Iran Red Crescent Med J. 2017 February; 19(2):e29663. doi: 10.5812/ircmj.29663.

Published online 2015 December 28. **Research Article**

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

Neda Gilani,[1,2] Anoshirvan Kazemnejad,[1,*] Farid Zayeri,[3] Mohammad Asghari Jafarabadi,[4] and Fatemeh Sadat Izadi Avanji[5]

[1]Department of Biostatistics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[2]Department of Statistics and Epidemiology, Faculty of Health, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Department of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Road Traffic Injury Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[5]Department of Medical Surgical Nursing, Faculty of Nursing, Kashan University of Medical Sciences, Kashan, Iran

[*]*Corresponding author*: Anoshirvan Kazemnejad, Department of Biostatistics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, IR Iran. Tel: +98-2182883875, Fax: +98-2182884555, E-mail: kazem_an@modares.ac.ir

Received 2015 May 08; **Revised** 2015 June 13; **Accepted** 2015 July 11.

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 Jennet (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 GCS and TBI survival time. The patients were selected by simple random sampling in the (ICU) wards of the Shahid Beheshti hospital in Kashan, Iran between September 2008 and September 2010. This hospital has three ICUs, and one of them is exclusive to trauma patients. The ethical aspects of this study were approved by the institutional ethics committee of Kashan University of Medical Sciences, with code 9218 issued on August 13, 2008. All subjects provided written consent before participation. At admission, these patients were under treatment with an Advanced Traumatic Life Support (ATLS) protocol and, given their circumstances, they were transferred to the ICU. The inclusion criteria were as follows: 16 < age < 65 years, weight > 30 kg, length of stay in the ICU > 24 hours, lack of underlying chronic disorders, absence of corticosteroid use, no history of addiction and lack of trauma in other parts of the body. Patients who died during the 24 hours after admission; had a spinal cord injury, as determined on the basis of radiological or clinical findings; the existence of any type of neurological diseases before TBI; or brain injury with no traumatic causes, such as brain tumors, aneurismal, stroke, and other brain vascular incidences were excluded from the study. There were no limitations on gender, height, time of emergency room admission, traumatic lesions, leading causes of TBI, and type of head injury. After excluding patients with a spinal cord injury (n = 4), aneurismal (n = 3), brain tumor (n = 1), and lost to follow up (n = 4), 239 patients were recruited for analysis.

A checklist was used for data gathering; it consisted of demographic and clinical data (e.g., characteristics of external force, trauma outcome, and the level of consciousness). The level of consciousness was evaluated using GCS at admission, six hours after admission to the ICU, and time of discharge from the hospital. The primary outcomes of the study were patient status as TBI severity and a GCS score as prediction tools.

The Glasgow outcome score (GOS) was used to classify the global outcome in TBI survivors. Patients were assigned to one of five possible outcome categories: death, persistent vegetative state, severe disability, moderate disability, and good recovery (17). In this study, moderate disability and good recovery were considered the success outcomes, and death, persistent vegetative state, and severe disability were failures.

3.2. Statistical Analysis

In the first step, the individual trajectories of GCS obtained from the repeated estimates of the longitudinal explanatory variable were fitted using linear mixed-effect models. 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:

$$g\left[E\left\{\frac{y_i(t)}{b_i}\right\}\right] = \eta_i(t) = x_i^T(t)\beta + z_i^T(t)b_i \quad (1)$$

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, $x_i(t)$, and $z_i(t)$ denotes the time-dependent design vectors for the fixed-effects β 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).

$$h_i\left(\frac{t}{H_i}(t), w_i\right) = h_0(t)\exp\left[\gamma^T w_i + f\{\eta_i(t), b_i, \alpha\}\right] \quad (2)$$

Where, $H_i(t) = [_i(s), 0 \leq s < t]$ denoted the historical events of the underlying repeated measure process up to t, $h_0(t)$ denoted the baseline hazard function, w_i is a vector of baseline covariates with corresponding regression coefficients γ. Parameter vector α 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. IA 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.

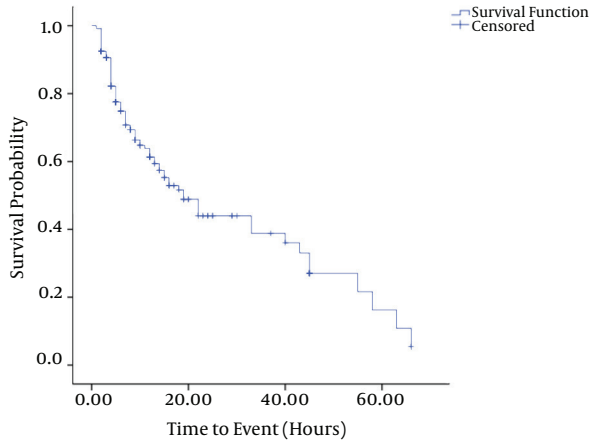

Figure 1. Kaplan-Meier Estimator of Survival Probabilities for the Patients

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

Variables	Values[a]	Mixed Model		Cox Model	
		Estimate (SE)	P Value	HR (95%CI)[b]	P Value
Gender					
Male	208 (87.00)	Reference Category			
Female	31 (13.00)	0.390 (0.012)	0.002	0.843 (0.452,1.573)	0.591
Marriage					
Single	101 (42.30)	Reference Category			
Married	138 (57.70)	-0.555 (0.599)	0.322	1.153 (0.755,1.784)	0.522
Primary anesthesia					
No	148 (61.90)	Reference Category			
Yes	89 (37.20)	-0.596 (0.374)	0.112	2.621 (1.582,4.342)	< 0.001
Trauma type					
None	120 (50.20)	Reference Category			
Blunt	108 (45.20)	-1.213 (0.454)	0.081	1.219 (0.887,1.887)	0.373
Penetrating	11 (4.60)	-1.868 (1.046)	0.075	2.478 (0.819,7.491)	0.108
Injury type					
Vehicle	207 (88.80)	Reference Category			
Fall and Boll	26 (11.2)	-0.108 (0.338)	0.751	1.370 (0.806,2.330)	0.244
Age					
NA	NA	-0.041 (1.162)	0.016	1.016 (1.005,1.027)	0.003
Time of emergency room admission					
NA	NA	-0.002 (0.008)	0.017	1.006 (1.003,1.009)	< 0.001
Time (trend)	NA	0.981 (0.188)	< 0.001	NA	NA

Abbreviation: NA, not available.
[a] Data are presented as No. (%).
[b] HR (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 (α = -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-

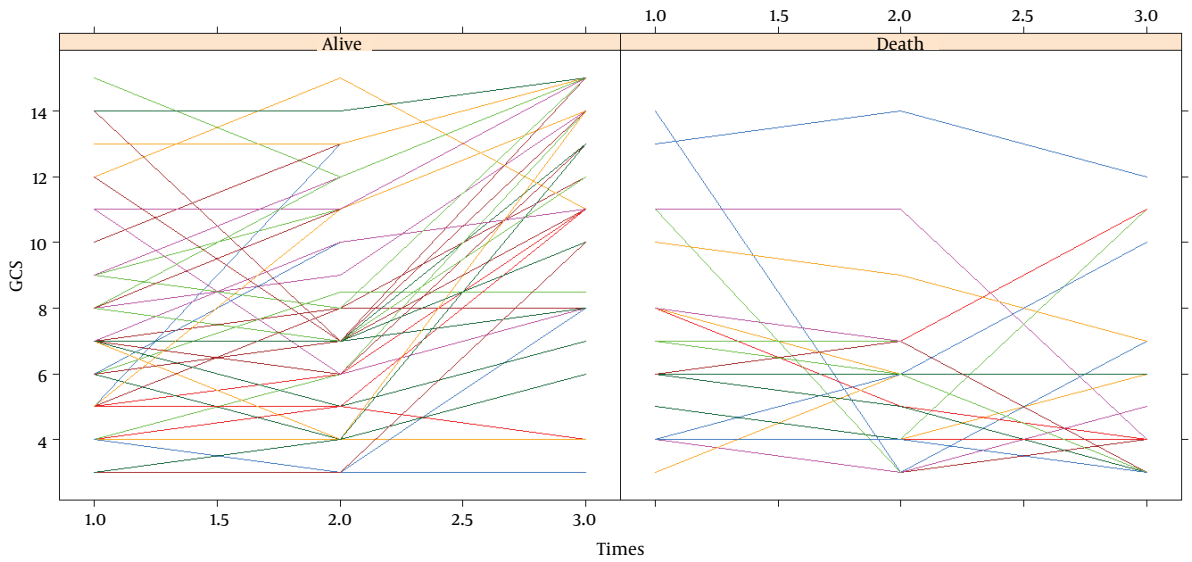

Figure 2. Subject-Specific Longitudinal Trajectories for Patients With and Without an Event

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

Covariate	Estimate	SE	CI, 95%		P Value
			2.5%	97.5%	
Longitudinal process					
Age	-0.045	.005	0.019	0.074	< 0.001
Gender (female)	0.476	.011	-0.834	1.648	0.435
Time of emergency room admission	-0.0008	.0002	-0.002	0.0001	0.167
Primary anesthesia	-0.779	.074	-1.541	-0.150	0.014
Time	0.576	.057	0.118	0.998	0.003
Survival process					
Age	0.010	.006	0.008	0.036	0.010
Gender (Female)	0.091	.353	-1.045	0.897	0.757
Time of emergency room admission	0.0021	.004	-0.0002	0.003	0.152
Primary anesthesia	0.493	.024	-1.230	0.223	0.153
α	-0.256	.064	-0.239	-0.079	< 0.001

sults 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

The authors thank the trauma research center of Kashan University of Medical Sciences for their invaluable assistance with data procurement.

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.

Funding/Support: This study was supported in part by the Medical Sciences Faculty of Tarbiat Modares University, Tehran, Iran.

References

1. Faul M, Xu L, Wald M, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths 2002-2006. Atlanta; National Center for Injury Prevention and Control. 2010.. .
2. Thurman DJ. The Epidemiology of Traumatic Brain Injury in Children and Youths: A Review of Research Since 1990. *J Child Neurol.* 2014 doi: 10.1177/0883073814544363. [PubMed: 25123531].
3. Corrigan JD, Selassie AW, Orman JA. The epidemiology of traumatic brain injury. *J Head Trauma Rehabil.* 2010;**25**(2):72–80. doi: 10.1097/HTR.0b013e3181ccc8b4. [PubMed: 20234226].
4. Prevention NCFI . Report to Congress on mild traumatic brain injury in the United States: Steps to prevent a serious public health problem. Centers for Disease Control and Prevention. 2003. .
5. Bryan-Hancock C, Harrison J. The global burden of traumatic brain injury: preliminary results from the Global Burden of Disease Project. *Injury Prevent.* 2011;**16**(Supplement 1):A17. doi: 10.1136/ip.2010.029215.61.
6. Andelic N. The epidemiology of traumatic brain injury. *Lancet Neurol.* 2013;**12**(1):28–9. doi: 10.1016/s1474-4422(12)70294-6.
7. Langlois JA, Rutland-Brown W, Thomas KE. The incidence of traumatic brain injury among children in the United States: differences by race. *J Head Trauma Rehabil.* 2005;**20**(3):229–38. [PubMed: 15908823].
8. Weiner MF, Lipton AM. The American Psychiatric Publishing textbook of Alzheimer disease and other dementias. American Psychiatric Pub; 2009.
9. Thurman DJ, Coronado VG, Selassie AW. The epidemiology of TBI: implications for public health. *Brain Injury Med Principles prac.* 2007:45–56.
10. fakharian S, Fazel M, Tabesh H, Navabi Z. The Incidence and Cost of mild traumatic brain injury in Kashan. *Feyz.* 2007;**11**(3):63–7.
11. Ponsford MJ, Medana IM, Prapansilp P, Hien TT, Lee SJ, Dondorp AM, et al. Sequestration and microvascular congestion are associated with coma in human cerebral malaria. *J Infect Dis.* 2012;**205**(4):663–71. doi: 10.1093/infdis/jir812. [PubMed: 22207648].
12. Roebuck-Spencer T, Cernich A. Epidemiology and societal impact of traumatic brain injury. Handbook on the neuropsychology of traumatic brain injury.: Springer;. ; 2014. pp. 3–23.
13. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet.* 1974;**2**(7872):81–4. [PubMed: 4136544].
14. Ishibe N, Wlordarczyk RC, Fulco C. Overview of the institute of medicine's committee search strategy and review process for gulf war and health: long-term consequences of traumatic brain injury. *J Head Trauma Rehabil.* 2009;**24**(6):424–9. doi: 10.1097/HTR.0b013e3181c13426. [PubMed: 19940675].
15. Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. *Lancet.* 2012;**380**(9847):1088–98. doi: 10.1016/S0140-6736(12)60864-2. [PubMed: 22998718].

16. Hsieh FY, Lavori PW. Sample-size calculations for the Cox proportional hazards regression model with nonbinary covariates. *Control Clin Trials.* 2000;**21**(6):552–60. [PubMed: 11146149].
17. Wright J. *Glasgow Outcome Scale. Encyclopedia of Clinical Neuropsychology: Springer;.* 2011:1150–1152.
18. Diggle P, Heagerty P, Liang KY, Zeger S. Analysis of longitudinal data. Oxford University Press; 2002.
19. Kleinbaum DG. Survival Analysis, a Self-Learning Text. *Biometrical Journal.* 1998;**40**(1):107–8.
20. Rizopoulos D. Joint models for longitudinal and time-to-event data: With applications in R. CRC Press; 2012.
21. Rizopoulos D. JMbayes: joint modeling of longitudinal and time-to-event data under a Bayesian approach. R package version 0.6-1 2014.. Available from: http://arxiv.org/abs/1404.7625.
22. Malehi AS, Hajizadeh E, Ahmadi K, Mansouri P. Assessing the Autoantibody levels in Relation to Recurrence of Pemphigus: Joint Modeling of Longitudinal Measurements and Recurrent Event Times. *Iran Red Crescent Med J.* 2014;**16**(2):e13812. .
23. Mansourian M, Kazemnejad A, Kazemi I, Zayeri F, Soheilian M. Bayesian analysis of longitudinal ordered data with flexible random effects using McMC: application to diabetic macular Edema data. *J Appl Statistics.* 2012;**39**(5):1087–100. doi: 10.1080/02664763.2011.638367.
24. Rizopoulos D. JM: An R Package for the Joint Modelling of Longitudinal and Time-to-Event Data. *J Statistical Software.* 2010;**35**(9):1–33. doi: 10.18637/jss.v035.i09.
25. Team RC. A Language and Environment for Statistical Computing (2014) 2015.. Available from: http://www. r-project.
26. Crowther MJ. Development and application of methodology for the parametric analysis of complex survival and joint longitudinal-survival data in biomedical research. Department of Health Sciences; 2015.
27. Ekinci EI, Moran JL, Thomas MC, Cheong K, Clarke S, Chen A, et al. Relationship between urinary sodium excretion over time and mortality in type 2 diabetes. *Diabetes Care.* 2014;**37**(4):e62–3. doi: 10.2337/dc13-1947. [PubMed: 24652730].
28. Njagi EN, Rizopoulos D, Molenberghs G, Dendale P, Willekens K. A joint survival-longitudinal modelling approach for the dynamic prediction of rehospitalization in telemonitored chronic heart failure patients. *Statistical Model.* 2013;**13**(3):179–98. doi: 10.1177/1471082x13478880.
29. Zangwill LM, Boer ER, Weinreb RN, Medeiros FA. Association Between Progressive Retinal Nerve Fiber Layer Loss and Longitudinal Change in Quality of Life in Glaucoma 2014.. Available from: http://archopht.jamanetwork.com/.
30. Leitgeb J, Mauritz W, Brazinova A, Majdan M, Janciak I, Wilbacher I, et al. Glasgow Coma Scale score at intensive care unit discharge predicts the 1-year outcome of patients with severe traumatic brain injury. *Eur J Trauma Emerg Surg.* 2013;**39**(3):285–92. doi: 10.1007/s00068-013-0269-3. [PubMed: 23762202].
31. Saha AK, Khan AH, Islam KMT, Hossain M, Sarker AC, Khair A, et al. A study of Correlation Between motor Component of GCS score on Admission and Glasgow Outcome scale Score at Discharge in head injured Patients who underwent Surgical intervention. *Bangladesh Medical Journal.* 2014;**40**(2) doi: 10.3329/bmj.v40i2.18509.
32. Barrett J, Diggle P, Henderson R, Taylor-Robinson D. Joint modelling of repeated measurements and time-to-event outcomes: flexible model specification and exact likelihood inference. *J R Stat Soc Series B Stat Methodol.* 2015;**77**(1):131–48. doi: 10.1111/rssb.12060. [PubMed: 25866468].
33. Levine JM, Kumar MA. Traumatic brain injury. Neurology Continuing Education Conference. Texas. .
34. Coimbra R, Hoyt DB, Potenza BM, Fortlage D, Hollingsworth-Fridlund P. Does sexual dimorphism influence outcome of traumatic brain injury patients? The answer is no!. *J Trauma.* 2003;**54**(4):689–700. doi: 10.1097/01.TA.0000058314.31655.5F. [PubMed: 12707530].
35. Farace E, Alves WM. Do women fare worse: a metaanalysis of gender differences in traumatic brain injury outcome. *J Neurosurg.* 2000;**93**(4):539–45. doi: 10.3171/jns.2000.93.4.0539. [PubMed: 11014529].
36. Kraus JF, Peek-Asa C, McArthur D. The independent effect of gender on outcomes following traumatic brain injury: a preliminary investigation. *Neurosurg FOCUS.* 2000;**8**(1):1–7. doi: 10.3171/foc.2000.8.1.156.
37. Chang VC, Ruseckaite R, Collie A, Colantonio A. Examining the epidemiology of work-related traumatic brain injury through a sex/gender lens: analysis of workers' compensation claims in Victoria, Australia. *Occup Environ Med.* 2014:102097.
38. Leitgeb J, Mauritz W, Brazinova A, Janciak I, Majdan M, Wilbacher I, et al. Effects of gender on outcomes after traumatic brain injury. *J Trauma.* 2011;**71**(6):1620–6. doi: 10.1097/TA.0b013e318226ea0e. [PubMed: 21808209].
39. Mosenthal AC, Lavery RF, Addis M, Kaul S, Ross S, Marburger R, et al. Isolated Traumatic Brain Injury: Age Is an Independent Predictor of Mortality and Early Outcome. *J Trauma Injury Infect Crit Care.* 2002;**52**(5):907–11. doi: 10.1097/00005373-200205000-00015.
40. Jeremitsky E, Omert LA, Dunham CM, Wilberger J, Rodriguez A. The Impact of Hyperglycemia on Patients With Severe Brain Injury. *J Trauma Injury Infect Crit Care.* 2005;**58**(1):47–50. doi: 10.1097/01.ta.0000135158.42242.b1.
41. Algattas H, Huang JH. Traumatic Brain Injury pathophysiology and treatments: early, intermediate, and late phases post-injury. *Int J Mol Sci.* 2014;**15**(1):309–41. doi: 10.3390/ijms15010309. [PubMed: 24381049].
42. Ripley DL, Morey CE, Gerber D, Harrison-Felix C, Brenner LA, Pretz CR, et al. Atomoxetine for attention deficits following traumatic brain injury: results from a randomized controlled trial. *Brain Inj.* 2014;**28**(12):1514–22. doi: 10.3109/02699052.2014.919530. [PubMed: 25180876].
43. Suehiro E, Koizumi H, Kunitsugu I, Fujisawa H, Suzuki M. Survey of brain temperature management in patients with traumatic brain injury in the Japan neurotrauma data bank. *J Neurotrauma.* 2014;**31**(4):315–20. doi: 10.1089/neu.2013.3057. [PubMed: 24047191].
44. Vavilala MS, Bowen A, Lam AM, Uffman JC, Powell J, Winn HR, et al. Blood pressure and outcome after severe pediatric traumatic brain injury. *J Trauma.* 2003;**55**(6):1039–44. doi: 10.1097/01.TA.0000101759.23607.57. [PubMed: 14676648].