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Prediction of Persistent Post-Concussion Symptoms after Mild Traumatic Brain Injury

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Abstract

Persistent post-concussion symptoms (PPCS) occur frequently after mild traumatic brain injury (mTBI). The identification of patients at risk for poor outcome remains challenging because valid prediction models are missing. The objectives of the current study were to assess the quality and clinical value of prediction models for PPCS and to develop a new model based on the synthesis of existing models and addition of complaints at the emergency department (ED). Patients with mTBI (Glasgow Coma Scale score 13–15) were recruited prospectively from three Dutch level I trauma centers between 2013 and 2015 in the UPFRONT study. PPCS were assessed using the Head Injury Severity Checklist at six months post-injury. Two prediction models (Stulemeijer 2008; Cnossen 2017) were examined for calibration and discrimination. The final model comprised variables of existing models with the addition of headache, nausea/vomiting, and neck pain at ED, using logistic regression and bootstrap validation.

Overall, 591 patients (mean age 51 years, 41% female) were included; PPCS developed in 241 (41%). Existing models performed poorly at external validation (area under the curve [AUC]: 0.57–0.64). The newly developed model included female sex (odds ratio [OR] 1.48, 95% confidence interval [CI] [1.01–2.18]), neck pain (OR 2.58, [1.39–4.78]), two-week post-concussion symptoms (OR 4.89, [3.19–7.49]) and two-week post-traumatic stress (OR 2.98, [1.88–4.73]) as significant predictors. Discrimination of this model was adequate (AUC after bootstrap validation: 0.75). Existing prediction models for PPCS perform poorly. A new model performs reasonably with predictive factors already discernible at ED warranting further external validation. Prediction research in mTBI should be improved by standardizing definitions and data collection and by using sound methodology.

Keywords: external validation; mild traumatic brain injury; post-concussion symptoms; prediction model

Introduction

MILD TRAUMATIC BRAIN INJURY (mTBI) is a common condition in the general population¹ and is associated with substantial burden to patients and relatives and high societal costs.² A considerable proportion of patients with mTBI report post-concussion symptoms (PCS), including cognitive (e.g., memory problems, cognitive deficits), somatic (e.g., headache, nausea), and emotional symptoms (e.g., depression, irritability) days to weeks after injury.^{2,3} Although it is generally assumed that these symptoms resolve within weeks to months,^{2,3} recent prospective studies indicate persistence of post-concussion symptoms (PPCS) in a large subset of patients six months to one year post-injury^{4,5} or even longer.⁶ PPCS is associated

with work absenteeism⁷ and a reduction in health-related quality of life.^{7,8} Given the high prevalence of mTBI in the general population,⁹ PPCS can be considered as a serious public health concern.

Patients with PPCS often seek help between three and six months after injury.¹⁰ Interventions to prevent and reduce PPCS, however—e.g., cognitive behavioral therapy—are especially promising when provided early post-injury.¹¹ The identification of risk-prone patients could be accomplished by the development of a prediction model—a mathematical tool estimating the risk of PPCS in individual patients with mTBI. Despite an abundant number of studies aiming to identify predictors for PPCS, no study to date has successfully developed a prediction model that could be implemented in clinical practice.^{12–14}

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A prerequisite for implementation is the external validation of a model in an independent set of patients. Yet, none of the existing models for PPCS has been validated externally.^{12,14} In addition, although prognostic research has focused extensively on pre-injury characteristics^{12,14} and post-injury characteristics,^{12,14} the role of acute complaints at the emergency department (ED, e.g., headache, nausea, vomiting, or neck pain) is studied less often. These complaints have the potential to be relevant predictors^{15,16} and could be applied easily to a prediction model as they are gathered during standard clinical assessment on ED examination.

Utilizing the Dutch multi-center prospective observational UPFRONT study, we aimed: (1) to assess the quality and clinical value of existing prediction models for six-month PPCS in patients with mTBI; and (2) to develop a new model ("The UPFRONT-PPCS model") based on relevant predictors from existing models and complaints at the ED.

Methods

This study was conducted and reported according to the criteria of the "Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis" (TRIPOD) statement.¹⁷

Patient population

Data were obtained from a prospective cohort study conducted in three level I trauma centers in the Netherlands (the UPFRONT study).¹⁸ Patients admitted to the EDs of these centers between 2013 and 2015 were included if they were 16 years or older, had an admission Glasgow Coma Scale (GCS) score of 13–15, had post-traumatic amnesia (PTA) or loss of consciousness (LOC), and had sufficient comprehension of the Dutch language. Exclusion criteria included drug or alcohol addiction, homelessness, and dementia. The UPFRONT study was approved by the local medical ethics committee of the University Medical Center Groningen, which acted as a central committee for the three participating centers. All patients provided written informed consent.

Measurements

Demographics, pre-injury characteristics and complaints at the ED. Demographics and clinical variables and the presence of a previous TBI were extracted from hospital records. Education was divided into low (<11 years of formal education), middle (11–14 years of formal education), and high (>14 years) of formal education; LOC and PTA were noted as present or absent. All patients received a computed tomography (CT) scan, which was scored as normal (Marshall score = 1) or abnormal (Marshall score >1 indicating any lesions, compressed cisterns, or midline shifts). The following complaints were examined during ED admission: headache, nausea/vomiting, and neck pain. Information on pre-injury characteristics was examined with a short questionnaire completed by patients.

PPCS. The PCS at two weeks and six months post-injury were assessed with the Head Injury Symptom Checklist (HISC).¹⁹ The HISC consists of 21 frequently reported symptoms, and patients were asked to complete each item, for both the pre-injury and current level, on a three-point scale (never, sometimes, often). The HISC can be directly mapped to the *International Statistical Classification of Diseases and Related Health Problems (ICD-10)* criteria for post-concussion syndrome, because all eight syndromic symptoms are examined. Patients were classified subsequently as having PCS (persisting for two weeks) and PPCS (persisting for six months) if they indicated that at least three of the following symptoms were worse than before the injury (difference score of 1 or 2): (1) headache; (2) dizziness; (3) fatigue; (4) irritability;

(5) difficulties falling asleep or staying asleep; (6) concentration problems; (7) memory difficulties; or (8) intolerance of alcohol or being anxious as indicator for the *ICD-10* symptom "reduced tolerance to stress, emotional excitement or alcohol."

Post-traumatic stress symptoms. Post-traumatic stress symptoms at two weeks were examined with the Impact of Event Scale (IES),²⁰ a 15-item questionnaire in which patients have to rate whether they experience intrusive and avoidant post-traumatic stress symptoms on a five-point Likert scale, resulting in a minimum score of 0 and a maximum score of 75. Scores above 26 were classified as severe, in line with recommendations.²¹

Selection of prediction models

Existing prediction models were identified by screening reference lists of systematic reviews on prognosis after mTBI^{12,14} and by updating the search strategy of Silverberg and associates¹² until March 2017. Models were considered eligible for our study if they were developed in prospectively collected data on adult patients (age ≥16 years) with mTBI (Supplementary Table A; see online supplementary material at ftp.liebertpub.com). To be included, studies had to fulfill at least one of three quality criteria²²: (1) a large sample size (N > 500 patients); (2) >10 cases (patients with PPCS) for each candidate predictor considered; or (3) the use of shrinkage or internal validation.

Two models met our eligibility and quality criteria (Supplementary Table B; see online supplementary material at ftp.liebertpub.com).^{23,24} Stulemeijer and coworkers²³ had developed a prediction model based on data from a level I trauma center in the Netherlands (2004–2006) to predict six-month PPCS using the Rivermead Post Concussion Questionnaire (RPQ). They investigated 201 patients among whom PPCS developed in 49. Among the 19 candidate predictors, three (pre-injury physical comorbidities, early PCS, early post-traumatic stress) were included in their final model. The final model had an area under the curve (AUC) of 0.82, which decreased to 0.73 after bootstrap validation.

Cnossen and colleagues²⁴ had developed a prediction model based on 277 patients from three level I trauma centers in the United States (2010–2012) applying the RPQ. The RPQ was used as a linear scale, and 14 candidate predictors available at the ED were considered. After least absolute shrinkage and selection operator (LASSO) procedure and bootstrap validation, the final model with eight predictors (age, sex, years of education, pre-injury migraine or headache, pre-injury psychiatric disorders, previous TBI, PTA, and LOC) explained 14% of the variation in outcome. The final set of predictors was examined in a logistic model with the RPQ dichotomized according to the *ICD-10* criteria, resulting in an AUC of 0.74. A list of included and excluded studies as well as detailed characteristics of the included prediction models are presented in Supplementary Tables C and D; see online supplementary material at ftp.liebertpub.com.

Statistical analyses

Patient characteristics were reported by medians and inter-quartile ranges (IQR) for continuous variables and frequencies and percentages for categorical variables. To assess the possible influence of loss to follow-up, we compared characteristics of patients who completed the six-month outcome assessment and patients who were lost to follow-up using chi-square and Mann-Whitney *U* tests, because all continuous variables had a skewed distribution. Missing data on candidate predictors were subsequently imputed using multiple imputation.

The quality and clinical value of the two existing prediction models were assessed by examining the external validity in terms of calibration and discrimination. Calibration refers to the agreement between observed and predicted outcomes. Calibration was

assessed graphically and expressed as calibration-in-the-large, indicating whether predictions are systematically too low (calibration-in-the-large >0) or too high (calibration-in-the-large <0) and calibration slope (indicating the average strength of predictor effects and ideally equal to 1). Discrimination refers to the ability of a model to distinguish between patients in whom PPCS will or will not develop and was expressed as the AUC. An AUC of 1 implies perfect discrimination and an AUC of 0.5 indicates that the model is no better than random chance.

All variables from the Stulemeijer and coworkers²³ and Cnossen and colleagues²⁴ models were available in the UPFRONT data. Education, however, was measured as a continuous variable in study by Cnossen and colleagues²⁴ but as a categorical variable in the UPFRONT dataset. Therefore, for the external validation, we used the mean years of education for each category (low education: 8 years, middle education: 12 years, higher education: 15 years).

To examine the role of complaints at the ED (headache, nausea or vomiting, neck pain), we developed a new model with all predictors from the Stulemeijer and coworkers²³ and Cnossen and colleagues²⁴ models in a backward selection procedure ($p < 0.157$).²⁵ We subsequently assessed whether the addition of complaints at the ED (headache, neck pain, nausea or vomiting) significantly improved this model by comparing goodness-of-fit of a model with and without complaints at the ED. To correct for optimism of the new model, we used bootstrap validation with 100 samples, where all modeling steps were repeated. Analyses were performed using SPSS statistics version 21.0 and R (version 3.2.2) using the *rms*, *foreign*, *PROC*, and *mice* packages.

Explorative analyses

Because the included prediction models did not contain all relevant predictors found in the literature (e.g., predictors identified by systematic reviews^{12,14} and recent publications^{5,6}), we explored the association between a set of additional potential relevant predictors and PPCS. We subsequently estimated the unadjusted OR and the adjusted OR, which was adjusted for the predictors included in the final model. Only those predictors that were measured in the UPFRONT study and occurred in at least 10% and maximum 90% of the patients were considered.

Results

Patient population

A total of 1151 patients were included in the UPFRONT study, of whom 591 (51%) completed the six-month HISC. Included patients had a median age of 51 years (IQR range 32–64), and 41% ($n = 241$) were female. Sixteen percent ($n = 94$) had intracranial traumatic abnormalities on the initial head CT scan. Patients included in the study were significantly older ($p < 0.01$), more often female ($p = 0.03$), and showed more CT abnormalities ($p = 0.01$) than patients lost to follow-up. In addition, patients included in the study less often reported pre-injury psychiatric disorders ($p = 0.04$) and more often reported pre-injury physical disorders ($p = 0.04$; Table 1).

TABLE 1. CHARACTERISTICS OF SUBJECTS INCLUDED IN THE STUDY AND SUBJECTS LOST TO FOLLOW-UP

Variable	Included subjects (n = 591)		Subjects lost to follow-up (n = 560)		p
	Missing	N (%)	Missing	N (%)	
Demographic and pre-injury characteristics					
Age (median, IQR range)	-	51 (32–64)	-	34 (22–53)	<0.01
Sex (female)	-	241 (41%)	-	194 (35%)	0.03
Education ^a	31		249		0.07
- Low		105 (19%)		66 (21%)	
- Middle		210 (37%)		134 (43%)	
- High		245 (44%)		111 (36%)	
Pre-injury psychiatric disorders ^b	30	58 (10%)	238	58 (18%)	<0.01
Pre-injury physical disorders ^c	-	185 (31%)	-	145 (26%)	0.04
Pre-injury headache or migraine	57	156 (29%)	279	87 (31%)	0.60
Prior TBI	131	15 (3%)	113	27 (6%)	0.05
ED characteristics					
CT abnormalities ^d	13	94 (16%)	8	61 (11%)	0.01
LOC	3	494 (84%)	3	483 (87%)	0.20
PTA	37	490 (88%)	41	440 (85%)	0.08
Headache	87	263 (52%)	63	259 (52%)	0.98
Nausea or vomiting	92	173 (35%)	78	174 (36%)	0.64
Neck pain	120	71 (15%)	97	91 (20%)	0.07
Early post-injury symptoms					
2-week PCS ^e	160	240 (56%)	348	108 (51%)	0.26
2-week post-traumatic stress ^f	117	114 (22%)	287	69 (25%)	0.20

IQR, interquartile range; TBI, traumatic brain injury; ED, emergency department; CT, computed tomography; LOC, loss of consciousness; PTA, post-traumatic amnesia; PCS, post-concussion symptoms.

^aLow education=less than 11 years of formal education; middle education=11–14 years of formal education; high education=15 or more years of formal education.

^bIncludes any psychiatric disorder necessitating treatment by a psychologist or psychiatrists or use of psychotropic medication, or both.

^cIncludes cerebrovascular accident, heart diseases, hypertension, diabetes, asthma or other respiratory diseases, epilepsy, or any malignant disorder.

^dAny lesions, compressed cisterns, or midline shifts.

^eMeeting the ICD-10 criteria for post-concussion symptoms, 2 weeks post-injury.

^fScore on the Impact of Events Scale above 26, 2 weeks post-injury.

PPCS

At six months post-injury, 370 (63%) patients reported at least one of eight symptoms. A total of 241 (41%) patients reported three or more symptoms, indicating PPCS according to our criteria. Fatigue (38%), concentration problems (36%), and memory problems (35%) were most frequently reported (Fig. 1).

Quality and clinical value of existing models

Both existing models performed poorly in external validation, with an AUC of 0.64 (95% CI 0.60–0.68) for the Stulemeijer and associates²³ model and an AUC of 0.57 (95% CI 0.52–0.62) for the Cnossen and colleagues²⁴ model (Fig. 2). Both models systematically underestimated the proportion of patients with PPCS (calibration-in-the-large >0) and average effects of the set of predictors were too low (calibration slopes <1).

Development of the UPFRONT-PPCS model

Backward selection ($p < 0.157$) with all variables from the Stulemeijer and associates²³ and Cnossen and colleagues²⁴ models resulted in the inclusion of three variables: female sex (OR 1.48, 95% CI 1.01–2.18), two-week PCS (OR 4.89, 95% CI 3.19–7.49), and two-week post-traumatic stress (OR 2.98, 95% CI 1.88–4.73; Table 2).

The addition of complaints at the ED (headache, nausea or vomiting, and neck pain) significantly improved the model ($p < 0.01$). Of these complaints, only neck pain was statistically significantly associated with six-month PPCS (OR 2.58, 95% CI 1.39–4.78). The AUC of the final prediction model was 0.77 and decreased to 0.75 after bootstrap validation (Table 2).

The PCS after two weeks was the strongest predictor in the model: among the 241 patients with six-month PPCS, 192 (80%) already reported three or more symptoms after two weeks, and almost all patients ($n = 233$, 97%) reported at least one symptom after two weeks. Among the patients reporting three or more symptoms after two weeks ($n = 333$), however, only half ($n = 192$) still reported three or more symptoms after six months. We identified seven patients who had the criteria for all risk factors in the prediction model, and PPCS developed in all of them after six months. A total of 73 patients did not have any of the risk factors, among whom PP still developed in 12 (16%). These 12 patients all

had a history of psychiatric disorders, and 10 patients (83%) also had sustained a previous TBI.

An overview of all uni- and multi-variable associations of predictors is shown in Table 3.

Explorative analyses

In the explorative analyses, we did not find an association between additional demographic and injury-related factors and the development of PPCS. In addition, CT abnormalities were not associated with a higher risk of PPCS. We found, however, that patients with a GCS score lower than 15, patients admitted to the hospital, patients reporting dizziness, and patients having enhanced scores on the symptom checklist (SCL)-90 or the hospital anxiety and depression scale (HADS) after two weeks had a higher odds of PPCS developing in both univariable and multi-variable analyses (Table 4).

Discussion

The aims of the present study were to assess the quality and clinical value of existing prediction models for PPCS and to develop a new model based on the synthesis of predictors from previous models and the addition of symptoms at the ED. Existing models for six-month PPCS performed poorly in an independent set of patients with mTBI. Our new model, including female sex, complaints at the ED, and two-week PCS and post-traumatic stress as predictors, performed reasonably and can therefore be potentially valuable for clinical practice. Yet, external validation in a new and independent set of patients with mTBI is necessary to confirm its validity and applicability.

In our newly developed model, we found that female sex, early PCS, and early post-traumatic stress were associated with six-month PPCS, which is congruent with a systematic review on prognosis after mTBI.¹² In addition, we found that neck pain was a significant predictor. Although the influence of neck pain on PPCS has not been studied in large-scale prospective studies before, our findings are in line with the emerging view that concomitant cervical soft tissue injury may contribute to prolonged sequelae after mTBI.²⁶ Headache and nausea or vomiting were not statistically significantly associated with PPCS in the final prediction model. We did find, however, a statistically significant association between

FIG. 1. Frequency of post-concussion symptoms six months post-injury. Figure shows the percentage of patients who reported that the symptom was worse than before the injury.

FIG. 2. Calibration plots for external validation Stulemeijer and associates²³ and Cnossen and colleagues²⁴ models. X-axis shows predicted probabilities by the model in quantiles of patients, and Y-axis shows observed proportion. The dotted diagonal lines represent perfect predictions. The triangles indicate the observed outcome frequency in quantiles of predicted probabilities, with 95% confidence interval. Calibration -i.t.l.=Calibration-in-the-large.

headache and PPCS in univariable analyses, in line with a previous study.¹⁵ The lack of significance in multi-variable analyses might be caused by the relatively strong association between headache and early PCS; among those patients with headache, 65% ($p < 0.01$) was classified as having PCS after two weeks.

Among the predictors in our final model, early PCS was the strongest predictor and showed high sensitivity—i.e., 80% of those patients with PPCS already reported three or more symptoms after two weeks. This was in line with a 2015 study stating that 82% of

TABLE 2. PREDICTION MODEL FOR SIX-MONTH BASED ON EXISTING MODELS AND THE ROLE OF EMERGENCY DEPARTMENT SYMPTOMS

Variable	OR (95% CI)
Female sex	1.48 (1.01 – 2.18)
Nausea or vomiting	0.88 (0.54 – 1.43)
Headache	0.94 (0.61 – 1.47)
Neck pain	2.58 (1.39 – 4.78)
2-week PCS	4.89 (3.19 – 7.49)
2-week post-traumatic stress	2.98 (1.88 – 4.73)
AUC	0.77
AUC after bootstrap validation	0.75

OR, odds ratio; CI, confidence interval; AUC, area under the curve; PCS, post-concussion symptoms.

Intercept: $B = -2.241$

the patients experiencing PPCS one year after mTBI already reported symptoms one month post-injury.²⁷ Specificity, however, was much lower, with approximately half of the patients reporting three or more symptoms after two weeks having PPCS develop after six months.

The feasibility of two-week PCS as predictor for PPCS is nevertheless hampered by the practical constraint that patients with mTBI are rarely followed-up routinely.²⁸ A history of psychiatric disorders and a previous TBI were not statistically significantly associated with PPCS in our study, despite being consistent predictors in previous investigations.^{12,24} Nevertheless, among the 12 patients in this study in whom PPCS developed despite having none of the risk factors from the prediction model, all had a history of psychiatric disorders, and the large majority also had sustained a previous TBI. Therefore, these predictors might still be important for a subset of patients and should therefore be included in future prediction models.

In our explorative analyses, we found an association between PPCS and mTBI severity, as indicated by a GCS score lower than 15 and/or hospital admission, which are probably inter-correlated. This association was not found in the studies by Stulemeijer and associates,²³ Cnossen and colleagues,²⁴ and neither in the systematic review by Silverberg and coworkers.¹² We found additionally that all symptoms measured after two weeks were statistically significantly associated with PPCS, even after adjusting for two-week PCS and two-week post-traumatic stress disorder. This finding strengthens current ideas that early symptoms are highly relevant in the prediction of long-lasting symptoms^{6,12,27} and may imply that future prediction modeling studies should incorporate a comprehensive list of early symptoms. The explorative analyses in Table 4 should be interpreted with caution, however, because we examined a large number of predictors without strong and pre-specified hypotheses. Consequently, some of the significant associations might be the result of chance.

The present study was the first that assessed the quality and clinical value of existing prediction models for PPCS after mTBI by performing an external validation study. Strengths of our study include the comprehensive search strategy for existing models and the large sample size, which is a requirement for external validation of logistic regression models.^{29,30} In addition, our final prediction model was developed according to methodological recommendations for prediction modeling.^{13,22,31,32} Further, we used the definition for mTBI as set by the American Congress of

TABLE 3. UNIVARIABLE AND MULTI-VARIABLE ASSOCIATIONS OF ALL PREDICTORS IN THIS STUDY AND SIX-MONTH PERSISTENT POST-CONCUSSION SYMPTOMS

Variable	Univariable association OR (95% CI)	Multivariable association OR (95% CI)
Age ^a	0.99 (0.99 – 1.00)	0.99 (0.98 – 1.01)
Female gender ^a	2.40 (1.60 – 3.14)	1.56 (1.05 – 2.32)
Education ^a		
- Low vs. medium/high	1.10 (0.69 – 1.73)	0.87 (0.54 – 1.72)
- Medium vs. low/high	1.26 (0.87 – 1.83)	1.39 (0.91 – 2.13)
Pre-injury physical comorbidities ^{ab}	1.05 (0.74 – 1.50)	1.20 (0.73 – 1.95)
Pre-injury migraine or headache ^a	1.06 (0.74 – 1.51)	0.96 (0.63 – 1.47)
Pre-injury psychiatric disorders ^a	1.63 (0.92 – 2.86)	1.18 (0.64 – 2.18)
Prior TBI ^a	1.22 (0.46 – 3.27)	1.25 (0.34 – 4.62)
PTA ^a	1.41 (0.82 – 2.40)	1.06 (0.55 – 2.03)
LOC ^a	0.92 (0.59 – 1.44)	0.89 (0.53 – 1.50)
2-week PCS ^b	5.82 (3.94 – 8.60)	5.18 (3.39 – 7.91)
2-week post-traumatic stress ^b	3.22 (2.12 – 4.50)	3.15 (1.93 – 5.16)
ED symptoms		
Headache	1.46 (1.03 – 2.07)	1.15 (0.73 – 1.75)
Nausea or vomiting	1.31 (0.85 – 2.01)	1.13 (0.73 – 1.76)
Neck pain	3.66 (2.23 – 6.01)	3.44 (2.05 – 5.78)

Note. In the multi-variable model, all variables are included. Therefore, the effect estimates might diverge slightly from the effect estimates in Table 4. OR, odds ratio; CI, confidence interval; TBI, traumatic brain injury; PTA, post-traumatic amnesia; LOC, loss of consciousness; PCS, post-concussion symptoms.

^aVariable derived from Cnossen and colleagues²⁴ model.

^bVariable derived from Stulemeijer and associates²³ model.

Rehabilitation Medicine,³³ and the study sample was relatively comparable to other studies including ED patients with mTBI in terms of demographics and mTBI severity. Therefore, the results of our study are probably generalizable to patients with mTBI admitted to the ED.

Limitations include the high percentage of patients lost to follow-up. Although follow-up rates were similar to other prospective studies in patients with mTBI,^{5,34} selection bias cannot be excluded, which could have influenced the significance of predictors.²⁴ Another limitation is that our outcome measurement (HISC)

TABLE 4. EXPLORATIVE ANALYSIS OF ADDITIONAL PREDICTORS

Predictor	Prevalence	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
<i>Demographics</i>			
Living alone	115 (20%) ¹	0.98 (0.65 – 1.49)	0.87 (0.54 – 1.41)
Working or studying	374 (67%) ²	1.23 (0.85 – 1.77)	1.43 (0.92 – 2.22)
<i>Injury mechanism</i>			
Injury involved violence	15 (2.5%)	1.68 (0.60 – 4.70)	0.98 (0.30 – 3.18)
Injury involved alcohol	183 (31%) ³	0.81 (0.57 – 1.16)	1.00 (0.66 – 1.52)
<i>Clinical characteristics and imaging</i>			
GCS score at SEH <15	202 (34%)	1.67 (1.19 – 2.36)	1.62 (1.08 – 2.44)
CT abnormalities (Marshall score >1)	96 (16%)	1.33 (0.84 – 2.04)	1.06 (0.64 – 1.77)
<i>Treatment</i>			
Hospital admission	366 (61.9%)	1.88 (1.33 – 2.67)	2.39 (1.58 – 3.63)
Neurosurgical intervention	4 (0.8%) ⁴	NA	NA
<i>2-week symptoms</i>			
Dizziness	304 (56%) ⁵	4.80 (3.26 – 7.06)	2.40 (1.44 – 4.00)
Relatively high score on the SCL-90 after two weeks	295 (59%) ⁶	4.57 (3.03 – 6.87)	2.15 (1.34 – 3.46)
HADS anxiety >7	87 (16%) ⁷	4.34 (2.64 – 7.14)	2.15 (1.21 – 3.83)
HADS depression >7	88 (16%) ⁷	4.79 (2.90 – 7.90)	2.58 (1.47 – 4.53)

*Odds ratio was adjusted for factors included in the final prediction model in Table 2 (sex, nausea or vomiting, headache, neck pain, 2-week PCS, and 2-week post-traumatic stress).

OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale; ED, emergency department; CT, computed tomography; SCL-90, symptom checklist-90; HADS, hospital anxiety and depression scale.

¹N total = 563

²N total = 555

³N total = 588

⁴N total = 580

⁵N total = 538

⁶N total = 501

⁷N total = 546

differed from the outcome measurement used in both development studies (RPQ). The HISC includes eight symptoms from the *ICD-10* criteria for post-concussion syndrome, whereas the RPQ includes only seven of eight symptoms. In addition, using the HISC, patients rated symptoms for both their current and pre-injury situation, and symptoms were only included if there was evidence of deterioration. In comparison, using the RPQ, patients had to provide one rating. The difference in outcome measurement may have contributed to the poor model performance. For example, poor calibration-in-the-large of both models may have resulted from differences in outcome measurement and subsequent differences in prevalence rates of PPCS among studies.

Another potential source for unsatisfactory model performance in external validation is poor modeling methodology in the development studies.^{32,35} In the model by Stulemeijer and coworkers,²³ the relatively small sample size, the consideration of a large number of candidate predictors and data-driven selection methods may have resulted in statistical overfitting.^{32,35} Statistical overfitting means that a model appears to predict outcome well in the development population, but performs poorly in new patients.³⁵ An example is the extreme and potentially imprecise effect estimate for early post-traumatic stress (OR = 10.0) in the development data, which was based on only 16 patients scoring above the cut-off point.²³ This may have contributed to the low calibration slope found in external validation. In the Cnossen and colleagues²⁴ study, modeling methodology was in line with recommendations.^{22,31,32}

Differences in the operationalization and coding of predictors might, however, have contributed toward poor external validity.³⁵ For example, pre-injury mental health and previous TBI, which were relevant predictors in the study by Cnossen and colleagues,²⁴ were no relevant predictors in the current study. In the study by Cnossen and colleagues,²⁴ these variables were based on self-report without a threshold for severity. In the current study, however, the presence of a previous TBI required documentation from medical records and pre-injury mental problems necessitated that a patient received treatment. This difference in assessment may have caused the large differences in baseline prevalence (pre-injury mental health problems: 32% vs. 10%; previous TBI: 54% vs. 3%) between the Cnossen and colleagues²⁴ study and the current study, influencing performance in external validation.

Next to model-related and measurement-related factors, differences in patient characteristics might further have contributed toward the poor model performance of both models. For example, the current study population is relatively old in comparison with both the Stulemeijer and Cnossen population (median age = 51 vs. 36 and 42) and has a relatively large number of patients in PTA (88% vs. 62% and 63%) and LOC (84% vs. 54% and 69%). The number of patients with CT abnormalities was, however, lower (16% vs. 20% and 34%). These differences might have affected the discriminative ability of the models.

In line with previous work,^{12,27} our study demonstrates the complexity in developing a prediction model for PPCS that is both valid and applicable for clinical practice. Given the heterogeneity of mTBI,² the multi-factorial and complex nature of PPCS,^{27,36} and the lack of unity for definitions and assessment of PPCS,³⁷ improvement in consensus on definitions and standardization of data collection might be necessary before advances in prediction modeling can be accomplished.

A recent initiative to standardize data collection in TBI is the Common Data Elements (CDEs), which have specific recommendations for the measurement of sociodemographic, pre-injury and clinical variables,³⁸ and thereby have the potential to enhance the

comparability of future prognostic studies. For outcome assessment, the CDEs recommend the RPQ to assess PPCS. No guidance is provided, however, on how the RPQ should be analyzed, while this varies widely in clinical practice.^{27,39–42} More detailed recommendations are therefore warranted.

Conclusion

Existing prediction models for persistent post-concussion symptoms perform poorly in an independent set of patients with mTBI. A new model based on factors already discernible at the ED, including female sex and complaints at the ED together with two week post-concussion and post-traumatic symptoms, performs reasonably. External validation is necessary, however, before this model can be considered for clinical practice. In addition, improvement in definition of post-concussion symptoms and standardization of data collection may further aid in future advances in this area.

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