PAPER

Severe head injury and the risk of early death

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J Neurol Neurosurg Psychiatry 2006;**77**:1054–1059. doi: 10.1136/jnnp.2005.087056

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Received 23 December 2005
Revised version received 11 April 2006
Accepted 18 May 2006
Published Online First 1 June 2006

Background: Severe head injury (SHI) is one of the most important health, social and economic problems in industrialised countries. Unfortunately, none of the neuroprotection trials for traumatic brain injury have shown efficacy. One of the reasons for this failure could be the inclusion of patients with high probability of early death. A population-based, retrospective study was conducted to develop a prognostic model for identification of these patients.
Methods: Between January 1987 and August 1999, a total of 895 patients (⩾15 years of age) with non-missile SHI were studied, in whom a computed tomography scan was carried out within the first 6 h of injury. The association between early death (first 48 h after injury) and independent prognostic factors was determined by logistic regression analysis. A scoring system was also constructed.
Results: The early-death rate was 20%. Independent predictors of early mortality after SHI were non-evacuated mass (odds ratio (OR) 65, 95% confidence interval (CI) 11 to 379), diffuse injury IV (OR 25, 95% CI 5 to 112), diffuse injury III (OR 8, 95% CI 3 to 22), flaccidity (OR 7, 95% CI 3 to 15), non-reactive bilaterally mydriasis (OR 6, 95% CI 3 to 12), evacuated mass (OR 4, 95% CI 1 to 11), age ⩾65 years (OR 4, 95% CI 1 to 9), decerebration (OR 3, 95% CI 2 to 7) and shock (OR 3, 95% CI 2 to 6). The prognostic model correctly identified 93% of the patients.
Conclusions: This prognostic model is based on simple clinical and radiological data readily available during the first 6 h after injury and is useful for identification of early death after SHI.

Severe head injury (SHI) remains the main cause of mortality and morbidity in people aged ⩽40 years in all westernised nations. The death rates of SHI nowadays range from 30% to 50%, figures very similar to those reported 30 years ago, despite efforts to better this. To improve the outcome of SHI, many phase III clinical trials have been developed in the past decade but, unfortunately, none has shown efficacy, in contrast with the success achieved in animal laboratory studies.[1] One of the reasons for this failure could rest on the inclusion of patients with high risk of death. Our study aimed to develop a prognostic model for identification of patients with high risk of death in order to exclude them from future clinical trials for SHI.

METHODS

Study setting

We conducted a retrospective, population-based study at the Hospital 12 de Octubre, Madrid, Spain, from 1 January 1987 to 31 August 1999. In this period, the Department of Neurosurgery at this hospital attended to a total of 1009 consecutive patients with non-missile SHI and age >14 years, in whom at least one computed tomography scan was carried out at any time after their admission. Of these patients, 114 were excluded because the computed tomography scan was carried out after the first 6 h of injury. Therefore, we included a total of 895 patients. Cases detected from 1 January 1987 to 31 December 1995 (652 patients) were used to derive the prognostic model, and those gleaned from 1 January 1996 to 31 August 1999 (the remaining 243 patients) were used to validate it.

Definitions

Head injury was defined as severe when the patient scored ⩽8 points on the Glasgow Coma Scale (GCS)[2] after non-surgical resuscitation, within the first 6 h of injury.

Total GCS score and motor response were assessed after non-surgical resuscitation through the first 6 h after trauma, provided the patients were not sedated or pharmacologically paralysed. We classified them into two categories: high (scores of 6, 7 or 8) and low (scores of 3, 4 or 5) total GCS score; likewise, high (4 or 5 points on motor GCS) and low (1 (flaccidity), 2 (decerebration) or 3 points) motor GCS score.

Pupils were classified after non-surgical resuscitation within the first 6 h after trauma as unknown (assessment inaccurate); not "pathological" both pupils equal and reactive or asymmetric (difference ⩾2 mm) or non-reactive pupils but non-mydriatic (mydriasis was assessed when the pupillary size was >4 mm)); non-reactive unilateral mydriasis; and non-reactive bilateral mydriasis.

Neurological worsening was defined as the spontaneous decrease in motor GCS score of ⩾2 points during the first 6 h after injury, and in those patients who were sedated or pharmacologically paralysed as the development of non-reactive unilateral or bilateral mydriasis or any major change on the control computed tomography scan that warranted immediate medical or surgical intervention.[3] In these patients, we considered the GCS score and pupillary category displayed after such neurological worsening as final.

Shock and hypoxia were defined by any episode recorded (including cardiorespiratory arrest) of systolic blood pressure ⩽90 mm Hg or arterial oxygen saturation ⩽90% within the first 6 h after trauma.

Findings on computed tomography scan were classified according to the Traumatic Coma Data Bank.[4] In those patients in whom changes could be outlined on the control computed tomography scan obtained during the first 6 h after injury, the final Traumatic Coma Data Bank category assessed was the one associated with the greatest overall mortality, in the following order from the worst to the best outcome: traumatic lesion type VI (non-evacuated mass), type IV (diffuse injury IV—shift), type III (diffuse injury III—swelling), type V (evacuated mass), type II (diffuse injury II) and type I (diffuse injury I—no visible pathology).[5]

Abbreviations: GCS, Glasgow Coma Scale; ROC, receiver–operator characteristic; SHI, severe head injury

Table 1 Prognostic factors of early death after severe head injury: summary of univariate analysis for patients in the derivation set

Variable	No (%) of patients (n = 652)		OR (95% CI)	p Value
	Dead within the first 48 h (n = 114)	Remaining patients (n = 538)		
Age (years)				
⩾65	19 (34.5)	36 (65.5)	3.12 (1.54 to 6.32)	<0.001
55–64	7 (13.2)	46 (86.8)	0.90 (0.34 to 2.28)	0.81
45–54	9 (14.5)	53 (85.5)	1.01 (0.42 to 2.33)	0.99
35–44	15 (20.0)	60 (80.0)	1.48 (0.72 to 3.01)	0.25
25–34	27 (17.9)	124 (82.1)	1.29 (0.72 to 2.29)	0.36
15–24*	37 (14.5)	219 (85.5)	1	—
Total GCS score				
3	62 (64.6)	34 (35.4)	67.5 (14.9 to 424)	<0.001
4	31 (26.7)	85 (73.3)	13.5 (2.99 to 84.5)	<0.001
5	13 (12.0)	95 (88.0)	5.06 (1.04 to 33.6)	0.02
6	3 (2.7)	110 (97.3)	1.01 (0.13 to 8.87)	1.00†
7	3 (2.1)	140 (97.9)	0.79 (0.10 to 6.95)	1.00†
8*	2 (2.6)	74 (97.4)	1	—
Low	106 (33.1)	214 (66.9)	20.1 (9.24 to 45.4)	<0.001
High*	8 (2.4)	324 (97.6)	1	—
Motor GCS score				
1	62 (64.6)	34 (35.4)	74.0 (26.1 to 227)	<0.001
2	31 (26.7)	85 (73.3)	14.8 (5.25 to 45.0)	<0.001
3	13 (11.8)	97 (88.2)	5.44 (1.74 to 18.1)	<0.001
4	3 (2.5)	119 (97.5)	1.02 (0.19 to 5.02)	1.00†
5*	5 (2.4)	203 (97.6)	1	—
Motor GCS score				
Low	106 (32.9)	216 (67.1)	19.8 (9.10 to 44.7)	<0.001
High*	8 (2.4)	322 (97.6)	1	—
Pupils				
Non-reactive bilateral mydriasis	80 (62.0)	49 (38.0)	37.8 (18.4 to 79.3)	<0.001
Non-reactive unilateral mydriasis	20 (9.5)	190 (90.5)	2.44 (1.11 to 5.44)	0.02
Unknown	2 (8.7)	21 (91.3)	2.21 (0.00 to 11.5)	0.27†
Not "pathological"*	12 (4.1)	278 (95.9)	1	—
Seizure				
Yes	2 (4.5)	42 (95.5)	0.21 (0.03 to 0.91)	0.02
No*	112 (18.4)	496 (81.6)	1	—
Shock				
Yes	82 (33.3)	164 (66.7)	5.84 (3.65 to 9.38)	<0.001
No*	32 (7.9)	374 (92.1)	1	—
Hypoxia				
Yes	59 (28.0)	152 (72.0)	2.72 (1.77 to 4.20)	<0.001
No*	55 (12.5)	386 (87.5)	1	–
Urgent extracranial surgery				
Yes	14 (35.0)	26 (65.0)	2.76 (1.32 to 5.72)	0.003
No*	100 (16.3)	512 (83.7)	1	–
Anaemia				
Unknown	29 (60.4)	19 (39.6)	19.2 (7.66 to 49.0)	<0.001
Yes	74 (16.3)	381 (83.7)	2.44 (1.21 to 5.01)	0.007
No*	11 (7.4)	138 (92.6)	1	—
Coagulopathy				
Unknown	28 (57.1)	21 (42.9)	34.4 (11.8 to 106)	<0.001
Yes	80 (18.1)	362 (81.9)	5.71 (2.34 to 14.9)	<0.001
No*	6 (3.7)	155 (96.3)	1	—
Type of traumatic lesion				
VI	13 (76.5)	4 (23.5)	150 (30.6 to 856)	<0.001†
V	43 (18.2)	193 (81.8)	10.3 (3.81 to 30.2)	<0.001
IV	12 (50.0)	12 (50.0)	46.2 (12.4 to 184)	<0.001†
III	41 (29.5)	98 (70.5)	19.3 (7.04 to 57.5)	<0.001
II*	5 (2.3)	210 (97.7)	1	—
I*	0 (0)	21 (100)	1	—
Epidural haematoma				
Yes	5 (5.7)	83 (94.3)	0.25 (0.09 to 0.66)	0.002
No*	109 (19.3)	455 (80.7)	1	—
Subdural haematoma				
Yes	66 (27.2)	177 (72.8)	2.80 (1.82 to 4.33)	<0.001
No*	48 (11.7)	361 (88.3)	1	—
Focal brain contusion				
Yes	17 (11.8)	127 (88.2)	0.57 (0.31 to 1.01)	0.04
No*	97 (19.1)	411 (80.9)	1	—
SAH				
Yes	46 (38.3)	74 (61.7)	4.24 (2.65 to 6.80)	<0.001
No*	68 (12.8)	464 (87.2)	1	—
IVH				
Yes	54 (27.7)	141 (72.3)	2.53 (1.64 to 3.92)	<0.001
No*	60 (13.1)	397 (86.9)	1	—
Brain swelling				
Yes	109 (27.2)	292 (72.8)	18.4 (7.09 to 51.9)	< 0.001
No*	5 (2.0)	246 (98.0)	1	—

Table 1 Continued

Variable	No (%) of patients (n = 652) Dead within the first 48 h (n = 114)	Remaining patients (n = 538)	OR (95% CI)	p Value
Cerebral ischaemia				
Yes	109 (27.2)	292 (72.8)	18.4 (7.09 to 51.9)	<0.001
Yes	26 (59.1)	18 (40.9)	8.54 (4.30 to 17.0)	<0.001
Basal cisterns compressed				
Yes	109 (27.2)	292 (72.8)	18.4 (7.09 to 51.9)	<0.001
No*	5 (2.0)	246 (98.0)	1	—
Midline shift				
Yes	57 (30.2)	132 (69.8)	3.08 (1.99 to 4.76)	<0.001
No*	57 (12.3)	406 (87.7)	1	—
Lesion volume >25 ml				
Yes	42 (30.2)	97 (69.8)	2.65 (1.67 to 4.21)	<0.001
No*	72 (14.0)	441 (86.0)	1	—

GCS, Glasgow Coma Scale; IVH, intraventricular haemorrhage; SAH, subarachnoid haemorrhage; —, data not applicable.
*Reference categories.
†Fisher's exact test.

Final outcome was considered as the dependent variable and dichotomised into patients who died within the first 48 h of injury (early death) versus the remainder. This latter group was graded at 6 months after injury according to the Glasgow Outcome Scale[6] categories: good recovery, moderate disability, severe disability, vegetative state and death.

Data analysis

The information provided by all the independent variables of the study was collected during the first 6 h after trauma. The results of the descriptive analysis were compared between both cohorts. Overall and early-death rates in the total sample as well as in both sets were also calculated.

In the derivation cohort, we identified those variables significantly associated with early death (first 48 h of injury). The χ^2 test, with Yates correction when indicated, and Fisher's exact test were used to compare categorical qualitative variables. Student's t test was used for comparison of continuous qualitative and quantitative variables. The association between variables was considered to be significant when the probability (p) value was <0.05.

Using the logistic regression method, we identified the independent prognostic factors of early death, applying a selection of variables ''directed'' so that the different indicators were tested until we found the set (prognostic model) that worked better. The risk was quantified using odds ratios (ORs) with 95% confidence intervals (CIs) for every prognostic factor. After identifying independent predictors, points were assigned to each prognostic factor by dividing the coefficient of each predictor (from the logistic regression analysis) by the smallest coefficient, and then rounding each quotient to the nearest integer.

Reliability, the concordance between predicted and observed outcomes, was analysed by groups of patients depending on their predicted risk and comparing the observed prevalence of the outcome in each group with the expected value. The goodness of fit of the logistic regression model was tested by the Hosmer–Lemeshow test in both cohorts. Receiver–operator characteristic (ROC) curves were constructed by a series of cut-off points from both the derivation and validation sets. Both curves were analysed by calculating the area under ROC curves and the 95% CI to establish whether model prediction was better than chance prediction. Discrimination, the ability to separate patients with and without the outcome of interest, was compared using the distribution of predictions for patients with and without the outcome of intent (early death *v* remainder).

Finally, we calculated a prediction score to estimate the likelihood of early death for each patient by summing the total number of points. Sensitivity, specificity, positive and negative predictive values, and overall accuracy of each score were also determined.

Statistical analyses were carried out using the SAS system statistical package.

RESULTS

A comparison between both cohorts was carried out without finding important differences, although early mortality was considerably greater in the validation set (data not shown). On the other hand, the overall mortality in this series was 46.8% (419 of the 895 patients, 314 in the derivation cohort and 105 in the validation cohort). Of these patients, 42.2% died within the first 48 h of injury (177 of 419, 114 in the derivation set and 63 in the validation set), yielding an early-death rate of 19.8% (177 of the 895 patients) (data not shown).

Univariate analysis for patients in the derivation set

Table 1 summarises the results of univariate analysis for patients in the derivation cohort. The variables markedly associated with early death (first 48 h) were: age ⩾65 years; total GCS scores of 3, 4 or 5, and low total GCS score; motor GCS scores of 1, 2 or 3, and low motor GCS score; non-reactive bilateral mydriasis and non-reactive unilateral mydriasis; shock; hypoxia; urgent extracranial surgery; anaemia; coagulopathy; traumatic lesion types VI, IV, III and V; subdural haematoma; subarachnoid haemorrhage; intraventricular haemorrhage; brain swelling; cerebral ischaemia; basal cisterns compressed (numbers equal to those of brain swelling); midline shift and lesion volume >25 ml. In contrast, other variables were strongly ''protective'' with respect to early death: seizure ($p = 0.02$); epidural haematoma ($p = 0.002$) and focal brain contusion ($p = 0.04$; marginally significant). The remaining variables did not show significant association with early death, and for that reason they are not shown in table 1.

Multivariate analysis

Multivariate analysis identified the independent prognostic factors of early death, assigning in addition a score to each of them depending on their logistic regression coefficients (table 2). Theoretically, the total score for each patient would range from 0 to 10. However, no patient of our study scored 10 points.

Table 2 Prognostic factors of early death after severe head injury: results of multivariate analysis

Variable	Coefficient	Standard error	OR (95% CI)	p Value	Points*
Age (years ⩾65)	1.29	0.48	3.62 (1.42 to 9.23)	0.007	1
Flaccidity	1.94	0.40	6.93 (3.15 to 15.3)	<0.001	2
Decerebration	1.24	0.37	3.44 (1.65 to 7.17)	0.001	1
Non-reactive bilateral mydriasis	1.85	0.34	6.33 (3.25 to 12.3)	<0.001	2
Shock	1.18	0.32	3.27 (1.76 to 6.07)	<0.001	1
Traumatic lesion type III	2.03	0.55	7.64 (2.61 to 22.4)	<0.001	2
Traumatic lesion type IV	3.20	0.77	24.5 (5.36 to 112)	<0.001	3
Traumatic lesion type V	1.37	0.54	3.92 (1.37 to 11.2)	0.01	1
Traumatic lesion type VI	4.17	0.90	64.6 (11.0 to 379)	<0.001	4

*Each coefficient was divided by 1.18 and the quotient rounded to the nearest integer to determine the number of points assigned to that independent predictor.

The prognostic model worked correctly when it was applied to the validation cohort. Thus, the predicted outcomes were compared with observed ones in groups of patients according to their predicted risk, obtaining similar values (derivation: $p = 0.27$, $df = 6$; validation: $p = 0.98$, $df = 7$; Hosmer–Lemeshow test). The areas under the ROC curves for the derivation set and the validation set were 0.93 (95% CI 0.90 to 0.95) and 0.94 (95% CI 0.90 to 0.97), respectively, without significant differences between them ($p = 0.66$; fig 1).

For the 895 patients in the study, we calculated the likelihood of early death for each score (table 3). Taking as reference the scores of 0 and 1, the risk of early death progressively increases as the score increases. All patients who had 9 points died within the first 48 h of injury. Patients with 7 or 8 points who did not die during the first 48 h (4 patients in total) eventually died, between the 3rd and 22nd days after injury. Of the patients who scored 6 points, only one survived, remaining severely disabled. Similarly, four patients who scored 5 points survived, two of them severely disabled and the other two moderately disabled.

In table 4, the sensitivity, specificity, positive predictive value, negative predictive value and the percentage of patients correctly classified are shown for each score or cut-off point in the 895 patients in the study. One of the most interesting matters rests on calculating the error of the model—in particular when it predicts that patients will survive after the first 48 h of trauma but in fact they die within this time (false-negative rate). If we do not apply any selection criterion, we will have all patients available but we have to assume an early-death rate of 19.8%. From another point of view, if the aim rests on accepting, for instance, an early-death rate of 4.6%, it will be necessary to exclude 26.6% of the patients.

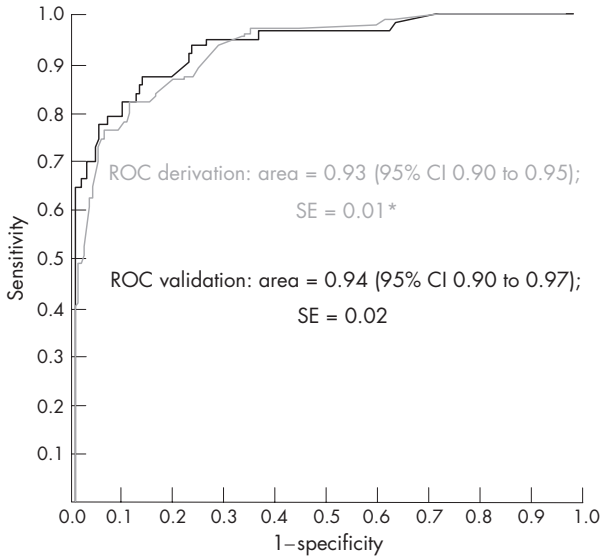

Figure 1 Receiver–operator characteristic (ROC) curves of the bedside scoring system using independent prognostic factors of early death after severe head injury: comparison between derivation set and validation set. CI, confidence interval; SE, standard error.

DISCUSSION

The final outcome regarding SHI is determined by the effect of prognostic factors, the treatment effect and the random effect. To reduce the random effect, different ''prognostic models'' have been carried out since the mid-70s, with the main objective of performing reliable predictions for future patients with SHI.[7–17] Up-to-date studies related to prediction for SHI have concluded that accurate prediction of outcome is impossible through the first 6 h of injury.[18 19] On the other hand, several reports[20 21] suggest that accuracy of predictions based on late assessments is greater when only two outcomes (death or survival) are considered; so the likelihood of death or SD state can usually be predicted accurately after the first 24 h of SHI. Therefore, it could be useful that these models estimate only the likelihood of death, identifying only that group of patients with high probability of dying.

In the past ''decade of the brain'', several neuroprotective agents have been tested in phase III clinical trials for SHI, but unfortunately the results have been disappointing.[1 22 23] Possibly, most of the clinical trials carried out till now have lacked a suitable sample size and perhaps they have not been well designed.[24 25] Two schools exist within the statistical community: the ''lumpers'', who argue that problems resulting from heterogeneity may be obviated in large megatrials, and the ''dividers'', who would prefer more targeted approaches—that is, clinical trials focused on patients with an ''intermediate'' risk.[1 25–27] To focus on this population with an ''intermediate'' risk, it would be necessary, at first, not to include in these clinical trials patients with high likelihood of dying, as they could dilute the potential benefit of the drug. Thus, we would try to design phase III studies ''custom made'' for the specific population to be studied.[22 23]

The overall mortality in our series was higher than that reported by others, a difference probably due to the inclusion of more severely injured patients in our study secondary to the aggressive measures of resuscitation used in our hospital to obtain the greatest number of potential organ donors. Given that the prognostic models are better correlated with mortality than with the overall prognosis, and as most patients with SHI die during the first days after

Table 3 Probability of early death depending on the observed score

Prediction score	Early deaths, No/no of patients	Early-death rate (%)	OR (95% CI)	p Value
0*	0/186	0		
1*	5/208	2.4	1	—
2	12/164	7.3	6.14 (1.97 to 20.4)	<0.001†
3	13/99	13.1	11.8 (3.78 to 38.9)	<0.001†
4	16/67	23.9	24.4 (7.94 to 80.0)	<0.001†
5	31/60	51.7	83.2 (28.0 to 265)	<0.001†
6	27/34	79.4	300 (79.1 to 1261)	<0.001†
7	46/49	93.9	1193 (239 to 7277)	<0.001
8	20/21	95.2	1556 (159 to 38114)	<0.001†
9	7/7	100	—	—

—, data not applicable.
*Reference categories.
†Fisher's exact test.

Table 4 Parameters for prediction of outcome related to the different scores

Prediction score	No (%) of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Patients correctly classified (%)
⩾0	895 (100)	100	—	19.8	—	19.8
⩾1	709 (79.2)	100	25.9	25.0	100	40.6
⩾2	501 (56.0)	97.2	54.2	34.3	98.7	62.7
⩾3	337 (37.7)	90.4	75.3	47.5	97.0	78.3
⩾4	238 (26.6)	83.1	87.3	61.8	95.4	86.5
⩾5	171 (19.1)	74.0	94.4	76.6	93.6	90.4
⩾6	111 (12.4)	56.5	98.5	90.1	90.2	90.2
⩾7	77 (8.6)	41.2	99.4	94.8	87.3	87.9
⩾8	28 (3.1)	15.3	99.9	96.4	82.7	83.1
⩾9	7 (0.8)	4.0	100	100	80.9	81.0
⩾10	0 (0)	—	100	—	80.2	80.2

PPV, positive predictive value; NPV, negative predictive value.
—, data not applicable.

trauma,[13 14 28 29] we decided to develop a simple prognostic model with an alternative final objective: the probability of early death after SHI.[30] We defined early mortality as death that occurs within the first 48 h of injury,[31] after observing the death of patients in our study, almost half of whom died in that time. These patients died due to the severity of their injuries and, as a whole, they represented about 20% of all patients in our series. In this context, not many studies that specifically contemplate the aspect of early death in SHI have been carried out, and as far as we know, a prognostic model with the characteristics and purposes similar to ours has not been published.[32–35]

Another feature of our model is the possibility of making accurate predictions about mortality within 6 h after SHI, in contrast with the prognostic models developed to date. The fact that patients in our study were in a coma for the first 6 h and it was possible to carry out a computed tomography scan in that time defines a minimum and a maximum level of severity, thus making the group that we studied well defined and relatively homogeneous.[12] Another reason to choose the interval of 6 h was that many of the trials carried out for SHI to date have generally used a therapeutic window of at least 8 h after trauma.[1]

The patients included in clinical trials for SHI are heterogeneous.[30] In these trials, the contingency that, for instance, patients have had episodes of shock or hypoxia (even cardiorespiratory arrest) before their inclusion is not considered. Similarly, it is not considered that their neurological states deteriorate through the first hours of injury or that their lesions seen on computed tomography scan change. Thus, we can state that some patients with SHI have greater likelihood of early death, as their outcomes strictly depend on the severity of the initial injury and, therefore, are hardly modifiable.[3 5 23 26 36–38] In fact, it is noteworthy that the only "avoidable" variable of our model is shock. The prediction score system developed from our study is simple to apply, as it only requires a correct neurological examination and a computed tomography scan during the first 6 h after injury, and thus can be used in any hospital without neurosurgical infrastructure. From this scoring system, it is possible to have a more precise idea of the real severity of these patients. Moreover, our prognostic model would rule out the greatest number of patients who are going to die within the first 48 h after injury, without losing an important number of people potentially suitable for inclusion in the clinical trials. Thus, it is possible to achieve inclusion of more homogeneous patients in these trials, optimisation of the type and number of people entered and, consequently, reduction in the costs. Although one potential drawback of more extreme targeting of trial participants is that it would limit the generalisability of the findings, perceived particularly as a problem by the pharmaceutical companies, this strategy has been found to allow a reduction in sample size by 30% for the same statistical power.[22 25 27]

Another consequence of our work rests in advocating extraordinary therapeutic measures in these patients who are going to die precociously, but managing them as potential organ donors.[14 33 39] Considering the ethical and legal connotations that a strategy of this type entails,[20] more databases and of sizes greater than that of ours are required to carry out absolutely reliable predictions on this matter.

Finally, it is important to remember that a very sensitive and specific model will be a poor predictor in a population in which the outcome is rare, or simply different from that observed in the model population.[9 40] For this reason, the generalisation of our model requires caution for the moment, as it has not been prospectively validated in a setting different from that of our hospital.

ACKNOWLEDGEMENTS

This study was supported by Mutua Madrileña Foundation.

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Competing innterests: None declared.

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