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Cytokines and inflammatory biomarkers and their association with post-operative delirium: a meta-analysis and systematic review

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Delirium is a prevalent cognitive disorder among older patients and a common phenomenon following major surgical procedures. This study aimed to identify the significant proteomic biomarkers and examine their association with postoperative delirium (POD). Four electronic databases were used to identify the published articles between 1st January 2000 and 31st December 2023. Among the included 40 studies, the meta-analysis investigated 13 potential cytokines and inflammatory biomarker proteins linked with postoperative delirium. The Hedge's *g* standardized mean difference (SMD) was applied to calculate the effect size, with 95% confidence intervals (CIs), under the fixed effect or random effect model based on the heterogeneity index of I^2. Patients with POD exhibited significantly higher elevated levels of inflammatory biomarkers IL-6 (SMD = 1.45), CRP (SMD = 1.26), GFAP (SMD = 1.15), IL-1B (SMD = 0.95), IL-10 (SMD = 0.57), IL-8 (SMD = 0.56), MCP-1 (SMD = 0.39), and NFL (SMD = 0.44), suggesting that these proteins may play an inevitable role in delirium-associated cytokines and inflammatory response, development and progression of delirium. Conversely, a reduction in IGF-1 protein level (SMD = −0.24) was also significantly associated with POD, suggesting a potential vulnerability to delirium. This study paves the way for future research aimed at early diagnosis, personalized treatment, and the development of novel therapeutic strategies to manage delirium effectively.

Keywords Post-operative delirium, Cytokines and inflammatory proteins, Systematic review and meta-analysis, Interleukins, C-reactive proteins

Delirium is a common neurological complication among hospitalized or intensive care unit (ICU) patients. It is characterized by temporary impairments in concentration, consciousness, and cognition, often leading to prolonged recovery, increased mortality, and higher healthcare costs[1–3]. Delirium can be triggered by various risk factors including pain, trauma, stress, inflammation, and other medical conditions. Recent studies suggest that both surgery and anesthesia have an adverse effect on cognitive function, contributing to the development of post-operative delirium (POD)[4,5]. Although the pathophysiology of delirium is largely unknown, it plays a significant role in the development and severity of delirium[6–8]. Delirium might be a modifiable risk factor for dementia which indicates a crucial interrelationship[9]. POD has been identified in 15–53% of elderly patients after surgery[10,11] despite the fact that, a significant number of cases remained undiagnosed. Currently, the clinical examination and symptom-based diagnosis are the only techniques that are being employed in medical settings to detect delirium.

Over the last few decades, there has been a rapid increase in molecular research indicating that delirium is correlated with different potential biomarkers such as different proteins, genes, genetic variation (i.e., Single Nucleotide Polymorphism), and others[12–14], although no single biomarker has been introduced so far

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to diagnose and predict delirium. The distinct theories, functional mechanism and pathologic process have been hypothesized to explain the onset and development of delirium including neuroinflammation, central nervous system dysfunction, neurotransmitter systems; inflammatory cytokine activity leading to blood–brain barrier permeabilization; and hypothalamic-pituitary axis disturbance following severe trauma[15]. Among them cytokines and inflammatory related proteomic biomarkers are considered to be one of the crucial influencers of delirium as they trigger inflammation and contribute to its onset[16–19]. A recent meta-analysis by Liu et al. and other research also suggest that some inflammatory markers (for example, IL-6, C-RP) are highly associated with POD and postoperative cognitive decline[20–23]. Since neurodegeneration results from stimulation of the systemic inflammatory cascade, it is believed that dysregulation of cytokines is the major cause of neurodegeneration and the consequent mental impairment in delirium[24–26]. The growing evidence clearly indicates that cytokines and inflammation related biomolecules play a significant role in delirium's development, progression, and pathophysiology.

Nevertheless, having no specific single biomarkers-based diagnosis, mysterious multifactorial pathophysiology of delirium reveals a huge knowledge blackhole. Considering this knowledge gap in this area, identifying, and analyzing specific protein biomarkers associated with postoperative delirium due to their immediate clinical relevance, dynamic nature, and potential for therapeutic targeting could be a possible way of further deeper investigation to detect any unique proteomic biomarker molecule to diagnose delirium as well as utilize for future therapeutic investigation. While genetic factors offer insight into long-term risk, protein biomarkers such as cytokines and inflammatory proteins provide real-time indicators of physiological changes and inflammatory responses directly linked to delirium. This focus enhances our understanding of the acute mechanisms driving delirium and informs the development of targeted interventions, complementing genetic research and offering a more comprehensive view of delirium management. Therefore, the primary objective of this study was to synthesize the existing literature that reports potential proteins associated with POD. The qualitative syntheses were reported to update the existing knowledge regarding delirium-associated proteins. Additionally, a quantitative meta-analysis would be conducted to investigate the hypothesis that cytokines and inflammatory proteins are significantly associated with POD.

Materials and methods

Systematic review

The study conducted a systematic literature review (SLR) of delirium-associated proteins/gene-encoded proteins. The review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[27] and the corresponding PRISMA flowchart and checklist. The well-established PICOS framework[28] was utilized to develop the search terms and inclusion and exclusion criteria for the review. This systematic review was registered on PROSPERRO (registration number: CRD42024566515).

A total of 1,746 records were retrieved from selected electronic bibliographic databases [PubMed, Scopus, and EBSCOhost (CINAHL, Medline)], of which 1365 were screened after removing 381 duplicates (Fig. 1). A total of 1232 articles did not meet the inclusion criteria during the title and abstract screening and were hence excluded. The full text of 133 studies were screened and finally, 78 studies were included in qualitative synthesis. After the qualitative synthesis, the selected 78 studies were further screened for quantitative synthesis and meta-analysis according to the inclusion criteria. The details of the methodology for qualitative review including search strategies and keywords, PICOS frameworks, inclusion–exclusion criteria, and the review outcome are provided in Supplementary File 1.

Study screening and selection process

A three-stage screening process was used to identify whether the research was eligible for inclusion. The first stage involved screening of studies by title to eliminate duplications. The second stage required reviewing titles and abstracts to determine their relevance to our study. Finally, the third stage necessitated reading the full texts of the retained studies, and those that met the set criteria were kept. The first author, MPM, carried out the title and abstract screening under the direct guidance and supervision of a supervisory team, including experienced researchers (RAM, KA, and JG). Then the eligibility of the full text articles was examined by two researchers, MPM and RAM. During the screening process, we addressed the disputes with the other researchers and resolved them by consensus.

Meta-analysis

In this study, we have conducted a meta-analysis of the cytokines and inflammatory biomarkers associated with delirium. Finally, 78 full-text articles in SLR (qualitative analysis) were further considered and screened for quantitative meta-analysis. For this purpose, we identified 13 most-studied delirium-associated proteins reported among the 78 studies (Supplementary Fig. 1). These 13 proteins were the key component of cytokines and inflammatory biomarkers namely, Interlukitin-6 (IL-6), C-reactive protein (CRP), Interlukitin-8 (IL-8), S100B calcium-binding protein, Interlukitin-10 (IL-10), Tumor necrosis factor-a (TNF-a), Interlukitin-1b (IL-1B), Cortisol, Monocyte chemoattractant protein 1 (MCP-1), Glial fibrillary acidic protein (GFAP), Insulin-like-growth-factor-1 (IGF-1), Interlukitin-1 receptor antagonist (IL-1ra), and Neurofilament light polypeptide (NFL) as found in qualitative synthesis. They were considered for conducting a meta-analysis to determine their association with delirium.

Inclusion and exclusion criteria for meta-analysis

The primary search strategy and inclusion and exclusion criteria for SLR were considered based on the PICOS framework (Supplementary File 1). In addition to the qualitative synthesis, the following inclusion criteria were utilized for screening the 78 studies for meta-analysis:

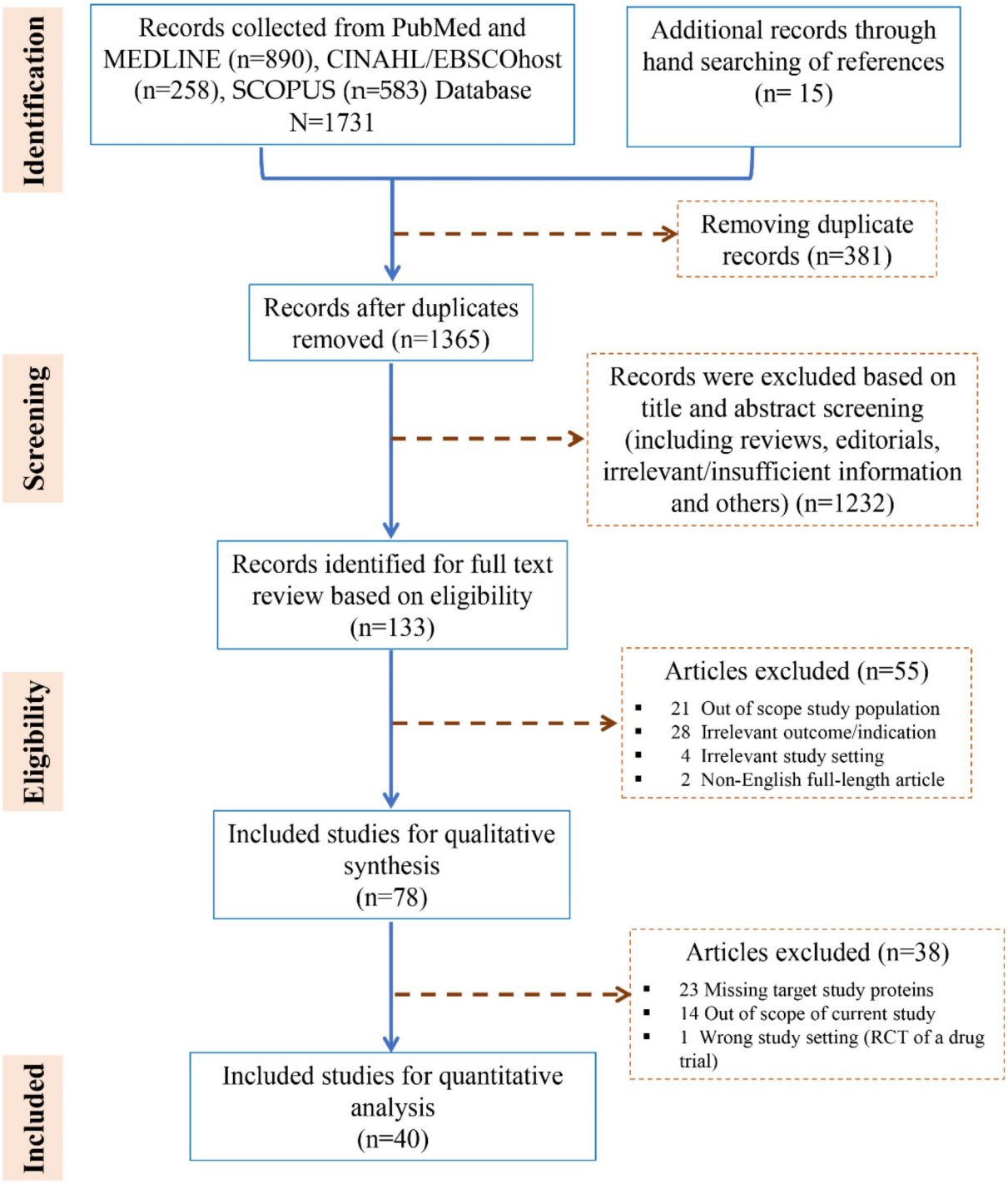


Fig. 1. The PRISMA flowchart of this study.

(1) Observational studies included the case (delirium) and control (non-delirium) of human subjects.
(2) Delirium is confirmed by any of the established scientific methods as described in the systematic review.
(3) The studies reported any of the top 13 cytokines and inflammatory biomarkers associated with delirium.
(4) The studies reported the biomarkers found in serum, plasma, or Cerebrospinal Fluid (CSF) in both delirium and non-delirium groups.

The exclusion criteria were:

(1) Any randomized control trial that reported any drug effect or any intervention effect along with the biomarker information.
(2) The delirium and non-delirium subgroups were not clearly defined and reported.
(3) Data presented by graph and any unavailable data format.
(4) Biomarker information presented in any other formats (such as, log fold change value, and regression coefficient)

A total of 40 studies met the inclusion criteria for meta-analysis.

Quality assessment

Quality assessment of the 40 included studies for meta-analysis was conducted because of the heterogeneity among the study designs of the included studies. In this systematic review and meta-analysis, the cohort, case–control, cross-sectional, randomized control trials, and longitudinal study designs were found among the included studies. The Joanna Briggs Institute (JBI)[29] provided critical quality assessment tools that have been utilized for quality assessment. The JBI quality appraisal tools are widely used in academic studies to assess the risk of bias (graded as high, moderate, or low)[30–33], where the higher quality scores demonstrate better confidence and vice versa. The JBI appraisal tool was used to evaluate the 38 cohort studies, ten case-controls, three randomized control trials, two cross-sectional, and one longitudinal study included in our review. The overall quality appraisal scores are summarized in Supplementary File 2.

Data extraction for meta-analysis

One reviewer extracted the data using inclusion and exclusion criteria for meta-analysis. The data matrix was shared within the group for review, and any discrepancy was discussed and resolved accordingly. The genes and proteins significantly related to delirium were mainly considered for this qualitative synthesis. During the data extraction, we considered the first author, publication year, country of study, study design, patient's medical or surgical information, and method of delirium diagnosis, and significant proteins associated with delirium. Further, the sample size, number of delirious and non-delirious patients, and the effect size (mean and standard deviation) for top 13 biomarkers' serum/plasma/CSF concentrations (pg/ML), method of examination/sample source of the proteins, and number of reported proteins were collected for meta-analysis.

The biomarkers expression or concentration in serum/plasma/CSF were collected in linear format units (such as pg/ML, ng/ML). For example, if any of the descriptive statistics were presented in log transformation, the value has been converted in linear format according to the guidance provided in the specific article. Most of the protein concentration data (70%) were presented in pg/ML format. Therefore, for a robust comparison, analysis and reporting purposes, we converted all other reported units into the base pg/ML format. The effect sizes presented in median, range, standard error, 95% confidence interval (CI), and interquartile range (IQR) were converted into mean and standard deviation (SD) using a suitable formula[20,34,35]. For a large sample size (n > 25), the median can be used for estimating the mean. The SD was calculated from the given IQR using the formula IQR/1.35. We used the following formula and conditions for calculating the optimal estimator for SD using range:

$$SD: \quad \begin{matrix} \frac{Range}{4}; & when, 15 < sample\ size \leq 70 \\ \frac{Range}{6}; & when,\ sample\ size > 70 \end{matrix}$$

If the 95% CI was given with the effect size, the standard error (SE) was calculated using the formula, SE = (*Upper limit of CI-Lower limit of CI*)/3.92. Then SD was calculated from the given SE using the following formula:

$$SD: \quad SE \times \sqrt{n}; When, sample\ size = n$$

Data extraction

Using the Mendeley library, the data were extracted by one researcher (MPM) under the direct supervision and guidance of another researcher (RAM), who also validated and reviewed the extracted data. Emerging differences in the data were discussed and resolved by consensus, and where the two researchers could not agree, other researchers (KA and JG) were consulted to resolve. The entire procedure was guided and completed by the systematic literature review tool Covidence (https://app.covidence.org). The meta-analysis data was collected from both the delirium and non-delirium groups, based on predetermined inclusion and exclusion criteria.

Meta-analysis

The meta-analysis was undertaken using the data available in SLR to examine the most extensively investigated proteins related to delirium where the aforementioned 13 biomarkers were reported. To perform the meta-analysis, the inverse-variance weights[36] technique was employed to calculate Hedges's g, a standardized mean difference (SMD) estimation suitable for small sample sizes with 95% CI, using the random effect model (REM). The Q-statistic was calculated through the Chi-square test for heterogeneity among the studies with a statistically significant p-value < 0.05[37]. To reveal the effect of the heterogeneity, the inconsistency index I^2 was evaluated[38]. When the studies showed homogeneity ($I^2 < 50\%$), the fixed effect model (FEM) was utilized for meta-analysis, employing the invariance-variance method, otherwise random effect model (REM) were used. The subgroup analysis was conducted for the proteins reported in more than five studies. Sensitivity analysis was performed considering the effect of between-study variance on overall effect size estimation. Egger's test was implemented to check publication bias and small study effect among the included studies which showed statistical significance with a p-value of less than 0.05. The trim-and-fill method was employed to determine any existing publication

bias effects and their impact on the total effect size[39]. All analysis was conducted using STATA/SE Version 17 for Windows (STATA Corp College Station, TX).

Results

Literature exploration and study population

The current SLR and meta-analysis included 78 and 40 articles for qualitative and quantitative synthesis, respectively. Figure 1 demonstrates the screening and selection process using the PRISMA guidelines. During the screening for meta-analysis, we excluded 38 articles selected for qualitative synthesis, using the exclusion criteria (Fig. 1). The included 40 studies used for meta-analysis were to investigate the relationship between the top 13 biomarker proteins and postoperative delirium (POD). In this analysis, we collected a total of N = 6644 study population where 29.6% (n = 1968) were found to experience POD. The average proportion of delirious patients among the included studies was 35% with a minimum of 10% to a maximum of 63% of the study sample. Most of the included studies reported the ages of delirious patients between the ages of 70 and 80, with two studies reporting young onset delirium at the mean age of 27 years (Table 1).

Study characteristics

Table 1 and Fig. 2 describe the key features of the selected studies. Most of the studies reported that the confusion assessment method (CAM) (n = 20) or CAM for the intensive care unit (CAM-ICU) (n = 12) version was used to diagnose delirium (Fig. 2A). Along with these two assessment methods, a few studies also used multiple methods to identify delirious patients including the DSM-IV and DSM-5, DRSR-98, and others (Fig. 2A). The included studies were conducted in 15 different countries (Fig. 2B) with most of them conducted in China (23%), the Netherlands (20%), and the USA (18%). Three studies were conducted in Poland, two were in India and Norway. Among the included studies for meta-analysis, most of the studies were cohort studies (80%; n = 32), followed by case–control (13%; n = 5) two cross-sectional studies, and one longitudinal study (Fig. 2C).

Risk of bias in studies

The quality scores for the included studies were obtained using the JBI quality evaluation checklists (Supplementary File 2) where the majority of included studies (n = 31; 77.5%) were of medium/moderate quality, and nine out of forty (22.5%) were high standard, demonstrating the robustness of the included research. For example, of the 32 cohort studies, 28 were rated as medium quality on the JBI scale and four were rated as high quality. Two case–control studies were of high quality and three were of medium quality, according to the JBI quality rating checklists. There were two high-quality cross-sectional studies and one longitudinal study. Not a single study in this review was excluded due to a low-quality assessment.

Association of cytokines and inflammatory protein with POD

The meta-analysis revealed nine cytokines and inflammatory-related proteins, namely IL-6, CRP, IL-8, IL-10, MCP-1, GFAP, IGF-1, IL-1B, and NFL showed statistically significant (p-value < 0.05) SMD of concentration level (pg/ML) between POD and non-delirium samples. The findings of the meta-analysis are displayed in Fig. 3 with the overall effect size (Hedges's g), 95% CI, p-values, p-value of heterogeneity test ($P_{Heterogeneity}$), heterogeneity index I^2, and the meta-analysis model used for each of the proteins. In contrast, the other four proteins, namely Cortisol, S100B, TNF-a, and IL-1ra did not show any significant difference in concentration level (pg/ML) between POD and non-delirium patients (Fig. 3).

There was a significant SMD Hedges's g between the patients from the delirium and non-delirium group with the increased level of IL-6 level (pg/ML) among the delirious patients (21 studies, Hedges's g = 1.35; 95% CI = 0.52, 2.18; p = 0.000; REM). The concentration level of CRP protein was found to be higher among delirious patients compared to non-delirious (12 studies, Hedges's g = 1.26; 95% CI = 0.34, 2.18; p = 0.01; REM). The increased concentration level of IL-8 (7 studies, Hedges's g = 0.56; 95% CI: 0.23, 0.89; p = 0.000; REM) and IL-10 (7 studies, Hedges's g = 0.57, 95% CI: 0.19, 0.95; p = 0.000; REM) proteins were also significantly associated with the POD found in meta-analysis with REM (Fig. 3).

Similarly, the statistically significant increased level of MCP-1 (5 studies, Hedges's g = 0.39, 95% CI: 0.18, 0.59; p = 0.000; FEM), GFAP (2 studies, Hedges's g = 1.15, 95% CI: 0.78, 1.52; p = 0.000; FEM), IL-1B (3 studies, Hedges's g = 0.95; 95% CI: 0.61, 1.29; p = 0.000; FEM) and NFL (2 studies; Hedge's g = 0.44; 95% CI: 0.23, 0.64; p = 0.00; FEM) among the delirious patients. Conversely, the decreased level of IGF-1 (3 studies, Hedges's g = − 0.24; 95% CI: − 0.47, − 0.01; p = 0.03; FEM) among post-operative delirious patients were found in meta-analysis (Fig. 3).

For the four statistically significant proteins (IL-6, CRP, IL-8, and IL-10), the REM was employed for the meta-analysis while for the rest of the significant proteins (MCP-1, GFAP, IGF-1, IL-1B, and NFL), the FEM was utilized based on the heterogeneity index I^2 (< 50%) and the $P\text{-}value_{(heterogeneity)}$ > 0.05 of heterogeneity test (Q-test) (Fig. 3). Moreover, Egger's test was performed to assess publication bias for all the analyses (Table 2). Based on our meta-analysis, the four proteins (Cortisol, S100B, TNF-a, and IL-1ra) were found to be statistically insignificant in relation to POD showing insignificant Hedge's g (Fig. 3). For all these proteins, the REM was utilized for meta-analysis based on the heterogeneity index I^2 > 50% (Fig. 3).

Subgroup analysis

As per the selection criteria we have conducted subgroup analysis for the proteins IL-6, CRP, IL-8, IL-18 and S100B as they were reported by more than five studies. The subgroup analysis was conducted based on the study type, delirium assessment method, and the source of protein detection (CSF vs peripheral plasma/serum concentration) since other variables were highly heterogenous. The subgroup analysis revealed that the overall effect sizes for the proteins are more homogeneous for cohort studies than the other type of studies (Fig. 4). The studies that identified delirium using the CAM method revealed the significant overall size effect for protein IL-6

References	Source of protein detection	Patient's medical/surgical information	Country	Type of study	Delirium assessment methods	Age	Delirious case/ Sample size	# of reported proteins	Reported associated proteins/genes
Hirsch et al.[40]	Plasma and CSF Concentration	Patients underwent orthopedic surgery	USA	Cohort Study	CAM	Mean (SD): 70.3 (8.7)	1/10	13	IL-5, IL-6, RAGE, IL-8, MCP-1, IL-10, IFN-a, IL-4, IFN-γ, IL-12, TNF-a, MIP-1α, MIP-1β
Kazmierski et al.[41]	Serum biomarker concentration	Patients underwent coronary-artery bypass graft surgery	Poland	Cohort Study	CAM-ICU	Median (IQR): 64 (59, 71)	41/113	2	IL-2, TNF-a
Miao et al.[42]	Plasma biomarker concentration	Patients underwent open abdominal surgery	China	Cohort Study	DSM-IV	NR	49/112	4	Neopterin, CRP, IL-6, IGF-1
Ritter et al.[16]	Plasma biomarker concentration	All ICU Patients	Brazil	Cohort Study	CAM-ICU	Median (IQR): 56 (42, 67)	31/78	4	STNFR1, STNFR2, adiponectin, IL-1B
Sun et al.[43]	Plasma biomarker concentration	Patients underwent tumor resection together with free flap surgery	China	Cohort Study	CAM	NR	56/112	5	IL-6, CRP, procalcitonin, Cortisol, ABI-40
Van Munster et al.[44]	Serum biomarker concentration	Patients underwent hip fracture surgery	Netherlands	Cohort Study	CAM	NR	50/98	2	IL-6, IL-8
Vasunilashorn et al.[45]	Plasma biomarker concentration	Patients underwent major elective surgery	USA	Case–Control Study	CAM	Mean (SD): 77.3 (5.0)	95/517	5	IL-6, IL-2, TNF-a, IL-12, VEGF
Westhoff et al.[46]	Cerebrospinal Fluid (CSF) concentration	Elderly patients underwent hip fracture surgery	Netherlands	Cohort Study	CAM	Mean (SD): 84.6 (5.2)	23/61	3	IL-6, IL-1ra, FLT-31
Ballweg et al.[47]	Plasma biomarker concentration	Patients underwent major elective non-intracranial, noncardiac surgery	USA	Cohort Study	CAM-ICU	Mean: 69.2	37/103	3	IL-8, IL-10, MCP-1
Van Munster et al.[48]	Plasma biomarker concentration	Patients underwent orthopedic surgery	Netherlands	Cohort Study	CAM	Mean (SD): 84.8 (6.9)	62/120	4	Cortisol, IL-6, IL-8, S100B
Ka´zmierski et al.[49]	Serum biomarker concentration	Patients underwent cardiac surgery	Poland	Cohort Study	CAM	Median (IQR): 67 (63, 71)	61/177	2	MCP-1, CRP
Ye et al.[50]	Plasma biomarker concentration	Patients underwent elective laparoscopic surgery	China	Cohort Study	CAM-ICU	Mean (SD): 63.69 (7.21)	50/104	9	IL-6, CHI3L1, S100B, Lp-PLA2, MIF, ICAM-1, VCAM-1, BACE1, a-SYN
Ritchie CW et al.[51]	Plasma biomarker concentration	Acutely ill older patients	UK	Cross-Sectional Study	CAM	Mean (SD): 83.05 (7.4)	87/710	1	CRP
Erikson et al.[52]	Serum biomarker concentration	Patients with septic shock	Finland	Cohort Study	CAM-ICU	Median (IQR): 62.4 (49, 70.5)	10/22	2	S100B, IL-6
Khan et al.[53]	Serum biomarker concentration	Patients underwent esophagectomy	USA	Cohort Study	CAM-ICU	Median (IQR): 65.9 (57.8, 70.6)	26/71	3	CRP, IL-8, IL-10
Boogaard et al.[54]	Plasma biomarker concentration	All medical and surgical patients	Netherlands	Cross-Sectional Study	CAM-ICU	Median (IQR): 72 (38–86)	50/100	10	IL-8, MCP-1, PCT, Cortisol, TNF-a, MIF, IL-8, IL-1B, IL-1ra, IL-10
Hall et al.[55]	Cerebrospinal Fluid (CSF) concentration	Patients underwent hip fracture surgery	Scotland	Cohort Study	CAM	Mean (SD): 81.3 (6.7)	8/45	1	S100B
Chai et al.[56]	Plasma biomarker concentration	Patients underwent cardiac surgery	China	Cohort Study	CAM	Mean (SD): 56.48 (± 11.68)	31/221	1	IL-6
Mao et al.[57]	Serum biomarker concentration	Patients underwent elective orthopedic surgery	China	Cohort Study	CAM	Median (IQR): 77 (70, 82)	35/131	4	PGE2, NfL, S100B, GFAP
Neerland et al.[58]	Cerebrospinal Fluid (CSF) concentration	Patients underwent acute hip fracture	Norway	Cohort Study	CAM	Median (IQR): 85 (80, 89)	25/85	2	CRP, sIL-6R
Cerejeira et al.[59]	Plasma biomarker concentration	Patients underwent elective arthroplasty	Portugal	Cohort Study	CAM	Mean (SD):73 (±6.3)	37/101	4	CRP, IL-6, IL-8, IL-10
Rooij et al.[60]	Serum biomarker concentration	All acutely ill patients	Netherlands	Cohort Study	CAM	Mean (SD): 81.2 (7.1)	64/185	2	IL-6, IL-8
McNeil et al.[61]	Plasma biomarker concentration	All critically ill patients	USA	Cohort Study	CAM-ICU	Median (IQR): 74 (68, 82)	64/156	2	PAI-1, IL-6
Cape et al.[62]	Cerebrospinal Fluid (CSF) concentration	Patients underwent acute hip fracture	Netherlands	Cohort Study	CAM	Mean (SD): 81.3 (6.0)	9/43	2	IL-1B, IL-1ra
Lindblom et al.[63]	Serum and Cerebrospinal Fluid (CSF) concentration	Patients underwent complex surgery on the thoracic aorta	Sweden	Cohort Study	CAM-ICU	NR	8/23	10	TR4, EZH2, CHI3L1, IL-6, SFRP2, PMP2, RTN4R, GFAP, CX3CL1, ICAM-1
Skrede et al.[64]	Plasma biomarker concentration	Patients underwent acute hip fracture	Norway	Cohort Study	CAM	Median (IQR): 83 (79, 91)	12/19	1	MCP-1

Continued

References	Source of protein detection	Patient's medical/surgical information	Country	Type of study	Delirium assessment methods	Age	Delirious case/ Sample size	# of reported proteins	Reported associated proteins/genes
Brattinga et al.[65]	Plasma biomarker concentration	Patients underwent oncologic surgery	Netherlands	Cohort Study	DOS scale	Median (Range): 72 (65, 89)	38/311	3	IL-6, IL-10, NGAL
Chen et al.[66]	Serum biomarker concentration	Patients underwent coronary artery bypass graft	China	Cohort Study	CAM-ICU	Mean (SD): 67 (7.7)	85/266	1	IL-6
Shen et al.[67]	Serum biomarker concentration	Patients underwent open abdominal surgery	China	Cohort Study	CAM, DRS-R-98	Mean (SD): 73.8 (±5.9)	36/140	1	IGF-1
Egberts et al.[68]	Plasma and Serum Concentration	Acutely ill patients	Netherlands	Case–Control Study	DSM-IV	≥65	23/86	3	Neopterin, IL-6, IGF-1
Sun et al.[69]	Serum biomarker concentration	Patients underwent colorectal cancer surgery	China	Cohort Study	CAM	Mean (SD): 70.94 (±6.38)	112/643	1	CRP
Ruhnau et al.[70]	Serum biomarker concentration	Patients underwent spine surgery	Germany	Cohort Study	DSM-5, Nu-DESC	Mean (SD): 75.7 (±5.8)	19/44	5	sTREM2, Gasdermin D, IL-6, S100B, IL-1B
Zhang et al.[71]	Plasma biomarker concentration	Patients underwent major lower limb surgery	China	Longitudinal Study	CAM	Median (IQR): 81 (68–85)	31/126	2	IL-6, sIL-6R
Leung JM et al.[72]	Plasma biomarker concentration	Patients underwent elective noncardiac surgery	USA	Case–Control Study	CAM	Mean (SD): 73.22 (6.06)	102/204	1	NFL
Shyam et al.[73]	Serum biomarker concentration	Critically ill obstetric patients	India	Case–Control Study	CAM-ICU	Mean (SD): 27.46 ± 4.97	37/76	1	S100B
Kim et al.[74]	Serum biomarker concentration	Patients underwent acute hip fracture	South Korean	Cohort Study	DSM-V	Mean (SD): 80.1 ± 7.6	150/300	1	CRP
Shyam et al.[75]	Serum biomarker concentration	Critically ill obstetric patients	India	Case–Control Study	CAM-ICU	Mean (SD): 27.46 ± 4.97	37/76	1	CRP
Brown et al.[76]	Plasma biomarker concentration	Patients underwent cardiac surgery	USA	Cohort Study	CAM, CAM-ICU, DSM-5	Mean (SD): 72.3 (8.1)	88/175	1	NFL
Klimiec-Moskal et al.[77]	Serum biomarker concentration	Consecutive stroke patients	Poland	Cohort Study	bCAM, CAM-ICU	Median (IQR): 78 (68–85)	134/459	1	CRP
Imai et al.[78]	Serum biomarker concentration	Patients underwent head and neck surgery	Japan	Cohort Study	CAM	Mean (SD): 72.8 ± 7.3	54/221	1	IL-6

Table 1. Summary information of the forty selected studies for meta-analysis. SD: Standard Deviation; NR: Not Reported; IQR: Inter Quartile Range; ICU: Intensive Care Unit; (b) CAM/CAM-ICU: (Brief) Confusion Assessment Method (ICU), DSM-IV/5: Diagnostic and Statistical Manual of Mental Disorders (Version-IV/5); Nu-DESC: Nursing Delirium Screening Scale; DRS-R-98: Delirium Rating Scale-Revised-98; DOS scale: Delirium Observation Screening scale.

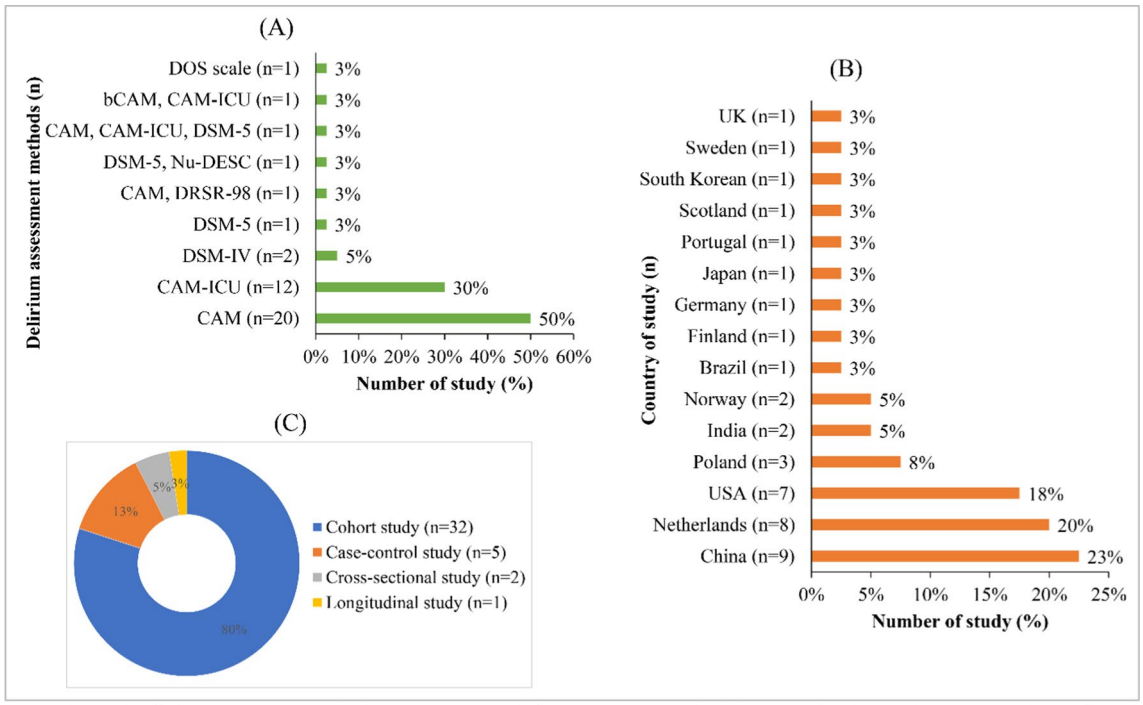
and S100B. The CAM-ICU method showed significant results for protein CRP and IL-10 when both delirium identification methods indicated significant outcomes for IL-8 protein in subgroup analysis (Fig. 4). Conversely, the subgroup analysis for IL-6, categorized by the source of protein concentration data, revealed that the effect size was insignificant for CSF samples (Hedges's g = 4.15; 95% CI: −2.73, 11.02), while a significant effect was observed for plasma/serum (PS) samples (Hedges's g = 1.20; 95% CI: 0.39, 2.02). The concentration samples for the other four proteins were mostly collected from plasma/serum, with only one sample collected from CSF for each protein (Supplementary Fig. 2). Despite the heterogeneity among the samples, the subgroup analysis showed that the PS samples were more homogeneous for the overall effect size and demonstrated significant differences in proteins compared to CSF samples (Supplementary Fig. 2).

Sensitivity analysis

In this meta-analysis, the robustness of the reported effect size was validated using sensitivity analysis. The analysis was performed to investigate the individual study's effect on overall effect size (Hedge's *g*). We utilized the oscillation between study variances and checked its effect on the overall effect size for the proteins utilizing the REM for meta-analysis. The analysis revealed that the overall effect size (Hedge's *g*) did not significantly fluctuate due to the between-study variation (Supplementary Fig. 3). The final reported overall effect sizes for the proteins were the stable points for the sensitivity analysis.

Publication bias

Due to the limited inclusion of funnel plots in the included studies (> 10), Egger's test was used to check the small study effect on overall estimation results. The test reveals publication bias and evaluates the irregularity of the included studies. For each protein, we found most of the studies had no publication bias, except the IL-6 and S100B (Table 2). There might be a small study effect for these two proteins as found by the Egger's test (*p*-value < 0.05). The Trim-and-fill method test results showed that the overall estimated effect size (Hedge's *g*) of these two proteins were not affected by the small study effect (Table 2).



[Here, CAM: Confusion Assessment Methods; CAM-ICU: Confusion Assessment Methods for Incentive Care Unit; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DOS scale: Delirium Observation Scale]

Fig. 2. (**A**) The distribution of delirium assessment methods reported in the included studies. (**B**) Country of Study and (**C**) The distribution of study types.

Discussion

The SLR and meta-analysis aimed to accumulate the delirium-associated significant proteins for qualitative and quantitative synthesis. The qualitative synthesis revealed 13 most studied cytokines and inflammatory-associated proteins that were significantly linked with POD. Then, a meta-analysis was conducted to identify the significant relationship of cytokines and inflammatory proteins with POD. The analysis revealed that nine of the 13 proteins exhibited a significant relationship between POD and their concentration levels (measured/converted in pg/ML) in plasma/serum/CSF.

Cytokines, inflammation and delirium

The current understanding of the pathophysiological pathway of delirium suggests that major surgeries and certain medicines used in anesthesia may trigger post-operative inflammation, leading to peripheral inflammation[79], which can finally cause neuroinflammation-mediated neuronal dysfunction[23,80,81]. On the other hand, the findings also revealed that the most studied 13 cytokines and inflammatory proteins are significantly involved with delirium pathomechanisms. The findings from the meta-analysis also support this inflammatory hypothesis of delirium[79], since significant evidence about the cytokines and inflammatory-associated proteins showed linkage with delirium.

Several review studies reported a significant association of IL-6, CRP, IL-8, and S100β protein concentration with POD[20,21,23,80]. Our findings were also consistent with this hypothesis for IL-6, CRP, and IL-8 whilst we did not find any significant relationship between TNF-α and S100β with POD. Also, the findings demonstrated the significant relationship of these proteins with delirium. Moreover, our results showed new findings indicating a significant correlation between delirium and certain inflammatory biomarkers (IL-10, IL-1B, and MCP-1), as well as the growth factor IGF-1 and the intermediate filament protein GFAP. This relationship was previously considered insignificant in some previous studies[20,80,82]. The proinflammatory cytokines IL-6 were reported by 21 articles describing a significant relationship with delirium which plays a significant role in pain development and inflammation[83–86]. Among critically ill patients, the plasma level of IL-6 is linked with systemic inflammation triggering delirium development and increased severity[22,50]. The cytokines IL-8, MCP-1, and anti-inflammatory marker IL-10 are associated with a major immune response, stimulating the T-cell and B-cell, the commencement of anti-inflammatory processes[87–89]. Another significant protein, CRP, is strongly associated with inflammation, stress, and neurotransmission[90,91]. In this qualitative synthesis, 12 articles showed a significant relationship between CRP and POD. Recent meta-analyses also reported that the higher CRP serum levels in the preoperative segment are significantly linked with POD[20,21,92]. The significantly associated protein IL-1B acts as an inevitable member of cholinergic activities which is crucial to delirium pathophysiology[93] as well as taking part in the etiology of onset delirium[62]. The neuroprotective and growth factor IGF-1 is involved in neurogenesis and may impede cytotoxic cytokines, which contribute to pro-inflammatory responses[94,95]. In this meta-analysis, two studies found a significant association between POD and GFAP protein[57,96]. The NFL

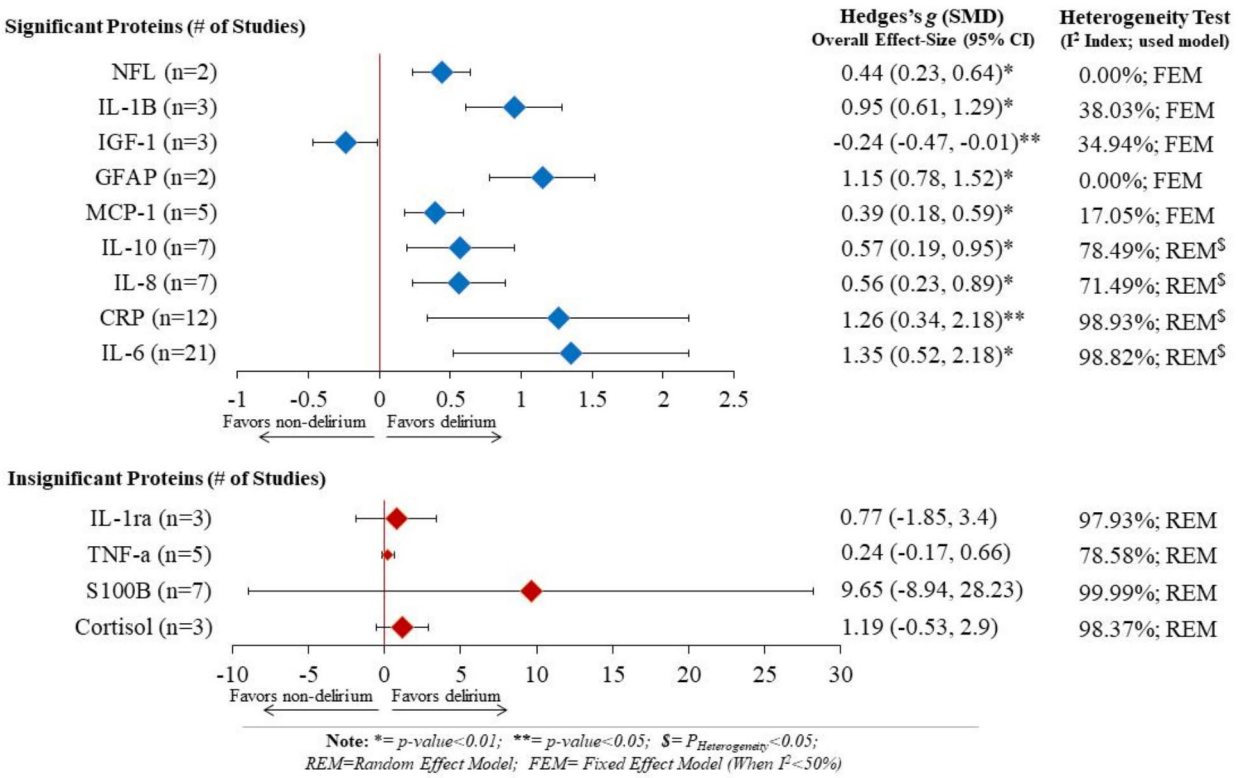


Fig. 3. Meta-analysis results (forest plot) for the association of the cytokines and inflammatory biomarkers proteins with delirium. The positive overall effect-size values indicate greater concentration levels among the delirium patients and negative values indicate higher concentration levels among the non-delirium. More detailed outcomes are provided in Supplementary File 3. The vertical red line (at zero point) shows the no-effect line and I^2 (> 50%) represents heterogeneity.

Protein's name	Egger's Test *P*-value	Trim-and-Fill method test	
		Observed	Observed + Imputed
		Hedges's *g* (95% CI)	Hedges's *g* (95% CI)
IL-6	0.0001	1.35 (0.52, 2.18)	1.35 (0.52, 2.18)
CRP	0.8811		
IL-8	0.8202		
IL-10	0.4319		
MCP-1	0.9263		
GFAP	0.8432		
IGF-1	0.0907		
IL-1B	0.443		
NFL	0.7536		
Cortisol	0.5969		
S100B	0.0000	9.65 (-8.94, 28.23)	9.65 (-8.94, 28.23)
TNF-a	0.6509		
IL-1ra	0.1097		

Table 2. Summary of publication bias of the included studies by Egger's test and Trim-and-fill method.

protein is linked to persistent axonal problems and is thought to be a novel biomarker for several neurological conditions[97,98], including Alzheimer's disease[99,100].

The meta-analysis revealed four proteins namely Cortisol, S100B, TNF-a, and IL-1ra as showing insignificant association with POD. Existing literature suggested that these proteins were associated with delirium. In our qualitative review, we also found a significant association of these proteins with delirium. S100B is connected with the central nervous system[52,101], and early symptoms of Alzheimer's disease and dementia[54]. TNF-a protein

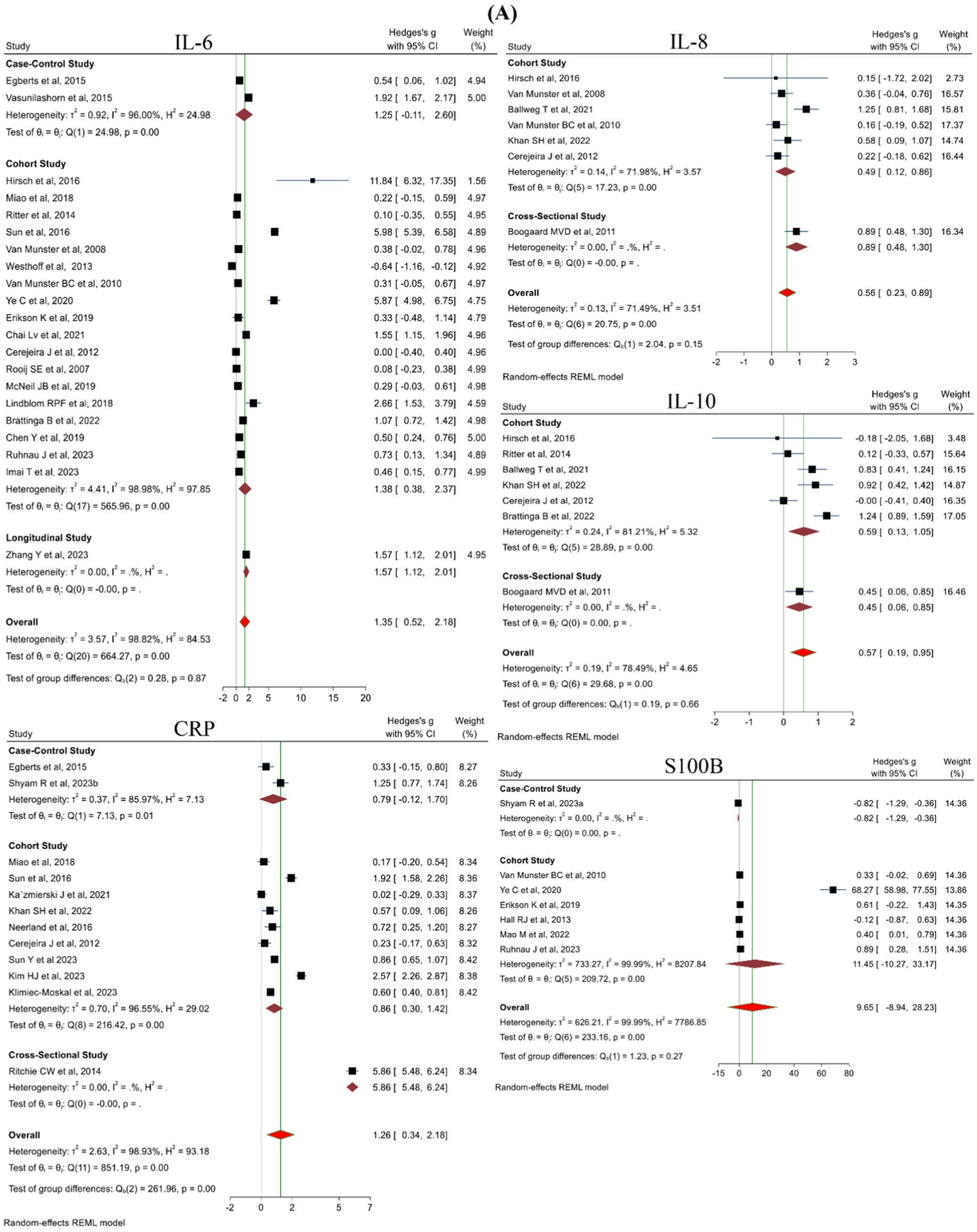


Fig. 4. The forest plot of subgroup analysis of proteins IL-6, CRP, IL-8, IL-10 and S100B (**A**) based on study type and (**B**) based on delirium assessment methods.

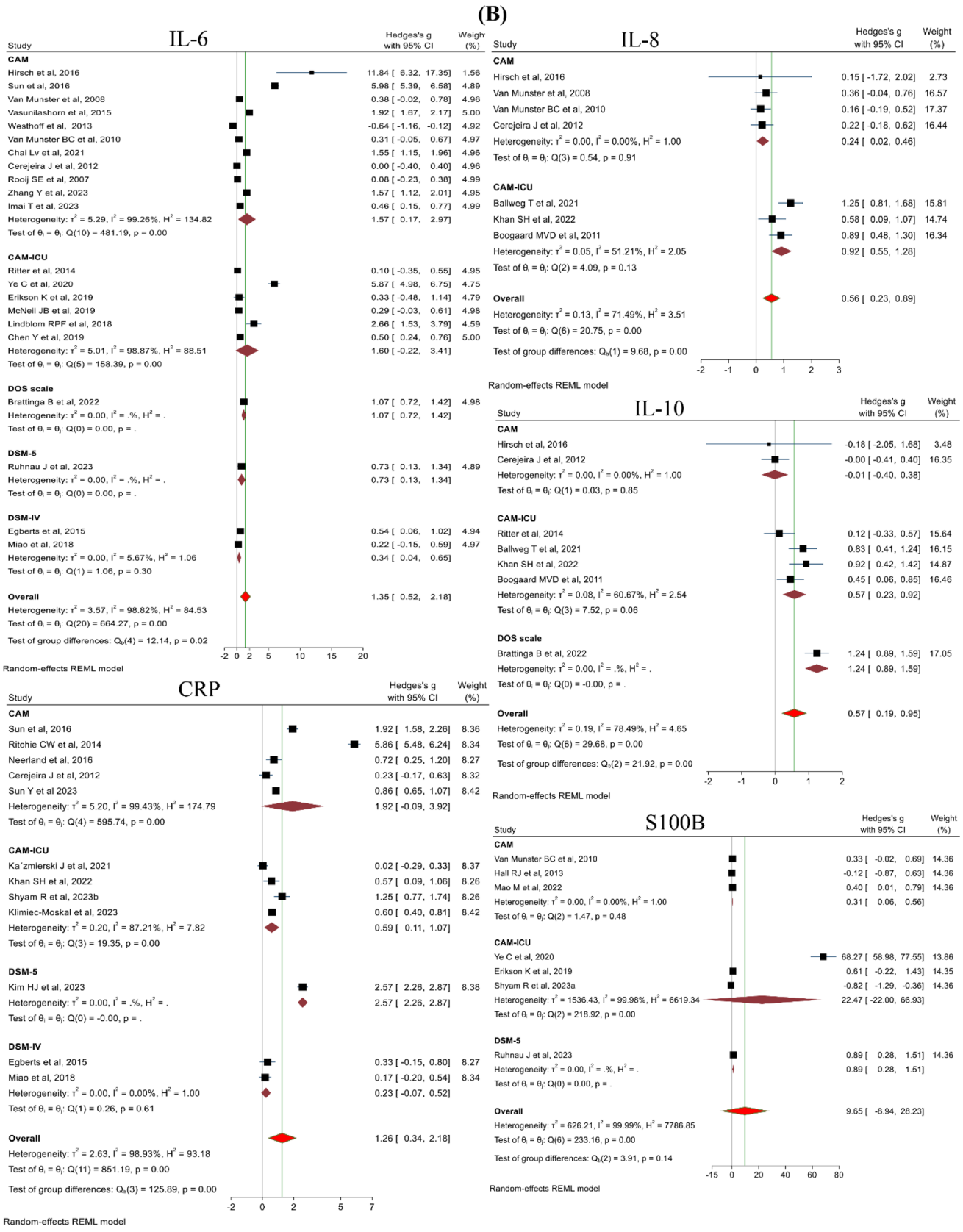


Figure 4. (continued)

is also known as a pleiotropic cytokine protein which is associated with apoptosis, inflammation, cognitive decline, and delirium[102–104]. An increased level of cortisol is related to a greater risk of dementia[105,106]. In this

review, three studies reported a significant relationship of IL-1ra with delirium, however, the meta-analysis revealed an insignificant relationship. IL-1ra proteins are highly connected with the brain and work as an anti-inflammatory marker that acts to inhibit IL-1B[107]. The patients having higher IL-1ra CSF have greater neuroprotective outcomes[108]. These properties of IL-1ra could be explored intensively for delirium whether its higher CSF level can mitigate the delirious episode and stimulate quick recovery. Moreover, recent studies suggest that delirium might have a possible influence on dementia through neurodegenerative functionality[9,109]. The blood–brain-barrier (BBB) mechanism is highly related with the CSF[110], the central nervous system, and the systematic inflammation[111,112]. The subgroup analysis of IL-6 inflammatory protein indicated that plasma/serum concentration samples are more homogeneous with the meta-analysis effect size than CSF samples. Significant sample heterogeneity was observed among the plasma/serum and CSF concentration samples for the studied proteins, indicating the need for more rigorous investigations of CSF-based samples to obtain precise results about cytokines and inflammation. The current findings regarding these inflammatory proteins are indicating their possible involvement in dementia induced by delirium, which requires further investigation, as inflammation is one of the fundamental components of neurodegeneration[113,114].

The findings regarding the association of elevated levels of cytokines and inflammatory proteins with POD provide substantial support for the inflammation theory as a significant contributor to delirium development. Another review by Dunne et al. also reported inconsistency among the biomarkers of delirium since delirium is a multifactorial critical medical phenomenon[23,115]. Although the biomarkers showed a significant relationship with delirium, more studies are required to enable further meta-analysis and, ideally, to identify any unique biomarker that might be used for the prognosis and diagnosis of delirium.

Implications

Our meta-analysis underscores the significant association of specific cytokines and inflammatory biomarkers with POD. Future research should focus on validating these findings in diverse patient populations and exploring the use of these biomarkers in preoperative screening to identify high-risk individuals. These biomarkers offer a foundation for the development of inflammation-targeted diagnosis and treatment strategies for delirium. Given that delirium is a multifactorial critical condition, there is a need for more rigorous studies focusing on its etiology, pathophysiology, preventative therapeutic drug development, and identification of molecular processes. The cohort study design with CAM/CAM-ICU delirium assessment methods are recommended for future studies. Furthermore, plasma and serum concentration data were more effective in identifying significant biomarker proteins associated with delirium. Further research should also focus on CSF samples to better understand the pathophysiological mechanisms associated with cytokines and systemic inflammation in relation to delirium.

While proteins such as Cortisol, S100B, TNF-a, and IL-1ra did not show significant associations, their roles in specific contexts or patient subgroups warrant further investigation. This study advances our understanding of the biological underpinnings of POD, establishing a framework for clinical trials targeting key biomarkers, such as IL-6 and CRP, to develop anti-inflammatory treatments that might transform perioperative care. Incorporating routine biomarker monitoring into clinical practice could reduce the POD risk and improve patient outcomes, facilitating the development of more precise and effective care strategies.

Study limitations

This review focused on delirium in humans whether they were identified in ICU or any hospital settings. Studies including Alzheimer's disease and dementia have not been included to keep the study rigorous and focused solely on delirium. This review's search for relevant studies may have been limited by the search timeframe and databases used, which might result in the potential for missing studies. In this study, the reported relationship between the proteins and delirium was only considered when the direction of the relationship (positive or negative) was ignored. Therefore, the properties of upregulation or downregulation of proteins could not be described in this review which demands further studies to investigate the differentially expressed genes/proteins identification.

The heterogeneity among the included studies for meta-analysis might potentially impact the overall outcomes, particularly for the Cortisol, S100β, IL-1ra, and TNF-α proteins. The study selection for meta-analysis was a nested process, which might omit any important studies with significant results. Also, the number of studies included for each protein was not proportionally adequate, since most of the analysis was conducted using a limited number of studies, which limited the exclusive meta-analytical comparisons and rendered the findings inadequate. Due to these disproportionate number of studies and the heterogeneity of the variables, the meta-regression analysis was not conducted, which constrained the overall comparison and interpretation. The concentration values of protein molecules were collected considering plasma/serum or CSF which might affect the overall comparison although they were converted into one common unit, pg/ML, before analysis. Moreover, the cofounding variables, estimation process variation, lack of random allocation, study setting were not considered and completely ignored.

This meta-analysis selected 40 studies from an initial pool of 78 to ensure data quality and relevance, particularly in evaluating the “top 13” protein biomarkers associated with postoperative delirium. This approach was chosen to provide a rigorous and targeted analysis of the most clinically significant biomarkers, aligning with the study's primary aim to understand specific inflammatory pathways involved in delirium. While this may limit the inclusion of other potentially novel biomarkers, it ensures a high level of precision in our findings. Future research is encouraged to explore a broader range of biomarkers to enhance the understanding of delirium’s multifactorial nature.

Conclusions

This study provides a comprehensive meta-analysis of the association between 13 cytokines and inflammatory proteins with postoperative delirium (POD), highlighting nine proteins (IL-6, CRP, IL-8, IL-10, MCP-1, GFAP, IL-1B, IGF-1, and NFL) as significantly linked to delirium. These findings underline the need for further molecular investigations to unravel the fundamental mechanisms driving delirium, given the variability in proteomic biomarkers and our limited understanding of their pathophysiology. The identified biomarkers present promising avenues for improving the diagnosis, classification, and potential treatment of delirium. However, more stringent studies are required to elucidate the molecular mechanisms underlying delirium and identify exclusive biomarkers. This study paves the way for future research aimed at early diagnosis, personalized treatment, and the development of novel therapeutic strategies to manage delirium effectively.

Data availability

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Author contributions

MPM conceptualized, collected data, analyzed, and wrote the first draft of the study. MPM and RAM screened the articles. KA, JG, and RAM supervised the study as well as revised and edited the manuscript.

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