

Acute Concussion Symptom Severity and Delayed Symptom Resolution



WHAT'S KNOWN ON THIS SUBJECT: Children are often evaluated in the emergency department after a concussion. Although prolonged symptoms are associated with higher initial symptom severity when measured 2 to 3 weeks after injury, a similar association with acute symptom severity has not been demonstrated.



WHAT THIS STUDY ADDS: Higher acute symptom severity is not associated with development of persistent post-concussion symptoms 1 month after injury, but persistent post-concussive symptoms affect a significant number of children after concussion. Outpatient follow-up is essential to identify children who develop persistent symptoms.

abstract

FREE

BACKGROUND AND OBJECTIVES: Up to 30% of children who have concussion initially evaluated in the emergency department (ED) display delayed symptom resolution (DSR). Greater initial symptom severity may be an easily quantifiable predictor of DSR. We hypothesized that greater symptom severity immediately after injury increases the risk for DSR.

METHODS: We conducted a prospective longitudinal cohort study of children 8 to 18 years old presenting to the ED with concussion. Acute symptom severity was assessed using a graded symptom inventory. Presence of DSR was assessed 1 month later. Graded symptom inventory scores were tested for association with DSR by sensitivity analysis. We conducted a similar analysis for post-concussion syndrome (PCS) as defined by the *International Statistical Classification of Diseases and Related Health Problems, 10th revision*. Potential symptoms characteristic of DSR were explored by using hierarchical cluster analysis.

RESULTS: We enrolled 234 subjects; 179 (76%) completed follow-up. Thirty-eight subjects (21%) experienced DSR. Initial symptom severity was not significantly associated with DSR 1 month after concussion. A total of 22 subjects (12%) had PCS. Scores >10 (possible range, 0–28) were associated with an increased risk for PCS (RR, 3.1; 95% confidence interval 1.2–8.0). Three of 6 of the most characteristic symptoms of DSR were also most characteristic of early symptom resolution. However, cognitive symptoms were more characteristic of subjects reporting DSR.

CONCLUSIONS: Greater symptom severity measured at ED presentation does not predict DSR but is associated with PCS. Risk stratification therefore depends on how the persistent symptoms are defined. Cognitive symptoms may warrant particular attention in future study. Follow-up is recommended for all patients after ED evaluation of concussion to monitor for DSR. *Pediatrics* 2014;134:54–62

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KEY WORDS

brain concussion, brain injury, acute, brain injury, traumatic, post-concussion symptoms, post-concussion syndrome, emergency medicine

ABBREVIATIONS

AUC—area under the curve
CI—confidence interval
DSR—delayed symptom resolution
ED—emergency department
GCS—Glasgow Coma Scale
IQR—interquartile range
LOC—loss of consciousness
ICD-10—*International Statistical Classification of Diseases and Related Health Problems, 10th revision*
OR—odds ratio
PCS—post-concussion syndrome
RR—relative risk

Dr Grubenhoff conceptualized and designed the study, designed the database, oversaw data collection and analysis, drafted the initial manuscript, and reviewed and revised the manuscript; Ms Deakne performed the primary statistical analysis, assisted with study design and database design, managed study personnel in recruitment and data acquisition, and co-authored, reviewed, and revised the manuscript; Ms Brou assisted with the cluster analysis and drafting and reviewed and revised the manuscript; Dr Bajaj assisted with study design and study personnel management, oversaw data analysis, and critically reviewed and revised the manuscript; Dr Comstock assisted with data analysis and interpretation and critically reviewed and revised the manuscript; Dr Kirkwood conceptualized and designed the study, assisted with data instrument design, and co-authored, reviewed, and revised the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-2988

doi:10.1542/peds.2013-2988

Accepted for publication Apr 10, 2014

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There are 630 000 emergency department (ED) visits annually for mild traumatic brain injury (concussion) among children ages 0 to 19 years.¹ The majority of those who have concussion experience symptom resolution in a few weeks.² However, a notable minority experience persistent post-concussive sequelae.

When examining post-concussive sequelae with standardized performance-based cognitive and behavioral tests, most prospective studies indicate that by 2 to 3 months post-injury, deficits are no longer apparent.^{2–6} Fewer studies have systematically examined outcomes using post-concussive symptom reports from children. However, available research suggests that some pediatric patients display more persistent symptoms than might be expected if examining performance-based test results alone.^{7,8} The acute injury risk factors predictive of delayed symptom resolution (DSR) in children are poorly understood.

Traditionally, determining the severity of concussion was predicated on the presence of certain signs and symptoms at the time of injury, most notably loss of consciousness (LOC).^{9,10} However, LOC occurs relatively infrequently after concussion and is no longer used to define injury severity as it is not consistently associated with neuropsychological deficits or DSR.^{11,12} In contrast, research in adults who have concussion has found that post-traumatic amnesia as well as higher overall symptom levels (ie, both number and severity of symptoms) are associated with DSR.^{13–17} In pediatric patients, greater symptom levels present a few weeks after injury are associated with a longer duration of post-concussive symptoms.¹⁸ Greater symptom levels have also been associated with objective signs of altered mental status (eg, post-traumatic amnesia) in pediatric ED patients immediately after injury.¹⁹ Taken together, these findings suggest that the number and

severity of acute concussion symptoms may be a useful indicator of overall severity, and therefore may constitute an easily measurable risk factor to predict DSR. Recent research among youth athletes who have sports-related concussion supports this concept.²⁰

DSR is a defining feature of post-concussive syndrome (PCS). However, it is important to highlight that there is no universally accepted definition of PCS. Indeed, whether the nonspecific symptoms typically attributed to this condition constitute a syndrome with a common pathophysiological explanation is controversial.^{21,22} Nonetheless, DSR affects children who have concussion, and evidence suggests that the risk for experiencing persistent symptoms is modifiable.^{23–25} Identifying children at increased risk for DSR at the time of injury would allow selective implementation of interventions earlier in the recovery phase.

The primary objective of this study was to determine whether greater symptom severity measured immediately after injury is associated with DSR. We hypothesized that higher scores on a graded symptom inventory immediately after injury would be associated with the DSR at 1 month in a pediatric ED cohort presenting for acute evaluation of concussion. Given the lack of a universally accepted definition of PCS, we also evaluated the performance of a graded symptom inventory for identifying the risk for meeting clinical criteria for PCS laid out in the *International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10)*.²⁶ Although ICD-10 has not yet been adopted in the United States for coding purposes, the clinical criteria for PCS have been investigated in concussion research.^{14,27}

METHODS

Study Design

We conducted a prospective cohort study from October 1, 2010 to March 31, 2013 of

a convenience sample of children ages 8 to 18 years who sustained concussions no >6 hours before presenting to Children's Hospital Colorado's trauma center ED, which has ~65 000 annual visits. Patients identified on the ED electronic track board presenting with complaints of head injury or symptoms associated with concussion were screened for enrollment 16 hours per day, 7 days per week by professional research assistants who enrolled subjects and administered all study procedures. Subjects were contacted by telephone 30 days after injury to complete follow-up procedures. Subjects were considered lost to follow-up if they failed to respond after 3 attempts. The study was approved by the Colorado Multiple Institutional Review Board.

Subjects

Children were considered to have concussion if they had a Glasgow Coma Scale (GCS) score of 13 or 14 or at least 2 of the following symptoms occurring after a direct blow to or rapid acceleration/deceleration of the head: bystander-witnessed LOC; post-traumatic amnesia; disorientation to person, place, or time; subjective feelings of slowed thinking; perseveration; vomiting/nausea; headache; diplopia/blurry vision; dizziness; or somnolence. This clinical definition of concussion has been used elsewhere.^{28,29} Children who had open head injuries, intoxication with alcohol or controlled substances, receipt of narcotics for pain control, injuries resulting from child abuse, multisystem injuries, or underlying central nervous system abnormalities were excluded.

Measurements

At the ED enrollment visit, the following demographic and injury characteristics were obtained: mechanism of injury; parental report of previous concussion; GCS score as determined by the treating provider; and presence of abnormalities on head CT scan as

reported by a board-certified pediatric neuroradiologist if obtained.

Self-reported concussion symptoms were quantified by using a graded concussion symptom inventory. The symptom inventory included the 12 items from the Concussion Symptom Inventory³⁰ plus 2 additional items regarding feeling irritable and sad. Subjects verbally rated to what degree they were experiencing 14 symptoms common to concussion. We modified the instrument for our pediatric population from a 0 to 6 point scale to a 0 to 2 point scale to ensure understanding (range, 0–28). Parents rated their child's symptom severity in the week before injury using the same instrument to provide a pre-injury baseline for these nonspecific symptoms. The primary outcome, DSR, was defined as the presence of 3 or more symptoms 1 month after injury that were absent or less severe in the week before injury reflective of findings in similar cohorts.¹⁸

ICD-10 criteria for PCS require the presence of 3 or more of the following 8 symptoms 1 month after injury: headache, dizziness, fatigue, irritability, difficulty in concentration or performing mental tasks, impairment of memory, insomnia, and reduced tolerance to stress, emotional excitement, or alcohol.⁵¹ The criteria do not adjust for symptoms present before injury as our clinical definition did. Patients were considered to have PCS if they reported 3 or more symptoms on the Concussion Symptom Inventory that aligned with PCS diagnostic criteria. There is no corollary for "reduced tolerance to stress, emotional excitement, or alcohol" on the Concussion Symptom Inventory, so that symptom was excluded during analysis.

Statistical Analysis

Based on a previous study examining symptom severity in ED patients who

have concussion, we planned to divide the cohort into low and high acute symptom groups based on a defined cut-off score on a graded symptom inventory.³² We hypothesized that DSR would be more prevalent in the high symptom group. Therefore, we estimated that a sample size of 202 subjects would be necessary to demonstrate a 15% absolute difference in prevalence of DSR between the low and high symptom group, using 90% power and 2-tailed α of 0.05.

Pre-injury scores for individual symptoms were subtracted from both the initial and 30-day follow-up scores to account for the presence of these nonspecific symptoms before injury. Symptoms present before injury but absent post-injury were scored as 0 (ie, a negative score was not assigned). Descriptive statistics for demographic and acute injury data were calculated as proportions or medians with interquartile ranges and compared by using a χ^2 test and Wilcoxon rank sum as appropriate. Because there is no defined point separating low from high symptoms, a sensitivity analysis was performed by using the χ^2 statistic to determine the best cut-point for initial symptom severity scores to divide the low and high groups using DSR as the outcome. After sensitivity analysis, the best cut-point score was used for multiple logistic regression, adjusting for gender and age, as symptom report may vary by both age and gender.^{32–34} The same methods were used substituting our clinical definition of DSR with the PCS criteria. Results of χ^2 analysis were considered significant if $P < .05$. Relative risk and odds ratios (OR) were considered significant if the 95% confidence interval (CI) did not include 1. Lastly, we conducted hierarchical clustering with average linkage analysis to determine if certain symptoms were more characteristic of delayed versus early symptom resolution.³⁵ Analyses

were conducted by using SAS 9.3 (SAS Institute, Inc, Cary, NC) and hierarchical clustering was conducted by using SPSS 22.0 (IBM SPSS Statistics, IBM Corporation, Chicago, IL).

RESULTS

Research assistants screened 1253 patients for participation; 273 met inclusion criteria and 234 subjects consented to participate in the study. Of those enrolled, 179 subjects (76%) completed the 30-day follow-up call and comprised the study cohort (Fig 1). Subjects who did not complete follow-up were similar to those who did in age, gender, initial GCS, mechanism of injury, and history of previous concussion. Subjects lost to follow-up had significantly lower initial graded symptom inventory scores (median score, 7; interquartile range [IQR], 4–12) compared with subjects completing the study (median score, 10; IQR, 7–13; $P = .01$).

Thirty-eight children (21%) from the study cohort met the study definition for DSR. The pre-injury baseline symptom score differed significantly in both groups, but the scores were low for both groups (Table 1). Two subjects in the early symptom resolution (ESR) group and 1 in the DSR group experienced a subsequent concussion in the follow-up period. Forty subjects underwent head CT scan with only 5 abnormal findings, all found in the ESR group (Table 2).

The results of sensitivity analysis of initial symptom inventory scores ranging from 8 to 14 are shown in Table 3. The receiver-operator characteristic curve is shown in Fig 2 (area under the curve [AUC], 0.508; 95% CI, 0.475–0.683; $P = .14$, rounded). The best cut point was a score of 11 with a sensitivity of 63% and a specificity of 50% for DSR. However, a score of 11 was not significantly associated with DSR ($P = .46$). In multivariate analysis, adjusting for age

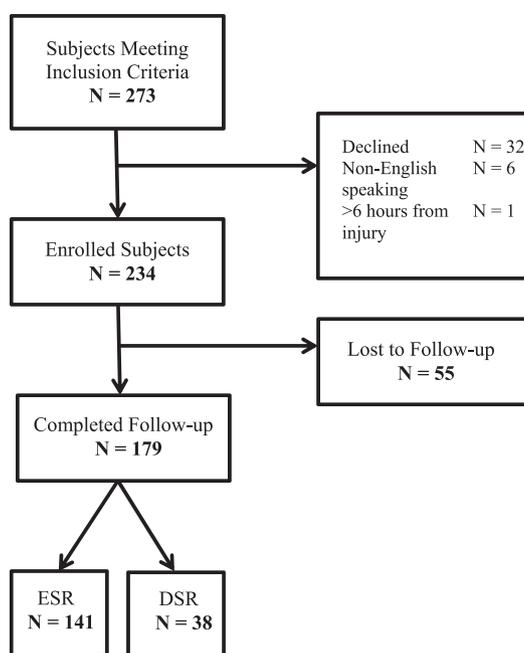


FIGURE 1
Study Participant Flow Diagram.

and gender, a score of 11 was still not associated with DSR (OR, 1.4; 95% CI, 0.7–2.8).

Twenty-two subjects (12%) met criteria for PCS. Sensitivity analysis for initial graded symptom scores ranging from 8 to 14 is shown in Table 4. The receiver-operator characteristic curve is shown

in Fig 2 (AUC, 0.629; 95% CI, 0.509–0.748; $P = .03$). The best cut point was 10 with a sensitivity of 77% and specificity of 51% for PCS ($P = .02$). The relative risk for PCS in subjects who had an initial symptom score >10 was 3.1 (95% CI, 1.2–8.0). In multivariate analysis, adjusting for age and gender, the OR for

PCS in the high symptom versus low symptom group was 3.7 (95% CI, 1.3–10.6).

Figures 3 and 4 show the results of cluster analysis. Three of the 6 most characteristic initial symptoms in the DSR and ESR groups (those in which the relative linkage distance on the x-axis are shortest) were similar (phonophobia, photophobia, blurred, or double vision). However, cognitive symptoms (difficulty remembering, difficulty concentrating, or “feeling foggy”) were more characteristic of the DSR group.

DISCUSSION

Our study of children 8 to 18 years old presenting to an ED <6 hours after concussion demonstrated that initial symptom severity is not associated with DSR. This is an important finding given evolving knowledge of concussion symptom resolution. In 1988, Lishman proposed that symptoms appearing shortly after a concussion were primarily the result of physiologic derangements directly related to the injury, whereas protracted symptoms were more likely related to latent psychological factors.³⁶ Two decades later, accumulated research suggests that “physiogenic” and “psychogenic” factors contribute to the constellation of symptoms present both immediately after injury as well as throughout recovery.³⁷

Intuitively, it is reasonable to assume that more severe acute physiologic injury will manifest as more severe symptomatology and likely require a longer recovery period. Recent research supports this assumption. A prospective cohort study of youth athletes evaluated in sports concussion clinics in the first 3 weeks after a concussion demonstrated that increasing initial graded symptom inventory scores were associated with increased odds of symptom resolution occurring beyond 28 days.²⁰ Similarly, pediatric ED patients who had high symptom

TABLE 1 Demographic and Injury Characteristics for Early and Delayed Symptom Resolution Groups

	ESR (n = 141)	DSR (n = 38)	P^a
Demographics			
Mean age, years (SD)	12.6 (2.5)	13.4 (2.2)	.79
Male, %	70	66	.69
History of previous concussion, %	24	29	.53
Injury characteristics			
Mechanism, %	—	—	.79
Sport	48	53	—
Fall	43	34	—
Assault	3	5	—
Motor vehicle collision	1	3	—
Other	5	5	—
LOC, %	26	29	0.68
Post-traumatic amnesia, %	26	34	0.42
Received head CT scan in ED, %	21	26	0.52
Abnormal head CT scan results, %	4	0	0.02
Initial GCS, median ^b	15	15	0.99
Preinjury graded symptom score, median (IQR)	1 (0–2)	2 (1–4)	0.002
Initial ED graded symptom score, median (IQR)	9 (6–13)	10.5 (7–15)	0.14

^a χ^2 was used to compare proportions and Wilcoxon rank sum to compare medians. χ^2 analysis compared the overall difference among mechanism for the ESR and DSR groups and only this single p-value is provided.

^b IQR for GCS was 15–15 for both groups.

TABLE 2 Characteristics of Subjects Who Had Abnormal Head CT Scans

Age (y)	Gender	GCS	LOC (+/-)	Injuries
10.8	F	15	-	Cerebral contusion
10.0	M	14	-	Subarachnoid and epidural hematoma, skull fracture
14.0	M	15	+	Subdural hematoma
9.4	M	14	-	Subarachnoid hematoma, skull fracture
10.1	M	15	+	Subarachnoid hematoma

TABLE 3 Sensitivity Analysis of Graded Symptom Inventory Scores for Identifying Delayed Symptom Resolution

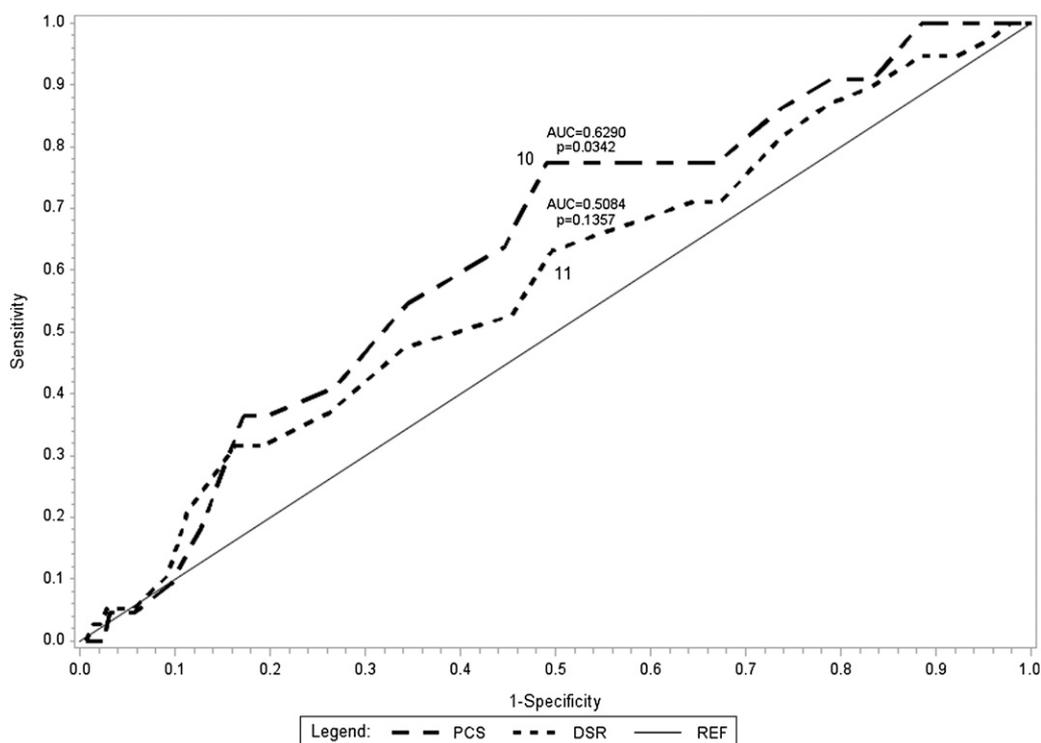
Cut Point	Sensitivity, %	Specificity, %	NPV, %	PPV, %	<i>P</i>
8	73	33	79	26	.66
9	71	33	81	22	.45
10	71	35	82	23	.14
11	63	50	84	26	.46
12	53	55	81	24	.13
13	47	66	82	27	.19
14	37	74	81	27	.10

levels measured in the early weeks after a concussion had significantly higher odds of symptoms persisting for up to 1 year.¹⁸ In both studies, initial symptom inventories were obtained an average of 11 days after concussion. Although both physiologic and psychological factors contribute to manifes-

tation of concussion symptoms, there is some evidence that the acute injury factors are stronger determinants of symptom reports early in recovery, whereas non-injury factors contribute more to persistent symptoms.³⁸ A strength of our study is that we enrolled subjects within 6 hours of injury,

but our results differed from these previous reports. This suggests that acute symptom report alone is not an accurate reflection of the physiologic and psychological factors that ultimately lead to DSR.

We defined DSR in terms relevant to clinical practice. Specifically, we developed a definition that would likely prompt a primary care provider to refer a child for specialist evaluation (at least 3 symptoms that are worse 1 month after injury than they were before injury). Although the clinical criteria for PCS also require the presence of at least 3 symptoms 1 month after concussion, the diagnostic accuracy of this definition is a topic of scientific debate as it is both subjective and imprecise.³⁹⁻⁴¹ There is also significant controversy as to whether the term “syndrome” is appropriate, given that common concussion symptoms are also found in patients who do not have concussion.⁴² Regardless of these shortcomings, PCS

**FIGURE 2**

ROC curves displaying sensitivity analysis of concussion symptom inventory scores for identifying delayed symptom resolution or post-concussive syndrome. Optimal scores (closest to upper left of graph) for each outcome are shown along with the AUC and associated *P* value for each curve.

TABLE 4 Sensitivity Analysis of Graded Symptom Inventory Scores for Identifying ICD-10 Post-Concussion Syndrome

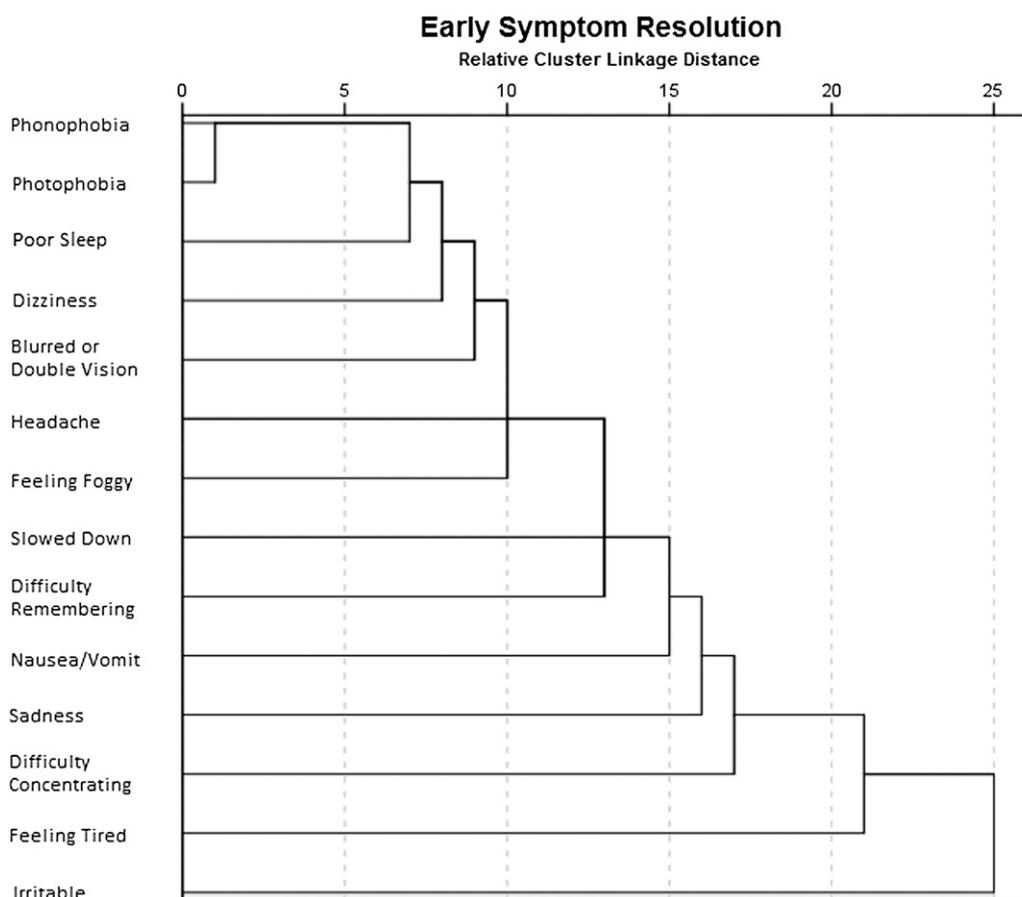
Cut Point	Sensitivity, %	Specificity, %	NPV, %	PPV, %	<i>P</i>
8	77	33	91	14	.46
9	77	36	92	14	.34
10	77	51	94	18	.02
11	64	55	92	17	.11
12	55	66	91	18	.10
13	41	73	90	18	.21
14	36	80	90	21	.10

has been studied as an outcome measure in studies of persistent symptoms.^{27,43,44} Therefore, we repeated our analysis using PCS as the outcome rather than our clinical definition of DSR. We noted 2 important findings. First, we found a 43% relative decrease in prevalence in the outcome (9% absolute difference) when applying this alternate definition. Second, we showed that a graded symptom inventory score

>10 was associated with a threefold increased risk for PCS in our cohort, whereas there was no association with our clinical definition.

One may conclude from these findings that the smaller subset of symptoms that meet criteria for PCS are more representative of a specific clinical entity characterized by persistent symptoms than those found on broader symptom inventories. An analysis comparing 3

different criteria for PCS showed that a subset of 6 symptoms common to all 3 criteria was specific to PCS owing to concussion among adults.⁴⁴ In contrast, other work calls into question whether the symptoms included in various diagnostic criteria are specific to concussion. Our results resemble those of McCauley, Boake, and colleagues, who found wide variations in the prevalence of PCS, depending on the criteria employed as well as a lack of specificity, because many adult patients who did not have head trauma also met PCS criteria.^{45,46} Additionally, although the PCS ROC curve showed a statistically significant association ($P = .034$) between an initial symptom severity score of 10 and PCS, the absolute AUC of 0.629 suggests no more than a modest relationship. Therefore, concluding that

**FIGURE 3**

Hierarchical cluster analysis for participants who had early symptom resolution. Shorter relative cluster linkage distances on the x-axis indicate symptoms (y-axis) that are more characteristic of the group, whereas longer distances indicate symptoms that are less characteristic.

Delayed Symptom Resolution

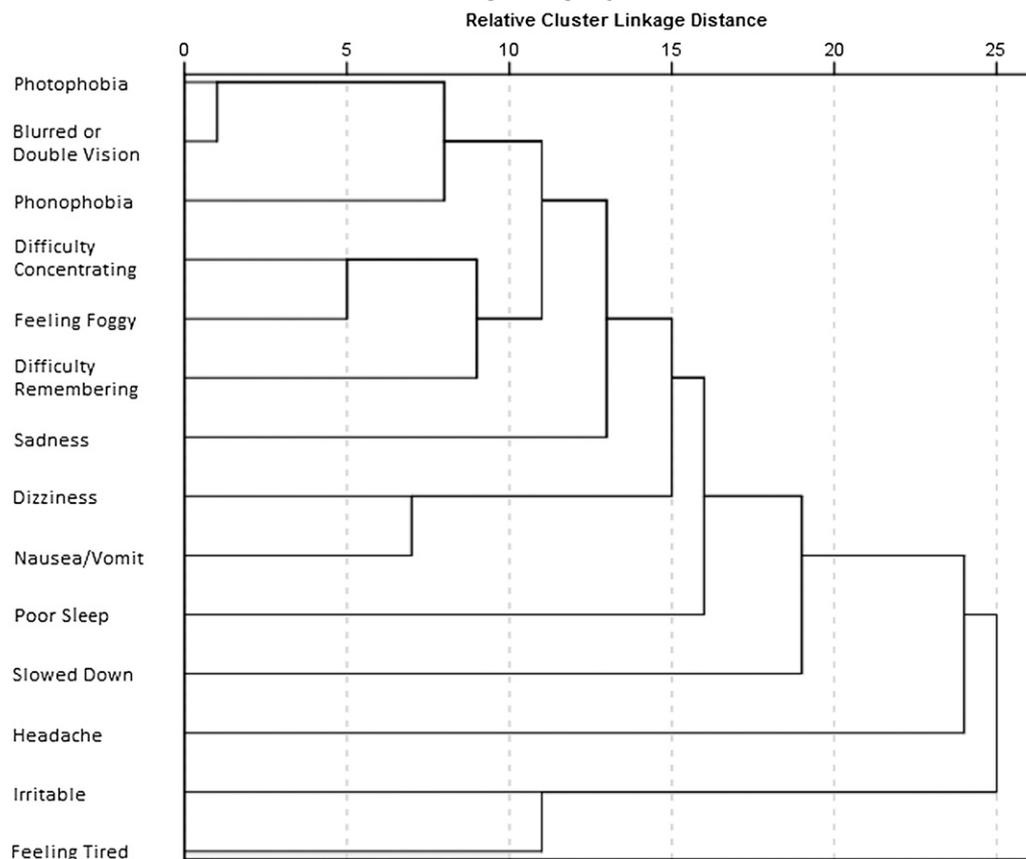


FIGURE 4

Hierarchical cluster analysis for participants who had delayed symptom resolution. Shorter relative cluster linkage distances on the x-axis indicate symptoms (y-axis) that are more characteristic of the group, whereas longer distances indicate symptoms that are less characteristic.

PCS criteria are more representative of a unique clinical syndrome is difficult to justify and suggests that accurate risk stratification is heavily dependent on how the outcome is defined.

Hierarchical cluster analysis is an exploratory method that aims to demonstrate which features are most characteristic of a group. Three of the 6 most characteristic symptoms for both the DSR and ESR groups were identical in our cohort, suggesting that these symptoms (phonophobia, photophobia, blurred or double vision) may not be useful in identifying those at risk for DSR. However, we found it interesting that cognitive symptoms were more characteristic of subjects who had DSR. Although some authors have found a stronger association between the number of initial symptoms and DSR,^{17,47} others have shown that

specific symptoms are more closely associated.^{14,48} The exploratory nature of cluster analysis prevents drawing firm conclusions regarding the ability of these symptoms to predict DSR. However, cognitive symptoms may warrant particular scrutiny when present.

We experienced a lost-to-follow-up rate of 24%. The subjects lost to follow-up had a significantly lower median initial symptom score than the final study cohort. It is plausible that most of these subjects would have fallen into the ESR group but did not complete the study owing to resolution of symptoms.⁴⁹ If true, the absence of these patients from analysis would tend to bias our results toward the null hypothesis.

Our follow-up period was limited to 30 days, as we were interested in identi-

fying children who, at the time of their concussion, are at risk for DSR. We did not perform serial assessments to determine the precise day of symptom resolution or the range of symptom duration. It is possible that some subjects in the DSR group had resolution of symptoms shortly after their 30-day follow-up call and were misclassified. However, the prevalence of DSR in this study was 21% compared with studies in other US pediatric ED cohorts 3 months after concussion, which ranged from 15% to 29%, so this limitation is unlikely to have had a significant impact on our results.^{50,51}

Finally, we did not include a control group who had injuries to body regions other than the head. Although children who have concussion tend to report more post-concussive symptoms than

children with orthopedic injuries, there is considerable overlap in symptom report, highlighting the non-specific nature of post-concussive symptoms.²⁹ We are therefore unable to evaluate what proportion of symptoms is simply attributable to injury in general and what proportion is attributable to concussion specifically. Our objective, however, was to determine whether acute symptom severity could be used for risk-stratification among head-injured children rather than as a diagnostic tool. Nonetheless, the issue of symptom

specificity further emphasizes the need for more accurate definitions related to sequelae after concussion.

CONCLUSIONS

Greater symptom severity at the time of injury does not predict DSR among children presenting to the ED for evaluation of concussion, but it is a risk factor for meeting criteria for PCS as defined by ICD-10. These findings underscore the need to refine the definition of post-concussive syndrome to one that is truly representative of concussion

sequelae and that accounts for the contribution of both physiologic and psychological processes. Given the inability to predict the resolution of post-concussive symptoms at the time of injury, outpatient follow-up and serial symptom assessment should be a cornerstone of concussion management for all children after ED discharge.

ACKNOWLEDGMENTS

We thank Kendra Kocher, BS, who provided study coordination and database management.

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Funding for the conduct of this study was provided by a Thrasher Research Fund Early Career Award to Dr Grubenhoff. Use of REDCap Database was supported by NIH/NCATS Colorado CTSI grant UL1 TR000154. Contents are the authors' sole responsibility and do not necessarily represent official NIH or Thrasher Research Fund views.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics 2014;134;54

DOI: 10.1542/peds.2013-2988 originally published online June 23, 2014;

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The online version of this article, along with updated information and services, is
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