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ORIGINAL RESEARCH

Outcome Prediction in Moderate and Severe Traumatic Brain Injury: A Focus on Computed Tomography Variables

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Abstract
Background With this study we aimed to design validated outcome prediction models in moderate and severe traumatic brain injury (TBI) using demographic, clinical, and radiological parameters.
Methods Seven hundred consecutive moderate or severe TBI patients were included in this observational prospective cohort study. After inclusion, clinical data were collected, initial head computed tomography (CT) scans were rated, and at 6 months outcome was determined using the extended Glasgow Outcome Scale. Multivariate binary logistic regression analysis was applied to evaluate the association between potential predictors and three different outcome endpoints. The prognostic models that resulted were externally validated in a national Dutch TBI cohort.
Results In line with previous literature we identified age, pupil responses, Glasgow Coma Scale score and the occurrence of a hypotensive episode post-injury as predictors. Furthermore, several CT characteristics were

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associated with outcome; the aspect of the ambient cisterns being the most powerful. After external validation using Receiver Operating Characteristic (ROC) analysis our prediction models demonstrated adequate discriminative values, quantified by the area under the ROC curve, of 0.86 for death versus survival and 0.83 for unfavorable versus favorable outcome. Discriminative power was less for unfavorable outcome in survivors: 0.69.

Conclusions Outcome prediction in moderate and severe TBI might be improved using the models that were designed in this study. However, conventional demographic, clinical and CT variables proved insufficient to predict disability in surviving patients. The information that can be derived from our prediction rules is important for the selection and stratification of patients recruited into clinical TBI trials.

Keywords Moderate traumatic brain injury · Severe traumatic brain injury · Outcome · Predictionmodel · CT-scan · Head injury

Introduction

The accuracy of prognostic models in moderate and severe traumatic brain injury (TBI) has risen during recent years, especially with the study of large patient cohorts within the IMPACT (International Mission on Prognosis and Clinical Trial Design in TBI) project [1] and MRC CRASH study [2]. Knowledge on the prognosis of a head injured patient in the early phase post-injury is essential to optimize treatment, for the possible withdrawal of treatment if an unfavorable outcome is anticipated, and to inform patients and their next-of-kin. Prognostic models may also be helpful to stratify patients for research purposes. Although literature on prognostic modeling is extensive and highly relevant, the methodological quality is subject to discussion and questions have been raised on the applicability, validity, and generalizability of current models [3–6].

Most studies on outcome prediction in TBI investigated the combination of demographic, clinical, and radiological characteristics [2, 4, 5, 7–9]. Age, total Glasgow Coma Scale (GCS) score or GCS-motor score, pupil reactivity, and the occurrence of a post-injury hypotensive and/or hypoxic period, proved the most powerful clinical predictors [2, 5, 7–11].

Various individual head computed tomography (CT) abnormalities have emerged as significant radiological outcome predictors after multivariable analyses, also including demographic and clinical covariates, such as: midline shift, compression of perimesencephalic cisterns, traumatic subarachnoid hemorrhage (SAH), and the presence and type of intracranial (mass) lesions [2, 9–14]. Several studies used the Traumatic Coma Databank (TCDB) CT classification [15] to incorporate CT characteristics in their prediction models [7–9, 11, 12]. Although widely used and acknowledged, the TCDB CT classification is criticized for being partly retrospective in nature and not addressing all radiological elements with prognostic value, in particular the presence of traumatic SAH [12, 16–18]. To meet this criticism the Rotterdam CT classification was introduced a few years ago [16] and more recently the Stockholm prediction score [18]. Combinations of individual CT characteristics, including intraventricular and traumatic subarachnoid hemorrhage, demonstrated a better discriminative performance than the original TCDB classification. Therefore, it has been suggested to use individual CT predictors instead of the TCDB classification for prognostic purposes in TBI [16].

In this prospective cohort study in moderate and severe TBI, we aimed to develop and externally validate new prognostic models, incorporating demographic, clinical and radiological variables for the prediction of death and unfavorable outcome, the latter also in the TBI survivors. A newly developed CT prediction rule was compared to the existing TCDB classification and Rotterdam CT score.

Methods

The present study is part of the Radboud University Brain Injury Cohort Study (RUBICS), an ongoing prospective observational cohort study that started on January 1st, 1998. The Radboud University Nijmegen Medical Centre (RUNMC) is a level I trauma centre in the Netherlands with a referral area of 2.5 million inhabitants. Since 1995 the RUNMC has been equipped with a regional 24-h physician-based Emergency Medical Service (EMS),

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staffed with trauma surgeons and anaesthesiologists, to support the local teams of highly trained ambulance paramedics. In 2001, a helicopter was added to the EMS. National Dutch protocol requires the dispatch of a regional physician-based (helicopter) EMS for all trauma patients with a GCS score of 3–8 [19].

All consecutive patients with a TBI diagnosis, including children, admitted to the emergency department (ED) of the RUNMC are included. The RUBICS databank comprises demographic data, various clinical and radiological injury variables, and outcome scores. The institutional ethics committee of the RUNMC waived the need for informed consent.

Moderate TBI was defined by a GCS score of 9–12 after initial resuscitation at the ED or an admission GCS of 9–12 followed by sedation and intubation during resuscitation for a non-neurological cause. Severe TBI was characterized by an ED GCS score of $\leq$8 after resuscitation, preferably obtained before sedation and intubation. Patients suffering from penetrating head injury were excluded.

Subjects

For the current study, all patients, aged above 16, with moderate and severe TBI, admitted to the ED of our hospital between January 1998 and January 2006, were selected from the RUBICS database. Patient characteristics that were selected included: Mechanism of injury, the presence of hypotension (systolic RR $<$ 90 mmHg, equal to shock class III–IV [20] or hypoxia (O_2 saturation $<$ 90 %, measured with pulse oximeter) during the pre-hospital period or at the ED. Furthermore, we included the GCS score, pupil responses, the Abbreviated Injury Scale score of the Head (AISH) and the Injury Severity Score (ISS) [21]. Finally, our study incorporated information on the clinical suspicion of day-of-injury alcohol intoxication or definite day-of-injury intoxication, when blood alcohol level (BAL) exceeded 0.1 promille (equal to $\geq$100 mg/l), and the use of oral anticoagulants. To adequately quantify additional extracranial injuries we calculated an alternative modified ISS score based on the three most severely injured body areas excluding the head: the "ISS-extracranial score" (ISSe).

Computed Tomography

All patients underwent CT scanning of the head after initial (surgical) resuscitation. Only the initial CT-scans of patients admitted to the hospital within 24 h after sustaining the head injury were analyzed in this study. Each CT-scan was scored, based on visual inspection, by one of three raters (B.J., T.B. and P.V.) using a predefined structured format, published previously [22]. All scans were classified according to the TCDB classification and Rotterdam CT score [15, 16]. Based on the results of two of our earlier reports the following CT outcome predictors were preselected: the status of the fourth ventricle and ambient cisterns—the status of the perimesencephalic or basal cisterns was not included [23], lesion (hematoma) volume and midline shift. The latter two were considered as continuous variables instead of using cutoff values [24]. To eventually design straightforward prediction models, i.e., to prevent selection of predictors subject to possible high interrater disagreement, we primarily used a binary—present versus absent—score of several variables, e.g., SAH, petechial hemorrhages, edema and skull(base) fracture.

We have described the results of various interobserver and intraobserver variability analyses of two of the raters (B.J. and P.V.) before: concerning ventricles and cisterns [23], and regarding hematoma volume, midline shift, and the TCDB CT classification [24].

Outcome Assessment

Outcome was assessed at 6 months post injury according to the Glasgow Outcome Score Extended (GOSE) using a structured interview during regular visits to the out-patient clinic or during consultation by telephone [25, 26]. The GOSE is an eight point scale expressing functional outcome ranging from 1: death to 8: complete recovery. Patients not visiting the outpatient clinic were sent a GOSE questionnaire by regular mail, and when not returned a reminder was sent [27]. Finally, we attempted to reach all non-responding patients by telephone to acquire an outcome score. Outcomes obtained within a 3 months range were also accepted if no outcome at exactly 6 months was available. When a patient was dismissed from follow-up before 6 months because of a favorable GOSE score of 7 or 8, this observation was carried forward and considered a definitive outcome.

Statistical Analysis

We used binary logistic regression analysis to evaluate the univariate relationship between the demographic, clinical, and CT characteristics and: (1) death (GOSE 1); (2) unfavorable outcome including death (GOSE: 1–4); and (3) unfavorable outcome excluding death (GOSE 2–4). Age was analyzed per year; GCS, AISH, ISS, and ISSe per point scored on each scale. Concerning the CT parameters midline shift was analyzed per millimeter (mm), the volume of the dominant intracranial lesions per milliliter (ml) and the number of hematomas/contusions per individual patient. Subsequently, the variables significantly associated with outcome were analyzed per category—demographic

and clinical parameters combined, and CT characteristics—using multivariable logistic regression analysis with forward variable selection to derive prediction rules for the different outcome scores. Both the AISH and ISS were not included in the multivariable analyses since they are based on a combination of clinical and CT information. To finish, the demographic, clinical, and CT predictors were combined and their predictive value was subsequently re-determined to design "combination" models.

Throughout the binary logistic regression analysis, both uni- and multivariable, we used a two-sided p value of 0.01 as criterion for significance. This in order to avoid that, irrelevant differences which would be statistically significant due to the large number of observations.

The discriminative power of the prediction rules was calculated using Receiver Operating Characteristic (ROC) analysis and quantified by the area under the receiver operating curve (AUC). We compared the AUCs of our CT rules with the AUCs of the TCDB CT classification and Rotterdam CT score [15, 16]. In addition, we calculated the Nagelkerke's R^2, representing the amount of variance in outcome explained by our prediction rules, and the Hosmer and Lemeshow goodness-of-fit statistic, reflecting the agreement between observed and predicted outcomes of our models.

Our prediction models were also externally validated in a population of 442 moderate and severe TBI patients from a recent Dutch multicenter observational cohort study: The Prospective Observational COhort Neurotrauma (POCON) study, executed in 5 out of 11 specialized (Level I) trauma centers in the Netherlands [28].

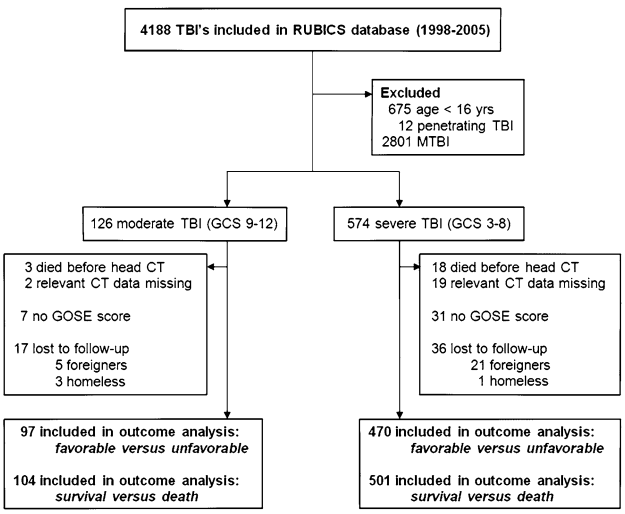

Fig. 1 Diagram shows the inclusion and exclusion of the patients in this study. *TBI* traumatic brain injury, *RUBICS* Radboud University Nijmegen Brain Injury Cohort Study; yrs: years, *MTBI* mild traumatic brain injury, *GCS* Glasgow Coma Scale, *CT* computed tomography, *GOSE* Glasgow Outcome Scale Extended

Results

Figure 1 shows the in- and exclusion flow-chart of this study: 700 Consecutive patients were included; 126 moderate and 574 severe TBI patients. Sufficient head CT data were available for 658 patients and of 605 patients survival data was known.

The demographic, acute clinical, radiological, and outcome characteristics of all included patients are represented in Table 1. Demographic and clinical data were missing in less than 0.5 % of these patients. In 81 % (433) of the severe and 60 % (73) of the moderate TBI patients CT abnormalities were found. Less than 4 % of all individual CT characteristics was missing.

Neurosurgical intervention (placement of an intracranial ICP monitoring device was not regarded as such) was performed in 12 (9.5 %) moderate TBI patients (craniotomy for acute SDH: $n = 6$; EDH: $n = 5$; hemorrhagic contusion: $n = 1$) and in 71 (12 %) of the severe TBI patients (SDH: $n = 38$; EDH: $n = 22$; hemorrhagic contusion: $n = 7$; depressed skull fracture: $n = 4$). In our moderate TBI patients death rate was 23 % ($n = 29$) and 222 (39 %) patients died after severe TBI.

After univariate binary logistic regression analysis all demographic and clinical variables but gender, extracranial trauma (represented by ISSe) and day-of-injury alcohol intoxication, were associated with death at 6 months post-injury (data not shown). Furthermore, all CT characteristics, except for the presence and type of petechial hemorrhages and the presence of facial fractures, demonstrated a relationship with mortality at 6 months (not shown). Associations were also found between clinical, demographic, and CT variables and unfavorable outcome, comparable to those found for death. The presence of punctate hemorrhages was merely moderately associated with unfavorable outcome (data not shown). Remarkably, the GCS score and pupillary responses were not associated with unfavorable outcome in the survivors.

Age, GCS score at the ED, occurrence of a hypotensive episode and pupil reactivity surfaced as independent outcome predictors of both death and unfavorable outcome after multivariate analysis. Trauma mechanism, the occurrence of a hypoxic episode and the use of anticoagulants were not included in both clinical prediction models. Unfavorable outcome in surviving patients was only associated with age and the occurrence of a hypotensive episode, whereas post-injury hypoxia was excluded form the eventual clinical prediction rule.

Multivariate analysis of the CT characteristics identified five predictors of death: aspect of ambient cisterns, number of contusions, aspect of the fourth ventricle, the presence of intraventricular or subarachnoid hemorrhage and volume of the largest intracranial lesion; largest lesion type, total number of epidural, and subdural

Table 1 Demographic, clinical and CT characteristics of the included moderate and severe TBI patients ($n = 700$)

Characteristic	Moderate TBI ($n = 126$)[a]	Severe TBI ($n = 574$)[a]
Gender—male	77 (61)	419 (73)
Age[b]	47.7 (22.3)	42.9 (19.9)
Trauma mechanism		
Traffic	60 (48)	403 (70)
Fall	50 (40)	123 (21)
Other/missing	16 (12)	48 (8.4)
GCS at ED—median	11	3
Intubated at arrival ED	6 (4.8)	364 (63)
AIS head [b]	3.5 (1.1)	4.3 (4.1)
ISS[b]	20.5 (12.6)	31.6 (14.8)
ISSe[b]	7.2 (8.2)	14.3 (14.1)
Multitrauma patients	73 (58)	427 (74)
Hypotensive episode	7 (5.6)	133 (23)
Hypoxic episode	12 (9.5)	165 (29)
Hypotensive and hypoxic	2 (1.6)	69 (12)
Pupil reactivity—normal	117 (93)	374 (65)
One abnormal pupil	6 (4.8)	74 (13)
Both pupils abnormal	3 (2.4)	126 (22)
Intoxication ethanol	39 (31)	99 (17)
Ethanol ‰ at ED[b]	2.5 (1.2)	2.1 (3.8)
Use of anticoagulants	7 (5.6)	46 (8.0)
Neurosurgical intervention	12 (9.5)	71 (12)
Outcome		
Death (GOSE 1)	29 (23)	222 (39)
Missing	16 (13)	39 (6.8)
Unfavorable (GOSE 1-4)	39 (31)	289 (50)
Unfavorable within survivors (GOSE 2-4)	10 (7.9)	67 (12)
Missing	25 (20)	71 (12)
TCDB classification	$n = 121$	$n = 537$
Diffuse injury I	48 (40)	104 (19)
Diffuse injury II	38 (31)	156 (29)
Diffuse injury III	5 (4.1)	88 (16)
Diffuse injury IV	–	17 (3.2)
Evacuated mass lesion/Neurosurgical intervention	12 (9.9)	71 (13)
Non-evacuated mass lesion	18 (15)	101 (19)
Missing	0	0

CT computed tomography, *TBI* traumatic brain injury, *sd* standard deviation, *GCS* Glasgow Coma Scale, *ED* emergency department, *AIS* Abbreviated Injury Scale, *ISS* Injury Severity Score, *ISSe* Injury Severity Scale extracranial injuries, *GOSE* Glasgow Outcome Scale Extended, *TCDB* Traumatic Coma Databank

[a] All variables expressed in number (percentage), except for [b] Mean (sd)

hematomas, the presence of edema, the presence of vault and skull base fractures, pneumocephalus and midline shift were excluded by means of the multivariate analysis. Three CT predictors of unfavorable outcome (GOSE 1–4) were identified: aspect of ambient cisterns, the presence of intraventricular or subarachnoid hemorrhage and dominant lesion type; volume of the largest lesion, aspect of the fourth ventricle, number of lesions (SDH, contusion), the presence of vault and skull base fractures, the presence of edema, the presence of punctate hemorrhages, pneumocephalus and midline shift were not selected for the CT model. Merely two CT predictors—aspect of ambient cisterns and dominant lesion type—were predictors of unfavorable outcome (GOSE 2–4) in survivors; the aspect of the fourth ventricle, the volume of the largest lesion, the presence of SAH and edema, the number of intracranial lesions (SDH, contusion), and midline shift were excluded by this model.

Table 2 shows the results of the final multivariable analysis combining the demographic, clinical, and CT predictors that constituted the individual "clinical" and "CT" prediction models mentioned above. Based on these predictors three prognostic models were designed for each endpoint.

Table 2 Association of demographic, clinical, and CT variables and death (a; $n = 605$), unfavorable outcome including death (b; $n = 567$) and unfavorable outcome within survivors (c; $n = 567$) in moderate and severe TBI: Results of multivariate binary logistic regression analysis

Characteristic	OR	(99 % CI)	Coefficient
(a)[a,b]			
Ambient cisterns—normal	Ref.		–
Compressed	2.1	(1.0–4.5)	0.741
Absent	7.0	(2.2–22.0)	1.943
Age	1.05	(1.03–1.07)	0.047
Pupil reactivity—normal	Ref.		–
One abnormal pupil	1.4	(0.5–3.6)	0.321
Both pupils abnormal	6.0	(2.3–15.9)	1.795
Number of contusions	1.7	(1.1–2.4)	0.501
Hypotensive episode	2.9	(1.3–6.4)	1.067
Fourth ventricle—abnormal	2.9	(1.1–7.6)	1.065
Constant			−4.795
(b)[c,d]			
Ambient cisterns—normal	Ref.		–
Compressed	2.1	(1.03–4.3)	0.744
Absent	19.9	(6.0–65.7)	2.989
Age	1.04	(1.03–1.06)	0.043
Hypotensive episode	3.7	(1.7–8.3)	1.311
Dominant lesion (type)—none	Ref.		–
Epidural hematoma	0.7	(0.2–2.5)	-0.343
Acute subdural hematoma	2.3	(1.04–5.0)	0.823
Hemorrhagic contusion	3.2	(1.5–6.9)	1.153
Pupil reactivity—normal	Ref.		–
One abnormal pupil	1.2	(0.5–2.9)	0.147
Both pupils abnormal	4.2	(1.4–12.9)	1.436
Constant			−3.269
(c)[e,f]			
Ambient cisterns—normal	Ref.		–
Compressed	1.3	(0.5–3.1)	0.223
Absent	5.9	(1.5–23.5)	1.779
Dominant lesion (type)—none	Ref.		–
Epidural hematoma	1.5	(0.3–6.2)	0.372
Acute subdural hematoma	4.1	(1.6–10.7)	1.415
Hemorrhagic contusion	3.7	(1.4–10.1)	1.320
Hypotensive episode	3.3	(1.3–8.7)	1.198
Constant			−2.213

CT computed tomography, *TBI* traumatic brain injury, *OR* odds ratio, *CI* confidence interval, *Ref* reference, *GOSE* Glasgow Outcome Scale Extended

[a] Excluded by this model: GCS score, volume of the largest lesion, presence of SAH

[b] The probability of death (GOSE 1) at 6 months can be calculated with the formula: $1/(1 + e^{-y})$. $Y = -4.795 + (0.741 \times$ ambient cisterns compressed$) + (1.943 \times$ absent ambient cisterns$) + (0.047 \times$ age$) + (0.321 \times$ one abnormal pupil$) + (1.795 \times$ both pupils abnormal$) + (0.501 \times$ number of contusions$) + (1.067 \times$ hypotensive episode$) + (1.065 \times$ abnormal fourth ventricle)

[c] Excluded by this model: GCS score, presence of SAH

[d] The probability of unfavorable outcome (GOSE 1–4) at 6 months can be calculated with the formula: $1/(1 + e^{-y})$. $Y = -3.269 + (0.744 \times$ ambient cisterns compressed$) + (2.989 \times$ absent ambient cisterns$) + (0.043 \times$ age$) + (1.311 \times$ hypotensive episode$) + (-0.343 \times$ EDH dominant lesion$) + (0.823 \times$ SDH dominant lesion$) + (1.153 \times$ contusion dominant lesion$) + (0.147 \times$ one abnormal pupil$) + (1.436 \times$ both pupils abnormal)

[e] Excluded by this model: age

[f] The probability of unfavorable outcome (GOSE: 2–4) at 6 months can be calculated with the formula: $1/(1 + e^{-y})$. $Y = -2.213 + (0.223 \times$ ambient cisterns compressed$) + (1.779 \times$ absent ambient cisterns$) + (0.372 \times$ EDH dominant lesion$) + (1.415 \times$ SDH dominant lesion$) + (1.320 \times$ contusion dominant lesion$) + (1.198 \times$ hypotensive episode)

The discriminative values (AUC), amount of explained variance in outcome (R^2), and degree of calibration (Hosmer and Lemeshow goodness-of-fit statistic) of the various prognostic models are presented in Table 3, next to the results of the external validation in the POCON data set. Due to the missing data, we ultimately included 333 of the original 442 patients from the POCON database with outcome data available at 6 months in the external validation analysis. The discriminative power of the TCDB classification and Rotterdam CT score in the RUBICS and POCON studies was computed for mutual comparison with our "CT" models (Table 3). Figure 2 depicts the ROC curves (discriminative value) of our different models when tested in the external POCON cohort.

For a more easy use of our models in daily clinical practice a web-based calculator that is available at: http://www.tbi-prognosis.com/, was built.

Discussion

This prospective cohort study in unselected moderate and severe TBI patients introduces new outcome prediction rules. Although the demographic and clinical predictors we identified are in line with previous research, we found several new CT outcome predictors. In addition to the conventional dichotomized outcome endpoints, death and unfavorable outcome, we also evaluated unfavorable outcome in surviving patients as an outcome of interest.

Not surprisingly, pupil reactivity, age, GCS, and the presence of a hypotensive post-injury event surfaced as predictors for both death and unfavorable outcome after multivariate analysis consistent with literature [2, 5, 7–11, 14, 29]. We used the complete GCS score instead of merely the GCS-motor score because we think the eye and verbal scores of the GCS also contain prognostic information as has been demonstrated before [9], although the additive prognostic value of these scores to the GCS-motor score was probably higher in moderate than in severe TBI patients. Interestingly, neither the GCS score nor the pupillary responses were predictors of unfavorable outcome in survivors, and therefore may be only relevant to predict death versus survival.

The presence of extracranial injuries, as represented by an extracranial ISS (ISSe) score, was not associated with outcome in contrast to a recently published prediction model [2]. This may be caused by the fact that around 30 % of the patients included in that study suffered from mild TBI. And, as we have shown before, specifically in mild TBI patients recovery and 6 months outcome is to a large part determined by extracranial injuries [22, 30]. In moderate and severe TBI the extent of the brain damage by

Table 3 Area under the receiver operating characteristic curve (AUC) and the Hosmer and Lemeshow goodness-of-fit test statistic of different prognostic models for three outcome scores in RUBICS and POCON

Outcome category	Model	RUBICS (AUC)	R^2	Hosmer and Lemeshow statistic			External validation in POCON dataset (AUC [95 % CI])		R^2	Hosmer and Lemeshow statistic		
				Chi^2	df	p				Chi^2	df	p
Death												
	Clinical	0.84	0.43	7.460	8	0.488	0.82	(0.78–0.87)	0.39	6.464	8	0.595
	CT	0.85	0.49	7.591	6	0.270	0.79	(0.74–0.84)	0.31	7.710	6	0.260
	TCDB	0.79	–	–	–	–	0.76	(0.71–0.82)	–	–	–	–
	RCTS	0.81	–	–	–	–	0.79	(0.74–0.84)	–	–	–	–
	Combination	0.90	0.58	9.075	8	0.336	0.86	(0.82–0.90)	0.49	7.071	8	0.529
Unfavorable outcome												
	Clinical	0.82	0.40	14.099	8	0.079	0.81	(0.76–0.86)	0.37	7.096	8	0.526
	CT	0.82	0.42	2.519	7	0.926	0.78	(0.73–0.83)	0.31	9.648	7	0.209
	TCDB	0.79	–	–	–	–	0.77	(0.72–0.83)	–	–	–	–
	RCTS	0.77	–	–	–	–	0.79	(0.75–0.84)	–	–	–	–
	Combination	0.87	0.53	6.087	8	0.637	0.83	(0.79–0.88)	0.41	10.824	8	0.212
Unfavorable outcome in survivors												
	Clinical	0.65	0.08	2.809	8	0.946	0.61	(0.52–0.70)	0.04	4.109	8	0.847
	CT	0.71	0.11	0.922	4	0.921	0.71	(0.62–0.79)	0.11	8.521	4	0.074
	Combination	0.74	0.20	1.985	5	0.851	0.69	(0.61–0.78)	0.11	12.005	5	0.035

AUC Area Under the Curve, *RUBICS* Radboud University Brain Injury Cohort Study, *POCON* Prospective Observational COhort Neurotrauma, R^2 Nagelkerke's R^2, *df* degrees of freedom, *CI* confidence interval, *CT* computed tomography, *TCDB* Traumatic Coma Databank CT classification, *RCTS* Rotterdam CT Score

itself may be sufficient to determine, and explain differences in functional outcome and return to work.

Consistent with previous studies demonstrating the value of CT characteristics in prediction models [8, 11, 12, 16], both in our and in the POCON cohort the TCDB CT classification showed strong predictive power (AUC's 0.76–0.79, Table 3). Other authors have suggested that the prognostic power of the head CT-scan is not fully utilized with the TCDB CT classification [9, 12, 16, 18]. Despite of its shortcomings the TCDB classification performed only slightly worse than the Rotterdam CT score (AUC's 0.77–0.81, Table 3) and our CT prognostic models (AUC's 0.78–0.79, Table 3), challenging those statements. The discriminative power of our "CT" models predicting unfavorable outcome in the surviving patients was somewhat disappointing (AUC 0.71), suggesting that CT characteristics are more important for the prediction of death and survival than of disability.

The discriminative abilities of our "combination" models were highly adequate even after external validation for both death (AUC: 0.86, Table 3) and unfavorable outcome (AUC: 0.83, Table 3), also when compared to recently published outcome prediction studies [2, 7, 8, 11]. In the surviving patients the predictive power of these models was limited (AUC 0.69, Table 3), again suggesting that disability is probably predicted by other variables than is death. Goodness-of-fit of our models was also sufficient, except from the "combination" model in the surviving patients (Table 3).

Two recent studies: IMPACT and MRC CRASH, introduced several prognostic models for mortality and unfavorable outcome in moderate and severe TBI [2, 7]. And although they are the two largest studies in moderate and severe TBI, some aspects need to be considered. The prognostic models resulting from these studies are largely based on patients enrolled in clinical trials and not on prospective observational cohort studies [31, 32]. Furthermore, the IMPACT database exists of studies executed between 1984 and 1997 [32]: The last patient was enrolled in these studies more than 15 years ago. Finally, both studies, and this is true for most studies on outcome prediction in moderate and severe TBI, aimed at the prediction of death and unfavorable outcome, but not at favorable versus unfavorable outcome in the surviving patients [2, 7].

The prediction models described in this study still rely on conventional demographic and clinical parameters, and a number of CT characteristics. Though certainly adequate, the discriminative values (AUCs) of our prediction rules are still not reaching the maximum of 1.0. Hence, we think that there is room for improvement and new outcome predictors are ready to hand. First, laboratory parameters have been found to add prognostic value. Serum glucose, platelet count, and hemoglobin levels proved independent predictors after multivariate analysis [7, 9, 33, 34]. In the widely applied intensive care prognostic system APACHE, laboratory parameters are of great importance in predicting mortality for critically ill adult patients [35]. Further, various biomarkers, like the brain-specific proteins GFAP and S100B, in cerebrospinal fluid and serum have been identified as parameters associated with outcome after TBI [36, 37]. Genetic polymorphisms, for example the apolipoprotein E4 polymorphism, are also considered to play a role in the prognosis of TBI outcome [38]. Finally, most current prognostic models are designed to predict death or unfavorable outcome (including death) [2, 7, 8, 11]. We found that the predictors constituting these models are insufficient for the prediction of severe disability in survivors. Research on more relevant predictors is warranted.

Limitations

We recognize some limitations of this study. Missing data in this prospective study may have weakened the association of these variables with outcome. Furthermore, not for every included patient outcome data was available. Of 31 (5.4 %) severe TBI patients only information on survival was available and 36 (6.3 %) patients were lost to follow-up. The main reason for this was the inclusion of patients from abroad, unable to be present at follow-up consultation. In the moderate TBI group 17 (13.5 %) patients were lost to follow-up, whereas in 7 (5.6 %) patients insufficient data to determine the GOSE score were available. For the complete study the loss to follow-up rate was 7.6 %, which is still less than the 10 % considered an acceptable loss to follow-up rate in a review on prognostic models in TBI [4].

The generalizability of our prognostic models may be impeded by the fact that the derivation part of this study was executed in a single centre and the external validation was performed using an exclusive Dutch cohort. On the other hand, in contrast to earlier studies we investigated an unselected cohort consisting of a heterogeneous and realistic patient population which minimized potential selection bias [2, 7, 9, 11].

Brain damage after severe and moderate TBI is a dynamic pathological process in which clinical and CT variables may change over time. This is best illustrated for the GCS score where a prediction model based on the best GCS-motor score within the first 24 h post-trauma demonstrated superior accuracy over the worst GCS score [8]. Progression of traumatic intracerebral hematomas and contusions, brain swelling, and edema, midline shift and post-traumatic cerebral infarction after the initial CT-scan is common [39–43]. Prediction of eventual outcome becomes more accurate using information from sequential rather than initial CT-scans [41]. Nevertheless, we used the clinical parameters at the ED and the information obtained

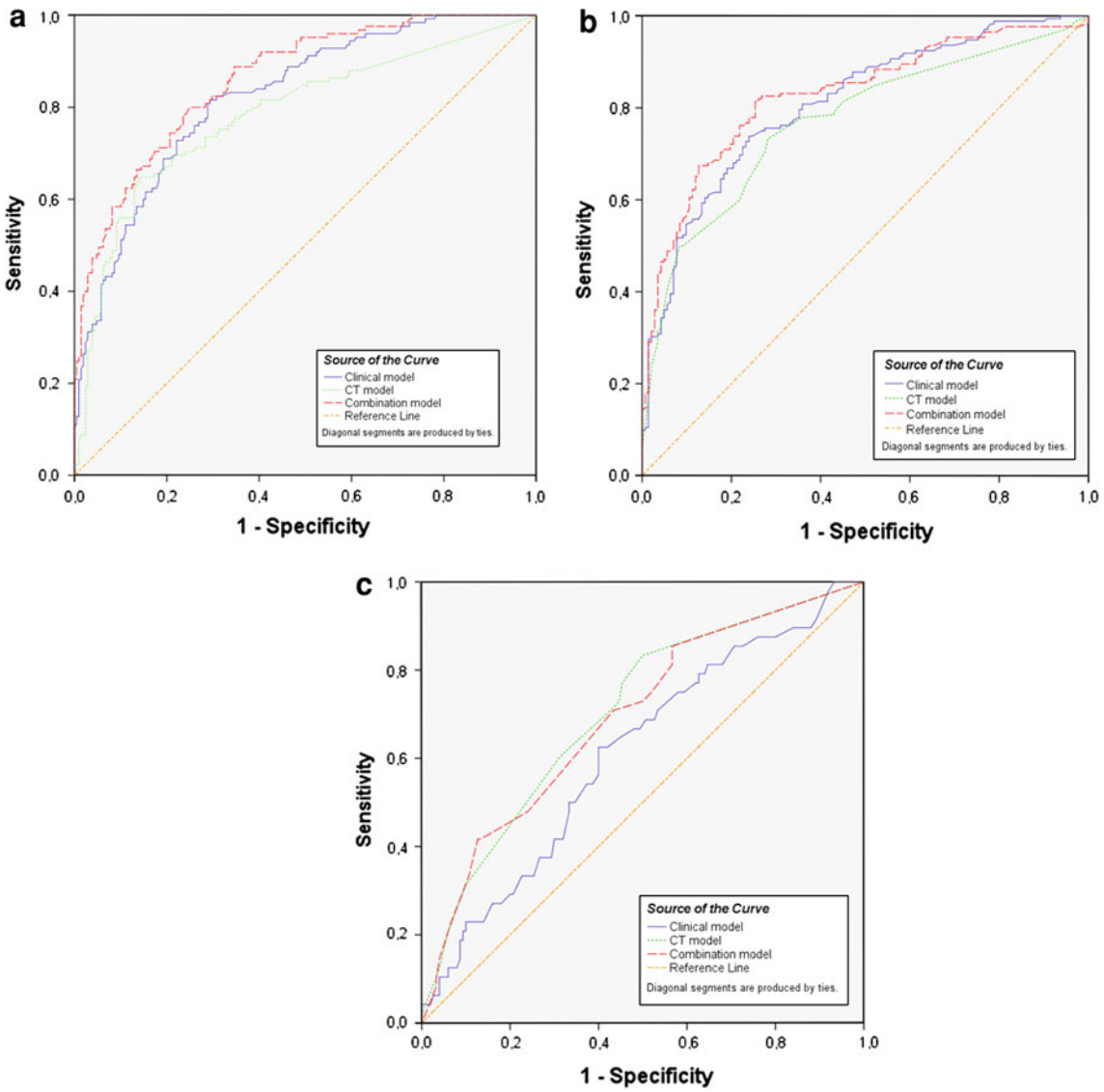

Fig. 2 Receiver operating characteristic (ROC) curves of our prognostic models for three outcome scores in the external POCON validation cohort: **a** death (GOSE 1), **b** unfavorable outcome (GOSE 1–4), and **c** unfavorable outcome in the TBI survivors (GOSE 2–4).

Note: Corresponding AUCs shown in Table 3. *CT* computed tomography, *AUC* area under the curve, *POPCON* Prospective Observational Cohort Neurotrauma

from initial CT-scans, while we think that indices of the primary injury are most essential in clinical decision-making and for prognostic purposes in daily practice.

An inclusion bias may have been introduced because of the GCS score, we applied to define TBI severity. We used the GCS score after initial resuscitation or the admission GCS score before intubation and sedation if these procedures were performed during resuscitation. However, a large proportion of especially the severe TBI patients was already intubated (63 %), and mainly also sedated, at the moment of clinical evaluation, as a result of pre-hospital management, complicating a reliable neurological assessment. We did not correct for GCS scores determined at the injury scene, of which the reliability has been questioned before [44]. Hence, it is possible that a less severely injured TBI patient was wrongly categorized as severe due to a falsely low GCS score.

Finally, the number of surviving patients with an unfavorable outcome (GOSE 2–4) was relatively small ($n = 77$), especially when compared to the number of patients that died ($n = 251$), which may have influenced model derivation and validation for this outcome category.

Conclusion

With this study of an unselected cohort of moderate and severe TBI patients we introduce several new and

externally validated outcome prediction rules. We also evaluated unfavorable outcome in surviving patients as an outcome of interest besides the conventional dichotomized outcome endpoints, death, and unfavorable outcome.

The information our prediction models provide, will be helpful in clinical research for the selection of patients for enrollment in clinical trials for example on neuroprotective therapies, as well as for stratifying participants by injury severity. To further improve the discriminative abilities of outcome prediction models in TBI, future research should focus on the identification of new potential outcome predictors, like serum or cerebrospinal fluid biomarkers of brain damage or genetic polymorphisms.

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Conflict of interest All authors declare no conflict of interest to disclose.

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