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Original Article

Traumatic Brain Injury: in-hospital Survival Rates and the Main Predictors of in-hospital Mortality in Northeastern Brazil*

Traumatismo cranioencefálico: taxas de sobrevida intrahospitalar e os principais preditores de mortalidade intrahospitalar no nordeste do Brasil

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Abstract

Background Upper middle-income countries have epidemiological peculiarities that should be considered to identify the main predictive factors of intrahospital mortality regarding traumatic brain injury (TBI) to address modifiable problems.

Objective To assess the in-hospital survival of patients with TBI and to identify the predictors of in-hospital death.

Methods This is a retrospective dynamic cohort study of victims of TBI who were admitted to the Hospital de Urgência de Sergipe (HUSE, in the Portuguese acronym) between March 1, 2017 and April 29, 2018. The outcome considered was in-hospital death from any cause. Cox regression was used to assess predictors of in-hospital mortality.

Results The sample comprised 596 patients, with a median age of 31.0 (12–94) years old, 504 (84%) of whom were men. Regarding TBI severity, 250 had mild TBI; 121 had moderate TBI; and 225 had severe TBI. The average follow-up was 20.6 ± 4.0 days, with 60 in-hospital deaths and a 30-day mortality of 22.9%. Four independent predictors of in-hospital death were identified: acute subdural hemorrhage (ASDH) (risk ratio [RR] = 1.926; 95% confidence interval [CI] = 1.15–3.22; $p = 0.013$), swelling (risk ratio

Keywords
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- mortality
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[RR] = 3.706; 95%CI = 2.21–6.19; $p < 0.001$), skull fracture (RR = 2.551; 95%CI = 1.36–4.75; $p = 0.003$), and severe TBI (RR = 2.039; 95%CI = 1.29–4.12; $p = 0.005$).
Conclusions Acute subdural hemorrhage, swelling, skull cap fracture, and a Glasgow Coma Scale score of < 9 at admission were independent predictors of in-hospital mortality in patients with TBI.

Resumo

Introdução Os países de renda média alta possuem peculiaridades epidemiológicas que devem ser levadas em consideração para identificar os principais fatores preditivos de mortalidade intrahospitalar por traumatismo cranioencefálico (TCE) a fim de abordar problemas modificáveis.
Objetivo Avaliar a sobrevida hospitalar de pacientes com TCE e identificar os preditores de óbito hospitalar.
Métodos Trata-se de um estudo de coorte dinâmico retrospectivo de vítimas de TCE que deram entrada no Hospital de Urgência de Sergipe (HUSE) entre 1° de março de 2017 e 29 de abril de 2018. O desfecho considerado foi óbito hospitalar por qualquer causa. A regressão de Cox foi usada para avaliar os preditores de mortalidade hospitalar.
Resultados A amostra foi composta por 596 pacientes, com idade mediana de 31,0 (12–94) anos, sendo 504 (84%) homens. Em relação à gravidade do TCE, 250 tiveram TCE leve; 121 tiveram TCE moderado, e 225 tiveram TCE grave. O seguimento médio foi de 20,6 ± 4,0 dias, com 60 óbitos hospitalares e mortalidade em 30 dias de 22,9%. Quatro preditores independentes de morte hospitalar foram identificados: hemorragia subdural aguda (ASDH, na sigla em inglês) (risk ratio [RR] = 1,926; intervalo de confiança [IC] 95% = 1,15–3,22; $p = 0{,}013$), inchaço (RR = 3,706; IC95% = 2,21–6,19; $p < 0{,}001$), fratura de crânio (RR = 2,551; IC95% = 1,36–4,75; $p = 0{,}003$) e TCE grave (RR = 2,039, IC95% = 1,29–4,12; $p = 0{,}005$).
Conclusões Hemorragia subdural aguda, edema, fratura da calota craniana e pontuação na Escala de Coma de Glasgow < 9 na admissão foram preditores independentes de mortalidade hospitalar em pacientes com TCE.

Palavras-chave
- país em desenvolvimento
- mortalidade
- sobrevivência
- traumatismo cranioencefálico

Introduction

Trauma is one of the main causes of global morbidity and mortality, and traumatic brain injury (TBI) is responsible for more global death and disability than any other traumatic injury,[1] especially among adolescents and young adults.[2,3] The rates are highest in low- and middle income countries (LMICs), such as Brazil, mainly for socioeconomic reasons.[3] Moreover, TBI victims put great pressure on health services, not only regarding their initial emergency treatment, but also the treatment of long-term sequelae such as motor and cognitive deficits. In Brazil, the estimated incidence of TBI ranges from 26.2 to 65.7 per 100,000 inhabitants, with overall lethality rate estimated at 7.7%, and 33.3% for those with severe TBI.[4] Hospital mortality has been estimated to be 5.1 per 100,000 inhabitants per year.[3]

The hospital considered in the present study is located in the Northeast of Brazil, an area which is marked by poor education, poverty, and increased levels of violence. The incidence of traffic accidents in the region is high and is the main cause of TBI. Frequent cases of driving while intoxicated by alcohol or riding a motorcycle without a helmet result in significant levels of severe TBI cases. Despite efforts to reduce these behaviors, limited resources mean that the oversight of traffic is still poor. Furthermore, the Northeast of Brazil is the most violent region in the country, which results in more cases of TBI caused by aggression and the use of firearms.

Another important factor in LMICs is the lack of resources in health units, such as the equipment required to undertake a computed tomography (CT) scan, especially outside major urban centers, where there is less access to healthcare and emergency medical services. Patients, therefore, have to be transferred to referral hospitals, which can delay treatment, resulting in reduced survival rates when compared with high-income countries.

In general, there is a lack of studies on TBI in LMICs, including in Brazil. The present study, therefore, aims to assess the in-hospital survival of patients with TBI and to identify the predictors of in-hospital death from any cause in a reference hospital in Northeastern Brazil.

Methods

Study Design

This is a dynamic retrospective cohort study comprising 596 TBI patients admitted to the Hospital de Urgência de Sergipe (HUSE, in the Portuguese acronym), a tertiary care center in the city of Aracaju, state of Sergipe, in Northeastern Brazil, between March 1, 2017, and April 29, 2018. The survival of patients suffering from acute TBI was investigated using demographic, clinical, and tomographic parameters. The outcome was in-hospital death from any cause. Patients were censored at discharge.

Data Collection

For each patient, their clinical and tomographic records at admission and during hospitalization were evaluated. Epidemiological data and information on the trauma mechanism were also collected. The Glasgow Coma Scale (GCS) assessment was performed by the neurosurgeon at the initial assessment and TBI was considered mild when the GCS score was 14 to 15, moderate when between 9 and 13, and severe when ≤ 8.

Headache, nausea, vomiting, and dizziness were not evaluated in patients who arrived at the hospital with an altered level of consciousness and without companions, unless it was reported in the prehospital evaluation record. Alcohol and drug intoxication were considered positive when reported by the patient or described in the medical record by a companion. Hypoxia at admission was measured by pulse oximeter and only considered when saturation was $< 92\%$.

Data that could not be obtained in the initial interview or from medical records were considered missing values. Mild cases who did not require hospitalization or patients who lacked tomographic data were excluded from the study.

Statistical Analysis

Categorical variables were presented as percentages and continuous variables were represented by means $\pm$ standard deviation (SD). Cox regression in a univariate and multivariate manner was used to assess the risks factors for in-hospital death from any cause. The variables included in the multivariate model were all those with $p < 0.05$ in the univariate analysis. Any multicollinearity problems were solved before the variables were inserted in the model. The backward method of variable selection was used. The variables that remained in the model were tested for possible interactions. The risk proportionality assumption was tested using Schoenfeld residues for each of the variables that remained in the final model. The method that was used to estimate the probabilities of survival was the Kaplan-Meier method. Values of $p < 0.05$ were considered significant. IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis.

Results

The median age of the patients was 31.0 (12–94) years old, 504 (84%) being male. Out of the total of 596 patients, 225 were considered severe on admission (►**Table 1**).

The direct photomotor reflex (DPR) was absent in at least 1 eye in 76 (12.7%) cases, but it was not an independent predictor of in-hospital mortality (►**Table 2**).

Regarding tomographic data, there were 316 (52.5%) cases of traumatic subarachnoid hemorrhage (SAH), 125 (20.9%) cases of epidural hematoma (EDH), 166 (27.8%) cases of acute subdural hematoma (ASDH), 76 (12.7%) cases of swelling, 332 (55.3%) of skull cap fractures, and 315 (52.8%) skull base fractures.

Using Cox regression, potential risk factors for in-hospital death from any cause were identified (►**Table 2**). After multivariate analysis, the study identified 4 independent predictors of in-hospital death in this cohort: ASDH (risk ratio [RR] = 1.926; 95% confidence interval [CI] = 1.15–3.22; $p = 0.013$); swelling (RR = 3.706; 95%CI = 2.21–6.19; $p < 0.001$), skull cap fracture (RR = 2.551; 95%CI = 1.36–4.75; $p = 0.003$), and severe TBI (RR = 2.039; 95%CI = 1.29–4.12; $p = 0.005$) (►**Table 3**).

Most clinical data were not independent predictors of death, except for severe TBI. The mean follow-up was 20.6 ± 4.0 days, with a death rate in 30 days of 22.9%. At the end of the period, there were 60 in-hospital deaths. (►**Fig. 1**). The median survival of patients suffering from ASDH was 58 days with a standard error of 49 days (►**Fig. 2**); from skull cap fracture, it was 172 days with a standard error of 82 days (►**Fig. 3**); from swelling, it was 41 days with a standard error of 20 days (►**Fig. 4**); and from severe TBI, it was 172 days with a standard error of 62 days (►**Fig. 5**).

Discussion

The present dynamic cohort study aimed to analyze the in-hospital survival of TBI victims, as well as the main predictors of in-hospital mortality from any cause. The 30-day survival rate was 22.9%. Independent predictors of death were both variables associated with primary damage (skull cap fracture and ASDH), and characteristics related to secondary injury (swelling). In addition, severe TBI proved to be a predictor of death in these patients, being an important indicator of severity on admission.

The number of cases of TBI increases each year in Brazil; the main cause is automobile accidents, both in adolescents and young adults,[1,5] and in the age group from 21 to 60 years old. Falls are the second major cause, affecting mainly the pediatric and geriatric population.[5] Some studies indicate that there is a relationship between older age and higher mortality,[6,7] even in cases of mild TBI.[6] However, there is no consensus on an appropriate cutoff; an age between 45 and 50 years old is generally suggested, with higher mortality in the first 14 days in this age group.[8,9] In other studies, age has been more related to functional recovery than mortality.[10] In the present cohort, age was not a significant predictor of mortality, even when different extracts were explored. This may result from the limitations of the power of the study', or it may correspond to particular characteristics of the population. In Northeastern Brazil, it is common for young people to drive at high speed, to drive when intoxicated, and to not use a helmet when riding a motorbike; this is reflected in the

Table 1 Characteristics of the population hospitalized by TBI

Characteristics	Value
Number of patients	596
Age (median)	31.0 (12–94) Years old
Sex	
Male	504
Female	92
GCS at admission	
Mild (14–15)	250 (41,7%)
Moderate (9–13)	121 (20,2%)
Severe (3–8)	225 (37,5%)
Pupillary reactivity	
Absence of DPR	76 (12,7%)
Anisocoria	68 (11,3%)
Alcohol	246 (41,0%)
Loss of consciousness	481 (80,2%)
Hypoxemia	275 (46,1%)
OTI	250 (41,7%)
Racoon Sign	119 (19,8%)
Battle Sign	31 (5,2%)
Eyelid edema	307 (51,2%)
Otorrhagia	153 (25,5%)
Rhinorrhagia	192 (32,0%)
CT findings	
EDH	125 (20,9%)
AHSD	166 (27,8%)
SAH	316 (52,5%)
Swelling	76 (12,7%)
Skull cap fracture	332 (55,3%)
Skull base fracture	315 (52,8%)
Depressed skull fracture	83 (13,8%)
MLS > 5mm	75 (12,5%)
Unlit Cisterns	61 (10,2%)
Unlit Sulcus	210 (35,0%)
Marshall	
I	100 (16,7%)
II	353 (58,8%)
III	72 (12,0%)
IV	72 (12,0%)
Neurological surgery	110 (18,3%)

Abbreviations: ASDH, acute subdural hemorrhage; CT, computed tomography; DPR, direct photomotor reflex; EDH, epidural hematoma; GCS, glasgow coma scale; MLS, midline shift; OTI, orotracheal intubation; SAH, subarachnoid hemorrhage.

cohort of the present study, with 41% of the patients being intoxicated at the time of admission. This may lead to more severe traumas than those caused by falls in older adults. Otherwise, the elderly seem to have the worst recovery from TBI.[11]

Traumatic brain injury is responsible for 30% of trauma deaths, and those who survive may remain extremely debilitated.[1] Survival and life expectancy in patients suffering from TBI are reported as being significantly reduced when compared with the general population.[12] It depends on prehospitalization and treatments that can control intracerebral pressure.[13,14] A study in Finland that included 5 neurosurgery intensive care units (ICUs), showed 30-day mortality rates after TBI of 18%,[15] ranging from 23 to 26% in cases of moderate-to-severe TBI. Falls were the main cause of trauma in this study, followed by traffic accidents. Age and GCS scores were the strongest predictors of mortality rates.[15] A study that used data from the Brain Trauma Foundation database in New York showed that 23% of the patients died within 14 days of the TBI,[16] with older age, unreactive pupils, and poor GCS motor scores being associated with mortality. In contrast, a study of a Chinese cohort of 13,138 patients showed that the overall 30-day mortality rate was 5%, and 20% in cases of severe TBI.[17] A study performed in São Paulo, Brazil's largest city, located in the Southeastern region of the country, showed intrahospital mortality rates from TBI of 10.2%,[18] with 1-to-7-day mortality of 60.9%, with falls being the main cause. In the present study, the mortality rates were of 10.6%, and the 30-day mortality was of 22.9%, with mortality being associated with four factors: ASDH, swelling, skull cap fracture, and severe TBI with swelling being the factor with the strongest association with mortality. Severe TBI may be more related to traffic accidents and violence, factors that are more prevalent in the Northeast region of Brazil. This can be seen in another study from the state of Maranhão, in which 58.1% of hospital admissions were for TBI resulting from a traffic accident, and 14.5% resulting from aggression.[19]

The incidence of TBI is around five times higher in men than in women.[1,3] This is because men have greater risk behaviors for TBI, such as traffic accidents and violence.[20] However, some studies show that women have higher mortality rates.[21] The influence of gender on survival remains controversial, and does not appear to be a significant predictor of mortality, as was found in the present study. Likewise, despite the well-known association between intoxication and TBI, the use of drugs and alcohol was not reflected in increased mortality, which was also reported in a study by Signorini[9] undertaken in the United Kingdom.

Among the clinical prognostic factors, pupillary reaction, hypoxemia, and arterial hypotension have previously been shown to be significant prognostic factors in several studies.[8,22–24] These factors are highly prevalent, occurring in ~ 80% of cases, both before and after hospital admission.[24] The absence of pupillary reaction, for example, is an important sign of severity in clinical practice,[23,24] being a clinical indication of intracranial hypertension. This is especially significant in cases of bilateral mydriasis, which is associated with increased mortality at 48 hours, 6 months, and 1 year.[25]

Hypoxemia is also related to higher mortality. This, perhaps, is due to the fact that it is frequently accompanied by

Table 2 Univariate analysis of predictors of in-hospital death from any cause (Cox regression)

Variable	RR	CI 95%	*p-value*
GCS	0.87	0.82–0.92	< 0.001
Severity	1.91	1.36–2.67	< 0.001
Hypoxemia	3.27	1.72–6.24	< 0.001
OTI	3.51	1.91–6.42	< 0.001
Face trauma	0.62	0.40–0.96	0.034
Presence of DPR	0.27	0.16–0.43	< 0.001
Contusion	1.91	1.20–3.05	0.006
ASDH	1.92	1.15–3.22	0.013
SAH	2.56	1.50–4.38	0.001
Skull cap fracture	2.55	1.36–4.75	0.003
Depressed skull fracture	1.71	1.02–2.88	0.041
MLS > 5mm	3.24	2.05–5.12	< 0.001
Unlit sulcus	2.46	1.55–3.91	< 0.001
Swelling	3.70	2.21–6.19	< 0.001
Conduct	1.67	1.05–2.65	0.028
Neurosurgical conduct	1.65	1.03–2.63	0.036
Severe TBI	2.03	1.29–4.12	0.005

Abbreviations: ASDH, acute subdural hemorrhage; CT, computed tomography; DPR, direct photomotor reflex; EDH, epidural hematoma; GCS, glasgow coma scale; MLS, midline shift; OTI, orotracheal intubation; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.

hypercapnia, which, in turn, promotes cerebral edema, and consequently increases intracranial pressure.[24] A previous study showed that patients who are submitted to endotracheal intubation have higher mortality rates compared with patients who do not need such measure.[26]

Arterial hypotension was not evaluated in the present cohort, but has been shown to be a relevant predictor of survival in other studies, and is strongly associated with worse outcomes.[7] In some studies, it has been reported to be the clinical parameter most strongly associated with mortality.[23,24] In our study, the absence of DPR and hypoxemia were predictors of mortality in the univariate analysis, but did not remain as such in the multivariate analysis. This may be due to the fact that the absence of DPR and hypoxemia are closely related to the severity of TBI variable, which ended up performing better in the statistical model. In other words, DPR and hypoxemia, in this population, did not confer an additional mortality risk to the proposed statistical model.

Although GCS is one of the main tools for assessing patients with |TBI, some studies suggest that it is not a good predictor of mortality, with an area under the receiver operating characteristic (ROC) curve of 0.64.[8] However, some studies show that the GCS has an almost linear relationship with mortality in the first 14 days of TBI,[8] and there seems to be a clear association between a decreased GCS score and lethality in polytrauma patients.[9,27] A GCS of 15 would be equivalent to 1% lethality. In those with an GCS of 4, we would have a lethality of 27%,[27] with an increase in continuous and almost linear lethality over the entire scale.[7] In our cohort, GCS severity proved to be an independent predictor of mortality and was an easy clinical parameter to obtain. Patients who had a GCS score < 9 had a 2-fold greater risk of dying during hospitalization.

Tomographic aspects have also been shown to be good predictors of mortality in the literature.[7] The appearance of the subarachnoid cisterns, the number of contusions, the appearance of the 4th ventricle, swelling, midline deviation, the presence of subdural hematoma, subarachnoid hemorrhage or intraventricular hemorrhage, and the volume of cranial injury have already been described as predictors of death

Table 3 Multivariate analysis of predictors of in-hospital death from any cause (Cox regression)

Variable	RR	95%CI	*p-value*
ASDH	1.926	1.150–3.224	0.013
Skull cap fracture	2.551	1.368–4.755	0.003
Swelling	3.706	2.218–6.192	< 0.001
Severe TBI	2.039	1.292–4.127	0.005

Abbreviations: ASDH, acute subdural hemorrhage; CI, confidence interval; RR, risk ratio; TBI, traumatic brain injury.

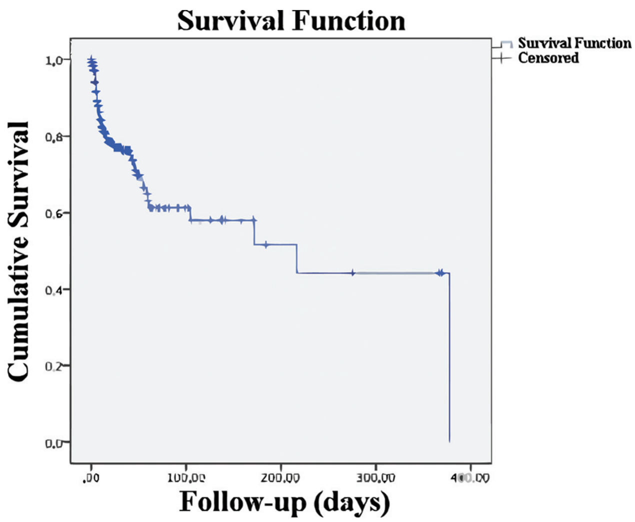

Fig. 1

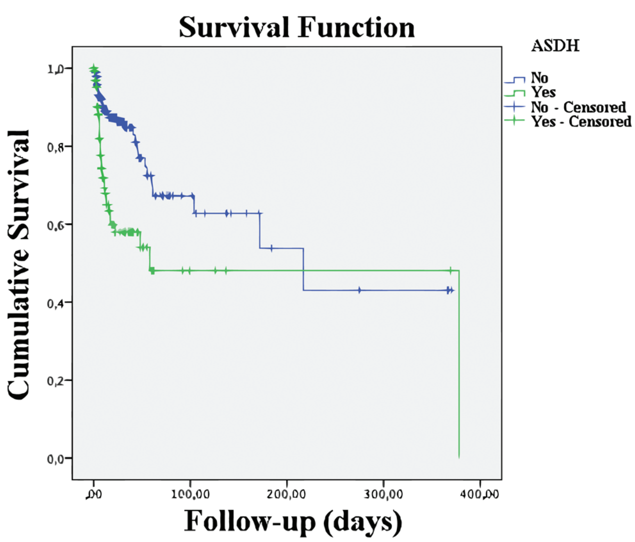

Fig. 2

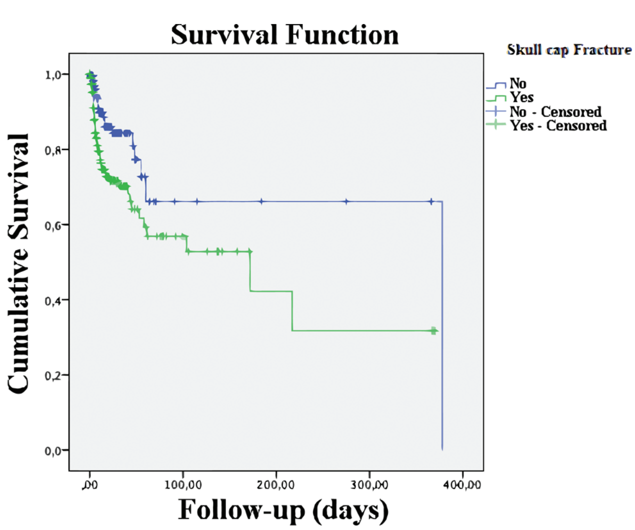

Fig. 3

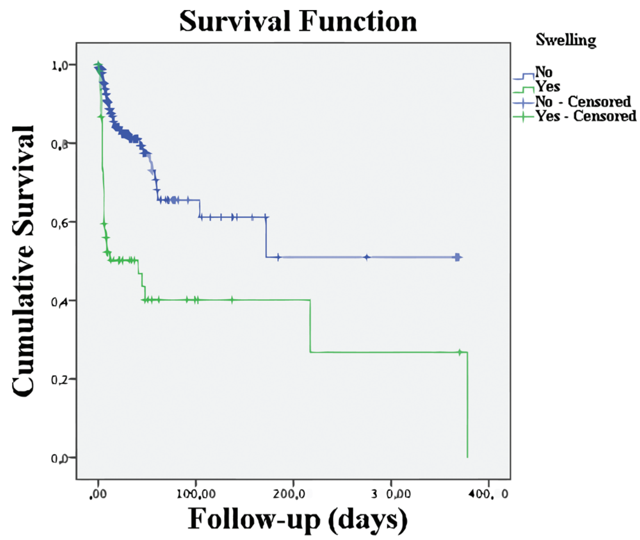

Fig. 4

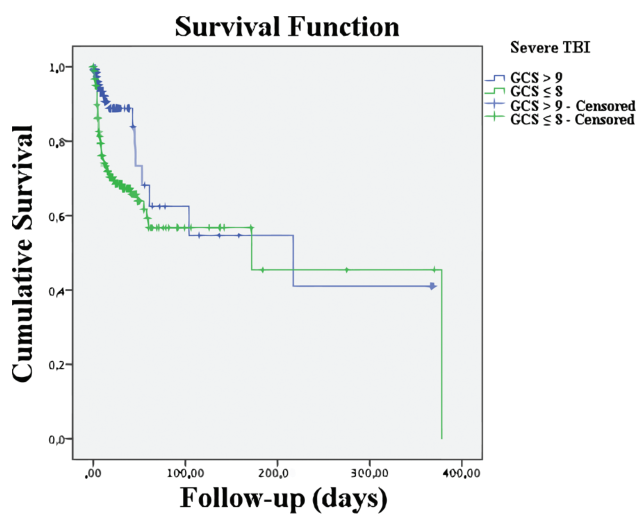

Fig. 5

associated with higher mortality in the first 48 hours after the injury.[8,9] In addition, cerebral edema detected on initial CT is considered an independent predictor of intrahospital mortality.[28] In the current study, skull cap fracture, swelling, and ASDH were important independent predictors of mortality in the multivariate analysis that were identified by tomography. Probably the skull cap fracture implies a worse prognosis, as a factor equivalent to a trauma of greater energy.

Other predictors of outcome scores are available, such as the Injury Severity Score (ISS), the CRASH basic score and the IMPACT core score, which have already proved effective in other populations. The ISS has been shown to present great sensitivity and specificity to predict in-hospital death in patients suffering from severe TBI, with AUC of 0.76 on the ROC curve.[25] Regarding the CRASH and IMPACT scores, a study by Maeda et al., which researched the applicability of these scores in the Japanese population in victims of severe TBI, found that they were both effective, with AUC scores of 0.86 and 0.81, respectively.[29]

De Silva et al. showed in their study using the CRASH score that patients in LMICs had a greater chance to die following a TBI than patients in high-income countries, with patients with severe TBI being twice (OR 2,23; 95%CI) as likely to die.[30] Unfortunately, a lack of information made it impossible to use these scores in this cohort. The applicability of these scores in northeastern Brazil must be tested in future studies.

Despite not being investigated in this cohort, laboratory parameters deserve due attention, since serum glucose, platelet count, and hemoglobin levels have also been shown to be independent predictors of survival.[23]

Conclusion

Understanding the independent predictors of mortality is of fundamental importance for the survival of patients suffering from TBI, in addition to serving as a substrate for clinical practices and informing public health policies. Acute subdural hematoma, swelling, skull cap fracture, and a GCS score < 9 at admission were independent predictors of intrahospital mortality from any cause in in patients hospitalized for TBI at the HUSE.

Conflict of Interests
The authors have no conflict of interests to declare.

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