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Quantitative pupillometry as a biomarker for prediction of return to play in mild traumatic brain injury: a Military Traumatic Brain Injury Initiative study

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OBJECTIVE This study aimed to determine the validity of quantitative pupillometry to predict the length of time for return to full activity/duty after a mild traumatic brain injury (mTBI) in a cohort of injured cadets at West Point.

METHODS Each subject received baseline (T0) quantitative pupillometry, in addition to evaluation with the Balance Error Scoring System (BESS), Standardized Assessment of Concussion (SAC), and Sport Concussion Assessment Tool 5th Edition Symptom Survey (SCAT5). Repeat assessments using the same parameters were conducted within 48 hours of injury (T1), at the beginning of progressive return to activity (T2), and at the completion of progressive return to activity protocols (T3). Pupillary metrics were compared on the basis of length of time to return to full play/duty and the clinical scores.

RESULTS The authors' statistical analyses found correlations between pupillometry measures at T1, including end-initial diameter and maximum constriction velocity, with larger change and faster constriction predicting earlier return to play. There was also an association with maximum constriction velocity at baseline (T0), predicting faster return to play.

CONCLUSIONS The authors conclude that that pupillometry may be a valuable tool for assessing time to return to duty from mTBI by providing a measure of baseline resiliency to mTBI and/or autonomic dysfunction in the acute phase after mTBI.

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KEYWORDS concussion; mild traumatic brain injury; mTBI; return to play; quantitative pupillometry

Traumatic brain injuries affected over 417,503 US service members from 2009 to 2017. Of these, the large majority—approximately 88%—were classified as mild traumatic brain injuries (mTBIs), known in the sports world as concussions.[1] In addition to the problems that result from the large numbers of TBI overall, this high rate of "mild" injury represents a substantial burden both to combat power and to the medical evacuation system because it leads to evacuation of personnel for injuries that could be treated without evacuation. Approximately 68% of service members with mTBI are evacuated for a head CT because the concussion assessment tools available in the field—specifically Military Acute Concussion Evaluation Version 2 (MACE2), which was made standard through Department of Defense Instruction (DODI) 6490.11 (2012, updated 2021)—are not sensitive enough to provide reliable diagnostic information to distinguish between individuals who could be treated on site and those who require evacuation to more advanced care.[1,2] Although MACE2 is easy to use and does provide some information about the possible presence of brain injury, the current version takes up to 30 minutes to administer, has

ABBREVIATIONS ADV = average dilation velocity; BESS = Balance Error Scoring System; End-Initial = difference between constricted and initial pupillary diameter; KM = Kaplan-Meier; MACE2 = Military Acute Concussion Evaluation Version 2; MCV = maximum constriction velocity; mTBI = mild traumatic brain injury; SAC = Standardized Assessment of Concussion; SCAT5 = Sport Concussion Assessment Tool 5th Edition Symptom Survey; Time_to_RTD = time to return to duty; T0 = baseline; T1 = within 48 hours after mTBI; T2 = progressive return to activity; T3 = return to duty; VOMS = vestibular ocular motor screening.

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limited ability to diagnose concussion, and has no predictive ability regarding when service members may be able to return to duty.[2] These weaknesses substantially limit the usefulness of MACE2 in combat operations, particularly in determining service members' readiness for full duty after mTBI.

Other concussion assessments, including vestibular ocular motor screening (VOMS), have been shown to be more predictive of return to play among athletes,[3–5] showing that objective measures of visual-oculomotor system functions can predict return to play after a concussion. Unfortunately, the major limitation of VOMS to its practical application in austere conditions is its relative complexity that requires appropriate examiner training for its reliable application. Pupillometry, which involves the measurement of pupillary responses after a standard flash of light is delivered and can produce a result in 6 seconds or less, is a similarly reliable objective assessment of the visual system that is also faster than VOMS and less dependent on an assessor's training.[6] Particularly promising pupillometry parameters in the diagnosis of concussion seem to be increased maximum pupillary diameter and higher constriction velocities in injured subjects.[7] Additionally, there is evidence that prior head injuries do not result in a significantly different pupillary light response compared to those of subjects without a prior head injury.[8] The combination of these factors—the accuracy with which it identifies individuals with mTBI, the evidence that it is not altered by prior concussion histories, and the rapidity and ease of its use—suggests that quantitative pupillometry is an ideal candidate for use in predicting return to duty. The main objective of this study was to validate the use of quantitative pupillometry (i.e., measurements of changes in pupillary light reflex) to predict the length of time to return to full activity, specifically the time to return to play for a cohort of injured cadets at West Point, whose demographic characteristics and other similarities make them a valid comparison to service members who are injured in combat.

Methods

Study Design

The study was conducted from August 2021 to December 2022 at the United States Military Academy at West Point and was approved by the Institutional Review Board at Naval Medical Center Portsmouth. Written informed consent was obtained from all participants prior to data collection. Freshmen cadets were recruited during the first 2 weeks of the academic year, and baseline concussion assessments were conducted at the time of consent. Participants were followed from the time of consent until the end of the follow-up period to document incident cases of mTBI in the cohort. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.

Clinical Baseline and Follow-Up Data Collection

Preinjury baseline (T0) data included all of the following characteristics: past medical and concussion history and scores on the Balance Error Scoring System (BESS) (score range 0–60, with higher scores indicating worse static postural stability), Sport Concussion Assessment Tool 5th Edition Symptom Survey (SCAT5) (symptom severity score range 0–132, with higher scores indicating worse symptoms), and Standardized Assessment of Concussion (SAC) (score range 0–30, with higher scores demonstrating improved cognitive function). The first postinjury clinical assessment using these scoring systems was within 48 hours of mTBI (T1). When the cadets were symptom free, as determined by their treating physician, they were started on the progressive return-to-activity protocol (T2) and were released to unrestricted activity after the completion of this protocol (T3). The clinical assessment included these scoring systems at all postinjury time points.

Pupillometry Parameters and Time to Return to Duty

Baseline (T0) pupillary responses were obtained using the NeurOptics PLR-3000 Pupillometer set with a recording time of 6 seconds and light pulse duration of 0.8 msec with an intensity of 121 μW. Recordings were taken starting with the left eye followed immediately by the right eye, and all recordings were taken with standard overhead fluorescent lighting. We obtained an average of both the left and right eyes for the following pupillometry parameters: 1) starting pupillary diameter (maximum, in millimeters); 2) end pupillary diameter (minimum, in millimeters); 3) percent of pupillary constriction; 4) latency time to the initiation of pupillary constriction (seconds); 5) average constriction velocity (negative millimeters per second); 6) maximum constriction velocity (MCV) (negative millimeters per second); 7) average dilation velocity (ADV) (millimeters per second); and 8) time of return to 75% of the pupillary starting diameter (seconds). 9) We also calculated the difference between the constricted (minimum) and initial (maximum) pupillary diameter (End-Initial) (in negative millimeters).

In a previous study, 3 of 9 pupillary measures (End-Initial, MCV, ADV) correlated significantly with the dichotomized (< 21 days or ≥ 21 days) time of recovery after concussion (B.A. Dengler, unpublished data, December 2023). Therefore, the goal of the present study was to examine the individual associations of these 3 pupillometry parameters with time to return to duty (Time_to_RTD), as a further refinement of the previously submitted analysis. Time_to_RTD of each individual represents the number of days between the time of injury (T1) and the time when the cadet completed the return-to-activity protocol and resumed unrestricted activity (T3).

Data Standardization

The 3 pupillometry parameters were examined with respect to Time_to_RTD, both as original pupillometry data observed in the concussed group and as standardized pupillometry measures. Standardization applied to the 3 pupillometry measures i ($i = 1, \ldots, 3$) in participant j ($j = 1, \ldots, n$) at time point k ($k = 1, \ldots, 4$) and was calculated as follows: observed pupillometry (i, j, k) – mean pupillometry in nonconcussed (i, k)/standard deviation pupillometry in nonconcussed (i, k).

TABLE 1. Nonstandardized pupillary measures and clinical variables by time point

	Baseline (T0)	<48 hrs After mTBI (T1)	Asymptomatic (T2)	Return to Duty (T3)
Pupillary measure				
End-Initial	−1.4 (0.4)	−1.6 (0.4)	−1.6 (0.4)	−1.4 (0.4)
MCV	−4.2 (1.0)	−4.4 (0.9)	−4.3 (0.9)	−3.9 (0.9)
ADV	1.3 (0.3)	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)
Clinical score				
BESS	13.3 (7.4)	17.5 (10.6)	14.3 (7.1)	10.6 (6.2)
SAC	27.7 (1.7)	26.7 (1.9)	27.0 (1.9)	27.5 (1.8)
SCAT5	3.4 (4.5)	11.0 (5.6)	3.7 (4.4)	0.4 (0.9)*
Time_to_RTD†	25 (16.5) (4–71)			

Values are shown as mean (SD) in days unless indicated otherwise.
* At T3, all values for SCAT5 total ≤ 4, reflecting return-to-duty status.
† Time_to_RTD represents days between time of injury (T1) and time of return to duty (T3). It is a fixed (not time dependent) variable in the data for individuals, where each individual has 1 value representing their return-to-duty status. Mean (SD) (range) is shown.

Standardization rescales the pupillometry measures as z-scores in the concussed group, so differences in the levels of the measures are relative with respect to the healthy population—i.e., "better" pupillometry values relative to the mean pupillometry in a healthy population may represent resilience and "worse" values compared to the average in a healthy population may indicate vulnerability. The potential associations of these pupillometry measures with respect to Time_to_RTD could then be thought of in terms of "better than average" or "worse than average" for a healthy pupillary response and the implications this may have for an individual's prognosis.

Statistical Analysis

First, we examined correlations between standardized pupillary measures and Time_to_RTD (days) using the Spearman method. Correlations between the 3 pupillary measures and Time_to_RTD were assessed for the 4 study time points, at which these pupillary data were collected in participants. Additionally, correlations between the clinical assessments measured at the study time points and 1) Time_to_RTD and 2) standardized pupillary measures were examined.

Next, using Kaplan-Meier (KM) estimation, we examined the association between these pupillary measures, respectively, and the probability of individuals returning to duty by a given time. Briefly, individuals' pupillary responses were grouped into tertiles for each of the 4 time points. The order of the tertiles would represent potentially "best" (first tertile) to "worst" (third tertile) pupillary response (e.g., standardized End-Initial, standardized MCV), or the opposite for standardized ADV ("worst" first tertile, "best" third tertile). KM curves were generated to assess the proportion of individuals within each of these tertiles who had not yet returned to duty by a given day. Given that the second tertile represents an intermediate group between the first and third tertiles, we applied a nonparametric statistical rank test of the individuals' probability of Time_to_RTD for the first and third tertiles—i.e., a "best" versus "worst" comparison—based on the individuals' standardized pupillometry scores. We assumed that extended Time_to_RTD (> 2 months) may have been related to other factors (e.g., delayed scheduling for screening inpatient visits); therefore, we performed sensitivity analyses to examine the associations of interest in participants whose Time_to_RTD did not exceed 2 months (≤ 60 days). The 60-day cutoff time was chosen on the basis of observational evidence that the time to symptom resolution after a sport-related first concussion was 21.2 ± 16.3 days and after a repeated concussion 41.7 ± 86 days.[9]

Analyses were conducted using SAS version 9.4 (SAS Institute), R version 4.3.2 (R Foundation for Statistical Computing), and Stata software version Stata BE 18.0 (StataCorp).

Results

Demographic Characteristics

The mean ± SD (range) age of study participants was 18.5 ± 1.0 (17–23) years, and 77.3% were men and 22.7% women. The distribution based on race and ethnicity showed that 70.4% of participants were White, 10.9% Asian, 0.9% American Indian, 7.9% African American, 8.2% multiple races, 1.7% unknown race, 84.0% non-Hispanic/Latino, 10.8% Hispanic/Latino, and 5.2% unknown ethnicity. Participants whose Time_to_RTD was within 2 months (mean ± SD [range] 23.4 ± 12.7 [4–59] days) represented 94% of the sample (n = 64/68) compared with 4 individuals (6%) whose Time_to_RTD exceeded 2 months (range [61–71] days). Three individuals with Time_to_RTD > 100 days, for whom the expected delay in return to duty was due to other clinical considerations, were excluded.

Spearman Correlation Analysis

The summary of nonstandardized pupillometry measures (End-Initial, MCV, and ADV) and clinical scores at respective time points is shown on Table 1. All participants returned to unrestricted activity by day 100 after injury.

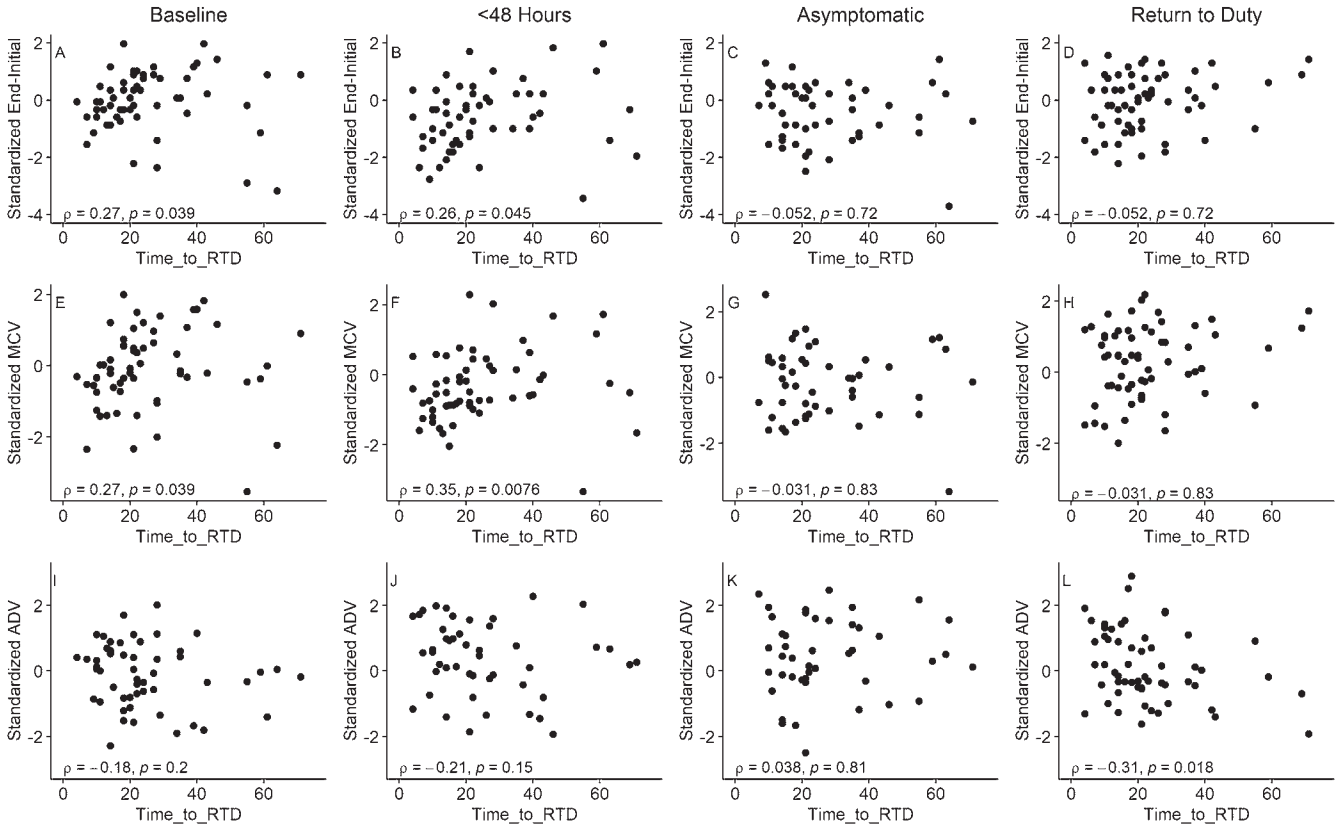

FIG. 1. Three standardized pupillometry measures (End-Initial [**A–D**], MCV [**E–H**], ADV [**I–L**]) and Time_to_RTD (days).

The analysis of correlations between standardized pupillary measures and Time_to_RTD was performed using the Spearman method, showing that in the acute phase after concussion (T1) both End-Initial and MCV were significantly correlated with Time_to_RTD: the larger the pupillary constriction (End-Initial rho = 0.26, p = 0.045) and the higher the MCV (rho = 0.35, p = 0.0076), the shorter the time until return to full activity (Fig. 1). In addition to the T1 time point, there were also significant associations between both End-Initial and MCV and Time_to_RTD at baseline (T0) (End-Initial rho = 0.27, p = 0.039; MCV rho = 0.27, p = 0.039). In contrast, ADV was significantly correlated with Time_to_RTD only at T3 (rho = –0.31, p = 0.018), meaning that earlier returning cadets had higher ADVs (Fig. 1).

Examination of the clinical concussion scores (BESS, SAC, and clinical SCAT5) and Time_to_RTD revealed that only SCAT5 was correlated positively with the time to return to full activity, and this occurred at T1 (rho 0.34, p = 0.0099) and T2 (rho = 0.45, p = 0.0017). The data indicate that cadets with lower clinical SCAT5 scores (fewer and less severe symptoms) at both time points returned earlier to unrestricted activity (Fig. 2). Interestingly, neither the BESS nor the SAC scores showed any correlation at any postinjury time point. For example, a cadet returning to duty earlier may have had higher BESS error scores than the individual returning later. The same applies to the SAC scores.

The analysis of correlation between the clinical scores for concussion (BESS, SAC, SCAT5) and the 3 selected standardized pupillometry parameters (End-Initial, MCV, ADV) revealed that only BESS correlated significantly with the 3 pupillary variables, and only at the time when cadets became asymptomatic (T2): End-Initial (rho = –0.39, p = 0.006), ADV (rho = 0.36, p = 0.019), and MCV (rho = –0.37, p = 0.01) (Supplemental Figs. 1–3).

KM Estimation Analysis

For the purpose of KM analysis, we represented the standardized pupillometry variables as tertiles (Fig. 3). For standardized End-Initial, the first tertile represents better scores (end minus initial pupil size provides more negative scores) and the third tertile represents worse scores. For standardized MCV, the first tertile represents better scores (larger negative value) and the third tertile represents worse scores (positive values relative to the group mean for MCV). For standardized ADV, the first tertile represents worse scores (negative values relative to group mean for dilation velocity) and the third tertile represents better scores (positive values relative to the group mean for dilation velocity).

As shown in Fig. 1, MCV had the strongest correlation with Time_to_RTD at T1. We used KM curves to compare individuals' probability of Time_to_RTD based on the first and third tertiles of the participants' standardized

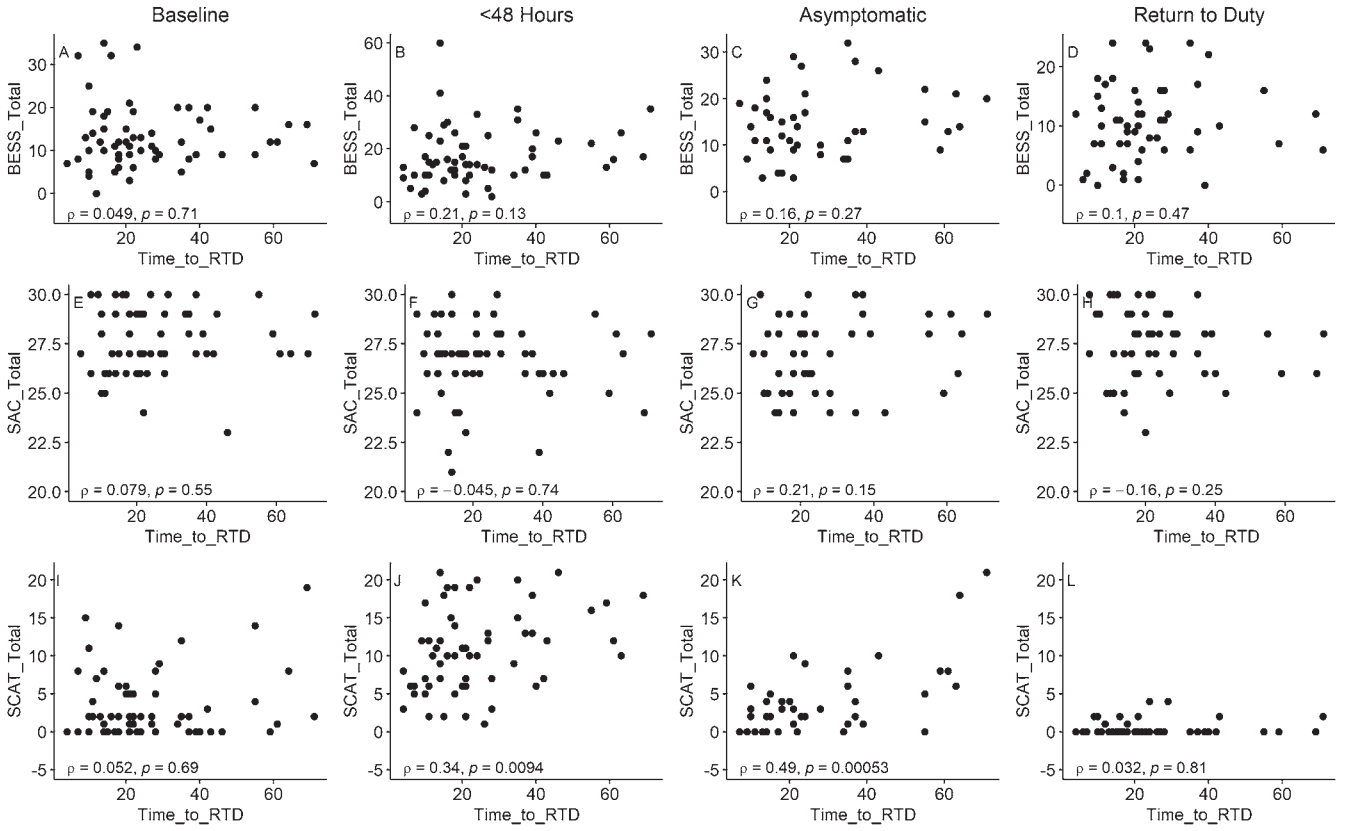

FIG. 2. Correlation of clinical concussion scores (BESS total [**A–D**], SAC total [**E–H**], SCAT total [**I–L**]) and Time_to_RTD (days).

MCV scores, where the first tertile represents the lowest 33% of MVC (negative values, the best pupillometry response for this measure) and the third tertile represents the highest 33% (poor pupillometry response for this measure). Two analyses were performed: one analysis included all participants where the latest Time_to _RTD was within 100 days, and the sensitivity analysis included those who returned to full duty within 60 days. KM curves are shown for the analysis that included all participants (Fig. 4).

There is a significant separation of the first and third tertiles in the acute phase of injury (T1) ($p < 0.049$), which becomes more significant with the sensitivity analysis (subgroup with Time_to_RTD < 60 days, $p < 0.005$). There was no significant separation of curves at the remaining time points (T0, $p < 0.42$; T2, $p < 0.88$; T3, $p < 0.21$). Sensitivity analyses indicated no differences between the curves at these other time points as well (T0, $p < 0.63$; T2, $p < 0.72$; T3, $p < 0.80$). As an illustration, the T1 time point in Fig. 4 can be interpreted as follows: the probability of participants whose MCV is represented by the first tertile having not yet returned to duty by day 20 after injury is roughly 30%. In contrast, the probability of participants represented by the third tertile of the MCV measure not yet returning to duty by day 20 after injury is roughly 75%.

The KM curves for the variables End-Initial and ADV are shown in Supplemental Figs. 4 and 5. There was no significant separation of the KM curves for End-Initial. A significant separation was observed based on the sensitivity analysis for the first and third tertiles of the pupillometry measure at the T1 time point ($p < 0.03$). For ADV, no significant separations of the KM curves were observed for the first and third tertiles, except at the T3 time point only.

Discussion

This study reflects a deeper analysis of our previous work evaluating the overall pupillary light reflex after concussion, which is pending publication and demonstrated significant changes in the pupillary light reflex after mTBI along with an ability to dichotomize cadets returning to play or duty before or after 21 days. This study is a further refinement of those data, specifically examining 3 pupillary parameters that correlated with return to play and breaking them up into a more predictive model. At the first postinjury time point, larger change in the diameter of the pupil and faster MCV both correlated with faster return to play. Given that the autonomic nervous system affects the pupillary light reflex, faster speed demonstrates more regulation by the autonomic nervous system. This has been demonstrated in other studies evaluating the risk of postinduction hypotension prior to anesthesia, which reported that higher MCV values were associated with

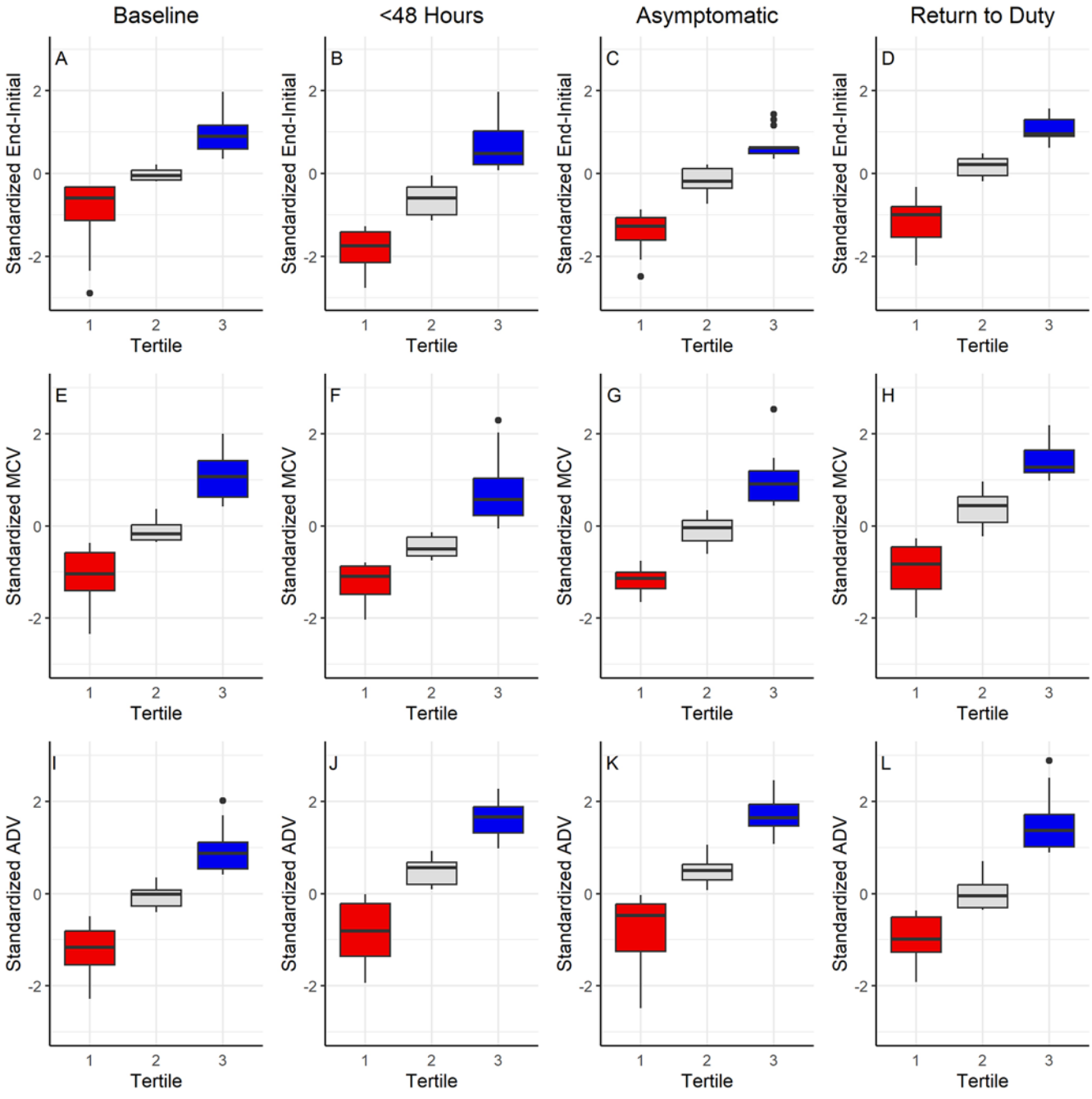

FIG. 3. Boxplot representation of tertiles for the standardized pupillary measures at different time points. Tertiles of each standardized measure for each time point are represented, where standardized values are based on individual measures (mean measure at the group level) divided by the standard deviation of the measure at the group level. For standardized End-Initial (**A–D**), the first tertile represents better scores (end minus initial pupil size provides a negative score) and the third tertile represents worse scores. For standardized MCV (**E–H**), the first tertile represents better scores (larger negative value) and the third tertile represents worse scores (positive values relative to the group mean for MCV). For standardized ADV (**I–L**), the first tertile represents worse scores (negative values relative to the group mean for dilation velocity) and the third tertile represents better scores (positive values relative to the group mean for dilation velocity). Median (*middle line*), interquartile range (*box*), minimum and maximum (*whiskers*), and outliers (*dots*) are shown.

less chance of hypotension and therefore improved function of the autonomic nervous system to maintain hemodynamic parameters.[10] This finding demonstrating tighter autonomic nervous system control after injury and faster return to play is also predicted in studies evaluating heart rate variability after mTBI. In these studies, subjects who had less heart rate variability had faster return to play than those with more variability, reflecting increased sympa-

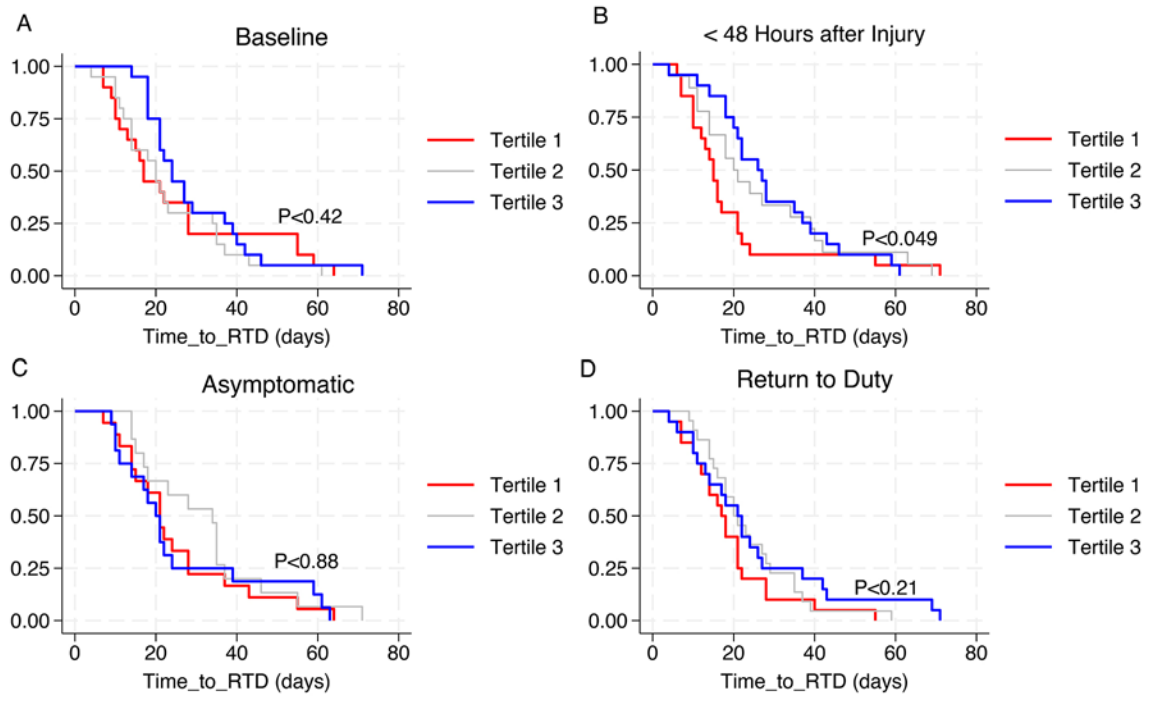

FIG. 4. KM estimation curves for MCV and Time_to_RTD after injury (in days along the x-axis). **A:** At baseline (T0). **B:** In the acute phase of injury (T1). **C:** When asymptomatic (T2). **D:** At the time of return to full activity (T3). The first tertile of the distribution of the standardized MCV represents a better score, and the third tertile represents a worse score. A statistical test was conducted to compare Time_to_RTD between the first and third tertiles. The second tertile of the MCV (intermediate between the first and third tertiles) is shown in the graphs but was not included in the analysis.

thetic control.[11,12] Given these findings, MCV and End-Initial could serve as prognostic indicators soon after mTBI.

In addition to predicting the recovery trajectory after an mTBI has occurred, another area of great interest is to determine who is at risk for delayed recovery prior to sustaining an mTBI. Some studies have reported that preinjury factors such as history of mental health problems, high school age, or female sex all predict longer-lasting symptoms.[4,13] In our study, the same variables that predicted faster return to play at the T1 time point, namely MCV and End-Initial, were also both predictive of faster recovery after an mTBI at the T0 time point. This is an interesting finding that could represent the overall preinjury brain health of the participant. This could be a more objective marker than a self-reported concussion history because, as we have previously demonstrated, there was no difference in pupillary parameters between those with a prior history of head injury and those without such history at baseline.[8]

As with other studies, our data confirm that the more symptoms reported on the SCAT5 predicted a longer time until return to full duty or play.[14] The SCAT5 symptoms demonstrated a significant positive correlation with the time to return to play. This internally validates our data and is also not surprising because the decision to start the progressive return-to-activity protocol at T2 is made when cadets are asymptomatic or have minimal symptoms. Both SAC and BESS showed no ability to predict postinjury return to play, which parallels findings from other larger-scale studies.[15]

An interesting correlation occurred in the comparison of the selected pupillary measures to the clinical parameters. At the initiation of the return-to-activity protocol (T2), the faster MCV and ADV values along with the larger End-Initial measure demonstrated significant correlations with the BESS scores. This would suggest that the higher error rates on BESS would correspond to faster return to play than lower BESS scores. It is possible that the BESS overall is a poor tool and has poor test and retest reliability, which has been demonstrated in other studies.[16,17] Also of interest was that the pupillary parameters did not correlate with any of the scores on the SAC or SCAT5. This demonstrates that each one is independent of the other at predicting return to play and that each clearly evaluates different functional domains after injury. This finding could also suggest that autonomic nervous system dysfunction does not necessarily correlate with symptom severity.

Conclusions

These findings suggest that pupillometry metrics, specifically magnitude of change in diameter and MCV, may be appropriate predictors of return to play/duty when the test is performed in the acute phase after mTBI (T1). Furthermore, End-Initial pupil diameter and MCV were also associated with faster recovery from mTBI, even when the data for those parameters were collected at baseline (T0). These differences observed at baseline could indicate a level of predictability for how much recovery time may be

required for an individual if they have an mTBI, providing valuable information for risk mitigation and unit readiness from a commander's perspective.

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Disclosures

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Author Contributions

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Supplemental Information

Online-Only Content

Supplemental material is available online.

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