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Prognostic models for depression and post-traumatic stress disorder symptoms following traumatic brain injury: a CENTER-TBI study

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ABSTRACT

Background Traumatic brain injury (TBI) is associated with an increased risk of major depressive disorder (MDD) and post-traumatic stress disorder (PTSD). We aimed to identify predictors and develop models for the prediction of depression and PTSD symptoms at 6 months post-TBI.

Methods We analysed data from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury study. We used linear regression to model the relationship between predictors and depression (Patient Health Questionnaire-9) and PTSD symptoms (PTSD Checklist for Diagnostic and Statistical Manual for Mental Health Disorders Fifth Edition). Predictors were selected based on Akaike's Information Criterion. Additionally, we fitted logistic models for the endpoints 'probable MDD' and 'probable PTSD'. We also examined the incremental prognostic value of 2–3 weeks of symptoms.

Results We included 2163 adults (76% Glasgow Coma Scale=13–15). Depending on the scoring criteria, 7–18% screened positive for probable MDD and about 10% for probable PTSD. For both outcomes, the selected models included psychiatric history, employment status, sex, injury cause, alcohol intoxication and total injury severity; and for depression symptoms also preinjury health and education. The performance of the models was modest (proportion of explained variance=R^2 8% and 7% for depression and PTSD, respectively). Symptoms assessed at 2–3 weeks had a large incremental prognostic value (delta R^2=0.25, 95% CI 0.24 to 0.26 for depression symptoms; delta R^2=0.30, 95% CI 0.29 to 0.31 for PTSD).

Conclusion Preinjury characteristics, such as psychiatric history and unemployment, and injury characteristics, such as violent injury cause, can increase the risk of mental health problems after TBI. The identification of patients at risk should be guided by early screening of mental health.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The rates of depression and post-traumatic stress disorder (PTSD) are high in the first year after traumatic brain injury (TBI).

WHAT THIS STUDY ADDS

⇒ This study identified baseline predictors of depression and PTSD after TBI and developed prognostic models.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Assessing risk for depression and PTSD before hospital discharge may support early referrals to mental health assessment and specialist care. Screening for mental health symptoms in the first weeks after injury would enable more accurate predictions of depression and PTSD after TBI.

INTRODUCTION

Traumatic brain injury (TBI), generally defined as 'an alteration in brain function or other evidence of brain pathology, caused by an external force',[1] is a leading cause of death and disability worldwide. After a TBI, mental health symptoms are common.[2–4] Approximately 9%–30% of adults meet diagnostic criteria for major depressive disorder (MDD) within the first year post-TBI,[5–9] compared with a 12-month prevalence of 6% in the general population.[10] Similarly, post-traumatic stress disorder (PTSD) is more prevalent after TBI (16%)[11] than in the general population (1%–12%).[12] The prevalence of psychiatric disorders may be higher among individuals who sustain TBI even before the TBI occurs.[13]

Depression and PTSD are causes of burden on their own,[14] but co-occurrence with a TBI can lead to greater disability[15–17] and healthcare use.[18 19] Addressing mental health early after TBI may prevent poor clinical outcomes.[20 21] Accurately identifying who is at risk of mental health complications at hospital presentation or in the first weeks after injury can support a timely referral to a mental health specialist for diagnosis and treatment. Nevertheless, in contrast to other outcomes after TBI,[22 23] prognostic models for mental health disorders are lacking.

A systematic review and meta-analysis of predictors of mental health disorders following TBI[2] identified female sex/gender, preinjury depression, postinjury unemployment, and lower brain volume

as risk factors for MDD. Additionally, shorter post-traumatic amnesia (PTA), memory of the traumatic event and early post-traumatic stress symptoms were identified as risk factors for PTSD. However, the majority of analysed studies had important methodological limitations and only a few used multivariable models to predict MDD or PTSD. More recently, Stein *et al*[7] investigated risk factors for probable MDD and PTSD after mild TBI (Glasgow Coma Scale (GCS) Score 13–15) in a large US-based cohort. The authors identified lower education, being black, prior mental health problems and injury cause involving violence as the strongest multivariable predictors of probable PTSD and, except injury cause, of probable MDD.

We aimed to identify predictors of depression and PTSD symptoms after TBI of all severities and to develop prognostic models for the early identification of at-risk adults. Additionally, we aimed to develop prognostic models for MDD and PTSD, using criteria on validated screening questionnaires that showed satisfactory diagnostic accuracy for clinical diagnosis (referred to as 'probable MDD' and 'probable PTSD').

METHODS

Study population

We analysed data from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI, Core V.3.0) study.[24] CENTER-TBI is a prospective, multicentre, longitudinal, observational study. The participants' data were collected in 65 sites (trauma centres) in Europe and Israel from December 2014 to December 2017. Patients with a clinical diagnosis of TBI, who presented to study centre within 24 hours of injury and had an indication for CT scan were included in the study. Patients with a pre-existing severe neurological disorder that would confound outcome assessments were excluded. In CENTER-TBI, participants were differentiated by care pathway into three strata: emergency room (ER) stratum (assessed in the ER and discharged), admission stratum (admitted to a hospital ward) or intensive care unit (ICU) stratum (admitted to the ICU).[25]

For this study, we included participants aged 16 years or older who completed at least one of the outcome assessments at 6 months post-TBI. In subgroup analyses, we analysed participants with baseline GCS=3–12 and 13–15 separately. Further, we analysed a subgroup of participants assessed at 2–3 weeks (according to the study protocol, assessment was scheduled for all patients enrolled in the ER stratum and a proportion of the admission stratum).

Outcomes

Patients were asked to complete self-report questionnaires measuring depression and PTSD symptoms at 6 months post injury. If not available in local languages, the questionnaires were translated and linguistically validated.[26] The assessments could take place face to face, by telephone or by (postal) questionnaire.

Depression symptoms and probable diagnosis of MDD

The Patient Health Questionnaire-9 (PHQ-9)[27] was used to assess the presence and the severity of depressive symptoms. It is a self-report instrument containing nine items that can be scored on a 4-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). The range of the total score is 0–27, with a higher score indicating more severe symptoms. The cut-off scores of 10 and 15 indicate moderate and moderately severe symptoms of depression, respectively.[27] We operationalised probable MDD in three ways. We used a cut-off score≥10 that demonstrated excellent diagnostic sensitivity and specificity for MDD.[28–30] In line with Stein *et al*,[7] we also used the cut-off score≥15 as indicative of probable MDD. Finally, following the Diagnostic and Statistical Manual for Mental Health Disorders Fifth Edition (DSM-5),[31] we defined probable MDD by five or more items checked at least 'several days' (except suicidal ideation that can be checked 'some days'), with at least one measuring depressive mood or anhedonia (items 1 or 2).[28]

PTSD symptoms and probable diagnosis of PTSD

The PTSD Checklist for DSM-5 Score (PCL-5) was used to assess PTSD symptoms.[32] It contains 20 items measuring PTSD symptoms across four clusters, as defined in the DSM-5. Each item is scored on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). The total score ranges from 0 to 80, with a higher score indicating more pronounced symptoms. A score of ≥33 is considered indicative of probable PTSD.[7 33] We also employed an alternative definition of probable PTSD according to the DSM-5 criteria: a score of 2 (moderate) or higher on at least one item from criterion B (questions 1–5), one item from criterion C (questions 6–7), two items from criterion D (questions 8–14) and two items from criterion E (questions 15–20). As a sensitivity analysis, we defined PTSD as positive only for those who responded positively to: 'Were your answers in reference to the stressful experience which caused your traumatic brain injury?'.

Candidate predictors

Candidate predictors were prespecified based on the previous studies[2 4 7 9 34–36]: age (years), sex ('male'/'female'), education (years), employment status ('employed'/'not working'/'retired'/'student'), psychiatric history ('yes'/'no'), prior TBI ('yes'/'no'), cause of injury ('traffic accidents'/'falls or other incidental injuries'/'violence'), GCS (3–15), PTA ('yes or suspected'/'no'), loss of consciousness (LOC, 'yes or suspected'/'no'), alcohol intoxication at the time of injury ('yes or suspected'/'no'), total Injury Severity Score (ISS) (1–75 for brain-injured patients), any intracranial abnormality on CT ('yes'/'no'). In addition, preinjury physical health ('healthy'/'systemic disease') was considered as a candidate predictor for depression,[37] and retrograde amnesia[2] ('yes or suspected'/'no') for PTSD. Because of skewed distribution, race/ethnicity[7] was only analysed as a predictor in univariable analyses.

Baseline variables were prospectively collected. Detailed description of candidate predictors is available in online supplemental table 1. In subgroups in whom these symptoms were assessed (ER stratum and part of admission stratum), we examined the predictive value of PHQ-9 total score and PCL-5 total score at 2–3 weeks (median 20 days) following injury. The Generalized Anxiety Disorder 7-item scale (GAD-7)[38] was also administered at the 2–3 weeks of assessment. The GAD-7 consists of 7 items that can be answered from 0=not at all to 3=nearly every day, and the total score (sum of all items) ranges 0–21. Postconcussion symptoms at 2–3 weeks were assessed using the Rivermead Post-concussion Symptoms Questionnaire (RPQ). The RPQ[39] includes 16 items that represent common symptoms after a (mild) TBI and can be rated from 0=not experienced at all to 4=severe. The total score was calculated as a sum of all items, with responses '1' (same as before the injury) treated as 0.

Statistical analysis

We described candidate predictors and outcomes in terms of medians with IQRs for continuous variables and percentages for categorical variables. For other analysis, missing values in

baseline predictor variables were imputed using multiple imputation (multivariate imputation by chain equations, mice)[40] with 10 iterations and all predictors, outcomes and auxiliary variables (online supplemental table 1). If scores on all analysed 2–3 weeks of questionnaires were missing, they were not imputed because they were not measured for over half of participants (>60%). Imputed 6-month outcomes were used when only one of the two questionnaires (PHQ-9 or PCL-5) were missing (<4%).

Model development

We used linear regression to model the relationship between all baseline predictors, and depression (PHQ-9 total score) and PTSD symptoms (PCL-5 total score). We examined associations in univariable and multivariable regression analyses and quantified them by regression coefficients.

We assessed non-linear terms with polynomials for age and ISS. To account for potentially different predictor effects by TBI severity, we assessed the interaction terms between GCS (continuous) and other variables in multivariable analyses. To develop a more robust model, we only included interactions when the p value for all interactions with GCS (overall interaction term) and individual interaction term(s) were significant ($p<0.05$).[41 42] To select the strongest predictors in the final model while balancing out the model fit with model complexity, we used backward selection based on Akaike's Information Criterion (AIC) as a stopping rule (see online supplemental table 2–3 for more details). The strength of predictors was also reported in terms of statistical significance (online supplemental table 2–3) and by partial R^2: overall and separately in GCS=13–15 and GCS=3–12 subgroups.

To estimate a uniform shrinkage factor and model optimism, we used an internal validation procedure with 500 bootstrap samples. We reported model equations with optimism-corrected regression coefficients of the final models (coefficient multiplied by a shrinkage factor) and re-estimated model intercept (online supplemental table 4). The performance was quantified with the proportion of explained variance (R^2) and calculated across imputed datasets. CIs were estimated using 500 bootstrap samples.

The selected model for depression symptoms was refitted to an endpoint 'probable MDD' by using cut-off≥10 on PHQ-9; cut-off≥15 on PHQ-9 and mapping items to DSM-5 criteria. The selected model for PTSD symptoms was refitted to an endpoint 'probable PTSD' by using cut-off≥33 on PCL-5; and mapping items to DSM-5 diagnosis. The equations of these logistic models were multiplied by the same shrinkage factor obtained for linear models (online supplemental table 4). The classification performance of binary logistic models was quantified with the area under the receiver operating characteristic curve (AUC) across imputed datasets, with optimism and CIs estimated using bootstrapping. To illustrate model performance and utility, we presented contingency tables for selected risk thresholds, and reported sensitivity, specificity and net benefit[43] (online supplemental table 5–6).

To assess the incremental value of 2–3-week symptoms for the prediction of depression in a subset for whom these were assessed, we compared the performance (delta R^2) of the following models: (1) final baseline model, (2) final baseline model + 2–3-week PHQ-9, (3) final model + all 2-3-week questionnaires (PHQ-9, PCL-5, GAD-7 and RPQ). To assess the incremental value of 2–3-week symptoms for the prediction of PTSD, the same approach was taken with the PCL-5 instead of the PHQ-9.

RESULTS

Study population

The CENTER-TBI Core study included 4509 participants. Of 4306 adults (age 16+ years), n=2163 (50%) had completed 6-month questionnaires and were included in the analysis. The majority of included participants were men (65%), had white race (97%) and GCS=13–15 (table 1). About 12% reported a history of psychiatric disorder. Participants who survived to 6 months but did not respond to the questionnaires did not substantially differ from the participants who responded; however, they were somewhat younger, more frequently unemployed and with higher rates of psychiatric history, intoxication at the time of injury and injuries due to violence.

At 6 months, 18% had probable MDD according to the PHQ-9≥10, 7% according to PHQ-9≥15 and 9% based on mapping to the DSM-5 criteria (online supplemental table 7). The prevalence of probable PTSD was 10% according to both criteria. When counting only participants who responded to PCL-5 in reference to their TBI, that percentage was slightly lower (8%). There were no large differences in the prevalence of MDD/PTSD based on the TBI severity; however, symptoms of depression and PTSD and the rates of PHQ-9≥10 were somewhat higher after more severe TBI.

Depression: predictors and model development

In univariable analyses, female sex, identifying as black/Asian, fewer years of education, unemployment, systemic disease, psychiatric history, being intoxicated at the time of injury, more severe injuries (by GCS, ISS and CT abnormalities) and injuries due to traffic accidents and violence were associated with more severe depression symptoms. In multivariable analyses, according to our prespecified criteria, the interactions between GCS and other candidate predictors (overall F=0.86, df=16, p=0.62), and non-linear effects of age (p=0.63) and ISS (p=0.22) were not included in the model. The following predictors were selected based on the AIC: psychiatric history, employment, ISS, sex, education, preinjury health, injury cause and alcohol intoxication (figure 1). Psychiatric history was the strongest predictor (figure 1online supplemental figure 1). The overall model performance was very modest (optimism-corrected R^2=0.08, 95% CI 0.08 to 0.08).

Based on the partial R^2, psychiatric history and employment were the strongest predictors of depression symptoms in GCS=13–15. In the GCS=3–12 subgroup, the strongest predictor was injury cause, followed by employment and psychiatric history (online supplemental figure 1).

For probable MDD, the optimism-corrected AUC ranged 0.64–0.66 (table 2). Similar predictors were important for all endpoints, with psychiatric history and unemployment being associated with the highest odds of probable MDD (table 2).

In the subset of participants with 2–3 weeks of symptoms assessed (n=655), the baseline model for depression symptoms had an R^2=0.11, 95% CI 0.10 to 0.12; after validation R^2=0.07, 95% CI 0.07 to 0.08. The addition of 2–3 weeks of PHQ-9 markedly improved the performance (delta R^2=0.25, 95% CI 0.24 to 0.26). The extension with additional questionnaires (PCL-5, GAD-7 and RPQ) did not further improve the model (delta R^2=0.00, 95% CI 0.00 to 0.01).

PTSD: predictors and model development

In univariable analyses, female sex, identifying as black/Asian, unemployment, psychiatric history, injuries caused by traffic accidents and violence, sustaining LOC, intoxication at the time

Table 1 CENTER-TBI participants by the response to 6-month questionnaires

	Responders to 6-month questionnaires	Missing %	Not responded to 6-month questionnaires	Death by 6 months
N	2163		1726	471
Baseline variables				
Age (median (IQR))	51 (32, 64)	0	47 (29, 65)	68 (52, 78)
Sex=M (%)	1413 (65.3)	0	1186 (68.7)	335 (71.1)
Race=white (%)	2034 (97.2)	3.3	1569 (96.0)	419 (97.2)
Education, years (median (IQR))	13 (11, 16)	18.5	12 (10, 15)	12 (8, 14)
Employment (%)		6.3		
Working	1156 (57.0)		745 (49.7)	75 (23.3)
Retired	496 (24.5)		403 (26.9)	213 (66.1)
Student	202 (10.0)		156 (10.4)	8 (2.5)
Not working*	173 (8.5)		196 (13.1)	26 (8.1)
Psychiatric history (%)	265 (12.4)	1.2	257 (15.6)	75 (17.9)
Preinjury health=no systemic disease (%)	866 (40.4)	0.9	716 (43.3)	284 (66.7)
Prior TBI/concussions (%)	217 (10.5)	4.7	145 (9.2)	29 (7.8)
Cause of injury (%)		2.1		
Fall and other unintentional cause	1124 (53.1)		911 (54.6)	273 (60.8)
Traffic	886 (41.9)		600 (35.9)	148 (33.0)
Violence	107 (5.1)		158 (9.5)	28 (6.2)
GCS (median (IQR))	15 (13, 15)	2.9	15 (11, 15)	6 (3, 11)
GCS<13 (%)	507 (24.1)	2.9	479 (28.9)	347 (79.6)
Total Injury Severity Score (median (IQR))	14 (9, 26)	1.1	16 (8, 26)	34 (25, 57)
Loss of consciousness (%)	1278 (65.7)	10.1	954 (63.0)	329 (82.2)
Post-traumatic amnesia (%)	891 (53.2)	22.6	500 (42.0)	49 (36.0)
Retrograde amnesia (%)	637 (40.3)	27	419 (37.0)	28 (23.3)
Alcohol intoxication	466 (22.9)	8	468 (29.8)	103 (25.6)
Any intracranial traumatic abnormality (%)	1163 (57.5)	6.5	826 (54.2)	375 (93.5)
2–3- week symptoms (median (IQR))				
PHQ-9 Total Score (min–max: 0–27)	5 (2, 10)	78.3	5 (0.50, 10)	/†
PCL-5 Total Score (min–max: 0–33)	9 (3, 19)	78.2	8 (2, 17.25)	/
GAD-7 Total Score (min–max: 0–21)	2 (0, 6)	78.4	2 (0, 7)	/
RPQ Total Score (min–max: 0–64)	8 (2, 21)	77.9	6 (0, 18.25)	/

*Unemployed, looking for work, unable to work, homemaker.
†Small frequencies.
CENTER-TBI, Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury; GAD-7, Generalized Anxiety Disorder-9; GCS, Glasgow Coma Scale Score; PCL-5, Post-Traumatic Stress Disorder Checklist for Diagnostic and Statistical Manual for Mental Health Disorders Fifth Edition; PHQ-9, Patient Health Questionnaire-9; RPQ, Rivermead Post-concussion Symptoms Questionnaire.

of injury and more severe injuries (lower GCS, higher ISS and CT abnormalities) were associated with more severe PTSD symptoms. Being retired and an increase in age after 40 were associated with less severe PTSD symptoms (table 3; online supplemental figure 2). In multivariable analysis, the overall interaction terms for GCS (overall F=1.14, df=16, p=0.315) were not significant. The non-linear effects of age (p=0.34) and ISS (p=0.70) were weak. The selected model had optimism-corrected R^2 of 0.07 and included: cause of injury, psychiatric history, employment status, sex, total ISS and alcohol intoxication (figure 1). The strongest predictors that explained the largest proportion of the variance in PTSD symptoms were injury cause, psychiatric history and employment status (online supplemental figure 3).

For probable PTSD, the model performance was modest (AUC=0.62–0.64; table 3). Psychiatric history, unemployment and traffic and violence as injury cases were associated with higher odds of PTSD, while being retired was associated with lower odds of PTSD. The sensitivity analysis of TBI-related probable PTSD showed mostly consistent results for both endpoints; however, while psychiatric history remained a significant predictor of PCL-5≥33, it was not a significant predictor for PTSD mapped to DSM-5 (OR=1.22, 95% CI 0.8 to 1.9; Online supplemental table 8). In both GCS=13–15 and GCS=3–12, injury cause was the strongest predictor with the largest partial R^2, followed by psychiatric history (GCS=13–15) and employment (GCS=3–12; online supplemental figure 3).

In the subset with patients whose symptoms were assessed at 2–3 weeks (n=655), the performance of the model for PTSD symptoms with baseline variables was R^2=0.08, 95% CI 0.08 to 0.09; after validation R^2=0.05, 95% CI 0.05 to 0.06). The addition of 2–3- week PCL-5 increased the performance substantially (delta R^2=0.30, 95% CI 0.29 to 31). The addition of other 2–3- week questionnaires (PHQ-9, GAD-7 and RPQ) to baseline variables and PCL-5 led to a delta R^2 of 0.005, 95% CI 0.003 to 0.007.

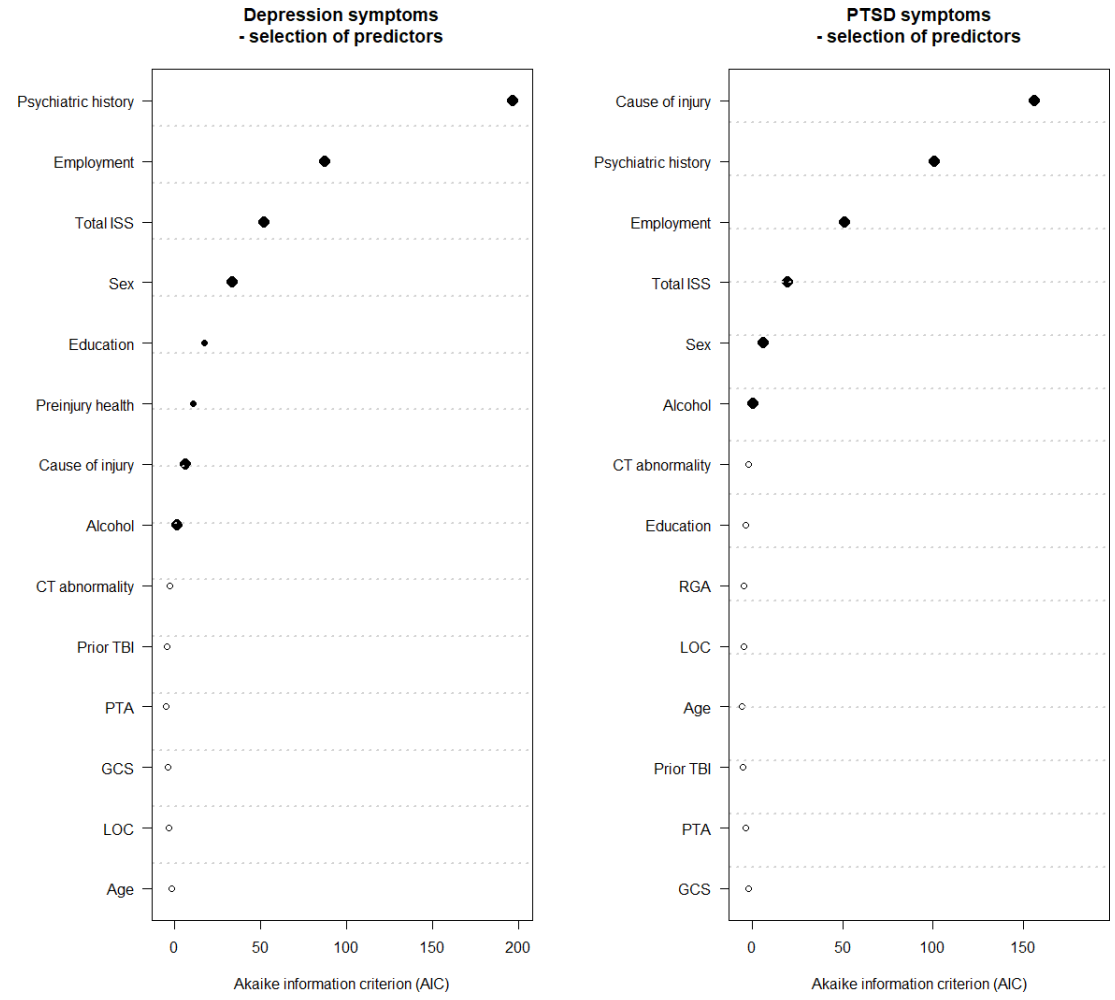

Figure 1 Prediction of depression and post-traumatic stress disorder symptoms: selection of predictors based on the Akaike information criterion for the pooled residual χ^2. Selected predictors are indicated with black circles. Predictors selected for both outcomes are shown with larger circles. GCS, Glasgow Coma Score; ISS, Injury Severity Score; LOC, loss of consciousness; PTA, post-traumatic amnesia; PTSD, post-traumatic stress disorder; RGA, retrograde amnesia; TBI, traumatic brain injury.

DISCUSSION

We examined predictors and developed prognostic models for depression symptoms (including probable MDD) and PTSD symptoms (including probable PTSD) at 6 months post-TBI. Using validated screening questionnaires, between 7% and 18% of patients (dependent on chosen cut-off value) had an indication for MDD and about 10% for PTSD. Psychiatric history was a strong predictor of both depression and PTSD symptoms following TBI. Although the baseline models for the prediction of both outcomes had only modest performance, some sociodemographic variables (eg, employment status) and injury variables (eg, injury cause) were associated with outcomes. Including 2–3-week symptoms for predicting later depression/PTSD symptoms improved model performance.

The strong incremental value of 2–3-weeks symptoms confirms the importance of screening for mental health symptoms in the weeks after TBI, which has been recommended by clinical practice guidelines.[44] Brief validated screening questionnaires for mental health disorders could be used in primary care settings[21] or using remote assessment[45], or after more severe TBIs, in hospital and rehabilitation settings. Without the screening, it is difficult to identify patients at risk of depression and PTSD symptoms at 6 months.

Although baseline variables do not enable accurate predictions on postinjury mental health, the presence of some risk factors can suggest a need for systematic follow-up. We found an association between psychiatric history and mental health problems after TBI, as supported by other evidence.[7 46] Further, the importance of social determinants of health for outcomes after TBI[7 47 48] has been confirmed in this study. Unemployment at the time of injury may increase the risk of mental health problems by elevated financial burden and levels of stress, hindering the ability to cope with an unexpected condition and further lowering the possibility to find paid employment. Similarly, lower education may be an indicator of lower socioeconomic status. Race,[47] one of the most studied factors, was not examined in our multivariable models due to a highly skewed distribution (97% white); however, the results from our univariable analyses suggest that racial minorities in Europe may have a higher likelihood of mental health disorders after TBI, echoing findings from other regions.[7 49] As in most previous studies, female sex was associated with higher risk of mental health problems after TBI.[2]

In line with the TRACK-TBI cohort, violent injury cause was a prominent predictor of PTSD, but a weaker predictor of depression.[7] While the TRACK-TBI study combined other injury causes, we examined traffic incidents separately and found them

Table 2 Predictors and model performance for depression symptoms and probable major depressive disorder according to three criteria (n=2163)

	Depression symptoms (Patient Health Questionnaire-9, (PHQ-9) total score)			PHQ-9≥10	PHQ-9≥15	PHQ-9 DSM-5
	Regression coefficient (95% CI)			Odds ratio (95% CI)		
	Univariable analyses	Full model	Selected model	Selected model		
Age, 67 vs 32 years*	−0.2 (−0.61, 0.21)	−0.18 (−0.87, 0.51)	Not selected			
Sex, female versus male	1.04 (0.56, 1.51)	1.06 (0.60, 1.53)	1.05 (0.58, 1.51)	1.47 (1.15 to 1.87)	1.43 (1.00 to 2.02)	1.55 (1.13 to 2.13)
Race, black/Asian versus white	2.2 (0.77, 3.63)	Not assessed	Not assessed			
Education, 16 vs 11 years*	−0.59 (−0.88, −0.29)	−0.42 (−0.72, −0.13)	−0.45 (−0.75, −0.16	0.85 (0.72 to 1.01)	0.76 (0.59 to 0.97)	0.83 (0.66 to 1.03)
Employment, ref=working						
Retired	−0.18 (−0.72, 0.37)	−0.39 (−1.13, 0.34)	−0.45 (−1.03, 0.13)	0.84 (0.61 to 1.16)	1.13 (0.71 to 1.78)	0.92 (0.61 to 1.41)
Student	−0.07 (−0.86, 0.73)	−0.05 (−0.97, 0.87)	0.05 (−0.74, 0.83)	1.30 (0.87 to 1.95)	1.14 (0.61 to 2.14)	1.07 (0.61 to 1.89)
Not working†	3.08 (2.25, 3.91)	2.06 (1.23, 2.90)	2.07 (1.24, 2.90)	2.39 (1.65 to 3.46)	2.38 (1.46 to 3.89)	1.99 (1.23 to 3.21)
Psychiatric history, yes versus no	3.53 (2.85, 4.21)	2.64 (1.94, 3.34)	2.71 (2.01, 3.41)	2.37 (1.75 to 3.22)	1.82 (1.20 to 2.78)	2.02 (1.37 to 2.98)
Preinjury systemic disease versus healthy	0.9 (0.44, 1.36)	0.69 (0.17, 1.20)	0.65 (0.16, 1.15)	1.46 (1.13 to 1.89)	1.31 (0.91 to 1.91)	1.39 (0.98 to 1.96)
Prior TBI, yes versus no	0.64 (−0.11, 1.39)	0.65 (−0.08, 1.38)	Not selected			
Cause of injury, ref=fall						
Traffic	0.71 (0.24, 1.17)	0.72 (0.24, 1.20)	0.70 (0.23, 1.17)	1.26 (0.98 to 1.63)	1.46 (1.01 to 2.12)	1.52 (1.08 to 2.12)
Violence	1.53 (0.46, 2.60)	0.82 (−0.26, 1.90)	0.81 (−0.25, 1.87)	1.35 (0.81 to 2.24)	1.77 (0.97 to 3.44)	1.21 (0.60 to 2.43)
Glasgow Coma Scale, 15 vs 9*	−0.76 (−1.12, −0.4)	−0.28 (−0.75, 0.18)	Not selected			
Total Injury Severity Score, 29 vs 9*	0.7 (0.4, 1)	0.41 (0.01, 0.80)	0.66 (0.36, 0.96)	1.18 (1.01 to 1.38)	1.20 (0.97 to 1.49)	1.08 (0.88 to 1.33)
Loss of consciousness, yes or suspected versus no	0.08 (−0.41, 0.57)	−0.15 (−0.67, 0.38)	Not selected			
Post-traumatic amnesia, yes or suspected versus no	−0.07 (−0.59, 0.45)	−0.31 (−0.89, 0.27)	Not selected			
Alcohol intoxication, yes or suspected versus no	1.11 (0.57, 1.65)	0.64 (0.08, 1.19)	0.67 (0.13, 1.21)	1.40 (1.07 to 1.84)	1.58 (1.09 to 2.30)	1.43 (1.00 to 2.04)
Intracranial abnormality, present versus absent	0.93 (0.47, 1.39)	0.54 (0.03, 1.05)	Not selected			
Model performance, 95% CI		R^2=0.10, 0.10 to 0.10	R^2=0.10, 0.09 to 0.10	AUC=0.68 0.66 to 0.70	AUC=0.68, 0.65 to 0.73	AUC=0.66, 0.63 to 0.70
Optimism-corrected performance, 95% CI			R^2=0.08, 0.08 to 0.09	AUC=0.66, 0.64 to 0.68	AUC=0.64, 0.61 to 0.69	AUC=0.62, 0.59 to 0.66

*IQR coefficients, scaled to 75:25 percentile.
†Unemployed, unable to work, homemaker.
DSM-5, Diagnostic and Statistical Manual for Mental Health Disorders Fifth Edition; TBI, traumatic brain injury.

predictive of PTSD at 6 months post-TBI. Our findings suggest that TBIs caused by psychologically traumatic events that induce fear and feeling of loss of control should trigger follow-up screening for PTSD. Interestingly, we also found associations between higher total injury severity (including extracranial injuries) and lower GCS (in univariable analyses) with more severe PTSD/depression symptoms, while we did not find strong associations between retrograde/PTA and PTSD symptoms. It was previously hypothesised that amnesia for injury event decreases the likelihood of PTSD by preventing memory encoding; however, it is now more widely accepted that amnesia/LOC do not preclude post-traumatic reactions.[17] While our finding is consistent with some studies,[7] considerable missingness and lack of granularity (eg, assessment by standardised instruments, incorporation of duration) prevent strong conclusions.

The baseline models developed in this study had only modest performance. However, they contain predictors identified in other studies.[7 50] As preinjury mental health problems are consistent predictors of postinjury symptoms, particular attention should be given to patients with this comorbidity. Given the small proportion of variance explained by the baseline models, we recommend improving the model fit by refining the assessment of predictors identified by this study and including additional variables. Future studies should include a detailed

Table 3 Predictors and model performance for post-traumatic stress disorder (PTSD) symptoms and probable PTSD according to two criteria (n=2163)

	PTSD symptoms (PTSD Checklist for DSM-5 (PCL-5) total score)			PCL-5≥33	PCL-5 DSM-5
	Regression coefficient (95% CI)			Odds ratio (95% CI)	
	Univariable	Full model	Selected	Selected	
Age, 67 vs 32 years*	−2.5 (−3.55, −1.44)	−1.21 (−2.99, 0.57)	Not selected		
Sex, female versus male	1.25 (0.03 to 2.48)	1.84 (0.62 to 3.05)	1.81 (0.60 to 3.02)	1.11 (0.81 to 1.52)	1.21 (0.89 to 1.64)
Race, black/Asian versus white	7.01 (3.36, 10.66)	Not assessed	Not assessed		
Education, 16 vs 11 years*	−0.85 (−1.66, −0.03)	−0.79 (−1.59, 0.01)	Not selected		
Employment, ref=working					
Retired	−2.72 (−4.13, −1.31)	−1.22 (−3.12, 0.68)	−1.78 (−3.19, −0.38)	0.58 (0.38 to 0.91)	0.53 (0.34 to 0.83)
Student	−0.12 (−2.21, 1.97)	−0.97 (−3.47, 1.53)	0.03 (−2.00, 2.06)	0.84 (0.48 to 1.47)	0.80 (0.46 to 1.39)
Not working†	6.97 (4.68, 9.25)	4.96 (2.71, 7.22)	5.30 (3.05, 7.56)	1.85 (1.18 to 2.90)	2.15 (1.37 to 3.36)
Psychiatric history, yes versus no	6.65 (4.88, 8.42)	5.05 (3.28, 6.82)	5.17 (3.41, 6.93)	2.23 (1.55 to 3.23)	1.58 (1.11 to 2.33)
Prior TBI, yes versus no	0.53 (−1.39, 2.46)	0.57 (−1.29, 2.44)	Not selected		
Cause of injury, ref=fall					
Traffic	3.52 (2.32, 4.72)	3.16 (1.90 to 4.42)	2.94 (1.72, 4.16)	1.51 (1.09, 2.10)	1.36 (0.99 to 1.88)
Violence	9.12 (6.35, 11.89)	6.63 (3.84 to 9.41)	6.96 (4.20, 9.72)	2.39 (1.39, 4.10)	2.02 (1.14 to 3.58)
Glasgow Coma Scale, 15 vs 9*	−1.78 (−2.7, −0.86)	0.18 (−1.00, 1.36)	Not selected		
Total Injury Severity Score, 29 vs 9*	2.13 (1.36, 2.91)	1.35 (0.33, 2.37)	1.70 (0.92, 2.47)	0.95 (0.78, 1.17)	0.98 (0.81 to 1.20)
Loss of consciousness, yes or suspected versus no	1.59 (0.34, 2.83)	1.21 (−0.14, 2.57)	Not selected		
Post-traumatic amnesia, yes or suspected versus no	0.62 (−0.66, 1.9)	−0.40 (−1.87, 1.07)	Not selected		
Retrograde amnesia, yes or suspected versus no	−0.19 (−1.67, 1.28)	−1.20 (−2.82, 0.43)	Not selected		
Alcohol intoxication, yes or suspected versus no	2.68 (1.26, 4.1)	1.33 (−0.14, 2.80)	1.43 (−0.01, 2.87)	1.39 (0.97, 1.97)	1.17 (0.81 to 1.68)
Intracranial abnormality, present versus absent	2.34 (1.14, 3.54)	1.46 (0.14, 2.79)	Not selected		
Model performance, 95% CI		R^2=0.09, 0.09 to 0.09	R^2=0.08, 0.08 to 0.08	AUC=0.66, 0.63 to 0.70	AUC=0.64, 0.61 to 0.68;
Optimism-corrected performance, 95% CI			R^2=0.07, 0.07 to 0.08	AUC=0.64, 0.61 to 0.68	AUC=0.62, 0.59 to 0.66

*IQR coefficients, scaled to 75:25 percentile.
†Unemployed, unable to work, homemaker.
AUC, area under the receiver operating characteristic curve; DSM-5, The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; TBI, traumatic brain injury.

assessment of preinjury mental health and the psychological impact of the TBI. Using tools developed for screening of trauma survivors, such as the Predictive Screening Tool for Depression and PTSD[51] or the Injured Trauma Survivor Screen,[52] within the hospital setting may also improve the prediction of depression and PTSD before discharge and optimise follow-up.[53] The feasibility of these instruments and their predictive performance should be examined in the TBI population. In larger datasets, analysing more granular baseline variables (eg, detailed medical history, specific lesions and medical procedures) using modern analytical techniques, including machine learning, may enable more satisfactory baseline models.

This study has limitations. The outcomes were not assessed by structured clinical interviews, which are necessary for confirming the diagnosis of mental health disorders. Nevertheless, we used validated screening questionnaires that showed satisfactory sensitivity and specificity for clinical diagnosis of MDD and PTSD.[28 29 54] Further, there was a substantial proportion of missing data on outcomes, with participants with the highest and lowest disability levels having more missing data.[55]

Imputation of missing predictor values was performed under missing at random assumption, which would lead to bias under missing not at random mechanism. We did not consider clustering or random effects for sites in the imputation of missing values and modelling. Our sample consisted mostly of patients with GCS=13–15, and 2–3-week symptoms were not assessed in patients admitted to ICU. Our findings, in particular the predictive value of early symptoms and the optimal timing to assess them after more severe TBI, require validation.

In conclusion, we identified baseline predictors of depression and PTSD symptoms after TBI, such as psychiatric history, employment status and injury cause. Prognostic models that include only sociodemographic and baseline clinical variables have modest performance. Screening for mental health symptoms 2–3 weeks after TBI strongly improves prognostication of later mental health problems and it should guide systematic follow-up after TBI.

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Ethics approval This study involves human participants. The CENTER-TBI study (EC grant 602150) has been conducted in accordance with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws of the country where the recruiting sites were located, including but not limited to, the relevant privacy and data protection laws and regulations (the 'Privacy Law'), the relevant laws and regulations on the use of human materials and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ('ICH GCP') and the World Medical Association Declaration of Helsinki entitled 'Ethical principles for medical research involving human subjects'. Informed consent by the patients and/or the legal representative/next of kin was obtained, accordingly to the local legislations, for all patients recruited in the Core Dataset of CENTER-TBI and documented in the e-CRF. Ethical approval was obtained for each recruiting sites. The list of sites, ethical committees, approval numbers and approval dates can be found below: https://www.center-tbi.eu/project/ethical-approval. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data may be obtained from a third party and are not publicly available. Access to the CENTER-TBI dataset can be granted after approval of a study plan proposal, submitted through the online system: https://www.center-tbi.eu/data.

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