Moderate Traumatic Brain Injury: Clinical Characteristics and a Prognostic Model of 12-Month Outcome

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■ BACKGROUND: **Patients with moderate traumatic brain injury (TBI) often are studied together with patients with severe TBI, even though the expected outcome of the former is better. Therefore, we aimed to describe patient characteristics and 12-month outcomes, and to develop a prognostic model based on admission data, specifically for patients with moderate TBI.**

■ METHODS: **Patients with Glasgow Coma Scale scores of 9–13 and age ≥16 years were prospectively enrolled in 2 level I trauma centers in Europe. Glasgow Outcome Scale Extended (GOSE) score was assessed at 12 months. A prognostic model predicting moderate disability or worse (GOSE score ≤6), as opposed to a good recovery, was fitted by penalized regression. Model performance was evaluated by area under the curve of the receiver operating characteristics curves.**

■ RESULTS: **Of the 395 enrolled patients, 81% had intracranial lesions on head computed tomography, and 71% were admitted to an intensive care unit. At 12 months, 44% were moderately disabled or worse (GOSE score ≤6), whereas 8% were severely disabled and 6% died (GOSE score ≤4). Older age, lower Glasgow Coma Scale score, no day-of-injury alcohol intoxication, presence of a subdural hematoma, occurrence of hypoxia and/or hypotension, and preinjury disability were significant predictors of GOSE score ≤6 (area under the curve = 0.80).**

■ CONCLUSIONS: **Patients with moderate TBI exhibit characteristics of significant brain injury. Although few patients died or experienced severe disability, 44% did not experience good recovery, indicating that follow-up is needed. The model is a first step in development of prognostic models for moderate TBI that are valid across centers.**

INTRODUCTION

Few studies have specifically focused on characteristics and prognosis in patients with moderate traumatic brain injury (TBI),[1-5] which in existing classifications is either defined by a Glasgow Coma Scale (GCS) score of 9–12 or 9–13 at emergency department (ED) admission.[6-9] Previous studies of patients

Key words
- Cohort studies
- Comparative study
- Craniocerebral trauma
- Prognosis
- Statistical models

Abbreviations and Acronyms
AUC: Area under the curve
CI: Confidence interval
CT: Computed tomography
ED: Emergency department
EDH: Epidural hematoma
GCS: Glasgow Coma Scale
GOSE: Glasgow Outcome Scale Extended
HL test: Hosmer-Lemeshow goodness-of fit-test
ICP: Intracranial pressure
ICU: Intensive care unit
ISS: Injury Severity Score
ISSe: Modified ISS score for extracranial injuries
IQR: Interquartile range
SDH: Subdural hematoma
TBI: Traumatic brain injury
tSAH: Traumatic subarachnoid hemorrhage

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with moderate TBI have found that approximately 60% of patients had intracranial traumatic findings on admission computed tomography (CT) of the head,[1-3] 20%–84% were admitted to an intensive care unit (ICU),[1-4] and approximately 15% had surgery for a mass lesion or a depressed skull fracture.[3,4] However, case-fatality rates were low (0.9%–8%).[2,3,5,10] Furthermore, the vast majority of the patients experienced only moderate or no disability, indicating independency in daily life (74%–85%),[2,5] and many even a good recovery, indicating no disability (55%–75%).[1,2,5]

Despite the fact that the expected outcome is better after moderate than severe TBI, patients with moderate TBI are mostly studied together with patients with severe TBI in outcome prediction studies.[8,11-14] The largest validated prognostic models so far using the Glasgow Outcome Scale Extended (GOSE) as outcome measure are the models from the Corticosteroid randomization after significant head injury (CRASH) Trial and the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT).[11,15] The models have consistently identified age, GCS score, pupillary reactivity, and CT characteristics as predictors for an unfavorable outcome.

These models, however, have been developed for prediction of death and severe disability (GOSE score $\leq$4), outcomes that are less likely after moderate TBI. Moreover, it has been demonstrated that these models performed better in cohorts with a high proportion of patients with poor outcomes. This was especially observed in prediction of death.[16] This may indicate that accurate outcome prediction in patients with better outcomes may be more challenging. Hence, there is a need for studies aiming at developing models for the prediction of outcome specifically in patients with moderate TBI, where many patients will have good recovery at follow-up. This gap in the literature also was acknowledged in a recent review.[17] To our knowledge, no earlier studies have constructed models for the prediction of moderate disability or worse (GOSE score $\leq$6) in contrast to a good recovery specifically in patients with moderate TBI.

Our first aim was to describe and compare clinical characteristics, head CT findings, and 12-month outcome in observational prospective cohorts of patients with moderate TBI from 2 European level I trauma centers. The second aim was to develop a prognostic model based on admission data for prediction of GOSE score $\leq$6, 12 months after the injury. Prognostic models also were developed for each center separately to identify important predictors, and hence it was possible to externally validate these in the opposite dataset.

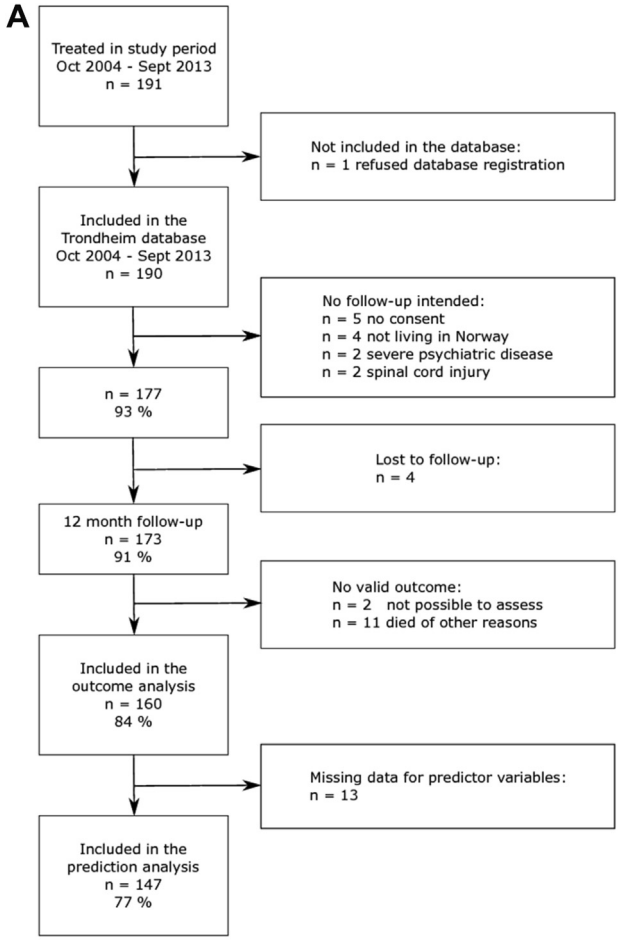

Figure 1. (**A**) Flowchart of patients with moderate traumatic brain injury admitted to the Trondheim University Hospital, Trondheim, Norway, during the study period. (**B**) Flowchart of patients with moderate traumatic brain injury patients admitted to the University Medical Center, Groningen, The Netherlands, during the study period. GCS, Glasgow Coma Scale. (continues)

MATERIAL AND METHODS

The Two Centers

St. Olavs Hospital, Trondheim University Hospital (referred to as Trondheim) is a regional level I trauma center and a tertiary referral center for all neurosurgical activities for 3 counties in mid-Norway, with approximately 700,000 inhabitants and 6 general hospitals. Regarding 1 of the counties (approximately 300,000 inhabitants), patients with all severities of TBI are admitted to Trondheim. Regarding the 2 other counties, patients with severe TBI, patients with moderate TBI in need of neurosurgical assessments and/or intervention, and patients with additional major extracranial injuries are admitted to Trondheim.

The University Medical Center in Groningen (referred to as Groningen) is 1 of 11 regional level I trauma centers in the Netherlands, serving 3 counties with 1,500,000 inhabitants in total. The area also has 12 general hospitals. Patients with all severities of TBI and patients in need for observation for neurosurgical assessments or intervention are admitted to Groningen.

Patients and Inclusion Procedures

Patients $\geq$16 years of age with a moderate TBI defined by GCS score 9–13 were included. Inclusion and exclusion into the databases and follow-up in the 2 centers are described in **Figure 1A** and **B**. The GCS score was determined after stabilization in the ED. In case of intubation or sedation at the scene of accident, at

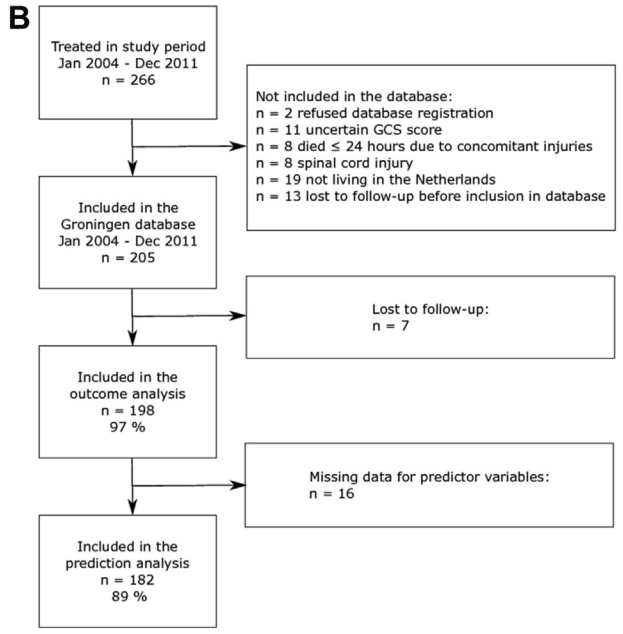

Figure 1. (continued).

the local hospital or at the trauma center, the last nonsedated GCS score was reported ($n = 79$). In Trondheim, 190 patients were enrolled prospectively in the Trondheim TBI studies during 9 years (October 2004 to September 2013) (Figure 1A). Of these patients 94, 46, and 84 have been included in previous studies from the Trondheim TBI group.[4,18,19] In Groningen, 205 patients were enrolled prospectively in their neurotrauma database during 8 years (January 2004 to December 2011) (Figure 1B), and 19 and 49 of these patients were included in previous studies.[1,20]

Clinical Variables

Preinjury disability was defined as present if daily functioning was affected by alcohol and/or drug abuse, psychiatric or neurologic disease, developmental disorders, or severe somatic disease. Cause of injury was categorized into traffic accidents, falls, and others (including violence, ski accidents, and being struck by an object). Day-of-injury alcohol intoxication was recorded as yes or no based on the serum value of ethanol or clinical judgment, both methods have been found valid for classifying a person as sober or not.[21,22] Pupillary status was categorized into normal or unilaterally dilated. A secondary event was defined as occurrence of hypoxia (saturation <92%) and/or hypotension (systolic blood pressure <90 mm Hg) at the scene of accident or at ED admission. Transfer of patients from other hospitals to the trauma centers also was recorded. Other clinical variables were being intubated, days on ventilator, treatment in a neurointensive or general intensive care unit (ICU), including the length of stay in the ICU, evacuation of any intracranial mass lesion (subdural [SDH], epidural [EDH], or intracerebral hematomas) and insertion of intracranial pressure (ICP) monitoring device (parenchymal ICP sensor and/or external ventricular drain).

The Injury Severity Score (ISS) was used to indicate overall trauma severity and was assessed by residents in neurosurgery (K.G.M. and S.H.) in Trondheim, and by the research nurse (A.C.) in Groningen.[23] To quantify extracranial injuries, a modified extracranial score (ISS_e) was calculated based on the total ISS score minus the squared Abbreviated Injury Scale Head score.[24]

Head CT

Most head CTs were acquired with a Siemens Somatom Sensation 64-row scanner (Siemens AG, Erlangen, Germany) in both Trondheim and Groningen. CT examinations were performed as standardized care at ED admission and during follow-up if needed. Both the first and the worst CT examinations were reviewed for the current study by a consultant or resident in neurosurgery or radiology (I.H.S., K.G.M., S.F.D., or J.X.) in Trondheim and in Groningen by a neurologist (J.V.N. or B.J.).

At both centers, head CT characteristics of the worst CT examination were categorized into: any intracranial finding, SDH, EDH, traumatic subarachnoid hemorrhage (tSAH), including intraventricular hemorrhage, punctate hemorrhage <2 mm, contusion (single or multiple lesions), fracture (base, skull, and impression fractures merged), midline shift > or ≤5 mm, and degree of compression of basal cisterns (normal, compressed, or absent). In addition, Rotterdam CT score (best score 1, worst score 6) using the worst scan was computed by consultant or resident in neurosurgery or radiology (I.H.S., K.G.M., S.F.D., or J.X.) in Trondheim and in Groningen by a consultant in physical medicine and rehabilitation (C.E.) based on the CT variables.[25] This score is based on midline shift, compression of basal cisterns, tSAH, or intraventricular hemorrhage and EDH.

Outcome

Length of stay was defined as time from the first hospital ED admission to discharge from the level I trauma center. Case-fatality rate was defined as the percentage of patients who died from the head injury during the hospital stay. Discharge destinations were home (with or without outpatients' rehabilitation services), other clinical departments (including psychiatry), other hospitals, rehabilitation center (including rehabilitation at hospital, rehabilitation in private institutions or municipal rehabilitation), or nursing home (including sheltered housing 24 hours a day).

Functional outcome was assessed at 12 months after the injury using the structured interview for the GOSE.[26-29] The GOSE score in survivors was assessed based on the functional outcome from the injury as a whole and not specifically the brain injury. Outcome was assessed by phone (most of the patients at Trondheim) or in-person interview (most of the patients at Groningen) with the patients and relatives or caregivers. Both phone and in-person interview for the GOSE assessment have been validated and good agreement has been found, especially after standardizing procedures and training.[26,30,31] The outcome assessors were not blinded for clinical information.

The GOSE score was dichotomized into being moderately disabled or worse (GOSE score ≤6) versus good recovery (GOSE score 7–8), and into being severely disabled or worse (GOSE score ≤4) versus moderate or no disability (GOSE score 5–8).

Statistical Analysis

The statistical analyses were conducted with IBM SPSS Statistics version 22 (IBM Corp., Armonk, New York, USA), STATA/SE

Table 1. All Patients: Clinical Characteristics and Injury-Related Variables

Variable	Total	Trondheim	Groningen	*P* Value
No. of patients, %	395	190 (48)	205 (52)	
Age, years				**0.002**
Median (range, IQR)	46 (16–97, 25–63)	51 (16–97, 28–67)	39 (16–88, 23–60)	
Mean ± SD	46 ± 21	50 ± 22	43 ± 39	
Male/female sex, *n* (%)	280/115 (71/29)	123/67 (65/35)	157/48 (77/23)	**0.010**
Preinjury disability, *n* (%)*	92 (24)	49 (26)	43 (22)	0.305
Cause of injury, *n* (%)*				**0.006**
Traffic accidents	174 (45)	71 (39)	103 (50)	
Fall	166 (43)	94 (51)	72 (35)	
Other	49 (13)	19 (10)	30 (15)	
GCS score, *n* (%)				0.921
13	171 (43)	84 (44)	87 (42)	
12	79 (20)	39 (21)	40 (20)	
11	44 (11)	22 (12)	22 (11)	
10	40 (10)	19 (10)	21 (10)	
9	61 (15)	26 (14)	35 (17)	
Alcohol intoxication, *n* (%)†	109 (28)	48 (26)	61 (31)	0.277
Intoxicated, S-ethanol known	51 (13)	41 (22)	10 (5)	
Intoxicated, S-ethanol unknown	58 (15)	7 (4)	51 (26)	
Transferred from other hospitals, *n* (%)	64 (16)	41 (22)	23 (11)	**0.005**
Secondary event, *n* (%)‡	50 (13)	22 (12)	28 (14)	0.609
Unilateral pupillary dilation, *n* (%)§	42 (11)	15 (8)	27 (13)	0.086
Median ISS score (IQR)	17 (9–25)	20 (13–25)	17 (8–24)	**<0.001**
Median ISS_e score (IQR)	4 (0–9)	1 (0–8)	4 (1–9)	**<0.001**
Intracranial findings, *n* (%)	320 (81)	173 (91)	147 (72)	**<0.001**
SDH, *n* (%)	136 (34)	88 (46)	48 (23)	**<0.001**
EDH, *n* (%)	62 (16)	29 (15)	33 (16)	0.820
tSAH, *n* (%)	195 (49)	106 (56)	89 (43)	**0.014**
Punctate hemorrhage, *n* (%)	108 (27)	48 (25)	60 (29)	0.372
Contusion(s), *n* (%)	181 (46)	107 (56)	74 (36)	**<0.001**
Cranial fracture, *n* (%)	174 (44)	87 (46)	87 (42)	0.503
Midline shift >5 mm, *n* (%)	66 (17)	34 (18)	32 (16)	0.543
Basal cisterns, *n* (%)				0.374
Normal	300 (76)	150 (79)	150 (73)	
Compressed	84 (21)	36 (19)	48 (23)	
Absent	11 (3)	4 (2)	7 (3)	
Median Rotterdam CT score (IQR)	3 (2–3)	3 (2–3)	2 (2–3)	**0.030**
Admitted to ICU, *n* (%)	279 (71)	167 (88)	112 (55)	**<0.001**
Median days ICU LOS (IQR)‖	4 (2–8)	3 (1–7)	5 (2–12)	**<0.001**
Intubated, *n* (%)	164 (42)	87 (46)	77 (38)	0.097

Continues

Table 1. Continued

Variable	Total	Trondheim	Groningen	*P* Value
Median days on ventilator (IQR)¶	4 (1—10)	2 (1—9)	6 (1—11)	**0.045**
ICP monitoring, *n* (%)#	66 (17)	44 (23)	22 (11)	**0.001**
Evacuation of mass lesion, *n* (%)	60 (15)	39 (21)	21 (10)	**0.004**
Median days LOS (range, IQR)**	8 (0—142, 3—16)	6 (1—94, 4—12)	10 (0—142, 3—20)	0.055
In-hospital case-fatality rate, n (%)	13 (3)	6 (3)	7 (3)	0.886
Discharge destination, *n* (%)††				**<0.001**
Home	280 (48)	57 (31)	123 (63)	
Other hospital	93 (25)	68 (37)	25 (27)	
Rehabilitation	74 (20)	37 (20)	37 (19)	
Nursing home	24 (6)	14 (8)	10 (5)	
Other departments	7 (2)	6 (3)	1 (1)	

Significant *P* values are marked in bold.
IQR, interquartile range; SD, standard deviation; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; ISSe, modified ISS score for extracranial injuries; SDH, subdural hematoma; EDH, epidural hematoma; tSAH, traumatic subarachnoid hemorrhage; CT, computed tomography; ICU, Intensive care unit; LOS, length of hospital stay; ICP, intracranial pressure.
Number of patients in analysis due to lacking data: *$n = 389$, †$n = 388$, ‡$n = 380$, §$n = 394$.
||Only patients treated in ICU included, $n = 275$.
¶Only ventilated patients included, $n = 163$.
#Reasons for ICP monitoring were high-risk brain injury (79%) or monitoring of the brain injury in sedated patients (21%).
**Only surviving patients included, $n = 380$.
††Only surviving patients included, $n = 378$.

version 13 (StataCorp LLC, College Station, Texas, USA), and the R statistical package.[32] Demographic and injury characteristics are presented as percentages, median with interquartile range (IQR), or mean with standard deviation. Between-group differences were analyzed with the Mann—Whitney U test for variables with non-normal distributions and for ordinal variables. The χ^2 test or Fisher exact test was used for comparison of proportions. Two-sided P values of < 0.05 were considered statistically significant.

A common model was generated based on the data from Trondheim and Groningen combined and one for each of the Trondheim and Groningen datasets. We included 9 clinical and 8 CT variables commonly used in previous outcome prediction studies. We chose to use the individual CT characteristics rather than the Rotterdam CT score, because they are more easily interpreted in a clinical context. Age, GCS score, and ISS_e score were analyzed as continuous variables, and the remaining clinical and CT variables were binary. In addition, center was included as a

Table 2. All Patients: 12 Months' Outcome

GOSE Score at 12 Months	Total	Trondheim	Groningen	*P* Value
No. of patients	358	160 (45)	198 (55)	
GOSE 1 (Death), *n* (%)	20 (6)	10 (6)	10 (5)	
GOSE 3 (Severe disability, lower), *n* (%)	16 (4)	12 (8)	4 (2)	
GOSE 4 (Severe disability, upper), *n* (%)	14 (4)	4 (3)	10 (5)	
GOSE 5 (Moderate disability, lower), *n* (%)	45 (13)	17 (11)	28 (14)	
GOSE 6 (Moderate disability, upper), *n* (%)	63 (18)	24 (15)	39 (20)	
GOSE 7 (Good recovery, lower), *n* (%)	82 (23)	25 (16)	57 (29)	
GOSE 8 (Good recovery, upper), *n* (%)	118 (33)	68 (43)	50 (25)	
GOSE score $\leq$6 (%), *n* (%)	158 (44)	67 (42)	91 (46)	0.439
GOSE score $\leq$4 (%), *n* (%)	50 (14)	26 (16)	24 (12)	0.263

GOSE, Glasgow Outcome Scale Extended.

Table 3. Patients Included in the Prediction Analysis: Clinical Characteristics, Injury-Related Variables, and 12 Months' Outcome

Variable	Total	Trondheim	Groningen	*P* Value
No. of patients (%)	329	147 (45)	182 (55)	
Age, years				0.138
Median (range, IQR)	45 (16–97, 24–62)	48 (16–97, 25–63)	39 (16–88, 23–61)	
Mean ± SD	45 ± 21	47 ± 21	43 ± 21	
Male/female sex, *n* (%)	232/97 (71/30)	93/54 (63/37)	139/43 (76/24)	**0.010**
Preinjury disability, *n* (%)	69 (21)	30 (20)	39 (21)	0.821
Cause of injury, *n* (%)				0.094
Traffic accident	155 (47)	61 (42)	94 (52)	
Fall	133 (40)	69 (47)	64 (35)	
Other	41 (13)	17 (12)	24 (13)	
Median GCS score (IQR)	12 (10–13)	12 (10–13)	12 (10–13)	0.399
Alcohol intoxication, n (%)	93 (28)	39 (27)	54 (30)	0.530
Secondary event, *n* (%)	39 (12)	12 (8)	27 (15)	0.063
Unilateral pupillary dilation, *n* (%)	34 (10)	11 (8)	23 (13)	0.127
Median ISS_e (IQR)	4 (1–9)	4 (0–8)	4 (1–9)	**0.001**
SDH, *n* (%)	109 (33)	65 (44)	44 (24)	**<0.001**
EDH, *n* (%)	56 (17)	25 (17)	31 (17)	0.995
tSAH, *n* (%)	164 (50)	82 (56)	82 (45)	0.053
Punctate hemorrhage, *n* (%)	98 (30)	40 (27)	58 (32)	0.358
Contusion(s), *n* (%)	148 (45)	81 (55)	67 (37)	**0.001**
Cranial fracture, *n* (%)	146 (44)	66 (45)	80 (44)	0.864
Midline shift >5 mm, *n* (%)	65 (17)	27 (18)	29 (16)	0.559
Basal cisterns, *n* (%)				0.446
Normal	246 (75)	114 (78)	132 (73)	
Compressed	73 (22)	30 (20)	43 (24)	
Absent	10 (3)	3 (2)	7 (4)	
Median Rotterdam CT score (IQR)	3 (2–3)	3 (2–3)	2 (2–3)	0.068
GOSE score ≤6, *n* (%)	147 (45)	62 (42)	85 (47)	0.412

Significant *P* values are marked in bold.
IQR, interquartile range; SD, standard deviation; GCS, Glasgow Coma Scale; ISS_e, modified ISS score for extracranial injuries; SDH, subdural hematoma; EDH, epidural hematoma; tSAH, traumatic subarachnoid hemorrhage; CT, computed tomography; GOSE, Glasgow Outcome Scale Extended.

binary covariate (fixed effect) in the common model, in effect accounting for within-center dependencies. Missing data were handled by listwise deletion (13 patients in Trondheim: 5 cause of injury and 8 secondary event [Figure 1A] and 16 patients in Groningen: 5 preinjury disability, 5 day-of-injury alcohol intoxication, 5 secondary event, 1 pupillary dilation [Figure 1B]). A total of 329 patients were included in the analysis.

The models were fitted by penalized logistic regression using the lasso (least absolute shrinkage and selection operator) method as implemented in the R package glmnet.[33] This method shrinks the values of the regression coefficients to obtain less extreme values, as a means towards improving the external validity of the model. For variables with low predictive value, the coefficients could be shrunk to zero, and the variables thus left out of the final model. The degree of shrinkage was determined by 10-fold cross-validation. In effect, the method performs simultaneous estimation of the coefficients and variable selection. It should be noted that the lasso method focuses on the overall fit rather than statistical significance of individual predictors. Consequently, predictors with a *P* value > 0.05 could still be included in the final model.

The uncertainty in the estimated coefficients from the lasso was assessed by bootstrapping the penalized regression procedure

Table 4. Common Model Selected by Lasso

Variable	Coefficient	OR (95% CI)	*P* Value
Intercept	0.84		
Age	0.02	1.02 (1.02–1.04)	**<0.001**
Female	0.09	1.09 (0.76–2.26)	0.324
Preinjury disability	0.40	1.50 (1.02–3.40)	**0.043**
Traffic accident	0.06	1.06 (0.71–2.08)	0.480
GCS score	−0.24	0.65 (0.65–0.90)	**0.001**
Alcohol intoxication	−0.83	0.44 (0.20–0.65)	**0.001**
Secondary event	0.62	1.86 (1.05–5.14)	**0.037**
Pupillary dilation	0.37	1.44 (0.85–4.45)	0.113
ISS_e	0	1 (0.97–1.05)	0.628
SDH	0.62	1.86 (1.31–4.14)	**0.004**
EDH	0.12	1.13 (0.63–2.53)	0.520
tSAH	0.26	1.30 (0.91–2.63)	0.107
Punctate hemorrhage	0	1 (0.67–2.05)	0.574
Contusion	0	1 (0.51–1.57)	0.710
Cranial fracture	0.17	1.19 (0.71–2.26)	0.433
Midline shift >5 mm	0.13	1 (0.67–3.34)	0.323
Basal cisterns compressed/absent	0.18	1.20 (0.68–2.63)	0.404
Center	0.23	1.26 (0.92–2.54)	0.102

Significant *P* values are marked in bold.
Models selected by lasso show the estimated shrunk regression coefficients for the combined Trondheim and Groningen data. A coefficient of 0 means that the variable was not included in the model and values different from 0, was included. OR was the odds for GOSE score ≤6 versus odds for GOSE score >6.
OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale; ISS_e, Injury Severity Scale extracranial; SDH, subdural hematoma; EDH, epidural hematoma; tSAH, traumatic subarachnoid hemorrhage.

using 1000 bootstrap samples. A bootstrap sample is generated by resampling with replacement from the original data set. The penalized regression procedure, including the selection of the degree of shrinkage, was run for each bootstrap sample. The uncertainty was illustrated for each of the variables by the proportion of the 1000 bootstrap samples that gave a value of zero for that coefficient. Proportions closer to zero indicate greater probability for the variable to be included in the model and contribute to the outcome prediction. In addition, P values for the regression coefficients were calculated using the de-sparsified lasso method implemented in the R package hdi.[34] This method takes the shrinkage and variable selection into account. P values < 0.05 were considered statistically significant. Because the statistical analysis was aimed at obtaining the best predictor model, the statistical significance for the regression coefficients was not of major importance, and no formal adjustment for multiple testing was included.

The model fit was assessed by the Hosmer–Lemeshow goodness-of fit-test (HL test), for which a P value less than 0.05 indicates a poor fit. The Nagelkerke pseudo-R^2 was also calculated for the models. The area under the curve (AUC) of the receiver operating characteristics curves was used to assess discrimination. The 95% confidence intervals (CIs) for the AUCs and the P values for comparing AUCs were calculated by bootstrapping using 10,000 bootstrap samples. To calculate the performance measures for external validation, the Groningen outcomes were predicted based on the model fitted in the Trondheim data, and vice versa.

Ethics

In Trondheim, the Regional Committee for Medical Research Ethics (2013/1977) approved the study. Written consent was obtained from the surviving patients or their next of kin if the patient was incapacitated. In Groningen, the study was approved by the local Medical Ethical Committee, and informed consent was waived as only de-identified clinical data were registered.

RESULTS

All Patients with Moderate TBI

In the total study population of 395 patients, the median age was 46 years, 71% of the patients were male, and 24% reported preinjury disability (Table 1). Falls and traffic accidents were the main causes of injury. Intracranial traumatic lesions on head CT were seen in 81% of the patients, 71% were treated in an ICU (median 4 days (IQR = 2–8 days), and median days on ventilator were 4 (IQR = 1–10). The in-hospital case-fatality rate was 3%. At 12-month follow-up, 56% had good recovery (GOSE score 7 and 8), 31% moderate disability (GOSE score 5 and 6), 8% severe disability (GOSE score 3 and 4), and 6% had died from their head injury (GOSE score 1). Hence, 44% were moderately disabled or worse (GOSE score ≤6), whereas 14% were severely disabled or worse (GOSE score ≤4) (Table 2).

The GCS score was 13 in 43% of the patients. In general, the GCS 9–12 group were significantly different from the GCS 13 group, with a greater proportion of intracranial lesions (73% vs. 88%, $P \leq 0.001$), treatment in ICU (56% vs. 82%, $P \leq 0.001$), and GOSE score ≤6 at follow-up (35% vs. 51%, $P = 0.003$). Still, the GCS 13 group had high prevalence of lesions on CT, more than 50% were treated in the ICU, and approximately one third did not achieve a good recovery.

Differences Between the Two Centers

In Trondheim, the patients were older (median 51 years vs. 39 years), the proportion of women was greater, and more injuries were caused by falls than in Groningen. The patients in Trondheim had more often been transferred from other hospitals and traumatic intracranial lesions were more often present on head CT (91% vs. 72%). They had greater ISS scores, but ISS_e was lower. The patients in Trondheim were more often admitted to the ICU and more often had ICP monitoring (Table 1). More patients were discharged directly home in Groningen than in Trondheim (63% vs. 31%), whereas discharge to other hospitals was more common in Trondheim (37% vs. 27%). Outcome at 12 months was not significantly different between the centers.

Prediction of Outcome

Characteristics of the patients included in the outcome prediction analysis are presented in Table 3. The combined dataset of both

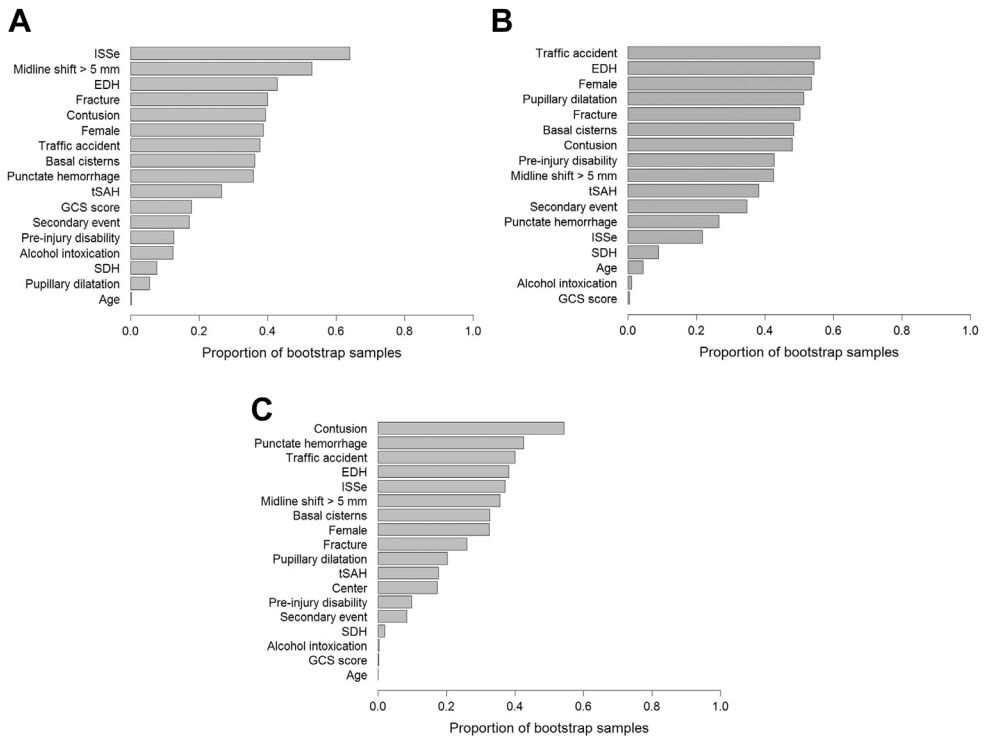

Figure 2. (**A**) The histogram shows the proportion of the 1000 bootstrap samples that gave coefficients equal to zero for each variable in the combined dataset of patients from both centers. Proportions closer to zero indicate data greater probability for the variable to be included in the model. (**B**) The histogram shows the proportion of the 1000 bootstrap samples that gave coefficients equal to zero for each variable in the model fitted in the Trondheim data. Proportions closer to zero indicate greater probability for the variable to be included in the model. (**C**) The histogram shows the proportion of the 1000 bootstrap samples that gave coefficients equal to zero for each variable in the model fitted in the Groningen data. Proportions closer to zero indicate greater probability for the variable to be included in the model. EDH, Epidural hematoma; ISSe, Injury Severity Scale extracranial; tSAH, traumatic subarachnoid hemorrhage; SDH, subdural hematoma; GCS, Glasgow Coma Scale.

Trondheim and Groningen was used to develop a model for prediction of a GOSE score ≤6, including center as an additional categorical variable (Table 4, Figure 2A). Of the variables selected as predictors for GOSE score ≤6, older age ($P < 0.001$), lower GCS score ($P = 0.001$), no day-of-injury alcohol intoxication ($P = 0.001$), presence of SDH ($P = 0.004$), occurrence of a secondary event ($P = 0.037$), and preinjury disability ($P = 0.043$) were significant associated with outcome. The HL test for the common model indicated a good model fit ($P = 0.143$). The Nagelkerke pseudo-R^2 was 0.34, and AUC for the common prognostic model was 0.80 (95% CI 0.75–0.85) (Figure 3).

In the Trondheim cohort, older age ($P < 0.001$), pupillary dilation ($P = 0.005$), the presence of a SDH ($P = 0.012$), and preinjury disability ($P = 0.049$) were significantly associated with a GOSE score ≤6 (Figure 2B). The Nagelkerke pseudo-R^2 was 0.43, the HL test indicated a good model fit ($P = 0.325$), and the AUC from the internal validation was 0.85 (95% CI 0.78–0.91) (Figure 3). In Groningen, a lower GCS score ($P = 0.001$), no day-of-injury alcohol intoxication ($P = 0.002$), older age ($P = 0.007$), and the presence of a SDH ($P = 0.030$) were significantly associated with the outcome (Figure 2C). The Nagelkerke pseudo-R^2 was 0.31, the HL test indicated a good model fit ($P = 0.270$), and the AUC from the internal validation was 0.79 (95% CI 0.72–0.85) (Figure 3).

When the Trondheim model was tested in the Groningen data, the AUC value was 0.75 (95% CI 0.68–0.82), and the P value of the HL-test was 0.038. When the Groningen model was tested in the Trondheim data, the AUC value was 0.76 (95% CI 0.67–0.83) and the P value for the HL-test was 0.362.

DISCUSSION

In this follow-up study performed exclusively in patients with moderate TBI from 2 European level 1 trauma centers, approximately three quarters of the patients had intracranial findings on head CT, and many needed intensive care treatments. Few patients died or experienced severe disability. Still, 44% of the patients did not achieve good recovery at 12 months. Older age, lower GCS score, no day-of-injury alcohol intoxication, SDH, occurrence of secondary event, and preinjury disability were predictors for GOSE score ≤6 in a model that was constructed from the combined dataset.

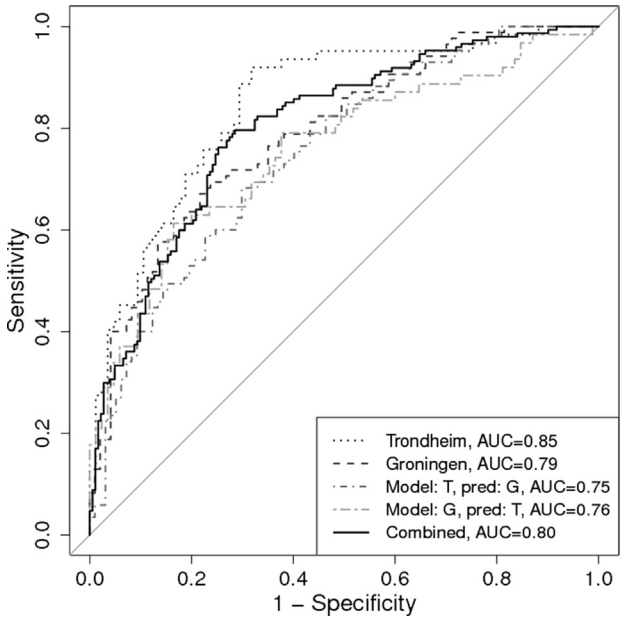

Figure 3. Receiver operating characteristics (ROC) curves and the area under the curve (AUC) for different prognostic models for patients with moderate traumatic brain injury in Trondheim (T) and Groningen (G) and the combined dataset of patients from both centers. ROC curves are given for internal validation for the Trondheim and Groningen models, and for external validation predicting the Groningen outcomes based on the model fitted in the Trondheim data (Model: T, pred: G) and predicting the Trondheim outcomes based on the model fitted in the Groningen data (Model: G, pred: T). Finally, internal validation of the model is based on the combined dataset.

We found that 81% had intracranial traumatic lesions on head CT, which is somewhat greater than previously reported.[1-3,10] The lowest frequency was reported in the oldest study and may be explained by lower detection rates with older scanners. The most frequent intracranial findings in the present study were tSAH and contusions, in line with other studies on patients with moderate TBI.[1,10] Acute SDH was reported less frequently, only in 34%, whereas this lesion type is more common in severe TBI.[1,35]

Further, the patients with moderate TBI often were treated in an ICU and many underwent neurosurgical interventions. ICP monitoring was performed in several patients as might not be expected in patients with moderate TBI. In most of these cases, the patients had a high-risk brain injury, whereas some patients needed sedation for other reasons, and the ICP measurement was implemented to monitor the evolution of the brain injury. Despite all these indicators of significant brain injury, the in-hospital case-fatality rate was low (3%), in line with other studies on patients with moderate TBI (0.9%–8%).[2,3,5,10] This finding lends validity to the debated GCS score as a clinically useful tool for classification of injury severity in the acute setting.[36] The current study also demonstrated that the patients with GCS score 13 suffered significant injures as they had a high rate of intracranial CT findings and 35% had a disability at 12 month follow-up. Indeed, it is debated whether patients with GCS score 13 should be classified as mild or moderate TBI.[8,37] Based on the current results in a large sample, the clinical characteristics of patients with GCS score 13 provide evidence for these individuals as belonging to the moderate TBI rather than mild TBI category. This classification scheme is in line with the Head Injury Severity Scale and also has been used in previous studies.[1,2,9]

The significant cohort effects between the cohorts from Trondheim and Groningen underline the necessity for multicenter studies. Ongoing international multisite studies, like the TRACK-TBI and the CENTER-TBI, are important in this respect. The approach of comparative effectiveness research in these studies will hopefully increase our understanding of the provided care and measured outcomes of patients across centers.

A GOSE score ≤4, i.e., death or severe disability, was observed in only 14% in the present study. This was in accordance with 2 Italian studies reporting GOSE score ≤4 at 6 months, in 15% and 26%, respectively.[2,5] Hence, supported by results from our study, we argue that the existing models like CRASH and IMPACT, which are designed to predict such poor outcomes, have low relevance for patients with moderate TBI. In contrast, a GOSE score of ≤6, i.e., worse than good recovery, was observed in 44% of the patients in the present study, quite similar to the 55% reported in a previous Dutch multicenter study from 5 level I trauma centers in which patients with GCS score 13 also were included.[1] The high number of patients with moderate TBI with persistent functional problems call for routine follow-up in these patients, who are often discharged to their homes.[20]

Prediction of Outcome

This is the first study specifically to develop a prognostic model in a sample of only patients with moderate TBI. Moreover, we applied a cut-off at moderate disability or worse (GOSE score ≤6), unlike previous studies, which have developed and validated models that predict severe disability or death (GOSE score of ≤4). In the model fitted based on the combined dataset, older age, lower GCS score, no day-of-injury alcohol intoxication, SDH, occurrence of a secondary event, and preinjury disability were significant predictors of GOSE score ≤6.

Age is a well-known prognostic factor for outcome in patients with TBI.[15,16,38] Studies on patients with severe TBI show greater case-fatality rate for elderly patients,[39,40] as well as worse long-term outcome.[40,41] The present study clearly shows that this is also the case for patients with moderate TBI. Also in accordance with findings in severe TBI, the GCS score, occurrence of a secondary event, and SDH were related to worse outcome.[11,15,16,42]

The variable "pre-injury disability" was associated with worse outcome in the entire sample and the Trondheim cohort but not in the Groningen cohort. This variable might have been defined differently and hence subject to between-center variations. Still, this result indicates that adding variables describing preinjury health may increase the prognostic performance of a model, as also has been shown for mild TBI.[43,44] Therefore, we suggest that future prognostic studies of patients with moderate TBI should explore the impact of pre- and comorbidity.

A more surprising finding was that not being influenced by alcohol was associated with worse outcome, most prominent in the Groningen cohort. However, positive serum ethanol has previously also been associated with a better outcome.[45,46] One

explanation of this finding could be that the depressant effects of alcohol on the central nervous system was falsely ascribed to the head injury.[19] If so, patients with only mild TBI could be included in cohorts of moderate and severe TBI due to falsely low GCS score and present with a good recovery at follow-up. In contrast, alcohol has also been hypothesized to have a neuroprotective effect previous studies.[47,48] Regardless, influence of alcohol is an example of clinical information that probably should be systematically collected at admission and controlled for in future studies of prognosis.

The common outcome prediction model performed adequately with an AUC value of 0.80, but the discriminative ability needs to be proven by external validation. Yet, we believe that the model presented here comprises variables that represent important risk factors for disability after moderate TBI. The modest Nagelkerke pseudo-R^2 of the model indicates that the outcome after moderate TBI may depend also on factors that are not measured in regular moderate-severe TBI cohort studies. Future studies could address this shortcoming by collection of a broader set of variables embracing a biopsychosocial understanding of the TBI patient in line with the insight from the field of mild TBI.[44,49]

In the external validations of the 2 separate models, the models performed similarly, with AUC values of 0.76 (Trondheim) and 0.75 (Groningen), compared with 0.85 and 0.79, respectively, for the internal validations. Thus, the AUC values indicate that the models show an acceptable strength of discrimination between moderate disability or worse in contrast to good recovery.[50] However, to arrive at a predictive model with sufficient discriminative ability to be used in clinical practice, further studies are needed. We believe that an important challenge regarding prognostication in moderate TBI is to identify and incorporate the best set of factors that may influence outcome in the individual patients. Especially important is it to extend future studies to middle- and low-income countries, and the International Initiative for TBI Research (InTBIR) is promising in this respect.[51]

Strengths and Limitations

A strength of this study is the large number of prospectively registered patients with moderate TBI. Since we specifically studied patients with moderate TBI, we could choose the level of dichotomization of the GOSE that we believe is the most relevant, according to the baseline risk of patients with moderate TBI. Moreover, the chosen statistical method, penalized regression using the lasso method, is an important strength. It performs simultaneous estimation of the coefficients and the variable selection, determining the best combination of variables with reduced risk of overfitting of the models.

One limitation of the study was that inclusion and data collection was planned and completed separately in the 2 centers. Moreover, both cohorts comprise only patients who have been treated at neurosurgical referral centers, and the study results may not apply to patients who are treated in general hospitals. We doubt, however, that this has caused a large bias in this study, because both hospitals also serve as general hospitals, and because most patients with moderate TBI are referred to a neurosurgical center in both countries. Another limitation is the wide time-span of data-collection, which can have impact on performance of the model, but is difficult to avoid when a large sample is needed. Finally, it is important to bear in mind that this study describes patients treated in 2 high-income countries, and our conclusions may therefore not be valid in middle and low-income countries.

CONCLUSIONS

In this prospective study from 2 European centers, a high proportion of the patients with moderate TBI had characteristics of significant brain injury and needed advanced hospital care. Therefore, it is important to secure appropriate acute care. Even if few patients died, a high proportion (44%) did not experience a good recovery, which substantiates the need of appropriate follow-up for patients with moderate TBI.

Older age, lower GCS score, no day-of-injury alcohol intoxication, SDH, occurrence of secondary event, and preinjury disability were predictors for GOSE score $\leq$6. Future studies should incorporate an even broader set of variables, which can hopefully increase the predictive power of a prognostic model. We believe that this study can serve as a first step in future development of valid prognostic models for patients with moderate TBI.

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