RESEARCH SUBMISSION

Developing multivariable models for predicting headache improvement in patients with acute post-traumatic headache attributed to mild traumatic brain injury: A preliminary study

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Abstract

Objectives/Background: Post-traumatic headache (PTH) is a common symptom after mild traumatic brain injury (mTBI). Although there have been several studies that have used clinical features of PTH to attempt to predict headache recovery, currently no accurate methods exist for predicting individuals' improvement from acute PTH. This study investigated the utility of clinical questionnaires for predicting (i) headache improvement at 3 and 6 months, and (ii) headache trajectories over the first 3 months.

Methods: We conducted a clinic-based observational longitudinal study of patients with acute PTH who completed a battery of clinical questionnaires within 0–59 days post-mTBI. The battery included headache history, symptom evaluation, cognitive tests, psychological tests, and scales assessing photosensitivity, hyperacusis, insomnia, cutaneous allodynia, and substance use. Each participant completed a web-based headache diary, which was used to determine headache improvement.

Results: Thirty-seven participants with acute PTH (mean age = 42.7, standard deviation [SD] = 12.0; 25 females/12 males) completed questionnaires at an average of 21.7 (SD = 13.1) days post-mTBI. The classification of headache improvement or non-improvement at 3 and 6 months achieved cross-validation area under the curve (AUC) of 0.72 (95% confidence interval [CI] 0.55 to 0.89) and 0.84 (95% CI 0.66 to 1.00). Sub-models trained using only the top five features still achieved 0.72 (95% CI 0.55 to 0.90) and 0.77 (95% CI 0.52 to 1.00) AUC. The top five contributing features were from three questionnaires: Pain Catastrophizing Scale total score and helplessness sub-domain score; Sports Concussion Assessment Tool Symptom Evaluation total score and number of symptoms; and the State-Trait Anxiety Inventory score. The functional regression model achieved $R = 0.64$ for modeling headache trajectory over the first 3 months.

Conclusion: Questionnaires completed following mTBI have good utility for predicting headache improvement at 3 and 6 months in the future as well as the evolving

Abbreviations: AUC, area under the curve; BDI, Beck Depression Inventory; CI, confidence interval; CV, cross-validated; LOOCV, leave-one-out cross-validation; mTBI, mild traumatic brain injury; PC, principal components; PCA, principal component analysis; PC-PTSD, Primary Care Post-traumatic Stress Disorder Screen; PCS, Pain Catastrophizing Scale; PTH, post-traumatic headache; SCAT5, Sport Concussion Assessment Tool; SD, standard deviation; STAI, State-Trait Anxiety Inventory; VA, Veterans Administration.

headache trajectory. Reducing the battery to only three questionnaires, which assess post-concussive symptom load and biopsychosocialecologic factors, was helpful to determine a reasonable prediction accuracy for headache improvement.

KEYWORDS
headache diary, headache frequency, mild traumatic brain injury, post-traumatic headache, predictive modeling

INTRODUCTION

Post-traumatic headache (PTH) is the most common symptom following mild traumatic brain injury (mTBI) and is associated with significant disability and long-term health burden.[1–4] Whereas some patients improve and recover quickly from acute PTH, a significant proportion of patients continue to have headache for months or even years. It is a common clinical dilemma that patients with acute PTH would like to know how quickly their headaches will improve, yet clinicians lack ways of making accurate predictions about patients' headache improvement trajectories.

Although several studies have identified factors such as older age, female sex, migraine history, and history of prior mTBI as risk factors for *developing* PTH,[1,2,5,6] there are insufficient methods for predicting headache *improvement* in the months following the onset of PTH. This study developed multivariable models that predict headache improvement at 3 and 6 months using baseline clinical questionnaires completed within 0–59 days post-mTBI. Additionally, we assessed whether the clinical questionnaires could predict patients' headache frequency trajectory over the course of 3 months to complement the binary headache status calculations (headache improvement/non-improvement) with a more granular assessment of how each patient's headache pattern changes over time.

METHODS

This clinic-based observational longitudinal study was approved by Mayo Clinic Arizona and the Phoenix Veterans Administration (VA) institutional review boards. Participants were male and female adults between the ages of 18 and 70. All participants were enrolled from the Mayo Clinic in Arizona or the Phoenix VA Health Care System and provided written informed consent prior to participation. Participants included in this study were enrolled over a period of 3 years (2019–2022). A subset of individuals included in this study were included in a prior publication.[7] However, this is the primary analysis aimed at predicting headache improvement based on clinical questionnaires completed within 0–59 days post-mTBI. No portions of this analysis have been previously published using the same or a subset of the participants included in this study. All individuals had headaches that began within 7 days of injury and met criteria for acute PTH attributed to mTBI in accordance with the 2018 International Classification of Headache Disorders, 3rd edition criteria.[8] Individuals were enrolled between 0 and 59 days post-mTBI. PTH patients with a history of moderate or severe TBI were excluded from study participation. History of migraine (prior to mTBI) was allowed.

Baseline questionnaires

All individuals with PTH completed the following questionnaires during their baseline study visit (0–59 days post-mTBI): a detailed headache history, the Ohio State University Traumatic Brain Injury Identification Method for determining the history of TBI; the Symptom Evaluation Subtest of the Sport Concussion Assessment Tool (SCAT5); the Photosensitivity Assessment Questionnaire; the Hyperacusis Questionnaire; the Insomnia Severity Index; the 12-item Allodynia Symptom Checklist, a questionnaire assessing substance use history; cognitive tests (Trail-Making Test Parts A and B [TRAILS A and B]); and questionnaires assessing psychological symptoms including the Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory (STAI), the Pain Catastrophizing Scale (PCS), and the Primary Care Post-traumatic Stress Disorder Screen (PC-PTSD). The questionnaires used as part of this study were selected because of their validity and reliability qualities and prevalent use in headache research.[9–19] From these questionnaires, 42 clinical variables were extracted and used as features to build multivariable models for predicting headache status. Missing values were imputed using single-imputation based on the mode of each variable among remaining patients.

Outcome variables

Individuals completed a web-based daily headache diary over the first 3 months after enrollment and over 30 days prior to their 6-month follow-up visit. In each daily entry, individuals indicated whether they had a headache (1 = headache; 0 = no headache). Headache diary entries were used to determine headache improvement/non-improvement at 3 and 6 months post-mTBI. We developed a novel algorithm that adequately captured headache improvement and considered headache history prior to mTBI. First, we defined "additional headaches" as the number of headaches an individual had post-mTBI compared to the number of headaches experienced pre-mTBI. An individual with pre-existing headaches was considered to

have "headache improvement" if the number of additional headaches 3 months post-mTBI was reduced by 50% or less compared to the first month post-mTBI, OR if the additional headaches 3 months post-mTBI reduced to 2.5 or less. For example, an individual who had 4 headache days per month prior to mTBI and 10 headache days per month post-mTBI, would be considered to have 6 "additional" headaches. If the same individual then had 7 or fewer headache days per month at 3 months post-mTBI they would have a 50% reduction of "additional" headaches and considered to have "headache improvement." For an individual with zero headache days prior to mTBI and 10 headache days in the first month following enrollment, they would need to have 5 or fewer headache days at 3 months post-mTBI to meet the same criteria and be considered to have headache improvement.

In addition to the aforementioned binary labels (improvement vs. non-improvement) assessed at 3 and 6 months for each patient, we also considered the trajectory of headache frequency over the course of the first 3 months to be an outcome variable. Specifically, we computed each patient's headache frequency for a 7-day window as the percentage of days the patient reported headaches and slid the window day by day over the first 3 months. If a patient's headache data are missing for an entire 7-day window, we imputed the headache frequency of that window using linear interpolation of the two windows nearest in time. This operation extracted the trajectory of headache frequency as a function of a continuous variable over time, which is then used as the response variable in a regression model. The methodology for this analysis is described further below.

Statistical analysis

Patient characteristics were summarized by computing the mean and standard deviation (SD) for continuous variables and frequency counts for categorical variables. Next, we describe two prediction models developed using questionnaire data, one aiming to classify whether a patient's headache will improve or not at 3 months and at 6 months in the future, and another aiming to model patients' trajectory of headaches in the first 3 months.

Multivariable classification of headache improvement

The questionnaire variables are high dimensional relative to the sample size. Therefore, we used principal component analysis (PCA) to reduce the dimension of the questionnaire variables into fewer predictors, called principal components (PC). Then, logistic regression models were trained based on the questionnaire PCs, age, sex, and enrollment time post-mTBI (measured in days) to classify the binary improvement/non-improvement outcome at 3 and 6 months. PCA assumes that all variables are provided on the same scale. Thus, all variables were standardized by subtracting the mean and dividing by the SD. In addition, PCA assumes that the PCs with the highest variance retain the most information that should be used downstream, and the PCs with lower variance are discarded as noise. The number of

PCs was selected using leave-one-out cross-validation (LOOCV) and based on the one-standard-error rule, that is, selecting the most parsimonious model whose prediction performance is within one standard error of the best choice. This strategy has been reported to avoid overfitting under a small sample size.[20] To assess the accuracy of the classification, we computed the area under the curve (AUC) metric under the LOOCV scheme, that is, one patient is left out for validation while remaining patients are used to train the model and the process is repeated for all patients. We computed the 95% confidence intervals (CIs) of the AUCs using Delong's method and the algorithm by Sun and Xu,[21,22] which does not rely on normality assumptions. Also, we used the loadings of PCA to assess the contribution of each clinical variable. The predictive accuracy of sub-models was assessed using *only* the top 10 or the top 5 contributing features from PCA. For better interpretability of the regression coefficients, the questionnaire PC was min-max scaled to [0, 1] range and age was mean-centered.

Modeling headache trajectories using functional regression

As improvement patterns likely differ between patients, we aimed to predict the headache trajectory of each patient over time to reveal the temporal granularity of headache change. This analysis uses clinical questionnaires collected at baseline to predict patients' headache trajectories over the first 3 months. As an extension of traditional regression, functional regression is designed to handle the high dimensionality and autocorrelation of data collected as functions, such as applications that involve growth curves, 2D/3D images, spectral domains, and even genomic locations.[23,24] Function-on-scalar regression is one category of functional regression in which the response is in the form of a function, that is, for each participant, the response variable is recorded continuously over a compact time interval. We fit a function-on-scalar regression model using the 7-day headache frequency trajectory as the functional response; the questionnaire PC as a scalar regressor with time-varying coefficients; the covariates age, sex, and enrollment time post-mTBI as scalar regressors with constant coefficients; and a time-varying intercept. Under this formulation, the time-varying coefficient of the questionnaire PC provides an estimate of how the relationship between the questionnaire variables and headache frequency changes over time and this relationship is assumed to be smooth over time. We used a popular class of splines called penalized cubic splines to represent the functional coefficients of the model.[22] Specifically, we used cubic splines with five evenly spread knots and penalty for unsmoothness measured as integrated square of the second derivative. Full details of this penalized spline–based functional regression model can be found in section 3.2. of Wood.[25] For sub-analyses, we fit functional regression models for headache trajectories for the first 2 weeks, for the first month, and for the first 2 months. This aims to help understand the temporal length of headache trajectory that baseline questionnaire variables can best predict. The goodness-of-fit of the functional regression model was assessed based on R^2.

The PCA and logistic regression were conducted using the *sklearn* and *statsmodels* packages in Python. The functional regression was conducted using the pffr function in the *refund* package for R.[22] Multicollinearity was not present in the logistic regression and functional regression models, as confirmed by a variance inflation factor of less than 4 across all predictors. A *p*-value of less than 0.05 was considered statistically significant for the two-tailed regression coefficient tests.

RESULTS

According to the enrollment criteria, 37 patients with acute PTH due to mTBI were included (mean age = 42.7, SD = 12.0; 25 females/12 males), see Table 1. All participants completed a battery of questionnaires at an average of 21.7 days (SD = 13.1) post-mTBI. Among this cohort, 16 patients had TBI due to falls, 17 patients due to motor vehicle accidents, 1 patient due to sports-related injuries, and 3 patients due to other mechanisms; 24 individuals had a single lifetime mTBI, 6 individuals had one prior mTBI, 6 individuals had two prior mTBIs, and 1 had five prior mTBIs. The timing of PTH onset relative to the mTBI was as follows: less than 1 h for 16 individuals, between 1–9 h for 10 individuals, between 10–23 h for 2 individuals, between 24–47 h for 5 individuals, between 48–71 h for 0 individuals, and after 72 h for 2 individuals. Thirteen individuals reported not having headache prior to their most recent mTBI. Eight individuals had tension-type headache, 3 had probable migraine, and 13 had migraine prior to mTBI. Nine individuals had aura with headache prior to mTBI. The headache phenotype acutely following mTBI was as follows: 11 individuals had tension-type headache, 9 had probable

TABLE 1 Participant demographics and baseline questionnaire scores (0–59 days post-mTBI)

Category	Characteristic	Mean (SD)
Demographics	Age (*years*)	42.7 (12.0)
	[a]Sex (*f/m*)	*f* = 25 (67.6%); *m* = 12 (32.4%)
	[a]Ethnicity (*Hispanic/Non-Hispanic*)	Hispanic = 5 (13.5%) Non-Hispanic = 32 (86.5%)
	Education (*years*)	17.4 (1.3)
Headache history	Headache pain (*average*)	4.5 (2.1)
	[a]Headache continuous since onset (*y/n*)	*y* = 23 (62.2%); *n* = 14 (37.8%)
Cognitive measures	TRAILS A (*z-score*)	0.3 (1.1)
	TRAILS B (*z-score*)	0.6 (1.0)
	RAVLT Immediate Recall (*z-score*)	−0.2 (1.1)
	RAVLT Delayed Recall (*z-score*)	−0.7 (1.1)
	SCAT Symptom Evaluation (*symptom severity*)	30.8 (25.5)
	SCAT Symptom Evaluation (*number of symptoms*)	12.0 (6.7)
Psychological measures	BDI (*total score*)	9.6 (8.3)
	[a]PTSD present (*y/n*)	*y* = 8 (21.6%); *n* = 29 (78.4%)
	PCS (*total score*)	11.7 (10.3)
	STATE Anxiety Inventory (*total score*)	35.1 (12.1)
	TRAIT Anxiety Inventory (*total score*)	37.4 (13.5)
	PCA helplessness (*subdomain score*)	4.8 (4.5)
	PCS magnification (*subdomain score*)	2.1 (2.1)
	PCS rumination (*subdomain score*)	4.7 (4.5)
Physical measures	Hyperacusis (*total score*)	15.9 (10.3)
	Photophobia (*total score*)	2.4 (2.2)
	Allodynia Ictal (*total score*)	3.4 (3.8)
	Insomnia (*total score*)	11.2 (7.0)

Note: *z*-score = *z*-score calculations for normed questionnaire criteria; Headache Pain (*average*) = average headache intensity of post-traumatic headaches on a scale of 0 = no pain to 10 = worst pain; RAVLT = Rey Auditory Verbal Learning task; BDI = Beck Depression Inventory, total score; SCAT Symptom Evaluation (*symptom severity*) = Sport Concussion Assessment Tool (SCAT5), total score calculated by adding all sub-scores (maximum is 132); SCAT Symptom Evaluation (*number of symptoms*) = Sport Concussion Assessment Tool (SCAT5), total number of symptoms (maximum is 22); PCS = Pain Catastrophizing Scale; Photophobia = Photosensitivity Assessment (PAQ), total score; PTSD present = Post-traumatic Stress Disorder Screen (PC-PTSD); Hyperacusis = Hyperacusis Questionnaire, total score; Insomnia = Insomnia Severity Index, total score; Allodynia Ictal = Allodynia Symptom Checklist 12 Ictal, total score.

Abbreviations: f, female; m, male; mTBI, mild traumatic brain injury; n, no; SD, standard deviation; y, yes.

[a]Data is reported as frequency count and percentage within total patients (*N* = 37).

migraine, and 17 had migraine. Five individuals reported aura with headache after mTBI.

At 3 months post-enrollment, 23 patients had headache improvement and 14 patients did not have headache improvement. At the reassessment at 6 months, 17 patients had headache improvement, and 9 individuals did not have headache improvement; the remaining patients were not classified as they had not yet completed their 6-month follow-up at the time of this analysis.

One individual had missing headache frequency for one 7-day window and was imputed by linear interpolation as described in the previous section. Two individuals had missing response for immediate nausea, vomiting, visual disturbance, and dizziness symptoms after injury and were imputed using mode as described in the Methods section.

Prediction of headache improvement at 3 and 6 months post-mTBI

Headache prediction at 3 months

The classification model was trained using all 37 patients and achieved 0.72 (95% CI 0.55 to 0.89) cross-validated (CV) AUC for predicting the headache improvement/non-improvement outcome of each patient at 3 months. The questionnaire PC was a significant predictor for headache status (coefficient $= -0.87$, $p = 0.046$) in the logistic regression model, whereas age (coefficient $= -0.28$, $p = 0.520$), sex (coefficient $= 0.66$, $p = 0.163$), enrollment time post-mTBI (coefficient $= 0.74$, $p = 0.103$), and intercept (coefficient $= 0.76, p = 0.101$) were not significant. It is worth noting that, based on the LOOCV scheme, only the first questionnaire PC was included as a predictor. Thus, the questionnaire PC can be interpreted as an overall symptom score of each patient at baseline. Figure 1 shows the contributions of each questionnaire variable to the model prediction. The 10 most predictive variables included the following: PCS (total score and sub-domain scores for helplessness, magnification, and rumination), SCAT5 (Symptom Evaluation; total score, and total number of symptoms), STAI (Trait Anxiety total score), BDI (total score), and hyperacusis (total score). The five most predictive variables included: PCS (total score and subdomain score for helplessness), SCAT5 (Symptom Evaluation; total score and total number of symptoms), and STAI (Trait Anxiety total score). The reduced model using the top 10 or the top 5 contributing features both achieved 0.72 CV AUC.

Headache prediction at 6 months

For predicting headache improvement/non-improvement at 6 months, the classification model was trained using 26 patients who had the 6-month label and achieved a higher accuracy, 0.84 CV AUC (95% CI 0.66 to 1.00). Similar to the prediction at 3 months, the first questionnaire PC was a significant predictor (coefficient $= -2.02$,

$p = 0.026$) in the logistic regression model whereas age (coefficient $= -1.15$, $p = 0.085$), sex (coefficient $= 0.41$, $p = 0.509$), enrollment time post-mTBI (coefficient $= -0.41$, $p = 0.471$), and intercept (coefficient $= 1.26$, $p = 0.122$) were not significant. The reduced models using the same top 10 or the top 5 predictive features as the previous analysis both achieved 0.77 CV AUC. Figure 2 shows the AUC plots of the predictions of the full model and the reduced models at 3 and 6 months.

Error analysis

The prediction of headache improvement/non-improvement outcome using baseline questionnaires was less accurate at 3 months (AUC 0.72) than at 6 months (AUC 0.84). To investigate the reason for this discrepancy, we examined the two subgroups of patients that had a different headache status at 3 and 6 months: (1) patients with slow improvement, that is, those without improvement at 3 months but with headache improvement at 6 months (four patients, two correctly classified by the 3-month prediction), and (2) patients with headache relapse, that is, those whose headaches appeared improved at 3 months but not at 6 months (three patients, none classified correctly by the 3-month prediction). The 3-month headache status of these two subgroups of patients was more difficult to classify compared to other patients who had more consistent headache patterns.

PREDICTION OF HEADACHE TRAJECTORY OVER THE COURSE OF 3 MONTHS

The functional regression model that predicts the 7-day headache frequency trajectory over the course of 3 months post-mTBI was trained using all patients and achieved $R = 0.64$ ($R^2 = 0.41$). These results suggest that the questionnaire PC has predictive value for the trajectory of headache frequency over the first 3 months post-enrollment. The estimated coefficients for the scalar regressors age, sex, enrollment time after mTBI, and constant intercept were 0.01 ($p < 0.001$), -0.003 ($p = 0.729$), 0.002 ($p < 0.001$), 0.67 ($p < 0.001$), respectively. Figure 3 shows the estimated time-varying intercept and time-varying coefficient of the clinical PC with their 95% CIs. The estimated intercept can be interpreted as the mean headache frequency when all other regressors are zero (for example, a female, average-aged patient enrolled 0 days after mTBI and with the worst clinical symptoms at baseline). Figure 3A shows that the mean headache frequency for patients with this profile is decreasing linearly over time, that is, headaches are improving at a constant rate. From Figure 3B, there are two main observations. (1) Overall, the time-varying coefficient is negative, which implies that a lower score on the questionnaire PC (representing a worse overall clinical symptom at baseline) is associated with a higher headache frequency. (2) The magnitude of the time-varying coefficient is the smallest at the beginning of the
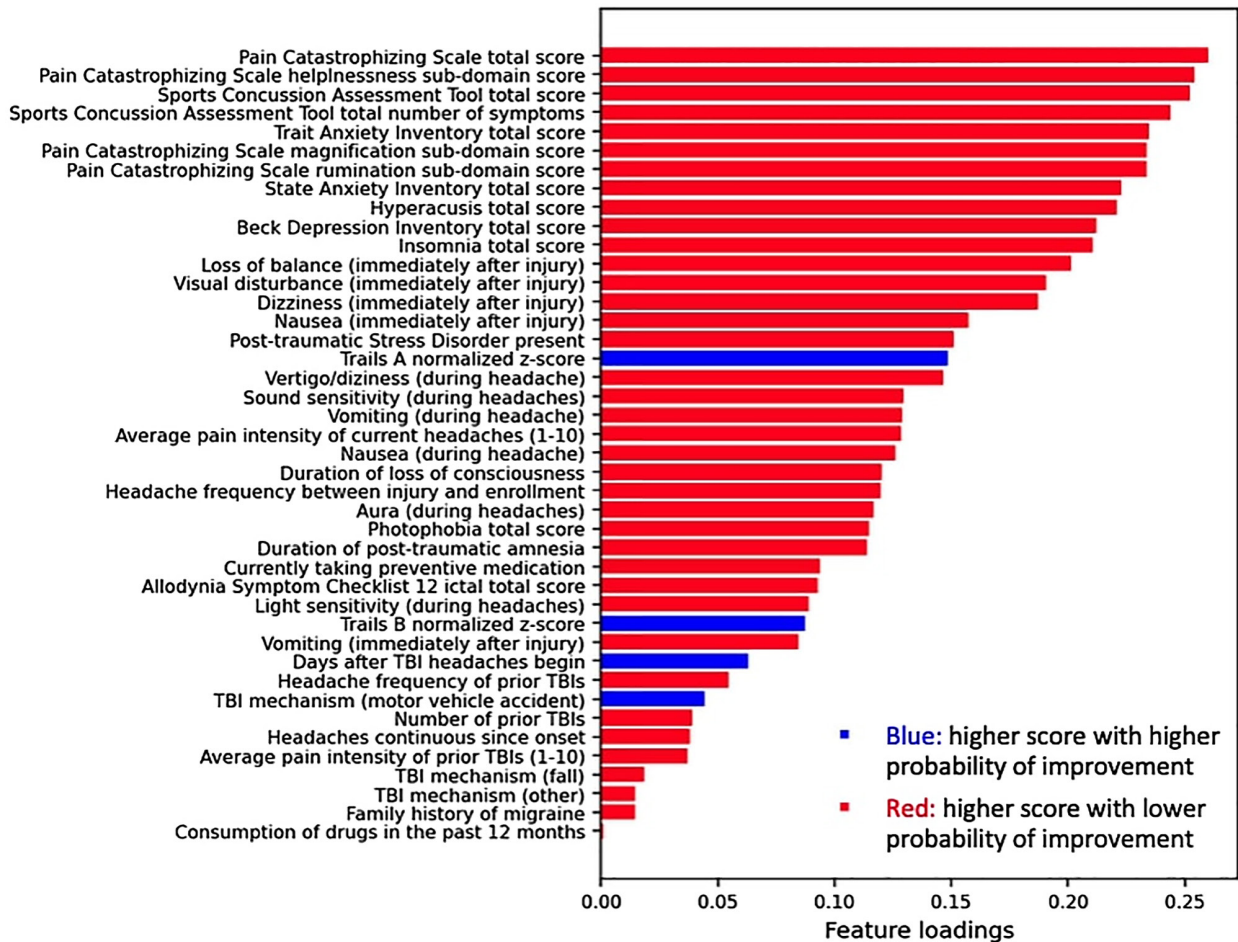
FIGURE 1 Contribution of clinical variables to the prediction of headache improvement/non-improvement obtained from PCA loadings. Blue bars = variables with higher scores have higher predicted probability of headache improvement; red bars = variables with higher scores have higher predicted probability of non-improving headache. Higher scores contributed more positively or negatively to the probability of headache improvement or non-improvement. PCA, principal components analysis; TBI, traumatic brain injury.

time course and peaks around 20 days. This suggests that the association between baseline clinical symptoms and headache frequency is initially weaker but strengthens over time as headache frequency patterns become more stable.

Furthermore, Figure 4 visualizes the headache frequency trajectories of each patient over the first 3 months post-enrollment predicted by the functional regression model. The model predicted different trajectories of headache frequency among these individuals based on questionnaires completed at baseline. For example, patients A (red) and B (blue) started at a similar level of headache frequency. Patient A was predicted to have a slowly improving headache frequency trajectory, whereas patient B was predicted to have a fast improvement in the first month post-enrollment.

In the sub-analysis, the functional regression models achieved *R* of 0.63, 0.66, and 0.65 for predicting headache evolving during the first 2 weeks, 1 month, and 2 months, respectively. These results show that goodness of fit increases in the first weeks, remains at a similar level within the first 2 months, and decreases as the time

course extends beyond, indicating that the best time window of prediction using functional regression is 1 or 2 months post-enrollment. These results imply that clinical variables collected at baseline may start losing predictive power for headache frequency beyond 2 months.

In summary, these two types of models based on clinical questionnaires can be helpful to provide an early prediction of the patients' likelihood for headache improvement/non-improvement at 3 and 6 months in the future and to project patients' potential headache trajectory over the first 3 months.

DISCUSSION

Measures from six questionnaires measuring pain catastrophizing (PCS), situational and general anxiety (STAI), depression (BDI), hyperacusis, and mTBI-related symptoms (SCAT5, Symptom Evaluation) were the top 10 predictors for headache improvement.
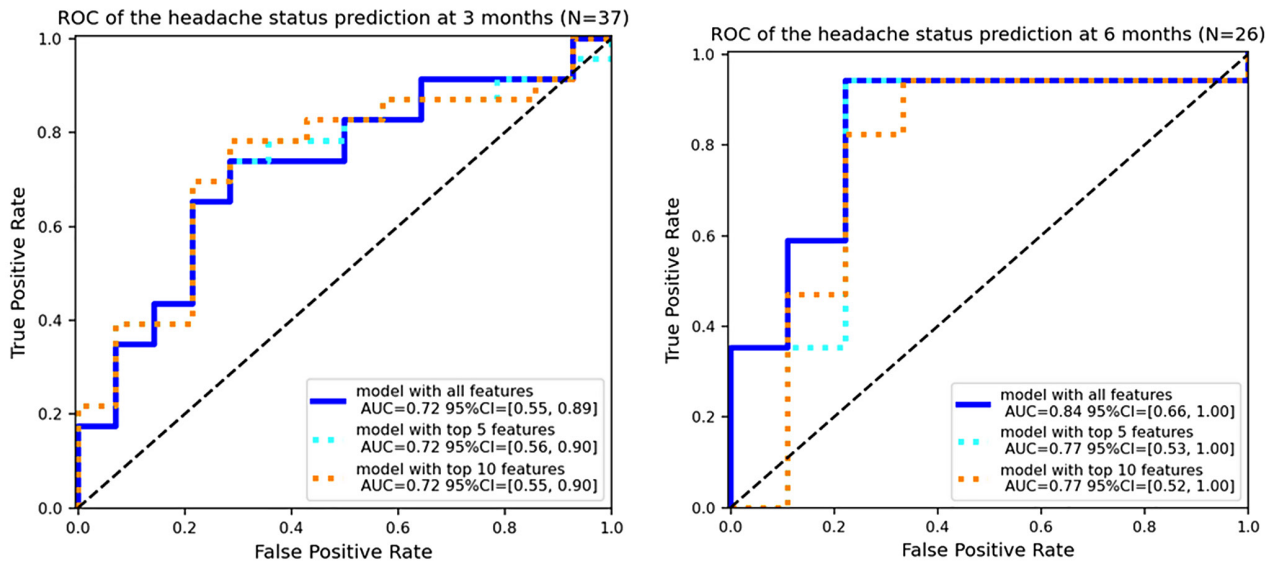
FIGURE 2 Receiver operating characteristic (ROC) curves and area under the curve (AUC) of the multivariate classification model's predictions of headache improvement/non-improvement at 3 months (left) and at 6 months (right) post-enrollment using only clinical characteristics at baseline. The solid blue line shows the ROC curve of the model trained using all 42 features; and the dotted lines show the ROC curve of the reduced models trained using only the top 10 and the top 5 contributing features. 95%CI, 95% confidence interval.
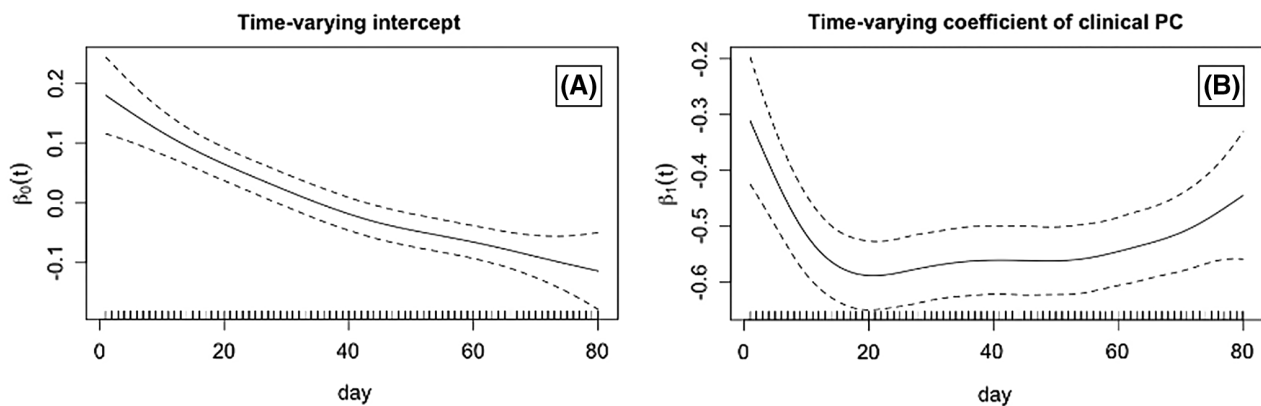
FIGURE 3 Estimated time-varying intercept (A) and time-varying coefficient of clinical principal components (PC; B) with their 95% confidence intervals of the functional regression model to predict headache trajectory over the first 3 months post-enrollment.

The top five predictors were measures of pain catastrophizing, general anxiety, and mTBI-related symptoms. Results indicate that trimming down the testing battery to only three questionnaires (PCS; SCAT5, Symptom Evaluation; STAI) yields good accuracy for predicting headache improvement at 3 months (AUC = 0.72) and at 6 months (AUC = 0.77).

Biopsychosocialecologic factors play a critical role in the pain experience.[26] Pain catastrophizing including rumination, magnification, and helplessness are closely linked to anxiety and depression,[27,28] related to poor outcome,[29] and are a predictor of chronic pain, regardless of the type of physical pain that is experienced.[30] The Symptom Evaluation subtest of the SCAT5, a standardized tool designed originally as a sideline test to assess sports-related concussion symptoms, captures physical (including headache), cognitive and psychological concussion-related symptoms. In this study, the symptom total score (and number of symptoms) were strong predictors for non-improving headache. Previous data suggest that more symptoms (including headache) reported immediately after mTBI predicts more severe symptoms at 1-week follow-up and longer recovery from post-concussive symptoms.[31,32] Hyperacusis is a common symptom in migraine and has been reported in patients with persistent PTH.[33] Tinnitus (but not hyperacusis) was also found to be a predictor for headache persistence in a cohort study among veterans with acute PTH.[34]

In contrast to previous findings,[6,35,36] in this study female sex, migraine history, and concussion history were not strong predictors for non-improving headache relative to other predictors. These discrepancies in findings may be due to differences in

Predicted headache frequency trajectories over the first three months post-enrollment
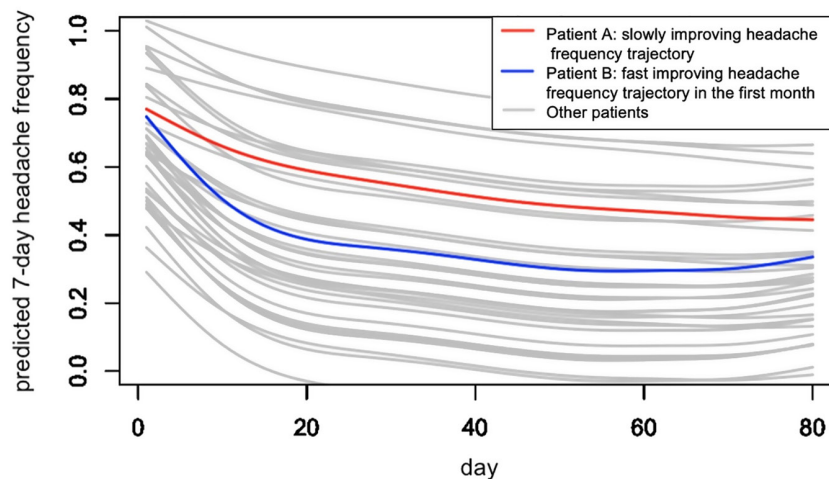
FIGURE 4 Predicted headache frequency of each patient over the first 3 months post-enrollment by functional regression. The predicted curves of two patients, A and B, are highlighted as examples.

cohort selection or related to differences in outcome prediction measures.

The observation that the prediction of headache status at 6 months had a higher AUC than at 3 months suggests that clinical questionnaires completed on an average of 3 weeks post-mTBI inform more about long-term improvement/non-improvement when headache status is more stabilized. Furthermore, a comparison of the 3- and 6-month headache status assessment of each patient reveals that there may exist more nuanced subgroups of patients beyond the binary status, such as subgroups of slow or fast improvement, relapse, and stable persistence, thus indicating the need for more refined classification models in the future.

The functional regression results indicate that clinical variables collected at baseline can be used to predict patients' trajectories of headache frequency over time. Specifically, the best time window of headache trajectory prediction using functional regression was during the first 1 or 2 months post-enrollment ($R = 0.65$) when patients' headache patterns are beginning to stabilize. This trajectory prediction can complement the binary headache status prediction with more granular visualization of headache changes over time.

Note that only the first PC from PCA was included as a predictor in the downstream regression models. While including more components as predictors would allow capturing a greater proportion of variance (i.e., information) of the original data, using more predictors would increase the overfitting risk given the small sample size. Our conservative choice of only including the first component assumes that the major source of variability in the data comes from major patterns that are useful to classify headache improvement versus non-improvement, whereas the remaining components capture minor sources of variability due to patient heterogeneity.

This study has several limitations. Only 26 out of 37 individuals with PTH had 6-month follow-up recovery status, which was due to

loss of follow-up or due to individuals not yet having completed their 6-month follow-up visit. This study has a small sample size. While several strategies were adopted to avoid the risk of overfitting such as including a minimal number of predictors and using a LOOCV scheme, it will be an important task to validate the findings using an external validation dataset in future studies. A significant proportion of information contained in the original data was discarded after dimension reduction. Future studies with a larger sample size will allow development of models that can better exploit the predictive ability of the clinical questionnaires for headache improvement. To reduce the number of features (to prevent model overfitting), we did not include individual questions from each questionnaire in the model, and instead included only total scores (or sub-scores) from each of the questionnaires in the model. Although this approach was reasonable from a statistical standpoint, it may have prevented us from capturing specific symptoms that have relevance for predicting patient outcomes. Furthermore, we also did not include PTH phenotype or headache severity in the model, which could have further improved prediction accuracy as indicated by a recent, large-scale study by Kamins et al.[36] To achieve enrollment success, we purposefully enrolled individuals between 0 and 59 days post-mTBI. It is therefore likely that those individuals that were enrolled after a longer interval post-mTBI have a higher likelihood of developing PTH persistence compared to individuals that enrolled within days after mTBI.

CONCLUSION

Three questionnaires that assess post-concussive symptom load (SCAT5 Symptom Evaluation total score and number of symptoms) and biopsychosocialecologic factors (PCS total score and helplessness sub-domain score, and the Trait Anxiety total score) are helpful for determining headache improvement at 3 months (AUC = 0.72)

and at 6 months (AUC = 0.77) post-mTBI. The early identification and treatment of these physical and biopsychosocialecologic symptoms could be beneficial to headache recovery. The questionnaires also provide value to predict headache frequency trajectories over the course of the first 3 months ($R = 0.64$), which offers more temporal granularity of how patients' headache patterns change over time. Future studies with larger sample sizes and an independent testing group are needed to confirm these results.

AUTHOR CONTRIBUTIONS

Study concept and design: Lingchao Mao, Gina Dumkrieger, Dohyun Ku, Katherine Ross, Visar Berisha, Todd J. Schwedt, Jing Li, Catherine D. Chong. *Acquisition of data*: Gina Dumkrieger, Todd J. Schwedt, Catherine D. Chong. *Analysis and interpretation of data*: Lingchao Mao, Gina Dumkrieger, Dohyun Ku, Katherine Ross, Visar Berisha, Todd J. Schwedt, Jing Li, Catherine D. Chong. *Drafting of the manuscript*: Lingchao Mao, Gina Dumkrieger, Dohyun Ku, Katherine Ross, Visar Berisha, Todd J. Schwedt, Jing Li, Catherine D. Chong. *Revising it for intellectual content*: Lingchao Mao, Gina Dumkrieger, Dohyun Ku, Katherine Ross, Visar Berisha, Todd J. Schwedt, Jing Li, Catherine D. Chong. *Final approval of the completed manuscript*: Lingchao Mao, Gina Dumkrieger, Dohyun Ku, Katherine Ross, Visar Berisha, Todd J. Schwedt, Jing Li, Catherine D. Chong.

CONFLICTS OF INTEREST

Lingchao Mao, **Dohyun Ku**, **Katherine Ross**, and **Jing Li** declare no conflicts of interest. **Gina Dumkrieger** declares research funding from Amgen. **Catherine D. Chong** has received research funding from Amgen. **Visar Berisha** is co-founder and has equity in Aural Analytics, Inc. Within the last 12 months, **Todd J. Schwedt** has served as a consultant for Abbvie, Allergan, Biohaven, Click Therapeutics, Eli Lilly, Equinox, Lundbeck, Novartis, and Tonix. He has stock options in Aural Analytics and Nocira. He has received royalties from UpToDate. He has received research funding from Amgen, American Migraine Foundation, Henry Jackson Foundation, National Institutes of Health, Patient Centered Outcomes Research Institute, and U.S. Department of Defense. He serves on the Board of Directors for the American Headache Society and the International Headache Society.

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