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Comparison of two simple models for prediction of short term mortality in patients after severe traumatic brain injury

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ABSTRACT

Introduction: The subscale motor score of Glasgow Coma Scale (msGCS) and the Abbreviated Injury Score of head region (HAIS) are validated prognostic factors in traumatic brain injury (TBI). The aim was to compare the prognostic performance of a HAIS-based prediction model including HAIS, pupil reactivity and age, and the reference prediction model including msGCS in emergency department (ED), pupil reactivity and age.
Methods: Secondary analysis of a prospective epidemiological study including patients after severe TBI (HAIS > 3) with follow-up from the time of accident until 14 days or earlier death was performed in Switzerland. Performance of prediction, based on accuracy of discrimination [area under the receiver-operating curve (AUROC)], calibration (Hosmer-Lemeshow test) and validity (bootstrapping with 2000 repetitions to correct) for optimism of the two prediction models were investigated. A non-inferiority approach was performed and an a priori threshold for important differences was established.
Results: The cohort included 808 patients [median age 56 {inter-quartile range (IQR) 33–71}, median motor part of GCS in ED 1 (1–6), abnormal pupil reactivity 29.0%] with a death rate of 29.7% at 14 days. The accuracy of discrimination was similar (AUROC HAIS-based prediction model: 0.839; AUROC msGCS-based prediction model: 0.826, difference of the 2 AUROC 0.013 (−0.007 to 0.037). A similar calibration was observed (Hosmer-Lemeshow X^2 11.64, p = 0.168 vs. Hosmer-Lemeshow X^2 8.66, p = 0.372). Internal validity of HAIS-based prediction model was high (optimism corrected AUROC: 0.837).
Conclusions: Performance of prediction for short-term mortality after severe TBI with HAIS-based prediction model was non-inferior to reference prediction model using msGCS as predictor.

Introduction

Traumatic brain injury (TBI) is a major burden affecting 10 million people per year worldwide [1]. TBI diminishes life expectancy related to attributable mortality rate ranging between 30 and 70% [2–4]. Following severe TBI, most deaths occur early with mortality rates at 14 days reaching 24.5% in adults (16–65 years) and up to 40.9% in the elderly (>65 years) [5]. Precise classification of patients with TBI early after injury is essential not only to optimize medical resources management and initiate appropriate diagnostic and therapeutic interventions, but also to accurately predict outcome, perform comparative audits, and conduct pertinent research. Early stratification should be simple and feasible for clinicians.

Assessment using the initial Glasgow Coma Scale (GCS) score, which is regularly included in predictor models [6], may be affected by several factors such as alcohol intoxication, maxillo-facial fractures, pre-existing cognitive limitations, sedation and intubation, and limited training of health care providers for GCS assessment [7,8]. The GCS score may thus have limited predictive validity; while it correlates with survival and functional outcome, the association is weak and inconsistent [9–11]. In elderly patients specifically, the GCS score is a controversial outcome predictor due to observed discrepancies between the GCS score and anatomical measures of TBI severity [12–14]. Furthermore, the GCS score does not predict the need for neurosurgical interventions [15]. Several approaches have been developed to improve the predictive power of the GCS score following TBI [16,17]. Bayesian network analyses have identified age and pupil reactivity to light as significant outcome predictors following TBI [18]. Predictive models including GCS are improved when they include these two independent variables. Alternatively, the GCS score can be replaced by its subscale motor component in order to simplify assessment of consciousness. Evidence shows that the subscale motor score of GCS (msGCS) is equivalent to the GCS total score for prediction of outcome after TBI [18–20].

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Whereas the GCS quantifies the physiological or functional consequences of TBI, the Abbreviated Injury Score (AIS) is an anatomical or structural scoring diagnostic system that is less affected by external factors. Using the AIS, severity of injury is classified by body region on a 6 points ordinal scale. In most cases, accurate grading requires diagnostic imaging [21,22]. Similar to GCS scoring, limited inter-rater agreement on the degree of severity using the AIS was observed [23], however the Abbreviated Injury Score of head region (HAIS) is a validated outcome predictor following TBI [24]. In the few studies comparing the initial GCS to the HAIS the two scores were poorly correlated, and the prediction of mortality was different [13,25–28].

We hypothesized that models including HAIS are non-inferior to "traditional" reference models including the msGCS for the prediction of mortality within 14 days following severe TBI [16,17]. The aim was to compare the prognostic performance of two prediction models: one including HAIS, pupil reactivity, and age, another including msGCS, pupil reactivity and age (refitted IMPACT core model).

Materials and methods

This report complies with the TRIPOD guideline [29].

Source of data

We used an existing dataset from a prospective epidemiological cohort study including patients with severe TBI who were followed up for 14 days (or till time of death) from the time of accident [5]. The study was approved by the ethics committees of each participating trauma center. Because eligible patients were unable to give informed consent on enrolment, local study coordinators contacted their legal representatives (proxies) to inform them of the study within 14 days following injury. Written consent was requested from patients or proxies. Follow-up was discontinued, and all collected data discarded, any time consent was not granted or withdrawn.

Study population and inclusion criteria

We included patients ≥16 years who sustained severe TBI from both blunt and penetrating trauma in Switzerland between May1, 2007 and April 30, 2010. Severe TBI was defined by a HAIS > 3. The neurosurgeon or radiologist in charge was responsible for HAIS scoring based on clinical assessments and head computer tomography imaging. The worst head CT scan within the first 24 h was used and assessed using a standardized data sheet. Patients who died before neurosurgical or radiological diagnosis were excluded. Additionally, patients with unclear brain trauma history (for instance, comatose patients found on a public area without observation by bystanders) or absence of brain trauma (for instance, fatal multi-trauma patients with abdominal and thoracic injuries without visual injuries to the head) were excluded. Finally, patients who died during the prehospital phase, as well as those with missing predictors [subscale motors score of GCS in emergency department (ED), pupil reactivity in ED, age] were also excluded.

Outcomes and predictors

Outcome: mortality at 14 days.
Predictors:

i Patient characteristics: Age
ii Initial physiological and biological variables: GCS total score and msGCS, pupil reactivity at hospital admission in the ED
iii Severity of TBI: HAIS score based on clinical assessment and head CT scan performed within 24 h of injury

Sample size and missing data

The sample size was prespecified [5]. To improve predictive accuracy and to decrease bias in regression coefficient, we limited potential predictors to variables with sufficient events per variable [30]. A total of 11 patients who died on scene were excluded. We excluded 102 patients with missing predictive factors. The msGCS was not available in 77 (8.4%) patients. Assessment of pupil reaction was missing in 31 (3.4%) patients (Fig. 1 and Supplementary Table S1).

Statistical analysis

Patients' baseline characteristics were described as distribution with medians and inter-quartile ranges (IQR) for continuous variables and frequencies and percentages for categorical variables. Descriptive statistics were conducted for the entire population and for two subgroups: survivors versus non-survivors at 14 days.

The predictor "age" was presented as a distribution (median, IQR). The predictor "msGCS" was presented as a distribution and as categories (1–2, 3–4, 5–6). The predictor "HAIS" was presented as a distribution and as categories (HAIS 4, HAIS 5, HAIS 6). Relationship between categories of msGCS and HAIS were presented graphically and assessed with a X^2 test. We compared "survivors" and "non-survivors" using non-parametric Wilcoxon t-tests for continuous variables and, X^2 tests for categorical variables (univariate analyses).

Development of the two prediction models

There was pre hoc decision to develop a prediction model based on data from the ED similar to the reference prediction model (IMPACT core model) [16,17]. Age was used continuously; msGCS, and HAIS were categorized for the purpose of this study.

First, we refitted the IMPACT core model [16,17] by including the following 3 predictors: msGCS on ED admission, pupillary reactivity on ED admission and age. This prediction model was considered as our reference model.

Second, we tested the performance of another prediction model similar to the refitted IMPACT core model, replacing the

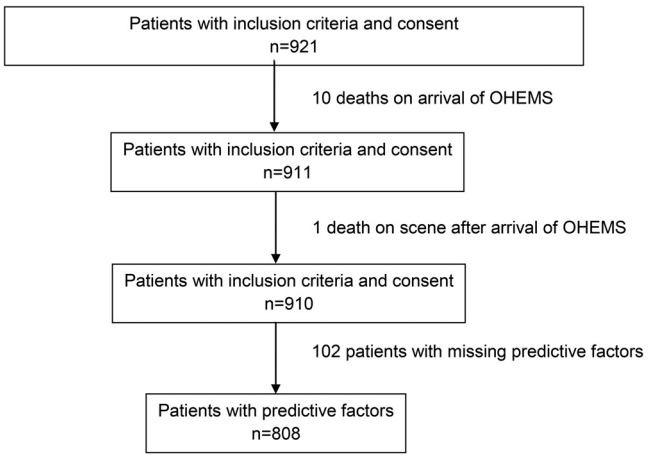

Fig. 1. Flow chart of enrolled and included patients.

msGCS with HAIS. In both cases, we used multivariate logistic regression methods to predict the outcome of death within 14 days.

To assess the performance of each prediction model, we determined their amount of explained variation (by Nagelkerke's pseudo R2 and deviance models), their level of discrimination [area under the receiver-operating curve (AUROC)] and calibration (by calibration slope and intercept).

While the Nagelkerke's R2 measures the explained variation of a model, the deviance estimates the 'goodness-of-fit' of a model. It is defined as twice the difference between the log likelihoods of two models: a fitted model and a full model representing "the most complete model we could fit". The better the goodness of fit, the smaller the deviance.

Models' discrimination and comparison of models' AUROCs

The AUROCs of the two fitted models (reference prediction model and HAIS-based prediction model) were calculated to evaluate their discriminative ability. The AUROC values range from 0.5 to 1.0, where 1.0 indicates perfect discrimination and 0.5 means that the model does not perform any better than chance alone. Generally, AUROCs >0.90 are considered excellent, >0.80 good, >0.70 modest and ≤0.70 poor [31].

To compare the AUROC curves of each model, we calculated the difference in AUROCs by subtracting the AUROC of the reference prediction model from the AUROC of the HAIS-based prediction modes. We expressed the difference with a 95% confidence interval (95% CI) derived from a bootstrapping procedure with 1000 repetitions.

We then proceeded to test the hypothesis of non-inferiority of these two prediction models. There is no consensus on non-inferiority margins for models predicting mortality following TBI; Gill et al, for instance, proposed that differences in AUROC less than −0.10 or −10% would be small enough to lack clinical importance [32]. We adopted a more conservative approach to non-inferiority: we considered any difference of −0.05 or more between the AUROCs (non-inferiority margin), or any difference of 5% or more between the discriminative abilities, to be clinically relevant. As a result, the HAIS-based prediction model would be non-inferior to the reference prediction model if the lower bound of the 95% CI of the difference AUROCs remains above −0.05 or −5.0% [33].

Calibration of prediction models

Calibration of the two fitted models, which verifies that, predicted and observed outcomes remain concordant across all risk categories. We used the Hosmer-Lemeshow test to test concordance [31]. The test first divides the data points into equally sized deciles based on estimated mortality risk, then calculates a X^2 for each decile. The smaller the value of X^2, the larger the p-value, the better the calibration.

To graphically express the level of calibration of the HAIS-based prediction model, we plotted the predicted death rate at 14 days (x-axis) against the observed death rate at 14 days (y-axis). When calibration is perfect, the predicted and observed death rates are linearly related along a 45° line. We also plotted the observed death rate at 14 days by decile of predicted death rate to graphically illustrate the Hosmer-Lemeshow goodness-of-fit test. We repeated the same procedure for the reference prediction model.

Validation of the HAIS-based prediction model

We used a bootstrapping procedure with 2000 repetitions to correct for optimistic HAIS-based prediction model's AUROC estimates [34]. This method aims to avoid issues related to overfitting. Whenever optimistic AUROCs are close to initial AUROCs, overfitting is unlikely.

We used STATA Release 12.1 (Stata Statistical Software: Release 12.1 Stata Corporation, College Station, USA) for all statistical analyses. The significance level was set at $P < 0.05$ for all analyses.

Results

Baseline characteristics

A total of 808 patients were included in this study (Fig. 1). The median age was 56 (IQR 33-71), the median GCS on ED admission was 3 (IQR 3-14), the median msGCS on ED admission was 1 (IQR 1-6), 432 patients (53.5%) had a msGCS equal to 1 or 2. Abnormal pupil reactivity was observed in 234 patients (29.0%). The overall mortality rate at 14 days for the entire study population was 29.7% (240 out of 808 patients) (Table 1).

Non-survivors were significantly older and presented with worse brain injuries in univariate analyses (Table 1). HAIS scores and msGCS scores were inversely related: the greater the HAIS

Table 1
Description of surviving and not surviving patients after severe TBI at 14 days.

	N (%) N = 808	Survivors N (%) N = 568	Non survivors N (%) N = 240	P values
Age (median, IQR)	56 (33–71)	53 (30–68)	63 (42–79)	<0.0001
msGCS on ED admission (median, IQR)	1 (1–6)	5 (1–6)	1(1–1)	<0.0001
msGCS 5-6 on ED admission	344 (42.5)	307 (54.1)	37 (15.4)	<0.0001
msGCS 3-4 on ED admission	32 (4.0)	24 (4.2)	8 (3.3)	
msGCS 1-2 on ED admission	432 (53.5)	237 (41.7)	195 (81.3)	
Abnormal pupil reaction on ED admission	234 (29.0)	88 (15.5)	146 (60.8)	<0.0001
HAIS (median, IQR)	5(4–5)	4 (4-5)	5 (5-5)	<0.0001
HAIS 4	341 (42.2)	307 (54.1)	34 (14.2)	<0.0001
HAIS 5	442 (54.7)	261 (45.9)	181 (75.4)	
HAIS 6	25 (3.1)	0 (0)	25 (10.4)	
Multiple trauma	248 (30.7)	157 (27.6)	91 (37.9)	0.004
ISS (median, IQR)	25 (20-33)	25 (20–29)	28 (25–42)	<0.0001
Falls	427 (52.9)	296 (52.1)	131 (54.6)	0.752
Road traffic accidents	254 (31.4)	183 (32.2)	71 (29.6)	
Other mechanisms	127 (15.7)	89 (15.7)	38 (15.8)	

IQR: Inter-quartile range; ED: emergency department; msGCS: subscale motor score of Glasgow Coma Scale; HAIS: Abreviated injury score of the head region; ISS: injury severity score.

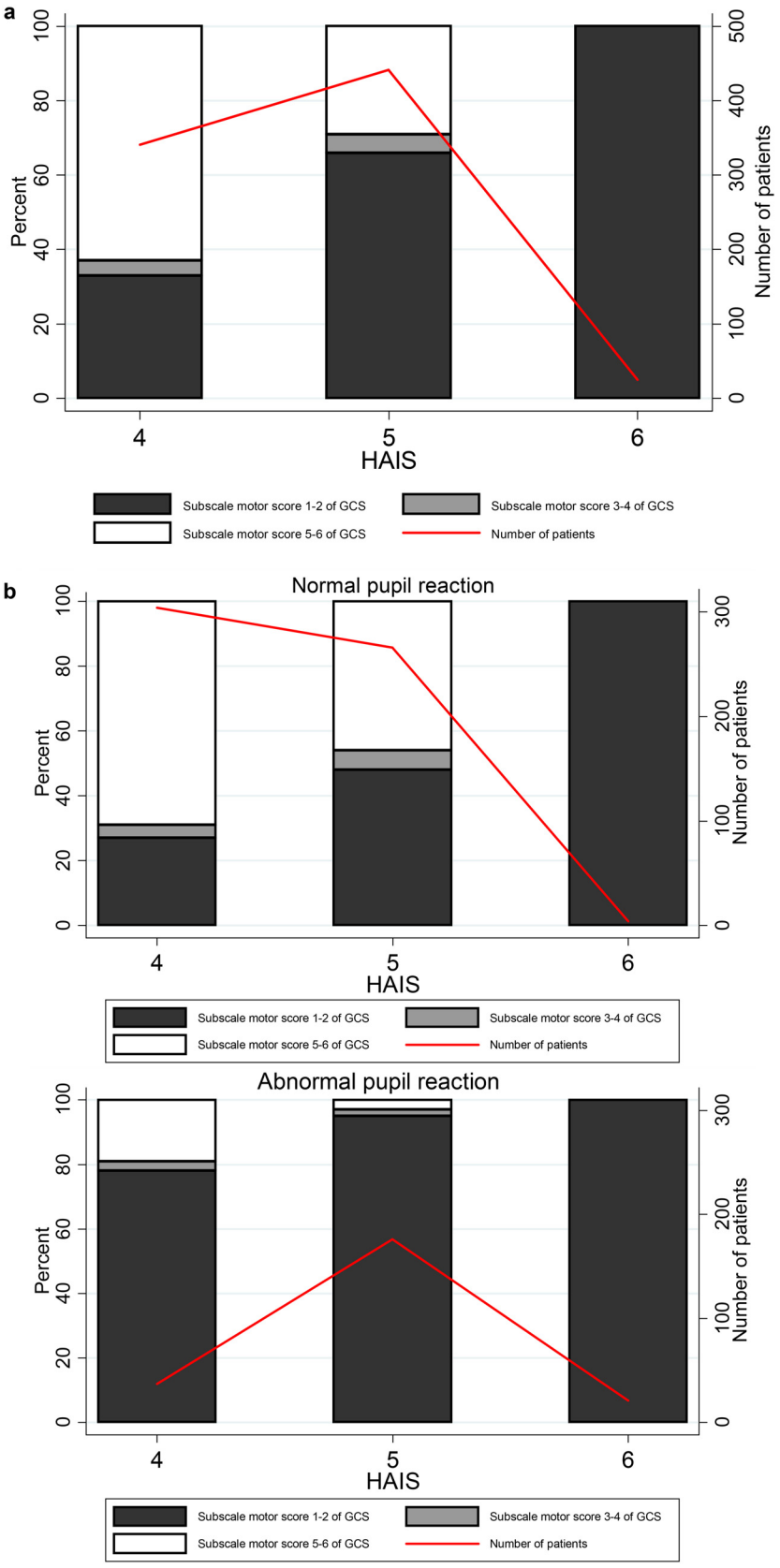

Fig. 2. (a) Distribution of the categories of HAIS and motor GCS at ED. (b) Distribution of the categories of subscale motor score of GCS on ED and HAIS stratified in patients with normal pupil reactivity and abnormal pupil reactivity.

Table 2
Predictors of death at 14 days. Univariate analyses and mutlivariate logistic regression for the two predictive models.

	Univariate model OR (95% CI)	P values	Multivariate model HAIS-based predictive model OR (95% CI)	P values	Mutivariate reference predictve model OR (95% CI)	P values
Age	1.02 (1.01–1.03)	<0.0001	1.03 (1.02–1.04)	<0.0001	1.03 (1.02–1.04)	<0.0001
msGCS 5-6 on ED admission (reference)	1				1	
msGCS 3-4 on ED admission	2.77 (1.16–6.60)	<0.0001			2.87 (1.10–7.46)	0.031
msGCS 1-2 on ED admission	6.83 (4.62–10.09)	0.022			4.03 (2.55–6.36)	<0.0001
Abnormal pupil reaction on ED admission (versus normal)	8.47 (6.00–11.96)	<0.0001	7.23 (4.90–10.65)	<0.0001	5.70 (3.80–8.56)	<0.0001
HAIS = 4 (reference)	1		1			
HAIS = 5/6	7.13 (4.78–10.62)	<0.0001	5.06 (3.27–7.83)	<0.0001		

OR: Odds ratio; CI: confidential interval; ED: emergency department; msGCS: subscale motor score of Glasgow Coma Scale; HAIS: Abreviated injury score of the head region.

score, the lower the msGCS ($p < 0.0001$; Fig. 2a). This association remained valid irrespective of pupil reactivity ($p_{\text{normal pupil reaction}} < 0.0001$ and $p_{\text{abnormal pupil reaction}} = 0.001$; Fig. 2b).

Model development

The odds ratios for age and for pupil reaction were similar in both models (Table 2). Compared to the reference prediction model, the HAIS-based model had a similar predictive power (Nagelkerke's pseudo R2: 39.5% vs. 36.6%; deviance 720 vs 742).

Models' discrimination and comparison of model's AUROCs

Both models reached good levels of discrimination with AUROCs $\geq$ 0.800 (Table 3, Fig. 3). The difference between the 2 AUROCs was 0.013 (95%CI −0.007 to +0.037). Since the lower bound of the 95% CI was inferior to the pre-specified non-inferiority margin of -0.05, the HAIS-based prediction model was judged non-inferior to the reference prediction model.

Calibration of the prediction models

Overall, both prediction models were appropriately calibrated (Hosmer-Lemeshow X^2 11.64, $p = 0.168$; Hosmer-Lemeshow X^2 8.66, $p = 0.372$; Table 3, Fig. 4a and b).

Validation of the HAIS-based prediction model

The optimism corrected AUROC value of the HAIS-based prediction model was 0.837, which is close to the non-corrected AUROC value of 0.839. Therefore, the risk of overfitting is low and we expect that the model will maintain discriminative accuracy in external populations.

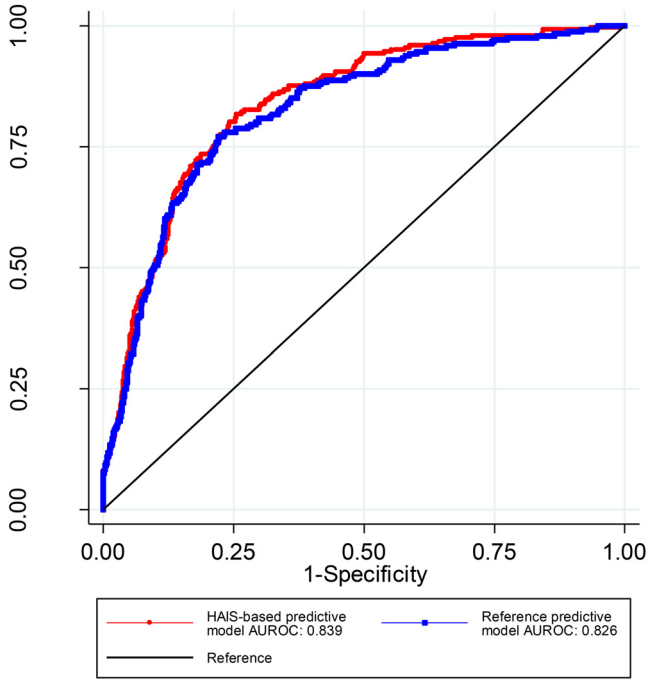

Fig. 3. Accuracy of discrimination (AUROC) for the HAIS-based predictive model and the reference predictive model.

Table 3
Discrimination, explained variation and calibration of the two predictive models.

	HAIS-based predictive model (M1) (95% CI)	Reference predictive model (M2) (95% CI)	Difference (M1–M2) (95% CI)[a]
Discrimination			
Sensitivity	51.3% (44.7%–57.7%)	50.4% (43.9%–56.9%)	
Specificity	90.0% (87.2%–92.3%)	90.0% (87.2%–92.3%)	
Positive predictive value	68.3% (61.0%–75.1%)	68.0% (60.6%–74.8%)	
Negative predictive value	81.4% (78.1%–84.3%)	81.1% (77.8%–84.1%)	
AUROC	0.839 (0.810–0.869)	0.826 (0.795–0.857)	0.013 (−0.007–0.037)
Explained variation			
Nagelkerke's R2	39.5	36.6	
Deviance	720	742	
Calibration			
Hosmer Lemeshow	$X^2 = 11.64$; $p = 0.168$	$X^2 = 8.66$, $p = 0.372$	

[a] Bootstrap estimation; CI: confidence interval; AUROC: area under the receiver-operating curve.

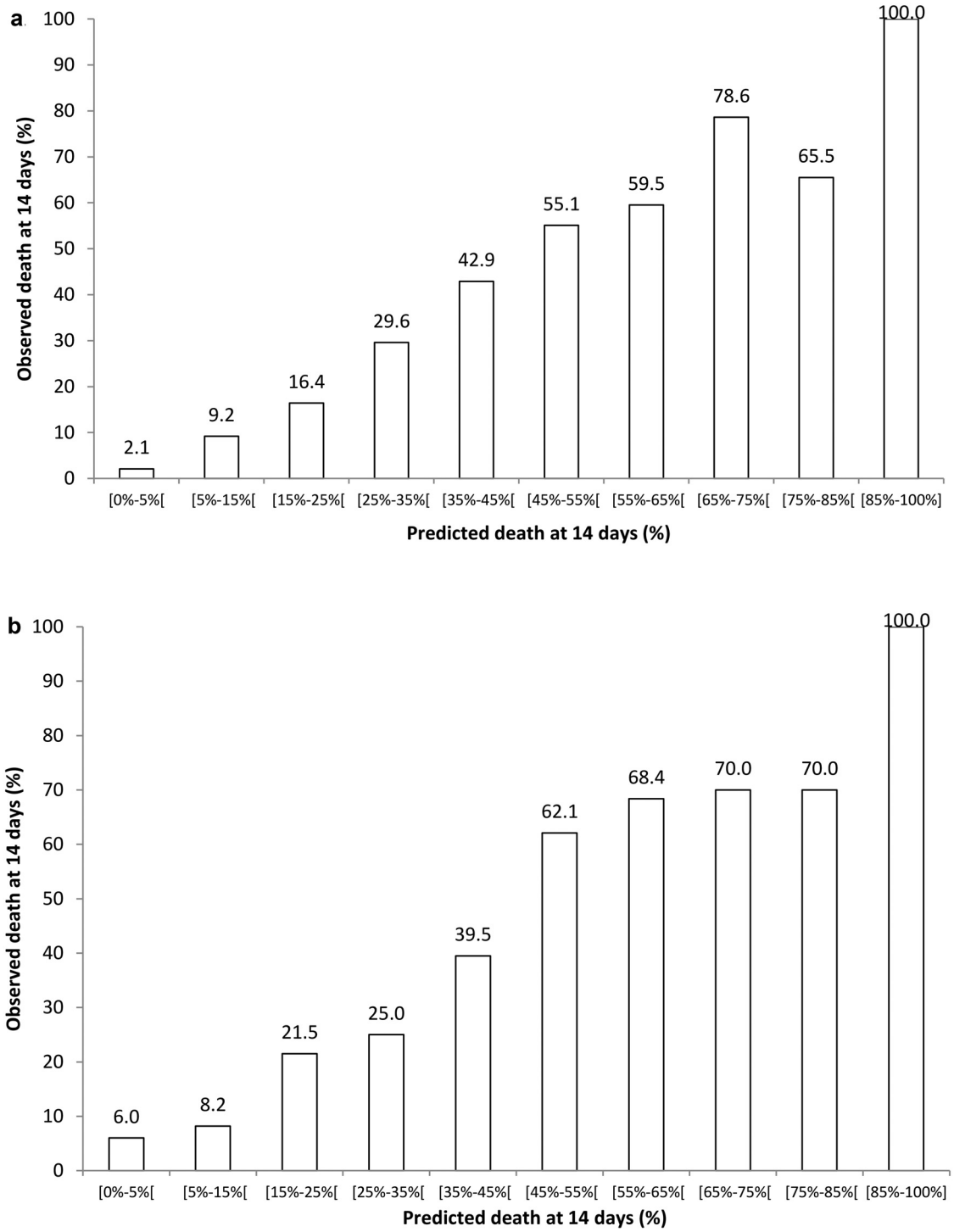

Fig. 4. (a) Calibration of the HAIS-based predictive model. (b) Calibration of the reference predictive model.

Discussion

Key findings

The study observed a robust relationship between the anatomical or structural description of TBI using the HAIS and the physiological of functional description using the msGCS. This association was observed for patients with normal and abnormal pupil reactivity. Therefore, there is evidence that the msGCS may be substitutable by HAIS in prediction models for mortality within 14 days after TBI.

The discriminative accuracy of the HAIS-based prediction model was not inferior to the reference prediction model for the prediction of death at 14 days. Both models had good discrimination and appropriate calibration for short-term mortality prediction.

Interpretation of the results and implications

The observation that the HAIS-based model is non-inferior to the reference prediction model has several implications. First, accurate prediction of early mortality following TBI is feasible even

in absence of an initial total or msGCS assessment. Since HAIS is often assessed for coding and accounting reasons, it should be readily available. Second, should external validation studies confirm the discriminative accuracy of the HAIS-based prediction model, risk assessment following TBI will be also achievable using this additional, simple approach. The armamentarium of mortality prediction will be more varied and may lead to more, early and adequate decision-making including an appropriate resources management. By reducing the over- and underestimation of risk after TBI, this clinically important aspect will contribute to improve our ability to predict early mortality following TBI. HAIS is particularly meaningful in cases where the GCS on admission is normal or near normal, as is often the case with elderly patients [13,35]. Third, while initial GCS assessment are often missing in clinical studies and registers with TBI patients, HAIS is often available. We propose that it can be used to minimize the amount of missing neurological information in clinical datasets. Larger, robust datasets facilitate clinical research, audits, quality-of-care assessments and benchmarking between trauma centers.

A strength and originality of the study was that it relied on a non-inferiority comparative study of two prediction models using a large cohort. When selecting the non-inferiority boundary, both statistical reasoning and clinical judgment were used. The one available study comparing the total GCS vs. a simplified GCS to estimate the non-inferiority boundary concluded that any predictive performance difference inferior to 10% is clinically non-relevant [32]. Given the little evidence available, we used a more conservative approach and we declared any predictive performance difference inferior to 5% clinically non-relevant.

Comparison with previous studies

MsGCS was a much stronger predictor of death within 14 days than HAIS in 2808 patients suffering from TBI and admitted to 8 U. S. Level I trauma centers [28]. Timmons et al. analyzed this data with Cox proportional hazards regressions methods, but failed to formally investigate the predictive performance of their model, which may decrease the validity of their conclusions.

In a single center study including 270 patients a multi-linear regression analyses was performed with the outcome Glasgow Outcome Scale extended (GOSE) at 1 year [26]. The authors concluded that HAIS and ISS outperformed GCS as predictor of GOSE. Again, in this smaller study, no formal analyses of the predictive performances were tested.

Limitations

This study has several limitations. First, we had to exclude some patients with missing data. Patients excluded due to missing predictive factors were demographically comparable to those without predictive factors, thereby reducing the risk of systematic bias. Second, the study was performed in a high-income country, it cannot be generalized to middle or low income countries were limited access to CT imaging may complicate HAIS assessment. Third, the study used a reference prediction model which was established with younger patients (IMPACT model) [16,17]; the median age in our cohort was higher introducing a potential risk of a case-mix bias. But the IMPACT model was also valid in a high-income country with a similar older population [36]. Forth, our HAIS-based prediction model was not formally validated in an external cohort. A low risk of overfitting can be expected with an external population because the optimism corrected value of AUROC was similar to the original AUROC of the HAIS-based prediction model.

Future implications

Although both prediction models have good prediction performance of mortality, they are not perfect. The following candidate predictors should be tested for further improvement: multiple trauma [37], pre-existing co-morbidities assessed with the Charlson score [38] and post-injury complications such as pneumonia [39] and/or transfusion of platelets [40].

Conclusions

In this large multicenter cohort study, a HAIS-based prediction model is non-inferior to a reference prediction model using the msGCS for prediction of short-term mortality after severe TBI. An external validation is needed to confirm this finding.

Conflict of interest and sources of funding

The authors have no conflict of interest to declare. This study was partially funded by the Swiss Accident Insurance Foundation (SUVA, Switzerland). The funding agency had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.injury.2018.08.022.

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