Validation of Visual Objective Biomarkers for Acute Concussion

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ABSTRACT Objective: Despite an increase in the awareness and diagnosis of mild traumatic brain injury (mTBI), there remains a paucity of data examining the comparative efficacy of available assessments. This study aims to validate visual functions as potential biomarkers for mTBI. Methods: This case–control correlational design utilizes military personnel diagnosed with acute (≤72 h post-injury) mTBI (n = 100) and age-matched controls (n = 100) to examine the relative effectiveness of the pupillary light reflex (PLR), near point of convergence (NPC) break, King-Devick (KD) test time, and Convergence Insufficiency Symptom Survey (CISS) score to discriminate between participants with mTBI. Results: Three of the eight PLR parameters (i.e., average constriction velocity (ACV), average dilation velocity (ADV), and 75% re-dilation time; all $p < 0.001$) were affected in mTBI participants. Similarly, NPC break, KD test time, and CISS scores showed a statistically significant difference between groups (all $p < 0.001$). Area under the curve showed that ADV (0.82) and NPC (0.74) have the higher predictive values of all objective parameters. Conclusions: ADV, ACV, and NPC break are objective visual functions markedly affected in the acute mTBI group compared with controls; therefore, we proposed that they could be used as biomarkers for acute mTBI.

INTRODUCTION

Traumatic brain injury (TBI) is a significant public health issue in the United States. The Department of Defense reported 370,688 cases of clinically confirmed TBI from 2000 to the second quarter of 2017, with mild TBI (mTBI) accounting for 82.3% of all cases.[1] Similarly, the Centers for Disease Control and Prevention reported that TBI affects approximately 1.7 million people in the United States annually.[2] The total combined rates of TBI-related hospitalizations, emergency department visits, and deaths climbed from a rate of 521.0 per 100,000 in 2001 to a rate of 823.7 per 100,000 in 2010, with mTBI accounting for at least 75% of all TBIs in the United States.[3,4] Unfortunately, mTBI continues to be a perennial challenge for the medical community primarily due to the lack of objective assessment tools.[5] This challenge makes elucidating objective biomarkers of mTBI a top priority not only for providers but also for the patients they treat.[5,6] Valid and objective biomarkers of acute mTBI are of particular importance in forward deployed situations for military clinicians to make accurate and immediate determination of return to duty (RTD) or evacuation for further evaluation.[7]

There is increasing evidence that mTBI triggers complex biological changes including neuronal, inflammatory, metabolic, vascular, and axonal abnormalities. Therefore, molecular biomarkers in blood, saliva, and urine as well as vascular and structural imaging (e.g., diffuse tensor imaging, transcranial Doppler, hemodynamic vascular analysis, transcranial ultrasound shear mode and C-scan, and near-infrared imaging) can be potential objective biomarkers to accurately identify and monitor mTBI recovery.[6,8,9]

Similarly, visual processing and eye movements are frequently affected by mTBI. Common problems among patients presenting with mTBI include pupillary response deficit, visual processing delays (poor attention to detail, poor visual attention, and poor visual memory), photosensitivity, impaired oculomotor convergence (difficulty focusing on nearby objects or images), and related oculomotor-based reading dysfunctions. Given that approximately 30 areas of the brain and 7 of the 12 cranial nerves are utilized by the visual system, it is not unexpected that the patient with an injury to the brain typically presents with a variety of visual problems. Sensory stimuli from the retinas are primarily routed to the visual cortex with numerous connections in disparate areas among the frontal, parietal, and temporal lobes.[10] The functional integrity of connections between these areas is vital for proper eye movement function and demonstrates the fragility of the visual system. Pathology at any point in the network risks disrupting the functional pathway, thus producing errors or degrading performance.[11] Therefore, tests involving the visual system are well suited for detecting the neurophysiological effects of brain injury.[12]

The assessment of a patient's pupillary light reflex (PLR) is a long established and heavily relied upon indicator of

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neurological function in severely brain-injured patients.[13] The PLR refers to the involuntary response of the pupil that is evoked by an increase in illumination of the retina. The PLR, however, is unique in that it is not under volitional control and therefore is unaffected by the motivation, effort, or bias from either the patient or the provider.

Initial studies in patients with repeated blast exposure have demonstrated the potential application of the PLR as an objective indicator and potential to aide in the diagnosis of mTBI. Advances in technology have significantly improved the accuracy and repeatability of automated infrared pupillometry allowing for more precise quantification of pupil dynamics.[14–16] Two recently published studies evaluated PLR with a handheld monocular pupillometer, NeurOptics PLR-200, as a potential objective test for subacute and chronic mTBI/concussions.[17,18] Both studies showed significant differences between the control and mTBI groups on some of the eight data measurements provided by the pupillometer in relative small populations.

Due to the diffuse nature of typical mTBIs, a wide range of vergence dysfunctions often manifest during the acute phase of injury.[19] Another assessment used to evaluate potential brain trauma has been the presence of convergence insufficiency (CI). Neurological damage to the system that controls the muscles of the eyes may cause the image to fall on disparate locations on the retina; this may manifest as blurred vision, double vision, fatigue, difficulty reading, or headaches. In multiple studies, CI has been shown to be commonly associated with brain injury.[20–22] Convergence insufficiency is characterized by a receded near point of convergence (NPC). An NPC break beyond 10 cm is considered receded and indicative of convergence dysfunction.[23] In addition to physical observation of CI, surveys have been developed for patient self-assessment of symptoms. The Convergence Insufficiency Symptom Survey (CISS) is a commonly used assessment for symptoms related to mTBI. The CISS has been validated and standardized for use in randomized clinical trials to subjectively measure the recovery of near-vision symptoms in adults.[20,24,25]

Lastly, tests involving the visual system that probe saccades and higher cortical functioning are well suited for detecting the neurophysiological effects of brain injury.[12] Saccades refer to the quick, simultaneous movements of both eyes between two phases of fixation in the same direction. Among the more prominent and established assessments used in cases of suspected head trauma is the King-Devick (KD) test.[26] The KD test is designed to assess an individual's saccades and has demonstrated consistently high levels of test–retest reliability.[26–28] King-Devick test is subjective in nature; however, it has proven effective in identifying acute concussive athletes on the sidelines when compared with pre-injury baseline data.

The purpose of the present study is to validate PLR parameters and NPC break as objective biomarkers for acute mTBI and to use them in combination with the KD test time and CISS score to increase their predictive power.

METHODS

Subjects

Two hundred active duty service members seeking care at Womack Army Medical Center (WAMC) in Fort Bragg, NC, were included in this study. One hundred participants with acute mTBI (≤72 h post-injury) were recruited at the Department of Brain Injury Medicine's Concussion Care Clinic and 100 age-matched controls were recruited while receiving routine care at the Department of Optometry. The diagnosis of mTBI was made by primary care providers based on the following criteria: loss of consciousness of no more than 30 min, post-traumatic amnesia of no more than 24 h, any alteration of mental state, a Glasgow Coma Scale score from 13 to 15, and normal structural brain imaging. The study was approved by WAMC Institutional Review Board and the Human Research Protection Office of the US Army Medical Research and Materiel Command. Each subject provided written informed consent before participating in the study.

Pupillary Light Reflex

The PLR functions were measured with the NeuroOptics PLR-200 infrared pupillometer (Fig. 1) as previously described.[17] PLR was assessed under binocular conditions with dim illumination (~3 cd/m^2) while the subject fixated with the non-tested eye on a high-contrast target located at 3 m to avoid changes in pupil size due to accommodation. The PLR was recorded twice in each eye, alternating between eyes with an interval of no less than 45 s between the recordings. Table I shows the eight PLR variables measured with the pupillometer: (1) maximum diameter, (2) minimum diameter, (3) percent constriction, (4) constriction latency, (5) average constriction velocity (ACV), (6) maximum constriction velocity, (7) average dilation velocity (ADV), and (8) 75% re-dilation recovery time (T75). PLR administration took approximately 5 s per eye.

Near Point of Convergence

The objective break in NPC was measured using the Royal Air Force near point rule (Fig. 2). The Royal Air Force rule consists of a 50-cm long ruler with a slider holding a rotating four-sided rectangle. The test was administered in a well-lit room and participants were instructed to focus on a single high-contrast 20/30 size letter target. The examiner moved the slider with the accommodative target toward the subject's eyes and stopped when one of the eyes deviated out. If neither eye deviated, the NPC value was reported as "5" cm, which reflects the minimum value on the convergence rule. The distance (in cm) at which the eye deviated was recorded by noting the distance listed on the ruler. The break in NPC was measured twice with a 5-min interval between test administrations. Each NPC measure took approximately 10 s.

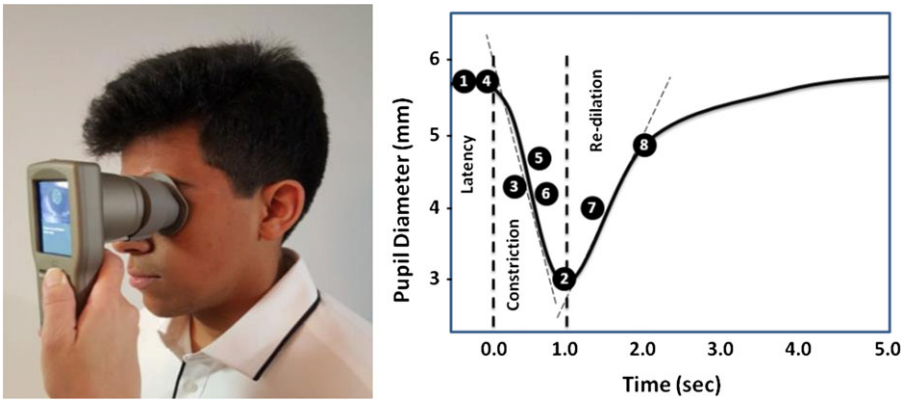

FIGURE 1. Left, demonstration of pupil assessment with PLR (pupillary light reflex)-200 monocular pupillometer. Right, schematic diagram of the typical pupillary reaction curve illustrating PLR-recorded parameters: (1) maximum diameter, (2) minimum diameter, (3) percent of constriction, (4) constriction latency, (5) average constriction velocity, (6) maximum constriction velocity, (7) average dilation velocity, (8) 75% recovery time.

TABLE I. Summary of Objective and Subjective Visual Functions Assessed in the Current Study

Objective Visual Functions				
Visual Function and Measure	Abbreviation	Unit	Instrument	Administration Time
Pupillary light reflex	PLR	—	PLR-200®	10 s
Maximum diameter	MAX	mm		
Minimum diameter	MIN	mm		
Percent constriction	CON%	%		
Constriction latency	LAT	ms		
Average constriction velocity	ACV	mm/s		
Maximum constriction velocity	MCV	mm/s		
Average dilation velocity	ADV	mm/s		
75% Recovery time	T75	s		
Convergence eye movement				
Near point of convergence break	NPC break	cm	Royal Air Force Rule	10 s
Subjective Visual Functions				
Measure	Abbreviation	Unit	Instrument	Administration Time
Saccadic eye movement				
King-Devick test time	KD test	s	KD Test	40–120 s
Visual symptoms				
Convergence Insufficiency Symptom Survey Score	CISS Score	—	CISS	60–120 s Total time = 120–260 s

King-Devick Test

The KD test was used to evaluate saccadic eye movement performance. The KD test involves reading aloud a series of single-digit numbers from left to right on three test cards (Figure 3). Standardized instructions provided with the instrument were used, and testing was administered in a well-lit room at approximately a 40 cm reading distance. The participants were instructed to read the numbers aloud as fast as possible without making errors. If errors were made, the subject returned to correct the errors. The participants were instructed not to use their fingers on the card to assist during the testing. The cumulative time to read the three test cards were measured by the examiner using a stopwatch. The test was administered twice with a 5-min interval between test administrations. King-Devick administration took between 40 and 120 s.

FIGURE 2. Royal Air Force near point rule.

Convergence Insufficiency Symptoms Survey

The 15-question Convergence Insufficiency Symptoms Survey (CISS) was used to document symptoms associated

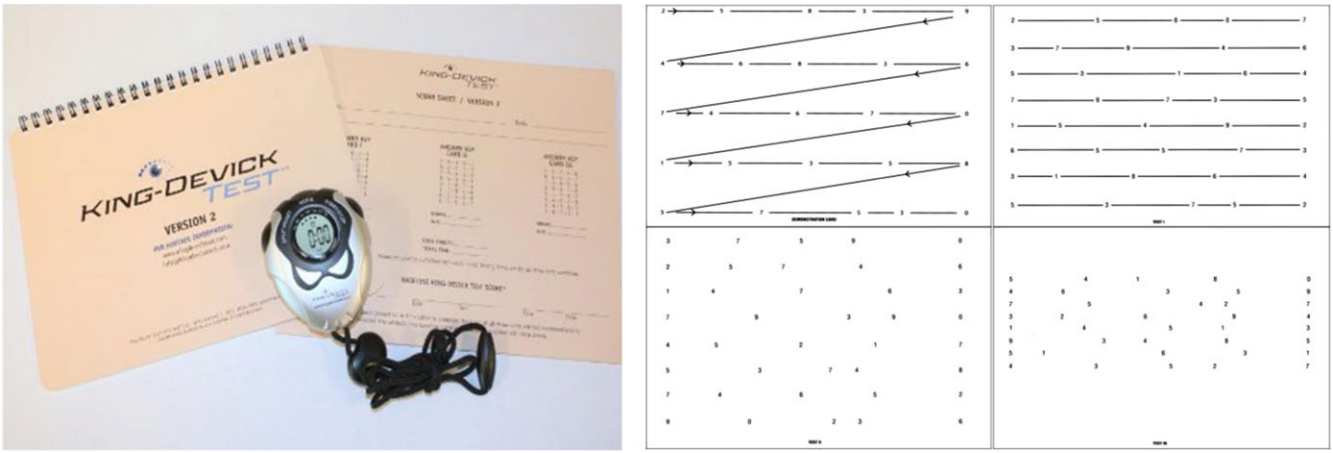

FIGURE 3. Left, King-Devick Test. Right, top left, Demo card; top right Test 1 card; lower left, Test 2 card; lower right, Test 3 card.

with near-visual tasks. Participants were asked to rate the 15-symptom questions on a 5-point Likert-type scale. Each symptom question had five possible answers with an associated value, where 4 = always, 3 = frequently, 2 = sometimes, 1 = rarely, and 0 = never. Thus, the cumulative symptoms score can vary from 0 to 60. A healthy adult should score <21 points. The survey was completed only once and there was no time limit for this activity. PLR administration took between 60 and 120 s.

Statistical Analysis

Demographic data, clinical characteristics, and assessment outcomes were assessed for normality using the Shapiro–Wilk test. The Kruskal–Wallis test was used to check for underlying demographic and clinical differences between the two groups as well as between the first and second trial. To assess the data for fatigue effects due to three assessments (PLR, NPC, and KD test) being conducted twice for each participant, Wilcoxon signed rank tests were used to examine the significance of any differences between the first and second trial.

Receiver operating characteristic (ROC) curves were used to investigate the relationship between diagnostic sensitivity and specificity for two significant PLR parameters (ACV and ADV), NPC break, KD test time, and CISS score. The area under the curve (AUC) was calculated for all significant objective and subjective predictors. Selecting instruments with an area AUC > 0.60, a logistic regression analysis was performed. Based on the ROC AUC analysis, optimal cutoff values were determined for each significant predictor. Finally, a second regression analysis was performed using the identified cutoff values as predictors to determine the overall discriminate efficacy.

All data were analyzed by using IBM SPSS version 20 (IBM Corporation, Armonk NY, USA) and GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA). p-Values <0.05 were considered statistically significant. No cases with missing data were included in the analysis.

RESULTS

Demographics and Mechanisms of Injury

A total of 224 patients were recruited for participation. Twenty-four participants were excluded from the acute-phase mTBI group due to missing data. Consequently, 200 patients were included in the analyses and comprised the study sample of 100 participants with acute-phase mTBI and 100 age-matched controls.

Demographic information of both groups is shown in Table II. Data were included from 100 service members with acute mTBI (87 males and 13 females) and 100 age-matched controls (79 males and 21 females). The mean age was 26 ± 6 yr and ranged from 19 to 44 yr of age. No significant differences were found between the mTBI group and the age-matched controls on the basis of sex ($p = 0.13$) or race/ethnicity ($p = 0.70$). There was a significant difference in rank between the two groups ($p < 0.001$) with the mTBI group containing fewer officers than were present in the control group. Additionally, differences were observed in the distribution of eye color ($p = 0.01$). The mTBI group contained fewer individuals with blue eyes than were present in the control group. Neither of these was considered to be a relevant factor relating to mTBI and thus neither was included as a predictor in later regression analyses.

To qualify for participation individuals in the mTBI group must have been in the acute phase of injury (≤72 h post-injury). Thirty-one percent of the mTBI group presented to the clinic within 24 h, 40% presented within 48 h, and 29% presented within 72 h. The most common mechanism of injury was airborne-training activities (jump), 69%. The remaining injuries were attributed to fall (7%), motor vehicle accident (6%), other (6%), blunt force (5%), sports/recreation (5%), and combative training (2%).

Among the mTBI group, current medications were evaluated for potential confounding effects on pupillary dynamics. Of specific interest were mydriatic drugs and amphetamines, which may artificially dilate the pupils, anticholinergics that

may impede normal constriction and dilation, and opiates that may lead to artificial pupillary miosis (constriction). None of the medications prescribed to the participants in the mTBI group were considered to potentially affect the PLR measures. The most common medication used by participants was acetaminophen ($n = 26$) followed by ibuprofen ($n = 25$).

To further confirm that undisclosed medications were not significantly affecting pupillary dynamics in the either group, the latency and maximum pupillary dilations were examined.

TABLE II. Participant Demographics and Characteristics

Characteristic	Control, *n* (%)	mTBI, *n* (%)	*p*-Value
Age (yr)			
18-22	29 (50.0)	29 (50.0)	1.00
23-27	40 (50.0)	40 (50.0)	
28-32	17 (50.0)	17 (50.0)	
33+	14 (50.0)	14 (50.0)	
Sex			
Male	79 (47.6)	87 (52.4)	0.13
Female	21 (61.8)	13 (38.2)	
Race/ethnicity			
White	58 (49.2)	60 (50.8)	0.70
Black	18 (56.2)	14 (43.8)	
Hispanic	13 (48.1)	14 (51.9)	
Asian	6 (66.7)	3 (33.3)	
Other	5 (35.7)	9 (64.3)	
Rank			
Junior Enlisted (E1–E3)	25 (58.1)	18 (41.9)	<0.001[a]
NCO (E4–E8)	50 (40.3)	74 (59.7)	
Officer (O1–O5)	25 (75.8)	8 (24.2)	
Eye color			
Light brown	9 (45.0)	11 (55.0)	0.01[a]
Brown	47 (43.1)	62 (56.9)	
Green	11 (52.4)	10 (47.6)	
Blue	33 (66.0)	17 (34.0)	

[a]Statistically significant ($p \leq 0.05$).

The mean latency between light stimulus and pupillary constriction was 215.85 ± 22.17 ms for the right eye and 213.80 ± 22.45 ms for the left eye as measured by the PLR-200. These results were in accordance with previous research,[29,30] which indicates that latencies between 200 and 450 ms are indicative of normal pupillary function. To confirm age-related decline in pupil size, Spearman correlations were produced for age and maximum pupil diameter. Both the right and the left eyes were significantly correlated with age ($r = -0.31$, $n = 100$, $p = 0.002$; and $r = -0.38$, $n = 100$, $p < 0.001$, respectively).[29,30]

Pupillary Light Reflex

There was no statistically significant difference (all $p > 0.05$) for any of the PLR parameters between the right and the left eye nor between trials. Therefore, PLR data from trial 1 and 2 for the right and left eye were combined for further between-group comparison. Results indicate that three of the eight PLR parameters are suited to objectively differentiate between normal and mTBI participants (Table III). The ACV and ADV were slower in the mTBI group ($p < 0.001$, $\eta^2 = 0.07$; and $p < 0.001$, $\eta^2 = 0.30$, respectively). In addition, it took longer for pupils to reach 75% of prestimulated size (i.e., T75) among the acute mTBI group compared with controls, $p < 0.001$, $\eta^2 = 0.30$.

Near Point of Convergence

The mean NPC break for the acute mTBI and the control groups was 13.25 ± 8.07 cm and 8.18 ± 2.15 cm, respectively. Statistically significant results indicate that the acute mTBI group had receded NPC compared with controls, $p < 0.001$ (Table IV). Based on the guideline that scores greater than 10 cm indicate receded convergence, the sensitivity and specificity of the NPC break were 0.81 and 0.49, respectively. This indicates a high number of false positives (51%).

TABLE III. Summary Statistics for PLR Parameters[a]

Variable Group		*N*	Mean	Standard Deviation	95% Confidence Interval		*p*-Value
					Lower Bound	Upper Bound	
Maximum diameter (mm)	Control	100	5.97	0.73	5.83	6.12	0.14
	mTBI	100	5.74	0.97	5.56	5.94	
Minimum diameter (mm)	Control	100	4.00	0.61	3.89	4.13	0.19
	mTBI	100	3.87	0.64	3.73	4.03	
Percent constriction (%)	Control	100	33.19	3.87	32.40	33.98	0.45
	mTBI	100	32.69	4.54	31.79	33.57	
Constriction latency (ms)	Control	100	218.93	18.00	215.50	222.61	0.18
	mTBI	100	214.83	19.56	211.08	218.61	
Average constriction velocity (mm/s)	Control	100	4.05	0.53	3.95	4.16	<0.001[b]
	mTBI	100	3.65	0.76	3.50	3.81	
Maximum constriction velocity (mm/s)	Control	100	5.31	0.67	5.18	5.46	0.69
	mTBI	100	5.24	0.78	5.08	5.39	
Average dilation velocity (mm/s)	Control	100	0.94	0.19	0.90	0.98	<0.001[b]
	mTBI	100	0.62	0.27	0.56	0.66	
75% Recovery time (s)	Control	100	2.60	0.60	2.47	2.71	<0.001[b]
	mTBI	100	4.00	1.09	3.78	4.22	

[a]Results based on mean of two trials. [b]Statistically significant ($p \leq 0.05$).

TABLE IV. Summary Statistics for NPC Break, KD Test Time, and CISS

Variable		N	Mean	Standard Deviation	95% Confidence Interval		p-Value
					Lower Bound	Upper Bound	
NPC break (cm)	Control	100	8.18	2.15	7.75	8.6	< 0.001[a]
	mTBI	100	13.24	8.07	11.64	14.84	
KD test time (s)	Control	100	44.53	8.05	42.93	46.12	< 0.001[a]
	mTBI	100	60.28	19.5	56.41	64.15	
CISS score	Control	100	8.82	7.42	7.35	10.29	< 0.001[a]
	mTBI	100	24.76	12.06	22.37	27.15	

mTBI, mild traumatic brain; NPC, near point of convergence; KD, King-Devick; CISS, Convergence Insufficiency Symptom Survey. [a]Statistically significant ($p \leq 0.05$).

TABLE V. Area Under the Curve (AUC) Values for All Statistically Significant Variables

Variable	AUC	SD	95% Confidence Interval	
			Lower Bound	Upper Bound
Average dilation velocity	0.815	0.030	0.756	0.874
Average constriction velocity	0.650	0.039	0.574	0.725
Near point convergence break	0.744	0.034	0.676	0.811
King-Devick test time	0.777	0.033	0.711	0.842
Convergence Insufficiency Symptom Survey Score	0.860	0.027	0.808	0.912

King-Devick Test

The mean KD test completion time for participants in the acute mTBI group was 60.28 ± 19.50 s and the mean KD completion time for controls was 44.53 ± 8.05 s. Statistically significant results indicate that the acute mTBI group took longer to complete the KD test $p < 0.001$ (Table IV). Based on KD test guidelines for injury determination, the sensitivity and specificity of the KD test were 0.45 and 0.92, respectively. This indicates a high number of false negatives (55%).

Convergence Insufficiency Symptoms Survey

The mean CISS score was 24.76 ± 12.06 among participants in the acute-phase mTBI group and 8.82 ± 7.42 for the controls. Results indicate that the higher CISS scores for the acute-phase mTBI group represent a statistically significant difference, $p < 0.001$ (Table IV). Using the cutoff score of 20, the sensitivity and specificity of the CISS were 0.59 and 0.91, respectively. The number of false negatives among the acute mTBI participants closely mirrors the results of the KD test.

Area Under the Curve (AUC)

The AUC was calculated for two of the PLR measures (ACV and ADV) as well as for the NPC break, KD test time, and CISS score. Although T75 was statistically different between the groups, it was not included within the ROC analysis since it is dependent on dilation velocity. Table V shows that ADV (0.82) and NPC (0.74) have the higher predictive values of all objective parameters. However, the highest predictable values of all parameters were subjective in nature: CISS (0.86) and KD test (0.78). Figure 4 depicts the ROC curves for all significant variables. Using their respective ROC curves, cutoff scores for ADV, KD test time, and CISS score were determined to be 0.84 mm/s, 47 s, and 14, respectively.

Regression Analysis

Binary logistic regression was used to predict injury status (acute-phase mTBI or control) using participant's PLR parameters (ADV and ACV), NPC break, KD test time, and CISS score. A test of the full model was statistically significant, indicating that the predictor variables reliably discriminated between the groups ($p < 0.001$). The resulting Nagelkerke R^2 of 0.71 indicates a moderately strong relationship between the predictor variables and the group variable. Prediction success overall was 87.5% (91.0% for controls and 84.0% for acute-phase mTBI participants). Regression coefficients are presented in Table VI. ROC curve analysis indicates an AUC for the model of 0.93, which indicates very good overall accuracy for the model.

Finally, a second binary logistic regression was used to predict injury status (acute-phase mTBI or control) using previously determined cutoff scores for the KD test time, CISS score, and ADV. A test of the full model was statistically significant, indicating that the predictor variables reliably discriminated between the groups ($p < 0.001$) with a Nagelkerke R^2 of 0.61. Prediction success overall was 84.0% (86.0% for controls and 82.0% for acute-phase mTBI participants). ROC curve analysis of the model indicates an AUC of 0.90, which indicates very good overall accuracy for the model.

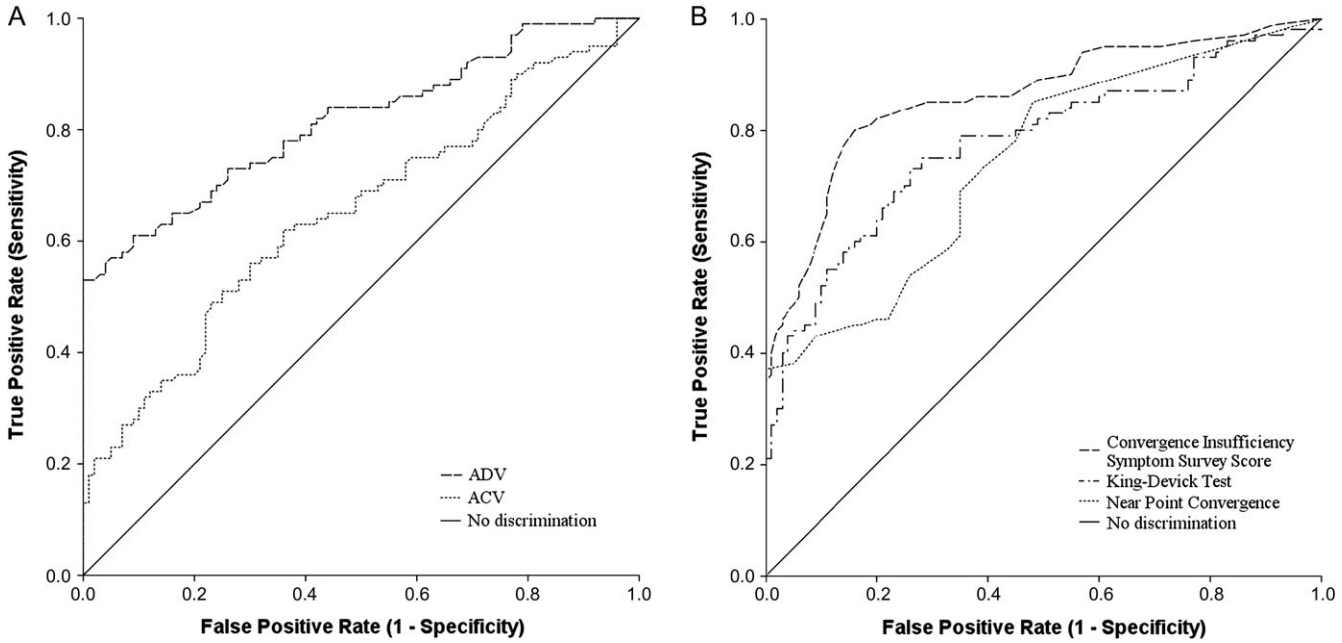

FIGURE 4. Receiver operating characteristic (ROC) curves showing the diagnostic performance for (A) PLR parameters: ADV and ACV; (B) NPC break, King-Devick test time, and CISS score.

TABLE VI. Regression Coefficients

							95% Confidence Interval	
Predictor	*B*	S.E.	*Wald*	df	*p*	OR	Lower Bound	Upper Bound
ACV	5.54	4.72	1.38	1	0.24			
ADV	3.35	0.84	16.07	1	<0.001[a]	28.61	5.55	147.48
KD test time	0.06	0.03	5.39	1	0.02[a]	1.06	1.01	1.11
NPC break	−0.01	0.08	0.02	1	0.88			
CISS score	0.13	0.03	22.83	1	<0.001[a]	1.14	1.08	1.20
Constant	−10.46	1.88	30.91	1	<0.001[a]	0.00		

ACV, average constriction velocity; ADV, average dilation velocity; KD, King-Devick; NPC, near point of convergence; CISS, Convergence Insufficiency Symptom Survey; S.E., standard error; OR, odds ratio. [a]Statistically significant ($p \leq 0.05$).

DISCUSSION

Cognitive and neurosensory degradation resulting from mTBI is significant to each patient but is of unique concern among military service members. Peak cognitive and physical performance is often crucial for military personnel as lives may depend on their ability to perform both physically and cognitively. Due to the relatively mild symptomology and transient nature of the injury, service members are frequently returned to full duty within 24 h. However, misdiagnosis or premature RTD potentially places service members at greater safety risks as well as increase chance for long-term disabilities should they suffer further concussive events before complete recovery.[31] This sometimes premature discharge risks exposing service members to repeat injuries with possible long-term consequences. Consequently, a quick and accurate diagnosis of mTBI could result in a better prognosis for the individual as well as increased safety for others operating within the unit.[32]

The present study validated the use of the PLR (i.e., ACV and ADV) and NPC break as objective biomarkers for acute mTBI. These visual functions can be accurately and quickly measured using instrumentation that is portable, non-invasive, causes no discomfort or risk to patient, requiring minimal user training, deployable, commercially available, and relatively low cost. Objective biomarkers, such as these visual function assessments, are needed to assist frontline medical providers in making RTD decisions after a suspected acute mTBI.

However, given the variety of visual deficits resulting from mTBI and the broad range of injury severity within the mTBI category, it is unrealistic to expect that a single visual function can serve as a universal concussion biomarker. This study shows that a combination of visual functions increases the sensitivity to correctly identify acute mTBI than any one test alone. Results of the present study indicate that the ADV and ACV of the PLR are better suited for discriminating between individuals with and without acute-phase mTBI than other

commonly used instruments. The PLR re-dilation deficit demonstrated in acute-phase mTBI patients is not surprising given the diffuse nature of vision in neural structures. This is in agreement with two previous studies evaluating PLR using the same device, but in blast-induced subacute military[17] and non-blast chronic civilian populations with mTBI.[18] Both of these studies were performed in relatively small population of mTBI subjects ($\leq$ 20). The autonomic nervous system governs the process of pupil dilation and constriction. Previous research has hypothesized that mTBI-related PLR deficits may result from disequilibrium in the autonomic nervous systems due to diffuse injury or transient neuroendocrine dysfunction.[17]

Although the exact neurocognitive mechanism(s) affecting individuals with acute mTBI are unclear, it is clear that new objective diagnostic techniques are needed for screening of mTBI. The standard penlight technique of assessing visual function lacks the objective precision needed to inform such a crucial decision as RTD or return to play. Although all the measures used in this study are established as objective measures, only the PLR is truly free from patient and provider bias. Thus, assessment of the PLR represents a quick, noninvasive, and objective method by which disruptions to the autonomic nervous systems such as acute mTBI may be identified.

Previous studies have validated the use of screening instruments such as the KD test, although often among athletes who also received baseline assessments for comparison. Research done without the use of baseline assessments has been more mixed. A study of acute-phase mTBI patients presenting to an emergency department failed to find significant differences in KD test performance, potentially due to small sample size.[33] A more recent study in a larger population showed the benefit of KD test as an acute mTBI screening tool in the absence of a baseline score,[34] particularly when used in conjunction with other objective screening tools. In addition, the CISS score increase observed in the present study is also in agreement with a previous study examining military personnel diagnosed with blast-induced subacute mTBI.[24] Therefore, whether in a warzone, training environment, or sports field, results suggest that assessment of the PLR is the most effective method of screening for acute-phase mTBI. Incorporating an assessment of the PLR into mTBI screening protocols may improve the accuracy of injury assessments not only in a military setting but also in sports and emergency care situations. This may result in a reduction of false negatives, thereby allowing affected individuals to recover rather than continuing activities and risking exacerbating the injury. Lastly, these results may assist with the development of a weighted neuropyschometric testing battery for the diagnosis of acute mTBI.

Several limitations to the study were identified and should be considered when evaluating the results. The participants were sampled for convenience from clinics in a military setting. Therefore, the data cannot be assumed to be representative of the greater civilian population given differences in age, gender distribution, and fitness level. In addition, the majority of acute-phase mTBI participants in this study suffered injury after jumping from an airplane, a mechanism of injury not likely to be the primary cause of mTBI in the civilian population. However, this injury modality still represents blunt force trauma to the head and diagnostic criteria for mTBI were similar to those used in civilian populations. Additionally, none of the acute-phase mTBI injuries resulted from blast exposure. Consequently, the results of this study cannot be assumed to hold for samples of individuals with blast injuries or polytrauma as may occur in motor vehicle accidents or assaults. Finally, the instruments used in this study have been demonstrated to be effective screening tools for mTBI during the acute injury phase. However, the ability to assess the severity of injury or provide prognosis information was not evaluated. Thus, although the results of this study can inform injury evaluation in general, no claim can be made regarding the clinical utility of these screening tools for determining injury severity or likely persistence of symptoms and recovery times.

CONCLUSION

Our findings demonstrate that ADV, ACV, and NPC break are objective visual functions markedly affected in the acute mTBI group compared with controls and therefore appear to be useful objective biomarkers for acute mTBI. The study results also support the added benefit of using vision-related subjective instruments, such as the KD test and CISS, in conjunction with abovementioned objective biomarkers, to increase the predictability to identify acute mTBI. Thus, although each instrument can accurately differentiate the injury and control groups, results suggest that they differ with regard to their sensitivity and specificity. Where available, objective assessment (i.e., ADV, ACV, and NPC) should be considered preferable to subjective assessments and those based on self-report. Health care providers should consider the relative differences of available assessment tools when screening for acute mTBI and consider the use of multiple assessments when feasible to aide in making RTD and return to play determinations or to monitor the recovery of post-concussive syndrome.

PRESENTATIONS

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