Predicting Outcomes in Traumatic Brain Injury Using the Glasgow Coma Scale: A Joint Modeling of Longitudinal Measurements and Time to Event

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Abstract

Background: Traumatic brain injury (TBI) is an important public health problem throughout the world. Objectives: The aim of this study was to assess repeated glasgow coma scale (GCS) scores in predicting the severity of TBI and patients’ survival.

Patients and Methods: In this longitudinal study used a total sample of 239 patients, all of whom were hospitalized with traumatic brain injuries. Subjects were selected by simple random sampling in intensive care unit (ICU) wards of the Shahid Beheshti hospital in Kashan, Iran between September 2008 and September 2010. The patients’ level of consciousness was evaluated using GCS at admission, six hours after admission to the ICU, and at the time of discharge from the hospital. A Glasgow outcome score (GOS) is used to classify the global outcomes in TBI survivors. A joint modeling approach was utilized for data analysis using R software.

Results: The results showed that female patients had the risk of occurrence, slightly more than men, but this was not significant (HR =1.095 P = 0.757). The mortality risk was significantly higher in older patients (HR = 1.010, P = 0.010). In addition, the results indicated a significant increasing linear trend in GCS values over time (HR=1.78, P=0.003). Higher age was also associated with lower GCS values over time (P < 0.001). The severity of TBI decreases with increasing GCS values (P < 0.001).

Conclusions: By jointly modeling longitudinal data with time-to-event outcomes, our findings supported the use of the GCS scores in predicting the severity of TBI.

Keywords: Glasgow Coma Scale, Brain Injuries, Glasgow Coma Scale, Brain Injuries, Glasgow Coma Scale, Survival Analysis

1. Background

Traumatic brain injury (TBI) is an important public health problem worldwide. It is often referred to as the “silent epidemic” since the complications from TBI, such as changes affecting sensation, thinking, emotions, or language, may not be readily apparent. Moreover, understanding of TBI among the general public is limited (1-4).

The global incidence rate of TBI is estimated at 200 per 100,000 people per year (5, 6). According to the centers for disease control and prevention (CDC), about 1.1 million emergency room visits; 235,000 hospitalizations; and 50,000 deaths occur each year as a result of TBI. Still, the actual incidence of TBI may be even higher, because many mild TBIs are never seen in the emergency room (7, 8). Rutland-Brown reported an annual estimated 1.6 million TBIs. Thurman estimates that more than 80,000 individuals become disabled from TBIs each year (9). In Iran, the incidence of TBIs is estimated 429 per 100,000 of the population per year (10). The etiological studies in this field are very sparse, in spite of their high incidence rate in Iran.

In fact, TBI consists of a heterogeneous group of pathological disorders, as a result of an external force, and each has its own clinical presentation, pathophysiology, natural history, treatment, and prognosis. Motor vehicle accidents, falls, acts of violence, lightening strikes, sports and recreational injuries, electric shocks, and blows to the head are the leading causes of TBI. Lower socioeconomic status, psychiatric disease, and pre-morbid cognitive, and male gender are the main risk factors for TBI. It may be classified by mechanism of clinical severity, injury, pathology, radiological appearance, or distribution (focal vs. diffuse) (11, 12)
TBI is indicated by new onset of at least of the following clinical signs, quickly following an event: any period of loss of or a reduced level of consciousness, any change in mental status at the time of the injury, any loss of memory of events immediately before or after the injury, neurological deficits that may or may not be transient, intracranial lesion, posttraumatic amnesia (PTA), and length of loss of consciousness (LOC) are the most common clinical indicators used to assess acute brain injury severity. The Glasgow Coma Scale (GCS) is the most widely used tool for assessing the severity of a TBI (13-15).

The GCS was introduced in 1974 by Teasdale and Jennett (13). Scores of GCS are one of the important aspects of classifying TBI severity. Since the GCS scores are regularly monitored over time, more complex statistical methods are needed to determine the relationship between repeated GCS scores and the severity of TBI, in addition to patients’ survival times.

2. Objectives

In this study we utilized a joint modeling of longitudinal measures of GCS scores and TBI survival time, to know whether these indices can be a significant indicator of predicting TBI survival time.

3. Patients and Methods

3.1. Study Participants and Outcomes

In this longitudinal study, the sample size was obtained (n = 232) using the Hsieh and Lavori formula; B = -0.34, α = 0.05 and Design parameter = 0.30 (16), including a five-percent loss, 251 patients hospitalized with traumatic brain injuries were recruited to assess the relationship between repeated GCS scores and the severity of TBI, in addition to patients’ survival times.

In the second step, rejection-free survival was studied using a non-linear specific evolution for the GCS (18). To embed different longitudinal sub-models were analyzed with an only intercept, intercept, and slope analysis and a non-linear specific evolution for the GCS (18). To embed these different kinds of longitudinal submodels in a unified frame, the conditional distribution of (GCS scores for patients) given a vector of random effects was assumed to be a member of the exponential family, given by the following Equation:

\[
g \left[ E \left\{ \frac{y_i(t)}{b_i} \right\} \right] = \eta_i(t)
\]

\[
= x_i^T(t) \beta + z_i^T(t) b_i
\]

Where g denotes a known one-to-one monotonic link function, and \( y_i(t) \) denotes the value of the longitudinal outcome for the i-th subject at time point t, \( x_i(t) \) denotes the time-dependent design vectors for the fixed-effects \( \beta \) and for the random effects \( b_i \), respectively. In the second step, rejection-free survival was studied using...
a Cox model (19). The patient's age, gender (1: male, 2: female), marital status (1: single, 2: married), time reaching the emergency room, having primary anesthesia, trauma type, and injury type were tested as covariates, both in the longitudinal process (which describes the trajectories of GCS) and in the survival process. In each of the processes, the covariate was maintained if its inclusion modified the log-likelihood significantly (P < 0.05). In the last step, the joint model with shared random-effects method was applied (20-23). For this study, we assumed that the risk for an event depended on a function of the subject-specific linear predictor. More specifically (Equation 2).

$$h_i \left( \frac{t}{T_i} (t), w_i \right) = h_0 \left( t \right) \exp \left[ \gamma^T w_i + f \{ \eta_i (t), b_i, \alpha \} \right]$$

(2)

Where, $H_i(t) \in [0, s \leq t]$ denoted the historical events of the underlying repeated measure process up to $t$, $h_0 \left( t \right)$ denoted the baseline hazard function, $w_i$ is a vector of baseline covariates with corresponding regression coefficients $\gamma$. Parameter vector $\alpha$ quantified the association between features of the repeated process up to time $t$ and the hazard for an event at the same time point. So, we proposed a joint model under the maximum likelihood estimation method. The baseline hazard and the survival function were approximated using penalized B-splines and the Gauss-Kronrod quadrature rule, respectively (24). Data were analyzed using R for Windows software (version 3.2.1) (25).

4. Results

In this study, of 241 patients, eight patients were excluded according to the above-detailed criteria. A total sample of 239 TBI patients was assessed. Among them, 208 patients (89.0%) were male. The mean ± SD age of these patients was 35.4 ± 8.6 (from 16.0 to 85.0) years. Table 1 shows more details about the characteristics of the patients under study.

The mean ± SD GCS scores were 7.9 ± 3.7, 7.3 ± 3.2, and 9.5 ± 4.6, respectively at admission, six hours after admission to the ICU, and time of discharge from the hospital. Also, the mean follow up time for each patient was 12.3 ± 13.9 days.

Figures 1 and 2 show Kaplan-Meier estimates and the observed trajectories of GCS, according to the occurrence of the event during the follow-up. We can observe that the GCS scores had random intercept and random trend over time. Therefore, we used a random intercept-random time mixed effects model to assess the effect of different factors on GCS scores over time.

The results of mixed model showed that gender (P = 0.002), time reaching the emergency room (P = 0.017), patient’s age (P = 0.016), and time (P < 0.001) were significantly associated with GCS scores over time (Table 1). We therefore used these significant variables in the advanced joint analysis.

On the other hand, the number of patients with failure and censored outcomes were 92 (38.5%) (72 deaths, 9 persistent vegetative, and 11 severe disability) and 147 (61.5%), respectively. The univariate Cox analysis in Table 1 showed that mortality risk was significantly higher in older patients (P = 0.003), patients with greater time to reach the emergency room (P < 0.001), and patients with primary anesthesia (P < 0.001). There was no apparent relationship between the cause of injury and survival (P = 0.751). Significant variables in this model were added to the joint modeling analysis. The results of the joint model are observed in Table 2. Based on the obtained results, having primary anesthesia (HR = 1.637, P = 0.153) and time to reaching the emergency room were not significantly associated with the hazard of events in the joint model (HR = 1.002, P = 0.152). Female patients had a little more hazard of event than male patients, but it was not significant (HR = 1.095, P = 0.757). The mortality risk was significantly higher in older patients (HR = 1.010, P = 0.010). Additionally, the results demonstrated a significant linear increasing trend in GCS scores over time (HR = 1.78, P = 0.003). Age and anesthesia were associated with GCS values. Higher age was significantly related to lower GCS values over time (P < 0.001). Patients with primary anesthesia (P = 0.014) had a lower mean of GCS values. Moreover, the joint model constructed...
Table 1. Results of Linear Mixed Model and Cox Model for Assessing the Effect of Different Characteristics on GCS Scores

<table>
<thead>
<tr>
<th>Variables</th>
<th>Valuesa</th>
<th>Mixed Model</th>
<th>Cox Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Estimate (SE)</td>
<td>P Value</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>208 (87.00)</td>
<td>Reference Category</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>31 (13.00)</td>
<td>0.390 (0.012)</td>
<td>0.002</td>
</tr>
<tr>
<td>Marriage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>101 (42.30)</td>
<td>Reference Category</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>138 (57.70)</td>
<td>-0.555 (0.599)</td>
<td>0.322</td>
</tr>
<tr>
<td>Primary anesthesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>148 (61.90)</td>
<td>Reference Category</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>89 (37.20)</td>
<td>-0.596 (0.374)</td>
<td>0.112</td>
</tr>
<tr>
<td>Trauma type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>120 (50.20)</td>
<td>Reference Category</td>
<td></td>
</tr>
<tr>
<td>Blunt</td>
<td>108 (45.20)</td>
<td>-1.211 (0.454)</td>
<td>0.081</td>
</tr>
<tr>
<td>Penetrating</td>
<td>11 (4.60)</td>
<td>-1.868 (1.046)</td>
<td>0.075</td>
</tr>
<tr>
<td>Injury type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>207 (88.80)</td>
<td>Reference Category</td>
<td></td>
</tr>
<tr>
<td>Fall and Boll</td>
<td>26 (11.2)</td>
<td>-0.108 (0.338)</td>
<td>0.751</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>-0.041 (1.162)</td>
<td>0.016</td>
</tr>
<tr>
<td>Time of emergency room admission</td>
<td></td>
<td>-0.002 (0.008)</td>
<td>0.007</td>
</tr>
<tr>
<td>Time (trend)</td>
<td></td>
<td>0.981 (0.188)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.

aData are presented as No. (%).
bHR (95%CI) = Hazard rate (95% confidence interval).

by incorporating the mixed-effects process and the survival process showed a significant association between the GCS trajectories and failure outcomes. The risk of failure outcome decreases with increasing GCS values \((\alpha = -0.256, P < 0.001)\).

5. Discussion

The joint modeling of longitudinal and time-to-event data is an active area of statistical research that has received a lot of attention in the recent years \((26-29)\). This study demonstrated that the repeated use of GCS scores could predict the severity of TBI and patients’ survival. Since predictors such as age, gender, and time affect the relationship between the GCS score and TBI severity, we used the joint modeling approach to evaluate the effect of GCS scores on the survival of patients. Our study revealed a strong association between the GCS trajectories and failure outcomes (death and severe disability) \((Table 2)\). Leitgeb showed that patients with low GCS scores had a poor chance of favorable results \((30)\). In a cross-sectional study, Saha et al. had reported that the GCS scores were significantly correlated with GOS in head injury patients \((31)\). The reason for this increased interest is that joint models can be used when focusing or on the survival outcome and we wish to correct for non-random dropout or on the survival outcome \((32)\).

In this study, we observed that the standard error estimates of age, gender, and other covariates in the joint model are less than the Cox model \((Tables 1 and 2)\). Although some studies have demonstrated the male gender as a risk factor for TBI \((33)\), female patients had a little more, yet significant, hazard of event than male patients in our study \((Table 2)\).

Epidemiological studies have produced conflicting re-
Figure 2. Subject-Specific Longitudinal Trajectories for Patients With and Without an Event

Table 2. Results of the Joint Modeling of Time to Events and Longitudinal GCS Scores

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Estimate</th>
<th>SE</th>
<th>CI, 95%</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.5%</td>
<td>97.5%</td>
</tr>
<tr>
<td>Longitudinal process</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.045</td>
<td>0.005</td>
<td>0.019</td>
<td>0.074</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>0.476</td>
<td>0.011</td>
<td>-0.834</td>
<td>1.648</td>
</tr>
<tr>
<td>Time of emergency room admission</td>
<td>-0.0008</td>
<td>0.002</td>
<td>-0.002</td>
<td>0.0001</td>
</tr>
<tr>
<td>Primary anesthesia</td>
<td>-0.779</td>
<td>0.074</td>
<td>-1.541</td>
<td>-0.150</td>
</tr>
<tr>
<td>Time</td>
<td>0.576</td>
<td>0.057</td>
<td>0.118</td>
<td>0.098</td>
</tr>
<tr>
<td>Survival process</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.010</td>
<td>0.006</td>
<td>0.008</td>
<td>0.036</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>0.091</td>
<td>0.353</td>
<td>-0.045</td>
<td>0.897</td>
</tr>
<tr>
<td>Time of emergency room admission</td>
<td>0.0021</td>
<td>0.004</td>
<td>-0.0002</td>
<td>0.003</td>
</tr>
<tr>
<td>Primary anesthesia</td>
<td>0.493</td>
<td>0.024</td>
<td>-1.230</td>
<td>0.223</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>-0.256</td>
<td>0.064</td>
<td>-0.239</td>
<td>-0.079</td>
</tr>
</tbody>
</table>

Results with respect to the effect of gender on mortality and morbidity after trauma (34, 35). Kraus et al. in a prospective cohort of severely and moderately brain injured subjects, reported that deaths from brain injury in females was 1.75 times (95% confidence interval, 1.09 to 2.82). Moreover, females experience poor outcomes (severe disability or persistent vegetative status) 1.57 times more often than males do (36). Chang et al. found that males and females were significantly different in various risk factors and outcomes of work-related traumatic brain injury (wrTBI). They stated that the rate of TBI for males was 1.43 (95% CI 1.35 to 1.53) times that of females (37). In another study, a logistic regression analysis disseminated that gender had no significant effect on TBI mortality (38). Although the impact of gender on TBI outcomes is controversial, it may be concluded that the differences in outcomes were because of the higher mean age of females under studies. Our finding showed that age was associated with GCS values and TBI outcome (Table 2). The obtained results from the linear mixed model and the Cox model showed that increasing...
age decreases GCS scores and increases TBI severity. Mosenthal et al. have reported that, at all levels of head injury, the mortality from TBI is higher in older people (39). Jeremitsky et al. in a retrospective study of patients with severe traumatic brain injury, showed that mortality was related to age and injury severity scores (40).

In this study, we found that patients with primary anesthesia had a lower mean of GCS values. In this context, several studies have reported other factors of TBI (41-43). In addition, another study revealed that early hyperglycemia is associated with poor outcomes for patients with TBI (40). In a prospective cohort study, moderate to severe traumatic brain injury had the greatest incidence of impaired cerebral autoregulation. In addition, impaired cerebral autoregulation and poor outcome were related with hyperemia (44).

The present study has a few limitations that should be considered. As a prospective cohort study, selection bias may have occurred due to loss to follow up; this may affect the association of GCS with severity of TBI and patients’ survival. We calculated a random intercept effect of follow-up for any participant. In this way, differential selection bias was reduced. We did not take into account socioeconomic status or other factors in our analysis. Moreover, this study assessed admitted patients until their discharge from the hospital Therefore, performing a study with longer period of assessment is suggested. Finally, samples were only from a hospital in Kashan, so our findings might not be extrapolated to other parts of Iran.

5.1. Conclusions

Our study revealed a strong association between the GCS trajectories and failure outcome. By jointly modeling longitudinal data with time-to-event outcomes, our findings supported the use of the GCS scores in predicting the severity of TBI. On the other hand, providing preventive programs (such as increasing the amount of people’s awareness and paying more attention to traffic regulations) aimed at decreasing traumatic brain injury could be helpful. Also, different aspects of trauma nursing should be paid more attention.

Acknowledgments

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Footnotes

Authors’ Contribution: Analysis and date interpretation: Neda Gilani, Mohammad Asghari Jafarabadi, Anoshirvan Kazemnejad; drafting of the manuscript: Neda Gilani, Farid Zayeri, Anoshirvan Kazemnejad; critical revision of the manuscript for important intellectual content: Fateme Sadat Izadi Avanji, Anoshirvan Kazemnejad; statistical analysis: Neda Gilani, Mohammad Asghari Jafarabadi; administrative, technical, and material support: Fateme Sadat Izadi Avanji, Anoshirvan Kazemnejad.

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