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Original Article

Developing Insights for Possible and Probable Acute Concussions Using Cluster Analysis

Gian-Gabriel P. Garcia,[1] Caroline M. Schumb,[2] Mariel S. Lavieri,[2] Hendrik Koffijberg,[3] Thomas W. McAllister,[4] Michael A. McCrea,[5] Steven P. Broglio[6]; and Concussion Assessment, Research, and Education Consortium Investigators*

Abstract

Few studies have analyzed the Sport Concussion Assessment Tool's (SCAT) utility among athletes whose concussion assessment is challenging. Using a previously published algorithm, we identified possible and probable concussions at <6 h ($n = 393$ males, $n = 265$ females) and 24–48 h ($n = 323$ males, $n = 236$ females) post-injury within collegiate student-athletes and cadets from the Concussion Assessment, Research, and Education (CARE) Consortium. We applied cluster analysis to characterize performance on the Standard Assessment of Concussion (SAC), Balance Error Scoring System (BESS), and the SCAT symptom checklist for these athletes. Among the cluster sets that best separated acute concussions and normal performances, total symptom number raw score and change and post-traumatic migraine raw score and change score were the most frequent clustering variables across males and females at <6 h and 24–48 h. Similarly, total symptom number raw score and change score and post-traumatic migraine raw score and change score were most significantly different between clusters for males and females at <6 h and 24–48 h. Our results suggest that clinicians should focus on total symptom number, post-traumatic migraine symptoms, and cognitive-fatigue symptoms when assessing possible and probable concussions, followed by the SAC and BESS scores.

Keywords: clustering; concussion; possible/probable concussion; Sport Concussion Assessment Tool

Introduction

Concussion, the most common type of traumatic brain injury, affects millions of people in the United States each year.[1] Concussion has recently emerged as a major public health issue, partly because of its association with potential long-term consequences, including cognitive impairment, psychological disorders, and neurodegenerative diseases.[2–6] An important step in reducing long-term risk is accurately diagnosing concussion so that the injury can be properly managed. However, clinical diagnosis of concussion continues to be challenging.[7]

Currently, there is no gold standard test that can perfectly detect concussion.[8] However, current guidelines[9,10] recommend multidimensional standardized testing batteries, such as the Sport Concussion Assessment Tool (SCAT),[11] to support the traditional clinical examination when assessing sports-related concussion. Although previous research has demonstrated the accuracy of such batteries for identifying sports-related concussion,[12–17] they are still imperfect and could lead to misdiagnoses. Misdiagnoses may stem from variability in the presentation of concussion across different athletes. Specifically, assessments that may identify significant impairments in the majority of concussed athletes may not identify the same degree of impairment in others, making diagnosis difficult for this smaller subset of athletes. Few studies aim to identify and analyze this subset of athletes. To this end, we have previously developed a data-driven approach[18] to classify athletes by diagnostic certainty (i.e., unlikely, possible, probable, or definite concussion). Specifically, we compared athletes who were algorithmically difficult to identify with acute concussion (i.e., possible and probable concussions) against athletes who could be readily identified as having concussion (i.e., definite concussion) and no concussion (i.e., unlikely concussion). This analysis compared these groups based on composite scores for the Standardized Assessment of Concussion (SAC), full Balance Error Scoring System (BESS), and the SCAT symptom checklist. However, a more granular characterization of athletes with possible and probable concussions would benefit clinicians.

[1]MGH Institute for Technology Assessment, Harvard Medical School, Boston, Massachusetts, USA.
[2]Department of Industrial and Operations Engineering, and [6]Michigan Concussion Center, University of Michigan, Ann Arbor, Michigan, USA.
[3]Department of Health Technology and Services Research, Technical Medical Centre, University of Twente, Enschede, the Netherlands.
[4]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana, USA.
[5]Departments of Neurosurgery and Neurology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA.
*Concussion Assessment, Research, and Education Consortium Investigators are listed after the Acknowledgments.

The goal of this research is to characterize performance on the SAC, BESS, and SCAT symptom checklist for athletes with possible and probable concussions. We achieve this goal by first using our previously developed framework to classify athletes as having possible and probable concussion, and then applying cluster analysis within this group to identify variables that can best characterize differences between athletes with acute concussion and those who are considered to have normal performance. The results and insights from this study provide a reference for clinicians when assessing athletes for whom a diagnosis decision is unclear.

Methods

Study population and design

We analyze data from the Concussion Assessment, Research, and Education (CARE) Consortium,[19] wherein concussion is defined as ''a change in brain function following a force to the head, which may be accompanied by temporary loss of consciousness, but is identified in awake individuals with measures of neurologic and cognitive dysfunction.''[20] These data were collected during the 2014–2019 academic years and contained 38,379 player-seasons from male (57.1%) and female (42.9%) student-athletes (hereafter referred to as athletes) across 30 National College Athletic Association (NCAA) universities and military service academies. Non-varsity cadets from the military service academies were not included in these data. Within this data, 29,712 athletes completed a pre-season baseline evaluation, with 8667 athletes completing a second baseline evaluation. These data also contain 2971 concussions sustained by 2629 athletes. All concussion diagnoses were made by and at the discretion of the local institution's medical staff (e.g., team physicians). If someone was diagnosed with concussion, additional post-injury data were collected within 6 h of the injury (i.e., < 6h), 24–48 h post-injury, at initiation of the return-to-play (RTP) protocol, when cleared for unrestricted RTP, and 6 months post-RTP. All participants provided written informed consent, which was approved by their local institutional review board and the United States Army Human Research Protection Office.

Sample selection

We selected assessments performed at <6 h and 24–48 h (i.e., acute concussions) and at baseline and unrestricted RTP (i.e., normal performance). Baseline data were used only to compute change scores (defined subsequently) for the SAC, BESS, and symptom checklist. Therefore, we only included baseline data that could be matched to an athlete's post-injury assessment(s).

Study variables

We obtained each athlete's sex and scores on the SAC, BESS, and SCAT symptom checklist, which are considered to be among the most useful tools for evaluating acute concussion.[11]

The SAC is a neurocognitive assessment that measures impairment in orientation, immediate memory, concentration, and delayed recall.[21] Each of these domains is scored from 0 to 5, except for immediate memory, which is scored from 0 to 15, with lower scores indicating greater impairment. In our analysis, we consider the SAC total score, which ranges from 0 to 30 and is obtained by summing the score obtained in each domain.

The full BESS is an assessment of postural control, which is scored by counting the number of ''errors'' committed by an athlete in six 20-sec trials.[22] Each trial is defined by a combination of a stance (single leg, double leg, and tandem stance) and surface (firm and foam). Our analysis considers the BESS total score, which sums the total number of errors across all six trials. Higher BESS total scores indicate a greater degree of impairment in postural control.

The SCAT symptom checklist is a 22-item graded symptom checklist, in which the severity of each symptom is scored by athletes from 0 to 6 based on how they feel at the time of assessment.[23] Scores of 0 indicate that they do not feel the symptom at all whereas a score of 6 indicates the most severe possible manifestation of that symptom. Our analysis considers the total number of symptoms reported and the severity score from each individual symptom.

Compared with the SCAT total symptom severity score, the use of specific symptoms or symptom groups has been shown to improve the accuracy of acute concussion assessment protocols.[24] Therefore, we aggregated symptoms into ocular-vestibular, cognitive-fatigue, post-traumatic migraine, and anxiety-mood symptom groups (see Table 1). These symptom groups have shown strong reliability and validity for concussion screening.[25,26] We obtained the score for each symptom group by adding the severity scores of the symptoms within each group. We included the raw score for each symptom group along with the total number of symptoms reported.

For each of the post-injury assessments, we also computed a change score by taking the difference between the raw score obtained at the time of post-injury assessment and the score obtained during the baseline assessment for that athlete. A positive change score indicates an increase in that measure compared with baseline and vice versa. Therefore, positive change scores for the SAC indicate ''better'' performance compared with baseline, whereas positive change scores for the BESS and symptom scores indicate ''worse'' performance. For assessments at each time point, all missing data elements were filled using multiple imputation by chained equations (MICE), with imputation performed within each time point (e.g., only data from <6 h were used to impute missing data at <6 h).[27] MICE applies a sequence of conditional regression models to impute missing variables based on the values of all other variables. By sequentially applying regression and repeating this process over several iterations, uncertainty in the estimates of missing variables is more properly reflected compared with other methods, such as mean or mode substitution.[28] This process is repeated multiple times to create multiple imputed data sets. Most variables were missing at <5%, except for BESS total score at baseline (5.4%), <6 h (24.5%), and 24–48 h (10.3%). Imputation was performed using the mice package within the software R, Version 3.2.2. Our implementation of this package used five iterations and created five imputed data sets, with the first imputed data set presented for each time point. We note that there are no

Table 1. Description of Symptom Groups

Symptom group	*SCAT symptoms*
Ocular-vestibular	Blurred vision, dizziness, balance problems
Cognitive-fatigue	Feeling like ''in a fog,'' difficulty concentrating, difficulty remembering, feeling slowed down, fatigue, drowsiness, confusion, ''don't feel right''
Post-traumatic migraine	Headache, trouble falling asleep, ''pressure in the head,'' sensitivity to light, sensitivity to noise
Anxiety-mood	Nervous or anxious, sadness, more emotional, irritability

SCAT, Sport Concussion Assessment Tool.

significant differences or large effect sizes in comparing these remaining imputed data sets with the one used in this analysis, suggesting that similar results would be obtained with these data.

Data analysis

Analysis was performed in three stages, as illustrated in Figure 1, with separate analyses for assessments at <6 h and 24–48 h. In stage 1, we randomly divided the data into training ($\sim$ 60%) and testing ($\sim$ 40%) sets. We then used two-sample non-parametric bootstrap *t* tests[29] to compare training and testing sets with a significance level of $\alpha = 0.05$. We also computed Cohen's *d* to quantify the effect size of these differences. We then applied a previously published framework[18,30] on the training set to develop an algorithm for classifying athletes suspected of concussion as having unlikely, possible, probable, or definite concussions. Finally, we applied this algorithm to the testing set to identify possible and probable concussions.

In stage 2, we performed an exploratory cluster analysis to characterize differences between concussions and normal performances. Specifically, we applied two-means clustering on the possible and probable concussions where two-means clustering would place each athlete into one of two different clusters based on which cluster the athlete is ''closest'' to. For assessments at both <6 h and 24–48 h, we separated the possible and probable concussions by sex, producing four subsets: male <6 h, female <6 h, male 24–48 h, and female 24–48 h. Because clustering is sensitive to outliers,[31] we excluded a small subset of athletes ($n = 14$–21 athletes at each sex and time point) whose change score in SCAT total symptom severity and/or total number of symptoms were >2.5 standard deviations from the mean. These outliers had much lower symptom burden post-injury than at baseline. We used a two-sample non-parametric bootstrap *t* test to identify significant differences, and Cohen's *d* to quantify effect sizes for all modeling variables across each subset of possible and probable concussions by sex and time mpoint. Following best practices for clustering based on the size of our data,[32] we performed two-means clustering using every combination of modeling variables up to seven clusters. This analysis produced 63,003 clusters at both <6 h and 24–48 h. Hereafter, we refer to each group of clusters formed by a specified set of variables as a *cluster set*.

In stage 3, we evaluated the cluster sets. First, we computed silhouette scores[33] and sample-weighted Gini indices for each cluster set.[34] Silhouette scores range from -1 to 1 and measure the dissimilarity between clusters in a cluster set, where greater silhouette scores indicate greater dissimilarity. Gini indices range from 0 to 1 and measure the purity of clusters within a cluster set, with lower Gini indices indicating ''purer'' clusters, implying better separation between acute concussions and normal performances. We restricted our attention to the cluster sets that had a silhouette score of at least 0.1 and a Gini index within the lowest 200 of all Gini indices (approximately the top 0.32% of all clusters). With these 200 cluster sets, we analyzed which variables were used in clustering and which of these variables were significantly different between the two clusters in each cluster set. Finally, for each sex and time point, we analyzed the cluster sets with the least Gini index to illustrate the differences between the two purest clusters.

Results

Characteristics of study data

Table 2 summarizes the study data with respect to modeling variables. There were no significant differences between training and testing data at baseline, <6 h, and 24–48 h. At unrestricted RTP, the number of previous concussions ($p = 0.085$, $d = 0.11$), total number of symptoms raw score ($p = 0.038$, $d = 0.09$) and the anxiety-mood symptom group raw score ($p = 0.031$, $d = 0.09$) were significantly different between training and testing data, although the effect sizes are small.

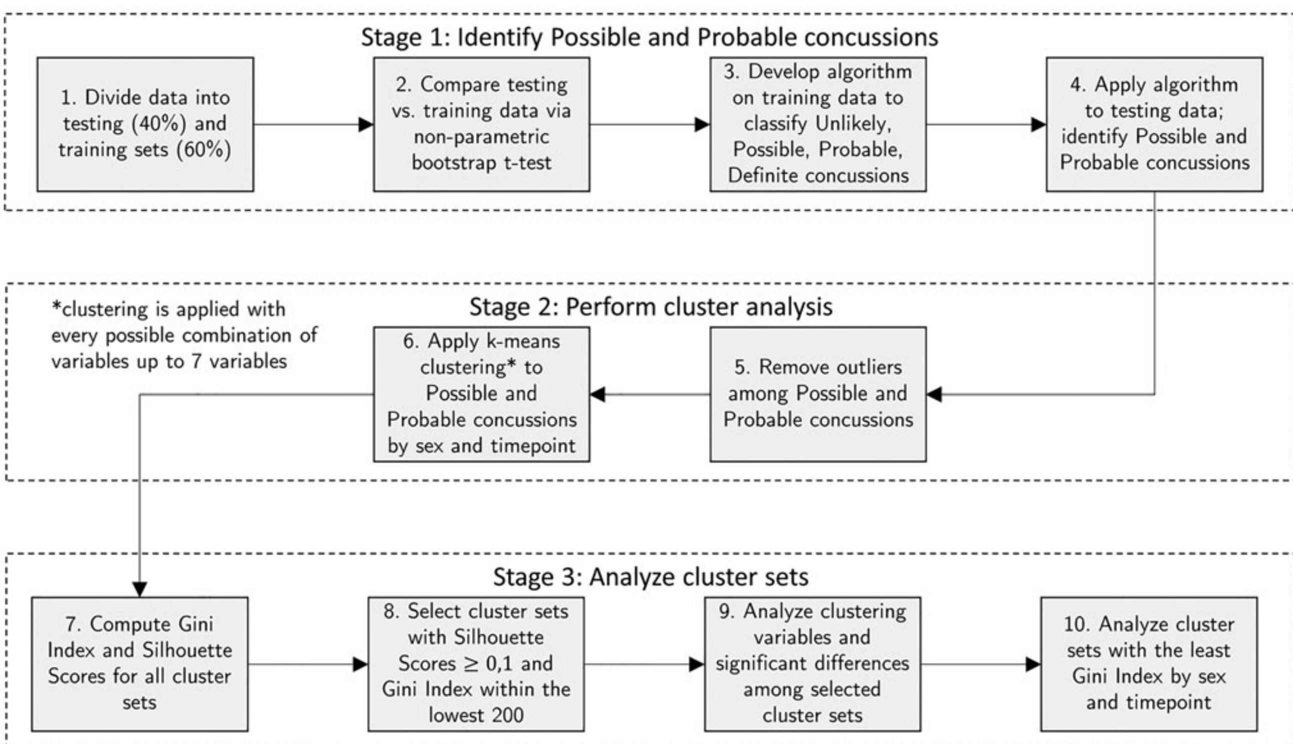

FIG. 1. Summary of data analysis.

Table 2. Characteristics of Study Data by Time Point

Variable	*Baseline*			*<6h*			*24-48h*			*Unrestricted RTP*		
	Training	*Testing*	d	*Training*	*Testing*	d	*Training*	*Testing*	d	*Training*	*Testing*	d
n	1623	964		831	625		1432	962		1346	832	
Male sex (% yes)	58.1%	60.79%	0.05	62.33%	63.84%	0.03	57.96%	59.98%	0.04	56.98%	58.89%	0.04
Age, years (SD)	19.10 (1.25)	19.16 (1.30)	0.05	19.23 (1.34)	19.23 (1.31)	0.00	19.06 (1.25)	19.07 (1.24)	0.01	19.12 (1.25)	19.12 (1.29)	0.00
Height, m (SD)	1.79 (0.11)	1.79 (0.12)	0.02	1.80 (0.11)	1.79 (0.12)	0.03	1.79 (0.11)	1.79 (0.12)	0.02	1.78 (0.11)	1.79 (0.12)	0.01
Weight, kg (SD)	82.33 (21.55)	83.12 (21.97)	0.04	84.67 (22.23)	83.84 (21.89)	0.04	82.50 (21.77)	82.86 (22.09)	0.02	81.78 (21.24)	82.62 (21.97)	0.04
Number of previous concussions (SD)	0.60 (0.88)	0.62 (0.88)	0.02	0.65 (0.91)	0.68 (0.90)	0.04	0.59 (0.86)	0.66 (0.93)	0.08	0.64 (0.88)	0.54 (0.81)**	0.11
SAC RS (SD)	27.30 (1.95)	27.22 (1.98)	0.04	26.01 (2.96)	25.87 (3.21)	0.05	26.56 (2.67)	26.52 (2.61)	0.01	28.11 (1.68)	28.11 (1.75)	0.00
SAC CS (SD)				–1.10 (3.05)	–1.35 (3.33)	0.08	–0.66 (2.73)	–0.77 (2.64)	0.04	0.83 (2.03)	0.78 (2.04)	0.02
BESS RS (SD)	13.31 (6.28)	13.74 (6.64)	0.07	17.11 (8.47)	16.69 (8.38)	0.05	15.13 (7.80)	15.13 (8.15)	0.00	10.81 (5.65)	10.70 (5.73)	0.02
BESS CS (SD)				3.58 (8.57)	3.15 (8.52)	0.05	1.59 (8.12)	1.64 (8.08)	0.01	–2.91 (6.23)	–2.59 (6.51)	0.05
SCAT total symptoms RS (SD)	2.79 (3.84)	2.82 (3.95)	0.01	10.52 (5.64)	11.07 (5.45)	0.10	11.01 (6.03)	10.83 (5.78)	0.03	0.40 (1.29)	0.30 (0.98)*	0.09
SCAT total symptoms CS (SD)				7.95 (6.42)	8.01 (6.61)	0.01	8.06 (6.66)	7.85 (6.80)	0.03	–2.47 (3.94)	–2.51 (3.85)	0.01
Ocular-vestibular RS (SD)	0.36 (1.22)	0.34 (1.27)	0.02	4.09 (4.19)	4.34 (4.27)	0.06	3.18 (3.90)	2.89 (3.54)	0.08	0.02 (0.21)	0.02 (0.16)	0.03
Ocular-vestibular CS (SD)				3.77 (4.33)	3.88 (4.27)	0.03	2.78 (4.05)	2.47 (3.92)	0.08	–0.31 (1.16)	–0.29 (1.31)	0.01
Cognitive-fatigue RS (SD)	2.52 (4.83)	2.41 (4.54)	0.02	12.56 (10.66)	13.18 (10.54)	0.06	11.77 (10.26)	11.32 (9.78)	0.04	0.22 (1.06)	0.15 (0.70)	0.08
Cognitive-fatigue CS (SD)				10.10 (11.80)	10.25 (11.77)	0.01	9.01 (10.91)	8.55 (10.83)	0.04	–2.35 (4.80)	–2.60 (5.41)	0.05
Post-traumatic Migraine RS (SD)	1.03 (2.13)	1.13 (2.18)	0.05	7.66 (5.20)	8.05 (5.43)	0.07	8.17 (5.99)	7.74 (5.49)	0.07	0.18 (0.74)	0.13 (0.55)	0.08
Post-traumatic Migraine CS (SD)				6.70 (5.31)	6.94 (5.55)	0.04	7.10 (6.06)	6.63 (5.67)	0.08	–0.90 (2.14)	–0.92 (2.15)	0.01
Anxiety-mood RS (SD)	1.00 (2.48)	0.98 (2.48)	0.01	2.44 (4.07)	2.57 (4.16)	0.03	2.58 (4.12)	2.27 (3.73)	0.08	0.07 (0.52)	0.03 (0.38)*	0.09
Anxiety-mood CS (SD)				1.68 (4.57)	1.38 (4.85)	0.06	1.56 (4.56)	1.26 (4.25)	0.07	–0.97 (2.48)	–0.96 (2.62)	0.00

*$p < 0.05$, **$p < 0.01$, significantly different from training data at same time point using two-sample non-parametric bootstrap *t* test.

RTP, return to play; *n*, sample size; SD, standard deviation; RS, raw score; CS, change score; SAC, Standard Assessment of Concussion; BESS, Balance Error Scoring System; SCAT, Sport Concussion Assessment Tool.

Table 3. Characteristics of Possible and Probable Concussions at <6h and 24-48h

	<6h						24-48h					
	Male			Female			Male			Female		
Variable	*Normal performance*	*Concussed*	d	*Normal performance*	*Concussed*	d	*Normal performance*	*Concussed*	d	*Normal performance*	*Concussed*	d
n	322	71		226	39		236	87		182	54	
SAC RS (SD)	27.67 (1.90)	27.28 (1.77)	0.21	28.17 (1.65)	28.13 (1.69)	0.03	27.86 (1.93)	27.03 (2.23)**	0.41	28.34 (1.63)	27.65 (1.71)*	0.42
SAC CS (SD)	0.76 (2.15)	–0.35 (2.31)***	0.51	0.72 (2.06)	0.23 (2.34)	0.23	0.74 (2.13)	–0.38 (2.14)***	0.52	0.66 (2.00)	–0.02 (1.84)*	0.35
BESS RS (SD)	11.55 (5.23)	12.62 (6.35)	0.20	10.49 (5.49)	11.97 (4.83)	0.28	11.24 (6.44)	13.10 (7.50)*	0.28	10.69 (6.24)	11.67 (5.09)	0.16
BESS CS (SD)	–2.20 (6.19)	1.06 (7.32)**	0.51	–2.51 (6.74)	0.97 (4.84)***	0.54	–2.17 (6.29)	1.71 (8.67)***	0.55	–2.38 (7.05)	–1.44 (5.95)	0.14
SCAT total symptoms RS (SD)	0.26 (0.85)	4.13 (2.34)***	3.09	0.39 (1.07)	4.72 (2.67)***	3.05	0.31 (0.88)	2.95 (1.74)***	2.25	0.42 (1.04)	3.85 (1.88)***	2.68
SCAT total symptoms CS (SD)	–1.71 (2.65)	2.69 (3.32)***	1.58	–2.19 (2.70)	0.95 (4.49)**	1.04	–1.55 (2.59)	1.26 (3.29)***	1.01	–2.24 (2.77)	1.31 (3.41)***	1.22
Ocular-vestibular RS (SD)	0.01 (0.08)	0.82 (1.30)**	1.46	0.01 (0.11)	1.62 (2.09)***	2.00	0.01 (0.09)	0.16 (0.48)*	0.59	0.01 (0.10)	0.30 (0.66)*	0.87
Ocular-vestibular CS (SD)	–0.11 (0.71)	0.52 (1.52)**	0.70	–0.20 (0.79)	1.23 (2.06)***	1.34	–0.10 (0.63)	–0.18 (1.38)	0.10	–0.19 (0.83)	0.00 (1.17)	0.20
Cognitive-fatigue RS (SD)	0.15 (0.67)	2.52 (2.89)***	1.74	0.18 (0.66)	2.46 (2.14)***	2.25	0.18 (0.75)	1.48 (2.02)***	1.06	0.18 (0.62)	1.85 (1.98)***	1.54
Cognitive-fatigue CS (SD)	–1.59 (2.86)	1.13 (4.40)***	0.85	–1.85 (2.98)	–0.74 (4.48)	0.34	–1.44 (2.80)	–0.11 (4.04)**	0.42	–2.11 (3.67)	–0.35 (3.49)**	0.48
Post-traumatic migraine RS (SD)	0.11 (0.52)	3.37 (2.91)***	2.47	0.19 (0.61)	3.79 (2.47)***	3.29	0.13 (0.57)	2.29 (2.38)***	1.63	0.21 (0.67)	2.94 (2.41)***	2.13
Post-traumatic migraine CS (SD)	–0.52 (1.38)	2.94 (3.22)***	1.88	–0.83 (1.82)	2.64 (3.43)***	1.63	–0.52 (1.44)	1.71 (2.75)***	1.18	–0.77 (1.69)	2.06 (3.06)***	1.36
Anxiety-mood RS (SD)	0.02 (0.25)	0.06 (0.23)	0.14	0.06 (0.64)	0.41 (1.23)	0.46	0.03 (0.30)	0.14 (0.73)	0.23	0.08 (0.72)	0.46 (1.55)	0.39
Anxiety-mood CS (SD)	–0.48 (1.31)	–0.30 (1.55)	0.14	–0.86 (2.11)	–1.13 (2.90)	0.12	–0.44 (1.25)	–0.43 (1.65)	0.01	–0.91 (2.25)	–0.26 (2.36)	0.29

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, significantly different from normal performance within the same sex and time point using two-sample non-parametric bootstrap *t* test.

n, sample size; SD, standard deviation; RS, raw score; CS, change score; SAC, Standard Assessment of Concussion; BESS, Balance Error Scoring System; SCAT, Sport Concussion Assessment Tool.

Characteristics of possible and probable concussion

In Table 3, we describe the possible and probable concussions identified in our testing data. For males at <6 h, mean values were significantly different between the concussed and normal performance groups for SCAT total symptoms raw score ($p = 0.0005$, $d = 3.09$) and change score ($p = 0.0005$, $d = 1.58$), post-traumatic migraine raw score ($p = 0.0005$, $d = 2.47$) and change score ($p = 0.0005$, $d = 1.88$), cognitive-fatigue raw score ($p = 0.0005$, $d = 1.74$) and change score ($p = 0.0005$, $d = 0.85$), ocular-vestibular raw score ($p = 0.002$, $d = 1.46$) and change score ($p = 0.002$, $d = 0.70$), SAC change score ($p < 0.001$, $d = 0.51$), and BESS change score ($p = 0.0015$, $d = 0.51$). For females at <6 h, there were significant differences between the concussed and normal performance groups in mean values for post-traumatic migraine raw score ($p = 0.0005$, $d = 3.29$) and change score ($p = 0.0005$, $d = 1.63$), SCAT total symptoms raw score ($p = 0.0005$, $d = 3.05$) and change score ($p = 0.002$, $d = 1.04$), cognitive-fatigue raw score ($p = 0.0005$, $d = 2.25$), ocular-vestibular raw score ($p = 0.001$, $d = 2.00$) and change score ($p = 0.0005$, $d = 1.34$), and BESS change score ($p = 0.001$, $d = 0.54$). For males at 24–48 h, mean values were significantly different between the concussed and normal performance groups for SCAT total symptoms raw score ($p = 0.0005$, $d = 2.25$) and change score ($p = 0.0005$, $d = 1.01$), post-traumatic migraine raw score ($p = 0.0005$, $d = 1.63$) and change score ($p = 0.0005$, $d = 1.18$), cognitive-fatigue raw score ($p = 0.0005$, $d = 1.06$) and change score ($p = 0.0085$, $d = 0.42$), ocular-vestibular raw score ($p = 0.028$, $d = 0.59$), BESS raw score ($p = 0.047$, $d = 0.28$) and change score ($p = 0.0005$, $d = 0.55$), and SAC raw score ($p = 0.0035$, $d = 0.41$) and change score ($p = 0.0005$, $d = 0.52$). For females at 24–48 h, mean values were significantly different between the concussed and normal performance groups for SCAT total symptoms raw score ($p = 0.0005$, $d = 2.68$) and change score ($p = 0.0005$, $d = 1.22$), post-traumatic migraine raw score ($p = 0.0005$, $d = 2.13$) and change score ($p = 0.0005$, $d = 1.36$), cognitive-fatigue raw score ($p = 0.0005$, $d = 1.54$) and change score ($p = 0.0015$, $d = 0.48$), ocular-vestibular raw score ($p = 0.013$, $d = 0.87$), and SAC raw score ($p = 0.012$, $d = 0.42$) and change score ($p = 0.024$, $d = 0.35$).

Analysis of clustering variables

Figure 2 illustrates the frequency by which each variable was chosen for clustering among the 200 cluster sets with the lowest Gini Indices by sex and time point. The lowest 200 Gini indices ranged from 0.224 to 0.231 for males at <6 h, 0.176–0.186 for females at <6 h, 0.362–0.371 for males at 24–48 h, and 0.299–0.309 for females at 24–48 h. At <6 h, the most frequently chosen clustering variables for males were post-traumatic migraine raw score (200/200, females) and change score (162/200, males; 149/200 females), and the total number of symptoms raw score (190/200, males; 163/200, females) and change score (145/200, males). At 24–48 h, the most frequently chosen clustering variables were the total number of symptoms raw score (200/200, males; 200/200 females), Post-traumatic migraine change score (145/200, males), cognitive-fatigue change score (103/200, females), anxiety-mood change score (102/200, females), and BESS change score (101/200, males).

Analysis of significant differences

Figure 3 illustrates the frequency by which each variable was significantly different between the two clusters among the 200 clusters sets with the lowest Gini Indices by sex and time point. At <6 h, the variables that were most often significantly different between clusters were total number of symptoms raw score (150/200, males) and change score (145/200, males; 148/200 females), post-traumatic migraine change score (148/200, males; 145/200 females), and ocular-vestibular change score (145/200, females). At 24–48 h, total number of symptoms raw score (153/200, males; 152/200 females) and change score (153/200, males; 155/200 females) and the post-traumatic migraine raw score (150/200, males) and change score (150/200, males; 149/200 females) were most often significantly different between clusters.

Analysis of clusters with the lowest Gini index

Table 4 describes the cluster sets with the lowest Gini Index by sex and time point. For males at <6 h (Gini Index = 0.224), the first cluster contained 334 athletes (4.49% with concussion) and the second cluster contained 59 athletes (94.92% with concussion). Mean values were significantly different between the clusters for SCAT total symptoms raw score ($p = 0.0005$, $d = 4.34$) and change score ($p = 0.0005$, $d = 2.04$), post-traumatic migraine raw score ($p = 0.0005$, $d = 3.57$) and change score ($p = 0.0005$, $d = 2.66$), cognitive-fatigue raw score ($p = 0.0005$, $d = 2.16$) and change score ($p = 0.0005$, $d = 1.01$), ocular-vestibular raw score ($p = 0.0005$, $d = 1.78$) and change score ($p = 0.0005$, $d = 0.84$), SAC change score ($p = 0.0035$, $d = 0.45$), and BESS change score ($p = 0.029$, $d = 0.36$). For females at <6 h (Gini Index = 0.176), the first cluster had 228 athletes (2.19% with concussion) and the second cluster had 37 athletes (91.89% with concussion). Between the two clusters, mean values were significantly different for SCAT total symptoms raw score ($p = 0.0005$, $d = 4.37$) and change score ($p = 0.0005$, $d = 1.28$), post-traumatic migraine raw score ($p = 0.0005$, $d = 3.73$) and change score ($p = 0.0005$, $d = 1.60$), cognitive-fatigue raw score ($p = 0.0005$, $d = 3.16$), ocular-vestibular raw score ($p = 0.0015$, $d = 2.21$) and change score ($p = 0.0005$, $d = 1.59$), and BESS change score ($p = 0.001$, $d = 0.48$). For males at 24–48 h (Gini Index = 0.362), the first cluster had 81 athletes (82.72% with concussion) and the second cluster had 242 athletes (8.26% with concussion). Mean values were significantly different between the two clusters for SCAT total symptoms raw score ($p = 0.0005$, $d = 4.33$) and change score ($p = 0.0005$, $d = 1.17$), post-traumatic migraine raw score ($p = 0.0005$, $d = 2.16$) and change score ($p = 0.0005$, $d = 1.49$), cognitive-fatigue raw score ($p = 0.0005$, $d = 1.78$) and change score ($p = 0.002$, $d = 0.56$), ocular-vestibular raw score ($p = 0.02$, $d = 0.70$), BESS change score ($p = 0.0015$, $d = 0.57$), and SAC change score ($p = 0.014$, $d = 0.32$). Finally, for females at 24–48 h (Gini Index = 0.299), the first cluster contained 179 athletes (4.47% with concussion) and the second cluster contained 57 athletes (80.70%) with concussion. Between the two clusters, there were significant differences in the mean values for SCAT total symptoms raw score ($p = 0.0005$, $d = 4.59$) and change score ($p = 0.0005$, $d = 1.38$), post-traumatic migraine raw score ($p = 0.0005$, $d = 2.35$) and change score ($p = 0.0005$, $d = 1.19$), cognitive-fatigue raw score ($p = 0.0005$, $d = 1.96$) and change score ($p = 0.0005$, $d = 0.55$), ocular-vestibular raw score ($p = 0.0095$, $d = 0.98$), SAC raw score ($p = 0.008$, $d = 0.41$), and anxiety-mood change score ($p = 0.0325$, $d = 0.36$).

We now provide a brief example illustrating how these clusters might be useful in practice; for example, in the case of a female athlete with possible or probable concussion being assessed at <6 h. We would direct our attention to the total number of symptoms raw

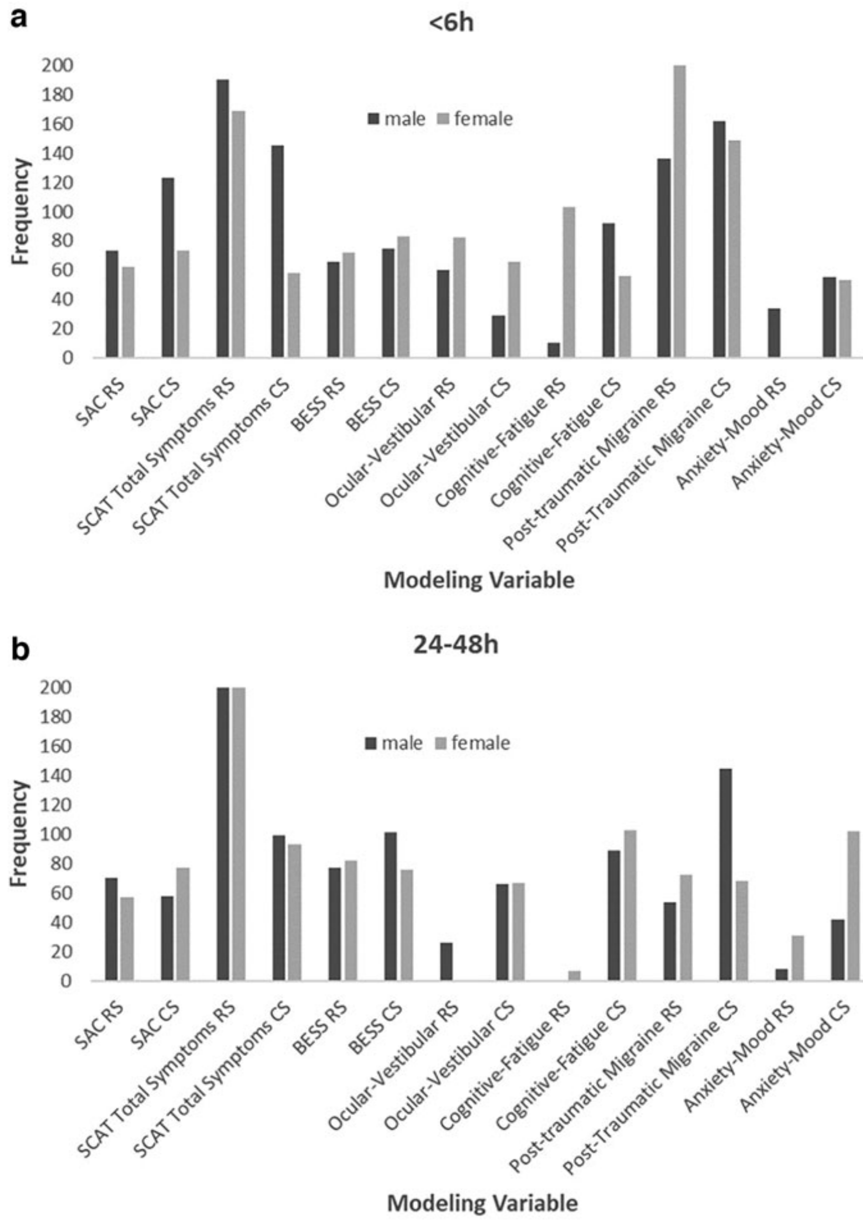

FIG. 2. Frequency of clustering variables among cluster sets with the 200 lowest Gini Indices at **(a)** < 6h and **(b)** 24–48h. RS, raw score; CS, change score; SAC, Standard Assessment of Concussion; BESS, Balance Error Scoring System; SCAT, Sport Concussion Assessment Tool.

score, ocular-vestibular change score, cognitive-fatigue raw score, and post-traumatic migraine raw and change scores. One can then assess whether she looks more like an athlete in cluster 1 or cluster 2. This process can be performed using clinical judgment and/or by computing her normalized distance to each cluster center and estimating the probability that she belongs to each cluster (Supplementary Text S1). Then, the results of this analysis can inform clinical decision making. For example, if she is ''closer'' to cluster 2, she may be more likely to have a concussion than if she were assigned to cluster 1.

Discussion

Previously, we developed a data-driven framework for classifying athletes suspected of having concussion as having an unlikely, possible, probable, or definite concussion.[18] We extend this prior work using cluster analysis to characterize possible and probable concussions. This analysis is one of the few that focuses specifically on the subgroup of athletes whose concussions are both clinically and algorithmically hard to diagnose. Our findings provide valuable guidance for clinicians by identifying key components of the SCAT that best characterize differences between concussions and normal performances among those with possible and probable concussions.

For males and females at both <6 h and 2–48 h, the post-traumatic migraine symptom group (both raw and change scores) was an important differentiator between athletes with acute concussion and those with normal performance. Further, the anxiety-mood symptom group was rarely clustered on or significantly different among clusters. These results aligns with the findings

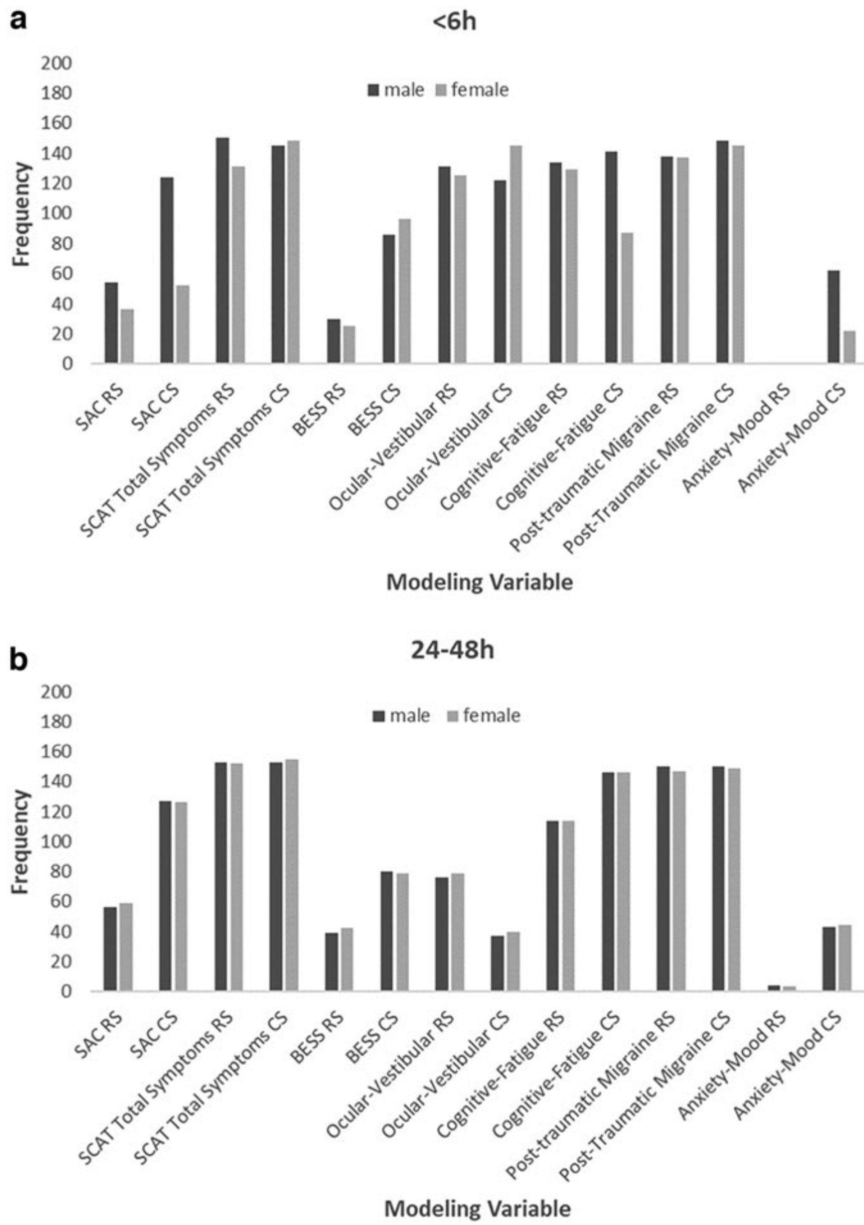

FIG. 3. Frequency of significant differences among cluster sets with the 200 lowest Gini Indices at **(a)** < 6h and **(b)** 24–48h. RS, raw score; CS, change score; SAC, Standard Assessment of Concussion; BESS, Balance Error Scoring System; SCAT, Sport Concussion Assessment Tool.

by Kontos et al., who found that, compared with all symptom groups in this study, the post-traumatic migraine symptom group could most accurately discriminate between concussed athletes and controls whereas the anxiety-mood symptom group was the worst performing.[26] In our analysis, the ocular-vestibular group played a small role whereas the cognitive-fatigue symptom group appeared to be the most important after the post-traumatic migraine symptom group. In contrast, they found that ocular and vestibular symptom groups had the second and third highest discriminative ability, respectively, among all symptom groups. These differences may be attributed to differences in sample selection, in which they considered a general population sample of athletes 12–19 years of age, whereas we studied collegiate varsity athletes who were algorithmically difficult to identify as having concussion.

Considering these results, incorporating specific symptom groups into the original classification algorithm for unlikely, possible, probable, and definite concussions would likely improve its performance. Specifically, the original algorithm only incorporated symptom severity through the total symptom severity score. Yet, focusing on specific symptoms rather than aggregate symptom severity has been shown to improve acute concussion assessment.[24] Hence, we anticipate that revising the original algorithm by placing more weight (e.g., via logistical regression) on an athlete's post-traumatic migraine and cognitive-fatigue symptoms would result in a greater proportion of acute concussions in the probable concussion group and a greater proportion of normal performances in the possible concussion group.

In previous research, the SAC and BESS have been found to perform similarly for identifying concussion in collegiate

Table 4. Cluster Sets with the Lowest Gini Index for Males and Females at <6 h and 24-48 h

	<6h						24-48h					
	Male			*Female*			*Male*			*Female*		
Variable	*Cluster 1*	*Cluster 2*	d	*Cluster 1*	*Cluster 2*	d	*Cluster 1*	*Cluster 2*	d	*Cluster 1*	*Cluster 2*	d
n	334	59		228	37		81	242		179	57	
% concussed	4.49%	94.92%		2.19%	91.89%		82.72%	8.26%		4.47%	80.70%	
SAC RS (SD)	27.63 (1.93)	27.44 (1.55)	0.10	28.18 (1.64)	28.11 (1.78)	0.04	27.32 (1.95)	27.75 (2.07)	0.21	28.35 (1.65)	27.67 (1.66)**	0.41
SAC CS (SD)[a]	0.71 (2.19)	−0.27 (2.22)**	0.45	0.68 (2.09)	0.41 (2.19)	0.13	−0.09 (2.04)	0.61 (2.21)*	0.32	0.63 (2.03)	0.14 (1.80)	0.25
SCAT total symptoms RS (SD)[a,b,c,d]	0.27 (0.81)	4.85 (1.93)***	4.34	0.33 (0.84)	5.35 (2.28)***	4.37	3.56 (1.34)	0.17 (0.46)***	4.33	0.23 (0.60)	4.25 (1.43)***	4.59
SCAT total symptoms CS (SD)[a]	−1.72 (2.59)	3.64 (2.88)***	2.04	−2.25 (2.76)	1.51 (3.92)***	1.28	1.60 (3.34)	−1.60 (2.49)***	1.17	−2.37 (2.74)	1.53 (3.09)***	1.38
BESS RS (SD)	11.71 (5.29)	11.92 (6.37)	0.04	10.45 (5.44)	12.30 (5.07)	0.34	13.02 (7.53)	11.31 (6.47)	0.25	10.80 (6.17)	11.26 (5.50)	0.08
BESS CS (SD)[c,d]	−1.96 (6.27)	0.37 (7.58)*	0.36	−2.43 (6.74)	0.68 (5.00)***	0.48	1.88 (8.89)	−2.13 (6.26)**	0.57	−2.03 (7.03)	−2.60 (6.16)	0.08
Ocular-Vestibular RS (SD)[a]	0.01 (0.09)	0.97 (1.38)***	1.78	0.01 (0.09)	1.73 (2.09)**	2.21	0.19 (0.50)	0.00 (0.06)*	0.70	0.00 (0.00)	0.32 (0.66)**	0.98
Ocular-Vestibular CS (SD)[b]	−0.11 (0.70)	0.64 (1.63)***	0.84	−0.22 (0.80)	1.43 (1.94)***	1.59	−0.15 (1.42)	−0.11 (0.62)	0.04	−0.17 (0.80)	−0.05 (1.22)	0.13
Cognitive-Fatigue RS (SD)[b]	0.15 (0.64)	2.97 (3.01)***	2.16	0.13 (0.49)	2.89 (2.01)***	3.16	1.96 (2.10)	0.05 (0.28)***	1.78	0.09 (0.36)	2.04 (1.92)***	1.96
Cognitive-Fatigue CS (SD)[a,d]	−1.58 (2.81)	1.61 (4.69)***	1.01	−1.92 (2.97)	−0.30 (4.46)	0.50	0.23 (3.97)	−1.52 (2.82)**	0.56	−2.18 (3.68)	−0.21 (3.35)***	0.55
Post-traumatic Migraine RS (SD)[a,b]	0.10 (0.42)	4.10 (2.73)***	3.57	0.19 (0.59)	4.03 (2.35)***	3.73	2.64 (2.33)	0.07 (0.32)***	2.16	0.15 (0.53)	3.00 (2.30)***	2.35
Post-traumatic Migraine CS (SD)[a,b]	−0.56 (1.33)	3.83 (2.87)***	2.66	−0.80 (1.84)	2.65 (3.52)***	1.60	2.07 (2.60)	−0.58 (1.42)***	1.49	−0.74 (1.69)	1.81 (3.16)***	1.19
Anxiety-Mood RS (SD)	0.02 (0.25)	0.07 (0.25)	0.19	0.04 (0.60)	0.54 (1.32)	0.67	0.19 (0.79)	0.02 (0.26)	0.36	0.00 (0.00)	0.70 (1.92)	0.75
Anxiety-Mood CS (SD)[d]	−0.51 (1.38)	−0.12 (1.19)*	0.29	−0.90 (2.11)	−0.92 (2.97)	0.01	−0.42 (1.66)	−0.44 (1.25)	0.01	−0.96 (2.16)	−0.14 (2.57)*	0.36

[a]Cluster variable for male <6 h; [b]Cluster variable for female <6 h; [c]Cluster variable for male 24–48 h; [d]Cluster variable for female 24–48 h.
*$p < 0.05$ **$p < 0.01$ ***$p < 0.001$, significantly different from Cluster 1 of the same sex and time point using two-sample non-parametric bootstrap *t* test.
n, sample size; SD, standard deviation; RS, raw score; CS, change score; SAC, Standard Assessment of Concussion; BESS, Balance Error Scoring System; SCAT, Sport Concussion Assessment Tool.

athletes.[12,14,17,35] Our analysis extends this literature by characterizing the clinical utility of the SAC and BESS among possible and probable concussions. Among males at <6 h and 24–48 h, the SAC change score seemed to play a more important role than the BESS raw score or change score. However, for females, this trend is reversed. That is, the BESS raw score and change score seemed to be more important than the SAC raw and change scores. Overall, the SAC and BESS appear to play a moderately important role in identifying concussion among possible and probable concussions, although they remain overshadowed by the total number of symptoms and the post-traumatic migraine symptoms. This finding bears similarity to the results by Broglio et al.,[36] who found that increased symptoms typically indicate concussion and that the SAC and/or BESS are beneficial for ascertaining the concussion assessment for athletes who report low or no symptoms. Overall, these findings support multidimensional approaches to concussion assessment.

Previous studies have attempted to quantify the value of change scores in acute concussion assessment, generally finding that they only have a small benefit over raw scores or standard normative references.[12,14,37–40] However, none of these studies specifically examined the utility of change scores within possible and probable concussions. This analysis shows that change scores for the total number of symptoms, post-traumatic migraine symptom group, and cognitive-fatigue symptom group were frequently used as clustering variables and were found to be significantly different across males and females at <6 h and 24–48 h. These results suggest that those with possible or probable concussions who exhibit elevated cognitive and migraine symptoms compared with baseline may be more likely to have concussion.

Differences in concussion presentation by sex have been identified in previous research.[41–45] Our analysis presented minimal sex-related differences and there were more similarities within time points than within sex. Although further investigation is warranted, these results suggest that similar injury assessment approaches can potentially be taken for male and female athletes with possible and probable concussion.

This study is not without limitations. Future studies should investigate whether our findings translate to populations beyond collegiate varsity athletes. Such studies should consider the development of population-specific risk estimation models and, when personalized baseline assessments are unavailable, change scores with reference to population-specific normative values warrant special attention. Additionally, future studies could extend this study by considering additional assessments beyond the SAC, BESS, and SCAT symptom checklist, such as the Vestibular/Ocular-Motor Screening (VOMS), King-Devick test, or Tandem Gait. Finally, future work can extend this current research by operationalizing our findings, which would facilitate its implementation in clinical settings.

Conclusion

To enhance the assessment and post-injury management of athletes, previous research has proposed a certainty-based diagnosis framework (i.e., possible, probable, and definite) for concussion based on clinical experience.[46] The present study builds on our prior work,[18] which aimed to develop a data-driven approach to quantifying these injury designations, paying particular attention to the subset of athletes whose injuries are most difficult to assess; that is, possible and probable concussions. Among this subgroup, clinicians should specifically direct their attention to post-traumatic migraine or cognitive-fatigue symptoms, as well as the SAC and BESS evaluations.

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Concussion Assessment, Research, and Education (CARE) Consortium Investigators

Scott Anderson, Holly J. Benjamin, M. Alison Brooks, Thomas Buckley, Kenneth Cameron, Darren E. Campbell, Sara P.D. Chrisman, James R. Clugston, Micky Collins, James T. Eckner, Carlos Estevez, Luis A. Feigenbaum, Joshua Goldman, Joseph B. Hazzard Jr, Megan Houston, April Marie (Reed) Hoy, Thomas W. Kaminski, Louise A. Kelly, Anthony P. Kontos, Laura Lintner, Christina L. Master, Gerald McGinty, Jason P. Mihalik, Christopher M. Miles, Nicholas Port, Steven Rowson, Julianne D. Schmidt, Adam J. Susmarski, and Christopher T Whitlow.

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Supplementary Material

Supplementary Text

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Address correspondence to:
Gian-Gabriel P. Garcia, PhD
MGH Institute for Technology Assessment
Harvard Medical School
Boston, MA 02114
USA

E-mail: ggarcia16@mgh.harvard.edu