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Review article

Biomarkers in delirium: A systematic review

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ABSTRACT

Background: Delirium is a common neuropsychiatric disorder associated with prolonged hospital stays, and increased morbidity and mortality. Diagnosis is frequently missed due to varying disease presentation and lack of standardized testing. We examined biomarkers as diagnostic or prognostic indicators of delirium, and provide a rational basis for future studies.

Method: Systematic review of literature published between Jan 2000 and June 2019. Searches included: PubMed; Web of Science; CINAHL; EMBASE; COCHRANE and Medline. Additional studies were identified by searching bibliographies of eligible articles.

Results: 2082 relevant papers were identified from all sources. Seventy-three met the inclusion criteria, all of which were observational. These assessed a range of fourteen biomarkers. All papers included were in the English language. Assessment methods varied between studies, including: DSM criteria; Confusion Assessment Method (CAM) or CAM-Intensive Care Unit (ICU). Delirium severity was measured using the Delirium Rating Scale (DRS). Delirium was secondary to post-operative dysfunction or acute medical conditions.

Conclusion: Evidence does not currently support the use of any one biomarker. However, certain markers were associated with promising results and may warrant evaluation in future studies. Heterogeneity across study methods may have contributed to inconclusive results, and more clarity may arise from standardization of methods of clinical assessment. Adjusting for comorbidities may improve understanding of the pathophysiology of delirium, in particular the role of confounders such as inflammation, cognitive disorders and surgical trauma. Future research may also benefit from inclusion of other diagnostic modalities such as EEG as well as analysis of genetic or epigenetic factors.

1. Background

Delirium is a serious neuropsychiatric condition affecting >15% of hospital inpatients [1]. It has been defined as a transient reversible syndrome that is acute and fluctuating, occurring in the setting of a medical condition. It is associated with increased morbidity, mortality and cognitive decline and contributes to longer hospital stays and increased healthcare costs [2,3]. Despite its importance, diagnosis remains challenging, with more than 50% of delirium cases estimated as undiagnosed [4–6] leading to decreased quality of care and poor patient outcomes.

Several factors contribute to this difficulty in diagnosis, including: lack of clarity on how diagnostic criteria should be tested; variance in presentation of delirium subtypes; and masking by comorbidities [7]. Additionally, the underlying pathophysiology of delirium remains poorly understood. The three primary hypotheses include: (1) disturbances in neurotransmitter pathways; (2) activation of pro-inflammatory cytokines resulting in breakdown of the blood brain

Abbreviations: 5'HIAA, hyroxyindole acetic acid; AchE, acetylcholinesterase; APOE, apolipoprotein; BuChe, Butylcholinesterase; CAM, Confusion Assessment Method; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CLIA, Chemiluminescent Immunoassay; CRP, Creactive protein; CSF, Cerebrospinal fluid; DSM, Diagnostic and Statistical Manual of Mental Health Disorders; ELISA, Enzyme linked immunosorbent assay; HPLC, High performance liquid chromatography; IGF, 1Insulin growth factor 1; IL, Interleukin; LNAA, Large Neutral Amino Acids; MDD, Major depressive disorder; NCD, neurocognitive disorder; Phe, Phenylalanine; Pre Cog Imp, Pre existing Cognitive Impairment; PREOP, pre operative; POD, post operative delirium; POP, post operative; S100B, S100 beta; Sig., significant; STNFR, Soluble Tumour Necrosis Factor Receptor; Trp, tryptophan; Tyr, tyrosine.

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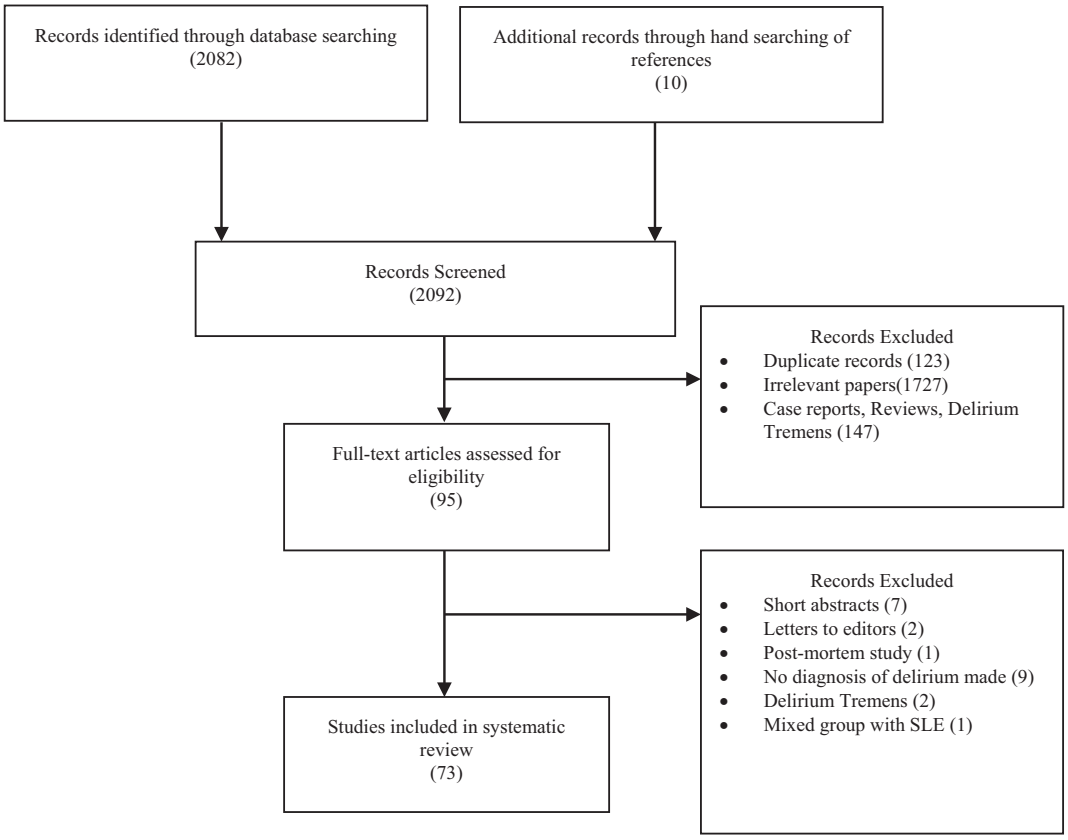

Fig. 1. PRISMA flow diagram of the process of (and reasons for) including and excluding studies.

barrier; or (3) disruption of the hypothalamic-pituitary-axis in reaction to acute stress [8].

Diagnosis currently relies on the Diagnosis and Statistics Manual 5th Edition (DSM-V). According to these criteria, delirium is characterized by acute onset disturbances in cognition, attention and awareness, fluctuating in severity throughout the day [9]. More specifically, disturbances in consciousness may manifest as reduced clarity of awareness of the environment, with reduced ability to focus or sustain attention. Its association with pre-existing, established or evolving neurocognitive disorders and perceptual disturbances and psychomotor behavioural changes are not well understood [10]. The DSM-V does not outline a specific clinical testing method.

The identification of biomarkers associated with delirium may provide insight into its elusive pathophysiology and aid in prediction, diagnosis and management. Biomarkers are biological or molecular traces that may indicate the presence or severity of disease [11]. They are categorized into three patterns [11]: (1) Risk markers, the presence of which indicates risk of a particular disease; (2) disease markers, correlating with the onset and recovery of disease; and (3) end-products that indicate disease resolution.

While biomarkers have been identified as associated with delirium, studies present conflicting results. For this reason, no biomarker(s) has been determined as specific to delirium. To date, there has been only one systematic review of molecular signals in delirium, which was limited to cerebrospinal fluid (CSF) markers [12]. Therefore, in performing this systematic review, we attempted to identify all available accessible literature examining biomarkers associated with delirium, and to critically appraise these studies in the context of current hypotheses of delirium pathophysiology. The objective was to assess the diagnostic and prognostic value of biomarkers of delirium and, if appropriate, to suggest a rational basis for future studies.

2. Methods

2.1. Systematic review tool

This review adheres to PRISMA (http://www.prisma-statement.org/) and Meta-analysis of Observational Studies in Epidemiology guidelines [13].

2.2. Study identification

An electronic search without restrictions (other than published in the English language) was performed for literature published between Jan 2000 and June 2019 that investigated biomarkers in delirium settings. Studies were identified from MEDLINE (beginning 1966), EMBASE (beginning 1974), CINAHL (beginning 1980), Web of Science (beginning 1980), and the COCHRANE databases. Primary key words included: “delirium” and “marker” used in combination with additional key words including: “biomarker”, “biological”, “biologic”, “marker”, “delirium”, “serum”, “plasma”, “genetic” and “protein”. Boolean operators were used to combine search terms above. Truncation and wildcards were applied to capture as many results as possible. Additional studies were identified by searching bibliographies in relevant articles identified in the searches. To avoid bias, results were based on analysis by SSD, CCC, SG and SK. Variations in interpretation were reviewed, and any disputes were resolved, by CPD. Final analysis was reviewed by JCC, GG, DM and CPD.

2.3. Selection criteria

Inclusion criteria were: (1) studies that investigated the relationship between biomarker(s) and delirium;(2) studies in which delirium was

assessed using a validated assessment tool; (3) any study methodology leading to publication within the topic of interest;and (4) full-text of original research papers.

Exclusion criteria were: (1) case reports, abstracts, letters and editorials; (2) studies before January 2000; (3) studies involving delirium tremens; (4) studies not written in the English language; or (5) animal model studies.

For the purposes of this review, pre-existing cognitive impairment is treated as undiagnosed dementia and is therefore not included as delirium. Additionally, this study makes a distinction between delirium-only studies, which will be referred to as "pure delirium", and delirium with comorbidities.

2.4. Data extraction

Titles and abstracts of searched articles were screened for relevance. Data extracted included: (1) study design; (2) objectives; (3) markers; (4) incidence or prevalence of delirium; (5) etiology of delirium;(6) delirium assessment tool; (7) timing of delirium assessment; (8) method of biomarker quantification; (9) timing of marker assessment; (10) sample size; (11) median/mean age of participants;(12) number of controls and cases; (13) assessment of variables/confounders; (14) outcome(s); (15) effect of variables/confounders; and (16) study limitations.

3. Results

A total of 2082 studies were identified from database searches of PubMed, CINAHL, EMBASE, COCHRANE and Medline. An additional ten articles were retrieved following review of bibliographies of eligible articles. Subsequent to review of titles and abstracts, 1997 records were discarded and the full manuscripts of 95 studies were examined in detail. Of the 95 papers, 22 papers were discarded as ineligible (Fig. 1).

Thus, 73 studies were included for full appraisal, all of which were observational in design. Delirium was assessed using the DSM criteria, Confusion Assessment Method (CAM) or CAM-Intensive Care Unit (ICU) for patients in the ICU. Delirium severity was measured using the Delirium Rating Scale (DRS). Across the 73 included studies, 14 markers of delirium were examined (Supplementary Table 1). Studies included markers (singly or combinations) from cerebrospinal fluid (CSF), serum, or plasma.

3.1. Study characteristics

There was significant diversity between the studies included, such as patient populations and settings, study design, and biomarker(s) examined. With regard to setting, participants included patients from either medical or surgical setting. Surgical patients varied from cardiac to orthopaedic. Medical patients were either acutely or critically ill. The notable Flacker et al. study [14], which examined febrile patients in a long-term care facility was included in the medical setting category. Study designs included either or both cross-sectional and longitudinal data. Within studies, delirium and marker(s) were assessed at single or multiple time points.

Study outcomes included statistically significant changes in biomarker levels "pre-delirium", "during-delirium", and/or "post-delirium" compared to control groups with no delirium. The most frequently studied marker was Interleukin-6 (IL-6) ($n = 23$) followed by C-reactive protein (CRP) ($n = 17$), cortisol ($n = 11$), S—100B ($n = 10$), IGF-1 ($n = 10$) and TNF-alpha ($n = 9$). Thirty-three studies investigated markers associated with delirium-only and 40 studies investigated markers in patients with other comorbidities, including depression and/or pre-existing cognitive dysfunction/dementia.

Amongst the delirium-only studies, authors either excluded patients with comorbidities or did not evaluate neurocognition to determine the presence or absence of comorbidities. Studies including additional comorbidities did not adjust consistently for the presence of these confounders. As noted below, pre-existing cognitive impairment is treated as dementia in this study. With regard to individual biomarkers, each is discussed briefly below, with considerable detail provided in Supplementary Tables dedicated to each separately. Each Table provides country of origin, clinical setting, sample type, number of samples utilized, number of control samples versus delirium cases, biomarkers assessed and study findings. Therefore, the following text details important summary details only.

Table 1 provides a list of all identified studies demonstrating an association, clarifying whether positive or negative, between delirium and specific biomarkers. A summary of all associations found is provided in Fig. 2.

3.2. Serum anticholinergic activity (SAA)

SAA was investigated as a marker of delirium in six studies (Supplementary Table 2). There were mixed results as three of the six papers demonstrated no association between SAA and delirium. SAA was studied alone in three papers [15–17], alongside EEG in two [18,19] and alongside other inflammatory markers in one paper [20]. It is worth noting that of the 73 studies eligible studies in this review, only three involved assessment of EEG [18,19,21]. There was no difference in the proportion of studies showing an association between those studies examining delirium alone and those that examined delirium with comorbidities. Delirium with comorbidities was the more broadly studied form, featuring in four of six studies. Similarly, studies in a surgical setting were more common in this group, involving four of six studies. Of note, the three studies [15,17,22] that found an association were performed in a surgical setting, and all three found that lower levels of cholinesterases in the pre-operative period were associated with incidences of delirium in the post-operative period. A fourth study, also involving surgical patients, by contrast found an increase in SAA activity in delirious patients, but the association lost significance after adjusting for pre-existing cognitive dysfunction [16]. All studies utilized serum samples, and used either a cholinesterase assay [17] [22], radioreceptor assay [18] [19] or an immunoassay [15] including radioimmunoassays [16] in their analyses.

3.2.1. Amino acids as a marker of delirium

Three studies assessed the value of homovanillic acid (HVA) as a marker of delirium, two of which adjusted for comorbidities including cognitive impairment [23] or cognitive impairment and depression [24]. Only Ramirez et al. [25] assessed an amino acid in the setting of pure delirium. HVA was either assessed alone [25], as part of a study involving neuropsychiatric patients, or as part of a suite of other amino acids in either medical [23] or surgical [24] patients. Two of three studies measuring HVA reported no association between this marker and delirium [23–25] while the third study [24] demonstrated elevated levels of HVA in pre-operative and post-operative surgical patients with delirium alongside elevated neopterin [24] as well as, in post-operative patients, phenylalanine to LNAA ratio and citrulline. The most common sampling method for HVA was serum, which was employed in two studies [23 24] while, in the third study, CSF samples were analyzed using HPLC.

All other amino acids were assessed as part of a group of two or more biomarkers and were assessed in delirium adjusting for comorbidities (Supplementary Table 3). Amongst these, tryptophan was the most common, featuring in six studies and with ambiguous results. Two of the six studies demonstrated a significant association between elevated levels of tryptophan and post-operative delirium [26 27], while three studies found significantly lower levels of tryptophan in delirious patients [24 28 29]. One study involving orthopaedic surgery patients reported no association [30] and had adjusted for cognitive impairment. This, in particular, is notable as orthopaedic surgery patients are sometimes affected by reduced oxygen saturation due to undiagnosed

Table 1
Identified studies demonstrating associations between delirium and specific biomarkers.

Authors (Year) (Origin) [Ref]	Markers with positive association	Markers with negative association
Adamis et al. (2007) (Ireland) [53]	–	IGF-1, recovery associated with lack of APOE allele
Adamis et al. (2009) (Ireland) [52]	–	IGF-1, IL-1ra
Al Tmimi et al. (2016) (Belgium) [71]	S100B	–
Alexander et al. (2014) (USA) [47]	IL-6, APOE4 allele	–
Avila-Funes et al. (2015) (Mexico) [86]	Estradiol (E2)	–
Baranyi et al. (2014) (Germany) [57]	SIL-2R	–
Cape et al. (2014) (UK) [56]	IL-1B, IL-RA	–
Capri et al. (2014) (Italy) [41]	IL-6	IL-2
Cerejeira et al. (2011) (Portugal) [17]	–	Cholinesterase
Cerejeira et al. (2012) (Portugal) [22]	IL-8	Acetylecholinesterase, butylcholinesterase
Cerejeira et al. (2013) (Portugal) [20]	Cortisol	–
Colkesen et al. (2013) (Turkey) [84]	Cortisol	–
De Jonghe et al. (2012) (The Netherlands) [30]	Kynurenine: Tryptophan ratio	–
De Rooij et al. (2007) (The Netherlands) [50]	IL-6, IL-8	–
Dillon et al. (2017) (USA) [60]	CRP	–
Egberts et al. (2015) (The Netherlands) [23]	Phenylalanine: LNAA ratio	Tryptophan:LNAA ratio, arginine
Egberts et al. (2015) (The Netherlands) [46]	Neopterin, IL-6	IGF-1
Erikson et al. (2019) (Finland) [43]	IL-6, *correlation between S100B and IL-6	–
Flacker et al. (2000) (USA) [14]	Phenylalanine: LNAA ratio	–
Girard et al. (2012) (USA) [59]	STNFR1	–
Hall et al. (2013) (UK) [72]	S100B	–
Hirsch et al. (2016) (USA) [36]	IL-6, RAGE, IL-5 (postop), IL-8, MCP-1	IFN-a, IL-4, IL-5 (preop), IGN-gamma, IL-12
Hughes et al. (2016) (USA) [75]	S100B (fewer delirium free days)	–
Jorge-Ripper et al. (2016) (Spain) [49]	TNF-alpha	–
Kazmierski et al. (2013)(Poland) [83]	Corstisol	–
Kazmierski et al. (2014)(Poland) [58]	IL-2, TNF-alpha	–
Knaak et al. (2019) (Germany) [65]	CRP	–
Lee et al. (2011) (Korea) [61]	CRP	–
Leung et al. (2007) (USA) [79]	APOE-4 allele	–
Liu et al. (2013) (Korea) [35]	IL-6	–
McManus et al. (2009) (UK) [63]	CRP	–
Miao et al. (2018) (China) [40]	Neopterin, CRP, IL-6, IGF-1	–
Mu et al. (2010) (China) [82]	Cortisol	–
Osse et al. (2012) (The Netherlands) [24]	Homovanillic acid, phenylalanine:LNAA ratio, citrulline	Tryptophan:LNAA ratio, methionine, tryptophan, serine
Pandharipande et al. (2009) (USA) [27]	Tryptophan	Tryptophan:LNAA ratio, Tyrosine:LNAA ratio
Pearson et al. (2010) (UK) [81]	Cortisol	–
Pfister et al. (2008) (Switzerland) [48]	CRP, S100B,cortisol	–
Piotrowicz et al. (2015) (Poland) [33]	Melatonin	–
Plaschke et al. (2010) (Germany) [21]	IL-6, cortisol	Mean BIS index
Pol et al. (2014) (The Netherlands) [67]	CRP	–
Ritchie et al. (2014) (UK) [62]	CRP	–
Ritter et al. (2014) (Brazil) [55]	STNFR1/2, adiponectin, IL-1B	–
Robinson et al. (2008) (USA) [29]	–	Tryptophan
Shen et al. (2016) (China) [68]	–	IGF-1
Shigeta et al. (2001) (Japan) [31]	Melatonin	–
Sun et al. (2016) (China) [38]	IL-6, CRP, procalcitonin, cortisol	–
Tsuruta et al. (2010) (Japan) [64]	CRP	–
Van der Boogaard et al. (2011) (The Netherlands) [54]	IL-8, cortisol	–
Van der Mast (2000) (The Netherlands) [28]	Phenylalanine: LNAA ratio	Tryptophan, Tryptophan:LNAA ratio
Van Munster et al. (2008) (The Netherlands) [42]	Il-6, Il-8	–
Van Munster et al. (2010) (The Netherlands) [34]	S100B, IL-6	–
Vasunilashorn et al. (2015) (USA) [39]	IL-6, I-2, TNF-alpha	–
Watne et al. (2016) (Norway) [26]	Tryptophan, tyrosine, methionine, phenylalanine, HIAA	–
Westhoff et al. (2013) (The Netherlands) [37]	IL-6 (serum)	IL-6 (CSF), IL-RA, Flt-3 l
Wilson et al. (2005) (UK) [69]	–	IGF-1
Yoshitaka et al. (2013) (Japan) [32]	–	Melatonin
Zhang et al. (2014) (China) [66]	CRP	–
Zhao et al. (2019) (China) [15]	–	Acetlycholinesterase, butylcholinesterase

pulmonary emboli (especially associated with hip fractures and, frequently, older patients). All except one of the studies [27] analyzing tryptophan were performed in surgical settings and most used serum samples only, with exception of two that also included CSF [26 27].

Four studies assessed the tryptophan/LNAA ratio, all of which found significant association between low levels of the tryptophan:LNAA ratios and delirium compared to non-delirious controls [23,24,27,28]. These included delirium in both surgical [24,28,30] and medical [23,27] settings. Comorbidities noted in the studies included dementia and depression. One study did not have significant findings after controlling for Mini Mental State Exam (MMSE) [23], one did not adjust for variables [28], and two remained statistically significant having controlled for variables[24,27]. Three studies demonstrated an association between elevated phenylalanine:LNAA ratio and delirium. These investigated medical [14] and post-operative delirium [24,28] using serum samples.

3.3. Melatonin

Three papers explored a link between melatonin and delirium, and found significant associations (Supplementary Table 4). The studies examining pure delirium, however, presented conflicting results. One described a positive association between melatonin and delirium in post-operative patients [31], while a second reported an association between decreased melatonin levels post-operatively and post-operative delirium [32]. Of note, the results of these two studies were hampered by low

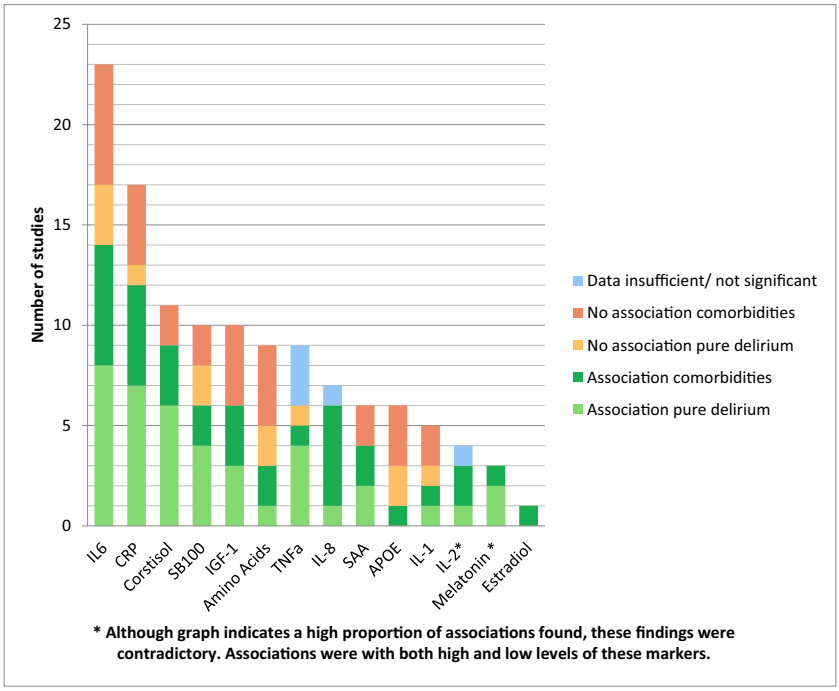

Fig. 2. Graphic summary of studies showing an association, lack of association, or insufficient data.

participant numbers. A third study involving medical patients reported a positive association between elevated levels of melatonin and delirium, accounting for dementia as a comorbidity [33]. The findings indicated a significant association irrespective of dementia state during acute delirium and post-resolution in non-demented patients. All three studies examining melatonin used serum samples and radio-immunoassays.

3.4. Interleukin-6 (IL-6)

IL-6 was the most studied biomarker (Supplementary Table 5). It featured in 23 studies with 14 of these demonstrating a significant association between elevated IL-6 and occurrence of delirium, while the remaining nine found no significant association. Van Munster et al. [34] initially showed an association between IL-6 and delirium, but this lost significance following adjustment for pre-existing cognitive impairment. In all but one study [35], IL-6 was analyzed alongside a panel other inflammatory markers.

Surgical settings accounted for 15 of the 23 studies, and surgical studies accounted for 10 of the 14 studies which showed an association between IL-6 and delirium. Notably, there was no clear time pattern of raised IL-6 relative to surgery. This marker was shown to be elevated in the pre-operative period[21,36–38], the post-operative period [39,40] or both[22,35,41] in patients who developed delirium although one surgical study noted specifically that the markers were higher in patients during delirium [42]. While results relating to IL-6 alone were generally significant, some studies [20,22,36,43] reported a correlation between IL-6 and other inflammatory markers, and many reported trends in IL-6 alongside other inflammatory markers. Sun et al. [38], for example, reported a general increase in all biomarkers in the post-operative delirium group, while Rudolph et al. [44] observed a difference between chemokines but not cytokines (including IL-6) in post-operative surgical patients. The significance of surgery-related trauma and its influence on inflammatory markers is extrapolated in the discussion section below.

Twelve of the 23 studies adjusted for comorbidities with cognitive impairment as a comorbidity common to all studies, except one that adjusted for depression [22]. All 23 studies in this group used serum samples while two [36 45] also included CSF. Analysis involved ELISA, multiplex assay, cytometric bead immunoassay, or CLIA immunoturbidimetric assay.

3.5. Interleukin-8 (IL-8)

The potential involvement of IL-8 in delirium was investigated in seven studies (Supplementary Table 6). Six [22,34,36,42,50,54] reported positive associations between elevated IL-8 and delirium, while one measured IL-8 levels below the detection limit, precluding meaningful analysis [41].

All seven studies assessed IL-8 alongside other inflammatory markers. While only one study assessed a correlation [20], trends of IL-8 in delirium in some studies matched those of other inflammatory markers such as IL-6 [36]. Van Munster et al. [42] found IL-8 to be highest in patients with delirium, with the greatest levels occurring in the days directly preceding delirium onset and remaining high during delirium, while Cerejeira et al. [20,22] described a small increase in IL-8 both pre-operatively and post-operatively in delirious patients [22]. One study detailed a significant elevation of IL-8 in medically delirious patients with inflammation, defined as a positive blood culture or presence of two or more SIRS criteria markers, compared to non-inflamed delirious patients [54]. This finding remained significant even after adjusting for multiple clinical variables.

Medical settings accounted for only two of these seven studies [50,54]. Both reported a positive association. Amongst the surgical studies, four of five [20,22,36,42] involved orthopaedic surgery patients, while one involved cardiac surgery patients [41] and three of five showed a positive association, with one returning non-significant data [41].

It was relatively common amongst studies assessing for IL-8 to adjust for comorbidities, which five of the seven studies did. Comorbidities included; depression [22], cognitive impairment [42,50], depression and dementia [22] and depression with neurocognitive disorder [36]. Four of these five found significant associations, while one [20] found no association between IL-8 and post-operative delirium after adjusting for comorbidities.

All assessed serum samples albeit one [36] also assessed for IL-8 in CSF. Samples were assayed using the xMAP Bio-Plex Suspension Array

System 200, cytometric-bead immunoassay, luminex assay. The study assessing both serum and CSF used ELISA [36].

3.6. Interleukin-1 (IL-1)

Five publications concentrated on IL-1 as a marker of delirium (Supplementary Table 7). Two cohort studies showed a significant association between elevated levels of IL-1 and delirium, with two studies finding no association and one showing varied results depending on the type of IL-1 assessed. In all five studies, IL-1 was assessed as one of a number of inflammatory markers.

There was no clear trend noted according to study setting. One of two studies involving medical patients showed an association, while one of three surgical studies showed an association. Similarly, there were no clear trends when assessing delirium or delirium with comorbidities. Of the two studies that explored the association of IL-1 and pure delirium, one showed an association [55]. This study was performed in a medical setting amongst septic and non-septic patients, demonstrating higher levels of IL-1B in delirious patients irrespective of the presence or absence of sepsis [55]. This finding remained significant after accounting for other variables. Of the three studies that adjusted for comorbidities, one found elevated IL-1B independent of dementia status [56]. Other comorbidities included depression [42].

Of note, many studies in this group assessed one of more variants of interleukin, including variants of IL-1. Capri et al., for example, presented divergent results for IL-1 and Il-6, measuring lower and higher respectively in patients with post-operative delirium [41]. Another study, performed in a medical setting, which adjusted for dementia found a positive association between low levels of the anti-inflammatory cytokine IL-1RA (interleukin 1 receptor antagonist) but not the pro-inflammatory IL1-alpha or IL-1beta and delirium [52].

All but one of the studies examining IL-1 analyzed serum samples only. The exception [56] also included CSF. Samples were analyzed using ELISA.

3.7. Interleukin-2 (IL-2)

IL-2 was the focus of four studies (Supplementary Table 8). Three of these found IL-2 to be a significant marker of delirium, with the final report failing to find significance. All four studies involved surgical patients who developed post-operative delirium, used serum samples and examined IL-2 as one of a group of inflammatory markers.

Of the two studies examining the association between IL-2 and pure delirium, one found elevated IL-2 both pre- and post-operatively. However, this research group did not adjust for other clinical variables [39]. This result was contradicted by a second study, which confirmed significantly lower IL-2 levels in patients with post-operative delirium. However, significance was lost following adjustment for other variables [41]. Conflicting results were also identified between the two studies that adjusted for comorbidities. One of these, adjusted for depression, found significantly decreased sIL-2R in delirious patients in the first 24-h post-operatively followed by a sharp rise in this marker [57]. The second study determined elevated IL-2 post-operatively in patients with post-operative delirium compared to controls, independent of other variables including dementia and depression [58]. Assay methods included CLIA and ELISA.

3.8. C-reactive protein (CRP)

Perhaps unsurprisingly, a relatively large number of researchers (17 reports) focused on the relationship between CRP and delirium in medical and surgical settings (Supplementary Table 9). Eleven of the papers demonstrated a significant correlation.

There were differences in the proportion of positive results amongst studies examining pure delirium compared with those examining delirium adjusted for comorbidities. Of the eight studies that examined the association with pure delirium, all of which assessed CRP as one of a panel of inflammatory markers, only one study found no association between levels of CRP and delirium [59], while seven demonstrated a positive association between raised levels of CRP and delirium [40,48,60–64]. By comparison, amongst the nine studies that investigated the association between CRP and delirium, accounting for dementia and/or depression, four studies, all of which recorded cognitive impairment as a comorbidity, detailed a positive association between elevated CRP and delirium [38,65–67] while the remainder stated no association between CRP and delirium [22,45,50,51,53]. The five studies that found no association reported cognitive dysfunction [45,50,53], as well as depression [22,51] as comorbidities.

Of the studies showing a positive association, six were performed in a surgical setting, examining pre-and post-operative levels [40,60,61] accounting for six of the nine surgical studies assessing CRP and delirium. These found elevated CRP in either or both the pre- and post-operative period. Five positive studies were conducted in medical settings with acutely ill patients [48,62–64,66], accounting for five of seven medical studies assessing CRP in delirium. One of these five studies adjusted for comorbidities [66]. Two of those in a medical setting did not evaluate the effect of covariates on the outcome [48,63]. Most of the studies assessing CRP analyzed serum samples, however two [38,51] assessed plasma samples and one [45] assessed CSF in addition to serum.

3.9. Insulin-like growth factor −1

Ten papers described work to determine an association between levels of insulin-like growth factor-1 (IGF-1) and delirium (Supplementary Table 10), three of which examined IGF-1 only [68–70] and seven which involved other inflammatory markers.

Results were varied, with five studies [46,52,53,68,69] concluding that there was an association between low levels of IGF-1 and delirium, one finding association between elevated levels of IGF-1 and delirium [40], and four describing no association[20,51,56,70]. Two of the studies describing an association between elevated IGF-1 and delirium were conducted in a medical setting examining pure delirium[40,46], while a third paper showed increased levels of IGF-1 in plasma samples from patients with post-operative delirium [40]. In contrast, three studies in a medical setting, which investigated delirium with comorbidities, specifically cognitive impairment, determined an association between low IGF-1 and delirium [52,53,69]. All of the studies that identified a positive association in the setting of delirium adjusted for comorbidities were conducted in medical settings. Four studies were unable to correlate IGF-1 and delirium. Three of these were performed with post-operative surgical orthopaedic patients, and one was performed in a medical setting [70]. All adjusted for comorbidities including dementia and pre-existing cognitive dysfunction.

All papers examining IGF-1 used serum samples. One also included CFS [56]. Assays included immulite analyzer [46], ELISA [20,40,52,53,56,68] or immunoassay[51,69,70].

3.10. S—100B

Ten studies investigated S—100B as a marker of delirium (Supplementary Table 11), with four analyzing S—100B alone [71–74] and six including other inflammatory markers [34,43,48,49,75,76].

Six studies demonstrated a positive association between elevated levels of S—100B and delirium, while four found no association. Research showing a positive association was performed in both medical [43,48,75] and post-operative surgical [34,71,72] settings. There was no pattern in positive studies with regard to medical vs surgical setting, or between studies that adjusted for comorbidities vs those that measured pure delirium. Al Tmimi et al. [71], Hughes et al. [75] and Erikson et al. [43], all detected elevated levels of S—100B independent of covariates, although Pfister et al. [48] made no adjustments for

variables amongst the sample of sepsis-associated delirium patients. Of note, Hughes [75] demonstrated an additional association between increased S100B and the duration of delirium. The most common co-morbidity in this group of studies was cognitive impairment, which was adjusted for in three studies [34,72,74], while neurocognitive disorder was adjusted for in one [73].

Four studies failed to determine association between S—100B and delirium; three in a medical setting[49,74,76] and one in a surgical setting [73]. Of these, Khan et al. [74] detected higher levels of S—100B in delirious patients, although the result was not significant. Beishuizen et al. [73] found that S100B was not associated with delirium, but was associated with cognitive decline or death in the first year following hip surgery.

All studies measuring S—100B used serum samples, except for Erikson et al. [43] who used whole blood and Hall et al. [72] who utilized CSF. ELISA and CLIA were used.

3.11. Apolipoprotein- E (APO-E)

APO-E in delirium was the focus of six studies (Supplementary Table 12), two of which [47,53] studied APO-E with other inflammatory markers. The others assessed APO-E alone. One demonstrated an association with occurrence of delirium while four did not. Five used serum sampling, while one [77] used whole blood.

Two studies examined the association of APO-E on pure delirium, demonstrating no significant association with occurrence of delirium. One was performed in a surgical setting [78] and one in a medical setting [47]. Four studies investigated APO-E as a marker of delirium, adjusting for co-morbidities. One demonstrated a positive association between APO-E epsilon4 allele and delirium in non-cardiac post-operative patients with delirium [79], and three demonstrated no association in either surgical patients[77,80] or medical patients [53]. Of note, Adamis et al. [53] indicated an association between lack of serum APOE and delirium recovery in medical patients.

These six studies account for the only direct analysis of genetic influence on delirium amongst the 73 studies included in this review. Methods involved PCR or genotype analysis.

3.12. Cortisol

Eleven studies (Supplementary Table 13) evaluated association between cortisol and delirium, with eight indicating a significant positive association between elevated plasma cortisol levels and delirium. The results of the remaining three studies did not support this observation. Cortisol was assessed alone in four studies, and alongside inflammatory markers in the remainder [20,21,34,38,48,54,85].

Results varied between studies that had adjusted for comorbidities and those that did not. All six studies evaluating cortisol as a marker of pure delirium indicated a positive association between cortisol and delirium [21,48,54,81,82,84], while amongst those adjusting for comorbidities three studies demonstrated a positive association [20,38,83], while two did not [34,85]. Kazmeirzski et al. [83] found pre- and post-operative cortisol significantly elevated in post-operative delirious patients compared to non-delirious controls. The significance of elevated cortisol remained after controlling for cognitive impairment, but not major depressive disorder. Elevation of cortisol in acute states of inflammation or trauma may be significant here and is extrapolated in the discussion section below. For example, Sun et al. [38] showed elevated levels of all inflammatory biomarkers tested in the study, including cortisol, in their patients and found no difference between patients with and without delirium. Similarly, van den Boogard et al. [54] noted that, as well as cortisol, elevated S100B and IL-8 were associated with delirium.

Surgical settings, either cardiac or orthopaedic surgery, were more common amongst the studies assessing cortisol in delirium, accounting for eight of eleven studies, of which five showed an association between cortisol and delirium. This included elevations in cortisol during delirium [21,81], in the postoperative period [20,82], or both the pre-operative and post-operative period [83]. All three studies in medical setting reported positive associations between cortisol and delirium. In the main, serum samples were assayed using ELISA and CLIA with the exception of one study that analyzed additional CSF samples [81].

3.13. Estradiol

One study investigated the relationship between estradiol (E2) and delirium in acute medically ill women [86](Supplementary Table 14). The study adjusted for covariates including age, pre-existing cognitive dysfunction and depression. Serum E2 was significantly elevated in delirious patients.

3.14. TNF-alpha

Nine studies investigated the relationship between either TNF-alpha or its related receptor, Soluble Tumour Necrosis Factor Receptor (STNFR), and delirium with five indicating a positive association, one showing no association and three returning marker levels below a sufficient threshold for meaningful analysis (Supplementary Table 15). In all cases, TNF-alpha was assessed as one of a panel of inflammatory markers.

Six studies measured TNF-alpha or its receptor in the setting of pure delirium. Four reported an association between pure delirium and elevated TNF-alpha in either surgical [39] or medical patients [49,55,59]. Of note, two of these four studies [55,59] measured the STNFR. One study [43] stated no association between TNF-alpha levels in blood samples between medical patient groups with and without delirium. One study [41] reported measurements below the detectable level unsuitable for analysis. Three studies measured TNF-alpha in the setting of delirium adjusting for comorbidities, all of which involved surgical patients. Only one of these [58] had viable samples and showed a positive association. Two [36,42] returned measurements below the detectable level unsuitable for analysis.

Studies investigating pure delirium made up the larger part of the group, accounting for six of nine studies. There was no pattern of positive results when comparing medical vs. surgical settings. Only one of three studies returned a viable sample in studies adjusting for comorbidities, precluding meaningful analysis of the effect of comorbidities on studies assessing associations between TNF-alpha and delirium. Studies assessing TNF alpha mainly used serum [34,39,41,42,49,58,59], although one used whole blood [43] and one used CSF [36].

4. Discussion

This is a comprehensive systematic review. Although not a meta-analysis, arising from the review, we determine that there is insufficient evidence to support the use of any single biomarker as a sole risk or disease marker of delirium. However, there are biomarkers with significance in some clinical settings, and these may provide direction for future studies and more in-depth analysis. This statement is made while cognizant of the fact that the underlying etiology of delirium is multifaceted, with potential pathologies ranging from peripheral inflammation, stress, or trauma to systems within the hypothalamic-pituitary-adrenal axis. Furthermore, challenges in ascertaining specific biomarkers' associations with delirium were evident, due to the heterogeneity of studies. More specifically, it was impossible to quantify strength of identified associations, positive or negative, due to the differences evident in methodologies, diverse patient populations, criteria for delirium diagnosis, involvement of confounding comorbidities (e.g., dementia)
[16–19,21,23–25,27,30,34,42–53,57–59,67,68,70,71,75–77,80,81,84–86,89,93], and analytical approaches adopted. Further complexity is added by the non-specificity of many of the investigated biomarkers.

Trauma relating to surgery, for example, is associated with alteration in many of the pro-inflammatory markers that are posited as having links to delirium, as further discussed in Hirsch et al. [36]. Similarly, many inflammatory markers are elevated in co-existing neuropsychiatric conditions. Despite this, appraisal of the papers identified the themes outlined below.

4.1. Disturbances in neurotransmitter pathways

The outcomes of several studies lend support to the hypothesis that delirium is attributable to, or at least contributed to by, disturbances in neurotransmitter pathways. Serotonin, dopamine and other neurotransmitters as well as neurotransmitter-like compounds such as the hormone melatonin, play roles in effective cognition, learning, memory, attention and sleep wake cycles. The neurotransmitter hypothesis suggests that imbalances in the levels of any neurotransmitter(s) or disruption of their mechanistic pathway impact pathogenesis of delirium [8]. Tryptophan, phenylalanine and tyrosine are all precursors to serotonin, dopamine and noradrenaline, respectively [87], and, therefore, may also be implicated.

In this context, cholinergic deficiency has been proposed as linked directly with the pathogenesis of delirium [11]. Adequate acetylcholine levels are required for regulation of sleep, memory, cognition, learning and selective attention [88]. An impairment of cholinergic activity could, thereby, plausibly lead to dementia and delirium. Three studies measuring the link between SAA and delirium found no associations in either medical or surgical settings [16 18 19]. This is in contrast to the finding of Flacker et al. [89] and Mussi et al. [90] who showed positive correlations between SAA and delirium. However, methods of detection were different and pre-existing cognitive dysfunction and age, well-known confounders of SAA activity and delirium, were not adjusted for in the findings. Overall, it is noteworthy that SAA is not necessarily aligned with central cholinergic function, which may be most relevant to delirium.

Cholinergic activity has also been linked to anti-inflammatory pathways through inhibition of pro-inflammatory cytokines [8,91]. A loss of cholinergic activity may lead to an increased inflammatory response, possibly contributing to delirium. Studies by Zhao et al. [15] and Cerejeira et al. [22] support a putative mechanism, demonstrating low plasma cholinesterase activity of AchE and BuChe prior to surgery in patients who developed post-operative delirium subsequently. In the Cerejeira et al. papers, a correlation between low cholinesterase activity and elevated levels of CRP and IL-6 was also present. This evidence contradicts the proposed mechanism that relies on cholinergic deficiency leading to inflammation. The studies do, however, state that pharmaceutical drugs interacting with cholinergic activity were not taken into account, which may have affected the outcomes.

Central serotonin deficiency has also been linked to the development of a delirious state via tryptophan depletion [92]. Reports have shown increased or decreased levels of tryptophan associated with delirium, either through direct measurement of the amino acid or its ratio to other large amino acids. These results are similar in both medical and surgical settings, both in pure-delirium studies and in those assessing delirium with comorbidities. While there is evidence to substantiate a tryptophan deletion theory, a randomized trial by Robinson et al. [93], in which patients undergoing hip surgery were administered supplementary tryptophan, did not result in any reduction of post-operative delirium compared to controls.

Dopamine plays a role in control of the features characterizing delirium including changes in movement, cognition, attention and memory [94,95]. Accordingly, dopamine excess has been hypothesized to contribute to pathophysiology of delirium [23,94,95]. Most studies of phenylalanine, a precursor of dopamine, as a possible biomarker of delirium observed elevated levels in patients with delirium compared to controls. Osse et al. [24] showed an association between delirium and a metabolite of dopamine (HVA),while Ramirez et al. [25] and Egberts et al. [23] did not.

Melatonin, a hormone produced by the pineal gland, affects circadian rhythms including the regulation of sleep-wake cycles [31]. One feature of delirium is the disturbed sleep-wake cycle and it is postulated that disturbed melatonin rhythms could be involved in delirium [96]. While all studies reviewed showed disturbances in melatonin concentrations during various stages of delirium, further research is needed to clarify the role of melatonin in delirium. Specifically, due to the low numbers of participants in eligible studies examining melatonin, larger group studies for this biomarker would be welcome.

4.2. Activation of pro-inflammatory cytokines resulting in the breakdown of the blood brain barrier

Several studies lend partial support to this hypothesis, albeit results are conflicting. The neuroinflammatory theory of delirium postulates that peripheral inflammation secondary to infections, surgery or trauma induces the activation of the pro-inflammatory cascade and suppression of anti-inflammatory markers [88]. The pro-inflammatory molecules cross the blood brain barrier (BBB), causing insult to the central nervous system, resulting in the neurobehavioral and cognitive symptoms associated with delirium [88].

IL-6 is one of the most studied cytokines with regard to its potential as a marker of delirium. Not all studies demonstrated an association between elevated levels of IL-6 and delirium, or the risk of developing delirium. Studies that demonstrated an association between high levels of pre-operative IL-6 and delirium [35,37,39,41] suggest that early manifestation of systemic inflammation leads to the onset of delirium. Infection, cognitive dysfunction and age have been shown to be independently associated with IL-6 [97–99], and not all of the studies adjusted for these variables, which may have influenced the significance and extent of association.

Similarly, studies of delirium with comorbidities had conflicting outcomes. There are many sources of heterogeneity between the studies investigating IL-6 as a marker including methods of IL-6 analysis, patient settings, and adjustment for known variables. However, because IL-6 is associated with age, infection, inflammation, cognitive dysfunction and many other systemic processes, using IL-6 as a potential marker will remain challenging.

Indeed, many of the studies investigated other pro-inflammatory cytokines and potential biomarkers of delirium. No consistency or conclusive marker was established. Research has identified relationships between levels of IL-8, cognition and age [100,101]. Cognition and age are both independent risk factors of delirium, suggesting a role for IL-8 in its development. However, the outcomes of our review highlighted conflicting data and opinions. In relation to both IL-6 and IL-8, this review supports the view that they continue to be measured alongside other inflammatory markers and that researchers work to adjust for inflammation. Doing so may help clarify the interaction between delirium and inflammation, and perhaps shed light on pathogenesis.

In addition to IL-1B being a pro-inflammatory cytokine, linking it to the inflammatory theory of delirium, it is further recognized as interfering with cholinergic signaling, a pathway thought to be involved in the pathogenesis of delirium [102]. IL-1B was assessed in four studies with conflicting results. Notably, animal research has proven that modulation of IL-1B through lipopolysaccharide(LPS) receptor blockade improves cognitive dysfunction [102]. It is not surprising then that studies on delirium with comorbidities [22,56] adjusted for pre-existing cognitive dysfunction, found no obvious difference in results. Overall, evidence does not support the use of IL-1 as a specific biomarker of delirium.

IL-2 is particularly important in T- cell activation [58]. It has also been shown to block acetylcholine stimulation in the CNS and to stimulate dopamine, two processes thought to be involved in the pathophysiology of delirium. Like the other cytokines, IL-2 results conflicted. However, Kazmierski et al. [58] showed independent associations

between levels of IL-2 and pre-existing cognitive dysfunction that remained significant after adjusting for comorbidities.

CRP is a circulating acute phase reactant and a common marker for infection and inflammation. Similar etiologies in delirium therefore suggest a role for CRP in the pathophysiology of delirium [45]. Evidence suggest that post-operative delirium, in which the mechanism of inflammation is known, CRP might play a role as a risk or disease marker of delirium [67] due partially to it being readily and easily measurable. However, as it is associated with many other inflammatory pathways, it is less likely to be specific to delirium.

IGF-1 is a neuroprotective cytokine with a role in promoting neurogenesis, proliferation, differentiation and synaptogenesis [103]. It is also thought to inhibit cytotoxic cytokines such as IL-6, IL-8 and IL-1 [104]. Low levels of IGF-1 are, therefore, thought to be associated with a loss or decline of its neuroprotective characteristics [70]. This suggested pathophysiology could lead to increased vulnerability of the brain to insults resulting in neurological injury and delirium. In addition, loss of inhibition of the cytotoxic cytokines leads to increased pro-inflammatory cytokines. In actuality, studies show inconsistencies in the association between levels of IGF-1 and delirium. Some indicated low levels of IGF-1 associated with delirium, which is in keeping with the neuroinflammatory hypothesis but, when separated into patient settings, there was no relationship between pre-operative and post-operative levels of IGF-1 and delirium, suggesting a role for IGF-1 in the medical setting only. In the medical setting, all but one study showed a positive association between low levels of IGF-1 and delirium onset. Therefore, IGF-1 may play a role as a diagnostic marker in acute medically ill patients but have less significance in post-operative delirium.IGF-1 has also been linked to the pathophysiology of Alzheimer's Dementia (AD) [105,106]. Lower levels of IGF-1 in AD lead to reduced clearance of amyloid beta plaques enhancing AD development. Studies of delirium with comorbidities, however, did not show consistency in outcomes.

S100—B, a calcium binding protein, is expressed mainly by astrocytes and is elevated after disturbances in the integrity of astrocytes [107]. S100—B plays a role in axonal growth and neuronal regeneration [86]. Elevated levels have been linked to traumatic brain injury, stroke and neuro-intensive care patients. Activation of astrocytes via systemic inflammation is thought to lead to raised levels of S100—B in the peripheral blood via increased permeability of the blood brain barrier [88]. In our review, results were found to be inconsistent and conflicting. One notable area of concordance was that all studies involving a post-operative setting found a significant positive association between S100B and delirium. Notably, the outcomes of one study [75] suggested that this marker may have a role in studying delirium over extended durations.

Apolipoprotein E4 allele (APOE) is a polymorphic protein that exists as three major isoforms, e2, e3, and e4 [108]. It is involved in the lipid transport and acetylcholine synthesis important in the repair, growth and maintenance of myelin and neuronal membranes during development or post injury [108].The e4 allele has been associated with earlier onset of AD [109], poor outcome post closed head injury and intracranial injury [110]. It has been hypothesized that patients with the e4 allele have a genetic predisposition to post-operative delirium after surgery. In addition, due to well-known relationship between delirium and dementia, it has been postulated that APOE4 contributes to the pathophysiology of delirium. Although there is suggested link between APOE and dementia, only one study involved pre-existing cognitive dysfunction as comorbidity [53]. With the known association between Alzheimer's and APOE, as well as its involvement in other possible neuropsychiatric conditions, APOE is a less than specific marker for delirium and researchers may consider evaluating other genes, as discussed under ‘implications for future study’ below.

TNF-alpha is a pleiotropic cytokine that signals several pathways relating to homeostasis and the pathogenesis of disease including inflammation, apoptosis and necrosis [111]. There is no consensus on the full extent of the role played by TNF-alpha and its receptor in inflammation, including in the CNS [112]. Despite this, studies have indicated a strong association of this marker with cognitive decline in the setting of Alzheimer's Disease [113], albeit that results have been equivocal [39] regarding an association with delirium. While some studies included in this review showed a positive association between TNF-alpha and its related receptor to delirium, one third of studies measuring these markers stated results that either did not reach significance or detected insufficient levels to determine a relationship between the marker and delirium. Given the strong associations with cognitive decline and the proportion of studies unable to reach a meaningful conclusion, this marker warrants further investigation. Wider biochemical research into its role in signaling pathways may help to elucidate its function in the CNS, shedding further light on the pathogenesis of delirium. Due to its association with inflammation, future studies may clarify its role in delirium further by adjusting for covariates, including inflammation, as is the case in van den Boogaard et al. [54]

4.3. Disruption of the hypothalamic-pituitary-axis in reaction to acute stress

The hypothalamic-pituitary-axis forms a response to stressful or traumatic insults to the body. Cortisol is the main effector of this process and rises as a result of these insults [114]. Elevated levels of cortisol affect the hippocampus and frontal lobe triggering neuropsychiatric characteristics and cognitive dysfunction seen in delirium [114,115]. Elevated levels of cortisol are not only associated with delirium but dementia, age and cognitive dysfunction [115]. Findings from this systemic review determine conflicting support for the hypothesis that delirium is associated with elevated cortisol levels. It should be noted, however, that all studies of pure delirium found an association between elevated levels of cortisol and delirium, identifying the connection between cortisol and pure delirium as an area for further study. The difference in positive results between studies of cortisol in this review that adjusted for comorbidities, and those that did not, suggest that further research into this marker may benefit from adjustment for confounders.

A 2015 study by Avila-Funes et al. [86] has found a link between elevated levels of estradiol and delirium in women. This result remained significant after adjusting for covariates including age, pre-existing cognitive dysfunction and depression. Estrogen has been implicated in cognitive dysfunction [116] and, therefore, thought to have a role in delirium. This warrants further investigation.

4.4. Limitations

The results of this systematic review highlight the lack of published studies with comparable methodologies examining biomarkers in delirium; at least up to June 2019. We did not attempt meta-analysis as it was impossible to quantify strength of identified associations, positive or negative, due to the differences evident in methodologies, diverse patient populations, criteria for delirium diagnosis, involvement of confounding comorbidities. Our review was limited to studies published in the English language. No unpublished literature was obtained. Although studies were retrieved through database searches and the citation lists of relevant articles reviewed for eligibility, it is possible that relevant articles may have been missed. However, the authors are confident that no significant articles have been missed. Publications reporting association with BDNF (brain-derived neurotrophic factor) (e.g.,[117,118]) were not included in this review as all trials of BDNF delivered into the CNS, even for special reasoning or memory, have failed (as of February 2021). Strengths of this review reflect the inclusion of the most-recent literature available in this field of study (up to June 2019) and assessment of delirium with standardized diagnostic tools.

5. Implications for future research

In brief, this review highlights the need for more focused research on this topic. The pathophysiology of delirium remains unclear. Future research should ensure use of standardized clinical criteria and assessment tools for delirium, adjust appropriately for comorbidities as well as consider generalizable populations, prospective designs and appropriate sample sizes. Analysis of delirium could also include delirium subtype. With regard to healthcare setting, these studies suggest there may be value in continuing to differentiate between medical and surgical patients when evaluating the efficacy of delirium biomarkers, and suggest a possible role for biomarkers in the prediction of post-operative delirium. It is, perhaps, in this setting that most immediate progress can be made. More specifically, effects of withdrawal from significant use of opioids (and epidural) in surgical procedures can impair cognition and be interpreted as delirium. Advances have been made recently in developing robust animal models relevant to surgery and, indeed, orthopaedic surgery in particular [119–122]. These have considerable potential in clarifying what appear to be tightly interwoven correlations between the varying biomarkers described here; for example, delirium and inflammatory markers such as CRP. Our review also concludes that while many studies attempted to establish the time-course of delirium, few involved long term follow up and only one [89] involved a long term care facility. Expansion of research into settings outside acute medical and surgical settings may be beneficial to understanding the time-course and patterns of delirium. [14]

Greater standardization of sampling and inclusion of other diagnostic modalities may benefit future research. To the authors' knowledge, this is one of two systematic reviews to examine biomarkers in delirium, and the only review to appraise samples other than CSF. Given that non-CNS sampling has been shown to yield information about the brain that differs from that gleaned from CSF [123], further studies involving peripheral, as well as CSF samples, may help to shed light on the pathophysiology of delirium. This may prove critical in understanding the interaction between the systemic and CNS inflammatory components, and the impact of delirium on the body as a whole. The diversity of reported sampling, including whole blood, serum, plasma and CSF in studies reviewed here is, therefore, welcome. It is noteworthy that of the 73 included studies, only three [18,19,21] combined biomarkers with other diagnostic modalities such as EEG. With current biomarker associations unclear, future research may benefit from combining biomarkers with diagnostic modalities such as EEG, which has proven benefit in diagnosis of delirium [124]. Epigenetic analysis remains an interesting proposition in potentially understanding and detecting delirium in clinical practice. More specifically, there has been elegant work published describing the emerging potential influence of DNA methylation on expression of genes encoding for pro-inflammatory cytokines in aging and delirious patients [125,126]. Association of DNA methylation with cholinergic synapse has also been suggested [127]. These warrant further focus. Future studies may also choose to include genetic analysis as this review found these to be limited, feature in only six studies, amongst which APOE was the only gene assessed. Stoicea et al. have described several genes known to be associated with delirium and may provide a helpful summary for researchers [128].

Overall, future research should be informed by, but healthily sceptical of, previous studies on biomarkers and factors demonstrated to have an association with delirium. Delirium is a complex multifaceted syndrome such that the relationship between particular elements of the syndrome (cognitive vs neuropsychiatric) and alterations in biomarkers or their levels warrant study. This may eventually illuminate our understanding of the pathophysiology of the various components of delirium. It is likely that, in time, the correlations described in this review will be clarified, and either confirmed or discarded, as systems biology approaches elucidate the pathways that involve multiple, interdependent biomarkers that most likely influence the complex mechanisms mediating delirium. Equally, this can be applied to exploring the genesis of different clinical presentations (e.g., motor subtypes) of delirium. In this context, however, confidence in any potential test arising from such a complex molecular milieu will likely require extensive and credible meta-analysis of proposed sensitivities, specificities and threshold values in a rigorous manner analogous to that proposed by Campbell et al. [129].

Ethical approval

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Consent to publish

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Data availability

Search data are available on request.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

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References

[1] S.D. Shenkin, C. Fox, M. Godfrey, et al., Delirium detection in older acute medical inpatients: a multicentre prospective comparative diagnostic test accuracy study of the 4AT and the confusion assessment method, BMC Med. 17 (1) (2019) 138, https://doi.org/10.1186/s12916-019-1367-9 [published Online First: Epub Date].

[2] J. Witlox, L.S. Eurelings, J.F. de Jonghe, K.J. Kalisvaart, P. Eikelenboom, W. A. van Gool, Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis, JAMA 304 (4) (2010) 443–451, https://doi.org/10.1001/jama.2010.1013 [published Online First: Epub Date].

[3] D.H. Davis, G. Muniz Terrera, H. Keage, et al., Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study, Brain 135 (Pt 9) (2012) 2809–2816, https://doi.org/10.1093/brain/aws190 [published Online First: Epub Date].

[4] J.H. Han, E.E. Zimmerman, N. Cutler, et al., Delirium in older emergency department patients: recognition, risk factors, and psychomotor subtypes, Acad. Emerg. Med. 16 (3) (2009) 193–200, https://doi.org/10.1111/j.1553-2712.2008.00339.x [published Online First: Epub Date].

[5] Y.C. Chin, G.C. Koh, Y.K. Tay, C.H. Tan, R.A. Merchant, Underdiagnosis of delirium on admission and prediction of patients who will develop delirium during their inpatient stay: a pilot study, Singap. Med. J. 57 (1) (2016) 18–21, https://doi.org/10.11622/smedj.2016007 [published Online First: Epub Date].

[6] P. Voyer, N. Champoux, J. Desrosiers, et al., RADAR: a measure of the sixth vital sign? Clin. Nurs. Res. 25 (1) (2016) 9–29, https://doi.org/10.1177/1054773815603346 [published Online First: Epub Date].

[7] E. Sepulveda, J.G. Franco, P.T. Trzepacz, et al., Delirium diagnosis defined by cluster analysis of symptoms versus diagnosis by DSM and ICD criteria: diagnostic accuracy study, BMC Psychiatry 16 (2016) 167, https://doi.org/10.1186/s12888-016-0878-6 [published Online First: Epub Date].

[8] J.R. Maldonado, Neuropathogenesis of delirium: review of current etiologic theories and common pathways, Am. J. Geriatr. Psychiatry 21 (12) (2013) 1190–1222, https://doi.org/10.1016/j.jagp.2013.09.005 [published Online First: Epub Date].

[9] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Publishing, Arlington, VA, 2013.

[10] World Health Organisation, The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines, World Health Organisation, Geneva, 1992.

[11] E.R. Marcantonio, J.L. Rudolph, D. Culley, G. Crosby, D. Alsop, S.K. Inouye, Serum biomarkers for delirium, J. Gerontol. A Biol. Sci. Med. Sci. 61 (12) (2006) 1281–1286, https://doi.org/10.1093/gerona/61.12.1281 [published Online First: Epub Date].

[12] R.J. Hall, L.O. Watne, E. Cunningham, et al., CSF biomarkers in delirium: a systematic review, Int. J. Geriatr. Psychiatry 33 (11) (2018) 1479–1500, https://doi.org/10.1002/gps.4720 [published Online First: Epub Date].

[13] D.F. Stroup, J.A. Berlin, S.C. Morton, et al., Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group, JAMA 283 (15) (2000) 2008–2012, https://doi.org/10.1001/jama.283.15.2008 [published Online First: Epub Date].

[14] J.M. Flacker, L.A. Lipsitz, Large neutral amino acid changes and delirium in febrile elderly medical patients, J. Gerontol. A Biol. Sci. Med. Sci. 55 (5) (2000), https://doi.org/10.1093/gerona/55.5.b249. B249-52; discussion B53-4. [published Online First: Epub Date].

[15] B. Zhao, Y. Ni, X. Tian, Low plasma cholinesterase activity is associated with postoperative delirium after noncardiac surgery in elderly patients: a prospective observational study, Psychosomatics 60 (2) (2019) 190–196, https://doi.org/10.1016/j.psym.2018.06.014 [published Online First: Epub Date].

[16] B.C. van Munster, C. Thomas, S.H. Kreisel, et al., Longitudinal assessment of serum anticholinergic activity in delirium of the elderly, J. Psychiatr. Res. 46 (10) (2012) 1339–1345, https://doi.org/10.1016/j.jpsychires.2012.06.015 [published Online First: Epub Date].

[17] J. Cerejeira, P. Batista, V. Nogueira, H. Firmino, A. Vaz-Serra, E.B. Mukaetova-Ladinska, Low preoperative plasma cholinesterase activity as a risk marker of postoperative delirium in elderly patients, Age Ageing 40 (5) (2011) 621–626, https://doi.org/10.1093/ageing/afr053 [published Online First: Epub Date].

[18] C. Thomas, U. Hestermann, J. Kopitz, et al., Serum anticholinergic activity and cerebral cholinergic dysfunction: an EEG study in frail elderly with and without delirium, BMC Neurosci. 9 (2008) 86, https://doi.org/10.1186/1471-2202-9-86 [published Online First: Epub Date].

[19] K. Plaschke, H. Hill, R. Engelhardt, et al., EEG changes and serum anticholinergic activity measured in patients with delirium in the intensive care unit, Anaesthesia 62 (12) (2007) 1217–1223, https://doi.org/10.1111/j.1365-2044.2007.05255.x [published Online First: Epub Date].

[20] J. Cerejeira, P. Batista, V. Nogueira, A. Vaz-Serra, E.B. Mukaetova-Ladinska, The stress response to surgery and postoperative delirium: evidence of hypothalamic-pituitary-adrenal axis hyperresponsiveness and decreased suppression of the GH/IGF-1 Axis, J. Geriatr. Psychiatry Neurol. 26 (3) (2013) 185–194, https://doi.org/10.1177/0891988713495449 [published Online First: Epub Date].

[21] K. Plaschke, P. Fichtenkamm, C. Schramm, et al., Early postoperative delirium after open-heart cardiac surgery is associated with decreased bispectral EEG and increased cortisol and interleukin-6, Intensive Care Med. 36 (12) (2010) 2081–2089, https://doi.org/10.1007/s00134-010-2004-4 [published Online First: Epub Date].

[22] J. Cerejeira, V. Nogueira, P. Luís, A. Vaz-Serra, E.B. Mukaetova-Ladinska, The cholinergic system and inflammation: common pathways in delirium pathophysiology, J. Am. Geriatr. Soc. 60 (4) (2012) 669–675, https://doi.org/10.1111/j.1532-5415.2011.03883.x [published Online First: Epub Date].

[23] A. Egberts, D. Fekkes, E.H. Wijnbeld, et al., Disturbed serotonergic neurotransmission and oxidative stress in elderly patients with delirium, Dement Geriatr. Cogn. Dis. Extra 5 (3) (2015) 450–458, https://doi.org/10.1159/000440696 [published Online First: Epub Date].

[24] R.J. Osse, D. Fekkes, J.H. Tulen, et al., High preoperative plasma neopterin predicts delirium after cardiac surgery in older adults, J. Am. Geriatr. Soc. 60 (4) (2012) 661–668, https://doi.org/10.1111/j.1532-5415.2011.03885.x [published Online First: Epub Date].

[25] J. Ramirez-Bermudez, A. Ruiz-Chow, I. Perez-Neri, et al., Cerebrospinal fluid homovanillic acid is correlated to psychotic features in neurological patients with delirium, Gen. Hosp. Psychiatry 30 (4) (2008) 337–343, https://doi.org/10.1016/j.genhosppsych.2008.01.007 [published Online First: Epub Date].

[26] L.O. Watne, A.V. Idland, D. Fekkes, et al., Increased CSF levels of aromatic amino acids in hip fracture patients with delirium suggests higher monoaminergic activity, BMC Geriatr. 16 (2016) 149, https://doi.org/10.1186/s12877-016-0324-0 [published Online First: Epub Date].

[27] P.P. Pandharipande, A. Morandi, J.R. Adams, et al., Plasma tryptophan and tyrosine levels are independent risk factors for delirium in critically ill patients, Intensive Care Med. 35 (11) (2009) 1886–1892, https://doi.org/10.1007/s00134-009-1573-6 [published Online First: Epub Date].

[28] R.C. van der Mast, W.W. van den Broek, D. Fekkes, L. Pepplinkhuizen, J. D. Habbema, Is delirium after cardiac surgery related to plasma amino acids and physical condition? J. Neuropsychiatr. Clin. Neurosci. 12 (1) (2000) 57–63, https://doi.org/10.1176/jnp.12.1.57 [published Online First: Epub Date].

[29] T.N. Robinson, C.D. Raeburn, E.M. Angles, M. Moss, Low tryptophan levels are associated with postoperative delirium in the elderly, Am. J. Surg. 196 (5) (2008) 670–674, https://doi.org/10.1016/j.amjsurg.2008.07.007 [published Online First: Epub Date].

[30] A. de Jonghe, B.C. van Munster, D. Fekkes, H.E. van Oosten, S.E. de Rooij, The tryptophan depletion theory in delirium: not confirmed in elderly hip fracture patients, Psychosomatics 53 (3) (2012) 236–243, https://doi.org/10.1016/j.psym.2011.09.009 [published Online First: Epub Date].

[31] H. Shigeta, A. Yasui, Y. Nimura, et al., Postoperative delirium and melatonin levels in elderly patients, Am. J. Surg. 182 (5) (2001) 449–454, https://doi.org/10.1016/s0002-9610(01)00761-9 [published Online First: Epub Date].

[32] S. Yoshitaka, M. Egi, H. Morimatsu, T. Kanazawa, Y. Toda, K. Morita, Perioperative plasma melatonin concentration in postoperative critically ill patients: its association with delirium, J. Crit. Care 28 (3) (2013) 236–242, https://doi.org/10.1016/j.jcrc.2012.11.004 [published Online First: Epub Date].

[33] K. Piotrowicz, A. Klich-Rączka, A. Pac, A. Zdzienicka, T. Grodzicki, The diurnal profile of melatonin during delirium in elderly patients–preliminary results, Exp. Gerontol. 72 (2015) 45–49, https://doi.org/10.1016/j.exger.2015.09.007 [published Online First: Epub Date].

[34] B.C. van Munster, P.H. Bisschop, A.H. Zwinderman, et al., Cortisol, interleukins and S100B in delirium in the elderly, Brain Cogn. 74 (1) (2010) 18–23, https://doi.org/10.1016/j.bandc.2010.05.010 [published Online First: Epub Date].

[35] P. Liu, Y.W. Li, X.S. Wang, et al., High serum interleukin-6 level is associated with increased risk of delirium in elderly patients after noncardiac surgery: a prospective cohort study, Chin. Med. J. 126 (19) (2013) 3621–3627 [published Online First: Epub Date].

[36] J. Hirsch, S. Vacas, N. Terrando, et al., Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery, J. Neuroinflammation 13 (1) (2016) 211, https://doi.org/10.1186/s12974-016-0681-9 [published Online First: Epub Date].

[37] D. Westhoff, J. Witlox, L. Koenderman, et al., Preoperative cerebrospinal fluid cytokine levels and the risk of postoperative delirium in elderly hip fracture patients, J. Neuroinflammation 10 (2013) 122, https://doi.org/10.1186/1742-2094-10-122 [published Online First: Epub Date].

[38] L. Sun, Peiyu Jia, Junfeng Zhang, Xin Zhang, H.J. Yiwei Zhang, Wei Jiang, Yong Guo, Production of inflammatory cytokines, cortisol, and Aβ1-40 in elderly oral cancer patients with postoperative delirium, Neuropsychiatr. Dis. Treat. 12 (October) (2016) 2789–2795 [published Online First: Epub Date].

[39] S.M. Vasunilashorn, L. Ngo, S.K. Inouye, et al., Cytokines and postoperative delirium in older patients undergoing major elective surgery, J. Gerontol. A Biol. Sci. Med. Sci. 70 (10) (2015) 1289–1295, https://doi.org/10.1093/gerona/glv083 [published Online First: Epub Date].

[40] S. Miao, P. Shen, Q. Zhang, et al., Neopterin and mini-mental state examination scores, two independent risk factors for postoperative delirium in elderly patients with open abdominal surgery, J. Cancer Res. Ther. 14 (6) (2018) 1234–1238, https://doi.org/10.4103/0973-1482.192764 [published Online First: Epub Date].

[41] M. Capri, S.L. Yani, R. Chattat, et al., Pre-operative, high-IL-6 blood level is a risk factor of post-operative delirium onset in old patients, Front Endocrinol. (Lausanne) 5 (2014) 173, https://doi.org/10.3389/fendo.2014.00173 [published Online First: Epub Date].

[42] B.C. van Munster, J.C. Korevaar, A.H. Zwinderman, M. Levi, W.J. Wiersinga, S. E. De Rooij, Time-course of cytokines during delirium in elderly patients with hip fractures, J. Am. Geriatr. Soc. 56 (9) (2008) 1704–1709, https://doi.org/10.1111/j.1532-5415.2008.01851.x [published Online First: Epub Date].

[43] Kristo A.K. Erikson, Koskenkari Teroİlmari, Liisanantti Juha, Janne Henrik, R. Kamakura, Karl Heinz Herzig, Hannu Syrjälä, Elevated serum S-100β in patients with septic shock Is associated with delirium, Acta Anaesthesiol. Scand. 63 (1 (January 2019)) (2019) 69–73 [published Online First: Epub Date].

[44] J.L. Rudolph, B. Ramlawi, G.A. Kuchel, et al., Chemokines are associated with delirium after cardiac surgery, J. Gerontol. A Biol. Sci. Med. Sci. 63 (2) (2008) 184–189, https://doi.org/10.1093/gerona/63.2.184 [published Online First: Epub Date].

[45] B.E. Neerland, R.J. Hall, I. Seljeflot, et al., Associations between delirium and preoperative cerebrospinal fluid C-reactive protein, Interleukin-6, and Interleukin-6 Receptor in individuals with acute hip fracture, J. Am. Geriatr. Soc. 64 (7) (2016) 1456–1463, https://doi.org/10.1111/jgs.14238 [published Online First: Epub Date].

[46] A. Egberts, E.H. Wijnbeld, D. Fekkes, et al., Neopterin: a potential biomarker for delirium in elderly patients, Dement. Geriatr. Cogn. Disord. 39 (1–2) (2015) 116–124, https://doi.org/10.1159/000366410 [published Online First: Epub Date].

[47] S.A. Alexander, D. Ren, S.R. Gunn, et al., Interleukin 6 and apolipoprotein E as predictors of acute brain dysfunction and survival in critical care patients, Am. J.

Crit. Care 23 (1) (2014) 49–57, https://doi.org/10.4037/ajcc2014578 [published Online First: Epub Date].
[48] D. Pfister, M. Siegemund, S. Dell-Kuster, et al., Cerebral perfusion in sepsis-associated delirium, Crit. Care 12 (3) (2008) R63, https://doi.org/10.1186/cc6891 [published Online First: Epub Date].
[49] C. Jorge-Ripper, M.R. Alemán, R. Ros, et al., Prognostic value of acute delirium recovery in older adults, Geriatr Gerontol Int 17 (8) (2017) 1161–1167, https://doi.org/10.1111/ggi.12842 [published Online First: Epub Date].
[50] S.E. de Rooij, B.C. van Munster, J.C. Korevaar, M. Levi, Cytokines and acute phase response in delirium, J. Psychosom. Res. 62 (5) (2007) 521–525, https://doi.org/10.1016/j.jpsychores.2006.11.013 [published Online First: Epub Date].
[51] A.W. Lemstra, K.J. Kalisvaart, R. Vreeswijk, W.A. van Gool, P. Eikelenboom, Pre-operative inflammatory markers and the risk of postoperative delirium in elderly patients, Int. J. Geriatr. Psychiatry 23 (9) (2008) 943–948, https://doi.org/10.1002/gps.2015 [published Online First: Epub Date].
[52] D. Adamis, M. Lunn, F.C. Martin, et al., Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients, Age Ageing 38 (3) (2009) 326–332, discussion 251, https://doi.org/10.1093/ageing/afp014 [published Online First: Epub Date].
[53] D. Adamis, A. Treloar, F.C. Martin, N. Gregson, G. Hamilton, A.J. Macdonald, APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients, Int. J. Geriatr. Psychiatry 22 (7) (2007) 688–694, https://doi.org/10.1002/gps.1732 [published Online First: Epub Date].
[54] M. van den Boogaard, M. Kox, K.L. Quinn, et al., Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients, Crit. Care 15 (6) (2011) R297, https://doi.org/10.1186/cc10598 [published Online First: Epub Date].
[55] C. Ritter, C.D. Tomasi, F. Dal-Pizzol, et al., Inflammation biomarkers and delirium in critically ill patients, Crit. Care 18 (3) (2014) R106, https://doi.org/10.1186/cc13887 [published Online First: Epub Date].
[56] E. Cape, R.J. Hall, B.C. van Munster, et al., Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1β in delirium after hip fracture, J. Psychosom. Res. 77 (3) (2014) 219–225, https://doi.org/10.1016/j.jpsychores.2014.06.014 [published Online First: Epub Date].
[57] A. Baranyi, H.B. Rothenhäusler, The impact of soluble interleukin-2 receptor as a biomarker of delirium, Psychosomatics 55 (1) (2014) 51–60, https://doi.org/10.1016/j.psym.2013.06.004 [published Online First: Epub Date].
[58] J. Kazmierski, A. Banys, J. Latek, J. Bourke, R. Jaszewski, Raised IL-2 and TNF-α concentrations are associated with postoperative delirium in patients undergoing coronary-artery bypass graft surgery, Int. Psychogeriatr. 26 (5) (2014) 845–855, https://doi.org/10.1017/S1041610213002378 [published Online First: Epub Date].
[59] T.D. Girard, L.B. Ware, G.R. Bernard, et al., Associations of markers of inflammation and coagulation with delirium during critical illness, Intensive Care Med. 38 (12) (2012) 1965–1973, https://doi.org/10.1007/s00134-012-2678-x [published Online First: Epub Date].
[60] S.T. Dillon, S.M. Vasunilashorn, L. Ngo, et al., Higher C-reactive protein levels predict postoperative delirium in older patients undergoing major elective surgery: a longitudinal nested case-control study, Biol. Psychiatry 81 (2) (2017) 145–153, https://doi.org/10.1016/j.biopsych.2016.03.2098 [published Online First: Epub Date].
[61] H.J. Lee, D.S. Hwang, S.K. Wang, I.S. Chee, S. Baeg, J.L. Kim, Early assessment of delirium in elderly patients after hip surgery, Psychiatry Investig. 8 (4) (2011) 340–347, https://doi.org/10.4306/pi.2011.8.4.340 [published Online First: Epub Date].
[62] C.W. Ritchie, T.H. Newman, B. Leurent, E.L. Sampson, The association between C-reactive protein and delirium in 710 acute elderly hospital admissions, Int. Psychogeriatr. 26 (5) (2014) 717–724, https://doi.org/10.1017/S1041610213002433 [published Online First: Epub Date].
[63] J. McManus, R. Pathansali, H. Hassan, et al., The course of delirium in acute stroke, Age Ageing 38 (4) (2009) 385–389, https://doi.org/10.1093/ageing/afp038 [published Online First: Epub Date].
[64] R. Tsuruta, T. Nakahara, T. Miyauchi, et al., Prevalence and associated factors for delirium in critically ill patients at a Japanese intensive care unit, Gen. Hosp. Psychiatry 32 (6) (2010) 607–611, https://doi.org/10.1016/j.genhosppsych.2010.09.001 [published Online First: Epub Date].
[65] C. Knaak, Gerald Vorderwülbecke, Spies S.K.P. Claudia, Daniel Hadzidiakos, Friedrich Borchers, Brockhaus F.M.R. Wolf-Rüdiger, Gunnar Lachmann, C-Reactive Protein for risk prediction of postoperative delirium and postoperative neurocognitive disorder, Acta Anaesthesiol. Scand. July 8 (2019) 2019, https://doi.org/10.1111/aas.13441 [published Online First: Epub Date].
[66] Z. Zhang, L. Pan, H. Deng, H. Ni, X. Xu, Prediction of delirium in critically ill patients with elevated C-reactive protein, J. Crit. Care 29 (1) (2014) 88–92, https://doi.org/10.1016/j.jcrc.2013.09.002 [published Online First: Epub Date].
[67] R.A. Pol, B.L. van Leeuwen, G.J. Izaks, et al., C-reactive protein predicts postoperative delirium following vascular surgery, Ann. Vasc. Surg. 28 (8) (2014) 1923–1930, https://doi.org/10.1016/j.avsg.2014.07.004 [published Online First: Epub Date].
[68] H. Shen, Y. Shao, J. Chen, J. Guo, Insulin-Like Growth Factor-1, a potential predicative biomarker for postoperative delirium among elderly patients with open abdominal surgery, Curr. Pharm. Des. 22 (38) (2016) 5879–5883, https://doi.org/10.2174/1381612822666160813234311 [published Online First: Epub Date].
[69] K. Wilson, C. Broadhurst, M. Diver, M. Jackson, P. Mottram, Plasma insulin growth factor-1 and incident delirium in older people, Int. J. Geriatr. Psychiatry 20 (2) (2005) 154–159, https://doi.org/10.1002/gps.1265 [published Online First: Epub Date].
[70] A. Morandi, I. Sleiman, R. Rozzini, M. Trabucchi, C-reactive protein and delirium in acute ill elderly patients, Age Ageing 36 (4) (2007) 473, https://doi.org/10.1093/ageing/afm060 [published Online First: Epub Date].
[71] L. Al Tmimi, M. Van de Velde, B. Meyns, et al., Serum protein S100 as marker of postoperative delirium after off-pump coronary artery bypass surgery: secondary analysis of two prospective randomized controlled trials, Clin. Chem. Lab. Med. 54 (10) (2016) 1671–1680, https://doi.org/10.1515/cclm-2015-1012 [published Online First: Epub Date].
[72] R.J. Hall, K.J. Ferguson, M. Andrews, et al., Delirium and cerebrospinal fluid S100B in hip fracture patients: a preliminary study, Am. J. Geriatr. Psychiatry 21 (12) (2013) 1239–1243, https://doi.org/10.1016/j.jagp.2012.12.024 [published Online First: Epub Date].
[73] S.J. Beishuizen, R.M. Scholtens, B.C. van Munster, S.E. de Rooij, Unraveling the relationship between delirium, brain damage, and subsequent cognitive decline in a cohort of individuals undergoing surgery for hip fracture, J. Am. Geriatr. Soc. 65 (1) (2017) 130–136, https://doi.org/10.1111/jgs.14470 [published Online First: Epub Date].
[74] B.A. Khan, M.O. Farber, N. Campbell, et al., S100 calcium binding protein B as a biomarker of delirium duration in the intensive care unit - an exploratory analysis, Int. J. Gen. Med. 6 (2013) 855–861, https://doi.org/10.2147/IJGM.S51004 [published Online First: Epub Date].
[75] C.G. Hughes, P.P. Pandharipande, J.L. Thompson, et al., Endothelial activation and blood-brain barrier injury as risk factors for delirium in critically ill patients, Crit. Care Med. 44 (9) (2016) e809–e817, https://doi.org/10.1097/CCM.0000000000001739 [published Online First: Epub Date].
[76] C. Grandi, C.D. Tomasi, K. Fernandes, et al., Brain-derived neurotrophic factor and neuron-specific enolase, but not S100β, levels are associated to the occurrence of delirium in intensive care unit patients, J. Crit. Care 26 (2) (2011) 133–137, https://doi.org/10.1016/j.jcrc.2010.10.006 [published Online First: Epub Date].
[77] F.J.F.V. Abelha, M. Botelho, P. Santos, A.M.J. Santos, et al., Apolipoprotein E e4 allele does not increase the, 2012 roepdamsJA. E e4 allele does not increase the risk of early postoperative delirium after major surgery, J. Anesth. 26 (2012) 412–421, https://doi.org/10.1007/s00540-012-1326-5 [published Online First: Epub Date].
[78] G.I. Tagarakis, F. Tsolaki-Tagaraki, M. Tsolaki, A. Diegeler, N.B. Tsilimingas, A. Papassotiropoulos, The role of apolipoprotein E in cognitive decline and delirium after bypass heart operations, Am. J. Alzheimers Dis. Other Dement. 22 (3) (2007) 223–228, https://doi.org/10.1177/1533317507299415 [published Online First: Epub Date].
[79] J.M. Leung, L.P. Sands, Y. Wang, et al., Apolipoprotein E e4 allele increases the risk of early postoperative delirium in older patients undergoing noncardiac surgery, Anesthesiology 107 (3) (2007) 406–411, https://doi.org/10.1097/01.anes.0000278905.07899.df [published Online First: Epub Date].
[80] G.L. Bryson, A. Wyand, D. Wozny, L. Rees, M. Taljaard, H. Nathan, A prospective cohort study evaluating associations among delirium, postoperative cognitive dysfunction, and apolipoprotein E genotype following open aortic repair, Can. J. Anaesth. 58 (3) (2011) 246–255, https://doi.org/10.1007/s12630-010-9446-6 [published Online First: Epub Date].
[81] A. Pearson, A. de Vries, S.D. Middleton, et al., Cerebrospinal fluid cortisol levels are higher in patients with delirium versus controls, BMC Res. Notes 3 (2010) 33, https://doi.org/10.1186/1756-0500-3-33 [published Online First: Epub Date].
[82] D.L. Mu, D.X. Wang, L.H. Li, et al., High serum cortisol level is associated with increased risk of delirium after coronary artery bypass graft surgery: a prospective cohort study, Crit. Care 14 (6) (2010) R238, https://doi.org/10.1186/cc9393 [published Online First: Epub Date].
[83] J. Kazmierski, A. Banys, J. Latek, J. Bourke, R. Jaszewski, Cortisol levels and neuropsychiatric diagnosis as markers of postoperative delirium: a prospective cohort study, Crit. Care 17 (2) (2013) R38, https://doi.org/10.1186/cc12548 [published Online First: Epub Date].
[84] Y. Colkesen, S. Giray, Y. Ozenli, N. Sezgin, I. Coskun, Relation of serum cortisol to delirium occurring after acute coronary syndromes, Am. J. Emerg. Med. 31 (1) (2013) 161–165, https://doi.org/10.1016/j.ajem.2012.07.001 [published Online First: Epub Date].
[85] P.H. Bisschop, S.E. de Rooij, A.H. Zwinderman, H.E. van Oosten, B.C. van Munster, Cortisol, insulin, and glucose and the risk of delirium in older adults with hip fracture, J. Am. Geriatr. Soc. 59 (9) (2011) 1692–1696, https://doi.org/10.1111/j.1532-5415.2011.03575.x [published Online First: Epub Date].
[86] J.A. Avila-Funes, J.P. Ledesma-Heyer, A.P. Navarrete-Reyes, R. Chavira-Ramírez, L. Boeck-Quirasco, S. Aguilar-Navarro, Association between high serum estradiol levels and delirium among hospitalized elderly women, Rev. Investig. Clin. 67 (1) (2015) 20–24 [published Online First: Epub Date].
[87] R.J. Wurtman, F. Hefti, E. Melamed, Precursor control of neurotransmitter synthesis, Pharmacol. Rev. 32 (4) (1980) 315–335 [published Online First: Epub Date].
[88] J. Cerejeira, H. Firmino, A. Vaz-Serra, E.B. Mukaetova-Ladinska, The neuroinflammatory hypothesis of delirium, Acta Neuropathol. 119 (6) (2010) 737–754, https://doi.org/10.1007/s00401-010-0674-1 [published Online First: Epub Date].
[89] J.M. Flacker, V. Cummings, J.R. Mach, K. Bettin, D.K. Kiely, J. Wei, The association of serum anticholinergic activity with delirium in elderly medical patients, Am. J. Geriatr. Psychiatry 6 (1) (1998) 31–41 [published Online First: Epub Date].

[90] C. Mussi, R. Ferrari, S. Ascari, G. Salvioli, Importance of serum anticholinergic activity in the assessment of elderly patients with delirium, J. Geriatr. Psychiatry Neurol. 12 (2) (1999) 82–86, https://doi.org/10.1177/089198879901200208 [published Online First: Epub Date].
[91] J. Cerejeira, L. Lagarto, E.B. Mukaetova-Ladinska, The immunology of delirium, Neuroimmunomodulation 21 (2–3) (2014) 72–78, https://doi.org/10.1159/000356526 [published Online First: Epub Date].
[92] M.C. Lewis, S.R. Barnett, Postoperative delirium: the tryptophan dyregulation model, Med. Hypotheses 63 (3) (2004) 402–406, https://doi.org/10.1016/j.mehy.2004.01.033 [published Online First: Epub Date].
[93] T.N. Robinson, C.L. Dunn, J.C. Adams, et al., Tryptophan supplementation and postoperative delirium–a randomized controlled trial, J. Am. Geriatr. Soc. 62 (9) (2014) 1764–1771, https://doi.org/10.1111/jgs.12972 [published Online First: Epub Date].
[94] A. Macdonald, D. Adamis, A. Treloar, F. Martin, C-reactive protein levels predict the incidence of delirium and recovery from it, Age Ageing 36 (2) (2007) 222–225, https://doi.org/10.1093/ageing/afl121 [published Online First: Epub Date].
[95] P.T. Trzepacz, Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine, Semin. Clin. Neuropsychiatry 5 (2) (2000) 132–148, doi: 10.153/SCNP005001132. [published Online First: Epub Date].
[96] D.J. Meagher, M. Leonard, S. Donnelly, M. Conroy, D. Adamis, P.T. Trzepacz, A longitudinal study of motor subtypes in delirium: relationship with other phenomenology, etiology, medication exposure and prognosis, J. Psychosom. Res. 71 (6) (2011) 395–403, https://doi.org/10.1016/j.jpsychores.2011.06.001 [published Online First: Epub Date].
[97] C. Franceschi, M. Capri, D. Monti, et al., Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans, Mech. Ageing Dev. 128 (1) (2007) 92–105, https://doi.org/10.1016/j.mad.2006.11.016 [published Online First: Epub Date].
[98] P. Sansoni, R. Vescovini, F. Fagnoni, et al., The immune system in extreme longevity, Exp. Gerontol. 43 (2) (2008) 61–65, https://doi.org/10.1016/j.exger.2007.06.008 [published Online First: Epub Date].
[99] J.D. Weaver, M.H. Huang, M. Albert, T. Harris, J.W. Rowe, T.E. Seeman, Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging, Neurology 59 (3) (2002) 371–378, https://doi.org/10.1212/wnl.59.3.371 [published Online First: Epub Date].
[100] M.Q. Xia, B.T. Hyman, Chemokines/chemokine receptors in the central nervous system and Alzheimer's disease, J. Neuro-Oncol. 5 (1) (1999) 32–41, https://doi.org/10.3109/13550289909029743 [published Online First: Epub Date].
[101] L. Rink, I. Cakman, H. Kirchner, Altered cytokine production in the elderly, Mech. Ageing Dev. 102 (2–3) (1998) 199–209, https://doi.org/10.1016/s0047-6374(97)00153-x [published Online First: Epub Date].
[102] N. Terrando, C. Monaco, D. Ma, B.M. Foxwell, M. Feldmann, M. Maze, Tumor necrosis factor-alpha triggers a cytokine cascade yielding postoperative cognitive decline, Proc. Natl. Acad. Sci. U. S. A. 107 (47) (2010) 20518–20522, https://doi.org/10.1073/pnas.1014557107 [published Online First: Epub Date].
[103] J.I. Jones, D.R. Clemmons, Insulin-like growth factors and their binding proteins: biological actions, Endocr. Rev. 16 (1) (1995) 3–34, https://doi.org/10.1210/edrv-16-1-3 [published Online First: Epub Date].
[104] D. Adamis, D. Meagher, Insulin-like growth factor I and the pathogenesis of delirium: a review of current evidence, J. Aging Res. 2011 (2011) 951403, https://doi.org/10.4061/2011/951403 [published Online First: Epub Date].
[105] G. Murialdo, A. Barreca, F. Nobili, et al., Relationships between cortisol, dehydroepiandrosterone sulphate and insulin-like growth factor-I system in dementia, J. Endocrinol. Investig. 24 (3) (2001) 139–146, https://doi.org/10.1007/BF03343833 [published Online First: Epub Date].
[106] E. Carro, J.L. Trejo, A. Gerber, et al., Therapeutic actions of insulin-like growth factor I on APP/PS2 mice with severe brain amyloidosis, Neurobiol. Aging 27 (9) (2006) 1250–1257, https://doi.org/10.1016/j.neurobiolaging.2005.06.015 [published Online First: Epub Date].
[107] S.S. Pinto, C. Gottfried, A. Mendez, et al., Immunocontent and secretion of S100B in astrocyte cultures from different brain regions in relation to morphology, FEBS Lett. 486 (3) (2000) 203–207, https://doi.org/10.1016/s0014-5793(00)02301-2 [published Online First: Epub Date].
[108] K.H. Weisgraber, A.D. Roses, W.J. Strittmatter, The role of apolipoprotein E in the nervous system, Curr. Opin. Lipidol. 5 (2) (1994) 110–116, https://doi.org/10.1097/00041433-199404000-00007 [published Online First: Epub Date].
[109] E.H. Corder, A.M. Saunders, W.J. Strittmatter, et al., Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families, Science 261 (5123) (1993) 921–923, https://doi.org/10.1126/science.8346443 [published Online First: Epub Date].
[110] J.R. Lynch, J.A. Pineda, D. Morgan, et al., Apolipoprotein E affects the central nervous system response to injury and the development of cerebral edema, Ann. Neurol. 51 (1) (2002) 113–117, https://doi.org/10.1002/ana.10098 [published Online First: Epub Date].
[111] G.D. Kalliolias, L.B. Ivashkiv, TNF biology, pathogenic mechanisms and emerging therapeutic strategies, Nat. Rev. Rheumatol. 12 (1) (2016) 49–62, https://doi.org/10.1038/nrrheum.2015.169 [published Online First: Epub Date].
[112] L. Probert, TNF and its receptors in the CNS: the essential, the desirable and the deleterious effects, Neuroscience 302 (2015) 2–22, https://doi.org/10.1016/j.neuroscience.2015.06.038 [published Online First: Epub Date].
[113] C. Holmes, C. Cunningham, E. Zotova, et al., Systemic inflammation and disease progression in Alzheimer disease, Neurology 73 (10) (2009) 768–774, https://doi.org/10.1212/WNL.0b013e3181b6bb95 [published Online First: Epub Date].
[114] T. Olsson, Activity in the hypothalamic-pituitary-adrenal axis and delirium, Dement. Geriatr. Cogn. Disord. 10 (5) (1999) 345–349, https://doi.org/10.1159/000017168 [published Online First: Epub Date].
[115] A.M. Maclullich, K.J. Ferguson, T. Miller, S.E. de Rooij, C. Cunningham, Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses, J. Psychosom. Res. 65 (3) (2008) 229–238, https://doi.org/10.1016/j.jpsychores.2008.05.019 [published Online First: Epub Date].
[116] V. Senanarong, S. Vannasaeng, N. Poungvarin, et al., Endogenous estradiol in elderly individuals: cognitive and noncognitive associations, Arch. Neurol. 59 (3) (2002) 385–389, https://doi.org/10.1001/archneur.59.3.385 [published Online First: Epub Date].
[117] J. Williams, K. Finn, V. Melvin, D. Meagher, G. McCarthy, D. Adamis, The association of serum levels of brain-derived neurotrophic factor with the occurrence of and recovery from delirium in older medical inpatients, Biomed. Res. Int. 2017 (2017) 5271395, https://doi.org/10.1155/2017/5271395 [published Online First: Epub Date].
[118] J. Wyrobek, A. LaFlam, L. Max, et al., Association of intraoperative changes in brain-derived neurotrophic factor and postoperative delirium in older adults, Br. J. Anaesth. 119 (2) (2017) 324–332, https://doi.org/10.1093/bja/aex103 [published Online First: Epub Date].
[119] P.T. Trzepacz, M. Leavitt, K. Ciongoli, An animal model for delirium, Psychosomatics 33 (4) (1992) 404–415, https://doi.org/10.1016/S0033-3182(92)71945-8 [published Online First: Epub Date].
[120] M. Peng, C. Zhang, Y. Dong, et al., Battery of behavioral tests in mice to study postoperative delirium, Sci. Rep. 6 (2016) 29874, https://doi.org/10.1038/srep29874 [published Online First: Epub Date].
[121] W.A.C. Mutch, R.M. El-Gabalawy, M.R. Graham, Postoperative delirium, learning, and anesthetic neurotoxicity: some perspectives and directions, Front. Neurol. 9 (2018) 177, https://doi.org/10.3389/fneur.2018.00177 [published Online First: Epub Date].
[122] R. Velagapudi, S. Subramaniyan, C. Xiong, et al., Orthopedic surgery triggers attention deficits in a delirium-like mouse model, Front. Immunol. 10 (2019) 2675, https://doi.org/10.3389/fimmu.2019.02675 [published Online First: Epub Date].
[123] B.M. Bettcher, S.C. Johnson, R. Fitch, et al., Cerebrospinal fluid and plasma levels of inflammation differentially relate to CNS markers of Alzheimer's disease pathology and neuronal damage, J. Alzheimers Dis. 62 (1) (2018) 385–397, https://doi.org/10.3233/JAD-170602 [published Online First: Epub Date].
[124] B.J.A. Palanca, T.S. Wildes, Y.S. Ju, S. Ching, M.S. Avidan, Electroencephalography and delirium in the postoperative period, Br. J. Anaesth. 119 (2) (2017) 294–307, https://doi.org/10.1093/bja/aew475 [published Online First: Epub Date].
[125] Shinozaki G, Braun PR, Hing BWQ, et al. Epigenetics of delirium and aging: potential role of DNA methylation change on cytokine genes in glia and blood along with aging. Front. Aging Neurosci. 2018;10: 311 doi: https://doi.org/10.3389/fnagi.2018.00311. [published Online First: Epub Date].
[126] T. Saito, P.R. Braun, S. Daniel, et al., The relationship between DNA methylation in neurotrophic genes and age as evidenced from three independent cohorts: differences by delirium status, Neurobiol. Aging 94 (2020) 227–235, https://doi.org/10.1016/j.neurobiolaging.2020.06.003 [published Online First: Epub Date].
[127] T. Saito, H. Toda, G.N. Duncan, et al., Epigenetics of neuroinflammation: Immune response, inflammatory response and cholinergic synaptic involvement evidenced by genome-wide DNA methylation analysis of delirious inpatients, J. Psychiatr. Res. 129 (2020) 61–65, https://doi.org/10.1016/j.jpsychires.2020.06.005 [published Online First: Epub Date].
[128] N. Stoicea, S. McVicker, A. Quinones, P. Agbenyefia, S.D. Bergese, Delirium-biomarkers and genetic variance, Front. Pharmacol. 5 (2014) 75, https://doi.org/10.3389/fphar.2014.00075 [published Online First: Epub Date].
[129] J.M. Campbell, M. Klugar, S. Ding, et al., Diagnostic test accuracy: methods for systematic review and meta-analysis, Int. J. Evid. Based Healthc. 13 (3) (2015) 154–162, https://doi.org/10.1097/XEB.0000000000000061 [published Online First: Epub Date].