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Review Article

Plasma Neurofilament Light Chain as a Marker of Axonal Injury in Traumatic Brain Injury

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Abstract

Background: Traumatic brain injury (TBI) spans concussion to severe injury, and axonal shearing is a shared pathway across this spectrum. Neurofilament light chain (NfL), an axonal protein, enters blood after axonal damage and is now measurable with ultrasensitive digital immunoassays.

Objective: To synthesise published evidence on plasma NfL as a marker of axonal injury across the TBI severity spectrum.

Methods: Narrative review of cohort studies, comparative biomarker studies, imaging-correlation studies and methodological reports.

Findings: Plasma NfL rises with injury severity, stays elevated longer than glial markers, correlates with diffusion imaging abnormalities, and predicts long-term outcome and progressive neurodegeneration. In sport-related concussion, NfL distinguishes injured athletes from controls and tracks recovery time. Age, renal function and neurological comorbidity confound interpretation, and NfL lacks injury-type specificity.

Conclusions: Plasma NfL is a promising, non-specific axonal injury marker complementing glial biomarkers, with growing but still incomplete evidence supporting clinical translation.

Keywords: Neurofilament light chain; Traumatic brain injury; Axonal injury; Biomarker; Concussion

Abstract

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Keywords: neurofilament light chain; traumatic brain injury; axonal injury; biomarker; concussion

Introduction

Traumatic brain injury (TBI) remains a leading cause of death and disability worldwide, encompassing an enormous clinical spectrum from transient concussion to devastating, life-altering severe injury. Across that spectrum, diffuse axonal injury is a common and often under-recognised pathological substrate, difficult to visualise on conventional computed tomography and only partially captured by structural magnetic resonance imaging. This diagnostic gap has driven decades of interest in blood-based biomarkers that could objectively index axonal damage at the bedside.

Neurofilaments are obligate cytoskeletal heteropolymers of neurons, providing structural support and radial axonal growth; the light subunit (NfL) is the most abundant and most extensively studied in biofluids [1]. When axons are sheared, stretched or otherwise damaged, NfL leaks from the axoplasm into the interstitium, cerebrospinal fluid (CSF) and ultimately peripheral blood, where it can be measured as a quantitative index of axonal injury burden [2]. For decades this measurement was confined to CSF, but the advent of single-molecule array (Simoa) digital enzyme-linked immunosorbent assay technology, capable of detecting proteins at subfemtomolar concentrations, made reliable blood-based NfL quantification practical [3]. This methodological advance transformed NfL from a research CSF marker restricted to lumbar puncture cohorts into a scalable, minimally invasive tool applicable across emergency, sports-medicine and outpatient settings [4].

This narrative review synthesises the published literature on plasma and serum NfL in TBI, covering axonal biology and assay methodology, diagnostic and prognostic performance across the injury-severity spectrum, comparison with other candidate blood biomarkers, correlation with neuroimaging and long-term outcome, application in sports-related concussion and repetitive head impact research, and the principal limitations that currently constrain clinical translation.

Neurofilament Biology and Assay Methodology

NfL forms the core scaffold of the neurofilament triplet, conferring axonal calibre and mechanical resilience; its release into extracellular fluid after axonal disruption is well established across traumatic, neurodegenerative and neuroinflammatory disease models [1,5]. Because axons throughout the central and peripheral nervous system contain neurofilaments, elevated blood NfL indicates axonal injury broadly rather than any single anatomical or aetiological process, a point developed further below [2].

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Blood NfL concentrations are one to two orders of magnitude lower than corresponding CSF concentrations, historically placing reliable serum measurement beyond the sensitivity of conventional immunoassays. Digital ELISA (Simoa) technology resolved this by isolating individual immunocomplexes in femtolitre-sized microwells, enabling single-molecule counting and pushing the limit of detection into the subfemtomolar range [3]. This capability underlies essentially all contemporary plasma and serum NfL studies in TBI. Because circulating NfL also rises physiologically with age and varies with several non-neurological factors, large reference cohorts spanning childhood to older adulthood have been assembled to define expected concentration ranges, an essential step for clinical interpretation [6,7].

Plasma NfL Across the Spectrum of TBI Severity

A substantial body of cohort evidence links circulating NfL concentration to TBI severity and to clinical outcome. In a mixed-severity cohort, serum NfL provided prognostic information independent of established clinical predictors, an early demonstration that it captures information not already contained in standard severity scores [8]. In severe TBI managed in intensive care, serum NfL sampled longitudinally predicted long-term clinical outcome, with concentrations that rose sharply after injury and remained elevated for a protracted period compared with typical laboratory markers [9].

At the milder end of the spectrum, serum NfL distinguished professional athletes with sport-related concussion from uninjured teammates and remained detectable for days after injury, well beyond the usual clearance window of glial markers [10]. A subsequent study in the same population found that NfL outperformed tau and other candidate markers for concussion identification and correlated with recovery time [11]. Complementary work characterising the time course of NfL alongside tau, glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) in subacute and chronic TBI found that NfL rises more slowly than glial markers but persists longer, consistent with ongoing or delayed axonal degeneration [12]. Across a cohort spanning multiple injury severities, plasma NfL concentrations tracked reported injury severity and correlated with other neurochemical and imaging measures of injury burden [13]. In mild TBI specifically, admission plasma NfL has been linked to subsequent development of axonal pathology detectable on follow-up imaging, suggesting acute-phase NfL carries information about evolving, not just baseline, axonal injury [14].

Table 1: Selected cohort studies of plasma or serum neurofilament light chain in traumatic brain injury reviewed here [9,10,11,13,12,8,20,22,23,14]; N = 10 studies.

Study	Population	Severity/setting	Key finding
Al Nimer 2015	Mixed-severity TBI cohort	Mild to severe	Serum NfL independently prognostic
Shahim 2016	ICU-managed TBI	Severe	Serum NfL predicts clinical outcome
Shahim 2017	Professional ice hockey	Concussion vs teammates	Serum NfL distinguishes concussion
Shahim 2018	Sport-related concussion	Mild/concussion	NfL outperforms tau; tracks recovery time
Shahim 2020a	Multi-severity TBI cohort	Mild to severe	Plasma NfL scales with severity
Shahim 2020b	Subacute/chronic TBI	Mixed	NfL rises slower, persists longer than glial markers
Graham 2021	Long-term follow-up TBI cohort	Mixed, up to 17 years	NfL predicts long-term outcome, neurodegeneration
McCrea 2020 (CARE)	Collegiate athletes	Acute sport-related concussion	Multimarker panel including NfL characterised acutely
Verduyn 2021	Contact-sport athletes	Cumulative exposure	CSF/blood NfL examined against exposure
Hossain 2023	Mild TBI cohort	Mild	Admission NfL predicts axonal pathology on imaging

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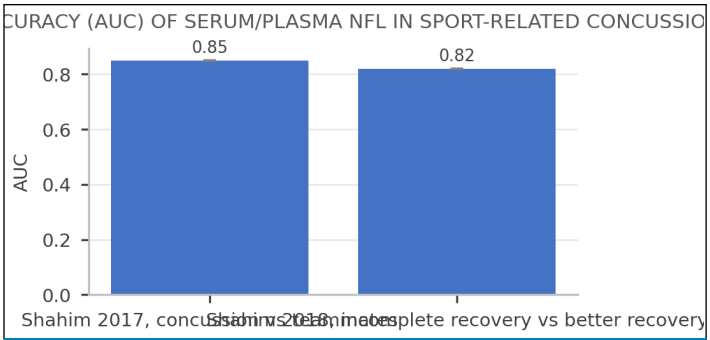

Figure 1: Reported diagnostic accuracy (area under the receiver operating characteristic curve, AUC) of serum/plasma NfL for distinguishing injury status in two published sport-related concussion cohorts: hockey players with concussion versus uninjured teammates [10]; athletes with sport-related concussion and incomplete recovery versus better recovery [11].

Comparison with Other Blood-Based Biomarkers

NfL is one of several candidate TBI blood biomarkers, alongside GFAP, UCH-L1 and tau, each reflecting a different injured cell compartment: GFAP is astrocytic, UCH-L1 is neuronal cytoplasmic, and both NfL and tau are axonal, though with differing release kinetics [15]. GFAP and UCH-L1 rise rapidly after injury and have been the most clinically advanced markers to date; a large multicentre study of their combined use to rule out intracranial injury on head computed tomography achieved high sensitivity and negative predictive value, underpinning regulatory clearance of a blood test for this indication [16]. Earlier work characterising GFAP and UCH-L1 kinetics in trauma patients with and without mild TBI established their diagnostic accuracy for acute CT-detectable pathology [17].

Where GFAP and UCH-L1 excel acutely, NfL appears comparatively more informative for subacute and long-term axonal injury burden. Day-of-injury plasma GFAP and UCH-L1 concentrations predicted six-month functional recovery in a large multicentre cohort, demonstrating that acute glial and neuronal markers also carry prognostic value extending well beyond the emergency encounter [18]. A multiplex assay directly comparing GFAP, UCH-L1, tau and NfL after sport-related concussion found each marker followed a distinct acute trajectory, reinforcing that no single biomarker captures the full pathophysiology and that a multimarker panel may be more informative than any single analyte [19].

Table 2: Principal blood-based protein biomarkers investigated in traumatic brain injury and their characteristics [2,17,16,15,19,12].

Biomarker	Cell/structure of origin	Acute kinetics	Principal established use	Source
NfL	Axonal cytoskeleton	Rises slowly, persists for weeks-months	Subacute/chronic axonal injury burden, prognosis	khalil2018; shahim2020b
GFAP	Astrocyte cytoskeleton	Rises within hours, peaks early	Acute CT-positive lesion detection	bazarian2018; papa2016
UCH-L1	Neuronal cytoplasm	Rises within hours, clears faster than GFAP	Acute CT-positive lesion detection (paired with GFAP)	bazarian2018; papa2016
Total tau	Axonal microtubule-associated	Variable, generally rapid	Adjunct axonal marker, less consistent than NfL	wang2018; asken2020

Correlation with Neuroimaging and Long-Term Outcome

Plasma NfL correlates with imaging measures of axonal and white-matter injury and with outcomes measured years, not just weeks, after TBI. In a large cohort followed from the acute phase to up to seventeen years post-injury, plasma NfL predicted long-term functional outcome and correlated with ongoing brain volume loss on serial imaging, providing some of the strongest evidence that TBI can trigger a chronic, biomarker-detectable neurodegenerative process rather than a purely static injury [20]. Complementary TRACK-TBI cohort work found plasma GFAP concentrations correlated with structural MRI abnormalities in patients whose initial computed tomography was negative, illustrating that blood biomarkers can detect injury imaging alone misses [21]. In mild TBI, admission plasma NfL predicted

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subsequent development of imaging-defined axonal pathology, further linking acute biomarker signal to structural injury evolution [14]. Taken together with the prognostic value of day-of-injury GFAP and UCH-L1 for functional recovery [18], these findings support a model in which combined biomarker and imaging assessment better captures injury burden and trajectory than either modality alone.

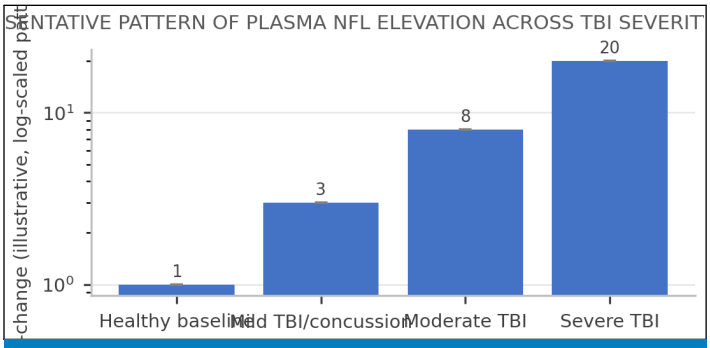

Figure 2: Representative pattern of plasma/serum NfL elevation relative to healthy baseline across increasing TBI severity categories, synthesised from cohorts spanning mild to severe injury; values are illustrative fold-changes rather than a single study's raw concentrations [13,8,9].

Sports-Related Concussion and Repetitive Head Impacts

Sports medicine has been an important proving ground for blood NfL, because athletes provide well-characterised injury timing, healthy comparator teammates and strong interest in objective return-to-play criteria. Beyond the ice hockey and mixed-sport cohorts already described [10,11], the multicentre NCAA and Department of Defense Concussion Assessment, Research and Education (CARE) Consortium evaluated a blood biomarker panel, including NfL, across several hundred collegiate athletes with acute sport-related concussion, providing one of the largest prospective assessments of biomarker behaviour in this population [22]. Studies in athletes across physical contact sports have similarly examined CSF and blood NfL concentrations in relation to cumulative exposure [23], while plasma GFAP and NfL, but not tau, distinguished professional rugby players with concussion from uninjured controls in another cohort [24].

Interest in repetitive, subconcussive head impact extends beyond single diagnosed concussions. Foundational work in Olympic boxing used CSF biomarkers to characterise the acute and cumulative effects of repetitive head trauma, establishing the conceptual basis for later blood-based repetitive-impact biomarker research [25]. Preclinical modelling supports the underlying premise: genetic mouse models of progressive axonal degeneration show that blood and CSF NfL concentrations scale with the burden of ongoing axonal loss, supporting NfL as a quantitative readout of cumulative, not only acute, axonal injury [5].

Limitations and Confounding Factors

Despite this accumulating evidence, several limitations temper enthusiasm for immediate clinical adoption. First and most fundamentally, NfL is not specific to TBI or even to trauma: it rises in numerous unrelated neurological conditions. Work in multiple sclerosis, for instance, shows serum NfL closely tracks CSF NfL and correlates with neuronal damage from an entirely different disease process, underscoring that an elevated value cannot by itself indicate traumatic axonal injury without appropriate clinical context [26]. Reviews of neurofilaments as biomarkers across neurological disease reach the same conclusion: NfL is best understood as a general index of neuroaxonal injury rather than a disease-specific test [2].

Second, physiological and non-neurological factors confound interpretation. Circulating NfL rises substantially with normal ageing, such that a concentration considered abnormal in a young adult may fall within the normal range for an older individual; large reference cohorts spanning childhood through older adulthood have been developed specifically to correct for this [6]. Renal function is an additional, clinically

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important confounder: reduced glomerular filtration is independently associated with higher blood NfL in older adults, plausibly reflecting reduced renal clearance rather than increased neurological injury, and comorbid renal impairment is common in trauma populations [27]. Assay and pre-analytical considerations, including sample handling and timing relative to injury, further affect measured concentrations and complicate cross-study comparison [7].

Conclusion

Across cohort studies spanning mild sport-related concussion to severe, intensive-care-managed TBI, plasma and serum NfL consistently tracks axonal injury burden, rises with severity, correlates with structural imaging abnormalities, and predicts both short-term recovery and long-term functional outcome, including evidence of ongoing post-traumatic neurodegeneration. Its slower rise and more prolonged elevation relative to glial markers such as GFAP and UCH-L1 make it a complementary rather than competing biomarker, best interpreted alongside these more acutely dynamic markers within a multimarker panel. However, NfL's lack of injury-type specificity, and its substantial confounding by age, renal function and unrelated neurological comorbidity, mean that reference-adjusted interpretation and further prospective validation are needed before plasma NfL can be routinely incorporated into TBI diagnostic or prognostic pathways.

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