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The Role of Acute Neuroinflammation in Patient Recovery Post-Traumatic Brain Injury: A Literature Review

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Abstract
Traumatic brain injury (TBI) is a leading cause of death and disability worldwide, affecting millions annually [1]. Acute neuroinflammation following traumatic brain injury (TBI) is an essential process for tissue repair and recovery. However, excessive, or prolonged inflammation can exacerbate damage, contributing to secondary brain injury. This review aims to consolidate the complex balance between beneficial and harmful inflammatory responses in TBI, exploring how this balance impacts patient outcomes. This review synthesizes findings from recent studies examining neuroinflammatory biomarkers during the first two weeks post-injury. A systematic search of PubMed, Nature, and related databases identified studies reporting cytokines, chemokines, cell activation markers, acute phase proteins, and oxidative stress indicators in the brain following closed-head TBI. After applying strict inclusion and exclusion criteria, ten studies were selected. These formed the basis for evaluating temporal patterns of inflammation and identifying biomarkers linked to secondary injury and recovery to understand the boundary between beneficial and harmful responses. Proinflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-8 (IL-8), and monocyte chemoattractant protein-1 (MCP-1), consistently rose within hours of injury and remained elevated for several days, with IL-6 and IL-8 often exceeding 1000 pg/mL – levels more than 100-fold above baseline, indicating severe immune activation and potential contribution to secondary injury [2]. The anti-inflammatory mediators interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1ra) also increased, but to a lesser degree. Markers of immune activation, such as cluster of differentiation 68 (CD68) and soluble intercellular adhesion molecule-1 (sICAM-1)) were elevated in brain tissue and cerebrospinal fluid (CSF). Biomarkers of axonal and neuronal injury, including neurofilament light chain (NFL) and ubiquitin carboxy-terminal hydrolase L1(UCH-L1),were significantly elevated within 24–72 hours. Neuroinflammation in TBI involves overlapping immune responses that vary with time, location, and severity. Cytokine activity may aid repair, but prolonged IL-6 and MCP-1 elevation can worsen damage. The complexity of immune activation and structural injury suggests that no single biomarker is sufficient. Multi-marker models may offer better tools to guide treatment. This review seeks to inform future approaches and support the development of targeted strategies for regulating inflammation in TBI.

Keywords: traumatic brain injury; neuroinflammation; cytokines; biomarkers; secondary brain injury; microglia; inflammatory regulation

Introduction

TBI is a major global health concern, contributing to substantial morbidity and mortality [1]. It affects an estimated 69 million people worldwide each year [3]. Among individuals under 45, TBI is a leading cause of death, and many survivors experience long-term disability as a result of its effects [4].

TBI results from external forces that cause structural or functional damage to the brain. It increases the risk of long-term neurological and psychiatric conditions, including Alzheimer's disease, Parkinson's disease, seizure disorders, depression, cognitive impairment, sleep disturbances, disorders of consciousness, and speech deficits [5]. TBI is typically classified into closed-head injuries, penetrating injuries, and blast-related injuries, which are more common in military settings. The severity of TBI is assessed using the Glasgow Coma Scale, which evaluates motor, eye, and verbal responses [6]. Each year in the United States, approximately 50,000 TBI cases result in death, 230,000 lead to hospitalization with survival, and 80,000 to 90,000 patients develop long-term disabilities [7].

Current TBI treatments focus on symptom management, in part because the secondary injury mechanisms main largely idiopathic, rather than directly addressing the

underlying pathology. Common interventions include the use of steroids to reduce inflammation, though these can suppress immune function and lead to systemic side effects [8]. Pain relievers are frequently prescribed to manage headaches and neurotic pain, while rehabilitation therapies, including physical, cognitive, and speech therapy, aim to improve functional recovery. However, despite these efforts, no treatments currently exist to prevent further neurological damage caused by TBI.

TBI progresses through two distinct phases that each contribute to neurological damage [9]. The primary injury occurs at the moment of impact and involves direct damage to brain tissue. This can include contusions and hemorrhaging from ruptured blood vessels, axonal shearing that disrupts neural pathways and white matter, and skull fractures that may cause additional complications including brain swelling or increased risk of infection.

Following the initial trauma, a cascade of biochemical and cellular responses leads to the secondary injury, which can further worsen brain damage [9]. Oxidative stress from the buildup of free radicals impairs cell function and can result in cell death. Excitotoxicity, caused by excessive release of neurotransmitters including glutamate, overstimulates neurons and leads to their degeneration. Neuroinflammation, driven by activated microglia and the release of proinflammatory cytokines, contributes to ongoing neurodegeneration and may negatively impact recovery. Although neuroinflammation can support repair, its prolonged or excessive activation is often harmful. The complexity of these secondary processes demonstrates the importance of strategies aimed at protecting neural tissue, limiting inflammation, and reducing the risk of long-term impairment.

While the outcomes and clinical effects of TBI have been extensively studied, increasing attention over the past two decades has focused on the role of inflammatory markers and immune mediators in guiding treatment development. These findings hold promise for creating more effective therapies that target the underlying mechanisms of TBI rather than just managing its symptoms.

Although the pathophysiological mechanisms of TBI are well documented, recent research emphasizes the importance of neuroinflammatory pathways in shaping both acute and long-term outcomes. However, the temporal dynamics and functional implications of specific inflammatory mediators remain incompletely understood. This review synthesizes current findings on inflammatory biomarkers during the acute phase of TBI and evaluates their association with secondary injury processes and recovery trajectories. In particular, it is aimed to examine how variations in cytokine and chemokine expression, immune cell activation, and related molecular signals distinguish beneficial from detrimental inflammatory responses in the acute stages following injury.

Methods

This literature review examines biomarkers associated with neuroinflammation during the acute phase of TBI, focusing on their temporal patterns and roles in recovery and secondary damage. Specifically, studies tracking fluctuations in cytokines, chemokines, and other molecular indicators over the first two weeks post-injury were analyzed to identify key markers influencing neuroinflammatory responses.

A broad literature search was conducted across major scientific databases, including PubMed, Nature, and other relevant sources, selecting clinical studies that investigated neuroinflammation and inflammatory biomarkers present in or around the brain after post-TBI. Key terms were searched, yielding 43 papers, which were further screened for relevance. Inclusion criteria included the presence of biomarker data in the report, studies on closed-head injuries without concurrent injuries, and a time frame of one week or less post-injury. Key search terms including ((acute) AND (traumatic brain injury)) AND (biomarker) were used, along with Medical Subject Headings terms including “Brain Injuries, Traumatic/physiopathology,” “Brain Injuries, Traumatic/complications,” and “Neuroprotection.” Each paper was independently screened by the reviewers. Studies that did not contain data on cytokines, chemokines, cell activation markers, acute phase proteins, or oxidative stress markers were excluded. Additionally, studies lacking clear temporal biomarker measurements within the first two weeks post-injury were excluded. Following the review, the final number of included studies was narrowed down to ten.

Results

Table 1 summarizes clinical findings from ten studies assessing reported changes in biomarkers within the first two weeks following TBI. Symbols indicate elevations (↑), decreases (↓), no changes (/), or unreported findings (—). Statistical significance is noted where available.

Table 1. Summary of Findings from Clinical Studies on Acute Inflammatory and Immune Markers Following Traumatic Brain Injury (TBI)

Markers/studies	Csuka et al. [1]	Kumar et al. [2]	Nessel et al. [5]	Jenkins et al. [10]	Semple et al. [11]	Cannon et al. [12]	Rowland et al. [13]	Abboud et al. [14]	Tsitsipanis et al. [15]	Nitta et al. [16]
IL-2	—	—	↑ ($p = 0.0191$)	—	—	—	—	—	—	—
IL-4	—	—	—	—	—	—	—	↑ ($p < 0.05$)	—	—
IL-5	—	—	—	—	—	—	—	↑ ($p < 0.05$)	—	—
IL-6	↑	↑ ($p < 0.001$)	↑ ($p = 0.0015$)	—	—	↑ ($p = 0.0551$)	↑ ($p < 0.05$)	↑ ($p < 0.05$)	↑ ($p = 0.001$)	↑ ($p < 0.001$)
IL-1β	—	—	—	—	—	↓	—	/	—	—
IL-8	—	—	—	—	—	↑ ($p = 0.0549$)	↑ ($p < 0.05$)	↑ ($p < 0.05$)	↑ ($p = 0.004$)	—
IL-10	/	—	—	—	—	—	↑	—	—	—
IL-ra	—	—	—	—	—	—	↑	—	—	↑ ($p \leq 0.001$)
IL-13	—	—	↑ ($p = 0.00094$)	—	—	—	—	↑ ($p < 0.05$)	—	—
TNF-α	↑	↑ ($p < 0.01$)	—	—	—	—	/	↑ ($p < 0.05$)	—	—
MCP-1	—	—	—	—	—	↑ ($p < 0.05$)	—	—	—	—
sICAM-1	—	↑ ($p < 0.01$)	—	—	—	—	—	—	—	—
sVCAM-1	—	↑ ($p < 0.01$)	—	—	—	—	—	—	—	—
sFAS	—	↑ ($p < 0.01$)	—	—	—	—	—	—	—	—
CD68	—	—	—	↑ ($p = 0.0002$)	—	—	—	—	—	—
CCL2	—	—	—	—	↑ ($p < 0.001$)	—	↑	↑ ($p < 0.05$)	—	—
IFN-γ	—	—	—	—	—	↑ ($p < 0.05$)	/	—	—	
CSF3	—	—	—	—	—	—	↑	—	—	—

/ = no change; ↑ = elevated; ↓ = decreased; — = unobserved

Pro-Inflammatory Cytokines

In the acute phase of TBI, CSF and serum levels of IL-6, IL-8, TNF-α, interferon-gamma (IFN-γ), MCP-1, interleukin-2 (IL-2), interleukin-5 (IL-5), and interleukin-11 (IL-11) are elevated compared to uninjured controls [1-2, 5, 10-14]. IL-6 rises within hours post-injury and remains elevated through days 3–5, with concentrations in CSF up to 7.2 times higher than in serum [2]. Peak levels are observed within 30 hours post-injury, with some cases exceeding 1,000 pg/mL [5, 14]. Elevated IL-6 is reported across mild and severe TBI cases [2].

IL-8 levels show an upward trend within the first 24–72 hours in plasma and are significantly elevated in CSF on Day 0 [11, 12, 14]. However, in one study of complicated TBI cases, IL-8 was significantly reduced relative to controls [15]. TNF-α is significantly elevated in CSF within the first five days post-injury [1, 2]. IFN-γ and MCP-1 are significantly increased in plasma and CSF respectively during the first 24–72 hours after injury, with MCP-1 peaking on Day 0 and remaining elevated through Day 9 [11, 12]. IL-2 is significantly increased from 0 to 24 hours post-injury, while IL-5 and IL-11 are elevated at acute time points in serum [5, 14]. Interleukin-1 beta (IL-1β) is inconsistently reported: some studies detected its presence but found no significant elevation, while other studies reported no change or did not measure it directly [12, 13].

Anti-Inflammatory Cytokines

IL-10 is significantly elevated in both CSF and plasma across studies [1, 2, 5, 15]. IL-10 peaks within the first three days post-injury and may persist longer than TNF-α or IL-6, with some evidence of a smaller secondary peak in the second week [1]. In CSF, IL-10 concentrations below 1.06 pg/mL were observed in healthy controls [1]. IL-1 receptor antagonist (IL-1ra) is significantly elevated by 6 hours post-injury [16]. Interleukin-13 (IL-13) is significantly elevated at 24 hours post-injury [14]. Interleukin-4 (IL-4) showed elevation in one study [14], while other studies did not report significant findings.

Cell Activation Markers

Increased microglial and macrophage activation is observed via elevated CD68 expression in brain tissue, with no corresponding rise in ionized calcium-binding adaptor molecule-1 (Iba-1) [10, 15]. The CD68 to Iba-1 ratio is significantly higher in TBI brain tissue and correlates with regions of fibrinogen deposition [10]. Additionally, soluble cell activation markers including sICAM-1, soluble vascular

cell adhesion molecule-1 (sVCAM-1), and soluble Fas protein (sFAS) are significantly elevated in CSF during the acute post-injury phase [2].

Additional Immune Mediators

NFL, a marker of axonal injury, is significantly elevated in plasma at 24 and 72 hours post-injury compared to controls, with levels averaging 269 pg/mL and 276 pg/mL respectively [5]. This increase is accompanied by reductions in lipid species including lysophosphatidylcholine, phosphatidylcholine, and hexosylceramide, and low omega-3 index (~4%) across all TBI patients.

Glial fibrillary acidic protein (GFAP) and UCH-L1 are also significantly elevated in blood within the first 12 hours post-injury and remain elevated through Day 7 [15].

Fibrinogen is deposited around cerebral blood vessels in TBI tissue more frequently than in controls and co-localizes with areas of reduced neuronal density, as shown by neuronal nuclei protein (NeuN) staining [10]. Beta-amyloid precursor protein (bAPP) is elevated in white matter regions including the corpus callosum and internal capsule, and immunoglobulin G (IgG) is also increased in TBI brain samples [10].

Finally, inflammatory network connectivity is increased post-injury, with enhanced inter-cytokine clustering and centrality of IL-6, IL-8, and IL-1α observed within 6 hours [13, 14].

Discussion

The inflammatory response following traumatic brain injury (TBI) involves a complex interaction of pro- and anti-inflammatory mediators, which may play both protective and damaging roles. Acute neuroinflammation varies by cell type, injury location, and severity. Inflammatory mediators released after the initial insult influence neuronal survival, glial activation, blood–brain barrier integrity, and longer-term recovery trajectories.

Rather than following a uniform pattern, cytokine responses differ across individuals and injury types. Elevations in IL-6, TNF-α, IL-8, IFN-γ, and MCP-1 are consistently reported in the acute phase, which may contribute to leukocyte infiltration and tissue remodeling. Their persistence beyond the initial phase of injury raises concern for ongoing immune activation.

Not all cytokines follow the same trajectory. Reduced levels of biomarkers including macrophage inflammatory protein-1 beta, interferon-gamma-induced protein-10, and interleukin-9 in complicated TBI suggest a divergence from typical inflammatory trajectories. These reductions may reflect suppressed signalling pathways or selective vulnerability of certain immune processes in severe or multifocal injuries. The absence of IL-1β elevation in several studies aligns with this variation and suggests that pro-inflammatory cytokine responses are not uniformly amplified after TBI.

Anti-inflammatory cytokines are also detectable during the acute phase, with IL-10 showing one of the most consistent responses. Its inhibitory effects on IL-1β, TNF-α, and other cytokines suggest a counter-regulatory role. A secondary IL-10 peak in the second week may indicate ongoing attempts to resolve inflammation. IL-1ra and IL-13 are also elevated, while IL-4 displays mixed findings. This variability may reflect differences in sampling time, patient heterogeneity, or technical limitations in measurement.

Markers of immune activation including CD68 are increased in tissue from TBI patients. Elevated CD68 and CD68 to Iba-1 ratios suggest enhanced microglial and macrophage presence, particularly in regions with high fibrinogen deposition. These findings suggest a localized inflammatory response linked to vascular disruption. The absence of Iba-1 elevation may reflect changes in cell phenotype rather than total microglial population.

The vascular endothelium also appears to be involved. Elevations in soluble adhesion molecules, namely sICAM-1 and sVCAM-1 indicate endothelial activation and a disrupted barrier, which may facilitate immune cell infiltration. Together with increased sFAS levels, these findings point to an interaction between immune and apoptotic signalling.

Elevations in GFAP, UCH-L1, and NFL reflect structural injury and glial activation. These markers may correlate with clinical severity in several studies, though further study is needed to determine their predictive reliability. The association of these markers with functional outcomes suggests they may be useful in prognosis, although further work is needed to determine their reliability across populations.

Histological patterns of increased fibrinogen, reduced NeuN staining, and elevated bAPP and IgG signal support the presence of ongoing inflammation and structural damage beyond the immediate injury site. These patterns are consistent with secondary injury mechanisms extending beyond the initial trauma.

Together, these findings support the view that neuroinflammation is a sustained feature of TBI. The inflammatory response is multifaceted, involving cytokine production, immune cell recruitment, endothelial activation, and glial involvement. Emerging research has linked these biomarkers to neurodegenerative conditions such as Alzheimer's and Parkinson's disease, suggesting that persistent inflammation may increase susceptibility to secondary disorders. Interactions between cytokine pathways, for example IL-6 affecting MCP-1 expression, may amplify neuroinflammatory responses and contribute to poorer outcomes. Disentangling these roles remains a key challenge.

The broad range of immune signals detected across studies suggests that a single biomarker is unlikely to capture the full extent of injury or predict recovery. A more informative approach may involve combining panels of

cytokines, structural proteins, and clinical indices to develop composite prognostic models. These could help stratify patients for interventions targeting inflammation. Future studies should consider the timing of sampling, injury heterogeneity, and regional variation in inflammation when evaluating potential therapeutic windows.

Outcomes

The inflammatory response following TBI in the acute phase has important implications for recovery. Prolonged elevation of IL-6 and MCP-1 has been associated with poorer functional outcomes, suggesting that unresolved neuroinflammation may contribute to secondary injury processes. In particular, persistent MCP-1 expression likely reflects ongoing recruitment of monocytes and macrophages into the central nervous system (CNS), which may exacerbate tissue damage [11].

The detection of activated microglia, especially in perivascular regions with fibrinogen deposition, indicates that inflammatory activity is not confined to the initial site of trauma. This spatial spread of immune activation may compromise neighboring neural circuits and disrupt global brain function. Overtime, this pattern of immune activation may interact with other inflammatory pathways and contribute to synaptic dysfunction or promote neurodegenerative cascades. Moreover, prolonged microglial activation has been implicated in the progression of neurodegeneration in other conditions, including Alzheimer's disease and multiple sclerosis, raising concern that similar mechanisms may operate post-TBI [10]. These findings support the view that inflammatory trajectories influence not only acute recovery but also the risk of chronic neurological decline.

Implications

While neuroinflammation is essential for initiating repair, clearing cellular debris, and supporting tissue recovery, unregulated or prolonged inflammation can have damaging effects. Elevated concentrations of proinflammatory cytokines IL-6 and TNF-α, along with chemokines like MCP-1, are not only linked to worse functional outcomes but may also promote sustained microglial activation and oxidative stress, contributing to long-term neurodegeneration [10, 17].

Chronic neuroinflammation following acute TBI has been associated with increased risk for neurodegenerative diseases including Alzheimer's and Parkinson's disease, due to its contribution to synaptic dysfunction, neuronal loss, and the spread of pathological protein aggregates [18]. In addition, ongoing glial activation, infiltration of peripheral immune cells, and blood–brain barrier disruption may facilitate the spread of inflammatory signals beyond the CNS, potentially affecting peripheral organ systems and impairing systemic recovery [19].

Given these risks, understanding the timing, intensity, and regulation of neuroinflammatory responses is essential for identifying therapeutic windows and developing targeted interventions. Modulating the immune response to preserve its protective functions while limiting its harmful consequences could improve recovery and reduce the risk of chronic neurological and systemic complications.

Conclusions

Neuroinflammatory biomarkers, including cytokines, chemokines, and acute-phase proteins, are consistently altered in the acute phase following traumatic brain injury. These changes are associated with increased immune activation, oxidative stress, and worse functional outcomes. Hyperinflammation, particularly persistent elevation of mediators, namely IL-6 and MCP-1, can drive secondary injury, disrupt neuronal repair processes, and contribute to long-term neurological decline. Understanding the timing, source, and magnitude of these inflammatory responses is critical to identifying therapeutic windows that can reduce harm while preserving repair mechanisms. This molecular understanding of acute inflammation provides a basis for moving beyond symptomatic treatment and toward targeted strategies that address the root causes of secondary brain injury. In doing so, they help close the gap between trauma and recovery in TBI care. Research going forward should focus on identifying specific thresholds that distinguish helpful from harmful inflammation. Efforts should prioritize the development of therapies that reduce excessive immune activation while preserving the beneficial effects of inflammatory signaling to support recovery and improve patient outcomes.

List of Abbreviations

bAPP: beta-amyloid precursor protein
CD68: cluster of differentiation 68
CNS: central nervous system
CSF: cerebrospinal fluid
GFAP: glial fibrillary acidic protein
Iba-1: ionized calcium-binding adaptor molecule-1
IFN-γ: interferon-gamma
IgG: immunoglobulin G
IL-10: interleukin-10
IL-11: interleukin-11
IL-13: interleukin-13tnf-α – tumor necrosis factor-alpha
IL-1ra: interleukin-1 receptor antagonist
IL-1β: interleukin-1 beta
IL-2: interleukin-2
IL-4: interleukin-4
IL-5: interleukin-5
IL-6: interleukin-6
IL-8: interleukin-8
MCP-1: monocyte chemoattractant protein-1
NeuN: neuronal nuclei protein
NFL: neurofilament light
sFas: soluble fas protein
sICAM-1: soluble intercellular adhesion molecule-1
sVCAM-1: soluble vascular cell adhesion molecule-1

TBI: traumatic brain injury
UCH-L1: ubiquitin carboxy-terminal hydrolase l1

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent
As this article was a review article, no permission was needed from an ethics committee, and no participants were consulted on its creation.

Authors' Contributions
EY: made contributions to the design and planning of the study, collected and analyzed data, reviewed the manuscript, and gave final approval of the version to be published.
HHK: made contributions to the design and planning of the study, collected and analyzed data, drafted and reviewed the manuscript, and gave final approval of the version to be published.

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