Association of Concussion History with Neuromechanical Responsiveness Asymmetry

ABSTRACT

Context: Detection of subtle changes in brain sensorimotor processes may identify athletes who would derive greatest benefit from interventions designed to reduce risk for future injury and progressive neurological or musculoskeletal dysfunction.

Objective: To derive a generalizable statistical model for identification of athletes who possess subtle alterations in sensorimotor processes that may be due to previous concussion.

Design: Cross-sectional cohort study.

Setting: Residential Olympic training center sports medicine clinic.

Participants: A primary cohort of 35 elite athletes, along with a second cohort of 40 different elite athletes who performed identical tests the preceding year.

Interventions: Two upper extremity tests of visual-motor reaction time and two tests of whole-body reactive agility were administered. The whole-body tests required lateral or diagonal responses to virtual reality targets, which provided measures of reaction time, speed, acceleration, and deceleration.

Main Outcome Measure: Sport-related concussion history (SRC Hx), which was reported by 54% (19/35) of the athletes in the primary cohort and 45% (18/40) of the athletes in the second cohort.

Results: Univariable analyses identified 12 strong predictors of SRC Hx, which we combined to create a composite metric with maximum predictive value. Composite lateral asymmetry for whole-body reactive movements and persisting effects of previous musculoskeletal injury yielded a logistic regression model with exceptionally good discrimination (AUC=.845) and calibration (predicted-observed probabilities within 7 subgroups: r=.959; *P*=.001). Application of the derived model to compatible data acquired from another cohort of elite athletes demonstrated very good discrimination (AUC=.772) and calibration (within 8 subgroups: r=.849, *P*=.008).

Conclusions: Asymmetry in whole-body reactive movement capabilities may be a manifestation of a subtle abnormality in the functional connectivity of brain networks that might be relevant to previously reported associations between SRC Hx and musculoskeletal injury occurrence.

Key Words: Reactive Agility, Logistic Regression, Musculoskeletal Injury Risk

INTRODUCTION

Emerging evidence strongly suggests that sport-related concussion (SRC) can have long-term adverse effects on neurocognitive function.[1-4] Current clinical assessment methods do not appear to be sufficiently sensitive for detection of subtle changes in functional connectivity of brain networks that have been documented by advanced neuroimaging and neurophysiological tests.[5] A self-reported history of SRC (SRC Hx) has been associated with a 5-fold relative risk for subsequent SRC,[6] but exact neurophysiological mechanisms have not been elucidated. An increasingly recognized consequence of SRC is 2-3 times greater risk for musculoskeletal (MSK) injury,[7] which is independent of MSK injury history (MSK Hx).[8] Slowed information processing may represent an important long-term effect of SRC that interferes with efficient performance of visually guided motor actions.[8-12] Because abnormalities have been found to persist beyond resolution of overt signs and symptoms,[13] the availability of a clinical test that provides evidence of impaired visual-motor performance capabilities could prove to be valuable.

The term perception-action coupling refers to interdependencies between perceiving and acting within an environment that affords opportunities and imposes constraints.[10] Neuromechanical responsiveness specifically refers to the generation of forces to meet the demands of rapidly changing environmental challenges, which includes maintenance of dynamic joint stability during exposure to unexpected external forces.[14] Advanced neuroimaging methods have identified the tempero-parietal cortex of the right hemisphere as a key area for interpretation of visual inputs from both visual hemifields,[15] as well as kinesthetic inputs from both extremities.[16] Disruption of neural signaling from the right tempero-parietal cortex to the prefrontal cortex could result in diminished, inaccurate, or absent responses to salient visual stimuli,[17] thereby leading to suboptimal reactive capabilities.

Both upper extremity visual-motor reaction time (VMRT) and whole-body reactive agility (WBRA) test metrics have been shown to discriminate between elite athletes who self-report versus deny SRC Hx.[18] A 3-factor prediction model that included metrics relating to peripheral-to-central VMRT ratio, left-to-right VMRT difference, and WBRA lateral movement speed asymmetry provided 100% positive predictive value and 90% negative predictive value. Slow responsiveness to peripheral visual stimuli has been associated with disruption of white matter tracts in the corpus callosum, which may represent an indirect measure of the time required to transfer information between brain hemispheres.[19] Right hemisphere specialization for processing of visual-spatial information from both visual hemifields is responsible for asymmetrical responsiveness to visual stimuli that normally favors the left visual hemifield.[20] Disruption of attention network connectivity can produce neglect of stimuli in the left visual hemifield,[21,22] which provides a plausible explanation for an observed reversal of responsiveness asymmetry that favored the right visual hemifield among athletes with SRC Hx.[18]

Previous studies have demonstrated strong associations of dichotomized VMRT and WBRA metrics with both self-reported SRC Hx and subsequent musculoskeletal injury.[14,18,23] Dichotomous categorization of continuous variables is a very common predictive modeling procedure that provides an easily interpretable estimation of relative risk for a positive diagnostic or prognostic outcome.[24] Model calibration is arguably the most important property of a predictive model, which refers to estimation of an individual's absolute risk for a specified outcome.[25] Unfortunately, determination of an optimal cut point for maximum discriminatory power typically has poor generalizability beyond the cohort used to derive the model,[26] and calibration is rarely assessed and reported.[24,25,27] Feature engineering refers to a machine learning classification procedure that creates new predictive variables from an existing set to develop a model that is both simpler and more generalizable.[28] In comparison to machine learning, regression modeling reflects human domain knowledge in model specification, and there is no evidence that machine learning provides superior models.[27] Thus, the purpose of this study was to develop a simple, well-calibrated, and generalizable logistic regression model for clinical identification of elite athletes with neuromechanical performance deficiencies that could be due to persisting effects of a previous SRC.

METHODS

A cohort of 35 healthy elite athletes who were temporarily residing at an Olympic training center volunteered to respond to survey questions and to participate in tests of neuromechanical responsiveness (Table 1). The Institutional Review Board of the University of Tennessee at Chattanooga approved all study procedures, which included the informed consent of each participant. Surveys included the Sport Fitness Index,[29] which included questions about SRC Hx and MSK Hx, and the Depression, Anxiety, and Stress Survey.[30] The athletes performed 60-s VMRT tests involving manual contact with randomly illuminated buttons on a height-adjustable board (Dynavision D2™ System; Dynavision International; West Chester, OH), and WBRA tests requiring lateral or diagonal movements in response to the appearance of visual targets on a virtual reality display (TRAZER® Sports Stimulator; Traq Global Ltd; Westlake, OH).

Following a practice trial, each athlete performed two different versions of a 60-s VMRT dual-task test that included the Eriksen flanker test on a centrally located tachistoscope (>>>>>, <<<<<, >>><>>, or <<><<). One test required the athlete to identify the direction of the center arrow of 20 displays with verbal responses, whereas a second test used the center arrow direction as a cue for the correct direction of 48 manual responses to pairs of illuminated buttons in corresponding locations on opposite sides of the board. One WBRA test required the athlete to perform 20 lateral (Lat) movements in response to virtual reality targets that were randomly displayed on the right (10 targets) or left (10 targets) of a 48 cm X 86 cm monitor. Whole-body displacement of 1.8 m was required to deactivate the targets. A second WBRA test required the athlete to perform 16 diagonal (Diag) movements in combinations of right-left and forward-backward (Fo-Ba) directions, which required 2.5 m of displacement to deactivate the targets. Time elapsed between target appearance and 0.2 m of body core displacement defined reaction time (RT), which was averaged for the 10 trials in each direction. Other measures derived from the virtual reality motion analysis system included averaged values for speed (Spd), acceleration (Acc), and deceleration (Dec). Asymmetry (Asym) represents the absolute difference between performance values for opposite movement directions divided by the better of the 2 performance values (RT Asym, Spd Asym, Acc Asym, and Dec Asym).

Statistical Analysis and Model Development

Receiver operating characteristic (ROC) analysis quantified the association of each continuous variable with SRC Hx. Variables that demonstrated a clearly definable cut point on the ROC curve were converted into binary variables to perform cross-tabulation analysis and calculation of the odds ratio (OR). Each binary predictor that demonstrated an OR > 3 was entered as a continuous variable to assess its possible contribution a multivariable logistic regression to a model. A backward-entry stepwise procedure identified the simplest model with good discrimination and calibration. Entry of various combinations of the continuous variables continued until no improvement in model performance was apparent. Predicted probabilities assigned to the individual athletes were used to create 7 subgroups of equal size, which grouped them from lowest to highest probability for SRC Hx. Predicted probabilities were plotted against the observed prevalence of SRC Hx within the subgroups to provide a visual representation of internal model calibration,[24,31] and a bivariate correlation coefficient was calculated to quantify the relationship. To assess the generalizability of a derived model that included variables measured in an earlier study,[20] the logistic regression intercept and beta coefficients were used to calculate predicted probabilities for SRC Hx within a validation cohort of 40 elite athletes (Table 2). Model discrimination was considered very good if predicted probability for SRC Hx yielded an area under the curve (AUC) value > .75.[25] Assessment of external model calibration for the validation cohort of 40 athletes followed the same procedure used for internal model calibration, which involved creation of 8 subgroups of equal size. All analyses were performed with SPSS® version 25 (IBM Corporation; Armonk, NY).

RESULTS

Sport-related concussion occurrence at 4.6 ±5.3 years prior to testing (range: 3 months to 18 years) was reported by 54% (19/35) of the athletes in the derivation cohort. The number of previous SRCs ranged from 1 to 3, with 32% (6/19) reporting a single SRC and 68% (13/19) reporting 2 or 3 SRCs. Concussion occurrence within the previous 12 months was reported by 37% (7/19). Table 3 presents the results of univariable analyses, with variables ordered by magnitude of AUC. Asymmetry metrics for WBRA tests represented 10 of the 12 strongest associations, with the two strongest from the Lat test. Exploratory analyses identified a composite value derived from the average of RT Asym, Spd Asym, Acc Asym, and Dec Asym for the WBRA Lat test as providing the best single-factor prediction model (AUC=.760, 65.7% accuracy, Nagelkerke R^2=.310, and Hosmer and Lemehsow Goodness of Fit P=.728). Further exploratory analyses identified persisting effects of previous MSK Hx as an important covariate. A 6-level response option to the first question of the 10-item Sport Fitness Index rated the extent to which moderate-to-severe joint or muscle injuries have limited participation in sport-related activities over the past several years (persistent, frequent, occasional, infrequent, rare, or never). Although the total score derived from responses to all 10 items was a strong predictor of SRC Hx, the response to the first item improved logistic regression model performance to the greatest extent. The addition of MSK Hx as a covariate with Composite Lat Asym provided a substantially improved model (AUC=.845, 77.1% accuracy, Nagelkerke R^2=.485, and Hosmer and Lemehsow Goodness of Fit *P*=.994).

Because WBRA Lat test data and Sport Fitness Index responses were available from a previous study,[18] the 2-factor logistic regression model intercept (0.07) and beta coefficients for Composite Lat Asym (20.33) and MSK Hx (-0.98) were used to calculate predicted probabilities for 40 athletes who were not among those who comprised the model derivation cohort. Sport-related concussion occurrence at 2.2 ±2.4 years prior to testing (range: 1 months to 7 years) was reported by 45% (18/40) of the athletes in the model validation cohort. The number of previous SRCs ranged from 1 to 8, with 39% (7/18) reporting a single SRC and 61% (11/18) reporting 2 or more SRCs. Concussion occurrence within the previous 12 months was reported by 56% (10/18).

Discrimination provided by the calculated probabilities was very good (AUC=.772; 75.0% classification accuracy). Figure 1 presents calibration plots for both the model derivation cohort (r=.959; *P*=.001; intercept=.001; beta=.999) and the model validation cohort (r=.849; P=.008; intercept=.115; beta=.881). Figure 2 provides a comparison of ROC curves derived from application of the same logistic regression model for calculation of SRC Hx probability for individual athletes in both cohorts. Table 4 presents a comparison of prediction accuracy for Composite Lat Asym cut points of ≥ 10% and ≥ 15%, without consideration of MSK Hx. To illustrate the practical implications of the study findings, ROC analysis was used to define optimal cut points for Composite Lat Asym (≥ 18% vs. < 18%) and MSK Hx (Adverse: persistent, frequent, or occasional response vs. Favorable: infrequent, rare, or never response) for the combined cohorts (n=83). Figure 3 depicts the prevalence of SRC Hx for combinations of the binary classifications of Composite Lat Asym and MSK Hx.

DISCUSSION

The combination of WBRA asymmetry and self-reported persisting effects of previous MSK injury demonstrated a strong association with SRC Hx. Our findings are consistent with those reported by other investigators who used virtual reality and motion tracking to detect an effect of SRC on the whole-body movement capabilities of athletes.[12,32] Slowing of neural processing speed is a well-documented long-term effect of SRC, which almost certainly affects visually guided movements that required integration of cognitive and motor processes.[11] Because the volume and spatial distribution of white matter is not symmetrical between brain hemispheres, diffuse axon injury could logically be expected to slow neural processing to a greater extent in one hemisphere compared to the other. This study identified the same ≥ 15 ms cut point for dual-task VMRT right – left difference reported previously,[18] but the strength of association did not meet the OR ≥ 3.0 criterion used to identify the set of strongest predictors.

The combination of WBRA values for RT Asym, SpdAsym, AccAsym, and DecAsym to create the continuous Composite Lat Asym variable appears to have provided ≥ 10% and ≥ 15% binary classifications with good generalizability for different cohorts.[26] Cut points differed substantially between the derivation and validation cohorts for separate analyses of the Lat WBRA metrics (RT Asym ≥ 30% vs. ≥ 23%, Spd Asym ≥ 10% vs. ≥ 8%, Acc Asym ≥ 12% vs. ≥ 3%, Dec Asym

≥ 14% vs. ≥ 22%). We derived the Composite Lat Asym cut point ≥ 18% from ROC analysis of continuous data for the combined cohorts to simplify test result interpretation. In contrast to the combination of WBRA metrics to create a composite variable, deconstruction of the Sport Fitness Index score to consider only its most discriminating item identified an important secondary factor that substantially improved model discrimination and calibration.

Previous literature pertaining to functional asymmetry has focused on differing lower extremity performance capabilities represented as non-dominant-to-dominant, injured-to-uninjured, or left-to-right ratios.[33,34] Although bilateral differences in isolated measures of strength, power, postural balance, gait, jump landing, and hopping appear to be important injury risk factors, measures of dynamic whole-body activity reflect complex sensorimotor integration that controls inter-limb coordination.[35] The observed WBRA asymmetry do not simply represent a bilateral difference in extremity performance capabilities, because both extremities contribute to the whole-body displacements in both lateral movement directions. For example, deactivation of a right-side target typically involves a left extremity push-off, a right extremity landing, a left extremity landing with push-off, and a right extremity landing for reversal of motion back toward the center starting position.

Persisting effects of prior MSK injury, such as joint laxity, muscle weakness, loss of proprioceptive afference, and restricted range of motion, could certainly contribute to asymmetrical whole-body movement capabilities. Thus, the WBRA asymmetry we observed may have been due to persisting effects of MSK injury, persisting effects of SRC, or a combination of both factors. Among athletes who exhibited a composite lateral movement asymmetry < 18% and who reported a favorable MSK Hx, the prevalence of SRC Hx was only 16.7% (6/32). Among those who exhibited ≥ 18% asymmetry and who reported a favorable

MSK Hx, the prevalence of SRC Hx was 91.7% (10/11). Among those who exhibited ≥ 18% asymmetry and who reported an adverse MSK Hx, the prevalence of SRC Hx was 100% (6/6). The cross-sectional design of this study did not allow for determination of the temporal order of previous SRC and MSK injury occurrences, but our analysis results suggest that either type of injury may be responsible for asymmetrical lateral movement capabilities. Despite the possible confounding effect of MSK Hx, composite WBRA asymmetry for lateral movements appears to have very good discriminatory value for identification of SRC Hx cases at asymmetry thresholds of 10% and 15% (Table 4).

The relatively small size of both the derivation and validation cohorts represents an important limitation, along with an insufficient number of female athletes for conclusive determination of an effect of sex on the measures. Reliance on athlete self-report of SRC Hx can be viewed as a limitation, but the strength of the association might have been equal or greater if a definitive record of past injuries had been available. Another limitation is lack of published data validating WBRA measures derived from the Kinect™ depth camera (Microsoft; Redmond, WA), which is a component of the virtual reality motion tracking system. However, the Kinect™ depth camera has been shown to provide 3-D coordinate measurements within 3 m at a level of accuracy comparable to that for measurements derived from a multiple-camera system for locating reflective markers.[36,37]

Unpublished data analyzed by the lead author of this report were recently acquired to assess test-retest reliability for 3 WBRA test sessions separated by 24 hours (Briles, Johnson, Hogg, et al.; report available at: https://www.utc.edu/graduate-athletic-training/pdfs/research/2019/trazer-validity-reliability.pdf). Eighteen college-age participants completed a total of 40 movement patterns per test session (5 each for forward, backward, right, left, forward-right, forward-left, backward-right, and backward-left). Intraclass correlation coefficients were .536 for RT, .847 for Spd, .919 for Acc, and .948 for Dec. The available evidence supports the validity and reliability of our WBRA measurements, but more research is needed to confirm that they are sufficiently precise for use as clinical indicators of impaired neural processing and elevated injury risk.

The long-term effect of SRC on visually guided motor actions may be an overlooked phenomenon that interferes with proper execution of complex movements.[8-12] Because SRC Hx appears to have a profound effect on risk for subsequent SRC,[6] as well as risk for MSK injury,[7,8] assessment and training of neuromechanical responsiveness may prove to be an important advance in the prevention of sports injuries. Future research involving advanced neuroimaging and electrophysiological methods might identify neural correlates of whole-body performance asymmetries, which would provide a means to assess the potential for neuroplastic adaptations to specific training protocols.

CONCLUSIONS

Our finding of a strong association between WBRA asymmetry and self-reported SRC Hx suggests that a subtle cognitive-motor impairment may persist long after complete resolution of overt signs and symptoms, which may elevate risk for a future injury. Persisting effects of previous MSK injury may explain WBRA asymmetry in the absence of SRC Hx, or SRC Hx and previous MSK injury may have an interactive effect. Our model demonstrated very good calibration and strong discriminatory power for both the derivation and validation cohorts, which support its potential use for identification of individual athletes who are most likely to derive greatest benefit from a targeted training intervention for improvement of whole-body reactive movement capabilities.

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Table 1. Characteristics of Model Derivation Cohort (N=35)

	Concussion History			No Concussion History		
N	19			16		
Age (years)	26.1 (18-34)			25.1 (18-35)		
	Male	Female		Male	Female	
Sex	10 (53%)	9 (47%)		10 (62%)	6 (38%)	
Height (cm)	176.0 ±10.8	162.6 ±6.0		175.0 ±8.8	167.6 ±4.8	
Mass (kg)	81.1 ±10.4	58.7 ±8.2		71.4 ±8.7	63.1 ±9.5	
	Right	Left	Neither	Right	Left	Neither
Hand Dominance	15	3	1	13	3	0
Sport Type:						
Bobsled/Skeleton	4			1		
Boxing	0			4		
Figure Skating	3			3		
Gymnastics	2			2		
Wrestling	9			4		
Modern Pentathlon	1			2		
Sport Fitness Index	67.0 (34-90)			75.4 (40-98)		
Depression, Anxiety, & Stress Scale	13.8 (0-44)			14.4 (2-48)		

Table 2. Characteristics of Model Validation Cohort (N=40)

	Concussion History			No Concussion History		
N	18			22		
Age (years)	25.3 (19-34)			23.0 (18-33)		
	Male		Female	Male		Female
Sex	11 (61%)		7 (39%)	17 (77%)		5 (23%)
Height (cm)	176.9 ±6.6		167.6 ±8.4	180.9 ±9.6		169.9 ±10.5
Mass (kg)	86.5 ±18.1		64.0 ±11.2	78.6 ±17.8		69.4 ±15.3
	Right	Left	Neither	Right	Left	Neither
Hand Dominance	17	0	1	17	4	1
Sport Type:						
Bobsled/Skeleton	4			2		
Boxing	0			6		
Figure Skating	3			4		
Gymnastics	1			1		
Wrestling	9			4		
Multi-Event*	1			5		
Sport Fitness Index	55.4 (30-94)			66.2 (24-98)		
Depression, Anxiety, & Stress Scale	12.4 (0-38)			11.9 (0-37)		

* Multi-Event includes Modern Pentathlon, Track & Field, Triathlon, and Weightlifting

Table 3. Results of Univariable Analyses

Variable	AUC	Cut point	*P*	PPV	NPV	+LR	−LR	OR	(90% CI)
WB Lat Acc Asym	.740	≥ .12	.012	77%	67%	2.74	0.42	6.50	(1.86, 22.67)
WB Lat RT Asym	.738	≥ .30	.031	72%	65%	2.19	0.46	4.77	(1.43, 15.87)
WB D/B Dec Asym	.717	≥ .24	.003	100%	59%	14.45*	0.58	24.39*	(2.05, ∞)*
WB D/F Dec Asym	.671	≥ .13	.034	70%	67%	1.97	0.42	4.67	(1.40, 15.60)
Sport Fitness Index	.666	≤ 64	.053	73%	59%	2.34	0.59	3.97	(1.20, 13.14)
WB D/B Spd Asym	.605	≥ .16	.037	88%	56%	5.90	0.67	8.75	(1.35, 56.79)
WB Lat Spd Asym	.602	≥ .10	.021	79%	62%	3.09	0.52	5.96	(1.62, 21.90)
WB D/F RT Asym	.566	≥ .08	.056	62%	83%	1.38	0.17	8.18	(1.21, 55.18)
WB Lat RT Avg	.561	≥ 460 ms	.037	88%	56%	5.90	0.67	8.75	(1.35, 56.79)
WB D/B Acc Asym	.559	≥ .21	.132	73%	54%	2.25	0.71	3.15	(0.86, 11.58)
WB D/B RT Asym	.549	≥ .75	.131	83%	52%	4.21	0.79	5.36	(0.80, 35.91)
WB Lat Dec Asym	.520	≥ .14	.104	79%	54%	2.95	0.72	4.08	(0.94, 17.74)

AUC: Area Under Curve; *P*: Fishers Exact Test One-Sided *P*-Value; PPV: Positive Predictive Value; NPV: Negative Predictive Value; +LR: Positive Likelihood Ratio; −LR: Negative Likelihood Ratio; OR: Odds Ratio; CI: Confidence Interval

WB: Whole-Body; D/B: Diagonal/Backward; D/B: Diagonal/Forward; Acc: Acceleration; Dec: Deceleration; RT: Reaction Time; Spd: Speed; Asym: Asymmetry; Avg: Average

* Values estimated by adding 0.5 to each 2 X 2 cell to eliminate division by zero

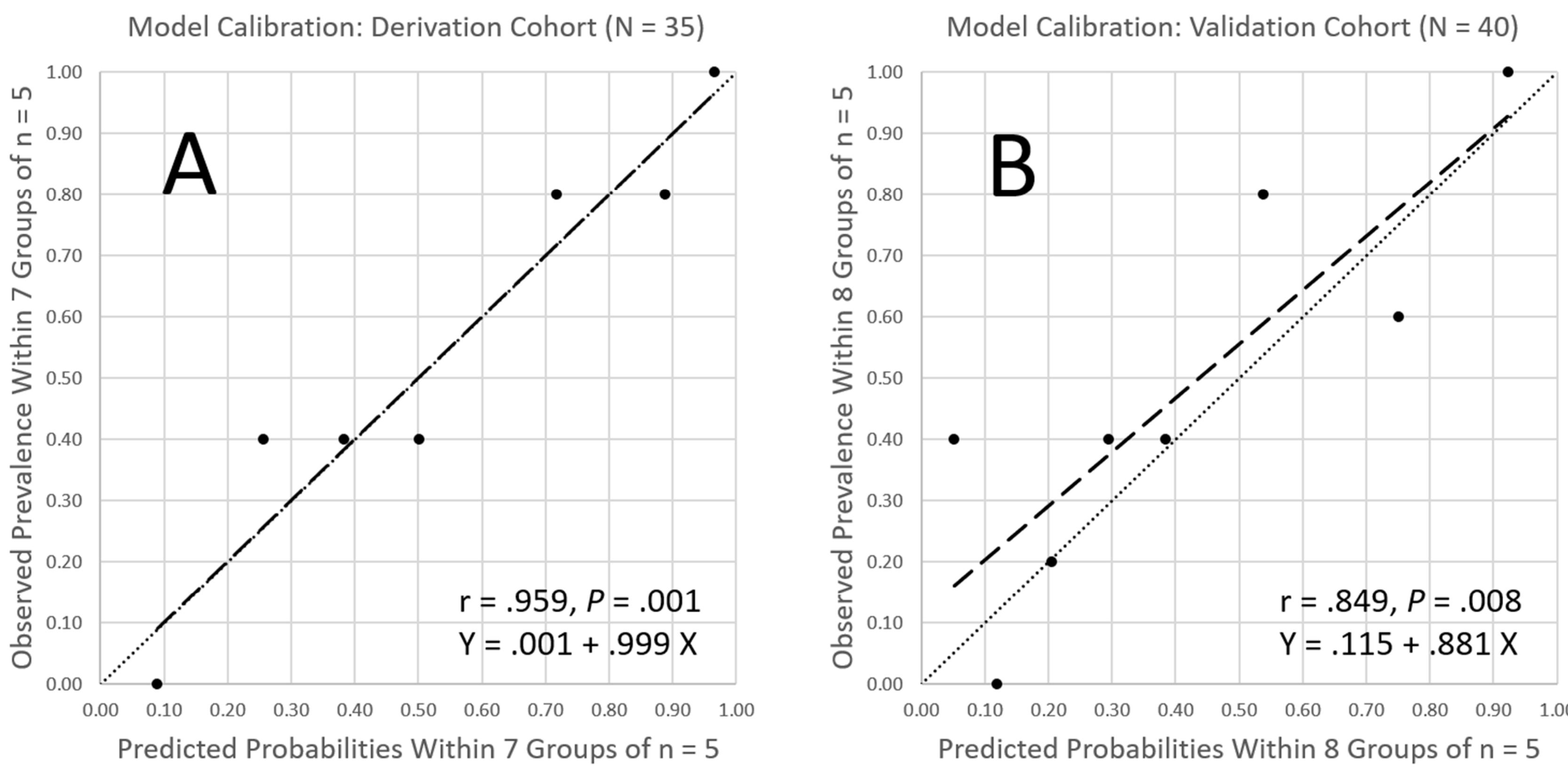

Figure 1. Logistic regression model predicted probabilities versus observed prevalence of sport-related concussion history within subgroups of equal size: A. Derivation cohort of 35 elite athletes. B. Validation cohort of 40 elite athletes.

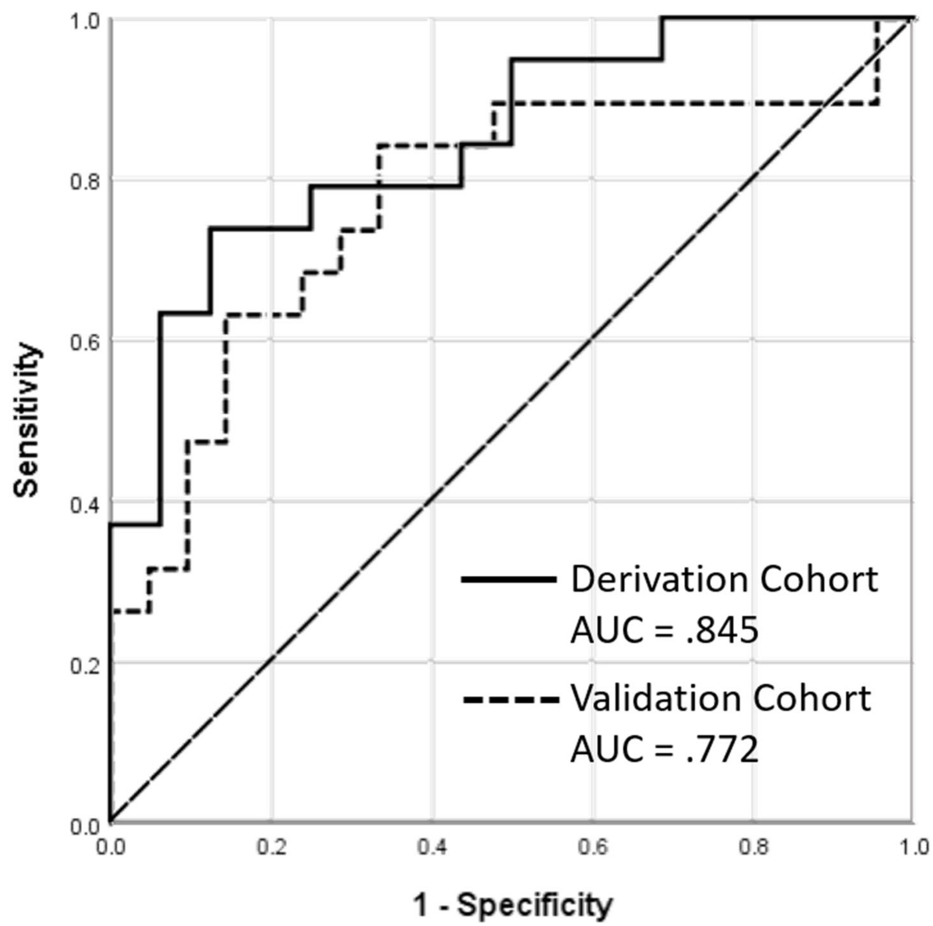

Figure 2. Receiver operating characteristic curve for logistic regression model predicted probability of SRC Hx within model derivation cohort (solid line) and model validation cohort (dashed line).

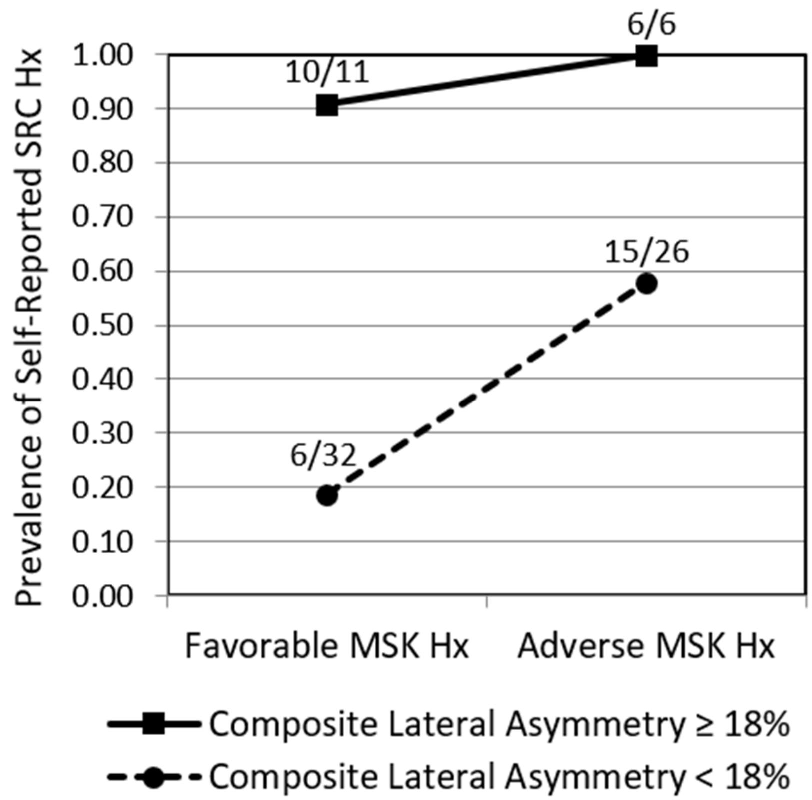

Figure 3. Prevalence of sport-related concussion history (SRC Hx) for combinations of binary classifications of WBRA Composite Lateral Asymmetry (< 18% versus ≥ 18%) and persisting effects of musculoskeletal injury history (Favorable MSK Hx versus Adverse MSK Hx).

Table 4. Identification of Sport-Related Concussion Cases by Lateral Whole-Body Reactive Agility Composite Asymmetry for Reaction Time, Speed, Acceleration, and Deceleration

Asymmetry	Cohort*	*P*	PPV	NPV	+LR	−LR	OR	(90% CI)
≥ 10%	Derivation	.074	64%	70%	1.50	0.36	4.15	(1.10, 15.62)
	Validation	.054	62%	68%	1.80	0.51	3.52	(1.17, 10.56)
≥ 15%	Derivation	.031	72%	65%	2.19	0.46	4.77	(1.43, 15.87)
	Validation	.089	75%	59%	3.32	0.76	4.39	(1.01, 19.03)

P: Fishers Exact Test One-Sided *P*-Value; PPV: Positive Predictive Value; NPV: Negative Predictive Value; +LR: Positive Likelihood Ratio; −LR: Negative Likelihood Ratio; OR: Odds Ratio; CI: Confidence Interval

* Sport-Related Concussion Prevalence: Derivation Cohort 54.3% (19/35); Validation Cohort 47.5% (19/40)