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Review Article

Mapping the acute trajectory of sport-related concussion outcomes across symptoms, cognition, and blood biomarkers

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ABSTRACT

Sport-related concussion (SRC) and its potential neurological sequela represent an emerging global health concern, requiring improved recovery management and strategies for return-to-play (RTP) to enhance brain health in athletes. Given the dynamic and multifaceted nature of SRC recovery, the purpose of this review is to synthesize existing literature on post-SRC outcomes in adult athletes, and to outline the temporal trajectories of key recovery indicators (symptoms, cognitive function, blood biomarkers) across distinct recovery phases until resolution. In the acute phase of SRC (first 48 h), symptom scores and brain damage markers peaked immediately, while cognitive impairments and neuroinflammation emerged with a slight delay. Following the initial rise, brain damage marker concentrations rapidly dropped below baseline levels at approximately 48 h following SRC injury. During the early recovery phase, neuroinflammation and most cognitive alterations resolved after 3–5 days, though symptom burden and attention deficits persisted for up to 7 days. Despite prolonged alterations reported in some individuals, recovery markers typically returned to pre-injury levels in the transition phase ($\leq$ 2 weeks), though mild attention deficits were detected up to 3 weeks, and TNF-α concentrations remained elevated throughout late recovery ($>$ 2 weeks). These results reveal distinct temporal discrepancies across recovery markers and emphasize that physiological disturbances can outlast symptom resolution, underscoring the need for both multimodal assessments and appropriately timed evaluations to accurately track recovery progression. Incorporating structured follow-ups at key time points, particularly beyond symptom resolution, may improve RTP decision-making and reduce the risk of premature return and long-term neurological consequences.

1. Introduction

Sport related concussion (SRC) and its adverse long-term effects on brain health have emerged as a globally significant public health concern.[1] A worldwide increase in SRC incidences over recent years and the established link between repeated head injury throughout an athletic career and potential neurological sequela underscores the demand for evidence-based injury management.[2–4] Incomplete recovery before returning to sport is reported to be a major risk factor of sustaining additional brain injury, prolonged concussion symptoms, and the onset of neurodegenerative disorders.[5,6] Therefore, early identification of SRC and the monitoring of recovery following injury are essential to prevent chronic brain damage and to improve athletes' brain health.[5,6]

As the clinical presentation of SRC is highly variable and encompasses a wide spectrum of physical, cognitive and mental symptoms during the acute phase of injury,[7,8] determining full clinical and physiological recovery is a complex and multifaceted task.[9,10] Post-injury recovery is commonly defined as the time required for symptoms to resolve and cognitive and motor function to return to baseline levels.[7,11] Frequently reported alterations besides clinical symptoms (e.g.

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headache, dizziness, and confusion) include impairments in vestibular and motor function, reaction time, attention, memory, and visual motor speed which may persist for several days or weeks,[6,11,12] with return-to-play (RTP) being recommended only after performance has returned to pre-injury levels.[7,13]

Baseline testing remains the best available practice of recovery assessment to date, as it facilitates individual detection of post-injury impairments and can assist the interpretation of recovery trajectory.[7,14] Although post-injury symptoms are still considered to be the most reliable predictor of recovery to date,[15] relying solely on self-reported symptoms carries a high risk for bias. Emerging evidence from multi-domain assessments suggests that physiological recovery may exceed clinical recovery indicated by symptom resolution,[6,11,15,16] emphasizing the need for multifaceted testing.

Nonetheless, cognitive function and its associated symptoms play a key role in determining RTP decisions, yet symptom-based assessments are often limited by subjectivity and variability across individuals.[17,18] To address this limitation, blood-based biomarkers have emerged as an objective tool for detecting SRC and assessing physiological recovery.[19] Compared to neuroimaging techniques such as computed tomography, positron emission tomography, and magnetic resonance imaging, blood-based biomarkers offer advantages in terms of accessibility, cost-effectiveness, and real-time monitoring capabilities.[20] However, blood-based biomarkers do not always exhibit a direct correlation with cognitive impairment or symptom resolution, emphasizing the complexity of post-concussion recovery.[21] While pro-inflammatory cytokines typically peak within the first few days post-injury, other damage-associated molecular patterns, such as the prolonged activation of neurotoxic M1-like microglia, may persist for several weeks or even months.[22] This discrepancy suggests that physiological recovery may extend well beyond the resolution of self-reported symptoms.[11,15,16,23] This dissociation between symptom resolution and underlying neurophysiological changes underscores the necessity for a multimodal approach that integrates cognitive testing, symptom tracking, and biomarker assessment to enhance RTP decision-making and prevent premature RTP.

To improve RTP decision-making, monitoring the progression of recovery markers throughout the rehabilitation process provides an objective framework for interpretation of recovery and is a critical step in establishing accurate recovery timelines.[6,16] There is a growing trend toward collecting clinical data across multiple time-points from baseline to full recovery and beyond.[18] Despite these advancements and the increasing interest in concussion recovery, existing research often lacks a comprehensive multimodal approach that integrates multiple domains associated with alterations after SRC.[18] As post-concussive outcomes are affected by multiple factors, individual management strategies implementing multi-domain assessments are needed rather than using a "one-size-fits-all" approach.[9,15,24] However, current literature is often limited to reporting only the total time until resolution of symptoms and alterations or focuses on single domains.[11,16,25]

Given the existing limitations in concussion research, this narrative review aims to provide a comprehensive overview of the progression of multiple sensitive recovery markers across various time points, from pre-injury to resolution. Mapping the temporal dynamics of each domain will enhance the understanding of SRC recovery, offering valuable insights for coaches, medical staff, and healthcare professionals in designing evidence-based rehabilitation protocols and making informed concussion management decisions. This approach represents a critical step toward a more holistic recovery framework, with the potential to prevent subsequent injuries and improve athlete safety.

2. Methods

This narrative review was conducted to provide a comprehensive overview on recovery trajectory following sport-related concussion at multiple time points, including a multi-domain approach. The main research question was how different recovery markers (clinical symptoms, cognitive function, blood biomarkers) proceed over time, when they return to baseline levels and/or normative scores from matched controls, and if there are differences in the timeline until resolution across markers. To address the research questions, a comprehensive literature search was performed using the following databases: PubMed, ResearchGate, and Google Scholar. Eligible articles were identified following a multi-step approach: In the initial step, the keywords 'concussion' OR 'sport-related concussion' OR 'traumatic brain injury' AND "recovery" OR "return to play" OR "return to baseline" OR "resolution" were used. To identify articles addressing specific recovery markers, the second step combined the mentioned keywords with the term 'biomarker' OR 'blood biomarker' OR 'symptoms' OR 'symptom score' OR 'cognition' OR 'cognitive function' OR 'cognitive performance'. Finally, reference lists of included articles and relevant reviews identified in the initial search process were examined for additional eligible studies. All studies retrieved through this multi-step approach underwent an initial screening of titles and abstracts by at least one reviewer to assess relevance and adherence to inclusion criteria. Studies passing this stage were independently reviewed by all four authors responsible for literature research, with any discrepancies in eligibility resolved through discussion. Given the narrative nature of this review, no record was kept of the number of abstracts and articles identified and screened by the authors.

As this study focuses on concussion recovery in adult sport athletes, only studies involving participants aged 18 years or older and SRC injury resulting from sports participation were included. The review covers research published between 2013 and 2024.

2.1. Search strategy and study selection

To address the research questions, a comprehensive literature search was performed using the following databases: PubMed, ResearchGate, and Google Scholar. The search process to identify eligible articles followed a multi-step approach. In the initial step, the primary keywords 'concussion' OR 'sport-related concussion' OR 'traumatic brain injury' AND "recovery" OR "return to play" OR "return to baseline" OR "resolution" were used to identify relevant studies. To identify articles addressing specific recovery markers, additional searches combined these keywords with the terms 'biomarker' OR 'blood biomarker' OR 'symptoms' OR 'symptom score' OR 'cognition' OR 'cognitive function' OR 'cognitive performance'. In the final step, reference lists of included articles and relevant reviews identified in the initial searches were examined for additional eligible studies. All studies retrieved through this multi-step approach underwent an initial screening of titles and abstracts by at least one reviewer to assess relevance and adherence to inclusion criteria. Studies passing this stage were independently reviewed by all four reviewers responsible for literature research, with any discrepancies in eligibility resolved through discussion.

2.2. Inclusion criteria

Studies were only included in this review if they were published in English and involved human participants, while articles conducting other types of research methodology, like assessing animal models or including brain injury simulation, were not included. To investigate concussion recovery in adult sport athletes, only studies involving participants aged 18 years or older were included, as age may significantly influence post-injury outcomes. Given the potential impact of injury mechanisms on recovery patterns, studies were eligible for inclusion only if the concussion resulted from sports participation, while injuries from non-sport-related incidents (e.g., traffic accidents, military injuries) were excluded. In studies reporting results for both athletes and non-athlete populations, only data specific to athletes were extracted for analysis. Finally, to examine the temporal trajectory of recovery markers, only articles reporting outcomes at a minimum of two distinct

time points, including baseline measurements, were included in this review.

3. Post-concussive symptoms

Symptom evaluation is an integral component of clinical assessment and supports clinicians in identifying the type and severity of functional disturbances.[26] The onset of clinical symptoms following a sport-related concussion is characterized by a clear temporal association with the injury mechanism, with symptoms manifesting either immediately or within minutes to hours post-injury, affecting multiple clinical domains.[15,27] Symptomatology is typically classified into four primary domains: affective/emotional (e.g., anxiety, sadness, nervousness), cognitive (e.g., confusion, disorientation, impaired concentration), sleep-related (e.g., drowsiness, difficulty initiating sleep), and somatic/-physical symptoms (e.g., headache, blurred vision, fatigue). Within these categories, clinical symptoms are often heterogeneous across individuals and sometimes challenging to distinguish from general fatigue following sport participation or depressive mood.[28] With a prevalence of approximately 90% post-injury, headache is the most frequently reported symptom by athletes suffering from SRC. Although amnesia and loss of consciousness were historically considered hallmark indicators of concussion, they are no longer seen as a mandatory requirement for the diagnosis of SRC. While concussion symptoms are generally described to be transient, typically resolving within 7–10 days in most cases, they may persist for weeks or months in certain individuals[12,15,29] with greater acute symptom severity and a higher symptom burden being associated with an increased risk of prolonged recovery and persistent symptoms. Given the considerable variability in symptom burden across individuals, this narrative review aims to provide an overview of total symptom scores to facilitate more meaningful comparisons (Supplement Table 1).

4. Cognitive function following SRC

Impairment of cognitive function is a common consequence resulting from SRC,[28] that can have a significant impact on daily functioning and performance.[30] Deficits in cognitive function refer to the impairment of mental processes involved in acquiring knowledge, which can affect various and broad domains[31] frequently including alterations in reaction time, attention, memory, executive function and visual motor speed which may persist for several days or weeks.[6,11,12,28] Although the occurrence of impairments and the time until resolution can vary among individuals, cognitive symptoms are often reported to resolve within a few days.[28,32] However, in rare cases cognitive alterations can persist beyond this period.[28,33] The assessment of neurocognitive function is routinely conducted to help practitioners manage SRC and make a safe RTP decision.[34] This review portrays the temporary trajectory of reaction, attention, memory, and motor speed performance (Supplement Table 2), as these domains are most commonly reported to show alterations following SRC.[6,12]

5. Blood biomarkers following SRC

Among blood-based biomarkers, this review includes glial fibrillary acidic protein (GFAP), neurofilament light chain (NFL), ubiquitin carboxyl-terminal esterase L1 (UCH-L1), S100 calcium-binding protein B (S100B), and Tau (Supplement Table 3), as well as inflammatory markers (Supplement Table 4), including C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), and interleukin-1 receptor antagonist (IL-1RA). GFAP is an astrocytic intermediate filament protein essential for blood-brain barrier (BBB) integrity, making it a key marker of astrocyte injury and traumatic brain injury (TBI).[35] UCH-L1, a neuronal enzyme involved in protein degradation and turnover, has been identified as an early biomarker for neuronal damage and mild traumatic brain injury (mTBI).[36] NFL, a major axonal structural protein, is widely recognized as an indicator of axonal injury and neurodegeneration, with elevated levels observed in neurodegenerative diseases and following repetitive head trauma.[37] Similarly, Tau, a microtubule-associated protein localized in axon terminals, has been associated with neurofibrillary pathology and chronic traumatic encephalopathy (CTE).[38] S100B, a calcium-binding protein predominantly expressed in astrocytes, serves as a biomarker for BBB disruption, astrocyte activation, and neuronal injury, though its levels may also rise due to extracranial trauma, limiting its specificity.

In addition to neurodegeneration markers, inflammatory markers have gained attention for their role in post-concussive pathology. CRP, a systemic inflammatory protein, rises rapidly following acute brain injury and is frequently used as a marker of injury severity and systemic inflammatory response.[39] TNF-α, a pro-inflammatory cytokine, is a key mediator of neuroinflammation, immune response activation, and secondary neuronal damage following SRC.[40] IL-6, a multifunctional cytokine, peaks early post-injury and contributes to BBB permeability, neuroinflammation, and immune modulation.[41] In contrast, IL-10 functions as an anti-inflammatory cytokine, counteracting neuroinflammation and promoting neuronal recovery.[42] Lastly, IL-1RA, a natural antagonist of IL-1, plays a neuroprotective role by mitigating excessive neuroinflammatory responses, thereby potentially reducing long-term brain damage.[43]

6. Temporal trajectory of recovery markers

Prior research suggests that acute neurometabolic disturbances and impairments in neuropsychological functioning typically resolve within 7–10 days post-injury.[12,19] However, persistent physiological changes, such as sustained neuroinflammation and elevated brain injury markers, are reported to extend beyond the timeframe of clinical symptom resolution.[11,15,16,23] This discrepancy highlights the limitations of relying on single biomarkers for predicting concussion recovery or guiding RTP decisions. A comprehensive understanding of the dynamic interplay between clinical symptoms and biological markers throughout the recovery process is essential for identifying critical recovery phases and optimizing rehabilitation strategies. Findings from the studies included in this review were synthesized and their results categorized according to critical phases of recovery to capture the dynamic progression of recovery. Based on these results, the following section provides a summary of the changes of total symptom scores, cognitive domains (reaction, attention, memory, motor speed, additional domains), and blood biomarkers (brain damage markers, inflammation markers), with their temporal flow illustrated in Fig. 1. While the results of studies included are presented in detail in the Supplementary Tables 1–4, practical recommendations and key points to consider for SRC recovery assessment and RTP decision-making are outlined in Table 1.

6.1. Acute phase following injury

Total symptom scores were reported to reach their peak values within the first 24 h in all studies providing data for this time point.[19,26,44–46] This increase was statistically significant in all studies that conducted a direct statistical comparison to baseline data,[19,26,45,46] underscoring that symptom burden emerges almost immediately or develops within hours following SRC.

Cognitive function data collected immediately following SRC were limited to the attention domain,[47–49] with no studies assessing memory, motor speed, or reaction performance in the acute phase. All studies evaluating attention used the King-devick test and consistently reported increased test completion times, indicating poorer performance, with increases ranging from 112.3% to 117.4% relative to baseline.[47,48] However, significant performance differences between time points were only reported by King et al.[47] Although the remaining studies reported no statistical comparison to baseline outcomes, Cheever et al.[49] found no difference in performance between concussed participants in the acute phase of injury and a control group of healthy matched participants.

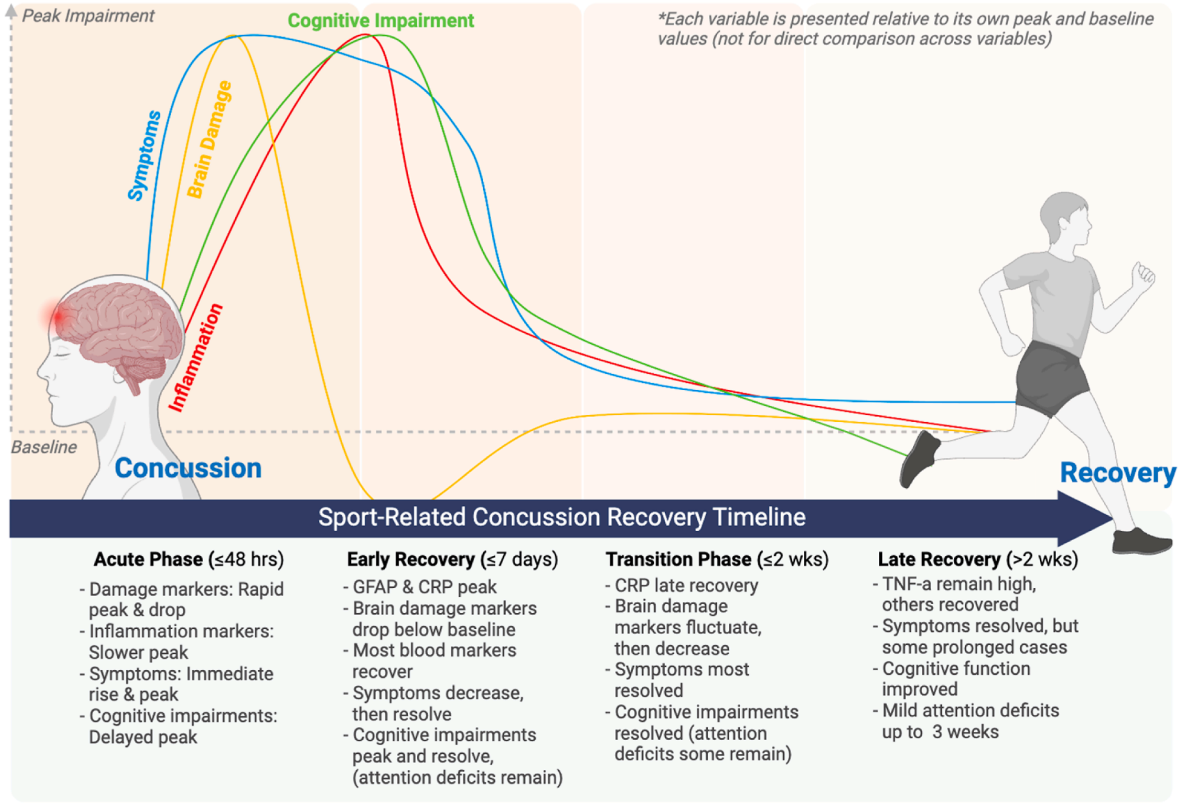

Fig. 1. Trajectories of symptoms, cognitive function, brain injury markers, and inflammatory markers during the recovery process following sport-related concussion (SRC) in adult athletes. The figure illustrates relative changes in each domain over time after SRC. The horizontal dotted gray line represents the x-axis (time since SRC), while the vertical dotted gray line represents the y-axis (relative increase from baseline). Each curve is normalized to its relative peak value for visual comparison. The sky-blue line indicates the total symptom score. The yellow line represents the combined levels of brain damage blood markers (Tau, GFAP, NFL, UCH-L1, and S100B). The green line reflects the composite score for cognitive impairment, and the red line represents the aggregated levels of inflammatory blood markers (IL-6, TNF-α, IL-10, and CRP). **Abbreviations**: SRC, sport-related concussion; GFAP, glial fibrillary acidic protein; NFL, neurofilament light chain; UCH-L1, ubiquitin C-terminal hydrolase-L1; S100B, S100 calcium-binding protein B; IL, interleukin; TNF-α, tumor necrosis factor-alpha; CRP, C-reactive protein.

Blood-based biomarkers of brain damage, including GFAP, UCH-L1, S100B, NFL, and Tau, showed an average increase of 49.70% ranging between 7.32% and 75.53% immediately following SRC.[19,21,50–52] However, an exception was noted in S100B, where Schulte et al.[71] reported a slight decrease of −1.88% compared to baseline. However, the remaining four studies of S100B showed similar increases,[21,50–52] suggesting that SRC primarily leads to damage in neurons and astrocytes, reflected by the elevation of GFAP, UCH-L1, NFL, and Tau, rather than S100B. The lack of a significant increase in S100B may also be attributed to its release following extracranial injuries, making it a less specific biomarker for direct neuronal damage in SRC.

Inflammatory markers including TNF-α, IL-6, IL-10, CRP, and IL-1RA, on average, increased by 27.15% ranging from −5.18% to 71.52% compared to baseline,[46,50,53] further supporting the presence of neuroinflammation following SRC. Interestingly, TNF-α was the only inflammatory marker that decreased, showing a 5.18% reduction compared to baseline. A closer examination of individual studies revealed some variability. Nitta et al.[53] reported a 16.31% reduction, whereas Meier et al.[46] observed a 5.95% increase. This discrepancy highlights the heterogeneous nature of inflammatory responses following SRC, suggesting that TNF-α dynamics may be influenced by individual recovery patterns, injury severity, or time-sensitive immune regulation.

6.2. Between 24 and 48 h post injury

All studies with available data within 24–48 h post-injury reported symptom scores remained elevated,[19,46,54–59] highlighting the increased vulnerability during this early stage of injury. Nevertheless, in the two studies that included assessments both immediately post-injury and again at 24–48 h,[19,46] symptom scores were slightly lower at the later time point, indicating that a slight resolution of symptoms might already occur during this timeframe. This early symptom improvement may be partly affected by the timing of both assessments: while the acute evaluation occurred after an average of 3.42 h,[19] the average time between injury and the later assessment was reported to be 41.25 h,[19] therefore providing sufficient time for early recovery to begin. Among all studies comparing symptom scores from baseline to values from 24 to 48 h post-injury, the increase in symptom burden varied highly ranging from 198.3%[19] to 580.8%.[58]

Reaction task performance was consistently worse than at baseline across all included studies,[7,50,55,60,61] apart from Glendon et al.,[59] which reported only a slight difference. Similarly, attention task completion times increased in most cases,[48,57,60,62] indicating attentional impairments resulting in poorer performance. Declines in motor speed composite scores during this phase ranged from 81.8%[55] to 98.8%[59] of baseline performance, while decreases in memory performance ranged from 78.8%[55] to 97.6%[58] for visual memory and from 84.7%[55] to 97.3%[58] for verbal memory compared to baseline values. Across the included studies providing data for this period, cognitive impairments were most pronounced within 24–48 h post SRC, indicating this period as the peak of cognitive dysfunction.

On average, brain damage biomarkers increased by 93.02% ranging between −21.01% and 119.79% compared to baseline, showing a substantial elevation relative to the acute phase.[19,21,50,52,63,64] However, the specific patterns of increase and decrease varied across different

Table 1
Considerations for SRC recovery assessment and RTP decision-making.

Phase	Key considerations	Recovery-marker monitoring
Acute phase (≤ 48 h)	Comprehensive assessment of symptom severity and cognitive impairments.	Use UCH-L1, S100B, and GFAP to confirm neuronal and astrocytic damage. Brain damage markers peak faster than inflammation markers. Immediate peak in symptom burden, prior to the occurrence of cognitive impairments.
Early recovery (≤ 7 days)	Recognize that cognitive impairments may persist despite symptom resolution. Cautious with Brain damage markers due to the rapid drop below the baseline.	UCH-L1 and S100B become less relevant, while GFAP and CRP peak at this point. Brain damage markers drop below baseline, therefore need to be cautious. Symptoms typically resolve during this phase. Reaction and motor speed returns to baseline within 3–5 days, while attention and memory deficits persist.
Transition phase (≤ 2 weeks)	Conduct cognitive assessments for possible delayed impairments.	Persistent TNF-α elevation may indicate prolonged neuroinflammation. NFL and Tau variability should be interpreted in the context of prior SRC history. Brain Damage Markers slightly increase again compared to the previous phase. Recovery of symptom burden in most individuals. Resolution of memory alterations, while deficits in attention might remain.
Late recovery (> 2 weeks)	TNF-a late recovery. Full recovery of symptoms and cognitive function, but prolonged burden in individuals possible.	Elevated TNF-α levels may suggest ongoing inflammation, warranting managing inflammation for longer time. Symptoms can remain consistent in some athletes. Resolution of attention deficits after 2–3 weeks.

markers. Notably, UCH-L1 (−21.01%)[19,21,50,63,64] and S100B (−11.62%)[21,50,52,64] showed a decrease, while other markers continued to rise. In the case of UCH-L1, all five studies that included 24–48 h data reported a decrease, suggesting a consistent trend that UCH-L1 levels peak during the acute phase and rapidly decline to below baseline levels. Similarly, S100B exhibited a rapid increase followed by a decline within 24–48 h, reinforcing its role as an early-phase biomarker of brain injury with transient dynamics. Only one study observed a slight increase (1.72%),[52] however, this increase seems to be a decrease from the previous phase. In contrast, NFL and Tau exhibited fluctuations, with only one study[63] reporting an exceptionally high increase (> 400%), while others showed a decrease. This inconsistency may reduce the reliability of these markers for SRC assessment and suggests that other factors, such as injury severity, individual variability, or secondary neurodegenerative processes, may influence these fluctuations.

Inflammatory markers showed an average increase of 7.92% ranging between −2.24% and 29.52% compared to baseline.[46,50,53] Among these markers, IL-1RA decreased by 2.24%, while all others exhibited an increase. However, results for IL-1RA varied across studies. Nitta et al.[53] reported a return to baseline, Meier et al. (2020)[50] showed an increase followed by a decline compared to the acute phase, and Meier et al. (2024)[46] reported a 12.91% decrease. Although the specific trends differed, all studies consistently showed a decline in IL-1RA levels compared to the acute phase. Among all inflammatory markers, IL-6 and IL-1RA exhibited the most significant decreases compared to the acute phase, suggesting a more transient role in the post-injury inflammatory response.

Overall, these findings indicate that UCH-L1, S100B, IL-6, and IL-1RA function as rapid-response biomarkers, as they peak early following SRC and rapidly decline. This suggests they may be most useful in detecting immediate neuronal and astrocytic stress and acute inflammatory responses, but not necessarily in tracking long-term recovery.

6.3. Between 3 and 13 days post injury

Results for total symptom scores varied highly across studies for assessments performed 3–13 days post injury. Three studies assessing symptoms at 3–5 days post injury reported significantly higher scores for concussed participants than for controls[65,66] or compared to baseline.[59] When assessed within 7–13 days, three included studies found no differences compared to baseline,[54,55,59] with one study reporting symptoms to be lower than baseline.[55] However, symptoms can persist beyond this period in some individuals as shown by two studies reporting total symptom scores to remain significantly higher in concussed participants when compared to a control group at 7 days.[56,67]

Reported reaction performance times showed a statistical difference to baseline levels in one study,[61] while two studies reported no impairments when assessed at 3 days[68] and 4 days[59,60] following SRC. Likewise, no differences were reported when assessed after 7–13 days in all studies that provided data for this period.[54,55,59,60,68] Glendon et al.[59] even reported improved reaction performance compared to baseline at 8 days post-injury. Similar results were reported for motor speed performance and memory scores. In motor speed performance, there were no meaningful differences to baseline reported after 3–4 days[59,68] following SRC. Reassessments performed within 7–13 days after SRC showed no differences in one study,[55] while the remaining studies reported performance to have increased compared to baseline levels.[59,68] Visual memory performance was reported to not differ significantly from baseline both at 3–4 days[59,68] and 7–13 days.[55,59,68] For verbal memory, two studies reported remaining impairment 3 days after injury,[67,68] while the remaining studies reported no such alterations over all included time points ranging from 4 to 13 days.[55,68] In contrast, working memory was evaluated in one study, which reported significant impairments compared to controls assessed 7 days post-SRC.[56] Likewise, attention performance remained impaired at 3–4 days,[47,60] with two studies reporting these alterations to still exist when reassessed after 7[47] and 10[60] days respectively. O'Brien et al.[56] on the other hand reported no differences to a healthy control group at 7 days following SRC. Interestingly, results reported by McDonald et al.[57] showed attention performance not to be different from within participant baseline scores but being worse than the performance of matched controls.

Among brain damage markers, no data were available for UCH-L1 and GFAP, likely due to their established role as acute-phase biomarkers for mTBI.[69] While other markers, including NFL and Tau, increased during this phase,[52,70] a slight decrease in S100B was observed.[52] Notably, each of these markers were reported in only one study, limiting the strength of this observation.

For inflammatory markers, an average reduction of 2.39% ranging between −12.34% and 21.19% was observed compared to baseline.[46,53] Among these, only TNF-α showed an increase, suggesting a slower recovery trajectory compared to other inflammatory markers. However, this finding is based on only two studies, highlighting the need for further validation. Specifically, Nitta et al.[53] reported a 43.56% increase, whereas Meier et al.[46] observed a 1.19% reduction. In other aspect, this variability may underscore the complexity of post-SRC inflammatory responses and suggests that individual differences or injury severity may influence TNF-α dynamics.[46,53]

6.4. After 2 weeks and long-term assessments

Among the identified studies, evaluation of symptom burden at 2 weeks post-injury and beyond was sparse, with only half of the studies included reporting outcomes for this prolonged phase. Within the available data, both Buttner et al.[66] and Howell et al.[67] reported persistently elevated symptoms, indicating an ongoing impairment.

Despite relatively small differences in symptom scores between concussed and non-concussed controls, O'Brien et al.[56] still reported these differences to be significant, suggesting that symptom burden may extend beyond two weeks in some individuals. In contrast, Glendon et al.[59] and Downey et al.[65] reported no differences in symptom scores compared to baseline at 14- and 21-day post-injury, respectively. Assessments performed at more than three weeks post-injury indicated no remaining symptom burden in four studies.[44,54,56,57] Despite symptoms still being slightly elevated following 1 month, Howell et al.[67] reported no significant difference to the control group at that time point. Notably, only Buttner et al.[66] reported sustained symptom elevation in concussed participants relative to controls at an average of 30 days post-SRC. According to the authors, this discrepancy between groups is likely to stem from methodological limitations, such as potential selection bias. In addition, the use of mean values to compare symptom severity might have contributed to the observed differences, as the elevated symptom burden in the concussion group appeared to be driven by a small subset of participants reporting unusually high scores, thereby significantly increasing the group's average. Nevertheless, these results demonstrate the high variability in symptom resolution observed across individuals.

Like symptom burden, a multitude of available research did not report cognitive outcomes for long-term assessments surpassing 2 weeks. Consistent with the results reported for prior assessment times, available outcomes of reaction performance showed increased outcomes both at 14 days[59] and one month[54] post SRC, with none of the included studies reporting remaining alterations. This indicates complete resolution of impairments in the reaction domain by that time. Memory assessments at 2 weeks or later were reported by only two authors, with no significant differences to baseline reported for visual and verbal memory at 14 days[59] and for working memory performance at several time points (2, 4, 6, 8, 12, and 26 weeks) post injury.[56] Visual motor speed results were reported only by one study[56] and showed no impairments at 14 days. The available results suggest that reaction, memory, and visual motor speed performance returned to baseline within 14 days with none of the included studies reporting contrary results. Again, results for attention domain remained contrary, complicating the interpretation of recovery trajectory. McDonald et al.[57] found no differences compared to both baseline performance and to matched controls after 1 month. Likewise, other studies reported no differences for 2 weeks, 4 weeks, and 6 weeks post assessments.[49,56] Nevertheless, despite the outcome scores being elevated only slightly, King et al.[47] reported a significant difference to baseline remaining at 2 weeks post injury, while performance improved in comparison to baseline when reassessed after 21 days. Similar to the findings for prolonged symptom burden, the remaining differences after 2 weeks were likely driven by only a few participants who exhibited declines in attention performance, while the majority had returned to baseline by that time. Additionally, the study categorized concussion cases as either witnessed or unwitnessed during play. These subgroups may therefore reflect differences in injury severity, as significant changes from baseline were observed only in the witnessed group but not in the participants with unwitnessed concussion. This suggests that injury severity plays a crucial role in recovery trajectories following SRC.

Among brain damage markers, UCH-L1 and GFAP were assessed in only one study at 7 days post- RTP, with UCH-L1 decreasing and GFAP increasing compared to baseline.[19] However, biomarker levels at 7 days post-RTP may be influenced by resumed training, making it difficult to draw definitive conclusions from post-RTP data. S100B showed a 22.10% reduction at RTP compared to baseline,[71] a trend consistent with its decline at 24–48 h post-SRC. This suggests that S100B may serve as a useful marker for detecting acute neuronal damage and monitoring early recovery. NFL showed a slight decrease (−0.24%) at the 2-week phase, potentially indicating recovery, but this finding was based on only one study.[70] Tau increased by 35.94% at 2 weeks, but this too was based on a single study, limiting interpretation.[70] Notably, NFL levels showed a significant outlier in another study, reporting a 484.21% increase at 24–48 h post-SRC, suggesting large fluctuations across studies. Given the limited number of studies and variability in Tau and NFL levels, these markers may be inconsistent indicators of SRC-related damage, but further research is needed to confirm their reliability.

For inflammatory markers, an average increase of 5.36% was observed at 2 weeks post-SRC, rising slightly to 8.36% at 1 month.[53] IL-1RA was the only marker that consistently decreased, with a 17.30% reduction at 2 weeks and 4.87% at 1 month, suggesting a faster recovery trajectory compared to other inflammatory markers. In contrast, TNF-α exhibited a slow but steady increase over time, with a 25.97% increase at 2 weeks and 43.56% at 1 month, supporting its role as a marker of prolonged inflammation. IL-6, which peaked acutely at 71.52%, showed a significant reduction over time, declining to 10.97% at 2 weeks and 1.94% at 1 month, suggesting a quicker resolution of inflammation. IL-10 demonstrated mild fluctuations but remained stable, showing a 4.13% increase from 2 weeks to 1 month, potentially indicating a stabilizing anti-inflammatory response. CRP levels peaked at 29.52% at 24–48 h post-SRC, followed by a reduction to 3.05% at 2 weeks and a slight decrease to −2.96% at 1 month, reflecting a transient inflammatory response that normalizes over time. However, all findings on blood-based biomarkers were derived from single-study data. In particular, inflammatory markers were reported in only one study, and each brain damage marker was reported in a different single study, underscoring the need for cautious interpretation and further validation in larger cohorts within this timeline (> 2 weeks).

7. Integrated approach to SRC recovery

Recovery following SRC is a dynamic and multifaceted process, characterized by distinct yet interrelated trajectories in symptom resolution, cognitive function, and blood biomarker fluctuations. The discrepancies in recovery patterns across these domains highlight the need for a multi-modal approach in SRC management, particularly in determining RTP readiness and long-term neurological outcomes. Given the differences in peak alterations and resolution rates, a framework that integrates clinical symptomatology, neurocognitive assessments, and blood-based biomarkers is essential for accurately assessing recovery and minimizing the risk of premature RTP.

7.1. Acute phase (0–48 h): immediate neurometabolic disruptions and clinical symptoms

During the initial 24–48 h post-SRC, symptoms exhibit an immediate and substantial increase with peak total symptom scores increasing significantly relative to baseline. Cognitive impairments are most pronounced in attention, reaction time, and motor speed, with alterations peaking around 24 h following injury. Simultaneously, blood biomarkers reflect acute neurometabolic disturbances and neuroinflammatory responses. GFAP, UCH-L1, NFL, and Tau show their highest elevations within this period, correlating with astrocyte activation, neuronal injury, and axonal disruption.[19,50,51] Inflammatory markers, including IL-6, TNF-α, IL-10, and CRP, peak acutely, reflecting a systemic neuroimmune response. Notably, S100B follows a different trajectory, peaking within hours post-injury and returning to baseline by 24–48 h, reinforcing its role as an early-phase marker of acute neuronal stress.[71] These findings suggest that acute-phase assessments should prioritize symptom severity, cognitive function (especially attention and reaction time), and early-phase biomarkers (UCH-L1, S100B, GFAP) to confirm neuronal and astrocytic injury. The inclusion of inflammatory markers (IL-6, CRP) may further aid in differentiating between transient and prolonged neuroinflammation.

7.2. Early recovery (3–7 days): persistent deficits despite symptom improvement

Between 3 and 7 days post-injury, symptom burden remains elevated in some individuals, though early improvements are often observed.[59,67]

Cognitive deficits in reaction time and motor function begin to resolve, but impairments in working memory and attention may persist longer than other cognitive domains.[47,60] This suggests that symptom resolution does not necessarily indicate full neurocognitive recovery and that cognitive performance outcomes have to be interpreted carefully due to inter-domain differences.

During this phase, UCH-L1 and S100B levels decline rapidly, reinforcing their utility as acute markers rather than indicators of long-term injury progression. However, GFAP remains elevated, suggesting ongoing astrocytic dysfunction and blood-brain barrier disruption.[19] NFL and Tau exhibit variability, with some studies reporting sustained elevations while others show decreases, indicating that axonal injury recovery patterns may differ across individuals.[63] Meanwhile, IL-6 and CRP levels begin to decrease, whereas TNF-α remains elevated, indicating that neuroinflammation may persist beyond the initial symptom resolution. Given these findings, early recovery assessments should integrate symptom reports, cognitive testing (especially for attention and executive function), and sustained biomarker monitoring (particularly GFAP and TNF-α) to identify individuals at risk for prolonged recovery.

7.3. Transition phase (2 weeks): recovery heterogeneity and persistent neuroinflammation

Within 2 weeks post-SRC, recovery trajectories begin to diverge, with some individuals achieving full symptom resolution while others continue to report lingering symptoms.[56,66] Cognitive performance, particularly in reaction time, motor function, and memory normalizes, but attention deficits remain detectable in some cases. IL-1RA is the only inflammatory marker that consistently decreases by this stage, aligning with symptom resolution and suggesting reduced neuroinflammation. However, TNF-α continues to rise, reaching a 43.56% increase at 1-month, indicating that some individuals may experience prolonged neuroimmune activation despite symptom resolution.[46,53] While NFL and Tau remain inconsistent across studies, GFAP levels remain elevated, reinforcing its role in tracking prolonged astrocytic stress. These findings highlight the limitations of symptom-based assessments in determining full neurophysiological recovery. Instead, persistent TNF-α elevation and GFAP stability should be considered indicators of prolonged neuroinflammation.

7.4. Late recovery: residual neurophysiological changes beyond symptom resolution

Beyond more than 2 weeks post-SRC, most individuals experience complete symptom resolution, and their cognitive function largely returns to baseline in most domains.[54,57] However, attention deficits remain inconsistent across studies, with some reporting persistent impairments and others demonstrating full recovery. TNF-α continues to rise, indicative of persistent neuroinflammation.[11] Meanwhile, CRP and IL-6 return to baseline, highlighting the transient nature of early-phase inflammation. These findings suggest that symptom-based recovery assessments alone may not accurately reflect underlying neurophysiological status and that continued monitoring of GFAP and TNF-α may be warranted, especially in high-risk populations.

8. Limitations

This review has several limitations, primarily related to heterogeneity and limited long-term data. First, inconsistencies in assessment timing and outcome measures across studies made it difficult to compare results at specific recovery phases. While some studies assessed only two time points, others used longitudinal designs. Notably, data within the first 24 h post-injury critical for detecting acute impairments were sparse. Second, only a limited number of studies assessed outcomes beyond 2 weeks post-injury, therefore restricting our ability to evaluate longer-term recovery trajectories. Especially in cases where athletes' outcomes returned to baseline within the first 2 weeks, follow-up assessments were often discontinued, likely due to high logistical or financial constraints. Third, variations in symptom, cognitive, and biomarker assessments (e.g., tool sensitivity, administration methods, reporting formats) further limited cross-study comparability. In addition, results may have been influenced by evaluator bias and platform-specific biomarker differences. Participant heterogeneity particularly age, sex, and concussion history also affected outcomes. Although we included only adult athletes to reduce variability, this restricts generalizability to youth, elderly, or non-athlete populations. Furthermore, SRC severity was rarely quantified beyond general diagnostic criteria, complicating interpretation of biomarker dynamics. Control group differences and lack of baseline comparisons in some studies added additional variability. Together, these limitations underscore the need for future studies to adopt standardized protocols, include diverse populations, report raw data, and extend assessments beyond the early recovery window. Such efforts will improve the accuracy of RTP decisions and our understanding of SRC recovery.

9. Conclusion

SRC presents a significant challenge due to its heterogeneity in symptomatology, cognitive impairments, and physiological disruptions. This review synthesized findings on SRC recovery across multiple domains, including clinical symptoms, cognitive function, and blood biomarkers highlights distinct temporal trajectories in each recovery marker. The evidence suggests that while symptom resolution often occurs within 7 days post-injury, cognitive deficits, particularly in attention, may persist beyond clinical recovery in adult athletes. Furthermore, blood-based biomarkers indicate that physiological disruptions, such as astrocyte activation (GFAP) and neuroinflammation (TNF-α), can extend well beyond the resolution of symptoms, emphasizing the potential dissociation between perceived and actual recovery.

Despite these insights, SRC recovery remains highly variable across different populations, with factors such as age, sex, concussion history, and injury severity influencing individual outcomes. Accordingly, the findings of this review are specific to adult athletes and should be interpreted carefully without generalizing them to other populations. Furthermore, inconsistencies in assessment timing, methodological heterogeneity, and a lack of standardized concussion severity metrics limit direct comparisons across studies. Given these challenges, a multimodal recovery framework that integrates symptom tracking, neurocognitive assessments, and biomarker profiling is essential to improve RTP decision-making and minimize the risk of premature RTP.

Future research should focus on establishing standardized assessment protocols, optimizing biomarker panels for tracking recovery, and identifying long-term consequences of SRC beyond the acute phase. Additionally, further longitudinal studies are needed to clarify the interactions between cognitive impairments and persistent neuroinflammatory responses. By integrating findings across clinical, cognitive, and physiological domains, a more comprehensive and individualized approach to SRC management can be achieved, ultimately enhancing athlete safety and reducing the long-term risks associated with repetitive head trauma.

CRediT authorship contribution statement

SoYoung Ahn: Writing – original draft, Methodology, Writing – review & editing, Project administration, Conceptualization, Visualization, Data curation. **Michael Prock:** Visualization, Data curation, Writing – original draft, Methodology, Writing – review & editing, Project administration, Conceptualization. **Ji-won Seo:** Data curation, Writing – original draft, Writing – review & editing. **Sanghyuk Han:** Data curation, Writing – original draft, Writing – review & editing. **David Michael O'Sullivan:** Writing – review & editing,

Conceptualization, Supervision, Validation. **Wook Song:** Validation, Writing – review & editing, Conceptualization, Supervision.

Declaration of Generative AI

During the preparation of this work the authors used ChatGPT in order to improve readability and language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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