15 Predicting Postconcussive Symptoms After Mild Traumatic Brain Injury in Children and Adolescents: 2020 Update

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Introduction

Mild traumatic brain injuries (TBI) are a common occurrence in children and adolescents. Annually, as many as 800,000 youth aged 0–17 in the United States are seen in emergency departments for TBI, and the large majority of these injuries are mild in severity [1]. The total number of youth sustaining mild TBI each year is far higher, however; many mild TBI are cared for outside of hospital settings—at least another 800,000 are seen as outpatients [2]—and even more likely never receive any formal medical attention. Indeed, estimates are that 1.1–1.9 million children and adolescents sustain sports-related concussions, a type of mild TBI, each year, with many never coming to medical attention [3].

Systematic reviews suggest that most children recover from mild TBI, at least in terms of clinical presentation, in a matter of weeks [4–6]. However, a substantial body of literature indicates that a small but significant proportion of children with mild TBI experience persistent postconcussive symptoms (PCS), and that persistent PCS occur more often after mild TBI than after injuries not involving the head or among healthy children [7–9]. PCS include a range of somatic (e.g., headache, dizziness), cognitive (e.g., inattention, forgetfulness), and affective (e.g., irritability, disinhibition) symptoms commonly reported after mild TBI, albeit not specific to that condition. Persistent PCS are linked to negative consequences for children's longer-term psychosocial functioning and quality of life [10–13].

A key issue for the purposes of clinical management is how to predict which children with mild TBI will go on to display persistent PCS [14]. This chapter

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represents an update of an earlier version in the first edition of this book, incorporating research published in the past 7 years. This chapter begins by describing a schematic model for predicting PCS following mild TBI in children and adolescents. It then reviews the existing literature regarding the prediction of PCS, examining both injury-related and non-injury-related factors as possible prognostic indicators. The chapter next summarizes conceptual and methodological issues that arise in research on the prediction of the outcomes of mild TBI and describes recent advances in the development of evidence-based decision rules that help to predict which children are at high risk for poor outcomes after mild TBI. The chapter concludes with suggestions for future research directions.

A Model for PCS

Figure 15.1 portrays a general schematic model for predicting PCS following mild TBI in youth [15]. The model draws on previous theories of children's adaptation to illness, including the Disability-Stress-Coping Model [16] and the Transactional Stress and Coping Model [17], as well as on models of adaptation specific to mild TBI [18, 19]. The model does not reflect the specificity or complexity of more recent systems science analyses of mild TBI [20] but is similar to other recent approaches in providing a broad biopsychosocial framework for understanding recovery [21].

The model presumes that the occurrence of PCS following mild TBI will depend on the combined influences of premorbid child and family factors, the nature of the injury, and post-injury child and family factors. The model also assumes that the influences of these factors can be both direct and indirect. For example, changes in brain structure or function associated with mild TBI may give rise to PCS directly because of the effect of brain impairment on behavior, but they also may result in PCS indirectly by affecting children's cognitive functioning or ability to cope with stress, which in turn mediates an increased risk of PCS.

Importantly, the relationship between various risk factors and PCS is assumed to vary as a function of time since injury [22]. Shortly after an injury, the onset of PCS is more likely to depend on premorbid child and family factors and injury characteristics. The likelihood that PCS will persist over time may depend more on children's

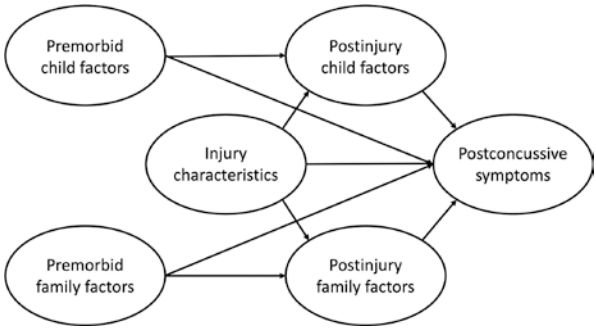

Fig. 15.1 Schematic biopsychosocial model for study of postconcussive symptoms in children with mild traumatic brain injury

and parents' post-injury responses to injury, as well as on the other stressors and resources in their lives. Premorbid factors and injury characteristics may be relevant to both acute and chronic symptoms. However, the influence of post-injury child and parent responses and other stressors and resources may be more pronounced than premorbid factors or injury characteristics for persistent symptoms. In other words, the way in which children and their parents react to the acute disruptions associated with mild TBI is likely to be a significant determinant of the persistence of PCS.

Predictors of PCS

In recent years, research examining the prediction of PCS in children after mild TBI has expanded significantly [14]. The research varies in methodological quality, however, with only a few studies involving prospective recruitment of representative samples of children with mild TBI and appropriate comparison groups who are followed longitudinally. Few studies have examined both injury and non-injury factors as potential predictors of PCS, much less compared their relative contributions at different times post-injury [22]. The following sections provide an overview of existing research about the predictors of PCS.

Injury Factors

A variety of injury factors have been considered as potential predictors of PCS. One is the occurrence of previous concussions or mild TBI. An early study of a national birth cohort suggested that multiple concussions did not result in specific cognitive deficits [23], but subsequent studies of sports concussions found evidence for cumulative effects [24]. Recent studies suggest that the impact of previous concussion may depend on how long it has been since the previous injury and whether the previous injury was associated with a longer time to recovery. Children whose previous concussions occurred more recently, or resulted in symptoms for at least 1 week, demonstrated more protracted symptoms after mild TBI than did children whose previous concussions occurred further in the past or did not result in PCS [25, 26].

Various indices of injury severity have also been studied as potential predictors of PCS. Acute symptom burden is perhaps the most consistent predictor of persistent PCS; some specific symptoms, such as headache/migraine and dizziness, also are predictive. Acute clinical signs that also have been shown to be associated with an increased risk of PCS include loss of consciousness [7, 8, 13, 27, 28], posttraumatic amnesia [28, 29], and balance problems [30]. The presence of intracranial abnormalities on acute neuroimaging has also been associated with increased PCS [8, 13, 27, 31]. Several indirect proxies for injury severity have also been associated with an increased likelihood of PCS, including hospital admission [8, 13, 32],

high-speed mechanism of injury—particularly motor vehicle collision [8, 33], referral for CT scanning [34], and the presence of associated injuries not involving the head [8, 29].

Non-injury Factors

Demographic factors such as age and sex are among the non-injury factors most commonly studied as predictors of PCS. The relationship of age to PCS is inconsistent. Several studies have found greater PCS among adolescents than younger children [7, 26, 30], while others have found evidence of more PCS among younger as compared to older children [8]. Differences in results across studies may reflect whether PCS were assessed by self-report or by parent ratings; adolescents tend to report more PCS than younger children, but parents may report more PCS for younger than older children. Few studies have specifically examined whether age moderates the effects of mild TBI on PCS; one showed evidence for larger group differences (mild TBI vs. orthopedic injury) for PCS among younger versus older children [8].

Sex has been a more consistent predictor of PCS, such that girls and their parents typically report more symptoms than boys [8, 26, 30]. However, differences in PCS between children with mild TBI and those with orthopedic injuries do not appear to be more pronounced for girls than boys, suggesting that sex is not a moderator of PCS after mild TBI, but instead that girls and their parents in general may report more symptoms than boys [8, 35].

Pre-injury symptoms are the non-injury factor that consistently accounts for the most variance in PCS [22, 36]. Pre-injury symptoms are typically assessed retrospectively after injury and so may be subject to bias, except in sports concussion research where pre-injury baselines are possible. However, retrospective ratings of pre-injury symptoms tend not to differ for children with mild TBI versus those with orthopedic injuries [22], suggesting that bias is likely minimal if the ratings are obtained shortly after the injury occurs. More generally, pre-injury psychiatric disorders increase the risk of PCS, although attention deficit hyperactivity disorder and learning disabilities specifically are not clearly prognostic [37].

Children's cognitive abilities may also be related to PCS after mild TBI. Although neurocognitive deficits typically resolve within a few weeks after mild TBI when measured using traditional paper-and-pencil tasks [4, 5], computerized testing has the potential to reveal longer lasting deficits in complex processing speed [38]. Neuropsychological testing can be used to identify not only those children who show acute post-injury decrements in their cognitive functioning, but also those who have low cognitive reserve, and both types of children may be at risk for PCS. Cognitive ability has been shown to be a significant moderator of PCS, such that children of lower cognitive ability with mild TBI-associated abnormalities on neuroimaging are especially prone to PCS [39]. More research is needed to determine whether post-acute cognitive deficits on neuropsychological testing are predictive of PCS.

Various aspects of children's psychological functioning also can help account for PCS. Children with mild TBI are at greater risk for PCS relative to children with orthopedic injuries if they rely on avoidance or wishful thinking to cope with their injuries as compared to more problem-focused coping strategies [40]. Children with high levels of psychological resilience also are less likely to demonstrate PCS [41], while those with higher levels of somatization and internalization of symptoms are more likely [42].

A variety of environmental factors may also predict PCS. For instance, family socioeconomic status is negatively correlated with self-reports of PCS [8], and parent psychological distress is positively correlated with PCS [36, 43]. Somewhat surprisingly, children whose families were higher functioning and had more environmental resources were more likely to demonstrate somatic PCS following mild TBI than those from poorer functioning homes with fewer resources [44]. This finding runs counter to previous research among children with severe TBI showing that the effects of TBI are exacerbated in the context of poorer premorbid family functioning [45].

Relative Contributions of Injury Versus Non-injury Factors

Few studies have directly compared injury versus non-injury factors as predictors of PCS. In a large prospective cohort study of children aged 0–18 years [7], family functioning and parent adjustment measured post-acutely did not account for differences in PCS across the first year post-injury as a function of injury status or severity, although the specific contributions of the former variables were not estimated statistically.

Another prospective cohort study examined the prediction of PCS during the first year post-injury in children aged 8–16 years with mild TBI or mild orthopedic injuries [22]. Predictors included demographic variables, premorbid child factors, family factors, and injury factors. Injury factors predicted parent and child ratings of PCS but showed a decreasing contribution over time. Demographic variables consistently predicted symptom ratings across time. Premorbid child factors, especially retrospective ratings of premorbid symptoms, accounted for the most variance in PCS. Family factors, particularly parent adjustment, consistently predicted parent, but not child, ratings of PCS.

In a third prospective cohort study [34], children aged 2–12 years with either mild TBI or minor bodily trauma were followed for 3 months post-injury. Potential predictors of PCS included injury and demographic variables, premorbid child behavior and sleep, and premorbid parental stress. Mild TBI was a stronger predictor of PCS in the first week compared to 1–3 months post-injury. Older age at injury and preexisting learning problems were significant predictors of PCS beyond 1 month post-injury. Family factors, including higher levels of parental stress, higher socioeconomic status, and Anglo-Saxon ethnicity, consistently predicted greater PCS.

Finally, in a recent prospective cohort study [46], children aged 4–15 years with mild TBI, complicated mild TBI, or orthopedic injury were studied across the first year post-injury. Potential predictors included preinjury demographic, child, and family factors. PCS were more common in the two mild TBI groups than in the orthopedic injury group; they also were associated with female sex, adolescence, preinjury symptoms and mood problems, lower family income, poorer family functioning, and lower social support.

Collectively, the findings from these studies suggest that mild TBI predicts increased PCS in the first weeks to months following injury but shows a decreasing contribution over time. In contrast, non-injury factors are more consistently related to PCS and may display an increasingly strong association over time.

Research Issues

Definition of Mild TBI

A variety of methodological shortcomings have characterized previous research on mild TBI [47]. One of the major limitations involves the definition of mild TBI, which has varied substantially across studies, along with associated inclusion/exclusion criteria [26, 48]. Most studies have defined mild TBI based on Glasgow Coma Scale scores ranging from 13 to 15 [49], but they have been inconsistent in applying other criteria, such as presence or duration of loss of consciousness (LOC) or posttraumatic amnesia (PTA) [50]. Some previous studies exclude children whose injuries are accompanied by positive findings on neuroimaging (i.e., complicated mild TBI), while some definitions of mild TBI include such children. Many studies have not clearly defined both the lower and upper limits of severity of mild TBI, which can range from brief alterations in mental status without loss of consciousness to more severe signs and symptoms (e.g., LOC, persistent PTA, seizures). Issues of definition and classification are especially problematic in studies of infants and younger children, for whom traditional measures of injury severity such as the Glasgow Coma Scale may not be valid [51].

A related nosological issue concerns the definition and relationship of concussion versus mild TBI [52, 53]. The terms are often used interchangeably. However, some have argued that they are distinct disorders, with concussion being less severe than mild TBI, while others see them as overlapping but not identical, most often viewing concussion as a subset of mild TBI; yet others have taken an opposing perspective, viewing mild TBI as a subset of all concussion. The lack of a single and specific diagnostic nosology for classifying the different types of mild TBI at different stages post-injury represents a significant barrier to progress in the field.

Outcome Measurement

PCS are typically measured using questionnaires and rating scales, often completed by both children and their parents. Parent–child agreement regarding PCS is significant but modest [54, 55], suggesting that both child and parent's reports should be explored in studies of mild TBI. Only parent ratings may be available for infants and younger children, but the validity of ratings in that age range warrants further investigation. The reporting of PCS may also depend on the format for symptom reporting. For example, in adults, rating scales elicit reports of more symptoms than do open-ended structured interviews [56, 57].

Previous studies have also frequently treated PCS as if they occur along a single dimension. However, research indicates that PCS in children with mild TBI are multidimensional, with clear distinctions between somatic, cognitive, and emotional symptoms [58, 59]. The dimensions of PCS not only can be distinguished psychometrically, but also follow distinct trajectories following mild TBI [8]. They also appear to be distinct from other kinds of symptoms, such as those associated with posttraumatic stress disorder [60, 61].

The definition and measurement of persistent PCS is a key methodological and conceptual issue. Many definitions of persistent PCS are based on a simple count of new or worse symptoms, while other definitions are based on standardized measures of change (e.g., reliable change or normative definitions). A recent study showed that misclassification rates among healthy children were higher for simple versus standardized change definitions [62]. Although inter-method agreement was superior among standardized change algorithms, significant variation existed for identifying children with mild TBI who had "recovered" (i.e., those who did not meet individual criteria for PPCS) across definitions, calling into question the true incidence rate of PPCS. Importantly, the findings raise significant concern about the use of simple change scores for diagnosis of PPCS in clinical settings.

Assessment of Risk Factors

The assessment of risk factors that predict outcomes following mild TBI has been problematic. Most studies have not adequately characterized the severity of children's injuries. Children with mild TBI are often treated as a homogenous group, without regard to whether factors such as LOC or abnormalities on neuroimaging increase the risk of negative outcomes. Advanced neuroimaging techniques, such as susceptibility-weighted and diffusion tensor imaging, may also provide a more sensitive assessment of injury severity in mild TBI [63–66].

Research also needs to incorporate measures of non-injury-related risk factors as possible predictors. In many cases, children with premorbid learning or behavior problems are omitted from studies, although they may be at particular risk for persistent postconcussive symptoms [14]. As noted earlier, a variety of non-injury factors are likely relevant to the prediction of PCS and may moderate its occurrence

after mild TBI, including children's premorbid cognitive ability and coping skills [39, 40], demographic factors and socioeconomic status [8, 22], and parent and family functioning [22, 36, 43, 44].

Prediction Versus Moderation

Research on the prediction of PCS often fails to distinguish between predictors and moderators, yet this distinction is critical to understanding whether a particular risk factor is specifically associated with worse outcomes among children with mild TBI versus children in general. A relevant example is the role of sex or gender as a risk factor for PCS. Many existing studies of sex differences lack a comparison group of healthy children or children with injuries not involving the head, and instead simply compare males and females with mild TBI. However, the absence of a comparison group precludes any determination of whether sex actually moderates the effects of mild TBI versus simply accounting for variation in outcomes in a nonspecific fashion, irrespective of mild TBI [35]. Similar concerns can be raised about many studies pertaining to other risk factors. The inclusion of appropriate comparison groups, and testing of statistical interactions between group status and risk factors, is necessary to conclude that any risk factor moderates the likelihood of PCS specifically after mild TBI.

Alternative Explanations

Previous research has rarely considered potential alternative explanations for persistent PCS, such as response validity, pain, and symptom exaggeration. Performance on response validity testing has been shown to account for substantial variance in cognitive test performance among children with mild TBI [67], although it did not account for group differences in PCS in other studies [38, 68]. Pain has not been widely examined, but it is a common consequence of mild TBI and may contribute to poor cognitive test performance and also exacerbate related symptom complaints [69]. Finally, some children or parents may be prone to symptom exaggeration, perhaps because of the lay expectations associated with mild TBI [70]. Research that incorporates indices of symptom exaggeration may help to determine whether reports of PCS after mild TBI are influenced by such expectations.

Timing of Outcome Assessment

Research on mild TBI has often been cross-sectional and focused on relatively short-term outcomes. This problem is compounded in some studies by retrospective recruitment of participants from among clinical referrals or hospital admissions, resulting in significant ascertainment bias. Prospective and longitudinal studies of

unselected samples are necessary to examine how the relationship of risk factors to PCS varies post-injury [22, 29].

The timing of assessments is particularly critical in longitudinal studies [71]. Acute post-injury assessments are often desirable, not only to document the immediate effects of mild TBI, but also to obtain retrospective measures of children's premorbid symptoms as soon as possible after the injury and thereby increase the validity of parent recall. The timing of subsequent assessments should be based in part on the expected course of recovery following mild TBI. Given that research suggests that PCS resolve in 2–3 months in most cases of mild TBI [6, 8], more frequent assessment during the first few weeks to months post-injury is warranted. However, longer-term assessments are needed to determine whether PCS result in significant ongoing impairment in children's social or academic functioning.

Prediction of Individual Outcomes

Studies of mild TBI have focused on outcomes at a group level, in part because most common statistical techniques yield results that are based on group averages. Thus, most research on the prediction of PCS is variable-centered and reflects only group trends [72]. In clinical practice, however, we want to know whether mild TBI is likely to be followed by persistent PCS in a particular patient. One way to focus on individual outcomes is to divide children with mild TBI into subgroups based on certain characteristics and then determine if outcomes are different for children in the different subgroups. Parsing a sample of children with mild TBI into those with versus those without LOC or neuroimaging abnormalities exemplifies this approach [8].

A second approach is to identify individuals with a given outcome, such as persistent PCS, and then determine the risk factors linked to this outcome [28]. For instance, analyses of reliable change also can be used to identify individual children who display unusually large increases in PCS compared to pre-injury estimates and to study the risk factors associated with such increases [73]. Figure 15.2 is drawn from a study of reliable change in PCS after mild TBI. The figure shows the proportion of children with mild TBI showing reliable increases in somatic symptoms as a function of loss consciousness or abnormalities on magnetic resonance imaging, as compared to children with orthopedic injuries [13].

Advanced statistical techniques can assist in the prediction of individual outcomes. Growth curve modeling permits the investigation of change at an individual level in relation to multiple risk factors [8]. Mixture modeling can be used to empirically derive latent classes of individuals [74]; for instance, subtypes of children with mild TBI can be identified based on initial clinical presentation or on different symptom trajectories [75]. Figure 15.3 provides an example of this approach; it shows symptom trajectories of PCS in children with mild TBI and orthopedic injuries [27]. In this study, children with mild TBI were more likely than those with orthopedic injuries to demonstrate trajectories involving high acute levels of PCS. Moreover, children with mild TBI whose acute clinical presentation reflected

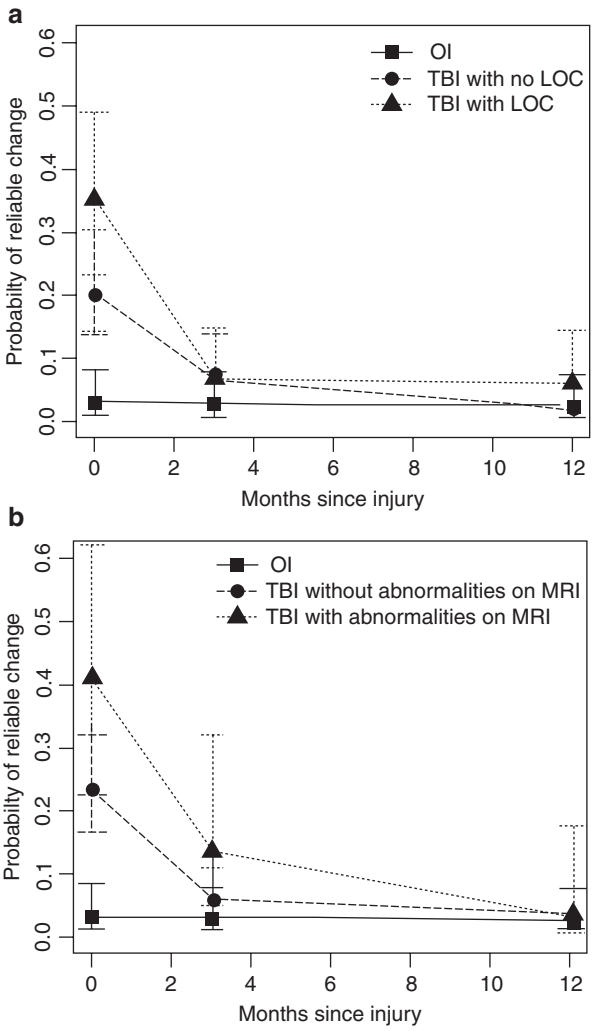

Fig. 15.2 Probability of reliable change in somatic symptoms as a function of group membership. Children with mild TBI are divided into those (**a**) with and without LOC and (**b**) with and without abnormalities on MRI. (Modified with permission from Yeates et al. [13]. © 2012 by American Medical Association)

more severe injury were especially likely to demonstrate such trajectories, in contrast to those with mild TBI with less severe acute presentations.

Building Prognostic Models and Decision Rules

In the long run, prognostic models and decision rules are needed so that clinicians can use them to predict which children with mild TBI will demonstrate persistent PCS. To be clinically useful, research on outcome prediction must be methodologically rigorous [76]. Sample sizes need to be relatively large. Predictors should be selected based on previous research and expert opinion. The number of predictors

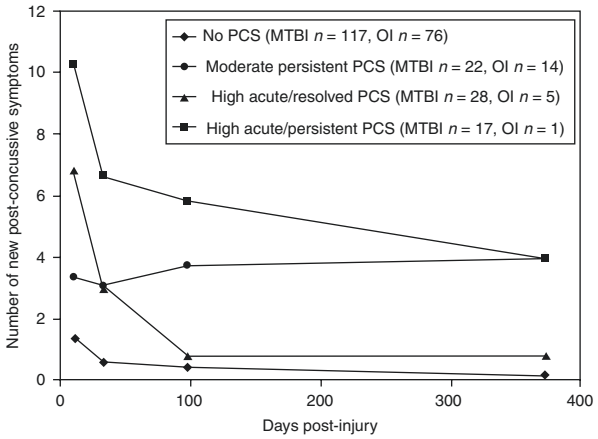

Fig. 15.3 Illustration of developmental trajectory analysis of postconcussive symptoms in children with mild TBI (mTBI) or orthopedic injuries (OI). Four latent groups were identified on the basis of the number of new postconcussive symptoms reported at four occasions post-injury, irrespective of whether participants were in the mTBI or OI group. (Modified with permission from Yeates et al. [27]. © 2009 by American Academy of Pediatrics)

should be kept reasonably small, to avoid overfitting of models. Both outcomes and predictors need to be defined precisely, measured with good reliability, and readily obtainable. Statistical models should use valid approaches to managing missing data and appropriate techniques for the selection of predictors and estimation of prognostic effects. Model performance needs to be assessed in terms of both calibration (i.e., agreement between observed outcome frequencies and predicted probabilities) and discrimination of those with versus without persistent PCS. Models need to be validated, and the results of modeling should be presented in a readily applicable format.

A recent seminal study that incorporated these features sought to derive and validate a clinical risk score for persistent PCS among children presenting to the emergency department (ED) with acute concussion [26]. The study included 3063 children aged 5–17 years who were seen at 9 EDs and were then assessed for PCS at 4 weeks post-injury. The sample was split into derivation and validation cohorts. Statistical modeling was used to develop a 12-point risk score, as shown in Table 15.1, based on the variables of female sex; age of 13 years or older; physician-diagnosed migraine history; prior concussion with symptoms lasting longer than 1 week; symptoms of headache, sensitivity to noise, fatigue; answering questions slowly on clinical exam; and errors on balance testing. The risk score discriminated between children with and without persistent PCS with modest accuracy and performed substantially better than physician prediction alone. The risk score holds significant promise as a tool for improving clinical care of mild TBI.

Table 15.1 Clinical risk score for predicting persistent postconcussive symptoms at 4 weeks post-injury in children presenting to the emergency department

Predictors	Number of risk points for persistent postconcussive symptoms
Age group, years	
5–7	0
8–12	1
13– < 18	2
Sex	
Male	0
Female	2
Prior concussion and symptom duration	
No prior concussion; symptom duration <1 week	0
Prior concussion; symptom duration ≥1 week	1
Physician-diagnosed migraine history	
No	0
Yes	1
Observed answering questions slowly	
No	0
Yes	1
Balance error scoring system tandem stance no. of errors	
0–3	0
≥ 4 or physically unable to undergo testing	1
Headache reported	
No	0
Yes	1
Sensitivity to noise reported	
No	0
Yes	1
Fatigue reported	
No	0
Yes	2

Future Directions

Future research on the prediction of PCS after mild TBI in children must adopt a biopsychosocial approach that acknowledges the contributions of risk factors at multiple levels of analysis—biological, psychological, and environmental. At the biological level, genetic and epigenetic variables may play an important role. The apolipoprotein E gene has not been found to predict PCS after mild TBI in children [77], but many other candidate genes should be examined [78]. Research at the biological level may also yield more sensitive and precise measures of brain injury that predict outcomes. For instance, various fluid biomarkers and advanced neuroimaging techniques are being considered both as indicators of underlying brain injury in mild TBI and possible predictors of PCS [79, 80].

At the psychological level, future research may identify more sensitive measures of the effects of mild TBI on cognitive functioning. Computerized testing has the

advantage of being able to assess reaction time, which has been shown to be sensitive to concussion [38]. More research is needed to determine if early post-injury cognitive deficits predict persistent PCS. Research on children's psychological characteristics, such as somatization and psychological resilience, also will be important for understanding the risk of persistent PCS.

Finally, at the environmental level, further research is needed to clarify which aspects of the family and broader social environment are related to the occurrence of PCS following mild TBI in children [22, 44]. The identification of interventions that can reduce the risk of PCS also will be critically important. Clinical trials and comparative effectiveness studies of both pharmacological and non-pharmacological interventions are needed [81].

For future research to have the greatest impact, the methodological issues reviewed earlier need to be addressed. Researchers need to find a common diagnostic nosology with clear criteria, and also a shared definition of persistent PCS. Large prospective studies of children with mild TBI and appropriate comparison groups that assess both injury-related and non-injury-related risk factors are needed to refine existing prognostic models and decision rules for predicting PCS [82]. The use of common data elements will enable harmonization of studies and pooling of data that can be assessed using advanced statistical techniques such as machine learning [83].

A key long-term goal for research on the outcomes of mild TBI is to further develop prognostic models and decision rules to incorporate developmental considerations and allow for individual variability in the importance of different risk factors. Ideally, these advances will enable clinicians to provide parents and children with evidence-based information regarding the effects of mild TBI and to identify those children who are most at risk for demonstrating negative outcomes. Healthcare providers can then target at-risk children and their families for appropriate management [84].

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