

SYSTEMATIC REVIEW

Blood-Brain Barrier Dysfunction after Traumatic Brain Injury: Molecular Pathways and Clinical Evidence -A Systematic Review

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ABSTRACT

Objective: The blood–brain barrier (BBB) is an important component of the secondary injury mechanism in traumatic brain injury (TBI), associated with changes in BBB permeability, neuroinflammation, impaired protein clearance, and neurological deterioration. This systematic review aimed to synthesize clinical evidence on BBB dysfunction and associated molecular pathways following TBI. **Data Sources:** This review was conducted following PRISMA 2020 guidelines. PubMed, Scopus, Web of Science, and Google Scholar were searched from January 2019 to February 2026. **Study Selection:** Studies having BBB disruption or molecular mechanisms associated with BBB in human TBI using imaging, serum or plasma, CSF, or cerebral microdialysis methods were selected. **Data Extraction:** Two reviewers independently extracted data. QUADAS-2, adapted PROBAST, QUIPS, and adapted JBI tools were used to assess risk of bias. The GRADE approach was used to assess certainty of evidence. **Data Synthesis:** Fifteen studies met the inclusion criteria. Studies demonstrated the presence of BBB or blood–CSF barrier disruption by DCE-MRI, gadolinium leakage, permeability mapping, and meningeal enhancement. Biomarker studies found links between TBI and neurofilament light chain, GFAP, UCH-L1, S100B, NSE, inflammatory cytokines and chemokines, MMPs, and microdialysis proteins. These markers were correlated with injury severity, CT abnormalities, post-concussion symptoms, axonal injury, cerebral blood flow changes, and functional outcomes. The risk of bias was mostly moderate. Certainty of evidence was low to moderate. **Conclusion:** BBB dysfunction following TBI is associated with altered permeability, neuroaxonal damage, inflammation, proteinase activity, and impaired protein clearance. Larger standardized studies are needed to validate BBB biomarkers and clarify underlying molecular pathways.

Keywords: Blood-Brain Barrier; Brain Injuries, Traumatic; Cerebrospinal Fluid; Magnetic Resonance Imaging; Neuroinflammation.

INTRODUCTION

Traumatic brain injury (TBI) causes high rates of neurological morbidity and chronic disability across all age groups and injury severities worldwide ¹. Primary mechanical injury occurs at the moment of the trauma; however, much of the post-trauma neurological injury is caused by secondary injury mechanisms, such as: neuroinflammation, oxidative stress, cerebrovascular dysfunction, excitotoxicity, and blood brain barrier (BBB) dysfunction ². The BBB is a highly selective vascular interface that regulates the cellular, protein, ion and inflammatory mediator flow between blood and brain tissue, maintaining the homeostasis of the central nervous system ³. Thus, BBB dysfunction has emerged as an issue of interest in TBI research as it can facilitate cerebral oedema, inflammatory cell infiltration, protein leakage and adverse neurological outcome ⁴.

There are several molecular and cellular mechanisms that impact BBB integrity following TBI such as disruption of tight junctions, injury to endothelial cells, activation of MMPs, dysfunction of astrocytes and pericyte cells, and release of inflammatory cytokines and injury to the neuroaxonal cells ⁵. Clinical studies have used imaging methods (dynamic contrast-enhanced magnetic resonance imaging, gadolinium leakage and meningeal enhancement), and biofluid biomarkers (S100B, neuron-specific enolase, GFAP, UCH-L1, neurofilament light chain and inflammatory proteins ⁵) to assess BBB dysfunction before ⁶.

Despite numerous clinical studies researching BBB pathologies following TBI, the evidence has been widely dispersed based on TBI severity, study design, assessment techniques and molecular markers ⁷. The assessment of BBB permeability can be done directly by neuro-imaging in some studies, or indirectly by serum/plasma markers or by cerebral microdialysis in CSF in other studies ⁸. Furthermore, differences in the timing after injury, patient population, panels of biomarkers and clinical outcome measures make it very difficult to draw consistent conclusions regarding the molecular mechanisms that underlie BBB disruption after TBI ⁹. Thus, it is necessary to carry out a systematic review of clinical evidence to summarize the current literature and select the most pertinent molecular pathways.

The objective of this systematic review was to synthesize clinical studies investigating BBB dysfunction and associated molecular pathways in TBI. This review aims at combining all these results and thus giving a more global picture of the role of BBB dysfunction in the pathophysiology of TBI and potential clinical parameters for biomarkers, imaging and therapeutic strategies for future research.

METHODOLOGY

The purpose of this systematic review was to comprehensively summarize the clinical evidence for the molecular mechanisms of blood–brain barrier (BBB) dysfunction in traumatic brain injury (TBI). The review was conducted in accordance with the PRISMA 2020 guidelines for a transparent and reproducible process¹⁰. A detailed systematic review protocol was developed, finalized, and verified internally prior to the commencement of data extraction to ensure research transparency and prevent reporting bias. A formal prospective registration code via external repositories was not sought for this specific cycle due to the rapid operational timeline.

Inclusion and Exclusion Criteria: Original human clinical studies that focused on BBB dysfunction and/or BBB-related molecular mechanisms following TBI were included. Studies that evaluated BBB permeability, BBB disruption, release (or clearance) of biomarkers, neuroinflammation, proteolytic pathways, endothelial injury, or molecular changes by microdialysis were eligible. Studies of mild, moderate, severe TBI, sport-related concussion, or repetitive subconcussive exposure were included. Articles published in English, since 2019 with clear methodology. Reviews, meta-analyses, editorials, conference abstracts, case reports, animal studies, in vitro studies, protocols and studies lacking molecular or clinical information relevant to BBB were not included.

Data Sources: A literature search was carried out using PubMed, Scopus, Web of Science and Google Scholar. The studies that were published between January 2019 and February 2026 were taken into account. Additionally, reference lists of eligible articles were hand-screened.

Search Strategy: Search terms included traumatic brain injury, TBI, concussion, blood–brain barrier, BBB disruption, blood–CSF barrier, permeability, DCE-MRI, gadolinium leakage, meningeal enhancement, GFAP, UCH-L1, NFL, S100B, NSE, matrix metalloproteinase, neuroinflammation, cytokines, cerebral microdialysis, and proteomics. Boolean operators AND and OR were used to combine search terms.

Study Selection: Titles and abstracts were screened by two reviewers independently for relevance following duplicate removal. Predefined criteria were then applied to full-text articles. Studies were included if they showed clinical evidence of association between TBI and BBB dysfunction or BBB-related molecular mechanisms. Disagreement was resolved by discussion.

Data Extraction: Data were obtained by the use of a standard data form. The information extracted by two reviewers independently comprised the author, the year of the study, the country where the study was conducted, the design of the study, the number of patients, the type of patients with TBI, severity of the injury, time since injury, the method used to assess BBB, molecular markers, clinical outcomes and major findings of the study. Disagreement was resolved by discussion.

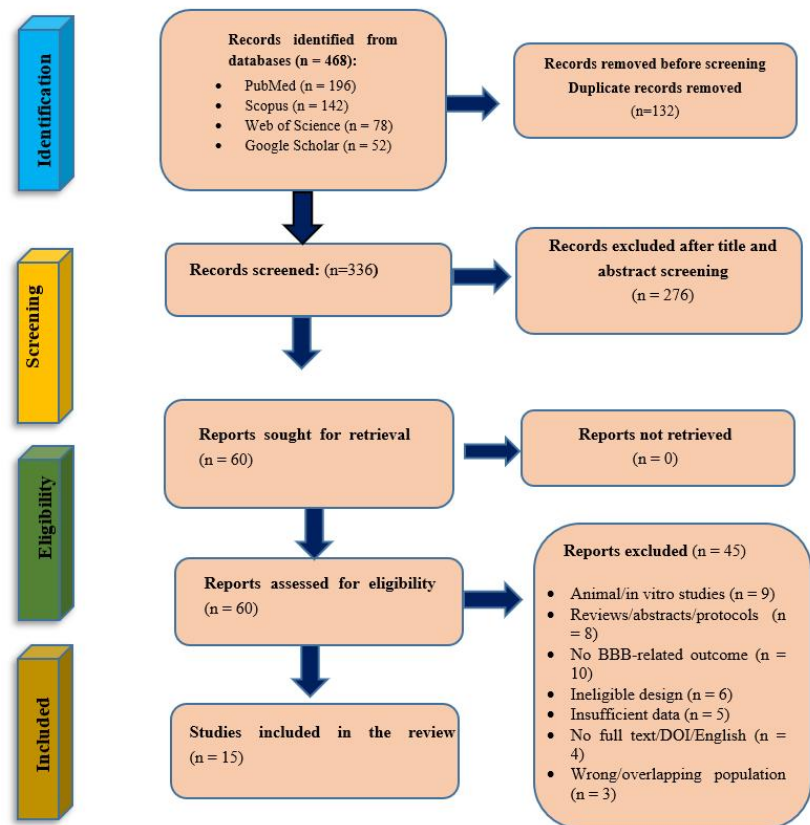


Figure 1: PRISMA 2020 flow diagram of study selection.

Outcome Measures: The main end point was BBB dysfunction following TBI, which was directly measured by imaging or indirectly by measuring molecular markers. Secondary outcomes included neuroaxonal injury, glial injury, inflammation, protein clearance, MMP activity, cerebral blood flow changes, severity of the TBI, imaging findings, post-concussion symptoms and functional outcome.

Quality Assessment: The risk of bias was done by QUADAS-2 tool for prognostic biomarker studies¹¹. An adapted PROBAST tool used for ROB analysis of prognostic-factor studies¹². The QUIPS tool was used for ROB analysis of exposure-outcome observational studies, and an adapted JBI case-series checklist was used for microdialysis studies^{13,14}. The overall risk was scored as low, moderate/some concerns, or high. GRADE approach was used for measuring certainty of evidence¹⁵.

Data Synthesis: Because of substantial heterogeneity in study designs, TBI severity, assessment methods, biomarkers, and reported outcomes, a meta-analysis was not considered appropriate. Findings were compiled narratively by BBB imaging, biofluid biomarker and neuroinflammatory, proteolytic or microdialysis-based molecular pathways.

RESULTS

Four hundred and sixty-eight records were found initially from four electronic databases: PubMed (n = 196), Scopus (n = 142), Web of Science (n = 78), and Google Scholar (n = 52). 132 duplicate records were eliminated and 336 articles were screened by title and abstract. A total of 276 articles were excluded at this step as they were irrelevant to BBB dysfunction in traumatic brain injury, not clinical studies in human patients or not focused on BBB-related molecular mechanisms, or did not meet the pre-established inclusion criteria. Next, 60 of the full-text articles were evaluated for inclusion. Of these, 45 articles were excluded because they were not suitable studies, included animal or experimental-only data, not included BBB-related outcomes, lacked methodological information, did not have full text, did not meet the criteria, were conference abstracts or were published before the selected time period. In the end, 15 studies fulfilled the inclusion criteria and were included in this systematic review. The selection process of the studies is described in the PRISMA flow diagram (Figure 1).

Table I provides a summary of the main features of the studies included, such as study design, population, severity of TBI, time since the injury, method used to assess BBB, molecular markers, and main clinical findings.

Table I: Characteristics of Included Clinical Studies Investigating Molecular Mechanisms and Assessment Approaches Related to BBB Dysfunction After Traumatic Brain Injury.

Author, Year	Study Design	Sample Size and TBI Population	TBI Severity / Type	Mechanistic Domain of BBB	BBB Assessment Method	Molecular Markers / Pathways Assessed	Clinical Outcomes and Factors Assessed	Key Findings
Country			Time Since Injury	Dysfunction				
O’Keeffe et al., 2020 ¹⁶	Prospective observational clinical study	MMA fighters and rugby players	Mild TBI / repetitive subconcussive exposure	Direct BBB permeability and imaging evidence	DCE-MRI; gadolinium leakage	BBB permeability; biomechanical strain	Head-impact exposure; concussion status	BBB disruption was detected after repetitive head impacts and correlated with biomechanical force exposure.
Ireland/USA			Pre- and post-exposure; within 120 h post-fight					
Veksler et al., 2020 ¹⁷	Observational DCE-MRI study with controls and validation cohorts	42 adult male amateur American football players; controls: 27 non-contact athletes and 26 non-athletes, 51 BBB-pathology patients	Repetitive mild TBI	Direct BBB permeability and imaging evidence	Modified DCE-MRI permeability mapping	Slow blood-to-brain transport; BBB permeability	Regional BBB permeability; DTI white-matter changes	A subset of football players showed persistent regional BBB dysfunction that correlated with white matter changes.
Israel		42 mTBI patients with PCS; 29 controls	On-season and off-season assessments					
Yoen et al., 2021 ¹⁸	Retrospective clinical imaging study	42 mTBI patients with PCS; 29 controls	Mild TBI with PCS	Direct BBB permeability and imaging evidence	DCE-MRI; whole-brain segmentation	Ktrans; vp; Patlak model	RPQ; neurocognitive tests	Increased cortical Ktrans and reduced vp in cerebellar WM/brainstem indicated subtle BBB disruption.
South Korea			Post-traumatic MRI; ≤3 vs >3 months subgroup					
Turtzo et al., 2020 ¹⁹	Prospective clinical imaging study	36 acute mTBI patients for DCE-MRI kinetics; 32 CT-negative mTBI patients for delayed MRI	Acute mild TBI	Direct meningeal BBB / blood–CSF barrier permeability evidence	DCE-MRI; delayed post-contrast MRI	Gadolinium extravasation; meningeal enhancement	CT-negative acute TBI; subarachnoid contrast redistribution	Meningeal enhancement occurred rapidly, and 18/32 patients showed delayed subarachnoid contrast spread, suggesting transient barrier disruption.
USA			Initial MRI within 6 h; delayed MRI several hours later					
Davis et al., 2020 ²⁰	Retrospective clinical imaging study	25 adults with suspected TBI	Mild TBI / suspected acute head injury	Direct meningeal BBB / blood–CSF barrier permeability evidence	Post-contrast FLAIR and T1 MRI	Gadolinium extravasation; traumatic meningeal enhancement	MRI sequence performance; TME detection	Post-contrast FLAIR detected TME more reliably than T1 MRI and may help identify acute TBI-related barrier injury.
USA			MRI within 48 h of injury					
Shahim et al., 2020 ²¹	Prospective observational	238 TBI/concussion participants;	Acute concussion, repetitive concussion, mild–severe TBI	Biofluid biomarkers of neuroaxonal injury	Serum and CSF biomarker analysis;	Neurofilament light chain	TBI severity, PCS duration,	Serum NfL correlated with CSF NfL,

Sweden/ USA	biomarker study	110 controls	6 days to 5 years after injury		MRI/DTI correlation		functional outcome, brain atrophy, traumatic axonal injury	distinguished TBI severity, and remained elevated for years after injury.
Lindblad et al., 2020 ²² Sweden	Longitudin al prospectiv e clinical study	17 severe TBI patients	Severe TBI; GCS 3–8 Repeated sampling for ~1 week after injury	Biofluid biomarkers of BBB-related protein clearance	CSF:blood albumin quotient; serial CSF/blood sampling	S100B; NSE; albumin quotient	GCS; CT injury severity; 6- month GOS	BBB integrity influenced S100B clearance from CSF to blood, while NSE appeared less dependent on BBB disruption. Day-of-injury GFAP and UCH-L1 predicted death and unfavorable outcome at 6 months, especially in GCS 3–12 TBI.
Korley et al., 2022 ²³ USA	Prospectiv e observatio nal cohort study	1,696 TRACK-TBI participants	TBI of all severities; GCS 3– 15 Day-of-injury blood sample; 6- month follow-up	Biofluid biomarkers of brain protein release after TBI	No direct BBB test; plasma biomarker assay	GFAP; UCH-L1; glial and neuronal injury	GOSE-TBI; mortality; unfavorable outcome; incomplete recovery	Day-of-injury GFAP and UCH-L1 predicted death and unfavorable outcome at 6 months, especially in GCS 3–12 TBI.
Tuure et al., 2024 ²⁴ Finland	Prospectiv e clinical biomarker study	178 TBI patients; 40 orthopedic injury controls	Mild and moderate- to-severe TBI Mean 9 months after injury	Biofluid biomarkers of neuroaxonal injury	No direct BBB test; plasma biomarker assay	Plasma NF- L; axonal injury	GOSE; GCS; CT positivity; PTA	Late plasma NF-L correlated with worse outcome in moderate-to- severe TBI and CT- positive mild TBI.
Koivikko et al., 2022 ²⁵ Finland	Prospectiv e clinical biomarker study	175 TBI patients; 40 orthopedic controls	Mild, moderate, and severe TBI Acute blood sampling after admission	Biofluid biomarkers of brain protein release after TBI	No direct BBB test; serum biomarker assay	S100B; NF- L; IL-10; H-FABP	TBI severity; CT-positive vs CT- negative injury; admission pathway	Biomarker levels were higher in moderate/sev ere TBI than mild TBI, but they could not reliably distinguish mild TBI from orthopedic trauma controls.
Dyhrfort et al., 2019 ²⁶ Sweden	Prospectiv e observatio nal neurointen sive-care study	10 severe TBI patients	Severe TBI; GCS ≤8 Microdialysis every 3 h for 5 days	Neuroinflamm atory and microdialysis pathways	Cerebral microdialys is; PEA protein profiling	92 inflammato ry proteins; cytokines, chemokines , MMP1, VEGFA	ICP/CP monitoring; 6-month GOSE	Sixty-nine proteins were analyzed, showing early, mid, late, biphasic, and stable inflammatory patterns after severe TBI.
Yue et al., 2023 ²⁷ USA	Prospectiv e multicente r observatio nal biomarker study	160 TBI patients; 28 orthopedic controls; 18 healthy controls	Mild to moderate/severe TBI; GCS 3–15 Blood draw within 24 h; outcomes at 3 and 6 months	Neuroinflamm atory biomarker pathways	Plasma inflammato ry biomarker assay	31 inflammato ry markers; HMGB-1, ILs, CRP, SAA, TNF, chemokines	TBI diagnosis, GCS severity, CT positivity, GOSE outcomes	Acute inflammatory markers showed diagnostic and prognostic value; IL-15 and SAA were priority

Dyhrfort et al., 2023 ²⁸	Prospective observational neurointensive-care biomarker study	10 severe TBI patients	Severe TBI; unconscious/intubated patients	Neuroinflammatory and microdialysis pathways	No direct BBB test; CMD-based cerebral protein profiling	21 proteins; IL-1 β , IL-6, IL-8, IL-1ra, MCP-2, MCP-3, VEGF, TAU, NF-H	Marshall CT grade; age; 6-month GOSE	markers across multiple outcome categories. Seventeen proteins showed significant temporal changes, with early, late, and biphasic inflammatory/axonal injury patterns after severe TBI.
Sweden			CMD monitoring up to 7 days after trauma					Higher MMP-2 and MMP-3 were associated with lower CBF during early symptomatic concussion, suggesting MMP-related cerebrovascular dysfunction.
Churchill et al., 2021 ²⁹	Longitudinal observational imaging-biomarker study	35 concussed athletes; 71 athletic controls	Sport-related concussion / mild TBI	Proteolytic/MMP-mediated cerebrovascular pathway	No direct BBB test; ASL-MRI CBF with plasma MMP assay	MMP-1, MMP-2, MMP-3, MMP-9, MMP-10; cerebral blood flow	SCAT symptoms; return-to-play; global/regional CBF	Inflammatory signatures were higher in CT-positive TBI and in patients with poor or incomplete recovery.
Canada			Median 5 days post-injury and 24 days at return-to-play					
Huie et al., 2019 ³⁰	Prospective multicenter proteomic biomarker study	130 TRACK-TBI patients	Acute TBI requiring head CT	Proteomic and inflammatory biomarker pathways	No direct BBB test; serum proteomic panel	72 serum proteins; 21-protein inflammatory signature	CT findings; GOSE; CVLT-II cognition	
USA			Blood within 24 h; outcomes at 3 and 6 months					

BBB, blood–brain barrier; CSF, cerebrospinal fluid; TBI, traumatic brain injury; mTBI, mild traumatic brain injury; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; DTL, diffusion tensor imaging; ASL-MRI, arterial spin labeling magnetic resonance imaging; CT, computed tomography; GCS, Glasgow Coma Scale; GOS/GOSE, Glasgow Outcome Scale/Extended; NFL/NF-L, neurofilament light chain; GFAP, glial fibrillary acidic protein; UCH-L1, ubiquitin C-terminal hydrolase L1; S100B, S100 calcium-binding protein B; NSE, neuron-specific enolase; MMP, matrix metalloproteinase; CMD, cerebral microdialysis; PEA, proximity extension assay; PCS, post-concussion syndrome.

The characteristics of the 15 clinical studies included in this review, which looked at blood–brain barrier dysfunction following traumatic brain injury, are summarized in Table I. The studies encompassed mild TBI, sport-related concussion, repetitive subconcussive exposure, acute TBI, and severe neurointensive-care TBI. The BBB breakdown or leakage of gadolinium and post-contrast MRI and meningeal enhancement were used in several studies to directly assess BBB, whereas serum, plasma, CSF and cerebral microdialysis biomarkers were used to assess BBB-related molecular mechanisms. These main molecular pathways involved were neuroaxonal injury markers (NfL, GFAP, UCH-L1, S100B and NSE), inflammatory cytokines/chemokines, MMP-related proteolytic pathways, and proteomic/microdialysis-based inflammatory signatures. The studies included in this review generally indicate that BBB disruption following TBI is associated with changes in BBB permeability, impaired protein clearance, neuroinflammation, cerebrovascular dysfunction, and decreased clinical or imaging outcomes.

Table II summarizes selected key studies that contributed the most distinctive evidence to the review. It highlights each study’s unique methodological or mechanistic value, including imaging evidence, biomarker prediction, protein clearance, neuroinflammation, MMP activity, and cerebral microdialysis findings.

Table II: Summary of Selected Key Studies and Their Unique Contribution to Understanding BBB Dysfunction After Traumatic Brain Injury

Author & Year	Unique Contribution to the Review	Study Strength	Clinical Significance	Limitation
O’Keeffe et al., 2020 ¹⁶	Linked repetitive head-impact exposure with dynamic BBB permeability changes in athletes	Combined biomechanical exposure data with DCE-MRI	Supports the role of subconcussive impacts in BBB disruption even without severe injury	Small sample and athlete-specific population
Veksler et al., 2020 ¹⁷	Demonstrated persistent regional BBB dysfunction in American football	Included athlete and non-athlete control groups with advanced DCE-MRI mapping	Suggests repeated mild head trauma may produce long-lasting BBB abnormalities	Male athlete cohort limits generalizability

Yoen et al., 2021 ¹⁸	players Evaluated BBB disruption in mTBI patients with post-concussion syndrome using regional DCE-MRI analysis	Used whole-brain segmentation and quantitative permeability parameters	Shows that persistent symptoms may be associated with subtle BBB changes	Retrospective design
Turtzo et al., 2020 ¹⁹	Identified meningeal BBB/blood–CSF barrier disruption in acute mild TBI	Early and delayed post-contrast MRI assessment	Highlights meningeal enhancement as a possible acute imaging marker of barrier injury	Optional delayed imaging reduced consistency
Shahim et al., 2020 ²¹	Showed that serum NfL reflects neuroaxonal injury across different TBI severities and time points	Prospective multicohort biomarker study with CSF and imaging correlation	Supports NfL as a clinically useful marker of persistent neuroaxonal injury	Heterogeneous cohorts and injury timing
Lindblad et al., 2020 ²²	Directly examined how BBB integrity influences brain protein biomarker clearance	Used CSF:blood albumin quotient with repeated CSF and blood sampling	Shows that circulating biomarkers may reflect both tissue injury and BBB transport/clearance	Very small severe-TBI sample
Korley et al., 2022 ²³	Provided strong prognostic evidence for day-of-injury GFAP and UCH-L1	Large multicenter TRACK-TBI cohort	Supports early biomarker-based prediction of 6-month outcome after TBI	Focused on prognostic value rather than direct BBB measurement
Yue et al., 2023 ²⁷	Identified inflammatory biomarkers associated with TBI diagnosis, severity, and outcome	Multicenter biomarker study with orthopedic and healthy controls	Supports neuroinflammation as a clinically relevant pathway after TBI	Pilot biomarker analysis requires validation
Churchill et al., 2021 ²⁹	Linked matrix metalloproteinases with cerebral blood flow changes after concussion	Combined plasma MMP assays with ASL-MRI perfusion imaging	Suggests proteolytic mechanisms may contribute to cerebrovascular dysfunction after concussion	Athlete-only population
Dyhrfort et al., 2019 ²⁶	Characterized temporal inflammatory protein patterns using cerebral microdialysis in severe TBI	Direct brain extracellular monitoring in neurointensive care	Shows that neuroinflammatory responses evolve over time after severe TBI	Very small uncontrolled sample

Table III showed the risk of bias for studies that primarily assessed BBB imaging or DCE-MRI/post-contrast FLAIR/traumatic meningeal enhancement, which were diagnostic-style methods. The majority of studies demonstrated minimal risk for the index test; imaging methods were well defined and objective. Several studies, however, were concerned or of high-risk in-patient selection and reference standard domains due to small sample size, selection, athlete-based, retrospective or lack of a true gold-standard test for BBB dysfunction. The overall certainty of evidence was rated as low to moderate. Evidence from larger multicenter biomarker studies provided moderate certainty, while certainty was reduced in small imaging, athlete-only, retrospective, and microdialysis studies because of limited sample size, heterogeneity, indirect BBB assessment, and risk-of-bias concerns.

Table III: Adapted QUADAS-2 for Diagnostic / Test-Evaluation Studies

Author & Year	Patient Selection	Index Test	Reference Standard / Comparator	Flow & Timing	Applicability	Overall Risk
Veksler et al., 2020 ¹⁷	Moderate (male volunteer sample)	Low (objective DCE mapping)	Moderate (no BBB gold standard)	Moderate (seasonal subset scans)	Moderate (athlete-specific cohort)	Moderate
Yoen et al., 2021 ¹⁸	Moderate (retrospective selection)	Low (automated DCE analysis)	Moderate (clinical PCS comparator)	Low (sample clearly defined)	Low (relevant mTBI-PCS)	Moderate
Turtzo et al., 2020 ¹⁹	Moderate (optional MRI component)	Low (standard contrast MRI)	Moderate (no independent standard)	Moderate (delayed scan optional)	Low (acute TBI relevant)	Moderate
Davis et al., 2020 ²⁰	High (selected MRI subset)	Low (blinded image reads)	Moderate (sequence comparison only)	Moderate (many exclusions)	Moderate (selected mild TBI)	Moderate
Koivikko et al., 2022 ²⁵	Moderate (CT-indicated patients)	Low (standard biomarker assays)	Moderate (CT/GCS imperfect)	Low (acute sampling clear)	Moderate (hospital-based cohort)	Moderate

This QUADAS-2 traffic-light plot demonstrates that there was a wide range of concerns across all imaging/test-evaluation studies, with a predominance of patient selection and lack of a clear reference standard for BBB dysfunction **Figure 2**. For all studies the domain of the index test was low risk, suggesting that imaging/biomarker methods were generally well described. The highest risk overall was in Davis et al., 2020²⁰, due to their highly selected patient sample.

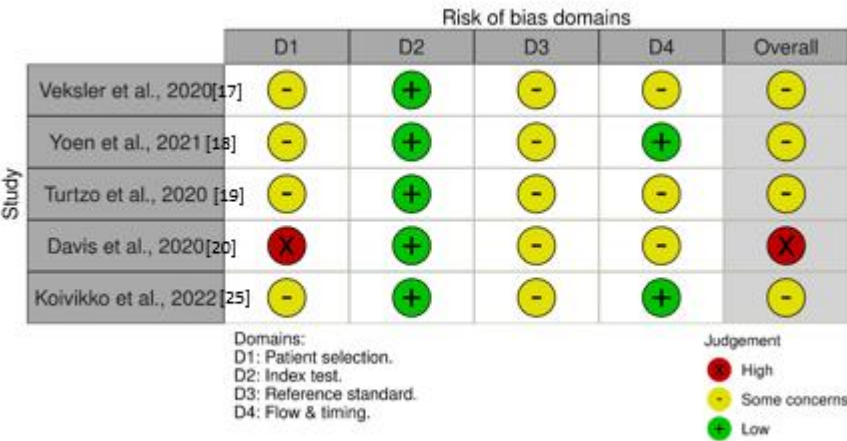


Figure 2: QUADAS-2 risk-of-bias traffic-light plot for diagnostic/test-evaluation studies.

Table IV summarized the studies that have used biomarkers to predict or evaluate clinical outcomes following TBI. Most studies were characterized by reliable measurement of the biomarker and clear outcomes, like GOSE, death, or functional outcome. The overall risk was mostly moderate/some concerns as some studies had heterogeneous populations, exploratory analyses or variable follow up. The best study in this group was the large TRACK-TBI study because it was better selected, presented with a standardized set of biomarker assays, and statistically analyzed.

Table IV: Adapted PROBAST for Prognostic Biomarker / Prediction Studies

Author & Year	Participants	Predictors / Biomarkers	Outcome Assessment	Analysis	Applicability	Overall Risk
Korley et al., 2022 ²³	Low (large multicenter cohort)	Low (standard GFAP/UCH-L1)	Low (blinded 6-month GOSE)	Low (adjusted models)	Low (broad TBI severity)	Low
Yue et al., 2023 ²⁷	Moderate (pilot subset sample)	Low (blinded inflammatory assays)	Low (3/6-month GOSE)	Moderate (exploratory AUCs)	Moderate (needs validation)	Moderate
Huie et al., 2019 ³⁰	Moderate (TRACK-TBI pilot)	Low (72-protein panel)	Low (CT, GOSE, CVLT)	Moderate (exploratory PCA)	Moderate (discovery analysis)	Moderate

The adapted PROBAST traffic light plot indicates that Korley et al., 2022²³ has the lowest risk of bias in the following domains: participant selection, biomarker assessment, outcome measurement, analysis, and applicability **Figure 3**. The domains in a biomarkers and in an outcomes assessment were low risk, but the domains in a participant selection and in an analysis were high, with some concerns, and the domain in applicability was high, with some concerns, as shown by Yue et al., 2023²⁷ and Huie et al., 2019³⁰.

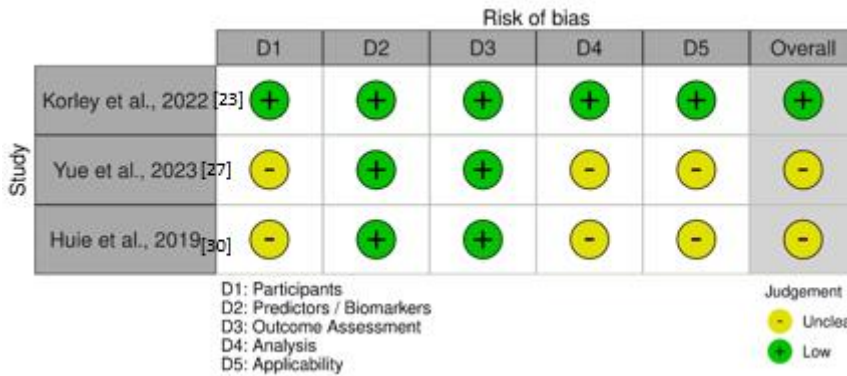


Figure 3: Adapted PROBAST risk-of-bias traffic-light plot for prognostic biomarker studies

Table V compares and contrasts studies that examined the relationships between various biomarkers, imaging results, injury exposure, and clinical outcomes. The primary sources of concern were with participation in the study, attrition from the study, confounding, and statistical adjustment primarily in athlete-based or single center cohorts. The risk of bias was generally low in most studies due to good exposure or to the measurement of the biomarkers, but was raised by the use of observational design and variable follow-up. The general trend of this table is moderate risk, with some higher risks for studies in very small samples or highly selected samples.

Table V: QUIPS for Prognostic-Factor / Exposure-Outcome Observational Studies

Author & Year	Study Participation	Attrition	Factor / Exposure Measurement	Outcome Measurement	Confounding	Analysis / Reporting	Overall Risk
O’Keeffe et al., 2020 ¹⁶	High (very small athletes)	High (rugby attrition)	Low (validated mouthguard/DCE)	Moderate (blinding unclear)	High (sports exposure variability)	Moderate (exploratory correlations)	High
Shahim et al., 2020 ²¹	Moderate (heterogeneous cohorts)	Moderate (variable follow-up)	Low (blinded NFL assay)	Low (MRI/DTI/GOS-E)	Moderate (mixed injury stages)	Moderate (complex associations)	Moderate
Lindblad et al., 2020 ²²	Moderate (17 severe TBI)	Low (serial sampling)	Moderate (different assay platforms)	Low (CT/GOS assessed)	Moderate (ICU confounding)	Moderate (interpolation/modeling)	Moderate
Tuure et al., 2024 ²⁴	Moderate (single-center cohort)	Moderate (late follow-up sample)	Low (single-batch NF-L)	Low (blinded neurologist)	Moderate (residual confounding)	Moderate (correlation analysis)	Moderate
Churchill et al., 2021 ²⁹	Moderate (athlete-only sample)	Moderate (partial paired data)	Low (MMP assay/ASL-MRI)	Low (CBF/SCAT measured)	Moderate (sport-related confounding)	Low (bootstrapped analysis)	Moderate

The overall risk of bias was moderate in most prognostic-factor studies, as indicated in this QUIPS traffic-light plot, primarily due to concerns regarding participation, attrition, confounding and statistical reporting. O’Keeffe et al., 2020¹⁶ was the highest risk of all because of high risk in study participation, attrition and confounding. Measurement of biomarker/ prognostic factors was generally higher across most studies, as compared to outcome measurement **Figure 4**.

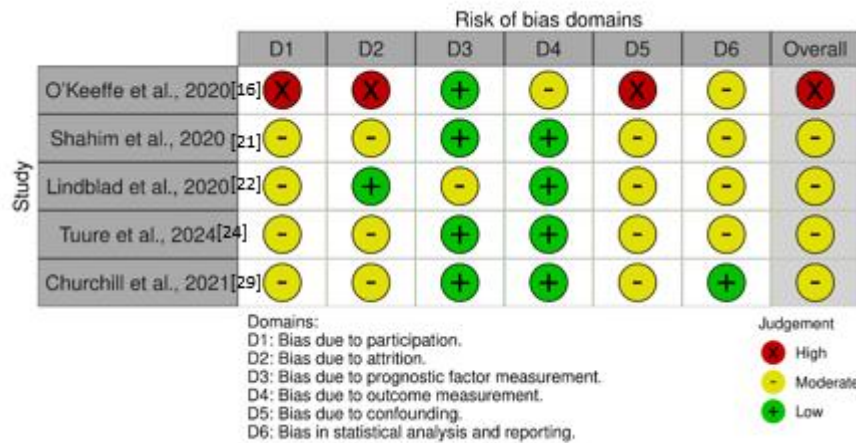


Figure 4: QUIPS risk-of-bias traffic-light plot for prognostic-factor observational studies

Table VI evaluates the small, uncontrolled case series microdialysis studies conducted in a JBI manner. The severe TBI populations were clearly defined in these studies, as were the measurement methods (e.g., cerebral microdialysis, PEA protein profiling). The overall risk was high, however, since only 10 patients were involved in both studies, there was no control group, and both studies were exploratory. These studies serve as a tool to provide insight into the mechanism, but should be taken with a grain of salt because it may not be generalizable.

Table VI: JBI Case Series Checklist for Small Uncontrolled Microdialysis Studies

Author & Year	Clear Inclusion Criteria	Consecutive / Complete Inclusion	Condition Measured Reliably	Biomarker Measurement	Outcome / Follow-up	Statistical Analysis	Overall Risk
Dyhrfort et al., 2019 ²⁶	Low (severe TBI defined)	High (convenience sample)	Low (GCS/CT/NIC defined)	Low (CMD + PEA)	Moderate (GOSE, blinding unclear)	Moderate (exploratory patterns)	High
Dyhrfort et al., 2023 ²⁸	Low (severe TBI defined)	High (10-case cohort)	Low (NIC monitoring clear)	Low (21-plex PEA)	Moderate (6-month GOSE)	Moderate (exploratory temporal analysis)	High

The overall risk of bias in both studies is high as seen in this JBI case-series traffic-light plot, primarily due to the high risk of bias in consecutive/complete inclusion and other sources of bias **Figure 5**. Both studies were of low risk, however, in various methodological domains in the studies such as inclusion criteria, condition measurement, biomarker measurement, outcome follow-up, and statistical analysis. Methods were well-resulted, however the small number of uncontrolled samples makes results unreliable and not generalizable.

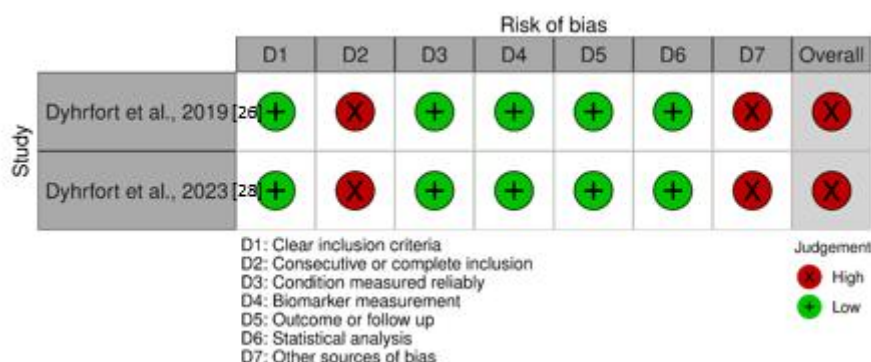


Figure 5: Adapted JBI case-series risk-of-bias traffic-light plot for microdialysis studies

Overall, the evidence indicates that BBB dysfunction after TBI is associated with altered permeability, impaired protein clearance, neuroaxonal injury, neuroinflammation, and cerebrovascular dysfunction. Imaging and biomarker studies support these associations across different TBI severities, although substantial methodological heterogeneity remains. Further large, multicenter studies using standardized BBB assessment methods are needed to validate biomarkers and clarify these mechanisms.

DISCUSSION

The results of the present systematic review suggest that blood–brain barrier (BBB) dysfunction is an important component of the pathophysiology of traumatic brain injury (TBI) ³¹. The studies included ranged from mild to sport related trauma to acute and severe TBI in a neurointensive care setting, to repetitive subconcussive head impacts ^{32,33}. Despite differences in study design, population, assessment method, and when the BBB dysfunction was measured following TBI, the overall evidence suggests that BBB dysfunction following TBI is linked to altered permeability, impaired brain protein clearance, neuroaxonal injury, neuroinflammation, proteolytic activity, and cerebrovascular dysfunction ³⁴.

Clinical evidence was obtained by direct imaging method that BBB disruption may occur even after mild or repetitive TBI ³⁵. Subtle barrier defects were found in athletes, patients with post-concussion syndrome, and acute mild TBI patients using dynamic contrast-enhanced MRI and gadolinium leakage and permeability mapping, and post-contrast MRI ³⁶. The relevance of these findings is important as many patients with mild TBI do not exhibit abnormalities on conventional CT or MRI but abnormalities may be found in advanced imaging, such as the imaging of subtle vascular or meningeal barrier abnormalities ³⁷. Delayed contrast redistribution and meningeal enhancement further indicate that barrier dysfunction might occur in both compartments of the blood–CSF barrier, the brain microvasculature, and the blood–CSF barrier ¹⁹. The biofluid biomarker studies corroborated the molecular changes associated with the TBI and BBB ³⁹. There were associations between biomarkers (specifically, neurofilament light chain, GFAP, UCH-L1, S100B, and neuron-specific enolase) and severity of TBI, CT positivity, post-concussion symptoms, brain atrophy, traumatic axonal injury and functional outcome ^{40,41}. These biomarkers primarily reflect neuronal, axonal, or glial injury and should not be interpreted as direct or specific biomarkers of BBB dysfunction. These markers may be indicators of glial injury, neuronal damage or axonal injury but interpretation is also dependent on the integrity of the BBB ⁴². Levels of circulating biomarkers therefore, should not be viewed solely as a measure of tissue damage, but also as a potential measure of changes in barrier transport and clearance ⁴³.

The review also revealed that inflammatory and proteolytic mechanisms play a key role in the dysfunction of the BBB in TBI ⁴⁴. Several studies have documented alterations in cytokines and chemokines, matrix metalloproteinases, inflammatory proteins and cerebral microdialysis markers in the acute and subacute time course of injury ⁴⁵. The matrix metalloproteinases could be responsible for breakdown of the extracellular matrix and tight-junction proteins, which would compromise vascular stability and permeability ⁴⁶. Microdialysis revealed that there are changes in inflammatory protein patterns over time in severe TBI, indicating that BBB dysfunction is not a single acute event ⁴⁷. The included studies have some limitations such as small sample sizes, substantial heterogeneity selected populations, cohorts of athletes only, retrospective designs or exploratory biomarker analyses. Lack of gold standard techniques for BBB analysis is another limitation. Like other systematic reviews, this has its limitations. As this study was based on full-text studies published in English since 2019, the results may not include relevant studies published prior to this period or those written in a language other than English. Moreover, some studies evaluated BBB-related mechanisms indirectly, instead of measuring barrier permeability directly.

Further studies are needed on large prospective multicenter studies that are powered by consistent protocols for BBB imaging, consistent panels of biomarkers and harmonized clinical outcome measures. There is a need for more longitudinal studies to define the nature of the changes in BBB dysfunction from the acute to chronic stage of TBI and its relationship to TBI outcome, chronic symptoms, and disability. Advanced imaging, biofluid biomarkers, microdialysis data, and clinical outcome data may be combined to gain a more comprehensive understanding of BBB dysfunction and future diagnostic, prognostic, and therapeutic targets may be discovered in TBI.

CONCLUSION

This systematic review supports blood–brain barrier (BBB) dysfunction as an important component of the pathophysiology of traumatic brain injury (TBI) across mild, repetitive, acute, and severe injury. Imaging, biofluid biomarker, and microdialysis studies indicate that BBB-related abnormalities are associated with altered permeability, neuroaxonal injury, inflammation, impaired protein clearance, and cerebrovascular dysfunction. However, small sample sizes, methodological heterogeneity, and the lack of standardized BBB assessment methods limit the strength of the available evidence. Large multicenter studies are needed to validate candidate biomarkers and clarify potential therapeutic targets related to BBB dysfunction in TBI.

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