Role of biomarkers and emerging technologies in defining and assessing neurobiological recovery after sport-related concussion: A systematic review

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ABSTRACT

Objective: Conduct a systematic review of scientific literature on the role of fluid-based biomarkers, advanced neuroimaging, genetic testing, and emerging technologies in defining and assessing neurobiological recovery after sport-related concussion (SRC).
Data Sources: Searches of 7 databases from 1/1/2001 through 3/24/2022 using keywords and index terms relevant to concussion, sports, and neurobiological recovery.
Eligibility Criteria for Selecting Studies: Studies were included if they: 1) were published in English; 2) represented original research; 3) involved human research; 4) pertained only to SRC; 5) included data involving neuroimaging (including electrophysiological testing), fluid biomarkers or genetic testing, or other advanced technologies used to assess neurobiological recovery after SRC; 6) had a minimum of 1 data collection point within 6 months post-SRC; and 7) contained a minimum sample size of 10 participants.
Data Extraction: Separate reviews were conducted for studies involving neuroimaging, fluid biomarkers, genetic testing, and emerging technologies. A standardized method and data extraction tool was used to document the study design, population, methodology and results Reviewers also rated the risk of bias and quality of each study.
Results: A total of 205 studies met criteria for inclusion in our review, including 81 neuroimaging, 50 fluid biomarkers, 5 genetic testing, 73 advanced technologies studies (4 studies overlapped two separate domains).
Summary/Conclusions: Advanced neuroimaging, fluid-based biomarkers, genetic testing, and emerging technologies continue to be valuable research tools for the study of SRC, but there is not sufficient evidence to recommend their use in clinical practice. Published work in recent years remains hindered by limitations in methodology and generalizability but represents significant progress and is expected to inform a translational pathway to clinical use in SRC.

What is already known?

- The evaluation and management of sport-related concussion (SRC) is hampered by the lack of advanced diagnostic testing capabilities and objective, biological markers of injury and recovery.
- Over the past 20 years, there has been extensive research and development focused on advanced neuroimaging, fluid-based biomarkers, and innovative technologies for the diagnosis and management of SRC.
- These technologies have shown promise in the research setting but have not been widely adopted in clinical practice.

What are the new findings?

- Our findings from largely group-level results indicate that advanced neuroimaging, fluid-based biomarkers, genetic testing, and emerging technologies are sensitive to the acute effects of SRC and tracking neurobiological recovery from concussion.
- The existing literature remains limited, however, in determining the clinical utility of these advanced technologies for the diagnosis and prognosis of SRC.
- The current body of evidence marks critical progress toward validating advanced neuroimaging, blood and fluid-based biomarkers, genetic testing, and emerging technologies for clinical use in SRC.

INTRODUCTION

Historically, the evaluation and management of sport-related concussion (SRC) has been hampered by the lack of advanced diagnostic testing capabilities and objective, biological markers of injury and recovery. Multiple challenges drive the need for objective testing and biomarkers to support the clinical management of SRC, most notably that signs and symptoms of injury can be both subtle and non-specific, conventional diagnostic tools have limited sensitivity, and clinicians often must rely on the subjective report of the athlete to establish diagnosis and assess recovery.[1]

There has been much effort to study and develop advanced technologies to support assessment and management of SRC over the past 20 years. Multiple lines of applied research have evaluated the utility of neuroimaging, blood-based biomarkers, genetic testing, and emerging technologies.[2, 3] In addition to assessing their added value toward improving diagnostic accuracy, studies have examined the prognostic utility of biomarkers and novel technologies in predicting and monitoring SRC recovery.[4]

As part of the 5th International Consensus Conference on Concussion in Sport (Berlin, 2016)[5], two reviews focused on the role of imaging and biomarker technologies to (a) support the diagnosis of SRC and (b) determine the duration of physiological recovery.[6, 7] Based on the 98 studies that met inclusion criteria, McCrea and colleagues concluded that these technologies showed early promise in the study of SRC, but that further research was required to recommend implementation in clinical practice.[7] Kamins et al. concluded that, while methodological variation across studies precluded them from determining a uniform window of physiological ("brain") recovery after SRC, evidence suggested the duration of recovery may extend beyond that of observed/reported signs and symptoms ("clinical recovery"), thereby supporting international consensus guidelines recommending a graded exertion strategy before returning to sport activities with contact or other risk of re-injury.[6] Both reviews called for further research to address scientific gaps and facilitate pathways for clinical translation.

Since the 2016 Berlin Consensus Conference, there has been a proliferation of research employing advanced magnetic resonance imaging (MRI) and blood-based biomarkers in studying the acute effects of and physiological recovery after SRC. Additionally, research has advanced on new technologies intended to provide a more objective means to diagnose concussion and assess an athlete's level of recovery and fitness for return to sport (RTS), beyond that of conventional clinical evaluations.[8] We conducted a systematic review of the existing literature on the role of blood-based biomarkers, advanced neuroimaging, genetic testing, and emerging technologies in defining and assessing neurobiological recovery after SRC.

METHODS

We conducted a comprehensive review of the published literature using systematic review methodology guided by the Cochrane Handbook.[9] This review is being reported following the PRISMA 2020 reporting guideline.[10] Our review was designed to address the following question from the Scientific Committee for the 6th International Consensus Conference on Concussion in Sport in Amsterdam, Netherlands:

"What is the role of biomarkers and emerging technologies in defining and assessing neurobiological recovery after SRC?"

We addressed this question within four domains:

- Advanced Neuroimaging
- Blood-based and Fluid-based Biomarkers
- Genetic Testing
- Emerging Technologies

The PRISMA Flow Diagram illustrating the methodology and workflow for our systematic review is summarized schematically in **Appendix 1.** The review protocol was created a priori and prospectively registered with PROSPERO (CRD42020164558).

Databases

The following databases were searched on November 14, 2019, and again on March 24, 2022: Medline (via Ovid), Embase (via Ovid), APA PsycInfo (via Ovid), Cochrane Central Register of Controlled Trials (via Ovid), CINAHL (via EBSCO), SportDISCUS (via EBSCO), and Scopus (Elsevier).

Period of Published Literature Reviewed

Given the rapid advancement of relevant literature in recent years, our search was limited to publications from January 1, 2001, to March 24, 2022.

Search Terms

The search strategy contained 3 search concepts; Sport, Concussion, and Recovery (which included neurobiological recovery, neuroimaging, biomarkers, and emerging technologies). The sport and concussion search concepts were created by expert librarians (Dr. Zahra Premji and Dr K. Alix Hayden) based on terms provided by the authors and search terms from the 5th International Consensus Conference on Concussion in Sport which are further described in the methods paper (see Schneider et al. 2023 in this special issue). The recovery concept was created (ZP) and peer reviewed (KAH) and tested against a set of known papers provided by the research team. Each search concept contained controlled vocabulary and keywords, and incorporated database-specific syntax and Boolean operators. The search strategy was designed for Medline (via Ovid) and translated to other databases. The search results were exported as RIS or txt files and imported into Covidence for deduplication and screening. References were managed in EndNote (Thomson Reuters, CA, USA). The complete reproducible search strategies for all database searches are included in **Appendix 3.**

Study Selection Criteria

Studies were eligible for inclusion if they met the following criteria: 1) published in English; 2) represented original research; 3) involved human research ; 4) pertained only to SRC (i.e., not non-sports TBI); 5) included data on one of the four domains listed above to assess neurobiological recovery after SRC; 6) evaluated participants at least once within 6 months post-SRC; and 7) contained a minimum sample size of 10 participants with SRC. Study selection

followed a three-step process. First, one reviewer performed a rapid screen of all records identified though database searches to exclude citations for clear violations of inclusion criteria. Second, the titles and abstracts of the remaining records were independently screened by two reviewers based on the established eligibility criteria. Third, the remaining studies underwent full-text screening independently by two reviewers. Discrepancies between reviewers at either steps 2 or 3 were resolved by a third reviewer.

Data Extraction and Analysis

Working groups comprising authors with subject area expertise extracted data from each of the included studies. Data were extracted via standardized data extraction tables for each domain (see **Supplementary Tables 1-4)**. Articles are listed chronologically by publication year to highlight the development of this literature over time. Subject matter working groups summarized the overall findings for each domain, as detailed below.

Assessment of Risk of Bias

Risk of bias (ROB) was performed independently by two authors using the study appropriate Scottish Intercollegiate Guidelines Network (SIGN) critical appraisal notes and checklist for case-control, cohort, and randomized clinical trial studies **(See Appendices 2a-c).** The SIGN checklist was considered suitable to assess ROB across multiple criteria, considering a study's methodology specific to study design, validity, and generalizability. Overall assessment of how well a study minimized ROB was assigned the following ratings: High quality (++), Acceptable (+), or Unacceptable (-). Disagreement between reviewers was resolved by consensus. Failure to reach consensus resulted in consultation with a third reviewer from the author group to resolve disagreement. Studies rated as unacceptable (high ROB) were deemed inadmissible for our review, therefore not included in data analysis. Overall ratings for each included study are listed in the table for each search domain. The overall quality of the body of evidence for each of the four search domains was rated using the Strength of Recommendation Taxonomy (SORT) framework.[11]

RESULTS

The electronic literature database search initially identified 3901 articles. A total of 205 studies met criteria for inclusion in our review (4 studies spanning multiple domains). **Supplementary Tables 1-4** provide a summary of key findings from studies in each domain that qualified for our review (81 neuroimaging, 50 biomarkers, 5 genetic testing, 73 advanced technologies).

Neuroimaging Studies

A total of 81 studies met criteria for review. Diffusion MRI (dMRI) was the most investigated modality (n=36) (see **Figure 1 and Supplementary Table 1**). Other commonly used measures including resting state fMRI (n=19), task fMRI (n=15, inclusive of cerebrovascular reactivity tasks), cerebral blood flow (n=15), magnetic resonance spectroscopy (MRS; n=9), structural MRI for quantitative analysis (e.g., volumetrics; n=8), structural MRI for qualitative analysis (e.g., clinical overreads, n=3), relaxometry for measuring myelin (n=2),

quantitative susceptibility mapping (n=2), and near infrared spectroscopy (NIRS; n=1). Twenty-two studies assessed more than one neuroimaging modality.

Three studies support current guidelines that routine clinical MRI following SRC has limited utility, unless patient signs or symptoms reflecting traumatic structural pathology are present.[12-14] A prospective cohort study extended these findings, showing that SRC was not associated with quantitative grey matter macroscopic differences following injury or changes (i.e., atrophy) through 6-months post-injury.[15] Together, these results suggest that most cases of SRC are not associated with acute changes in macrostructure or clinical pathology on traditional clinical MRI scanning.

Acute effects of concussion within 72 hours of injury are robustly observed at the group level across a wide range of advanced MRI sequences including: dMRI, fMRI (task and rest), measures of cerebral blood flow, quantitative susceptibility mapping, MRS, as well as non-MR imaging approaches such as NIRS. This reinforces that the pathophysiology of SRC reflects a diverse collection of pathological processes. Discrepancies exist, however, both in terms of direction of findings and regions most affected, possibly due to heterogeneity in study methods, sample composition, and the injury itself.

Study findings extend the conclusions from the previous review and highlight the possibility that physiological recovery may persist beyond clinical recovery.[6] Numerous studies demonstrated that group differences on advanced neuroimaging can be observed beyond 30-days. Differences beyond 30-days were commonly reported for dMRI, with varying levels of support for other markers. This is further supported by studies performing advanced neuroimaging at clinically defined timepoints (e.g., RTS), where significant group differences remained for dMRI, fMRI, and MRS.[16, 17] High-quality studies assessing recovery of these imaging metrics further from recovery (3-months to 1-years) are variable in regards to persistence of these effects, and further research is needed.

Finally, while progress has been achieved in terms of inclusion of larger sample sizes, wider sets of sport activities, and a greater range across levels of competitive sport, few studies individually showed a high degree of generalizability in isolation given their focus on specific age ranges. Similarly, female athletes (59/81 studies) and youth under 18 (25/81) remain underrepresented. Overall, the available literature on the role of advanced neuroimaging to define and assess neurobiological recovery after SRC was judged to be Level B according to SORT.[11]

Fluid Biomarker Studies

Fifty fluid biomarker papers met inclusion criteria (see **Figure 2.1, Figure 2.2, Supplementary Table 2**), most analysing blood (serum or plasma; n=43), followed by saliva (n=3), urine (n=2), and cerebrospinal fluid (CSF) (n=1). Sample sizes ranged from 12-264 concussions. Longitudinal follow-up sampling varied by study between 1-6 post-injury timepoints (single visit n=21; two visits n=6; three visits n=9; four visits n=7; five visits n=6; six visits n=1). Data collection typically occurred at clinically defined timepoints (e.g., early acute, sub-acute, symptom resolution, medical clearance to return-to-play/sport [RTP/RTS], one-week post-RTP) with only 10 studies sampling beyond 1-month post-injury.

Thirty-one papers found changes in blood biomarkers that significantly discriminated between SRC and controls (and/or pre-injury baseline levels).[18-48] Similar alterations were found in saliva,[49, 50] urine,[51, 52] and CSF[53, 54] studies. There is conflicting evidence concerning the discriminatory ability for some biomarkers[27, 31, 40, 55] [27, 47, 56, 57] while others specifically failed to distinguish between SRC and controls.[22, 45, 48, 58-60] Multiple studies showed a mix of longitudinally altered biomarker trajectories that either resolved by symptom recovery/RTP/RTS[23, 29, 33, 45, 61] while others were associated with prolonged recovery.[18, 30-32, 42, 48, 53, 54, 62-64] A summary of these biomarkers is presented in **Table 1**.

Many papers in recent years have made effort to investigate potential relationships between fluid biomarkers and clinical measures of SRC. These studies have associated various biomarkers to symptom burden[39, 47, 53, 65, 66] and specific psychological symptom domains (e.g., anxiety, depression, cognition, fatigue),[42, 43, 59, 65, 67] often implicating biomarkers involved in secondary injury processes following SRC (i.e., neuroinflammation and potentially altered neuroendocrine profiles). Lastly, recent investigations have revealed a possible dose-response relationship in blood GFAP, whereby concussed athletes with loss of consciousness (LOC) and/or post-traumatic amnesia (PTA) had elevated GFAP levels compared to athletes with neither LOC nor PTA acutely post-SRC.[26]

Overall, most studies included were rated as "+Acceptable", with only 9 papers rated as "++High Quality". Despite substantial improvement since the last iteration of this review[3] (particularly through larger sample sizes and longitudinal sampling), the field of SRC fluid biomarkers remains in infancy principally due to a lack of generalizability (30/50 studies including females and only 8 studies with mean age <18 years). Given the overall quality and consistency across studies, the available SRC fluid biomarker literature was judged to be Level B according to SORT.[11]

Table 1. Fluid biomarkers to detect and monitor recovery

Biomarkers demonstrating ability to discriminate between SRC and controls	- AMPAR[19] - Aβ-42,[20, 21] - BLBP[22] - C-proteins[23] - Extracellular-vesicle associated and depleted cytokines[32] - GFAP[24-27] - IgA autoantibodies[49]	- Inflammatory chemokines MCP-4,[28, 29] MIP-1β[29] - Inflammatory cytokines IL-6,[21, 30, 31] IL-1RA[30, 31] - Matrix metalloproteinases MMP-2 and MMP-3[33] - Metabolomic[34-36, 51] and proteomic[37, 52] panels - miRNAs[38, 39, 50] - Neuron-derived and astrocyte-derived exosome cargo proteins[21]	- PRDX-6[28, 41] - QUIN and KYNA[42-44] - s100B[20, 31, 40, 45] - SNTF[18, 31] - T-tau[20, 24-28, 41, 45-47] and tau-C[48] - UCH-L1[21, 26, 31, 40]

		- NF-L[24, 25, 27, 40, 53, 54]
Biomarkers failing to discriminate SRC from controls	- Cortisol[59] - CRP[31] - Fibrinogen[22] - GFAP,[27, 31, 40, 55] - HMGB1[22] - Inflammatory cytokines IL-6,[56] IL-18[58] - NFL[27, 47, 57] - NSE[45]	- PEA15[22] - T-tau[27, 57] and tau-A[48] - VILIP-1[60] - vWF[22]
Biomarkers trajectories post-SRC resolved by symptom resolution/return to play/return to sport	- C-proteins[23] - Inflammatory chemokines MCP-1, MCP-4, MIP-1B,[29] - Matrix metalloproteinases MMP-2 and MMP-3[33] - NFL[61] - s100B[45] - T-tau[45]	
Biomarkers associated with prolonged recovery post-SRC	- GFAP[62] - Inflammatory cytokines IL-1RA,[31] IL-6[30, 32] - NFL[53, 54] - QUIN and KYNA[42] - SNTF[18] - T-tau[62-64] and tau-A[48]	

AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; (Aβ)-42 = Amyloid β-42; BLBP = brain lipid binding protein; C-proteins = complement proteins (mediators and inhibitors); CRP = C-reactive protein; GFAP = glial fibrillary acidic protein; HMGB1 = high mobility group box protein 1; IgA = immunoglobulin A; IL = interleukin; IL-1RA = IL-1 receptor antagonist; MCP = monocyte chemoattractant protein; miRNA = microRNA; MIP-1β = macrophage inflammatory protein-1β; MMP = matrix metalloproteinase; NF-L = neurofilament-light; NSE = neuron specific enolase; PEA15 = phosphoprotein enriched astrocytes 15; PRDX-6 = peroxiredoxin-6; QUIN/KYNA = quinolinic acid/kynurenic acid; s100B = s100 calcium binding protein B; SNTF = α-II-spectrin N-terminal fragment; tau-A = tau A fragment; tau-C = tau C fragment; T-tau = total tau; UCH-L1 = ubiquitin C-terminal hydrolase-1; VILIP-1 = visinin-like protein-1; vWF = von Willebrand factor.

Genetic Testing Studies

Five genetic testing papers met inclusion criteria, all rated as "+Acceptable" (see **Supplementary Table 3**). Each study included female participants, but there were no studies that included participants with mean ages <18 years. Research characterizing the genetic aspects of concussion and recovery remains limited. Lines of inquiry being pursued include the genetic modulators of risk for concussion, modulators of response to trauma, and modulators of recovery from injury. For example, investigation into the apolipoprotein E ε4 (*APOE4* ε4) allele continues

to be intriguing. In addition to previous research investigating long-term outcomes, a 2015 study of 42 collegiate athletes across a variety of contact and collision sports showed that carriers of the ε4 allele reported greater SRC-related symptom burden shortly after injury, particularly in the physical and cognitive symptom domains.[68] A separate study revealed greater headache severity among carriers of the ε4 allele post-concussion.[69] A 2020 pilot study suggested that prolonged recovery time was perhaps associated with various polymorphisms of the promoter region for certain proteins.[70]

A prospective cohort study of collegiate athletes studied mRNA expression in peripheral blood mononuclear cells at the start of the season, within 6 hours and again at 7-days post-SRC. Their findings may offer some insight into the acute and subacute pathological changes that occur after concussion.[71] Similarly, Gill et al. studied peripheral blood mononuclear cells, finding changes from before to 7 days post-injury in the expression of 71 genes (more than a third involved in the inflammatory response to concussion) from before to 7 days post-injury.[72] Based on the limited available literature concerning the use of genetic testing to inform neurobiological recovery after SRC, we judged the body of evidence to be Level B according to SORT.[11]

Advanced Technologies

Twenty-nine papers measured electroencephalograms (EEG) or brain event-related potentials (ERP; see **Figure 3 and Supplementary Table 4**). Studies consistently found lower resting EEG power in one or more frequency bands (ranging from delta to gamma) post-SRC,[73-75] with SRC-related effects potentiated in standing (versus seated) positions.[73, 74] Similarly, 7 studies found altered amplitudes of numerous ERPs to auditory and visual stimuli after SRC,[76-82] with all but one[80] finding *lower* amplitude in SRC (versus non-SRC) groups and concussed athletes with more severe symptoms. P3/P300 was the most commonly studied ERP;[76-78, 80-82] others were N1, P2, N4, and a brainstem potential to speech sounds (FFR).[77, 79, 80] Studies have been mixed in whether[80, 82] or not[76, 81] ERP latency was associated with SRC. Five studies indexed functional connectivity using various indices extracted from the proprietary brain network algorithm (BNA), all of which reported either significant SRC versus control group differences or different trajectories of BNA scores across groups.[83-87]

Efforts have progressed to develop portable quantitative EEG systems (QEEG) that might become feasible to implement at the time of suspected injury. Five studies using BrainScope's QEEG system were reviewed.[88-92] Taken together, these studies support other work finding changes in resting EEG features acutely post-SRC; group differences were generally not significant at day 45 post-injury.[88, 89, 92] Other efforts have used complex signal processing methods and multivariate analysis approaches (including machine learning) to derive EEG/ERP-based classifiers of SRC. These studies have reported various classifiers to be significantly associated with concussion.[91, 93-97] While promising and informative about the natural history of physiological recovery from concussion, the proposed classifiers require independent cross-validation.

Thirteen studies examined autonomic nervous system (ANS; e.g., heart rate [HR], blood pressure [BP]) reactivity to tasks post-SRC; four studied ANS measures at rest. HR variability (HRV) studies have consistently found decreased HRV, particularly in high frequency (HF)

power band, after physical or cognitive tasks.[98-101] Findings of resting ANS have been mixed; 2 studies found no differences in HRV metrics between SRC and controls during rest,[102, 103] although one revealed differences in baroreceptor sensitivity.[103] Conflicting evidence exists between SRC and control groups in BP or HRV during the acute injury period.[104-108] Interestingly, a randomized controlled trial found a ΔHR cut-off metric (<50 bpm) to predict prolonged recovery.[109] Pilot studies employing physiological stressors such as lower body negative and positive pressure[110] and the Cold Pressure Test[111] found group differences in cerebrovascular reactivity (CVR)[110] and HR and BP[111]. One study found a significantly elevated Mayer wave proportion (cMW) in the concussion group compared to control.[112]

Six studies utilized transcranial doppler ultrasound to assess cerebral autoregulation (CA) or neurovascular coupling (NVC) during a task; 2 studies examined middle cerebral artery velocity (MCAv) and CVR during rest. Blunted NVC, CA, and CVR responses in concussed versus control groups were present during task and resting conditions at various timepoints post-SRC that appeared to extend beyond clinical recovery.[113-117][118] Finally, 2 studies by the same group found hypercapnia induced differences between SRC and controls in MCAv.[119, 120]

Several papers examined oculomotor and vestibular functioning following SRC. Various eye tracking technologies discriminated SRC and controls using pupillary light reflex metrics,[121] eye skew,[122] reaction time,[123, 124] gaze stability, and saccade errors.[124, 125] No deficits in the vestibulo-ocular reflex using a video head impulse test were found.[126] Two studies combined visual tracking tests with rotary chair systems,[124] measures of cervical vestibular evoked myogenic potential, and the Sensory Organization Test.[127] While most eye-tracking studies demonstrated diagnostic potential, only 2 studies found moderate associations with symptom burden and the ability to predict recovery time.[128, 129]

Emerging technologies such as robotic devices, virtual reality (VR) modalities, and inertial sensors have been used to examine a wide range of post-concussion deficits with variable results. One study using the KINARM robotic device was able to detect marginal impairments in neurological functioning which subsided by symptom resolution.[130] Conversely, a VR tool assessing postural stability continued to find residual concussion-related deficits up to 30-days post injury.[131] A similar study employing a neuropsychological VR tool also detected lasting cognitive deficits that discriminated SRC from controls.[132] Novel studies using inertial sensors to assess alterations in dynamic movement post-SRC also show promise when combined with measures such as the Y-balance test.[133] The commercially available FitBit has been used in studies to objectively monitor post-concussion changes in step-count adjusted metabolic energy balance,[134, 135] and sleep/wake disturbances.[136]

Overall, there has been a steep increase in the number of advanced technology studies examining electrophysiological, physiological, and ANS disruptions following SRC. Most studies included in this portion of this review were rated "+Acceptable", with only 12 being rated "++High Quality". Generalizability of these advanced technologies remains limited as only 48/73 studies included females, and 25/73 studies contained data from participants of mean ages <18 years. Using the SORT framework, the quality of the body of evidence for advanced technologies to define and assess neurobiological recovery after SRC was judged to be Level B.[11]

DISCUSSION

Conventional clinical tools for diagnosing and managing SRC are limited by subjectivity and lack of sensitivity and specificity. Consequently, there exists a need for objective measures to improve diagnosis, prognosis and RTS decision-making. The past 20 years have witnessed major growth in the number and scope of studies on the neurobiological underpinnings of SRC. This is reflected in the 205 studies included in the current systematic review assessing the role of biomarkers, genetic testing, and emerging technologies in defining and assessing neurobiological recovery after SRC, compared to fewer than 100 studies in a similar 2017 review. The interim work summarized in our current review reflects significant progress in the field. Despite evident growth in research interest and productivity, however, several gaps toward achieving clinical translation remain, driven mainly by limited generalizability and heterogeneity across studies. Notwithstanding these limitations, the balance of literature reviewed continues to advance our understanding of the complex neuropathophysiology of SRC, while generating key hypotheses that work toward the goal of developing objective tools for eventual clinical use. The discussion on the current state of biomarkers and advanced technologies could be split into multiple categories in terms of diagnostic utility, prognostic ability to predict and monitor recovery, determining time-windows of physiological recovery, and assessing possible associations between physiology to clinical symptomology.

Objective diagnosis of SRC

Findings of neuroimaging studies reviewed continue to support widely accepted guidelines that standard imaging (i.e., clinical MRI or CT) following SRC is not useful in detecting the microstructural changes that can be found when employing more advanced neuroimaging capabilities such as diffusion and functional MRI.

Blood-based biomarkers also show promising sensitivity to SRC, with numerous studies demonstrating the ability of these biomarkers to discriminate athletes with and without SRC. Most of the available evidence comes from studies that report results at the group level, as opposed to studies that determined diagnostic or prognostic accuracy at the level of the individual athlete. While consistent patterns have emerged in the literature for advances in imaging and fluid biomarkers, there exists conflicting evidence in many of the individual modalities, likely due to inconsistent sample compositions and study methods layered onto an already heterogenous injury.

Advanced technologies assessing both electrophysiological measures and autonomic dysfunction show promise, especially considering their non-invasive, cost-effective, and in some cases mobile and/or commercially available nature. Yet, studies using these modalities require replication in larger, independent samples to determine diagnostic accuracy at the level of the individual athlete, which is also essential to determining whether biomarkers and advanced technologies should eventually be incorporated into the case definition for SRC. Finally, there is also need for independent validation of many emerging technologies that have only been studied to date by individuals involved in their development and who hold commercial interests in them.

Monitoring recovery

Beyond the diagnostic domain, a key area of growth germane to our review featured recent studies investigating the prognostic utility of biomarkers and their potential to monitor recovery after SRC. Many studies in this review have prospectively collected data longitudinally

throughout SRC recovery, providing further evidence toward defining a physiological time-window of cerebral vulnerability. The sport concussion research model has moved toward collecting data at clinically defined timepoints ranging from acute injury to unrestricted RTS and beyond. This has enabled investigators to evaluate biomarker trajectories, which may provide insight into the natural physiological time course of recovery from concussion. An objective tool that could aid in both monitoring recovery and supporting RTS decisions is highly sought after, but yet to be adequately validated for clinical use. More recently, key biomarkers have emerged that may demonstrate the ability to predict normal versus prolonged recovery, which would be useful for early prescription of targeted interventions to promote recovery. Genetic research has shown that certain genes (and their products) may modulate an athlete's risk for and recovery from SRC, but remains too limited to predict the future role of genetic testing in SRC management.

While it is encouraging that multiple studies followed athletes throughout clinical recovery, few persisted to more chronic timepoints (i.e., >1-month post-injury). Regardless, multiple advanced neuroimaging, electrophysiological, and fluid biomarker studies demonstrated group differences remaining at both symptom resolution and/or medical clearance, further demonstrating that underlying physiological effects of SRC may persist beyond symptom resolution and functional recovery. These findings are mixed across studies, and it remains unknown whether residual alterations in physiology reflect clinically significant pathology, or perhaps indicate pre-injury vulnerabilities, benign effects, or even adaptive changes. Importantly, increased research has associated biomarkers with clinical measures of recovery, further enhancing our understanding of the neurobiology of concussion. In particular, biomarkers linked to inflammation (both central and peripheral) recurrently appear in the context of symptom burden in athletes following SRC. We also found relatively little research employing multi-modal approaches across domains which could an important new frontier for future research.

Research opportunities

Despite efforts to enhance quality and minimize ROB, inconsistent study methodology, varied data collection timepoints, and limited representation across populations persist in this current research space. For instance, timing of initial data collection ranged from hours to several weeks postinjury across studies in our review. Most papers included in our review were rated as "+Acceptable" with few meriting a "++High Quality" rating based on the methodologies employed. Further, given the procedures followed for the current systematic review, many papers with a high ROB were excluded, further emphasizing systemic issues that need to be addressed prior to the clinical validation of advanced technologies to evaluate recovery from SRC. Overall, the body of evidence in each of the four search domains was judged as inconsistent and of limited quality (Level B) based on the SORT framework.[11]

In general, most studies lack generalizability given the restricted age ranges and levels of competition (often collegiate level athletes only), limited number of sports (typically high contact only), and an unbalanced representation of athletic populations and racial/ethnic groups. While noticeable improvements have been made in recent years, there is still a sizeable gap in research on sex differences in SRC biomarkers and physiological recovery. This sex and gender disparity hinders movement toward clinical use of these advanced tools given the known biopsychosocial differences between male and female athletes. Furthermore, there were very few studies focusing on pediatric populations. Despite the known influences of puberty and development on the brain, we have little data on how these objective tools perform in pediatric

athletes. The current pediatric literature predominantly examines North American male adolescents, and further research is required addressing children 5-12 years of both sexes from different geographical backgrounds.

Lastly, there is a pressing need for better standardization of study design, methodologies, and common data elements across domains. The amount of data produced in recent years is formidable, but it remains difficult to compare results between studies given the lack of homogeneity in the field. With the exponential growth and evolution of these novel technologies, investigators are urged to coalesce; multi-site prospective longitudinal study designs implementing standardized operating procedures, common data elements, consistent data collection timepoints, and sophisticated biostatistical approaches to analyzing large multimodal datasets are needed.

Limitations

Multiple limitations exist in our systematic search and review process. While our search produced twice the included number of studies compared to the previous systematic review, our studies were limited to those that had extractable data specific to SRC. Beyond the parameters of our review focused specifically on concussion in sport, there has been significant progress in research investigating the potential diagnostic and prognostic utility of blood-based biomarkers, advanced neuroimaging, and emerging technologies in civilian mild TBI (mTBI). Collaborative exchange between the parallel efforts in both civilian mTBI and SRC can be mutually beneficial to both fields and help accelerate the field forward. As in all areas of published research, it is also important to recognize publication bias for positive findings only. There may be unpublished evidence showing less promise for these advanced technologies that would dampen their clinical effectiveness. Future reviews of this type would benefit from searching the grey literature, so long as those reports meet criteria for inclusion. The definition of emerging technologies used in our literature search may have excluded some prototypes and other work in early development. Finally, articles in this review were only included if published in English, limiting the inclusion of data published in other languages.

Conclusion

Our findings indicate that advanced neuroimaging, fluid-based biomarkers, genetic testing, and emerging technologies continue to be valuable research tools for the investigation of SRC neurobiology in areas of diagnosis, prognosis, and recovery. Research using these modalities has proliferated in recent years, but the existing literature remains hindered by important limitations in generalizability and heterogenous study methods employed. The important work published by researchers in recent years marks major progress that further inform a translational pathway to determine the appropriateness and clinical utility of advanced neuroimaging, blood and fluid-based biomarkers, genetic testing, and emerging technologies in SRC.

KEY RECOMMENDATIONS

- Advances in neuroimaging, fluid biomarkers, genetic testing, and emerging technologies continue to provide valuable research tools for the investigation of SRC neurobiology in the areas of diagnosis, prognosis, and recovery.

- While these technologies show potential for eventual clinical use, their translation is limited by methodological inconsistencies and a lack of generalizability, based on the existing evidence.
- Progression to further validate their clinical utility will require large, multi-site, prospective longitudinal studies implementing standardized operating procedures, common data elements, consistent data collection timepoints, and more sophisticated biostatistical approaches to data analysis.

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Data Availability

Data extraction tables and relevant analytic code from this systematic review are available upon request from the corresponding author.

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Figures Legends

Figure 1. Neuroimaging Study Activity and Sample Sizes (2001-2022)

Figure 2.1. Fluid and Blood Biomarker Study Activity and Sample Sizes (2001-2022)

Figure 2.2. Fluid and Blood Biomarker Study Modalities (2001-2022)

Figure 3. Advanced Technologies Study Activity and Sample Sizes (2001-2022)