THE CHALLENGES OF PREDICTING POST-CONCUSSION SYMPTOMS

THE CHALLENGES ASSOCIATED WITH PREDICTING POST-CONCUSSION SYMPTOMS: A SCOPING REVIEW OF LITERATURE

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Descriptive Note

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TITLE: The Challenges Associated With Predicting Post-Concussion Symptoms: A Scoping Review of Literature

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Lay Abstract

Background: Despite countless reviews attempting to clarify the extensive list of predictors for post-concussion syndrome, there remains a great deal of uncertainty.

Objective: To determine the characteristics of the existing review studies on predictors for developing post-concussion syndrome and identify obstacles in quantitatively combining studies and translating the evidence into clinical practice.

Methods: Six databases were systematically searched to find relevant reviews examining predictors of post-concussion syndrome. Eligible studies went through multistage screening to determine whether they meet the eligibility criteria.

Results: 281 studies were eligible for screening, of which, 11 studies were included. Obstacles regarding definitions and diagnostic criteria and study methods were contributing to increased diversity across the studies.

Conclusions: The obstacles identified in this study all contribute to the challenges in combining individual studies into a quantitative synthesis that, in turn, limit the clear conclusions that can be drawn and the translation of research evidence to clinical use.

Abstract

Background: Up to 20% of concussion patients do not recover and develop a host of persisting cognitive, physical, behavioural, and/or emotional symptoms – collectively known as post-concussion syndrome (PCS) – lasting for many months to years. It is unclear why these patients have protracted recovery. Identifying factors that can predict patients at most risk can provide earlier targets for prevention and treatment. However, the wide-ranging list of predictors of PCS is creating confusion in the body of literature, and despite countless reviews attempting to clarify this growing list, there remains a great deal of uncertainty.

Objective: To systematically map the reviews on PCS predictors to determine the nature of the reviews and understand why this body of literature still lacks firm, conclusive evidence. We aimed to identify sources of clinical and methodological diversity that hinder meta-analytic syntheses, and in turn, limit the conclusions drawn and translated to clinical practice.

Methods: The Joanna Briggs Institute Reviewer's Manual and the PRISMA-ScR was used to develop our study design. Six databases were searched, including reference lists. Studies needed to sufficiently focus on predicting PCS and report challenges relevant to quantitative synthesis.

Results: 281 eligible studies were found. Eleven studies were included in the final qualitative analysis. Qualitative synthesis revealed definitions and diagnostic barriers, as well as methodological barriers, contribute to clinical and methodological diversity in studies.

Conclusions: Despite extensive research on PCS predictors, researchers are faced with definitions and diagnostic barriers and methodological barriers that influence the clinical and methodological diversity across studies. These sources of barriers and diversity impede the conduct of more meta-analytic approaches, and in turn, limits review studies from reaching more conclusive evidence that can reliably inform clinical practice. Understanding of the nature of literature reviews can help inform researchers of the sources of diversity and barriers to improve research contributions to evidence-based medicine.

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List of Figures and Tables

List of Abbreviations and Symbols

Abbreviation	Definition
ACEP	American College of Emergency Physicians
ACRM	American Congress of Rehabilitation Medicine
ADHD	Attention Deficit Hyperactivity Disorder
CDC	Centers for Disease Control and Prevention
CDSR	Cochran Database of Systematic Reviews
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CT	Computed Tomography
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4^{th} Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5^{th} Edition
EBM	Evidence-Based Medicine
ED	Emergency Department
EEG	Electroencephalography
GCS	Glasgow Coma Scale
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10^{th} Revision
LOC	Loss of consciousness
MRI	Magnetic Resonance Imaging
mTBI	Mild Traumatic Brain Injury

PCS	Post-Concussion Syndrome
PTA	Post-traumatic amnesia
REB	Research Ethics Board
RCT	Randomized Controlled Trial
TBI	Traumatic Brain Injury
U.S.	United States
WHO	World Health Organization

Declaration of Academic Achievement

I, Adrienne Lloyd Atayde, declare this thesis to be my own work. Under the supervision and guidance of Dr. Michel P. Rathbone and the support of Teresa Gambale, I was responsible for leading the reviewing team of students: Maxwell Ng, Angela Dong, and Anthony Wang, by establishing timelines for project milestones, leading and holding project meetings, creating files and resources for database searching, data extraction, assigning articles for each reviewer to review, and leading the qualitative analysis of included articles.

Chapter 1: Introduction

1.1 Mild Traumatic Brain Injuries & Post-Concussion Syndrome

1.1.1 Epidemiology

A traumatic brain injury (TBI) is characterized by an alteration in brain function due to an external force to the head or body[1]. Globally, the incidence rate of TBIs has been increasing over time, with over 50 million people sustaining a TBI annually[2–7]. It is a growing public health concern as it was estimated that about 50% of the global population would sustain at least one TBI in their lifespan[4,8]. According to the World Health Organization (WHO), TBI is – at present and forecasted up to the year 2030 – one of the top three neurological conditions, worldwide, causing neurodisability[9]. To put this into the context of cases in the United States (U.S.), about 3.17 million Americans are suffering from the prolonged and permanent sequelae of TBIs[10].

The severity of TBIs can range from mild to more moderate and severe TBIs. Of all the types of TBIs, mild traumatic brain injury (mTBI), used interchangeably with the term concussion, accounts for 80-90%[11]. The Centers for Disease Control and Prevention (CDC) estimate 1.6-3.8 million concussions occur in the U.S. annually[12]. In the province of Ontario, Canada alone, a total of 1.3 million concussion diagnoses occurred between 2008 and 2016, with about 150,000 diagnoses occurring each year[13]. Despite these staggering rates, the reported numbers are likely an underestimation of the true incidence rate of concussion. This may be partly explained by the prior assumption that this type of brain injury is "milder" in severity and tends to require more minimal clinical management compared to the more moderate to severe cases. Thus, some mTBI patients may not seek medical attention or report the injury[4,13]. However, there is increasing awareness that mTBIs can also have adverse consequences with patients burdened by chronic symptoms and disabilities. Thus, obtaining proper medical attention and earlier targeted treatments based on strong evidence-based guidelines to reduce or prevent the chronicity of symptoms and the likelihood of disability is warranted.

1.1.2 Mild TBI Definitions & Diagnostic Criteria

The most widely accepted mTBI definition and diagnostic criteria is the American Congress of Rehabilitation Medicine's (ACRM) definition[14,15]. It defines an mTBI as a physiological disruption of brain function due to brain trauma, – which includes the head being struck, the head striking an object, and the brain undergoing an acceleration or deceleration movement (i.e., whiplash) without direct external trauma to the head – and computed tomography (CT), magnetic resonance imaging (MRI), electroencephalogram (EEG), or routine neurological evaluations can be normal. This disruption is manifested by at least one of the following: (1) any period of loss of consciousness (LOC) that does not exceed 30 minutes (or after 30 minutes following injury, a Glasgow Coma Scale (GCS) score between 13-15); (2) any post-traumatic amnesia (PTA) for events immediately before or after the injury that does not exceed 24 hours; (3) any alteration of mental state at the time of the injury (e.g. feeling dazed, disoriented or confused); and (4) transient or non-transient focal neurologic deficit(s).

Another mTBI definition and diagnostic criteria is in the CDC's report to Congress on mTBI in the U.S. that provides a standard conceptual definition[16]. This conceptual definition also provides the basis for three operational definitions, which allows the assessors to obtain quantifiable criteria to consistently identify mTBI cases for interviews and surveys, healthcare administrative data sets, and clinical records. The conceptual definition defines an mTBI as a head injury due to blunt trauma or acceleration/deceleration forces. This results in one or more of the following: (i) any period of observed or self-reported: transient confusion, disorientation, or impaired consciousness; PTA around the time of injury; and LOC less than 30 minutes; (ii) observed signs of neurological or neuropsychological dysfunction (e.g., seizures acutely after a head injury). They also include specific symptoms in infants and very young children as well as in older children and adults that can be used to support the diagnosis of mild TBI only if there was the presence of LOC or altered consciousness.

Moreover, the WHO Collaborating Centre for Neurotrauma Task Force on mTBI provides its operational criteria for clinical identification of an mTBI that is derived from the ACRM and has similarities with the CDC[17]. The WHO defines an mTBI as an acute brain injury due to mechanical energy from external physical forces. This includes: (i) 1 or more of the following: confusion or disorientation, LOC for 30 minutes or less, PTA for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) GCS score of 13-15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations must not be due to: drugs, alcohol, medications, other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury.

In addition to these, the most commonly used concussion definition in sports concussion is the Consensus Statement from the Fifth International Conference in Berlin[14,18,19]. This group defines a concussion as a complex pathophysiologic process due to biomechanical forces resulting in the rapid onset of transient neurologic dysfunction. This dysfunction can spontaneously subside over a variable period of time, and may or may not involve LOC.

Altogether, there are some clear overlaps between these criteria; however, there are also distinct differences highlighted in the literature. For instance, the ACRM considers an alteration of mental state as feeling dazed, disoriented, or confused, whereas the WHO and the CDC criteria omit dazed, and the CDC alternatively requires impaired consciousness. Furthermore, the WHO defines the presence of neurologic abnormalities to be transient while the ACRM leaves the option of focal neurologic deficit(s) that may or may not be transient[20], while the CDC only specifies that confusion, disorientation, and impaired consciousness is transient. A critique of the WHO definition is that it leaves some ambiguity as to what constitutes an acute brain injury, according to Maas et al. (2017)[4]. Moreover, Holm et al. (2005)[17] address that the WHO criteria builds on to the ACRM's requirement of a GCS of 13-15 (assessed after 30 minutes has passed following injury) by allowing this assessment to also occur at the earliest possible opportunity by a healthcare provider as patients presenting to an emergency department (ED) may not be assessed within the ACRM's 30-minute time frame requirement. Lastly, according to Sussman et al. (2018)[14] the sports concussion definition is notably broader and more inclusive in comparison to the other criteria. However, the same critique of being too broad was given to the ACRM and the CDC's report to Congress by Jagoda et al. (2008)[21] from the American College of Emergency Physicians (ACEP)/CDC. These differences in criteria can lead to a largely variable patient sample diagnosed with mTBI depending on which criteria is used and may explain the likely underestimation of incidence rates. Therefore, further standardization of which criteria should be used in both clinical practice and research based on expert opinion and consensus is needed to clarify and address this variability.

1.1.3 Prognosis & Recovery from an mTBI

The majority of concussed patients generally have a full recovery within 14 days[22,23]; however, it is important to highlight that patients also experience varying recovery times from a concussion. For example, it has been reported that the duration of concussion recovery can vary greatly from a week to 3 months for most adults[22,24–27]. Recently, an article reported that the resolution of symptoms following a concussion was as little as 72 hours[18] while sports-related concussion recovery was within two weeks for adults and one to three months for children[18,19,28–30]. Although most concussed patients will recover within the shorter time frame, a subset of concussed patients will not and will experience persistent post-concussive symptoms that can last for many months (i.e., more than 3 months) to years. The percentage of the patients experiencing this protracted recovery can vary as well, ranging from as little as 5% up to as high as 58.5%[31–33]. It has been previously reported post-concussive symptoms persist for over three months in 15% of mTBI patients, while more recent studies reported that various inception cohort studies found 1 in 5 mTBI patients will experience post-concussion symptoms persisting for over one month[6]. Other reports suggested up to one-third of individuals were experiencing prolonged symptoms[18,27]. For children, it has been reported that symptoms can last for months to years in 10-20% of patients[19], while another study specified that 58.5% of children were symptomatic at one month post-injury, 11.0% at 3 months, and 2.3% over 1 year[34]. Generally, it is agreed upon that about 15-20% of concussed adult patients were frequently reported to not fully recover and go on to have a host of persisting physical, cognitive, behavioural, and/or emotional post-concussion symptoms[22,26,35]. Collectively, these symptoms are known as post-concussion syndrome (PCS).

1.1.4 PCS Definitions & Diagnostic Criteria

The two most widely known PCS diagnostic criteria are from the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) and the WHO International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). The DSM-IV uses the term 'postconcussional disorder' and includes: (i) TBI causing a significant cerebral concussion, (ii) attention and memory cognitive impairment, (iii) at least 3 of the following 8 symptoms (persisting for a minimum of 3 months): fatigue, headache, affective disturbance, sleep disturbance, irritability, dizziness, apathy, and personality change, (iv) a change in the condition manifested as symptoms appearing after injury or a significant worsening from baseline pre-existing conditions, (v) social/professional functioning interference, and (vi) the exclusion of other comorbid conditions with similar symptoms (e.g., dementia).

Meanwhile, the ICD-10 uses the term 'postconcussion syndrome' and has two PCS criteria, one for research and one for clinical use[36]. The clinical criteria require: (i) a history of head trauma severe enough to result in LOC and, (ii) 3 or more of the following symptoms: headache, fatigue, dizziness, irritability, insomnia, concentration and memory difficulty, as well as intolerance for alcohol, emotion and stress, (iii) complaints unassociated with compensation/litigation motives, (iv) the optional presence of depression or anxiety related to fear of brain damage. These symptoms are required to have been present within 4 weeks after the injury. The ICD-10 research criteria differ in broadening the list of symptoms to 12 manifestations: headache, dizziness, fatigue, noise intolerance, irritability, emotional lability, depression and/or anxiety, subjective complaints of difficulty in concentration and memory problems, insomnia, intolerance or reduced tolerance for alcohol, and the adoption of a hypochondriac-like preoccupation with symptoms and worries about brain damage.

In addition, it is important to consider that the DSM-5 (published in 2013) does not recognize PCS as a distinct diagnostic entity, but rather identifies problems relating to an mTBI as 'major or mild neurocognitive disorder'[37]. The DSM-5 is based on an objective assessment of a decline in cognitive function and does not include post-concussion symptoms or take into account the injury severity using the GCS score[37].

A fundamental challenge in defining and diagnosing PCS is its non-specificity to the brain injury itself and the lack of consensus on the true etiology of the syndrome[38]. This may explain why PCS has been a controversial topic in research and in the clinic. Post-concussion-like symptoms are common in healthy individuals, in patients with traumatic injuries not stemming from a head or brain injury, and other health conditions that can co-occur with an mTBI[6,28,39–41]. For example, these symptoms have been found in patients with general trauma, psychiatric complaints, neurology patients, and patients with chronic pain[42,43]. These preexisting and comorbid health conditions can further complicate recovery, and the poor specificity of these symptoms can weaken their diagnostic utility[6,35,44]. Similar to the definitions and diagnostic criteria for an mTBI, increased expert opinion and consensus on more standardized criteria or guideline on the preferred PCS criteria in research and in the clinic is needed.

1.1.5 Predictors of PCS

The reason why a subset of patients has protracted recovery and present with these post-concussion symptoms remains unclear. Genetic, environmental, socioeconomic and behavioural factors can predispose one to prolonged recovery, although studies have conflicting findings on their relative contributions. Previous literature shows a clear need for more evidence-based guidelines to establish treatment and management standards for PCS. Identifying factors that can predict and target patients who are most likely to develop prolonged PCS can provide earlier targets for the prevention and treatment of these symptoms and potentially improve risk stratification in research studies.

Over time, numerous studies have attempted to identify risk factors for PCS; however, there is conflicting evidence across studies on the predictive value of independent and multivariable predictors of PCS reported in the current literature[6,18,25,28,34,42,45–47]. For example, McCrea et al. (2013) found LOC and PTA as predictors of prolonged recovery while several studies reported that these traditional markers do not have a clear association with protracted recovery[18,28,46,48]. The severity of symptoms immediately after the injury has also been reported as the most consistent predictor of prolonged recovery[18,19,49–51], but this is in contrast to Chrisman et al. (2013)[48], Scopaz et al. (2013)[47], and Silverberg et al. (2020)[6] who suggest that the higher number of symptoms, as opposed to the severity, are more associated with the clinical outcome for prolonged concussion symptoms.

Furthermore, it has also been reported that persistent neurocognitive impairment and history of prior concussion are other likely predictors[52–57]. However, Silverberg et al. (2020)[6] suggest a history of concussion is an inconsistent predictor of clinical outcome[48,52,54,57–62]. Other reported predictors are: acute symptoms such as fatigue/fogginess, immediate or early onset of headache, amnesia, disorientation, or mental status change[19,24,54], females, mTBI with lower GCS score, mechanism of injury from an assault or alcohol intoxication[63], younger age[24,64], years of education, medication, and comorbidities such as sleep disorders, learning disabilities, and migraine[64]. However, the evidence for these reported factors has again been consistently criticized as limited or inconclusive. For instance, the recent review by Silverberg et al. (2020)[6] suggested that although females may take longer to recover, the evidence has been fairly mixed[22,25,46,47,49,51,53,55,57–59,65]. Another example is the association of attention deficit hyperactivity disorder (ADHD) as a predictor of prolonged recovery. Previously, Scopaz et al. (2013)[47] did not find an association with ADHD while in a recent retrospective cohort study on adolescents ADHD was found to be a predictor of prolonged recovery[55,57].

More recently, Silverberg et al.'s (2020)[6] review paper suggested that the most powerful and robust predictors of prolonged recovery are preinjury mental health problems and postinjury psychological distress (symptoms of depression and anxiety) in adults as well as mood symptoms following injury[40,52,56,58,62,66,67]. This finding falls in line with their previous systematic review[60], where they found that the most robust predictors were pre-injury mental health and acute post-injury neuropsychological functioning when considered alongside multivariable models. Moreover, research on potential biomarkers to help predict post-injury recovery and the risk of developing prolonged PCS have also been done; however, similar to the other potential predictors, strong evidence from well-designed confirmatory studies are still warranted[68].

Since post-concussion symptoms can persist for many months to years and some never fully recover, this protracted recovery can further add to the negative physical, psychosocial and economic impact on the individual following injury and the healthcare system due to the prolonged need for post-concussion care management and high health service use. To effectively inform clinical practice and help research studies risk stratify those most at risk for PCS, there is a clear need to summarize, clarify, and validate this extensive and expanding list of potential predictors using evidence-based guidelines.

1.2 Evidence-Based Medicine

1.2.1 Systematic Reviews & Meta-Analyses

The dynamic landscape of medical research and literature necessitates that healthcare professionals are provided with the strongest evidence available upon which to base their care. The principles of evidence-based medicine (EBM) show randomized control trials (RCT) at the top of the hierarchy of evidence for unfiltered, non-synthesized studies whereas systematic reviews and meta-analyses are at the top of the hierarchy of evidence for filtered and synthesized information.

A systematic review methodically aggregates empirical evidence to answer a specific research question aimed at minimizing bias and providing more reliable outcomes[69]. Meta-analyses – a type of quantitative systematic review – provide the advantage of a formal statistical approach when pooling data from multiple individual studies. This approach can provide far more robust and precise estimates of the effect size than any individual study contributing to the synthesized analysis. As such, meta-analyses can be objectively used to summarize and clarify large bodies of work on a specific topic.

It is not surprising that there have been countless reviews that have attempted to summarize the true predictors of PCS and resolve existing discrepancies; however, many qualitative systematic reviews experienced challenges in attempting to conduct a meta-analysis. And, despite the current literature reviews attempting to clarify the wide-ranging list of potentially predictive factors of PCS, there remains a great deal of uncertainty and inconclusive evidence.

There are several criteria associated with conducting high-quality meta-analyses that need to be taken into consideration[70]. It is crucial that meta-analyses are conducted on a group of sufficiently homogeneous studies (i.e., in terms of subjects, interventions, and outcomes) as pooling studies that have substantial variability (e.g., in study designs) can produce meaningless outcomes[69]. With complex and multi-faceted conditions such as mTBI and PCS, excessive heterogeneity across studies should be anticipated and may explain the uncertainty in the current literature on predictors of PCS.

1.2.2 Scoping Reviews

A scoping review is used for more broad research questions or goals that can investigate various objectives such as examining the extent, range, and nature of the evidence on a topic; determine the value of conducting a systematic review; summarize findings from a heterogeneous body of literature; or identify gaps in the literature[71,72]. Therefore, a scoping review was conducted to investigate the nature of the existing review studies on predictors of PCS to better understand why the current body of literature reviews still lack such conclusive evidence.

1.3 Study Aims

According to Haidich et al. (2010)[69], distinguishing between the variable sources of heterogeneity is crucial in order “to understand the nature of variability in studies". Although review studies on predictors of PCS have briefly reported on limitations and challenges with regards to conducting a meta-analysis, there have been no review studies that comprehensively dissects and distinguishes between the different sources of heterogeneity. Therefore, the purpose of this scoping review was to systematically map the existing reviews focusing on predictors of PCS to better understand the characteristics of these reviews and determine why despite numerous studies on predictors of PCS many uncertainties and inconclusive evidence remains evident in the current literature reviews. This study aimed to distinguish between the different sources of heterogeneity that may be impeding researchers from conducting high-quality meta-analyses, which in turn, influences the capacity of drawing strong conclusive evidence. The implications of this scoping review were to highlight the current shortcomings in the literature reviews on predictors of PCS to help improve and facilitate the translation of strong research evidence into clinical practice and improve uniformity across research studies.

Chapter 2: Methods

2.1 Study Design

The Joanna Briggs Institute Reviewer's Manual[73] and the PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation[72] was used to guide the development of our study design to ensure methodological transparency and for best practices for reporting and conducting scoping reviews. Approval from a local Research Ethics Board (REB) is not required as we will be using data from published literature reviews.

2.2 Eligibility Criteria

In this study, review articles meeting the inclusion criteria needed to focus on some aspect of predicting PCS and identifying predictors of PCS. Studies must also have sufficiently reported limitations, challenges and/or gaps in determining the true predictive value of predictors of PCS. Articles meeting the study inclusion criteria were: full-text literature review articles (narrative and systematic reviews that can include meta-analyses), published up to 2018, written in English, and involved human participants. Published abstracts with no available full text article do not provide sufficient information to satisfy our study aims and therefore will not be eligible in the final inclusion of articles for qualitative analysis. Articles were excluded if they did not meet any of the inclusion criteria. Adherence to the inclusion and exclusion criteria was maintained throughout the scoping review process with a detailed reasoning for exclusion.

2.3 Information Sources

To identify potentially relevant documents, the following six online databases were searched: (a) EMBASE (via Ovid) (1974 - 2018), (b) MEDLINE (via Ovid) (1946 - 2018), (c) PsycINFO (via Ovid) (1806 - 2018), (d) Web of Science (1976 - 2018), (e) Cumulative Index of Nursing and Allied Health Literature (CINAHL), and (f) Cochrane Database of Systematic Reviews (CDSR). The comprehensive search strategy was developed and refined by the research reviewing team (A.A., T.G., M.N., A.W., and A.D.) in collaboration with an experienced research librarian from McMaster University's Health Sciences Library where the librarian helped in enhancing the study methods and protocol. The search strategy was built off of key search terms relevant to the study aims (Table 1). The final search results were exported into Mendeley. Duplicates were first removed using Mendeley followed by the manual removal, by the reviewers, of any duplicates that may have been missed. The electronic database search was supplemented by scanning reference lists of included or relevant articles and hand-searching key databases.

Table 1. Key study search terms for the comprehensive search strategy

(#)	Key Search Terms	Reasoning for selection
1	Post-Concussion Syndrome OR Persistent Post-Concussion OR	Condition of focus

	Concussion OR mild Traumatic Brain Injury	
2	Prognostic Factors OR Risk Factors OR Predictors	Outcome assessment of focus
3	Review OR Meta-analysis OR Systematic Review	Study type

2.4 Search

An example of one full electronic search strategy used for the Embase (OVID) database searched from 1974 until May 25, 2018:

1 postconcussion syndrome/ (1609)
2 post concuss*.mp. (2215)
3 mild traumatic brain injur*.mp. (5204)
4 concussion/ (4306)
5 PCS.mp. (19887)
6 3 or 4 (8851)
7 5 and 6 (407)
8 1 or 2 (2932)
9 6 and 8 (1653)
10 7 or 9 (1700)
11 risk factor/ (874710)
12 prognosis/ (537553)
13 risk factor*.mp. (1144595)
14 prognos*.mp. (975686)
15 11 or 12 or 13 or 14 (2027518)
16 10 and 15 (246)
17 meta analysis/ (144547)
18 limit 16 to meta analysis (4)
19 limit 16 to "systematic review" (24)
20 "review"/ (2309916)
21 16 and 20 (53)
22 limit 16 to cochrane library (0)
23 limit 21 to exclude medline journals (5)
24 limit 19 to exclude medline journals (1)
25 limit 18 to exclude medline journals (0)

2.5 Selection of Sources of Evidence

Selection of study articles for inclusion was undertaken in a multistage process where four independent reviewers (A.A., M.N., A.W., and A.D.) first conducted the searches, followed by the title and abstract screening, full-text screening, and lastly the data charting using Microsoft Excel. Mendeley software was used to combine the search results from the six databases and to remove any duplicates. The screening was reviewed and verified by the lead reviewer (A.A.) throughout the multistage review process. Disagreements on study selection were resolved first through discussion with a third-party reviewer (T.G.) followed by a discussion with the broader researcher team if needed.

2.6 Data Charting Process & Data Items

A data charting form was developed by the lead reviewer in consultation with the reviewing team to determine the information that will be extracted and charted on Microsoft Excel from the screened articles. The data items extracted from the manuscript include: author(s), year of publication, title, journal, study characteristics (study origin, study design/review type, study population, number of studies included in the review, diagnostic criteria used for mTBI and PCS, prognostic factors reported, method of assessing prognostic factors, challenges, limitations, or gaps in predicting PCS and/or conducting a systematic review or meta-analysis, other key points relevant to the aims of this scoping review, and potentially relevant articles found in the included article's reference list. After the data items from the articles were logged onto the charting table, each reviewer's decision to include or exclude the article was also recorded and accompanied by the reviewer's reasoning for inclusion or exclusion. If the decision on whether to include or exclude an article was uncertain or undetermined a third-party reviewer (T.G.) was consulted to resolve any discrepancies. If required, the discussion was brought to the broader research team to come to a consensus decision.

2.7 Synthesis of Results

This data subsequently underwent qualitative synthesis and were grouped into major themes of heterogeneity according to Haidich et al. (2010)[69]: any variability in the participants or outcomes studied will be identified as clinical diversity, and variability in study design and outcome assessment methods will be categorized as methodological diversity.

2.8 Critical Appraisal of Individual Sources of Evidence

Given this study is a scoping review, a formal assessment to critically appraise the risk of bias of a cumulative body of evidence was not conducted.

Chapter 3: Results

3.1 Selection of Sources of Evidence

A total of 269 records were identified from searching the six electronic databases with an additional 12 records found from scanning reference lists of eligible studies or hand-searching relevant databases (Figure 1). Following the removal of duplicates, 204 records were screened for their title and abstracts to determine eligibility for full-text screening. Of the 96 records that went through the full-text screening, 85 were excluded due to several reasons listed in Figure 1. Following exclusion, 11 articles were included in the final qualitative review.

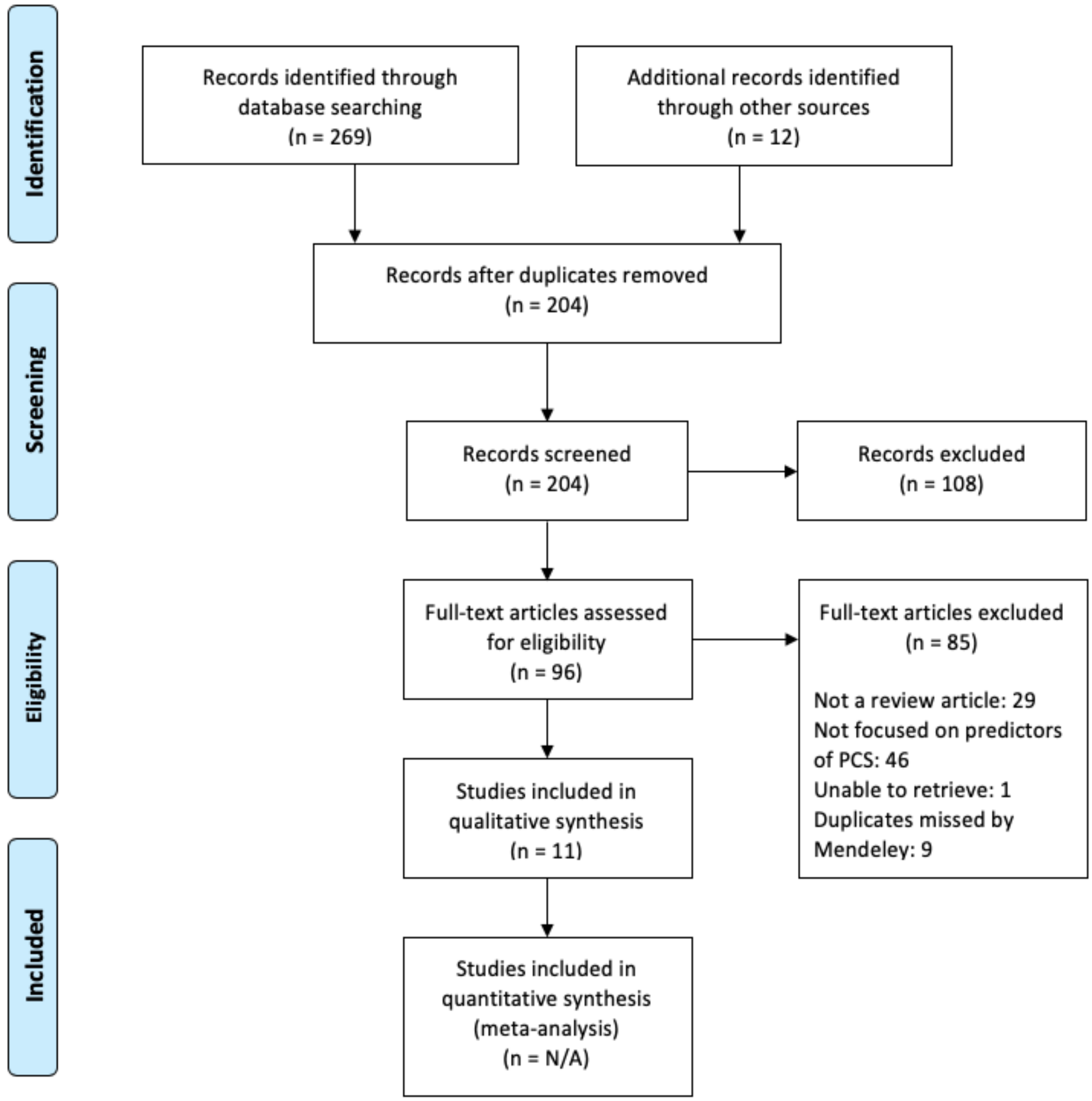

Figure 1. Flowchart of the scoping review process and study selection for this review study adapted from the PRISMA flowchart by Moher et al. (2009)

3.2 Characteristics of Sources of Evidence

The key study characteristics related to this scoping review is reported on Table 1. Out of the 11 included review studies, 6 were systematic reviews and the remaining 5 were non-systematic reviews. Interestingly, no meta-analytic studies were eligible for inclusion in this scoping review. Upon qualitative synthesis and identification of clinical and methodological diversity, review studies consistently reported a recurring pattern of barriers that are impeding systematic reviews from conducting meta-analyses, which in turn, limited their study conclusions from being translated into clinical practice. We categorized these barriers under definition and diagnostic barriers and methodological barriers and further breakdown these barriers in Chapter 4 as it relates to the clinical and methodological diversity found in the literature.

Table 2. Relevant Study Characteristics of the 11 Included Review Studies

Article (First author, Year, Reference)	Article Type	Number of studies included	Study sample	Study objective(s)
Blume 2012[53]	Review	Not specified	Pediatrics	To review the epidemiology, evaluation, and management of pediatric PCS
Cancelliere 2014[55]	Systematic review	19	Athletes	To update the WHO Collaborating Centre Task Force findings by

				synthesizing the best available evidence on prognosis of sport concussion and RTP
Cassidy 2014[42]	Systematic review	23	All ages	To update the WHO findings on course and prognosis in adults with respect to self-reported outcomes
Fayol 2009[43]	Review	Not specified	Not specified	To point out from the literature the issues in mild traumatic brain injury outcome
Jotwani 2010[31]	Review	Not specified	Athletes	To review the controversies and factors that predict PCS relating to issues in definition and pathophysiology
King 2014[25]	Systematic review	16	"Working-age" (16-65 years old)	To identify and examine those studies which have investigated working-age patients with prolonged PCS
Mayer 2017[37]	Review	Not specified	Not specified	To provide an in-depth overview of diagnostic schema and risk factors influencing recovery during the acute, subacute, and chronic injury phases across the full spectrum of individuals with mTBI
Mercier 2017[33]	Systematic review	36	Adults (>16 years old)	To describe populations included or enrolled in studies on the

				prognostic value of protein biomarkers for prediction of postconcussion symptoms following an mTBI and to describe the mTBI definition applied in these studies as well as the outcomes evaluated
Scopaz 2013[47]	Review	Not specified	Not specified	To review and identify risk factors of concussions and prolonged recovery
Silverberg 2015[60]	Systematic review	26	Patients from an acute care setting (school-aged children, adolescents, and/or adults)	To identify and evaluate existing multivariable prognostic models appropriate for clinical and research applications, and to clarify which individual factors independently predict mTBI outcome
Zemek 2013[32]	Systematic review	15	Pediatrics (2-18 years old)	To identify predictors of persistent concussion symptoms in children following concussion

Abbreviations: PCS, Post-Concussion Syndrome; mTBI, mild Traumatic Brain Injury; WHO, World Health Organization; RTP, return-to-play

Chapter 4: Discussion & Conclusions

4.1 Summary of Evidence

This scoping review found that literature reviews on predictors of PCS reported clear definition and diagnostic barriers as well as methodological barriers that influence the clinical and methodological diversity impeding the appropriate conduct of a meta-analytic approach, which in turn, affects the strength of conclusions that can be drawn from these studies. As a result, this limits the translation of strong evidence from review studies into the clinical context. Excessive variability in the participants, their characteristics, the outcomes assessed, and the methods for measuring and defining the outcomes differ for each individual study challenging the pooling of studies into a meta-analysis. Both the definition and diagnostic barriers as well as the methodological barriers reported across the studies clearly demonstrate how there is a need for a more balanced approach to ensuring internal and external validity is maintained in both the individual and review studies. Finding this balance is essential to overcome these barriers and reduce the clinical and methodological diversity. This scoping review discusses in subsequent sections how these barriers directly contribute to the clinical and methodological diversity in literature reviews on predictors of PCS.

4.2 Definition & Diagnostic Barriers

4.2.1 Mild TBI Definitions & Diagnostic Criteria

Unsurprisingly, the first barrier hindering the ability to conduct a meta-analysis and reach more consensus on PCS predictors is the variability in mTBI definitions and diagnostic criteria used across studies and in the clinical setting[25,31–33,37,43,47,53,60,74,75]. Historically, the most commonly used classification system for TBIs has been rooted in the GCS, a clinical score based on the level of consciousness. With regards to mTBI, it is diagnosed in patients with a GCS score of 13–15 and scores less than 13 are considered more moderate to severe cases[14]. The systematic review by Mercier et al. (2017)[33] found wide variations in the mTBI definitions used across the 36 studies included in their review. Specifically, despite the GCS being used in 86% of the studies, the specific GCS criteria differed between these studies. Most of their included studies (64%) used GCS criteria of 13-15 while 19% of studies used a GCS of 14-15, and 3% used a GCS of 15. Although these differences may appear subtle, Mercier et al. (2017)[33] emphasized that a wide range of injury severities can exist within mTBIs. Those with a GCS 13 could be argued as having more severe mTBIs compared to patients with a GCS of 15 implying that this comparison may be unsuitable due to the increased diversity in patient characteristics.

At present, other clinical factors have also been considered and incorporated in classifying the severity of a TBI such as LOC, PTA, and focal neurological signs[14]. However, the use of LOC, PTA, and focal neurological deficits as study criteria reportedly varied between studies as well, which again can inappropriately compare milder cases to more severe ones[33,60]. For example, a review study by Eliyahu et al. (2016)[45] found that one of their accepted studies used LOC for 15 minutes, while three others used a LOC for a maximum of 30 minutes. Furthermore, the duration of PTA varied between a maximum of one hour to that of 24 hours in this study[45], which also increases the diversity in patient characteristics. Similarly, some studies included in Silverberg et al.'s (2015)[60] systematic review used their distinct definition for mTBI, which had more narrow requirements for the duration of LOC that biased the sample toward less severe mTBIs.

As we discussed in Chapter 1, attempts at creating official definitions and diagnostic criteria – such as the ACRM, the CDC's Report to Congress, the WHO's definition, and the sports concussion definition, to name a few – have been made; however, the selection and use of these established definitions varied across both the primary studies as well the review studies included in this scoping review. Again, it has been reported that the most widely accepted definition is the ACRM's definition of an mTBI[14]. However, despite the ACRM being reported as the most widely used, the systematic review by Mercier et al. (2017)[33] reported only 16.7% of their included studies used the ACRM definition, while 8.3% used a definition from the ACEP/CDC – which differs from the CDC's report to Congress in that it requires a GCS score of 14-15 at the first ED assessment and is specifically for ages 16 years or older[21] –, and 2.8% used the European Federation of Neurological Societies. In comparison, the systematic review by Silverberg et al. (2015)[60] had 27% of the 26 included studies use the ACRM, while some of the other included studies modified the ACRM criteria to create their own mTBI criteria. Due to this heterogeneity, pooling of study results was made more difficult and limited the discussion of results to individual descriptive analyses[45]. Altogether, this lack of a universal, clearly defined definition for mTBI and concussions leads to confusion and inconsistencies in diagnosis and management of the injury[14,18] and is a clear barrier to quantitative synthesis as it increases the patient diversity across the individual studies[14].

4.2.2 Mild TBI Outcomes

The second barrier impeding a meta-analytic approach to predicting PCS is the disagreements and inconsistencies in defining the outcomes following an mTBI. For example, only 50% of the studies included in Mercier et al. (2017)[33] specifically used PCS as the outcome measure. Differences in mTBI endpoints limits the comparability of individual studies into a meta-analysis as it can create clear differences in the patients being investigated and how the outcomes are measured and defined. Similar to the heterogeneity in mTBI definitions and diagnostic criteria, there was considerable variability in PCS definitions and diagnostic criteria used across studies[33,60]. For instance, although official diagnostic criteria for PCS exist (i.e., the ICD-10 and the DSM-IV), there are marked differences between these guidelines that is discussed in Chapter 1. These differences can lead to underestimation or overestimation of the diagnosed sample. For example, there is a stark difference between the groups of patients identified with PCS from the same concussed population depending on which diagnostic criteria is being used[32,43]. There was a 6-fold increase in patients diagnosed with PCS when using the ICD-10 compared to the DSM-IV[43]. Furthermore, it was found that a 2-fold increase in patients diagnosed with PCS 3 months following injury when the ICD-10 was used compared to the DSM-IV[43]. This has significant implications in both the diagnosis and treatment of patients. From a research perspective, variations in diagnostic criteria result in heterogeneous patient populations that can confound study outcomes, and this may be one reason for the inconsistent predictors reported in the literature. Also, diverse patient groups as well as differences in defining outcomes and outcome measures reduce the scope of which the study findings can be generalizable and applicable to the general population.

i. Timeline Between mTBI & PCS

The differences between the current PCS criteria stem from the challenges in defining the duration between the injury, the natural course of symptom resolution, and the onset of PCS[31]. Some physicians refer to any symptoms following an mTBI as PCS[31] while consideration should be given to recognizing the presence of different stages of injury (e.g. acute versus chronic) when considering definitions and diagnostic criteria for PCS[32]. Blume et al. (2012)[53]

reported that what constitutes acute and subacute PCS is poorly defined. Although, they suggest that chronic PCS is generally known as PCS lasting for more than 3 months post-injury[53]. Whereas, King et al. (2014)[25] suggest there is a lack of consensus for the terms describing the continuous experience of post-concussion symptoms. ‘Persisting’, ‘chronic, ‘long-term’, and ‘late’ are used interchangeably and inconsistently to describe post-concussion symptoms lasting from 1 month to many years[25]. For example, ‘persisting’ was used to describe PCS lasting from between 1 month to 4 years[25] while Zemek et al. (2013)[32] used a 1-month criteria to consider PCS as ‘persistent’. King et al. (2014)[25] suggested ‘permanent’ is more appropriate for symptoms lasting 18 or more months while symptoms lasting for 12-18 months can be considered ‘prolonged’ PCS. In terms of the ICD-10 and DSM-IV diagnostic criteria, the ICD-10 requires symptoms to present within a one-month period following injury whereas the DSM-IV requires the symptoms to persist for a minimum of 3 months. But, even the time between the injury and when PCS assessment occurred varied – ranging from 7 days to more than 5 years – with 46% having an assessment criteria of greater than 3 months in the studies included in Mercier et al. (2017)[33].

These subtle differences in terminology can impact how definitions and diagnostic criteria are created and can lead to mixed interpretations if there is excessive diversity[32]. Thus, more awareness and guidelines are needed to delineate and define the timeline between the brain injury, the natural course of symptom resolution, and the onset of acute, subacute and chronic post-concussion symptoms to clarify and reduce confusion.

ii. Classifying Symptoms

Variations can also occur in the classification of symptoms themselves. As we noted in the Introduction, the DSM-IV and ICD-10 differ in the type and number of symptoms required for a PCS diagnosis[43]. In addition, some studies create their own classification criteria such as in a study included in the systematic review by Cassidy et al. (2014)[42]. A study used a PCS diagnostic criteria of 4 or more symptoms after 3 months since the injury and these symptoms can include any of the unique physical, cognitive or emotional symptoms listed in their study[42]. In a meta-analysis by Frencham et al. (2005)[74], the researchers noted that the categories used to identify different areas of neuropsychological functioning differed greatly between studies. This variability in clustering and pooling of categories may potentially cause biased results and erroneously attributed similarities with symptom clusters between studies. One example illustrating this was how the Binder et al. (1997)[76] study followed-up by Frencham et al. (2005)[74] classified “attention and concentration” as a single domain, in contrast to the re-categorization used by Frencham (2005)[74], which separated “attention and concentration” into two separate domains of “working memory/attention” and “speed of processing”, due to more recent research trends[76]. These differences in symptom categorization can impact the outcomes of the study[74] and can limit the comparison between studies that define symptoms differently.

Zemek et al.'s (2013)[32] review poses several important unanswered questions about the classification of PCS symptoms. They ask whether a minimum number of symptoms should even be a requirement such as in the ICD-10 and DSM-IV, which requires a minimum of 3 symptoms, or would taking into account the severity of the symptoms regardless of the number of presenting symptoms be used as a diagnostic criteria? This may stem from a criticism towards the DSM-IV and ICD-10 criteria, which states that a more categorical diagnosis is used rather than taking into account the range of symptom severity using a severity scale[43]. Iverson & Lange (2003)[39] argue that PCS diagnosis will likely occur 5-6 times less often if only moderate to severe symptoms are required for diagnosis. By taking into account the classification of symptom severity, this can capture the diagnostic and functional consequences of the injury on the individual[39,43]. Although the DSM-IV takes into account relevant impairment in social or occupational functioning, the ICD-10 does not. The complexity of PCS and the subjective nature of these symptoms creates a high risk of misdiagnosis. Therefore, expert consensus on clearly classifying symptoms is needed in order to reduce the largely diverse patient groups and outcome measurements used across studies. This will help to facilitate the quantitative synthesis and analysis of individual studies.

iii. Non-specificity & Skepticism of PCS

The challenges of defining PCS and ultimately creating a barrier to establishing true PCS predictors is rooted in the existence and diagnosis of PCS itself, which is under scrutiny as we highlighted in Chapter 1. There is uncertainty on whether PCS is a true biological condition specific to mTBI or whether PCS is more attributed to a psychological response to the stress of the injury[31,32,37,42,53,77,78]. The occurrence of post-concussion-like symptoms in non-mTBI individuals and the high rates of comorbidity with other pre-existing symptoms makes it difficult to separate injury-related and non-injury-related symptoms[42,43,53,78]. For example, in a group of healthy individuals, 79.6% of these healthy individuals received a PCS diagnosis following the DSM-IV criteria, and 72.1% according to the ICD-10[39,43].

Fayol et al. (2009)[43] suggested that although the syndrome is not specific to mTBI, some individual symptoms may be specific to the injury; however, the evidence on these reported symptoms appear to be inconsistent[43]. Cassidy et al. (2014)[42] stated their reluctance in using the term PCS as it was feared to be "misleading" due to contradictions in the current literature on the etiology of certain PCS symptoms. Suggestions on moving away from using the term syndrome is being more widely accepted. For example, Cassidy et al. (2014)[42] recommended using the term 'posttraumatic symptoms' rather than PCS. Zemek et al. (2013)[32] refer to PCS as 'persistent concussion symptoms' (previously known as postconcussive syndrome). Jotwani et al. (2010)[31] distinguished between post-concussive symptoms and post-concussive syndrome by the duration of symptoms persisting following injury suggesting that post-concussion symptoms are common post-injury symptoms while the syndrome is not[31]. This ambiguity can lead to variability and misinterpretation of the condition itself. Likewise, Iverson et al. (2019)[41] suggests that the symptoms do not arise from an underlying syndrome but rather "the symptoms are the syndrome" highlighting the fact that each symptom can stem from a multitude of inter-related factors that may not only stem from the injury itself. Mayer et al. (2017)[37] suggested that recovery is "complex, multi-faceted, and time-dependent", and thereby, diagnosis and prognosis should be assessed in a more "probabilistic, rather than definitive" manner.

4.3 Methodological Barriers

To best inform and contribute to evidence-based medicine, the goal of research should include the ability to translate research findings into clinical practice. To do this, more emphasis on external validity – whether the study conclusions can be generalized and applied to different measures, persons, settings, and times outside of the main study context – is required[79]. According to Steckler et al. (2008)[79], the general focus on maintaining internal validity (i.e., the reliability or accuracy of results by rigorously controlling variables) in research studies has contributed to the challenges in translating research into practice due to a lack of external validity. In addition, the authors reported that systematic reviews and meta-analyses are restricted in their conclusions when there is a lack of external validity[79]. Both internal and external validity is necessary to research, therefore finding a balance to ensure scientific rigor is maintained as well as generalizability of the evidence is crucial[80]. The challenge of balancing internal and external validity was evident in the review studies included in this scoping review. Many reported a lack of external validity due to the focus on maximizing internal validity, which likely contributed to the inconclusive evidence in the current PCS predictor literature. Below, we highlight the commonly reported methodological barriers affecting the methodological diversity and external validity in the review studies included in this scoping review.

4.3.1 Restricting Recruitment Settings

The first methodological barrier to consider is whether restricting a study's recruitment setting to one location is more beneficial than multi-centre recruitments. Recruited mTBI patients are often restricted to a single type of recruitment setting such as a trauma center or the ED[60]. Many mTBI studies tend to recruit from the ED, but this may not always be the first point of care following a concussion[32,60]. Silverberg et al. (2015)[60] suggested that patients recruited from the ED likely have more severe mTBIs compared to the general mTBI population as many mTBI patients may not even seek any medical attention if there are absent or minimal immediate symptoms, especially if these symptoms are perceived as not severe. In addition, the range of mTBI severity can also be seen in the groups of patients presenting to the ED as a patient triaged to a CT scan versus a patient that does not require further assessments and is sent home implies differing mTBI severities[60]. Relying on only one type of recruitment location limits the generalizability and applicability of the study results since the study sample may not always be representative of the general mTBI population. For example, Silverberg et al. (2015)[60] found about 50% of the enrolled patients recruited from the ED had LOC, but < 10% of mTBI patients had LOC.

In contrast, more recent studies showed that the ED is a popular first point of care for mTBIs. Out of 1.3 million Canadian-Ontarians diagnosed with a concussion between 2008 and 2016, 79% of these were diagnosed in the ED[13] and the CDC rates of TBI-related ED visits in 2016 increased by 70%[5]. It is also important to emphasize that the majority of the studies included in Silverberg et al. (2015)[60] were conducted in EDs located in North America (39%), in Europe (39%), and in Australia (19%) suggesting that the ED is a favoured recruitment location across different countries.

An already restricted pool of patients enrolled in individual studies may limit the likelihood of meeting the strict eligibility criteria of systematic reviews and meta-analyses if the review focuses on only one recruitment location reducing the external validity of review studies. Zemek et al's (2013)[32] systematic review demonstrates the diverse range of recruitment locations used in each of their included studies. Eight out of 15 included studies recruited from the ED, 3 from a referral sports medicine clinic, 3 from the sideline, and 1 study recruited patients admitted for observation after the injury. This diversity increases the heterogeneity across studies especially when the goal of a systematic review is to conduct a meta-analysis, which requires studies to be as homogeneous as possible. However, in the case of ED recruitment increasing in popularity, this may allow for a more balanced approach between internal and external validity. Recruiting from only EDs can maintain internal validity and reduce the likelihood of confounding variables affecting the final outcome. At the same time, recruiting from EDs found in different hospitals or locations can improve the external validity as well as help to facilitate the quantitative pooling of individual studies. Nevertheless, synthesis studies need to be aware of the diversity in recruitment locations when aggregating data and the potential differences in mTBI severity of patients recruited from different locations.

4.3.2 Restricting Recruited Samples

Another methodological barrier to be aware of is determining the ideal degree of restrictiveness of inclusion and exclusion criteria. Strict eligibility criteria are inherent to research studies to reduce the likelihood of confounding variables influencing the outcomes of a study and creating biases. Thus, restricting a study's sample has the advantage of improving the internal validity at the cost of limiting the generalizability and applicability of the results as certain patient populations are likely to be excluded or less likely to be enrolled. For example, the application of these strict inclusion and exclusion criteria has been associated with exclusion of up to 95% of the general mTBI population according to Mercier et al. (2017)[33]. For many studies, the focus tends to be predominantly on children or adults while patients with underlying comorbidities such as the geriatric population are more likely to be excluded[32,33,42,60,75]. Mercier et al. (2017)[33] systematically reviewed the inclusion and exclusion criteria and patient characteristics of individual studies looking at the prognostic value of biomarkers for post-concussion symptoms to understand the generalizability of the enrolled sample. They found that most of the included studies' recruited samples are unrepresentative and not generalizable to the overall mTBI population. Despite only 28% of their included studies excluding patients that were 65 years old or older, the average age of patients that were enrolled across their studies were 38.7 years old. However, the older patient group will likely represent a large portion of TBI incidences due to the ageing population, increased life expectancy, and mobility of individuals[33]. Moreover, epidemiological studies reported that >40% of the mTBI population is greater than 50 years old[33]. Thus, older patient groups are underrepresented in mTBI and PCS predictor studies despite the likelihood that they will have poorer functional outcomes and may have more protracted recovery from post-concussion symptoms[33].

Differences between "healthier" and comorbid patients in the association of predictor variables and patients' outcomes may vary. This can create barriers to the translation of study findings focused on non-comorbid patients into clinical practice[33]. Mercier et al. (2017)[33] suggested studies should aim to maximize the inclusion of these patients by broadening their inclusion criteria and limiting the exclusion criteria. However, researchers aiming to synthesize individual studies into a meta-analysis may have difficulty overcoming very diverse and broader samples as this will increase the heterogeneity across the studies challenging the conduct of a quantitative analysis. Heterogeneity among mTBI patients is intrinsic and should be expected given the complexity of mTBIs and the wide-ranging outcomes; therefore, complete homogeneity across studies may not be feasible or unattainable[33]. Perhaps an alternative perspective is to view restrictive exclusion and inclusion criteria as a more individualized approach towards addressing the complexity of mTBI patients. Since it has been reported that differences in the prognostic trajectory and outcomes of certain mTBI patient groups such as in children and comorbid patients exist[41], Sussman et al. (2018)[14] suggested stratifying concussion patients into specific age groups that are both diagnostic- and treatment-targeted to their specific age group. Stratifying can help balance and maximize both internal and external validity because the focus on a specific age group can help control specific age-effects, but can also facilitate the translation of study outcomes to clinical care for a more generalized age group[41].

4.3.3 Self-Reporting Biases

Another methodological barrier to consider is that many studies reported limited external validation of outcome assessment tools and prognostic models. The first of which is related to the lack of a preferred method of symptom reporting for post-concussion symptoms[60]. Self-reporting of symptoms is a method often used in mTBI and PCS studies since diagnosis is dependent on questionnaires, surveys, and interviews[37,42,60]. However, self-reports have been thought of as not very reliable since there is a likelihood that self-reporting biases such as social desirability and recall errors can arise[81]. For example, patients may be less likely to report drug use at the time of the mTBI or following the mTBI as this is perceived as socially disapproved. Moreover, shorter recall periods are preferred over longer recall periods as there is less likelihood for recall errors in memory for the event[81]. For PCS, the required recall period can range from days to months and even years since, generally, PCS diagnostic criteria require symptoms to persist for many months before a diagnosis of PCS is given. Recall errors are known to be associated with the length of the recall period, chronicity of the condition, patient characteristics, and study design[81]. A method to circumvent these biases is to externally validate self-reported data with medical record checks, reference family or caregiver reports, as well as using memory aids such as a diary for cases where PCS assessments will only take place after many weeks or months[81]. There are further unique considerations for the younger pediatric population since parents or caregivers may be the only source of symptom reporting for very young pediatric patients. The symptoms experienced and reported can be subjected to misinterpretation and misattribution resulting in inaccurate results[60]. Thus, it is important that researchers consider the benefits and consequences of symptom reporting as the disregard for the potential biases can either underestimate or overestimate the study outcomes[81].

4.3.4 Prognostic Models

Given the numerous studies on predictors of PCS, it is not surprising that there have been attempts at creating multivariable prognostic models to determine the risk of an mTBI patient developing PCS and to also clarify the relative importance of individual predictors[60]. The systematic review by Silverberg et al. (2015)[60] examined existing prognostic models for mTBI outcomes that can potentially be used in the clinic to triage patients at risk for poorer outcomes and for research to risk stratify participants in clinical trials. However, out of the 26 studies reviewed – with a combined total of 6939 participants ranging from 5 to over 80 years old –, the authors could not find a multivariable prognostic model that adequately predicts patient outcome following an mTBI. Their reason for this was largely due to poor methodology of the included studies, specifically the lack of external validation of these prognostic models outside of the study samples. Only one of their included studies attempted to externally validate their model, but the model failed when used in an external sample. Due to these reasons, out of the 49 models found in their study, the authors could not recommend any of the prognostic models to be used in clinical practice or in research for risk stratification[60]. Therefore, there is a clear need for expert consensus that involves national and international collaboration to help facilitate and improve the external validation of prognostic models.

4.3.5 Types of Study Phases

Another barrier highlighted by several systematic reviews included in this scoping review is the type of primary studies included in the reviews. Phase I and Phase II studies are considered exploratory analyses[42]. They differ in that Phase I studies investigate the associations between potential prognostic factors and disease outcomes in a descriptive or univariate way, are hypothesis generating, and considered as preliminary compared to a Phase II and III study. Phase II studies, by comparison, explore sets of prognostic factors to determine which factor has the highest independent prognostic value. Phase III studies are considered confirmatory studies with clear hypotheses focused on the strength, direction, and independence of the causal relationship. Phase III studies are considered the strongest evidence for prognostic factors followed by phase II studies. In Cancelliere et al.'s (2014)[55] systematic review, out of the 19 studies included in their review, they did not find any phase III studies investigating prognosis following sports concussion. Half were phase II and the rest were phase I providing only exploratory evidence. Similarly, Cassidy et al.'s (2014)[42] systematic review also found that only one out of the 23 studies included in their review was a phase III confirmatory prognostic study. Their review articles stated that the strength of their conclusions is dependent on the studies included in their reviews, and currently it is generally weak, heterogeneous, and lacks scientific rigour. There is still a great need for well-designed, long-term confirmatory studies in order to progress towards translation of research studies into clinical use[42,43,55].

4.4 Limitations

We implemented a thorough search and review strategy based on recent guidelines[72,73] that aim to standardize the methods and reporting of scoping reviews similar to that of existing guidelines for systematic reviews. Despite our efforts for comprehensive coverage, our scoping review is subject to the possibility of missing or omitting relevant sources of information. As such, we ensured that our search and review protocol included a wide range of databases and included further searching of reference lists and hand searching relevant databases. Furthermore, we used multidisciplinary databases (i.e., Embase, MEDLINE, and PsycINFO all via OVID, Web of Science, CINAHL, and CDSR) to ensure we are covering all relevant databases to PCS. It is also important to highlight our search restriction to English-only, which may have missed relevant articles in other languages. Finally, this scoping review did not conduct a formal assessment of study quality or level of evidence – which is inherent to the methods of scoping reviews – and therefore cannot provide recommendations for clinical practice. Nevertheless, our study brings to light the current nature of literature reviews on predictors of PCS and the current challenges and barriers affecting the qualitative and quantitative synthesis of studies.

4.5 Conclusions

This scoping review aimed to provide a comprehensive summary of the nature of the current literature reviews examining PCS predictors to better understand why inconclusive evidence and confusion still remain despite the extensive research done in this area. Our findings highlighted researchers are still faced with various diagnostic and methodological barriers that are contributing to excessive clinical and methodological diversity. This has been a major factor influencing the quality of evidence and the difficulties in conducting of more meta-analytic approaches that can better inform and determine patients at highest risk of developing PCS. This, in turn, is hindering the progress towards more consensus and conclusive evidence in the research on PCS predictors that can reliably inform clinical practice. The results from this study provide a unique perspective and improve our understanding of the current characteristics of the reviews done on PCS predictors. Specifically, we identify the barriers that remain to be overcome in order to increase standardization across studies and develop more cross-compatible studies. The implications of this study are to inform researchers of the sources of diversity and barriers in the literature on PCS predictors and highlight these areas for improvement as well as help facilitate the translation of research evidence into clinical practice and contributions to evidence-based medicine.

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