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Exploring Sex-Related Difference in Cerebrospinal Fluid/Blood Quotient of Albumin in Older Patients Undergoing Hip Fracture Surgery: Insight From the ORTODEL and BIODEL Study

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Abstract

Background: The blood-cerebrospinal fluid barrier (BCSFB) regulates substance exchange between the blood and cerebrospinal fluid (CSF).

Objectives: This study investigated sex-related differences in the CSF/blood quotient of albumin (QAlb), a BCSFB function biomarker, in older patients undergoing spinal anesthesia for hip fracture (HF) surgery.

Design: Seventy-eight patients aged ⩾65 years (18 males, 60 females) undergoing HF repair were enrolled.

Methods: Baseline variables, including age, sex, diagnosis of dementia, were collected. The BCSFB function was assessed using the CSF/blood quotient of albumin (QAlb).

Results: Dementia prevalence was similar in men (22.2%) and women (17.6%), as was postoperative delirium (POD) (men 27.8%, women 33.3%). Despite similar demographics, men exhibited significantly higher CSF albumin concentrations ($P = .031$) and QAlb values ($P = .023$) compared to women. No differences were found in QAlb value between patients with or without dementia in male ($P = .645$) and female ($P = .102$) subgroups. Moreover, no differences in QAlb value emerged between those with or without POD in males ($P = .173$) and females ($P = .225$).

Conclusion: Despite sample size and sex imbalance, our analyses highlight a sex-related discrepancy in BCSFB function in older patients underscoring the need for sex-specific QAlb reference ranges. Normalization of QAlb values by sex may be essential to prevent over- or underestimation of BCSFB dysfunction in the 2 sexes. Future studies with larger, balanced cohorts may clarify these differences.

Plain Language Summary

When someone has a hip fracture and needs surgery, doctors often use spinal anesthesia. This study looked at the fluid around the brain and spinal cord (called cerebrospinal fluid or CSF) and compared it to the blood in older patients who had this type of surgery. The wall between the blood and the CSF, called the blood-CSF barrier, controls what goes in and out of the brain fluid. We measured a specific marker, called QAlb, to see how well this barrier was working. We

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wanted to know if there were any differences between older men and women. We studied 78 patients aged 65 and older who had hip fracture surgery. We noted whether they were male or female and if they had dementia. We also checked if they developed confusion after surgery (delirium). We found that even though the men and women in our study were similar in age and how many had dementia or delirium, the men had higher levels of a protein called albumin in their CSF and higher QAlb values compared to the women. This suggests that the barrier between their blood and brain fluid might work differently. We didn't find a clear link between the QAlb levels and whether someone had dementia or developed delirium, in either men or women. Our findings suggest that there might be important differences in how the blood-CSF barrier functions in older men and women. This means that the normal ranges for the QAlb marker might need to be different for men and women. We need more research with a larger and more equal number of men and women to better understand these differences. This could help us improve care for older patients after hip fracture surgery.

Keywords
cerebrospinal fluid, quotient of albumin, over 65, sex differences, delirium, hip fracture

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Introduction

Sex differences in brain development, structure, function, and biochemistry influence diseases susceptibility and progression.[1,2] These anatomical variations, including cranial size, brain and cerebrospinal fluid (CSF) volume, and white and gray matter distribution, highlight the need for sex-specific diagnostic and therapeutic approaches to personalize healthcare.[3-5]

CSF is a clear, colorless fluid that permeates the central nervous system (CNS), resembling a plasma ultrafiltrate but with lower protein content and few leukocytes.[6] CSF and CNS homeostasis are maintained by the blood-brain barrier (BBB), at the level of the endothelium of cerebral blood vessels, and the blood-CSF barrier (BCSFB), at the level of the choroid plexus epithelial cells, which regulate the exchange of substances between the blood, brain, and CSF.[6] The age-related evaluation of the CSF/blood albumin quotient (QAlb) is preferred because of its greater accuracy than total CSF protein levels in detecting BCSFB dysfunction.[7-9] Following the initial years of life, QAlb progressively increases with advancing age, concurrent with a decrease in mean CSF production rate.[10]

Research indicates that CSF protein content is higher in males than in females, both in neurological patients and hospitalized individuals with undefined diagnoses. Males exhibit higher CSF density and impaired BCSFB function, as shown by elevated QAlb values, compared to females. This sex-related difference is consistent across various conditions including multiple sclerosis (MS), inflammatory and non-inflammatory diseases, psychiatric disorders, amyotrophic lateral sclerosis, and even in healthy individuals.[2,11-14] The observed sex-related differences in QAlb have been attributed to morphological variations between males and females, specifically differences in height, which are hypothesized to influence the rostro-caudal gradient.[15] However, a recent study investigating neurological patients, with data stratified by sex, found no statistically significant correlation between QAlb values and either weight or height.[16]

Isolated BCSFB dysfunction, as suggested by an elevated QAlb in the absence of other pathological CSF findings, is a frequent observation in CSF analysis. Its estimated prevalence is approximately 10% in patients undergoing lumbar puncture and 16% in patients with non-inflammatory central nervous system disorders.[17] Elevated QAlb has been associated with cognitive decline in both Alzheimer's Disease[18] and vascular cognitive impairment.[19] Furthermore, BCSFB dysfunction may contribute to clinical worsening in patients with cognitive decline.[19]

Delirium, an acute and fluctuating neuropsychiatric disorder, is a common complication of hip fracture (HF) surgery[20] potentially leading to adverse outcomes including death, cognitive and functional decline.[21-23] The pathophysiology of delirium remains speculative and may encompass various hypotheses.[24] Among these, the neuroinflammatory hypothesis suggests that inflammatory mediators, which may increase following traumatic event such as HF, can reach the blood-brain barrier via the bloodstream. If the barrier is compromised, these mediators can cross it, activate microglia, and causing varying degrees of neuronal damage, which may be transient or permanent.[24] Supporting this hypothesis, a cohort study involving 120 patients undergoing HF surgery found that development of post-operative delirium (POD) was associated with BCSFB dysfunction.[25]

Following these preliminary considerations, this study aimed to investigate sex-related differences in CSF albumin concentration and BCSFB function in older patients undergoing spinal anesthesia during HF surgery.

Methods

Study Design

Data were drawn from 2 cohorts of patients, 1 Italian and 1 Spanish, using a similar study design.[26] The Italian multicenter observational longitudinal ORTODEL study enrolled patients consecutively admitted to Orthogeriatric Units in

Monza and Ferrara from July 2021 to March 2024. The eligibility criteria for the ORTODEL cohort have been described elsewhere.[27] The Spanish study BIODEL enrolled patients consecutively admitted to the Orthogeriatric Unit of the Hospital Universitario de Navarra (Pamplona) between August 2021 and December 2021.[28] Variables used for this study were retrospectively harmonized according to current recommendations.[29]

Briefly, the eligibility criteria included patients aged ⩾65 years who underwent HF surgical repair. Patients were excluded from the analysis if they (1) had preoperative delirium, (2) had terminal disease (estimated life expectancy <3 months), (3) were unable to communicate, or (4) were unwilling or unable to provide informed consent. Written informed consent for study participation was obtained from patients at enrollment in all cohorts, according to procedures approved by the institutional review boards: Navarra Clinical Research Ethics Committee on June 25, 2021, PI_2021/68, and the Ethics Committee of Monza Brianza on May 6, 2021 (decree 691), study reference number 3505.

A comprehensive geriatric assessment was performed at the time of enrollment. Pre-surgical baseline variables, including age, sex, diagnosis of dementia, and delirium, were collected by interview or chart review. Diagnosis of dementia was obtained using multiple sources of information, including anamnestic history, caregiver interviews, medical records, sensitive tests (ie, AD8[30] and IQ-Code[31]), and medication use on admission. Delirium was assessed daily pre-operatively and up to 3 postoperative days by geriatricians using the Italian or Spanish version of the 4AT scale[32] and the final diagnosis of POD was confirmed by a senior geriatrician with expertise in delirium.

This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the institutional review boards: Navarra Clinical Research Ethics Committee on June 25, 2021, PI_2021/68, and the Ethics Committee of Monza Brianza on May 6, 2021 (decree 691), study reference number 3505. Written informed consent was obtained from all participants.

The study protocol follows the STROBE guidelines for Reporting Observational Studies[33] (Supplemental Materials).

Specimen Collection

Blood samples (4–5 mL) were collected preoperatively by venipuncture and processed within 1 hour. Blood samples were centrifuged at 2000 × *g* for 10 minute at 4°C to separate serum or plasma from cellular components. Aliquots (0.5–1.0 mL) were stored at −80°C until assays. CSF sampling was performed in patients during spinal anesthesia by spinal cannulation under standard monitoring in the operating room immediately before the administration of anesthetic agents for the planned surgical procedure. After confirming intrathecal placement and adequate CSF flow, 1.5 mL of CSF was collected by aspiration or directly dropwise into polypropylene tubes and stored at −80°C. CSF samples were centrifuged under the same conditions as blood, and the cell-free CSF was stored at −80°C until the assays. The reduced CSF volume to be collected was "imposed" by Institutional Review Board, as a condition for protocol approval. Rigorous quality control standards were used to ensure the integrity of the ORTODEL and BIODEL biospecimens. This study was conducted as an independent sub-analysis of the 2 aforementioned projects.[26] All measurements were performed on the residual biological samples collected for the primary studies. No further selection was performed. All available samples were included in the analysis.

Determination of Cerebrospinal Fluid/Blood Quotient of Albumin

BCSFB dysfunction was assessed using QAlb, which is calculated as the ratio of albumin concentrations in the CSF to those in the blood.[7] Overall, the QAlb was determined in 78 subjects (19 ORTODEL, 59 BIODEL): 18 males and 60 females.

Briefly, blood and CSF albumin levels were measured for research purposes using the Binding Site Optilite® benchtop analyzer (The Binding Site, Birmingham, UK) following the manufacturer's instructions. The Optilite® Low Level Albumin Kit (NK032.L.OPT), with a measuring range of 11 to 16 625 mg/L (CSF) and 2200 to 66 500 mg/L (blood), was used for all determinations.

For each patient, paired blood and CSF samples were analyzed in the same session using the same calibration curve. Albumin levels were expressed as g/L in the blood and mg/L in the CSF samples. The age-adjusted QAlb upper reference limit (URL) was calculated for each subject using the formula: age/15 + 4.[17] A QAlb value greater than the specific URL was suggestive of BCSFB dysfunction.

Statistical Analysis

All data were checked for normality with the Kolmogorov-Smirnov test. Descriptive statistics were conducted to summarize sample characteristics. Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR). Group comparisons stratified by sex were conducted using Student's *t*-test and Mann–Whitney *U* test, as appropriate. Categorical data are reported as counts (percentages) and were compared between the sexes using Fisher's exact test. Prism 10 software (GraphPad Software, La Jolla, CA, USA) was used to perform the statistical analyses.

Results

Demographic, clinical and laboratory characteristics of the study population are reported in Table 1. There was no difference in age between males (84.3 ± 7.6 years), and females (age: 85.0 ± 6.6 years) at enrollment. Dementia was present in 22.2% of men and 17.6% of women, while POD was found in 27.8% of men and 33.3% of women, without any statistical difference between the sexes. Median CSF albumin concentrations were higher in men than in

Table 1. Overview of the Demographic, Clinical, and Laboratory Characteristics of the Study Population.

Characteristics	Males	Females	*P*
Total, n	**18**	**60**	
Age (years), mean ± SD	84.3 ± 7.6	85.0 ± 6.6	.6831
Dementia, n (%)	4 (22.2)	9 (17.6)	.4832
Post-operative delirium, n (%)	5 (27.8)	20 (33.3)	.7777
Blood albumin concentrations (g/L)	36.24 (30.65−39.84)	35.75 (33.13-38.17)	.7177
CSF albumin concentrations (mg/L)	300.5 (266.7-343.4)	224.2 (162.0-316.8)	**.0307**
QAlb × 10^{-3}, median (IQR)	8.28 (6.89-12.58)	6.10 (4.85-9.84)	**.0231**
QAlb × 10^{-3} > age/15 + 4, n (%)	7 (38.9)	15 (25)	.3701

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range; QAlb, quotient of albumin; SD, standard deviation.
Bold *P*-values indicate statistical significance.

women (300.5 mg/L vs 224.2 mg/L; $P = .031$) with a consequent median QAlb value greater in men than in women (8.28 vs 6.10; $P = .023$). BCSFB dysfunction, characterized by a QAlb value greater than the age-adjusted URL, was found in 7 males (1 with dementia alone, 1 with POD alone, and 1 with both conditions) and in 15 females (3 with dementia alone, 4 with POD alone, and 2 with both conditions). A sex-disaggregated analysis was also performed to identify differences in QAlb values between patients with or without dementia and POD. No differences were found in QAlb value between patients with or without dementia in male (7.30 vs 8.29; $P = .645$) and female (7.88 vs 5.76; $P = .102$) subgroups. Moreover, no differences in QAlb value emerged between those with or without POD in males (7.53 vs 8.47; $P = .173$) and females (7.46 vs 5.79; $P = .225$).

Discussion

This study is the first to demonstrate a sex-related discrepancy in CSF albumin concentration and BCSFB function, measured by QAlb, in older patients undergoing spinal anesthesia for HF surgery. Moreover, sex-stratified analysis indicated no association between QAlb values and clinical characteristics like dementia or POD in either sex, suggesting that BCSFB dysfunction may not play a direct pathophysiological role in these patients.

Our data contribute to the increasing body of evidence indicating sex-related difference in BCSFB function,[2] extending these observations to very old patients.

While our data appears to confirm previous findings of BCSFB dysfunction in patient with delirium,[25] its low prevalence suggests that it is not a requisite condition for delirium development. Furthermore, our findings highlight the importance of sex-disaggregated analyses. In fact, while the prevalence of BCSFB dysfunction – defined as having a QAlb value above the established positivity threshold – did not differ statistically between sexes (38.9% in males vs 25% in females), the absolute QAlb values were statistically higher in males compared to females with values exceeding 25%.

QAlb is widely regarded as the most reliable tool for assessing individual BCSFB functions concerning blood-derived proteins in the CSF.[7] This is mainly because CSF albumin originates exclusively from the blood, making its CSF/blood concentration quotient a reliable marker of the various sources and diffusion mechanisms through which serum proteins reach the CSF. Sex differences in QAlb has been described in patients undergoing lumbar puncture for suspected neurological diseases, such as MS, other inflammatory and non-inflammatory neurological disorders,[13] psychiatric conditions,[11] amyotrophic lateral sclerosis,[14] and even in healthy volunteers,[12] this study is the first to demonstrate such differences in older people with HF, regardless of pre-existing dementia or POD. These findings suggest that the observed sex difference is not related to a particular neurological condition but likely reflects underlying physiological differences between sexes.[2]

Differences in BCSFB function between males and females may result from several mechanisms. Lifelong hormonal effects, such as 17β-estradiol's influence on BCSFB integrity, may explain sex differences in BCSFB function.[34,35] However, stable QAlb differences across lifespans indicate sex chromosome genes may be a stronger determinant.[12] Moreover, although a role for height in explaining the QAlb differences between males and females could be hypothesized,[36] our recent study did not find any correlation between QAlb values and anthropometric characteristics such as weight and height.[16] It is important to acknowledge that, given the clinical challenges of mobilizing elderly patients with hip fractures, we were unable to collect these anthropometric measurements or calculate body mass index in the present study.

Limitation

Due to the relatively small sample size and the observational design of this study, we cannot rule out the possibility of residual confounding from unmeasured factors. However, in line with the challenges inherent in studying this specific population of older subjects, our sample size, while small, is nevertheless comparable to other studies investigating BCSFB function in similar clinical settings, such as the work of Devinney et al (eg, 56 orthopedic surgery patients)[37] and Hov et al (120 patients with a delirium incidence like our study),[25] suggesting

that significant trends may be observed even within these constraints. Moreover, the study is limited by the lack of data on relevant comorbidities such as hypertension, diabetes, and other cerebrovascular risk factors, which could potentially influence the outcomes in this older population.

Another limitation of the study is the unbalanced sex ratio of the included sample. This was due to a consecutive patient enrollment and reflects the patient population presenting at our clinics during the study period. A more balanced cohort would be needed to more comprehensively analyse sex-related differences.

Future studies with significantly larger sample sizes and more comprehensive data collection will be crucial to address these limitations.

Conclusion

In conclusion, our study indicates that BCSFB dysfunction is unlikely to be a major contributor to POD in older patients undergoing HF surgery, given its low prevalence. Notably, the observed sex-related difference in absolute QAlb values, despite similar delirium prevalence (27.8% in males vs 33.3% in females), emphasizes the importance of sex-disaggregated analyses and warrants further investigation into the adequacy of current QAlb thresholds. Normalization of QAlb values by sex and age may be essential to prevent over- or underestimation of BCSFB dysfunction.

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Ethical Considerations

Navarra Clinical Research Ethics Committee on June 25, 2021, PI_2021/68, and the Ethics Committee of Monza Brianza on May 6, 2021 (decree 691), study reference number 3505.

Consent to Participate

Written informed consent for study participation was obtained from patients at enrollment in both cohorts, according to procedures approved by the institutional review boards (Ethics Committee of Monza Brianza on May 6, 2021 [decree 691], study reference number 3505, and Navarra Clinical Research Ethics Committee on June 25, 2021 [PI_2021/68]).

Consent for Publication

Not applicable.

Author Contributions

MC: Conceptualization, Formal analysis, Writing – original draft. MCF, BA, LL-V, EP, AMO, CO, and NM-V: Data curation. GB and SV: Supervision. All co-authors: Writing – review and editing.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability Statement

All datasets generated during this study are available from the corresponding author for reasonable request.

Supplemental Material

Supplemental material for this article is available online.

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