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Review Article

Correlation analysis between plasma biomarkers albumin, fibrinogen, and their ratio with postoperative delirium in patients undergoing non-cardiac surgery: a systematic review and meta-analysis

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Abstract: Objectives: This meta-analysis aimed to investigate the correlation between plasma biomarkers, such as albumin and fibrinogen, and their ratio with postoperative delirium (POD) in patients undergoing non-cardiac surgery. Methods: Relevant observational cohort studies were systematically searched in PubMed, EMBASE, CINAHL, and the Cochrane Library databases as of March 2023. This meta-analysis was conducted using RevMan 5.4.1 and Stata 15.0 software. For continuous variables with non-uniform units, the standardized mean difference (SMD) and 95% confidence intervals (CIs) were used; otherwise, the mean difference (MD) and 95% CIs were employed. The Newcastle-Ottawa Scale (NOS) was applied to assess the quality of included literature. Results: Eighteen studies encompassing 7,011 patients were included. The meta-analysis revealed significantly lower albumin levels (sixteen studies, 5,813 patients, SMD = -0.45, 95% CI = -0.64 to -0.26, $P < 0.00001$, $I^2 = 80\%$) and albumin-fibrinogen ratio (AFR) (four studies, 824 patients, MD = -0.62, 95% CI = -0.76 to -0.48, $P = 0.56$, $I^2 = 0\%$) in the delirious group. Conversely, higher fibrinogen concentrations (two studies, 441 patients, MD = 0.13, 95% CI = 0.02 to 0.24, $P = 0.69$, $I^2 = 0\%$) were observed in the delirious group. Due to high heterogeneity in albumin levels ($P < 0.00001$, $I^2 = 80\%$), we conducted a subgroup and sensitivity analysis, and confirmed that the association of albumin levels was not influenced by surgery type, design or delirium evaluation instruments. Conclusions: Preoperative albumin, fibrinogen and AFR levels were associated with POD, potentially aiding in identifying high-risk patients and playing a key role in preventing POD.

Keywords: Albumin, fibrinogen, albumin-fibrinogen ratio (AFR), postoperative delirium, plasma biomarkers, meta-analysis

Introduction

Postoperative delirium (POD) is an acute, reversible and common cerebral comprehensive complication following surgery, primarily characterized by attention deficits and overall cognitive decline [1]. The prevalence of POD ranges from 12% to 51% in non-cardiac surgeries, varying with patient age and surgical type [2]. POD can lead to highly unpleasant medical experience, including extended physical recovery time, prolonged hospitalization, increased incidence of other complications, additional care requirements and higher costs [3]. Therefore, early prevention and treatment strategies for POD are crucial for reducing detrimental outcomes and improving prognosis. However, the etiology of delirium remains unclear, posing significant challenges in treating POD [4]. Therefore, early identification and prevention of POD warrant increased attention.

In light of this, numerous studies have focused on POD risk prediction factors, such as age, the Age-adjusted Charlson Comorbidity Index and the Prognostic Nutritional Index [5, 6]. Notably, some plasma biomarkers have also been considered as risk factors for POD [7, 8]. Albumin, synthesized and secreted by the liver, constitutes over 50% of blood proteins [9]. Previous research has indicated that preoperative hypoalbuminemia is an effective predictor of deliri-

um in surgical patients [7, 10], although its predictive value has been disputed [11]. Fibrinogen, produced in response to proinflammatory cytokines, facilitates platelet aggregation [12]. Literature has highlighted that increased fibrinogen levels are linked to a higher incidence of neurodegenerative diseases, such as Alzheimer's disease and vascular dementia [13]. Recently, studies have begun to exploring fibrinogen's the predictive value for POD [5, 8]. The albumin-fibrinogen ratio (AFR), a composite index based on albumin and fibrinogen, is commonly used as a prognostic indicator for elective surgery [14]. Several studies indicated that AFR might be considered as a potential risk factor in forecasting the progression of POD [15, 16], although the overall effectiveness of this measure is not yet fully established.

Therefore, a meta-analysis was conducted to elucidate the association between plasma biomarkers including albumin, fibrinogen and their ratio with POD in patients undergoing non-cardiac surgery.

Materials and methods

Search strategy

Four online databases (PubMed, EMBASE, CINANL and Cochrane Library) were applied to establish a systematic search using PRISMA guidelines for relevant literatures [17]. The search, which included all studies published up to March 2023, utilized a combination of Medical Subject Headings (MeSH) and comprehensive text-word. The search terms included "delirium/post-operative delirium" in conjunction with "albumin" or "fibrinogen". The detailed search strategies are provided in Supplementary Materials. Additionally, the reference lists of initially included studies were examined to identify further relevant literature.

Inclusion and exclusion criteria

Eligible studies were obtained on the basis of following criteria: (1) Study type: Observational studies, containing cohort and case control study with non-delirium subjects as controls, were considered. There was no restriction on whether the literature was prospective or retrospective. (2) Study population: The population comprised adult patients (> 18 years old), with the age range of the subjects clearly stated in the studies. (3) Surgical type: All patients underwent some type of non-cardiac surgical treatment. (4) Outcomes: Serum biomarkers (albumin, fibrinogen and AFR) were quantified preoperatively, and complete data could be extracted, including mean and standard deviation ($x \pm sd$) or as median and interquartile ranges [M (IQR)]. POD was measured and diagnosed from the end of surgery until discharge using validated tools.

Exclusion criteria included: (1) Patients under 18 years old or those who underwent cardiac surgery. (2) Articles with incomplete data for statistical analysis. (3) Serum biomarkers in delirium patient were not collected and quantified preoperatively. Lack of clear diagnostic tools for delirium. (4) Studies that did not differentiate between delirium and non-delirium groups. (5) Publications in the form of randomized controlled trials, letters, case reports, review articles, conference summaries or other non-original research. (6) In cases of duplicate records, the most recently published record was used.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was chosen to evaluate the risk of bias in selected studies [18]. For observational studies, the NOS scale comprises four components: (1) Selection criteria: adequate case definition (1 point), representativeness of cases (1 point), selection and definition of controls (2 points); (2) Comparability: significant and other confounding elements controlled (2 points); (3) Exposure: ascertainment of exposure (1 point), same method of ascertainment for cases and controls (1 point) and no response rate (1 point). The maximum score is 9 points, with studies scoring 6 points or higher considered to be high quality and possess a low risk of bias.

Data extraction and analysis

Two investigators independently extracted data from the literature, including operation type, study design, patient age, number of cases per group, preoperative plasma biomarkers (albumin, fibrinogen, AFR), the diagnostic tool for delirium, and the timing, frequency and incidence of delirium. After the data were jointly extracted by both investigators, a third investigator reviewed the data, and any disagree-

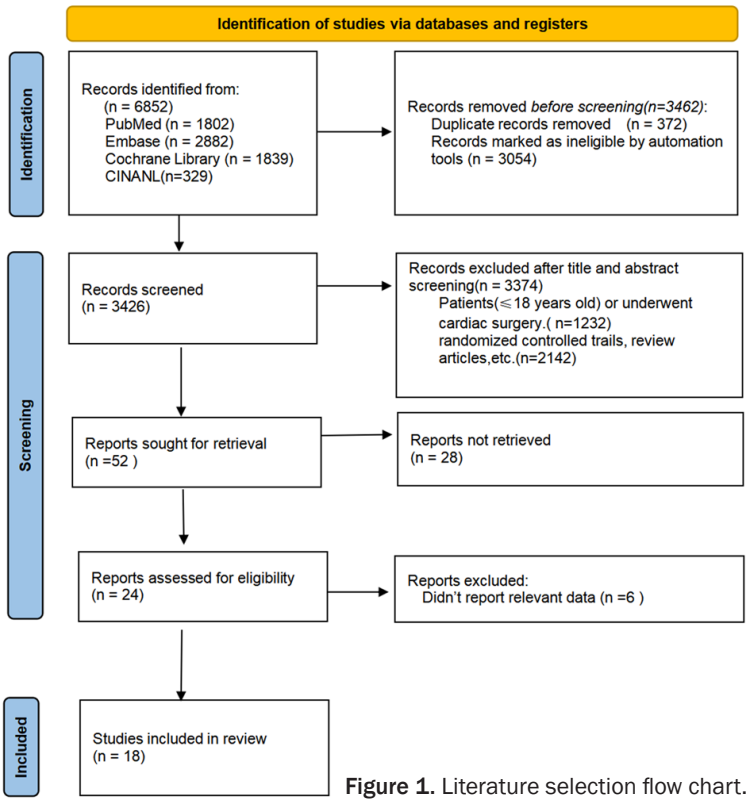

Figure 1. Literature selection flow chart.

ments were reconciled by discussion and consensus among all investigators. The protocol was registered on the PROSPERO website (CRD42023448913).

Statistical analysis

The meta-analysis was performed using RevMan 5.4.1 software to implement statistical analysis. For continuous variables with non-uniform units, the standardized mean difference (SMD) and 95% confidence intervals (CIs) were used; otherwise, the mean difference (MD) and 95% CIs were employed. Data presented as median (interquartile range [IQR]) were converted to mean (standard deviation [SD]) using methods describe by Luo [19] as well as Wan and colleagues [20]. The Q test was performed to assess heterogeneity among the studies, with $P < 0.05$ indicating significant heterogeneity. In cases of apparent heterogeneity ($P < 0.1$ and/or $I^2 > 50\%$), a random-effects model was used to analyze pooled data; otherwise, a fixed-effects model was selected. Subgroup analyses were conducted according to type of surgery, design as well as evaluation tools for POD, provided that each subgroup included two or more studies. Sensitivity analysis was performed by omitting one study at a time to re-evaluate the reliability of the evidence. A funnel plot was used to assess publication bias.

Results

Study selection

Initially, 6,852 records were identified from which 3,426 records were retained after removing duplicates and ineligible articles (**Figure 1**). Further review of titles and abstracts led to the exclusion of an additional 3,374 records. After full-text examination of 52 records, 18 studies were included in the quantitative statistical analysis.

Basic characteristics of literatures

As shown in **Table 1**, 18 cohort studies, up to March 2023, were selected, involving a total of 7,011 participants. These comprised 7 prospective studies [5, 7, 11, 21-24] and 11 retrospective studies [6, 8, 10, 15, 16, 25-30]. All studies concentrated on non-cardiac surgery, consisting of orthopedic surgery (9 studies) [6, 8, 11, 21, 24, 25, 27, 29, 30], thoracoabdominal surgery (6 studies) [5, 10, 15, 16, 22, 23], oral surgery (2 studies) [26, 28] and general non-cardiac surgery without specific classification (1 study) [7]. The Confusion Assessment Method (CAM) was used to assess delirium in seven articles [5-7, 23, 24, 27, 30], including one using the CAM-ICU [7]. Additionally, six studies used DSM-V [8, 10, 15, 16, 21, 25], three studies used DSM-IV [26, 28, 29], one study used the Intensive Care Delirium Screening Checklist [22], and one study used two measurement tools simultaneously [11]. Sample sizes of these studies ranged from 68 to 1933, with delirium prevalence varying from 3.4% to 51.3%.

Risk of bias assessment

The cases included in the mined studies for analysis were typical, with a low underlying risk of bias. The overall quality score of all litera-

Table 1. Characteristics of studies included in the meta-analysis

Author	Year	Type of surgery	Design type (pro or retro)	Age: mean ± SD or Median (IQR) (POD/Non-POD)	POD (N)	Non-POD (N)	Inflammatory mediator	Diagnostic tool for POD	Incident of POD	Timing and frequency of POD diagnosis
Chen J. [15]	2022	Gastric cancer glaparoscopic surgery	re	(75.8 ± 3.8)/(72.5 ± 3.8)	74	196	AFR	DSM-V	27.40%	Daily (no exactly time) within the postoperative 7 days
Guan HL. [7]	2022	Non-cardiac surgery	pro	71 (66-76)/68 (64-72)	107	293	Albumin	CAM-ICU	26.70%	At 2 h after the surgery and twice a day within the postoperative 3 days
Hasegawa T. [26]	2015	Oral cancer surgery	re	(49.0 ± 8.9)/(67.4 ± 12.9)	29	159	Albumin	DSM-IV	15.40%	Daily (no exactly time) until the discharge
Jiang L. [8]	2022	Total joint arthroplasty	re	(74.3 ± 3.1)/(72.1 ± 2.9)	43	293	Albumin, Fibrinoen, AFR	DSM-V	12.80%	Daily (no exactly time) within the postoperative 7 days
Jung JW. [21]	2022	Knee arthroplasty	pro	(76.4 ± 6.2)/(70.7 ± 6.8)	111	1820	Albumin	DSM-V	4.90%	Daily (no exactly time) within the postoperative 7 days
Lemstra AW. [11]	2008	Hip surgery	pro	80 (71-91)/78.5 (71-88)	18	50	Albumin	DSM-IV + CAM	26.50%	Daily (no exactly time) within the postoperative 5 days
Liu J. [5]	2022	Thoracic and abdominal surgery	pro	70.5 (67.0-75.0)/67.0 (64.0-72.0)	36	148	Albumin, Fibrinoen, AFR	CAM	19.60%	Twice a day within the postoperative 3 days
McAlpine JN. [23]	2008	Gynecologic malignancies	pro	76.61 (60.00-91.00)/69.01 (60.00-86.00)	18	85	Albumin	CAM	17.50%	Daily (no exactly time) until the discharge
Morino T. [29]	2018	Spine surgery	re	(77.6 ± 6.6)/(62.5 ± 17.3)	59	116	Albumin	DSM-IV	11.10%	Daily (in the evening) within the postoperative 7 days
Oe S. [6]	2019	Spinal deformity surgery	re	(73.1 ± 4.7)/(61.9 ± 16.9)	30	289	Albumin	CAM	9.40%	Daily (no exactly time) within the postoperative 30 days
Park SA. [10]	2017	Hepatectomy	re	(75 ± 6)/(67 ± 12)	44	152	Albumin	DSM-V	22.40%	Daily (no exactly time) until the discharge
Xiang D. [16]	2022	Gynecologic cancer glaparoscopic surgery	re	(71.7 ± 3.0)/(70.4 ± 2.7)	39	187	AFR	DSM-V	17.30%	Daily (no exactly time) within the postoperative 7 days
Yang Y. [30]	2022	Hip fracture surgery	re	(83.10 ± 7.77)/(81.42 ± 7.63)	30	200	Albumin	CAM	13.60%	Daily (no exactly time) until the discharge
Chen J. [25]	2021	Total joint arthroplasty	re	(71.1 ± 9.6)/(66.4 ± 9.7)	67	927	Albumin	DSM-V	6.7%	Daily (in the evening) within the postoperative 7 days
Makiguchi T. [28]	2020	Oral cancer resection	re	(60.5 ± 11.3)/(59.6 ± 12.0)	45	77	Albumin	DSM-IV	36.9%	/
Matsuki M. [22]	2020	Urological elective surgery	pro	(75.2 ± 6.1)/(74.6 ± 6.5)	32	914	Albumin	ICDSC	3.4%	Daily (no exactly time) within the postoperative 7 days
Shin JE. [24]	2016	Hip fracture	pro	(82.8 ± 6.2)/(80.4 ± 6.9)	40	38	Albumin	CAM	51.3%	Daily (in the morning) within the postoperative 7 days
Kong D. [27]	2022	Hip fracture	re	(78.84 ± 7.36)/(71.21 ± 5.83)	32	213	Albumin	CAM	13.06%	Twice a day until the discharge

Abbreviations: Pro, prospective; re, retrospective; SD, standard deviation; IQR, interquartile range; CAM, confusion assessment method; CAM-ICU, confusion assessment method-intensive care unit; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; DSM-V, Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; ICDSC, Intensive Care Delirium Screening Checklist.

Table 2. Quality assessment based on Newcastle-Ottawa Scale (NOS)

Literature	Selection criteria (/4)	Comparability (/2)	Expose (/3)	Total (/9)
Chen J. [15]	4	1	3	8
Guan HL. [7]	4	1	3	8
Hasegawa T. [26]	4	2	2	8
Jiang L. [8]	4	0	1	7
jung JW. [21]	4	2	1	7
Lemstra AW. [11]	4	1	1	6
Liu J. [5]	3	1	3	7
McAlpine JN. [23]	3	1	2	6
Morino T. [29]	3	2	3	8
Oe S. [6]	4	1	3	8
Park SA. [10]	4	2	2	8
Xiang D. [16]	3	1	3	7
Yang Y. [30]	3	1	2	6
Chen J. [25]	4	2	2	8
Makiguchi T. [28]	3	1	3	6
Matsuki M. [22]	3	1	2	6
Shin JE. [24]	4	2	2	8
Kong D. [27]	4	2	1	7

tures was between 6-8 points, indicating good quality, as shown in **Table 2**.

Meta-analysis

Comparison of plasma albumin levels (g/L) between POD and non-POD patients: Sixteen studies reported serum albumin levels in early post-admission POD and non-POD patients [5-8, 10, 11, 21-30]. Due to high heterogeneity, greater than 50% ($Chi^2 = 76.62$, $P < 0.00001$, $I^2 = 80\%$), random effects models were used. The pooled analysis demonstrated that preoperative plasma albumin concentration was remarkably lower in the POD group compared to the non-POD group [SMD = -0.45, 95% CI = -0.64 to -0.26, Z = 4.72, $P < 0.00001$], as revealed in **Figure 2A**.

Comparison of plasma fibrinogen (g/l) between POD and non-POD patients: Two studies [5, 8] compared fibrinogen levels between the POD and non-POD groups. With low heterogeneity ($Chi^2 = 0.16$, $P = 0.69$, $I^2 = 0\%$), a fixed-effect model was applied. Results indicated a significant correlation between higher fibrinogen levels and POD [MD = 0.13, 95% CI = 0.02 to 0.24, Z = 2.26, $P = 0.02$], as shown in **Figure 2B**.

Comparison of AFR between POD and non-POD patients: Four studies [5, 8, 15, 16] examined the AFR in POD and non-POD patients early post-admission. The meta-analysis showed a negative association between AFR and POD [MD = -0.62, 95% CI = -0.76 to -0.48, Z = 8.39, $P < 0.00001$], with no heterogeneity ($Chi^2 = 2.04$, $P = 0.56$, $I^2 = 0\%$), as shown in **Figure 2C**.

Subgroup analysis for albumin and POD: Subgroup analyses were conducted based on the type of surgery (**Figure 3A**), study design (**Figure 3B**), and delirium evaluation instruments (**Figure 3C**). These analyses consistently showed a negative correlation between albumin levels and POD, irrespective of these factors.

Sensitivity analysis and publication bias for albumin and POD: Due to the high heterogeneity, a sensitivity analysis was performed to assess the impact of each study on the combined estimate and the robustness of the effect size. Sequential removal of individual studies did not significantly influence the combined analysis results (**Figure 4A**), indicating stability in the meta-analysis findings. The funnel plots for albumin were symmetrical, suggesting a low risk of publication bias (**Figure 4B**).

Discussion

Our meta-analysis summarized 18 observational studies and examined the correlation between preoperative plasma biomarkers including albumin, fibrinogen and their ratio with POD in adult patients undergoing non-cardiac surgery. Notably, our results demonstrated plausible evidence for an association between albumin, fibrinogen and AFR with POD in this patient group.

As a postoperative neuropsychiatric behavioral syndrome, POD is mainly characterized by drastic fluctuations in mental status, including changes in consciousness, mood disturbances and inattention [29]. POD can lead to multiple adverse outcomes, such as increased complications and mortality, and decreased quality of life [7]. Since the underlying mechanism

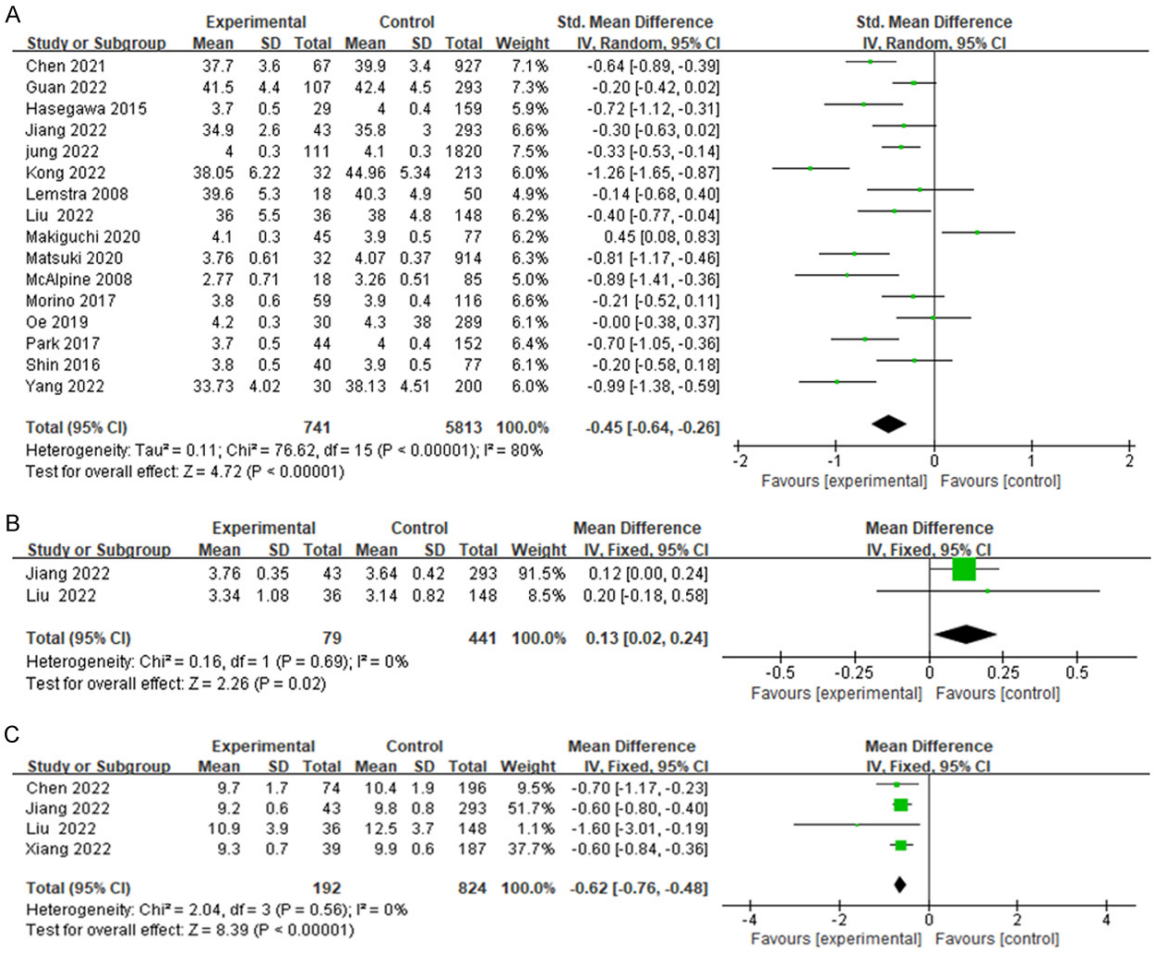

Figure 2. Comparison of serum albumin (A), fibrinogen (B) and AFR (C) between delirium patients and non-delirium patients.

remains poorly understood, treatment options are limited [31]. Early identification of risk factors could help clinicians optimize patient-specific management during the perioperative period. Several risk factors are associated with POD, including malnutrition, previous cerebrovascular history, blood loss and perioperative blood transfusion [32]. Plasma biomarkers, particularly albumin and fibrinogen, and their ratio, are considered potential risk factors for POD [8, 15].

Plasma albumin plays distinct roles, including maintaining physiological homeostasis, exerting anti-inflammatory effects, and displaying antioxidant activity. It is commonly used as an indicator for assessing malnutrition [8]. Interestingly, previous studies have reported that preoperative malnutrition increases the occurrence of POD [33] and that low plasma albumin levels are independently correlated with elevated odds of cognitive dysfunction in the elderly [34]. Our results show a negative correlation between albumin levels and the development of POD, unaffected by the type of surgery, study design, or POD evaluation instruments. Despite high heterogeneity (I^2 = 80%) in our findings sensitivity analysis confirmed the consistency of our results, suggesting their reliability. We speculated that heterogeneity might originate from clinical factors, such as the timing of blood sample collection and delirium assessment. Furthermore, a previous study showed that severe hypoalbuminemia (≤ 30.0 g/L) before surgery was an independent predictor of the occurrence of POD, but not mild and moderate hypoalbuminemia [35]. Unfortunately, only one of the included articles stratified albumin levels (≥ 40.0 g/L and < 40.0 g/L) and derived that lower albumin levels had a higher incidence of

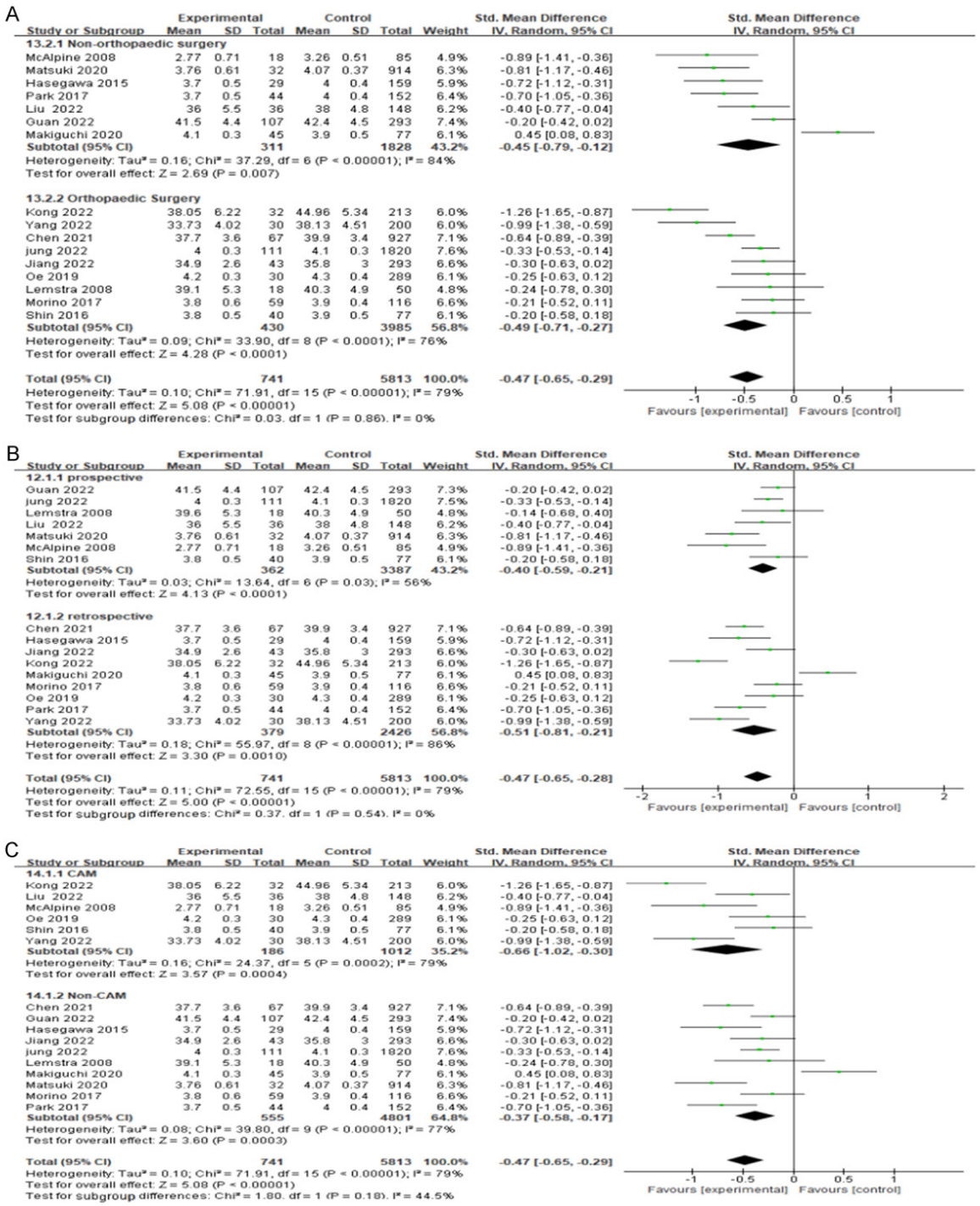

Figure 3. A. Subgroup analysis of orthopedic surgery versus non-orthopedic surgery; B. Subgroup analysis of prospective study versus retrospective study; C. Subgroup analysis of CAM versus Non-CAM.

postoperative delirium [10]. Due to the lack of available data, we could not draw an association between postoperative delirium and hypoalbuminemia, which warrants further exploration.

Fibrinogen, an important acute-phase protein, is widely recognized as a biomarker of coagulation and chronic inflammation [12]. Studies suggest that fibrinogen is deposited in the central nervous system when blood-brain barrier

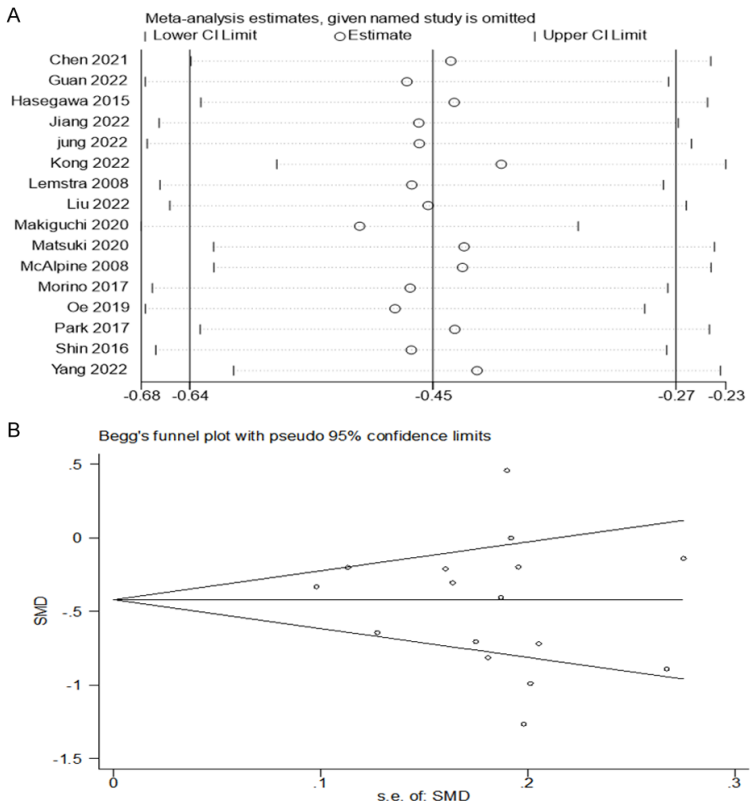

Figure 4. Sensitivity analysis (A) and publication bias (B) for albumin and POD.

function is compromised, leading to neuroinflammation and changes in synaptic plasticity, contributing to cognitive decline [36]. Recently, another study showed that high plasma fibrinogen levels could increase the incidence of cognitive impairment after stroke [37]. As POD is also a cognitive disorder, some studies have focused on whether fibrinogen could be a risk factor for POD [5, 8]. Our results demonstrated that fibrinogen is linked to POD, providing robust evidence for early intervention.

To the best of our knowledge, POD results from a combination of factors, including malnutrition, systemic inflammatory response and coagulation disorder [1]. Albumin is used to assess nutritional status, and fibrinogen is involved in inflammation as an acute-phase reactive protein. The AFR, representing the ratio of albumin and fibrinogen, is a comprehensive marker that simultaneously reflects inflammation and nutritional status [15]. Notably, one study demonstrated that value of AFR to assess prognosis is superior to that of albumin or fibrinogen alone, enhancing the sensitivity for evaluating nutritional status and inflammation [38]. Similarly, another study indicated that the efficacy of AFR in predicting nutritional status and postoperative outcomes among patients surpassed that of albumin or fibrinogen individually, possibly due to a reduction in confounding variables [39]. AFR has emerged as a valuable indicator to predict systemic inflammation, which was closely related to the pathogenesis of POD [16]. When the body experiences physical or surgical trauma, pro-inflammatory mediators are released into the circulation, triggering an inflammatory cascade that can disrupt the blood-brain barrier and potentially lead to POD [40]. Recent studies exploring the value of AFR for POD further point to its potential as a novel biomarker for POD [5, 8]. Interestingly, one study demonstrated that AFR was an independent predicator for POD in elderly patients undergoing total joint arthroplasty, whereas albumin and fibrinogen alone was not [8]. Similarly, our results confirm the predictive value of AFR for POD by pooling relevant literature.

This meta-analysis has several limitations. First, the timing of POD diagnosis varied across the selected studies, which could affect the interpretation of some outcomes. Second, plasma biomarkers were not collected at multiple points throughout the perioperative period, preventing observation of potential longitudinal changes in these markers. Finally, the included studies did not describe the severity or subtypes of delirium, limiting our understanding of whether these plasma biomarkers correlate with delirium severity or specific subtypes.

Conclusion

In summary, our meta-analysis revealed a significant association between preoperative levels of albumin, fibrinogen, and AFR with POD.

These findings underscore the importance of early intervention to prevent POD onset if abnormal plasma levels of these biomarkers are detected.

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Disclosure of conflict of interest

None.

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Supplementary Materials

Table 1. Search strategy

Cochrane	
#1	MeSH descriptor: [Fibrinogen] explode all trees
#2	(Fibrinogen*):ti,ab,kw OR (Blood Coagulation Factor I):ti,ab,kw OR (Coagulation Factor I):ti,ab,kw OR (Factor I, Coagulation):ti,ab,kw OR (Factor I):ti,ab,kw
#3	(gamma-Fibrinogen):ti,ab,kw OR (gamma Fibrinogen):ti,ab,kw
#4	#1 or #2 or #3
#5	MeSH descriptor: [Delirium] explode all trees
#6	(cognitive impairment):ti,ab,kw OR (cognitive dysfunction):ti,ab,kw OR (cognitive decline):ti,ab,kw OR (postoperative delirium):ti,ab,kw OR (delirious):ti,ab,kw
#7	(pod):ti,ab,kw OR (acute confusional syndrome):ti,ab,kw OR (confusion):ti,ab,kw
#8	#5 OR #6 OR #7
#9	MeSH descriptor: [Albumins] explode all trees
#10	(albumine):ti,ab,kw OR (albumines):ti,ab,kw OR (albumin):ti,ab,kw OR (albumin*):ti,ab,kw
#11	#9 or #10
#12	(#4 or #11) and #8
Embase	
#1	‘delirium’/exp
#2	delirium:ab,ti OR ‘cognitive impairment’:ab,ti OR ‘cognitive dysfunction’:ab,ti OR ‘cognitive decline’:ab,ti OR ‘postoperative delirium’:ab,ti OR delirious:ab,ti OR pod:ab,ti OR ‘acute confusional syndrome’:ab,ti OR confusion:ab,ti
#3	#1 OR #2
#4	‘albumin’/exp
#5	‘albumin’:ti,ab or ‘albumine’:ti,ab or ‘albumines’:ti,ab or ‘albumin*’:ti,ab
#6	#4 OR #5
#7	‘fibrinogen’/exp
#8	fibrinogen:ab,ti OR fibrinogen*:ab,ti OR ‘blood coagulation factor i’:ab,ti OR ‘coagulation factor i’:ab,ti OR ‘factor i, coagulation’:ab,ti OR ‘factor i’:ab,ti OR ‘gamma fibrinogen’:ab,ti
#9	#7 or #8
#10	(#6 or #9) and #3

Pubmed	
#1	(((((((Fibrinogen[MeSH Terms]) OR (Fibrinogen*[Title/Abstract])) OR (Blood Coagulation Factor I[Title/Abstract])) OR (Coagulation Factor I[Title/Abstract])) OR (Factor I, Coagulation[Title/Abstract])) OR (Factor I[Title/Abstract])) OR (gamma-Fibrinogen[Title/Abstract])) OR (gamma Fibrinogen[Title/Abstract]))
#2	(((((albumins[MeSH Terms]) OR (albumin's[Title/Abstract])) OR (albumine[Title/Abstract])) OR (albumines[Title/Abstract])) OR (albumins[Title/Abstract])) OR (albumin[Title/Abstract])
#3	(((((((Delirium[MeSH Terms]) OR (cognitive impairment[Title/Abstract])) OR (cognitive dysfunction[Title/Abstract])) OR (cognitive decline[Title/Abstract])) OR (postoperative delirium[Title/Abstract])) OR (delirious[Title/Abstract])) OR (pod[Title/Abstract])) OR (acute confusional syndrome[Title/Abstract])) OR (confusion[Title/Abstract])
#4	(#1 or #2) and #3
CINANL	
S1	MH albumins OR TI albumin's OR AB albumin's OR TI albumine OR AB albumine OR TI albumines OR AB albumines OR TI albumins OR AB albumins OR TI albumin OR AB albumin
S2	MH Fibrinogen OR TI Fibrinogen* OR AB Fibrinogen* OR TI Blood Coagulation Factor I OR AB Blood Coagulation Factor I OR TI Coagulation Factor I OR AB Coagulation Factor I OR TI Factor I, Coagulation OR AB Factor I, Coagulation OR TI Factor I OR AB Factor I OR TI gamma-Fibrinogen OR AB gamma-Fibrinogen OR TI gamma Fibrinogen OR AB gamma Fibrinogen
S3	MH delirium OR TI cognitive impairment OR AB cognitive impairment OR TI cognitive dysfunction OR AB cognitive dysfunction OR TI cognitive decline OR AB cognitive decline OR TI postoperative delirium OR AB postoperative delirium OR TI delirious OR AB delirious OR TI pod OR AB pod OR TI acute confusional syndrome OR AB acute confusional syndrome OR TI confusion OR AB confusion
S4	(S1 OR S2) AND S3

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 1-2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 2-3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 2; Supplementary Materials
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 2; **Figure 1**
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 2-3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	None
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 3
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	None
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 3
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 3
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	None

RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 3; **Figure 1**
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	**Figure 1**
Study characteristics	17	Cite each included study and present its characteristics.	Page 3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 3, 5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 5; **Figure 2**
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 5
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 5
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	None
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 5
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 5
	23b	Discuss any limitations of the evidence included in the review.	Page 6-7
	23c	Discuss any limitations of the review processes used.	Page 8
	23d	Discuss implications of the results for practice, policy, and future research.	Page 8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	None
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	None
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 9
Competing interests	26	Declare any competing interests of review authors.	Page 9
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	None

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