



Early predictors of outcome after mild traumatic brain injury (UPFRONT): an observational cohort study

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Summary

Background Mild traumatic brain injury (mTBI) accounts for most cases of TBI, and many patients show incomplete long-term functional recovery. We aimed to create a prognostic model for functional outcome by combining demographics, injury severity, and psychological factors to identify patients at risk for incomplete recovery at 6 months. In particular, we investigated additional indicators of emotional distress and coping style at 2 weeks above early predictors measured at the emergency department.

Methods The UPFRONT study was an observational cohort study done at the emergency departments of three level-1 trauma centres in the Netherlands, which included patients with mTBI, defined by a Glasgow Coma Scale score of 13–15 and either post-traumatic amnesia lasting less than 24 h or loss of consciousness for less than 30 min. Emergency department predictors were measured either on admission with mTBI—comprising injury severity (GCS score, post-traumatic amnesia, and CT abnormalities), demographics (age, gender, educational level, pre-injury mental health, and previous brain injury), and physical conditions (alcohol use on the day of injury, neck pain, headache, nausea, dizziness)—or at 2 weeks, when we obtained data on mood (Hospital Anxiety and Depression Scale), emotional distress (Impact of Event Scale), coping (Utrecht Coping List), and post-traumatic complaints. The functional outcome was recovery, assessed at 6 months after injury with the Glasgow Outcome Scale Extended (GOSE). We dichotomised recovery into complete (GOSE=8) and incomplete (GOSE≤7) recovery. We used logistic regression analyses to assess the predictive value of patient information collected at the time of admission to an emergency department (eg, demographics, injury severity) alone, and combined with predictors of outcome collected at 2 weeks after injury (eg, emotional distress and coping).

Findings Between Jan 25, 2013, and Jan 6, 2015, data from 910 patients with mTBI were collected 2 weeks after injury; the final date for 6-month follow-up was July 6, 2015. Of these patients, 764 (84%) had post-traumatic complaints and 414 (45%) showed emotional distress. At 6 months after injury, outcome data were available for 671 patients; complete recovery (GOSE=8) was observed in 373 (56%) patients and incomplete recovery (GOSE≤7) in 298 (44%) patients. Logistic regression analyses identified several predictors for 6-month outcome, including education and age, with a clear surplus value of indicators of emotional distress and coping obtained at 2 weeks (area under the curve [AUC]=0·79, optimism 0·02; Nagelkerke R^2 =0·32, optimism 0·05) than only emergency department predictors at the time of admission (AUC=0·72, optimism 0·03; Nagelkerke R^2 =0·19, optimism 0·05).

Interpretation Psychological factors (ie, emotional distress and maladaptive coping experienced early after injury) in combination with pre-injury mental health problems, education, and age are important predictors for recovery at 6 months following mTBI. These findings provide targets for early interventions to improve outcome in a subgroup of patients at risk of incomplete recovery from mTBI, and warrant validation.

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Introduction

Mild traumatic brain injury (mTBI) accounts for 80–90% of all cases of TBI worldwide.¹ Most patients recover within weeks to months after injury without specific therapy, but a subgroup of patients experience persistent post-traumatic complaints like forgetfulness, irritability, and problems with concentration.² One in three patients with mTBI will not resume work and activities 6 months after mTBI at a level similar to that observed before injury.^{3,4} Despite these residual complaints, structural brain damage in this population is often not seen using structural imaging techniques.⁵ Although some studies have found mild cognitive deficits in the acute stage of mTBI,^{6,7} it is

consistently found that neuropsychological ability returns to pre-injury levels in the long term.^{6,7} Moreover, studies investigating outcomes after mTBI found that indices of injury severity (CT-abnormalities, Glasgow Coma Score [GCS]) did not explain these post-traumatic complaints.^{8,9} Only age and educational level have been found to be reliable predictors of incomplete recovery so far.^{10,11}

There has been a long-standing debate on whether post-traumatic complaints result from either traumatic brain damage or psychological factors, or a combination of both.¹² Poor recovery after mTBI has been associated with pre-injury mental health status and emotional distress,^{8,13} probably because post-traumatic

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Research in context

Evidence before this study

We searched PubMed for articles in English on mild traumatic brain injury (mTBI) published between Jan 1, 1990, and Jan 1, 2015, with the following search terms for the patient category of mTBI: "mild traumatic brain injury", "mild head injury", or "minor head injury". We also identified all hospital-based and population-based studies on mTBI that reported data on the outcome of mTBI with search terms for outcome: "prediction", "predictors", "prediction model", or "outcome". We repeated the search combining the search terms for the patient category and outcome. We found 20585 articles on outcome and mTBI, and 3188 articles on mTBI and prediction, from which we identified only three studies that focused on the development of a prediction model for outcome after mTBI. The first study showed limited predictive value (0.57 area under the curve [AUC]) of a CT-model compared with a clinical model (0.71) in an mTBI group of 1069 patients; psychological factors were not assessed. The second study comprised 201 patients and identified the absence of premorbid physical problems, low number and severity of symptoms, and post-traumatic stress early after injury as predictors of good recovery (AUC 0.73) 6 months after injury. The third study aimed to externally validate all available studies and identified that existing prognostic models for mTBI were unsatisfactory, with risk of overfitting of the model, and suggested that larger cohorts of patients with more specific predictors for outcome were required.

Added value of this study

Previous studies investigating prediction models for incomplete recovery after mTBI have not used a multifactorial

approach that combines injury and demographic variables with psychological factors and, in particular, have not adequately studied the mediating role that coping style can have. Most studies have focused on patients of working age (ie, 18–64 years), neglecting the increasing incidence in elderly individuals who sustain mTBI. To our knowledge, this is the largest, prospectively followed cohort of mTBI to date. We found that psychological factors (ie, maladaptive coping and emotional distress), in addition to education and pre-injury mental health problems, were strong predictors of recovery. We developed a prediction model showing that psychological data obtained 2 weeks after injury have an additional predictive value above characteristics collected at the emergency department alone (demographic and injury-related factors) with good discriminative ability.

Implications of all the available evidence

Our study allows for a two-step approach to identify those patients who are at risk for incomplete recovery. Early identification of patients at risk of mTBI is already possible at the time of admission to the emergency department, with later assessment of psychological factors allowing more precise selection of patients at risk. This model might facilitate early identification of patients at risk for suboptimal recovery and indicates the need for the development of mental health interventions in these patients to improve their long-term outcomes. In view of the large numbers of patients sustaining mTBI, and the long-term personal, financial, and societal consequences of incomplete recovery, further research on potential predictors of outcome is needed.

complaints are strongly related to anxiety, depression, and post-traumatic stress.^{8,14–16} Maladaptive coping is also associated with incomplete recovery after any TBI, and with increased incidence of depression and anxiety.^{17,18} Although outcomes vary across patients with TBI of different ages,¹⁹ many studies focus only on patients of working age, and thus do not account for the effect of age on outcome despite that the incidence in elderly patients (aged 65 years and older) sustaining TBI is increasing,²⁰ and that, with older age, frailty and comorbidity might modulate outcome.

We aimed to create a prognostic model of 6-month functional outcome in adult patients with mTBI of different ages using a multifactorial approach that combined demographic and injury-related factors with psychological factors, namely indicators of emotional distress and coping style. This model was compared for prognostic accuracy with a prognostic model we created using only demographic and injury-related factors.

Methods

Study design and participants

This prospective, observational cohort study was done between Jan 25, 2013, and Jan 6, 2015, with 6-month

outcomes assessed by July 25, 2015. Patients were recruited on arrival at the emergency department of three level-1 trauma centres in the Netherlands (Groningen, Enschede, and Tilburg) by the attending physician or (in the case of admission) by the physician at the ward. Patients with mTBI, defined by a GCS score of 13–15, with post-traumatic amnesia lasting less than 24 h or loss of consciousness for less than 30 min were included. Patients were excluded if they were younger than 16 years, had history of drug or alcohol misuse, or had a major psychiatric or neurological disorder as identified by the attending or ward physician. Patients without a permanent home address or insufficient fluency of the Dutch language were also excluded. The Medical Ethical Committee of the University Medical Center Groningen approved the study. All patients gave written informed consent within 48 h after injury.

Procedures

In the UPFRONT study, data were collected at multiple time intervals after injury (at 2 weeks and 3, 6, and 12 months) covering several aspects of recovery of function after injury; data obtained at 2 weeks and 6 months after injury were analysed as the outcome for the current study.

The presence of post-traumatic amnesia, loss of consciousness, and GCS score were assessed at the emergency department by the attending physician. A CT scan was done on admission to the hospital and was classified into a normal versus abnormal CT by a board-certified radiologist. Demographic information, information about injury severity and trauma mechanism, and information on hospital admittance and discharge were obtained from digital medical records. Medical history included previous TBI and neurological history; presence of pre-injury mental health problems was defined by psychiatric or psychological symptoms necessitating treatment by a psychologist or psychiatrist or use of psychotropic medication; and educational level that was indicated on a Dutch 7-point scale, by years in education (YoE; 1=primary school [<6 YoE], 2=finished primary school [6 YoE], 3=did not finish secondary school [7–8 YoE], 4=finished secondary school [9 YoE], 5=finished secondary school [10–11 YoE], 6=finished secondary school [12–16 YoE], and 7=university degree [>16 YoE]).

At 2 weeks after recruitment in a trauma centre with mTBI, information about post-traumatic complaints, anxiety and depression, coping style, and post-traumatic stress levels was obtained by use of a questionnaire (web-based or printed, depending on the preference of the participant). Post-traumatic complaints were assessed using the Head Injury Symptom Checklist (HISC),²¹ which addresses 21 common post-traumatic complaints on a three-point Likert scale (sum scores 0–42), resulting in a sum score of current complaints corrected for pre-injury levels. Anxiety and depression were assessed using

the Hospital Anxiety and Depression Scale (HADS),²² a 14-item questionnaire that measures anxiety (HADS-A) and depression (HADS-D) separately on a four-point Likert scale (ranges 0–28), with cutoff values of seven for being considered clinically anxious or depressed. Coping Style was investigated using the Utrecht Coping List (UCL),²³ a 47-item questionnaire with seven subscales that represent different coping styles with scores ranging from low (1) to very high (5) use of that specific coping style relative to a historic group based on age and gender. In line with other studies,¹⁸ we used three of the seven scales (UCL-active, UCL-passive, and UCL-avoidant), with scores of four or five as indicating a high use of that specific coping style. Post-traumatic stress was assessed using the Impact of Event Scale, a 15-item questionnaire with a five-point Likert scale (sum scores 0–75),²⁴ with a cutoff score of 19 defining post-traumatic stress disorder.

Outcome

At 6 months after injury, recovery was assessed with the Glasgow Outcome Scale Extended (GOSE),²⁵ which measures functional outcome on an eight-point scale (8=complete recovery, 7=suboptimal recovery, 6=upper moderate disability, 5=lower moderate disability, 4=upper severe disability, 3=lower severe disability, 2=vegetative state, and 1=death). Outcome was dichotomised into complete (GOSE=8) and incomplete recovery (GOSE $\leq$ 7).

Statistical analysis

On the basis of studies on the effect of age on outcome after TBI,²⁶ we categorised patients into three age groups:

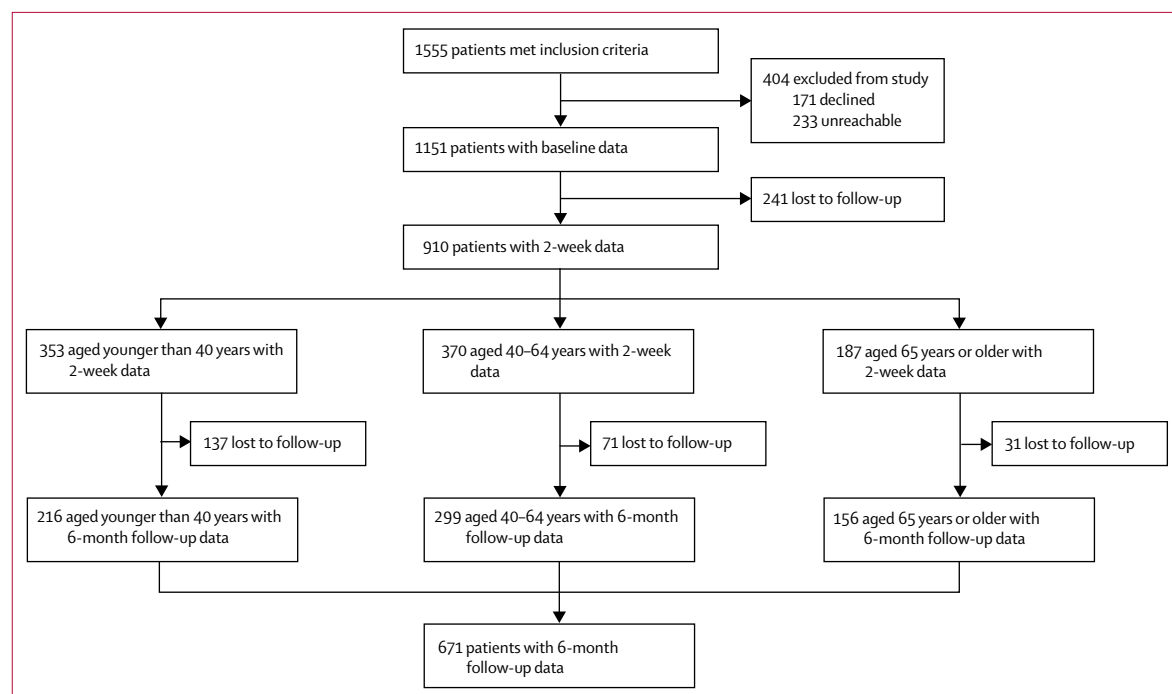


Figure 1: Study profile

younger than 40 years, 40–64 years, and aged 65 years or older. We analysed differences between age groups using ANOVA. Spearman correlations were calculated to determine the association between emotional distress and complaints variables. Patients with missing data for the 6-month after injury assessment were excluded.

For the prediction models, we considered the prognosis predictors in two blocks, measured either at time of admission to the emergency department—comprising injury severity (GCS score, post-traumatic amnesia, and CT abnormalities), demographics (age, gender, educational level, pre-injury mental health, and previous brain injury), and physical conditions (alcohol use on the day of injury, neck pain, headache, nausea, dizziness)—or measured at 2 weeks after injury, comprising indicators of emotional distress and coping style. Logistic regressions analyses were done with recovery (ie, GOSE $\leq$ 7 or GOSE=8) as the dependent variable in three steps to assess the predictive value of the individual predictors, and the two blocks. First, we did a regression analysis for each individual predictor. Second, we built the emergency department model by use of a step-down variable selection for emergency department-predictors, including all main effects and the two-way interactions of age with educational level and gender, because of a-priori expectations that both variables might behave differently across different age ranges in relation to outcome. We used a significance of $\alpha=0.15$ as the cutoff for each variable. Third, we built another model, termed the emergency department-plus model, that used the same step-down selection procedure as the emergency department model, which considered those selected emergency department predictors with the addition of predictors measured at 2 weeks after injury, and considered all main effects. In all of the regression analyses, for the predictor age, we modelled a possible non-linear association with outcome with a restricted cubic spline with three knots. After predictor selection, we tested whether the model with the non-linear term would fit better than the model with the linear term only using a χ^2 test ($\alpha=0.05$). If the non-linear term was not a better fit, we used the linear term to ease the interpretation of the model. We assessed associations between the predictors and the outcome of the resulting models using the odds ratios (OR) and graphical summaries. For continuous predictors, OR values were scaled to correspond to a change from the 25th to the 75th percentile, to allow for a direct comparison of the prognostic value.

We assessed the discriminatory power of the two models using the area under the curve (AUC), Nagelkerke's R^2 , and the calibration of risk predictions via the bias corrected calibration intercept (ie, predicted vs observed mean outcome) and slope (ie, slope of predicted log odds vs observed log odds) resulting from logistic regressions with the predicted value as predictor and the outcome as the dependent variable. We estimated the optimism for all measures by internal validation

	Total patients (n=910)	Patients aged <40 years (n=353)	Patients aged 40–64 years (n=370)	Patients aged ≥65 years (n=187)	p value*
Mean age, years	46.5 (19.2)	25.7 (6.6)	53.2 (7.0)	72.5 (6.0)	<0.0001
Sex					
Male	560 (62%)	223 (63%)	229 (62%)	108 (58%)	0.46
Female	350 (38%)	130 (37%)	141 (38%)	79 (42%)	
Mental health problems	106 (12%)	35 (10%)	56 (15%)	15 (8%)	0.030
Previous TBI	42 (5%)	14 (4%)	17 (5%)	11 (6%)	<0.0001
GCS on admission					<0.0001
15	585 (64%)	208 (59%)	237 (64%)	140 (75%)	
14	252 (28%)	110 (31%)	103 (28%)	39 (21%)	
13	73 (8%)	35 (10%)	30 (8%)	8 (4%)	
Cause of injury					
Traffic	468 (51%)	188 (53%)	187 (51%)	93 (50%)	0.88
MVA	153 (17%)	80 (23%)	56 (15%)	17 (9%)	<0.0001
Bicycle	287 (32%)	103 (29%)	117 (32%)	67 (36%)	0.079
Pedestrian	28 (3%)	5 (1%)	14 (4%)	9 (5%)	0.036
Fall	342 (38%)	96 (27%)	155 (42%)	91 (49%)	<0.0001
Violence	49 (5%)	40 (11%)	9 (2%)	0	0.009
Sport	20 (2%)	12 (3%)	8 (2%)	0	0.10
Other	31 (3%)	17 (5%)	11 (3%)	3 (2%)	0.17
Mean ISS	7.5 (5.3)	6.9 (4.4)	7.9 (5.7)	8.0 (5.9)	0.043
Alcohol consumed on the day of injury	300 (33%)	148 (42%)	118 (32%)	34 (18%)	0.003
CT abnormalities	137 (15%)	39 (11%)	59 (16%)	39 (21%)	0.098
Hospital admission	558 (61%)	194 (55%)	226 (61%)	138 (74%)	<0.0001

Data are n (%) or mean (SD). Mental health problems were defined as psychiatric or psychological symptoms necessitating treatment by a psychologist or psychiatrist or use of psychotropic medication. *p-value indicates differences between age groups measured by ANOVA. TBI=traumatic brain injury. GCS=Glasgow Coma Scale. ISS=injury severity score. MVA=motor vehicle accident.

Table 1: Demographics and baseline clinical characteristics

using 500 bootstrap samples. The statistical analyses were done in R (version 3.3.2), using the rms package. Missing values in the predictors at the time of admission and 2 weeks after injury were imputed using single imputation with the *aregImpute* function of the Hmisc package.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing the report. JvdN, MEdK, HJvdH, MES, MET, and JMS had full access to all the data, and JvdN had final responsibility for the decision to submit for publication.

Results

From the patients admitted to the three emergency departments, we identified 1555 patients who met inclusion criteria, of whom 1151 gave consent and had baseline data recorded (figure 1). 2 weeks after injury, 910 (79%) patients had filled out the first questionnaire. These patients were older (46.5 years) than those who did not complete the questionnaire (39.6 years; table 1).

For the rms package see
[https://CRAN.R-project.org/
package=rms](https://CRAN.R-project.org/package=rms)

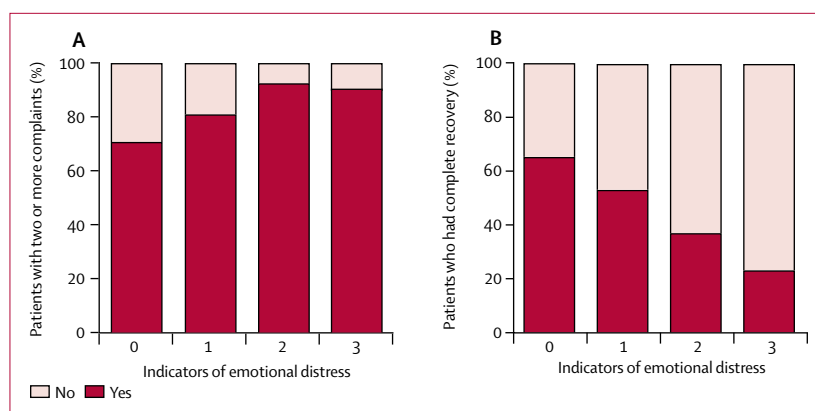


Figure 2: Proportion of patients with emotional distress

Percentage of patients reporting 2 or more complaints scored with the Head Injury Symptom Checklist at 2 weeks after injury (A) and percentage of patients with complete recovery at 6 months after injury (B) related to the number of indicators of emotional distress reported.

Predictor	Coding*	Univariable OR (95% CI)	Emergency department model OR (95% CI)	Emergency department-plus model OR (95% CI)
Baseline data				
Age*	33–51	0.67 (0.55–0.83)	0.77 (0.60–1.00)	..
Age*	51–64	1.09 (0.90–1.32)	1.19 (0.96–1.47)	..
Gender	Male–Female	0.62 (0.45–0.85)	0.74 (0.52–1.04)	..
Education*	4–6	1.79 (1.36–2.36)	1.47 (0.92–2.34)	2.06 (1.49–2.86)
Mental health†	No–Yes	0.30 (0.17–0.53)	0.31 (0.17–0.56)	0.39 (0.20–0.75)
Alcohol‡	No–Yes	2.18 (1.54–3.10)	2.17 (1.47–3.22)	2.14 (1.41–3.24)
Previous TBI	No–Yes	0.48 (0.20–1.18)	..	..
CT abnormalities	No–Yes	0.71 (0.47–1.07)	..	..
GCS*	13–15	1.78 (1.10–2.88)	4.20 (2.17–8.12)	3.26 (1.61–6.58)
PTA	<1h–≥1h	1.21 (0.86–1.70)	1.67 (1.06–2.63)	1.94 (1.20–3.15)
Headache	No–Yes	0.99 (0.73–1.35)	..	..
Nausea	No–Yes	0.86 (0.62–1.19)	..	..
Dizziness	No–Yes	0.83 (0.54–1.26)	..	..
Neck pain	No–Yes	0.41 (0.26–0.62)	0.40 (0.25–0.63)	0.42 (0.26–0.68)
2-week data				
Anxiety*	1–6	0.51 (0.41–0.64)	..	1.54 (1.07–2.22)
Depression*	1–5	0.40 (0.32–0.49)	..	0.44 (0.33–0.59)
PTS*	5–25	0.58 (0.47–0.71)	..	..
Complaints*	2–9	0.37 (0.28–0.48)	..	0.57 (0.40–0.81)
UCL-active*	3–4	1.12 (0.94–1.33)	..	..
UCL-passive*	2–4	0.56 (0.41–0.75)	..	0.65 (0.42–1.02)
UCL-avoidant*	3–4	1.09 (0.90–1.29)	..	1.29 (1.02–1.63)

*The values in this column indicate the 25th and 75th percentile of the continuous predictors, since OR are scaled to correspond to a change from the lower to the upper percentile. For age, values are scaled to changes from the 25th to 50th percentiles, and then from the 50th to the 75th percentile to reflect the non-linear association. An OR <1 favours the first presented condition, whereas an OR >1 favours the second presented condition of a given row. †Pre-injury mental health problems. ‡Alcohol consumed on the day of injury. GCS=Glasgow Coma Scale, PTA=post-traumatic amnesia, PTS=post-traumatic stress. TBI=traumatic brain injury. UCL=Utrecht coping list.

Table 2: Potential associations between predictors in three models and outcomes

From 671 (58%) of 1151 patients, outcome scores were available at the 6-month timepoint, and these data were used for further analysis. Neither severity of injury nor age differed between patients who filled out the 2-week and 6-month questionnaire (table 1). Mean age was 46.5 years (SD 19.2). Age groups comprised 353 (39%) of 910 patients aged less than 40 years, 370 (41%) of 910 patients aged 40–64 years, and 187 (21%) of 910 patients aged 65 years and older, with a response rate at 6 months of 216 (61%) of 353 patients in the group younger than 40 years, 299 (81%) of 370 patients in the group aged 40–64 years, and 156 (83%) of 187 patients in the group aged 65 years and older. There were significantly more falls ($p=0.0001$), CT abnormalities ($p=0.003$) and hospital admissions ($p=0.0001$) recorded in patients aged 65 years and older, and higher use of alcohol at day-of-injury for patients aged less than 40 years ($p=0.098$). CT abnormalities were present in 136 (15%) of 910 patients and mainly comprised of subarachnoid haemorrhage or oedema. Pre-injury TBIs were reported in 42 (5%) of 910 patients.

At 2 weeks after injury, 764 (84%) of 910 patients had one or more post-traumatic complaints (mean 5.8, SD 4.3), with the most common complaints being headache in 464 (51%) patients, dizziness in 505 (55%) patients, and fatigue in 514 (56%) patients. The total number of complaints correlated positively with sum scores of anxiety ($r=0.42$, $p=0.0001$), depression ($r=0.52$, $p=0.0001$), and post-traumatic stress ($r=0.30$, $p=0.0001$). At 2 weeks after injury, 167 (18%) patients scored above the cutoff for anxiety and 147 (16%) above the cutoff for depression, and 352 (39%) patients had post-traumatic stress.

6 months after injury, 481 (72%) of 671 patients had one or more complaints (mean 4.7, SD 4.8). At 6 months after injury, GOSE scores indicated complete recovery in 373 (56%) of 671 patients and incomplete recovery in 298 (44%) of 671 patients. Complete recovery was seen in 136 (63%) of 216 patients aged younger than 40 years, 147 (49%) of 299 patients 40–64 years, and 90 (58%) of 156 patients aged 65 years or older. 143 (28%) of 515 patients aged 16–64 years had not resumed work or study at a pre-injury level.

At 2 weeks after injury, we observed use of all three coping styles (active, passive, and avoidant; range 28–37%; appendix). The UCL scores correlated moderately with indicators of emotional distress and complaints, with significant correlations of passive coping with anxiety ($r=0.56$, $p=0.0001$) and with post-traumatic stress ($r=0.43$, $p=0.0001$). Post-hoc analyses showed a significantly higher use of passive and avoidant coping in patients aged younger than 40 years (35% passive coping, 48% avoidant coping) compared with those aged 40–64 years (29% passive coping, 28% avoidant coping) and older than 65 years (24% passive coping, 32% avoidant coping; $p<0.01$). At 2 weeks, 414 (45%) of 910 patients showed emotional distress, as indicated by one or more scores above the cutoff values

for anxiety, depression, or post-traumatic stress. With an increasing number of indicators for emotional distress, the percentage of patients with two or more complaints at 2 weeks increased, and percentage of patients with complete recovery (ie, GOSE=8) at 6 months decreased (figure 2).

Table 2 shows the predictors in the univariable logistic regression model, the emergency department model, and the emergency department-plus model. For the predictor age in the univariable model and the emergency department model, a non-linear association modelled with a restricted cubic spline with three knots fitted the data better than a linear association ($p=0.0041$).

For the emergency department model, we found that higher education, male sex, absence of mental health problems, presence of alcohol intoxication, absence of neck pain, higher GCS score, and a longer duration of post-traumatic amnesia contributed positively to the prediction of complete recovery. Furthermore, an interaction of age with education was present. The probability of recovery became more strongly related to age with increasing educational level (figure 3), resulting in a clear U-shape association, with the lowest probability of recovery around the age of 40–60 years.

In the emergency department-plus model, the procedure-selected predictors were identical to those of the emergency department model except for sex and age (which were excluded), and the additional variables of anxiety, depression, complaints, UCL-avoidant, and UCL-passive, which were all measured at 2 weeks after injury. For depression, complaints, and UCL-passive, a low score was associated with better outcome, though for anxiety and UCL-avoidant a higher score was associated with a better outcome. The estimated equation was:

$$\log[P/(1-P)] = -9.90 + 0.36 \text{ education} - 0.94 \text{ mental health} + 0.76 \text{ alcohol} + 0.59 \text{ GCS score} + 0.66 \text{ post-traumatic amnesia } (\geq 1 \text{ h}) - 0.88 \text{ neck} + (-0.20 \text{ depression}) + 0.09 \text{ anxiety} + (0.08 \text{ complaints}) + (-0.21 \text{ UCL-Passive}) + 0.25 \text{ UCL-Avoidance}$$

A nomogram summarises these effects (figure 4).

The AUC values indicate that the emergency department-plus model discriminates to a good extent ($\text{AUC}_{\text{sample}}=0.79$, with optimism 0.02; Nagelkerke $R^2=0.32$, with optimism 0.05), and the emergency department model discriminates to a moderate extent between recovery categories ($\text{AUC}_{\text{sample}}=0.72$, with optimism 0.03; Nagelkerke $R^2=0.19$, with optimism 0.05). The bias corrected calibration intercepts indicate a reasonable estimation of the mean probability of complete recovery for the emergency department model (0.03) and emergency department-plus model (0.04). The calibration slopes indicate slight deviations from the optimal calibration curve (0.83 emergency department model, and 0.78 emergency department-plus model).

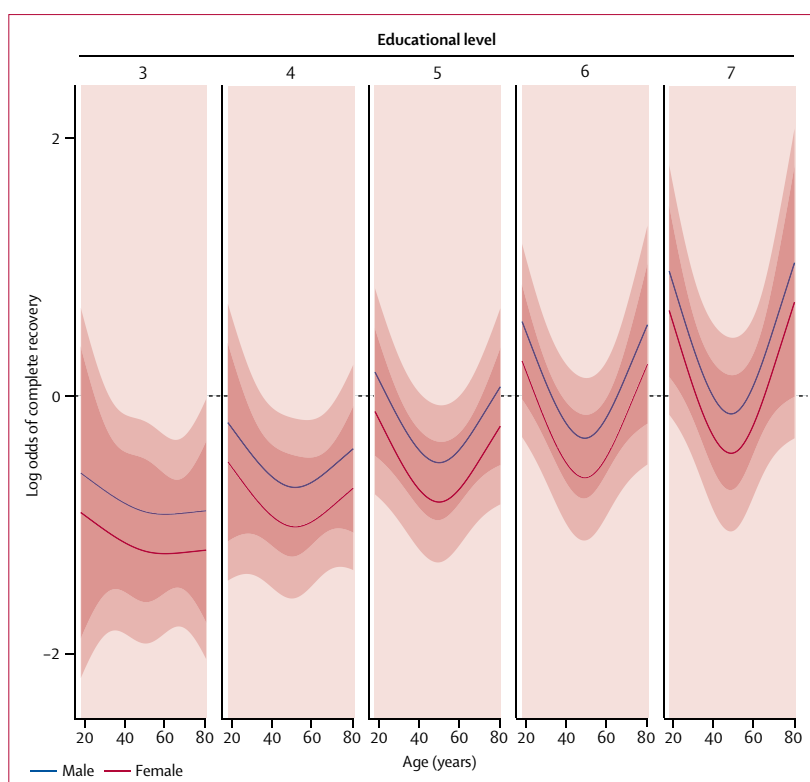


Figure 3: Log odds of complete recovery at 6 months according to level of education

Educational level indicated on a 7-point scale: 3=did not finish secondary school; 4=finished secondary school (low level); 5=finished secondary school (medium level); 6=finished secondary school (highest level or college degree); 7=university degree. No patients presented with an educational level of 1 or 2. This analysis is based on the emergency department model, and adjusted for absence of pre-injury mental health problems, absence of alcohol intoxication, absence of neck pain, Glasgow Coma Scale score equal to 14, and post-traumatic amnesia duration of less than 1 h. Shaded areas indicate the 95% CI bands around the estimated effects, with dark shading indicating an overlap between male and female patients and light shading indicating no overlap in 95% CI.

Discussion

See Online for appendix

In this study, we created a prognostic model for functional outcome at 6 months after mTBI, by combining demographics, injury severity, and psychological factors, to identify patients at risk for incomplete recovery. 6 months after injury, almost half of the patient population had not achieved complete recovery, with most patients still reporting post-traumatic complaints, and one in four patients having not resumed work or study at a pre-injury level. Emotional distress experienced early after injury, in combination with a maladaptive coping style and demographic variables (pre-injury mental health problems and education) were significant factors for incomplete recovery.

2 weeks after injury, the number of patients reporting post-traumatic complaints or emotional distress was similar to earlier studies.^{3,14,27} In our cohort, the percentage of patients reporting post-traumatic complaints decreased over time, whereas the incidence of anxiety, depression, or post-traumatic stress remained stable, although the earlier studies did not measure these factors simultaneously. The presence of one or

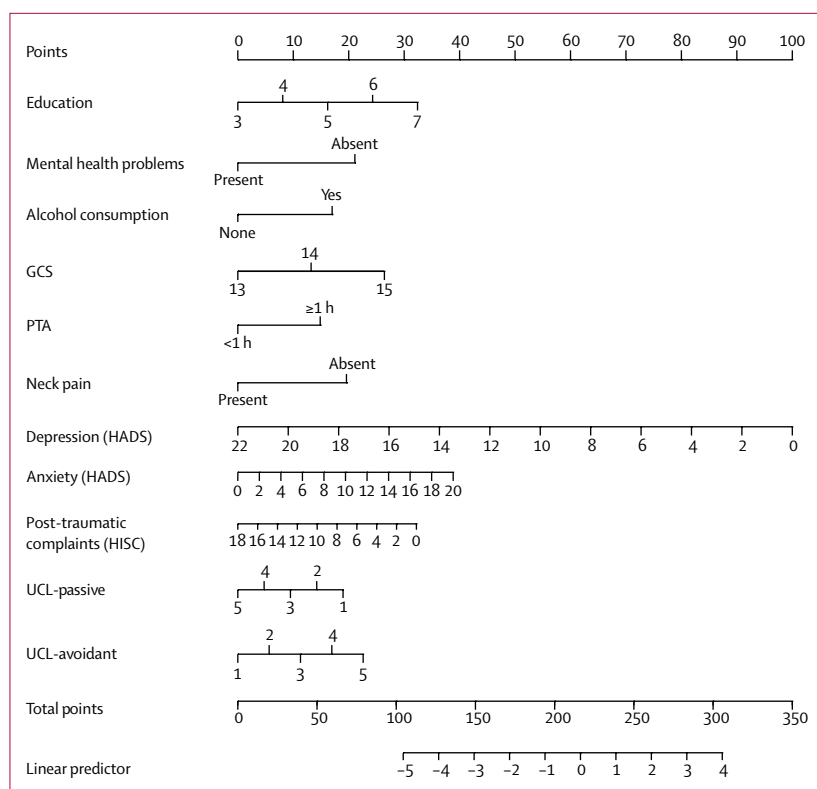


Figure 4: Nomogram to estimate probability of complete recovery at 6 months

Based on the emergency department-plus model. To predict the probability of outcome for an individual patient, for each predictor identify the number of points associated with the score of the patient. For example, an educational level of 6 would imply 24 points. Compute the sum of points for all predictors, and denote this value as the Total points. Identify the value of the Linear predictor (LP) associated with the total points by placing a vertical ruler on the nomogram. For example, a score of 215 on the Total points is associated with a value of 0 on the linear predictor. Calculate the probability of outcome (PO) as $PO = 1 / (1 + \exp(-LP))$. GCS=Glasgow Coma Scale. PTA=post-traumatic amnesia. HADS=Hospital Anxiety and Depression Scale. HISC=Head Injury Symptom Checklist. UCL=Utrecht Coping List.

more of these emotional distress factors after injury was related to higher rates of post-traumatic complaints and incomplete recovery. In line with previous research,²⁷ this suggests that, for the persistence of complaints, the specific type of emotional distress present (ie, anxiety, depression, or post-traumatic stress) was not relevant, but instead whether patients were able to cope adequately with this mental distress was the most important factor.

We identified several predictive factors for outcome with good discriminative ability compared with other models.^{11,28,29} In our emergency department model, which contained demographic and injury severity variables, outcome was related to age, which is in line with other studies.^{10,11} This association was non-linear, with complete recovery rates that were higher in patients aged 65 years and older than in those aged 40–64 years (58% vs 49%). This finding confirms earlier studies^{19,30} that reported a generally good outcome for patients aged 60 years and older. However, age interacted with educational level, showing that this effect of better recovery rates was mainly present for patients with higher educational

levels; it is likely that the lower recovery rates for the age group of 40–64 might be explained by a combination of increased age and higher vocational demands.

For the emergency department-plus model, which contained additional variables recorded at 2 weeks after injury, a higher score on the depression scale, a higher number of post-traumatic complaints, and a higher use of a passive coping style were found to be significant predictors of an incomplete recovery. Additionally, we found that a higher score on the anxiety scale and a higher use of an avoidant coping style apparently had some protective value, since these two variables were predictive for a better outcome. In the chronic phase of TBI, the use of an avoidant coping style has been found to increase; this coping style might have a protective effect because mentally challenging situations can be avoided in case of information overload.³¹ This assumption is confirmed in our study by the non-significant correlation of avoidant coping with post-traumatic stress in contrast to passive coping. Since age and sex, which were significant predictors in the emergency department model, were no longer significant predictors in the emergency department-plus model, we conclude that measures of emotional distress and coping style had a higher and more specific predictive power for recovery.

Injury severity identified by the variable CT abnormality was not found to be a predictor of incomplete recovery in either model. This finding can be explained by the fact that, in only 108 (16%) of 671 patients, CT abnormalities that mainly consisted of subarachnoid haemorrhage or oedema were present. In the TRACK-TBI study,³ it was also found that presence of post-traumatic complaints was not related to the presence of CT abnormalities, and although patients with CT abnormalities had worse GOSE scores at 3 months, this association was no longer present at 6 months. This suggests that factors other than CT abnormalities were predictive of long-term outcome, in accordance with previous work.^{8,9,11} Post-traumatic amnesia was also predictive for outcome but, counter-intuitively, a duration of less than 1 h was associated with a worse outcome, perhaps implying that the effect of the accident has been experienced more consciously by the patient. Similarly, the finding that presence of alcohol intoxication is associated with better outcome might be considered as a protective factor that dampens the memory of the traumatic event.

Several limitations of this study have to be mentioned, including the restricted generalisability of the results. Patients who did not fill out the first questionnaire at 2 weeks who were subsequently excluded from the analyses were substantially younger than those that completed the study, and this might have resulted in a bias towards worse outcome. Although the UPFRONT study comprised a high number of patients up to 92 years of age, which is possibly a cohort that is a good representation of the epidemiological trend of an ageing TBI population, a bias towards worse outcome was

unlikely to have been introduced by including these patients. The group of patients that filled out the first questionnaire were similar in age, injury severity, and sex to those patients for whom outcome at 6 months was available. There was loss to follow-up between 2 weeks and 6 months, which might relate to the fact that it can be difficult to motivate patients with an overall good outcome to participate in extensive follow-up, and might result in a bias towards worse outcome in the patients that remained in the study.^{32,33} However, this dropout rate was similar to those seen in other studies.^{3,11} Therefore, we believe that we have constructed a reliable prediction model and have provided results that are important for the interpretation of long-term outcome in this patient population.

For clinical practice, our analyses might allow a two-step approach to identify patients who are at risk of developing complaints that interfere with recovery, since indiscriminate treatment of all patients with mTBI would not be beneficial. This early identification could be done at discharge from the emergency department, using the model with emergency department variables only. At-risk patients subsequently could be contacted by phone or mail to inquire how they feel and how they are coping at 2 weeks after injury. Inclusion of measures of emotional distress and coping style allows for a more precise identification of who is at risk for an incomplete recovery using the emergency department-plus model than with variables only obtained at admission to the emergency department. With this approach, the selection of those patients who have to be seen at the outpatient clinic can be narrowed down. Several studies^{34–36} have suggested that early psychological interventions might be effective in preventing the development of persistent post-traumatic complaints. Therefore, we believe that application of the emergency department-plus model allows for early identification of high-risk patients with possibilities for timely treatment. Although our models have yet to be externally validated, internal validation, as expressed via the optimism values, was done using bootstrapping in this study. In a future validation study, it might be worthwhile to expand on these possibilities for early identification by investigating the sensitivity and specificity of specific cutoffs based on the emergency department model to follow up patients by phone or mail at 2 weeks after injury.

Contributors

JvdN and JMS put together the study design and conceived the idea for the study. JvdN, MEdK, HJvdH, MES, GH, GR, MET, JMS, and BJ drafted and revised the manuscript. JvdN, MET, MEdK, MES, HJvdH, BJ, TY, GR, GH, and JMS acquired and interpreted the collected data. MET, JMS, and JvdN did the statistical analyses.

Declaration of interests

We declare no competing interests.

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