Universidad Pública de Navarra

Departamento de Ciencias de la Salud

Delirium en el adulto mayor:

de los biomarcadores a la práctica clínica

TESIS DOCTORAL POR COMPENDIO DE PUBLICACIONES

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“Inténtalo y fracasa, pero no fracases en intentarlo”

Stephen Kaggwa

Tabla de contenidos

Tabla de contenidos 5
Índice de Tablas 6
Índice de figuras 7
Lista de abreviaturas 9
Financiación 11
Declaración, lista de publicaciones y comunicaciones a congresos 12
Listado de publicaciones 12
Comunicaciones presentadas a congresos internacionales 14
Agradecimientos 16
Resumen-Summary (Español-Inglés) 18
Introducción 29
Objetivos y diseño de la tesis 39
Chapter 1: Biomarkers of delirium risk in older adults: a systematic review and meta-analysis 45
Chapter 2: Association of postoperative delirium with serum and cerebrospinal fluid proteomic profiles: a prospective cohort study in older hip fracture patients 77
Chapter 3: The role of C-reactive protein as a risk marker of postoperative delirium in older hip fracture patients: a prospective cohort study 105
Chapter 4: Effectiveness of a multicomponent exercise training programme for the management of delirium in hospitalized older adults using Near-Infrared Spectroscopy (NIRS) as a biomarker of brain perfusion: study protocol for a randomized controlled trial 118
Chapter 5: Effects of exercise intervention for the management of delirium in acutely hospitalized older adults: a randomized clinical trial 141
Capítulo 6: Discusión general 168
Capítulo 7: Conclusiones, aplicaciones prácticas y futuras perspectivas. 181
Anexos 189

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Índice de Tablas

Chapter 1

Table 1. Risk markers of delirium 49

Table 2. Summary of main results of risk markers of delirium 52

Chapter 2

Table 1. Biomarkers analyzed with Olink® technology 82

Table 2. Biomarkers (cytokines and chemokines) within the analytic samples 85

Table 3. Baseline characteristics of patients with and without POD 88

Table 4. Characteristics after surgery of patients with and without POD 89

Chapter 3

Table 1. Logistic regression model between clinical variables and CRP 109

Chapter 4

Table 1. Time of measurement of the different variables on the subjects of the study .. 123

Table 2. Intervention group exercises 128

Chapter 5

Table 1. Main demographic, clinical, functional and cognitive characteristics at baseline by group 150

Table 2.a Results of primary end points: evolution of delirium 151

Table 2.b Results of primary end points: change in functional capacity 151

Table 3a. Results of secondary end points: in-hospital falls and length of stay 152

Table 3b. Results of secondary end points: 1- and 3-month follow-up 152

Table 3c. Results of secondary end points: 1- and 3-month follow up 153

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Índice de figuras

Introduction

Figura 1. Mecanismos fisiopatológicos implicados en el desarrollo del delirium 30

Figura 2. Factores predisponentes y precipitantes de delirium 31

Chapter 1

Figure 1. Flowchart 51

Figure 2. Forest plot 58

Figure 3. Recommendations for future research in delirium biomarkers 65

Chapter 2

Figure 1. Flowchart of study inclusion 87

Figure 2. Principal component (PCA) of POD and non-POD groups 90

Figure 3. Biomarkers identification according to serum and cerebrospinal fluid levels into POD and non-POD groups 91

Figure 4. Matrix of pairwise spearman correlations among biomarkers according to serum and cerebrospinal fluid levels for POD and non-POD groups adjusted by sex and age. 93

Chapter 3

Figure 1. Neuroinflammatory hypothesis of delirium: the difference between a healthy and a vulnerable brain in response to stressors in hip fracture..... 110

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Nafarroako Unibertsitate Publikoa

Chapter 4

Figure 1. Flow diagram of the study protocol 122
Figure 2. Sample collection and processing 124
Figure 3. Details of intervention 129
Figure 4. Training protocol 131

Chapter 5

Figure 1. Study design 145
Figure 2. Details of the study methodology 146
Figure 3. Flowchart of the study 149
Figure 4. The complex relationship between delirium and physical exercise 156

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Lista de abreviaturas

ABVD: Actividades Básicas de la Vida Diaria

4-AT: 4 'A's Test

BHE (BBB): Barrera hematoencefálica (Blood Brain Barrier)

CCL2: Quimiocina 2 (C-C motif chemokine 2)

CCL3: Quimiocina 3 (C-C motif chemokine 3)

CCL4: Quimiocina 4 (C-C motif chemokine 4)

CSF3: Factor Estimulante de Colonias 3 (Colony Stimulating Factor 3)

CXCL8: Quimiocina 8 (Chemokine C-X-C motif ligand 8)

CXCL9: Quimiocina 9 (Chemokine C-X-C motif ligand 9)

CXCR3: Receptor de quimiocinas CXCR3

DEAR: Delirium Elderly At Risk

DPO (POD): Delirium Postoperatorio (Postoperative Delirium)

DSD: Delirium Superimpuesto a Demencia (Delirium Superimposed Dementia)

EA (AD): Enfermedad de Alzheimer (Alzheimer Disease)

EGF: Factor de crecimiento epidérmico (Pro-epidermal growth factor)

HABAM scale: Hierarchical Assessment of Balance and Mobility scale

HELP: Hospital Elder Life Program

IL-6: Interleukina-6 (Interleukin-6)

IL-10: Interleukina-10 (Interleukin-10)

IQCODE-sf: Informant Questionnaire on COgnitive Decline in the Elderly-short form

LCR (CSF): líquido cefalorraquídeo (cerebrospinal fluid)

MDAS scale: Memorial Delirium Assessment Scale

NIRS: Espectroscopia de infrarrojo cercano

PCR (CRP): Proteína C-reactiva (C-reactive Protein)

PRE-DELIRIC: PREdiction of DELIRium in ICu patients

SIRS: Síndrome de respuesta inflamatoria sistémica (Systemic Inflammatory Response Syndrome)

SNC (CNS): Sistema Nervioso Central (Central Nervous System)

SPPB: Short Physical Performance Battery

TGFA: Factor de crecimiento protransformador α (Protransforming Growth Factor α)

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TNF-α: Factor de Necrosis tumoral-alpha (Tumour Necrosis Factor-alpha)

UCI: Unidad de Cuidados Intensivos

UGA (AGU): Unidad Geriátrica de Agudos (Acute Geriatric Unit)

VGI (CGA): Valoración Geriátrica Integral (Comprehension Geriatric Assessment)

Financiación

El proyecto titulado “Association of postoperative delirium with serum and cerebrospinal fluid proteomic profiles: a prospective cohort study in older hip fracture patients” fue financiado con una beca del Departamento de Desarrollo Económico y Empresarial del Gobierno de Navarra (Ref. 0011-1411-2020-000028).

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Declaración, lista de publicaciones y comunicaciones a congresos

Esta tesis doctoral es un compendio de tres artículos que han sido publicados en revistas nacionales e internacionales revisadas por pares y tres artículos que están bajo revisión para su publicación.

Lucía Lozano Vicario, como estudiante de doctorado es la autora principal de todos los artículos y ha sido la principal colaboradora en la concepción y diseño de los estudios, adquisición, análisis e interpretación de los datos, redacción de los artículos y aprobación final para su publicación.

Listado de publicaciones

1. Lozano-Vicario L, García-Hermoso A, Cedeno-Veloz BA, Fernández-Irigoyen J, Santamaría E, Romero-Ortuno R, Zambom-Ferraresi F, Sáez de Asteasu ML, Muñoz-Vázquez ÁJ, Izquierdo M, Martínez-Velilla N. Biomarkers of delirium risk in older adults: a systematic review and meta-analysis. Front Aging Neurosci. 2023 May 12;15:1174644. doi: 10.3389/fnagi.2023.1174644.

2. Lozano-Vicario L, Zambom-Ferraresi F, Zambom-Ferraresi F, de la Casa-Marín A, Ollo-Martínez I, Sáez de Asteasu ML, Cedeño-Veloz BA, Fernández-Irigoyen J, Santamaría E, Romero-Ortuno R, Izquierdo M, Martínez-Velilla N. Effectiveness of a multicomponent exercise training program for the management of delirium in hospitalized older adults using near-infrared spectroscopy as a biomarker of brain perfusion: Study protocol for a randomized controlled trial. Front Aging Neurosci. 2022 Dec 15;14:1013631. doi: 10.3389/fnagi.2022.1013631.

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3. Vicario-Lozano L, Martínez-Velilla N. Nuevos horizontes en el manejo del delirium [New horizons in the management of delirium]. Rev Esp Geriatr Gerontol. 2023 May-Jun;58(3):123-124. Spanish. doi: 10.1016/j.regg.2023.05.003.

4. Lozano-Vicario L, Muñoz-Vázquez AJ, Ramírez-Vélez R, Galbete-Jiménez A, Fernández-Irigoyen J, Santamaría E, Cedeno-Veloz BA, Zambom-Ferraresi F, Van Munster BC, Ortiz-Gómez JR, Hidalgo-Ovejero AM, Romero-Ortuno R, Izquierdo M, Martínez-Velilla N. Association of postoperative delirium with serum and cerebrospinal fluid proteomic profiles: a prospective cohort study in older hip fracture patients. Accepted in Geroscience.

5. Lozano-Vicario L, Muñoz-Vázquez AJ, Romero-Ortuno R, Galbete-Jiménez A, Fernández-Irigoyen J, Santamaría E, Cedeno-Veloz, BA; Zambom-Ferraresi F, Ortiz-Gómez JR, Hidalgo-Ovejero, AM; Martínez-Velilla N. The role of C-reactive protein as a risk marker of postoperative delirium in older hip fracture patients: a prospective cohort study. Submitted.

6. Lozano-Vicario L, Zambom-Ferraresi F, Zambom-Ferraresi F, de la Casa-Marín A, Ollo-Martínez I, Galbete-Jiménez, A; Sáez de Asteasu ML, Cedeño-Veloz BA, Fernández-Irigoyen J, Santamaría E, Izquierdo M, Martínez-Velilla N. Effects of exercise intervention for the management of delirium in acutely hospitalized older adults: a randomized clinical trial. Submitted.

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Comunicaciones presentadas a congresos internacionales

Comunicaciones orales:

1. "Delirium and surgery: pre, intra and post-surgical approach to manage delirium", 15th Annual Meeting of the European Delirium Association (EDA), 17-19 noviembre de 2021, Barcelona, España.
2. "Quality of life, cognitive and functional trajectories associated with postoperative delirium: a prospective cohort study in hip fracture patients with 1-and 3-month follow-up", 16th Annual Meeting of the European Delirium Association (EDA), 2-4 noviembre de 2022, Milán, Italia.

Poster:

1. "Impact of an exercise program in hospitalized older adults on the evolution of delirium: patient profile and benefits", 15th Annual Meeting of the European Delirium Association (EDA), 17-19 noviembre de 2021, Barcelona, España.
2. "Biomarkers of delirium risk in older adults: a systematic review and meta-analysis", 16th Annual Meeting of the European Delirium Association (EDA), 2-4 noviembre de 2022, Milán, Italia.
3. "In older hip fracture patients, postoperative delirium was significantly associated with pre-morbid cognition, but not with serum or cerebrospinal fluid cytokines", 16th Annual Meeting of the European Delirium Association (EDA), 2-4 noviembre de 2022, Milán, Italia.
4. "Prevalence of delirium in older adults with proximal hip fractures in Spain: a multicentric point prevalence study", 17th Annual Meeting of the European Delirium Association (EDA), 6-8 septiembre de 2023, Birmingham, Inglaterra.
5. "C-reactive protein as a risk marker of postoperative delirium in older hip fracture patients: a prospective cohort study", 19th International Congress of the European Geriatric Medicine Society (EuGMS), 20-22 septiembre de 2023, Helsinki, Finlandia.
6. "Effectiveness of a multicomponent exercise training program for the management of delirium in hospitalized older adults using Near-Infrared Spectroscopy (NIRS) as a biomarker of brain perfusion: study protocol", 19th International Congress of the

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European Geriatric Medicine Society (EuGMS), 20-22 septiembre de 2023, Helsinki, Finlandia.

7. “Postoperative delirium is significantly associated with a proteomic profile in serum and cerebrospinal fluid: a prospective cohort study in older hip fracture patients”, 19th International Congress of the European Geriatric Medicine Society (EuGMS), 20-22 septiembre de 2023, Helsinki, Finlandia.
8. “Clinical risk factors and baseline characteristics of patients with postoperative delirium after hip fracture surgery”, 19th International Congress of the European Geriatric Medicine Society (EuGMS), 20-22 septiembre de 2023, Helsinki, Finlandia.

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Si quieres ir rápido, camina solo; si quieres llegar lejos, ve acompañado.

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Resumen-Summary (Español-Inglés)

Resumen

La presente tesis doctoral gira en torno al potencial uso de los biomarcadores para predecir delirium en los adultos mayores y el uso de ejercicio físico como herramienta para modificar la evolución de éste una vez instaurado. El delirium es un síndrome neuropsiquiátrico grave y muy frecuente en los ancianos que conduce a la discapacidad y el deterioro cognitivo, entre otros. Los biomarcadores pueden ser una estrategia mínimamente invasiva y eficaz para predecir el delirium, ayudando a conocer mejor su fisiopatología y pudiendo contribuir al desarrollo de futuras dianas terapéuticas. Esta tesis doctoral se basa en 3 estudios publicados en distintas revistas nacionales e internacionales. En el primer estudio (Capítulo 1) nuestro objetivo fue evaluar la evidencia existente sobre los biomarcadores predictivos de delirium en el adulto mayor. En el segundo estudio (Capítulos 2 y 3) el objetivo principal fue analizar la asociación entre distintos biomarcadores en sangre y líquido cefalorraquídeo de pacientes con fractura de cadera y la incidencia de delirium. En el tercer estudio (Capítulos 4 y 5) el objetivo principal fue determinar la utilidad de un programa de ejercicio multicomponente en la evolución de pacientes mayores hospitalizados con delirium utilizando el NIRS como biomarcador de perfusión cerebral.

A continuación, se resume la metodología y los resultados más relevantes.

Capítulo 1: Biomarcadores de riesgo de delirium en adultos mayores: revisión sistemática y metaanálisis

El objetivo de este estudio fue realizar una revisión acerca de los biomarcadores predictivos del delirium en adultos mayores para profundizar en la fisiopatología de este síndrome y proporcionar una base para futuros estudios. Dos autores realizaron la búsqueda de forma independiente en las bases de datos MEDLINE, Embase, Cochrane Library, Web of Science y Scopus hasta agosto de 2021. Se incluyeron un total de 32 estudios. Solo 6 estudios fueron elegibles para el metaanálisis, y los resultados mostraron un aumento significativo en algunos biomarcadores en suero como la PCR, TNF-α e IL-6 entre los pacientes con delirium (razón de probabilidades = 1.88, IC del 95% 1.01 a 1.637; I^2 = 76.75%). Ésta es la primera revisión sistemática que se realiza acerca de biomarcadores predictivos de delirium sin restricción en año de publicación ni fluido analizado, teniendo

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en cuenta estudios de alta calidad. Sin embargo, presenta algunas limitaciones como son la heterogeneidad en la metodología de los estudios incluidos y la falta de consenso en la terminología asociada al delirium. Aunque la evidencia actual no apoya el uso de ningún biomarcador en particular, la PCR, el TNF-α y la IL-6 en suero fueron los biomarcadores más consistentes de delirium en pacientes mayores.

Capítulo 2: Asociación del delirium postoperatorio con un perfil proteómico en sangre y líquido cefalorraquídeo: un estudio de cohortes prospectivo en pacientes mayores con fractura de cadera

El propósito de este estudio fue investigar la relación entre los biomarcadores preoperatorios en suero y LCR y el desarrollo de DPO en pacientes mayores con fractura de cadera, explorando la posibilidad de integrar métodos objetivos en futuros modelos predictivos de delirium. Se reclutaron sesenta pacientes con fractura de cadera. Se tomaron muestras de sangre y LCR en el momento de la anestesia epidural cuando ninguno de los sujetos presentaba delirium. Los pacientes fueron evaluados diariamente utilizando la escala 4AT y, en función de estos resultados, se dividieron en grupos de DPO y sin DPO. Se utilizó la plataforma Olink® para analizar 45 citoquinas. Veintiún pacientes (35%) desarrollaron DPO. En la submuestra de 30 pacientes en la que se realizó análisis proteómicos, se encontró un perfil proteómico asociado con la incidencia de DPO. La quimiocina CXCL9 tuvo la correlación más fuerte entre las muestras de suero y LCR en pacientes con DPO (rho= 0.663; $p<0.05$). Aunque varias citoquinas en suero y LCR estuvieron asociadas con DPO después de la cirugía de fractura de cadera en adultos mayores, se encontró una asociación significativa con niveles preoperatorios más bajos de CXCL9 en LCR y suero. Este estudio aporta información valiosa sobre el delirium en una muestra bien definida y analizando no solamente suero (un fluido accesible), si no también LCR (un fluido en contacto directo con el parénquima cerebral), lo que permite establecer relaciones entre ambos, aproximando de una forma práctica los complejos procesos que tienen lugar en el SNC. Sin embargo, el tamaño muestral es pequeño y los resultados deben ser interpretados con cautela pues los biomarcadores inflamatorios no suelen ser específicos de una situación en concreto. A pesar del tamaño muestral reducido, este estudio proporciona evidencia del potencial papel de los biomarcadores moleculares en DPO, lo que podría sentar las bases para el desarrollo de nuevos modelos predictivos de

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delirium que incluyeran a los biomarcadores como herramienta diagnóstica no invasiva, objetiva y reproducible.

Capítulo 3: El papel de la proteína C-reactiva como marcador de riesgo de delirium postoperatorio en adultos mayores con fractura de cadera: un estudio de cohortes prospectivo

Los modelos predictivos actuales de delirium se basan en factores clínicos que pueden ser subjetivos e imprecisos. En este estudio, investigamos la asociación entre la PCR en suero y la aparición de DPO en pacientes mayores con fractura de cadera, y si la PCR era un mejor predictor de DPO en comparación con un modelo clínico. Se reclutaron pacientes de ≥75 años ingresados para cirugía tras una fractura de cadera. Se realizó una VGI al ingreso y se recogieron muestras de sangre antes de la cirugía en ausencia de delirium. El delirium se evaluó diariamente hasta el alta mediante la escala 4-AT. Comparamos los niveles de PCR en suero entre pacientes con y sin DPO y examinamos la asociación entre la PCR y la gravedad del delirium. Se utilizaron los test de Mann-Whitney U y Spearman para las comparaciones entre grupos. Sesenta pacientes fueron incluidos, de los cuales 21 (35%) desarrollaron DPO. Los niveles de PCR en suero fueron significativamente más altos en los pacientes que desarrollaron delirium (p=0.011), pero no se encontró una asociación significativa entre la PCR y la gravedad del delirium (p=0.079). En un modelo de regresión múltiple que incluyó las variables clínicas más representativas asociadas con el delirium (edad, comorbilidad, fuerza de prensión, fragilidad, infección y deterioro cognitivo) y la PCR, el deterioro cognitivo (p=0.003) y la infección (p=0.001) fueron los mejores predictores de DPO. Aunque niveles más altos de CRP en suero estuvieron significativamente asociados con el DPO en pacientes mayores con fractura de cadera, el deterioro cognitivo y las infecciones fueron los factores de riesgo más importantes para desarrollarlo.

Capítulo 4: Efectividad de un programa de ejercicio multicomponente para el manejo del delirium en adultos mayores hospitalizados usando la espectroscopia de infrarrojo cercano (NIRS) como un biomarcador de perfusión cerebral: protocolo de un ensayo aleatorizado controlado

Las intervenciones multicomponentes dirigidas a los factores de riesgo de delirium que incluyen el ejercicio físico y la movilización, han demostrado reducir la incidencia del

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mismo en un 30-40% en unidades de agudos. Sin embargo, se sabe poco sobre su papel en la evolución del delirium una vez establecido. Este estudio es un ensayo clínico aleatorizado que se llevará a cabo en la UGA del Hospital Universitario de Navarra (Pamplona, España). Los pacientes hospitalizados con delirium que cumplan con los criterios de inclusión serán asignados al azar al grupo de intervención o al grupo de control. La intervención consistirá en un programa de ejercicio físico multicomponente, que estará compuesto por un entrenamiento de resistencia y fuerza progresiva, de manera supervisada, durante 3 días consecutivos. Se utilizará el NIRS para evaluar el flujo sanguíneo cerebral y del tejido muscular. El objetivo será evaluar la efectividad de esta intervención en modificar los siguientes resultados primarios: duración y gravedad del delirium y estado funcional, contribuyendo a determinar la efectividad del ejercicio físico en el manejo del delirium. Será el primer estudio en evaluar el impacto de una intervención multicomponente basada en ejercicio físico en la evolución del delirium.

Registro del ensayo: Identificador de ClinicalTrials.gov: NCT05442892 (Fecha de registro 26.06.2022)

Capítulo 5: Efecto de una intervención basada en ejercicio físico para el manejo del delirium en adultos mayores hospitalizados: un ensayo clínico aleatorizado

Los tratamientos farmacológicos han mostrado efectividad limitada en el tratamiento del delirium. Por otro lado, y aunque los programas de ejercicio físico multicomponente han demostrado beneficios funcionales, el impacto del ejercicio en la evolución del delirium sigue siendo una incógnita. El objetivo de este estudio fue investigar el efecto de una intervención individualizada basada en ejercicio físico multicomponente en la evolución del delirium. Se llevó a cabo un ensayo clínico aleatorizado, unicéntrico y simple ciego, desde el 1 de febrero de 2022 hasta el 31 de mayo de 2023, en la UGA del Hospital Universitario de Navarra, España. Se reclutaron 36 pacientes médicos hospitalizados con delirium (media de edad de 87 años) y se asignaron aleatoriamente a dos grupos. El grupo control recibió la atención clínica habitual y el grupo intervención recibió ejercicio físico individualizado (1 sesión diaria) durante 3 días consecutivos. Las variables primarias que se evaluaron fueron la duración y gravedad del delirium (4-AT, MDAS) y el cambio en el estado funcional (Índice de Barthel, SPPB, HABAM y fuerza de prensión). Las variables secundarias incluyeron la estancia media hospitalaria, las caídas y

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otros resultados de salud al mes y a los 3 meses de seguimiento. El grupo de intervención mostró una mejoría funcional superior al alta (HABAM, p=0.015) y en el seguimiento (Barthel, p=0.041; Lawton p=0.027). Se observó un menor deterioro cognitivo al mes y a los 3 meses (IQCODE-sf, p=0.017). El ejercicio redujo la duración del delirium en 1 día y ayudó a la resolución del delirium al alta, aunque los hallazgos no alcanzaron significación estadística. No se produjeron eventos adversos relacionados con el ejercicio. Estos hallazgos sugieren que el ejercicio individualizado en pacientes mayores hospitalizados agudos con delirium es seguro, pudiendo mejorar el curso del delirium y contribuyendo a preservar la función y la cognición tras el alta hospitalaria.

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Summary

The current doctoral thesis focuses on the potential use of biomarkers to predict delirium in older adults and the use of physical exercise as a tool to modify its evolution once established. Delirium is a serious neuropsychiatric syndrome that is very common among older adults and can lead to disability and cognitive impairment. Biomarkers can be a minimally invasive and effective strategy for predicting delirium, helping to better understand its pathophysiology and potentially contributing to the development of future therapeutic targets. This doctoral thesis is based on three studies published in different national and international journals. In the first study (Chapter 1), our objective was to evaluate the existing evidence on predictive biomarkers of delirium in older adults. In the second study (Chapters 2 and 3), the main objective was to analyze the association between different biomarkers in blood and cerebrospinal fluid of patients with hip fracture and the incidence of delirium. In the third study (Chapters 4 and 5), the main objective was to determine the utility of a multicomponent exercise program in the evolution of hospitalized older patients with delirium using near-infrared spectroscopy (NIRS) as a biomarker of cerebral perfusion.

The most relevant methodology and results are summarized below.

Chapter 1: Biomarkers of delirium risk in older adults: a systematic review and meta-analysis

This study aimed to review predictive biomarkers of delirium in older patients to gain insights into the pathophysiology of this syndrome and provide guidance for future studies. Two authors independently and systematically searched MEDLINE, Embase, Cochrane Library, Web of Science and Scopus databases up to August 2021. A total of 32 studies were included. Only 6 studies were eligible for the meta-analysis, pooled results showed a significant increase in some serum biomarkers (CRP, TNF-α and IL-6) among patients with delirium (odds ratio = 1.88, 95% CI 1.01 to 1.637; I^2 = 76.75%). This is the first systematic review conducted on predictive biomarkers of delirium without restrictions on publication year or analyzed fluid, taking into consideration high-quality studies. However, it presents some limitations such as heterogeneity in the methodology of the studies included and lack of consensus in the terminology associated with delirium. Although

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current evidence does not favour the use of any particular biomarker, serum CRP, TNF-α, and IL-6 were the most consistent biomarkers of delirium in older patients.

Chapter 2: Association of postoperative delirium with serum and cerebrospinal fluid proteomic profiles: a prospective cohort study in older hip fracture patients

The purpose of this study was to investigate the relationship between preoperative biomarkers in serum and CSF and the development of POD in older hip fracture patients, exploring the possibility of integrating objective methods into future predictive models of delirium. Sixty hip fracture patients were recruited. Blood and CSF samples were collected at the time of spinal anesthesia when none of the subjects had delirium. Patients were assessed daily using the 4AT scale and based on these results, they were divided into POD and non-POD groups. The Olink® platform was used to analyze 45 cytokines. Twenty-one patients (35%) developed POD. In the subsample of 30 patients on whom proteomic analyses were performed, a proteomic profile was associated with the incidence of POD. CXCL9 had the strongest correlation between serum and CSF samples in patients with POD (rho= 0.663; $p<0.05$). Although several cytokines in serum and CSF were associated with POD after hip fracture surgery in older adults, there was a significant association with lower preoperative levels of CXCL9 in CSF and serum. This study provides valuable information about delirium in a well-defined sample, analyzing not only serum (an accessible fluid) but also cerebrospinal fluid (a fluid in direct contact with the brain parenchyma), allowing for the establishment of relationships between both fluids and providing a practical approach to the complex processes occurring in the CNS. However, the sample size is small, and the results should be interpreted with caution as inflammatory biomarkers are not typically specific to a particular situation. Despite the limited sample size, this study offers evidence of the potential role of molecular biomarkers in delirium prediction, potentially laying the groundwork for the development of new predictive models of delirium that incorporate biomarkers as non-invasive, objective, and reproducible diagnostic tools.

Chapter 3: The role of C-reactive protein as a risk marker of postoperative delirium in older hip fracture patients: a prospective cohort study

Current predictive models of delirium are based on clinical factors that can be subjective and imprecise. In this study we investigated the association between serum CRP

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and the occurrence of POD in older hip fracture patients, and whether CRP predicted POD better than a clinical model. Patients aged ≥75 years admitted for surgical repair of an acute hip fracture were recruited. A CGA was performed at admission and blood samples were collected preoperatively in the absence of delirium. Delirium was assessed daily until discharge with the 4-AT. We compared serum CRP levels between patients with and without POD and examined the association between CRP and delirium severity. Mann-Whitney U and Spearman tests were used for group comparisons. Sixty patients were included, of whom 21 (35%) developed POD. Serum CRP levels were significantly higher in patients who developed delirium (p=0.011), but no significant association was found between CRP and delirium severity (p=0.079). In a multiple regression model including the most representative clinical variables associated with delirium (age, comorbidity, grip strength, frailty, infection and pre-existing cognitive impairment) and CRP, cognitive impairment (p=0.003) and infection (p=0.001) were the best predictors of POD. Although higher levels of serum CRP were significantly associated with POD in older hip fracture patients, pre-existing cognitive impairment and infections were the most important risk factors for POD.

Chapter 4: Effectiveness of a multicomponent exercise training programme for the management of delirium in hospitalized older adults using Near-Infrared Spectroscopy (NIRS) as a biomarker of brain perfusion: study protocol for a randomized controlled trial

Multicomponent interventions targeting delirium risk factors, including physical exercise and mobilization, have been shown to reduce delirium incidence by 30-40% in acute care settings. However, little is known about its role in the evolution of delirium, once established. This study is a randomized clinical trial conducted in the ACU of Hospital Universitario de Navarra (Pamplona, Spain). Hospitalized patients with delirium who meet the inclusion criteria will be randomly assigned to the intervention or the control group. The intervention will consist of a multicomponent exercise training programme, which will be composed of supervised progressive resistance and strength exercise training during 3 consecutive days. NIRS will be used for assessing cerebral and muscle tissue blood flow. The objective is to assess the effectiveness of this intervention in modifying the following primary outcomes: duration and severity of delirium and functional status. This study will contribute to determine the effectiveness of physical exercise in the management of

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delirium. It will be the first study to evaluate the impact of a multicomponent intervention based on physical exercise in the evolution of delirium.

Trial registration: ClinicalTrials.gov Identifier: NCT05442892 (Date of registration 26.06.2022)

Chapter 5: Effects of exercise intervention for the management of delirium in acutely hospitalized older adults: a randomized clinical trial

Pharmacological treatments have shown limited effectiveness in the treatment of delirium. Although multicomponent physical exercise programs have demonstrated functional benefits, the impact of exercise on the course of delirium remains unexplored. The aim of this study was to investigate the effect of an individualized, multicomponent exercise intervention on the evolution of delirium and patient outcomes. A single-center, single-blind randomized controlled trial was conducted from February 1, 2022, to May 31, 2023, in an acute geriatric unit of a tertiary public hospital in Navarra, Spain. Thirty-six medical inpatients with delirium (mean age 87 years) were recruited and randomized into two groups. The control group received usual care and the intervention group received individualized physical exercise (1 daily session) during 3 consecutive days. Primary endpoints were the duration and severity of delirium (4-AT, MDAS) and change in functional status (Barthel Index, SPPB, HABAM and handgrip strength. Secondary endpoints included length of stay, falls, and health outcomes at 1 and 3-month follow-up. The intervention group showed more functional improvement at discharge (HABAM, p=0.015) and follow-up (Barthel, p=0.041; Lawton p=0.027). Less cognitive decline was observed at 1 and 3-months (IQCODE-sf, p=0.017). Exercise seemed to reduce delirium duration by 1 day and contribute to delirium resolution at discharge, although findings did not reach statistical significance. No exercise-related adverse events occurred. These findings suggest that individualized exercise in acutely hospitalized older patients with delirium is safe, may improve delirium course and help preserve post-hospitalization function and cognition.

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Introducción

Como consecuencia del desarrollo socioeconómico, la mejora en las condiciones de vida y la disminución de la natalidad se está produciendo un aumento del envejecimiento poblacional en distintos países. Dentro de la Unión Europea, el 21 % de la población tenía 65 años o más en el año 2020, frente al 16 % en 2001, lo que supone un aumento de 5 puntos porcentuales. Este crecimiento se observa especialmente en el grupo de personas mayores de 80 años, donde su cuota era del 6 % en 2020, mientras que en 2001 se encontraba en el 3,4 %, lo que significa que, prácticamente, se duplicó durante este periodo. En España, el porcentaje actual de personas mayores de 65 años es del 19,09% (algo más de 9 millones) y los estudios indican que este envejecimiento seguirá creciendo de forma exponencial hasta el año 2050 donde alcanzaría el 31,4%, superando la media europea que sería del 28,5%.[1]

El envejecimiento se caracteriza por la acumulación gradual de daño molecular y celular con el paso de los años, lo que se manifiesta como una disregulación de la respuesta fisiológica de diferentes órganos y sistemas, especialmente una disminución en la capacidad de adaptación a los estímulos o agresiones externas y una escasez de mecanismos compensatorios.[2] El acúmulo de factores predisponentes en múltiples dominios asociados al envejecimiento (disminución de la fuerza muscular y la capacidad aeróbica, inestabilidad vasomotora, insensibilidad barorreceptora, reducción de la densidad ósea, disminución de la ventilación y la capacidad sensorial …etc.) y la presencia de enfermedades crónicas, conducen a la vulnerabilidad y la aparición de diferentes síndromes geriátricos. Un síndrome geriátrico es, por tanto, un conjunto de cuadros clínicos de etiología diversa, caracterizados por su elevada prevalencia en el adulto mayor que conducen hacia una cascada de discapacidad donde una alteración funcional o clínica precipita otra, afectando, en último término, a la calidad de vida del paciente y limitando su autonomía. Dentro de los síndromes geriátricos, podríamos clasificarlos, atendiendo a los diferentes dominios como sería el deterioro funcional (caídas, úlceras por presión, fragilidad, sarcopenia, malnutrición…etc), la polifarmacia, la incontinencia, la deprivación sensorial o la disfunción cognitiva (deterioro cognitivo y delirium), entre otros.[3]

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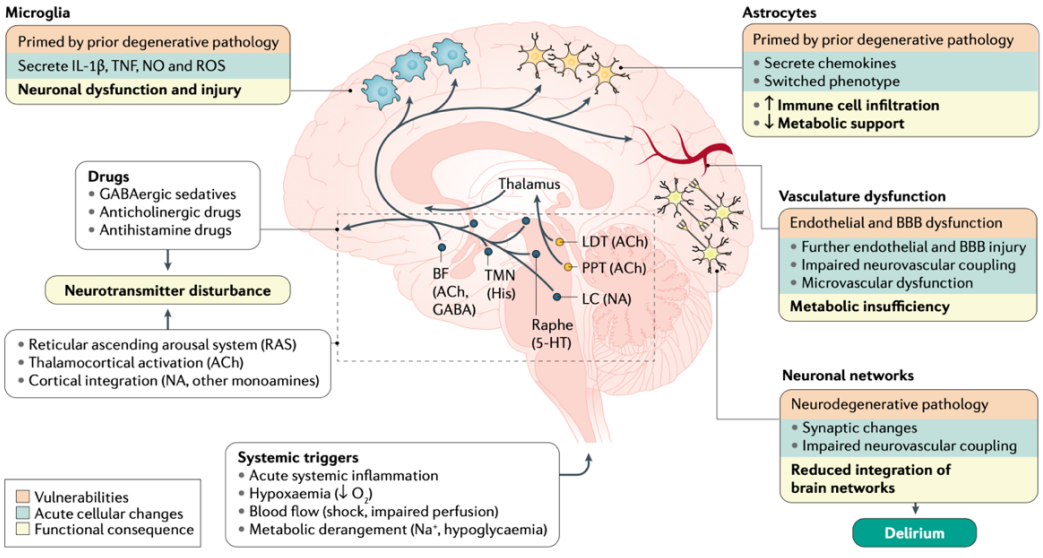
El término **"delirium"** deriva del latín *delirare*, que significa "desviarse del camino" y constituye un síndrome neuropsiquiátrico grave caracterizado por una alteración brusca en el nivel de consciencia, la atención y la cognición, causado en la mayoría de las ocasiones, por una enfermedad orgánica subyacente.[4] Esta entidad es especialmente importante por su alta prevalencia y el gran impacto de sus consecuencias en el adulto mayor. Aproximadamente, un tercio de los pacientes hospitalizados desarrollan delirium, pero su prevalencia aumenta en servicios quirúrgicos (20-50%), unidades de cuidados paliativos (59-88%) y cuidados intensivos (50-70%).[5] La aparición de delirium conlleva entre otras una mayor estancia hospitalaria, numerosas complicaciones médicas (inmovilismo, úlceras por presión, caídas, yatrogenia, deshidratación, malnutrición), deterioro funcional y cognitivo (cerca de un tercio de los pacientes que presentan delirium desarrollarán demencia), institucionalización, mayor mortalidad y consumo de recursos sanitarios.[6] También es interesante tener en cuenta el concepto de delirium subsindrómico, que comprende aquellos estados subumbrales de delirium, a menudo desapercibidos, pero que, al igual que el delirium, está relacionado con peores resultados de salud.[7,8]

A pesar de su importancia clínica y de existir herramientas eficaces validadas para su detección, el delirium es un síndrome habitualmente infradiagnosticado, sobre todo en pacientes con delirium hipoactivo, y, por tanto, no manejado adecuadamente. A ello se le suma el hecho de que la fisiopatología es muy compleja y sigue sin conocerse con exactitud, lo que dificulta enormemente su abordaje.[9]

Figura 1. Mecanismos fisiopatológicos implicados en el desarrollo del delirium (Wilson et al. 2020)



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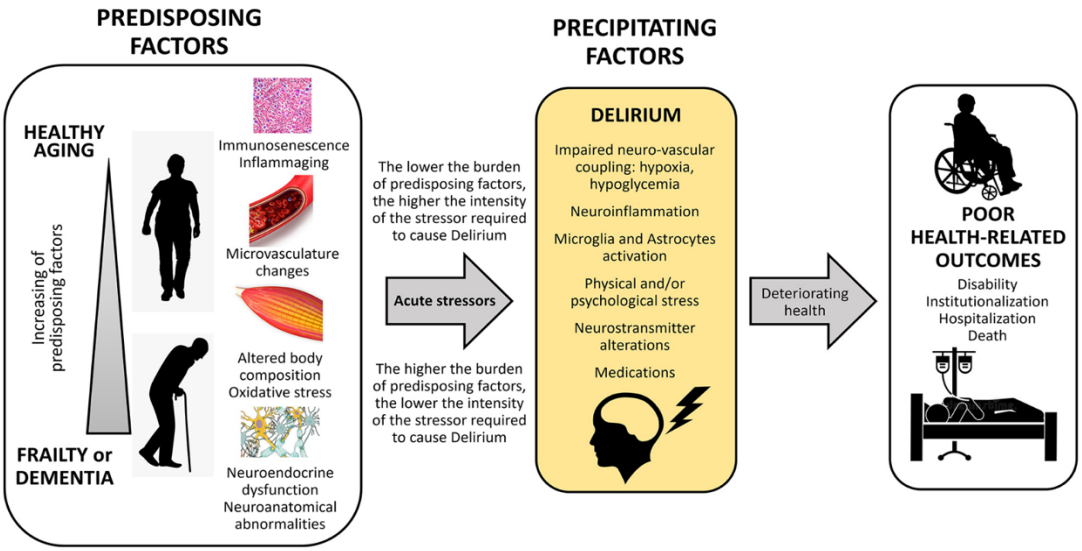
Ningún fármaco ha demostrado suficiente evidencia en el tratamiento del delirium, por lo que la mejor estrategia para minimizar el impacto de sus consecuencias es la prevención, identificando a los sujetos de alto riesgo para poder modificar su trayectoria cognitiva y funcional.[10]

Los modelos clásicos de predicción de delirium se han basado en la combinación de una serie de factores clínicos predisponentes (factores que confieren vulnerabilidad a un sujeto para desarrollar delirium como la edad, el deterioro cognitivo o la deprivación sensorial) y en factores precipitantes (aquellos que lo desencadenan como los procesos infecciosos, algunos fármacos o las descompensaciones metabólicas).[11] Herramientas como el PRE-DELIRIC[12] en UCI o la escala DEAR[13] en cirugía ortopédica, han demostrado ser útiles, sin embargo, presentan algunas limitaciones como son la subjetividad al tratarse de valoraciones clínicas, lo que les confiere cierta imprecisión.

Figura 2. Factores predisponentes y precipitantes de delirium (Bellelli et al. 2021)



En los últimos años, ha habido un interés creciente por el estudio de los biomarcadores en el contexto del delirium. Un biomarcador es una sustancia utilizada como indicador de un estado biológico, es decir, una molécula cuantificable que podemos medir de forma objetiva en relación con un proceso biológico normal, un estado patológico o como respuesta a un tratamiento farmacológico. Los biomarcadores son parte de las nuevas

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herramientas usadas en la medicina de precisión y pueden ser de tipo molecular, celular o de imagen[14,15]. Éstos podrían tener distintas aplicaciones en el ámbito del delirium como la implementación en la prevención identificando biomarcadores predictivos de delirium, la mejora del diagnóstico o el seguimiento durante recuperación, en fluidos accesibles como el suero, que complementarían las limitaciones de los actuales modelos clínicos disponibles.[16,17] También serían de gran ayuda en el diagnóstico, fundamentalmente en aquellos casos complejos como el DSD o pacientes intubados en UCI donde se están empezando a realizar estudios con técnicas de ecografía doppler a pie de cama o NIRS como biomarcadores de perfusión cerebral no invasivos, con resultados prometedores.[18–21] De hecho, cada vez se utilizan más técnicas como el electroencefalograma o el NIRS como herramientas de neuromonitorización en el campo de la Anestesiología, para evitar sedaciones profundas y detectar precozmente la hipoperfusión cerebral con el objetivo de disminuir la incidencia de DPO.[22,23] Por otro lado, comprender mejor los mecanismos fisiopatológicos implicados en el desarrollo de este síndrome, podría abrir nuevas líneas de investigación en el tratamiento farmacológico de esta entidad, actuando sobre moléculas diana, como es el caso de la vía del ácido quinolínico y su asociación con el delirium en fractura de cadera[24] o la implicación del neurofilamento ligero como marcador de daño neuronal y su asociación con el deterioro cognitivo posterior al delirium.[25]

Con respecto al manejo farmacológico del delirium, y aunque ha cobrado importancia el uso de algunos fármacos en su tratamiento como son la melatonina, el ramelteon o la dexmedetomidina,[26,27] ningún fármaco ha demostrado ser eficaz en la prevención ni en el tratamiento del delirium en la actualidad.[28] Las estrategias basadas en identificar y corregir los factores de riesgo modificables predisponentes y precipitantes de delirium son las más efectivas tanto para la prevención como para el tratamiento de este síndrome. Dado que el delirium presenta una etiología multifactorial, la recomendación de un solo elemento para su prevención y tratamiento no es de gran utilidad. Por este motivo, las intervenciones que han demostrado más eficacia son los programas multicomponente, compuestos de distintas medidas que actúan sobre los desencadenantes y factores de riesgo del desarrollo de delirium modificables como son el trastorno del sueño, las alteraciones neurosensoriales o el inmovilismo, entre otras.[29]

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El proyecto HELP, fue el primer programa multicomponente que se desarrolló y cuya implantación, consiguió prevenir y reducir la incidencia de delirium en un 40%, disminuyendo, a su vez, las caídas, la estancia media hospitalaria y la institucionalización al alta, ahorrando importantes costes sanitarios.[30] Todos los programas multicomponente presentan intervenciones sobre la función física para reducir el inmovilismo como son la disminución del tiempo de reposo en cama de los pacientes, el fomento de la autonomía a través de la realización de las ABVD por los propios pacientes y la retirada, en la medida de lo posible, de catéteres, vías o sondas para facilitar los desplazamientos de los sujetos, entre otros[31]. Es por ello razonable pensar que el ejercicio físico podría ser en sí mismo, una posible vía de abordaje tanto en la prevención[32] como en el tratamiento del delirium[33,34] dadas sus propiedades antiinflamatorias, neuroprotectoras y angiogénicas, favoreciendo el flujo sanguíneo cerebral.

Aunque los estudios realizados hasta el momento explorando estas líneas de trabajo están ofreciendo resultados prometedores, presentan ciertas limitaciones como son la heterogeneidad en su metodología, la falta de caracterización de los síndromes geriátricos en la población estudiada y el escaso uso de herramientas validadas para la detección del delirium, así como la tipificación del mismo y su gravedad. Este es un punto crucial que abre la posibilidad a desarrollar estudios de calidad con nuevas estrategias que complementen y ayuden a implementar los actuales modelos de manejo de delirium.

Finalmente, esta tesis describe la justificación, el diseño, la metodología y los resultados de varios estudios realizados en adultos mayores hospitalizados con delirium. Se plantea la hipótesis de que pacientes con perfiles proteómicos alterados en fluidos como son la sangre y el líquido cefalorraquídeo tienen más riesgo de presentar delirium y que el ejercicio físico puede ser una estrategia que ayude a modificar positivamente la evolución del delirium una vez instaurado.

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Referencias

1. Instituto Nacional de Estadística. at https://www.ine.es/prodyser/demografia_UE/bloc-1c.html.
2. López-Otín, C. Hallmarks of aging: An expanding universe. *Cell* **186**, 243–278 (2023) doi:10.1016/j.cell.2022.11.001.
3. Inouye, S. K. Geriatric syndromes: Clinical, research, and policy implications of a core geriatric concept. *J. Am. Geriatr. Soc.* **55**, 780–791 (2007) doi:10.1111/j.1532-5415.2007.01156.x.
4. Sachdev, P. S. Classifying neurocognitive disorders: The DSM-5 approach. *Nat. Rev. Neurol.* **10**, 634–642 (2014) doi:10.1038/nrneurol.2014.181.
5. Bellelli, G. Delirium: A Marker of Vulnerability in Older People. *Front. Aging Neurosci.* **13**, 1–13 (2021) doi:10.3389/fnagi.2021.626127.
6. Welch, C. Delirium is prevalent in older hospital inpatients and associated with adverse outcomes: Results of a prospective multi-centre study on World Delirium Awareness Day. *BMC Med.* **17**, 1–11 (2019) doi:10.1186/s12916-019-1458-7.
7. Cole, M. G. Subsyndromal delirium in older people: A systematic review of frequency, risk factors, course and outcomes. *Int. J. Geriatr. Psychiatry* **28**, 771–780 (2013) doi:10.1002/gps.3891.
8. Gao, Y. Prevalence, risk factors, and outcomes of subsyndromal delirium in older adults in hospital or long-term care settings: A systematic review and meta-analysis. *Geriatr. Nurs. (Minneap).* **45**, 9–17 (2022) doi:10.1016/j.gerinurse.2022.02.021.
9. Wilson, J. E. Delirium. *Nat. Rev. Dis. Prim.* **6**, (2020) doi:10.1038/s41572-020-00223-4.
10. Fong, T. G. The inter-relationship between delirium and dementia: the importance of delirium prevention. *Nat. Rev. Neurol.* (2022) doi:10.1038/s41582-022-00698-7.
11. Ormseth, C. H. Predisposing and Precipitating Factors Associated with Delirium: A Systematic Review. *JAMA Netw. Open* **6**, E2249950 (2023) doi:10.1001/jamanetworkopen.2022.49950.
12. Linkaitė, G. Evaluation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for the patients in the intensive care unit. *Acta medica*

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Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

Litu. **25**, 14–22 (2018) doi:10.6001/actamedica.v25i1.3699.

13. Freter, S. Risk of pre- and post-operative delirium and the delirium elderly at risk (DEAR) tool in hip fracture patients. *Can. Geriatr. J.* **18**, 212–216 (2015) doi:10.5770/cgj.18.185.
14. Aronson, J. K. Biomarkers—a general review. *Curr. Protoc. Pharmacol.* **2017**, 9.23.1-9.23.17 (2017) doi:10.1002/cpph.19.
15. Strimbu, K. What are biomarkers? *Curr. Opin. HIV AIDS* **5**, 463–466 (2010) doi:10.1097/COH.0b013e32833ed177.
16. Oren, R. L. Age - dependent differences and similarities in the plasma proteomic signature of postoperative delirium. *Sci. Rep.* 1–13 (2023) doi:10.1038/s41598-023-34447-7.
17. Wiredu, K. Proteomics for the Discovery of Clinical Delirium Biomarkers: A Systematic Review of Major Studies. *Anesth. Analg.* **136**, 422–432 (2023) doi:10.1213/ane.0000000000006246.
18. Wood, M. D. The Use of Near-Infrared Spectroscopy and/or Transcranial Doppler as Non-Invasive Markers of Cerebral Perfusion in Adult Sepsis Patients With Delirium: A Systematic Review. *J. Intensive Care Med.* **37**, 408–422 (2022) doi:10.1177/0885066621997090.
19. Caplan, G. A. Transcranial doppler to measure cerebral blood flow in delirium superimposed on Dementia. A cohort study. *J. Am. Med. Dir. Assoc.* **15**, 355–360 (2014) doi:10.1016/j.jamda.2013.12.079.
20. Susano, M. J. Association Among Preoperative Cognitive Performance, Regional Cerebral Oxygen Saturation, and Postoperative Delirium in Older Portuguese Patients. *Anesth. Analg.* **132**, 846–855 (2021) doi:10.1213/ANE.0000000000005159.
21. Ding, L. Effects of electroencephalography and regional cerebral oxygen saturation monitoring on perioperative neurocognitive disorders: A systematic review and meta-analysis. *BMC Anesthesiol.* **20**, 1–13 (2020) doi:10.1186/s12871-020-01163-y.
22. Chan, M. T. V. American Society for Enhanced Recovery and Perioperative quality initiative joint consensus statement on the role of neuromonitoring in perioperative outcomes: Electroencephalography. *Anesth. Analg.* **XXX**, 1278–1291 (2020) doi:10.1213/ANE.0000000000004502.

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

23. Thiele, R. H. American society for enhanced recovery and perioperative quality initiative joint consensus statement on the role of neuromonitoring in perioperative outcomes: Cerebral near-infrared spectroscopy. *Anesth. Analg.* **131**, 1444–1455 (2020) doi:10.1213/ANE.0000000000005081.
24. Watne, L. O. Cerebrospinal fluid quinolinic acid is strongly associated with delirium and mortality in hip-fracture patients. *J. Clin. Invest.* **133**, (2023) doi:10.1172/JCI163472.
25. Krogseth, M. Delirium, neurofilament light chain and progressive cognitive impairment: analysis of a prospective Norwegian population-based cohort. **7568**, 1–10 (2023) doi:10.1016/S2666-7568(23)00098-3.
26. Qin, C. Perioperative dexmedetomidine administration to prevent delirium in adults after non-cardiac surgery: A systematic review and meta-analysis. *J. Clin. Anesth.* **73**, 110308 (2021) doi:10.1016/j.jclinane.2021.110308.
27. Yang, C. P. Melatonergic agents in the prevention of delirium: A network meta-analysis of randomized controlled trials. *Sleep Med. Rev.* **50**, 101235 (2020) doi:10.1016/j.smrv.2019.101235.
28. Burton, J. K. Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst. Rev.* **2021**, (2021) doi:10.1002/14651858.CD013307.pub2.
29. Gual, N. The role of physical exercise and rehabilitation in delirium. *Eur. Geriatr. Med.* **11**, 83–93 (2020) doi:10.1007/s41999-020-00290-6.
30. Hshieh, T. T. Hospital Elder Life Program: Systematic Review and Meta-analysis of Effectiveness. *Am. J. Geriatr. Psychiatry* **26**, 1015–1033 (2018) doi:10.1016/j.jagp.2018.06.007.
31. Wang, Y. Y. Effect of the Tailored, Family-Involved Hospital Elder Life Program on Postoperative Delirium and Function in Older Adults: A Randomized Clinical Trial. *JAMA Intern. Med.* **180**, 17–25 (2020) doi:10.1001/jamainternmed.2019.4446.
32. Janssen, T. L. A multicomponent prehabilitation pathway to reduce the incidence of delirium in elderly patients in need of major abdominal surgery: Study protocol for a before-and-after study. *BMC Geriatr.* **19**, 1–10 (2019) doi:10.1186/s12877-019-1101-7.
33. Sáez de Asteasu, M. L. Effects of Physical Exercise on the Incidence of Delirium and

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Nafarroako Unibertsitate Publikoa

Cognitive Function in Acutely Hospitalized Older Adults: A Systematic Review with Meta-Analysis. *J. Alzheimer's Dis.* **87**, 503–517 (2022) doi:10.3233/JAD-220103.

34. Martinez Velilla, N. Could a Tailored Exercise Intervention for Hospitalised Older Adults Have a Role in the Resolution of Delirium? Secondary Analysis of a Randomised Clinical Trial. *J. Frailty Aging* **12**, 84–85 (2023) doi:10.14283/jfa.2022.60.

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Objetivos y diseño de la tesis

Capítulo 1

Estudio 1

Título: Biomarcadores de riesgo de delirium en adultos mayores: revisión sistemática y metaanálisis

Objetivo de la investigación: Analizar de forma sistemática la literatura sobre biomarcadores de delirium e identificar aquellos que sean predictivos del mismo en adultos mayores con el fin de sintetizar el conocimiento existente hasta ahora y profundizar en el conocimiento de su fisiopatología, proporcionando una guía para futuros estudios.

Hipótesis: Algunos biomarcadores biológicos pueden ser capaces de predecir la incidencia de delirium. La gran heterogeneidad en la metodología de los estudios. La gran heterogeneidad en los aspectos metodológicos de los estudios dificultaría aclarar las discrepancias entre ellos.

Capítulo 2

Estudio 2

Título: Asociación del delirium postoperatorio con un perfil proteómico en sangre y líquido cefalorraquídeo: un estudio de cohortes prospectivo en pacientes mayores con fractura de cadera

Objetivo de la investigación: Caracterizar de manera exhaustiva a los pacientes con delirium desde un punto de vista clínico y proteómico, con el fin de evaluar si los cambios en el perfil inmunológico preoperatorio podrían estar asociados con el delirium postoperatorio tras la cirugía de fractura de cadera.

Hipótesis: Se planteó la hipótesis de que los adultos mayores con fractura de cadera que presentan perfiles alterados de citoquinas en suero y líquido cefalorraquídeo antes de la cirugía podrían tener un mayor riesgo de desarrollar delirium.

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Capítulo 3

Estudio 2

Título: El papel de la proteína C-reactiva como marcador de riesgo de delirium postoperatorio en adultos mayores con fractura de cadera: un estudio de cohortes prospectivo.

Objetivo de la investigación: Determinar si la proteína C-reactiva (PCR) se asocia con el desarrollo y la gravedad del delirium tras la cirugía de fractura de cadera en una muestra de adultos mayores homogénea y bien definida, evaluando otros síndromes geriátricos con el fin de saber cuál de los dos modelos (bioquímico o clínico) es el más efectivo para predecir delirium.

Hipótesis: Se planteó la hipótesis de que los pacientes mayores con fractura de cadera que presentan niveles alterados de PCR en suero antes de la cirugía podrían tener un mayor riesgo de desarrollar delirium, y esto podría contribuir a mejorar los modelos clínicos predictivos del delirium, que a menudo pueden ser subjetivos e imprecisos.

Capítulo 4

Estudio 3

Título: Efectividad de un programa de ejercicio multicomponente para el manejo del delirium en adultos mayores hospitalizados usando la espectroscopia de infrarrojo cercano (NIRS) como un biomarcador de perfusión cerebral: protocolo de un ensayo aleatorizado controlado.

Objetivo de la investigación: Evaluar la efectividad de una intervención basada en ejercicio multicomponente para modificar la duración y gravedad del delirium, así como la capacidad funcional en adultos mayores hospitalizados con delirium en una Unidad Geriátrica de Agudos.

Hipótesis: Se plantea la hipótesis de que estrategias que ayudan a mejorar el aporte de oxígeno al cerebro, como el ejercicio físico, podrían ser útiles en el tratamiento del delirium, y que la espectroscopia de infrarrojo cercano (NIRS) podría utilizarse como biomarcador del flujo sanguíneo cerebral.

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Capítulo 5

Estudio 3

Título: Efecto de una intervención basada en ejercicio físico para el manejo del delirium en adultos mayores hospitalizados: un ensayo clínico aleatorizado.

Objetivo de la investigación: Evaluar el efecto de un programa basado en ejercicio físico multicomponente individualizado, en el estado funcional y cognitivo de los adultos mayores hospitalizados con delirium en una UGA.

Hipótesis: Se planteó la hipótesis de que estrategias que favorecen la perfusión cerebral, como el ejercicio físico, podrían mejorar potencialmente la evolución del delirium una vez que éste se ha desarrollado.

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Aims and layouts of the thesis

Chapter 1

Study 1

Title: Biomarkers of delirium risk in older adults: a systematic review and meta-analysis.

Research aim: To systematically analyze the current literature on delirium biomarkers and identify risk markers in older adults to summarize the existing knowledge, enhance our understanding regarding the pathophysiology and provide methodological guidance for future studies.

Hypothesis: It was hypothesized that some biological biomarkers can predict delirium incidence. The large heterogeneity in the methodological aspects of the studies would make it difficult to clarify the discrepancies between them.

Chapter 2

Study 2

Title: Association of postoperative delirium with serum and cerebrospinal fluid proteomic profiles: a prospective cohort study in older hip fracture patients.

Research aim: to comprehensively characterize patients with delirium both from a clinical point of view and using a proteomic approach, in order to evaluate whether changes in the preoperative immunological profile could be associated with POD after hip fracture surgery.

Hypothesis: It was hypothesized that older hip fracture patients with altered cytokine profiles in serum and cerebrospinal fluid before surgery could be at higher risk of developing delirium.

Chapter 3

Study 2

Title: The role of C-reactive protein as a risk marker of postoperative delirium in older hip fracture patients: a prospective cohort study.

Research aim: to investigate whether CRP was associated with the development and severity of delirium after hip fracture surgery in a homogeneous and well-defined older population, measuring other geriatric syndromes in order to assess which of the two models (biochemical or clinical) was more effective in predicting delirium.

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Hypothesis: It was hypothesized that older hip fracture patients with altered CRP in serum before surgery could be at higher risk of developing delirium, and this could help to improve clinical predictive models of delirium that can be subjective and imprecise.

Chapter 4

Study 3

Title: Effectiveness of a multicomponent exercise training programme for the management of delirium in hospitalized older adults using Near-Infrared Spectroscopy (NIRS) as a biomarker of brain perfusion: study protocol for a randomized controlled trial

Research aim: to assess the effectiveness of a multicomponent exercise intervention in modifying the duration and severity of delirium and functional status of hospitalized older adults with delirium in an Acute Geriatric Unit.

Hypothesis: we hypothesized that strategies that help improve oxygen supply to the brain, such as physical exercise, could be useful in treating delirium and NIRS could be used as a biomarker of cerebral blood flow.

Chapter 5

Study 3

Title: Effects of exercise intervention for the management of delirium in acutely hospitalized older adults: a randomized clinical trial.

Research aim: To evaluate the effect of a multicomponent physical exercise program on cognitive and functional status among hospitalized older adults with delirium in an AGU.

Hypothesis: We hypothesized that strategies capable of enhancing cerebral perfusion, such as physical exercise, could potentially improve the evolution of delirium once it has developed.

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Chapter 1
Biomarkers of delirium risk in older adults: a systematic review and meta-analysis

Capítulo 1
Biomarcadores de riesgo de delirium en adultos mayores: revisión sistemática y metaanálisis

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1. Introduction

The risk of delirium is determined by predisposing factors (for example, pre-existing cognitive impairment, advanced age or frailty) and precipitating factors (acute insults such as surgery, infections or metabolic decompensations).[1] Because multiple factors are implicated in the aetiology of delirium, there are likely several neurobiological processes that contribute to its pathophysiology, that remains unclear. During delirium, a reversal of the relationship between the dorsolateral prefrontal cortex (part of the executive network)[2] and the posterior cingulate cortex (involved in the default mode network)[3] has been observed, contributing to changes in behaviour and attention. In addition, reduced brain efficiency and connectivity strength (especially in subcortical regions related to arousal) have been found in patients with delirium. Delirium can be defined as a failure of a vulnerable brain to show resilience in response to an acute stressor.[4] This vulnerability can be caused by several processes such as impaired brain network connectivity which leads to neurotransmitter disturbance in cholinergic and noradrenergic neurons[5], neuroinflammatory and glial cell changes which causes an exacerbated pro-inflammatory response to noxious insults[6] and vasculature dysfunction which produces endothelial injury, blood-brain barrier (BBB) damage and impaired brain perfusion.[7]

Given the complexity of these processes, the use of biomarkers has become widespread for identification of delirium and its risk. The World Health Organization (WHO) defines a biomarker as any substance, structure, or process that can be measured in the body or its products that can influence or predict the incidence of outcome or disease.[8] Biomarkers are objective and quantifiable characteristics of biological processes, which makes them a reliable and reproducible measure.[9]They are categorized into three patterns: (1) risk markers, which indicate the risk of a particular disease; (2) disease markers, which are correlated with the onset or recovery of a disease; and (3) end-products, which indicate disease resolution.[10] The identification of biomarkers associated with delirium may help clarify its pathophysiology and aid in the prediction, diagnosis and management of this syndrome. Although few systematic reviews have been recently carried out on delirium biomarkers, they present important limitations, such as restriction to a single fluid[11–13] or a

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single biomarker,[14,15] different types of mixed biomarkers[16,17] and the absence of a focus on older adults, in whom delirium risk is the greatest.

Thus, the aim of this study was to systematically review the current literature on delirium biomarkers and identify risk markers in older adults to summarize the existing knowledge, enhance our understanding regarding the pathophysiology and provide methodological guidance for future studies.

2. Material and methods

2.1. Search strategy

This systematic review was undertaken in accordance with the guidelines described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. We asked the question whether incident delirium was associated with biomarkers and summarized data extracted from included studies.

Two reviewers searched studies published before 17 August 2021 that investigated delirium biomarkers. Searches were performed using a comprehensive text-word and Medical Subject Headings-based electronic search of MEDLINE, EMBASE, The Cochrane Library, Web of Science and Scopus. Primary key words included: “delirium” and “biomarker” used in combination with additional key words as: “cognitive dysfunction”, “acute confusion state”, “acute brain failure”, “postoperative delirium” or “postoperative cognitive disorder”. Boolean operators were used to combine search terms above. Authors with specialist knowledge of the subject extracted the data. The review protocol was registered in PROSPERO (CRD42021281272).

2.2. Selection criteria

The inclusion criteria were: study design (case-control, cohort study or case series with non-delirious subjects as controls), language of publication (english or spanish), year of publication: all studies until 17.08.2021, study subjects: mean patient aged ≥65 years, diagnostic criteria of delirium (Diagnostic Statistical Manual of Mental Disorders (DSM), International Classification of Diseases (ICD), Delirium assessment tool based on DSM or ICD), source of biomarker (cerebrospinal fluid, blood or other body fluids), measurement methods (methods that provide quantitative or detailed qualitative data), and full text available with detailed information.

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The exclusion criteria were: study design (reviews, case reports or comments, letters, personal opinions, book chapters and conference abstracts), randomized controlled trials (RCTs) measuring the effects of drugs on delirium incidence, studies where biomarkers were not identified, experimental studies (in vitro or in vivo animal studies), no identifiable delirium/no delirium subgroups or delirium of other specific causes (delirium tremens or other alcohol withdrawal states, Wernicke´s encephalopathy, neuropsychiatric systematic lupus erythematosus).

2.3. Data extraction and synthesis

Two authors independently screened the remaining literature for useable data and extracted it, and this was checked by another reviewer. Articles that met the inclusion criteria were reviewed and we recorded (if available) the following information: (1) Author and year of publication (2) study design and setting (i.e. orthopedics, cardiac surgery, ICU patients…) (3) number and characteristics of patients included (age, sex, delirious/no delirious) (4) method used to diagnose delirium and delirium severity (5) presence of cognitive impairment and method of assessment (6) type of biomarker analyzed and levels (7) method of obtaining the samples (8) analytical laboratory methodology (9) main study findings. In cases in which more than one publication of the same trial existed, only the latest publication with the most complete data was included. Disagreements were settled by consensus.

In the case of studies that included both people younger and older than 65 years and specific data for older adults were included in the publication, we only used data from individual participants ≥65 years. If individual participant data for the subgroup of interest could not be obtained, we included studies if greater than or equal to 80% of the participants were ≥65 years.

2.4. Endpoints

The main risk markers of delirium are shown in **Table 1**.

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Tabla 1. Risk markers of delirium

TYPE OF BIOMARKER	BIOMARKERS ANALYZED	NUMBER OF STUDIES	AUTHORS
NEUROTRANSMITTERS	AChE, BChE, Ach, Kyneurine/Tryptophan, IDO, HVA	5	Adam et al. (2020), Cerejeira et al. (2012), Dejonghe et al. (2012), Ma et al. (2020), Osse et al. (2012)
HORMONES	Estradiol, cortisol, leptin	3	Ávila-Funes et al. (2015), Li et al. (2018), Ma et al. (2020)
BIOMARKERS OF NEURONAL DAMAGE	S100B, NfL, pNfLH, UCHL-1, neurogranin	5	Fong et al. (2020), Halaas et al. (2021), Hov et al. (2017), Saller et al. (2019), Szwed et al. (2019)
BIOMARKERS OF NEUROINFLAMMATION	IFN-γ, IFN-α2, IGF-1, GFAP, CRP, hsCRP, CAR, TNF-α, IL-1ra, IL-1ß, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, MCP-1, MIP-1α, MIP-1β, RAGE, calprotectin, MRP8/14, CHI3L1, neopterin	17	Cape et al. (2014), Cerejeira et al. (2012), Chen et al. (2020), Chen et al. (2019), Chu et al. (2016), Çinar et al. (2014), Dillon et al. (2016), Fong et al. (2020), Hirsch et al. (2016), Katsumi et al. (2020), Kazmierski et al. (2021), Osse et al. (2012), Peng et al. (2019), Sajjad et al. (2020), Saller et al. (2019), Shen et al. (2016), Szwed et al. (2019)
BIOMARKERS OF DEMENTIA	t-tau, p-tau, tau, Aß40, Aß42	5	Fong et al. (2020), Hirsch et al. (2016), Hov et al. (2017), Pan et al. (2019), Saller et al (2019).
GENETICS	miR-210	1	Chen et al. (2020)
METABOLOMICS, LIPIDOMICS AND PROTEOMICS	PE (40:7e), PE (40:6), PE (38:7e), PC (40:6), PC (33:1), Cer-NS, SM VSTM2B, FA5, Spermidine, Glutamine, Putrescine, AZGP1, CHI3L1/YKL-40	5	Han, Zhang et al. (2020), Han, Chen et al. (2020), Pan et al. (2019), Vasunilashorn et al. (2018), Vasunilashorn et al. (2021)
OTHERS	Creatinine, PLR and PWR, NSP, VILIP-1, BDNF	4	Bakker et al. (2012), Kotfis et al. (2019), Szwed et al. (2019), Wyrobek et al. (2017)

AChE= acetylcholinesterase; BChE= butyrylcholinesterase; Ach=acetylcholine; IDO=indoleamine 2,3-dioxygenase; HVA=homovanillic acid; IFN=human interferon; IGF-I=insulin-like growth factor-1; CRP=C-reactive protein; CAR=C-reactive protein-to- albumin ratio; hsCRP=high-sensitivity C-reactive protein; IL=interleukin; TNF=tumor necrosis factor; S100(B)=calcium-binding protein (B); GFAP= glial fibrillary acidic protein; MCP-1=monocyte chemoattractant protein 1; NfL=neurofilament light; pNfLH= phosphorylated axonal neurofilament subunit H; NSE=neuron specific enolase; Aß=amyloid-beta; t-tau= total tau; p-tau=phosphorylated tau; miRNAs=MicroRNAs; UCHL-1=ubiquitin carboxyl-terminal hydrolase L1; PE=phosphatidylethanolamine; PC=phosphatidylcholine; SM=sphingomyelin; Cer-NS=ceramide non-hydroxyfatty acid-sphingosine; VSTM2B=transmembrane domain-containing protein 2B; FA5=coagulation factor V; MIP= macrophage inflammatory protein; RAGE=Receptor for advanced glycation end products; WDC=white blood cell count; PWR=lower platelet-to-white blood cell ratio; PLR=lower platelet-to-lymphocyte ratio; CHI3L1=Chitinase 3-Like 1 glycoprotein (also known as YKL-40 [tyrosine (Y), lysine (K), leucine (L) with molecular weight of 40); NSP=neuroserpin; VILIP-1=visinin-like protein-1; AZGP1=zinc alpha-2 glycoprotein; MRP=Macrophage inflammatory protein; BDNF=Brain-derived neurotrophic factor

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2.5. Assessment of study quality

Study quality and risk of bias were assessed independently by two of the authors using the Newcastle-Ottawa scale (NOS), which is designed for assessing common causes of bias in cohort studies. The NOS score ranges from 0-9 stars. A quality score was calculated based on three major components: (1) the selection of study groups (0-4 stars), (2) the comparability of study groups (0-2 stars), and (3) ascertainment of the exposure and outcome of interest. Overall, the quality of studies was deemed as poor (0 to 3 stars), fair (4 to 6 stars) or excellent (7 to 9 stars). Disagreement was resolved by discussion and consensus.

2.6. Statistical analyses

All analyses were conducted using the DerSimonian-Laird random-effects inverse variance model using STATA software (version 17; StataCorp, College Station, TX, USA). Data were pooled only if biomarkers were reported in at least two studies. We used the odds ratios (OR) as the main effect size for the present study. We converted other estimations (e.g., standardized regression coefficients, standardized mean differences) to OR according to their corresponding formulas. A subgroup analysis according to inflammatory parameters was also included for CRP, TNF-α, and IL-6 data.

Heterogeneity across studies was calculated using the inconsistency index (I^2)[19], and Egger's regression intercept test was used to detect small-study effects bias[20,21]. No other sub-group analysis was performed due to the limited number of studies.

3. Results

3.1. Results of the literature search

We located 2518 records, of which 1644 remained after removing duplicates. After screening the titles and abstracts, 217 studies remained for full text review. Ultimately, 32 articles were included (shown in **Figure 1**) and a summary of the main results is shown in **Table 2**.

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Figure 1. Flowchart

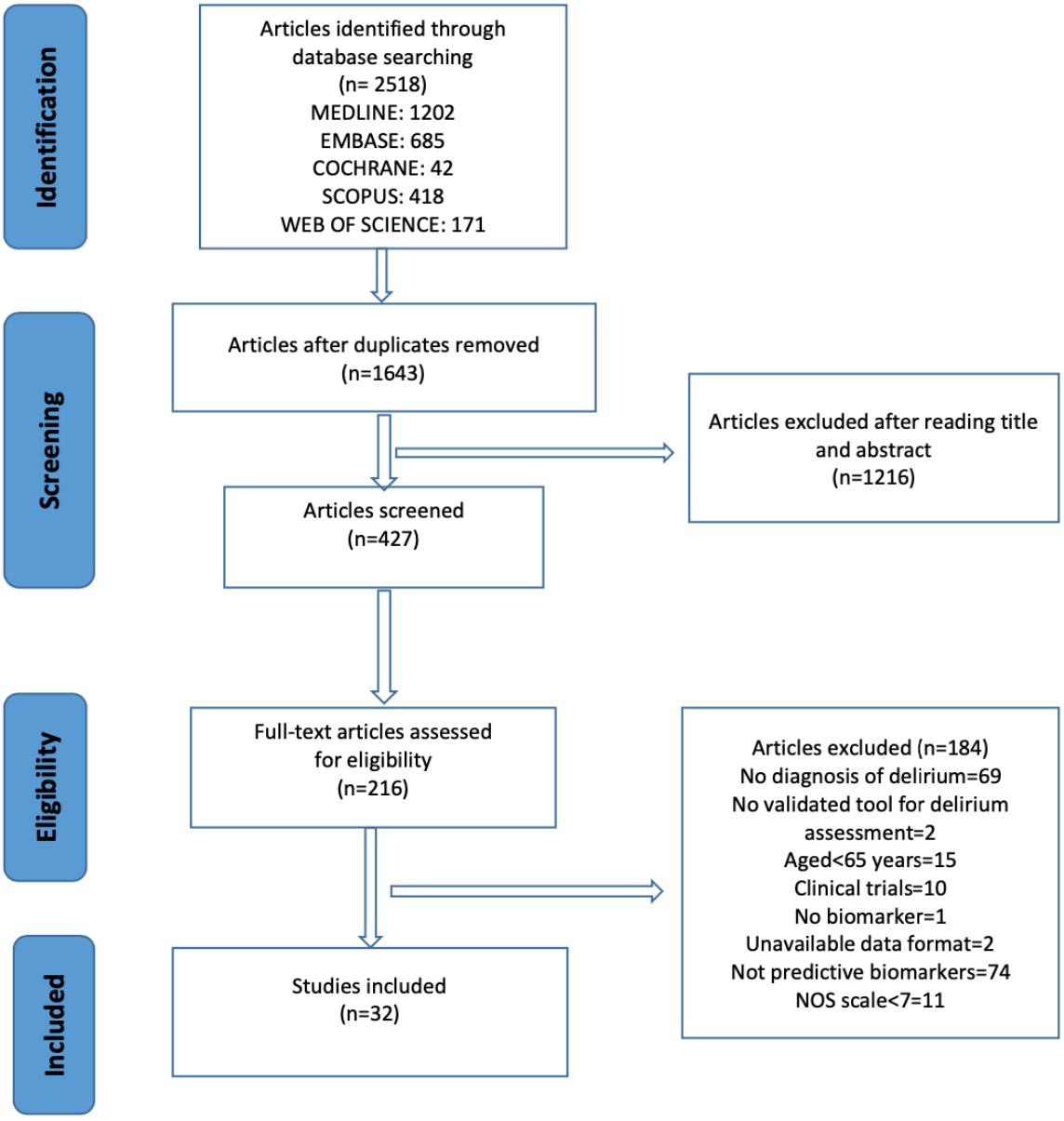

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Tabla 2. Summary of main results of risk markers of delirium

BIOMARKER	TYPE OF BIOMARKER	NUMBER OF STUDIES	RESULTS
AChE	Neurotransmitter	2	↓
BChE	Neurotransmitter	2	In one study ↓ but in the other study no association was found
Ach	Neurotransmitter	1	↓
Kynurenine/Tryptophan	Neurotransmitter	1	↑
IDO	Neurotransmitter	1	↑
HVA	Neurotransmitter	1	↑
Estradiol	Hormone	1	↑
Cortisol	Hormone	2	In one study ↑ but in the other study no association was found
Leptin	Hormone	1	↓
S100B	Neuronal damage	1	↑
NfL and pNfLH	Neuronal damage	3	In one study ↑ predicted POD and in 2 studies no association was found
UCHL-1	Neuronal damage	1	No association
Neurogranin	Neuronal damage	1	No association
IFN-γ	Neuroinflammation	2	In one study ↓ and in the other study, no association was found
IFN-α2	Neuroinflammation	1	↓
IGF-1	Neuroinflammation	4	In 2 studies ↓ and in other 2 studies no association was found
GFAP	Neuroinflammation	4	No association
CRP	Neuroinflammation	7	In 5 studies ↑ predicted delirium but in other 2 studies no association was found
hsCRP	Neuroinflammation	1	↑
CAR	Neuroinflammation	1	↑
TNF-α	Neuroinflammation	6	In 1 study ↑ predicted delirium but in other 5 studies no association was found
IL-1ra	Neuroinflammation	1	No association
IL-1ß	Neuroinflammation	3	In 1 study ↑ predicted delirium but in other 2 studies no association was found
IL-2	Neuroinflammation	1	No association
IL-4	Neuroinflammation	1	↓
IL-5	Neuroinflammation	1	↓
IL-6	Neuroinflammation	7	In 4 studies ↑ predicted delirium but in other 3 studies no association was found

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IL-8	Neuroinflammation	3	In 2 studies ↑ predicted delirium but in 1 study, no association was found
IL-10	Neuroinflammation	2	No association
IL-12p70	Neuroinflammation	1	↓
MCP-1	Neuroinflammation	2	In 1 study ↑ predicted delirium but in other study no association was found
MIP-1α	Neuroinflammation	1	↑
MIP-1 ß	Neuroinflammation	1	↑
RAGE	Neuroinflammation	1	↓
Calprotectin	Neuroinflammation	1	↑
MRP8/14	Neuroinflammation	1	No association
CHI3L1	Neuroinflammation	1	No association
Neopterin	Neuroinflammation	1	↑
t-tau	Dementia	2	No association
p-tau	Dementia	2	In 1 study ↑ but in other study no association was found
tau	Dementia	1	↑
Aß40	Dementia	1	↓
Aß42	Dementia	2	↓
miR-210	Genetics	1	↑
PE (40:7e)	Lipidomics	1	↓
PE (40:6)	Lipidomics	1	↓
PE (38:7e)	Lipidomics	1	↓
PC (40:6)	Lipidomics	1	↓
PC (33:1)	Lipidomics	1	↓
Cer-NS	Lipidomics	1	↑
SM	Lipidomics	1	↑
VSTM2B	Proteomics	1	↓
FA5	Proteomics	1	↓
Spermidine	Metabolomics	1	↑
Glutamine	Metabolomics	1	↑
Putrescine	Metabolomics	1	↑
AZGP1	Proteomics	1	↓
CHI3L1/YKL-40	Proteomics	1	↑
Creatinine	Other	1	↑
PLR and PWR	Other	1	↓
NSP	Other	1	↑
VILIP-1	Other	1	No association
BDNF	Other	1	↓

↓=low levels of this biomarker were associated with delirium

↑=high levels of this biomarker were associated with delirium

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3.2. Study population

There was diversity between the clinical settings of the studies included in this systematic review. Most of them (30 studies) were carried out in surgical patients: 10 studies in cardiac surgery patients, 14 in orthopaedic surgery patients, 2 in cancer surgery and 4 in other surgery patients. Only 2 studies were conducted among medical inpatients (1 in the hospital ward and the other in the ICU).

The age of the patients included in the studies varied between 67 and 88 years. Seventeen studies included more males than females, while females were more prevalent in 15 studies.

3.3. Delirium assessment, delirium severity and delirium subtype

The Confusion Assessment Method was the most commonly used tool for assessing delirium,[22,23] followed by the Confusion Assessment Method for Intensive Care Unit (CAM-ICU),[24] DSM and Delirium Rating Scale (DRS).[25] Eighteen studies applied the CAM to define delirium, nine studies used the CAM-ICU, three studies assessed delirium with the DSM criteria, one study used the DRS and DSM criteria and one study used both the CAM and the CAM-ICU.

The severity of delirium was assessed in ten studies. The most used tool was the Memorial Delirium Assessment Scale (MDAS), followed by the Confusion Assessment Method-Severity (CAM-S) and the DRS.

The subtype of delirium was only evaluated in one study, which used the Richmond Agitation-Sedation Scale (RASS).

3.4. Sample characteristics

Most of the studies collected blood samples. Cerebrospinal fluid (CSF) was collected in 4 studies and both blood and CSF were collected in 5 studies.

3.5. Risk markers of delirium

Neurotransmitters

Serum anticholinergic activity (SAA) was investigated as a risk marker of delirium in three studies. There were mixed results, as 2 studies[26,27] demonstrated that lower

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preoperative acetylcholinesterase (AChE) activity was related to postoperative delirium (POD). One study showed that lower preoperative butyrylcholinesterase (BChE) activity was correlated with POD [27], but another study did not find an association.[26] Low levels of acetylcholine (Ach) before surgery were an independent risk factor for POD.[28] De Jonghe et al. found that a higher preoperative kynurenine/tryptophan ratio and higher indoleamine 2,3-dioxygenase (IDO) activity were risk markers for POD.[29] Higher postoperative levels of homovanillic acid (HVA) were associated with POD.[30]

Hormones

Three papers explored a link between serum hormones and incident delirium. One study found that medical inpatients with higher levels of estradiol had an increased risk of developing delirium.[31] Two studies investigated cortisol; Ma et al. found that higher preoperative cortisol levels were an independent risk factor for delirium,[28] but Ávila-Funes et al. did not find any associations between cortisol in medical inpatients and incident delirium.[31] Li et al. found that low leptin levels at ICU admission were independently associated with delirium.[32]

Neuronal damage biomarkers

Five studies focused on the relationship between biomarkers of neuronal damage and delirium. Hov et al. found that higher preoperative levels of S100 calcium-binding protein B (S100B) in CSF correlated with POD in patients who also had pathological levels of p-tau.[33] Serum Neurofilament light (NfL) was assessed in two studies. Fong et al. found that higher preoperative levels were associated with POD and POD severity,[34] but Saller et al. did not find differences.[35] Szwed et al. evaluated serum phosphorylated axonal neurofilament subunit H (pNfLH), but no association with delirium was found.[36] One study investigated serum ubiquitin carboxyl-terminal hydrolase L1 (UCHL-1)[34] and another study examined CSF neurogranin,[37] but no differences were reported between these biomarkers and delirium.

Neuroinflammatory markers

Nineteen studies analysed the role of biomarkers of neuroinflammation in delirium. The most investigated biomarkers in this field were C-reactive protein (CRP), tumour

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necrosis factor (TNF) and interleukin-6 (IL-6). Seven studies explored CRP. Five studies found that higher preoperative CRP in serum correlated with POD;[27,38–41] however, two studies did not find differences.[42,43] Kazmierski et al. found that high levels of high-sensitivity C-reactive protein (hsCRP) in serum were also associated with POD,[44] and Peng et al. also analysed the C-reactive protein-to-albumin ratio (CAR), showing that higher preoperative levels of serum CAR were an independent risk factor for POD.[45] TNF-α was analysed in six studies; only one found that higher preoperative levels of TNF-α were related to POD but not significantly;[45] in the rest of the studies, no differences were found.[27,38,42,46,47] Seven studies investigated IL-6: four studies found that higher preoperative levels of IL-6 were related to delirium,[40,45,46,48] while three studies found no differences.[27,38,43]

Other interleukins were explored, such as IL-1ra,[49] IL-2,[46] and IL-10,[46] but they were not found to be related to the incidence of delirium. Cape et al. found that higher IL-1ß in CSF correlated with POD,[49] but in two other studies, no association was found.[27,47] Hirsch et al. also showed that lower levels of IL-4, IL-5 and IL-12p70 were related to POD.[46] IL-8 was analysed in three studies; in two of them, higher preoperative levels in CSF correlated with POD,[46,47] but in one study, no differences were found.[27] Monocyte chemoattractant protein 1 (MCP-1) was analysed in two studies; one of them found that higher serum levels before surgery were associated with delirium,[44] but the other one did not find any difference.[46] Hirsch et al. also studied macrophage inflammatory protein (MIP), macrophage inflammatory protein (MRP), receptor for advanced glycation end products (RAGE) and calprotectin and found that POD was related to higher preoperative levels of MIP-1α MIP-1ß and calprotectin but not RAGE or MRP8/14.[46] Preoperative chitinase 3-like 1 glycoprotein (CHI3L1) was evaluated in one study, but no association was found with delirium.[43]

Human interferon-γ (IFN-γ) was investigated in two studies; one study found that lower preoperative IFN-γ in plasma was related to POD,[46] but the other one did not find any differences in CSF and blood.[49] Hirsch et al. also found that lower preoperative human interferon-α2 (IFN-α2) in CSF was implicated in the development of POD.[46] Four studies explored insulin-like growth factor-1 (IGF-1). Two studies found that lower preoperative levels of IGF-1 were associated with POD,[40,42] but the other two studies did not find any differences.[49,50] Glial fibrillary acidic protein (GFAP) was also investigated in 4 studies, but

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no association was found in any of them.[34–36,49] Only IL-6, TNF-α and CRP could be examined via meta-analysis, as each biomarker was investigated in 6 or more studies.

The major findings of this meta-analysis are presented in **Figure 2**. Overall, pooled analysis showed a significant increase in some serum biomarkers (i.e., CRP, TNF-α, and IL-6) of patients who developed delirium (OR = 1.88, 95% CI 1.01 to 1.637; I^2 = 76.75%). Egger's test indicated no small-study effects bias for pooled analysis (p=0.178). Four studies could be included in the meta-analysis of IL-6; the results showed a significant increase in this biomarker in serum (OR = 1.88, 95% CI 1.01 to 1.637) in patients who developed delirium, with high heterogeneity (τ^2 = 0.31, I^2 = 76.75%). Four studies were included in the meta-analysis of CRP, but Dillon et al. evaluated three different cohorts with three independent analyses, so we included all of them in this meta-analysis [39]. Serum preoperative CRP was significantly high in patients with later POD (OR = 1.75; 95% CI 1.04 to 2.93), with high heterogeneity (τ^2 = 0.29, I^2 = 72.92%).

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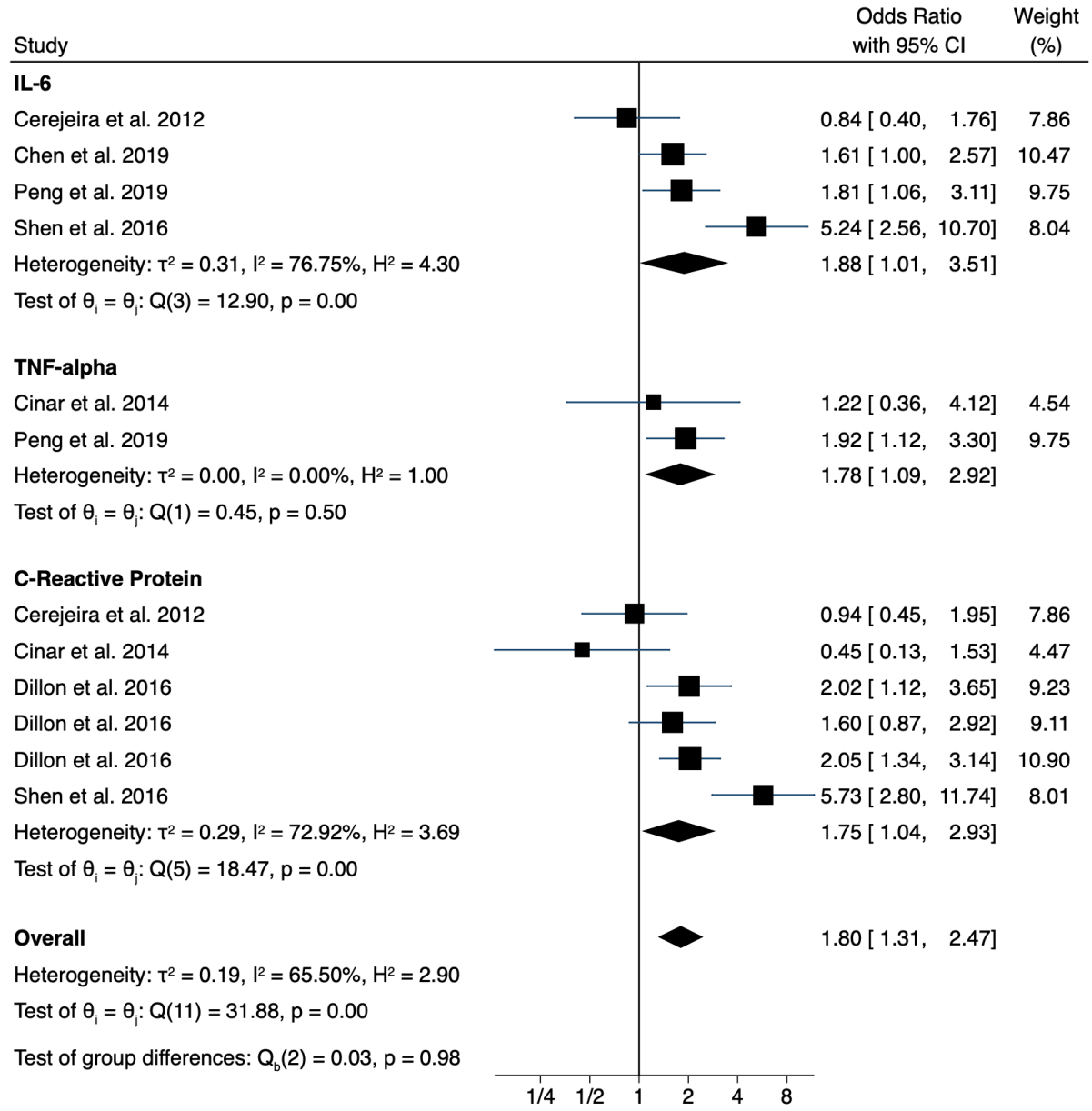
Figure 2. Forest plot



Biomarkers of dementia

Five studies investigated the relationship between biomarkers of dementia and delirium. Two studies analysed total tau (t-tau), but no differences were found between this biomarker and delirium in either blood[34] or CSF.[51] Two studies evaluated phosphorylated tau (p-tau); in one study, higher CSF p-tau correlated with POD,[33] but in another study, no differences were found between CSF p-tau and delirium.[51] However, Saller et al. found that higher preoperative tau in serum correlated with POD.[35] Hirsch et al. showed that lower preoperative Aβ40 in plasma predicted POD.[46] Aß42 was investigated in two studies; one

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found that lower preoperative Aß42 in plasma correlated with incident POD,[46] and the other found that lower preoperative Aß42 in CSF predicted POD.[51]

Genetics

Only one study evaluated the implication of genetics in the development of delirium[38] showing that higher preoperative expression of miR-210 in blood was a predictor of POD.

Metabolomics, lipidomics and proteomics

Five studies explored the role of -omics approaches in delirium. Han et al., showed that CSF lipidomics and metabolomics pointed out that phosphatidylethanolamine (PE), phosphatydilcholine (PC), sphingomyelin (SM) and ceramide non-hydroxyfatty acid-sphingosine (Cer-NS) were related with delirium.[52] In this study, lower preoperative levels of PE (40:7e), PE (40:6), PE (38:7e), PC (40:6) and PC (33:1) but higher preoperative levels of CER-NS and SM were associated with incident POD. A CSF proteomic study found that lower preoperative levels of transmembrane domain-containing protein 2B (VSTM2B) and coagulation factor V (FA5) were positively correlated with delirium severity.[53] Vasunilashorn et al., showed that lower preoperative serum levels of zinc alpha-2 glycoprotein (AZGP1) were associated with POD.[41] Moreover, a serum proteomic study found that higher preoperative chitinase 3-like 1 glycoprotein (CHI3LI/KYL-40) were associated with POD.[54] Pan et al., showed that higher preoperative levels of spermidine, glutamine and putrescine in CSF were related with incident delirium.[51]

Others

Bakker et al., showed that higher levels of serum creatinine prior to surgery were an independent predictor of POD.[55] Kotfis et al., found that lower preoperative levels of platelet-to-white blood cell ratio (PWR) and lower platelet-to-lymphocyte ratio (PLR) were associated with POD in serum.[56] Szwed et al., investigated the relationship between neuroserpin (NSP) or visinin-like protein-1 (VILIP-1) and delirium[36] in serum. Higher end of surgery to baseline ratio of NSP predicted the occurrence of POD but no differences were

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found between VILIP-1 and POD. Wyrobeck et al., showed that lower levels of serum Brain-derived neurotrophic factor (BDNF) during surgery were associated with delirium.[57]

4. Discussion

To the best of our knowledge, **this is the first review that focuses on predictive biomarkers of delirium in older patients**, considering all clinical settings and all types of biological fluids with high-quality studies. The multi-etiological nature of delirium is likely to be reflected in the wide range of biomarkers identified by our study.

Ach

The neurotransmitter hypothesis suggests that disturbances in neurotransmitter pathways can lead to delirium.[58] Although precursors of serotonin (tryptophan, phenylalanine and tyrosine), dopamine and noradrenaline may be implicated in the development of delirium, anticholinergic deficiency has been directly related to its pathophysiology.[59] Ach is involved in sleep regulation, cognition and attention. It is well known that an impairment in cholinergic activity is associated with cognitive and attentional changes; current literature also suggests that an impairment in cholinergic activity is associated with delirium.[60–63] In addition, anticholinergic effects are common among several drugs, and a previous study found that increased anticholinergic burden increases delirium risk.[64]

Cortisol

A disruption of the hypothalamic-pituitary-axis with an increase in cortisol levels has been related to a higher risk of dementia[65] and delirium, particularly in critically ill patients,[66,67] but evidence is not conclusive. Other hormones, such as estradiol or leptin, may have a role in delirium pathophysiology, but additional research is needed to confirm this hypothesis.

S100B and NfL

Markers of neuronal damage, such as S100B and NfL (related to disturbances in astrocytic integrity), have been associated with delirium,[68,69] but these markers of brain injury could be associated with established, and not necessarily incident, delirium.[70]

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However, higher levels have been associated with higher severity and worse prognosis of delirium.[15,71,72]

Tau and Aß

It is well known that cognitive impairment is a clinical risk factor for delirium.[73–76] Nevertheless, few studies have been carried out in this field, pointing out that typical markers of dementia, such as tau or Aβ, are associated with delirium development.[77,78]

Genetics

Another pathway that yields promising results is genetic research in delirium.[79] Although studies in this field are scarce, genetic studies could be interesting translational tools for elucidating the pathophysiology of this syndrome. In addition, genetics are not influenced by the causal combination of predisposing and precipitating factors that affects delirium, so they can offer a more reliable value compared to other biomarkers.[80]

Proteomics and metabolomics

Research in proteomics and metabolomics aims to provide a protein or metabolic profile to contribute to delirium diagnosis and prevention.[81] There are few and heterogeneous studies in this field due to the technological difficulty associated with mapping the whole molecular landscape of biofluids. However, omics technologies are complementary to the genetic toolbox, detecting, identifying and quantifying alternative molecular biomarkers necessary to understand the dynamics and interactions that occur during delirium development.

Although acetylcholine deficiency, hormonal influence, markers of dementia and biochemical changes observed through proteomics and metabolomics may play an important role in predicting delirium, neuroinflammation theory seems to be the most relevant pathway, at least in the population of this review (most of the studies were carried out in older surgical populations). These findings are consistent with previous reviews that found an association between delirium and neuroinflammation biomarkers.[13,14,16,82,83] This hypothesis suggests that peripheral inflammation due to surgery, trauma or infection leads to the activation of the proinflammatory cascade and suppression of anti-inflammatory

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markers. These stimuli trigger tissue macrophage and blood monocyte activation and secretion of inflammatory mediators such as IL-1, IL-1ß, IL-6, TNF-α and prostaglandin E_2 (PGE_2). These proinflammatory molecules penetrate the BBB, producing cerebral injury through the activation of microglia that causes brain dysfunction and delirium [1]. Interestingly, we conducted a meta-analysis with IL-6, TNF-α and CRP, which were the most investigated biomarkers, and we found that they were statistically significant predictors of delirium.

IL-6

IL-6 is a cytokine involved in the immune response and has a notorious role in adult neurogenesis, the process of creating new neurons and glial cells from neural stem cells (oligodendrogliogenesis and astrogliogenesis) in the central nervous system (CNS).[84] IL-6 expression is involved in the synthesis of beta-amyloid precursor protein being altered in the brains of Alzheimer's disease (AD) patients and it is also upregulated whenever neuroinflammation is expected, such as infection or injury.[85] Noah et al. found that higher preoperative IL-6 was associated with postoperative delirium.[82] Another meta-analysis performed among surgical patients also found this association.[14,83] Dunne et al. showed that early manifestation of systemic inflammation with elevated levels of IL-6 leads to the onset of delirium.[16] However, Hall et al. did not find a significant correlation between IL-6 measured in CSF and delirium.[13]

TNF-α

TNF-α is a proinflammatory cytokine[86] that has been associated with more rapid cognitive decline in patients with AD.[87] Analysis of the same cohort showed that elevated systemic TNF-α was associated with an increase in psychobehavioural alterations such as apathy, anxiety, depression and agitation**,** suggesting that increased systemic TNF-α may also have a role in hippocampal neurodegeneration.[88] The association of TNF-α and delirium is unclear. While some studies showed a positive correlation between TNF-α and delirium and our study revealed a significant association, previous meta-analyses by Noah et al. and Liu et al. found that preoperative TNF-α was significantly higher in the POD group in univariate analysis but not in multivariate analysis.[14,82]

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CRP

CRP is a pentameric protein whose circulating concentrations rise in response to inflammation.[89] It is an acute-phase protein of hepatic origin that increases following IL-6 secretion.[90] In the same way that IL-6 is altered in patients with cognitive impairment, a recent review found that CRP is also involved in this mechanism.[91] Moreover, several meta-analyses have shown that higher preoperative serum CRP levels are significantly associated with later POD.[14,16,82,83]

4.1. Strengths and limitations

One of the main limitations of the studies included in this systematic review and meta-analysis is their small sample size and the lack of consistent terminology about delirium which has negatively affected the research (different terms such as organic brain syndrome, encephalopathy or acute brain failure can be misleading). Another important drawback is the lack of diversity in patient populations. Most of the studies were carried out in surgical populations, so their results may not be extrapolated to other clinical scenarios (medical inpatients, critically ill patients, etc.). On the other hand, there was little information about geriatric syndromes (frailty, malnutrition, polypharmacy) that may be directly involved not only in the development of delirium but also in the delirium characteristics (severity, subtype, duration, etc.). In addition, it is important to note that the methodological heterogeneity observed across studies might have an impact on the overall outcomes; therefore, the information should be considered with caution when drawing conclusions.

Importantly, this study provides several strengths. Firstly, there was no restriction by year of publication, and only high-quality studies (7 to 9 stars in NOS) with formal delirium diagnosis (DSM criteria, ICD criteria or a tool based on these criteria) with a lower risk of bias were included. Secondly, only studies on risk markers for delirium were included, excluding studies on disease markers or end-products of delirium. Thirdly, we also compared the preoperative state of patients who had not yet developed delirium in the studies that had more than one sample collected at different time points, focusing on predictive biomarkers of delirium and minimizing the risk of bias.

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4.4. Challenges and implications for future research

These findings could contribute to the implementation of the International Drive to Illuminate Delirium (IDID) initiative, [92] providing a **new prevention strategy for delirium** and, subsequently, helping to preserve cognitive function. Although biomarkers could be an instrument to predict delirium, there are some unanswered questions. Blood-based biomarkers are little invasive, fast and reproducible, giving a quantitative value, and could be easy to measure in routine analysis (accessible in hands of surgeons, primary care physicians or other clinics). However, the validation of these biomarkers in terms of accuracy, sensitivity and specificity remains unknown because many of these inflammatory mediators are elevated in patients with sepsis, trauma or surgery and not only in those who develop delirium. In addition, their affordability and cost-efficiency are also unexplored.

Based on the limitations of the studies included in this systematic review and meta-analysis, we identified five major action areas to advance this research, designing better quality studies: (1) detailed planning and informed consent; (2) proper choice of target population; (3) blinding; (4) protocolization of biomarker collection and analysis; and (5) standardized reporting, which are summarized in **Figure 3.** and could be useful to improve the "Core Outcome Set" (COMET) in the field of delirium.[93]

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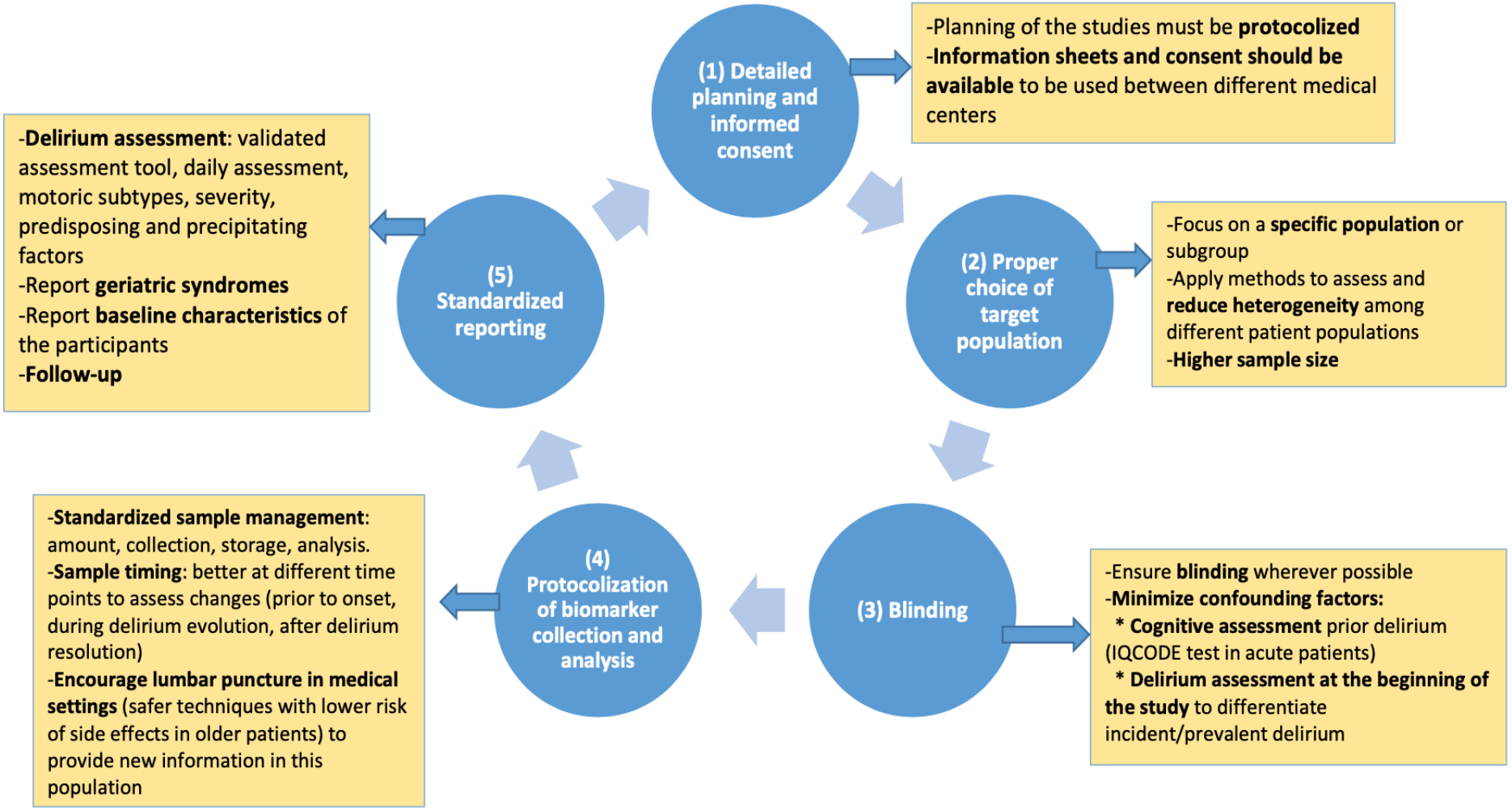
Figure 3. Recommendations for future research in delirium biomarkers.



5. Conclusions

The relevance of delirium in older patients, both for its long- and short-term adverse consequences, provides a compelling reason to investigate its pathophysiology to prevent its appearance and improve the approach.

Despite the recent surge in studies on delirium biomarkers, there is not consistent evidence in the obtained results given the great heterogeneity that reflects the complexity of its pathophysiological mechanisms. Our data identified **a significant association between biomarkers of neuroinflammation, such as CRP, IL-6 or TNF-α, and the risk of delirium**, but further research is needed to standardize the methodology, improve scientific evidence and translate the current knowledge into pragmatic tools for routine clinical practice in the field of delirium.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Wilson, J. E. Delirium. *Nat. Rev. Dis. Prim.* **6**, (2020) doi:10.1038/s41572-020-00223-4.
2. Choi, S. H. Neural network functional connectivity during and after an episode of delirium. *Am. J. Psychiatry* **169**, 498–507 (2012) doi:10.1176/appi.ajp.2012.11060976.
3. Raichle, M. E. The Brain's Default Mode Network. *Annu. Rev. Neurosci.* **38**, 433–447 (2015) doi:10.1146/annurev-neuro-071013-014030.
4. van Montfort, S. J. T. Brain network disintegration as a final common pathway for delirium: a systematic review and qualitative meta-analysis. *NeuroImage Clin.* **23**, 101809 (2019) doi:10.1016/j.nicl.2019.101809.
5. Morandi, A. The relationship between delirium duration, white matter integrity, and cognitive impairment in Intensive Care Unit survivors as determined by diffusion tensor imaging: the VISIONS prospective cohort magnetic resonance imaging study. *Crit. Care Med.* **40**, 2182–2189 (2012) doi:10.1097/CCM.0b013e318250acdc.The.
6. Murray, C. Systemic inflammation induces acute working memory deficits in the primed brain: relevance for delirium. *Neurobiol. Aging* **33**, 603-616.e3 (2012) doi:10.1016/j.neurobiolaging.2010.04.002.
7. Cavallari, M. Neural substrates of vulnerability to postsurgical delirium as revealed by presurgical diffusion MRI. *Brain* **139**, 1282–1294 (2016) doi:10.1093/brain/aww010.
8. World Health Organization (WHO). Biomarkers In Risk Assessment: Validity And Validation. *Environ. Heal.* 144 (2001).
9. Strimbu, K. What are biomarkers? *Curr. Opin. HIV AIDS* **5**, 463–466 (2010) doi:10.1097/COH.0b013e32833ed177.
10. Aronson, J. K. Biomarkers—a general review. *Curr. Protoc. Pharmacol.* **2017**, 9.23.1-9.23.17 (2017) doi:10.1002/cpph.19.
11. Hall, R. J. A systematic literature review of cerebrospinal fluid biomarkers in delirium. *Dement. Geriatr. Cogn. Disord.* **32**, 79–93 (2011) doi:10.1159/000330757.
12. Ida, M. Preoperative serum biomarkers in the prediction of postoperative delirium

upna
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Nafarroako Unibertsitate Publikoa

following abdominal surgery. *Geriatr. Gerontol. Int.* **20**, 1208–1212 (2020) doi:10.1111/ggi.14066.

13. Hall, R. J. CSF biomarkers in delirium: a systematic review. *Int. J. Geriatr. Psychiatry* **33**, 1479–1500 (2018) doi:10.1002/gps.4720.
14. Liu, X. Inflammatory markers in postoperativedelirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. *PLoS One* **13**, (2018) doi:10.1371/journal.pone.0195659.
15. Narayanan, S. Neurofilament light: a narrative review on biomarker utility. *Fac. Rev.* **10**, 46 (2021) doi:10.12703/r/10-46.
16. Dunne, S. S. Biomarkers in delirium: A systematic review. *J. Psychosom. Res.* **147**, 110530 (2021) doi:10.1016/j.jpsychores.2021.110530.
17. Chu, C.-L. C. L. Biomarkers of delirium: Well evidenced or not? *J. Clin. Gerontol. Geriatr.* **2**, 100–104 (2011) doi:10.1016/j.jcgg.2011.11.005.
18. Liberati, A. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Med.* **6**, (2009) doi:10.1371/journal.pmed.1000100.
19. Cooper H, Hedges LV, Valentine JC, E. *Rosenthal R. Parametric measures of effect size. The handbook of research synthesis. New York, NY: Russell Sage Foundation*. (1994).
20. Egger, M. Bias in meta-analysis detected by a simple, graphical test. *Br. Med. J.* **315**, 629–634 (1997) doi:10.1136/bmj.315.7109.629.
21. Higgins, J. P. Measuring inconsistency in meta-analyses. *Br. Med. J.* **327**, 557–560 (2003) doi:10.1136/bmj.315.7109.629.
22. Helfand, B. K. I. Detecting Delirium: A Systematic Review of Identification Instruments for Non-ICU Settings. *J. Am. Geriatr. Soc.* **69**, 547–555 (2021) doi:10.1111/jgs.16879.
23. Inouye, S. K. Clarifying confusion: The confusion assessment method: A new method for detection of delirium. *Ann. Intern. Med.* **113**, 941–948 (1990) doi:10.7326/0003-4819-113-12-941.
24. Gusmao-Flores, D. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. *Crit. Care* **16**,

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

2–11 (2012) doi:10.1186/cc11407.

25. Trzepacz, P. T. The delirium rating scale. Its use in consultation-liaison research. *Psychosomatics* **40**, 193–204 (1999) doi:10.1016/S0033-3182(99)71235-1.

26. Adam, E. H. Cholinesterase alterations in delirium after cardiosurgery: a German monocentric prospective study. *BMJ Open* **10**, e031212 (2020) doi:10.1136/bmjopen-2019-031212.

27. Cerejeira, J. The cholinergic system and inflammation: common pathways in delirium pathophysiology. *J. Am. Geriatr. Soc.* **60**, 669–675 (2012) doi:10.1111/j.1532-5415.2011.03883.x.

28. Ma, J. R. Age, preoperative higher serum cortisol levels, and lower serum acetylcholine levels predict delirium after percutaneous coronary intervention in acute coronary syndrome patients accompanied with renal dysfunction. *Indian J. Psychiatry* **62**, 172–177 (2020) doi:10.4103/psychiatry.IndianJPsychiatry_37_19.

29. de Jonghe, A. The tryptophan depletion theory in delirium: not confirmed in elderly hip fracture patients. *Psychosomatics* **53**, 236–243 (2012) doi:10.1016/j.psym.2011.09.009.

30. Osse, R. J. High preoperative plasma neopterin predicts delirium after cardiac surgery in older adults. *J. Am. Geriatr. Soc.* **60**, 661–668 (2012) doi:10.1111/j.1532-5415.2011.03885.x.

31. Avila-Funes, J. A. Association between high serum estradiol levels and delirium among hospitalized elderly women. *Rev. Investig. Clin. organo del Hosp. Enfermedades la Nutr.* **67**, 20–24 (2015).

32. Li, G. Low plasma leptin level at admission predicts delirium in critically ill patients: A prospective cohort study. *Peptides* **93**, 27–32 (2017) doi:10.1016/j.peptides.2017.05.002.

33. Hov, K. R. Cerebrospinal fluid S100B and Alzheimer's disease biomarkers in hip fracture patients with delirium. *Dement. Geriatr. Cogn. Dis. Extra* **7**, 374–385 (2017) doi:10.1159/000481853.

34. Fong, T. G. Association of Plasma Neurofilament Light with Postoperative Delirium. *Ann. Neurol.* **88**, 984–994 (2020) doi:10.1002/ana.25889.

35. Saller, T. A case series on the value of tau and neurofilament protein levels to predict and detect delirium in cardiac surgery patients. *Biomed. Pap. Med. Fac.*

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

Univ. Palacky, Olomouc, Czechoslov. **163**, 241–246 (2019) doi:10.5507/bp.2019.043.

36. Szwed, K. Novel Markers for Predicting Type 2 Neurologic Complications of Coronary Artery Bypass Grafting. *Ann. Thorac. Surg.* **110**, 599–607 (2020) doi:10.1016/j.athoracsur.2019.10.071.
37. Halaas, N. B. Cerebrospinal Fluid Concentration of Neurogranin in Hip Fracture Patients with Delirium. *J. Alzheimers. Dis.* **81**, 667–677 (2021) doi:10.3233/JAD-201341.
38. Chen, Y. Preoperative Circulating MiR-210, a Risk Factor for Postoperative Delirium Among Elderly Patients with Gastric Cancer Undergoing Curative Resection. *Curr. Pharm. Des.* **26**, 5213–5219 (2020) doi:10.2174/1381612826666200617163857.
39. Dillon, S. T. Higher C-Reactive Protein Levels Predict Postoperative Delirium in Older Patients Undergoing Major Elective Surgery: A Longitudinal Nested Case-Control Study. *Biol. Psychiatry* **81**, 145–153 (2017) doi:10.1016/j.biopsych.2016.03.2098.
40. Shen, H. Insulin-Like Growth Factor-1, a Potential Predicative Biomarker for Postoperative Delirium Among Elderly Patients with Open Abdominal Surgery. *Curr. Pharm. Des.* **22**, 5879–5883 (2016) doi:10.2174/1381612822666160813234311.
41. Vasunilashorn, S. M. Development of a Dynamic Multi-Protein Signature of Postoperative Delirium. *J. Gerontol. A. Biol. Sci. Med. Sci.* **74**, 261–268 (2019) doi:10.1093/gerona/gly036.
42. Çinar, M. A. Role of CRP, TNF-a, and IGF-1 in Delirium Pathophysiology. *Noro Psikiyatr. Ars.* **51**, 376–382 (2014) doi:10.5152/npa.2014.6999.
43. Katsumi, Y. The Role of Inflammation after Surgery for Elders (RISE) study: Examination of [11C]PBR28 binding and exploration of its link to post-operative delirium. *NeuroImage Clin.* **27**, (2020) doi:10.1016/j.nicl.2020.102346.
44. Kaźmierski, J. Elevated Monocyte Chemoattractant Protein-1 as the Independent Risk Factor of Delirium after Cardiac Surgery. A Prospective Cohort Study. *J. Clin. Med.* **10**, (2021) doi:10.3390/jcm10081587.
45. Peng, J. Preoperative C-Reactive Protein/Albumin Ratio, a Risk Factor for Postoperative Delirium in Elderly Patients After Total Joint Arthroplasty. *J. Arthroplasty* **34**, 2601–2605 (2019) doi:10.1016/j.arth.2019.06.042.
46. Hirsch, J. Perioperative cerebrospinal fluid and plasma inflammatory markers after

upna
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Nafarroako Unibertsitate Publikoa

orthopedic surgery. *J. Neuroinflammation* **13**, 211 (2016) doi:10.1186/s12974-016-0681-9.

47. Sajjad, M. U. Cerebrospinal Fluid Levels of Interleukin-8 in Delirium, Dementia, and Cognitively Healthy Patients. *J. Alzheimers. Dis.* **73**, 1363–1372 (2020) doi:10.3233/JAD-190941.

48. Chen, Y. Change in Serum Level of Interleukin 6 and Delirium After Coronary Artery Bypass Graft. *Am. J. Crit. care an Off. Publ. Am. Assoc. Crit. Nurses* **28**, 462–470 (2019) doi:10.4037/ajcc2019976.

49. Cape, E. Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1β in delirium after hip fracture. *J. Psychosom. Res.* **77**, 219–225 (2014) doi:10.1016/j.jpsychores.2014.06.014.

50. Chu, C.-S. Lack of Association between Pre-Operative Insulin-Like Growth Factor-1 and the Risk of Post-Operative Delirium in Elderly Chinese Patients. *Psychiatry Investig.* **13**, 327–332 (2016) doi:10.4306/pi.2016.13.3.327.

51. Pan, X. Cerebrospinal Fluid Spermidine, Glutamine and Putrescine Predict Postoperative Delirium Following Elective Orthopaedic Surgery. *Sci. Rep.* **9**, 4191 (2019) doi:10.1038/s41598-019-40544-3.

52. Han, Y. Metabolomic and Lipidomic Profiling of Preoperative CSF in Elderly Hip Fracture Patients With Postoperative Delirium. *Front. Aging Neurosci.* **12**, (2020) doi:10.3389/fnagi.2020.570210.

53. Han, Y. Proteomic Analysis of Preoperative CSF Reveals Risk Biomarkers of Postoperative Delirium. *Front. psychiatry* **11**, 170 (2020) doi:10.3389/fpsyt.2020.00170.

54. Vasunilashorn, S. M. Proteome-Wide Analysis using SOMAscan Identifies and Validates Chitinase-3-Like Protein 1 as a Risk and Disease Marker of Delirium Among Older Adults Undergoing Major Elective Surgery. *J. Gerontol. A. Biol. Sci. Med. Sci.* (2021) doi:10.1093/gerona/glaa326.

55. Bakker, R. C. Preoperative and operative predictors of delirium after cardiac surgery in elderly patients. *Eur. J. cardio-thoracic Surg. Off. J. Eur. Assoc. Cardio-thoracic Surg.* **41**, 544–549 (2012) doi:10.1093/ejcts/ezr031.

56. Kotfis, K. The practical use of white cell inflammatory biomarkers in prediction of postoperative delirium after cardiac surgery. *Brain Sci.* **9**, (2019)

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

doi:10.3390/brainsci9110308.

57. Wyrobek, J. Association of intraoperative changes in brain-derived neurotrophic factor and postoperative delirium in older adults. *Br. J. Anaesth.* **119**, 324–332 (2017) doi:10.1093/bja/aex103.

58. Maldonado, J. R. Neuropathogenesis of delirium: Review of current etiologic theories and common pathways. *Am. J. Geriatr. Psychiatry* **21**, 1190–1222 (2013) doi:10.1016/j.jagp.2013.09.005.

59. Wang, Y. Postoperative delirium in the elderly: the potential neuropathogenesis. *Aging Clin. Exp. Res.* **30**, 1287–1295 (2018) doi:10.1007/s40520-018-1008-8.

60. Lisibach, A. Evaluation of the association of anticholinergic burden and delirium in older hospitalised patients – A cohort study comparing 19 anticholinergic burden scales. *Br. J. Clin. Pharmacol.* 0–2 (2022) doi:10.1111/bcp.15432.

61. Oudewortel, L. The Association of Anticholinergic Drugs and Delirium in Nursing Home Patients With Dementia: Results From the SHELTER Study. *J. Am. Med. Dir. Assoc.* **22**, 2087–2092 (2021) doi:10.1016/j.jamda.2021.05.039.

62. Pasina, L. Relation Between Delirium and Anticholinergic Drug Burden in a Cohort of Hospitalized Older Patients: An Observational Study. *Drugs and Aging* **36**, 85–91 (2019) doi:10.1007/s40266-018-0612-9.

63. Vondeling, A. M. Anticholinergic drug exposure at intensive care unit admission affects the occurrence of delirium. A prospective cohort study. *Eur. J. Intern. Med.* **78**, 121–126 (2020) doi:10.1016/j.ejim.2020.04.062.

64. Egberts, A. Anticholinergic Drug Burden and Delirium: A Systematic Review. *J. Am. Med. Dir. Assoc.* **22**, 65-73.e4 (2021) doi:10.1016/j.jamda.2020.04.019.

65. Ouanes, S. High cortisol and the risk of dementia and alzheimer's disease: A review of the literature. *Front. Aging Neurosci.* **11**, (2019) doi:10.3389/fnagi.2019.00043.

66. Michels, M. Biomarker Predictors of Delirium in Acutely Ill Patients: A Systematic Review. *J. Geriatr. Psychiatry Neurol.* **32**, 119–136 (2019) doi:10.1177/0891988719834346.

67. Mattar, I. Factors causing acute delirium in critically ill adult patients: a systematic review. *JBI Libr. Syst. Rev.* **10**, 187–231 (2012) doi:10.11124/jbisrir-2012-3.

68. Mietani, K. Elevated neuron-specific enolase level is associated with postoperative delirium and detection of phosphorylated neurofilament heavy subunit: A

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prospective observational study. *PLoS One* **16**, 1–10 (2021) doi:10.1371/journal.pone.0259217.

69. Mietani, K. Dysfunction of the blood-brain barrier in postoperative delirium patients, referring to the axonal damage biomarker phosphorylated neurofilament heavy subunit. *PLoS One* **14**, e0222721 (2019) doi:10.1371/journal.pone.0222721.
70. Khan, B. A. Biomarkers for deliriuma - A review. *J. Am. Geriatr. Soc.* **59**, S256–S261 (2011) doi:10.1111/j.1532-5415.2011.03702.x.
71. Gao, Y. Levels of S100 calcium binding protein B (S100B), neuron-specific enolase (NSE), and cyclophilin A (CypA) in the serum of patients with severe craniocerebral injury and multiple injuries combined with delirium transferred from the ICU and their prognosti. *Ann. Palliat. Med.* **10**, 3371–3378 (2021) doi:10.21037/apm-21-424.
72. Page, V. J. Plasma neurofilament light chain protein as a predictor of days in delirium and deep sedation, mortality and length of stay in critically ill patients. *eBioMedicine* **80**, 1–12 (2022) doi:10.1016/j.ebiom.2022.104043.
73. Fong, T. G. Delirium and Alzheimer disease: A proposed model for shared pathophysiology. *Int. J. Geriatr. Psychiatry* **34**, 781–789 (2019) doi:10.1002/gps.5088.
74. Fong, T. G. The interface between delirium and dementia in elderly adults. *Lancet Neurol.* **14**, 823–832 (2015) doi:10.1016/S1474-4422(15)00101-5.
75. Racine, A. M. Alzheimer's-related cortical atrophy is associated with postoperative delirium severity in persons without dementia. *Neurobiol. Aging* **59**, 55–63 (2017) doi:10.1016/j.neurobiolaging.2017.07.010.
76. Fong, T. G. Delirium, dementia, and decline. *JAMA Psychiatry* **74**, 212–213 (2017) doi:10.1001/jamapsychiatry.2016.3812.
77. Wang, S. A Systematic Review of Delirium Biomarkers and Their Alignment with the NIA-AA Research Framework. *J. Am. Geriatr. Soc.* **69**, 255–263 (2021) doi:10.1111/jgs.16836.
78. Wang, S. Postoperative delirium and its relationship with biomarkers for dementia: a meta-analysis. *Int. Psychogeriatrics* **34**, 377–390 (2022) doi:10.1017/S104161022100274X.
79. Van Munster, B. C. The role of genetics in delirium in the elderly patient. *Dement.*

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Nafarroako Unibertsitate Publikoa

Geriatr. Cogn. Disord. **28**, 187–195 (2009) doi:10.1159/000235796.

80. Sepulveda, E. The complex interaction of genetics and delirium: a systematic review and meta-analysis. *Eur. Arch. Psychiatry Clin. Neurosci.* **271**, 929–939 (2021) doi:10.1007/s00406-021-01255-x.

81. Sfera, A. Proteomic and epigenomic markers of sepsis-induced delirium (SID). *Front. Mol. Biosci.* **2**, (2015) doi:10.3389/fmolb.2015.00059.

82. Noah, A. M. Preoperative inflammatory mediators and postoperative delirium: systematic review and meta-analysis. *Br. J. Anaesth.* **127**, 424–434 (2021) doi:10.1016/j.bja.2021.04.033.

83. Adamis, D. Consistent patterns in the inconsistent associations of Insulin-like growth factor 1 (IGF-1), C-Reactive Protein (C-RP) and Interleukin 6 (IL-6) levels with delirium in surgical populations. A systematic review and meta-analysis. *Arch. Gerontol. Geriatr.* **97**, 104518 (2021) doi:10.1016/j.archger.2021.104518.

84. Kang, S. Historical overview of the interleukin-6 family cytokine. *J. Exp. Med.* **217**, 1–10 (2020) doi:10.1084/jem.20190347.

85. Erta, M. Interleukin-6, a major cytokine in the central nervous system. *Int. J. Biol. Sci.* **8**, 1254–1266 (2012) doi:10.7150/ijbs.4679.

86. Idriss, H. T. TNFα and the TNF receptor superfamily: Structure-function relationship(s). *Microsc. Res. Tech.* **50**, 184–195 (2000) doi:10.1002/1097-0029(20000801)50:3<184::AID-JEMT2>3.0.CO;2-H.

87. Holmes, C. Systemic inflammation and disease progression in Alzheimer disease. *Neurology* **73**, 768–774 (2009) doi:10.1212/WNL.0b013e3181d5df7f.

88. Holmes, C. Proinflammatory cytokines, sickness behavior, and Alzheimer disease. *Neurology* **77**, 212–218 (2011) doi:10.1212/WNL.0b013e318225ae07.

89. Pathak, A. Evolution of C-reactive protein. *Front. Immunol.* **10**, (2019) doi:10.3389/fimmu.2019.00943.

90. Sproston, N. R. Role of C-reactive protein at sites of inflammation and infection. *Front. Immunol.* **9**, 1–11 (2018) doi:10.3389/fimmu.2018.00754.

91. Qiao, S. Research progress on cognitive impairment and the expression of serum inflammatory markers in patients with white matter hyperintensities: a narrative review. *Ann. Transl. Med.* **10**, 421–421 (2022) doi:10.21037/atm-22-1016.

92. Khachaturian, A. S. International drive to illuminate delirium: A developing public

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Nafarroako Unibertsitate Publikoa

health blueprint for action. *Alzheimer's Dement.* **16**, 711–725 (2020) doi:10.1002/alz.12075.

93. Williamson, P. R. The COMET Handbook: Version 1.0. *Trials* **18**, 1–50 (2017) doi:10.1186/s13063-017-1978-4.

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Chapter 2
Association of postoperative delirium with serum and cerebrospinal fluid proteomic profiles: a prospective cohort study in older hip fracture patients

Capítulo 2
Asociación del delirium postoperatorio con un perfil proteómico en sangre y líquido cefalorraquídeo: estudio de cohortes prospectivo en pacientes mayores con fractura de cadera

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1. Introduction

The term postoperative delirium (POD) refers to a condition of acute cognitive dysfunction that occurs in hospital up to one week after surgery and is a frequent perioperative complication, especially among older adults.[1] The incidence of POD after hip fracture has been reported to range from 11% to 51% and occurs in up to 50–70% of high-risk patient groups.[2] Furthermore, POD is associated with adverse outcomes such as longer length of stay, functional decline, persistent cognitive impairment, institutionalization, decrease in quality of life, premature mortality and increased healthcare expenditure.[3,4]

Although studies have contributed some evidence in recent years, the pathophysiological mechanism of delirium remains largely unknown, and a multifactorial etiology has been suggested.[5,6] Evidence supports that maladaptive neuroinflammatory response plays an important role in the development of POD.[7,8] Several precipitating factors of delirium such as surgery, infection or trauma cause endothelial damage, which increases blood brain barrier (BBB) permeability allowing immune cells, cytokines and other neuroinflammatory products to penetrate the brain parenchyma. These mediators activate the microglia, leading to neuronal dysfunction and delirium [9]. This mechanism has been observed particularly in older adults and patients with cognitive impairment undergoing hip fracture surgery.[10,11] Some studies have found that Tumour Necrosis Factor-α (TNF-α), proinflammatory cytokines such us Interleukins (IL1, IL6 and IL8), and other novel neuroinflammatory biomarkers (neopterin) are elevated in the serum of these patients before surgery, but their study in cerebrospinal fluid (CSF) has yielded mixed results.[12,13] However, studies carried out so far have important limitations because most do not account for geriatric syndromes, nor they measure delirium in a daily pattern during hospitalization; furthermore, delirium characteristics such as subtype and severity are seldom assessed.

Importantly, there is no effective treatment for POD once it is established, so the best approach is its prevention. Several clinically-based predictive models of delirium have been developed in recent years such as the Delirium Elderly At-Risk (DEAR) tool,[14–16] but they have some limitations because their application depends on the interpretation of the clinician who performs them and, consequently, they can be subjective and imprecise. For this reason, the possibility of integrating objective measures into predictive models of delirium needs to be explored. Serum biomarkers are quantifiable, reproducible and

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minimally invasive and could be useful to better understand the pathophysiology of delirium and identify patients at higher risk of developing it.

The present study aimed to comprehensively characterize patients with delirium both from a clinical point of view and using a proteomic approach, in order to evaluate whether changes in the preoperative immunological profile could be associated with POD after hip fracture surgery. We hypothesized that older hip fracture patients with altered cytokine profiles before surgery could be at higher risk of developing delirium.

2. Material and methods

2.1. Study design and participants

This was a prospective cohort study. Between August 2021 and December 2021, we approached sixty consecutive hip fracture patients aged 75 years or older undergoing subarachnoid anesthesia, who were admitted to the Orthopedic ward of Hospital Universitario de Navarra (Pamplona, Spain). Patients were excluded if: 1) they had preoperative delirium, 2) advanced dementia (a score >5 at Global Deterioration Scale),[17] 3) severe dependence (a score <20 at Barthel Index),[18] 4) terminal disease (life expectancy <3 months), 5) were unable to communicate in Spanish, and 6) were not willing or not capable to provide informed consent.

2.2. Clinical assessments

Medical records were reviewed and patients and relatives were interviewed preoperatively and daily after surgery. A Comprehensive Geriatric Assessment (CGA) was performed at the time of enrolment that included functional status (Barthel Index and Lawton and Brody scale),[19] frailty (FRAIL scale),[20] nutrition (Mini-Nutritional Assessment-Short Form, MNA-SF),[21] grip strength (measured with JAMAR 5030J1 Hand Dynamometer), quality of life (EuroQol Scale-5D),[22] falls, sensory impairment, depression (Yesavage Geriatric Depression Scale),[23] polypharmacy and demographic factors such as provenance and education level. Possible confounding factors, including fracture characteristics, type of anesthesia, type of surgery, peri- and post-operative complications such as infectious events or postoperative anemia were registered for all patients.

The presence or absence of delirium was scored daily until discharge by two geriatricians using the Spanish version of the 4AT scale.[24,25] Information for the 4AT was

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based on a psychiatric examination of the patient, review of medical and nursing records, and information given by the patient's closest relative. All 60 patients were non-delirious before surgery. Delirium symptom severity was assessed postoperatively with the validated Memorial Delirium Assessment Scale (MDAS).[26] The peak MDAS was defined as the highest total delirium severity score recorded in the postoperative period. Delirium subtype was assessed using the Delirium Motor Subtype Scale-4.[27] Preexisting cognitive impairment was based on medical history and Informant Questionnaire on Cognitive Decline short form (IQCODE-sf). The informant was asked to recall the cognitive situation 2 weeks prior to the hip fracture and compare it with the situation 10 years earlier. Patients with a mean score of 3.9 or higher were considered to have global cognitive impairment.[28,29]

2.3. Sample collection and laboratory assessments

Blood and CSF were collected before surgery and processed in no more than 1 hour from their sampling. The blood sample (8 mL obtained by venous puncture) was collected the morning prior to surgery and placed in a polypropylene plastic tube at room temperature (25ºC) for 30 minutes until blood coagulation occurred; then, the tube was centrifuged in a fixed-angle rotor at 1960 *g* for 10 minutes at room temperature. After centrifugation, the serum in the upper layer was carefully extracted and divided into 0.5mL aliquots and immediately stored at -80ºC. CSF samples were collected during canulation for the introduction of spinal anesthesia, prior to administration of any anesthetic. Lumbar punctures were performed with a 25-gauge needle between the L3-L4 or L4-L5 intervertebral space. From each patient, 2 mL of CSF was collected in polypropylene tubes which were transported to the laboratory and centrifuged at 720 *g* for 10 minutes at 4ºC, divided into 0.5 µL aliquots and stored at -80ºC. Samples of 30 patients (both serum and CSF) in which 15 had delirium and 15 did not, were selected and sent on dry ice for analysis at Cobiomic Bioscience (Parque Científico Tecnológico de Córdoba, Córdoba, Spain). We used Olink® technology to assess cytokine and chemokine levels. The Olink® reagents are based on the Proximity Extension Assay (PEA) technology, where 45 oligonucleotide labeled antibody probe pairs are each allowed to bind to their respective target protein present in the sample. Following hybridization of the matched oligo sequences, a PCR reporter sequence is formed by a proximity-dependent DNA polymerization event. This is then amplified, and subsequently detected and quantified using real time Polymerase Chain

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Reaction (PCR). The assay is performed in a 48-plex format without any need for washing steps, and results are reported in standard concentration units (pg/mL). When cytokines are within the lower and upper limits of quantification (LLOQ and ULOQ) for each assay, the values are not included in the analysis. Details about PEA technology, assays performance and validation data are available from the manufacturer (www.olink.com) and all the biomarkers analyzed with this technology are detailed in **Table 1**.

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Table 1. Biomarkers analyzed with Olink® technology

Biomarker name (Abbreviation)
C-C motif chemokine 2 (CCL2)
C-C motif chemokine 3 (CCL3)
C-C motif chemokine 4 (CCL4)
C-C motif chemokine 7 (CCL7)
C-C motif chemokine 8 (CCL8)
C-C motif chemokine 13 (CCL13)
C-C motif chemokine 19 (CCL19)
C-X-C motif chemokine 9 (CXCL9)
C-X-C motif chemokine 10 (CXCL10)
C-X-C motif chemokine 11 (CXCL11)
Eotaxin (CCL11)
Fms-related tyrosine kinase 3 ligand (FLT3LG)
Granulocyte colony-stimulating factor (CSF3)
Granulocyte-macrophage colony-stimulating factor (CSF2)
Hepatocyte growth factor (HGF)
Interferon gamma (IFNG)
Interleukin-1 beta (IL1B)
Interleukin-2 (IL2)
Interleukin-4 (IL4)
Interleukin-6 (IL6)
Interleukin-7 (IL7)
Interleukin-8 (CXCL8)
Interleukin-10 (IL10)
Interleukin-13 (IL13)
Interleukin-15 (IL15)
Interleukin-17A (IL17A)
Interleukin-17C (IL17C)
Interleukin-17F (IL17F)
Interleukin-18 (IL18)
Interleukin-27 (IL27)
Interleukin-33 (IL33)
Interstitial collagenase (MMP1)
Lymphotoxin-alpha (LTA)
Macrophage colony-stimulating factor 1 (CSF1)
Macrophage metalloelastase (MMP12)
Oncostatin-M (OSM)
Oxidized low-density lipoprotein receptor 1 (OLR1)
Pro-epidermal growth factor (EGF)
Protransforming growth factor alpha (TGFA)
Stromal cell-derived factor 1 (CXCL12)
Tumor necrosis factor (TNF)
Tumor necrosis factor ligand superfamily member 10 (TNFSF10)
Thymic stromal lymphopoietin (TSLP)
Tumor necrosis factor ligand superfamily member 12 (TNFSF12)
Vascular endothelial growth factor A (VEGFA)

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2.4. Standard protocol approval, registration and patient consents

This study was conducted in accordance with the Declaration of Helsinki (World Medical Association) and was approved by the Navarra Clinical Research Ethics Committee on June 25, 2021 (PI_2021/68). Data and samples were collected after informed consent from patients at the time of enrolment. There was no financial compensation for the participants.

2.5. Statistical analyses

Variables were tested for normality using the Shapiro-Wilk method. Consequently, non-parametric (Mann–Whitney U) or parametric (independent t-test) tests were used to compare the two groups (patients who developed POD versus patients who did not develop POD) regarding baseline characteristics measured in continuous variables. For dichotomous or nominal variables, Fisher's exact or Pearson X^2 were used. Data were presented as mean and standard deviation unless stated otherwise. For descriptives and testing of group differences, the statistical software used was SPSS version 26 (International Business Machines Corporation (IBM), Armonk, New York, USA). P-value of <0.05 was considered significant.

We used the Tukey's fences method to detect observations out of the normal range by using interquartile ranges, which is often used for detecting outliers in various fields.[30] 122 outliers were excluded from the analysis out of the 2700 values analyzed using the Olink platform. Before performing Tukey's fences, normality of the data was checked before fitting the curve. Features with >70% missing values in the real samples or >10% outlier values in the serum and CSF samples were deleted first. 38 biomarkers passed quality control in serum and 27 passed quality control in CSF (**Table 2**). Serum biomarkers in pg/mL values were analyzed using two unpaired t-tests, *Benjamini–Hochberg* method for p value correction with 5% false discovery rate, and a distribution boxplot. P values <0.05 were considered statistically significant after correction with the *Benjamini–Hochberg* method. A principal component analysis (PCA) and Volcano plot assessed the distribution of the groups, using singular value decomposition with imputation (pre-normalized data, no transformation), and visualized using ClustVis [31]. Spearman's correlation matrices were calculated including clinical variables, sex and age, and significant biomarkers for patients

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who developed POD versus patients who did not develop POD, using the R package Corrplot (version 0.84. https://cran.r-project.org/package=corrplot).

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Table 2. Biomarkers (cytokines and chemokines) within the analytic samples

Variable	SERUM			CSF		
	Delirium (n=15)	No Delirium (n=15)	p-value	Delirium (n=15)	No Delirium (n=15)	p-value
CCL8	44.2 (40.3, 58.0)	48.3 (39.7, 64.8)	0.511	1.7 (1.3, 1.9)	1.4 (1.3, 1.7)	0.347
IL33	0.4 (0.3, 0.6)	0.6 (0.5, 0.7)	0.075	Undetectable	Undetectable	
CXCL12	199.9 (182.0, 223.1)	173.8 (143.7, 195.9)	0.046	Undetectable	Undetectable	
OLR1	163.6 (88.7, 316.3)	103.7 (83.5, 236.0)	0.254	176.3 (155.5, 247.1)	224.2 (163.7, 250.2)	0.780
IL27	22.1 (9.1, 39.0)	17.6 (15.8, 25.9)	0.821	Undetectable	Undetectable	
IL2	Undetectable	Undetectable		Undetectable	Undetectable	
CXCL9	88.1 (70.8, 96.9)	155.0 (108.4, 289.7)	0.001*	5.9 (5.6, 6.9)	11.6 (8.7, 14.6)	**0.006**
TGFA	20.4 (13.1, 30.7)	17.9 (13.4, 21.3)	0.616	49.7 (42.5, 58.6)	37.9 (33.1, 39.7)	**0.002**
IL1B	Undetectable	Undetectable		Undetectable	Undetectable	
IL6	35.6 (26.5, 45.1)	42.7 (26.2, 61.8)	0.377	3.0 (2.3, 8.0)	2.6 (2.2, 4.4)	0.187
IL4	Undetectable	Undetectable		Undetectable	Undetectable	
TNFSF12	553.3 (403.9, 649.6)	522.0 (409.2, 615.2)	0.935	1,151.4 (900.6, 1,700.0)	1,125.6 (921.1, 1,238.5)	0.451
TSLP	Undetectable	Undetectable		Undetectable	Undetectable	
CCL11	93.6 (87.2, 125.1)	132.7 (69.5, 196.6)	0.539	1.7 (1.3, 2.1)	1.6 (1.5, 2.1)	1.000
HGF	1,151.6 (951.3, 1,414.7)	1,001.9 (608.2, 1,331.2)	0.533	287.3 (253.1, 344.9)	279.6 (250.3, 352.2)	0.902
FLT3LG	59.6 (53.6, 73.5)	84.1 (58.6, 98.5)	0.112	72.6 (65.8, 94.8)	76.3 (64.8, 98.8)	0.806
IL17F	Undetectable	Undetectable		Undetectable	Undetectable	
IL7	6.0 (4.4, 7.3)	6.0 (4.3, 7.3)	0.910	0.3 (0.3, 0.4)	0.3 (0.3, 0.4)	0.696
IL13	Undetectable	Undetectable		Undetectable	Undetectable	
IL18	287.9 (227.9, 409.9)	274.9 (204.9, 338.6)	0.345	7.1 (5.4, 10.8)	7.5 (5.8, 11.4)	0.838
CCL13	127.9 (96.2, 168.5)	187.2 (111.2, 227.6)	0.172	0.4 (0.4, 0.6)	0.5 (0.5, 0.7)	0.367
TNFSF10	363.4 (307.7, 439.1)	319.7 (287.7, 458.2)	0.595	6.2 (5.1, 7.3)	5.6 (4.3, 6.8)	0.567
CXCL10	112.6 (101.7, 118.8)	112.4 (103.2, 176.2)	0.650	89.1 (53.2, 116.3)	106.4 (51.9, 124.0)	0.683
IFNG	0.2 (0.1, 0.2)	0.2 (0.1, 0.4)	0.350	Undetectable	Undetectable	
IL10	11.3 (7.8, 13.0)	17.4 (13.9, 26.1)	0.007	Undetectable	Undetectable	
CCL19	113.3 (86.6, 136.4)	114.1 (85.2, 128.2)	0.943	33.4 (21.7, 56.8)	25.4 (18.8, 32.6)	0.158
TNF	29.2 (26.1, 30.8)	30.5 (28.3, 32.5)	0.434	Undetectable	Undetectable	
IL15	16.1 (15.2, 18.8)	17.8 (16.3, 22.5)	0.081	13.7 (10.4, 19.3)	12.3 (10.1, 15.3)	0.539

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CCL3	14.8 (10.2, 18.3)	17.0 (13.9, 17.4)	0.595	1.7 (1.6, 2.1)	2.6 (1.9, 2.8)	**0.009**
CXCL8	22.2 (19.8, 25.6)	26.6 (18.6, 43.2)	0.270	47.1 (41.9, 60.2)	57.1 (46.2, 64.4)	0.294
MMP12	436.5 (359.4, 541.2)	386.5 (320.3, 508.2)	0.683	22.6 (11.3, 32.4)	31.4 (13.8, 40.7)	0.315
CSF2	Undetectable	Undetectable		Undetectable	Undetectable	
CSF3	115.0 (69.5, 140.7)	200.4 (125.8, 262.5)	0.004	21.2 (14.2, 25.6)	12.4 (11.1, 15.5)	0.060
VEGFA	930.3 (638.9, 1,130.9)	835.8 (730.1, 1,121.0)	0.653	154.1 (127.2, 203.2)	154.0 (126.6, 185.7)	0.425
IL17C	31.8 (20.2, 45.7)	33.7 (23.8, 62.7)	0.946	Undetectable	Undetectable	
EGF	112.8 (75.0, 188.6)	99.4 (61.1, 110.0)	0.155	Undetectable	Undetectable	
CCL2	501.3 (426.1, 578.2)	637.4 (498.8, 1,198.4)	0.063	421.4 (366.0, 509.6)	413.6 (398.6, 668.9)	0.713
IL17A	1.0 (0.6, 1.7)	1.2 (0.6, 2.0)	0.590	Undetectable	Undetectable	
OSM	11.4 (6.0, 12.2)	6.1 (4.5, 10.2)	0.270	Undetectable	Undetectable	
CSF1	169.8 (150.5, 183.4)	171.4 (153.6, 185.0)	0.838	71.4 (66.1, 81.6)	70.6 (65.3, 74.3)	0.591
CCL4	169.1 (159.3, 220.5)	197.0 (160.1, 294.6)	0.488	8.5 (6.7, 10.5)	11.6 (7.3, 13.7)	0.067
CXCL11	50.3 (34.3, 57.9)	51.2 (43.0, 74.3)	0.560	1.6 (1.3, 2.7)	1.5 (1.1, 2.0)	0.377
LTA	4.1 (3.7, 4.9)	5.0 (3.8, 5.6)	0.402	0.5 (0.4, 0.6)	0.6 (0.5, 0.7)	0.105
CCL7	2.7 (2.2, 4.4)	3.1 (2.1, 4.5)	0.744	Undetectable	Undetectable	
MMP1	5,173.7 (1,844.2, 6,810.9)	4,904.6 (3,141.2, 6,161.3)	0.879	6.6 (5.3, 8.4)	8.5 (6.0, 12.4)	0.088

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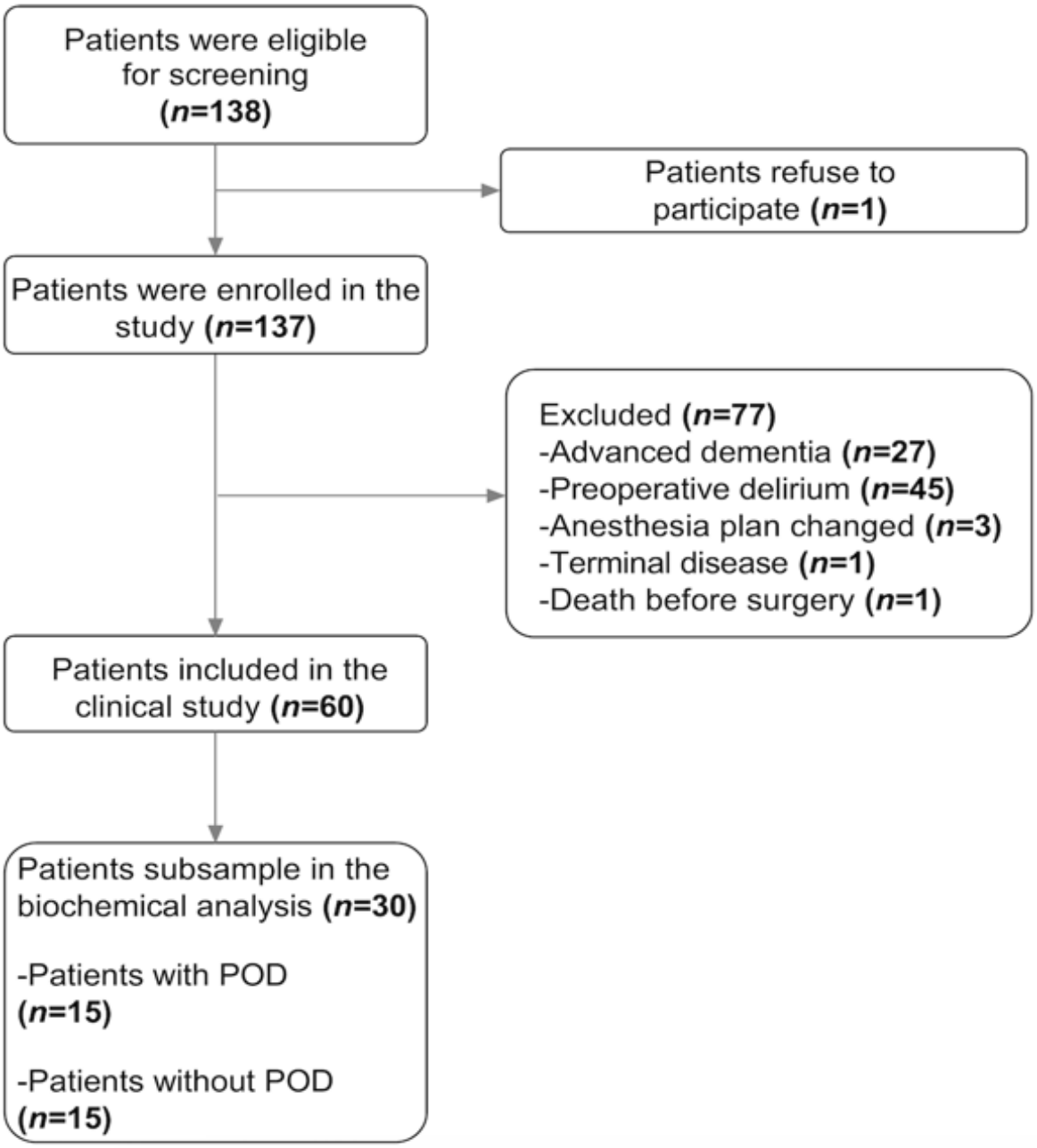
3. Results

3.1. Clinical results

From August 2021 to December 2021, 60 of 138 hip fracture patients fulfilled criteria for participation and provided informed consent (**Figure 1**). Twenty-one of these 60 patients developed POD (35%) and thirty-nine did not (65%).

Figure 1. Flowchart of study inclusion



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The characteristics of patients with and without POD are shown in **Table 3**. Patients who developed POD had more cognitive impairment (p<0.001), higher dependency (p=0.005) and worse nutritional status (p=0.013).

Table 3. Baseline characteristics of patients with and without POD

		Without POD n=39 (65%)	**POD n=21(35%)**	**p-value**
Age (years)	mean (sd)	84.9 (6.6)	87.9 (5.2)	0.085[a]
Sex	Male	6 (15.4%)	4 (19.0%)	
	Female	33 (84.6%)	17 (81.0%)	0.729[b]
Comorbidity (Charlson)	median (Q1-Q3)	5.0 (4.0-7.0)	5.0 (5.0-6.5)	0.814
ASA	2	9 (23.1%)	5 (23.8%)	
	3	26 (66.7%)	14 (66.7%)	1.0[b]
	4	4 (10.3%)	2 (9.5%)	
Number of drugs at admission	median (Q1-Q3)	7.0 (4.0-9.0)	8.0 (6.0-11.0)	0.181[d]
DBI at admission	median (Q1-Q3)	0.5 (0.0-1.17)	1.0 (0.5-1.4)	0.073[d]
Barthel index	mean (sd)	88.8 (12.6)	81.7 (15.8)	0.059[a]
Lawton and Brody	median (Q1-Q3)	6.0 (4.0-8.0)	3.0 (1.5-5.0)	0.005[d]
Grip strenght (Handgrip)	mean (sd)	14.1 (6.1)	12.0 (6.8)	0.216[a]
Nutritional condition (MNA)	median (Q1-Q3)	27.0 (25.0-28.5)	25.5 (19.8-27.5)	0.013[d]
Frailty (FRAIL)	median (Q1-Q3)	1.0 (1.0-2.0)	2.0 (1.0-3.0)	0.194[d]
Admission location	Home	36 (92.3%)	18 (85.7%)	
	Nursing home	3 (7.7%)	3 (14.3%)	0.655[b]
QoL at admission (EuroQoL-5D)	mean (sd)	77.3 (20.4)	71.0 (17.6)	0.118[a]
Visual impairment	No	11 (28.2%)	5 (23.8%)	
	Yes	28 (71.8%)	26 (76.2%)	0.713[c]
Hearing impairment	No	25 (64.1%)	8 (38.1%)	
	Yes	14 (35.9%)	13 (61.9%)	0.053[c]
Educational level	Primary studies	9 (23.1%)	7 (33.3%)	
	Secondary studies	28 (71.8%)	10 (47.6%)	0.101[b]
	University	2 (5.1%)	4 (19.0%)	
Depression (Yesavage)	median (Q1-Q3)	3.0 (1.0-5.0)	5.0 (2.5-8.0)	0.055[d]
Cognitive impairment (IQCODE-sf at admission)	mean (sd)	52.1 (4.9)	60.0 (8.8)	<0.001[a]
Previous episodes of delirium	No	34 (87.2%)	15 (71.4%)	
	Yes	5 (12.8%)	6 (28.6%)	0.169[b]

Characteristics of the surgery and clinical complications after surgery are shown in **Table 4**. No significant differences were found between type of hip fracture, time from surgery to sitting, femoral nerve block, blood transfusion or bladder catheterization and the incidence of POD. However, patients who spent a longer period of time without walking after surgery had higher incidence of POD (*p*=0.003). In addition, patients who developed delirium had more infections (*p*<0.001), needed more psychotropic drugs (*p*<0.001) and more opioids (*p*=0.013) during hospitalization than patients without delirium.

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Table 4. Characteristics after surgery of patients with and without POD

		Without POD n=39 (65%)	POD n=21 (35%)	p-value
Type of hip fracture	Subcapital	15 (38.5%)	8 (38.1%)	
	Pertrochanteric	18 (46.2%)	8 (38.1%)	
	Subtrochanteric	3 (7.7%)	1 (4.8%)	0.659[b]
	Basicervical	3 (7.7%)	4 (19.0%)	
Time from surgery to sitting (hours)	median (Q1-Q3)	36.0 (36.0-36.0)	36.0 (36.0-36.0)	0.618[a]
Time from surgery to walking (hours)	median (Q1-Q3)	48.0 (48.0-72.0)	72.0 (60.0, 120.0)	0.003[a]
Femoral nerve block	No	21 (53.8%)	11 (52.4%)	0.914[c]
	Yes	18 (46.2%)	10 (47.6%)	
Blood transfusion (number of packed red blood cells)	median (Q1-Q3)	0.0 (0.0, 1.0)	1.0 (0.0, 2.0)	0.058[a]
Infection	No	33 (84.6%)	6 (28.6%)	
	Yes	6 (15.4%)	15 (71.4%)	<0.001[c]
Type of infection	None	33 (84.6%)	6 (28.6%)	
	Respiratory	2 (5.1%)	4 (19.0%)	
	Urinary	2 (5.1%)	6 (28.6%)	
	Bacteraemia	1 (2.6%)	0 (0.0%)	
	Sepsis	0 (0.0%)	2 (9.5%)	<0.001[b]
	Respiratory+Urinary	0 (0.0%)	1 (2.8%)	
	Another focus	1 (2.6%)	2 (9.5%)	
Bladder catheterization	No	20 (51.3%)	9 (42.9%)	
	Yes	19 (48.7%)	12 (57.1%)	0.533[c]
Poor pain control during hospitalization	No	33 (84.6%)	11 (52.4%)	
	Yes	6 (15.4%)	10 (47.6%)	0.013[c]
Use of opioids during hospitalization	No	36 (92.3%)	11 (52.4%)	
	Yes	3 (7.7%)	10 (47.6%)	<0.001[b]
Need of psychotropic drugs during hospitalization	No	26 (66.7%)	6 (28.6%)	
	Yes	13 (33.3%)	15 (71.4%)	0.005[c]

3.2. Laboratory results

Serum and CSF samples of 30 patients were analyzed (15 patients with POD and 15 patients without POD) and the results are shown in **Table 2.** A score plot was generated to show the separation between the POD and non-POD groups. The PCA analysis did not reveal any abnormal deviations between the two groups (**Figure 2).**

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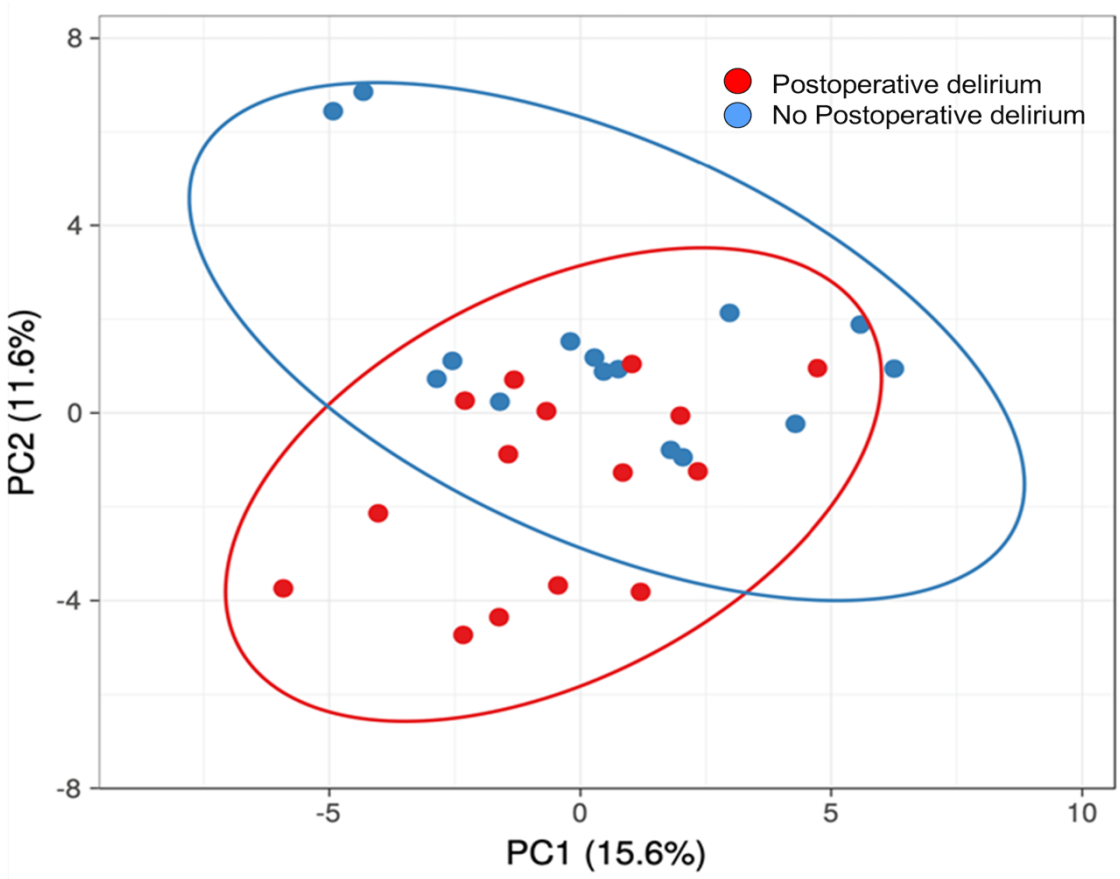
Figure 2. Principal component (PCA) of POD and non-POD groups



Principal component analysis (PCA) was created to investigate possible outliers in the data set. Score plot showing the separation between the POD and without POD group. The red points correspond to patients with POD, and the blue points correspond to patients without POD.

The volcano plot in **Figure 3** shows the differences between POD and non-POD groups. Those who developed POD had significantly higher levels of CXCL12 and EGF in serum as well as higher levels of CSF3 and TGFA in CSF compared to patients without POD. However, patients who developed POD had significantly lower levels of CSF3, CXCL9, IL10, CCL2 and CXCL8 in serum and lower levels of CCL3, CXCL9 and CCL4 in CSF compared to patients without POD.

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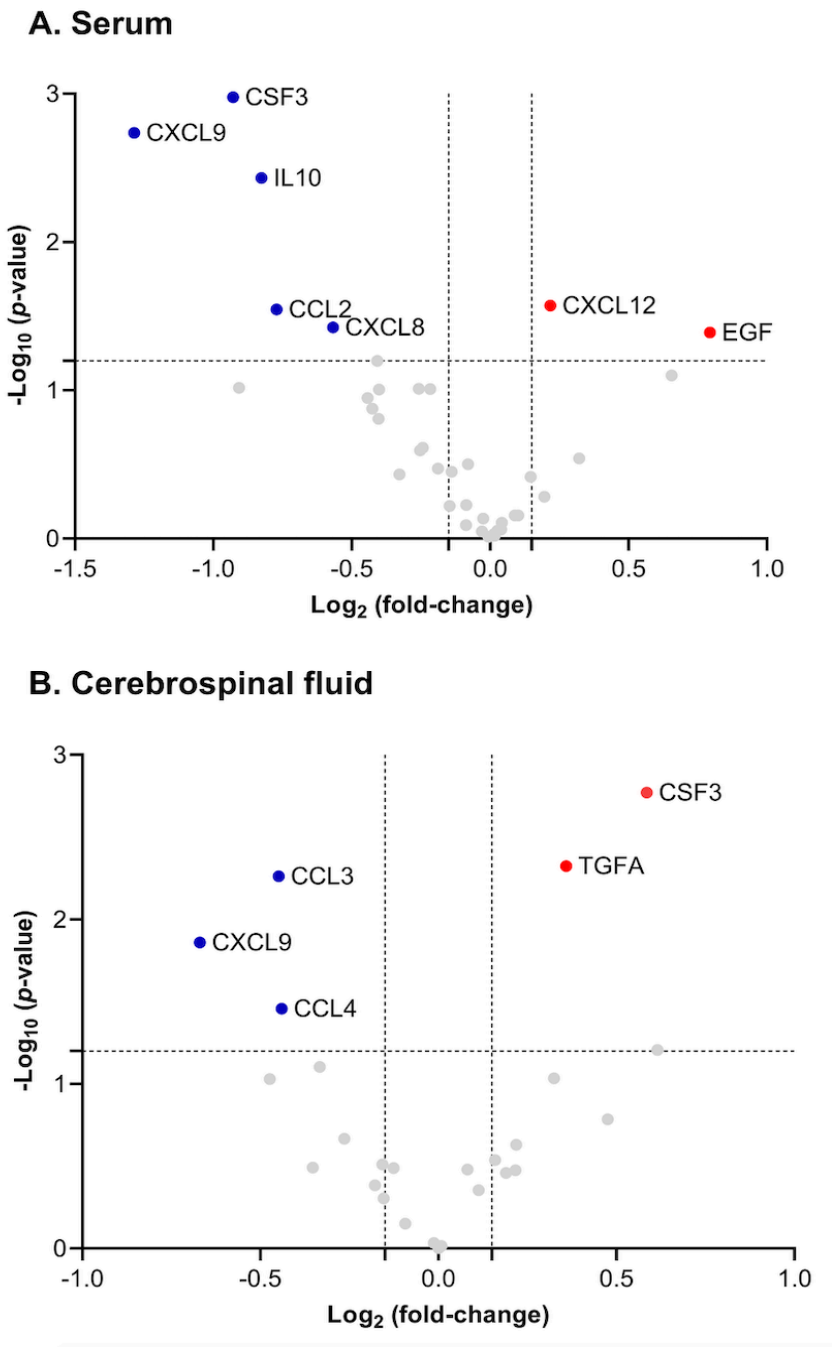
Figure 3. Biomarkers identification according to serum and cerebrospinal fluid levels into POD and non-POD groups



The volcano plot for detected biomarkers; the X-axis represents the $\log_2$ fold-change value, while the Y-axis represents the $-\log_{10}$ P value; the gray point represents the biomarkers without significant difference. The red point represents the biomarkers increase with significant difference, while blue point represents the biomarkers decrease with significant difference, in patients with POD compared to patients without POD.

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The association between cytokine concentrations in serum and CSF in POD and non-POD groups, adjusted by sex and age, were investigated using Spearman rank (Rho) correlation. This analysis revealed significant negative relationships between levels of serum EGF and serum CXCL9 (rho= -0.754; $p<0.05$), CSF TGFA and CSF CXCL9 (rho= -0.714; $p<0.01$), CSF CSF3 and CSF CCL3 (rho= -0.843; $p<0.05$) in the non-POD group. We found other significant positive relationships between serum CSF3 and serum IL10 (rho= 0.603; $p<0.05$), CSF CSF3 and serum CXCL12 (rho= 0.737, $p<0.05$), CSF CSF3 and serum CXCL8 (rho= 0.816, $p<0.05$), CSF CCL4 and CSF CCL3 (rho= 0.64, $p<0.05$) in the non-POD group.

On the other hand, significant negative relationships were found between serum CSF3 and serum CXCL9 (rho= -0.688; $p<0.05$), serum EGF and serum CXCL9 (rho= -0.635; $p<0.05$), serum EGF and serum CXCL8 (rho= -0.605; $p< 0.05$) in POD group. Similarly, other significant positive relationships were found between serum CXCL8 and serum IL10 (rho= 0.538; $p<0.05$), serum CSF3 and serum CXCL8 (rho= 0.597; $p<0.05$), serum CCL2 and serum CSF3 (rho= 0.599; $p<0.05$), CSF CCL3 and serum CXCL12 (rho= 0.621; $p<0.05$), CSF CCL4 and serum CCL2 (rho= 0.596; $p<0.05$), CSF CCL4 and CSF CCL3 (rho= 0.812; $p<0.001$) in POD group.

The only cytokine that had a significantly positive correlation in both serum and CSF of patients with POD was CXCL9 (rho= 0.663; $p<0.05$) (**Figure 4**).

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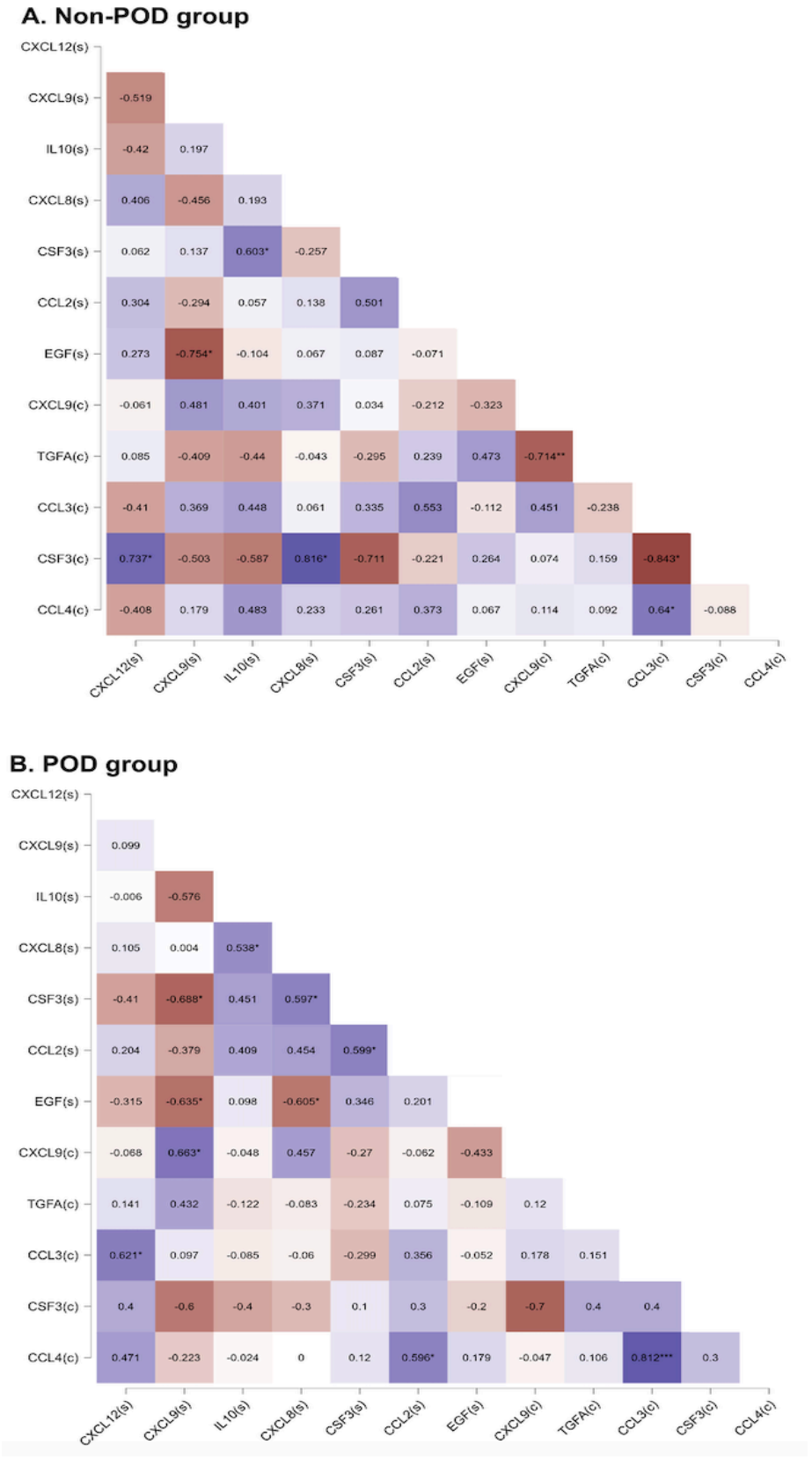
Figure 4. Matrix of pairwise spearman correlations among biomarkers according to serum (s) and cerebrospinal fluid (c) levels for POD and non-POD groups adjusted by sex and age. Color represents the level of Spearman's correlations (blue means positive correlation and red means negative correlation).



Significant protein pairs correlations were indicated as *** p<0.001, ** p<0.01, * p<0.05.

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4. Discussion

In this study, we investigated the association between POD and 45 cytokines and chemokines in preoperative serum and CSF in older hip fracture patients and we identified 12 potential biomarkers of delirium risk. Four of them were found to be up-regulated (serum CXCL12, serum EGF, CSF CSF3 and CSF TGFA) and eight were down-regulated (serum CSF3, serum CXCL9, serum CXCL8, serum IL10, serum CCL2, CSF CCL3, CSF CXCL9, and CSF CCL4). An interesting finding was the significant correlation between lower levels of CXCL9 in serum and CSF in patients with POD compared to patients without POD.

Chemokine (C-X-C motif) ligand 9 (CXCL9) is a small cytokine belonging to the CXC chemokine family that is also known as monokine induced by gamma interferon (MIG). CXCL9 induces chemotaxis, promotes differentiation and multiplication of leukocytes and causes tissue extravasation. It has been found that CXCL9 increases with age[32] and is an important factor in age-related chronic inflammation, being involved in cardiac aging, adverse cardiac remodeling and poor vascular function. Age-related elevation in CXCL9 leads to endothelial cell senescence and predicts subclinical levels of cardiovascular aging in healthy individuals.[33] CXCL9 has also been shown to be associated with falls and hip fracture in older population[34] and frailty.[35,36] Furthermore, data in the literature indicates a significant role of CXCL9 and its receptor (CXCR3) in the Central Nervous System (CNS), in both physiological and pathological processes.[37,38] CXCL9 is expressed in human brain-derived microvascular endothelial cells and astrocytes and is especially involved in Th1 response. In addition, it has been shown that CXCL9 is able to induce the activation of extracellular signal-regulated kinases (ERK1/2) in cortical neurons and might be involved in a neuronal-glial interaction. The up-regulation of this chemokine and its receptor was also identified in Alzheimer Disease (AD) brains, finding higher levels of CXCL9 in AD patients compared to patients with mild cognitive impairment or without cognitive impairment.[39,40] On the other hand, CXCL9 exhibited lowest levels in participants with 1 or more ε4 alleles in a study carried out to identify a panel of plasma biomarkers of AD.[41] These dissenting results support the fact that lower levels of CXCL9 were associated with POD in our study. These discrepancies could be justified by the multiple mechanisms implicated in delirium development (tissue damage, infection, pain, polypharmacy, hypoxia…), the heterogeneity in the methodology of the studies carried out (different biochemical analysis and clinical assessments) and the small sample size of our study. Other factors to consider are the

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systemic inflammatory response syndrome of our patients (all of them had hip fracture, with the consequent tissue damage compared to other studies where the patients did not have it) and the complexity for chemokine receptor CXCR3 activation that is involved in wound healing with different signaling pathways.[42]

Serum Stromal cell-derived factor 1 (CXCL12) is involved in Alzheimer Disease (AD) pathophysiology[43] and pro-epidermal growth factor (EGF), whose up-regulation has been associated with cognitive impairment in Parkinson´s disease,[44,45] showed higher levels in patients with POD compared to patients without POD in our study. These findings support the possible relationship between CXCL12, EGF and POD.

Granulocyte colony-stimulating factor (CSF3) showed significantly higher levels in CSF but lower levels in serum of patients with POD in our study. Previous studies have found that its up-regulation improves neuroplasticity[46] and its administration in rats protects against cognitive impairment.[47]

Transforming growth factor alpha (TGFA) showed higher levels in CSF of patients who developed POD in our study and has been associated with AD and vascular dementia,[48,49] which could explain the pathophysiological substrate for delirium.

Interleukin-10 (IL10) whose down-regulation has been found in patients with AD and delirium,[50,51] showed lower levels in serum of patients who developed POD in our study, which is consistent with previous literature.

C-C motif chemokine 2 (CCL2), Interleukin-8 (CXCL8), C-C motif chemokine 3 (CCL3) and C-C motif chemokine 4 (CCL4) showed significantly lower levels in patients with POD in our study. However, higher levels have been associated with dementia,[52,53] delirium among critically ill patients[54] and neuropsychiatric disorders in Parkinson's disease[55,56] in previous literature.

Although the etiology of POD is both complex and elusive, in our study, age, comorbidity, sensory impairment, depression, worse functional status, cognitive impairment, malnutrition, frailty and polypharmacy were identified as clinical predisposing factors of POD, which is consistent with previous literature.[57,58] In addition, infections and immobility after hip fracture surgery were the only significant precipitating factors of POD during the postoperative period, according to similar results obtained in other studies.[16,59]

However, these predisposing and precipitating clinical factors are often difficult to quantify because they are subjective and, consequently, less accurate. In contrast,

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biomarkers are quantifiable, objective and potentially reproducible. Moreover, serum biomarkers are minimally invasive what makes them accessible in different clinical settings. Although further research is needed, these findings emphasize the role of biomarkers in POD after hip fracture and its potential use through the development of integrating objective methods into future predictive models of delirium.

We highlight several study strengths such as the collection of blood and CSF and the well-defined sample. However, some study limitations warrant mention. First, the small sample size requires that the results be interpreted with caution. Second, our set of inflammatory biomarkers might not be an appropriate indicator of inflammation in the CNS because most of the cytokines and chemokines analyzed are not characteristic of a specific condition or process, thus further testing and evaluation with robust studies in larger surgical population may be necessary to identify specific markers of delirium in order to implement the understanding of the CNS disorders pathophysiology.

5. Conclusion

In summary, we found 12 biomarkers associated with POD and lower levels of CXCL9 had the most significant correlation between serum and CSF. These findings suggest that altered proteomic profile before surgery could be associated with POD development. Although further research is needed to confirm these results, biomarkers may offer a valuable tool for delirium risk assessment in addition to current predictive clinical models.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Founding

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References

1. Marcantonio, E. R. Delirium in Hospitalized Older Adults. *N. Engl. J. Med.* **377**, 1456–1466 (2017) doi:10.1056/nejmcp1605501.
2. Bruce, A. J. The incidence of delirium associated with orthopedic surgery: A meta-analytic review. *Int. Psychogeriatrics* **19**, 197–214 (2007) doi:10.1017/S104161020600425X.
3. Zhou, J. Cognitive disorders associated with hospitalization of COVID-19: Results from an observational cohort study. *Brain. Behav. Immun.* **91**, 383–392 (2021) doi:10.1016/j.bbi.2020.10.019.
4. Oberai, T. Is delirium associated with negative outcomes in older patients with hip fracture: analysis of the 4904 patients 2017–2018 from the Australian and New Zealand hip fracture registry. *ANZ J. Surg.* **92**, 200–205 (2022) doi:10.1111/ans.17421.
5. Maldonado, J. R. Neuropathogenesis of delirium: Review of current etiologic theories and common pathways. *Am. J. Geriatr. Psychiatry* **21**, 1190–1222 (2013) doi:10.1016/j.jagp.2013.09.005.
6. Wilson, J. E. Delirium. *Nat. Rev. Dis. Prim.* **6**, (2020) doi:10.1038/s41572-020-00223-4.
7. Wang, Y. Postoperative delirium in the elderly: the potential neuropathogenesis. *Aging Clin. Exp. Res.* **30**, 1287–1295 (2018) doi:10.1007/s40520-018-1008-8.
8. Alam, A. Surgery, neuroinflammation and cognitive impairment. *EBioMedicine* **37**, 547–556 (2018) doi:10.1016/j.ebiom.2018.10.021.
9. Subramaniyan, S. Neuroinflammation and Perioperative Neurocognitive Disorders. *Anesth. Analg.* **128**, 781–788 (2019) doi:10.1213/ANE.0000000000004053.
10. Liu, X. Inflammatory markers in postoperativedelirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. *PLoS One* **13**, (2018) doi:10.1371/journal.pone.0195659.
11. Beloosesky, Y. Cytokines and C-reactive protein production in hip-fracture-operated elderly patients. *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* **62**, 420–426 (2007) doi:10.1093/gerona/62.4.420.
12. Hirsch, J. Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. *J. Neuroinflammation* **13**, 211 (2016) doi:10.1186/s12974-016-

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Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

0681-9.

13. Miao, S. Neopterin and mini-mental state examination scores, two independent risk factors for postoperative delirium in elderly patients with open abdominal surgery. *J. Cancer Res. Ther.* **14**, 1234–1238 (2018) doi:10.4103/0973-1482.192764.
14. Freter, S. Risk of pre- and post-operative delirium and the delirium elderly at risk (DEAR) tool in hip fracture patients. *Can. Geriatr. J.* **18**, 212–216 (2015) doi:10.5770/cgj.18.185.
15. Zhao, S. Risk factors and prognosis of postoperative delirium in nonagenarians with hip fracture. *Sci. Rep.* **13**, 1–7 (2023) doi:10.1038/s41598-023-27829-4.
16. Smith, T. O. Factors predicting incidence of post-operative delirium in older people following hip fracture surgery: a systematic review and meta-analysis. *Int. J. Geriatr. Psychiatry* **32**, 386–396 (2017) doi:10.1002/gps.4655.
17. Auer, S. The GDS/FAST staging system. *Int. Psychogeriatrics* **9**, 167–171 (1997) doi:10.1017/S1041610297004869.
18. Barthel, M. Functional evaluation: the Barthel Index. *Md. State Med. J.* **14**, 56–61 (1965).
19. Lawton, M. Assessment of older people: selfmaintaining and instrumental activities of daily living. Gerontologist. 1969;9:179–86. *Gerontologist* **9**, 1979–1986 (1969).
20. Woo, J. Frailty screening in the community using the FRAIL scale. *J. Am. Med. Dir. Assoc.* **16**, 412–419 (2015) doi:10.1016/j.jamda.2015.01.087.
21. Kaiser, M. . Validation of the mini nutritional assessment short-form (MNA®-SF): a practical tool for identification of nutritional status. *J. Nutr. Health Aging* **13**, 782–788 (2009).
22. Herdman, M. EuroQol-5D: a simple alternative for measuring health-related quality of life in primary care. *Aten. Primaria* **28**, 425–430 (2001) doi:10.1016/s0212-6567(01)70406-4.
23. Yesavage, J. A. Geriatric Depression Scale. *Psychopharmacol. Bull.* **24**, 709–710 (1988) doi:10.1007/978-3-319-69892-2_736-1.
24. Tieges, Z. Diagnostic accuracy of the 4AT for delirium detection in older adults: systematic review and meta-analysis. *Age Ageing* **50**, 733–743 (2021) doi:10.1093/ageing/afaa224.
25. Delgado-Parada, E. Diagnostic accuracy of the Spanish version of the 4AT scale (4AT-

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ES) for delirium screening in older inpatients. *Eur. J. Psychiatry* **36**, 182–190 (2022) doi:10.1016/j.ejpsy.2022.01.003.

26. Barahona, E. The Diagnostic Sensitivity of the Memorial Delirium Assessment Scale—Spanish Version. *J. Pain Symptom Manage.* **55**, 968–972 (2018) doi:10.1016/j.jpainsymman.2017.11.013.
27. Meagher, D. Development of an abbreviated version of the Delirium Motor Subtyping Scale (DMSS-4). *Int. Psychogeriatrics* **26**, 693–702 (2014) doi:10.1017/S1041610213002585.
28. Harrison, J. K. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the early detection of dementia across a variety of healthcare settings. *Cochrane Database Syst. Rev.* **2021**, (2021) doi:10.1002/14651858.CD011333.pub3.
29. Blandfort, S. The short IQCODE as a predictor for delirium in hospitalized geriatric patients. *Aging Clin. Exp. Res.* **32**, 1969–1976 (2020) doi:10.1007/s40520-019-01412-2.
30. Luo, J. Using the variogram for vector outlier screening: application to feature-based image registration. *Int. J. Comput. Assist. Radiol. Surg.* **13**, 1871–1880 (2018) doi:10.1007/s11548-018-1840-5.
31. Metsalu, T. ClustVis: A web tool for visualizing clustering of multivariate data using Principal Component Analysis and heatmap. *Nucleic Acids Res.* **43**, W566–W570 (2015) doi:10.1093/nar/gkv468.
32. Torres, K. C. L. Immune senescence and biomarkers profile of Bambuí aged population-based cohort. *Exp. Gerontol.* **103**, 47–56 (2018) doi:10.1016/j.exger.2017.12.006.
33. Sayed, N. *An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging*. *Nature Aging* vol. 1 (2021). doi:10.1038/s43587-021-00082-y.
34. Phan, Q. T. CXCL9 Predicts the Risk of Osteoporotic Hip Fracture in a Prospective Cohort of Chinese Men—A Matched Case–Control Study. *J. Bone Miner. Res.* **37**, 1843–1849 (2022) doi:10.1002/jbmr.4646.
35. de Amorim, J. S. C. Inflammatory markers and occurrence of falls: Bambuí Cohort Study of Aging. *Rev. Saude Publica* **53**, 1–11 (2019) doi:10.11606/S1518-8787.2019053000855.

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Nafarroako Unibertsitate Publikoa

36. de Amorim, J. S. C. Inflammatory markers associated with fall recurrence and severity: The Bambuí Cohort Study of Aging. *Exp. Gerontol.* **132**, 110837 (2020) doi:10.1016/j.exger.2020.110837.
37. Watson, A. E. S. Regulation of CNS precursor function by neuronal chemokines. *Neurosci. Lett.* **715**, 134533 (2020) doi:10.1016/j.neulet.2019.134533.
38. Satarkar, D. Evolution, Expression and Functional Analysis of CXCR3 in Neuronal and Cardiovascular Diseases: A Narrative Review. *Front. Cell Dev. Biol.* **10**, 1–17 (2022) doi:10.3389/fcell.2022.882017.
39. Lee, K. S. Bioplex analysis of plasma cytokines in Alzheimer's disease and mild cognitive impairment. *Immunol. Lett.* **121**, 105–109 (2008) doi:10.1016/j.imlet.2008.09.004.
40. Koper, O. M. CXCL9, CXCL10, CXCL11, and their receptor (CXCR3) in neuroinflammation and neurodegeneration. *Adv. Clin. Exp. Med.* **27**, 849–856 (2018) doi:10.17219/acem/68846.
41. Soares, H. D. Plasma biomarkers associated with the apolipoprotein E genotype and alzheimer disease. *Arch. Neurol.* **69**, 1310–1317 (2012) doi:10.1001/archneurol.2012.1070.
42. Berchiche, Y. A. CXC chemokine receptor 3 alternative splice variants selectively activate different signaling pathways. *Mol. Pharmacol.* **90**, 483–495 (2016) doi:10.1124/mol.116.105502.
43. Li, H. A focus on CXCR4 in Alzheimer's disease. *Brain Circ.* **3**, 199 (2017) doi:10.4103/bc.bc_13_17.
44. Pellecchia, M. T. Serum epidermal growth factor predicts cognitive functions in early, drug-naive Parkinson's disease patients. *J. Neurol.* **260**, 438–444 (2013) doi:10.1007/s00415-012-6648-6.
45. Yasar, Z. Sprint interval training (SIT) reduces serum epidermal growth factor (EGF), but not other inflammatory cytokines in trained older men. *Eur. J. Appl. Physiol.* **121**, 1909–1919 (2021) doi:10.1007/s00421-021-04635-2.
46. Sanchez-Ramos, J. Granulocyte Colony Stimulating Factor (G-CSF) Decreases Brain Amyloid Burden and Reverses Cognitive Impairment in Alzheimer's Mice. *Neuroscience* **163**, 55–72 (2009) doi:10.1016/j.neuroscience.2009.05.071.
47. Tuo, M. Role of Granulocyte-colony Stimulating Factor in the Protection of Cerebral

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Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

Vascular Endothelium, White Matter, and Cognition. *Curr. Neurovasc. Res.* **16**, 425–432 (2019) doi:10.2174/1567202616666191029115113.

48. Khedr, E. M. Cognitive Impairment, P300, and Transforming Growth Factor β1 in Different Forms of Dementia. *J. Alzheimer's Dis.* **78**, 837–845 (2020) doi:10.3233/JAD-200885.

49. Estrada, L. D. Transforming Growth Factor Beta Type I Role in Neurodegeneration: Implications for Alzheimer´s Disease. *Curr. Protein Pept. Sci.* **19**, 1180–1188 (2018) doi:10.2174/1389203719666171129094937.

50. Khan, S. H. Serum Biomarkers in Postoperative Delirium After Esophagectomy. *Ann. Thorac. Surg.* **113**, 1000–1007 (2022) doi:10.1016/j.athoracsur.2021.03.035.

51. Culjak, M. The Association between TNF-alpha, IL-1 alpha and IL-10 with Alzheimer's Disease. *Curr. Alzheimer Res.* **17**, 972–984 (2020) doi:10.2174/1567205017666201130092427.

52. Ahmad, M. A. Neuroinflammation: A Potential Risk for Dementia. *Int. J. Mol. Sci.* **23**, (2022) doi:10.3390/ijms23020616.

53. Lee, W. J. Plasma MCP-1 and cognitive decline in patients with Alzheimer's disease and mild cognitive impairment: A two-year follow-up study. *Sci. Rep.* **8**, 4–11 (2018) doi:10.1038/s41598-018-19807-y.

54. Smith, R. J. Cytokine profiles in intensive care unit delirium. *Acute Crit. Care* **37**, 415–428 (2022) doi:10.4266/acc.2021.01508.

55. Perna, L. Risk of Late-Onset Depression and Cognitive Decline: Results From Inflammatory Proteome Analyses in a Prospective Population-Based Cohort Study. *Am. J. Geriatr. Psychiatry* **30**, 689–700 (2022) doi:10.1016/j.jagp.2021.12.001.

56. Lindqvist, D. Cerebrospinal fluid inflammatory markers in Parkinson's disease - Associations with depression, fatigue, and cognitive impairment. *Brain. Behav. Immun.* **33**, 183–189 (2013) doi:10.1016/j.bbi.2013.07.007.

57. Dogrul, R. T. Does Preoperative Comprehensive Geriatric Assessment and Frailty Predict Postoperative Complications? *World J. Surg.* **44**, 3729–3736 (2020) doi:10.1007/s00268-020-05715-8.

58. Yang, Y. Incidence and associated factors of delirium after orthopedic surgery in elderly patients: a systematic review and meta-analysis. *Aging Clin. Exp. Res.* **33**, 1493–1506 (2021) doi:10.1007/s40520-020-01674-1.

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

59. Inouye, S. K. Delirium in elderly people. *Lancet* **383**, 911–922 (2014) doi:10.1016/S0140-6736(13)60688-1.

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Chapter 3
The role of C-reactive protein as a risk marker of postoperative delirium in older hip fracture patients: a prospective cohort study

Capítulo 3
El papel de la proteína C-reactiva como marcador de riesgo de delirium postoperatorio en adultos mayores con fractura de cadera: un estudio de cohortes prospectivo

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1. Introduction

Delirium is a common neuropsychiatric syndrome characterized by an alteration in the level of consciousness and a disturbance in cognition and attention that appears abruptly.[1] Its incidence increases in patients aged 65 and older, reaching 15-53% after surgery but it can be higher in hip fracture patients with an incidence of 16-62%.[2] Postoperative delirium (POD) is a serious complication that is associated with higher mortality and morbidity, prolonged hospitalization,[3] greater risk of new institutionalization,[4] worse functional recovery[5] and increased risk of future dementia.[6]

The pathophysiological mechanisms that lead to delirium remain unclear.[7] There is an emerging interest in serum inflammatory proteins and their possible association with the development of delirium.[8] In this context, CRP has been traditionally used as a marker of inflammation, infection and tissue damage. An association between CRP levels and delirium has been reported but results are controversial.[9,10]

On the other hand, clinical predictive models of delirium such as the Delirium Elderly At-Risk (DEAR) tool, which assesses risk factors of delirium (age, cognitive impairment, functional status, polypharmacy and sensory impairment) have demonstrated their utility in delirium prediction identifying patients at high risk of POD, but some report that at times they may be subjective and imprecise.[11]

Despite the research in this field, the effectiveness of both biochemical and clinical models of delirium risk is unknown due to important limitations in the studies such as the methodology, the small sample size and a poor characterization of geriatric syndromes, which implies high heterogeneity.

The aim of this study was to investigate whether CRP was associated with the development and severity of delirium after hip fracture surgery in a homogeneous and well-defined older population, measuring other geriatric syndromes in order to assess which of the two models (biochemical or clinical) was more effective in predicting delirium.

2. Material and methods

2.1. Study design and participants

This was a prospective cohort study. Sixty hip fracture patients aged ≥75 years undergoing subarachnoid anesthesia, were recruited between August 2021 and December

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2021, in the Orthopedic ward of Hospital Universitario de Navarra (Pamplona, Spain). Patients were excluded if 1) had preoperative delirium, 2) had advanced dementia (a score > 5 in the Global Deterioration Scale),[12] 3) had severe dependence (a score <20 in the Barthel Index),[13] 4) had a terminal disease (life expectancy < 3 months), 5) were unable to communicate in Spanish and 6) were not willing or not capable to provide informed consent.

2.2. Clinical assessments

A Comprehensive Geriatric Assessment (CGA) was performed at the time of enrolment evaluating functional status (Barthel Index and Lawton and Brody scale),[14] pre-existing cognitive impairment (Informant Questionnaire on Cognitive Decline short form (IQCODE-sf)),[15] frailty (FRAIL index)[16] and grip strength (measured with JAMAR 5030J1 Hand Dynamometer). The presence or absence of delirium was scored daily until discharge by two geriatricians using the Spanish version of 4AT scale.[17] Delirium severity was assessed with the Memorial Delirium Assessment Scale (MDAS).[18]

2.3. Sample collection and laboratory assessments

Blood samples were collected before surgery and processed in no more than 1-2 hours from their extraction. Eight mL of blood were obtained by venous puncture. We used MULTIGENT CRP Vario assay (Abbott Laboratories, Wiesbaden, Germany) to analyze CRP levels. This technology is based on immunoturbidimetric methodology. When an antigen-antibody reaction occurs between CRP and anti-CRP antibody, which has been adsorbed to latex particles, agglutination results. This agglutination is detected as an absorbance change (572 nm), with the rate of change being proportional to the quantity of CRP in the sample.

2.4. Standard protocol approval, registration and patient consent

This study was conducted in accordance with the Declaration of Helsinki (World Medical Association) and was approved by the Navarra Clinical Research Ethics Committee on June 25, 2021 (PI_2021/68). Data and samples were collected after obtaining written informed consent from each patient at the time of enrolment. There was no financial compensation for the participants.

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2.5. Statistical analyses

We first compared preoperative CRP serum levels between patients with and without POD. In addition, we investigated the association between the levels of CRP and delirium severity. Furthermore, we analyzed the relationship between baseline clinical characteristics and the incidence of POD. Statistics were performed using SPSS (SPSS for Windows, version 20, IBM Corporation, Armonk, NY, USA). Continuous non-normal variables were tested with the Mann-Whitney U test. Spearman´s correlation was used for correlation analysis. Statistical significance was set at P <0.05. The figure was created with BioRender® (https://www.biorender.com).

3. Results

Sixty hip fracture patients were recruited at the Orthopedic Surgery and Traumatology ward in Hospital Universitario de Navarra (HUN). Twenty-one patients developed delirium after surgery (35%) and thirty-nine did not (65%).

Serum CRP was analyzed in all patients; the mean value was 32.5 mg/L and the range was 0 to 176 mg/L. Mean level of CRP in patients with POD was 47.2 mg/L (median 38.7 mg/L), 95% CI (26.76 - 67.53), whereas mean CRP level in patients without POD was 24.7 mg/L (median 9.2 mg/L), 95% CI (14.75 - 34.60), with a statistically significant difference (p=0.011). When comparing CRP levels with the severity of delirium, a positive but not significant association was observed. The 2-sided Spearman's correlation coefficient between CRP and MDAS was 0.228, p=0.079.

The most significant clinical variables associated with POD were age, comorbidity, grip strength, frailty, infections and cognitive impairment. When performing a multiple regression model with these clinical variables and CRP, cognitive impairment measured with IQCODE-sf and infections were the strongest predictor variables. Results are shown in **Table 1**.

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Table 1. Logistic regression model between clinical variables and CRP

	OR	95% CI OR		p-value
		Lower	Upper	
Age	1.06	0.90	1.25	0.465
Comorbidity (Charlson index)	0.60	0.36	1.00	0.050
Grip strenght	1.07	0.91	1.26	0.440
Frailty (FRAIL)	1.00	0.41	2.42	0.995
Cognitive impairment (IQCODE-sf)	1.29	1.09	1.53	**0.003***
Serum CRP	1.00	0.98	1.03	0.810
Infection	29.28	3.69	232.12	**0.001***

4. Discussion

This study investigated serum CRP as a predictive biomarker of delirium in a well-defined cohort of older hip fracture patients and compared these findings with a model based on clinical risk factors of delirium. We found significantly higher levels of serum CRP in hip fracture patients who developed POD, however, clinical variables such as cognitive impairment and infections were better predictors of delirium.

CRP is a pentameric protein whose circulating concentrations rise in response to inflammation and increases following IL-6 secretion by macrophages and T cells [19,20]. Although higher levels of CRP have been shown in inflammatory and infectious processes, CRP is also altered in patients with cognitive impairment and Alzheimer disease, which is a risk factor for delirium development [21,22]. Some studies have found that levels of CRP are significantly increased in older patients undergoing surgery who subsequently develop delirium [23–26], but others did not find this association [27–29]. Our data supports the neuroinflammatory hypothesis of delirium suggesting that inflammatory stimulation in the periphery goes through the blood-brain barrier (BBB), inducing the activation of brain parenchymal cells such as microglia and astroglia and producing a dysfunctional neuroinflammatory response with an expression of proinflammatory cytokines, which may lead to neurocognitive changes and delirium [30]. This pathway is explained in **Figure 1.**

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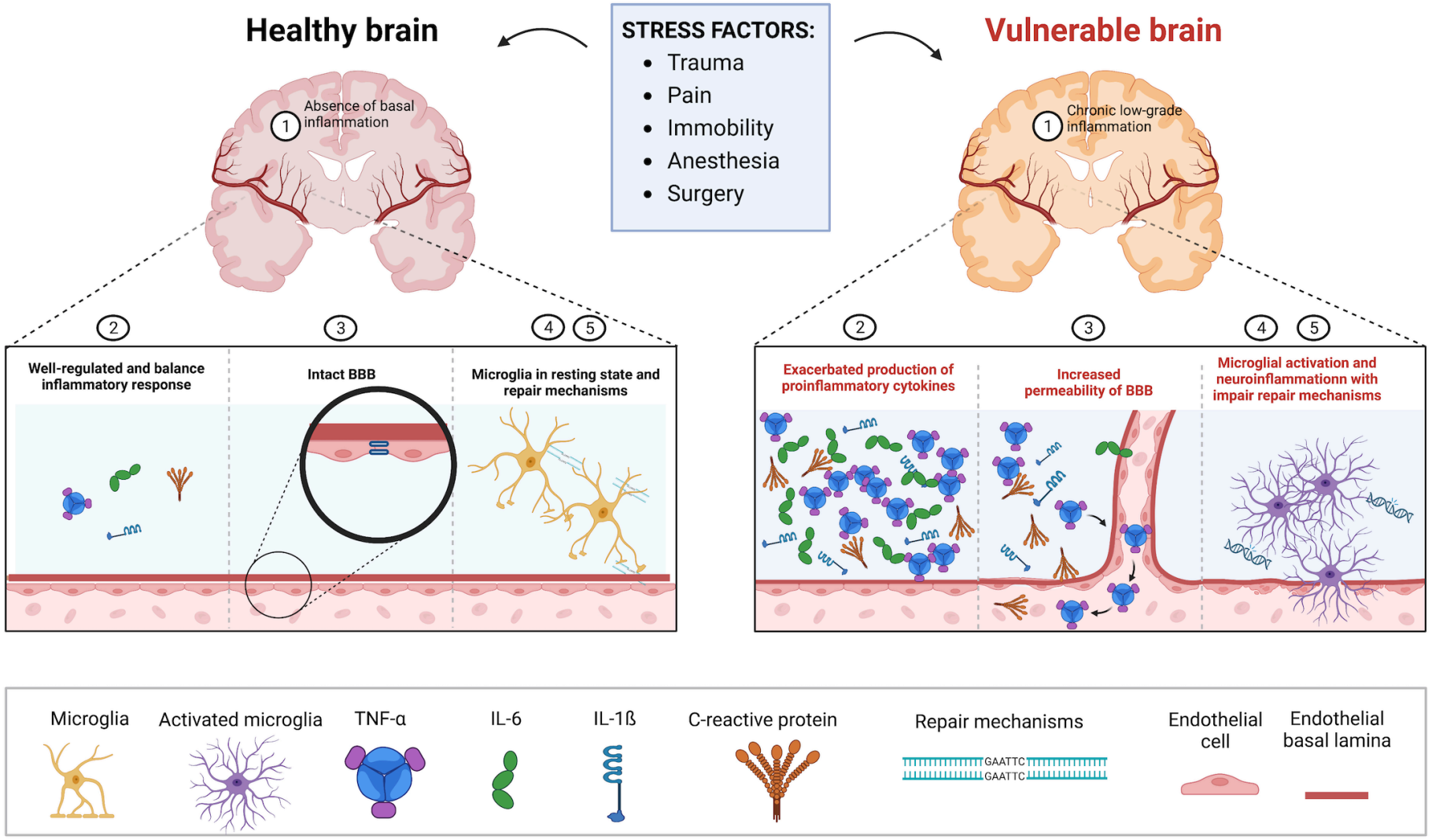
Figure 1. Neuroinflammatory hypothesis of delirium: the difference between a healthy and a vulnerable brain in response to stressors in hip fracture



1. *Chronic inflammation* in a vulnerable brain can result in sustained activation of proinflammatory pathways, leading to the production of additional cytokines, chemokines, and reactive oxygen species (ROS). This sustained neuroinflammation can damage neurons, disrupt synaptic function, and contribute to neurodegenerative processes seen in cognitive impairment.
2. *Inflammatory response:* In a healthy brain, the inflammatory response is typically well-regulated and balanced. However, in a vulnerable brain, there is an exacerbated production of proinflammatory cytokines such us tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1 beta (IL-1β). These cytokines act as mediators of inflammation and stimulate the production of CRP.
3. *BBB integrity:* The BBB is a protective barrier between the bloodstream and the brain, regulating the passage of molecules and cells. In a healthy brain, the BBB is generally intact, limiting the entry of inflammatory mediators and maintaining brain homeostasis. In contrast, in a frail brain, the BBB may be compromised, allowing increased permeability and the infiltration of inflammatory cells and molecules into the brain.
4. *Microglial activation and neuroinflammation:* Microglia, the resident immune cells of the brain, play a critical role in the inflammatory response. In a healthy brain, microglia are kept in a resting state, with balanced activation levels. In a vulnerable brain, microglia may exhibit a more activated and dysregulated state, leading to excessive release of proinflammatory cytokines and oxidative stress, contributing to neuroinflammation and delirium.
5. *Impaired repair mechanisms:* In a healthy brain, there are mechanisms for resolving inflammation and promoting tissue repair. However, in a vulnerable brain, these repair mechanisms may be impaired or dysregulated, leading to prolonged inflammation and reduced ability to restore normal brain function.

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However, when we performed a logistic regression model combining clinical variables and CRP, infections and pre-morbid cognitive impairment were the best predictors of POD. This can be explained by the advanced age of the patients with a high rate of comorbidity and frailty that confers brain vulnerability and lower resilience to stressors, developing more perioperative complications such as infections. In addition, all the patients had a fracture-induced systemic inflammatory response before surgery, when samples were collected, that may affect CRP levels and their interpretation.

Although a clinical predictive model of delirium including the infection rate and a cognitive assessment seems to be the best predictor of POD, serum CRP could be a valuable tool to complement its limitations such as subjectivity and complexity of performance, providing accessibility and reproducibility because it is minimally invasive and quantifiable.

We highlight several study strengths such as the detailed characterization of POD and the homogeneous and well-defined sample, including the measurement of several geriatric syndromes. However, some study limitations warrant mention. Firstly, the small sample size means that the results should be interpreted with caution. Secondly, we did not collect follow-up samples after POD to examine changes in different time moments. Thirdly, CRP has low specificity and may be related with other conditions or processes beyond delirium such us infections. More studies with larger sample sizes will be needed to define the potential role of these molecules in predictive models of delirium, combined with the classical clinical models in order to improve its accuracy.

5. Conclusions

Preoperative serum CRP was significantly associated with POD in older hip fracture patients. However, pre-morbid cognitive impairment and infections were the most important risk markers of POD. Although further research is needed to validate these results, the influence of neuroinflammation in the development of POD could help improve its prevention by targeting this pathway and creating delirium predictive models with both clinical and biochemical variables to improve predictive accuracy.

Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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References

1. Inouye, S. K. Delirium in elderly people. *Lancet* **383**, 911–922 (2014) doi:10.1016/S0140-6736(13)60688-1.
2. Yang, Y. Incidence and associated factors of delirium after orthopedic surgery in elderly patients: a systematic review and meta-analysis. *Aging Clin. Exp. Res.* **33**, 1493–1506 (2021) doi:10.1007/s40520-020-01674-1.
3. Israni, J. Delirium as a predictor of mortality in US Medicare beneficiaries discharged from the emergency department: A national claims-level analysis up to 12 months. *BMJ Open* **8**, 1–7 (2018) doi:10.1136/bmjopen-2017-021258.
4. Welch, C. Delirium is prevalent in older hospital inpatients and associated with adverse outcomes: Results of a prospective multi-centre study on World Delirium Awareness Day. *BMC Med.* **17**, 1–11 (2019) doi:10.1186/s12916-019-1458-7.
5. Marcantonio, E. R. Delirium Is Independently Associated with Poor Functional Recovery After Hip Fracture. *J. Am. Geriatr. Soc.* **48**, 618–624 (2000).
6. Lee, S. J. Postoperative delirium after hip surgery is a potential risk factor for incident dementia: A systematic review and meta-analysis of prospective studies. *Arch. Gerontol. Geriatr.* **87**, 103977 (2020) doi:10.1016/j.archger.2019.103977.
7. Wilson, J. E. Delirium. *Nat. Rev. Dis. Prim.* **6**, (2020) doi:10.1038/s41572-020-00223-4.
8. Subramaniyan, S. Neuroinflammation and Perioperative Neurocognitive Disorders. *Anesth. Analg.* **128**, 781–788 (2019) doi:10.1213/ANE.0000000000004053.
9. Liu, X. Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. *PLoS One* **13**, e0195659 (2018) doi:10.1371/journal.pone.0195659.
10. Lopez, D. A. Serum biomarkers associated with post-operative delirium in patients undergoing non-cardiac major thoracic surgery. *Am. J. Respir. Crit. Care Med.* **201**, (2020).
11. Freter, S. Risk of pre- and post-operative delirium and the delirium elderly at risk (DEAR) tool in hip fracture patients. *Can. Geriatr. J.* **18**, 212–216 (2015) doi:10.5770/cgj.18.185.
12. Auer, S. The GDS/FAST staging system. *Int. Psychogeriatrics* **9**, 167–171 (1997) doi:10.1017/S1041610297004869.

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

13. Barthel, M. Functional evaluation: the Barthel Index. *Md. State Med. J.* **14**, 56–61 (1965).
14. Lawton, M. Assessment of older people: selfmaintaining and instrumental activities of daily living. Gerontologist. 1969;9:179–86. *Gerontologist* **9**, 1979–1986 (1969).
15. Burton, J. K. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the detection of dementia within a secondary care setting. *Cochrane Database Syst. Rev.* **2021**, (2021) doi:10.1002/14651858.CD010772.pub3.
16. Woo, J. Frailty screening in the community using the FRAIL scale. *J. Am. Med. Dir. Assoc.* **16**, 412–419 (2015) doi:10.1016/j.jamda.2015.01.087.
17. Delgado-Parada, E. Diagnostic accuracy of the Spanish version of the 4AT scale (4AT-ES) for delirium screening in older inpatients. *Eur. J. Psychiatry* **36**, 182–190 (2022) doi:10.1016/j.ejpsy.2022.01.003.
18. Barahona, E. The Diagnostic Sensitivity of the Memorial Delirium Assessment Scale—Spanish Version. *J. Pain Symptom Manage.* **55**, 968–972 (2018) doi:10.1016/j.jpainsymman.2017.11.013.
19. Sproston, N. R. Role of C-reactive protein at sites of inflammation and infection. *Front. Immunol.* **9**, 1–11 (2018) doi:10.3389/fimmu.2018.00754.
20. Pathak, A. Evolution of C-reactive protein. *Front. Immunol.* **10**, (2019) doi:10.3389/fimmu.2019.00943.
21. Rentería, M. A. C-reactive protein and risk of cognitive decline: The REGARDS study. *PLoS One* **15**, 1–15 (2020) doi:10.1371/journal.pone.0244612.
22. Leng, F. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nat. Rev. Neurol.* **17**, 157–172 (2021) doi:10.1038/s41582-020-00435-y.
23. Cerejeira, J. The cholinergic system and inflammation: common pathways in delirium pathophysiology. *J. Am. Geriatr. Soc.* **60**, 669–675 (2012) doi:10.1111/j.1532-5415.2011.03883.x.
24. Chen, Y. Preoperative Circulating MiR-210, a Risk Factor for Postoperative Delirium Among Elderly Patients with Gastric Cancer Undergoing Curative Resection. *Curr. Pharm. Des.* **26**, 5213–5219 (2020) doi:10.2174/1381612826666200617163857.
25. Dillon, S. T. Higher C-Reactive Protein Levels Predict Postoperative Delirium in Older Patients Undergoing Major Elective Surgery: A Longitudinal Nested Case-Control

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

Study. *Biol. Psychiatry* **81**, 145–153 (2017) doi:10.1016/j.biopsych.2016.03.2098.

26. Slor, C. J. The trajectory of C-reactive protein serum levels in older hip fracture patients with postoperative delirium. *Int. J. Geriatr. Psychiatry* **34**, 1438–1446 (2019) doi:10.1002/gps.5139.

27. Çinar, M. A. Role of CRP, TNF-a, and IGF-1 in Delirium Pathophysiology. *Noro Psikiyatr. Ars.* **51**, 376–382 (2014) doi:10.5152/npa.2014.6999.

28. Katsumi, Y. The Role of Inflammation after Surgery for Elders (RISE) study: Examination of [11C]PBR28 binding and exploration of its link to post-operative delirium. *NeuroImage Clin.* **27**, (2020) doi:10.1016/j.nicl.2020.102346.

29. Lemstra, A. W. Pre-operative inflammatory markers and the risk of postoperative delirium in elderly patients. *Int. J. Geriatr. Psychiatry* **23**, 943–948 (2008) doi:10.1002/gps.2015.

30. Maldonado, J. R. Neuropathogenesis of delirium: Review of current etiologic theories and common pathways. *Am. J. Geriatr. Psychiatry* **21**, 1190–1222 (2013) doi:10.1016/j.jagp.2013.09.005.

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Chapter 4
Effectiveness of a multicomponent exercise training programme for the management of delirium in hospitalized older adults using Near-Infrared Spectroscopy (NIRS) as a biomarker of brain perfusion: study protocol for a randomized controlled trial

Capítulo 4
Efectividad de un programa de ejercicio multicomponente para el manejo del delirium en adultos mayores hospitalizados usando la espectroscopia de infrarrojo cercano (NIRS) como un biomarcador de perfusión cerebral: protocolo de un ensayo aleatorizado controlado

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Introduction

Delirium is highly prevalent among older adults across healthcare settings (8–17% reported in emergency departments, 20-29% in geriatric acute care, 13-50% in surgical patients and 19-82% in intensive care units).[1] Furthermore, delirium is particularly important in older patients not only for its high incidence and prevalence but also for the great impact of its consequences including longer hospital stay, increased risk of institutionalization at discharge, higher cognitive and functional impairment, higher mortality, and greater healthcare costs.[2] In addition, geriatric inpatients often experience accelerated functional decline during hospitalization associated with the long bed-rest episodes. Some studies have shown that more than 83% of these patients are bedridden and only 4% are permitted to stand or walk, which increases the risk of delirium and hinders its resolution once it is established.[3–6] Multicomponent interventions such as the Hospital Elder Life Program (HELP) have been shown to reduce delirium incidence in the acute care setting by 43%, by acting on modifiable risk factors such as dehydration, pain, sensory impairment, malnutrition, and immobility, compared to usual care.[7–9]

However, there is little evidence on treatments for delirium. According to current clinical guidelines, the non-pharmacological approach focused on correcting the underlying causes should always be the first option, reserving pharmacological treatment for cases of extreme agitation.[10,11] The scarce evidence is due to the fact that the pathophysiology of delirium remains unclear. Several mechanisms have been proposed to explain the development of delirium involving certain processes such as neuroinflammation, neuronal damage, neurotransmitter disturbance and acute cerebral failure caused by hypoxia-ischemia. In the hypoxia-ischemia theory, there is a vascular dysfunction that produces endothelial injury and blood-brain barrier (BBB) damage, causing low oxygen delivery to the brain parenchyma and contributing to a metabolic insufficiency that allows delirium development.[12]

Physical exercise has been shown to improve cerebral blood flow, increasing neurogenesis and neuroplasticity through the release of neurotransmitters and neurotrophic factors such as insulin-like growth factor-1 (IGF-1) and Brain Derived Neurotrophic Factor (BDNF),[13] providing synaptic transmission and improving cognitive

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function. Physical exercise also decreases the accumulation of amyloid plaques and tau protein which has been shown to improve cognitive functions such as attention, memory, executive tasks and information processing speed.[14–18] In fact, an individualized, multicomponent exercise training program may be an effective therapy for improving cognitive function in very old patients during acute hospitalization,[19,20] cognitive impairment[21] and depression.[22] Therefore, we hypothesized that strategies that help improve oxygen supply to the brain, such as physical exercise, could be useful in treating delirium.

Although there are several techniques to monitor brain activity and cerebral blood flow (e.g., brain magnetic resonance, positron emission tomography, electroencephalogram), Near-Infrared Spectroscopy (NIRS) could potentially be effective. NIRS is a non-invasive physiological monitoring method that measures light absorbance to calculate oxy-hemoglobin (oxy-HB) and deoxy-hemoglobin (deoxy-HB), which provide an indirect measure of tissue oxygenation, often in the frontal cortex of the brain and muscle. Some of the advantages that NIRS can offer are that is a non-invasive technology, which provides real-time continuous measurement of regional cerebral blood oxygenation and indirect blood flow indicating perfusion adequacy. Being a portable device, it can be moved to the place where the patient is, which facilitates its use. In addition, NIRS does not emit ionizing radiation and is less expensive than brain neuroimaging tests such as magnetic resonance imaging, providing added advantages such as the analysis of functional brain parameters while the patient performs different physical or cognitive tasks.[23–26]

Even though NIRS is used in different areas of Medicine, it has reached its greatest interest in Intensive Care and Anesthesiology for monitoring brain perfusion to avoid hypoxemia, which is associated with cognitive dysfunction and delirium.[27,28] Some studies have recently been published using NIRS as a predictive biomarker of postoperative delirium with promising results, where it has been observed that patients with low levels of cerebral oxygen saturation prior to surgery and during surgical intervention, had a higher incidence of postoperative delirium.[29–32] On the other hand, NIRS has been used to monitor hemodynamic response in the prefrontal cortex region and in lower-limb muscle tissue doing physical exercise and functional tasks in acutely hospitalized older patients.[33]

In spite of the growing number of studies published on the application of NIRS in delirium over the last few years, there are currently significant limitations so this evidence

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should be interpreted with caution.[34] These studies often include a low sample size, are usually carried out in the field of surgery or the Intensive Care Unit (ICU), are heterogeneous in their composition and have a high risk of bias. In addition, most of them do not consider the peculiarities of the older population, which is where delirium is most frequent. In most studies, essential information about older adults is not systematically collected, including geriatric syndromes (frailty, falls, malnutrition...), predisposing factors (comorbidity, functional and cognitive status) and precipitating factors of delirium (pain, polypharmacy, use of urinary catheters....).

The objective of this clinical trial is to evaluate the effect of a multicomponent exercise program on the development of delirium assessing cerebral and muscle perfusion using NIRS in hospitalized older adults. This study may help to understand the mechanisms underlying delirium, which are not yet totally clear in the literature, considering tissue oxygenation hypothesis.

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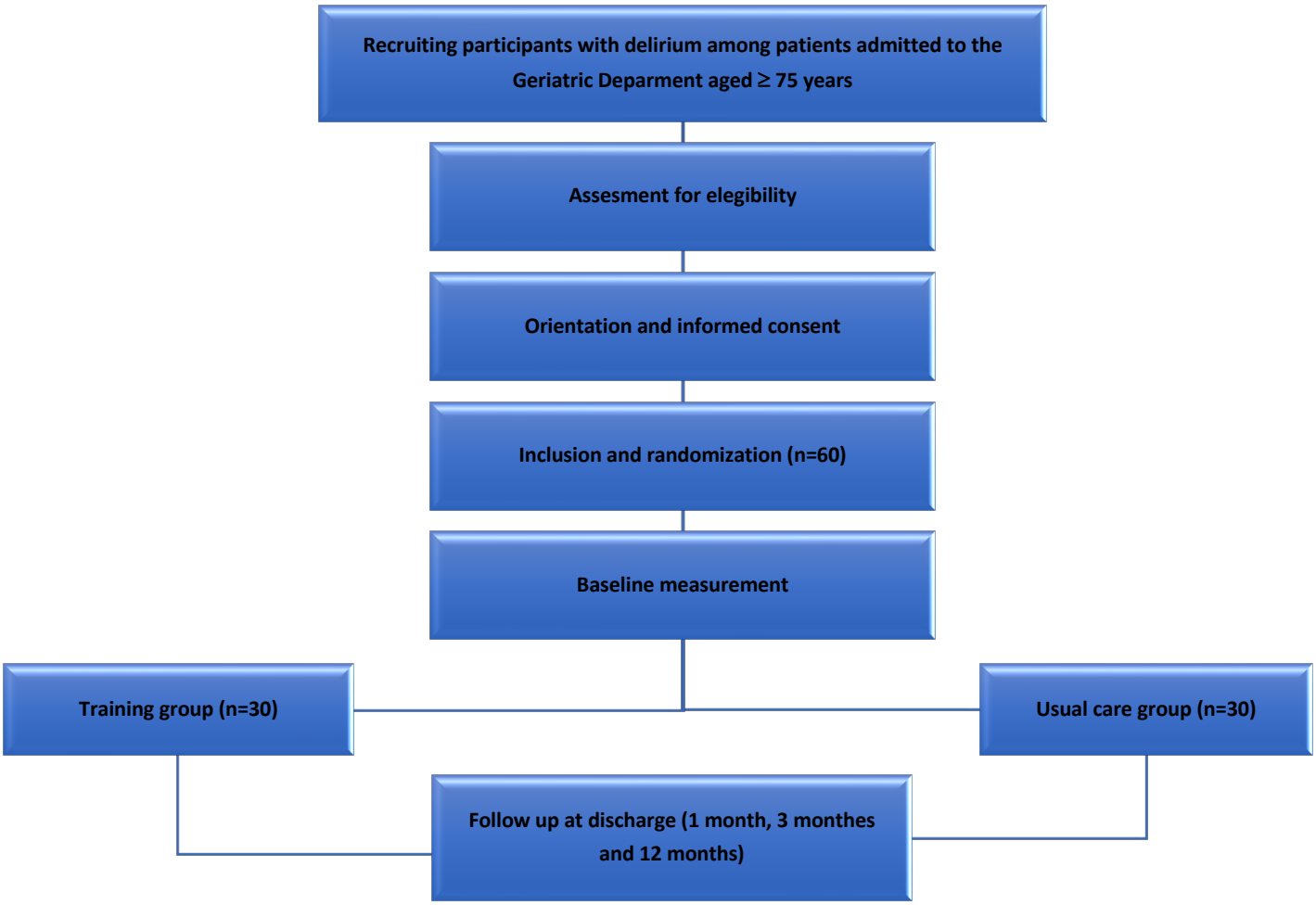
1. Materials and methods

1.1. Study design

This study is a randomized clinical trial conducted in the 40-bedded Acute Geriatric Unit (AGU) of Hospital Universitario de Navarra (Pamplona, Spain). Hospitalized patients who meet the inclusion criteria will be randomly assigned to the intervention or control group. The study flow diagram is shown in **Figure 1**.

Figure 1. Flow diagram of the study protocol



After obtention of written informed consent, patients will be randomly assigned to either the intervention or control group. The data for both the intervention group and the control group will be obtained at five different times: the initial visit during the acute hospitalization, at discharge and at one, three and twelve months after discharge through

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phone call and clinical history. The times of measurement of the different outcomes is shown in **Table 1**.

Table 1. Time of measurement of the different variables on the subjects of the study

Measurement	**T1 Baseline**	**T2 Daily**	**T3 After training or control period**	**T4 1 month**	**T5 3months**	**T6 12 months**
Barthel Index	X		X	X	X	X
Lawton and Brody Scale	X			X	X	X
HABAM	X	X	X			
Handgrip strength	X		X			
Short Physical Performance Battery (SPPB)	X		X			
1RM (leg press, chest press and knee extension)	X		X			
Muscle power 10 repetitions at 50% 1RM in leg press	X		X			
Trail making test-part A (TMT-A)	X		X			
Regional cerebral oxygen saturation (Scto2) in the forehead and vastus lateralis at rest, TMT-A, 1RM, and 10 reps x 50% 1RM	X		X			
Delirium assessment (4AT)	X	X	X			
Delirium severity (MDAS)	X	X	X			
Delirium motor subtype scale (DMSS)	X	X	X			
Global Deterioration Scale (GDS/FAST)	X			X	X	X
Informant Questionnaire on Cognitive Decline in the Elderly (*IQCODE*)	X			X	X	X
Geriatric depression Scale of Yasavage	X					
Geriatrics syndromes	X	X	X	X	X	X
FRAIL scale and Clinical Frailty Scale (CFS)	X			X	X	X
Mini Nutritional Assessment (MNA)	X					
Falls	X	X	X	X	X	X
Quality of life (EQ-5D)	X			X	X	X
Pharmacological Treatment and Drug Burden Index (DBI)	X		X	X	X	X
Laboratory parameters	X		X			

Peripheral blood (PB) samples will be obtained from all patients at baseline and at discharge. EDTA blood collection tubes (Vacuette®, Greiner Bio-One) will be used. All PB

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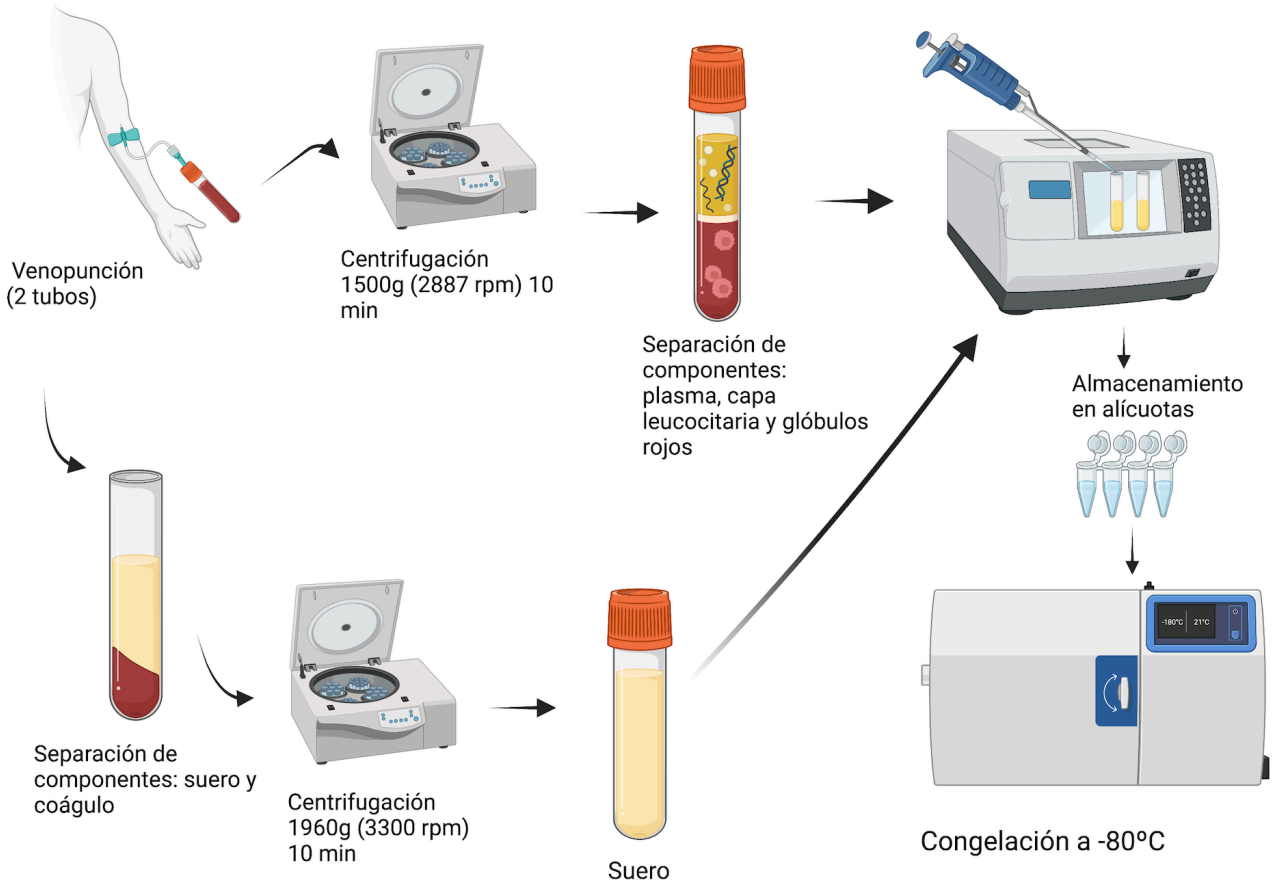
samples will be centrifuged in a fixed-angle rotor at room temperature. After centrifugation, the serum in the upper layer will be carefully extracted from the plasma in the bottom layer, divided into 100µL and immediately stored at -80ºC. Plasma and buffy coat will be also extracted and stored in polypropylene plastic tubes at -80ºC. Details are shown in **Figure 2.**

Figure 2. Sample collection and processing



We aim to examine the brain function during delirium and the effects of an intra-hospital exercise program on the prefrontal cortex region and on muscle function with the use of NIRS. Regional oxygen saturation (rSO2) in the forehead and vastus lateralis muscle will be recorded using NIRS using the by placing one optode on the patient's forehead above the eyebrow and the other optode on the vastus lateralis muscle.[35,36] The measurements will be made with the patients resting in the sitting position after 60 seconds, doing trail making test part A and physical exercise at the beginning of the study and the 4th day of the study, in both intervention and control group. There are some factors which may alter NIRS parameters because they influence cerebral perfusion such us drugs, blood pressure,

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hemoglobin or oxygen saturation. Although we will evaluate all of them, this is an important limitation of the study.

Delirium will be assessed using the European Spanish version of the 4AT[37] daily during hospitalization until discharge. This tool has been validated for the Spanish population and is a reliable instrument for delirium detection in older patients. The 4AT scale is designed to be used as a delirium detection tool in general clinical settings. The 4AT has 4 parameters: Alertness, Abbreviated mental test-4 (AMT4), Attention (months backwards test) and Acute change or fluctuating course. The score range is 0–12, with scores of 4 or more suggesting possible delirium. Scores of 1-3 suggest possible cognitive impairment.[38,39] Delirium severity will be evaluated daily with the Memorial Delirium Assessment Scale (MDAS) which is also validated in Spain.[40,41] MDAS was designed to diagnose delirium as well as classify delirium severity. The instrument reflects delirium diagnostic criteria from DSM. It has 10 severity items rated 0 to 3 points for a maximum total score of 30 points, with higher scores representing more severe delirium.[42]

The protocol employs relevant standard protocol items for clinical trials according to the SPIRIT 2013 statement[43] and follows the CONSORT statement.[44] The trial is registered at ClinicalTrials.gov, identifier NCT05442892. This study was approved by the Navarra Clinical Research Ethics Committee (PI_2021/94).

1.2. Study participants and eligibility criteria

Medical inpatients admitted to the AGU of Hospital Universitario de Navarra (Pamplona, Spain) between February 2022 and February 2023.

The inclusion criteria are:

- Age: 75 years or older with delirium during hospitalization
- Able to ambulate with or without personal/technical assistance
- Barthel Index $\geq$ 45 points two weeks before admission
- Informed consent by patients (if possible), relatives or legal representatives

The exclusion criteria are:

- Duration of hospitalization < 5 days
- Severe dementia (GDS 6-7)
- Terminal illness (life expectancy less than 3 months)
- Any factor precluding performance of physical exercise. These factors include:

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- Acute myocardial infarction in the past three months or unstable angina
- Severe heart valve insufficiency
- Arrhythmia or uncontrolled arterial hypertension
- Pulmonary embolism in the past 3 months
- Hemodynamic instability

- Pathology that could interfere with NIRS registration:
  - Facial dermal pathology (front)
  - Acute intracranial pathology (hemorrhages, cerebral infarcts)

1.3. Randomization and blinding

The study participants will be randomized (www.randomizer.org) into intervention or control group. Assessment staff will be blinded to the participant randomization assignment, as well as to the main study design and to what changes we expect to occur in the study outcomes in each group. It will not be possible to conceal the group assignment from the staff involved in the training of the intervention group. Patients and their families will be informed of the random inclusion in one group but will not be informed as to which group they belong.

1.4. Sample size

Assuming a standard deviation in MDAS scale of 6 points, for a power of 80% and a significance level of 0.05, 24 patients per group (a total of 48) will be necessary to detect a mean difference of 5 points between groups. Assuming 20% losses, 30 patient per group will be necessary.

1.5. Statistics

The baseline value of the included variables will be described for the whole sample and separated by group using frequencies and percentages for the categorical ones and via mean and standard deviation or median and interquartile range for continuous ones. In order to assess the extent of the therapeutic effect, we will compute for every patient the difference between final and initial level of the continuous outcome variables. Then, these differences will be compared by intervention group, using t-tests or Mann Whitney U tests. For the mortality outcome, the percentage mortality of both groups will be compared using

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the chi-square test. In case of observing relevant differences at baseline, these comparisons will be adjusted by the baseline value, using linear models or generalized linear models. The level of statistical significance will be 0.05. Data will be analyzed with SPSS package 28.0.

1.6. Detailed description

Usual care group (control)

Participants randomly assigned to the usual care group will receive normal hospital care, which includes physical rehabilitation when needed.

Intervention group (training)

The intervention will consist of a multicomponent exercise training program adapted from Vivifrail to prevent muscle weakness and falls[45,46] and the training protocol was detailed in previous literature.[3,47–49] It will be composed of supervised progressive resistance exercise training, balance-training, and walking for 3 consecutive days. During the training period, patients will be trained in 30 min sessions once a day (morning). The supervised multicomponent exercise training program will be comprised of upper and lower body strengthening exercises, tailored to the individual's functional capacity, using weight machines and aiming for 2–3 sets of 8–10 repetitions at an intensity of 50–70 % of 1RM (Matrix, Johnson Health Tech, Ibérica, S.L. Torrejón de Ardoz, Madrid, Spain). A "1RM" signifies the maximum resistance a person can move in one repetition of an exercise. The resistance exercises focused on the major upper and lower limb muscles. On the second and third training days, patients do 2 sets of 10 chair squats. Each resistance training session will include 2 exercises for the leg extensor muscles (bilateral leg press and bilateral knee extension machines) and 1 exercise for upper limbs (seated bench press machine). During the progressive resistance training, instruction will be provided to the participants to perform the exercises at a high velocity of motion. However, care will be taken to ensure that exercises are executed with correct form. In the first assessment, the patients will warm up with specific movements for the exercise test. Each subject´s maximal load will be determined in no more than five attempts. During all neuromuscular performance tests, a strong verbal encouragement will be given to each subject to motivate them to perform each test action as optimally and rapidly as possible. Three experienced physical trainers

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(FZF, IOM, ADM) will carefully monitor and supervise all training sessions and provide instruction and encouragement. Adherence to the exercise intervention programme will be documented in a daily register of sessions and adverse events including muscle pain, fatigue, falls and general aches will be recorded by the training staff. Participants and their family members will be carefully familiarized with the training procedures in advance. The intervention exercises are detailed in **Table 2** and the training protocol is shown in **Figures 3 and 4**.

Table 2. Intervention group exercises

Exercise	Day 1	Day 2	Day 3	Day 4
Rises from a chair	1x5	2x10	2x10	1x5
Leg press	1RM + 2x10 (50% 1RM)	3x10 (60% 1RM)	3x8 (70% 1RM)	1RM + 1x10 (50%1RM)
Chest press	1RM + 2x10 (50% 1RM)	3x10 (60% 1RM)	3x8 (70% 1RM)	1RM
Leg extension	1RM + 2x10 (50% 1RM)	3x10 (60% 1RM)	3x8 (70% 1RM)	1RM

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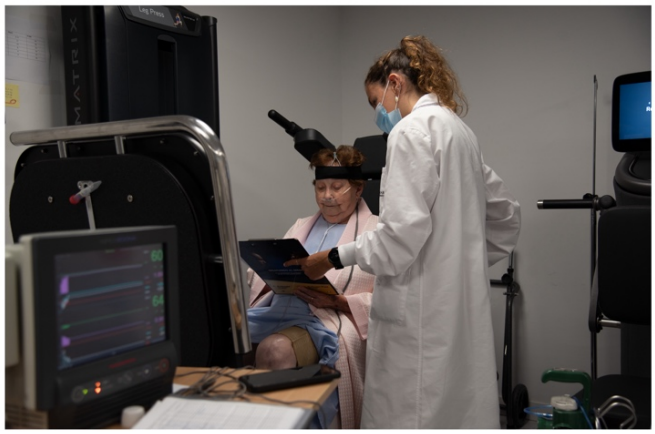
Figure 3. Details of intervention

Optode on patient´s forehead to assess rSO2

NIRO-200NX C10448 monitor (Hamamatsu, Japan)

Trail making test part A

Trail making test part A



An experienced fitness specialist leads each session, providing instructions and encouragement to the patient

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1.7. Outcome measures

Primary outcome

- Duration and severity of delirium during the hospitalization between both intervention and control group and the change in functional status: 4AT and MDAS scale.
- Functional capacity of patients will be evaluated by the Short Physical Performance Battery (SPPB), which evaluates, balance, gait ability, and leg strength using a single tool. The total score will range from 0 (worst) to 12 points (best). The SPPB test has been shown to be a valid instrument for screening frailty and predicting disability, institutionalization, and mortality [50]. Daily functional status will be also assess with the Hierarchical Assessment of Balance and Mobility (HABAM) with is an instrument that provides a clinical assessment of in-bed mobility, transfers and ambulation [51,52]. The lowest number, a value of 0, is equal to the lowest or no performance. Changes in these abilities can then be compared with patient progress.
- Regional oxygen saturation (rSO2) will be measured using NIRS [53,54].

Secondary outcome

- Cognitive status: Global Deterioration Scale (GDS) which describes 7 clinically distinguishable global stages, from normality to severe dementia of the Alzheimer type [55,56] and the Informant Questionnaire on Cognitive Decline in the Elderly short form (IQCODE) which is a 16-question form, each question is scored from 1 (much improved) to 5 (much worse) and a cut-off point (average score) of 3.31/3.38 achieves a balance of sensitivity and specificity of cognitive impairment [57,58].
- Functional status: Barthel Index of independence during activities of daily living (ADLs). This index ranges from 0 worst to 100 best [59].
- Mortality.
- Quality of life: EuroQol Scale-5D. This instrument measures 5 dimensions of health status: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [60,61].
- Use of health sources: new admissions to the hospital, admission to nursing homes, visits to the general practitioner and to the emergency department.
- Falls.

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Figure 4. Training protocol

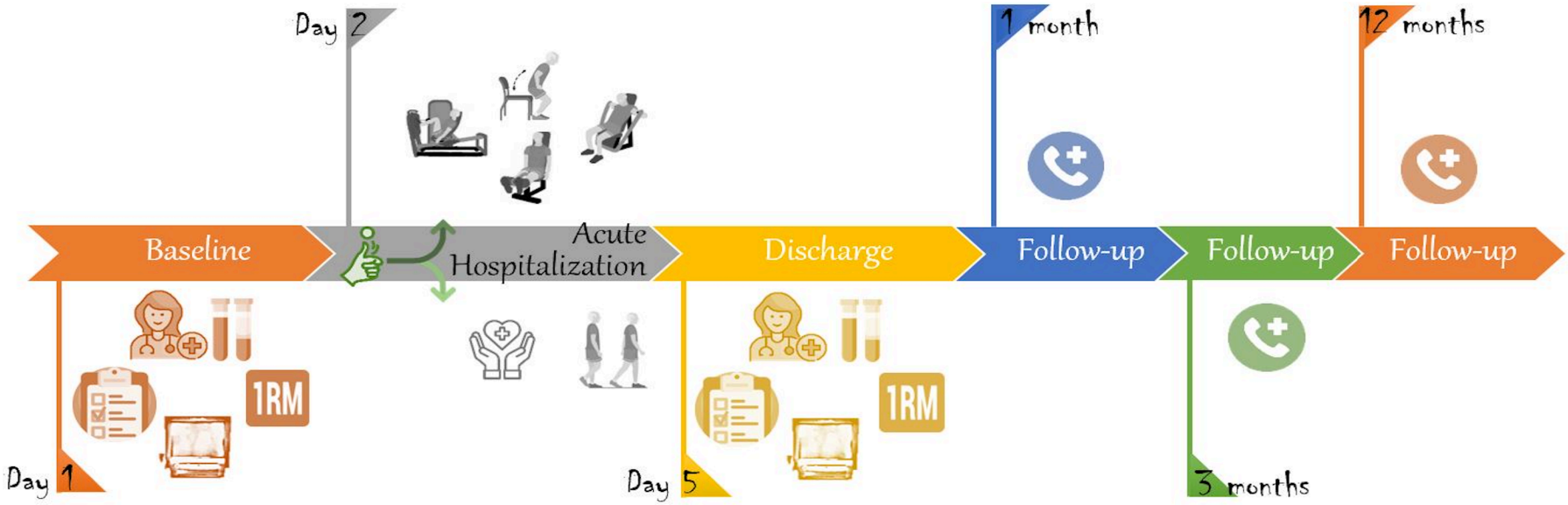

Figure 1. Intervention timeline

- Baseline assessment
- Clinical assessment
- 1RM: 1 Repetition Maximum
- Near-Infrared Spectroscopy (NIRS)
- Blood sample
- Randomized Controlled Trial
- Follow-up phone call
- Usual Care
- Walking
- Rise-up from the chair
- Leg Press
- Chest Press
- Knee Extension

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2. Discussion

Given that the pathophysiology of delirium remains unclear and its pharmacological treatment once established has not been shown to be effective in addition to having serious side effects (extrapyramidal symptoms, sedation, arrhythmias…) physical exercise, due to its anti-inflammatory component and improvement of cerebral perfusion, can open as a new therapeutic option to explore. Other important aspect of our trial is the inclusion of older patients with mild cognitive decline and dementia. So far, most of trials in aged frail participants with these conditions are routinely excluded. The inclusion of participants with cognitive impairment in addition to frailty makes the trial novel with notable external validity compared with other previous trials in assessing the effect of individualized exercise programmes on functional capacity, activities of daily living and cognitive function. This study will both advanced delirium-related knowledge and improve health outcomes through a program based on physical exercise. Moreover, this project will try to find new biomarkers of delirium that could be extrapolated to the usual clinical practice and help in its monitoring. Due to the high prevalence of delirium in this population and its serious consequences on morbidity and mortality, this intervention opens the possibility of a new therapeutic approach that can mitigate its impact. If our hypothesis is correct and shows that a multicomponent, individualized and progressive exercise programme in hospitalized older adults with delirium improve cognitive and functional status, a possible new targeted and therapeutic tool during hospitalization could be developed to implement delirium management.

Ethics statement

This study follows the principles of the Declaration of Helsinki (World Medical Association) and was approved by the Navarra Clinical Research Ethics Committee on September 15, 2021 (PI_2021/94). All volunteers or their legal representatives will be asked to sign a written informed consent form, also approved in advance by the Ethics Committee. There will be no financial compensation.

Conflict of interest

The authors declare that they have no competing interests.

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Author contributions

L-LV, Fa-ZF, A-CM and I-OM developed the protocol in consultation with Fr-ZF, M-LA, M-IR and N-MV. LLV, Fa-ZF, A-CM and I-OM are involved in the recruitment and evaluation of the patients.

All authors listed had an intellectual contribution to the work and approved it for publication.

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Nafarroako Unibertsitate Publikoa

References

1. Inouye, S. K. Delirium in elderly people. *Lancet* **383**, 911–922 (2014) doi:10.1016/S0140-6736(13)60688-1.
2. Jackson, T. A. Challenges and opportunities in understanding dementia and delirium in the acute hospital. *PLoS Med.* **14**, 1–9 (2017) doi:10.1371/journal.pmed.1002247.
3. Martínez-Velilla, N. An exercise program with patient's involvement and family support can modify the cognitive and affective trajectory of acutely hospitalized older medical patients: a pilot study. *Aging Clin. Exp. Res.* **28**, 483–490 (2016) doi:10.1007/s40520-015-0434-0.
4. Brummel, N. E. Delirium in the ICU and subsequent long-term disability among survivors of mechanical ventilation. *Crit. Care Med.* **42**, 369–377 (2014) doi:10.1097/CCM.0b013e3182a645bd.
5. Covinsky, K. E. Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: Increased vulnerability with age. *J. Am. Geriatr. Soc.* **51**, 451–458 (2003) doi:10.1046/j.1532-5415.2003.51152.x.
6. Zisberg, A. Hospital-Associated Functional Decline: The Role of Hospitalization Processes Beyond Individual Risk Factors. *J. Am. Geriatr. Soc.* **63**, 55–62 (2015) doi:10.1111/jgs.13193.
7. Hshieh, T. T. Hospital Elder Life Program: Systematic Review and Meta-analysis of Effectiveness. *Am. J. Geriatr. Psychiatry* **26**, 1015–1033 (2018) doi:10.1016/j.jagp.2018.06.007.
8. Burton, J. K. Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst. Rev.* **2021**, (2021) doi:10.1002/14651858.CD013307.pub2.
9. Wang, Y. Y. Effect of the Tailored, Family-Involved Hospital Elder Life Program on Postoperative Delirium and Function in Older Adults: A Randomized Clinical Trial. *JAMA Intern. Med.* **180**, 17–25 (2020) doi:10.1001/jamainternmed.2019.4446.
10. Davis, D. The Scottish Intercollegiate Guidelines Network: Risk reduction and management of delirium. *Age Ageing* **48**, 486–488 (2019) doi:10.1093/ageing/afz036.
11. National Institute for Health and Care Excellence (NICE). Delirium : prevention ,

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

diagnosis and management. (2022).

12. Wilson, J. E. Delirium. *Nat. Rev. Dis. Prim.* **6**, (2020) doi:10.1038/s41572-020-00223-4.
13. Ben-Zeev, T. The effect of exercise on neurogenesis in the brain. *IMAJ* **24**, (2022).
14. Del Pozo Cruz, B. Association of Daily Step Count and Intensity with Incident Dementia in 78430 Adults Living in the UK. *JAMA Neurol.* 6–11 (2022) doi:10.1001/jamaneurol.2022.2672.
15. Rai, M. Muscle-to-Brain Signaling Via Myokines and Myometabolites. *Brain Plast.* **8**, 1–21 (2022) doi:10.3233/bpl-210133.
16. Bliss, E. S. Benefits of exercise training on cerebrovascular and cognitive function in ageing. *J. Cereb. Blood Flow Metab.* **41**, 447–470 (2021) doi:10.1177/0271678X20957807.
17. Erickson, K. I. Physical Activity, Cognition, and Brain Outcomes: A Review of the 2018 Physical Activity Guidelines. *Med. Sci. Sports Exerc.* **51**, 1242–1251 (2019) doi:10.1249/MSS.0000000000001936.
18. Da Silva, J. L. Effects of Chronic Physical Exercise or Multicomponent Exercise Programs on the Mental Health and Cognition of Older Adults Living in a Nursing Home: A Systematic Review of Studies From the Past 10 Years. *Front. Psychol.* **13**, 1–9 (2022) doi:10.3389/fpsyg.2022.888851.
19. Sáez de Asteasu, M. L. Assessing the impact of physical exercise on cognitive function in older medical patients during acute hospitalization: Secondary analysis of a randomized trial. *PLoS Med.* **16**, 1–14 (2019) doi:10.1371/journal.pmed.1002852.
20. Sáez de Asteasu, M. L. Effects of Physical Exercise on the Incidence of Delirium and Cognitive Function in Acutely Hospitalized Older Adults: A Systematic Review with Meta-Analysis. *J. Alzheimer's Dis.* **87**, 503–517 (2022) doi:10.3233/JAD-220103.
21. Venegas-Sanabria, L. C. Effect of multicomponent exercise in cognitive impairment: a systematic review and meta-analysis. *BMC Geriatr.* **22**, (2022) doi:10.1186/s12877-022-03302-1.
22. Li, L. Effects of exercise on depressive symptoms among nursing home residents: a meta-analysis. *Aging Ment. Heal.* **26**, 1514–1523 (2022) doi:10.1080/13607863.2021.1951658.

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

23. Sakudo, A. Near-infrared spectroscopy for medical applications: Current status and future perspectives. *Clin. Chim. Acta* **455**, 181–188 (2016) doi:10.1016/j.cca.2016.02.009.

24. Hogue, C. W. Clinical Applications of Near-infrared Spectroscopy Monitoring in Cardiovascular Surgery. *Anesthesiology* **134**, 784–791 (2021) doi:10.1097/ALN.0000000000003700.

25. Milej, D. Quantification of cerebral blood flow in adults by contrast-enhanced near-infrared spectroscopy: Validation against MRI. *J. Cereb. Blood Flow Metab.* **40**, 1672–1684 (2020) doi:10.1177/0271678X19872564.

26. Nguyen, T. N. Hyperspectral near-infrared spectroscopy assessment of the brain during hypoperfusion. *J. Biomed. Opt.* **24**, 1 (2019) doi:10.1117/1.jbo.24.3.035007.

27. Hori, D. Arterial pressure above the upper cerebral autoregulation limit during cardiopulmonary bypass is associated with postoperative delirium. *Br. J. Anaesth.* **113**, 1009–1017 (2014) doi:10.1093/bja/aeu319.

28. Schoen, J. Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: A prospective observational trial. *Crit. Care* **15**, (2011) doi:10.1186/cc10454.

29. Susano, M. J. Association Among Preoperative Cognitive Performance, Regional Cerebral Oxygen Saturation, and Postoperative Delirium in Older Portuguese Patients. *Anesth. Analg.* **132**, 846–855 (2021) doi:10.1213/ANE.0000000000005159.

30. Semrau, J. S. Cerebral oximetry and preventing neurological complication post-cardiac surgery: A systematic review. *Eur. J. Cardio-thoracic Surg.* **C**, 1–11 (2021) doi:10.1093/ejcts/ezaa485.

31. Khan, J. M. Delirium, Cerebral Perfusion, and High-Frequency Vital-Sign Monitoring in the Critically Ill the CONFOCAL-2 Feasibility Study. *Ann. Am. Thorac. Soc.* **18**, 112–121 (2021) doi:10.1513/AnnalsATS.202002-093OC.

32. Wood, M. D. Low brain tissue oxygenation contributes to the development of delirium in critically ill patients: A prospective observational study. *J. Crit. Care* **41**, 289–295 (2017) doi:10.1016/j.jcrc.2017.06.009.

33. Sáez de Asteasu, M. L. Exercise Effects on Brain and Muscle Function in Acutely Hospitalized Older Patients Assessed by Functional Near-Infrared Spectroscopy. *J.*

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Nafarroako Unibertsitate Publikoa

Am. Med. Dir. Assoc. **22**, 875–876 (2021) doi:10.1016/j.jamda.2020.12.027.

34. Chen, W. L. Functional Near-Infrared Spectroscopy and Its Clinical Application in the Field of Neuroscience: Advances and Future Directions. *Front. Neurosci.* **14**, 1–15 (2020) doi:10.3389/fnins.2020.00724.
35. Udina, C. Functional Near-Infrared Spectroscopy to Study Cerebral Hemodynamics in Older Adults During Cognitive and Motor Tasks: A Review. *Front. Aging Neurosci.* **11**, 1–19 (2020) doi:10.3389/fnagi.2019.00367.
36. Koyama, Y. A new method to detect cerebral blood flow waveform in synchrony with chest compression by near-infrared spectroscopy during CPR. *Am. J. Emerg. Med.* **31**, 1504–1508 (2013) doi:10.1016/j.ajem.2013.07.002.
37. Delgado-Parada, E. Diagnostic accuracy of the Spanish version of the 4AT scale (4AT-ES) for delirium screening in older inpatients. *Eur. J. Psychiatry* **36**, 182–190 (2022) doi:10.1016/j.ejpsy.2022.01.003.
38. Tieges, Z. Diagnostic accuracy of the 4AT for delirium detection in older adults: systematic review and meta-analysis. *Age Ageing* **50**, 733–743 (2021) doi:10.1093/ageing/afaa224.
39. Jeong, E. Diagnostic test accuracy of the 4AT for delirium detection: A systematic review and meta-analysis. *Int. J. Environ. Res. Public Health* **17**, 1–15 (2020) doi:10.3390/ijerph17207515.
40. Barahona, E. The Diagnostic Sensitivity of the Memorial Delirium Assessment Scale—Spanish Version. *J. Pain Symptom Manage.* **55**, 968–972 (2018) doi:10.1016/j.jpainsymman.2017.11.013.
41. Noguera, A. First spanish version of the memorial delirium assessment scale: Psychometric properties, responsiveness, and factor loadings. *J. Pain Symptom Manage.* **47**, 189–197 (2014) doi:10.1016/j.jpainsymman.2013.02.020.
42. Jones, R. N. Assessment of Instruments for Measurement of Delirium Severity: A Systematic Review. *JAMA Intern. Med.* **179**, 231–239 (2019) doi:10.1001/jamainternmed.2018.6975.
43. Chan, A. W. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* **346**, 1–42 (2013) doi:10.1136/bmj.e7586.
44. Moher, D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group reandomized trials. *BMC Med. Res. Methodol.*

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Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

91, 437–442 (2001).

45. Casas-Herrero, Á. Effects of Vivifrail multicomponent intervention on functional capacity: a multicentre, randomized controlled trial. *J. Cachexia. Sarcopenia Muscle* **13**, 884–893 (2022) doi:10.1002/jcsm.12925.

46. Izquierdo M, Casas-Herrero A, Zambom-Ferraresi F, et al. *Multicomponent physical exercise program VIVIFRAIL*. (2017).

47. Martínez-Velilla, Nicolás, PhD, MD; Casas-Herrero, Álvaro, PhD, MD; Zambom-Ferraresi, Fabricio, PhD; L. Sáez de Asteasu, Mikel , MSc; Lucia, Alejandro PhD, MD; Galbete, Arkaitz PhD; García-Baztán, Agurne MD; Alonso-Renedo, Javier MD; González-Glaría, Bele, M. P. Effect of Exercise Intervention on Functional Decline in Very Elderly Patients During Acute Hospitalization: A Randomized Clinical Trial. *JAMA Intern. Med.* **179**, 28–36 (2019) doi:10.1001/jamainternmed.2018.4869.

48. Martínez-Velilla, N. Functional and cognitive impairment prevention through early physical activity for geriatric hospitalized patients: Study protocol for a randomized controlled trial. *BMC Geriatr.* **15**, 1–9 (2015) doi:10.1186/s12877-015-0109-x.

49. Martínez-Velilla, N. Effect of an Exercise Intervention on Functional Decline in Very Old Patients during Acute Hospitalizations: Results of a Multicenter, Randomized Clinical Trial. *JAMA Intern. Med.* **182**, 345–347 (2022) doi:10.1001/jamainternmed.2021.7654.

50. Guralnik, J. M. A Short Physical Performance Battery Assessing Lower Extremity Function: Association With Self-Reported Disability and Prediction of Mortality and Nursing Home Admission Energetic cost of walking in older adults View project IOM committee on cognitive agi. *Artic. J. Gerontol.* **49**, 85–94 (1994).

51. Gual, N. Impairments in balance and mobility identify delirium in patients with comorbid dementia. *Int. Psychogeriatrics* **31**, 749–753 (2019) doi:10.1017/S1041610218001345.

52. Richardson, S. Delirium and delirium severity predict the trajectory of the Hierarchical Assessment of Balance and Mobility (HABAM) in hospitalised older people: findings from the DECIDE Study. *Journals Gerontol. Ser. A* **XX**, 1–5 (2021) doi:10.1093/gerona/glab081.

53. Luo, X. Prefrontal cortex dysfunction during verbal fluency task after atypicalantipsychotic treatment in schizophrenia: A near-infrared spectroscopy

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imaging study. *Neurosci. Lett.* **686**, 101–105 (2018) doi:10.1016/j.neulet.2018.09.001.

54. Pfeifer, M. D. Signal processing in functional near-infrared spectroscopy (fNIRS): Methodological differences lead to different statistical results. *Front. Hum. Neurosci.* **11**, (2018) doi:10.3389/fnhum.2017.00641.

55. Reisberg, B. The Global Deterioration Scale for Assessment of Primary Degenerative Dementia. *Am. J. Psychiatry* **139**, 1136–1139 (1982).

56. Auer, S. The GDS/FAST staging system. *Int. Psychogeriatrics* **9**, 167–171 (1997) doi:10.1017/S1041610297004869.

57. Harrison, J. K. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the early detection of dementia across a variety of healthcare settings. *Cochrane Database Syst. Rev.* **2021**, (2021) doi:10.1002/14651858.CD011333.pub3.

58. Blandfort, S. The short IQCODE as a predictor for delirium in hospitalized geriatric patients. *Aging Clin. Exp. Res.* **32**, 1969–1976 (2020) doi:10.1007/s40520-019-01412-2.

59. Barthel, M. Functional evaluation: the Barthel Index. *Md. State Med. J.* **14**, 56–61 (1965).

60. García-Gordillo, M. Á. Validación y comparación de los instrumentos EQ-5D-3L y SF-6D en una muestra de población española con enfermedad de Parkinson. *Nutr. Hosp.* **32**, 2808–2821 (2015) doi:10.3305/nh.2015.32.6.9765.

61. Herdman, M. EuroQol-5D: a simple alternative for measuring health-related quality of life in primary care. *Aten. Primaria* **28**, 425–430 (2001) doi:10.1016/s0212-6567(01)70406-4.

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Chapter 5
Effects of exercise intervention for the management of delirium in acutely hospitalized older adults: a randomized clinical trial

Capítulo 5
Efecto de una intervención basada en ejercicio físico para el manejo del delirium en adultos mayores hospitalizados: un ensayo clínico aleatorizado

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1. Background

Delirium is a severe neuropsychiatric syndrome characterized by disturbances in attention, perception, awareness and cognition, attributable to an organic condition, which usually develops acutely and has a fluctuating course.[1] Its prevalence is high, especially among older adults, reaching 59–88% in palliative care units,[2] 50-70% in intensive care units,[3] and 23% in medical hospitalization services.[4] Hospitalized patients who experience delirium have higher risk of functional decline, cognitive impairment, prolonged hospitalization, institutionalization and mortality.[5–9]

Despite the growing number of studies on delirium management, pharmacological therapy has shown to have limited effectiveness for either preventing or treating delirium.[10,11] Pharmacological treatment is only indicated in cases of hyperactive delirium to address symptoms like severe agitation. However, in the case of hypoactive delirium, which is the most prevalent subtype among older people, medication is not indicated.[12,13]

Therefore, given the multifactorial etiology of delirium, current clinical guidelines advocate a non-pharmacological, multicomponent approach.[14] In this regard, non-pharmacological multicomponent programs based on identifying and addressing modifiable predisposing and precipitating risk factors of delirium, such as the Hospital Elder Life Program (HELP),[15,16] can reduce the incidence of delirium by 43% compared to usual care.[17] However, the management of established delirium remains controversial. According to the literature, identifying and treating the underlying organic cause of delirium should be the primary intervention to implement once delirium develops.[18,19] However, there is limited evidence on the impact of other non-pharmacological measures for treating this syndrome.

Several studies highlight the importance of early mobilization to prevent delirium[20–24]. However, the implementation of individualized physical exercise programs in established delirium has been constrained by the limitations within this population, such as functional and cognitive impairment, aberrant motor disturbances, lack of attention, and cooperation. This poses a significant clinical challenge.

Physical exercise has shown benefits not only in enhancing the functional status of hospitalized older patients but also in improving cognition, mental health, and preventing delirium.[25–31] These improvements could be due to its properties in increasing tissue

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oxygenation and the synthesis of growth factors that support the proper functioning of the body, particularly the brain.[32,33]

Our hypothesis was that strategies capable of enhancing cerebral perfusion, such as physical exercise, could potentially improve the evolution of delirium once it has developed.[34] The aim of this randomized clinical trial (RCT) was to evaluate the effect of a multicomponent physical exercise program on cognitive and functional status among hospitalized older adults with delirium in an Acute Geriatric Unit (AGU).

2. Material and methods

Study design

This single-center, single-blind RCT followed SPIRIT 2013 and CONSORT reporting guidelines.[35,36] It was conducted from February 1, 2022, to May 31, 2023, in the AGU of Hospital Universitario de Navarra (Pamplona, Spain). The 40-bed AGU is staffed by 16 geriatricians covering inpatient, orthogeriatrics and outpatient care. Most AGU admissions originate from the Emergency Department for heart failure and infectious diseases.

This study followed the principles of the Declaration of Helsinki (World Medical Association)[37] and obtained ethical approval from the Navarra Clinical Research Ethics Committee (PI_2021/94). All participants or their authorized representatives provided written informed consent. This trial was registered on ClinicalTrials.gov (NCT05442892).

Participants and randomization

All patients admitted to the AGU were evaluated by geriatricians. Inclusion criteria were age ≥ 75 years with delirium and able to ambulate (Barthel Index >45 points prior to admission). Patients were excluded if: 1) expected length of stay < 5 days, 2) severe dementia, 3) terminal illness (life expectancy less than 3 months) and 4) contraindications to exercise including acute myocardial infarction in the past three months or unstable angina, severe heart valve insufficiency, arrhythmia or uncontrolled arterial hypertension, pulmonary embolism in the past 3 months or hemodynamic instability.

Patients who met the inclusion criteria within 48 hours of admission were randomly assigned in a 1:1 ratio to either the intervention group or the usual care control group.

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Assessment staff were blinded to group assignment and protocol details. Patients and families were aware of randomization but not group allocation.

Intervention

Controls received usual hospital care, which included physical therapy when needed. Patients assigned to the intervention group were trained daily in a 30-min morning session for 3 consecutive days (including weekends). A session was considered completed when 90% or more of the programmed exercises were successfully performed.

Each session was conducted in a room equipped with variable resistance strength machines (Matrix; Johnson Health Tech and Exercycle S.L., BH Group). The multicomponent program adapted from Vivifrail® (www.vivifrail.com/resources) comprised progressive resistance training, balance exercises, and walking tailored to each patient´s baseline functional capacity.

Adjustable resistance training machines targeted major muscle groups through 2-3 sets of 8-10 repetitions at 30%- 70% of the 1-repetition maximum (1 RM). Exercises focused on lower limbs (squats, leg press, knee extension) and upper body (chest press). Staff documented adherence and any adverse events. The intervention timeline is showed in **Figure 1** and all the details of the study design are explained in the previously published protocol, as well as in **Figure 2**.[38]

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Figure 1. Study design

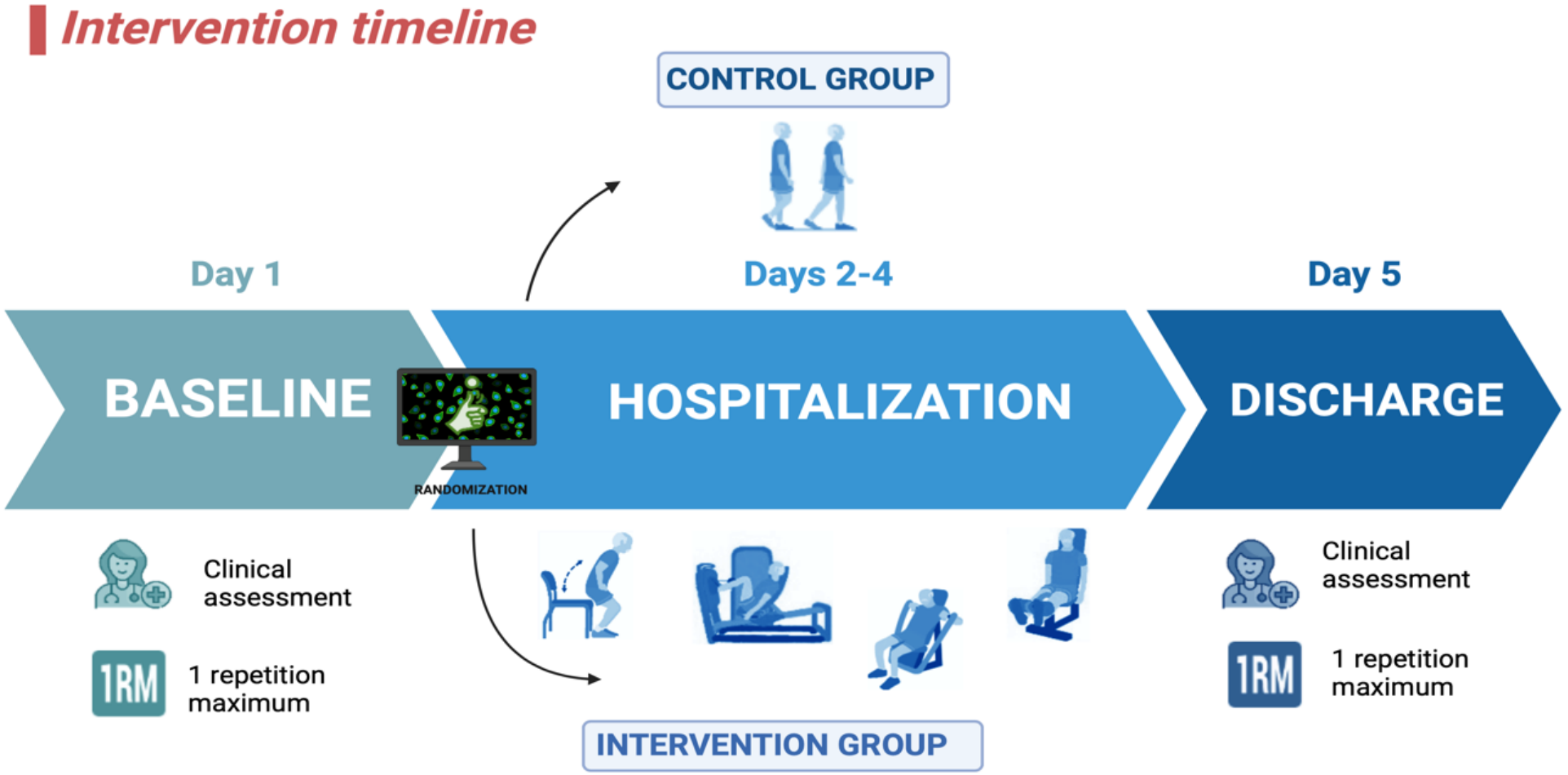
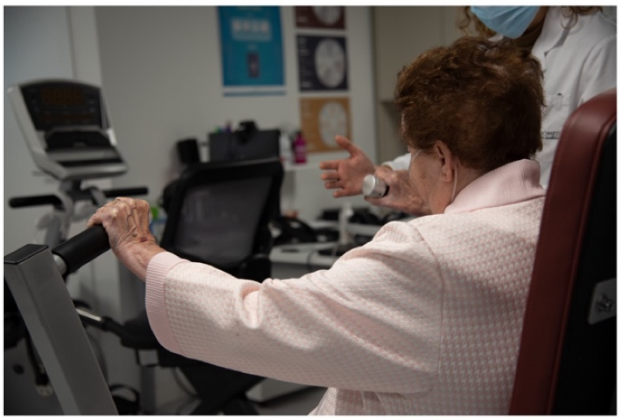


Figure 2. Details of the study methodology

An experienced fitness specialist led each session, providing instructions and encouragement to the patient

The patient was monitored during the exercise session to ensure his security



Patient with delirium doing upper body exercises (chest press) and leg press/extension knee with a machine

1 RM was calculated for each patient in order to provide an individualized exercise program

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Endpoints

The primary endpoints were the duration and severity of delirium during hospitalization and change in functional status from baseline to hospital discharge.

Delirium was assessed daily until discharge by two geriatricians using the Spanish version of the 4AT scale.[39] Delirium symptom severity was evaluated with the validated Memorial Delirium Assessment Scale (MDAS)[40] and delirium subtype was assessed using the Delirium Motor Subtype Scale-4.[41] Preexisting cognitive impairment was based on medical history, Global Deterioration Scale FAST (GDS-fast)[42] and Informant Questionnaire on Cognitive Decline short form (IQCODE-sf).[43]

Functional measures on admission and at discharge included Short Physical Performance Battery (SPPB),[44] grip strength (measured with JAMAR 5030J1 Hand Dynamometer), Barthel Index, and Hierarchical Assessment of Balance and Mobility (HABAM)[45,46]. Individual´s strength was also evaluated using the 1 Repetition Maximum (1 RM) for leg press, chest press and knee extension. This is the maximum amount of weight (Kilograms, Kg) that a person can lift, push, or pull in a single repetition for a given exercise.

Medical records were reviewed and a Comprehensive Geriatric Assessment (CGA) was performed at the time of enrolment that included functional status (Barthel Index and Lawton and Brody scale),[47,48] frailty (FRAIL scale and Clinical Frailty Scale),[49] nutrition (Mini-Nutritional Assessment-Short Form, MNA-SF),[50] quality of life (EuroQol Scale-5D),[51] falls in the previous 12 months, sensory impairment, depression (Yesavage Geriatric Depression Scale),[52] polypharmacy, drug burden index (DBI) and demographic factors such as provenance and education level.

Secondary endpoints were changes in length of stay and in-hospital falls. A 1 and 3-month post-discharge follow-ups were performed to ascertain instances of readmission, visits to emergency department or primary care, functional status, cognitive status, falls, quality of life, and mortality.

Statistics

Given a standard deviation of 6 points on the MDAS scale, and with power of 80% and a significance level of 0.05, a total of 48 patients, or 24 patients per group, were needed to

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identify a mean difference of 5 points between the groups. Considering potential losses of 20%, this implies that 30 patients per group were required.

The participants in the study were randomly assigned, using www.randomizer.org, to either the intervention group or the control group. The evaluation team did not have access to the participant randomization assignment, as well as the main study design and the anticipated alterations in the study outcomes for each group. However, it could not be feasible to hide the group assignment from the staff responsible for the intervention group's training.

Baseline demographic and clinical characteristics were presented for the entire sample and categorized by group. Frequencies and percentages were utilized for categorical variables, while continuous variables were presented using mean and standard deviation or median and interquartile range. Group comparisons were performed using t-test, Mann-Whitney U test, chi-square test, or Fisher's exact test as appropriate.

To investigate the impact of the intervention on outcome variables during hospitalization, ANCOVA models were employed, incorporating the discharge value as the dependent variable and utilizing admission value and group as independent variables. Additionally, to examine the between-group effect at 1- and 3-month follow-ups, linear mixed models were utilized. These models included time, group, time and group interaction as independent variables, with adjustment by baseline outcome value. All comparisons were 2-sided, with a significance level of 0.05. All statistical analyses were made with SPSS, version 28.0 (IBM Corp) and R, version 4.2.1 (R Foundation) software.

All figures were created with BioRender® (https://www.biorender.com).

3. Results

The study flow diagram is shown in **Figure 3**. Baseline characteristics of patients in both groups are detailed in **Table 1**. No statistically significant differences were found between the medical and demographic characteristics of both groups, except for frailty as measured by the FRAIL scale. Patients in the control group exhibited higher levels of frailty (median 3.5 [IQR 1.0]) compared to the intervention group (median 3 [IQR 1]), with a p-value of 0.047. Out of the 36 patients included in the analyses, 21 were women, accounting for 58.3% of the sample. The mean age of the participants was 87.4 years with a standard

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deviation of 6.7 years. Adherence to the intervention reached 95.8%. There were no recorded adverse effects associated with the prescribed exercise program, and no patients necessitated discontinuation of the program or change in their hospital stay.

Figure 3. Flowchart of the study

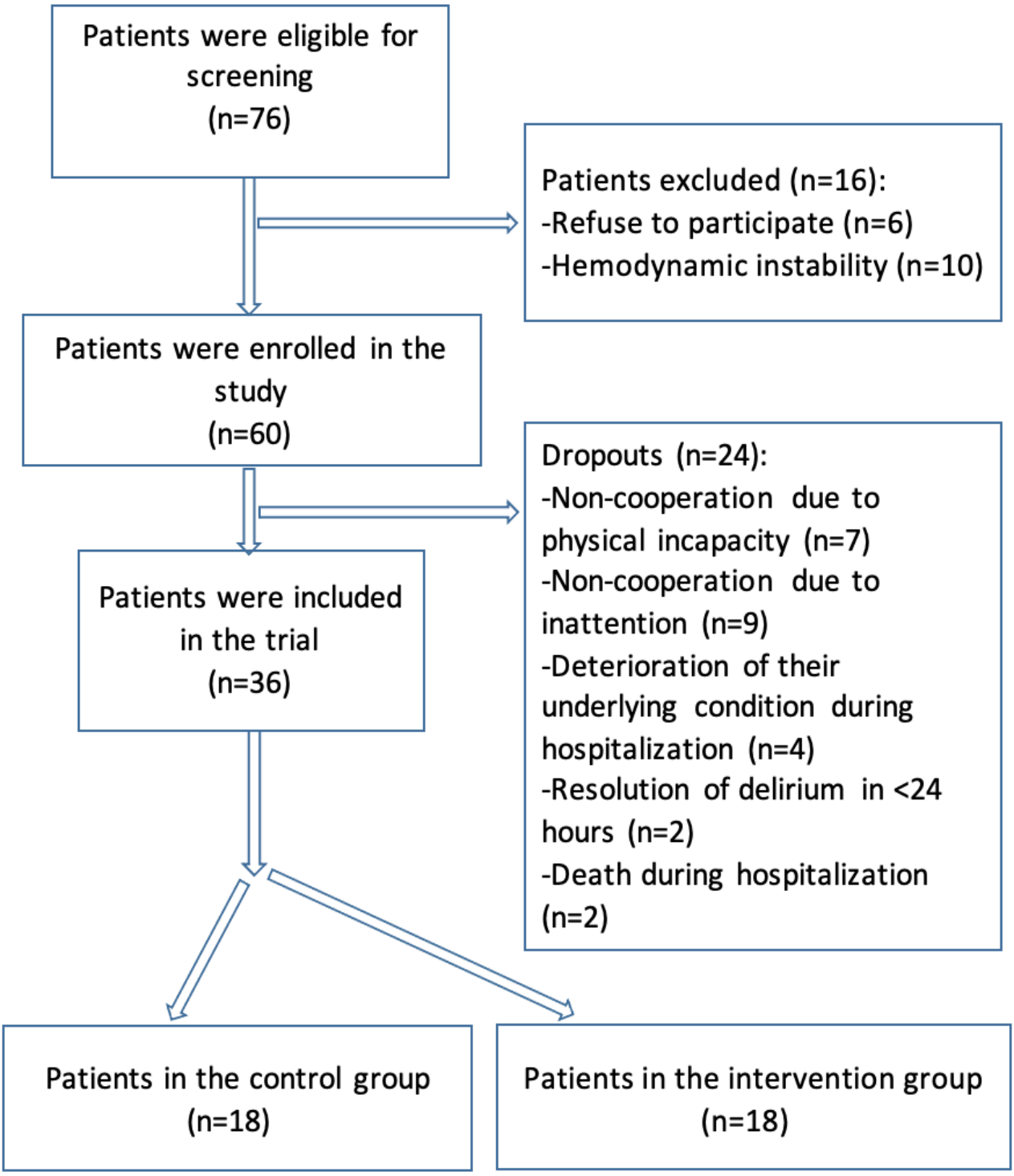

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Table 1. Main demographic, clinical, functional and cognitive characteristics at baseline by group

Variable	Category	Control group (n=18)	Intervention group (n=18)	p-value
Demographic data				
Age	mean (SD)	87.6 (7.8)	87.3 (5.5)	0.719[1]
Sex	Male	9 (50.0%)	6 (33.3%)	
	Female	9 (50.0%)	12 (66.7%)	0.310[2]
BMI	mean (SD)	27.3 (5.7)	25.4 (5.1)	0.495[1]
Clinical data				
CIRS[a]	mean (SD)	16.0 (4.5)	14.1 (3.7)	0.116[1]
MNA[b]	mean (SD)	21.0 (4.8)	21.9 (3.9)	0.419[1]
FRAIL[c]	median (IQR)	3.5 (1.0)	3.0 (1.0)	**0.047***[4]
Nº of drugs	mean (SD)	8.8 (4.4)	10.3 (3.2)	0.286[1]
Nº of active ingredients	mean (SD)	9.2 (4.7)	10.9 (3.6)	0.277[1]
Polypharmacy	No	2 (11.1%)	0 (0.0%)	
	Yes	16 (88.9%)	18 (100.0%)	0.486[3]
DBI[d] at admission	mean (SD)	0.94 (0.87)	0.73 (0.56)	0.407[1]
Quality of life (EuroQol-5D)	mean (SD)	67.5 (26.7)	70.3 (19.6)	0.724[1]
Functional and cognitive data				
SPPB[e]	mean (SD)	3.3 (1.7)	4.4 (2.9)	0.150[1]
Handgrip	mean (SD)	17.0 (6.8)	14.5 (6.6)	0.274[1]
1 RM leg press, Kg	mean (SD)	58.6 (22.3)	59.1 (24.5)	0.818[1]
1 RM chest press, Kg	mean (SD)	17.8 (9.4)	17.9 (8.8)	0.972[1]
1 RM knee extension, Kg	mean (SD)	26.2 (9.4)	24.2 (8.5)	0.561[1]
Handgrip	mean (SD)	13.9 (7.7)	13.2 (6.9)	0.890[1]
HABAM[f]	mean (SD)	20.8 (4.0)	20.9 (5.8)	0.947[1]
Barthel before admission[g]	mean (SD)	77.5 (12.2)	80.8 (13.3)	0.438[1]
Barthel at admission	mean (SD)	19.7 (14.1)	19.2 (11.4)	0.896[1]
MDAS[h]	mean (SD)	20.6 (8.2)	20.8 (7.5)	0.950[1]
Lawton[i]	median (IQR)	2.5 (5.0)	1.0 (4)	0.719[4]
GDS[j]	median (IQR)	4.0 (2.0)	4.0 (1.0)	0.521[4]
IQCODE-sf[k]	mean (SD)	4.1 (0.7)	4.3 (0.6)	0.386[1]
Falls in the last 12 months	median (IQR)	1.0 (2.0)	1.0 (3.0)	0.628[4]

[1] t-test [2] chi-square test [3] Fisher test [4] U Mann-Whitney

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CIRS, Cumulative Illness Rating Scale; IQR, interquartile range; MNA, Mini-Nutritional Assessment; DBI, Drug Burden Index; EuroQol-5d, EuroQol-5 Dimension ; SPPB, Short Physical Performance Battery; 1RM, 1 repetition maximum; HABAM, Hierarchical Assessment of Balance and Mobility; GDS, Global Deterioration Scale; IQCODE-sf, Informant Questionnaire on Cognitive Decline in the Elderly-short form;

[a]The CIRS scale evaluates individual body systems, ranging from 0 (best) to 56 (worst). The most prevalent diseases were hypertension, heart failure, osteoarthritis, arrhythmias, chronic gastritis/gastroesophageal reflux, chronic kidney disease, and urinary incontinence.

[b]The MNA scale ranges from normal nutritional status (24-30 points), risk of malnutrition (17-23.5 points), or malnourished (<17 points).

[c]The FRAIL scale ranges from robust (0 points), prefrail (1-2 points), or frail (3-5 points)

[d]The DBI scale is dose-related measure of anticholinergic and sedative drug exposure.

[e]The SPPB scale ranges from 0 (worst) to 12 (best).

[f]The HABAM scale evaluates mobility, transfers and balance, ranging from 0 (worst) to 67 (best)

[g]The Barthel Index ranges from 0 (severe functional dependence) to 100 (functional independence).

[h]The MDAS scale evaluates the severity of delirium (0 no delirium) to 30 (severe delirium)

[i]The Lawton scale evaluates instrumental activities and ranges from 0 (dependance) to 8 (independence).

[j]The GDS scale provides stages of cognitive function for those suffering from a primary degenerative dementia and ranges from 0 (no cognitive impairment) to 7 (severe dementia)

[k]The IQCODE-sf evaluates cognitive impairment. A cut-off point (average score) of 3.31/3.38 achieves a balance of sensitivity and specificity of cognitive impairment.

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The majority of the patients included exhibited hypoactive delirium, accounting for 77.8% in the control group and 66.7% in the intervention group. Initial analysis suggested that the physical exercise intervention had some benefit in managing delirium, reducing its duration by one day during hospitalization (mean delirium days in control group (SD) = 7 (2.1) versus 6 (3.0) in the intervention group; p=0.344). Furthermore, it appeared to facilitate delirium resolution at discharge (resolved in 66.7% of the control group versus 77.8% of the intervention group; p=0.457); however, these differences did not reach statistical significance. Primary delirium endpoints are outlined in **Table 2.a**.

Table 2.a Results of primary end points: evolution of delirium

Variable	Category	Control group(n=18)	Intervention group (n=18)	p-value
Duration of delirium	mean (SD)	7.0 (2.1)	6.2 (3.0)	0.344[1]
Delirium subtype	hypoactive	14 (77.8%)	12 (66.7%)	
	hyperactive	2 (11.1%)	2 (111.1%)	0.862[3]
	mixed	2 (11.1%)	4 (22.2%)	
Resolution of delirium at discharge	No	6 (33.3%)	4 (22.2%)	
	Yes	12 (66.7%)	14 (77.8%)	0.457[2]

[1] t-test [2] chi-square test [3]Fisher test

Regarding functional status, the intervention group showed a statistically significant improvement in HABAM score (9.84 points, 95% CI, 2.04 to 17.6 points; *p*=0.015). None of the other functional endpoints reached statistical significance (**Table 2.b.**).

Table 2.b Results of primary end points: change in functional capacity

Variable	Change in Control Group	Change in Intervention Group	Change between-group differences (95% CI)	p-value
SPPB	1.18 (0.21, 2.14)	0.67 (-0.48, 1.18)	-0.34 (-1.84, 1.16)	0.649
Barthel	43.9 (38. 49.8)	49.2 (36.1, 62.2)	5.72 (-6.46, 17.9)	0.346
Handgrip	0.05 (-1.21, 1.31)	0.99 (-0.37, 2.36)	0.68 (-1.26, 2.51)	0.457
HABAM	20.1 (14.3, 25.9)	29.9 (24.5, 35.4)	9.84 (2.04, 17.6)	**0.015***
1 RM leg press	0.91 (-3.34, 5.15)	4.83 (-0.47, 10.1)	3.80 (2-90, 10.5)	0.256
1 RM chest press	1.53 (-0.03, 3.10)	0.67 (-1.32, 2.65)	-0.85 (-3.18, 1.48)	0.460
1 RM knee extension	1.25 (-2.85, 5.34)	4.11 (1,87, 6.34)	2.94 (-1.42, 7.30)	0.176

Abbreviations: SPPB, Short Physical Performance Battery; HABAM, Hierarchical Assessment of Balance and Mobility; 1RM, 1 repetition maximum

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Secondary endpoints are presented in **Table 3a, 3b and 3c.** Although there were no significant changes in in-hospital falls and length of hospital stay between groups, significant differences were observed in activities of daily living (ADLs), instrumental activities (IADLs), and cognitive decline during follow-up. From admission, the intervention group showed a 12.2-point greater improvement on Barthel index versus control group (p=0.041) at 3-month follow-up. For IADLs, although both groups deteriorated over time, the intervention group had 1.23 points less on the Lawton scale than controls (p=0.027) at 1-month follow-up. For cognition, the intervention group showed less deterioration on the GDS and IQCODE-sf scales, scoring 5.75 points lower in IQCODE-sf than the control group at the 1-month follow-up (p=0.017) and 4.96 points lower at the 3-month follow-up (p=0.043).

Table 3a. Results of secondary end points: in-hospital falls and length of stay

Variable	Category	Control group (n=18)	Intervention group (n=18)	p-value
In-hospital falls	No	17 (94.4%)	16 (88.9%)	
	Yes	1 (5.6%)	2 (11.1%)	1.0[1]
Length of stay	mean (SD)	8.4 (1.9)	7.9 (2.7)	0.572[3]

[1]Test Fisher [3] T-test

Table 3b. Results of secondary end points: 1- and 3-month follow-up

Variable	Months of follow-up	Change in Control Group	Change in Intervention Group	Change between-group differences (95% CI)	p-value
Barthel	M1	43.6 (36.1, 51.1)	51.8 (44.0, 59.6)	8.25 (-2.59, 19.1)	0.148
	M3	38.5 (30.7, 46.3)	50.6 (42.6, 58.7)	12.2 (0.99, 23.4)	**0.041 ***
Lawton	M1	-1.71 (-2.44, -0.99)	-0.49 (--1.24, 0.26)	1.23 (0.18, 2.27)	**0.027 ***
	M3	-1.95 (-2.70, -1.20)	-0.94 (-2.08, 0.06)	1.01 (-0.06, 2.08)	0.075
GDS	M1	0.58 (0.30, 0.86)	0.20 (-0.09, 0.49)	-0.38 (-0.79, 0.02)	0.074
	M3	0.80 (0.51. 1.09)	0.51 (0.21, 0.81)	-0.29 (-0.71, 0.12)	0.182
IQCODE-sf	M1	4.39 (1.26, 7.51)	-1.37 (-4.61, 1.88)	-5.75 (-10.25, -1.24)	**0.017 ***
	M3	6.99 (3.76, 10.25)	2.03 (-1.31, 5.34)	-4.96 (-9.64, -0.34)	**0.043 ***
Nº drugs	M1	-0.13 (-1.14, 0.87)	-0.22 (-1.29, 0.85)	-0.08 (-1.55, 1.38)	0.912
	M3	-0.23 (-1.26, 0.79)	-0.29 (-1.43, 1.54)	-0.06 (-1.54, 1.43)	0.942
Nº of active ingredients	M1	-0.01 (-1.13, 1.12)	0.00 (-1.20, 1.20)	0.01 (-1.64, 1.65)	0.994
	M3	-0.10 (-1.26, 1.04)	-0.14 (-1.35, 1.05)	-0.04 (-1.70, 1.62)	0.963
DBI	M1	-0.25 (-0.47, -0.03)	0.01 (-0.22, 0.25)	0.26 (-0.06, 0.59)	0.122
	M3	-0.29 (-0.52, -0.07)	-0.06 (-0.30, 0.18)	0.23 (-0.09, 0.56)	0.176
EuroQol-5D	M1	-8.47 (-17.8, 0.86)	2.97 (-6.75, 12.7)	11.4 (-2.03, 24.9)	0.107
	M3	-11.3 (-21.0, -1.60)	1.48 (-8.41, 11.42)	12.8 (-1.07, 26.7)	0.082

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In the first column, the change for the control group from admission (from admission to 1 month (1M) and from admission to 3 months (3M)) is shown. The second column represents the same change for the intervention group, and the third column indicates the difference between these changes, known as the between-group difference, which reflects the effect of the intervention. For example, from admission, the intervention group shows an improvement of 51.8 points at one month, while the control group shows an improvement of 43.6 points. The difference between groups is 8.25 points, meaning the intervention group has a change 8.25 points greater than the control group.

Table 3c. Results of secondary end points: 1- and 3-month follow up

Variable	Months of follow-up	Category	Control group (n=18)	Intervention group (n=18)	p-value
Location		Home	16 (94.1%)	10 (66.7%)	
	M1	Nursing home	1 (5.9%)	3 (20.0%)	0.142[1]
		Intermediate Care Unit	0 (0.0%)	2 (13.3%)	
		Home	10 (66.7%)	11 (78.6%)	
	M3	Nursing home	4 (26.7%)	3 (21.4%)	0.507[1]
		Intermediate Care Unit	1 (6.7%)	0 (0.0%)	
Death	M1	No	17 (94.4%)	15 (88.2%)	
		Yes	1 (5.6%)	2 (11.8%)	0.603[1]
	M3	No	15 (93.8%)	14 (93.3%)	
		Yes	1 (6.3%)	1 (6.7%)	1.0[1]
New institutionalization	M1	No	16 (94.1%)	13 (86.7%)	
		Yes	1 (5.9%)	2 (13.3%)	0.589[1]
	M3	No	14 (93.3%)	14 (100.0%)	
		Yes	1 (6.7%)	0 (0.0%)	1.0[1]
Readmission	M1	No	13 (76.5%)	13 (86.7%)	
		Yes	4 (23.5%)	2 (13.3%)	0.659[1]
	M3	No	13 (86.7%)	14 (100.0%)	
		Yes	2 (13.3%)	0 (0.0%)	0.483[1]
Nº Emergency department visit	M1	median (IQR)	1.0 (3.0)	0.0 (2.0)	0.602[2]
	M3	median (IQR)	0.0 (1.0)	0.0 (0.0)	0.949[2]
Nº Primary Care Physician visit	M1	median (IQR)	1.0 (2.0)	1.0 (1.0)	0.313[2]
	M3	median (IQR)	0.0 (0.0)	0.0 (0.0)	0.683[2]
Nº Falls	M1	median (IQR)	0.0 (0.0)	0.0 (0.0)	0.953[2]
	M3	median (IQR)	0.0 (1.0)	0.0 (0.0)	0.769[2]

[1]Fisher exact test [2]Mann Whitney U test

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4. Discussion

To our knowledge, this is the first RCT evaluating the effect of a multicomponent tailored physical exercise program on the evolution of established in-hospital delirium in older adults. Our study shows that individualized, multicomponent exercise intervention adapted from VIVIFRAIL, improves the evolution of delirium and functional status during hospitalization and this improvement is maintained upon discharge. This is important, not only because it opens a new line of approach in the treatment of delirium in hospitalized older adults (especially the hypoactive type), but also because it prevents nosocomial dysfunction in this patient profile, which is typically excluded from studies.

Hospitalization, particularly among patients experiencing delirium, significantly contributes to functional decline and cognitive impairment in older adults. As a result, it is imperative not only to address the acute illness of these patients but also to safeguard and maintain their functional and cognitive capabilities throughout their acute admission. Some RCTs have evaluated the effects of physical exercise on functional outcomes and cognition in acutely hospitalized older adults finding that exercise is an effective and safe intervention to reverse the functional decline associated to hospitalization and prevent delirium.[53–57] Although their SPPB and Barthel scores surpassed ours, their cohort had better baseline functional and cognitive status compared to our patients, and excluded those with delirium. Exercise interventions have also shown functional, cognitive, and mood benefits in community-dwelling older adults with cognitive impairment, but again excluded those with delirium.[58–60]

Our hypothesis regarding how physical exercise may positively influence the course of delirium is illustrated in **Figure 4**. Physical exercise is postulated to have an anti-inflammatory effect, leading to increased levels of anti-inflammatory cytokines and other molecules, such as Brain-Derived Neurotrophic Factor (BDNF), Insulin-Like Growth Factor-1 (IGF-1), Vascular Endothelial Growth Factor A (VEGFA), and enhanced mitochondrial function. This effect also potentially decreases the levels of inflammatory cytokines and cortisol.[61,62] Physiologically, these processes might contribute to increased neurotransmission and neuroplasticity, thereby promoting neurogenesis and angiogenesis while reducing oxidative stress and neuronal damage.[63,64] In functional terms, these changes could potentially enhance cerebrovascular capacity, cognition (including attention

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and memory), connectivity (in terms of executive functions), and contribute to improved mood (by reducing anxiety and depression) and better facilitation of sleep.[65]

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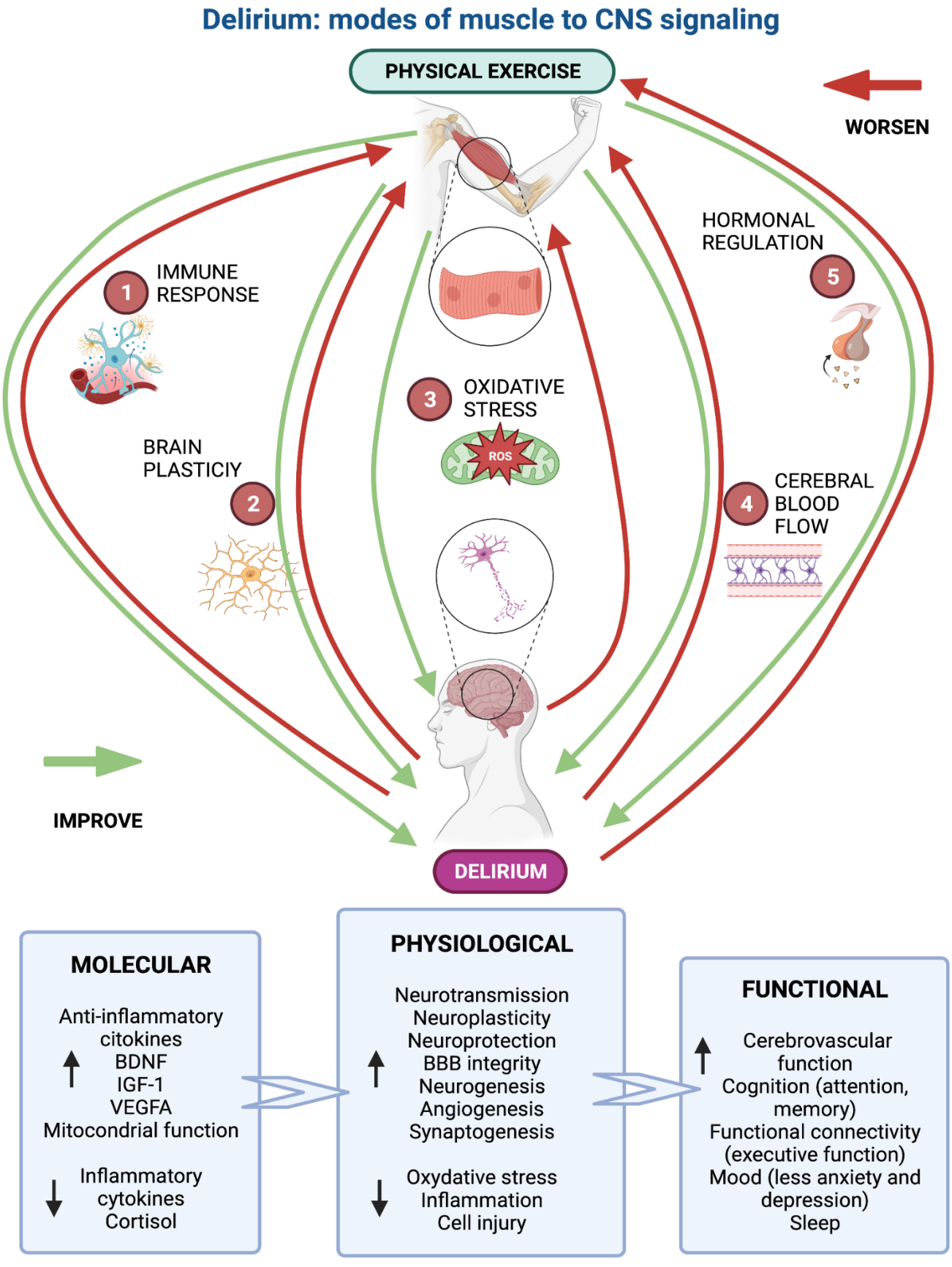
Figure 4. The complex relationship between delirium and physical exercise.



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1. **Inflammation and immune response:** delirium is associated with an increase in inflammatory markers in the brain and blood. Physical exercise has anti-inflammatory effects and can modulate the immune system, which may help reduce excessive inflammation associated with delirium. Exercise has been implicated in the release of anti-inflammatory cytokines that can counteract the inflammatory cascade in the brain.
2. **Neurotrophins and brain plasticity:** delirium leads to microglia activation, however, physical exercise promotes the release of neurotrophins, such as Brain-Derived Neurotrophic Factor (BDNF), which are associated with brain plasticity and neuronal growth. This could be relevant in improving cognitive function and reducing the severity of delirium.
3. **Regulation of oxidative stress:** delirium can lead to increased oxidative stress, damaging brain cells. Physical exercise has demonstrated antioxidant effects, improving mitochondrial function, which could help protect the brain from oxidative damage and reduce delirium severity.
4. **Improvement of cerebral blood flow:** damage on brain blood barrier (BBB) produces endothelial damage and migration of molecules to brain parenchyma causing delirium. Physical exercise increases cerebral blood flow and brain oxygenation and promotes the release of cerebral vascular endothelial growth factor A (VEGFA), which may be beneficial in maintaining optimal cognitive function and mitigating delirium symptoms.
5. **Hormonal regulation:** delirium has been associated with hormonal imbalances such as increased cortisol. Physical exercise can influence hormonal regulation and stress response. Exercise might contribute to maintaining a proper hormonal balance and reduce vulnerability to delirium.

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Limitations

Our study has limitations. The compromised health condition of several patients led to a high rate of dropouts, subsequently reducing the study's sample size and resulting in underpowering. This dropout trend was primarily due to the severity of many patients' underlying conditions and the complexity associated with patients experiencing delirium, including symptoms such as inattention and a fluctuating course. These challenges made it difficult for them to actively cooperate and participate in the study. Furthermore, this is a single RCT, so replication is needed in other cohorts to validate these results, exploring alternative exercise regimens and determining the optimal timing during the day to implement this intervention, given the fluctuating nature of delirium.

However, our study has several strengths, including its novelty. Most physical exercise interventions are conducted in stable patients (prehabilitation, residential care, community) and generally involve individuals with good baseline functional and cognitive status, excluding those with dementia or delirium.[66,67] In this study, not only patients with delirium were included, but also those with moderate dementia, frailty, and advanced age. Furthermore, to minimize potential bias, the researchers did not have access to a patient's previous test results during the retesting and end point assessment was performed following a standardized test protocol.

5. Conclusions

Multicomponent individualized exercise holds promise as a safe and effective treatment strategy for delirium in hospitalized older adults, particularly those with the hypoactive subtype. It appears to aid in delirium resolution and in preventing hospital-associated disability. These results suggest a potentially new approach to delirium management, especially in cases where pharmacological interventions have been less effective. While additional studies with larger sample sizes and comparative protocols are warranted, our findings suggest the feasibility of conducting clinical trials with patients experiencing delirium, a population often excluded from research studies.

Consent for publication

The authors have obtained consent from the participants to publish individual patient data.

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Conflict of interest

The authors declare that they have no competing interests.

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Nafarroako Unibertsitate Publikoa

References

1. Wilson, J. E. Delirium. *Nat. Rev. Dis. Prim.* **6**, (2020) doi:10.1038/s41572-020-00223-4.
2. Watt, C. L. The incidence and prevalence of delirium across palliative care settings: A systematic review. *Palliat. Med.* **33**, 865–877 (2019) doi:10.1177/0269216319854944.
3. Krewulak, K. D. Incidence and prevalence of delirium subtypes in an adult ICU: A systematic review and meta-analysis. *Crit. Care Med.* **46**, 2029–2035 (2018) doi:10.1097/CCM.0000000000003402.
4. Gibb, K. The consistent burden in published estimates of delirium occurrence in medical inpatients over four decades: A systematic review and meta-analysis study. *Age Ageing* **49**, 352–360 (2020) doi:10.1093/ageing/afaa040.
5. Dharmarajan, K. Pathway from Delirium to Death: Potential In-Hospital Mediators of Excess Mortality. *J. Am. Geriatr. Soc.* **65**, 1026–1033 (2017) doi:10.1111/jgs.14743.
6. Han, Q. Y. C. Prevalence, Risk Factors, and Impact of Delirium on Hospitalized Older Adults With Dementia: A Systematic Review and Meta-Analysis. *J. Am. Med. Dir. Assoc.* **23**, 23-32.e27 (2022) doi:10.1016/j.jamda.2021.09.008.
7. Welch, C. Delirium is prevalent in older hospital inpatients and associated with adverse outcomes: Results of a prospective multi-centre study on World Delirium Awareness Day. *BMC Med.* **17**, 1–11 (2019) doi:10.1186/s12916-019-1458-7.
8. Madrigal, C. Delirium and functional recovery in patients discharged to skilled nursing facilities after hospitalization for heart failure. *JAMA Netw. Open* **4**, 1–11 (2021) doi:10.1001/jamanetworkopen.2020.37968.
9. Fong, T. G. The inter-relationship between delirium and dementia: the importance of delirium prevention. *Nat. Rev. Neurol.* (2022) doi:10.1038/s41582-022-00698-7.
10. Oh, E. S. Delirium in older persons: Advances in diagnosis and treatment. *JAMA - J. Am. Med. Assoc.* **318**, 1161–1174 (2017) doi:10.1001/jama.2017.12067.
11. Kim, M. S. Comparative efficacy and acceptability of pharmacological interventions for the treatment and prevention of delirium: A systematic review and network meta-analysis. *J. Psychiatr. Res.* **125**, 164–176 (2020) doi:10.1016/j.jpsychires.2020.03.012.

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Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

12. Cerveira, C. C. T. Delirium in the elderly: A systematic review of pharmacological and non-pharmacological treatments. *Dement. e Neuropsychol.* **11**, 270–275 (2017) doi:10.1590/1980-57642016dn11-030009.
13. Sadlonova, M. Pharmacologic treatment of delirium symptoms: A systematic review. *Gen. Hosp. Psychiatry* **79**, 60–75 (2022) doi:10.1016/j.genhosppsych.2022.10.010.
14. National Institute for Health and Care Excellence (NICE). Delirium : prevention , diagnosis and management. (2022).
15. Hshieh, T. T. Hospital Elder Life Program: Systematic Review and Meta-analysis of Effectiveness. *Am. J. Geriatr. Psychiatry* **26**, 1015–1033 (2018) doi:10.1016/j.jagp.2018.06.007.
16. Wang, Y. Y. Effect of the Tailored, Family-Involved Hospital Elder Life Program on Postoperative Delirium and Function in Older Adults: A Randomized Clinical Trial. *JAMA Intern. Med.* **180**, 17–25 (2020) doi:10.1001/jamainternmed.2019.4446.
17. Burton, J. K. Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst. Rev.* **2019**, (2019) doi:10.1002/14651858.CD013307.
18. Davis, D. The Scottish Intercollegiate Guidelines Network: Risk reduction and management of delirium. *Age Ageing* **48**, 486–488 (2019) doi:10.1093/ageing/afz036.
19. National Institute for Health and Care Excellence (NICE). Delirium: prevention, diagnosis and management in hospital and long-term care. *NICE Guidel.* (2023).
20. Rengel, K. F. Delirium Prevention and Management in Frail Surgical Patients. *Anesthesiol. Clin.* **41**, 175–189 (2023) doi:10.1016/j.anclin.2022.10.011.
21. Hshieh, T. T. Effectiveness of multicomponent nonpharmacological delirium interventions: A meta-analysis. *JAMA Intern. Med.* **175**, 512–520 (2015) doi:10.1001/jamainternmed.2014.7779.
22. Oberai, T. Effectiveness of multicomponent interventions on incidence of delirium in hospitalized older patients with hip fracture: A systematic review. *Int. Psychogeriatrics* **30**, 481–492 (2018) doi:10.1017/S1041610217002782.
23. Gual, N. The role of physical exercise and rehabilitation in delirium. *Eur. Geriatr. Med.* **11**, 83–93 (2020) doi:10.1007/s41999-020-00290-6.

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

24. Sáez de Asteasu, M. L. Effects of Physical Exercise on the Incidence of Delirium and Cognitive Function in Acutely Hospitalized Older Adults: A Systematic Review with Meta-Analysis. *J. Alzheimer's Dis.* **87**, 503–517 (2022) doi:10.3233/JAD-220103.
25. Karamacoska, D. Brain function effects of exercise interventions for cognitive decline: a systematic review and meta-analysis. *Front. Neurosci.* **17**, (2023) doi:10.3389/fnins.2023.1127065.
26. Da Silva, J. L. Effects of Chronic Physical Exercise or Multicomponent Exercise Programs on the Mental Health and Cognition of Older Adults Living in a Nursing Home: A Systematic Review of Studies From the Past 10 Years. *Front. Psychol.* **13**, 1–9 (2022) doi:10.3389/fpsyg.2022.888851.
27. Haley, M. N. Delirium management: Let's get physical? A systematic review and meta-analysis. *Australas. J. Ageing* **38**, 231–241 (2019) doi:10.1111/ajag.12636.
28. Susie S. Lee, Yungtai Lo, J. V. Physical activity and risk of postoperative delirium. *J Am Geriatr. Soc.* **67(11)**, 2260–2266 (2019) doi:10.1111/jgs.16083.
29. Li, L. Effects of exercise on depressive symptoms among nursing home residents: a meta-analysis. *Aging Ment. Heal.* **26**, 1514–1523 (2022) doi:10.1080/13607863.2021.1951658.
30. Sáez de Asteasu, M. L. Cognitive Function Improvements Mediate Exercise Intervention Effects on Physical Performance in Acutely Hospitalized Older Adults. *J. Am. Med. Dir. Assoc.* **22**, 787–791 (2021) doi:10.1016/j.jamda.2020.08.024.
31. Valenzuela, P. L. Effects of exercise interventions on the functional status of acutely hospitalised older adults: A systematic review and meta-analysis. *Ageing Res. Rev.* **61**, 101076 (2020) doi:10.1016/j.arr.2020.101076.
32. Bliss, E. S. Benefits of exercise training on cerebrovascular and cognitive function in ageing. *J. Cereb. Blood Flow Metab.* **41**, 447–470 (2021) doi:10.1177/0271678X20957807.
33. Rojas-Valverde, D. Examining the interaction between exercise, gut microbiota, and neurodegeneration: future research directions. *Biomedicines* **11**, 1–17 (2023) doi:10.3390/biomedicines11082267.
34. Martinez Velilla, N. Could a Tailored Exercise Intervention for Hospitalised Older Adults Have a Role in the Resolution of Delirium? Secondary Analysis of a Randomised Clinical Trial. *J. Frailty Aging* **12**, 84–85 (2023)

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Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

doi:10.14283/jfa.2022.60.

35. Chan, A. W. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* **346**, 1–42 (2013) doi:10.1136/bmj.e7586.

36. Moher, D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group reandomized trials. *BMC Med. Res. Methodol.* **91**, 437–442 (2001).

37. Review, C. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J. Am. Coll. Dent.* **81**, 14–18 (2014) doi:10.1093/acprof:oso/9780199241323.003.0025.

38. Lozano-Vicario, L. Effectiveness of a multicomponent exercise training program for the management of delirium in hospitalized older adults using near-infrared spectroscopy as a biomarker of brain perfusion: Study protocol for a randomized controlled trial. *Front. Aging Neurosci.* **14**, 1–9 (2022) doi:10.3389/fnagi.2022.1013631.

39. Delgado-Parada, E. Diagnostic accuracy of the Spanish version of the 4AT scale (4AT-ES) for delirium screening in older inpatients. *Eur. J. Psychiatry* **36**, 182–190 (2022) doi:10.1016/j.ejpsy.2022.01.003.

40. Noguera, A. First spanish version of the memorial delirium assessment scale: Psychometric properties, responsiveness, and factor loadings. *J. Pain Symptom Manage.* **47**, 189–197 (2014) doi:10.1016/j.jpainsymman.2013.02.020.

41. Meagher, D. Development of an abbreviated version of the Delirium Motor Subtyping Scale (DMSS-4). *Int. Psychogeriatrics* **26**, 693–702 (2014) doi:10.1017/S1041610213002585.

42. Auer, S. The GDS/FAST staging system. *Int. Psychogeriatrics* **9**, 167–171 (1997) doi:10.1017/S1041610297004869.

43. Burton, J. K. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the detection of dementia within a secondary care setting. *Cochrane Database Syst. Rev.* **2021**, (2021) doi:10.1002/14651858.CD010772.pub3.

44. Guralnik, J. M. A Short Physical Performance Battery Assessing Lower Extremity Function: Association With Self-Reported Disability and Prediction of Mortality and Nursing Home Admission Energetic cost of walking in older adults View project IOM committee on cognitive agi. *Artic. J. Gerontol.* **49**, 85–94 (1994).

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Nafarroako Unibertsitate Publikoa

45. Gual, N. Impairments in balance and mobility identify delirium in patients with comorbid dementia. *Int. Psychogeriatrics* **31**, 749–753 (2019) doi:10.1017/S1041610218001345.
46. Richardson, S. Delirium and delirium severity predict the trajectory of the Hierarchical Assessment of Balance and Mobility (HABAM) in hospitalised older people: findings from the DECIDE Study. *Journals Gerontol. Ser. A* **XX**, 1–5 (2021) doi:10.1093/gerona/glab081.
47. Barthel, M. Functional evaluation: the Barthel Index. *Md. State Med. J.* **14**, 56–61 (1965).
48. Lawton, M. Assessment of older people: selfmaintaining and instrumental activities of daily living. Gerontologist. 1969;9:179–86. *Gerontologist* **9**, 1979–1986 (1969).
49. Gleason, L. J. FRAIL Questionnaire Screening Tool and Short-Term Outcomes in Geriatric Fracture Patients. *J. Am. Med. Dir. Assoc.* **18**, 1082–1086 (2017) doi:10.1016/j.jamda.2017.07.005.
50. Kaiser, M. . Validation of the mini nutritional assessment short-form (MNA®-SF): a practical tool for identification of nutritional status. *J. Nutr. Health Aging* **13**, 782–788 (2009).
51. Herdman, M. EuroQol-5D: a simple alternative for measuring health-related quality of life in primary care. *Aten. Primaria* **28**, 425–430 (2001) doi:10.1016/s0212-6567(01)70406-4.
52. Yesavage, J. A. Geriatric Depression Scale. *Psychopharmacol. Bull.* **24**, 709–710 (1988) doi:10.1007/978-3-319-69892-2_736-1.
53. Martínez-Velilla, N. Effect of Exercise Intervention on Functional Decline in Very Elderly Patients During Acute Hospitalization: A Randomized Clinical Trial. *JAMA Intern. Med.* **179**, 28–36 (2019) doi:10.1001/jamainternmed.2018.4869.
54. Martínez-Velilla, N. Effect of an Exercise Intervention on Functional Decline in Very Old Patients during Acute Hospitalizations: Results of a Multicenter, Randomized Clinical Trial. *JAMA Intern. Med.* **182**, 345–347 (2022) doi:10.1001/jamainternmed.2021.7654.
55. Martínez-Velilla, N. An exercise program with patient's involvement and family support can modify the cognitive and affective trajectory of acutely hospitalized older medical patients: a pilot study. *Aging Clin. Exp. Res.* **28**, 483–490 (2016)

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

doi:10.1007/s40520-015-0434-0.

56. L. Sáez de Asteasu, M. Role of physical exercise on cognitive function in healthy older adults: A systematic review of randomized clinical trials. *Ageing Res. Rev.* **37**, 117–134 (2017) doi:10.1016/j.arr.2017.05.007.

57. Ortiz-Alonso, J. Effect of a Simple Exercise Program on Hospitalization-Associated Disability in Older Patients: A Randomized Controlled Trial. *J. Am. Med. Dir. Assoc.* **21**, 531-537.e1 (2020) doi:10.1016/j.jamda.2019.11.027.

58. Casas-Herrero, Á. Effects of Vivifrail multicomponent intervention on functional capacity: a multicentre, randomized controlled trial. *J. Cachexia. Sarcopenia Muscle* **13**, 884–893 (2022) doi:10.1002/jcsm.12925.

59. Sáez de Asteasu, M. L. Assessing the impact of physical exercise on cognitive function in older medical patients during acute hospitalization: Secondary analysis of a randomized trial. *PLoS Med.* **16**, 1–14 (2019) doi:10.1371/journal.pmed.1002852.

60. Sánchez-Sánchez, J. L. Effects of a 12-week Vivifrail exercise program on intrinsic capacity among frail cognitively impaired community-dwelling older adults: secondary analysis of a multicentre randomised clinical trial. *Age Ageing* **52**, 1–10 (2023) doi:10.1093/ageing/afad050.

61. Rai, M. Muscle-to-Brain Signaling Via Myokines and Myometabolites. *Brain Plast.* **8**, 1–21 (2022) doi:10.3233/bpl-210133.

62. Cooper, J. Quantification of Neurological Blood-Based Biomarkers in Critically Ill Patients With Coronavirus Disease 2019. *Crit. care Explor.* **2**, e0238 (2020) doi:10.1097/CCE.0000000000000238.

63. Isaac, A. R. How does the skeletal muscle communicate with the brain in health and disease? *Neuropharmacology* **197**, 108744 (2021) doi:10.1016/j.neuropharm.2021.108744.

64. Ben-Zeev, T. The effect of exercise on neurogenesis in the brain. *IMAJ* **24**, (2022).

65. Cooper, C. On the run for hippocampal plasticity. *Cold Spring Harb. Perspect. Med.* **8**, (2018) doi:10.1101/cshperspect.a029736.

66. Humeidan, M. L. Effect of Cognitive Prehabilitation on the Incidence of Postoperative Delirium among Older Adults Undergoing Major Noncardiac Surgery: The Neurobics Randomized Clinical Trial. *JAMA Surg.* **156**, 148–156 (2021)

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

doi:10.1001/jamasurg.2020.4371.

67. Venegas-Sanabria, L. C. Effect of multicomponent exercise in cognitive impairment: a systematic review and meta-analysis. *BMC Geriatr.* **22**, (2022) doi:10.1186/s12877-022-03302-1.

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Capítulo 6: Discusión general

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El papel de los biomarcadores en la predicción del delirium (estudio 1)

La etiología multifactorial del delirium se refleja en la amplia variedad de biomarcadores identificados en el desarrollo del mismo. El déficit de acetilcolina y la alteración de neurotransmisores (serotonina, dopamina y noradrenalina) se han asociado a la presencia delirium al estar directamente implicados en la cognición, las fluctuaciones del nivel de atención y el patrón del sueño.[1–4] Por otro lado, la disregulación hormonal en el eje hipotálamo-hipofisario produciendo aumento de cortisol o secreción inadecuada de estradiol y leptina, también se han visto implicadas en la etiopatogenia del delirium.[5,6] Marcadores de daño neuronal como la proteína S100B o el neurofilamento ligero, relacionados con el funcionamiento de la microglía y los astrocitos, se han identificado en el desarrollo de delirium, si bien están más ligados al daño tisular que se produce en el cerebro durante el delirium y no necesariamente a los factores predisponentes del mismo.[7–9] Las proteínas Tau y beta-amiloide, identificadas en la patogénesis del deterioro cognitivo, también han sido halladas en algunos estudios, confirmando la relación bidireccional entre delirium y demencia.[10,11] Finalmente, técnicas basadas en el mapeo genético y la identificación de perfiles proteómicos y metabolómicos, han conseguido aportar nueva información sobre otros factores implicados el delirium, aunque los estudios son escasos y heterogéneos.[12–15]

La hipótesis neuroinflamatoria es la más estudiada y validada, en parte por la accesibilidad de biomarcadores durante las intervenciones quirúrgicas (sangre y LCR de fácil obtención en procedimientos anestésicos). Esta teoría sugiere que una noxa externa (cirugía, traumatismo o infección) conduce a la activación de una cascada inflamatoria y a la supresión de moléculas anti-inflamatorias que contrarrestarían estos efectos, segregándose mediadores proinflamatorios como interleuquinas, prostaglandinas y marcadores de necrosis tumoral. Estas moléculas penetrarían en el parénquima cerebral al perderse la integridad de la barrera hematoencefálica y producirían una hiperactivación de la microglía que, en último término, contribuiría al desarrollo de delirium.[16–19] En este contexto, biomarcadores como la IL-6, el TNF-α y la PCR han sido los más investigados, encontrándose diferencias estadísticamente significativas entre niveles elevados en suero y la incidencia de delirium.[20–24]

A pesar del creciente número de estudios que se están llevando a cabo en este ámbito, no existe suficiente evidencia que apoye el uso de biomarcadores actualmente.

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Algunas de las limitaciones que presentan estos estudios son el bajo tamaño muestral y la gran heterogeneidad en su metodología, así como la imprecisión en la terminología referente al delirium y la falta de uso de herramientas validadas para su detección. Además, la mayoría de estos estudios tienen lugar en pacientes quirúrgicos, lo que dificultaría la extrapolación de sus resultados a otro tipo de pacientes. Por lo tanto, deberían de implementarse estrategias con el fin de mejorar la calidad de los futuros estudios sobre biomarcadores de delirium como serían la protocolización en la toma de muestras y el diseño del estudio, la utilización de escalas validadas para la detección del delirium y las características del mismo, la definición de la población diana, la valoración de los síndromes geriátricos y la realización de un seguimiento en el tiempo de los sujetos.

Aunque se necesitan más estudios que confirmen estos hallazgos y profundicen en las propiedades de los biomarcadores en términos de sensibilidad, especificidad y coste-eficiencia, el uso de estas moléculas podría ser de gran utilidad en la predicción del delirium al constituir una herramienta objetiva, reproducible y poco invasiva (en el caso del suero) que podría complementar a la práctica clínica habitual.

La alteración de perfiles proteómicos se asocia al desarrollo de DPO en ancianos con fractura de cadera (estudio 2)

La existencia de DPO tras una fractura de cadera conlleva una peor recuperación funcional, un mayor riesgo de deterioro cognitivo, mayor estancia hospitalaria, mortalidad y consumo de recursos.[25,26] La identificación de sujetos de alto riesgo para modificar su trayectoria cognitiva y funcional es esencial para poder prevenirlo y detectarlo de manera eficaz. Hasta ahora, esta valoración se ha realizado a través de modelos clínicos basados en factores de riesgo predisponentes y precipitantes de delirium, como la escala DEAR, sin embargo, estas herramientas son en ocasiones imprecisas, subjetivas y complejas de utilizar para personal no entrenado.[27,28] Es por ello, que se deben explorar otras opciones que aporten mayor objetividad y sean más sencillas de utilizar en la práctica clínica habitual.

En este sentido, hemos identificado 12 biomarcadores asociados al riesgo de delirium tras fractura de cadera. Cuatro de ellos estaban aumentados (CXCL12 en suero, EGF en suero, CSF3 en LCR y TGFA en LCR) y ocho estaban disminuidos (CSF3 en suero, CXCL9 en suero, CXCL8 en suero, IL10 en suero, CCL2 en suero, CCL3 en LCR, CXCL9 en LCR

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y CCL4 en LCR). Un hallazgo interesante fue la correlación significativa entre niveles más bajos de CXCL9 en suero y LCR en pacientes con DPO en comparación con pacientes sin DPO.

La quimioquina (C-X-C) ligando 9 (CXCL9) es una pequeña citoquina que pertenece a la familia de quimoquinas, también conocida como monocina inducida por interferón gamma (MIG). CXCL9 induce quimiotaxis, promueve la diferenciación y multiplicación de leucocitos y provoca la extravasación de los tejidos. La CXCL9 aumenta con la edad y es un factor importante en la inflamación crónica relacionada con el envejecimiento cardiovascular.[29] El aumento de CXCL9 relacionado con la edad incrementa la senescencia de las células endoteliales y está asociado con caídas y fracturas de cadera en la población mayor, así como con la fragilidad.[30,31] El aumento de esta quimioquina y su receptor (CXCR3) también se han descrito en cerebros de pacientes con EA, encontrando niveles más altos de CXCL9 en pacientes con EA en comparación con pacientes con deterioro cognitivo leve o sin deterioro cognitivo.[32,33] Sin embargo, también existen hallazgos contradictorios en la literatura pues en algunos estudios, se han observado que niveles más bajos de CXCL9 en participantes con 1 o más alelos ε4 de EA.[34] Estos resultados discordantes respaldan el hecho de que niveles más bajos de CXCL9 en nuestro estudio estuviesen asociados a DPO tras fractura de cadera. Estas discrepancias podrían justificarse por los múltiples mecanismos implicados en el desarrollo del DPO (daño tisular, infección, dolor, polifarmacia, hipoxia...), la heterogeneidad en la metodología de los estudios realizados (diferentes análisis bioquímicos y evaluaciones clínicas) y el pequeño tamaño muestral de nuestro estudio. A ello se le añade que todos los pacientes de nuestro estudio presentaban SIRS (todos ellos tenían fractura de cadera, en comparación con otros estudios realizados en población sana) lo que podría ser un indicador no específico de delirium y más relacionado con el estado de inflamación periférica.

Aunque se necesitan realizar más estudios que apoyen estos hallazgos en poblaciones con mayor número de pacientes y evaluando la especificidad concreta de los biomarcadores, éstos podrían ayudar a conocer mejor la fisiopatología del delirium e implementar su predicción y detección en la práctica clínica habitual desde un punto de vista objetivo y mínimamente invasivo.

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Niveles elevados de PCR en suero se asocian a un mayor riesgo de DPO en el anciano con fractura de cadera (estudio 2)

La PCR es una proteína pentamérica cuyas concentraciones aumentan en respuesta a la inflamación y se elevan tras la secreción de IL-6 por parte de macrófagos y células T.[35,36] Aunque se han observado niveles más altos de PCR en procesos inflamatorios e infecciosos, la PCR también se encuentra alterada en pacientes con deterioro cognitivo y EA, lo que es un factor de riesgo para el desarrollo del delirium.[37,38] Algunos estudios han encontrado que los niveles de PCR aumentan significativamente en pacientes mayores sometidos a cirugía que posteriormente desarrollan delirium,[23,39,40] y otros no encuentran esta asociación.[41–43] Nuestros datos respaldan la hipótesis neuroinflamatoria del delirium, sugiriendo que la estimulación inflamatoria periférica atraviesa la BHE, induce la activación de las células del parénquima cerebral como la microglía y los astrocitos, y, en consecuencia, se produce una respuesta neuroinflamatoria disfuncional, lo que conlleva cambios neurocognitivos y desarrollo del delirium.[44]

Sin embargo, cuando realizamos un modelo de regresión logística que combinaba las variables clínicas más importantes implicadas en el desarrollo de delirium (edad, comorbilidad, fuerza de prensión, fragilidad, deterioro cognitivo e infecciones) y PCR, las infecciones y el deterioro cognitivo previo a la enfermedad fueron los mejores predictores de DPO. Esto puede explicarse por la edad avanzada de los pacientes, con una alta tasa de comorbilidad y fragilidad que confieren vulnerabilidad cognitiva y menor resistencia a los factores estresantes, lo que ocasiona más complicaciones perioperatorias, como las infecciones. Además, todos los pacientes de este estudio experimentaron SIRS inducido por la fractura antes de la cirugía cuando se recogieron las muestras, lo que podría haber afectado a los niveles de PCR y su interpretación.

De estos hallazgos se deduce que, aunque los niveles altos de PCR en suero están relacionados con un mayor riesgo de delirium, las variables clínicas en este caso son más potentes a la hora de predecir el delirium. Por ello, un modelo predictivo que combinase ambos tipos de variables (clínicas y bioquímicas) podría resultar una herramienta valiosa al complementar las limitaciones que unos y otros poseen. Por un lado, las variables clínicas parecen ser más consistentes, pero son, en muchas ocasiones, complicadas de evaluar en la práctica clínica habitual por falta de tiempo o de personal entrenado. Por otra parte, los

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biomarcadores, aunque aún no se conoce bien su especificidad concreta, son moléculas cuantificables y por ello objetivas, reproducibles y accesibles a todos los profesionales.

Aunque se necesitan más estudios que apoyen estas conclusiones, este es el primer paso para implementar la detección del delirium y anticiparse a él de una forma más eficaz.

La intervención con ejercicio físico multicomponente como medida de tratamiento en el abordaje del delirium (estudio 3)

Las consecuencias del delirium tras un ingreso hospitalario son devastadoras. A pesar de numerosos estudios, actualmente no existe ningún fármaco eficaz para su tratamiento y únicamente están indicados en el control sintomático del delirium hiperactivo con agitación grave no reconducible, pero no en el delirium hipoactivo, que es el que, con mayor frecuencia, presentan los adultos mayores.[45,46]

Este es el primer ensayo clínico aleatorio que evalúa el efecto de un programa de ejercicio físico individualizado y multicomponente en la evolución del delirium establecido durante la hospitalización en adultos mayores. Nuestro estudio demuestra que la intervención con ejercicio físico adaptado del programa VIVIFRAIL mejora la evolución del delirium y el estado funcional durante la hospitalización, y esta mejora se mantiene al alta. Esto es relevante no solo porque abre una nueva línea de enfoque en el tratamiento del delirium en adultos mayores hospitalizados (sobre todo en el tipo hipoactivo), sino también porque previene la disfunción nosocomial en este perfil de pacientes, que típicamente se excluye de los estudios.

La hospitalización, especialmente en pacientes que experimentan delirium, contribuye significativamente al deterioro funcional y cognitivo en adultos mayores. Por lo tanto, es imperativo no solo abordar la enfermedad aguda de estos pacientes, sino también salvaguardar y mantener sus capacidades funcionales y cognitivas a lo largo del ingreso. Algunos estudios han evaluado los efectos del ejercicio físico en mayores hospitalizados en una UGA, encontrando que es una intervención eficaz y segura para revertir el deterioro funcional asociado a la hospitalización y prevenir el delirium.[47–51] Aunque las puntuaciones de SPPB y Barthel de los pacientes incluidos en estos estudios superaron a las nuestras, sus cohortes tenían un estado funcional y cognitivo basal mejor que el de nuestros pacientes, y se excluyeron a aquellos pacientes que presentaban delirium. Las intervenciones con ejercicio físico también han demostrado beneficios funcionales, cognitivos y del estado de

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ánimo en adultos mayores que viven en la comunidad con deterioro cognitivo, pero, nuevamente, estos estudios también excluyeron a pacientes con delirium.[52–54]

Este estudio tiene varias fortalezas, además de su originalidad. La mayoría de las intervenciones con ejercicio físico se realizan en pacientes estables (prehabilitación, entorno residencial, comunidad) y generalmente con personas que presentan un buen estado funcional y cognitivo basal, excluyendo a aquellos con demencia o delirium.[55,56] En este estudio, no solo se incluyeron pacientes con delirium, sino también aquellos con demencia moderada, fragilidad y edad avanzada, propios de nuestra práctica clínica habitual.

Sin embargo, es importante destacar que la condición de salud comprometida de varios pacientes llevó a una alta tasa de abandono en el estudio, reduciendo así el tamaño muestral y la validez de los resultados. Esta tasa de abandono se debió principalmente a la gravedad de las enfermedades de base de muchos pacientes y a la complejidad intrínseca al delirium, como la falta de atención y el curso fluctuante, lo que dificultó en gran medida la adecuada cooperación de los participantes. Además, hay que tener en cuenta que éste fue un único ensayo clínico, por lo que se necesitaría replicarlo en otras cohortes para validar estos resultados. Por otro lado, sería interesante explorar otros protocolos de ejercicio alternativos y determinar el momento óptimo del día para implementar esta intervención, dada la naturaleza fluctuante del delirium, así como el perfil de paciente que más podría beneficiarse de ella.

Aunque se necesitan más estudios que refrenden estas conclusiones, este es el primer paso para implementar el tratamiento del delirium desde un punto de vista no farmacológico a través del ejercicio físico.

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References

1. Liu, C. Relationship between cholinergic biomarkers and postoperative delirium in elderly patients . *Chinese J. Anesthesiol.* **40**, 787–790 (2020) doi:10.3760/cma.j.cn131073.20191028.00705.
2. Wang, Y. Postoperative delirium in the elderly: the potential neuropathogenesis. *Aging Clin. Exp. Res.* **30**, 1287–1295 (2018) doi:10.1007/s40520-018-1008-8.
3. Lisibach, A. Evaluation of the association of anticholinergic burden and delirium in older hospitalised patients – A cohort study comparing 19 anticholinergic burden scales. *Br. J. Clin. Pharmacol.* 0–2 (2022) doi:10.1111/bcp.15432.
4. Egberts, A. Anticholinergic Drug Burden and Delirium: A Systematic Review. *J. Am. Med. Dir. Assoc.* **22**, 65-73.e4 (2021) doi:10.1016/j.jamda.2020.04.019.
5. Michels, M. Biomarker Predictors of Delirium in Acutely Ill Patients: A Systematic Review. *J. Geriatr. Psychiatry Neurol.* **32**, 119–136 (2019) doi:10.1177/0891988719834346.
6. Ouanes, S. High cortisol and the risk of dementia and alzheimer's disease: A review of the literature. *Front. Aging Neurosci.* **11**, (2019) doi:10.3389/fnagi.2019.00043.
7. Mietani, K. Elevated neuron-specific enolase level is associated with postoperative delirium and detection of phosphorylated neurofilament heavy subunit: A prospective observational study. *PLoS One* **16**, 1–10 (2021) doi:10.1371/journal.pone.0259217.
8. Gao, Y. Levels of S100 calcium binding protein B (S100B), neuron-specific enolase (NSE), and cyclophilin A (CypA) in the serum of patients with severe craniocerebral injury and multiple injuries combined with delirium transferred from the ICU and their prognosti. *Ann. Palliat. Med.* **10**, 3371–3378 (2021) doi:10.21037/apm-21-424.
9. Page, V. J. Plasma neurofilament light chain protein as a predictor of days in delirium and deep sedation, mortality and length of stay in critically ill patients. *eBioMedicine* **80**, 1–12 (2022) doi:10.1016/j.ebiom.2022.104043.
10. Fong, T. G. The inter-relationship between delirium and dementia: the importance of delirium prevention. *Nat. Rev. Neurol.* (2022) doi:10.1038/s41582-022-00698-7.
11. Wang, S. Postoperative delirium and its relationship with biomarkers for dementia: a meta-analysis. *Int. Psychogeriatrics* **34**, 377–390 (2022) doi:10.1017/S104161022100274X.

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

12. Sepulveda, E. The complex interaction of genetics and delirium: a systematic review and meta-analysis. *Eur. Arch. Psychiatry Clin. Neurosci.* **271**, 929–939 (2021) doi:10.1007/s00406-021-01255-x.
13. Sfera, A. Proteomic and epigenomic markers of sepsis-induced delirium (SID). *Front. Mol. Biosci.* **2**, (2015) doi:10.3389/fmolb.2015.00059.
14. Van Munster, B. C. Genetic polymorphisms in the DRD2, DRD3, and SLC6A3 gene in elderly patients with delirium. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* **153**, 38–45 (2010) doi:10.1002/ajmg.b.30943.
15. Van Munster, B. C. The role of genetics in delirium in the elderly patient. *Dement. Geriatr. Cogn. Disord.* **28**, 187–195 (2009) doi:10.1159/000235796.
16. Hall, R. J. CSF biomarkers in delirium: a systematic review. *Int. J. Geriatr. Psychiatry* **33**, 1479–1500 (2018) doi:10.1002/gps.4720.
17. Liu, X. Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. *PLoS One* **13**, e0195659 (2018) doi:10.1371/journal.pone.0195659.
18. Dunne, S. S. Biomarkers in delirium: A systematic review. *J. Psychosom. Res.* **147**, 110530 (2021) doi:10.1016/j.jpsychores.2021.110530.
19. Noah, A. M. Preoperative inflammatory mediators and postoperative delirium: systematic review and meta-analysis. *Br. J. Anaesth.* **127**, 424–434 (2021) doi:10.1016/j.bja.2021.04.033.
20. Peng, J. Preoperative C-Reactive Protein/Albumin Ratio, a Risk Factor for Postoperative Delirium in Elderly Patients After Total Joint Arthroplasty. *J. Arthroplasty* **34**, 2601–2605 (2019) doi:10.1016/j.arth.2019.06.042.
21. Hshieh, T. T. The Role of Inflammation after Surgery for Elders (RISE) study: Study design, procedures, and cohort profile. *Alzheimer's Dement. (Amsterdam, Netherlands)* **11**, 752–762 (2019) doi:10.1016/j.dadm.2019.09.004.
22. Chen, Y. Change in Serum Level of Interleukin 6 and Delirium After Coronary Artery Bypass Graft. *Am. J. Crit. care an Off. Publ. Am. Assoc. Crit. Nurses* **28**, 462–470 (2019) doi:10.4037/ajcc2019976.
23. Dillon, S. T. Higher C-Reactive Protein Levels Predict Postoperative Delirium in Older Patients Undergoing Major Elective Surgery: A Longitudinal Nested Case-Control Study. *Biol. Psychiatry* **81**, 145–153 (2017) doi:10.1016/j.biopsych.2016.03.2098.

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Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

24. Vasunilashorn, S. M. Development of a Dynamic Multi-Protein Signature of Postoperative Delirium. *J. Gerontol. A. Biol. Sci. Med. Sci.* **74**, 261–268 (2019) doi:10.1093/gerona/gly036.

25. Oberai, T. Is delirium associated with negative outcomes in older patients with hip fracture: analysis of the 4904 patients 2017–2018 from the Australian and New Zealand hip fracture registry. *ANZ J. Surg.* **92**, 200–205 (2022) doi:10.1111/ans.17421.

26. Sieber, F. Postoperative delirium and its sequelae. *Alzheimer's Dement.* **11**, P212 (2015).

27. Freter, S. Risk of pre- and post-operative delirium and the delirium elderly at risk (DEAR) tool in hip fracture patients. *Can. Geriatr. J.* **18**, 212–216 (2015) doi:10.5770/cgj.18.185.

28. Freter, S. Predicting post-operative delirium in elective orthopaedic patients: the Delirium Elderly At-Risk (DEAR) instrument. *Age Ageing* **34**, 169–184 (2005) doi:10.1093/ageing/afh245.

29. Sayed, N. *An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging*. *Nature Aging* vol. 1 (2021). doi:10.1038/s43587-021-00082-y.

30. Phan, Q. T. CXCL9 Predicts the Risk of Osteoporotic Hip Fracture in a Prospective Cohort of Chinese Men—A Matched Case–Control Study. *J. Bone Miner. Res.* **37**, 1843–1849 (2022) doi:10.1002/jbmr.4646.

31. de Amorim, J. S. C. Inflammatory markers and occurrence of falls: Bambuí Cohort Study of Aging. *Rev. Saude Publica* **53**, 1–11 (2019) doi:10.11606/S1518-8787.2019053000855.

32. Satarkar, D. Review: The chemokine receptor CXCR3 and its ligands CXCL9, CXCL10 and CXCL11 in neuroimmunity - A tale of conflict and conundrum. *Int. J. Mol. Sci.* **23**, 748 (2022) doi:10.1038/s41584-021-00694-z.

33. Satarkar, D. Evolution, Expression and Functional Analysis of CXCR3 in Neuronal and Cardiovascular Diseases: A Narrative Review. *Front. Cell Dev. Biol.* **10**, 1–17 (2022) doi:10.3389/fcell.2022.882017.

34. Soares, H. D. Plasma biomarkers associated with the apolipoprotein E genotype and alzheimer disease. *Arch. Neurol.* **69**, 1310–1317 (2012)

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Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

doi:10.1001/archneurol.2012.1070.

35. Sproston, N. R. Role of C-reactive protein at sites of inflammation and infection. *Front. Immunol.* **9**, 1–11 (2018) doi:10.3389/fimmu.2018.00754.

36. Pathak, A. Evolution of C-reactive protein. *Front. Immunol.* **10**, (2019) doi:10.3389/fimmu.2019.00943.

37. Rentería, M. A. C-reactive protein and risk of cognitive decline: The REGARDS study. *PLoS One* **15**, 1–15 (2020) doi:10.1371/journal.pone.0244612.

38. Leng, F. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nat. Rev. Neurol.* **17**, 157–172 (2021) doi:10.1038/s41582-020-00435-y.

39. Cerejeira, J. The cholinergic system and inflammation: common pathways in delirium pathophysiology. *J. Am. Geriatr. Soc.* **60**, 669–675 (2012) doi:10.1111/j.1532-5415.2011.03883.x.

40. Chen, Y. Preoperative Circulating MiR-210, a Risk Factor for Postoperative Delirium Among Elderly Patients with Gastric Cancer Undergoing Curative Resection. *Curr. Pharm. Des.* **26**, 5213–5219 (2020) doi:10.2174/1381612826666200617163857.

41. Slor, C. J. The trajectory of C-reactive protein serum levels in older hip fracture patients with postoperative delirium. *Int. J. Geriatr. Psychiatry* **34**, 1438–1446 (2019) doi:10.1002/gps.5139.

42. Çinar, M. A. Role of CRP, TNF-a, and IGF-1 in Delirium Pathophysiology. *Noro Psikiyatr. Ars.* **51**, 376–382 (2014) doi:10.5152/npa.2014.6999.

43. Katsumi, Y. The Role of Inflammation after Surgery for Elders (RISE) study: Examination of [11C]PBR28 binding and exploration of its link to post-operative delirium. *NeuroImage Clin.* **27**, (2020) doi:10.1016/j.nicl.2020.102346.

44. Wilson, J. E. Delirium. *Nat. Rev. Dis. Prim.* **6**, (2020) doi:10.1038/s41572-020-00223-4.

45. National Institute for Health and Care Excellence (NICE). Delirium: prevention, diagnosis and management in hospital and long-term care. *NICE Guidel.* (2023).

46. Davis, D. The Scottish Intercollegiate Guidelines Network: Risk reduction and management of delirium. *Age Ageing* **48**, 486–488 (2019) doi:10.1093/ageing/afz036.

47. Martínez-Velilla, N. Effect of Exercise Intervention on Functional Decline in Very

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Nafarroako Unibertsitate Publikoa

Elderly Patients During Acute Hospitalization: A Randomized Clinical Trial. *JAMA Intern. Med.* **179**, 28–36 (2019) doi:10.1001/jamainternmed.2018.4869.

48. Sáez de Asteasu, M. L. Effects of Physical Exercise on the Incidence of Delirium and Cognitive Function in Acutely Hospitalized Older Adults: A Systematic Review with Meta-Analysis. *J. Alzheimer's Dis.* **87**, 503–517 (2022) doi:10.3233/JAD-220103.
49. Martínez-Velilla, N. An exercise program with patient's involvement and family support can modify the cognitive and affective trajectory of acutely hospitalized older medical patients: a pilot study. *Aging Clin. Exp. Res.* **28**, 483–490 (2016) doi:10.1007/s40520-015-0434-0.
50. L. Sáez de Asteasu, M. Role of physical exercise on cognitive function in healthy older adults: A systematic review of randomized clinical trials. *Ageing Res. Rev.* **37**, 117–134 (2017) doi:10.1016/j.arr.2017.05.007.
51. Ortiz-Alonso, J. Effect of a Simple Exercise Program on Hospitalization-Associated Disability in Older Patients: A Randomized Controlled Trial. *J. Am. Med. Dir. Assoc.* **21**, 531-537.e1 (2020) doi:10.1016/j.jamda.2019.11.027.
52. Casas-Herrero, Á. Effects of Vivifrail multicomponent intervention on functional capacity: a multicentre, randomized controlled trial. *J. Cachexia. Sarcopenia Muscle* **13**, 884–893 (2022) doi:10.1002/jcsm.12925.
53. Sánchez-Sánchez, J. L. Effects of a 12-week Vivifrail exercise program on intrinsic capacity among frail cognitively impaired community-dwelling older adults: secondary analysis of a multicentre randomised clinical trial. *Age Ageing* **52**, 1–10 (2023) doi:10.1093/ageing/afad050.
54. Sáez de Asteasu, M. L. Assessing the impact of physical exercise on cognitive function in older medical patients during acute hospitalization: Secondary analysis of a randomized trial. *PLoS Med.* **16**, 1–14 (2019) doi:10.1371/journal.pmed.1002852.
55. Humeidan, M. L. Effect of Cognitive Prehabilitation on the Incidence of Postoperative Delirium among Older Adults Undergoing Major Noncardiac Surgery: The Neurobics Randomized Clinical Trial. *JAMA Surg.* **156**, 148–156 (2021) doi:10.1001/jamasurg.2020.4371.
56. Venegas-Sanabria, L. C. Effect of multicomponent exercise in cognitive impairment: a systematic review and meta-analysis. *BMC Geriatr.* **22**, (2022) doi:10.1186/s12877-022-03302-1.

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Capítulo 7
Conclusiones, aplicaciones prácticas y futuras perspectivas

Chapter 7
Conclusions, practical applications and future perspectives

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Estudio 1 (Capítulo 1)

Conclusión:

Biomarcadores inflamatorios en suero como la PCR, la IL-6 o el TNF-α, parecen tener una asociación significativa con el riesgo de desarrollo de delirium en el anciano.

Aplicación práctica:

Aunque no existe evidencia suficiente para apoyar el uso rutinario de biomarcadores de delirium en la actualidad, esta revisión destaca la existencia de biomarcadores en sangre y líquido cefalorraquídeo asociados a la incidencia de delirium en el anciano, especialmente los de tipo proinflamatorio. El uso de biomarcadores podría ayudar a profundizar en el conocimiento de los procesos fisiopatológicos implicados en el desarrollo de delirium y en la creación de herramientas objetivas y mínimamente invasivas que pudiesen complementar a la práctica clínica habitual en el manejo del delirium.

Perspectiva futura:

Es necesario estandarizar la metodología de los estudios para clarificar la relación entre los biomarcadores y la incidencia de delirium, así como comprender mejor la especificidad y sensibilidad de éstos.

Estudio 2 (Capítulo 2):

Conclusión:

Un perfil proteómico alterado en suero y líquido cefalorraquídeo se asocia a la aparición de delirium postoperatorio en el adulto mayor con fractura de cadera.

Aplicación práctica:

A pesar del pequeño tamaño muestral, este estudio proporciona evidencia del potencial uso de los biomarcadores moleculares en la predicción de riesgo de delirium postoperatorio, concretamente 12 biomarcadores relacionados con la inflamación, destacando la asociación más significativa con la quimiocina CXCL-9 tanto en suero como en líquido cefalorraquídeo. Estos biomarcadores podrían ser

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de utilidad en la detección del delirium, al ser una alternativa objetiva, cuantificable, reproducible y mínimamente invasiva, en el caso del suero.

Perspectiva futura:

Los resultados obtenidos en este estudio abren la posibilidad a realizar un cambio en el modo actual en el que se lleva a cabo la predicción del delirium, basado en modelos exclusivamente clínicos. Además, conocer estos biomarcadores ayudaría a comprender mejor la fisiopatología del delirium e identificar futuras dianas terapéuticas. Sin embargo, se necesitan realizar más estudios en el futuro con otras moléculas, identificando su especificidad para la detección este síndrome.

Estudio 2 (Capítulo 3):

Conclusión:

La PCR en suero se asocia de forma significativa con la incidencia de delirium postoperatorio en el anciano con fractura de cadera. Sin embargo, la existencia de deterioro cognitivo y la presencia de infecciones son los factores de riesgo más importantes para el desarrollo de delirium en este contexto.

Aplicación práctica:

Aunque se necesitan más estudios que ayuden a consolidar estos hallazgos, identificar biomarcadores implicados en la neuroinflamación cerebral, podría ayudar a detectar a los sujetos de alto riesgo y prevenir su aparición.

Perspectiva futura:

Nuestros hallazgos respaldan la necesidad de un cambio en el enfoque metodológico de los modelos de predicción de delirium, incluyendo no solamente las tradicionales variables clínicas si no también variables bioquímicas, para mejorar su eficacia. Futuros estudios deberán determinar si estas moléculas también podrían constituir una potencial diana terapéutica para el delirium.

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Estudio 3 (Capítulos 4 y 5):

Conclusión:

El ejercicio individualizado multicomponente es una estrategia segura y prometedora para el tratamiento del delirium en adultos mayores hospitalizados, especialmente en aquellos con el subtipo hipoactivo. No solamente previene la discapacidad nosocomial si no que también podría contribuir a la resolución del delirium, beneficios que se mantendrían al alta.

Aplicación práctica:

Nuestro estudio destaca la importancia de implementar el ejercicio físico durante la hospitalización, no solo para prevenir la discapacidad física, sino también para mejorar la cognición. Esto se aplicaría a todos los pacientes, incluidos aquellos con delirium que habitualmente son excluidos de los estudios, pero que también se benefician de esta intervención.

Perspectiva futura:

Teniendo en cuenta que las intervenciones farmacológicas no han demostrado eficacia en el tratamiento del delirium, estos hallazgos abren la posibilidad de un nuevo enfoque en su manejo. Sin embargo, se necesitan más estudios con tamaños muestrales más grandes y protocolos con distintos tipos de ejercicios para validar estos resultados. Será crucial identificar el tipo más eficaz de intervención con ejercicio físico así como el momento de realizarla y el perfil de pacientes que más se beneficia de ella.

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Study 1 (Chapter 1)

Conclusion:

Serum biomarkers such as PCR, IL-6, or TNF-α seem to have a significant association with the risk of delirium development in the elderly.

Practical Application:

Although there is insufficient evidence to support the routine use of delirium biomarkers, this review highlights the existence of blood and cerebrospinal fluid biomarkers associated with the incidence of delirium in the elderly, particularly those of a proinflammatory nature. The use of biomarkers could contribute to a deeper understanding of the pathophysiological processes involved in delirium and the development of objective and minimally invasive tools that could complement routine clinical practice in delirium management.

Future Perspective:

It is essential to standardize the methodology of studies to clarify the relationship between biomarkers and delirium incidence, as well as to better understand their specificity and sensitivity.

Study 2 (Chapter 2)

Conclusion:

An altered proteomic profile in serum and cerebrospinal fluid is associated with the development of POD in older adults with hip fracture.

Practical Application:

Despite the small sample size, this study provides evidence for the potential use of molecular biomarkers in predicting the risk of POD, specifically 12 biomarkers related to inflammation, with the most significant association found with the chemokine CXCL-9, both in serum and CSF. Biomarkers could be useful in delirium prediction, as they offer an objective, quantifiable, reproducible, and minimally invasive alternative, particularly in the case of serum.

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Future Perspective:

The results obtained in this study open the possibility of a shift in the current approach to delirium prediction, which relies solely on clinical models. Furthermore, understanding these biomarkers would contribute to a better comprehension of delirium's pathophysiology and the identification of potential therapeutic targets. However, further research is needed to identify other molecules associated with delirium incidence and its specificity in this field.

Study 2 (Chapter 3)

Conclusion:

Serum CRP is significantly associated with the incidence of POD in older adults with hip fracture. However, the presence of cognitive impairment and infections are the most important risk factors for delirium development in this context.

Practical Application:

Although further research is needed to strengthen these findings, identifying biomarkers involved in cerebral neuroinflammation could aid in recognizing patients at risk of delirium and prevent its occurrence.

Future Perspective:

Our findings support the need to implement the methodological approach of delirium prediction models, incorporating not only traditional clinical variables but also biochemical variables to enhance their effectiveness. Future studies will need to determine whether these molecules could also constitute a potential therapeutic target for delirium.

Study 3 (Chapter 4 and 5)

Conclusion:

Multicomponent individualized exercise is a safe and possible effective treatment strategy for delirium in hospitalized older adults, particularly those with the

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hypoactive subtype. It appears to aid in delirium resolution and in preventing hospital-associated disability.

Practical Application:

Our study highlights the importance of implementing physical exercise during hospitalization as a measure not only for the prevention of physical disability but also for improving cognition, without excluding patients with delirium, as they also benefit from this intervention.

Future Perspective:

These findings open the possibility of a new approach to delirium treatment, where pharmacological interventions have not proven effective. However, additional studies with larger sample sizes and comparative protocols are warranted, to validate these results, identifying the most effective type of physical exercise intervention, as well as the best moment to implement it and the patient profile that benefits the most from it.

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Anexos

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Biomarkers of delirium risk in older adults: a systematic review and meta-analysis

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Delirium is a neuropsychiatric syndrome associated with increased morbidity and mortality in older patients. The aim of this study was to review predictive biomarkers of delirium in older patients to gain insights into the pathophysiology of this syndrome and provide guidance for future studies. Two authors independently and systematically searched MEDLINE, Embase, Cochrane Library, Web of Science and Scopus databases up to August 2021. A total of 32 studies were included. Only 6 studies were eligible for the meta-analysis, pooled results showed a significant increase in some serum biomarkers (C-reactive protein [CRP], tumour necrosis factor alpha [TNF-α] and interleukin-6 [IL-6]) among patients with delirium (odds ratio=1.88, 95% CI 1.01 to 1.637; I2=76.75%). Although current evidence does not favour the use of any particular biomarker, serum CRP, TNF-α, and IL-6 were the most consistent biomarkers of delirium in older patients.

KEYWORDS

delirium, cognitive impairment, biomarkers, neuroinflammation, older people

Introduction

Delirium is a severe neuropsychiatric syndrome characterized by an acute change in attention and other aspects of cognition such as altered arousal, disorientation, psychosis or mood disturbance (Sachdev et al., 2014). Approximately 23% of hospitalized older adults develop delirium in medical settings (Gibb et al., 2020); this proportion increases to 13–50% in noncardiac surgical settings (Inouye et al., 2014), 6–74% in inpatient palliative care units (Watt et al., 2019) and 50–70% among mechanically ventilated patients (Krewulak et al., 2018). Delirium is associated with multiple adverse outcomes, such as higher length of stay, higher risk of iatrogenic and medical complications during hospitalization (falls, malnutrition, dehydration, aspiration pneumonia, immobility, bedsores), increased disability, cognitive impairment, mental illnesses (depression, anxiety, posttraumatic stress disorder) and mortality (Abelha et al., 2013; Martínez-Velilla et al., 2016; Dharmarajan et al., 2017; Altman et al., 2018; Israni et al., 2018; Sillner et al., 2019; Welch et al., 2019; Hayhurst et al., 2020).

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The risk of delirium is determined by predisposing factors (for example, pre-existing cognitive impairment, advanced age or frailty) and precipitating factors (acute insults such as surgery, infections or metabolic decompensations) (Wilson et al., 2020). Because multiple factors are implicated in the aetiology of delirium, there are likely several neurobiological processes that contribute to its pathophysiology, that remains unclear. During delirium, a reversal of the relationship between the dorsolateral prefrontal cortex (part of the executive network) (Choi et al., 2012) and the posterior cingulate cortex (involved in the default mode network) (Raichle, 2015) has been observed, contributing to changes in behaviour and attention. In addition, reduced brain efficiency and connectivity strength (especially in subcortical regions related to arousal) have been found in patients with delirium. Delirium can be defined as a failure of a vulnerable brain to show resilience in response to an acute stressor (van Montfort et al., 2019). This vulnerability can be caused by several processes such as impaired brain network connectivity which leads to neurotransmitter disturbance in cholinergic and noradrenergic neurons (Morandi et al., 2012), neuroinflammatory and glial cell changes which causes an exacerbated pro-inflammatory response to noxious insults (Murray et al., 2012) and vasculature dysfunction which produces endothelial injury, blood–brain barrier (BBB) damage and impaired brain perfusion (Cavallari et al., 2016).

Given the complexity of these processes, the use of biomarkers has become widespread for identification of delirium and its risk. The World Health Organization (WHO) defines a biomarker as any substance, structure, or process that can be measured in the body or its products that can influence or predict the incidence of outcome or disease [World Health Organization (WHO), 2001]. Biomarkers are objective and quantifiable characteristics of biological processes, which makes them a reliable and reproducible measure (Strimbu and Tavel, 2010). They are categorized into three patterns: (1) risk markers, which indicate the risk of a particular disease, (2) disease markers, which are correlated with the onset or recovery of a disease, and (3) end-products, which indicate disease resolution (Aronson and Ferner, 2017). The identification of biomarkers associated with delirium may help clarify its pathophysiology and aid in the prediction, diagnosis and management of this syndrome. Although few systematic reviews have been recently carried out on delirium biomarkers, they present important limitations, such as restriction to a single fluid (Hall et al., 2011, 2018; Ida et al., 2020) or a single biomarker (Liu et al., 2018; Narayanan et al., 2021), different types of mixed biomarkers (Chu et al., 2011; Dunne et al., 2021) and the absence of a focus on older adults, in whom delirium risk is the greatest.

Thus, the aim of this study was to systematically review the current literature on delirium biomarkers and identify risk markers in older adults to summarize the existing knowledge, enhance our understanding regarding the pathophysiology and provide methodological guidance for future studies.

Materials and methods

Search strategy

This systematic review was undertaken in accordance with the guidelines described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al., 2009). We asked the question whether incident delirium was associated with biomarkers and summarized data extracted from included studies.

Two reviewers (LL and BAC) searched studies published before 17 August 2021 that investigated delirium biomarkers. Searches were performed using a comprehensive text-word and Medical Subject Headings-based electronic search of MEDLINE, EMBASE, The Cochrane Library, Web of Science and Scopus. Primary key words included: "delirium" and "biomarker" used in combination with additional key words as: "cognitive dysfunction," "acute confusion state," "acute brain failure," "postoperative delirium" or "postoperative cognitive disorder." Boolean operators were used to combine search terms above (Supplementary material). Authors with specialist knowledge of the subject extracted the data. To avoid bias, results were based on analysis by LL, AC, NM, and AG. Variations in interpretation were reviewed, and any disputes were resolved by NM. The review protocol was registered in PROSPERO (CRD42021281272).

Selection criteria

The inclusion criteria were:

- Study design: case–control, cohort study or case series with non-delirious subjects as controls
- Language of publication: English or Spanish
- Year of publication: all studies until 17.08.2021
- Study subjects: mean patient aged ≥65 years
- Diagnostic criteria of delirium:
  - o Diagnostic Statistical Manual of Mental Disorders (DSM)
  - o International Classification of Diseases (ICD)
  - o Delirium assessment tool based on DSM or ICD
- Source of biomarker: cerebrospinal fluid, blood or other body fluids.
- Measurement methods: methods that provide quantitative (i.e., ELISA, RIA) or detailed qualitative data (i.e., proteomics)
- Full text available (detailed information)

The exclusion criteria were:

- Reviews, case reports or comments, letters, personal opinions, book chapters and conference abstracts
- Randomized controlled trials (RCTs) measuring the effects of drugs on delirium incidence
- Studies where biomarkers were not identified
- Association between biomarkers and delirium in experimental studies (*in vitro* or *in vivo* animal studies)
- No identifiable delirium/no delirium subgroups
- Delirium of other specific causes (delirium tremens or other alcohol withdrawal states, Wernicke's encephalopathy, neuropsychiatric systematic lupus erythematosus).

Data extraction and synthesis

Two authors independently screened the remaining literature for useable data and extracted it, and this was checked by another reviewer. Articles that met the inclusion criteria were reviewed and we recorded (if available) the following information: (1) Author and year of publication, (2) study design and setting (i.e.,

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TABLE 1 Risk markers of delirium.

Type of biomarker	Biomarkers analyzed	Number of studies	Authors
Neurotransmitters	AChE, BChE, Ach, Kyneurine/Tryptophan, IDO, HVA	5	Adam et al. (2020), Cerejeira et al. (2012), de Jonghe et al. (2012), Ma et al. (2020), Osse et al. (2012)
Hormones	Estradiol, cortisol, leptin	3	Avila-Funes et al. (2015), Li et al. (2017), Ma et al. (2020)
Biomarkers of neuronal damage	S100B, NfL, pNfLH, UCHL-1, neurogranin	5	Fong et al. (2020), Halaas et al. (2021), Hov et al. (2017), Saller et al. (2019), Szwed et al. (2020)
Biomarkers of neuroinflammation	IFN-γ, IFN-α2, IGF-1, GFAP, CRP, hsCRP, CAR, TNF-α, IL-1ra, IL-1ß, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, MCP-1, MIP-1α, MIP-1β, RAGE, calprotectin, MRP8/14, CHI3L1, neopterin	17	Cape et al. (2014), Cerejeira et al. (2012), Chen et al. (2020), Chen et al. (2019), Chu et al. (2016), Çinar et al. (2014), Dillon et al. (2017), Fong et al. (2020), Hirsch et al. (2016), Katsumi et al. (2020), Kaźmierski et al. (2021), Osse et al. (2012), Peng et al. (2019), Sajjad et al. (2020), Saller et al. (2019), Shen et al. (2016), Szwed et al. (2020)
Biomarkers of dementia	t-tau, p-tau, tau, Aß40, Aß42	5	Fong et al. (2020), Hirsch et al. (2016), Hov et al. (2017), Pan et al. (2019), Saller et al. (2019)
Genetics	miR-210	1	Chen et al. (2020)
Metabolomics, lipidomics and proteomics	PE (40:7e), PE (40:6), PE (38:7e), PC (40:6), PC (33:1), Cer-NS, SM VSTM2B, FA5, Spermidine, Glutamine, Putrescine, AZGP1, CHI3L1/YKL-40	5	Han et al. (2020a,b), Pan et al. (2019), Vasunilashorn et al. (2019), Vasunilashorn et al. (2021)
Others	Creatinine, PLR and PWR, NSP, VILIP-1, BDNF	4	Bakker et al. (2012), Kotfis et al. (2019), Szwed et al. (2020), Wyrobek et al. (2017)

AChE, acetylcholinesterase; BChE, butyrylcholinesterase; Ach, acetylcholine; IDO, indoleamine 2,3-dioxygenase; HVA, homovanillic acid; IFN, human interferon; IGF-I, insulin-like growth factor-1; CRP=C-reactive protein; CAR, C-reactive protein-to-albumin ratio; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; TNF, tumor necrosis factor; S100(B), calcium-binding protein (B); GFAP, glial fibrillary acidic protein; MCP-1, monocyte chemoattractant protein 1; NfL, neurofilament light; pNfLH, phosphorylated axonal neurofilament subunit H; NSE, neuron specific enolase; Aß, amyloid-beta; t-tau, total tau; p-tau, phosphorylated tau; miRNAs, MicroRNAs; UCHL-1, ubiquitin carboxyl-terminal hydrolase L1; PE, phosphatidylethanolamine; PC, phosphatidylcholine; SM, sphingomyelin; Cer-NS, ceramide non-hydroxyfatty acid-sphingosine; VSTM2B, transmembrane domain-containing protein 2B; FA5, coagulation factor V; MIP, macrophage inflammatory protein; RAGE, Receptor for advanced glycation end products; WDC, white blood cell count; PWR, lower platelet-to-white blood cell ratio; PLR, lower platelet-to-lymphocyte ratio; CHI3L1, Chitinase 3-Like 1 glycoprotein (also known as YKL-40 [tyrosine (Y), lysine (K), leucine (L)] with molecular weight of 40); NSP, neuroserpin; VILIP-1, visinin-like protein-1; AZGP1, zinc alpha-2 glycoprotein; MRP, Macrophage inflammatory protein; BDNF=Brain-derived neurotrophic factor.

orthopedics, cardiac surgery, ICU patients…), (3) number and characteristics of patients included (age, sex, delirious/no delirious), (4) method used to diagnose delirium and delirium severity, (5) presence of cognitive impairment and method of assessment, (6) type of biomarker analyzed and levels, (7) method of obtaining the samples, (8) analytical laboratory methodology, and (9) main study findings. In cases in which more than one publication of the same trial existed, only the latest publication with the most complete data was included. Disagreements were settled by consensus.

In the case of studies that included both people younger and older than 65 years and specific data for older adults were included in the publication, we only used data from individual participants ≥65 years. If individual participant data for the subgroup of interest could not be obtained, we included studies if greater than or equal to 80% of the participants were ≥ 65 years.

Endpoints

The main risk markers of delirium are shown in Table 1.

Assessment of study quality

Study quality and risk of bias were assessed independently by two of the authors using the Newcastle-Ottawa scale (NOS), which is designed for assessing common causes of bias in cohort studies. The NOS score ranges from 0 to 9 stars. A quality score was calculated based on three major components: (1) the selection of study groups (0–4 stars), (2) the comparability of study groups (0–2 stars), and (3) ascertainment of the exposure and outcome of interest. Overall, the quality of studies was deemed as poor (0 to 3 stars), fair (4 to 6 stars) or excellent (7 to 9 stars). Disagreement was resolved by discussion and consensus. The summary of assessment of risk of bias and additional comments on study quality are shown in Supplementary material.

Statistical analyses

All analyses were conducted using the DerSimonian-Laird random-effects inverse variance model using STATA software (version 17; StataCorp, College Station, TX, United States). Data were pooled only if biomarkers were reported in at least two studies. We used the odds ratios (OR) as the main effect size for the present study. We converted other estimations (e.g., standardized regression coefficients, standardized mean differences) to OR according to their corresponding formulas. A subgroup analysis according to inflammatory parameters was also included for CRP, TNF-α, and IL-6 data. Heterogeneity across studies was calculated using the inconsistency index (I^2) (Cooper et al., 1994), and Egger's regression intercept test was used to detect small-study effects bias (Egger et al., 1997; Higgins et al., 2003). No

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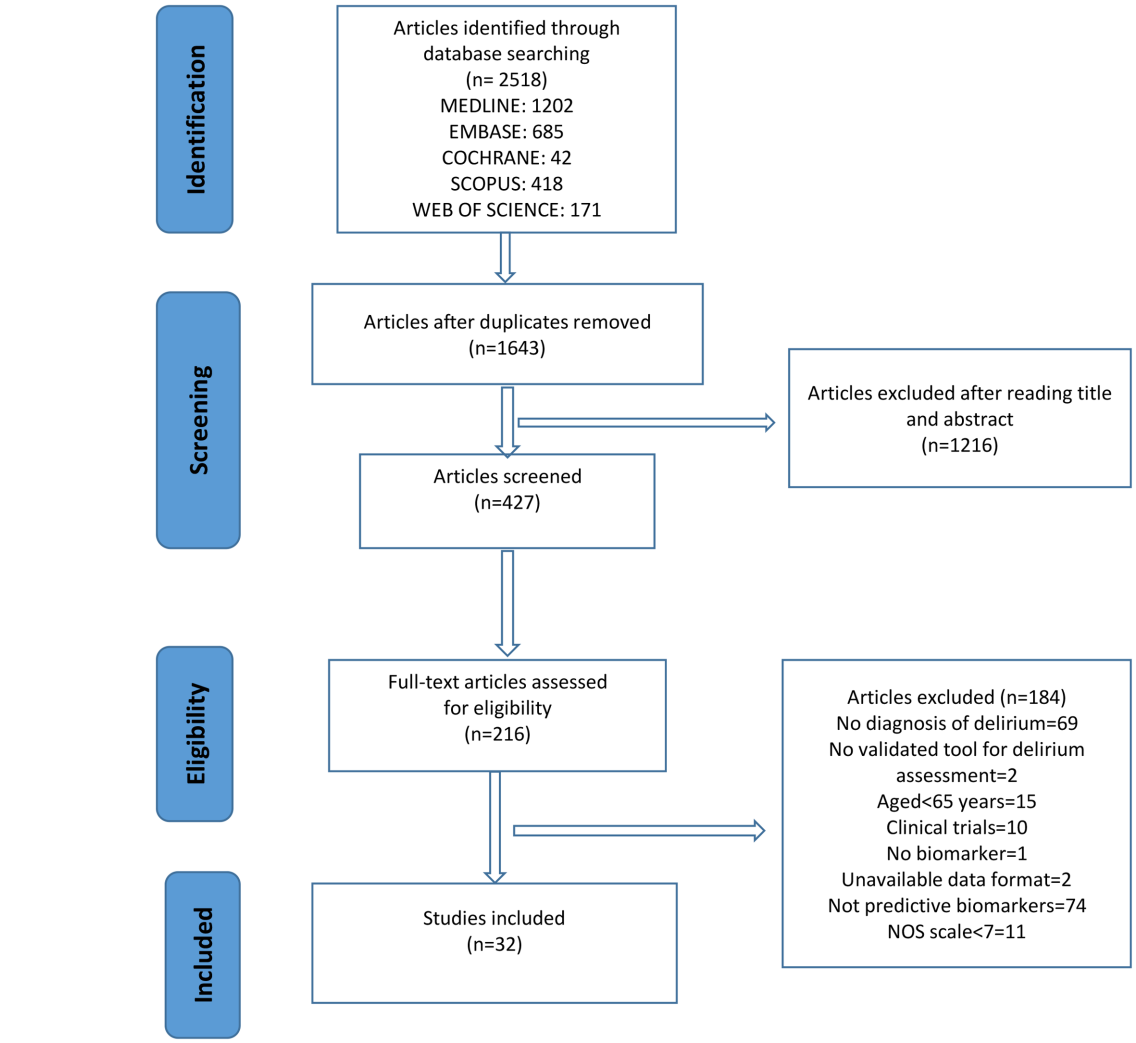

FIGURE 1
Flowchart.

other sub-group analysis was performed due to the limited number of studies.

Results

Results of the literature search

We located 2,518 records, of which 1,644 remained after removing duplicates. After screening the titles and abstracts, 217 studies remained for full text review. Ultimately, 32 articles were included (shown in Figure 1). The major characteristics of the included studies are presented in Supplementary material, and a summary of the main results is shown in Table 2.

Study population

There was diversity between the clinical settings of the studies included in this systematic review. Most of them (30 studies) were carried out in surgical patients: 10 studies in cardiac surgery patients, 14 in orthopaedic surgery patients, 2 in cancer surgery and 4 in other surgery patients. Only 2 studies were conducted among medical inpatients (1 in the hospital ward and the other in the ICU).

The age of the patients included in the studies varied between 67 and 88 years. Seventeen studies included more males than females, while females were more prevalent in 15 studies.

Delirium assessment, delirium severity and delirium subtype

The Confusion Assessment Method was the most commonly used tool for assessing delirium (Inouye et al., 1990; Helfand et al., 2021), followed by the Confusion Assessment Method for Intensive Care Unit (CAM-ICU) (Gusmao-Flores et al., 2012), DSM and Delirium Rating Scale (DRS) (Trzepacz, 1999). Eighteen studies applied the CAM to define delirium, nine studies used the CAM-ICU, three studies assessed delirium with the DSM criteria, one study used the

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TABLE 2 Summary of main results of risk markers of delirium.

Biomarker	Type of biomarker	Number of studies	Results
AChE	Neurotransmitter	2	↓
BChE	Neurotransmitter	2	In one study ↓ but in the other study no association was found
Ach	Neurotransmitter	1	↓
Kynurenine/Tryptophan	Neurotransmitter	1	↑
IDO	Neurotransmitter	1	↑
HVA	Neurotransmitter	1	↑
Estradiol	Hormone	1	↑
Cortisol	Hormone	2	In one study ↑ but in the other study no association was found
Leptin	Hormone	1	↓
S100B	Neuronal damage	1	↑
NfL and pNfLH	Neuronal damage	3	In one study ↑ predicted POD and in 2 studies no association was found
UCHL-1	Neuronal damage	1	No association
Neurogranin	Neuronal damage	1	No association
IFN-γ	Neuroinflammation	2	In one study ↓ and in the other study, no association was found
IFN-α2	Neuroinflammation	1	↓
IGF-1	Neuroinflammation	4	In 2 studies ↓ and in other 2 studies no association was found
GFAP	Neuroinflammation	4	No association
CRP	Neuroinflammation	7	In 5 studies ↑ predicted delirium but in other 2 studies no association was found
hsCRP	Neuroinflammation	1	↑
CAR	Neuroinflammation	1	↑
TNF-α	Neuroinflammation	6	In 1 study ↑ predicted delirium but in other 5 studies no association was found
IL-1ra	Neuroinflammation	1	No association
IL-1ß	Neuroinflammation	3	In 1 study ↑ predicted delirium but in other 2 studies no association was found
IL-2	Neuroinflammation	1	No association
IL-4	Neuroinflammation	1	↓
IL-5	Neuroinflammation	1	↓
IL-6	Neuroinflammation	7	In 4 studies ↑ predicted delirium but in other 3 studies no association was found
IL-8	Neuroinflammation	3	In 2 studies ↑ predicted delirium but in 1 study, no association was found
IL-10	Neuroinflammation	2	No association
IL-12p70	Neuroinflammation	1	↓
MCP-1	Neuroinflammation	2	In 1 study ↑ predicted delirium but in other study no association was found
MIP-1α	Neuroinflammation	1	↑
MIP-1ß	Neuroinflammation	1	↑
RAGE	Neuroinflammation	1	↓
Calprotectin	Neuroinflammation	1	↑
MRP8/14	Neuroinflammation	1	No association
CHI3L1	Neuroinflammation	1	No association
Neopterin	Neuroinflammation	1	↑
t-tau	Dementia	2	No association
p-tau	Dementia	2	In 1 study ↑ but in other study no association was found
tau	Dementia	1	↑
Aß40	Dementia	1	↓
Aß42	Dementia	2	↓

(Continued)

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TABLE 2 (Continued)

Biomarker	Type of biomarker	Number of studies	Results
miR-210	Genetics	1	↑
PE (40:7e)	Lipidomics	1	↓
PE (40:6)	Lipidomics	1	↓
PE (38:7e)	Lipidomics	1	↓
PC (40:6)	Lipidomics	1	↓
PC (33:1)	Lipidomics	1	↓
Cer-NS	Lipidomics	1	↑
SM	Lipidomics	1	↑
VSTM2B	Proteomics	1	↓
FA5	Proteomics	1	↓
Spermidine	Metabolomics	1	↑
Glutamine	Metabolomics	1	↑
Putrescine	Metabolomics	1	↑
AZGP1	Proteomics	1	↓
CHI3L1/YKL-40	Proteomics	1	↑
Creatinine	Other	1	↑
PLR and PWR	Other	1	↓
NSP	Other	1	↑
VILIP-1	Other	1	No association
BDNF	Other	1	↓

↓ = low levels of this biomarker were associated with delirium.
↑ = high levels of this biomarker were associated with delirium.

DRS and DSM criteria and one study used both the CAM and the CAM-ICU.

The severity of delirium was assessed in ten studies. The most commonly used tool was the Memorial Delirium Assessment Scale (MDAS), followed by the Confusion Assessment Method-Severity (CAM-S) and the DRS.

The subtype of delirium was only evaluated in one study, which used the Richmond Agitation-Sedation Scale (RASS).

Sample characteristics

Most of the studies collected blood samples. Cerebrospinal fluid (CSF) was collected in 4 studies and both blood and CSF were collected in 5 studies.

Risk markers of delirium

Neurotransmitters

Serum anticholinergic activity (SAA) was investigated as a risk marker of delirium in three studies. There were mixed results, as 2 studies (Cerejeira et al., 2012; Adam et al., 2020) demonstrated that lower preoperative acetylcholinesterase (AChE) activity was related to postoperative delirium (POD). One study showed that lower preoperative butyrylcholinesterase (BChE) activity was correlated with POD (Cerejeira et al., 2012), but another study did not find an association (Adam et al., 2020). Low levels of acetylcholine (Ach) before surgery were an independent risk factor for POD (Ma et al., 2020). de Jonghe et al. (2012) found that a higher preoperative kynurenine/tryptophan ratio and higher indoleamine 2,3-dioxygenase (IDO) activity were risk markers for POD. Higher postoperative levels of homovanillic acid (HVA) were associated with POD (Osse et al., 2012).

Hormones

Three papers explored a link between serum hormones and incident delirium. One study found that medical inpatients with higher levels of estradiol had an increased risk of developing delirium (Avila-Funes et al., 2015). Two studies investigated cortisol; Ma et al. (2020) found that higher preoperative cortisol levels were an independent risk factor for delirium, but Avila-Funes et al. (2015) did not find any associations between cortisol in medical inpatients and incident delirium. Li et al. (2017) found that low leptin levels at ICU admission were independently associated with delirium.

Neuronal damage biomarkers

Five studies focused on the relationship between biomarkers of neuronal damage and delirium. Hov et al. (2017) found that higher preoperative levels of S100 calcium-binding protein B (S100B) in CSF correlated with POD in patients who also had pathological levels of p-tau. Serum Neurofilament light (NfL) was assessed in two studies. Fong et al. (2020) found that higher preoperative levels were associated with POD and POD severity, but Saller et al. (2019) did not find

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differences. Szwed et al. (2020) evaluated serum phosphorylated axonal neurofilament subunit H (pNfLH), but no association with delirium was found. One study investigated serum ubiquitin carboxyl-terminal hydrolase L1 (UCHL-1) (Fong et al., 2020) and another study examined CSF neurogranin (Halaas et al., 2021), but no differences were reported between these biomarkers and delirium.

Neuroinflammatory markers

Nineteen studies analysed the role of biomarkers of neuroinflammation in delirium. The most investigated biomarkers in this field were C-reactive protein (CRP), tumour necrosis factor (TNF) and interleukin-6 (IL-6). Seven studies explored CRP. Five studies found that higher preoperative CRP in serum correlated with POD (Cerejeira et al., 2012; Shen et al., 2016; Dillon et al., 2017; Vasunilashorn et al., 2019; Chen et al., 2020); however, two studies did not find differences (Çinar et al., 2014; Katsumi et al., 2020). Kaźmierski et al. (2021) found that high levels of high-sensitivity C-reactive protein (hsCRP) in serum were also associated with POD, and Peng et al. (2019) also analysed the C-reactive protein-to-albumin ratio (CAR), showing that higher preoperative levels of serum CAR were an independent risk factor for POD. TNF-α was analysed in six studies; only one found that higher preoperative levels of TNF-α were related to POD but not significantly (Peng et al., 2019); in the rest of the studies, no differences were found (Cerejeira et al., 2012; Çinar et al., 2014; Hirsch et al., 2016; Chen et al., 2020; Sajjad et al., 2020). Seven studies investigated IL-6: four studies found that higher preoperative levels of IL-6 were related to delirium (Hirsch et al., 2016; Shen et al., 2016; Chen et al., 2019; Peng et al., 2019), while three studies found no differences (Cerejeira et al., 2012; Chen et al., 2020; Katsumi et al., 2020).

Other interleukins were explored, such as IL-1ra (Cape et al., 2014), IL-2 (Hirsch et al., 2016) and IL-10 (Hirsch et al., 2016), but they were not found to be related to the incidence of delirium. Cape et al. (2014) found that higher IL-1ß in CSF correlated with POD, but in two other studies, no association was found (Cerejeira et al., 2012; Sajjad et al., 2020). Hirsch et al. (2016) also showed that lower levels of IL-4, IL-5 and IL-12p70 were related to POD. IL-8 was analysed in three studies; in two of them, higher preoperative levels in CSF correlated with POD (Hirsch et al., 2016; Sajjad et al., 2020), but in one study, no differences were found (Cerejeira et al., 2012). Monocyte chemoattractant protein 1 (MCP-1) was analysed in two studies; one of them found that higher serum levels before surgery were associated with delirium (Kaźmierski et al., 2021), but the other one did not find any difference (Hirsch et al., 2016). Hirsch et al. (2016) also studied macrophage inflammatory protein (MIP), macrophage inflammatory protein (MRP), receptor for advanced glycation end products (RAGE) and calprotectin and found that POD was related to higher preoperative levels of MIP-1α MIP-1ß and calprotectin but not RAGE or MRP8/14. Preoperative chitinase 3-like 1 glycoprotein (CHI3L1) was evaluated in one study, but no association was found with delirium (Katsumi et al., 2020).

Human interferon-γ (IFN-γ) was investigated in two studies; one study found that lower preoperative IFN-γ in plasma was related to POD (Hirsch et al., 2016), but the other one did not find any differences in CSF and blood (Cape et al., 2014). Hirsch et al., 2016 also found that lower preoperative human interferon-α2 (IFN-α2) in CSF was implicated in the development of POD. Four studies explored insulin-like growth factor-1 (IGF-1). Two studies found that lower preoperative levels of IGF-1 were associated with POD (Çinar et al., 2014; Shen et al., 2016), but the other two studies did not find any differences (Cape et al., 2014; Chu et al., 2016). Glial fibrillary acidic protein (GFAP) was also investigated in 4 studies, but no association was found in any of them (Cape et al., 2014; Saller et al., 2019; Fong et al., 2020; Szwed et al., 2020). Only IL-6, TNF-α and CRP could be examined *via* meta-analysis, as each biomarker was investigated in 6 or more studies.

The major findings of this meta-analysis are presented in Figure 2. Overall, pooled analysis showed a significant increase in some serum biomarkers (i.e., CRP, TNF-α, and IL-6) of patients who developed delirium (OR = 1.88, 95% CI 1.01 to 1.637; I^2 = 76.75%). Egger's test indicated no small-study effects bias for pooled analysis (p = 0.178). Four studies could be included in the meta-analysis of IL-6; the results showed a significant increase in this biomarker in serum (OR = 1.88, 95% CI 1.01 to 1.637) in patients who developed delirium, with high heterogeneity (τ^2 = 0.31, I^2 = 76.75%). Four studies were included in the meta-analysis of CRP, but Dillon et al. (2017) evaluated three different cohorts with three independent analyses, so we included all of them in this meta-analysis. Serum preoperative CRP was significantly high in patients with later POD (OR = 1.75; 95% CI 1.04 to 2.93), with high heterogeneity (τ^2 = 0.29, I^2 = 72.92%).

Biomarkers of dementia

Five studies investigated the relationship between biomarkers of dementia and delirium. Two studies analysed total tau (t-tau), but no differences were found between this biomarker and delirium in either blood (Fong et al., 2020) or CSF (Pan et al., 2019). Two studies evaluated phosphorylated tau (p-tau); in one study, higher CSF p-tau correlated with POD (Hov et al., 2017), but in another study, no differences were found between CSF p-tau and delirium (Pan et al., 2019). However, Saller et al. (2019) found that higher preoperative tau in serum correlated with POD. Hirsch et al. (2016) showed that lower preoperative Aβ40 in plasma predicted POD. Aß42 was investigated in two studies; one found that lower preoperative Aß42 in plasma correlated with incident POD (Hirsch et al., 2016), and the other found that lower preoperative Aß42 in CSF predicted POD (Pan et al., 2019).

Genetics

Only one study evaluated the implication of genetics in the development of delirium (Chen et al., 2020) showing that higher preoperative expression of miR-210 in blood was a predictor of POD.

Metabolomics, lipidomics and proteomics

Five studies explored the role of -omics approaches in delirium. Han et al., showed that CSF lipidomics and metabolomics pointed out that phosphatidylethanolamine (PE), phosphatydilcholine (PC), sphingomyelin (SM) and ceramide non-hydroxyfatty acid-sphingosine (Cer-NS) were related with delirium (Han et al., 2020b). In this study, lower preoperative levels of PE (40:7e), PE (40:6), PE (38:7e), PC (40:6) and PC (33:1) but higher preoperative levels of CER-NS and SM were associated with incident POD. A CSF proteomic study found that lower preoperative levels of transmembrane domain-containing protein 2B (VSTM2B) and coagulation factor V (FA5) were positively correlated with delirium severity (Han et al., 2020a). Vasunilashorn et al., showed that lower preoperative serum levels of zinc alpha-2 glycoprotein (AZGP1) were associated with POD (Vasunilashorn et al., 2019). Moreover, a serum proteomic study found that higher

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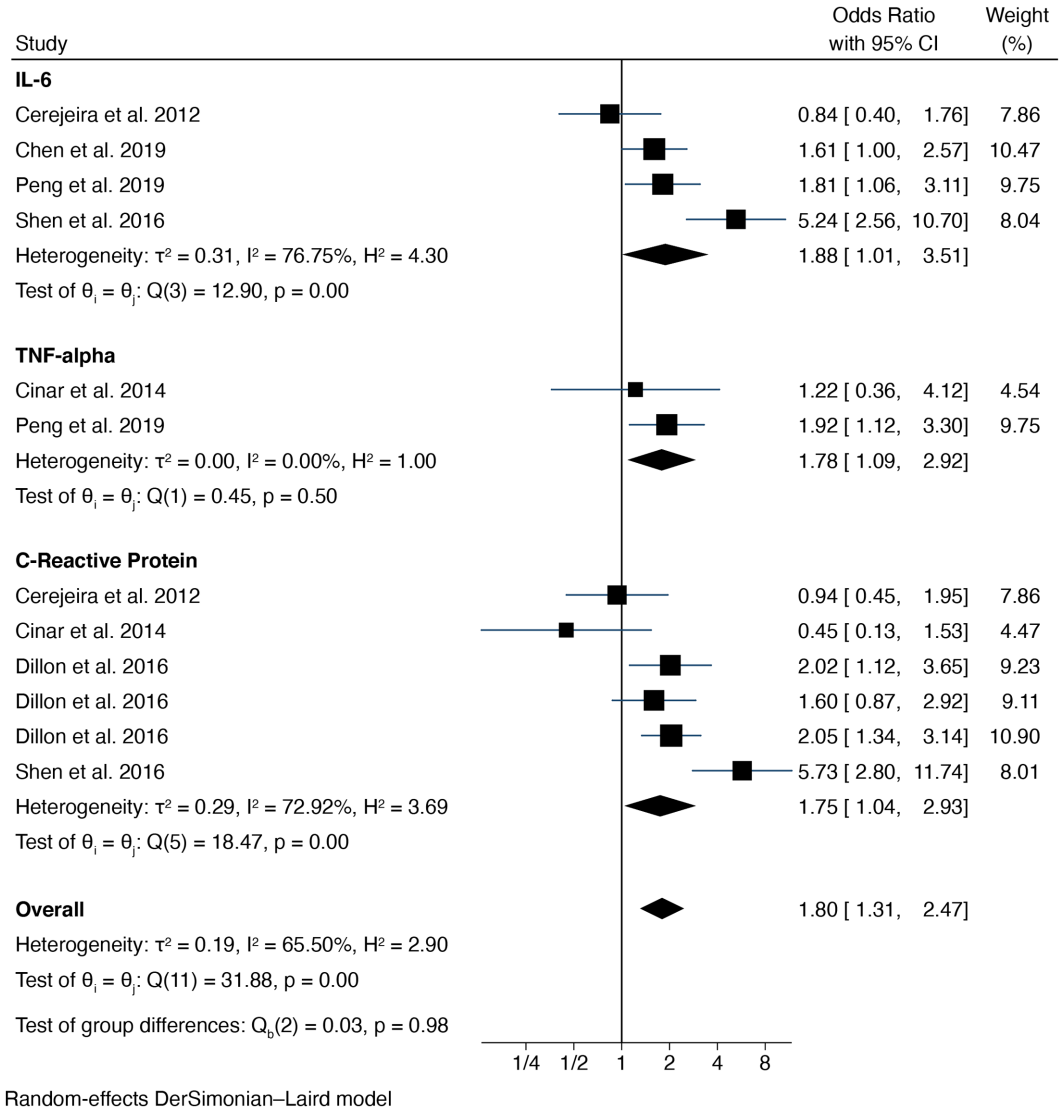

FIGURE 2
Forest plot.

preoperative chitinase 3-like 1 glycoprotein (CHI3LI/KYL-40) were associated with POD (Vasunilashorn et al., 2021). Pan et al., showed that higher preoperative levels of spermidine, glutamine and putrescine in CSF were related with incident delirium (Pan et al., 2019).

Others

Bakker et al., showed that higher levels of serum creatinine prior to surgery were an independent predictor of POD (Bakker et al., 2012). Kotfis et al., found that lower preoperative levels of platelet-to-white blood cell ratio (PWR) and lower platelet-to-lymphocyte ratio (PLR) were associated with POD in serum (Kotfis et al., 2019). Szwed et al., investigated the relationship between neuroserpin (NSP) or visinin-like protein-1 (VILIP-1) and delirium (Szwed et al., 2020) in serum. Higher end of surgery to baseline ratio of NSP predicted the occurrence of POD but no differences were found between VILIP-1 and POD. Wyrobeck et al., showed that lower levels of serum Brain-derived neurotrophic factor (BDNF) during surgery were associated with delirium (Wyrobek et al., 2017).

Discussion

To the best of our knowledge, this is the first review that focuses on predictive biomarkers of delirium in older patients, considering all clinical settings and all types of biological fluids with high-quality studies. The multi-etiological nature of delirium is likely to be reflected in the wide range of biomarkers identified by our study.

Ach

The neurotransmitter hypothesis suggests that disturbances in neurotransmitter pathways can lead to delirium (Maldonado, 2013). Although precursors of serotonin (tryptophan, phenylalanine and tyrosine), dopamine and noradrenaline may be implicated in the development of delirium, anticholinergic deficiency has been directly related to its pathophysiology (Wang and Shen, 2018). Ach is involved in sleep regulation, cognition and attention. It is well known that an

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impairment in cholinergic activity is associated with cognitive and attentional changes; current literature also suggests that an impairment in cholinergic activity is associated with delirium (Pasina et al., 2019; Vondeling et al., 2020; Oudewortel et al., 2021; Lisibach et al., 2022). In addition, anticholinergic effects are common among several drugs, and a previous study found that increased anticholinergic burden increases delirium risk (Egberts et al., 2021).

Cortisol

A disruption of the hypothalamic–pituitary-axis with an increase in cortisol levels has been related to a higher risk of dementia (Ouanes and Popp, 2019) and delirium, particularly in critically ill patients (Mattar et al., 2012; Michels et al., 2019), but evidence is not conclusive. Other hormones, such as estradiol or leptin, may have a role in delirium pathophysiology, but additional research is needed to confirm this hypothesis.

S100B and NfL

Markers of neuronal damage, such as S100B and NfL (related to disturbances in astrocytic integrity), have been associated with delirium (Mietani et al., 2019, 2021), but these markers of brain injury could be associated with established, and not necessarily incident, delirium (Khan et al., 2011). However, higher levels have been associated with higher severity and worse prognosis of delirium (Gao et al., 2021; Narayanan et al., 2021; Page et al., 2022).

Tau and Aß

It is well known that cognitive impairment is a clinical risk factor for delirium (Fong et al., 2015, 2017, 2019; Racine et al., 2017). Nevertheless, few studies have been carried out in this field, pointing out that typical markers of dementia, such as tau or Aβ, are associated with delirium development (Wang et al., 2021, 2022).

Genetics

Another pathway that yields promising results is genetic research in delirium (Van Munster et al., 2009). Although studies in this field are scarce, genetic studies could be interesting translational tools for elucidating the pathophysiology of this syndrome. In addition, genetics are not influenced by the causal combination of predisposing and precipitating factors that affects delirium, so they can offer a more reliable value compared to other biomarkers (Sepulveda et al., 2021).

Proteomics and metabolomics

Research in proteomics and metabolomics aims to provide a protein or metabolic profile to contribute to delirium diagnosis and prevention (Sfera et al., 2015). There are few and heterogeneous studies in this field due to the technological difficulty associated with mapping the whole molecular landscape of biofluids. However, omics technologies are complementary to the genetic toolbox, detecting, identifying and quantifying alternative molecular biomarkers necessary to understand the dynamics and interactions that occur during delirium development.

Although acetylcholine deficiency, hormonal influence, markers of dementia and biochemical changes observed through proteomics and metabolomics may play an important role in predicting delirium, neuroinflammation theory seems to be the most relevant pathway, at least in the population of this review (most of the studies were carried out in older surgical populations). These findings are consistent with previous reviews that found an association between delirium and neuroinflammation biomarkers (Hall et al., 2018; Liu et al., 2018; Adamis et al., 2021; Dunne et al., 2021; Noah et al., 2021). This hypothesis suggests that peripheral inflammation due to surgery, trauma or infection leads to the activation of the proinflammatory cascade and suppression of anti-inflammatory markers. These stimuli trigger tissue macrophage and blood monocyte activation and secretion of inflammatory mediators such as IL-1, IL-1ß, IL-6, TNF-α and prostaglandin E_2 (PGE_2). These proinflammatory molecules penetrate the BBB, producing cerebral injury through the activation of microglia that causes brain dysfunction and delirium (Wilson et al., 2020). Interestingly, we conducted a meta-analysis with IL-6, TNF-α, and CRP, which were the most investigated biomarkers, and we found that they were statistically significant predictors of delirium.

Il-6

IL-6 is a cytokine involved in the immune response and has a notorious role in adult neurogenesis, the process of creating new neurons and glial cells from neural stem cells (oligodendrogliogenesis and astrogliogenesis) in the central nervous system (CNS) (Kang et al., 2020). IL-6 expression is involved in the synthesis of beta-amyloid precursor protein being altered in the brains of Alzheimer's disease (AD) patients and it is also upregulated whenever neuroinflammation is expected, such as infection or injury (Erta et al., 2012). Noah et al. (2021) found that higher preoperative IL-6 was associated with postoperative delirium. Another meta-analysis performed among surgical patients also found this association (Liu et al., 2018; Adamis et al., 2021). Dunne et al. (2021) showed that early manifestation of systemic inflammation with elevated levels of IL-6 leads to the onset of delirium. However, Hall et al. (2018) did not find a significant correlation between IL-6 measured in CSF and delirium.

TNF-α

TNF-α is a proinflammatory cytokine (Idriss and Naismith, 2000) that has been associated with more rapid cognitive decline in patients with AD (Holmes et al., 2009). Analysis of the same cohort showed that elevated systemic TNF-α was associated with an increase in psychobehavioural alterations such as apathy, anxiety, depression and agitation, suggesting that increased systemic TNF-α may also have a role in hippocampal neurodegeneration (Holmes et al., 2011). The association of TNF-α and delirium is unclear. While some studies showed a positive correlation between TNF-α and delirium and our study revealed a significant association, previous meta-analyses by Liu et al. (2018) and Noah et al. (2021) found that preoperative TNF-α was significantly higher in the POD group in univariate analysis but not in multivariate analysis.

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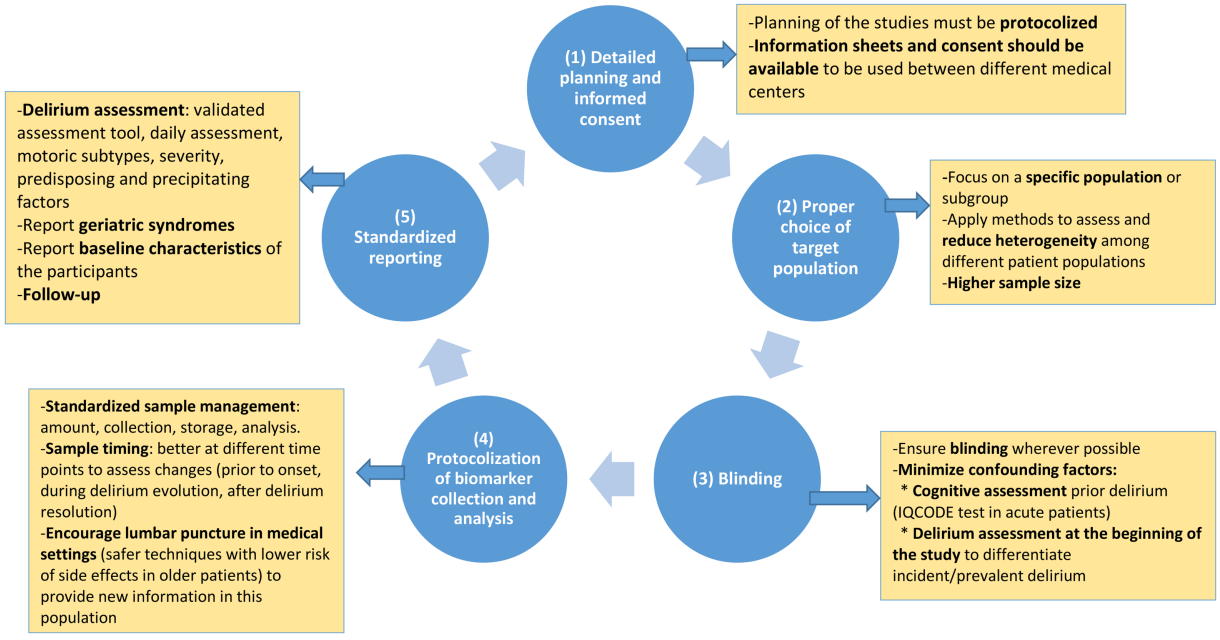

FIGURE 3
Recommendations for future research in delirium biomarkers.

CRP

CRP is a pentameric protein whose circulating concentrations rise in response to inflammation (Pathak and Agrawal, 2019). It is an acute-phase protein of hepatic origin that increases following IL-6 secretion (Sproston and Ashworth, 2018). In the same way that IL-6 is altered in patients with cognitive impairment, a recent review found that CRP is also involved in this mechanism (Qiao et al., 2022). Moreover, several meta-analyses have shown that higher preoperative serum CRP levels are significantly associated with later POD (Liu et al., 2018; Adamis et al., 2021; Dunne et al., 2021; Noah et al., 2021).

Strengths and limitations

One of the main limitations of the studies included in this systematic review and meta-analysis is their small sample size and the lack of consistent terminology about delirium which has negatively affected the research (different terms such as organic brain syndrome, encephalopathy or acute brain failure can be misleading). Another important drawback is the lack of diversity in patient populations. Most of the studies were carried out in surgical populations, so their results may not be extrapolated to other clinical scenarios (medical inpatients, critically ill patients, etc.). On the other hand, there was little information about geriatric syndromes (frailty, malnutrition, polypharmacy) that may be directly involved not only in the development of delirium but also in the delirium characteristics (severity, subtype, duration, etc.). In addition, it is important to note that the methodological heterogeneity observed across studies might have an impact on the overall outcomes; therefore, the information should be considered with caution when drawing conclusions.

Importantly, this study provides several strengths. Firstly, there was no restriction by year of publication, and only high-quality studies (7 to 9 stars in NOS) with formal delirium diagnosis (DSM criteria, ICD criteria or a tool based on these criteria) with a lower risk of bias were included. Secondly, only studies on risk markers for delirium were included, excluding studies on disease markers or end-products of delirium. Thirdly, we also compared the preoperative state of patients who had not yet developed delirium in the studies that had more than one sample collected at different time points, focusing on predictive biomarkers of delirium and minimizing the risk of bias.

Challenges and implications for future research

These findings could contribute to the implementation of the International Drive to Illuminate Delirium (IDID) initiative (Khachaturian et al., 2020), providing a new prevention strategy for delirium and, subsequently, helping to preserve cognitive function. Although biomarkers could be an instrument to predict delirium, there are some unanswered questions. Blood-based biomarkers are little invasive, fast and reproducible, giving a quantitative value, and could be easy to measure in routine analysis (accessible in hands of surgeons, primary care physicians or other clinics). However, the validation of these biomarkers in terms of accuracy, sensitivity and specificity remains unknown because many of these inflammatory mediators are elevated in patients with sepsis, trauma or surgery and not only in those who develop delirium. In addition, their affordability and cost-efficiency are also unexplored.

Based on the limitations of the studies included in this systematic review and meta-analysis, we identified five major action areas to advance this research, designing better quality studies: (1) detailed planning and informed consent; (2) proper choice of target population; (3) blinding; (4) protocolization of biomarker collection and analysis; and (5) standardized reporting, which are summarized in Figure 3.

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and could be useful to improve the "Core Outcome Set" (COMET) in the field of delirium (Williamson et al., 2017).

Conclusion

The relevance of delirium in older patients, both for its long- and short-term adverse consequences, provides a compelling reason to investigate its pathophysiology to prevent its appearance and improve the approach.

Despite the recent surge in studies on delirium biomarkers, there is not consistent evidence in the obtained results given the great heterogeneity that reflects the complexity of its pathophysiological mechanisms. Our data identified a significant association between biomarkers of neuroinflammation, such as CRP, IL-6, or TNF-α, and the risk of delirium, but further research is needed to standardize the methodology, improve scientific evidence and translate the current knowledge into pragmatic tools for routine clinical practice in the field of delirium.

Author contributions

LL-V, BC-V, and NM-V: conception and design of the work. LL-V and BC-V: acquisition of data. AG-H: analysis. AG-H and LL-V: interpretation of data. LL-V, NM-V, and RR-O: drafting of manuscript. JF-I, ES, FZ-F, MS, ÁM-V, and MI: critical revision. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1174644/full#supplementary-material

References

Abelha, F. J., Luís, C., Veiga, D., Parente, D., Fernandes, V., Santos, P., et al. (2013). Utcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery. *Crit. Care* 17:R257. doi: 10.1186/cc13084

Adam, E. H., Haas, V., Lindau, S., Zacharowski, K., and Scheller, B. (2020). Cholinesterase alterations in delirium after cardiosurgery: a German monocentric prospective study. *BMJ Open* 10:e031212. doi: 10.1136/bmjopen-2019-031212

Adamis, D., van Gool, W. A., and Eikelenboom, P. (2021). Consistent patterns in the inconsistent associations of insulin-like growth factor 1 (IGF-1), C-reactive protein (C-RP) and interleukin 6 (IL-6) levels with delirium in surgical populations. A systematic review and meta-analysis. *Arch. Gerontol. Geriatr.* 97:104518. doi: 10.1016/j.archger.2021.104518

Altman, M. T., Knauert, M. P., Murphy, T. E., Ahasic, A. M., Chauhan, Z., and Pisani, M. A. (2018). Association of intensive care unit delirium with sleep disturbance and functional disability after critical illness: an observational cohort study. *Ann. Intensive Care* 8:63. doi: 10.1186/s13613-018-0408-4

Aronson, J. K., and Ferner, R. E. (2017). Biomarkers—a general review. *Curr. Protoc. Pharmacol.* 76, 9.23.1–9.23.17. doi: 10.1002/cpph.19

Avila-Funes, J. A., Ledesma-Heyer, J. P., Navarrete-Reyes, A. P., Chavira-Ramírez, R., Boeck-Quirasco, L., and Aguilar-Navarro, S. (2015). Association between high serum estradiol levels and delirium among hospitalized elderly women. *Rev. Investig. Clin. organo del Hosp. Enfermedades la Nutr.* 67, 20–24.

Bakker, R. C., Osse, R. J., Tulen, J. H. M., Kappetein, A. P., and Bogers, A. J. J. C. (2012). Preoperative and operative predictors of delirium after cardiac surgery in elderly patients. *Eur. J. cardio-thoracic Surg. Off. J. Eur. Assoc. Cardio-thoracic Surg.* 41, 544–549. doi: 10.1093/ejcts/ezr031

Cape, E., Hall, R. J., van Munster, B. C., de Vries, A., Howie, S. E. M., Pearson, A., et al. (2014). Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1β in delirium after hip fracture. *J. Psychosom. Res.* 77, 219–225. doi: 10.1016/j.jpsychores.2014.06.014

Cavallari, M., Dai, W., Guttmann, C. R. G., Meier, D. S., Ngo, L. H., Hshieh, T. T., et al. (2016). Neural substrates of vulnerability to postsurgical delirium as revealed by presurgical diffusion MRI. *Brain* 139, 1282–1294. doi: 10.1093/brain/aww010

Cerejeira, J., Nogueira, V., Luís, P., Vaz-Serra, A., and Mukaetova-Ladinska, E. B. (2012). The cholinergic system and inflammation: common pathways in delirium pathophysiology. *J. Am. Geriatr. Soc.* 60, 669–675. doi: 10.1111/j.1532-5415.2011.03883.x

Chen, Y., Lu, S., Wu, Y., Shen, Y., Zhao, H., Ding, S., et al. (2019). Change in serum level of interleukin 6 and delirium after coronary artery bypass graft. *Am. J. Crit. care an Off. Publ. Am. Assoc. Crit. Nurses* 28, 462–470. doi: 10.4037/ajcc2019976

Chen, Y., Zheng, J., and Chen, J. (2020). Preoperative circulating MiR-210, a risk factor for postoperative delirium among elderly patients with gastric Cancer undergoing curative resection. *Curr. Pharm. Des.* 26, 5213–5219. doi: 10.2174/1381612826666200617163857

Choi, S. H., Lee, H., Chung, T. S., Park, K. M., Jung, Y. C., Kim, S. I., et al. (2012). Neural network functional connectivity during and after an episode of delirium. *Am. J. Psychiatry* 169, 498–507. doi: 10.1176/appi.ajp.2012.11060976

Chu, C.-L., Liang, C.-K., Lin, Y.-T., Chow, P. C., Pan, C.-C., Chou, M.-Y., et al. (2011). Biomarkers of delirium: well evidenced or not? *J. Clin. Gerontol. Geriatr.* 2, 100–104. doi: 10.1016/j.jcgg.2011.11.005

Chu, C.-S., Liang, C.-K., Chou, M.-Y., Lin, Y.-T., Hsu, C.-J., Chu, C.-L., et al. (2016). Lack of association between pre-operative insulin-like growth Factor-1 and the risk of post-operative delirium in elderly Chinese patients. *Psychiatry Investig.* 13, 327–332. doi: 10.4306/pi.2016.13.3.327

Çinar, M. A., Balikçi, A., Sertoğlu, E., Mehmet, A. K., Serdar, M. A., and Özmenler, K. N. (2014). Role of CRP, TNF-a, and IGF-1 in delirium pathophysiology. *Noro Psikiyatr. Ars.* 51, 376–382. doi: 10.5152/npa.2014.6999

Cooper, H., Hedges, L. V., Valentine, J. C., and Rosenthal, R. E. (1994). *Parametric Measures of Effect Size. The Handbook of Research synthesis.* New York, NY: Russell Sage Foundation.

de Jonghe, A., van Munster, B. C., Fekkes, D., van Oosten, H. E., and de Rooij, S. E. (2012). The tryptophan depletion theory in delirium: not confirmed in elderly hip fracture patients. *Psychosomatics* 53, 236–243. doi: 10.1016/j.psym.2011.09.009

Dharmarajan, K., Swami, S., Gou, R. Y., Jones, R. N., and Inouye, S. K. (2017). Pathway from delirium to death: potential in-hospital mediators of excess mortality. *J. Am. Geriatr. Soc.* 65, 1026–1033. doi: 10.1111/jgs.14743

Dillon, S. T., Vasunilashorn, S. M., Ngo, L., Otu, H. H., Inouye, S. K., Jones, R. N., et al. (2017). Higher C-reactive protein levels predict postoperative delirium in older patients undergoing major elective surgery: a longitudinal nested case-control study. *Biol. Psychiatry* 81, 145–153. doi: 10.1016/j.biopsych.2016.03.2098

Dunne, S. S., Coffey, J. C., Konje, S., Gasior, S., Clancy, C. C., Gulati, G., et al. (2021). Biomarkers in delirium: a systematic review. *J. Psychosom. Res.* 147:110530. doi: 10.1016/j.jpsychores.2021.110530

Egberts, A., Moreno-Gonzalez, R., Alan, H., Ziere, G., and Mattace-Raso, F. U. S. (2021). Anticholinergic drug burden and delirium: a systematic review. *J. Am. Med. Dir. Assoc.* 22, 65–73.e4. doi: 10.1016/j.jamda.2020.04.019

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Egger, M., Smith, G. D., Schneider, M., and Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *Br. Med. J.* 315, 629–634. doi: 10.1136/bmj.315.7109.629

Erta, M., Quintana, A., and Hidalgo, J. (2012). Interleukin-6, a major cytokine in the central nervous system. *Int. J. Biol. Sci.* 8, 1254–1266. doi: 10.7150/ijbs.4679

Fong, T. G., Davis, D., Growdon, M. E., Albuquerque, A., and Inouye, S. K. (2015). The interface between delirium and dementia in elderly adults. *Lancet Neurol.* 14, 823–832. doi: 10.1016/S1474-4422(15)00101-5

Fong, T. G., Inouye, S. K., and Jones, R. N. (2017). Delirium, dementia, and decline. *JAMA Psychiat.* 74, 212–213. doi: 10.1001/jamapsychiatry.2016.3812

Fong, T. G., Vasunilashorn, S. M., Libermann, T., Marcantonio, E. R., and Inouye, S. K. (2019). Delirium and Alzheimer disease: a proposed model for shared pathophysiology. *Int. J. Geriatr. Psychiatry* 34, 781–789. doi: 10.1002/gps.5088

Fong, T. G., Vasunilashorn, S. M., Ngo, L., Libermann, T. A., Dillon, S. T., Schmitt, E. M., et al. (2020). Association of Plasma Neurofilament Light with postoperative delirium. *Ann. Neurol.* 88, 984–994. doi: 10.1002/ana.25889

Gao, Y., Duan, J., Ji, H., and Lu, W. (2021). Levels of S100 calcium binding protein B (S100B), neuron-specific enolase (NSE), and cyclophilin a (CypA) in the serum of patients with severe craniocerebral injury and multiple injuries combined with delirium transferred from the ICU and their prognosti. *Ann. Palliat. Med.* 10, 3371–3378. doi: 10.21037/apm-21-424

Gibb, K., Seeley, A., Quinn, T., Siddiqi, N., Shenkin, S., Rockwood, K., et al. (2020). The consistent burden in published estimates of delirium occurrence in medical inpatients over four decades: a systematic review and meta-analysis study. *Age Ageing* 49, 352–360. doi: 10.1093/ageing/afaa040

Gusmao-Flores, D., Figueira Salluh, J. I., Chalhub, R. T., and Quarantini, L. C. (2012). The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. *Crit. Care* 16, R115–R111. doi: 10.1186/cc11407

Halaas, N. B., Zetterberg, H., Idland, A.-V., Knapskog, A.-B., Watne, L. O., and Blennow, K. (2021). Cerebrospinal fluid concentration of Neurogranin in hip fracture patients with delirium. *J. Alzheimers Dis.* 81, 667–677. doi: 10.3233/JAD-201341

Hall, R. J., Shenkin, S. D., and Maclullich, A. M. J. (2011). A systematic literature review of cerebrospinal fluid biomarkers in delirium. *Dement. Geriatr. Cogn. Disord.* 32, 79–93. doi: 10.1159/000330757

Hall, R. J., Watne, L. O., Cunningham, E., Zetterberg, H., Shenkin, S. D., Wyller, T. B., et al. (2018). CSF biomarkers in delirium: a systematic review. *Int. J. Geriatr. Psychiatry* 33, 1479–1500. doi: 10.1002/gps.4720

Han, Y., Chen, W., Song, Y., Yuan, Y., Li, Z., Zhou, Y., et al. (2020a). Proteomic analysis of preoperative CSF reveals risk biomarkers of postoperative delirium. *Front. Psych.* 11:170. doi: 10.3389/fpsyt.2020.00170

Han, Y., Zhang, W., Liu, J., Song, Y., Liu, T., Li, Z., et al. (2020b). Metabolomic and Lipidomic profiling of preoperative CSF in elderly hip fracture patients with postoperative delirium. *Front. Aging Neurosci.* 12:570210. doi: 10.3389/fnagi.2020.570210

Hayhurst, C. J., Marra, A., Han, J. H., Patel, M. B., Brummel, N. E., Thompson, J. L., et al. (2020). Association of Hypoactive and Hyperactive Delirium with cognitive function after critical illness. *Crit. Care Med.* 48, E480–E488. doi: 10.1097/CCM.0000000000004313

Helfand, B. K. I., D'Aquila, M. L., Tabloski, P., Erickson, K., Yue, J., Fong, T. G., et al. (2021). Detecting delirium: a systematic review of identification instruments for non-ICU settings. *J. Am. Geriatr. Soc.* 69, 547–555. doi: 10.1111/jgs.16879

Higgins, J. P., Thompson, S. G., Deeks, J. J., and Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *Br. Med. J.* 327, 557–560. doi: 10.1136/bmj.315.7109.629

Hirsch, J., Vacas, S., Terrando, N., Yuan, M., Sands, L. P., Kramer, J., et al. (2016). Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. *J. Neuroinflammation* 13:211. doi: 10.1186/s12974-016-0681-9

Holmes, C., Cunningham, C., and Perry, V. H. (2009). Systemic inflammation and disease progression in Alzheimer disease. *Neurology* 73, 768–774. doi: 10.1212/WNL.0b013e3181d5df7f

Holmes, C., Cunningham, C., Zotova, E., Culliford, D., and Perry, V. H. (2011). Proinflammatory cytokines, sickness behavior, and Alzheimer disease. *Neurology* 77, 212–218. doi: 10.1212/WNL.0b013e318225ae07

Hov, K. R., Bolstad, N., Idland, A.-V., Zetterberg, H., Blennow, K., Chaudhry, F. A., et al. (2017). Cerebrospinal fluid S100B and Alzheimer's disease biomarkers in hip fracture patients with delirium. *Dement. Geriatr. Cogn. Dis. Extra* 7, 374–385. doi: 10.1159/000481853

Ida, M., Takeshita, Y., and Kawaguchi, M. (2020). Preoperative serum biomarkers in the prediction of postoperative delirium following abdominal surgery. *Geriatr Gerontol Int* 20, 1208–1212. doi: 10.1111/ggi.14066

Idriss, H. T., and Naismith, J. H. (2000). TNFα and the TNF receptor superfamily: structure-function relationship(s). *Microsc. Res. Tech.* 50, 184–195. doi: 10.1002/1097-0029(20000801)50:3<184::AID-JEMT2>3.0.CO;2-H

Inouye, S. K., Van Dyck, C. H., Alessi, C. A., Balkin, S., Siegal, A. P., and Horwitz, R. I. (1990). Clarifying confusion: the confusion assessment method: a new method for detection of delirium. *Ann. Intern. Med.* 113, 941–948. doi: 10.7326/0003-4819-113-12-941

Inouye, S. K., Westendorp, R. G. J., Saczynski, J. S., Naeije, G., and Pepersack, T. (2014). Delirium in elderly people. *Lancet* 383, 911–922. doi: 10.1016/S0140-6736(13)60688-1

Israni, J., Lesser, A., Kent, T., and Ko, K. (2018). Delirium as a predictor of mortality in US Medicare beneficiaries discharged from the emergency department: a national claims-level analysis up to 12 months. *BMJ Open* 8, 1–7. doi: 10.1136/bmjopen-2017-021258

Kang, S., Narazaki, M., Metwally, H., and Kishimoto, T. (2020). Historical overview of the interleukin-6 family cytokine. *J. Exp. Med.* 217, 1–10. doi: 10.1084/jem.20190347

Katsumi, Y., Racine, A. M., Torrado-Carvajal, A., Loggia, M. L., Hooker, J. M., Greve, D. N., et al. (2020). The role of inflammation after surgery for elders (RISE) study: examination of [11C]PBR28 binding and exploration of its link to post-operative delirium. *NeuroImage Clin.* 27:102346. doi: 10.1016/j.nicl.2020.102346

Kaźmierski, J., Miler, P., Pawlak, A., Jerczyńska, H., Woźniak, J., Frankowska, E., et al. (2021). Elevated monocyte Chemoattractant Protein-1 as the independent risk factor of delirium after cardiac surgery. A prospective cohort study. *J. Clin. Med.* 10:1587. doi: 10.3390/jcm10081587

Khachaturian, A. S., Hayden, K. M., Devlin, J. W., Fleisher, L. A., Lock, S. L., Cunningham, C., et al. (2020). International drive to illuminate delirium: a developing public health blueprint for action. *Alzheimers Dement.* 16, 711–725. doi: 10.1002/alz.12075

Khan, B. A., Zawahiri, M., Campbell, N. L., and Boustani, M. A. (2011). Biomarkers for deliriuma - A review. *J. Am. Geriatr. Soc.* 59, S256–S261. doi: 10.1111/j.1532-5415.2011.03702.x

Kotfis, K., Ślozowska, J., Safranow, K., Szylińska, A., and Listewnik, M. (2019). The practical use of white cell inflammatory biomarkers in prediction of postoperative delirium after cardiac surgery. *Brain Sci.* 9:308. doi: 10.3390/brainsci9110308

Krewulak, K. D., Stelfox, H. T., Leigh, J. P., Wesley Ely, E., and Fiest, K. M. (2018). Incidence and prevalence of delirium subtypes in an adult ICU: a systematic review and meta-analysis. *Crit. Care Med.* 46, 2029–2035. doi: 10.1097/CCM.0000000000003402

Li, G., Lei, X., Ai, C., Li, T., and Chen, Z. (2017). Low plasma leptin level at admission predicts delirium in critically ill patients: a prospective cohort study. *Peptides* 93, 27–32. doi: 10.1016/j.peptides.2017.05.002

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., et al. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 6:e1000100. doi: 10.1371/journal.pmed.1000100

Lisibach, A., Gallucci, G., Benelli, V., Kälin, R., Schulthess, S., Beeler, P. E., et al. (2022). Evaluation of the association of anticholinergic burden and delirium in older hospitalised patients – a cohort study comparing 19 anticholinergic burden scales. *Br. J. Clin. Pharmacol.* 88, 4915–4927. doi: 10.1111/bcp.15432

Liu, X., Yu, Y., and Zhu, S. (2018). Inflammatory markers in postoperativedelirium (POD) and cognitive dysfunction (POCD): a meta-analysis of observational studies. *PLoS One* 13:e0209284. doi: 10.1371/journal.pone.0195659

Ma, J. R., Fan, M. M., and Wang, Z. S. (2020). Age, preoperative higher serum cortisol levels, and lower serum acetylcholine levels predict delirium after percutaneous coronary intervention in acute coronary syndrome patients accompanied with renal dysfunction. *Indian J. Psychiatry* 62, 172–177. doi: 10.4103/psychiatry.IndianJPsychiatry_37_19

Maldonado, J. R. (2013). Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am. J. Geriatr. Psychiatry* 21, 1190–1222. doi: 10.1016/j.jagp.2013.09.005

Martínez-Velilla, N., Herrero, A. C., Cadore, E. L., Sáez de Asteasu, M. L., and Izquierdo, M. (2016). Iatrogenic nosocomial disability diagnosis and prevention. *J. Am. Med. Dir. Assoc.* 17, 762–764. doi: 10.1016/j.jamda.2016.05.019

Mattar, I., Chan, M. F., and Childs, C. (2012). Factors causing acute delirium in critically ill adult patients: a systematic review. *JBI Libr. Syst. Rev.* 10, 187–231. doi: 10.11124/jbisrir-2012-3

Michels, M., Michelon, C., Damásio, D., Vitali, A. M., Ritter, C., and Dal-Pizzol, F. (2019). Biomarker predictors of delirium in acutely ill patients: a systematic review. *J. Geriatr. Psychiatry Neurol.* 32, 119–136. doi: 10.1177/0891988719834346

Mietani, K., Hasegawa-Moriyama, M., Inoue, R., Ogata, T., Shimojo, N., Kurano, M., et al. (2021). Elevated neuron-specific enolase level is associated with postoperative delirium and detection of phosphorylated neurofilament heavy subunit: a prospective observational study. *PLoS One* 16, e0259217–e0259210. doi: 10.1371/journal.pone.0259217

Mietani, K., Sumitani, M., Ogata, T., Shimojo, N., Inoue, R., Abe, H., et al. (2019). Dysfunction of the blood-brain barrier in postoperative delirium patients, referring to the axonal damage biomarker phosphorylated neurofilament heavy subunit. *PLoS One* 14:e0222721. doi: 10.1371/journal.pone.0222721

Morandi, A., Rogers, B. P., Gunther, M. L., Merkle, K., Pandharipande, P., and Girard, T. D. (2012). The relationship between delirium duration, white matter integrity,

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and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging: the VISIONS prospective cohort magnetic resonance imaging study. *Crit. Care Med.* 40, 2182–2189. doi: 10.1097/CCM.0b013e318250acdc.The

Murray, C., Sanderson, D. J., Barkus, C., Deacon, R. M. J., Rawlins, J. N. P., Bannerman, D. M., et al. (2012). Systemic inflammation induces acute working memory deficits in the primed brain: relevance for delirium. *Neurobiol. Aging* 33, 603–616.e3. doi: 10.1016/j.neurobiolaging.2010.04.002

Narayanan, S., Shanker, A., Khera, T., and Subramaniam, B. (2021). Neurofilament light: a narrative review on biomarker utility. *Fac. Rev.* 10:46. doi: 10.12703/r/10-46

Noah, A. M., Almghairbi, D., Evley, R., and Moppett, I. K. (2021). Preoperative inflammatory mediators and postoperative delirium: systematic review and meta-analysis. *Br. J. Anaesth.* 127, 424–434. doi: 10.1016/j.bja.2021.04.033

Osse, R. J., Fekkes, D., Tulen, J. H. M., Wierdsma, A. I., Bogers, A. J. J. C., van der Mast, R. C., et al. (2012). High preoperative plasma neopterin predicts delirium after cardiac surgery in older adults. *J. Am. Geriatr. Soc.* 60, 661–668. doi: 10.1111/j.1532-5415.2011.03885.x

Ouanes, S., and Popp, J. (2019). High cortisol and the risk of dementia and alzheimer's disease: a review of the literature. *Front. Aging Neurosci.* 11:43. doi: 10.3389/fnagi.2019.00043

Oudewortel, L., van der Roest, H. G., Onder, G., Wijnen, V. J. M., Liperoti, R., Denkinger, M., et al. (2021). The Association of Anticholinergic Drugs and Delirium in nursing home patients with dementia: results from the SHELTER study. *J. Am. Med. Dir. Assoc.* 22, 2087–2092. doi: 10.1016/j.jamda.2021.05.039

Page, V. J., Watne, L. O., Heslegrave, A., Clark, A., McAuley, D. F., Sanders, R. D., et al. (2022). Plasma neurofilament light chain protein as a predictor of days in delirium and deep sedation, mortality and length of stay in critically ill patients. *EBioMedicine* 80, 104043–104012. doi: 10.1016/j.ebiom.2022.104043

Pan, X., Cunningham, E. L., Passmore, A. P., McGuinness, B., McAuley, D. F., Beverland, D., et al. (2019). Cerebrospinal fluid Spermidine, glutamine and Putrescine predict postoperative delirium following elective Orthopaedic surgery. *Sci. Rep.* 9:4191. doi: 10.1038/s41598-019-40544-3

Pasina, L., Colzani, L., Cortesi, L., Tettamanti, M., Zambon, A., Nobili, A., et al. (2019). Relation between delirium and anticholinergic drug burden in a cohort of hospitalized older patients: an observational study. *Drugs Aging* 36, 85–91. doi: 10.1007/s40266-018-0612-9

Pathak, A., and Agrawal, A. (2019). Evolution of C-reactive protein. *Front. Immunol.* 10:943. doi: 10.3389/fimmu.2019.00943

Peng, J., Wu, G., Chen, J., and Chen, H. (2019). Preoperative C-reactive protein/albumin ratio, a risk factor for postoperative delirium in elderly patients after Total joint Arthroplasty. *J. Arthroplast.* 34, 2601–2605. doi: 10.1016/j.arth.2019.06.042

Qiao, S., Li, H., Guo, F., Cai, G., and Zhang, Y. (2022). Research progress on cognitive impairment and the expression of serum inflammatory markers in patients with white matter hyperintensities: a narrative review. *Ann. Transl. Med.* 10:421. doi: 10.21037/atm-22-1016

Racine, A. M., Fong, T. G., Travison, T. G., Jones, R. N., Gou, Y., Vasunilashorn, S. M., et al. (2017). Alzheimer's-related cortical atrophy is associated with postoperative delirium severity in persons without dementia. *Neurobiol. Aging* 59, 55–63. doi: 10.1016/j.neurobiolaging.2017.07.010

Raichle, M. E. (2015). The Brain's default mode network. *Annu. Rev. Neurosci.* 38, 433–447. doi: 10.1146/annurev-neuro-071013-014030

Sachdev, P. S., Blacker, D., Blazer, D. G., Ganguli, M., Jeste, D. V., Paulsen, J. S., et al. (2014). Classifying neurocognitive disorders: the DSM-5 approach. *Nat. Rev. Neurol.* 10, 634–642. doi: 10.1038/nrneurol.2014.181

Sajjad, M. U., Blennow, K., Knapskog, A. B., Idland, A.-V., Chaudhry, F. A., Wyller, T. B., et al. (2020). Cerebrospinal fluid levels of Interleukin-8 in delirium, dementia, and cognitively healthy patients. *J. Alzheimers Dis.* 73, 1363–1372. doi: 10.3233/JAD-190941

Saller, T., Petzold, A., Zetterberg, H., Kuhle, J., Chappell, D., von Dossow, V., et al. (2019). A case series on the value of tau and neurofilament protein levels to predict and detect delirium in cardiac surgery patients. *Biomed. Pap. Med. Fac. Univ. Palacky, Olomouc, Czechoslov.* 163, 241–246. doi: 10.5507/bp.2019.043

Sepulveda, E., Adamis, D., Franco, J. G., Meagher, D., Aranda, S., and Vilella, E. (2021). The complex interaction of genetics and delirium: a systematic review and meta-analysis. *Eur. Arch. Psychiatry Clin. Neurosci.* 271, 929–939. doi: 10.1007/s00406-021-01255-x

Sfera, A., Price, A. I., Gradini, R., Cummings, M., and Osorio, C. (2015). Proteomic and epigenomic markers of sepsis-induced delirium (SID). *Front. Mol. Biosci.* 2:59. doi: 10.3389/fmolb.2015.00059

Shen, H., Shao, Y., Chen, J., and Guo, J. (2016). Insulin-like growth Factor-1, a potential predicative biomarker for postoperative delirium among elderly patients with open abdominal surgery. *Curr. Pharm. Des.* 22, 5879–5883. doi: 10.2174/1381612822666160813234311

Sillner, A. Y., Holle, C. L., and Rudolph, J. L. (2019). The overlap between falls and delirium in hospitalized older adults: a systematic review. *Clin. Geriatr. Med.* 35, 221–236. doi: 10.1016/j.cger.2019.01.004

Sproston, N. R., and Ashworth, J. J. (2018). Role of C-reactive protein at sites of inflammation and infection. *Front. Immunol.* 9, 1–11. doi: 10.3389/fimmu.2018.00754

Strimbu, K., and Tavel, J. A. (2010). What are biomarkers? *Curr. Opin. HIV AIDS* 5, 463–466. doi: 10.1097/COH.0b013e32833ed177

Szwed, K., Słomka, A., Pawliszak, W., Szwed, M., Anisimowicz, L., Żekanowska, E., et al. (2020). Novel markers for predicting type 2 neurologic complications of coronary artery bypass grafting. *Ann. Thorac. Surg.* 110, 599–607. doi: 10.1016/j.athoracsur.2019.10.071

Trzepacz, P. T. (1999). The delirium rating scale. Its use in consultation-liaison research. *Psychosomatics* 40, 193–204. doi: 10.1016/S0033-3182(99)71235-1

van Montfort, S. J. T., van Dellen, E., Stam, C. J., Ahmad, A. H., Mentink, L. J., Kraan, C. W., et al. (2019). Brain network disintegration as a final common pathway for delirium: a systematic review and qualitative meta-analysis. *NeuroImage Clin.* 23:101809. doi: 10.1016/j.nicl.2019.101809

Van Munster, B. C., De Rooij, S. E., and Korevaar, J. C. (2009). The role of genetics in delirium in the elderly patient. *Dement. Geriatr. Cogn. Disord.* 28, 187–195. doi: 10.1159/000235796

Vasunilashorn, S. M., Dillon, S. T., Chan, N. Y., Fong, T. G., Joseph, M., Tripp, B., et al. (2021). Proteome-wide analysis using SOMAscan identifies and validates Chitinase-3-like protein 1 as a risk and disease marker of delirium among older adults undergoing major elective surgery. *J. Gerontol. A Biol. Sci. Med. Sci.* 77, 484–493. doi: 10.1093/gerona/glaa326

Vasunilashorn, S. M., Ngo, L. H., Chan, N. Y., Zhou, W., Dillon, S. T., Otu, H. H., et al. (2019). Development of a dynamic multi-protein signature of postoperative delirium. *J. Gerontol. A Biol. Sci. Med. Sci.* 74, 261–268. doi: 10.1093/gerona/gly036

Vondeling, A. M., Knol, W., Egberts, T. C. G., and Slooter, A. J. C. (2020). Anticholinergic drug exposure at intensive care unit admission affects the occurrence of delirium. A prospective cohort study. *Eur. J. Intern. Med.* 78, 121–126. doi: 10.1016/j.ejim.2020.04.062

Wang, S., Greene, R., Song, Y., Chan, C., Lindroth, H., Khan, S., et al. (2022). Postoperative delirium and its relationship with biomarkers for dementia: a meta-analysis. *Int. Psychogeriatrics* 34, 377–390. doi: 10.1017/S104161022100274X

Wang, S., Lindroth, H., Chan, C., Greene, R., Serrano-Andrews, P., Khan, S., et al. (2021). A systematic review of delirium biomarkers and their alignment with the NIA-AA research framework. *J. Am. Geriatr. Soc.* 69, 255–263. doi: 10.1111/jgs.16836

Wang, Y., and Shen, X. (2018). Postoperative delirium in the elderly: the potential neuropathogenesis. *Aging Clin. Exp. Res.* 30, 1287–1295. doi: 10.1007/s40520-018-1008-8

Watt, C. L., Momoli, F., Ansari, M. T., Sikora, L., Bush, S. H., Hosie, A., et al. (2019). The incidence and prevalence of delirium across palliative care settings: a systematic review. *Palliat. Med.* 33, 865–877. doi: 10.1177/0269216319854944

Welch, C., McCluskey, L., Wilson, D., Chapman, G. E., Jackson, T. A., Treml, J., et al. (2019). Delirium is prevalent in older hospital inpatients and associated with adverse outcomes: results of a prospective multi-Centre study on world delirium awareness day. *BMC Med.* 17, 1–11. doi: 10.1186/s12916-019-1458-7

Williamson, P. R., Altman, D. G., Bagley, H., Barnes, K. L., Blazeby, J. M., Brookes, S. T., et al. (2017). The COMET handbook: version 1.0. *Trials* 18, 1–50. doi: 10.1186/s13063-017-1978-4

Wilson, J. E., Mart, M. F., Cunningham, C., Shehabi, Y., Girard, T. D., Maclullich, A. M. J., et al. (2020). Delirium. *Nature* 11. doi: 10.1038/s41572-020-00223-4

World Health Organization (WHO) (2001). *Biomarkers in Risk Assessment: Validity and Validation*. World Health Organization, Geneva, 144.

Wyrobek, J., LaFlam, A., Max, L., Tian, J., Neufeld, K. J., Kebaish, K. M., et al. (2017). Association of intraoperative changes in brain-derived neurotrophic factor and postoperative delirium in older adults. *Br. J. Anaesth.* 119, 324–332. doi: 10.1093/bja/aex103

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EDITORIAL

Nuevos horizontes en el manejo del delirium

New horizons in the management of delirium

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El término "delirium" deriva del latín *delirare*, que significa "desviarse del camino" y constituye un síndrome neuropsiquiátrico grave caracterizado por una alteración brusca en el nivel de consciencia, la atención y la cognición, causado en la mayoría de las ocasiones, por una enfermedad orgánica subyacente[1]. Esta entidad es especialmente importante por su alta prevalencia y el gran impacto de sus consecuencias en el adulto mayor. Aproximadamente, un tercio de los pacientes hospitalizados desarrollan delirium, pero su prevalencia aumenta en servicios quirúrgicos (20-50%), unidades de cuidados paliativos (59-88%) y cuidados intensivos (50-70%)[2]. La aparición de delirium conlleva entre otras una mayor estancia hospitalaria, numerosas complicaciones médicas (inmovilismo, úlceras por presión, caídas, yatrogenia, deshidratación, malnutrición), deterioro funcional y cognitivo (cerca de un tercio de los pacientes que presentan delirium desarrollarán demencia), institucionalización, mayor mortalidad y consumo de recursos sanitarios[3]. También es interesante tener en cuenta el concepto de delirium subsindrómico, que comprende aquellos estados subumbrales de delirium, a menudo desapercibidos, pero que, al igual que el delirium, está relacionado con peores resultados de salud[4].

A pesar de su importancia clínica y de existir herramientas eficaces validadas para su detección, el delirium es un síndrome habitualmente infradiagnosticado, sobre todo en pacientes con delirium hipoactivo, y, por tanto, no manejado adecuadamente. A ello se le suma el hecho de que la fisiopatología es muy compleja y sigue sin conocerse con exactitud, lo que dificulta enormemente su abordaje[5]. Ningún fármaco ha demostrado suficiente evidencia en el tratamiento del delirium, por lo que la mejor estrategia para minimizar el impacto de sus consecuencias es la prevención, identificando a los sujetos de alto riesgo para poder modificar su trayectoria cognitiva y funcional[6].

Los modelos clásicos de predicción de delirium se han basado en la combinación de una serie de factores clínicos predisponentes (factores que confieren vulnerabilidad a un sujeto para desarrollar delirium como la edad, el deterioro cognitivo o la deprivación sensorial) y en factores precipitantes (aquellos que lo desencadenan como los procesos infecciosos, algunos fármacos o las descompensaciones metabólicas)[7]. Herramientas como el PRE-DELIRIC[8] en unidades de cuidados intensivos (UCI) o la escala DEAR[9] en cirugía ortopédica, han demostrado ser útiles, sin embargo, presentan algunas limitaciones como son la subjetividad al tratarse de valoraciones clínicas, lo que les confiere cierta imprecisión.

En los últimos años, ha habido un interés creciente por el estudio de los biomarcadores en el contexto del delirium. Un biomarcador es una sustancia utilizada como indicador de un estado biológico, es decir, una molécula cuantificable que podemos medir de forma objetiva en relación con un proceso biológico normal, un estado patológico o como respuesta a un tratamiento farmacológico. Los biomarcadores son parte de las nuevas herramientas usadas en la medicina de precisión y pueden ser de tipo molecular, celular o de imagen. Éstos podrían tener distintas aplicaciones en el ámbito del delirium como la implementación en la prevención identificando biomarcadores predictivos de delirium en fluidos accesibles como el suero, que complementarían las limitaciones de los actuales modelos clínicos disponibles[10]. También serían de gran ayuda en el diagnóstico, fundamentalmente en aquellos casos complejos como el delirium superimpuesto a demencia (DSD) o pacientes intubados en UCI donde se están empezando a realizar estudios con técnicas de ecografía Doppler a pie de cama o espectroscopia de infrarrojo cercano (NIRS) como biomarcadores de perfusión cerebral no invasivos[11,12], con resultados prometedores. Por otro lado, comprender mejor los mecanismos fisiopatológicos implicados en su desarrollo, podría abrir nuevas líneas de investigación en el tratamiento farmacológico de esta entidad, actuando sobre moléculas diana, como es el caso de la vía del ácido quinolínico y su asociación con el delirium en fractura de cadera[13].

Con respecto al manejo farmacológico del delirium, y aunque ha cobrado importancia el uso de algunos fármacos en su tratamiento

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como son la melatonina, el ramelteon o la dexmedetomidina[14], ningún fármaco ha demostrado ser eficaz en la prevención ni en el tratamiento del delirium en la actualidad. Las estrategias multicomponente basadas en identificar y corregir los factores de riesgo modificables predisponentes y precipitantes de delirium son las más efectivas tanto para la prevención como para el tratamiento de este síndrome[15]. En este contexto, estudios basados en la movilización precoz y el ejercicio físico podrían mejorar el abordaje del delirium en el adulto mayor hospitalizado[16,17].

En conclusión, el delirium es sin duda uno de los síndromes geriátricos por excelencia sobre el que queda aún un largo camino por recorrer. Herramientas como los biomarcadores, si bien necesitan más estudios que pongan de manifiesto su especificidad y su coste-eficiencia, podrían complementar nuestra práctica clínica habitual mediante técnicas objetivas, accesibles y poco invasivas, arrojando luz sobre la fisiopatología del delirium e implementando así su prevención, diagnóstico y tratamiento.

Bibliografía

1. Sachdev PS, Blacker D, Blazer DG, et al. Classifying neurocognitive disorders: The DSM-5 approach. Nat Rev Neurol. 2014;10:634–42, http://dx.doi.org/10.1038/nrneurol.2014.181.
2. Bellelli G, Brathwaite JS, Mazzola P. Delirium: A Marker of Vulnerability in Older People. Front Aging Neurosci. 2021;13(April):1–13, http://dx.doi.org/10.3389/fnagi.2021.626127.
3. Welch C, McCluskey L, Wilson D, et al. Delirium is prevalent in older hospital inpatients and associated with adverse outcomes: Results of a prospective multi-centre study on World Delirium Awareness Day. BMC Med. 2019;17:1–11, http://dx.doi.org/10.1186/s12916-019-1458-7.
4. Cole MG, Ciampi A, Belzile E, Dubuc-Sarrasin M. Subsyndromal delirium in older people: A systematic review of frequency, risk factors, course and outcomes. Int J Geriatr Psychiatry. 2013;28:771–80, http://dx.doi.org/10.1002/gps.3891.
5. Wilson JE, Mart MF, Cunningham C, et al. Delirium. Nature. 2020:11, http://dx.doi.org/10.1038/s41572-020-00223-4.
6. Fong TG, Inouye SK. The inter-relationship between delirium and dementia: the importance of delirium prevention. Nat Rev Neurol. Published online. 2022, http://dx.doi.org/10.1038/s41582-022-00698-7.
7. Ormseth CH, Lahue SC, Oldham MA, Josephson SA, Whitaker E, Douglas VC. Predisposing and Precipitating Factors Associated with Delirium: A Systematic Review. JAMA Netw Open. 2023;6:E2249950, http://dx.doi.org/10.1001/jamanetworkopen.2022.49950.
8. Linkaitė G, Riauka M, Bunevičiūtė I, Vosylius S. Evaluation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for the patients in the intensive care unit. Acta medica Litu. 2018;25:14–22, http://dx.doi.org/10.6001/actamedica.v25i1.3699.
9. Freter S, Dunbar M, Koller K, MacKnight C, Rockwood K. Risk of pre- and postoperative delirium and the delirium elderly at risk (DEAR) tool in hip fracture patients. Can Geriatr J. 2015;18:212–6, http://dx.doi.org/10.5770/cgj.18.185.
10. Lozano-Vicario L, García-hermoso A, Cedeno-veloz BA, et al. Biomarkers of delirium risk in older adults?: a systematic review and meta-analysis. Front Aging Neurosci. 2023;(May):1–13, http://dx.doi.org/10.3389/fnagi.2023.1174644.
11. Wood MD, Boyd JG, Wood N, et al. The Use of Near-Infrared Spectroscopy and/or Transcranial Doppler as Non-Invasive Markers of Cerebral Perfusion in Adult Sepsis Patients With Delirium: A Systematic Review. J Intensive Care Med. 2022;37:408–22, http://dx.doi.org/10.1177/0885066621997090.
12. Caplan GA, Lan ZZ, Newton L, Kvelde T, McVeigh C, Hill MA. Transcranial doppler to measure cerebral blood flow in delirium superimposed on Dementia. A cohort study. J Am Med Dir Assoc. 2014;15:355–60, http://dx.doi.org/10.1016/j.jamda.2013.12.079.
13. Watne LO, Pollmann CT, Neerland BE, et al. Cerebrospinal fluid quinolinic acid is strongly associated with delirium and mortality in hip-fracture patients. J Clin Invest. 2023;133(2.), http://dx.doi.org/10.1172/JCI163472.
14. Qin C, Jiang Y, Lin C, Li A, Liu J. Perioperative dexmedetomidine administration to prevent delirium in adults after non-cardiac surgery: A systematic review and meta-analysis. J Clin Anesth. 2021;73(January):110308, http://dx.doi.org/10.1016/j.jclinane.2021.110308.
15. Burton JK, Craig LE, Yong SQ, et al. Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients. Cochrane Database Syst Rev. 2021;2021(7.), http://dx.doi.org/10.1002/14651858.CD013307.pub2.
16. Lozano-Vicario L, Zambom-Ferraresi F, Zambom-Ferraresi F, et al. Effectiveness of a multicomponent exercise training program for the management of delirium in hospitalized older adults using near-infrared spectroscopy as a biomarker of brain perfusion: Study protocol for a randomized controlled trial. Front Aging Neurosci. 2022;14(December):1–9, http://dx.doi.org/10.3389/fnagi.2022.1013631.
17. Martinez Velilla N, Lozano-Vicario L, Sáez de Asteasu ML, et al. Could a Tailored Exercise Intervention for Hospitalised Older Adults Have a Role in the Resolution of Delirium? Secondary Analysis of a Randomised Clinical Trial. J Frailty Aging. 2023;12:84–5, http://dx.doi.org/10.14283/jfa.2022.60.

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ASSOCIATION OF POSTOPERATIVE DELIRIUM WITH SERUM AND CEREBROSPINAL FLUID PROTEOMIC PROFILES:A PROSPECTIVE COHORT STUDY IN OLDER HIP FRACTURE PATIENTS

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Abstract:	Background Postoperative delirium (POD) is a common neuropsychiatric complication in geriatric inpatients after hip fracture surgery and its occurrence is associated with poor outcomes. The purpose of this study was to investigate the relationship between preoperative biomarkers in serum and cerebrospinal fluid (CSF) and the development of POD in older hip fracture patients, exploring the possibility of integrating objective methods into future predictive models of delirium.

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Methods

Sixty hip fracture patients were recruited. Blood and CSF samples were collected at the time of spinal anesthesia when none of the subjects had delirium. Patients were assessed daily using the 4AT scale and based on these results, they were divided into POD and non-POD groups. The Olink® platform was used to analyze 45 cytokines.

Results

Twenty-one patients (35%) developed POD. In the subsample of 30 patients on whom proteomic analyses were performed, a proteomic profile was associated with the incidence of POD. Chemokine (C-X-C motif) ligand 9 (CXCL9) had the strongest correlation between serum and CSF samples in patients with POD (rho= 0.663; $p<0.05$).

Conclusion

Although several cytokines in serum and CSF were associated with POD after hip fracture surgery in older adults, there was a significant association with lower preoperative levels of CXCL9 in CSF and serum. Despite of the small sample size, this study provides preliminary evidence of the potential role of molecular biomarkers in POD, which may provide a basis for the development of new delirium predictive models.

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ASSOCIATION OF POSTOPERATIVE DELIRIUM WITH SERUM AND CEREBROSPINAL FLUID PROTEOMIC PROFILES: A PROSPECTIVE COHORT STUDY IN OLDER HIP FRACTURE PATIENTS

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ABSTRACT

Background:

Postoperative delirium (POD) is a common neuropsychiatric complication in geriatric inpatients after hip fracture surgery and its occurrence is associated with poor outcomes. The purpose of this study was to investigate the relationship between preoperative biomarkers in serum and cerebrospinal fluid (CSF) and the development of POD in older hip fracture patients, exploring the possibility of integrating objective methods into future predictive models of delirium.

Methods:

Sixty hip fracture patients were recruited. Blood and CSF samples were collected at the time of spinal anesthesia when none of the subjects had delirium. Patients were assessed daily using the 4AT scale and based on these results, they were divided into POD and non-POD groups. The Olink® platform was used to analyze 45 cytokines.

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Twenty-one patients (35%) developed POD. In the subsample of 30 patients on whom proteomic analyses were performed, a proteomic profile was associated with the incidence of POD. Chemokine (C-X-C motif) ligand 9 (CXCL9) had the strongest correlation between serum and CSF samples in patients with POD (rho= 0.663; $p<0.05$).

Conclusion:

Although several cytokines in serum and CSF were associated with POD after hip fracture surgery in older adults, there was a significant association with lower preoperative levels of CXCL9 in CSF and serum. Despite of the small sample size, this study provides preliminary evidence of the potential role of molecular biomarkers in POD, which may provide a basis for the development of new delirium predictive models.

Keywords: Biomarkers, Cognitive impairment, CXCL9, Delirium, Neuroinflammation, Hip fracture

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BACKGROUND

Delirium is a neuropsychiatric disorder characterized by an acute change in attention, awareness, and cognition **[1]**. The term postoperative delirium (POD) refers to a condition of acute cognitive dysfunction that occurs in hospital up to one week after surgery and is a frequent perioperative complication, especially among older adults **[2]**. The incidence of POD after hip fracture has been reported to range from 11% to 51% and occurs in up to 50–70% of high-risk patient groups **[3]**. Furthermore, POD is associated with adverse outcomes such as longer length of stay, functional decline, persistent cognitive impairment, institutionalization, decrease in quality of life, premature mortality and increased healthcare expenditure **[4,5]**.

Although studies have contributed some evidence in recent years, the pathophysiological mechanism of delirium remains largely unknown, and a multifactorial etiology has been suggested **[6,7]**. Evidence supports that maladaptive neuroinflammatory response plays an important role in the development of POD **[8,9]**. Several precipitating factors of delirium such as surgery, infection or trauma cause endothelial damage, which increases blood brain barrier (BBB) permeability allowing immune cells, cytokines and other neuroinflammatory products to penetrate the brain parenchyma. These mediators activate the microglia, leading to neuronal dysfunction and delirium **[10]**. This mechanism has been observed particularly in older adults and patients with cognitive impairment undergoing hip fracture surgery **[11,12]**. Some studies have found that Tumour Necrosis Factor-α (TNF-α), proinflammatory cytokines such us Interleukins (IL1, IL6 and IL8), and other novel neuroinflammatory biomarkers (neopterin) are elevated in the serum of these patients before surgery, but their study in cerebrospinal fluid (CSF) has yielded mixed results **[13,14]**. However, studies carried out so far have important limitations because most do not account for geriatric syndromes, nor they measure delirium in a daily pattern during hospitalization; furthermore, delirium characteristics such as subtype and severity are seldom assessed.

Importantly, there is no effective treatment for POD once it is established, so the best approach is its prevention. Several clinically-based predictive models of delirium have been developed in recent years such as the DEAR tool **[15–17]**, but they have some limitations because

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their application depends on the interpretation of the clinician who performs them and, consequently, they can be subjective and imprecise. For this reason, the possibility of integrating objective measures into predictive models of delirium needs to be explored. Serum biomarkers are quantifiable, reproducible and minimally invasive and could be useful to better understand the pathophysiology of delirium and identify patients at higher risk of developing it.

The present study aimed to comprehensively characterize patients with delirium both from a clinical point of view and using a proteomic approach, in order to evaluate whether changes in the preoperative immunological profile could be associated with POD after hip fracture surgery. We hypothesized that older hip fracture patients with altered cytokine profiles before surgery could be at higher risk of developing delirium.

METHODS

Study design and participants

This was a prospective cohort study. Between August 2021 and December 2021, we approached sixty consecutive hip fracture patients aged 75 years or older undergoing subarachnoid anesthesia, who were admitted to the Orthopedic ward of Hospital Universitario de Navarra (Pamplona, Spain). Patients were excluded if: 1) they had preoperative delirium, 2) advanced dementia (a score >5 at Global Deterioration Scale **[18]**), 3) severe dependence (a score <20 at Barthel Index **[19]**), 4) terminal disease (life expectancy <3 months), 5) were unable to communicate in Spanish, and 6) were not willing or not capable to provide informed consent.

Clinical assessments

Medical records were reviewed and patients and relatives were interviewed preoperatively and daily after surgery. A Comprehensive Geriatric Assessment (CGA) was performed at the time of enrolment that included functional status (Barthel Index and Lawton and Brody scale **[20]**), frailty (FRAIL scale **[21]**), nutrition (Mini-Nutritional Assessment-Short Form, MNA-SF **[22]**), grip strength (measured with JAMAR 5030J1 Hand Dynamometer), quality of

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life (EuroQol Scale-5D **[23]**), falls, sensory impairment, depression (Yesavage Geriatric Depression Scale **[24]**), polypharmacy and demographic factors such as provenance and education level. Possible confounding factors, including fracture characteristics, type of anesthesia, type of surgery, peri- and post-operative complications such as infectious events or postoperative anemia were registered for all patients.

The presence or absence of delirium was scored daily until discharge by two geriatricians using the Spanish version of the 4AT scale **[25,26]**. Information for the 4AT was based on a psychiatric examination of the patient, review of medical and nursing records, and information given by the patient's closest relative. All 60 patients were non-delirious before surgery. Delirium symptom severity was assessed postoperatively with the validated Memorial Delirium Assessment Scale (MDAS) **[27]**. The peak MDAS was defined as the highest total delirium severity score recorded in the postoperative period. Delirium subtype was assessed using the Delirium Motor Subtype Scale-4 **[28]**. Preexisting cognitive impairment was based on medical history and Informant Questionnaire on Cognitive Decline short form (IQCODE-sf). The informant was asked to recall the cognitive situation 2 weeks prior to the hip fracture and compare it with the situation 10 years earlier. Patients with a mean score of 3.9 or higher were considered to have global cognitive impairment **[29,30]**.

Sample collection and laboratory assessments

Blood and CSF were collected before surgery and processed in no more than 1 hour from their sampling. The blood sample (8 mL obtained by venous puncture) was collected the morning prior to surgery and placed in a polypropylene plastic tube at room temperature (25ºC) for 30 minutes until blood coagulation occurred; then, the tube was centrifuged in a fixed-angle rotor at 1960 *g* for 10 minutes at room temperature. After centrifugation, the serum in the upper layer was carefully extracted and divided into 0.5mL aliquots and immediately stored at -80ºC. CSF samples were collected during canulation for the introduction of spinal anesthesia, prior to administration of any anesthetic. Lumbar punctures were performed with a 25-gauge needle between the L3-L4 or L4-L5 intervertebral space. From each patient, 2 mL of CSF was collected in polypropylene

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tubes which were transported to the laboratory and centrifuged at 720 *g* for 10 minutes at 4ºC, divided into 0.5 µL aliquots and stored at -80ºC. Samples of 30 patients (both serum and CSF) in which 15 had delirium and 15 did not, were selected and sent on dry ice for analysis at Cobiomic Bioscience (Parque Científico Tecnológico de Córdoba, Córdoba, Spain). We used Olink® technology to assess cytokine and chemokine levels. The Olink® reagents are based on the Proximity Extension Assay (PEA) technology, where 45 oligonucleotide labeled antibody probe pairs are each allowed to bind to their respective target protein present in the sample. Following hybridization of the matched oligo sequences, a PCR reporter sequence is formed by a proximity-dependent DNA polymerization event. This is then amplified, and subsequently detected and quantified using real time Polymerase Chain Reaction (PCR). The assay is performed in a 48-plex format without any need for washing steps, and results are reported in standard concentration units (pg/mL). When cytokines are within the lower and upper limits of quantification (LLOQ and ULOQ) for each assay, the values are not included in the analysis. Details about PEA technology, assays performance and validation data are available from the manufacturer (www.olink.com) and all the biomarkers analyzed with this technology are detailed in **Supplementary Table 1**.

Standard protocol approval, registration and patient consents

This study was conducted in accordance with the Declaration of Helsinki (World Medical Association) and was approved by the Navarra Clinical Research Ethics Committee on June 25, 2021 (PI_2021/68). Data and samples were collected after informed consent from patients at the time of enrolment. There was no financial compensation for the participants.

Statistical analyses

Variables were tested for normality using the Shapiro-Wilk method. Consequently, non-parametric (Mann–Whitney U) or parametric (independent t-test) tests were used to compare the two groups (patients who developed POD versus patients who did not develop POD) regarding baseline characteristics measured in continuous variables. For dichotomous or nominal variables,

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Fisher's exact or Pearson X^2 were used. Data were presented as mean and standard deviation unless stated otherwise. For descriptives and testing of group differences, the statistical software used was SPSS version 26 (International Business Machines Corporation (IBM), Armonk, New York, USA). P-value of <0.05 was considered significant.

We used the Tukey's fences method to detect observations out of the normal range by using interquartile ranges, which is often used for detecting outliers in various fields **[31]**. 122 outliers were excluded from the analysis out of the 2700 values analyzed using the Olink platform. Before performing Tukey's fences, normality of the data was checked before fitting the curve. Features with >70% missing values in the real samples or >10% outlier values in the serum and CSF samples were deleted first. 38 biomarkers passed quality control in serum and 27 passed quality control in CSF (**Supplementary Table 2**). Serum biomarkers in pg/mL values were analyzed using two unpaired t- tests, *Benjamini–Hochberg* method for p value correction with 5% false discovery rate, and a distribution boxplot. P values <0.05 were considered statistically significant after correction with the *Benjamini–Hochberg* method. A principal component analysis (PCA) and Volcano plot assessed the distribution of the groups, using singular value decomposition with imputation (pre-normalized data, no transformation), and visualized using ClustVis **[32]**. Spearman's correlation matrices were calculated including clinical variables, sex and age, and significant biomarkers for patients who developed POD versus patients who did not develop POD, using the R package Corrplot (version 0.84 https://cran.r-project.org/package=corrplot).

RESULTS

Clinical results

From August 2021 to December 2021, 60 of 138 hip fracture patients fulfilled criteria for participation and provided informed consent (**Figure 1**). Twenty-one of these 60 patients developed POD (35%) and thirty-nine did not (65%).

***** Insert Figure 1 here *****

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The characteristics of patients with and without POD are shown in **Table 1**. Patients who developed POD had more cognitive impairment (p<0.001), higher dependency (p=0.005) and worse nutritional status (p=0.013).

***** Insert Table 1 here *****

Characteristics of the surgery and clinical complications after surgery are shown in **Table 2**. No significant differences were found between type of hip fracture, time from surgery to sitting, femoral nerve block, blood transfusion or bladder catheterization and the incidence of POD. However, patients who spent a longer period of time without walking after surgery had higher incidence of POD (p=0.003). In addition, patients who developed delirium had more infections (p<0.001), used more psychotropic drugs (p<0.001) and more opioids (p=0.013) during hospitalization than patients without delirium.

***** Insert Table 2 here *****

Laboratory results

Serum and CSF samples of 30 patients were analyzed (15 patients with POD and 15 patients without POD) and the results are shown in **Supplementary Table 2.** A score plot was generated to show the separation between the POD and non-POD groups. The PCA analysis did not reveal any abnormal deviations between the two groups (**Figure 2).**

***** Insert Figure 2 here *****

The volcano plot in **Figure 3** shows the differences between POD and non-POD groups. Those who developed POD had significantly higher levels of CXCL12 and EGF in serum as well as higher levels of CSF3 and TGFA in CSF compared to patients without POD. However, patients who developed POD had significantly lower levels of CSF3, CXCL9, IL10, CCL2 and CXCL8

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in serum and lower levels of CCL3, CXCL9 and CCL4 in CSF compared to patients without POD.

***** Insert Figure 3 here*****

We examined the correlation between cytokine concentrations in serum and CSF in both POD and non-POD groups, with adjustments made for sex and age using Spearman rank (Rho) correlation. The analysis unveiled significant negative associations between serum EGF and serum CXCL9 levels (rho= -0.754; $p<0.05$), CSF TGFA and CSF CXCL9 (rho= -0.714; $p<0.01$), as well as CSF CSF3 and CSF CCL3 (rho= -0.843; $p<0.05$) in the non-POD group. Furthermore, other noteworthy positive relationships were observed between serum CSF3 and serum IL10 (rho= 0.603; $p<0.05$), CSF CSF3 and serum CXCL12 (rho= 0.737, $p<0.05$), CSF CSF3 and serum CXCL8 (rho= 0.816, $p<0.05$), as well as CSF CCL4 and CSF CCL3 (rho= 0.64, $p<0.05$) in the non-POD group.

On the other hand, significant negative relationships were found between serum CSF3 and serum CXCL9 (rho= -0.688; $p<0.05$), serum EGF and serum CXCL9 (rho= -0.635; $p<0.05$), serum EFG and serum CXCL8 (rho= -0.605; $p< 0.05$) in POD group. Similarly, other significant positive relationships were found between serum CXCL8 and serum IL10 (rho= 0.538; $p<0.05$), serum CSF3 and serum CXCL8 (rho= 0.597; $p<0.05$), serum CCL2 and serum CSF3 (rho= 0.599; $p<0.05$), CSF CCL3 and serum CXCL12 (rho= 0.621; $p<0.05$), CSF CCL4 and serum CCL2 (rho= 0.596; $p<0.05$), CSF CCL4 and CSF CCL3 (rho= 0.812; $p<0.001$) in POD group.

The only cytokine that had a significantly positive correlation in both serum and CSF of patients with POD was CXCL9 (rho= 0.663; $p<0.05$) (**Figure 4**).

***** Insert Figure 4 here *****

DISCUSSION

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In this study, we investigated the association between POD and 45 cytokines and chemokines in preoperative serum and CSF in older hip fracture patients and we identified 12 potential biomarkers of delirium risk. Four of them were found to be up-regulated (serum CXCL12, serum EFG, CSF CSF3 and CSF TGFA) and eight were down-regulated (serum CSF3, serum CXCL9, serum CXCL8, serum IL10, serum CCL2, CSF CCL3, CSF CXCL9, and CSF CCL4). An interesting finding was the significant correlation between lower levels of CXCL9 in serum and CSF in patients with POD compared to patients without POD.

Chemokine (C-X-C motif) ligand 9 (CXCL9) is a small cytokine belonging to the CXC chemokine family that is also known as monokine induced by gamma interferon (MIG). CXCL9 induces chemotaxis, promotes differentiation and multiplication of leukocytes and causes tissue extravasation. It has been found that CXCL9 increases with age **[33]** and is an important factor in age-related chronic inflammation, being involved in cardiac aging, adverse cardiac remodeling and poor vascular function. Age-related elevation in CXCL9 leads to endothelial cell senescence and predicts subclinical levels of cardiovascular aging in healthy individuals **[34]**. CXCL9 has also been shown to be associated with falls and hip fracture in older population **[35]** and frailty **[36,37]**. Furthermore, data in the literature indicates a significant role of CXCL9 and its receptor (CXCR3) in the Central Nervous System (CNS), in both physiological and pathological processes **[38,39]**. CXCL9 is expressed in human brain-derived microvascular endothelial cells and astrocytes and is especially involved in Th1 response. In addition, it has been shown that CXCL9 is able to induce the activation of extracellular signal-regulated kinases (ERK1/2) in cortical neurons and might be involved in a neuronal–glial interaction. The up-regulation of this chemokine and its receptor was also identified in Alzheimer Disease (AD) brains, finding higher levels of CXCL9 in AD patients compared to patients with mild cognitive impairment or without cognitive impairment **[40,41]**. On the other hand, CXCL9 exhibited lowest levels in participants with 1 or more ε4 alleles in a study carried out to identify a panel of plasma biomarkers of AD **[42]**. These dissenting results support the fact that lower levels of CXCL9 were associated with POD in our study. These discrepancies could be justified by the multiple mechanisms implicated in delirium development (tissue damage, infection, pain, polypharmacy, hypoxia…), the

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heterogeneity in the methodology of the studies carried out (different biochemical analysis and clinical assessments) and the small sample size of our study. Other factors to consider are the systemic inflammatory response syndrome of our patients (all of them had hip fracture, with the consequent tissue damage compared to other studies where the patients did not have it) and the complexity for chemokine receptor CXCR3 activation that is involved in wound healing with different signaling pathways **[43]**.

Serum Stromal cell-derived factor 1 (CXCL12) is involved in Alzheimer Disease (AD) pathophysiology **[44]** and pro-epidermal growth factor (EGF), whose up-regulation has been associated with cognitive impairment in Parkinson´s disease **[45,46]**, showed higher levels in patients with POD compared to patients without POD in our study. These findings support the possible relationship between CXCL12, EGF and POD.

Granulocyte colony-stimulating factor (CSF3) showed significantly higher levels in CSF but lower levels in serum of patients with POD in our study. Previous studies have found that its up-regulation improves neuroplasticity **[47]** and its administration in rats protects against cognitive impairment **[48]**.

Transforming growth factor alpha (TGFA) showed higher levels in CSF of patients who developed POD in our study and has been associated with AD and vascular dementia **[49,50]**, which could explain the pathophysiological substrate for delirium.

Interleukin-10 (IL10) whose down-regulation has been found in patients with AD and delirium **[51,52]**, showed lower levels in serum of patients who developed POD in our study, which is consistent with previous literature.

C-C motif chemokine 2 (CCL2), Interleukin-8 (CXCL8), C-C motif chemokine 3 (CCL3) and C-C motif chemokine 4 (CCL4) showed significantly lower levels in patients with POD in our study. However, higher levels have been associated with dementia **[53,54]**, delirium among critically ill patients **[55]** and neuropsychiatric disorders in Parkinson's disease **[56,57]** in previous literature.

Although the etiology of POD is both complex and elusive, in our study age, comorbidity, sensory impairment, depression, worse functional status, cognitive impairment, malnutrition,

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frailty and polypharmacy were identified as clinical predisposing factors of POD, which is consistent with previous literature **[58,59]**. In addition, infections and immobility after hip fracture surgery were the only significant precipitating factors of POD during the postoperative period, according to similar results obtained in other studies **[1,17]**.

However, these predisposing and precipitating clinical factors are often difficult to quantify because they are subjective and, consequently, less accurate. In contrast, biomarkers are quantifiable, objective and potentially reproducible. Moreover, serum biomarkers are minimally invasive what makes them accessible in different clinical settings. Although further research is needed, these findings emphasize the role of biomarkers in POD after hip fracture and its potential use through the development of integrating objective methods into future predictive models of delirium.

Strengths and limitations

We highlight several study strengths such as the collection of blood and CSF and the well-defined sample. However, some study limitations warrant mention. First, the small sample size requires that the results be interpreted with caution. Additionally, the sampling at a single time point results in the loss of information regarding the course of delirium during hospitalization. Second, our set of inflammatory biomarkers might not be an appropriate indicator of inflammation in the CNS because most of the cytokines and chemokines analyzed are not characteristic of a specific condition or process, thus, additional testing and evaluation might be required to identify specific markers of delirium in order to implement the understanding of the CNS disorders pathophysiology. Further research with larger sample sizes, and comprehensive assessments of confounding factors is needed to validate these findings and determine the clinical utility of molecular biomarkers in predicting and managing POD.

CONCLUSION

In summary, we found 12 biomarkers associated with POD and lower levels of CXCL9 had the most significant correlation between serum and CSF. These findings suggest that altered proteomic profile before surgery could be associated with POD development. Although further

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research is needed to confirm these results, biomarkers may offer a valuable tool for delirium risk assessment in addition to current predictive clinical models.

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Authors' contributions

LLV, NMV, JROG, RSME and BACV designed the study. RRV and AGJ performed statistical analyses and interpreted data. LLV acquired interpreted data and drafted the manuscript. MMV, RRV, MI, FZ, BAC, BVM, JROG, RSME, AMHO, AJMV, JFI, RRO and ESM critically revised the manuscript. All authors read and approved the final version of the manuscript.

Founding

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Statements and Declarations

Conflict of interest

The authors declare that no competing interest exists.

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REFERENCES

1. Inouye SK, Westendorp RGJ, Saczynski JS, Naeije G, Pepersack T. Delirium in elderly people. Lancet. 2014;383(9920):911–22. DOI: 10.1016/S0140-6736(13)60688-1
2. Marcantonio ER. Delirium in Hospitalized Older Adults. N Engl J Med. 2017;377(15):1456–66. DOI: 10.1056/nejmcp1605501
3. Bruce AJ, Ritchie CW, Blizard R, Lai R, Raven P. The incidence of delirium associated with orthopedic surgery: A meta-analytic review. Int Psychogeriatrics. 2007;19(2):197–214. DOI: 10.1017/S104161020600425X
4. Zhou J, Liu C, Sun Y, Huang W, Ye K. Cognitive disorders associated with hospitalization of COVID-19: Results from an observational cohort study. Brain Behav Immun. 2021;91:383–92. DOI: 10.1016/j.bbi.2020.10.019
5. Oberai T, Woodman R, Laver K, Crotty M, Kerkhoffs G, Jaarsma R. Is delirium associated with negative outcomes in older patients with hip fracture: analysis of the 4904 patients 2017–2018 from the Australian and New Zealand hip fracture registry. ANZ J Surg. 2022;92(1–2):200–5. DOI: 10.1111/ans.17421
6. Maldonado JR. Neuropathogenesis of delirium: Review of current etiologic theories and common pathways. Am J Geriatr Psychiatry. 2013;21(12):1190–222. DOI: 10.1016/j.jagp.2013.09.005
7. Wilson JE, Mart MF, Cunningham C, Shehabi Y, Girard TD, MacLullich AMJ, et al. Delirium. Nat Rev Dis Prim. 2020;6(1). DOI: 10.1038/s41572-020-00223-4
8. Wang Y, Shen X. Postoperative delirium in the elderly: the potential neuropathogenesis. Aging Clin Exp Res. 2018;30(11):1287–95. DOI: 10.1007/s40520-018-1008-8
9. Alam A, Hana Z, Jin Z, Suen KC, Ma D. Surgery, neuroinflammation and cognitive impairment. EBioMedicine. 2018;37:547–56. DOI: 10.1016/j.ebiom.2018.10.021
10. Subramaniyan S, Terrando N. Neuroinflammation and Perioperative Neurocognitive Disorders. Anesth Analg. 2019;128(4):781–8. DOI: 10.1213/ANE.0000000000004053

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

11. Liu X, Yu Y, Zhu S. Inflammatory markers in postoperativedelirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. PLoS One. 2018;13(4). DOI: 10.1371/journal.pone.0195659

12. Beloosesky Y, Hendel D, Weiss A, Hershkovitz A, Grinblat J, Pirotsky A, et al. Cytokines and C-reactive protein production in hip-fracture-operated elderly patients. Journals Gerontol - Ser A Biol Sci Med Sci. 2007;62(4):420–6. DOI: 10.1093/gerona/62.4.420

13. Hirsch J, Vacas S, Terrando N, Yuan M, Sands LP, Kramer J, et al. Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. J Neuroinflammation. 2016;13(1):211. DOI: 10.1186/s12974-016-0681-9

14. Miao S, Shen P, Zhang Q, Wang H, Shen J, Wang G, et al. Neopterin and mini-mental state examination scores, two independent risk factors for postoperative delirium in elderly patients with open abdominal surgery. J Cancer Res Ther. 2018;14(6):1234–8. DOI: 10.4103/0973-1482.192764

15. Freter S, Dunbar M, Koller K, MacKnight C, Rockwood K. Risk of pre- and post-operative delirium and the delirium elderly at risk (DEAR) tool in hip fracture patients. Can Geriatr J. 2015;18(4):212–6. DOI: 10.5770/cgj.18.185

16. Zhao S, Sun T, Zhang J, Chen X, Wang X. Risk factors and prognosis of postoperative delirium in nonagenarians with hip fracture. Sci Rep. 2023;13(1):1–7. DOI: 10.1038/s41598-023-27829-4

17. Smith TO, Cooper A, Peryer G, Griffiths R, Fox C, Cross J. Factors predicting incidence of post-operative delirium in older people following hip fracture surgery: a systematic review and meta-analysis. Int J Geriatr Psychiatry. 2017;32(4):386–96. DOI: 10.1002/gps.4655

18. Auer S, Reisberg B. The GDS/FAST staging system. Int Psychogeriatrics. 1997;9(SUPPL. 1):167–71. DOI: 10.1017/S1041610297004869

19. Barthel M. Functional evaluation: the Barthel Index. Md State Med J. 1965;14:56–61.

20. Lawton M, Brody E. Assessment of older people: selfmaintaining and instrumental

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Nafarroako Unibertsitate Publikoa

activities of daily living. Gerontologist. 1969;9:179–86. Gerontologist. 1969;9:1979–86.

21. Woo J, Yu R, Wong M, Yeung F, Wong M, Lum C. Frailty screening in the community using the FRAIL scale. J Am Med Dir Assoc. 2015;16(5):412–9. DOI: 10.1016/j.jamda.2015.01.087

22. Kaiser M., Bauer J. Validation of the mini nutritional assessment short-form (MNA®-SF): a practical tool for identification of nutritional status. J Nutr Health Aging. 2009;13(9):782–8.

23. Herdman M, Badia X, Berra S. EuroQol-5D: a simple alternative for measuring health-related quality of life in primary care. Aten Primaria. 2001;28(6):425–30. DOI: 10.1016/s0212-6567(01)70406-4

24. Yesavage JA. Geriatric Depression Scale. Psychopharmacol Bull. 1988;24(4):709–10. DOI: 10.1007/978-3-319-69892-2_736-1

25. Tieges Z, Maclullich AMJ, Anand A, Brookes C, Cassarino M, O'connor M, et al. Diagnostic accuracy of the 4AT for delirium detection in older adults: systematic review and meta-analysis. Age Ageing. 2021;50(3):733–43. DOI: 10.1093/ageing/afaa224

26. Delgado-Parada E, Morillo-Cuadrado D, Saiz-Ruiz J, Cebollada-Gracia A, Ayuso-Mateos JL, Cruz-Jentoft AJ. Diagnostic accuracy of the Spanish version of the 4AT scale (4AT-ES) for delirium screening in older inpatients. Eur J Psychiatry. 2022;36(3):182–90. DOI: 10.1016/j.ejpsy.2022.01.003

27. Barahona E, Pinhao R, Galindo V, Noguera A. The Diagnostic Sensitivity of the Memorial Delirium Assessment Scale—Spanish Version. J Pain Symptom Manage. 2018;55(3):968–72. DOI: 10.1016/j.jpainsymman.2017.11.013

28. Meagher D, Adamis D, Leonard M, Trzepacz P, Grover S, Jabbar F, et al. Development of an abbreviated version of the Delirium Motor Subtyping Scale (DMSS-4). Int Psychogeriatrics. 2014;26(4):693–702. DOI: 10.1017/S1041610213002585

29. Harrison JK, Stott DJ, McShane R, Noel-Storr AH, Swann-Price RS, Quinn TJ. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the early detection of dementia across a variety of healthcare settings. Cochrane Database Syst

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

Rev. 2021;2021(7). DOI: 10.1002/14651858.CD011333.pub3

30. Blandfort S, Gregersen M, Rahbek K, Juul S, Damsgaard EM. The short IQCODE as a predictor for delirium in hospitalized geriatric patients. Aging Clin Exp Res. 2020;32(10):1969–76. DOI: 10.1007/s40520-019-01412-2

31. Luo J, Frisken S, Machado I, Zhang M, Pieper S, Golland P, et al. Using the variogram for vector outlier screening: application to feature-based image registration. Int J Comput Assist Radiol Surg. 2018;13(12):1871–80. DOI: 10.1007/s11548-018-1840-5

32. Metsalu T, Vilo J. ClustVis: A web tool for visualizing clustering of multivariate data using Principal Component Analysis and heatmap. Nucleic Acids Res. 2015;43(W1):W566–70. DOI: 10.1093/nar/gkv468

33. Torres KCL, Rezende VB de, Lima-Silva ML, Santos LJ de S, Costa CG, Mambrini JV de M, et al. Immune senescence and biomarkers profile of Bambuí aged population-based cohort. Exp Gerontol. 2018;103(December 2017):47–56. DOI: 10.1016/j.exger.2017.12.006

34. Sayed N, Huang Y, Nguyen K, Krejciova-Rajaniemi Z, Grawe AP, Gao T, et al. An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging. Vol. 1, Nature Aging. 2021. 598–615 p. DOI: 10.1038/s43587-021-00082-y

35. Phan QT, Chua KY, Jin A, Winkler C, Koh WP. CXCL9 Predicts the Risk of Osteoporotic Hip Fracture in a Prospective Cohort of Chinese Men—A Matched Case–Control Study. J Bone Miner Res. 2022;37(10):1843–9. DOI: 10.1002/jbmr.4646

36. de Amorim JSC, Torres KCL, Teixeira-Carvalho A, Martins-Filho OA, Lima-Costa MF, Peixoto SV. Inflammatory markers and occurrence of falls: Bambuí Cohort Study of Aging. Rev Saude Publica. 2019;53:1–11. DOI: 10.11606/S1518-8787.2019053000855

37. de Amorim JSC, Torres KCL, Carvalho AT, Martins-Filho OA, Lima-Costa MF, Peixoto SV. Inflammatory markers associated with fall recurrence and severity: The Bambuí Cohort Study of Aging. Exp Gerontol. 2020;132(January):110837. DOI: 10.1016/j.exger.2020.110837

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Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

38. Watson AES, Goodkey K, Footz T, Voronova A. Regulation of CNS precursor function by neuronal chemokines. Neurosci Lett. 2020;715:134533. DOI: 10.1016/j.neulet.2019.134533

39. Satarkar D, Patra C. Evolution, Expression and Functional Analysis of CXCR3 in Neuronal and Cardiovascular Diseases: A Narrative Review. Front Cell Dev Biol. 2022;10(June):1–17. DOI: 10.3389/fcell.2022.882017

40. Lee KS, Chung JH, Lee KH, Shin MJ, Oh BH, Hong CH. Bioplex analysis of plasma cytokines in Alzheimer's disease and mild cognitive impairment. Immunol Lett. 2008;121(2):105–9. DOI: 10.1016/j.imlet.2008.09.004

41. Koper OM, Kaminska J, Sawicki K, Kemona H. CXCL9, CXCL10, CXCL11, and their receptor (CXCR3) in neuroinflammation and neurodegeneration. Adv Clin Exp Med. 2018;27(6):849–56. DOI: 10.17219/acem/68846

42. Soares HD, Potter WZ, Pickering E, Kuhn M, Immermann FW, Shera DM, et al. Plasma biomarkers associated with the apolipoprotein E genotype and alzheimer disease. Arch Neurol. 2012;69(10):1310–7. DOI: 10.1001/archneurol.2012.1070

43. Berchiche YA, Sakmar TP. CXC chemokine receptor 3 alternative splice variants selectively activate different signaling pathways. Mol Pharmacol. 2016;90(4):483–95. DOI: 10.1124/mol.116.105502

44. Li H, Wang R. A focus on CXCR4 in Alzheimer's disease. Brain Circ. 2017;3(4):199. DOI: 10.4103/bc.bc_13_17

45. Pellecchia MT, Santangelo G, Picillo M, Pivonello R, Longo K, Pivonello C, et al. Serum epidermal growth factor predicts cognitive functions in early, drug-naive Parkinson's disease patients. J Neurol. 2013;260(2):438–44. DOI: 10.1007/s00415-012-6648-6

46. Yasar Z, Elliott BT, Kyriakidou Y, Nwokoma CT, Postlethwaite RD, Gaffney CJ, et al. Sprint interval training (SIT) reduces serum epidermal growth factor (EGF), but not other inflammatory cytokines in trained older men. Eur J Appl Physiol. 2021;121(7):1909–19. DOI: 10.1007/s00421-021-04635-2

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Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

47. Sanchez-Ramos J, Song S, Sava V. Granulocyte Colony Stimulating Factor (G-CSF) Decreases Brain Amyloid Burden and Reverses Cognitive Impairment in Alzheimer's Mice. Neuroscience. 2009;163(1):55–72. DOI: 10.1016/j.neuroscience.2009.05.071.

48. Tuo M, Xiao Y, Xu Y, Wang L, Wei X, Zhang L. Role of Granulocyte-colony Stimulating Factor in the Protection of Cerebral Vascular Endothelium, White Matter, and Cognition. Curr Neurovasc Res. 2019;16(5):425–32. DOI: 10.2174/1567202616666191029115113

49. Khedr EM, Gomaa AMS, Ahmed OG, Sayed HMM, Gamea A. Cognitive Impairment, P300, and Transforming Growth Factor β1 in Different Forms of Dementia. J Alzheimer's Dis. 2020;78(2):837–45. DOI: 10.3233/JAD-200885

50. Estrada LD, Oliveira-Cruz L, Cabrera D. Transforming Growth Factor Beta Type I Role in Neurodegeneration: Implications for Alzheimer´s Disease. Curr Protein Pept Sci. 2018;19(12):1180–8. DOI: 10.2174/1389203719666171129094937

51. Khan SH, Lindroth H, Jawed Y, Wang S, Nasser J, Seyffert S, et al. Serum Biomarkers in Postoperative Delirium After Esophagectomy. Ann Thorac Surg. 2022;113(3):1000–7. DOI: 10.1016/j.athoracsur.2021.03.035

52. Culjak M, Perkovic MN, Uzun S, Strac DS, Erjavec GN, Leko MB, et al. The Association between TNF-alpha, IL-1 alpha and IL-10 with Alzheimer's Disease. Curr Alzheimer Res. 2020;17(11):972–84. DOI: 10.2174/1567205017666201130092427

53. Ahmad MA, Kareem O, Khushtar M, Akbar M, Haque MR, Iqubal A, et al. Neuroinflammation: A Potential Risk for Dementia. Int J Mol Sci. 2022;23(2). DOI: 10.3390/ijms23020616

54. Lee WJ, Liao YC, Wang YF, Lin IF, Wang SJ, Fuh JL. Plasma MCP-1 and cognitive decline in patients with Alzheimer's disease and mild cognitive impairment: A two-year follow-up study. Sci Rep. 2018;8(1):4–11. DOI: 10.1038/s41598-018-19807-y

55. Smith RJ, Lachner C, Singh VP, Trivedi S, Khatua B, Cartin-Ceba R. Cytokine profiles in intensive care unit delirium. Acute Crit Care. 2022;37(3):415–28. DOI: 10.4266/acc.2021.01508

upna
Universidad Pública de Navarra
Nafarroako Unibertsitate Publikoa

56. Perna L, Trares K, Perneczky R, Tato M, Stocker H, Möllers T, et al. Risk of Late-Onset Depression and Cognitive Decline: Results From Inflammatory Proteome Analyses in a Prospective Population-Based Cohort Study. Am J Geriatr Psychiatry. 2022;30(6):689–700. DOI: 10.1016/j.jagp.2021.12.001

57. Lindqvist D, Hall S, Surova Y, Nielsen HM, Janelidze S, Brundin L, et al. Cerebrospinal fluid inflammatory markers in Parkinson's disease - Associations with depression, fatigue, and cognitive impairment. Brain Behav Immun. 2013;33:183–9. DOI: 10.1016/j.bbi.2013.07.007

58. Dogrul RT, Dogrul AB, Konan A, Caglar O, Sumer F, Caliskan H, et al. Does Preoperative Comprehensive Geriatric Assessment and Frailty Predict Postoperative Complications? World J Surg. 2020;44(11):3729–36. DOI: 10.1007/s00268-020-05715-8

59. Yang Y, Zhao X, Gao L, Wang Y, Wang J. Incidence and associated factors of delirium after orthopedic surgery in elderly patients: a systematic review and meta-analysis. Aging Clin Exp Res. 2021;33(6):1493–506. DOI: 10.1007/s40520-020-01674-1

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LEGENT TO FIGURES

Fig. 1 Flowchart of study inclusion.

Figure 2. Principal component (PCA) of POD and non-POD groups.

Footnote: Principal component analysis (PCA) was created to investigate possible outliers in the data set. Score plot showing the separation between the POD and without POD group. The red points correspond to patients with POD, and the blue points correspond to patients without POD.

Figure 3. Biomarkers identification according to serum and cerebrospinal fluid levels into POD and non-POD groups.

Footnote: The volcano plot for detected biomarkers; the X-axis represents the $\log_2$ fold-change value, while the Y-axis represents the $-\log_{10}$ P value; the gray point represents the biomarkers without significant difference. The red point represents the biomarkers increase with significant difference, while blue point represents the biomarkers decrease with significant difference, in patients with POD compared to patients without POD.

Figure 4. Matrix of pairwise spearman correlations among biomarkers according to serum (s) and cerebrospinal fluid (c) levels for POD and non-POD groups adjusted by sex and age. Color represents the level of Spearman's correlations (blue means positive correlation and red means negative correlation).

Footnote: Significant protein pairs correlations were indicated as *** $p<0.001$, ** $p<0.01$, * $p<0.05$.

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TABLES

Table 1. Baseline characteristics of patients with and without POD

		Without POD n=39 (65%)	**POD n=21(35%)**	**p-value**
Age (years)	mean (sd)	84.9 (6.6)	87.9 (5.2)	0.085[a]
Sex	Male	6 (15.4%)	4 (19.0%)	
	Female	33 (84.6%)	17 (81.0%)	0.729[b]
Comorbidity (Charlson)	median (Q1-Q3)	5.0 (4.0-7.0)	5.0 (5.0-6.5)	0.814
ASA	2	9 (23.1%)	5 (23.8%)	
	3	26 (66.7%)	14 (66.7%)	1.0[b]
	4	4 (10.3%)	2 (9.5%)	
Number of drugs at admission	median (Q1-Q3)	7.0 (4.0-9.0)	8.0 (6.0-11.0)	0.181[d]
DBI at admission	median (Q1-Q3)	0.5 (0.0-1.17)	1.0 (0.5-1.4)	0.073[d]
Barthel index	mean (sd)	88.8 (12.6)	81.7 (15.8)	0.059[a]
Lawton and Brody	median (Q1-Q3)	6.0 (4.0-8.0)	3.0 (1.5-5.0)	0.005[d]
Grip strenght (Handgrip)	mean (sd)	14.1 (6.1)	12.0 (6.8)	0.216[a]
Nutritional condition (MNA)	median (Q1-Q3)	27.0 (25.0-28.5)	25.5 (19.8-27.5)	0.013[d]
Frailty (FRAIL)	median (Q1-Q3)	1.0 (1.0-2.0)	2.0 (1.0-3.0)	0.194[d]
Admission location	Home	36 (92.3%)	18 (85.7%)	
	Nursing home	3 (7.7%)	3 (14.3%)	0.655[b]
QoL at admission (EuroQoL-5D)	mean (sd)	77.3 (20.4)	71.0 (17.6)	0.118[a]
Visual impairment	No	11 (28.2%)	5 (23.8%)	
	Yes	28 (71.8%)	26 (76.2%)	0.713[c]
Hearing impairment	No	25 (64.1%)	8 (38.1%)	
	Yes	14 (35.9%)	13 (61.9%)	0.053[c]
Educational level	Primary studies	9 (23.1%)	7 (33.3%)	
	Secondary studies	28 (71.8%)	10 (47.6%)	0.101[b]
	University	2 (5.1%)	4 (19.0%)	
Depression (Yesavage)	median (Q1-Q3)	3.0 (1.0-5.0)	5.0 (2.5-8.0)	0.055[d]
Cognitive impairment (IQCODE-sf at admission)	mean (sd)	52.1 (4.9)	60.0 (8.8)	<0.001[a]
Previous episodes of delirium	No	34 (87.2%)	15 (71.4%)	
	Yes	5 (12.8%)	6 (28.6%)	0.169[b]

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Table 2. Characteristics after surgery of patients with and without POD

		Without POD n=39 (65%)	POD n=21 (35%)	p-value
Type of hip fracture	Subcapital	15 (38.5%)	8 (38.1%)	
	Pertrochanteric	18 (46.2%)	8 (38.1%)	
	Subtrochanteric	3 (7.7%)	1 (4.8%)	0.659[b]
	Basicervical	3 (7.7%)	4 (19.0%)	
Time from surgery to sitting (hours)	median (Q1-Q3)	36.0 (36.0-36.0)	36.0 (36.0-36.0)	0.618[a]
Time from surgery to walking (hours)	median (Q1-Q3)	48.0 (48.0-72.0)	72.0 (60.0, 120.0)	0.003[a]
Femoral nerve block	No	21 (53.8%)	11 (52.4%)	0.914[c]
	Yes	18 (46.2%)	10 (47.6%)	
Blood transfusion (number of packed red blood cells)	median (Q1-Q3)	0.0 (0.0, 1.0)	1.0 (0.0, 2.0)	0.058[a]
Infection	No	33 (84.6%)	6 (28.6%)	
	Yes	6 (15.4%)	15 (71.4%)	<0.001[c]
Type of infection	None	33 (84.6%)	6 (28.6%)	
	Respiratory	2 (5.1%)	4 (19.0%)	
	Urinary	2 (5.1%)	6 (28.6%)	
	Bacteraemia	1 (2.6%)	0 (0.0%)	
	Sepsis	0 (0.0%)	2 (9.5%)	<0.001[b]
	Respiratory+Urinary	0 (0.0%)	1 (2.8%)	
	Another focus	1 (2.6%)	2 (9.5%)	
Bladder catheterization	No	20 (51.3%)	9 (42.9%)	
	Yes	19 (48.7%)	12 (57.1%)	0.533[c]
Poor pain control during hospitalization	No	33 (84.6%)	11 (52.4%)	
	Yes	6 (15.4%)	10 (47.6%)	0.013[c]
Use of opioids during hospitalization	No	36 (92.3%)	11 (52.4%)	
	Yes	3 (7.7%)	10 (47.6%)	<0.001[b]
Need of psychotropic drugs during hospitalization	No	26 (66.7%)	6 (28.6%)	
	Yes	13 (33.3%)	15 (71.4%)	0.005[c]

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Figure 1. Flow diagram

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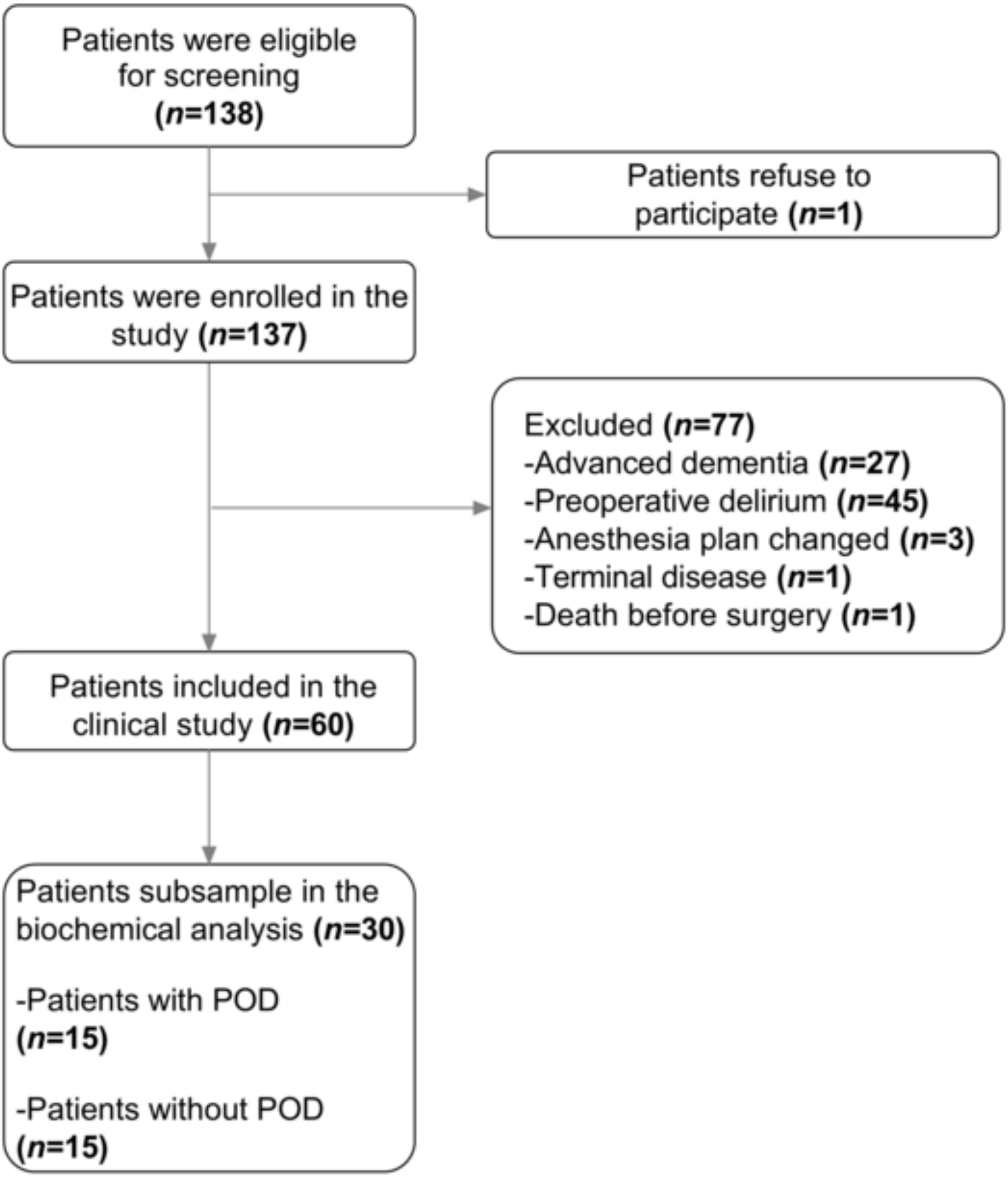

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Figure 2. PCA

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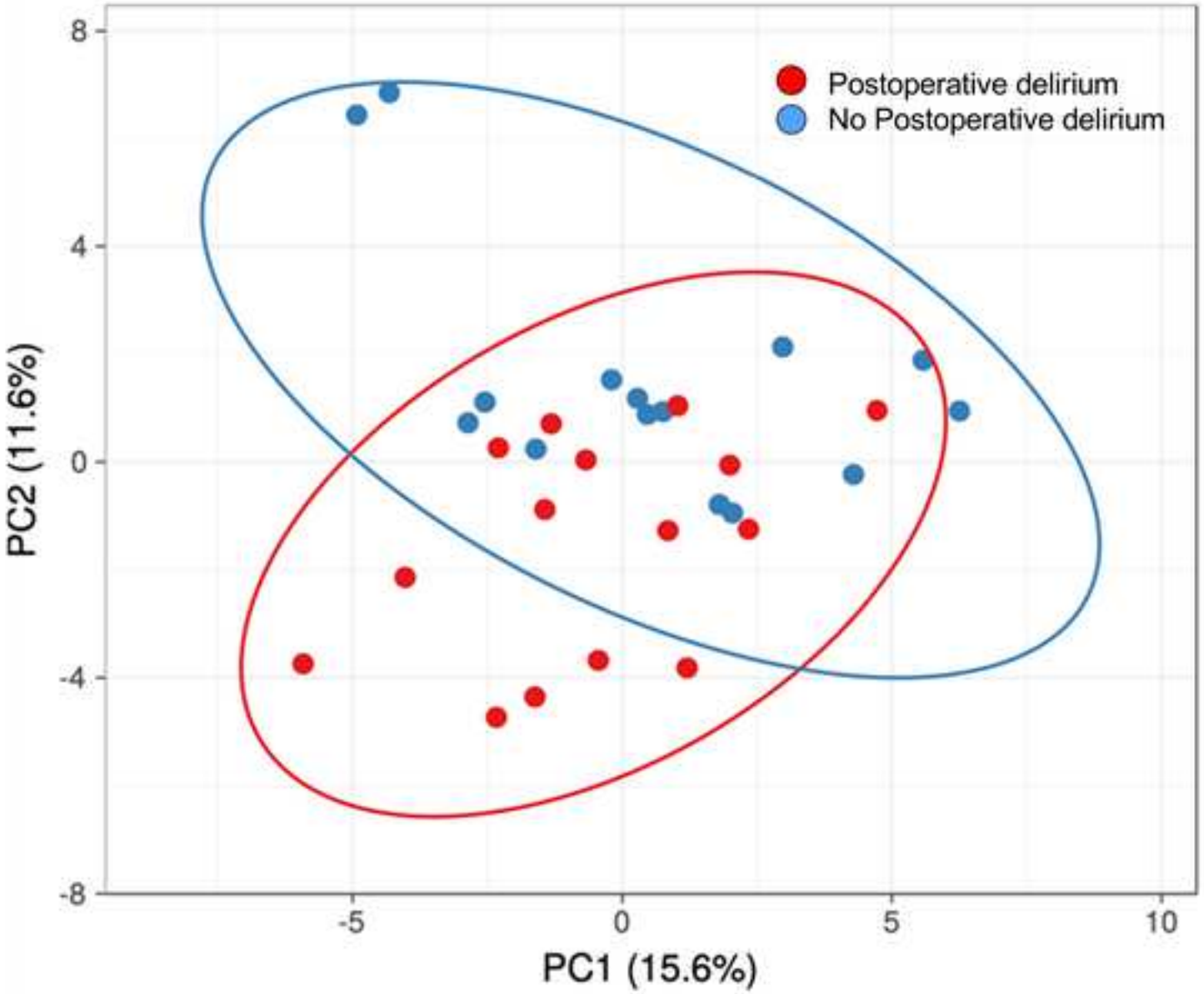

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Figure 3. Volcano plot

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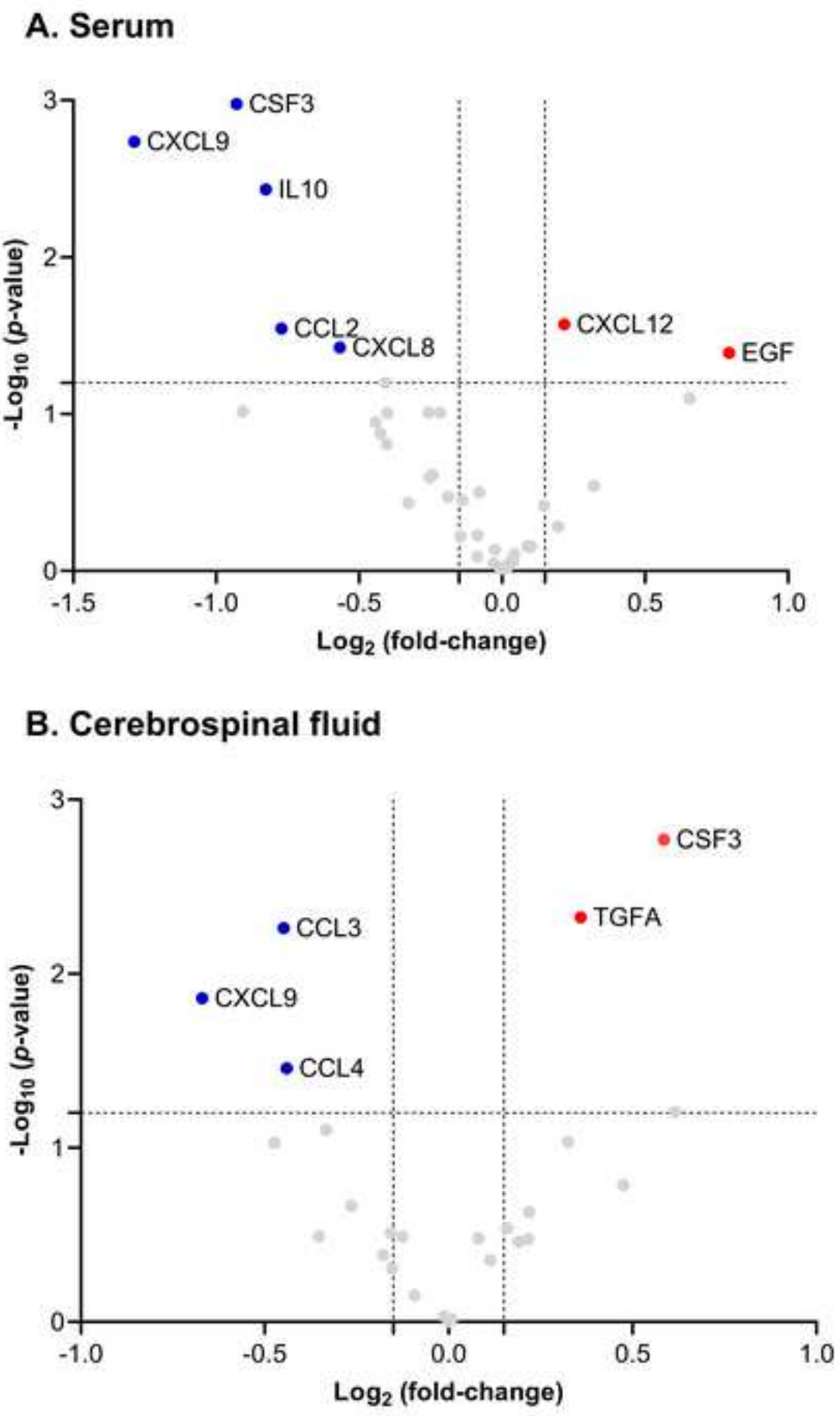

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Figure 4. Correlation plot

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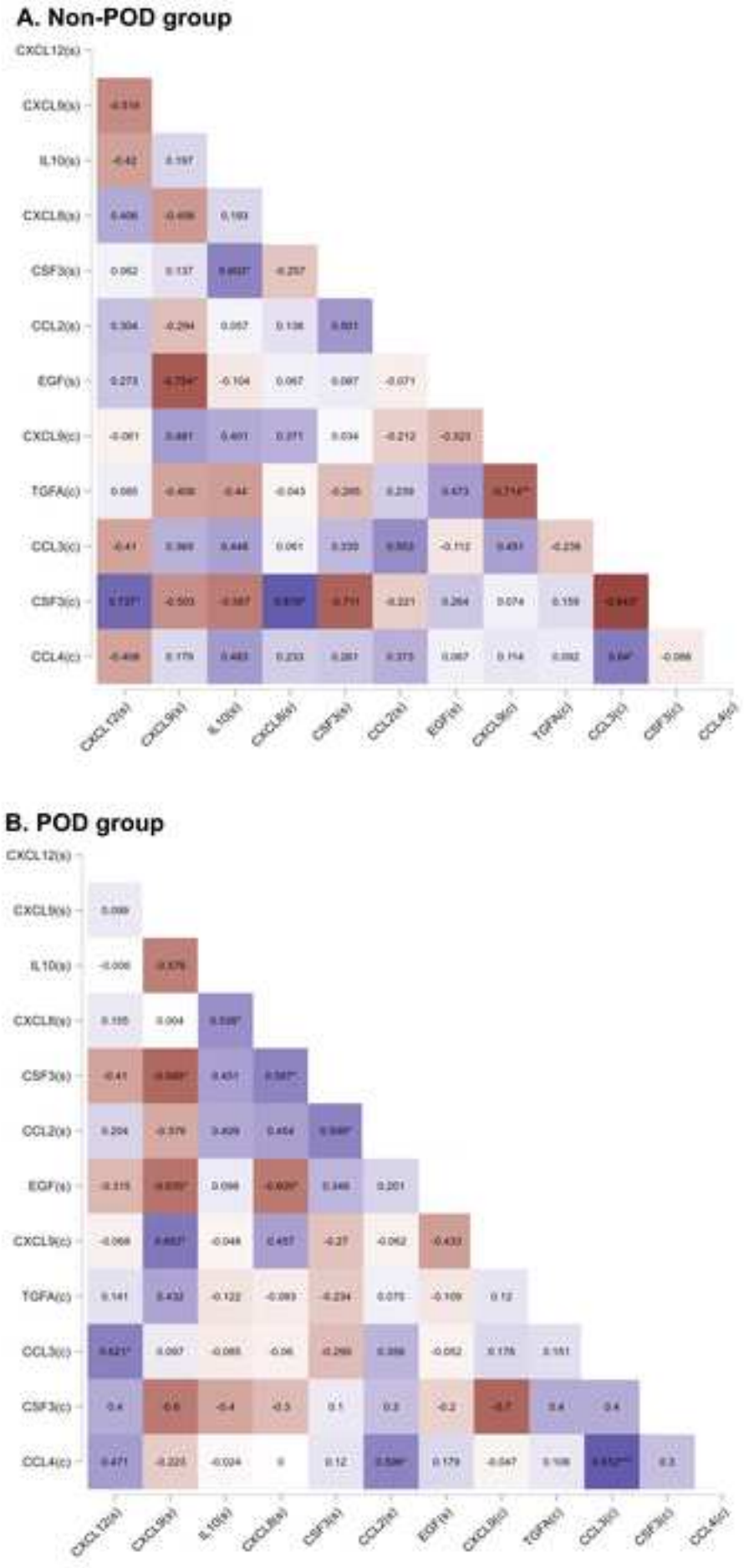

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Response to reviewer's comments
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Pamplona November, 2023

Dear Editor,
Many thanks for your decision letter related to Manuscript JAAA-D-23-00335 entitled "Association of postoperative delirium with serum and cerebrospinal fluid proteomic profiles: A prospective cohort study in older hip fracture patients" submitted to Geroscience.
Your comments and those made by the reviewers are much appreciated. We have revised the manuscript in depth following all the editorial and reviewers' recommendations. We have included a detailed point by point response to reviewers' comments below.

REVIEWER #1:
This study investigated biomarkers for predicting and understanding postoperative delirium in hip fracture patients. The study's findings contribute to the growing body of research on the use of objective measures, such as biomarkers, in improving the prediction and management of delirium in the geriatric population.
While this study provides preliminary evidence of the potential role of molecular biomarkers, specifically CXCL9, in predicting postoperative delirium (POD) in older hip fracture patients, there are several limitations to consider.

1) Small sample size: The study only included a total of sixty hip fracture patients, and proteomic analyses were performed on a subsample of thirty patients. The small sample size might limit the generalizability of the findings and increase the risk of statistical biases.
-Author response: Indeed, the sample size of the study is small, making it challenging to categorically extrapolate the results. Although this limitation is discussed in the "strengths and limitations" section of the manuscript, we would like to emphasize that the clinical characterization of the subjects and the performance of the proteomic profiling on samples not only from blood but also from cerebrospinal fluid bring novelty to this topic.
Unfortunately, this type of studies often have small sample sizes due to the complexity of sample collection, especially of cerebrospinal fluid. Such is the case of DOI: 10.1186/1742-2094-10-122 (61 patients), DOI: 10.1016/j.neulet.2018.11.014 (21 patients), DOI: 10.1007/s12265-018-9835-8 (23 patients), DOI: 10.1186/s12974-016-0681-9 (10 patients) or DOI: 10.1186/s12974-021-02145-8 (29 patients).

2) Single time point for sample collection: Blood and CSF samples were collected at the time of spinal anesthesia when none of the subjects had delirium. However, the development of delirium is a dynamic process, and a single time point may not fully capture the changes in biomarker levels over time.
-Author response: Thank you for your comment, we agree with your statement. While obtaining more samples throughout the hospitalization could provide more information about delirium, we initially planned to collect samples in the preoperative period with the idea of identifying predictive biomarkers for delirium in both serum and cerebrospinal fluid. Moreover, obtaining cerebrospinal fluid during the postoperative period would be difficult due to the

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condition of the patients after surgery. However, we add this limitation to the "strengths and limitations" section of the manuscript.

3) Potential confounding factors: The study does not provide information about potential confounding factors, such as comorbidities, medications, or perioperative management, which could influence the occurrence of POD. Failure to account for these factors may limit the interpretation of the results.
-Author response: Although some potential confounding factors during the postoperative period were not collected, a comprehensive characterization of the patients has been conducted, detailed in Tables 1 and 2, with variables that we believe could be sufficient to provide information about the development of delirium in this type of patients.

4) Lack of follow-up data: The study does not followed up with the patients beyond the immediate postoperative period. Long-term outcomes and the persistence of POD were not assessed, which could provide valuable insights into the clinical relevance of the biomarkers.
-Author response: The reviewer is right. In fact, we are working with that data, which I have already presented at the 2022 European Delirium Association (EDA) Congress in Milan as an oral presentation titled "Quality of Life, Cognitive and Functional Trajectories Associated with Postoperative Delirium: A Prospective Cohort Study in Hip Fracture Patients with 1- and 3-Month Follow-Up" https://smc-media.eu/web/eda2022/abstractbook/ *and I hope to finally publish it. However, in this manuscript, we focused on the short-term evolution of patients given the space limitations.*

5) Overall, while the study suggests a potential association between CXCL9 levels in serum and CSF and the development of POD, these limitations should be taken into account. Further research with larger sample sizes, and comprehensive assessments of confounding factors is needed to validate these findings and determine the clinical utility of molecular biomarkers in predicting and managing POD.
-Author response: Thank you for your comment. I add this clarification to the "limitations" section.

REVIEWER #2:
This is an interesting manuscript that aims to investigate the relationship between preoperative biomarkers in serum and cerebrospinal fluid (CSF) and the development of POD in older hip fracture patients. One of the biggest strengths of this study is the capability of obtaining CSF from 60 very old patients. Moreover, the sample is very well characterized and the clinical variables are well documented and explained in the manuscript. In spite of the caution that needs to be exercised, this study provides preliminary evidence of the potential role of molecular biomarkers in POD in a very old population, which is the most likely to develop delirium, even though it is the least studied.

As a recommendation to the authors, I would also add:

1) Page 8, lines 22-26: "In addition, patients who developed delirium had more infections […] during hospitalization than patients without delirium". Infections, drugs, and opioids can also precipitate delirium, so I would not put them as a consequence of delirium, but as associated factors.
-Author response: Thank you for your comment. Indeed, infections, polypharmacy, and the use of opioids are triggers for delirium. This is detailed in Table 2, which includes variables collected in the postoperative period (among them are precipitating factors of delirium such as infections and postoperative medications, as well as others that are not, for example the type of surgery or type of fracture). To avoid misunderstandings, I replace the phrase "need drugs" with "use drugs" to clarify that it is not a consequence of delirium.

2) Page 9, lines 11-49: "The association between cytokine concentrations in serum and CSF […] and CSF CCL3 (rho= 0.812; p<0.001) in POD group. ><0.001) in POD group". It is hard to read and understand this paragraph. Considering the challenge of explaining the correlation between the different biomarkers, I recommend rephrasing this paragraph and making it more simple to understand, using Figure 3 to guide you.
-Author response: Thank you for your comment. Following the reviewer´s suggestion, I have rephrased the paragraph as follows:
"We examined the correlation between cytokine concentrations in serum and CSF in both POD and non-POD groups, with adjustments made for sex and age using Spearman rank (Rho) correlation. The analysis unveiled significant negative associations between serum EGF and serum CXCL9 levels (rho= -0.754; p<0.05), CSF TGFA and CSF CXCL9 (rho= -0.714; p<0.01), as well as CSF CSF3 and CSF CCL3 (rho= -0.843; p<0.05) in the non-POD group. Furthermore, other noteworthy positive relationships were observed between serum CSF3 and serum IL10 (rho= 0.603; p<0.05), CSF CSF3 and serum CXCL12 (rho= 0.737, p<0.05), CSF CSF3 and serum CXCL8 (rho= 0.816, p<0.05), as well as CSF CCL4 and CSF CCL3 (rho= 0.64, p<0.05) in the non-POD group."

Thank you very much for your comments.

Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

The role of C-reactive protein as a risk marker of postoperative delirium in older hip fracture patients: a prospective cohort study

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Research Article

Keywords: delirium, risk marker, C-reactive protein, cognitive impairment, hip fracture

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Abstract

Background:

Postoperative delirium (POD) after hip fracture surgery is a common and serious neuropsychiatric syndrome that leads to higher morbidity and mortality. Current predictive models of delirium are based on clinical factors that can be subjective and imprecise. In this study we investigated the association between serum C-reactive protein (CRP) and the occurrence of POD in older hip fracture patients, and whether CRP predicted POD better than a clinical model.

Methods:

Patients aged ≥75 years admitted for surgical repair of an acute hip fracture were recruited. A Comprehensive Geriatric Assessment (CGA) was performed at admission and blood samples were collected preoperatively in the absence of delirium. Delirium was assessed daily until discharge with the 4-AT. We compared serum CRP levels between patients with and without POD and examined the association between CRP and delirium severity. Mann-Whitney U and Spearman tests were used for group comparisons.

Results:

Sixty patients were included, of whom 21 (35%) developed POD. Serum CRP levels were significantly higher in patients who developed delirium ($p = 0.011$), but no significant association was found between CRP and delirium severity ($p = 0.079$). In a multiple regression model including the most representative clinical variables associated with delirium (age, comorbidity, grip strength, frailty, infection and pre-existing cognitive impairment) and CRP, cognitive impairment ($p = 0.003$) and infection ($p = 0.001$) were the best predictors of POD.

Conclusions:

Although higher levels of serum CRP were significantly associated with POD in older hip fracture patients, pre-existing cognitive impairment and infections were the most important risk factors for POD.

Background

Delirium is a common neuropsychiatric syndrome characterized by an alteration in the level of consciousness and a disturbance in cognition and attention that appears abruptly (Inouye et al. 2014). Its incidence increases in patients aged 65 and older, reaching 15–53% after surgery but it can be higher in hip fracture patients with an incidence of 16–62% (Yang et al. 2021). POD is a serious complication that is associated with higher mortality and morbidity, prolonged hospitalization (Israni et al. 2018), greater

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risk of new institutionalization (Welch et al. 2019), worse functional recovery (Marcantonio et al. 2000) and increased risk of future dementia (Lee et al. 2020).

The pathophysiological mechanisms that lead to delirium remain unclear (Wilson et al. 2020). There is an emerging interest in serum inflammatory proteins and their possible association with the development of delirium (Subramaniyan and Terrando 2019). In this context, CRP has been traditionally used as a marker of inflammation, infection and tissue damage. An association between CRP levels and delirium has been reported but results are controversial (Liu et al. 2018; Lopez et al. 2020).

On the other hand, clinical predictive models of delirium such as the Delirium Elderly At-Risk (DEAR) tool, which assesses risk factors of delirium (age, cognitive impairment, functional status, polypharmacy and sensory impairment) have demonstrated their utility in delirium prediction identifying patients at high risk of POD, but some report that at times they may be subjective and imprecise (Freter et al. 2015).

Despite the research in this field, the effectiveness of both biochemical and clinical models of delirium risk is unknown due to important limitations in the studies such as the methodology, the small sample size and a poor characterization of geriatric syndromes, which implies high heterogeneity.

The aim of this study was to investigate whether CRP was associated with the development and severity of delirium after hip fracture surgery in a homogeneous and well-defined older population, measuring other geriatric syndromes in order to assess which of the two models (biochemical or clinical) was more effective in predicting delirium.

Methods

Study design and participants

This was a prospective cohort study. Sixty hip fracture patients aged ≥75 years undergoing subarachnoid anesthesia, were recruited between August 2021 and December 2021, in the Orthopedic ward of Hospital Universitario de Navarra (Pamplona, Spain). Patients were excluded if 1) had preoperative delirium, 2) had advanced dementia (a score > 5 in the Global Deterioration Scale (Auer and Reisberg 1997)), 3) had severe dependence (a score < 20 in the Barthel Index (Barthel 1965)), 4) had a terminal disease (life expectancy < 3 months), 5) were unable to communicate in Spanish and 6) were not willing or not capable to provide informed consent.

Clinical assessments

A Comprehensive Geriatric Assessment (CGA) was performed at the time of enrolment evaluating functional status (Barthel Index and Lawton and Brody scale (Lawton and Brody 1969)), pre-existing cognitive impairment (Informant Questionnaire on Cognitive Decline short form (IQCODE-sf) (Burton et al. 2021)), frailty (FRAIL index (Woo et al. 2015)) and grip strength (measured with JAMAR 5030J1 Hand Dynamometer). The presence or absence of delirium was scored daily until discharge by two geriatricians

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using the Spanish version of 4AT scale (Delgado-Parada et al. 2022). Delirium severity was assessed with the Memorial Delirium Assessment Scale (MDAS) (Barahona et al. 2018).

Sample collection and laboratory assessments

Blood samples were collected before surgery and processed in no more than 1–2 hours from their extraction. Eight mL of blood were obtained by venous puncture. We used MULTIGENT CRP Vario assay (Abbott Laboratories, Wiesbaden, Germany) to analyze CRP levels. This technology is based on immunoturbidimetric methodology. When an antigen-antibody reaction occurs between CRP and anti-CRP antibody, which has been adsorbed to latex particles, agglutination results. This agglutination is detected as an absorbance change (572 nm), with the rate of change being proportional to the quantity of CRP in the sample.

Standard protocol approval, registration and patient consent

This study was conducted in accordance with the Declaration of Helsinki (World Medical Association) and was approved by the Navarra Clinical Research Ethics Committee on June 25, 2021 (PI_2021/68). Data and samples were collected after obtaining written informed consent from each patient at the time of enrolment. There was no financial compensation for the participants.

Statistical analyses

We first compared preoperative CRP serum levels between patients with and without POD. In addition, we investigated the association between the levels of CRP and delirium severity. Furthermore, we analyzed the relationship between baseline clinical characteristics and the incidence of POD. Statistics were performed using SPSS (SPSS for Windows, version 20, IBM Corporation, Armonk, NY, USA). Continuous non-normal variables were tested with the Mann-Whitney U test. Spearman´s correlation was used for correlation analysis. Statistical significance was set at $P < 0.05$. The figure was created with BioRender® (https://www.biorender.com).

Results

Sixty hip fracture patients were recruited at the Orthopedic Surgery and Traumatology ward in Hospital Universitario de Navarra (HUN). Twenty-one patients developed delirium after surgery (35%) and thirty-nine did not (65%).

Serum CRP was analyzed in all patients; the mean value was 32.5 mg/L and the range was 0 to 176 mg/L. Mean level of CRP in patients with POD was 47.2 mg/L (median 38.7 mg/L), 95% CI (26.76–67.53), whereas mean CRP level in patients without POD was 24.7 mg/L (median 9.2 mg/L), 95% CI (14.75–34.60), with a statistically significant difference ($p = 0.011$). When comparing CRP levels with the severity of delirium, a positive but not significant association was observed. The 2-sided Spearman's

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correlation coefficient between CRP and MDAS was 0.228, $p = 0.079$. Baseline characteristics of both groups are detailed in **Supplementary material**.

The most significant clinical variables associated with POD were age, comorbidity, grip strength, frailty, infections and cognitive impairment. When performing a multiple regression model with these clinical variables and CRP, cognitive impairment measured with IQCODE-sf and infections were the strongest predictor variables. Results are shown in Table 1.

Table 1
Logistic regression model between clinical variables and CRP

	OR	95% CI OR		p-value
		Lower	Upper	
Age	1.06	0.90	1.25	0.465
Comorbidity (Charlson index)	0.60	0.36	1.00	0.050
Grip strenght	1.07	0.91	1.26	0.440
Frailty (FRAIL)	1.00	0.41	2.42	0.995
Cognitive impairment (IQCODE-sf)	1.29	1.09	1.53	**0.003***
Serum CRP	1.00	0.98	1.03	0.810
Infection	29.28	3.69	232.12	**0.001***

Discussion

This study investigated serum CRP as a predictive biomarker of delirium in a well-defined cohort of older hip fracture patients and compared these findings with a model based on clinical risk factors of delirium. We found significantly higher levels of serum CRP in hip fracture patients who developed POD, however, clinical variables such as cognitive impairment and infections were better predictors of delirium.

CRP is a pentameric protein whose circulating concentrations rise in response to inflammation and increases following IL-6 secretion by macrophages and T cells (Sproston and Ashworth 2018; Pathak and Agrawal 2019). Although higher levels of CRP have been shown in inflammatory and infectious processes, CRP is also altered in patients with cognitive impairment and Alzheimer disease, which is a risk factor for delirium development (Rentería et al. 2020; Leng and Edison 2021). Some studies have found that levels of CRP are significantly increased in older patients undergoing surgery who subsequently develop delirium (Cerejeira et al. 2012; Dillon et al. 2017; Slor et al. 2019; Chen et al. 2020), but others did not find this association (Lemstra et al. 2008; Çinar et al. 2014; Katsumi et al. 2020). Our data supports the neuroinflammatory hypothesis of delirium suggesting that inflammatory stimulation in the periphery goes through the blood-brain barrier (BBB), inducing the activation of brain parenchymal cells such as microglia and astroglia and producing a dysfunctional neuroinflammatory response with an

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expression of proinflammatory cytokines, which may lead to neurocognitive changes and delirium (Maldonado 2013). This pathway is explained in Fig. 1.

However, when we performed a logistic regression model combining clinical variables and CRP, infections and pre-morbid cognitive impairment were the best predictors of POD. This can be explained by the advanced age of the patients with a high rate of comorbidity and frailty that confers brain vulnerability and lower resilience to stressors, developing more perioperative complications such as infections. In addition, all the patients had a fracture-induced systemic inflammatory response before surgery, when samples were collected, that may affect CRP levels and their interpretation.

Although a clinical predictive model of delirium including the infection rate and a cognitive assessment seems to be the best predictor of POD, serum CRP could be a valuable tool to complement its limitations such as subjectivity and complexity of performance, providing accessibility and reproducibility because it is minimally invasive and quantifiable.

We highlight several study strengths such as the detailed characterization of POD and the homogeneous and well-defined sample, including the measurement of several geriatric syndromes. However, some study limitations warrant mention. Firstly, the small sample size means that the results should be interpreted with caution. Secondly, we did not collect follow-up samples after POD to examine changes in different time moments. Thirdly, CRP has low specificity and may be related with other conditions or processes beyond delirium such us infections. More studies with larger sample sizes will be needed to define the potential role of these molecules in predictive models of delirium, combined with the classical clinical models in order to improve its accuracy.

Conclusions

Preoperative serum CRP was significantly associated with POD in older hip fracture patients. However, pre-morbid cognitive impairment and infections were the most important risk markers of POD. Although further research is needed to validate these results, the influence of neuroinflammation in the development of POD could help improve its prevention by targeting this pathway and creating delirium predictive models with both clinical and biochemical variables to improve predictive accuracy.

Declarations

Acknowledgments

We would like to thank the patients and staff at the Orthopedic and the Anesthesiology Department of Hospital Universitario de Navarra.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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References

1. Auer S, Reisberg B (1997) The GDS/FAST staging system. Int Psychogeriatrics 9:167–171. https://doi.org/10.1017/S1041610297004869
2. Barahona E, Pinhao R, Galindo V, Noguera A (2018) The Diagnostic Sensitivity of the Memorial Delirium Assessment Scale—Spanish Version. J Pain Symptom Manage 55:968–972. https://doi.org/10.1016/j.jpainsymman.2017.11.013
3. Barthel M (1965) Functional evaluation: the Barthel Index. Md State Med J 14:56–61
4. Burton JK, Fearon P, Noel-Storr AH, et al (2021) Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the detection of dementia within a secondary care setting. Cochrane Database Syst Rev 2021:. https://doi.org/10.1002/14651858.CD010772.pub3
5. Cerejeira J, Nogueira V, Luís P, et al (2012) The cholinergic system and inflammation: common pathways in delirium pathophysiology. J Am Geriatr Soc 60:669–675. https://doi.org/10.1111/j.1532-5415.2011.03883.x
6. Chen Y, Zheng J, Chen J (2020) Preoperative Circulating MiR-210, a Risk Factor for Postoperative Delirium Among Elderly Patients with Gastric Cancer Undergoing Curative Resection. Curr Pharm Des 26:5213–5219. https://doi.org/10.2174/1381612826666200617163857
7. Çinar MA, Balikçi A, Sertoğlu E, et al (2014) Role of CRP, TNF-a, and IGF-1 in Delirium Pathophysiology. Noro Psikiyatr Ars 51:376–382. https://doi.org/10.5152/npa.2014.6999
8. Delgado-Parada E, Morillo-Cuadrado D, Saiz-Ruiz J, et al (2022) Diagnostic accuracy of the Spanish version of the 4AT scale (4AT-ES) for delirium screening in older inpatients. Eur J Psychiatry 36:182–190. https://doi.org/10.1016/j.ejpsy.2022.01.003
9. Dillon ST, Vasunilashorn SM, Ngo L, et al (2017) Higher C-Reactive Protein Levels Predict Postoperative Delirium in Older Patients Undergoing Major Elective Surgery: A Longitudinal Nested Case-Control Study. Biol Psychiatry 81:145–153. https://doi.org/10.1016/j.biopsych.2016.03.2098
10. Freter S, Dunbar M, Koller K, et al (2015) Risk of pre- and post-operative delirium and the delirium elderly at risk (DEAR) tool in hip fracture patients. Can Geriatr J 18:212–216. https://doi.org/10.5770/cgj.18.185
11. Inouye SK, Westendorp RGJ, Saczynski JS, et al (2014) Delirium in elderly people. Lancet 383:911–922. https://doi.org/10.1016/S0140-6736(13)60688-1
12. Israni J, Lesser A, Kent T, Ko K (2018) Delirium as a predictor of mortality in US Medicare beneficiaries discharged from the emergency department: A national claims-level analysis up to 12 months. BMJ Open 8:1–7. https://doi.org/10.1136/bmjopen-2017-021258

13. Katsumi Y, Racine AM, Torrado-Carvajal A, et al (2020) The Role of Inflammation after Surgery for Elders (RISE) study: Examination of [11C]PBR28 binding and exploration of its link to post-operative delirium. NeuroImage Clin 27:. https://doi.org/10.1016/j.nicl.2020.102346
14. Lawton M, Brody E (1969) Assessment of older people: selfmaintaining and instrumental activities of daily living. Gerontologist. 1969;9:179–86. Gerontologist 9:1979–1986
15. Lee SJ, Jung SH, Lee SU, et al (2020) Postoperative delirium after hip surgery is a potential risk factor for incident dementia: A systematic review and meta-analysis of prospective studies. Arch Gerontol Geriatr 87:103977. https://doi.org/10.1016/j.archger.2019.103977
16. Lemstra AW, Kalisvaart KJ, Vreeswijk R, et al (2008) Pre-operative inflammatory markers and the risk of postoperative delirium in elderly patients. Int J Geriatr Psychiatry 23:943–948. https://doi.org/10.1002/gps.2015
17. Leng F, Edison P (2021) Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nat Rev Neurol 17:157–172. https://doi.org/10.1038/s41582-020-00435-y
18. Liu X, Yu Y, Zhu S (2018) Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. PLoS One 13:e0195659. https://doi.org/10.1371/journal.pone.0195659
19. Lopez DA, Khan SH, Jawed Y, et al (2020) Serum biomarkers associated with post-operative delirium in patients undergoing non-cardiac major thoracic surgery. Am J Respir Crit Care Med 201:
20. Maldonado JR (2013) Neuropathogenesis of delirium: Review of current etiologic theories and common pathways. Am J Geriatr Psychiatry 21:1190–1222. https://doi.org/10.1016/j.jagp.2013.09.005
21. Marcantonio ER, Flacker JM, Michaels M, Resnick NM (2000) Delirium Is Independently Associated with Poor Functional Recovery After Hip Fracture. J Am Geriatr Soc 48:618–624
22. Pathak A, Agrawal A (2019) Evolution of C-reactive protein. Front Immunol 10:. https://doi.org/10.3389/fimmu.2019.00943
23. Rentería MA, Gillett SR, McClure LA, et al (2020) C-reactive protein and risk of cognitive decline: The REGARDS study. PLoS One 15:1–15. https://doi.org/10.1371/journal.pone.0244612
24. Slor CJ, Witlox J, Adamis D, et al (2019) The trajectory of C-reactive protein serum levels in older hip fracture patients with postoperative delirium. Int J Geriatr Psychiatry 34:1438–1446. https://doi.org/10.1002/gps.5139
25. Sproston NR, Ashworth JJ (2018) Role of C-reactive protein at sites of inflammation and infection. Front Immunol 9:1–11. https://doi.org/10.3389/fimmu.2018.00754
26. Subramaniyan S, Terrando N (2019) Neuroinflammation and Perioperative Neurocognitive Disorders. Anesth Analg 128:781–788. https://doi.org/10.1213/ANE.0000000000004053
27. Welch C, McCluskey L, Wilson D, et al (2019) Delirium is prevalent in older hospital inpatients and associated with adverse outcomes: Results of a prospective multi-centre study on World Delirium Awareness Day. BMC Med 17:1–11. https://doi.org/10.1186/s12916-019-1458-7

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28. Wilson JE, Mart MF, Cunningham C, et al (2020) Delirium. Nature 11:
29. Woo J, Yu R, Wong M, et al (2015) Frailty screening in the community using the FRAIL scale. J Am Med Dir Assoc 16:412–419. https://doi.org/10.1016/j.jamda.2015.01.087
30. Yang Y, Zhao X, Gao L, et al (2021) Incidence and associated factors of delirium after orthopedic surgery in elderly patients: a systematic review and meta-analysis. Aging Clin Exp Res 33:1493–1506. https://doi.org/10.1007/s40520-020-01674-1

Figures

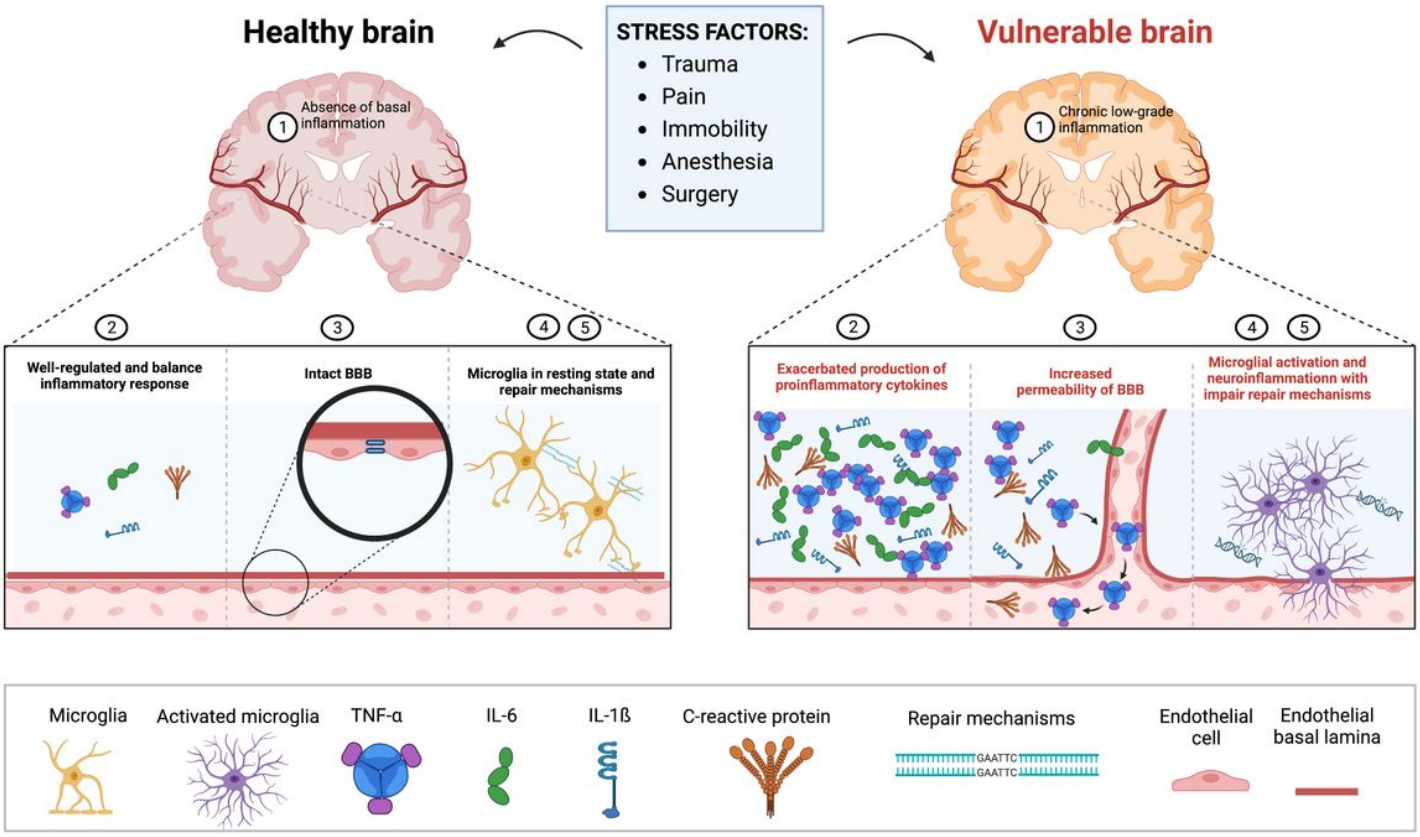

Figure 1

Neuroinflammatory hypothesis of delirium: the difference between a healthy and a vulnerable brain in response to stressors in hip fracture

1. Chronic inflammation in a vulnerable brain can result in sustained activation of proinflammatory pathways, leading to the production of additional cytokines, chemokines, and reactive oxygen species (ROS). This sustained neuroinflammation can damage neurons, disrupt synaptic function, and contribute to neurodegenerative processes seen in cognitive impairment.

2. Inflammatory response: In a healthy brain, the inflammatory response is typically well-regulated and balanced. However, in a vulnerable brain, there is an exacerbated production of proinflammatory cytokines such us tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6) and interleukin-1 beta (IL-1b). These cytokines act as mediators of inflammation and stimulate the production of CRP.

3. BBB integrity: The BBB is a protective barrier between the bloodstream and the brain, regulating the passage of molecules and cells. In a healthy brain, the BBB is generally intact, limiting the entry of inflammatory mediators and maintaining brain homeostasis. In contrast, in a frail brain, the BBB may be compromised, allowing increased permeability and the infiltration of inflammatory cells and molecules into the brain.

4. Microglial activation and neuroinflammation: Microglia, the resident immune cells of the brain, play a critical role in the inflammatory response. In a healthy brain, microglia are kept in a resting state, with balanced activation levels. In a vulnerable brain, microglia may exhibit a more activated and dysregulated state, leading to excessive release of proinflammatory cytokines and oxidative stress, contributing to neuroinflammation and delirium.

5. Impaired repair mechanisms: In a healthy brain, there are mechanisms for resolving inflammation and promoting tissue repair. However, in a vulnerable brain, these repair mechanisms may be impaired or dysregulated, leading to prolonged inflammation and reduced ability to restore normal brain function.

Supplementary Files

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Effectiveness of a multicomponent exercise training program for the management of delirium in hospitalized older adults using near-infrared spectroscopy as a biomarker of brain perfusion: Study protocol for a randomized controlled trial

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Delirium is an important cause of morbidity and mortality in older adults admitted to hospital. Multicomponent interventions targeting delirium risk factors, including physical exercise and mobilization, have been shown to reduce delirium incidence by 30–40% in acute care settings. However, little is known about its role in the evolution of delirium, once established. This study is a randomized clinical trial conducted in the Acute Geriatric Unit of Hospital Universitario de Navarra (Pamplona, Spain). Hospitalized patients with delirium who meet the inclusion criteria will be randomly assigned to the intervention or the control group. The intervention will consist of a multicomponent exercise training program, which will be composed of supervised progressive resistance and strength exercise over 3 consecutive days. Functional Near-Infrared Spectroscopy (NIRS) will be used for assessing cerebral and muscle tissue blood flow. The objective is to assess the effectiveness of this intervention in modifying the following primary outcomes: duration and severity of delirium and functional status. This study will contribute to determine the effectiveness of physical exercise in the management of delirium. It will be the first study

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to evaluate the impact of a multicomponent intervention based on physical exercise in the evolution of delirium.

Clinical trial registration: ClinicalTrials.gov. identifier: NCT05442892 (date of registration June 26, 2022).

KEYWORDS

delirium, near-infrared spectroscopy, multicomponent intervention, older adults, physical exercise, geriatric acute care unit

Introduction

Delirium is an acute onset and fluctuating syndrome that is characterized by disturbances in level of awareness, attention, and other cognitive functions (Helfand et al., 2021). It is highly prevalent among older adults across healthcare settings (8–17% reported in emergency departments, 20–29% in geriatric acute care, 13–50% in surgical patients, and 19–82% in intensive care units; Inouye et al., 2014). Furthermore, delirium is particularly important in older patients not only for its high incidence and prevalence but also for the great impact of its consequences including longer hospital stay, increased risk of institutionalization at discharge, higher cognitive and functional impairment, higher mortality, and greater healthcare costs (Jackson et al., 2017). In addition, geriatric inpatients often experience accelerated functional decline during hospitalization associated with long bed-rest episodes. Some studies have shown that more than 83% of these patients are bedridden and only 4% are permitted to stand or walk, which increases the risk of delirium and hinders its resolution once it is established (Covinsky et al., 2003; Brummel et al., 2014; Zisberg et al., 2015; Martínez-Velilla et al., 2016). Multicomponent interventions such as the Hospital Elder Life Program (HELP) have been shown to reduce delirium incidence in the acute care setting by 43%, by acting on modifiable risk factors such as dehydration, pain, sensory impairment, malnutrition, and immobility, compared to usual care (Hshieh et al., 2018; Wang et al., 2020; Burton et al., 2021).

However, there is little evidence on treatments for delirium. According to current clinical guidelines, the non-pharmacological approach focused on correcting the underlying causes should always be the first option, reserving pharmacological treatment for cases of extreme agitation [Davis et al., 2019; National Institute for Health and Care Excellence (NICE), 2022]. The scarce evidence is due to the fact that the pathophysiology of delirium remains unclear. Several mechanisms have been proposed to explain the development of delirium involving certain processes such as neuroinflammation, neuronal damage, neurotransmitter disturbance, and acute cerebral failure caused by hypoxia-ischemia. In the hypoxia-ischemia theory, there is a vascular dysfunction that produces endothelial injury and blood–brain barrier (BBB) damage, causing low oxygen delivery to the brain parenchyma and contributing to a metabolic insufficiency that allows delirium development (Wilson et al., 2020).

Physical exercise has been shown to improve cerebral blood flow, increasing neurogenesis and neuroplasticity through the release of neurotransmitters and neurotrophic factors such as insulin-like growth factor-1 (IGF-1) and Brain-Derived Neurotrophic Factor (BDNF; Ben-Zeev, 2022), providing synaptic transmission and improving cognitive function. Physical exercise also decreases the accumulation of amyloid plaques and tau protein which has been shown to improve cognitive functions such as attention, memory, executive tasks, and information processing speed (Erickson et al., 2019; Bliss et al., 2021; Cruz et al., 2022; Rai and Demontis, 2022; Silva et al., 2022). In fact, an individualized, multicomponent exercise training program may be an effective therapy for improving cognitive function in very old patients during acute hospitalization (de Asteasu et al., 2019, 2022), cognitive impairment (Venegas-Sanabria et al., 2022), and depression (Li et al., 2022). Therefore, we hypothesized that strategies that help improve oxygen supply to the brain, such as physical exercise, could be useful in treating delirium.

Although there are several techniques to monitor brain activity and cerebral blood flow (e.g., brain magnetic resonance, positron emission tomography, and electroencephalogram), Near-Infrared Spectroscopy (NIRS) could potentially be effective.

NIRS is a non-invasive physiological monitoring method that measures light absorbance to calculate oxy-hemoglobin (oxy-HB) and deoxy-hemoglobin (deoxy-HB), which provide an indirect measure of tissue oxygenation, often in the frontal cortex of the brain and muscle.

Some of the advantages that NIRS can offer are that is a non-invasive technology, which provides real-time continuous measurement of regional cerebral blood oxygenation and indirect blood flow indicating perfusion adequacy. Being a portable device, it can be moved to the place where the patient is, which facilitates its use. In addition, NIRS does not emit ionizing radiation and is less expensive than brain neuroimaging tests such as magnetic resonance imaging, providing added advantages such as the analysis of functional brain parameters while the patient performs different physical or cognitive tasks (Sakudo, 2016; Nguyen et al., 2019; Milej et al., 2020; Hogue et al., 2021).

Even though NIRS is used in different areas of Medicine, it has reached its greatest interest in Intensive Care and Anesthesiology for monitoring brain perfusion to avoid hypoxemia, which is

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associated with cognitive dysfunction and delirium (Schoen et al., 2011; Hori et al., 2014). Some studies have recently been published using NIRS as a predictive biomarker of postoperative delirium with promising results, where it has been observed that patients with low levels of cerebral oxygen saturation prior to surgery and during surgical intervention, had a higher incidence of postoperative delirium (Wood et al., 2017; Khan et al., 2021; Semrau et al., 2021; Susano et al., 2021). On the other hand, NIRS has been used to monitor hemodynamic response in the prefrontal cortex region and in lower-limb muscle tissue doing physical exercise and functional tasks in acutely hospitalized older patients (de Asteasu et al., 2021).

In spite of the growing number of studies published on the application of NIRS in delirium over the last few years, there are currently significant limitations so this evidence should be interpreted with caution (Chen et al., 2020). These studies often include a low sample size, are usually carried out in the field of surgery or the Intensive Care Unit (ICU), are heterogeneous in their composition, and have a high risk of bias. In addition, most of them do not consider the peculiarities of the older population, which is where delirium is most frequent. In most studies, essential information about older adults is not systematically collected, including geriatric syndromes (frailty, falls, and malnutrition), predisposing factors (comorbidity, functional, and cognitive status), and precipitating factors of delirium (pain, polypharmacy, use of urinary catheters).

The objective of this clinical trial is to evaluate the effect of a multicomponent exercise program on the development of delirium assessing cerebral and muscle perfusion using NIRS in hospitalized older adults. This study may help to understand the mechanisms underlying delirium, which are not yet totally clear in the literature, considering tissue oxygenation hypothesis.

Materials and methods

Study design

This study is a randomized clinical trial conducted in the 40-bedded Acute Geriatric Unit (AGU) of Hospital Universitario de Navarra (Pamplona, Spain). Hospitalized patients who meet the inclusion criteria will be randomly assigned to the intervention or control group. The study flow diagram is shown in Figure 1. After obtention of written informed consent, patients will be randomly assigned to either the intervention or control group. The data for both the intervention group and the control group will be obtained at five different times: the initial visit during the

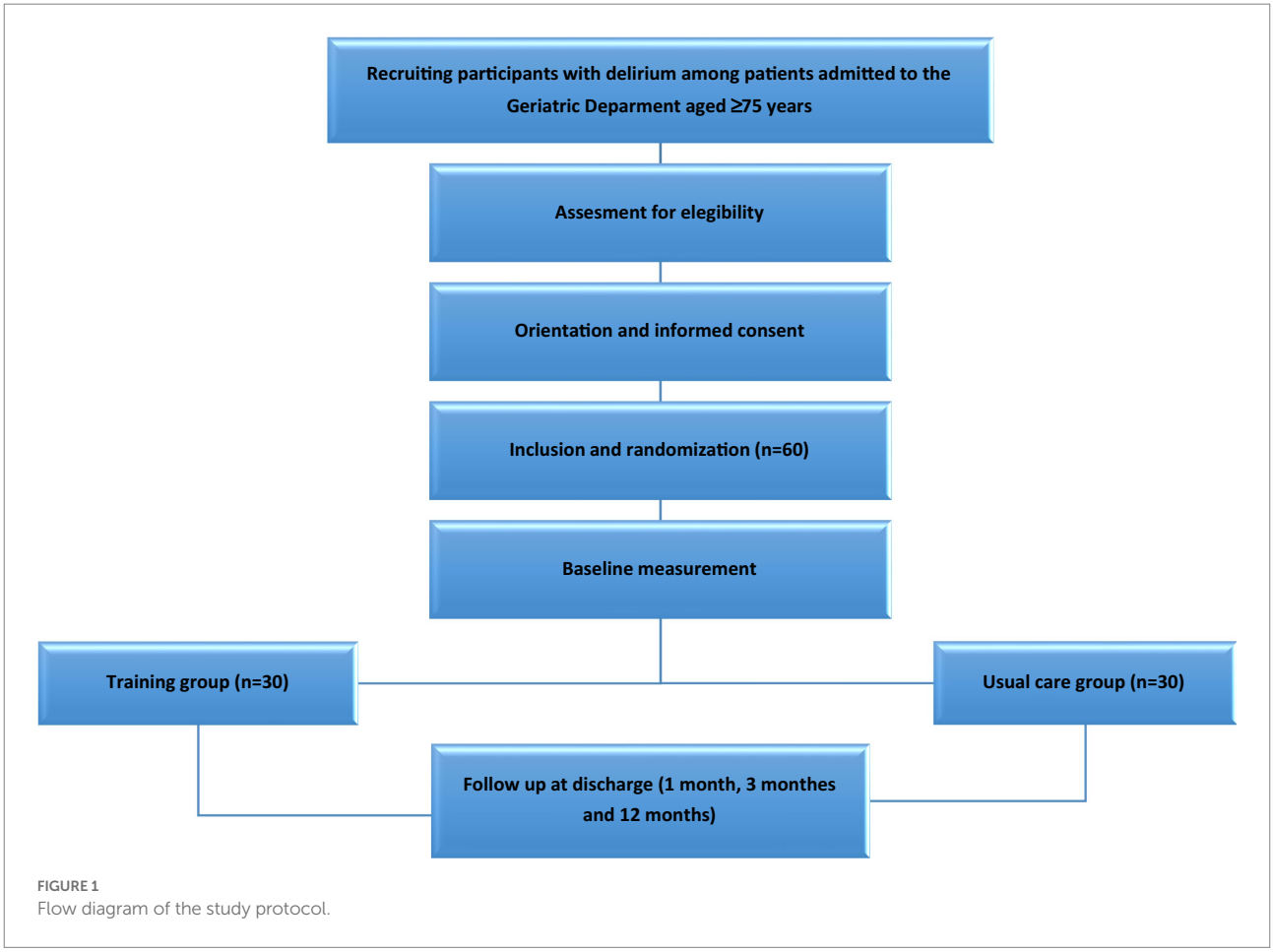

FIGURE 1
Flow diagram of the study protocol.

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TABLE 1 Time of measurement of the different variables on the subjects of the study.

Measurement	T1 baseline	T2 daily	T3 After training or control period	T4 1 month	T5 3months	T6 12 months
Barthel Index	X		X	X	X	X
Lawton and Brody Scale	X			X	X	X
Hierarchical Assessment of Balance and Mobility (HABAM)	X	X	X			
Handgrip strength	X		X			
Short Physical Performance Battery (SPPB)	X		X			
1RM (leg press, chest press and knee extension)	X		X			
Muscle power 10 repetitions at 50% 1RM in leg press	X		X			
Trail making test-part A (TMT-A)	X		X			
Regional cerebral oxygen saturation (Scto2) in the forehead and vastus lateralis at rest, TMT-A, 1RM, and 10 reps x 50% 1RM	X		X			
Delirium assessment (4AT)	X	X	X			
Delirium severity (MDAS)	X	X	X			
Delirium Motor Subtype Scale (DMSS)	X	X	X			
Global Deterioration Scale (GDS/FAST)	X			X	X	X
Informant questionnaire on cognitive decline in the elderly (*IQCODE*)	X			X	X	X
Yesavage Geriatric Depression Scale	X					
Geriatrics syndromes	X	X	X	X	X	X
FRAIL scale and Clinical Frailty Scale (CFS)	X			X	X	X
Mini nutritional assessment (MNA)	X					
Falls	X	X	X	X	X	X
Quality of life (EQ-5D)	X			X	X	X
Pharmacological treatment and drug burden index (DBI)	X		X	X	X	X
Laboratory parameters	X		X			

acute hospitalization, at discharge and at 1, 3, and 12 months after discharge through phone call and clinical history. The times of measurement of the different outcomes is shown in Table 1.

Peripheral blood (PB) samples will be obtained from all patients at baseline and at discharge. EDTA blood collection tubes (Vacuette®, Greiner Bio-One) will be used. All PB samples will be centrifuged in a fixed-angle rotor at 3,300 *rpm* for 10 min at room temperature. After centrifugation, the serum in the upper layer will be carefully extracted from the plasma in the bottom layer, divided into 100 µL, and immediately stored at −80°C. Plasma and buffy coat will be also extracted and stored in polypropylene plastic tubes at −80°C.

We aim to examine the brain function during delirium and the effects of an intra-hospital exercise program on the prefrontal cortex region and on muscle function with the use of NIRS. Regional oxygen saturation (rSO2) in the forehead and vastus lateralis muscle will be recorded using NIRS using the NIRO-200NX C10448 monitor (Hamamatsu, Japan) by placing one optode on the patient's forehead above the eyebrow and the other optode on the vastus lateralis muscle (Koyama et al., 2013; Udina et al., 2020). The measurements will be made with the patients resting in the sitting position during 60 s, doing trail making test part A and the assessment of 10 reps x 50% 1RM at the beginning of the study and the 4th day of the study, in both intervention and control groups. There are some factors which may alter NIRS parameters because they influence cerebral perfusion such as drugs, blood pressure, hemoglobin, or oxygen saturation. Although we will evaluate all of them, this is an important limitation of the study.

Delirium will be assessed using the European Spanish version of the 4AT (Delgado-Parada et al., 2022) daily during hospitalization until discharge. This tool has been validated for the Spanish population and is a reliable instrument for delirium detection in older patients. The 4AT scale is designed to be used as a delirium detection tool in general clinical settings. The 4AT has four parameters: Alertness, Abbreviated mental test-4 (AMT4), Attention (months backward test), and Acute change or fluctuating

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course. The score range is 0–12, with scores of 4 or more suggesting possible delirium. Scores of 1–3 suggest possible cognitive impairment (Jeong et al., 2020; Tieges et al., 2021). Delirium severity will be evaluated daily with the Memorial Delirium Assessment Scale (MDAS) which is also validated in Spain (Noguera et al., 2014; Barahona et al., 2018). MDAS was designed to diagnose delirium as well as classify delirium severity. The instrument reflects delirium diagnostic criteria from DSM. It has 10 severity items rated 0 to 3 points for a maximum total score of 30 points, with higher scores representing more severe delirium (Jones et al. 2019).

The protocol employs relevant standard protocol items for clinical trials according to the SPIRIT 2013 statement (Chan et al., 2013) and follows the CONSORT statement (Moher et al., 2001). The trial is registered at ClinicalTrials.gov, identifier NCT05442892. This study was approved by the Navarra Clinical Research Ethics Committee (PI_2021/94).

Study participants and eligibility criteria

Medical inpatients admitted to the AGU of Hospital Universitario de Navarra (Pamplona, Spain) between February 2022 and February 2023.

The inclusion criteria are:

- Age: 75 years or older with delirium during hospitalization.
- Able to ambulate with or without personal/technical assistance.
- Barthel Index ≥45 points 2 weeks before admission.
- Informed consent by patients (if possible), relatives, or legal representatives.

The exclusion criteria are:

- Duration of hospitalization <5 days.
- Severe dementia (GDS 6–7).
- Terminal illness (life expectancy less than 3 months).
- Any factor precluding performance of physical exercise. These factors include:
- Acute myocardial infarction in the past 3 months or unstable angina
- Severe heart valve insufficiency.
- Arrhythmia or uncontrolled arterial hypertension.
- Pulmonary embolism in the past 3 months.
- Hemodynamic instability.
- Pathology that could interfere with NIRS registration:
- Facial dermal pathology (front).
- Acute intracranial pathology (hemorrhages, cerebral infarcts).

Randomization and blinding

The study participants will be randomized[1] into intervention or control group. Assessment staff will be blinded to the participant randomization assignment, as well as to the main study design and to what changes we expect to occur in the study outcomes in each group. It will not be possible to conceal the group assignment from the staff involved in the training of the intervention group. Patients and their families will be informed of the random inclusion in one group but will not be informed as to which group they belong.

Sample size

Assuming a standard deviation in MDAS scale of 6 points, for a power of 80% and a significance level of 0.05, 24 patients per group (a total of 48) will be necessary to detect a mean difference of 5 points between groups. Assuming 20% losses, 30 patients per group will be necessary.

Statistics

The baseline value of the included variables will be described for the whole sample and separated by group using frequencies and percentages for the categorical ones and *via* mean and standard deviation or median and interquartile range for continuous ones. In order to assess the extent of the therapeutic effect, we will compute for every patient the difference between final and initial levels of the continuous outcome variables. Then, these differences will be compared by intervention group, using *t*-tests or Mann–Whitney U tests. For the mortality outcome, the percentage mortality of both groups will be compared using the Chi-square test. In case of observing relevant differences at baseline, these comparisons will be adjusted by the baseline value, using linear models or generalized linear models. The level of statistical significance will be 0.05. Data will be analyzed with SPSS package 28.0.

Detailed description

Usual care group (control)

Participants randomly assigned to the usual care group will receive normal hospital care, which includes physical rehabilitation when needed.

Intervention group (training)

The intervention will consist of a multicomponent exercise training program adapted from Vivifrail to prevent muscle weakness and falls (Izquierdo et al., 2017; Casas-Herrero et al., 2022) and the training protocol was detailed in previous literature (Martínez-Velilla et al., 2015, 2016, 2019, 2022). It will be composed of supervised progressive resistance exercise training, balance training, and walking for 3 consecutive days. During the training period, patients will be trained in 30 min sessions once a day (morning). The supervised multicomponent exercise training program will be comprised of upper and lower body strengthening exercises, tailored to the

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TABLE 2 Intervention group exercises.

Exercise	Day 1	Day 2	Day 3	Day 4
Rises from a chair	1 × 5	2 × 10	2 × 10	1 × 5
Leg press	1RM + 2 × 10 (50% 1RM)	3 × 10 (60% 1RM)	3 × 8 (70% 1RM)	1RM + 1 × 10 (50%1RM)
Chest press	1RM + 2 × 10 (50% 1RM)	3 × 10 (60% 1RM)	3 × 8 (70% 1RM)	1RM
Leg extension	1RM + 2 × 10 (50% 1RM)	3 × 10 (60% 1RM)	3 × 8 (70% 1RM)	1RM

individual's functional capacity, using weight machines and aiming for 2–3 sets of 8–10 repetitions at an intensity of 50–70% of 1RM (Matrix, Johnson Health Tech, Ibérica, S.L. Torrejón de Ardoz, Madrid, Spain). A "1RM" signifies the maximum resistance a person can move in one repetition of an exercise. The resistance exercises focused on the major upper and lower limb muscles. On the second and third training days, patients do 2 sets of 10 chair squats. Each resistance training session will include 2 exercises for the leg extensor muscles (bilateral leg press and bilateral knee extension machines) and 1 exercise for upper limbs (seated bench press machine). During the progressive resistance training, instruction will be provided to the participants to perform the exercises at a high velocity of motion. However, care will be taken to ensure that exercises are executed with correct form. In the first assessment, the patients will warm up with specific movements for the exercise test. Each subject's maximal load will be determined in no more than five attempts. During all neuromuscular performance tests, a strong verbal encouragement will be given to each subject to motivate them to perform each test action as optimally and rapidly as possible. Three experienced physical trainers (FZF, IOM, and ADM) will carefully monitor and supervise all training sessions and provide instruction and encouragement. Adherence to the exercise intervention program will be documented in a daily register of sessions and adverse events including muscle pain, fatigue, falls and general aches will be recorded by the training staff. Participants and their family members will be carefully familiarized with the training procedures in advance. The intervention exercises are detailed in Table 2 and the training protocol is shown in Figure 2.

Outcome measures

Primary outcome

- Duration and severity of delirium during the hospitalization between both intervention and control group and the change in functional status: 4AT and MDAS scale.
- Functional capacity of patients will be evaluated by the Short Physical Performance Battery (SPPB), which evaluates, balance, gait ability, and leg strength using a single tool. The total score will range from 0 (worst) to 12 points (best). The SPPB test has been shown to be a valid instrument for screening frailty and predicting disability, institutionalization, and mortality (Guralnik et al., 1994). Daily functional status will be also assessed with the Hierarchical Assessment of Balance and Mobility (HABAM) with is an instrument that provides a clinical assessment of in-bed mobility, transfers, and ambulation (Gual et al., 2019; Richardson et al., 2021). The lowest number, a value of 0, is equal to the lowest or no performance. Changes in these abilities can then be compared with patient progress.
- Regional oxygen saturation (rSO2) will be measured using NIRS (Luo et al., 2018; Pfeifer et al., 2018).

Secondary outcome

- Cognitive status: Global Deterioration Scale (GDS) which describes 7 clinically distinguishable global stages, from normality to severe dementia of the Alzheimer type (Reisberg et al., 1982; Auer and Reisberg, 1997) and the Informant Questionnaire on Cognitive Decline in the Elderly short form (IQCODE) which is a 16-question form, each question is scored from 1 (much improved) to 5 (much worse) and a cutoff point (average score) of 3.31/3.38 achieves a balance of sensitivity and specificity of cognitive impairment (Blandfort et al., 2020; Harrison et al., 2021).
- Functional status: Barthel Index of independence during activities of daily living (ADLs). This index ranges from 0 worst to 100 best (Barthel, 1965).
- Mortality.
- Quality of life: EuroQol Scale-5D. This instrument measures 5 dimensions of health status: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman et al., 2001; García-Gordillo et al., 2015).
- Use of health sources: New admissions to the hospital, admission to nursing homes, visits to the general practitioner, and to the emergency department.
- Falls.

Discussion

Given that the pathophysiology of delirium remains unclear and its pharmacological treatment once established has not been shown to be effective in addition to having serious side effects (extrapyramidal symptoms, sedation, arrhythmias…) physical exercise, due to its anti-inflammatory component and improvement of cerebral perfusion, can open as a new therapeutic option to explore. Other important aspect of our trial is the inclusion of older patients with mild cognitive decline and dementia. So far, most of trials in aged frail participants with these conditions are routinely excluded. The inclusion of participants with cognitive impairment in addition to frailty makes the trial novel with notable external validity compared with other previous

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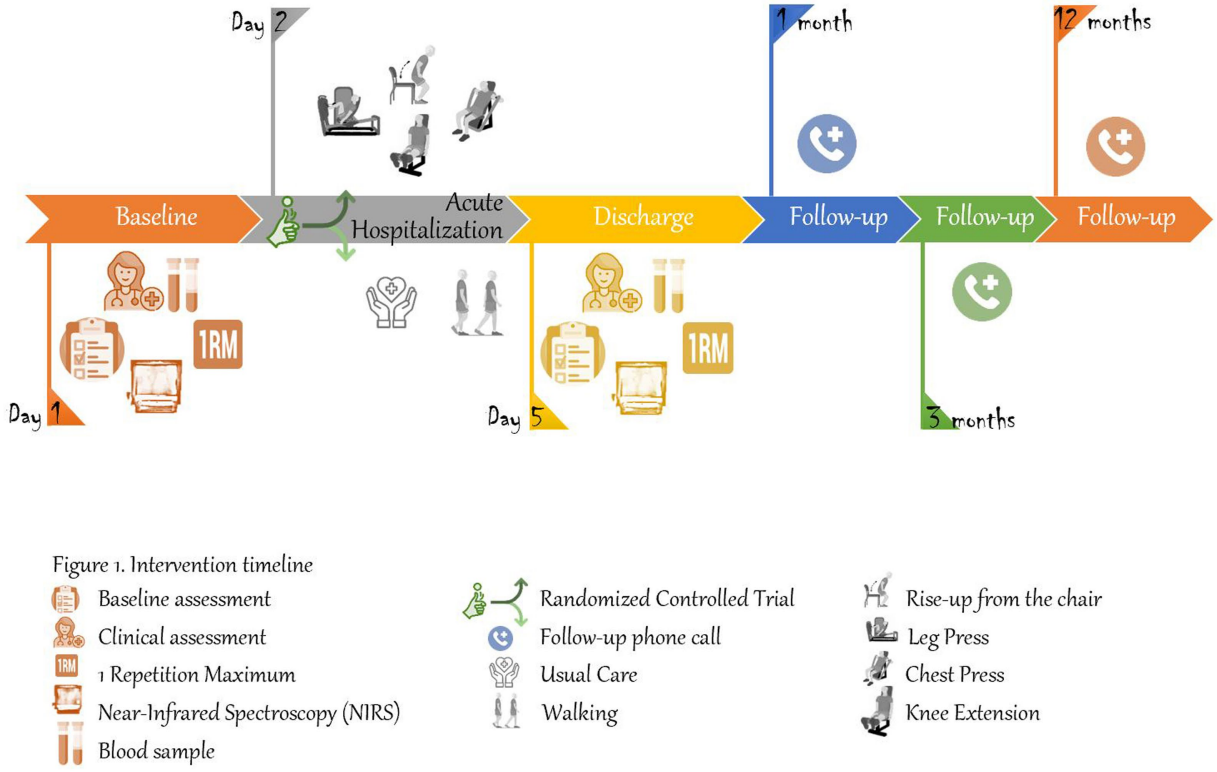

FIGURE 2
Intervention timeline.

trials in assessing the effect of individualized exercise programs on functional capacity, activities of daily living, and cognitive function. This study will both advance delirium-related knowledge and improve health outcomes through a program based on physical exercise. Moreover, this project will try to find new biomarkers of delirium that could be extrapolated to the usual clinical practice and help in its monitoring. Due to the high prevalence of delirium in this population and its serious consequences on morbidity and mortality, this intervention opens the possibility of a new therapeutic approach that can mitigate its impact. If our hypothesis is correct and shows that a multicomponent, individualized, and progressive exercise program in hospitalized older adults with delirium improves cognitive and functional status, a possible new targeted and therapeutic tool during hospitalization could be developed to implement delirium management.

Trial status

The trial commenced recruitment on 7 February 2022 and is currently open for recruitment. Recruitment will cease when 60 participants have been randomized. It is anticipated this target will be reached by February 2023.

Ethics statement

This study follows the principles of the Declaration of Helsinki (World Medical Association) and was approved by the Navarra Clinical Research Ethics Committee on September 15, 2021 (PI_2021/94). The patients/participants provided their written informed consent to participate in this study.

Author contributions

L-LV, FabiZ-F, AC-M, and IO-M developed the protocol in consultation with FabrZ-F, MS, MI, and NM-V. LL-V, FabiZ-F, AC-M, and IO-M were involved in the recruitment and evaluation of the patients. All authors contributed to the article and approved the submitted version.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.1013631/full#supplementary-material

References

Auer, S., and Reisberg, B. (1997). The GDS/FAST staging system. *Int. Psychogeriatr.* 9, 167–171. doi: 10.1017/S1041610297004869

Barahona, E., Pinhao, R., Galindo, V., and Noguera, A. (2018). The diagnostic sensitivity of the memorial delirium assessment scale—Spanish version. *J. Pain Symptom Manag.* 55, 968–972. doi: 10.1016/j.jpainsymman.2017.11.013

Barthel, M. (1965). Functional evaluation: the Barthel index. *Md. State Med. J.* 14, 56–61.

Ben-Zeev, T. (2022). The effect of exercise on neurogenesis in the brain. *IMAJ* 24, 533–538. PMID: 35971998

Blandfort, S., Gregersen, M., Rahbek, K., Juul, S., and Damsgaard, E. M. (2020). The short IQCODE as a predictor for delirium in hospitalized geriatric patients. *Aging Clin. Exp. Res.* 32, 1969–1976. doi: 10.1007/s40520-019-01412-2

Bliss, E. S., Wong, R. H. X., Howe, P. R. C., and Mills, D. E. (2021). Benefits of exercise training on cerebrovascular and cognitive function in ageing. *J. Cereb. Blood Flow Metab.* 41, 447–470. doi: 10.1177/0271678X20957807

Brummel, N. E., Jackson, J. C., Pandharipande, P. P., Thompson, J. L., Shintani, A. K., Dittus, R. S., et al. (2014). Delirium in the ICU and subsequent long-term disability among survivors of mechanical ventilation. *Crit. Care Med.* 42, 369–377. doi: 10.1097/CCM.0b013e3182a645bd

Burton, J. K., Craig, L. E., Yong, S. Q., Siddiqi, N., Teale, E. A., Woodhouse, R., et al. (2021). Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst. Rev.* 7:CD013307. doi: 10.1002/14651858.CD013307.pub2

Casas-Herrero, Á., Mikel, L., de Asteasu, S., Antón-Rodrigo, I., Sánchez-Sánchez, J. L., Montero-Odasso, M., et al. (2022). Effects of Vivifrail multicomponent intervention on functional capacity: a multicentre, randomized controlled trial. *J. Cachexia. Sarcopenia Muscle* 13, 884–893. doi: 10.1002/jcsm.12925

Chan, A. W., Tetzlaff, J. M., Gøtzsche, P. C., Altman, D. G., Mann, H., Berlin, J. A., et al. (2013). SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 346, 1–42. doi: 10.1136/bmj.e7586

Chen, W. L., Wagner, J., Heugel, N., Jeffrey Sugar, Y., Lee, W., Conant, L., et al. (2020). Functional near-infrared spectroscopy and its clinical application in the field of neuroscience: advances and future directions. *Front. Neurosci.* 14, 1–15. doi: 10.3389/fnins.2020.00724

Covinsky, K. E., Palmer, R. M., Fortinsky, R. H., Counsell, S. R., Stewart, A. L., Kresevic, D., et al. (2003). Loss of Independence in activities of daily living in older adults hospitalized with medical illnesses: increased vulnerability with age. *J. Am. Geriatr. Soc.* 51, 451–458. doi: 10.1046/j.1532-5415.2003.51152.x

Cruz, P., Del, B., Ahmadi, M., Naismith, S. L., and Stamatakis, E. (2022). Association of Daily Step Count and Intensity with incident dementia in 78430 adults living in the UK. *JAMA Neurol.* 79, 1059–1063. doi: 10.1001/jamaneurol.2022.2672

Davis, D., Searle, S. D., and Tsui, A. (2019). The Scottish intercollegiate guidelines network: risk reduction and Management of Delirium. *Age Ageing* 48, 485–488. doi: 10.1093/ageing/afz036

de Asteasu, S., Mikel, L., Cuevas-Lara, C., García-Hermoso, A., Ramírez-Vélez, R., Martínez-Velilla, N., et al. (2022). Effects of physical exercise on the incidence of delirium and cognitive function in acutely hospitalized older adults: a systematic review with meta-analysis. *J. Alzheimers Dis.* 87, 503–517. doi: 10.3233/JAD-220103

de Asteasu, S., Mikel, L., Martínez-Velilla, N., Zambom-Ferraresi, F., Casas-Herrero, Á., Cadore, E. L., et al. (2019). Assessing the impact of physical exercise on cognitive function in older medical patients during acute hospitalization: secondary analysis of a randomized trial. *PLoS Med.* 16, e1002852–e1002814. doi: 10.1371/journal.pmed.1002852

de Asteasu, S., Mikel, L., Martínez-Velilla, N., Zambom-Ferraresi, F., Ramírez-Vélez, R., García-Hermoso, A., et al. (2021). Exercise effects on brain and muscle function in acutely hospitalized older patients assessed by functional near-infrared spectroscopy. *J. Am. Med. Dir. Assoc.* 22, 875–876. doi: 10.1016/j.jamda.2020.12.027

Delgado-Parada, E., Morillo-Cuadrado, D., Saiz-Ruiz, J., Cebollada-Gracia, A., Ayuso-Mateos, J. L., and Cruz-Jentoft, A. J. (2022). Diagnostic accuracy of the Spanish version of the 4AT scale (4AT-ES) for delirium screening in older inpatients. *Eur. J. Psychiatry* 36, 182–190. doi: 10.1016/j.ejpsy.2022.01.003

Erickson, K. I., Hillman, C., Stillman, C. M., Ballard, R. M., Bloodgood, B., Conroy, D. E., et al. (2019). Physical activity, cognition, and brain outcomes: a review of the 2018 physical activity guidelines. *Med. Sci. Sports Exerc.* 51, 1242–1251. doi: 10.1249/MSS.0000000000001936

García-Gordillo, M. Á., Del Pozo-Cruz, B., Adsuar, J. C., Cordero-Ferrera, J. M., Abellán-Perpiñán, J. M., and Sánchez-Martínez, F. I. (2015). Validación y Comparación de Los Instrumentos EQ-5D-3L y SF-6D En Una Muestra de Población Española Con Enfermedad de Parkinson. *Nutricion Hospitalaria* 32, 2808–2821. doi: 10.3305/nh.2015.32.6.9765

Gual, N., Richardson, S. J., Davis, D. H. J., Bellelli, G., Hasemann, W., Meagher, D., et al. (2019). Impairments in balance and mobility identify delirium in patients with comorbid dementia. *Int. Psychogeriatr.* 31, 749–753. doi: 10.1017/S1041610218001345

Guralnik, J. M., Simonsick, E. M., Ferrucci, L., Glynn, R. J., Berkman, L. F., Blazer, D. G., et al. (1994). A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission energetic cost of walking in older adults view project IOM committee on cognitive Agi. *J. Gerontol.* 49, M85–M94. Available online at: http://www.ncbi.nlm.nih.gov/pubmed/8126356. doi: 10.1093/geronj/49.2.M85

Harrison, J. K., Stott, D. J., McShane, R., Noel-Storr, A. H., Swann-Price, R. S., and Quinn, T. J. (2021). Informant questionnaire on cognitive decline in the elderly (IQCODE) for the early detection of dementia across a variety of healthcare settings. *Cochrane Database Syst. Rev.* 7:CD011333. doi: 10.1002/14651858.CD011333.pub3

Helfand, B. K. I., D'Aquila, M. L., Tabloski, P., Erickson, K., Yue, J., Fong, T. G., et al. (2021). Detecting delirium: a systematic review of identification instruments for non-ICU settings. *J. Am. Geriatr. Soc.* 69, 547–555. doi: 10.1111/jgs.16879

Herdman, M., Badia, X., and Berra, S. (2001). EuroQol-5D: a simple alternative for measuring health-related quality of life in primary care. *Atencion Primaria/Sociedad Española de Medicina de Familia y Comunitaria* 28, 425–429. doi: 10.1016/s0212-6567(01)70406-4

Hogue, C. W., Levine, A., Hudson, A., and Lewis, C. (2021). Clinical applications of near-infrared spectroscopy monitoring in cardiovascular surgery. *Anesthesiology* 134, 784–791. doi: 10.1097/ALN.0000000000003700

Hori, D., Brown, C., Ono, M., Rappold, T., Sieber, F., Gottschalk, A., et al. (2014). Arterial pressure above the upper cerebral autoregulation limit during cardiopulmonary bypass is associated with postoperative delirium. *Br. J. Anaesth.* 113, 1009–1017. doi: 10.1093/bja/aeu319

Hshieh, T. T., Yang, T., Gartaganis, S. L., Yue, J., and Inouye, S. K. (2018). Hospital elder life program: systematic review and meta-analysis of effectiveness. *Am. J. Geriatr. Psychiatr.* 26, 1015–1033. doi: 10.1016/j.jagp.2018.06.007

Inouye, S. K., Westendorp, R. G. J., Saczynski, J. S., Naeije, G., and Pepersack, T. (2014). Delirium in elderly people. *Lancet* 383, 911–922. doi: 10.1016/S0140-6736(13)60688-1

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Nafarroako Unibertsitate Publikoa

Izquierdo, M., Casas-Herrero, A., Zambom-Ferraresi, F., Martínez-Velilla, N., Alonso-Bouzón, C., Rodríguez-Mañas, L., et al. (2017). Multicomponent physical exercise program VIVIFRAIL. Available at: http://www.vivifrail.com/resources/

Jackson, T. A., Gladman, J. R. F., Harwood, R. H., MacLullich, A. M. J., Sampson, E. L., Sheehan, B., et al. (2017). Challenges and opportunities in understanding dementia and delirium in the acute hospital. *PLoS Med.* 14, e1002247–e1002249. doi: 10.1371/journal.pmed.1002247

Jeong, E., Park, J., and Lee, J. (2020). Diagnostic test accuracy of the 4AT for delirium detection: a systematic review and meta-analysis. *Int. J. Environ. Res. Public Health* 17, 1–15. doi: 10.3390/ijerph17207515

Jones, R. N., Cizginer, S., Pavlech, L., Albuquerque, A., Daiello, L. A., Dharmarajan, K., et al. Assessment of instruments for measurement of delirium severity: a systematic review. *JAMA Intern. Med.* 179, 231–239. doi: 10.1001/jamainternmed.2018.6975

Khan, J. M., Wood, M. D., Lee, K. F. H., Maslove, D., Muscedere, J., English, S. W., et al. (2021). Delirium, cerebral perfusion, and high-frequency vital-sign monitoring in the critically ill the CONFOCAL-2 feasibility study. *Ann. Am. Thorac. Soc.* 18, 112–121. doi: 10.1513/AnnalsATS.202002-093OC

Koyama, Y., Wada, T., Lohman, B. D., Takamatsu, Y., Matsumoto, J., Fujitani, S., et al. (2013). A new method to detect cerebral blood flow waveform in synchrony with chest compression by near-infrared spectroscopy during CPR. *Am. J. Emerg. Med.* 31, 1504–1508. doi: 10.1016/j.ajem.2013.07.002

Li, L., Luo, J., Reangsing, C., and Schneider, J. K. (2022). Effects of exercise on depressive symptoms among nursing home residents: a meta-analysis. *Aging Ment. Health* 26, 1514–1523. doi: 10.1080/13607863.2021.1951658

Luo, X., Qi, Y., Wang, H., Wang, Y., He, T., and Rong, B. (2018). Prefrontal cortex dysfunction during verbal fluency task after Atypicalantipsychotic treatment in schizophrenia: a near-infrared spectroscopy imaging study. *Neurosci. Lett.* 686, 101–105. doi: 10.1016/j.neulet.2018.09.001

Martínez-Velilla, N., Abizanda, P., Gómez-Pavón, J., Zambom-Ferraresi, F., Sáez, M. L., Asteasu, D., et al. (2022). Effect of an exercise intervention on functional decline in very old patients during acute hospitalizations: results of a multicenter, randomized clinical trial. *JAMA Intern. Med.* 182, 345–347. doi: 10.1001/jamainternmed.2021.7654

Martínez-Velilla, N., Casas-Herrero, Á., Zambom-Ferraresi, F., De Asteasu, L. S., Mikel, L., Ga/lbete Arkaitz, A., et al. (2019). Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: a randomized clinical trial. *JAMA Intern. Med.* 179, 28–36. doi: 10.1001/jamainternmed.2018.4869

Martínez-Velilla, N., Casas-Herrero, A., Zambom-Ferraresi, F., Suárez, N., Alonso-Renedo, J., Contín, K. C., et al. (2015). Functional and cognitive impairment prevention through early physical activity for geriatric hospitalized patients: study protocol for a randomized controlled trial. *BMC Geriatr.* 15, 1–9. doi: 10.1186/s12877-015-0109-x

Martínez-Velilla, N., Garrués-Irisarri, M., Ibañez-Beroiz, B., Gil-Cabañas, J., Richarte-García, A., Idoate-Saralegui, F., et al. (2016). An exercise program with Patient's involvement and family support can modify the cognitive and affective trajectory of acutely hospitalized older medical patients: a pilot study. *Aging Clin. Exp. Res.* 28, 483–490. doi: 10.1007/s40520-015-0434-0

Milej, D., He, L., Abdalmalak, A., Baker, W. B., Anazodo, U. C., Diop, M., et al. (2020). Quantification of cerebral blood flow in adults by contrast-enhanced near-infrared spectroscopy: validation against MRI. *J. Cereb. Blood Flow Metab.* 40, 1672–1684. doi: 10.1177/0271678X19872564

Moher, D., Schulz, K. F., and Altman, D. G. CONSORT Group (2001). The CONSORT statement: revised recommendations for improving the quality of reports of parallel group Reandomized trials. *BMC Med. Res. Methodol.* 91, 437–442. doi: 10.1186/1471-2288-1-2

National Institute for Health and Care Excellence (NICE) (2022). "Delirium: prevention, diagnosis and management," www.nice.org.uk/guidance/cg103 (Accessed March 2019).

Nguyen, T. N., Wen, W., Woldemichael, E., Toronov, V., and Lin, S. (2019). Hyperspectral near-infrared spectroscopy assessment of the brain during Hypoperfusion. *J. Biomed. Opt.* 24, 1–6. doi: 10.1117/1.jbo.24.3.035007

Noguera, A., Carvajal, A., Alonso-Babarro, A., Chisholm, G., Bruera, E., and Centeno, C. (2014). First Spanish version of the memorial delirium assessment scale: psychometric properties, responsiveness, and factor loadings. *J. Pain Symptom Manag.* 47, 189–197. doi: 10.1016/j.jpainsymman.2013.02.020

Pfeifer, M. D., Scholkmann, F., and Labruyère, R. (2018). Signal processing in functional near-infrared spectroscopy (FNIRS): methodological differences Lead to different statistical results. *Front. Hum. Neurosci.* 11:641. doi: 10.3389/fnhum.2017.00641

Rai, M., and Demontis, F. (2022). Muscle-to-brain signaling via Myokines and Myometabolites. *Brain Plasticity* 8, 43–63. doi: 10.3233/bpl-210133

Reisberg, B., Ferris, S., De Leon, M., and Crook, T. (1982). The global deterioration scale for assessment of primary degenerative dementia. *Am. J. Psychiatr.* 139, 1136–1139. doi: 10.1176/ajp.139.9.1136

Richardson, S., Murray, J., Davis, D., Stephan, B. C. M., Robinson, L., Brayne, C., et al. (2021). Delirium and delirium severity predict the trajectory of the hierarchical assessment of balance and mobility (HABAM) in hospitalized older people: findings from the DECIDE study. *J. Gerontol.* 77, 531–535. doi: 10.1093/gerona/glab081

Sakudo, A. (2016). Near-infrared spectroscopy for medical applications: current status and future perspectives. *Clin. Chim. Acta* 455, 181–188. doi: 10.1016/j.cca.2016.02.009

Schoen, J., Meyerrose, J., Paarmann, H., Heringlake, M., Hueppe, M., and Berger, K. U. (2011). Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: a prospective observational trial. *Crit. Care* 15:R218. doi: 10.1186/cc10454

Semrau, J. S., Motamed, M., Ross-White, A., and Gordon Boyd, J. (2021). Cerebral oximetry and preventing neurological complication post-cardiac surgery: a systematic review. *Eur. J. Cardiothorac. Surg.* 59, 1144–1154. doi: 10.1093/ejcts/ezaa485

Silva, Jason Leonardo, Da, Nounagnon Frutueux, Agbangla, ChristineLe, Page, Wahiba Ghernout, and Andrieu, Bernard. (2022). "Effects of chronic physical exercise or multicomponent exercise programs on the mental health and cognition of older adults living in a nursing home: a systematic review of studies from the past 10 years." *Front. Psychol.* 13, 1–9. doi: 10.3389/fpsyg.2022.888851.

Susano, M. J., Dias, M., Seixas, F. S., Vide, S., Grasfield, R., Abelha, F. J., et al. (2021). Association among preoperative cognitive performance, regional cerebral oxygen saturation, and postoperative delirium in older Portuguese patients. *Anesth. Analg.* 132, 846–855. doi: 10.1213/ANE.0000000000005159

Tieges, Z., Maclullich, A. M. J., Anand, A., Brookes, C., Cassarino, M., O'connor, M., et al. (2021). Diagnostic accuracy of the 4AT for delirium detection in older adults: systematic review and meta-analysis. *Age Ageing* 50, 733–743. doi: 10.1093/ageing/afaa224

Udina, C., Avtzi, S., Durduran, T., Holtzer, R., Rosso, A. L., Castellano-Tejedor, C., et al. (2020). Functional near-infrared spectroscopy to study cerebral hemodynamics in older adults during cognitive and motor tasks: a review. *Front. Aging Neurosci.* 11, 1–19. doi: 10.3389/fnagi.2019.00367

Venegas-Sanabria, L. C., Cavero-Redondo, I., Martínez-Vizcaino, V., Cano-Gutierrez, C. A., and Álvarez-Bueno, C. (2022). Effect of multicomponent exercise in cognitive impairment: a systematic review and meta-analysis. *BMC Geriatr.* 22:617. doi: 10.1186/s12877-022-03302-1

Wang, Y. Y., Yue, J. R., Xie, D. M., Carter, P., Li, Q. L., Gartaganis, S. L., et al. (2020). Effect of the tailored, family-involved hospital elder life program on postoperative delirium and function in older adults: a randomized clinical trial. *JAMA Intern. Med.* 180, 17–25. doi: 10.1001/jamainternmed.2019.4446

Wilson, J. E., Mart, M. F., Cunningham, C., Shehabi, Y., Girard, T. D., Maclullich, A. M. J., et al. (2020). Delirium. *Nat. Rev. Dis. Primers* 6:90. doi: 10.1038/s41572-020-00223-4

Wood, M. D., Maslove, D. M., Muscedere, J. G., Day, A. G., and Gordon Boyd, J. (2017). Low brain tissue oxygenation contributes to the development of delirium in critically ill patients: a prospective observational study. *J. Crit. Care* 41, 289–295. doi: 10.1016/j.jcrc.2017.06.009

Zisberg, A., Shadmi, E., Gur-Yaish, N., Tonkikh, O., and Sinoff, G. (2015). Hospital-associated functional decline: the role of hospitalization processes beyond individual risk factors. *J. Am. Geriatr. Soc.* 63, 55–62. doi: 10.1111/jgs.13193

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Effects of exercise intervention for the management of delirium in hospitalized older adults: a randomized clinical trial

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Impact Statement

We certify that this work is novel.

Key points

- Delirium is a serious neuropsychiatric disorder in which drugs have shown limited efficacy.

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- Findings from this randomized controlled trial suggest that multicomponent individualized exercise in acutely hospitalized older patients with delirium is safe and may improve delirium resolution and functional status.
- This benefit is also observed at 1 and 3-months follow-up, where patients in the intervention group exhibited better cognitive and functional capacity.

Why does this paper matter?

Findings identify the need to consider individualized multicomponent physical exercise as a new approach in the treatment of delirium, as patients with delirium (often excluded from clinical trials) also show functional and cognitive improvement with this type of intervention.

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1. Background

Delirium is a severe neuropsychiatric syndrome characterized by disturbances in attention, perception, awareness and cognition, attributable to an organic condition, which usually develops acutely and has a fluctuating course.[1] Its prevalence is high, especially among older adults, reaching 59–88% in palliative care units, 50-70% in intensive care units and 23% in medical hospitalization services.[2] Hospitalized patients who experience delirium have higher risk of functional decline, cognitive impairment, prolonged hospitalization, institutionalization and mortality.[3,4]

Despite the growing number of studies on delirium management, pharmacological therapy has shown to have limited effectiveness for either preventing or treating delirium.[5,6] Pharmacological treatment is only indicated in cases of hyperactive delirium to address symptoms like severe agitation. However, in the case of hypoactive delirium, which is the most prevalent subtype among older people, medication is not indicated.[7,8]

Therefore, given the multifactorial etiology of delirium, current clinical guidelines advocate a non-pharmacological, multicomponent approach.[9] In this regard, non-pharmacological multicomponent programs based on identifying and addressing modifiable predisposing and precipitating risk factors of delirium, such as the Hospital Elder Life Program (HELP), can reduce the incidence of delirium by 43% compared to usual care.[10] However, the management of established delirium remains controversial. According to the literature, identifying and treating the underlying organic cause of delirium should be the primary intervention to implement once delirium develops.[11] However, there is limited evidence on the impact of other non-pharmacological measures for treating this syndrome.

Several studies highlight the importance of early mobilization to prevent delirium[12–14]. However, the implementation of individualized physical exercise programs in

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established delirium has been constrained by the limitations within this population, such as functional and cognitive impairment, aberrant motor disturbances, lack of attention, and cooperation. This poses a significant clinical challenge.

Physical exercise has shown benefits not only in enhancing the functional status of hospitalized older patients but also in improving cognition, mental health, and preventing delirium.[15–21] These improvements could be due to its properties in increasing tissue oxygenation and the synthesis of growth factors that support the proper functioning of the body, particularly the brain.[22,23]

Our hypothesis was that strategies capable of enhancing cerebral perfusion, such as physical exercise, could potentially improve the evolution of delirium once it has developed.[24] The aim of this randomized clinical trial (RCT) was to evaluate the effect of a multicomponent physical exercise program on cognitive and functional status among hospitalized older adults with delirium in an Acute Geriatric Unit (AGU).

2. Methods

Study design

This single-center, single-blind RCT followed SPIRIT 2013 and CONSORT reporting guidelines. It was conducted from February 1, 2022, to May 31, 2023, in the AGU of Hospital Universitario de Navarra (Pamplona, Spain). The 40-bed AGU is staffed by 16 geriatricians covering inpatient, orthogeriatrics and outpatient care. Most AGU admissions originate from the Emergency Department for heart failure and infectious diseases.

This study followed the principles of the Declaration of Helsinki (World Medical Association) and obtained ethical approval from the Navarra Clinical Research Ethics

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Committee (PI_2021/94). All participants or their authorized representatives provided written informed consent. This trial was registered on ClinicalTrials.gov (NCT05442892).

Participants and randomization

All patients admitted to the AGU were evaluated by geriatricians. Inclusion criteria were age ≥ 75 years with delirium and able to ambulate (Barthel Index >45 points prior to admission). Patients were excluded if: 1) expected length of stay < 5 days, 2) severe dementia, 3) terminal illness (life expectancy less than 3 months) and 4) contraindications to exercise including acute myocardial infarction in the past three months or unstable angina, severe heart valve insufficiency, arrhythmia or uncontrolled arterial hypertension, pulmonary embolism in the past 3 months or hemodynamic instability.

Patients who met the inclusion criteria within 48 hours of admission were randomly assigned in a 1:1 ratio to either the intervention group or the usual care control group. Assessment staff were blinded to group assignment and protocol details. Patients and families were aware of randomization but not group allocation.

Intervention

Controls received usual hospital care, which included physical therapy when needed. Patients assigned to the intervention group were trained daily in a 30-min morning session for 3 consecutive days (including weekends). An experienced fitness specialist led each session, providing instructions and encouragement. A session was considered completed when 90% or more of the programmed exercises were successfully performed.

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Each session was conducted in a room equipped with variable resistance strength machines (Matrix; Johnson Health Tech and Exercycle S.L., BH Group). The multicomponent program adapted from Vivifrail® (www.vivifrail.com/resources) comprised progressive resistance training, balance exercises, and walking tailored to each patient´s baseline functional capacity.

Adjustable resistance training machines targeted major muscle groups through 2-3 sets of 8-10 repetitions at 30%- 70% of the 1-repetition maximum (1 RM). Exercises focused on lower limbs (squats, leg press, knee extension) and upper body (chest press). Staff documented adherence and any adverse events. The intervention timeline is showed in **Figure 1** and all the details of the study design are explained in the previously published protocol.[25]

Endpoints

The primary endpoints were the duration and severity of delirium during hospitalization and change in functional status from baseline to hospital discharge.

Delirium was assessed daily until discharge by two geriatricians using the Spanish version of the 4AT scale.[26] Delirium symptom severity was evaluated with the validated Memorial Delirium Assessment Scale (MDAS)[27] and delirium subtype was assessed using the Delirium Motor Subtype Scale-4.[28] Preexisting cognitive impairment was based on medical history, Global Deterioration Scale FAST (GDS-fast)[29] and Informant Questionnaire on Cognitive Decline short form (IQCODE-sf).[30]

Functional measures on admission and at discharge included Short Physical Performance Battery (SPPB),[31] grip strength (measured with JAMAR 5030J1 Hand Dynamometer), Barthel Index, and Hierarchical Assessment of Balance and Mobility (HABAM)[32,33]. Individual´s strength was also evaluated using the 1 Repetition Maximum

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(1 RM) for leg press, chest press and knee extension. This is the maximum amount of weight (Kilograms, Kg) that a person can lift, push, or pull in a single repetition for a given exercise.

Medical records were reviewed and a Comprehensive Geriatric Assessment (CGA) was performed at the time of enrolment that included functional status (Barthel Index and Lawton and Brody scale),[34,35] frailty (FRAIL scale and Clinical Frailty Scale),[36] nutrition (Mini-Nutritional Assessment-Short Form, MNA-SF),[37] quality of life (EuroQol Scale-5D),[38] falls in the previous 12 months, sensory impairment, depression (Yesavage Geriatric Depression Scale),[39] polypharmacy, drug burden index (DBI) and demographic factors such as provenance and education level.

Secondary endpoints were changes in length of stay and in-hospital falls. A 1 and 3-month post-discharge follow-ups were performed to ascertain instances of readmission, visits to emergency department or primary care, functional status, cognitive status, falls, quality of life, and mortality.

Statistics

Given a standard deviation of 6 points on the MDAS scale, and with power of 80% and a significance level of 0.05, a total of 48 patients, or 24 patients per group, were needed to identify a mean difference of 5 points between the groups. Considering potential losses of 20%, this implies that 30 patients per group were required.

The participants in the study were randomly assigned, using www.randomizer.org, to either the intervention group or the control group. The evaluation team did not have access to the participant randomization assignment, as well as the main study design and the anticipated alterations in the study outcomes for each group. However, it could not be

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feasible to hide the group assignment from the staff responsible for the intervention group's training.

Baseline demographic and clinical characteristics were presented for the entire sample and categorized by group. Frequencies and percentages were utilized for categorical variables, while continuous variables were presented using mean and standard deviation or median and interquartile range. Group comparisons were performed using t-test, Mann-Whitney U test, chi-square test, or Fisher's exact test as appropriate.

To investigate the impact of the intervention on outcome variables during hospitalization, ANCOVA models were employed, incorporating the discharge value as the dependent variable and utilizing admission value and group as independent variables. Additionally, to examine the between-group effect at 1- and 3-month follow-ups, linear mixed models were utilized. These models included time, group, time and group interaction as independent variables, with adjustment by baseline outcome value. All comparisons were 2-sided, with a significance level of 0.05. All statistical analyses were made with SPSS, version 28.0 (IBM Corp) and R, version 4.2.1 (R Foundation) software.

All figures were created with BioRender® (https://www.biorender.com).

3. Results

The study flow diagram is shown in **Figure 2**. Baseline characteristics of patients in both groups are detailed in **Table 1**. No statistically significant differences were found between the medical and demographic characteristics of both groups, except for frailty as measured by the FRAIL scale. Patients in the control group exhibited higher levels of frailty (median 3.5 [IQR 1.0]) compared to the intervention group (median 3 [IQR 1]), with a p-value of 0.047. Out of the 36 patients included in the analyses, 21 were women,

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accounting for 58.3% of the sample. The mean age of the participants was 87.4 years with a standard deviation of 6.7 years. Adherence to the intervention reached 95.8%. There were no recorded adverse effects associated with the prescribed exercise program, and no patients necessitated discontinuation of the program or change in their hospital stay.

The majority of the patients included exhibited hypoactive delirium, accounting for 77.8% in the control group and 66.7% in the intervention group. Initial analysis suggested that the physical exercise intervention had some benefit in managing delirium, reducing its duration by one day during hospitalization (mean delirium days in control group (SD) = 7 (2.1) versus 6 (3.0) in the intervention group; p=0.344). Furthermore, it appeared to facilitate delirium resolution at discharge (resolved in 66.7% of the control group versus 77.8% of the intervention group; p=0.457); however, these differences did not reach statistical significance. Primary delirium endpoints are outlined in **Table 2.a**.

Regarding functional status, the intervention group showed a statistically significant improvement in HABAM score (9.84 points, 95% CI, 2.04 to 17.6 points; *p*=0.015). None of the other functional endpoints reached statistical significance (**Table 2.b.**).

Secondary endpoints are presented in **Table 3a, 3b and supplementary material**. Although there were no significant changes in in-hospital falls and length of hospital stay between groups, significant differences were observed in activities of daily living (ADLs), instrumental activities (IADLs), and cognitive decline during follow-up. From admission, the intervention group showed a 12.2-point greater improvement on Barthel index versus control group (p=0.041) at 3-month follow-up. For IADLs, although both groups deteriorated over time, the intervention group had 1.23 points less on the Lawton scale than controls (p=0.027) at 1-month follow-up. For cognition, the intervention group showed less deterioration on the GDS and IQCODE-sf scales, scoring 5.75 points lower

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in IQCODE-sf than the control group at the 1-month follow-up (p=0.017) and 4.96 points lower at the 3-month follow-up (p=0.043).

4. Discussion

To our knowledge, this is the first RCT evaluating the effect of a multicomponent tailored physical exercise program on the evolution of established in-hospital delirium in older adults. Our study shows that individualized, multicomponent exercise intervention adapted from VIVIFRAIL, improves the evolution of delirium and functional status during hospitalization and this improvement is maintained upon discharge. This is important, not only because it opens a new line of approach in the treatment of delirium in hospitalized older adults (especially the hypoactive type), but also because it prevents nosocomial dysfunction in this patient profile, which is typically excluded from studies.

Hospitalization, particularly among patients experiencing delirium, significantly contributes to functional decline and cognitive impairment in older adults. As a result, it is imperative not only to address the acute illness of these patients but also to safeguard and maintain their functional and cognitive capabilities throughout their acute admission. Some RCTs have evaluated the effects of physical exercise on functional outcomes and cognition in acutely hospitalized older adults finding that exercise is an effective and safe intervention to reverse the functional decline associated to hospitalization and prevent delirium.[40–43] Although their SPPB and Barthel scores surpassed ours, their cohort had better baseline functional and cognitive status compared to our patients, and excluded those with delirium. Exercise interventions have also shown functional, cognitive, and mood benefits in community-dwelling older adults with cognitive impairment, but again excluded those with delirium.[44–46]

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Our hypothesis regarding how physical exercise may positively influence the course of delirium is illustrated in **Figure 3**. Physical exercise is postulated to have an anti-inflammatory effect, leading to increased levels of anti-inflammatory cytokines and other molecules, such as Brain-Derived Neurotrophic Factor (BDNF), Insulin-Like Growth Factor-1 (IGF-1), Vascular Endothelial Growth Factor A (VEGFA), and enhanced mitochondrial function. This effect also potentially decreases the levels of inflammatory cytokines and cortisol.[47] Physiologically, these processes might contribute to increased neurotransmission and neuroplasticity, thereby promoting neurogenesis and angiogenesis while reducing oxidative stress and neuronal damage.[48,49] In functional terms, these changes could potentially enhance cerebrovascular capacity, cognition (including attention and memory), connectivity (in terms of executive functions), and contribute to improved mood (by reducing anxiety and depression) and better facilitation of sleep.[50]

Limitations

Our study has limitations. The compromised health condition of several patients led to a high rate of dropouts, subsequently reducing the study's sample size and resulting in underpowering. This dropout trend was primarily due to the severity of many patients' underlying conditions and the complexity associated with patients experiencing delirium, including symptoms such as inattention and a fluctuating course. These challenges made it difficult for them to actively cooperate and participate in the study. Furthermore, this is a single RCT, so replication is needed in other cohorts to validate these results, exploring alternative exercise regimens and determining the optimal timing during the day to implement this intervention, given the fluctuating nature of delirium.

However, our study has several strengths, including its novelty. Most physical exercise interventions are conducted in stable patients (prehabilitation, residential care,

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community) and generally involve individuals with good baseline functional and cognitive status, excluding those with dementia or delirium. In this study, not only patients with delirium were included, but also those with moderate dementia, frailty, and advanced age. Furthermore, to minimize potential bias, the researchers did not have access to a patient's previous test results during the retesting and end point assessment was performed following a standardized test protocol.

5. Conclusions

Multicomponent individualized exercise holds promise as a safe and effective treatment strategy for delirium in hospitalized older adults, particularly those with the hypoactive subtype. It appears to aid in delirium resolution and in preventing hospital-associated disability. These results suggest a potentially new approach to delirium management, especially in cases where pharmacological interventions have been less effective. While additional studies with larger sample sizes and comparative protocols are warranted, our findings suggest the feasibility of conducting clinical trials with patients experiencing delirium, a population often excluded from research studies.

Authors' contributions

LL-V, FaZ-F, FoZ-F, AD-M, I-OM, MSA, BAC-V, JO-G, RSE, MI and NM-V designed the study. AG-J performed statistical analyses and interpreted data. LL-V, FaZ-F, AD-M, I-OM, MSA and RSE acquired, interpreted data and drafted the manuscript. MI, NM-V, RR-O, JF-I, ES and AM-V critically revised the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that they have no competing interests.

Sponsor's role

Study funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; nor the decision to submit the manuscript for publication.

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Nafarroako Unibertsitate Publikoa

References

1. Wilson JE, Mart MF, Cunningham C, et al. Delirium. *Nat Rev Dis Prim*. 2020;6(1). doi:10.1038/s41572-020-00223-4
2. Gibb K, Seeley A, Quinn T, et al. The consistent burden in published estimates of delirium occurrence in medical inpatients over four decades: A systematic review and meta-analysis study. *Age Ageing*. 2020;49(3):352-360. doi:10.1093/ageing/afaa040
3. Han QYC, Rodrigues NG, Klainin-Yobas P, Haugan G, Wu XV. Prevalence, Risk Factors, and Impact of Delirium on Hospitalized Older Adults With Dementia: A Systematic Review and Meta-Analysis. *J Am Med Dir Assoc*. 2022;23(1):23-32.e27. doi:10.1016/j.jamda.2021.09.008
4. Fong TG, Inouye SK. The inter-relationship between delirium and dementia: the importance of delirium prevention. *Nat Rev Neurol*. Published online 2022. doi:10.1038/s41582-022-00698-7
5. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in older persons: Advances in diagnosis and treatment. *JAMA - J Am Med Assoc*. 2017;318(12):1161-1174. doi:10.1001/jama.2017.12067
6. Kim MS, Rhim HC, Park A, et al. Comparative efficacy and acceptability of pharmacological interventions for the treatment and prevention of delirium: A systematic review and network meta-analysis. *J Psychiatr Res*. 2020;125(March):164-176. doi:10.1016/j.jpsychires.2020.03.012
7. Cerveira CCT, Pupo CC, dos Santos SDS, Santos JEM. Delirium in the elderly: A systematic review of pharmacological and non-pharmacological treatments. *Dement e Neuropsychol*. 2017;11(3):270-275. doi:10.1590/1980-57642016dn11-030009

For Review Only

upna Universidad Pública de Navarra Nafarroako Unibertsitate Publikoa

8. Sadlonova M, Duque L, Smith D, et al. Pharmacologic treatment of delirium symptoms: A systematic review. *Gen Hosp Psychiatry*. 2022;79(September):60-75. doi:10.1016/j.genhosppsych.2022.10.010

9. National Institute for Health and Care Excellence (NICE). Delirium : prevention , diagnosis and management. 2022;(March 2019). www.nice.org.uk/guidance/cg103

10. Burton JK, Siddiqi N, Teale EA, Barugh A, Sutton AJ. Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev*. 2019;2019(4). doi:10.1002/14651858.CD013307

11. National Institute for Health and Care Excellence (NICE). Delirium: prevention, diagnosis and management in hospital and long-term care. *NICE Guidel*. 2023;(January). https://www.ncbi.nlm.nih.gov/books/NBK553009/

12. Rengel KF, Wahl LA, Sharma A, Lee H, Hayhurst CJ. Delirium Prevention and Management in Frail Surgical Patients. *Anesthesiol Clin*. 2023;41(1):175-189. doi:10.1016/j.anclin.2022.10.011

13. Gual N, García-Salmones M, Brítez L, et al. The role of physical exercise and rehabilitation in delirium. *Eur Geriatr Med*. 2020;11(1):83-93. doi:10.1007/s41999-020-00290-6

14. Sáez de Asteasu ML, Cuevas-Lara C, García-Hermoso A, et al. Effects of Physical Exercise on the Incidence of Delirium and Cognitive Function in Acutely Hospitalized Older Adults: A Systematic Review with Meta-Analysis. *J Alzheimer's Dis*. 2022;87:503-517. doi:10.3233/JAD-220103

15. Karamacoska D, Butt A, Leung IHK, et al. Brain function effects of exercise interventions for cognitive decline: a systematic review and meta-analysis. *Front Neurosci*. 2023;17. doi:10.3389/fnins.2023.1127065

For Review Only

upna Universidad Pública de Navarra Nafarroako Unibertsitate Publikoa

16. Da Silva JL, Agbangla NF, Le Page C, Ghernout W, Andrieu B. Effects of Chronic Physical Exercise or Multicomponent Exercise Programs on the Mental Health and Cognition of Older Adults Living in a Nursing Home: A Systematic Review of Studies From the Past 10 Years. *Front Psychol*. 2022;13(May):1-9. doi:10.3389/fpsyg.2022.888851

17. Haley MN, Casey P, Kane RY, Dārziņš P, Lawler K. Delirium management: Let's get physical? A systematic review and meta-analysis. *Australas J Ageing*. 2019;38(4):231-241. doi:10.1111/ajag.12636

18. Susie S. Lee, Yungtai Lo JV. Physical activity and risk of postoperative delirium. *J Am Geriatr Soc*. 2019;67(11):2260-2266. doi:10.1111/jgs.16083

19. Li L, Luo J, Reangsing C, Schneider JK. Effects of exercise on depressive symptoms among nursing home residents: a meta-analysis. *Aging Ment Heal*. 2022;26(8):1514-1523. doi:10.1080/13607863.2021.1951658

20. Sáez de Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F, Ramírez-Vélez R, García-Hermoso A, Izquierdo M. Cognitive Function Improvements Mediate Exercise Intervention Effects on Physical Performance in Acutely Hospitalized Older Adults. *J Am Med Dir Assoc*. 2021;22(4):787-791. doi:10.1016/j.jamda.2020.08.024

21. Valenzuela PL, Morales JS, Castillo-García A, et al. Effects of exercise interventions on the functional status of acutely hospitalised older adults: A systematic review and meta-analysis. *Ageing Res Rev*. 2020;61(April):101076. doi:10.1016/j.arr.2020.101076

22. Bliss ES, Wong RHX, Howe PRC, Mills DE. Benefits of exercise training on cerebrovascular and cognitive function in ageing. *J Cereb Blood Flow Metab*. 2021;41(3):447-470. doi:10.1177/0271678X20957807

For Review Only

upna Universidad Pública de Navarra Nafarroako Unibertsitate Publikoa

23. Rojas-Valverde D, A. Bonilla D, Gómez-Miranda LM. Examining the interaction between exercise, gut microbiota, and neurodegeneration: future research directions. *Biomedicines*. 2023;11(2267):1-17. doi:10.3390/biomedicines11082267

24. Martinez Velilla N, Lozano-Vicario L, Sáez de Asteasu ML, et al. Could a Tailored Exercise Intervention for Hospitalised Older Adults Have a Role in the Resolution of Delirium? Secondary Analysis of a Randomised Clinical Trial. *J Frailty Aging*. 2023;12(1):84-85. doi:10.14283/jfa.2022.60

25. Lozano-Vicario L, Zambom-Ferraresi F, Zambom-Ferraresi F, et al. Effectiveness of a multicomponent exercise training program for the management of delirium in hospitalized older adults using near-infrared spectroscopy as a biomarker of brain perfusion: Study protocol for a randomized controlled trial. *Front Aging Neurosci*. 2022;14(December):1-9. doi:10.3389/fnagi.2022.1013631

26. Delgado-Parada E, Morillo-Cuadrado D, Saiz-Ruiz J, Cebollada-Gracia A, Ayuso-Mateos JL, Cruz-Jentoft AJ. Diagnostic accuracy of the Spanish version of the 4AT scale (4AT-ES) for delirium screening in older inpatients. *Eur J Psychiatry*. 2022;36(3):182-190. doi:10.1016/j.ejpsy.2022.01.003

27. Noguera A, Carvajal A, Alonso-Babarro A, Chisholm G, Bruera E, Centeno C. First spanish version of the memorial delirium assessment scale: Psychometric properties, responsiveness, and factor loadings. *J Pain Symptom Manage*. 2014;47(1):189-197. doi:10.1016/j.jpainsymman.2013.02.020

28. Meagher D, Adamis D, Leonard M, et al. Development of an abbreviated version of the Delirium Motor Subtyping Scale (DMSS-4). *Int Psychogeriatrics*. 2014;26(4):693-702. doi:10.1017/S1041610213002585

29. Auer S, Reisberg B. The GDS/FAST staging system. *Int Psychogeriatrics*.

For Review Only

upna Universidad Pública de Navarra Nafarroako Unibertsitate Publikoa

1997;9(SUPPL. 1):167-171. doi:10.1017/S1041610297004869

30. Burton JK, Fearon P, Noel-Storr AH, McShane R, Stott DJ, Quinn TJ. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the detection of dementia within a secondary care setting. *Cochrane Database Syst Rev*. 2021;2021(7). doi:10.1002/14651858.CD010772.pub3

31. Guralnik JM, Simonsick EM, Ferrucci L, et al. A Short Physical Performance Battery Assessing Lower Extremity Function: Association With Self-Reported Disability and Prediction of Mortality and Nursing Home Admission Energetic cost of walking in older adults View project IOM committee on cognitive agi. *Artic J Gerontol*. 1994;49(2):85-94. https://www.researchgate.net/publication/15073609%0Ahttp://www.ncbi.nlm.nih.gov/pubmed/8126356

32. Gual N, Richardson SJ, Davis DHJ, et al. Impairments in balance and mobility identify delirium in patients with comorbid dementia. *Int Psychogeriatrics*. 2019;31(5):749-753. doi:10.1017/S1041610218001345

33. Richardson S, Murray J, Davis D, et al. Delirium and delirium severity predict the trajectory of the Hierarchical Assessment of Balance and Mobility (HABAM) in hospitalised older people: findings from the DECIDE Study. *Journals Gerontol Ser A*. 2021;XX(Xx):1-5. doi:10.1093/gerona/glab081

34. Barthel M. Functional evaluation: the Barthel Index. *Md State Med J*. 1965;14:56-61.

35. Lawton M, Brody E. Assessment of older people: selfmaintaining and instrumental activities of daily living. Gerontologist. 1969;9:179–86. *Gerontologist*. 1969;9:1979-1986.

36. Gleason LJ, Benton EA, Alvarez-Nebreda ML, Weaver MJ, Harris MB, Javedan

For Review Only

upna Universidad Pública de Navarra Nafarroako Unibertsitate Publikoa

H. FRAIL Questionnaire Screening Tool and Short-Term Outcomes in Geriatric Fracture Patients. *J Am Med Dir Assoc*. 2017;18(12):1082-1086. doi:10.1016/j.jamda.2017.07.005

37. Kaiser M., Bauer J. Validation of the mini nutritional assessment short-form (MNA®-SF): a practical tool for identification of nutritional status. *J Nutr Health Aging*. 2009;13(9):782-788.

38. Herdman M, Badia X, Berra S. EuroQol-5D: a simple alternative for measuring health-related quality of life in primary care. *Aten Primaria*. 2001;28(6):425-430. doi:10.1016/s0212-6567(01)70406-4

39. Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull*. 1988;24(4):709-710. doi:10.1007/978-3-319-69892-2_736-1

40. Martínez-Velilla N, Casas-Herrero A, Zambom-Ferraresi F. Effect of Exercise Intervention on Functional Decline in Very Elderly Patients During Acute Hospitalization: A Randomized Clinical Trial. *JAMA Intern Med*. 2019;179(1):28-36. doi:10.1001/jamainternmed.2018.4869

41. Martínez-Velilla N, Abizanda P, Gómez-Pavón J, et al. Effect of an Exercise Intervention on Functional Decline in Very Old Patients during Acute Hospitalizations: Results of a Multicenter, Randomized Clinical Trial. *JAMA Intern Med*. 2022;182(3):345-347. doi:10.1001/jamainternmed.2021.7654

42. L. Sáez de Asteasu M, Martínez-Velilla N, Zambom-Ferraresi F, Casas-Herrero Á, Izquierdo M. Role of physical exercise on cognitive function in healthy older adults: A systematic review of randomized clinical trials. *Ageing Res Rev*. 2017;37:117-134. doi:10.1016/j.arr.2017.05.007

43. Ortiz-Alonso J, Bustamante-Ara N, Valenzuela PL, et al. Effect of a Simple Exercise Program on Hospitalization-Associated Disability in Older Patients: A

For Review Only

upna Universidad Pública de Navarra Nafarroako Unibertsitate Publikoa

Randomized Controlled Trial. *J Am Med Dir Assoc*. 2020;21(4):531-537.e1. doi:10.1016/j.jamda.2019.11.027

44. Casas-Herrero Á, Sáez de Asteasu ML, Antón-Rodrigo I, et al. Effects of Vivifrail multicomponent intervention on functional capacity: a multicentre, randomized controlled trial. *J Cachexia Sarcopenia Muscle*. 2022;13(2):884-893. doi:10.1002/jcsm.12925

45. Sáez de Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F, et al. Assessing the impact of physical exercise on cognitive function in older medical patients during acute hospitalization: Secondary analysis of a randomized trial. *PLoS Med*. 2019;16(7):1-14. doi:10.1371/journal.pmed.1002852

46. Sánchez-Sánchez JL, de Souto Barreto P, Antón-Rodrigo I, et al. Effects of a 12-week Vivifrail exercise program on intrinsic capacity among frail cognitively impaired community-dwelling older adults: secondary analysis of a multicentre randomised clinical trial. *Age Ageing*. 2023;52(4):1-10. doi:10.1093/ageing/afad050

47. Rai M, Demontis F. Muscle-to-Brain Signaling Via Myokines and Myometabolites. *Brain Plast*. 2022;8(1):1-21. doi:10.3233/bpl-210133

48. Isaac AR, Lima-Filho RAS, Lourenco M V. How does the skeletal muscle communicate with the brain in health and disease? *Neuropharmacology*. 2021;197(July):108744. doi:10.1016/j.neuropharm.2021.108744

49. Ben-Zeev T. The effect of exercise on neurogenesis in the brain. *IMAJ*. 2022;24(533-538).

50. Cooper C, Moon HY, Van Praag H. On the run for hippocampal plasticity. *Cold Spring Harb Perspect Med*. 2018;8(4). doi:10.1101/cshperspect.a029736

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TABLES

Table 1. Main demographic, clinical, functional and cognitive characteristics at baseline by group

Variable	Category	Control group (n=18)	Intervention group (n=18)	p-value
Demographic data				
Age	mean (SD)	87.6 (7.8)	87.3 (5.5)	0.719[1]
Sex	Male	9 (50.0%)	6 (33.3%)	
	Female	9 (50.0%)	12 (66.7%)	0.310[2]
BMI	mean (SD)	27.3 (5.7)	25.4 (5.1)	0.495[1]
Clinical data				
CIRS[a]	mean (SD)	16.0 (4.5)	14.1 (3.7)	0.116[1]
MNA[b]	mean (SD)	21.0 (4.8)	21.9 (3.9)	0.419[1]
FRAIL[c]	median (IQR)	3.5 (1.0)	3.0 (1.0)	**0.047***[4]
Nº of drugs	mean (SD)	8.8 (4.4)	10.3 (3.2)	0.286[1]
Nº of active ingredients	mean (SD)	9.2 (4.7)	10.9 (3.6)	0.277[1]
Polypharmacy	No	2 (11.1%)	0 (0.0%)	
	Yes	16 (88.9%)	18 (100.0%)	0.486[3]
DBI[d] at admission	mean (SD)	0.94 (0.87)	0.73 (0.56)	0.407[1]
Quality of life (EuroQol-5D)	mean (SD)	67.5 (26.7)	70.3 (19.6)	0.724[1]
Functional and cognitive data				
SPPB[e]	mean (SD)	3.3 (1.7)	4.4 (2.9)	0.150[1]
Handgrip	mean (SD)	17.0 (6.8)	14.5 (6.6)	0.274[1]
1 RM leg press, Kg	mean (SD)	58.6 (22.3)	59.1 (24.5)	0.818[1]
1 RM chest press, Kg	mean (SD)	17.8 (9.4)	17.9 (8.8)	0.972[1]
1 RM knee extension, Kg	mean (SD)	26.2 (9.4)	24.2 (8.5)	0.561[1]
Handgrip	mean (SD)	13.9 (7.7)	13.2 (6.9)	0.890[1]
HABAM[f]	mean (SD)	20.8 (4.0)	20.9 (5.8)	0.947[1]
Barthel before admission[g]	mean (SD)	77.5 (12.2)	80.8 (13.3)	0.438[1]
Barthel at admission	mean (SD)	19.7 (14.1)	19.2 (11.4)	0.896[1]
MDAS[h]	mean (SD)	20.6 (8.2)	20.8 (7.5)	0.950[1]
Lawton[i]	median (IQR)	2.5 (5.0)	1.0 (4)	0.719[4]
GDS[j]	median (IQR)	4.0 (2.0)	4.0 (1.0)	0.521[4]
IQCODE-sf[k]	mean (SD)	4.1 (0.7)	4.3 (0.6)	0.386[1]
Falls in the last 12 months	median (IQR)	1.0 (2.0)	1.0 (3.0)	0.628[4]

[1] t-test [2] chi-square test [3] Fisher test [4] U Mann-Whitney

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CIRS, Cumulative Illness Rating Scale; IQR, interquartile range; MNA, Mini-Nutritional Assessment; DBI, Drug Burden Index; EuroQol-5d, EuroQol-5 Dimension ; SPPB, Short Physical Performance Battery; 1RM, 1 repetition maximum; HABAM, Hierarchical Assessment of Balance and Mobility; GDS, Global Deterioration Scale; IQCODE-sf, Informant Questionnaire on Cognitive Decline in the Elderly-short form;

[a]The CIRS scale evaluates individual body systems, ranging from 0 (best) to 56 (worst). The most prevalent diseases were hypertension, heart failure, osteoarthritis, arrhythmias, chronic gastritis/gastroesophageal reflux, chronic kidney disease, and urinary incontinence.

[b]The MNA scale ranges from normal nutritional status (24-30 points), risk of malnutrition (17-23.5 points), or malnourished (<17 points).

[c]The FRAIL scale ranges from robust (0 points), prefrail (1-2 points), or frail (3-5 points)

[d]The DBI scale is dose-related measure of anticholinergic and sedative drug exposure.

[e]The SPPB scale ranges from 0 (worst) to 12 (best).

[f]The HABAM scale evaluates mobility, transfers and balance, ranging from 0 (worst) to 67 (best)

[g]The Barthel Index ranges from 0 (severe functional dependence) to 100 (functional independence).

[h]The MDAS scale evaluates the severity of delirium (0 no delirium) to 30 (severe delirium)

[i]The Lawton scale evaluates instrumental activities and ranges from 0 (dependance) to 8 (independence).

[j]The GDS scale provides stages of cognitive function for those suffering from a primary degenerative dementia and ranges from 0 (no cognitive impairment) to 7 (severe dementia)

[k]The IQCODE-sf evaluates cognitive impairment. A cut-off point (average score) of 3.31/3.38 achieves a balance of sensitivity and specificity of cognitive impairment.

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Table 2.a Results of primary end points: evolution of delirium

Variable	Category	Control group(n=18)	Intervention group (n=18)	p-value
Duration of delirium	mean (SD)	7.0 (2.1)	6.2 (3.0)	0.344[1]
Delirium subtype	hypoactive	14 (77.8%)	12 (66.7%)	
	hyperactive	2 (11.1%)	2 (111.1%)	0.862[3]
	mixed	2 (11.1%)	4 (22.2%)	
Resolution of delirium at discharge	No	6 (33.3%)	4 (22.2%)	
	Yes	12 (66.7%)	14 (77.8%)	0.457[2]

[1] t-test [2] chi-square test [3]Fisher test

Table 2.b Results of primary end points: change in functional capacity

Variable	Change in Control Group	Change in Intervention Group	Change between-group differences (95% CI)	p-value
SPPB	1.18 (0.21, 2.14)	0.67 (-0.48, 1.18)	-0.34 (-1.84, 1.16)	0.649
Barthel	43.9 (38. 49.8)	49.2 (36.1, 62.2)	5.72 (-6.46, 17.9)	0.346
Handgrip	0.05 (-1.21, 1.31)	0.99 (-0.37, 2.36)	0.68 (-1.26, 2.51)	0.457
HABAM	20.1 (14.3, 25.9)	29.9 (24.5, 35.4)	9.84 (2.04, 17.6)	**0.015***
1 RM leg press	0.91 (-3.34, 5.15)	4.83 (-0.47, 10.1)	3.80 (2-90, 10.5)	0.256
1 RM chest press	1.53 (-0.03, 3.10)	0.67 (-1.32, 2.65)	-0.85 (-3.18, 1.48)	0.460
1 RM knee extension	1.25 (-2.85, 5.34)	4.11 (1,87, 6.34)	2.94 (-1.42, 7.30)	0.176

Abbreviations: SPPB, Short Physical Performance Battery; HABAM, Hierarchical Assessment of Balance and Mobility; 1RM, 1 repetition maximum

Table 3a. Results of secondary end points: in-hospital falls and length of stay

Variable	Category	Control group (n=18)	Intervention group (n=18)	p-value
In-hospital falls	No	17 (94.4%)	16 (88.9%)	
	Yes	1 (5.6%)	2 (11.1%)	1.0[1]
Length of stay	mean (SD)	8.4 (1.9)	7.9 (2.7)	0.572[3]

[1]Test Fisher [3] T-test

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Table 3b. Results of secondary end points: 1- and 3-month follow-up

Variable	Months of follow-up	Change in Control Group	Change in Intervention Group	Change between-group differences (95% CI)	p-value
Barthel	M1	43.6 (36.1, 51.1)	51.8 (44.0, 59.6)	8.25 (-2.59, 19.1)	0.148
	M3	38.5 (30.7, 46.3)	50.6 (42.6, 58.7)	12.2 (0.99, 23.4)	**0.041***
Lawton	M1	-1.71 (-2.44, -0.99)	-0.49 (--1.24, 0.26)	1.23 (0.18, 2.27)	**0.027***
	M3	-1.95 (-2.70, -1.20)	-0.94 (-2.08, 0.06)	1.01 (-0.06, 2.08)	0.075
GDS	M1	0.58 (0.30, 0.86)	0.20 (-0.09, 0.49)	-0.38 (-0.79, 0.02)	0.074
	M3	0.80 (0.51. 1.09)	0.51 (0.21, 0.81)	-0.29 (-0.71, 0.12)	0.182
IQCODE-sf	M1	4.39 (1.26, 7.51)	-1.37 (-4.61, 1.88)	-5.75 (-10.25, -1.24)	**0.017***
	M3	6.99 (3.76, 10.25)	2.03 (-1.31, 5.34)	-4.96 (-9.64, -0.34)	**0.043***
Nº drugs	M1	-0.13 (-1.14, 0.87)	-0.22 (-1.29, 0.85)	-0.08 (-1.55, 1.38)	0.912
	M3	-0.23 (-1.26, 0.79)	-0.29 (-1.43, 1.54)	-0.06 (-1.54, 1.43)	0.942
Nº of active ingredients	M1	-0.01 (-1.13, 1.12)	0.00 (-1.20, 1.20)	0.01 (-1.64, 1.65)	0.994
	M3	-0.10 (-1.26, 1.04)	-0.14 (-1.35, 1.05)	-0.04 (-1.70, 1.62)	0.963
DBI	M1	-0.25 (-0.47, -0.03)	0.01 (-0.22, 0.25)	0.26 (-0.06, 0.59)	0.122
	M3	-0.29 (-0.52, -0.07)	-0.06 (-0.30, 0.18)	0.23 (-0.09, 0.56)	0.176
EuroQol-5D	M1	-8.47 (-17.8, 0.86)	2.97 (-6.75, 12.7)	11.4 (-2.03, 24.9)	0.107
	M3	-11.3 (-21.0, -1.60)	1.48 (-8.41, 11.42)	12.8 (-1.07, 26.7)	0.082

In the first column, the change for the control group from admission (from admission to 1 month (1M) and from admission to 3 months (3M)) is shown. The second column represents the same change for the intervention group, and the third column indicates the difference between these changes, known as the between-group difference, which reflects the effect of the intervention. For example, from admission, the intervention group shows an improvement of 51.8 points at one month, while the control group shows an improvement of 43.6 points. The difference between groups is 8.25 points, meaning the intervention group has a change 8.25 points greater than the control group.

Supplementary Material:

Table 3b. Results of secondary end points: 1- and 3-month follow up

Variable	Months of follow-up	Category	Control group (n=18)	Intervention group (n=18)	p-value
Location		Home	16 (94.1%)	10 (66.7%)	
	M1	Nursing home	1 (5.9%)	3 (20.0%)	0.142[1]
		Intermediate Care Unit	0 (0.0%)	2 (13.3%)	
		Home	10 (66.7%)	11 (78.6%)	
	M3	Nursing home	4 (26.7%)	3 (21.4%)	0.507[1]
		Intermediate Care Unit	1 (6.7%)	0 (0.0%)	
Death	M1	No	17 (94.4%)	15 (88.2%)	
		Yes	1 (5.6%)	2 (11.8%)	0.603[1]
	M3	No	15 (93.8%)	14 (93.3%)	
		Yes	1 (6.3%)	1 (6.7%)	1.0[1]
New institutionalization	M1	No	16 (94.1%)	13 (86.7%)	
		Yes	1 (5.9%)	2 (13.3%)	0.589[1]
	M3	No	14 (93.3%)	14 (100.0%)	
		Yes	1 (6.7%)	0 (0.0%)	1.0[1]
Readmission	M1	No	13 (76.5%)	13 (86.7%)	
		Yes	4 (23.5%)	2 (13.3%)	0.659[1]
	M3	No	13 (86.7%)	14 (100.0%)	

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		Yes	2 (13.3%)	0 (0.0%)	0.483[1]
Nº Emergency department visit	M1	median (IQR)	1.0 (3.0)	0.0 (2.0)	0.602[2]
	M3	median (IQR)	0.0 (1.0)	0.0 (0.0)	0.949[2]
Nº Primary Care Physician visit	M1	median (IQR)	1.0 (2.0)	1.0 (1.0)	0.313[2]
	M3	median (IQR)	0.0 (0.0)	0.0 (0.0)	0.683[2]
Nº Falls	M1	median (IQR)	0.0 (0.0)	0.0 (0.0)	0.953[2]
	M3	median (IQR)	0.0 (1.0)	0.0 (0.0)	0.769[2]

[1]Fisher exact test [2]Mann Whitney U test

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Legend to Figure 3:

The complex relationship between delirium and physical exercise.

1. **Inflammation and immune response:** delirium is associated with an increase in inflammatory markers in the brain and blood. Physical exercise has anti-inflammatory effects and can modulate the immune system, which may help reduce excessive inflammation associated with delirium. Exercise has been implicated in the release of anti-inflammatory cytokines that can counteract the inflammatory cascade in the brain.
2. **Neurotrophins and brain plasticity:** delirium leads to microglia activation, however, physical exercise promotes the release of neurotrophins, such as Brain-Derived Neurotrophic Factor (BDNF), which are associated with brain plasticity and neuronal growth. This could be relevant in improving cognitive function and reducing the severity of delirium.
3. **Regulation of oxidative stress:** delirium can lead to increased oxidative stress, damaging brain cells. Physical exercise has demonstrated antioxidant effects, improving mitochondrial function, which could help protect the brain from oxidative damage and reduce delirium severity.
4. **Improvement of cerebral blood flow:** damage on brain blood barrier (BBB) produces endothelial damage and migration of molecules to brain parenchyma causing delirium. Physical exercise increases cerebral blood flow and brain oxygenation and promotes the release of cerebral vascular endothelial growth factor A (VEGFA), which may be beneficial in maintaining optimal cognitive function and mitigating delirium symptoms.
5. **Hormonal regulation:** delirium has been associated with hormonal imbalances such as increased cortisol. Physical exercise can influence hormonal regulation and stress response. Exercise might contribute to maintaining a proper hormonal balance and reduce vulnerability to delirium.

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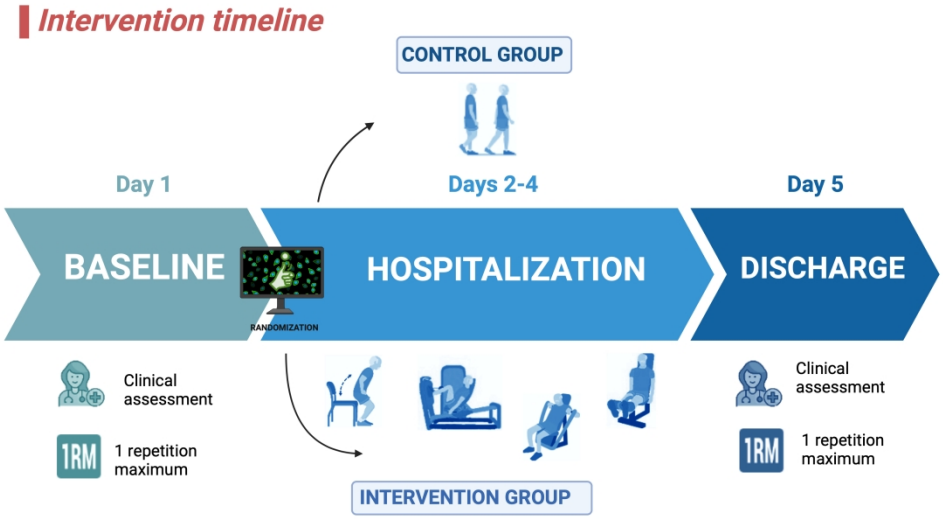

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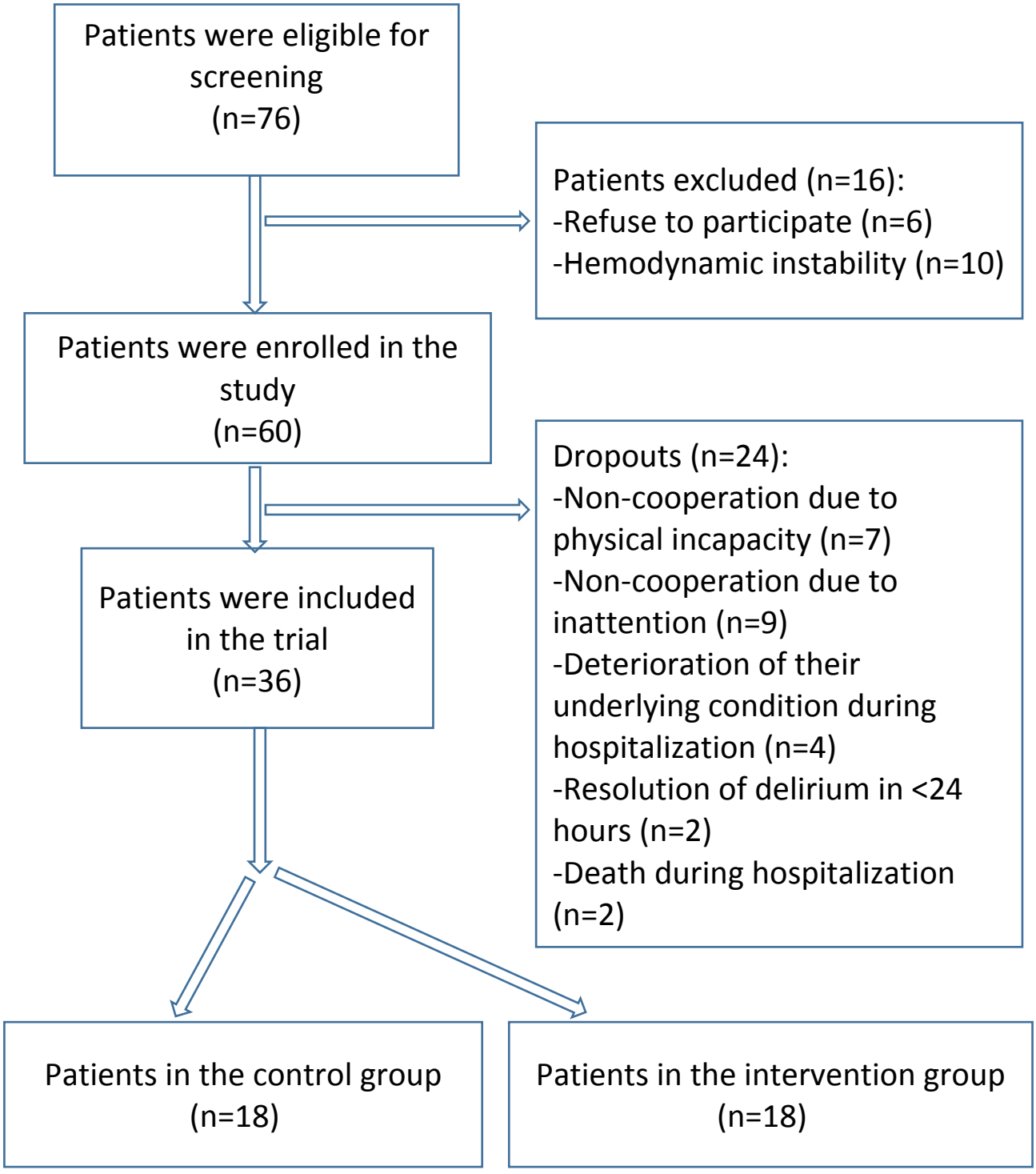
Figure 2. Flowchart of the study



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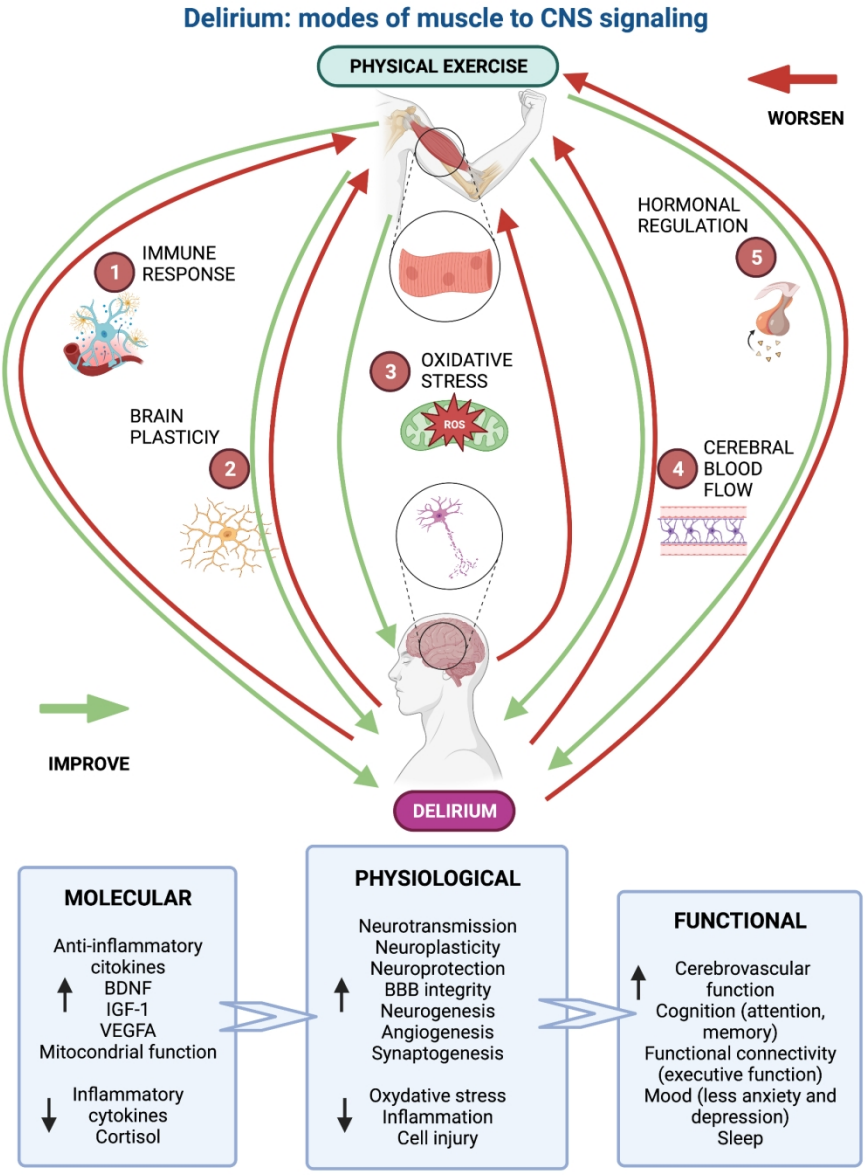

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