Cerebrospinal Fluid and Microdialysis Cytokines in Severe Traumatic Brain Injury: A Scoping Systematic Review

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Objective: To perform two scoping systematic reviews of the literature on cytokine measurement in: 1. cerebral microdialysis (CMD) and 2. cerebrospinal fluid (CSF) in severe traumatic brain injury (TBI) patients.

Methods: Two separate systematic reviews were conducted: one for CMD cytokines and the second for CSF cytokines. Both were conducted in severe TBI (sTBI) patients only.

Data sources: Articles from MEDLINE, BIOSIS, EMBASE, Global Health, Scopus, Cochrane Library (inception to October 2016), reference lists of relevant articles, and gray literature were searched.

Study selection: Two reviewers independently identified all manuscripts utilizing pre-defined inclusion/exclusion criteria. A two-tier filter of references was conducted.

Data extraction: Patient demographic and study data were extracted to tables.

Results: There were 19 studies identified describing the analysis of cytokines via CMD in 267 sTBI patients. Similarly, there were 32 studies identified describing the analysis of CSF cytokines in 1,363 sTBI patients. The two systematic reviews demonstrated: 1. limited literature available on CMD cytokine measurement in sTBI, with some preliminary data supporting feasibility of measurement and associations between cytokines and patient outcome. 2. Various CSF measured cytokines may be associated with patient outcome at 6–12 months, including interleukin (IL)-1b, IL-1ra, IL-6, IL-8, IL-10, and tumor necrosis factor 3. There is little to no literature in support of an association between CSF cytokines and neurophysiologic or tissue outcomes.

Conclusion: The evaluation of CMD and CSF cytokines is an emerging area of the literature in sTBI. Further, large prospective multicenter studies on cytokines in CMD and CSF need to be conducted.

Keywords: cytokines, traumatic brain injury, brain injury, systematic review, microdialysis, cerebrospinal fluid
INTRODUCTION

Neuroinflammation after traumatic brain injury (TBI) is postulated to be a key driver of secondary brain injury in the acute/subacute phase after injury (1, 2). Upregulation of various components of the inflammatory cascade have been associated with lesion expansion (3), cerebral edema (4), derangements in neural transmission (5), and subsequent tissue death (6) in animal models of stroke and TBI. In humans, the inflammatory process post-TBI has been of interest, since its therapeutic modulation can potentially lead to amelioration of pathophysiological processes. Serum cytokine levels are easily measured in TBI patients, and elevation in pro-inflammatory cytokines have been associated with worse patient outcome (7, 8). However, systemic cytokine levels can be confounded by extracranial pathology and variable blood-brain barrier leak of centrally derived mediators. Measurement of cerebral levels of cytokines provides a more direct metric of neuroinflammation following TBI, but, to date, the measurement of cerebral microdialysis (CMD) (11–29) and cerebrospinal fluid (CSF) (30–65) cytokines have been limited to small studies.

The goal of this study was to produce a scoping systematic review of the literature on both CMD and CSF cytokines in severe TBI (sTBI). Our hope was to produce a comprehensive overview of the literature on this emerging topic.

METHODS

Two separate scoping systematic reviews were conducted, using the methodology outlined in the Cochrane Handbook for Systematic Reviewers (66). Data were reported following the preferred reporting items for systematic reviews and meta-analyses (67). The review questions and search strategy were decided upon by the primary author (Frederick A. Zeiler) and supervisors (Adel Helmy and David K. Menon). This manuscript was conducted in concert with a similar review on cytokines in CMD and CSF for aneurysmal subarachnoid hemorrhage (SAH) patients.

Search Question and Population of Interest

Given that two separate systematic reviews were conducted, one for CMD cytokines and the other for CSF cytokines, two distinct questions were posed. The limited literature on CMD cytokines identified through a preliminary search of PubMed led us to conduct a scoping review for the CMD cytokine search. We attempted to identify all studies in this area to date, and all articles describing microdialysis cytokine measures in humans with sTBI included in our review in order to provide a comprehensive overview of this emerging area of literature. The key question for this part of the review was:

- What literature has been published on CMD of cytokines in sTBI?

The larger literature base for CSF cytokines in TBI led us to narrow our question for this scoping review, focusing on relevant outcomes (see below). The questions posed for this scoping systematic review were:

- Is there literature to suggest an association between CSF cytokine measures in sTBI and patient outcome, neurophysiologic outcome, or tissue outcome?

For the CSF cytokine review, the primary outcome measures were documented association between CSF cytokine levels and: patient outcome, neurophysiologic outcome (as measured via intensive care unit (ICU)-based monitoring; intracranial pressure (ICP)/cerebral perfusion pressure (CPP), brain tissue oxygen monitoring (PbtO2), thermal diffusion assessment of cerebral blood flow (CBF), transcranial Doppler (TCD) measure of cerebral blood flow velocity (CBFV), any neuroimaging based assessment of CBF/perfusion, and electroencephalography), and tissue outcome [as assessed on follow-up neuroimaging by either computed tomography (CT) or magnetic resonance imaging]. Any outcome score or mention of morbidity/mortality within the studies was deemed acceptable for documentation of patient outcome. Secondary outcome measures were complications associated with CSF monitoring of cytokines.

The list of included cytokines in CMD or CSF included: interleukin (IL)-1α, IL-1β, IL-1ra, IL-2, sIL-2ra, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-12p70, IL-13, IL-14, IL-15, IL-16, IL-17, inducible protein (IP)-10, etoxin, tumor necrosis factor (TNF), interferon gamma (INF-g), monocyte chemotactant proteins, macrophage inflammatory proteins (MIPs), transforming growth factor (TGF), nerve growth factor (NGF), brain-derived neurotrophic factor, glial-derived neurotrophic factor, soluble tumor necrosis factor receptor (sTNFR), granulocyte macrophage colony stimulating factor, soluble FAS, soluble vascular cell adhesion molecule (sVCAM)-1, and soluble intracellular adhesion molecule (sICAM)-1, platelet-derived growth factor, regulated on activation, normal T cell expressed and secreted (RANTES), macrophage-derived chemokine (MDC), fms-like tyrosine kinase 3 (Flt3), Fractalkine, and fibroblast growth factor receptor.

Inclusion/Exclusion Criteria

CMD Cytokine Review

Inclusion criteria were: all studies including human subjects with sTBI (GCS 8 or less), any study size, any age category, CMD analysis for cytokines, and mention of any outcome (patient based or otherwise). Exclusion criteria were: non-English studies and animal studies.

CSF Cytokine Review

Inclusion criteria were: all studies including human subjects with sTBI (GCS of 8 or less), studies with 10 or more patients, any age category, CSF analysis for cytokines, and documentation either: patient functional outcome, neurophysiologic outcome, or tissue outcome in relation to CSF cytokine measures. Exclusion criteria were: non-English studies, animal studies, and studies of less than 10 patients. Non-English studies were excluded given the small number identified.

Search Strategies

MEDLINE, BIOSIS, EMBASE, Global Health, SCOPUS, and Cochrane Library from inception to October 2016 were searched.
using individualized search strategies. The search strategy for the CMD scoping systematic review using MEDLINE can be seen in Appendix A in Supplementary Material, with a similar search strategy utilized for the other databases. Further, the search strategy for the CSF scoping systematic review using MEDLINE can be seen in Appendix B in Supplementary Material, with similar strategies employed for the other databases.

In addition, we surveyed relevant meeting proceedings for the last 5 years looking for ongoing and unpublished work based on cytokine analysis via CMD or CSF in sTBI patients. The meeting proceedings of the following professional societies were searched: Canadian Neurological Sciences Federation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, European Neurosurgical Society, World Federation of Neurological Surgeons, National Neurotrauma Society, American Neurology Association, American Academy of Neurology, European Federation of Neurological Science, World Congress of Neurology, Society of Critical Care Medicine, Neurocritical Care Society, European Society for Intensive Care Medicine, World Federation of Societies of Intensive and Critical Care Medicine, American Society for Anesthesiologists, World Federation of Societies of Anesthesiologist, Australian Society of Anesthesiologists, International Anesthesia Research Society, Society of Neurosurgical Anesthesiology and Critical Care, Society for Neuroscience in Anesthesiology and Critical Care, Japanese Society of Neuroanesthesia and Critical Care, International NeuroTrauma Society, International Brain Injury Association, and the College of Intensive Care Medicine Annual Scientific Meeting (CICMASM—Australia).

Finally, reference lists of any review articles on CSF or CMD cytokines were reviewed for any missed relevant studies.

Study Selection
Utilizing two reviewers, a two-step review of all articles returned by our search strategies was performed. First, the reviewers independently (Frederick A. Zeiler and Eric Peter Thelin) screened titles and abstracts of the returned articles to decide if they met the inclusion criteria. Second, full text of the chosen articles was then assessed to confirm if they met the inclusion criteria and that the primary outcomes of interest were reported in the study (Frederick A. Zeiler and Eric Peter Thelin). Any discrepancies between the two reviewers were resolved by a third reviewer if needed (Adel Helmy or David K. Menon).

Data Collection
Data were extracted from the selected articles and stored in an electronic database. Data fields included: patient demographics, type of study, article location, number of patients, CMD/CSF substrate measured, CMD/CSF measurement details (probe tissue location, sampling frequency), outcome measure described (patient, neurophysiologic, tissue), association between CMD/CSF cytokine measure to outcome, and complications. All extracted data can be found in Tables 1 through 4, with study designs in Tables 1 and 2, and study outcomes in Tables 3 and 4.

Bias Assessment
As the goal of this review was to produce a systematically conducted scoping review of the available literature on CMD and CSF cytokine measures in sTBI, formal bias assessment was not done. Our desire was to produce a comprehensive overview of the current literature on the topic of CMD/CSF cytokines in sTBI. Formal evidence grading was not conducted (given the limited and heterogeneous literature body), and thus we deemed formal bias risk assessment unnecessary for this emerging area of literature, which clearly suffers from standard biases associated with new areas of clinical research.

Statistical Analysis
A meta-analysis was not performed in this study due to the heterogeneity of data and study design within the articles identified.

RESULTS
Search Strategy Results

CMD Cytokine Search

Results of the search strategy for CMD cytokines in sTBI is shown in the flow diagram in Figure 1. In total, 259 articles were identified, with 255 from the database and 4 from meeting proceedings sources. After removal of the duplicates, there were 144 articles left for assessment in the first filter of title and abstract. Thirty-seven articles passed the first filter, requiring acquisition of the full manuscript to assess inclusion eligibility. After assessing the full manuscripts, 19 articles were deemed eligible for final inclusion in the scoping systematic review. No articles were added from the reference sections of either review papers or the parent manuscripts included in the systematic review.

CSF Cytokine Search

The search strategy flow diagram for the CSF cytokine scoping systematic review is shown in Figure 2. Overall, 3,218 articles were identified, with 3,214 from the database search and 4 from published meeting proceedings. There were 1,317 duplicates removed, leaving 1,901 references to review in the first filter. Applying the inclusion/exclusion criteria to the title and abstract of these articles, 105 manuscripts were selected for review of the full article. One additional reference was added from the reference sections of review papers. During the second filter of the full manuscript, 36 met the final inclusion criteria for the scoping systematic review. Remaining articles were excluded due to non-relevance.

Patient/Study Demographics

CDM Cytokine Review

Of the 19 articles included in the CMD cytokine portion of the systematic review (11–19), 15 were formal manuscript publications (14–24, 26–29) and 4 were meeting abstract publications (11–13, 25). There were 13 prospective studies (13–16, 18–21, 25–29), with 12 prospective observational studies (13–15, 18–21, 25–29) and 1 prospective randomized control trial (16). Four studies were retrospective case series or database reviews (11, 20, 22, 23). Finally, two studies were of “unknown” study design given a lack of information available within the methods (12, 24).

The study population described in CMD cytokine papers was generally poorly characterized sTBI patient populations, undergoing various ICU and surgical therapies for their heterogeneous
### TABLE 1 | CMD cytokine study characteristics and patient demographics.

| Reference                     | Number of patients | Study type                  | Article location  | Mean age (years) | Patient characteristics | Primary and secondary goal of study |
|-------------------------------|--------------------|-----------------------------|-------------------|------------------|------------------------|-------------------------------------|
| Cederberg et al. (11)         | 7                  | Retrospective case series   | Meeting abstract  | Unknown          | Severe TBI; 3 underwent DC | Primary: to compare CMD cytokines to common CMD measures, PbtO₂, and ICP  
Secondary: none mentioned |
| Figaji et al. (12)            | 5                  | Unknown                     | Meeting abstract  | Unknown          | Severe TBI             | Primary: to compare CMD cytokine and other CMD measures  
Secondary: none mentioned |
| Guilfoyle et al. (13)         | 12                 | Prospective observational   | Meeting abstract  | Unknown          | Severe TBI             | Primary: to compared CMD cytokine measures in healthy vs. peri-lesional tissue  
Secondary: none mentioned |
| Helmy et al. (14)             | 12                 | Prospective observational   | Manuscript        | Unknown          | Severe TBI             | Primary: to perform a principle component analysis of CMD cytokines to determine cytokine patterns and temporal profiles  
Secondary: none mentioned |
| Helmy et al. (15)             | 12                 | Prospective observational   | Manuscript        | Unknown          | Severe TBI             | Primary: 1. To compare crystalloid vs. albumin perfusate in CMD cytokine recovery.  
2. To compare the cytokine profile in sTBI  
Secondary: not specified |
| Helmy et al. (16)             | 20                 | Prospective RCT             | Manuscript        | 38.9 years (range: 18–61 years) | Severe diffuse TBI; randomized to subcutaneous rhIL-1ra | Primary: 1. To provide safety data in a randomized fashion on rhIL-1ra in sTBI  
2. To describe the impact of rhIL-1ra on CMD cytokine profiles  
Secondary: none mentioned |
| Helmy et al. (17)             | 20                 | Retrospective database analysis | Manuscript        | 38.9 years (range: 18–61 years) | Severe diffuse TBI; randomized to subcutaneous rhIL-1ra | Primary: to retrospectively analyze RCT data on rhIL-1ra administration, to better delineate the temporal change in cytokine profiles  
Secondary: none mentioned |
| Hillman et al. (18)           | 9 (10 total, but failed CMD catheter in 1) | Prospective observational | Manuscript        | Unknown          | Severe brain injury (undisclosed number of aSAH and sTBI patients) | Primary: to evaluate newer microdialysis catheters and their ability to measure various CMD macromolecules (including IL-6) vs. older catheters. Varied perfusates were also analyzed  
Secondary: none mentioned |
| Hillman et al. (19)           | 7 with TBI (14 total; mixed injury sources) | Prospective observational | Manuscript        | Unknown          | sTBI—5 requiring “surgery” | Primary: to determine the CMD cytokine patterns in TBI  
Secondary: none mentioned |
| Hutchinson et al. (20)        | 15                 | Prospective observational   | Manuscript        | 41 years (range: 17–68 years) | Severe TBI             | Primary: to determine the feasibility of measures IL-1α, IL-1β, and IL-1ra in CMD samples  
Secondary: correlation of cytokine to ICP, CPP, and patient outcome |
| Mellergard et al. (21)        | 7 (total 38 patients; only 7 with TBI) | Prospective observational | Manuscript        | Unknown          | Severe TBI             | Primary: to evaluate CMD cytokine profiles immediately after insertion of the CMD catheter  
Secondary: none mentioned |
| Mellergard et al. (22)        | 57 (total 145 patients; only 57 with TBI) | Retrospective case series | Manuscript        | Unknown          | Severe TBI             | Primary: to determine the CMD cytokine responds to TBI  
Secondary: none mentioned |
| Mellergard et al. (23)        | 57 (total 145 patients; only 57 with TBI) | Retrospective case series | Manuscript        | Unknown          | Severe TBI             | Primary: to determine the CMD cytokine responds to TBI  
Secondary: none mentioned |
| Mellergard et al. (24)        | 69                 | Unknown                     | Manuscript        | 45.9 years (range: unknown) | Severe TBI             | Primary: to determine if there is age-related difference in CMD cytokines  
Secondary: none mentioned |
| Mondello et al. (25)          | 6                  | Prospective observational   | Meeting abstract  | Unknown          | Severe TBI             | Primary: to evaluate the temporal profile of CMD and CSF cytokines in TBI  
Secondary: none mentioned |

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intracranial pathology (11–15, 18–25, 27–29). Three studies focused on only those patients with imaging defined “diffuse” brain injury, without extra-axial or large focal intraparenchymal lesions (16, 17, 26).

A total of 267 unique patients with sTBI were described across the 19 studies included in the CMD cytokine review. Thirty-six patients were “diffuse” sTBI only (16, 17, 26), with the remaining being unspecified heterogeneous sTBI pathology. We believe that some of the studies included within this portion of the review may contain duplicate patient information, as marked in Tables 1 and 3. Multiple publications from the same research groups likely were conducted on the same patient populations, yielding unique and separate manuscripts on the same group of patients. Though we must acknowledge it was difficult to determine, in some circumstances, whether CMD cytokine analysis was being conducted on new patient groups or existing banks of samples from previous prospective studies. With that said, our goal for the CMD cytokine scoring review was to provide an overview of all available literature in the area, hence we have included all published papers on CMD cytokines in sTBI within this review.

CSF Cytokine Review

Of the 36 articles included in the CSF cytokine systematic review (20–65), 32 were formal manuscript publications (30–36, 39, 40, 42–61, 63–65) and 4 were meeting abstract publications (37, 38, 41, 62). There were 34 prospective studies, all being observational studies (30–61, 64, 65). One study was a retrospective case series (63). Finally, one study had insufficient information to determine the design (62).

The populations described with in the CSF cytokine studies were almost all sTBI patients with unspecified heterogeneous injury patterns. Three studies documented the inclusion of both moderate-severe patients within the methods (39, 53, 62). We were unable to separate the moderate and sTBI patients within these studies, hence they were all included in the final descriptive statistics.

A total of 1,363 patients were described across all studies included in the CSF cytokine systematic review. The mean age for each study cohort varied significantly across studies. Twenty-one studies included pediatric patients within their studies, either as the primary population of interest or included with adult patients (31–35, 42, 44, 47–50, 52, 54, 55, 57, 59, 60, 63–65). Therapies received by these patients while in the ICU varied significantly, with profound heterogeneity in treatment provided. Details surrounding patient cohort, study design, and concurrent therapies can be found in Tables 2 and 4. We made substantial efforts to exclude duplicate patient data across studies. However, given that many of the papers came from centers of excellence for TBI research, some of the patient data may be cross reported in multiple studies. This could reduce the total overall number of unique patients. It was impossible based on the information provided within the parent studies to tease out all patients which were reported more than once.

Cytokine Measurement Technique

CMD Cytokine Review

Location of the CMD catheter was the following: mixed healthy/peri-lesional tissue in six studies (11, 13, 15, 21–23), peri-lesional in six studies (14, 16–19, 28), healthy tissue in two studies (27, 29), and unknown tissue location in five studies (12, 20, 24–26). Some studies utilized paired microdialysis catheters, one in healthy and one in peri-lesional tissue (13, 15, 22, 23). One study evaluated two catheters in one location (18). Analysis interval for CMD samples was as follows: every 6 h in 12 studies (14–24, 27), every 8 h in 1 study (26), every 3 h in 2 studies (28, 29), and unspecified in 4 studies (11–13, 25). The duration

| Reference | Number of patients | Study type | Article location | Mean age (years) | Patient characteristics | Primary and secondary goal of study |
|-----------|--------------------|------------|-----------------|-----------------|------------------------|-----------------------------------|
| Perez-Barcena et al. (20) | 16 | Prospective observational | Manuscript | 31.8 years (range: 16–65 years) | Severe diffuse TBI | Primary: to determine the cytokine profiles in severe diffuse TBI patients. Secondary: to determine the correlation between cytokines and ICP, PbtO₂, and CT changes. |
| Roberts et al. (27) | 8 | Prospective observational | Manuscript | 43.4 years (range: unknown) | Severe TBI | Primary: to measure the blood/CSF/CMD MMP and cytokine response post-TBI. Secondary: correlation to neurologic exam, ICP, PbtO₂, GOS at discharge. |
| Winter et al. (28) | 3 | Prospective observational | Manuscript | Unknown | Severe TBI | Primary: to describe the technique of cytokine measurement via CMD. Secondary: describe cytokine patterns in TBI. |
| Winter et al. (29) | 14 | Prospective observational | Manuscript | 43.1 years (range: 21–77 years) | Severe TBI | Primary: to evaluate the changes in CMD cytokines post-TBI. Secondary: correlation to patient outcome. |

TBI, traumatic brain injury; sTBI, severe TBI; aSAH, aneurysmal subarachnoid hemorrhage; DC, decompressive craniectomy; CMD, cerebral microdialysis; RCT, randomized control trial; ICP, intracranial pressure; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; LPR, lactate:pyruvate ratio; CT, computed tomography; PbtO₂, partial pressure of oxygen in brain tissue; MMPs, matrix metalloproteins; IL, interleukin; a, alpha; b, beta; ra, receptor analogonist; rh, recombinant human.

*Same patient population reported in both Helmy et al. (14) and Mellergard et al. (15).
*Same patient population described in Helmy et al. (19) and Helmy et al. (17).
*Same patient population reported in both Mellergard et al. (22) and Mellergard et al. (23).
### TABLE 2 | CSF cytokine study characteristics and patient demographics.

| Reference | Number of patients | Study type | Article location | Mean age (years) | Patient characteristics | Primary and secondary goal of study |
|-----------|--------------------|------------|------------------|------------------|------------------------|-----------------------------------|
| Abboud et al. (30) | 31 | Prospective observational | Manuscript | 31.6 years (range: unknown) | Severe TBI | Primary: to describe the correlation between CSF cytokine profiles and outcome at 6 and 12 months Secondary: none mentioned |
| Bell et al. (31) | 15 | Prospective observational | Manuscript | 6.1 years (range: 0.1–16 years) | Severe TBI | Primary: to determine the relationship between IL-6 and IL-10 with patient outcome Secondary: to compare CSF cytokine levels to non-TBI control subjects (n = 20) |
| Chiaretti et al. (32) | 29 | Prospective observational | Manuscript | 9.7 years (range: 1.3–15.6 years) | Severe TBI | Primary: to determine the association between IL-6 and patient outcome Secondary: to determine the correlation between IL-6 and NGF in CSF. Also to compare to non-TBI control patients (n = 31) |
| Chiaretti et al. (33) | 27 | Prospective observational | Manuscript | 8.8 years (range: 1.3–15.6) | Severe TBI | Primary: to determine the association between IL-1b, IL-6, NGF, BDNF, and GDNF with patient outcome Secondary: none mentioned |
| Chiaretti et al. (34) | 14 | Prospective observational | Manuscript | 7.8 years (range: 0.3–15.6 years) | Severe TBI | Primary: to determine the relationship between IL-1b and IL-6 with patient outcome Secondary: to compare cytokine expression to obstructive hydrocephalus controls |
| Hans et al. (35) | 11 | Prospective observational | Manuscript | 36.7 years (range: 16–67) | Severe TBI | Primary: to determine the association between IL-6 and sIL-6R to patient outcome Secondary: to compare these CSF cytokine levels to those in plasma |
| Hayakata et al. (36) | 53 | Prospective observational | Manuscript | 34–49 years | Severe TBI | Primary: to determine the association between TNF-a, IL-1, IL-6, IL-8, and IL-10 with patient outcome Secondary: to determine the association between cytokines and S100B expression in CSF. Also compare cytokines to ICP |
| Jamil et al. (37) | 61 | Prospective observational | Meeting abstract | Unknown “adults” | Severe TBI | Primary: to determine the relationship between acute measures of CSF cytokines and PTD at 6 and 12 months Secondary: none mentioned |
| Juengst et al. (38) | 25 | Prospective observational | Meeting abstract | Unknown “adults” | Severe TBI | Primary: to determine the association between acute cytokine levels and apathy at 6 and 12 months post-injury Secondary: none mentioned |
| Juengst et al. (39) | 37 | Prospective observational | Manuscript | “Adults” Unclear overall mean age | Moderate–severe TBI | Primary: to determine the relationship between TNF-a and disinhibition/suicidality post-TBI Secondary: compare levels in CSF and serum to healthy controls (n = 15) |
| Juengst et al. (40) | 50 | Prospective observational | Manuscript | 31.3 years (range: unknown) | Severe TBI | Primary: to determine the relationship between acute CSF cytokine profiles and the risk of PTD at 6 and 12 months post-injury Secondary: none mentioned |
| Kirchhoff et al. (41) | 23 | Prospective observational | Meeting abstract | Unknown | Severe TBI | Primary: to determine the IL-10 response in CSF in TBI patients. Also determine the relationship to outcome. Secondary: compared CSF in TBI to elective surgical patients (n = 10) |
| Kossman et al. (42) | 22 | Prospective observational | Manuscript | 41 years (range: 17–73) | Severe TBI | Primary: to determine the relationship between CSF IL-6 and NGF. Also determine the association to patient outcome. Secondary: compare IL-6 and NGF in controls (n = 3) |

(Continued)
### TABLE 2 | Continued

| Reference | Number of patients | Study type | Article location | Mean age (years) | Patient characteristics | Primary and secondary goal of study |
|-----------|-------------------|------------|-----------------|-----------------|------------------------|-----------------------------------|
| Kumar et al. (43) | 114 | Prospective observational | Manuscript | Unclear overall mean age | Severe TBI | Primary: to determine the relationship of IL-6 in CSF to serum values and patient outcome  
Secondary: compare CSF levels in non-TBI controls (*n* = 23) |
| Kumar et al. (44) | 111 | Prospective observational | Manuscript | Unknown (range: 16–75) | Severe TBI | Primary: to utilize PCA to determine clusters of cytokines associated with patient outcome  
Secondary: to determine a temporal pattern of cytokine clusters and relationship to outcome |
| Kushi et al. (45) | 22 | Prospective observational | Manuscript | 45 years (range: unknown) | Severe TBI | Primary: to compare CSF and Serum IL-6/IL-8 levels and determine the association to patient outcome  
Secondary: none mentioned |
| Nwachuku et al. (46) | 32 | Prospective observational | Manuscript | 31 years (range: unknown) | Severe TBI | Primary: to determine the association between various CSF cytokines and patient outcome  
Secondary: none mentioned |
| Santarsei et al. (47) | 91 | Prospective observational | Manuscript | 35.8 years (range: 16–73) | Severe TBI | Primary: to identify CSF cytokines associated with patient outcome. Also determine association between cytokines and neuroendocrine cortisol function  
Secondary: none mentioned |
| Shiozaki et al. (48) | 35 | Prospective observational | Manuscript | 39 years (range: 14–77 years) | Severe TBI | Primary: to determine the association between CSF cytokine profiles and patient outcome  
Secondary: to determine the association between cytokines and ICP |
| Singhal et al. (49) | 36 | Prospective observational | Manuscript | 34.4 years (range: 17–68 years) | Severe TBI | Primary: to determine the association between cytokines and electrophysiologic/functional patient outcome  
Secondary: none mentioned |
| Whalen et al. (50) | 27 | Prospective observational | Manuscript | Unknown “children” | Severe TBI | Primary: to determine the association between CSF IL-8 levels and patient outcome  
Secondary: to determine the association between CSF IL-8 in TBI patients and non-TBI controls (*n* = 24) |

**Neurophysiologic association**

| Reference | Number of patients | Study type | Article location | Mean age (years) | Patient characteristics | Primary and secondary goal of study |
|-----------|-------------------|------------|-----------------|-----------------|------------------------|-----------------------------------|
| Muller et al. (51) | 25 | Prospective observational | Manuscript | 41 years (range: unknown) | Severe TBI | Primary: to evaluate the relationship between CSF IL-6, IL-8, and IL-10 with TCD defined CBF  
Secondary: none mentioned |
| Stein et al. (52) | 14 with CSF cytokines | Prospective observational | Manuscript | 31.6 years (range: unknown) | Severe TBI | Primary: to determine the relationship between CSF cytokines with ICP and patient outcome  
Secondary: none mentioned |

**Nil association studies**

| Reference | Number of patients | Study type | Article location | Mean age (years) | Patient characteristics | Primary and secondary goal of study |
|-----------|-------------------|------------|-----------------|-----------------|------------------------|-----------------------------------|
| Amick et al. (53) | 24 | Prospective observational | Manuscript | 5.4 years (range: 0.2–16 years) | Moderate–severe TBI | Primary: to determine the association between IL-2, IL-4, IL-6 and IL-12 with patient outcome  
Secondary: compare IL levels in CSF to non-TBI controls (*n* = 12) |
| Buttram et al. (54) | 36 | Prospective observational | Manuscript | 6.9 years (range: unknown) | Severe TBI | Primary: to measure CSF cytokines and determine the impact of moderate hypothermia on expression. Also determine the link between CSF cytokines and outcome  
Secondary: compared CSF cytokine profile to non-TBI controls (*n* = 10) |
| Cauka et al. (55) | 28 | Prospective observational | Manuscript | 36 years (range: 16–67 years) | Severe TBI | Primary: to determine the association between various CSF and serum cytokines  
Secondary: to determine the association between CSF cytokines with outcome and ICP |

(Continued)
of sample collection varied as well, with the typical collection period of 5–7 days.

Numerous different panels of cytokines were evaluated within the CMD samples, across the studies included within the review. The most commonly studied cytokines included IL-1b, IL-1ra, IL-6, IL-8, and IL-10. Details of CMD technique and catheter locations are listed in Table 3.

### CSF Cytokine Review

Sampling of CSF was conducted through external ventricular drains (EVDs) in almost all patients described within the studies included in the CSF cytokine systematic review (30–65). Sampling and analysis frequency varied significantly from study to study with sampling occurring from every 6 h to daily. Duration of sampling varied as well, up to 21 days post-injury (35).

| Reference | Number of patients | Study type | Article location | Mean age (years) | Patient characteristics | Primary and secondary goal of study |
|-----------|--------------------|------------|------------------|------------------|------------------------|-------------------------------------|
| Diamond et al. (66) | 59 with CSF cytokines | Prospective observational | Manuscript | Unclear mean age for CSF cytokine cohort | Moderate–severe TBI | Primary: to determine the association between serum and CSF cytokine levels with the development of PTE <br>Secondary: to compare serum and CSF levels with healthy control values. Also assess genetic IL-1b associations with PTE |
| Goodman et al. (57) | 23 | Prospective observational | Manuscript | 32.7 years (range: 15–67 years) | Severe TBI | Primary: to compare CSF and jugular venous cytokine profiles <br>Secondary: to compare cytokine profiles to ICP and CPP |
| Gopcevic et al. (58) | 20 | Prospective observational | Manuscript | 53 years (range: unknown) | Severe TBI | Primary: to determine the association between jugular serum and CSF IL-8 levels with in-hospital mortality <br>Secondary: to determine the association between jugular plasma and CSF IL-8 levels |
| Lenzlinger et al. (59) | 41 | Prospective observational | Manuscript | 38 years (range: 15–74 years) | Severe TBI | Primary: to determine the association between CSF and serum cytokines with patient outcome <br>Secondary: to compared serum and CSF cytokine profiles |
| Maier et al. (60) | 29 | Prospective observational | Manuscript | 54.8 years (range: 16–85 years) | Severe TBI | Primary: to determine the CSF profile for two soluble tumor necrosis factor receptors (TNFR's) <br>Secondary: to determine the association between CSF sTNFR levels and patient outcome |
| Maier et al. (61) | 29 | Prospective observational | Manuscript | 45.5 years (range: 18–75 years) | Severe TBI | Primary: to evaluate the correlation between CSF and serum cytokine levels <br>Secondary: to determine the association between cytokine profile and patient outcome. Also, compare to CSF from healthy volunteers (n = 35) |
| Morganti-Kossmann et al. (62) | 42 | Unclear | Meeting abstract | Unknown | Severe TBI with various primary and secondary injuries | Primary: to determine the association between serum and CSF cytokines with injury patterns <br>Secondary: to determine the association between cytokine profiles and patient outcome. Also, compare levels to healthy controls |
| Newell et al. (63) | 66 | Retrospective case series | Manuscript | 6 years (range: 0.1–16 years) | Severe TBI | Primary: to measure inflammatory markers in the CSF linked to T-cell activation <br>Secondary: to comment on the association between these markers and patient outcome. Also compare levels to healthy controls |
| Ross et al. (64) | 50 | Prospective observational | Manuscript | 21 years (range: 4–70 years) | Severe TBI | Primary: to compare serum and CSF TNF-a in TBI patients to healthy controls (n = 46) <br>Secondary: to compare TNF-a levels to patient outcome |
| Uzan et al. (65) | 11 | Prospective observational | Manuscript | 28.5 years (range: 2.5–53 years) | Severe TBI | Primary: to determine the association between NO metabolic products and IL-8 <br>Secondary: to determine the association between NO and IL-8 with patient outcome |

TBI, traumatic brain injury; sTBI, severe TBI; RCT, randomized control trial; ICP, intracranial pressure; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CBF, cerebral blood flow; PbtO2, partial pressure of oxygen in brain tissue; TCD, Transcranial Doppler; DC, decompressive craniectomy; IL, interleukin; a, alpha; b, beta; ra, receptor antagonist; TNF, tumor necrosis factor; NO, nitrous oxide; TNFR, tumor necrosis factor receptor; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; GDNF, glial-derived neurotrophic factor; PTE, post-traumatic epilepsy; PTD, post-traumatic depression; PCA, principle component analysis.
| Reference          | Catheter location and measured CMD cytokines | Intervenional therapies applied during measurement | Primary outcome | Secondary outcome | Complications to CMD | Conclusions                                                                 |
|--------------------|---------------------------------------------|--------------------------------------------------|-----------------|------------------|----------------------|-----------------------------------------------------------------------------|
| Cederberg et al.   | Mixed locations IL-6/IL-8                   | Not specified                                    | 6/7 patients survived IL-6 and IL-8 was increased in survivors Peri-lesional location of CMD catheter yielded higher IL-6 and IL-8 levels | N/A              | Not specified         | IL-6/IL-8 are increase in CMD both in “healthy” and peri-lesional tissue   |
| Figaji et al.      | Unclear locations IL-1a, IL-1b, IL1-ra, IL-6, IL-8, and IL-10; VEGF, and MCP-1 | Not specified                                    | Variable individual cytokine responses IL-6 and IL-8 were the most consistently elevated across all patients | N/A              | Not specified         | IL-6/IL-8 are consistently increased in CMD in pediatric sTBI              |
| Guilfoyle et al.   | 2x CMD catheters per patients (1 healthy tissue, 1 peri-lesional) “42 cytokines” IL-7 and IL-8 | Not specified                                    | IL-7 (p < 0.05) and IL-8 (<0.05) were found to be higher in peri-lesional tissue IL-1b and interferon gamma (INF-g) were higher in peri-lesional tissue within the first 72 h post-injury | N/A              | Not specified         | IL-7/IL-8 are higher in peri-lesional tissue IL-1b and INF-g are higher in peri-lesional tissue within the first 72 h |
| Helmy et al.       | Area of “diffuse injury” EGF, Eotaxin, FGF-2, fms-like tyrosine kinase 3 (Flt3) Ig, Frac, G-CSF, GM-CSF, GRO, IFN-a2, IFN-g, IL-1a, IL-1b, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-17, inducible protein (IP)-10, MCP-1, MCP-3, MDC, MIP-1a, MIP-1b, PDGF-AA, PDGF-AAAB, regulated on activation, normal T cell expressed and secreted (RANTES), sCD40L, sIL-2R, TGF-a, TNF q6 h pooled sampling over 5 days 3.5% human abumin solution perfusate | Not specified | IL-1b and TNF are covariate IL-1ra and IL-1a are covariate MIP-1a and MIP-1b were coexpressed Earlier temporal expression of IL-6, GRO, G-CSF, IP10 compared to IL-10, MCP-3, IL-17 | N/A | Not specified | PCA of CMD cytokine profiles yields covariate relationships between specific cytokines and temporal expression pattern |
| Helmy et al.       | Double side-by-side in six patients (to analyze perfusate), and single catheter in six patients—unclear tissue location EGF, Eotaxin, FGF-2, Rt3 Ig, Frac, G-CSF, GM-CSF, GRO, IFN-a2, IFN-g, IL-1a, IL-1b, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-17, IP-10, MCP-1, MCP-3, MDC, MIP-1a, MIP-1b, PDGF-AA, PDGF-AAAB, regulated on activation, normal T cell expressed and secreted (RANTES), sCD40L, sIL-2R, TGF-a, TNF q6 h pooled sampling over 5 days Assessed both crystalloid and 3.5% human abumin solution perfusate | Unclear; two patients under went DC for refractory ICP | 1. Albumin perfusate led to significantly higher fluid recovery compared to crystalloid. Albumin perfusate led to significantly higher cytokine recovery (18 cytokines) 2. Brain concentrations of 23 cytokines were significantly higher than jugular plasma concentrations (ex. IL-1ra, IL-1a, IL-1b, IL-6, IL-8, IL-10, IL-12p70, MCP-1) Many cytokines displayed a temporal expression, with expression within the first 72 h [e.g., TNF, IL-7, IL-8, MIP1a, sCD40L, IL-1β, GRO, PDGF, AA, RANTES, MIP-1b, IL-1ra, G-CSF, IP10, IL-6] | N/A | Not specified | 1. Albumin CMD perfusate led to increased fluid and cytokine recovery 2. Brain cytokine concentrations were significantly higher than jugular plasma for 23 cytokines. Many cytokines displayed a temporal expression pattern with early expression post-injury (72 h) |
| Reference               | Catheter location and measured CMD cytokines                                                                 | Interventional therapies applied during measurement                                                                 | Primary outcome                                                                                                                                                                                                                                                                                                                                 | Secondary outcome | Complications to CMD | Conclusions                                                                                                                                                                                                                     |
|------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| bHelmy et al. (16)     | Right frontal location (in setting of diffuse injury) 42 cytokine array q6 h pooled sampling for 5 days Isotonic central nervous system perfusate | Group 1 (n = 10): after baseline 6 h CMD samples; received 100 mg rhIL-1ra subcut Repeated q24 h for total of five doses Group 2 (n = 10): control group No specifics on other ICU therapies | 1. No complications secondary to rhIL-1ra were seen. 2. CMD IL-1ra concentrations were significantly higher in the treatment group vs. control (p = 0.02), with variation over time (p < 0.0001) 3. MDC was significantly lower in the rhIL-1ra (p = 0.05)                                                                 | N/A               | Not specified          | 1. rhIL-1ra appears safe in severe diffuse TBI 2. rhIL-1ra reaches the brain extracellular fluid 3. MDC was lower in the rhIL-1ra group                                                                                                                                                            |
| bHelmy et al. (17)     | Right frontal location (in setting of diffuse injury) 42 cytokine array q6 h pooled sampling for 5 days 3.5% human albumin perfusate | Group 1 (n = 10): after baseline 6 h CMD samples; received 100 mg rhIL-1ra subcut Repeated q24 h for total of five doses Group 2 (n = 10): control group No specifics on other ICU therapies | Based on PCA it was found that cytokines associated with macrophage recruitment were decreased in the rhIL-1ra group (MIP-1a, MCP-3, Fractalkine, GM-CSF)                                                                                                                                                         | N/A               | Not specified          | CMD macrophage base cytokines are decreased in rhIL-1ra-treated patients                                                                                                                                                      |
| Hillman et al. (18)    | Paired CMD catheter placement in peri-lesional tissue IL-6 q6 h pooled analysis Ringer/s/dextran 60 or human albumin perfusate | Not specified                                                                                                                                                                      | CMD IL-6 concentrations varied depending on underlying condition and secondary injury (i.e., ischemia) The temporal expression of CMD measured IL-6 varied between patients                                                                                                                                                                    | N/A               | 1 catheter membrane failure | CMD IL-6 concentrations varied from patient to patient and depending on initial and secondary injury patterns                                                                                                                                                                      |
| Hillman et al. (19)    | Peri-lesional tissue IL-1b, IL-6 q6 h pooled analysis 3.5% human albumin perfusate                                | Not specified                                                                                                                                                                      | CMD biochemical evidence of ischemia (LPR > 30 and glutamate >80 μmol/L for 24 h period) was associated with significant IL-6 increase (p < 0.01), which subsided after ~90 h post-injury (p < 0.001) In those patients without biochemical ischemia, IL-6 levels spiked in the first 48 h (p < 0.01) IL-1b activation was less commonly observed (only 53% of measures) | N/A               | Not specified          | CMD IL-6 displays a correlation with CMD biochemical ischemia and a temporal correlation post-injury (in the absence of biochemical ischemia)                                                                                                                       |

(Continued)
| Reference | Catheter location and measured CMD cytokines | Interventional therapies applied during measurement | Primary outcome | Secondary outcome | Complications to CMD | Conclusions |
|-----------|----------------------------------------------|---------------------------------------------------|-----------------|------------------|----------------------|-------------|
| Hutchinson et al. (20) | Unclear tissue location (“frontal cortex”) IL-1a, IL-1b, IL-1ra q6 h pooled samples (mean no. samples = 9.1; range = 4–23) Isotonic central nervous system perfusate | Not specified | IL-1a and IL-1b concentrations were lower than IL-1ra A positive correlation between IL-1ra and IL-1b was seen (p = 0.028) No correlation between IL-1b and IL-1ra was found No correlation between cytokines and CMD glucose, glutamate, LPR | ICP: ICP was negatively correlated to IL-1ra (p = 0.041) No correlation between other cytokines and ICP No correlation between cytokines and CPP Outcome: significant relationship between mean IL-1ra levels and poor outcome (dichotomized GOS at 6 months) (p = 0.018)—high IL-1ra was associated with good outcome No relationship between IL-1a and IL-1b with outcome | Not specified | 1. The appears to be a correlation between IL-1ra and IL-1b 2. There is a negative correlation between ICP and IL-1ra 3. Mean IL-1ra levels correlate to patient outcome at 6 months |
| Mellergard et al. (21) | Mixed locations; some patients with two catheters (unclear which patients) IL-1b, IL-6, IL-8, FGF-2, MIP-1b, RANTES, VEGF, IL-10 q6 h pooled samples for 36 h Ringer-dextran 60 perfusate | Not specified | IL-1b peaked in the first 12 h period IL-6 peaked after 12 h post-insertion IL-8 peaked within the first 6 h post-insertion MIP-1b peaked within the first 6 h post-insertion FGF-2 peaked within the first 6 h post-insertion IL-10, VEGF, and RANTES did not show a temporal profile | N/A | Not specified | CMD catheter insertion leads to IL-1b/IL-6/IL-8/MIP-1b within the first 6–12 h, which then decreases during the subsequent time afterward |
| Reference | Catheter location and measured CMD cytokines | Interventional therapies applied during measurement | Primary outcome | Secondary outcome | Complications to CMD | Conclusions |
|-----------|---------------------------------|-----------------------------------------------|----------------|----------------|---------------------|-------------|
| Mellergard et al. (22) | Paired catheters (1 peri-lesional; 1 healthy tissue) — used the catheter with highest glycerol levels for measuring cytokines | Not specified; various surgical procedure for hemotomas in TBI group | IL-1β increased during the first 48 h, and then decreased | N/A | Not specified | IL-1β and IL-6 display a peak elevation during the first 48 h post-TBI and IL-10 remains elevated through the first 7 days post-TBI |
| | | | IL-6 increased over the first 48 h, and then decreased | | | |
| | | | IL-10 remained elevated throughout the measurement period | | | |
| Mellergard et al. (23) | Paired catheters (1 peri-lesional; 1 healthy tissue) — used the catheter with highest glycerol levels for measuring cytokines | Not specified; various surgical procedure for hemotomas in TBI group | FGF-2 levels peaked at day 3 post-TBI VEGF levels peaked on day 2 post-TBI | N/A | Not specified | FGF-2/VEGF levels peaked on days 3 and 2 post-TBI |
| Mellergard et al. (24) | Unclear location | Local protocols; not otherwise specified | IL-1β, IL-8, and IL-10 did not display age-related differences VEGF, MIP-1β, and RANTES were different in the <25 years age group vs. over 25 years age FGF-2 levels were significantly higher in the >65-year-old group (p < 0.0001) | N/A | Not specified | There may be an age-related difference in the expression of VEGF, MIP-1β, RANTES, and FGF-2 post-TBI |
| Mondello et al. (25) | Unclear location | Not specified | IL-6 showed high initial values that then decreased, in contrast IL-1beta, TNF-alpha and INF-gamma showed later elevations UCH-L1 levels negatively correlated (p < 0.05) with IL-1beta, widely used biomarker of inflammation | N/A | Not specified | Variable cytokine temporal profiles are seen post-TBI |
| Perez-Barcena et al. (26) | Right frontal location; unclear tissue quality | Varied ICP/CPP directed therapies; some use of barbiturates | IL-1β, IL-6, and IL-8 peaked during first 24 h post-injury IL-10 remained unchanged during the sampling period | ICP: no correlation between IL-1β, IL-6, IL-8 and IL-10 with ICP PbtO₂: no clear correlation between cytokines and PbtO₂ | Not specified | 1. IL-1β, IL-6 and IL-8 peaked within the first 24 h post-injury 2. No clear association was found between cytokines and ICP PbtO₂, CT changes |

(Continued)
### TABLE 3 | Continued

| Reference               | Catheter location and measured CMD cytokines                                                                 | Intervventional therapies applied during measurement | Primary outcome                                                                 | Secondary outcome | Complications to CMD | Conclusions                                                                 |
|-------------------------|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|---------------------------------------------------------------------------------|-------------------|-----------------------|-----------------------------------------------------------------------------|
| Roberts et al. (27)     | Healthy tissue IL-1a, IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, and TNF-a q6 h pooled analysis (up to 156 h of monitoring) Isotonic central nervous system perfusate | Varied; one patient had DC                          | IL-1a, IL-1b, and TNF-a were elevated initially after injury                     | CT: no association found between cytokines and subsequent CT defined swelling or lesion change |
|                         |                                                                                                               |                                                     | IL-6 and IL-8 were substantially higher in the CMD compared to other cytokines  |                   |                       | IL-1a, IL-1b, TNF-a, IL-6 and IL-8 predominate the cytokine response post TBI |
|                         |                                                                                                               |                                                     | IL-5 was barely detectable                                                     |                   |                       | 2. Various patterns of MMP changes are seen in correlation with changes in cytokine expression |
|                         |                                                                                                               |                                                     | Similar cytokine concentrations were seen in CSF and CMD, which were both substantially higher than jugular plasma sampled |                   |                       | 3. IL-1b, IL-4 and TNF-a levels were higher in those with loss of pupillary reactivity |
|                         |                                                                                                               |                                                     | Increase CMD concentrations of MMP-8 and MMP-9 were seen with increases in the levels of IL-1a, IL-2, and IL-1a and -2 and TNF-a, respectively. In contrast, the CMD levels of MMP-7 decreased with increases in IL-1b, IL-2, and IL-6 |                   |                       | 4. IL-6 and IL-8 correlation with CPP. TNF-a correlations with ICP |
|                         |                                                                                                               |                                                     | Neuro Exam: IL-1b, IL-4 and TNF-a levels were substantially higher in those with loss of pupillary reactivity |                   |                       |                                                                   |
|                         |                                                                                                               |                                                     | ICP: IL-2 displayed a negative correlation to ICP                              |                   |                       |                                                                   |
|                         |                                                                                                               |                                                     | TNF-a displayed a negative correlation to ICP                                   |                   |                       |                                                                   |
|                         |                                                                                                               |                                                     | CPP: IL-6 and IL-8 displayed a negative correlation to CPP                      |                   |                       |                                                                   |
|                         |                                                                                                               |                                                     | PbtO₂: no correlation found between cytokines and PbtO₂                         |                   |                       |                                                                   |
|                         |                                                                                                               |                                                     | Outcome: no correlation between cytokines and GCS                              |                   |                       |                                                                   |

(Continued)
TABLE 3 | Continued

| Reference          | Catheter location and measured CMD cytokines | Interventional therapies applied during measurement | Primary outcome | Secondary outcome | Complications to CMD | Conclusions |
|--------------------|---------------------------------------------|-----------------------------------------------------|-----------------|-------------------|----------------------|-------------|
| Winter et al. (28) | Peri-lesional IL-1β, IL-6, NGF q3 h sampling for 6 days Normal saline perfusate | Not specified | CMD cytokine analysis is feasible and safe | Peak cytokine levels were seen within the first 36 h post-injury IL-1β predominated with substantially higher concentrations compared to IL-6 and NGF IL-6 was high in survivors, while NGF was lower in non-survivors | None | 1. CMD cytokine analysis is feasible 2. IL-1β may be the predominant CMD cytokine expressed 3. Unclear patterns in survivors vs. non-survivors |

| Winter et al. (29) | Healthy tissue IL-1β, IL-6, NGF q3 h sampling Normal saline perfusate | Not specified | Higher IL-6 was seen in survivors (p = 0.04) Peak IL-6 correlated to GOS at 6 months (p = 0.03) Peak NGF:IL-1β ratios were significantly lower in survivors (p = 0.01) | N/A | None | IL-6 levels in CMD samples may correlation to survival and GOS at 6 months |

TBI, traumatic brain injury; sTBI, severe TBI; GOS, Glasgow outcome scale; CMD, cerebral microdialysis; RCT, randomized control trial; ICP, intracranial pressure; CT, computed tomography; PbtO2, brain tissue oxygen monitoring; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; LPR, lactate:pyruvate ratio; DC, decompressive craniectomy; µmol, micromolar; mm Hg, millimeters of mercury; L, liter; µmol, micromolar; IL, interleukin; α, alpha; β, beta; γ, gamma; TNF, tumor necrosis factor; INF, interferon; MCP, monocyte chemoattractant protein; MIPs, macrophage inflammatory proteins; TGF, transforming growth factor; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; GDNF, glial-derived neurotrophic factor; TNFR, tumor necrosis factor receptor; GM-CSF, granulocyte macrophage colony stimulating factor; sVCAM, soluble vascular cell adhesion molecule; sICAM, soluble intracellular adhesion molecule; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; MDC, macrophage-derived chemokine; FGF, fibroblast growth factor receptor.

*aSame patient population reported in both Helmy et al. (14) and Helmy et al. (15).*

*bSame patient population described in Helmy et al. (16) and Helmy et al. (17).*

*cSame patient population reported in both Mellegard et al. (22) and Mellegard et al. (23).*
| Reference | Interval of cytokine measure | Measured CMD cytokines | Interventional therapies applied during measurement | Outcome(s) of interest (patient outcome, neurophysiologic outcome, tissue outcome) | Other outcomes | Conclusions |
|-----------|-----------------------------|------------------------|-----------------------------------------------------|---------------------------------------------------------------------------------|--------------|-------------|
| Abboud et al. (30) | q12-h Intervals for 5 days | IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, MIP-1α, MIP-1β, TNF-α, VEGF | Not specified | GOS at 6 and 12 months post-injury Statistically significant differences in IL-4, IL-5, IL-6, IL-8, IL-13, and TNF-α (all \( p < 0.05 \)) were observed between TBI survivors vs. non-survivors over 5 days | N/A | Elevated IL-4, IL-6, IL-8, IL-23, and TNF-α levels may be associated with poor outcome at 6 and 12 months Similarly, low IL-5 and IL-13 may be associated with poor outcome |
| Bell et al. (31) | q24-h Intervals for 3 days | IL-6, IL-10 | High variable; barbiturates and various ICP/CPP-directed therapies | Mortality (at unclear interval) IL-6 is not associated with mortality IL-10 is associated with mortality (\( p = 0.022 \)) | IL-6 and IL-10 levels were increased compared to controls | Elevated IL-10 levels may be associated with mortality |
| Chiaretti et al. (32) | At 2 and 48 h post-injury | IL-6, NGF | Highly protocolized therapy; seemingly homogenous between patients | GOS at 6 months Low IL-6 and NGF at 2 h post-injury was associated with good outcome (\( p < 0.01 \)) Increased IL-6 variation between the two time points was correlated with better outcome | IL-6 and NGF were both elevated and increased between the two sampling periods IL-6 and NGF were positively correlated at both time periods | Lower IL-6 and NGF levels early post-TBI may be associated with better outcome at 6 months |
| Chiaretti et al. (33) | At 2 and 48 h post-injury | IL-1β, IL-6, NGF, BDNF, GDNF | Highly protocolized therapy; seemingly homogenous between patients | GOS at 6 months Low NGF at 2 h (\( p < 0.01 \)) and high NGF/IL-6 (\( p = 0.02/p < 0.01 \)) at 48 h were associated with better outcome Low IL-1β at 48 h was associated with better outcome (\( p < 0.01 \)) | N/A | Low initial NGF, followed by increased NGF/IL-6 may be associated with good outcome at 6 months Low IL-1β at 48 h may be associated with better outcome at 6 months |
| Chiaretti et al. (34) | At 2 and 24 h post-injury | IL-1β and IL-6 | Highly protocolized therapy; seemingly homogenous between patients | Dichotomized GOS at 6 months (good = 4 or 5; poor = 3 or less) Higher CSF IL-1β and IL-6 at both 2 h and 24 h were seen in those patients with poor outcome at 6 months | IL-1β and IL-6 at 2 h were higher in the TBI cohort | Elevated IL-1β and IL-6 at both 2 and 24 h post-injury may be associated with poor outcome at 6 months |
| Hans et al. (35) | Daily CSF samples up to 21 days post-injury | IL-6 and sIL-6R | Not specified | Dichotomized GOS at 6 months (good = 4 or 5; poor = 3 or less) High IL6/sIL-6R was associated with poor outcome at 6 months | CSF levels of IL-6 and sIL-6R were higher than compared to plasma | Elevated IL-6/sIL-6R may be associated with poor outcome at 6 months |
| Hayakata et al. (36) | 6, 12, 24, 48, 72, and 96 h after injury | TNF-α, IL-1, IL-6, IL-8, and IL-10 | Varied therapies; hypothermia and other ICP/CPP-directed approaches | Dichotomized GOS at 6 months (good = 4 or 5; poor = 3 or less) CSF IL-1β was found to be higher in those with poor outcome | ICP: IL-1β was significantly positively correlated with ICP throughout the entire study (\( p < 0.05 \)) | 1. Elevated IL-1β may be associated with poor outcome at 6 months 2. Elevated IL-1β may be associated with elevated ICP |
### TABLE 4 | Continued

| Reference | Interval of cytokine measure | Measured CMD cytokines | Intervventional therapies applied during measurement | Outcome(s) of interest (patient outcome, neurophysiologic outcome, tissue outcome) | Other outcomes | Conclusions |
|-----------|-----------------------------|------------------------|-----------------------------------------------------|--------------------------------------------------------------------------------|--------------|-------------|
| Jamil et al. (37) | Unclear interval; *“acute”* period post-TBI | IL-1β, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, TNF-α, sICAM-1, sVCAM-1, sFAS | Not specified | Patient health questionnaire (PHQ-9) at 6 and 12 months post-injury Acute CSF IL-6 (p = 0.008), IL-8 (p = 0.034), and ICAM1 (p = 0.025) levels were higher among patients who would go on to develop depression 6 months after injury Acute CSF TNF-α (p = 0.036), IL-4 (p = 0.007), and IL-1β (p = 0.001) levels were individually associated with lower depression risk at 12 months post-injury | N/A | 1. Elevated IL-6 and IL-8 may be associated with depression at 6 2. TNF-α, IL-4, and IL-1β may be associated with lower chance of depression at 12 months |
| Juengst et al. (38) | Within first week of injury | IL-4, IL-5, IL-8, IL-12, TNF-α, sVCAM, sICAM | Not specified | Apathy subscale of the frontal systems behavior scale, collected at 6 and 12 months post-TBI Higher acute CSF IL5, sVCAM, and sICAM with apathy at 6 months and lower acute serum TNFalpha, IL8, and IL5 with apathy at 12 months (p < 0.05) | N/A | Higher acute CSF IL5, sVCAM, and sICAM with apathy at 6 months and lower acute serum TNFalpha, IL8, and IL5 with apathy at 12 months |
| Juengst et al. (39) | 2 times daily for 6 days | TNF-α | Not specified | At 6 and 12 months post-injury, FrSBe disinhibition subscale; suicidal endorsement was assessed by the PHQ-9 No relationship between TNF-α in CSF and suicidality at 6 or 12 months Acute serum TNFα levels were inversely associated with 12-month disinhibition (r = 0.520, p = 0.027) and achieved borderline significance with 6-month disinhibition (r = 0.470, p = 0.057) TBI patients had significantly higher CSF TNF-α levels compared to controls | | Acute levels of TNF-α may correlate to 6 and 12 month rates of disinhibition |
| Juengst et al. (40) | 2 times daily up to 6 days | IL-1β, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, TNF-α, sVCAM-1, sICAM-1, sFAS | Not specified | PHQ-9 was administered to participants at 6 and 12 months after injury The inflammatory cell surface markers sVCAM-1, sICAM-1, and sFAS in the CSF were each positively associated with PTD at 6 months (p < 0.02 for all comparisons). The cytokine IL-8 was positively associated with PTD at 12 months (p < 0.02), while the cytokine IL-7 was inversely associated with PTD at 12 months (p < 0.05) | IL-1β, IL-4, IL-6, IL-7, IL-8, IL-10, TNF-α, sVCAM-1, sICAM-1, and sFAS (p < 0.05) were significantly elevated compared to controls | 1. Elevated sVCAM-1, sICAM-1 and sFAS may be associated with PTD at 6 months 2. Elevated IL-7 and IL-8 may be associated with PTD at 12 months |
| Kirchhoff et al. (41) | Upon EVD insertion, then at 12, 24, and 48 h post-injury | IL-10 | Not specified | Mortality at unspecified interval IL-10 was significantly higher in non-survivors | IL-10 was higher at all time points compared to non-TBI controls | Elevated CSF IL-10 at admission was associated with mortality |

(Continued)
| Reference | Interval of cytokine measure | Measured CMD cytokines | Interventional therapies applied during measurement | Outcome(s) of interest (patient outcome, neurophysiologic outcome, tissue outcome) | Other outcomes | Conclusions |
|-----------|-----------------------------|------------------------|-----------------------------------------------------|---------------------------------------------------------------------------------|----------------|-------------|
| Kossmann et al. (42) | q24 h for unclear duration Control group: non-TBI patients (1 VPS and 2 Dx LP) | IL1b, IL-6, TNF-a, NGF | Various therapies; heterogeneous across population | Dichotomized GOS at 3 months (good = 4 or 5; poor = 3 or less) High IL-6 levels were associated with NGF presence in CSF NGF levels were elevated in those with better outcomes | IL-6 and NGF were high in TBI patients compared to control samples | N/A | 
| Kumar et al. (43) | 2 times daily for 5 days | IL-6 | Not specified | Dichotomized GOS at 6 and 12 months (good = 4 or 5; poor = 3 or less) Association between high IL-6 upon admission and 6-month GOS (p = 0.003) IL-6 levels were higher in TBI compared to controls | High IL-6 during the first 5 days of injury may be associated with poor outcome at 6 months |
| Kumar et al. (44) | 2 times daily for up to 5 days | IL-1β, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, TNF-a, sVCAM-1, sICAM-1, sFAS | Not specified | Trichotomized GOS at 6 and 12 months (good = 4 or 5; poor = 3 or 2; dead = 1) Individuals in cluster 1 (increased sICAM-1, sFAS, IL-10, IL-6, sVCAM-1, IL-5, and IL-8) had a 10.9 times increased likelihood of GOS scores of 2/3 vs. 4/5 at 6 months compared to cluster 2 (increased IL-12, IL7, IL-4) Cytokines were elevated in TBI patients compared to controls | Elevated IL-5, IL-6, IL-8, IL-10, sVCAM-1, and sICMA-1 may be associated with poor outcome at 8 months |
| Kushi et al. (45) | Admission, 24, 72, and 168 h post-injury | IL-6, IL-8 | High protocolized treatment; fairly homogeneous therapy | Mortality at unspecified interval IL-6 and IL-8 levels were significantly higher in CSF compared to serum IL-6 and IL-8 levels were significantly higher in non-survivors | N/A | Elevated IL-6 and IL-8 during the first week post-TBI may be associated with mortality |
| Nwachuku et al. (46) | q6 h for 5 days | IL-1b, IL-6, TNF-a, IFN-a, IL-12p70, IL-10, and IL-8 | Not specified | Dichotomized GOS at 3, 6, 12, and 24 months (good = 4 or 5; poor = 3 or less) Mean 5-day levels of IFN-a, IL-10, IL-12 p70, IL-1, IL-6, IL-8, and TNF-a were associated with outcome (p < 0.05) | N/A | Elevated mean 5-day levels of various cytokines may be associated with poor outcome at 3, 6, 12, and 24 months post-injury |
| Santaraseiri et al. (47) | 2 times daily for up to 6 days | IL-1β, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, TNF-a, sVCAM-1, sICAM-1, sFAS | Not specified | Dichotomized GOS at 6 months (good = 4 or 5; poor = 3 or less) Cortisol: high cortisol patients were more likely to have elevated IL-10, IL-1b, IL-6, sFas, sCAM-1, sVCAM-1 and TNFa (p < 0.01 all comparisons, except IL-1b, p < 0.05) compared to low cortisol patients Outcome: significant associations between GOS and mean levels of IL-10, IL-6, IL-8, sFas, sCAM-1 (p < 0.01) and TNF-a (p < 0.05), with lower levels associated with favorable outcome | N/A | Low mean IL-6, IL-8, IL-10, sICAM-1, and TNF-a may be associated with good outcome at 6 months post-injury |

(Continued)
| Reference                      | Interval of cytokine measure | Measured CMD cytokines                        | Intervventional therapies applied during measurement | Outcome(s) of interest (patient outcome, neurophysiologic outcome, tissue outcome) | Other outcomes | Conclusions |
|--------------------------------|------------------------------|-----------------------------------------------|------------------------------------------------------|-------------------------------------------------------------------------------------|----------------|--------------|
| Shiozaki et al. (48)           | q6 h for unclear duration    | IL-1b, IL-1ra, IL-10, TNF-a, sTNFr-I          | Highly Protocolized therapy                           | Dichotomized GOS at 6 months (good = 4 or 5; poor = 3 or less)                     | IL-1b, IL-1ra, IL-10, and sTNFr-I were significantly higher in patients with high ICP than those with low ICP (p = 0.002, p = 0.006, p = 0.009, and p = 0.009, respectively). However, the CSF concentrations of TNF-a did not differ between patients with high ICP and those with low ICP | 1. Elevated IL-1b, IL-1ra, IL-10, and sTNFr-I may be associated with poor outcome at 6 months 2. Elevated IL-1b, IL-1ra, IL-10, stTNFr-I may be associated with high ICP |
| Singhal et al. (49)            | Unclear interval             | IL-1b, IL-6                                   | Not specified                                        | SSEP: positive correlation between IL-6 and SSEP96 (mean change in SSEP over 96 h) (p = 0.0133) Outcome: GOS at 3 months Peak IL-6 levels were associated with good outcome (p = 0.026) | N/A            | 1. Elevated IL-6 may be positively correlated to SSEP over the first 96 h 2. Peak IL-6 levels may be associated with outcome at 3 months |
| Whalen et al. (50)             | Unclear sampling intervals   | IL-8                                          | Not specified                                        | Mortality at unspecified interval Elevated CSF IL-8 levels were associated with mortality (p = 0.01) | IL-8 levels were elevated compared to controls | Elevated IL-8 levels during the first week of injury may be associated with mortality |
| Muller et al. (51)             | Daily for 7 days             | IL-6, IL-8, IL-10                             | Not specified                                        | Transcranial doppler (TCD)-defined cerebral blood flow velocity Mean IL-6 and IL-8 level were significantly correlated to MCBFV (r = −0.341 and −0.361, respectively; p < 0.05) | N/A            | Elevated IL-6 and IL-8 in the first 7 days may be negatively correlated to TCD defined MCBFV |
| Stein et al. (52)              | 2 times daily for 7 days     | IL-1b, IL-6, IL-8, IL-10, and TNF-a           | High protocolized therapy                             | ICP: negative association between early (within first 12 h of injury) IL-6 and ICP (p = 0.004) Positive correlation between time spent with CPP below 60 mm Hg and IL-8 levels (p = 0.001) Outcome: dichotomized GOSE at 6 months (good = 5–8; poor = 1–4) No association between CSF cytokines and outcome | N/A            | 1. Elevated IL-6 within the first 12 h of injury may be associated with low ICP 2. Elevated IL-8 levels may be associated with low CPP |
| Nil association studies        |                              |                                               |                                                      |                                                      | IL-6 and IL-12 were increased compared to control group | No association between IL-2, IL-4, IL-6, and IL-12 with GOS at 6 months |

Continued
| Reference            | Interval of cytokine measure | Measured CMD cytokines | Intervenional therapies applied during measurement | Outcome(s) of interest (patient outcome, neurophysiologic outcome, tissue outcome) | Other outcomes | Conclusions |
|----------------------|-----------------------------|------------------------|---------------------------------------------------|--------------------------------------------------------------------------------|----------------|-------------|
| Banked samples from a non-TBI control group (n = 12); CSF gained from investigations for meningitis | | | | No correlation between measured CSF cytokines and GOS | | |
| Buttram et al. (54)  | Collected 18, 24, 48, and 72 h post-injury | IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-15, IL-17, IP-10, eotaxin, TNF-α, INF-γ, MCP-1, MIP-1α | Not well specified; half the groups was subjected to moderate hypothermia for 48 h (32–33°C) | Dichotomized GOS at 6 months, No association between CSF cytokines and outcome | Cytokine levels in TBI patients were significantly higher compared to controls | There is no association between CSF cytokines and outcome at 6 months |
| Csuka et al. (55)   | Daily until EVD removal | IL-6, IL-10, TNF-α, TGF-B1 | Unclear ICP/CPP-directed therapies | Outcome: GOS at 3–6 months | IL-10 was found in both CSF and serum during the measurement period | CSF cytokines do not correlate to outcome at 3–6 months, CSF cytokines do not correlate to ICP |
| Diamond et al. (56) | q12 h for 6 days | IL1b | Not specified | EEG and Epileptologist defined PTE, CSF IL-1b was not statistically associated with PTE | Serum IL-1b levels was associated with PTE | Serum IL-1b levels within the first week of injury is not associated with PTE |
| Goodman et al. (57) | Unclear sampling interval | IL-1, IL-6, IL-8, IL-10, IL-12, TNF | Not specified | ICP/CPP: no correlation between CSF cytokines and ICP or CPP | Serum and CSF IL-6 and IL-8 were both elevated consistently | CSF cytokines are not associated with changes in ICP and CPP |
| Gopcevic et al. (58) | Unclear sampling interval | IL-8 | Not specified | 30-day in-hospital mortality: no correlation between CSF IL-8 levels and patient outcome | | |
| Lenzinger et al. (59) | Daily for unclear duration | sIL-2R, B2M, neopterin | Unclear ICP direct therapy | GOS at 4–6 months | Neopterin levels were higher in CSF than serum, B2M and sIL-2R levels were higher in serum | sIL-2R, B2M, and neopterin in CSF have no correlation to outcome at 4–6 months |
| Maier et al. (60)   | Admission and daily up to day 10 | sTNFRp55, sTNFRp75 | Not specified | GOS at 6 months | sTNFRp55 and sTNFRp75 levels are not associated with outcome at 6 months | sTNFRp55 and sTNFRp75 |
| Maier et al. (61)   | Admission and daily up to day 14 | IL-6, IL-8, IL-10 | Not specified | Mortality at unspecified interval | IL-6 and IL-8 were directly correlated with each other with CSF level higher than serum, All measured cytokines were higher in TBI patients compared to controls | CSF IL-6, IL-8, and IL-10 levels do not correlated with mortality |
Other outcomes

Conclusions

TABLE 4 | Continued

| Reference | Interval of cytokine measurement | Measured CMD cytokines | Outcomes of interest (patient outcome, neurophysiologic or tissue outcome) | Goals and outcomes reported by the studies were heterogeneous, and are listed in Table 3.

One study described an intervention during the assessment of CMD cytokines. This study was a prospective RCT describing the application of subcutaneous rhIL-1ra post severe diffuse TBI (16). The results described both elevated CMD IL-1ra levels and a reduction in MDC in the IL-1ra treated group. The follow-up retrospective statistical analysis of all CMD measured cytokines described a trend toward an increase in M1-microglia related cytokine activation following administration of rhIL-1ra (17).

Three studies reported the correlation between CMD cytokines and patient outcome (11, 20, 29). Two studies reported a positive association between elevated CMD IL-6 and improved survival, with one describing improved Glasgow Outcome Scale (GOS) at 6 months ($p = 0.03$). One study reported the negative correlation between CMD IL-1ra and poor GOS at 6 months ($p = 0.018$).

Most studies reported the CMD cytokine profile post-TBI and temporal fluctuations (12, 14, 15, 21, 24, 26, 27). Given the myriad of cytokines measured across the studies, it is impossible to describe all of the relationships. Highlighted details can be found in Table 3. The main findings included elevated IL-1b, IL-6, and IL-8 within the first 48–72 h post-injury, with these cytokines also displaying peaks during these times (21–23). The CMD IL-10 levels were found to be more uniformly elevated during the sampling periods (22, 26). Finally, some coexpression relationships were found between IL-1b with TNF, IL-1ra with IL-1a, and MIP-1a with MIP-1b (14).

Two studies evaluated the CMD cytokine profile associated with secondary events while in the ICU (18, 19). CMD IL-6 levels were positively associated with episodes of ischemia/metabolic stress, as defined by a lactate:pyruvate ratio greater than 30 and glutamate levels greater than 80 μmol/L.

The relationship of catheter location to CMD cytokine levels was discussed in a couple of papers, with peri-lesional tissue displaying higher cytokine expressions than distant or healthy tissue locations (11, 13). Evaluation of catheter technology (18) and cytokine measure feasibility (28) were also described in a few studies.

CSF Cytokine Review

The 36 papers included in the CSF systematic review (30–65) included both manuscripts, which reported positive associations between CSF cytokine levels and neurophysiologic or patient outcome (30–52), and studies reporting no association (53–65).

Like the CMD cytokine papers, the CSF cytokine papers included in this review reported the measurement of various cytokines. The most commonly measured cytokines in CSF reported were IL-1b, IL-1ra, IL-6, IL-8, IL-10, and TNF. The details of CSF sampling and specific cytokines measured can be found in Table 4.
(i.e., “nil association”) between CSF cytokines and the outcomes of interest for the CSF cytokine systematic review. No studies reported an association, “nil” or otherwise, between CSF cytokine measures and tissue outcome as assessed by follow-up neuroimaging. The subsections below describe more details of these outcomes of interest, with further information found in Table 4.

Positive Association Studies
Twenty-three papers included within the CSF cytokine review found associations between cytokine levels and both neurophysiologic and patient outcomes. Twenty-one described the association between CSF cytokines and patient outcome (30–50). Five papers discussed the association between CSF cytokine measures and neurophysiologic outcomes (36, 48, 49, 51, 52).

Patient Outcome. Cerebrospinal fluid levels of several cytokines were related to functional patient outcomes. The most common outcomes specified were: overall mortality or GOS at 6–12 months post-injury. The strongest relationships between cytokines and patient outcome were for IL-1b, IL-1ra, IL-6, IL-8, IL-10, and TNF.

A strong positive correlation between CSF measured IL-6 and IL-8 with poor GOS was the most commonly described relation between CSF cytokines and patient outcome (30, 32, 35, 36, 42–47, 49, 50). Similarly, a strong association between elevated CSF measured IL-10 and poor patient outcome was described in five studies (31, 41, 46–48). Elevated CSF IL-1b was found to be associated with mortality and worse GOS at 6 months in four studies (33, 34, 36, 49). Finally, CSF TNF-alpha (TNF-a) levels were found to be associated with worse patient outcome in two studies (30, 46).

The relationship between CSF cytokine levels and neuropsychiatric outcome was described in four studies (37–40). These associations included: higher IL-6 and IL-8 were associated with a higher incidence of depression at 6 months (37), TNF-a levels with depression at 12 months (37), IL-5/IL-8/IL-12/TBF with
outcomes of interest (53–65). Eleven studies reported no association between various CSF cytokines and patient outcome, as reported by in-hospital mortality or GOS at 3–6 months (53–55, 58–65). The cytokines reported within these studies varied significantly, with the most common “nil associations” reported for IL-1b, IL-6, IL-8, IL-10, TNF-a, and sTNFR. A total of 376 patients were described within these studies. Two studies reported no association between CSF cytokine measures and ICP/CPP (55, 57), while one study failed to determine an association between CSF IL-1b and post-traumatic epilepsy (56). Further detail on the “nil association” studies can be found at the bottom of Table 4.

Complications
Within the CMD cytokine manuscripts, the majority failed to report whether complications were considered within the data collection. Only three papers disclosed complication reporting (18, 28, 29), with two reporting “no complications” (28, 29), and
one reporting a CMD catheter malfunction in one patient (19). The complication profiles may be under-reported within the CMD studies. Complication reporting within the CSF cytokine studies was essentially non-existent, with the focus of these studies the association between CSF cytokine measures and various outcomes.

**DISCUSSION**

**CMD Cytokines in sTBI**

Our scoping systematic review completed for CMD cytokine measures in sTBI allows limited conclusions. Despite 19 publications (11–29), this literature is based on very small numbers of patients with many studies conducted on the same patient populations with banked CMD samples. However, the limited conclusions are important. First, CMD-based measurement of cytokines is feasible. Second, CMD catheter location makes a difference in the levels of cytokines measured, with peri-lesional tissue producing high levels compared to distant or healthier tissue (11, 13). Third, peaks in CMD cytokine measures may occur within the first 48–72 h for IL-1b, IL-6, and IL-8 (21–23). Interestingly, IL-10 seems to remain elevated in CMD samples through the duration of the sampling periods described (22, 26). Fourth, IL-6 levels may prove to be predictive of ongoing second insults such as ischemia (18, 19). Fifth, the data from the rhIL-1ra studies (16, 17) shows that subcutaneous rhIL-1ra leads to both an increase in CMD IL-1ra and a modulation of microglial/macrophage based cytokine profiles. Sixth, CMD IL-1b/IL-1ra/IL-6/IL-8 may be associated with poor outcome (11, 20, 29), up to 6 months post-injury. Finally, complications related to the use of CMD catheters are likely to be under-reported.

**CSF Cytokines in sTBI**

Our systematic review of CSF cytokines in sTBI, focused on the association between cytokine measures and patient, tissue outcome, or neurophysiology outcomes identified some interesting trends. First, a large number of heterogeneous studies correlated CSF cytokine levels with patient outcome, defined as either mortality or GOS at 6–12 months post-injury. Various large panels of cytokines were described within these studies, but the strongest associations with outcome were found for IL-1b, IL-1ra, IL-6, IL-8, IL-10, and TNF. Most studies described an association between elevated levels of these cytokines and poor GOS/increased mortality. Second, psychiatric outcome at 6–12 months post-injury appears to have some association to CSF cytokine levels (37–40). Elevated CSF IL-6, IL-8, and TNF seem to have the strongest associations with depression, apathy, and disinhibition at 6–12 months. Third, analysis of the impact of CSF cytokine levels on neurophysiologic measures is limited, with only five studies documenting such data (36, 48, 49, 51, 52). The strongest relationship identified here was the link between elevated levels of various cytokines, such as IL-6 or IL-1b, and elevated ICP (36, 48, 52). Further work is required before robust conclusions can be drawn in this area. Fourth, none of the studies explored the link between CSF cytokine measures and tissue outcome, as assessed by follow-up neuroimaging. Fifth, despite the “positive” associations found in the previously described papers, 11 manuscripts found no relationship between CSF cytokines and patient outcome (53–55, 58–65). The patient numbers in the individual studies, which reported no associations was much smaller than that in the studies describing a positive association between CSF cytokines and patient outcome (mean of 28 vs. 41 patients/study, respectively), making lack of power a possible cause of a negative result. Further patients in the “nil association” studies represented an overall smaller sample, totaling 376 patients vs. 948 patients in the “positive association” studies. Finally, complication reporting within the CSF cytokine studies was absent. Selective reporting bias here is a major concern.

**Limitations**

Despite the interesting results of these two systematic reviews, there are significant study limitations, which need to be highlighted. Limitations with each separate review can be found within the subsections to follow.

**CMD Cytokine Review**

First, there were a small number of heterogenous studies found for the CMD review, with some manuscripts reporting on the same patient populations based on banked CMD samples. Most of these studies had patient cohort with unspecified heterogeneous patterns of injury in the setting of sTBI. The exceptions were the studies describing “diffuse” TBI patients only. These drawbacks limit the generalizability of the results to all patients with sTBI. Second, the ICU and surgical therapies received by these patients during CMD sample collection/processing was quite heterogeneous and poorly reported, and could have driven substantial variation in CMD cytokine measures. Third, there were variations in CMD catheter location between studies. This could impact the CMD cytokine measures obtained and the described relationships. Fourth, complications association with CMD monitoring was seldom reported. We believe there is significant selective harms reporting. Finally, given the studies and results identified for the CMD review, there is likely a large publication bias, favoring only studies with positive results.

**CSF Cytokine Review**

First, there were many quite heterogeneous studies identified in the CSF cytokine review. The included papers varied by study design, number of patients, patient inclusion criteria, ICU-based therapies offered/provided to patients, blinding during outcome assessment, and primary outcome of the studies. Information regarding the relationship between CSF cytokine measures and patient outcome was often buried within the text, and often not an explicit target for the study. Furthermore, selective outcome reporting with regards to individual CSF cytokine measures and their association to patient outcome was present in many studies. Thus, the conclusions that can be drawn from these studies and the strength of associations between CSF cytokines with patient outcome/neurophysiologic outcome are limited. Second, selective outcome reporting was an issue in many studies with preference to reporting significant association(s) only, making no reference to other CSF measures and the results of statistical analysis. Third, complication reporting was concerning within
the literature identified (as mentioned above). Significant under-reporting is suspected, with selective harms reporting the likely cause. Fourth, given all the above limitations and heterogeneity issues, a meta-analysis was not performed. Finally, though majority of studies report a positive association between cytokine levels and outcome, given that this is an emerging area of research, it is important to consider whether this might represent a publication bias toward positive studies.

Correlation with Clinical Parameters
Several studies attempt to correlate a specific mediator concentration with outcome. As these mediators are known to act in complex cascades and show a high degree of statistical collinearity, simple inferences cannot be made about the role of a given mediator in causing a particular outcome or relating to a clinical parameter such as ICP. As these mediators are induced by the initial traumatic insult, they are all confounded by severity of injury: it is, therefore, not surprising that a high concentration of cytokine relates to a worsened clinical parameter. Furthermore, the timing of monitoring in relation to the time of injury is not consistently reported. Several mediators, such as IL-6, can have differing biological effects depending on the milieu in which they are produced (68). Finally, many mediators are known to act in concert and regulate the same downstream pathways (e.g., IL-1β and IL-1ra) such that measuring a mediator in isolation does not reflect its true biological role, which is time and milieu dependent.

Future Directions
Given the significant heterogeneity in both study design, patient injury patterns, ICU/surgical treatments, and CMD/CSF cytokine measures identified within both systematic reviews, there is substantial room for more investigation into this emerging area of the literature in sTBI.

Although it is tempting to simply suggest that larger studies are done to overcome the heterogeneity in injury patterns following TBI, there are significant limitations to this approach. There are an ever-expanding list of mediators available for analysis over multiple time points in a range of biological fluids and without a robust understanding of the interaction between these mediators, it is unlikely that a meaningful pattern will emerge through brute force of numbers. More refined approaches that explore within patient comparisons with multiple sites of monitoring (69), interventional studies in which specific modulation of a biological pathway (16), and more sophisticated multivariate statistical methods (14).

Some studies have attempted to relate intensive care parameters such as ICP to the cytokine and chemokine response to TBI (26). This is not a simple relationship as the time frame over which cytokines and chemokines are produced occur over several days and weeks, rather than over the minutes and hours. There is insufficient evidence to stipulate, which intensive care interventions should be applied during monitoring of inflammatory mediators; however, it is important for individual studies to report their intensive care protocols and interventions.

As CMD is necessarily focal in nature, strict reporting of the method of localization is required and ideally 2 catheter studies, 1 in peri-lesional tissue and 1 in healthy tissue provides the most informative data (quote consensus paper).

When multiple mediators are measured, multivariate statistical methods must be employed, such as multivariate projection methods in order to model the potential interactions (14, 70).

This could potentially identify cytokine patterns of coexpression in CMD and CSF, highlighting target for future studies and therapeutic targets.

One deficit in the current CMD literature is complication reporting. In part, this relates to the difficulty in apportioning complications to CMD catheter insertion specifically. As patients will have invasive monitoring for ICP monitoring and brain tissue oxygenation in any circumstance for directing clinical therapy, the additional risk of inserting CMD through an existing cranial access device is small and difficult to quantify. Nevertheless, transparency dictates that complications are reported. Standardization of the methodologies employed allows multicenter prospective evaluation of cytokines within CMD and CSF and is necessary to improve patient recruitment and aid with spreading the substantial cost of cytokine analysis among centers. Without this collaboration, the limitations with single center recruitment and costs of cytokine processing in CMD and CSF limits the ability to combine datasets across units and studies. This would allow easier compilation of data sets and may add clarity to the associations highlighted within this manuscript. Finally, a consideration of the methodological factors that determine microdialysis catheter efficiency, including choice of perfusion fluid, catheter membrane, and pump flow rate all have an impact on the result obtained.

CONCLUSION
The evaluation of CMD and CSF cytokines is an emerging area of the literature in sTBI. The two scoping systematic reviews have demonstrated a limited literature available on CMD cytokine measurement in sTBI, with some preliminary data supporting feasibility of measurement and associations between cytokines and patient outcome. Second, a number CSF cytokine levels may be associated with patient outcome at 6–12 months, including IL-1β, IL-1ra, IL-6, IL-8, IL-10, and TNF. Third, there is little to no literature to date in support of an association between CSF cytokines and neurophysiologic or tissue outcomes. Ultimately, the aim of CMD monitoring of inflammatory mediators is to reveal the underlying pathophysiology of TBI rather than as a clinical tool.

AUTHOR CONTRIBUTIONS
FZ was involved in project conception, design, systematic review searching, data extraction/tabulation, data interpretation, manuscript composition, and editing. ET was involved with data extraction/tabulation, manuscript composition, and editing. MC was involved in manuscript composition and editing. PH was involved in design, data interpretation, and manuscript editing. DM and AH was involved in design, data interpretation, manuscript writing, and editing.
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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fneur.2017.00331/full#supplementary-material.

REFERENCES

1. Corps KN, Roth TL, McGavern DB. Inflammation and neuroprotection in traumatic brain injury. JAMA Neurol (2015) 72(3):355–62. doi:10.1001/ jamaneurol.2014.3538
2. Kumar A, Loane DJ. Neuroinflammation after traumatic brain injury: opportunities for therapeutic intervention. Brain Behav Immun (2012) 26(8): 1191–201. doi:10.1016/j.bbi.2012.06.008
3. Logan A, Frautschy SA, Gonzalez AM, Sporn MB, Baird A. Enhanced expression of transforming growth factor beta 1 in the rat brain after a localized cerebral injury. Brain Res (1992) 587(2):216–25. doi:10.1016/0006-8993(92)90100-5
4. Xiong XX, Gu LJ, Shen J, Kang XH, Zheng YY, Yue SB, et al. Probenecid protects against transient focal cerebral ischemic injury by inhibiting HMGB1 release and attenuating AQP4 expression in mice. Neurochem Res (2014) 39(1):216–24. doi:10.1007/s11006-013-1212-z
5. Mukandala G, Tynan R, Lanigan S, O'Connor JJ. The effects of hypoxia and inflammation on synaptic signaling in the CNS. Brain Sci (2016) 6(1):6. doi:10.3390/brainsci6010006
6. Luhehi NM, Kovácik KJ, Lopez-Castejon G, Brough D, Denes A. Interleukin-1α expression precedes IL-1β after ischemic brain injury and is localised to areas of focal neuronal loss and penumbral tissues. J Neuroinflammation (2011) 8:186. doi:10.1186/1742-2094-8-186
7. Plesnila N. The immune system in traumatic brain injury. Curr Opin Pharmacol (2016) 26:110–7. doi:10.1016/j.coph.2015.10.008
8. Goyneva S, Ransohoff RM. Inflammatory reaction after traumatic brain injury: therapeutic potential of targeting cell-cell communication by chemokines. Trends Pharmacol Sci (2015) 36(7):471–80. doi:10.1016/j.tips.2015.04.003
9. Sordillo PP, Sordillo LA, Nelson L. Bifunctional role of pro-inflammatory cytokines after traumatic brain injury. Brain Inj (2016) 30(9):1043–53. doi:10.3109/02699052.2016.1163618
10. Di Battista AP, Rhind SG, Hutchison MG, Hassan S, Shiu MY, Inaba K, et al. Inflammatory cytokine and chemokine profiles are associated with patient outcome and the hyperadrenergic state following acute brain injury. J Neuroinflammation (2016) 13:40. doi:10.1186/s12974-016-0500-3
11. Cederberg D, Figaji A, Siesjo P. Cytokine analysis in paediatric severe traumatic brain injury. Brain Inj (2012) 26(4–5):719–20. doi:10.3109/02699052.2012.681089
12. Figaji A, Ross S, Rohlwink U, Fiegen G, Padayachy L, Hoffman J. Metabolic and inflammatory changes in the injured brain. Childs Nerv Syst (2013) 29(9):1718–9.
13. Guilfoyle MR, Helmy A, Carpenter KLH, Hutchinson PJ. Localised cytokine responses in peri-contusional brain following traumatic injury – a paired microdialysis study. Br J Neurosurg (2015) 29(4):452.
14. Helmy A, Antoniades CA, Guilfoyle MR, Carpenter KL, Hutchinson PJ. Principal component analysis of the cytokine and chemokine response to human traumatic brain injury. PLoS One (2012) 7(6):e39677. doi:10.1371/journal.pone.0039677
15. Helmy A, Carpenter KL, Menon DK, Pickard JD, Hutchinson PJ. The cytokine response to human traumatic brain injury: temporal profiles and evidence for cerebral parenchymal production. J Cereb Blood Flow Metab (2011) 31(2):658–70. doi:10.1038/jcbfm.2010.142
16. Helmy A, Guilfoyle MR, Carpenter KL, Pickard JD, Menon DK, Hutchinson PJ. Recombinant human interleukin-1 receptor antagonist in severe traumatic brain injury: a phase II randomized control trial. J Cereb Blood Flow Metab (2014) 34(5):485–51. doi:10.1038/jcbfm.2014.23
17. Helmy A, Guilfoyle MR, Carpenter KL, Pickard JD, Menon DK, Hutchinson PJ. Recombinant human interleukin-1 receptor antagonist promotes M1 microglia biased cytokines and chemokines following human traumatic brain injury. J Cereb Blood Flow Metab (2016) 36(8):1434–48. doi:10.1038/jcbfm.2016.177
18. Hillman J, Aneman O, Andersson C, Sjogren F, Saberg C, Mellerlogg P. A microdialysis technique for routine measurement of macromolecules in the injured human brain. Neurosurgery (2005) 56(6):1264–8. doi:10.1227/01.NEU.0000159711.9392B
19. Hillman J, Aneman O, Persson M, Andersson C, Dabrosin C, Mellerlogg P. Variations in the response of interleukins in neurosurgical intensive care patients monitored using intracerebral microdialysis. J Neurosurg (2007) 106(5):820–5. doi:10.3171/ins.2007.106.5.820
20. Hutchinson PJ, O’Connell MT, Rothwell NJ, Hopkins SJ, Nortje J, Carpenter KL, et al. Inflammation in human brain injury: intracerebral concentrations of IL-1alpha, IL-1beta, and their endogenous inhibitor IL-1ra. J Neurotrauma (2007) 24(10):1545–57. doi:10.1089/neu.2007.0295
21. Mellerlogg P, Aneman O, Sjogren F, Pettersson P, Hillman J. Changes in extracellular concentrations of some cytokines, chemokines, and eutrophic factors after insertion of intracerebral microdialysis catheters in neurosurgical patients. Neurosurgery (2008) 62(1):151–7. doi:10.1227/01.NEU.0000311072.33615.3A
22. Mellerlogg P, Aneman O, Sjogren F, Saberg C, Hillman J. Differences in cerebral extracellular response of interleukin-1 beta, interleukin-6, and interleukin-10 after subarachnoid hemorrhage or severe head trauma in humans. Neurosurgery (2011) 68(1):12–9. doi:10.1227/NEU.0b013e3181ef2a40
23. Mellerlogg P, Sjogren F, Hillman J. Release of VEGF and FGF in the extracellular space following severe subarachnoidal haemorrhage or traumatic head injury in humans. Br J Neurosurg (2010) 24(3):261–7. doi:10.3109/ 02688690903521605
24. Mellerlogg P, Sjogren F, Hillman J. The cerebral extracellular release of glycerol, glutamate, and FGF2 is increased in older patients following severe traumatic brain injury. J Neurotrauma (2012) 29(1):112–8. doi:10.1089/neu.2010.1732
25. Mondello S, Jeromin A, Bullock R, Sweeney JM, Streeter J, Schmid K, et al. In vivo monitoring of cytokines and brain biomarker damage following severe traumatic brain injury: a microdialysis study. J Neurotrauma (2011) 28(6):A84
26. Perez-Barcena J, Ibanez J, Brell M, Crespi C, Frontera G, Llompart-Pou JA, et al. Lack of correlation among intracerebral cytokines, intracranial pressure, and brain tissue oxygenation in patients with traumatic brain injury and diffuse lesions. Crit Care Med (2011) 39(3):533–40. doi:10.1097/CCM. 0b013e318205c7a4
27. Roberts DJ, Jenne CN, Leger C, Kramer AH, Gallagher CN, Todd S, et al. Association between the cerebral inflammatory and matrix metalloproteinase responses after severe traumatic brain injury in humans. J Neurotrauma (2013) 30(20):1277–30. doi:10.1089/neu.2013.2842

28. Winter CD, Iannotti F, Pringle AK, Trikkas C, Cloughe GH, Church MK. A microdialysis method for the recovery of IL-1beta, IL-6, and nerve growth factor from human brain in vivo. J Neurosci Methods (2002) 119(1):45–50. doi:10.1016/S0165-0270(02)00153-X

29. Winter CD, Pringle AK, Cloughe GH, Church MK. Raised parenchymal interleukin-6 levels correlate with improved outcome after traumatic brain injury. Brain (2004) 127(2):315–20. doi:10.1093/brain/awh039

30. Abboud A, Mi Q, Puccio A, Okonkwo D, Buliga M, Constantine G, et al. Inflammation following traumatic brain injury in humans: insights from data-driven and mechanistic models into survival and death. Front Pharmacol (2016) 7:342. doi:10.3389/fphar.2016.00342

31. Bell MJ, Kochanek PM, Dougherty LA, Carricillo JA, Adelson PD, Clark RS, et al. Interleukin-6 and interleukin-10 in cerebrospinal fluid after severe traumatic brain injury in children. J Neurotrauma (1997) 14(7):451–7. doi:10.1089/neu.1997.14.451

32. Chiaretti A, Antonelli A, Mastrangelo A, Pezzotti P, Tortorolo L, Tosi F, et al. Interleukin-6 and nerve growth factor upregulation correlates with improved outcome in children with severe traumatic brain injury. J Neurotrauma (2008) 25(3):225–34. doi:10.1089/neu.2007.0405

33. Chiaretti A, Antonelli A, Riccardi R, Pezzotti P, Di Rocco C, et al. Nerve growth factor expression correlates with severity and outcome of traumatic brain injury in children. Eur J Paediatr Neurol (2008) 12(3):195–204. doi:10.1016/j.ejpn.2007.07.016

34. Chiaretti A, Genovese O, Aloe L, Antonelli A, Piastra M, Poldori G, et al. Interleukin ibeta and interleukin 6 relationship with paediatric head trauma severity and outcome. Childs Nerv Syst (2005) 21(3):185–93. doi:10.1007/s00381-004-1032-1

35. Hans VH, Kossman T, Joller H, Otto V, Morganti-Kossmann MC. Interleukin-6 and its soluble receptor in serum and cerebrospinal fluid after cerebral trauma. Neuroreport (1999) 10(2):409–12. doi:10.1097/00001756-199902050-00036

36. Hayakata T, Shiozaki T, Tasaki O, Hosotubo H, Fujita K, Mouri T, et al. Cerebrospinal fluid concentrations of anti-inflammatory mediators in early-phase severe traumatic brain injury. Shock (2005) 23(5):406–10. doi:10.1097/01.shk.0000161385.62758.24

37. Singhal A, Baker AJ, Hare GM, Reinders FX, Schlüchter LC, Moulton RJ. Association between cerebrospinal fluid interleukin-6 concentrations and outcome after severe human traumatic brain injury. J Neurotrauma (2002) 19(8):929–37. doi:10.1089/089771502X23017087

38. Whalen MJ, Carlos TM, Kochanek PM, Wisniewski SR, Bell MJ, Clark RS, et al. Interleukin-8 is increased in cerebrospinal fluid of children with severe head injury. Crit Care Med (2000) 28(4):929–34. doi:10.1097/00003246-200004000-00003

39. Shiozaki T, Hayakata T, Tasaki O, Hosotubo H, Fujita K, Mouri T, et al. Cerebrospinal fluid interleukin-6 levels correlate with improved outcome after traumatic brain injury. Brain Behav Immun (2015) 45:15–27. doi:10.1016/j.bbi.2014.05.020

40. Santarisi M, Kumar RG, Kochanek PM, Berga S, Wagner AK. Variable neuroendocrine-immune dysfunction in individuals with unfavorable outcome after severe traumatic brain injury. Brain Behav Immun (2015) 45:15–27. doi:10.1016/j.bbi.2014.05.020

41. Singhal A, Baker AJ, Hare GM, Reinders FX, Schlüchter LC, Moulton RJ. Association between cerebrospinal fluid interleukin-6 concentrations and outcome after severe human traumatic brain injury. J Neurotrauma (2002) 19(8):929–37. doi:10.1089/089771502X23017087

42. Whalen MJ, Carlos TM, Kochanek PM, Wisniewski SR, Bell MJ, Clark RS, et al. Interleukin-8 is increased in cerebrospinal fluid of children with severe head injury. Crit Care Med (2000) 28(4):929–34. doi:10.1097/00003246-200004000-00003

43. Stein DM, Lindell A, Murdock KR, Kufera JA, Menaker J, Keledjian K, et al. Relationship of serum and cerebrospinal fluid biomarkers with intracranial hypertension and cerebral hyperperfusion after severe traumatic brain injury. J Trauma (2011) 70(5):1096–103. doi:10.1097/TA.0b013e318216930d

44. Stein DM, Lindell A, Murdock KR, Kufera JA, Menaker J, Keledjian K, et al. Relationship of serum and cerebrospinal fluid biomarkers with intracranial hypertension and cerebral hyperperfusion after severe traumatic brain injury. J Trauma (2011) 70(5):1096–103. doi:10.1097/TA.0b013e318216930d

45. Cuika E, Morganti-Kossmann MC, Lenzlinger PM, Joller H, Trentz O, Kossman T. IL-10 levels in cerebral spinal fluid and serum of patients with severe traumatic brain injury: relationship to IL-6, TNF-alpha, TGF-beta and blood-brain barrier function. J Neuroimmunol (1999) 101(2):211–21. doi:10.1016/S0165-5728(99)00148-4

46. Buttrum SD, Wisniewski SR, Jackson EK, Adelson PD, Feldman K, Bayir H, et al. Multiplex assessment of cytokine and chemokine levels in cerebrospinal fluid following severe pediatric traumatic brain injury: effects of moderate hypothermia. J Neurotrauma (2007) 24(11):1707–17. doi:10.1089/neu.2007.0349

47. Cuika E, Morganti-Kossmann MC, Lenzlinger PM, Joller H, Trentz O, Kossman T. IL-10 levels in cerebral spinal fluid and serum of patients with severe traumatic brain injury: relationship to IL-6, TNF-alpha, TGF-beta and blood-brain barrier function. J Neuroimmunol (1999) 101(2):211–21. doi:10.1016/S0165-5728(99)00148-4

48. Diamond ML, Ritter AC, Failla MD, Boles JA, Conley YP, Kochanek PM, et al. IL-1beta associations with posttraumatic epilepsy development: a genetics and biomarker cohort study. Epilepsia (2014) 55(7):1109–19. doi:10.1111/epi.12714

49. Goodman JC, Van M, Gopinath SP, Robertson CS. Pro-inflammatory and pro-apoptotic elements of the neuroinflammatory response are activated in traumatic brain injury. Acta Neurochir Suppl (2008) 102:437–9. doi:10.1007/978-3-211-85578-2_83

50. Gopecevic A, Mazul-Sunko B, Marout J, Sekulic A, Antoljak N, Siranovic M, et al. Plasma interleukin-8 as a potential predictor of mortality in adult patients with severe traumatic brain injury. Tohoku J Exp Med (2007) 211(4):387–93. doi:10.1620/tjem.211.387

51. Lenzlinger PM, Hans VH, Joller-Jemelka HI, Trentz O, Morganti-Kossmann MC, Kossman T. Markers for cell-mediated immune response are elevated in cerebrospinal fluid and serum after severe traumatic brain injury in humans. J Neurotrauma (2001) 18(5):479–89. doi:10.1089/089771501300227288

52. Maier B, Lehmler M, Lauer HL, Mautes AE, Steudel WI, Marzi I. Delayed elevation of soluble tumor necrosis factor receptors p75 and p55 in cerebrospinal fluid and plasma after traumatic brain injury. Shock (2006) 26(2):122–7. doi:10.1097/01.shk.0000223127.41641.f4

53. Maier B, Schwertdfeger K, Mautes A, Holanda M, Muller M, Steudel WI, et al. Differential release of interleukines 6, 8, and 10 in cerebrospinal
fluid and plasma after traumatic brain injury. *Shock* (2001) 15(6):421–6. doi:10.1097/00024382-200115060-00002

62. Morganti-Kossmann C, Bye N, Nguyen P, Kossmann T, Rosenfeld J, Yan E. Cytokines and brain injury markers in TBI patients: differences in focal and diffuse brain damage, and normoxic or hypoxic status and their relation to neurological outcome. *J Neurotrauma* (2012) 29(10):A188.

63. Newell E, Shellington DK, Simon DW, Bell MJ, Kochanek PM, Feldman K, et al. Cerebrospinal fluid markers of macrophage and lymphocyte activation after traumatic brain injury in children. *Pediatr Crit Care Med* (2015) 16(6):549–57. doi:10.1097/PCC.0000000000000400

64. Ross SA, Halliday GP, Campbell GC, Brynes DP, Rowlands BJ. The presence of tumour necrosis factor in CSF and plasma after severe head injury. *Br J Neurosurg* (1994) 8(4):419–25. doi:10.3109/02688699408995109

65. Uzan M, Tanriover N, Bozkus H, Gumustas K, Guzel O, Kuday C. Nitric Oxide (NO) metabolism in the cerebrospinal fluid of patients with severe head injury: inflammation as a possible cause of elevated no metabolites. *Surg Neurol* (2001) 56(6):350–6. doi:10.1016/S0090-3019(01)00633-4

66. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. (2013). Available from: http://handbook.cochrane.org

67. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analysis: the PRISMA statement. *Ann Intern Med* (2009) 151(4):264–9. doi:10.7326/0003-4819-151-4-200908180-00135

68. Simon DW, McGreaghy MJ, Bayar H, Clark RS, Loane DJ, Kochanek PM. The far-reaching scope of neuroinflammation after traumatic brain injury. *Nat Rev Neurol* (2017) 13(3):171–91. doi:10.1038/nrneurol.2017.13

69. Guilfoyle MR, Carpenter KL, Helmy A, Pickard JD, Menon DK, Hutchinson PJ. Matrix metalloproteinase expression in contusional traumatic brain injury: a paired microdialysis study. *J Neurotrauma* (2015) 32(20):1553–9. doi:10.1089/neu.2014.3764

70. Helmy A, De Simoni MG, Guilfoyle MR, Carpenter KL, Hutchinson PJ. Cytokines and innate inflammation in the pathogenesis of human traumatic brain injury. *Prog Neurobiol* (2011) 95(3):352–72. doi:10.1016/j.pneurobiol.2011.09.003

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