**Predictors of Intensive Care Unit Length of Stay and Intracranial Pressure in Severe Traumatic Brain Injury**

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**Objective:** (300 words)

**Design:**

**Setting:**

**Patients:**

**Interventions:**

**Measurements and Main Results:**

**Conclusions:**

Traumatic brain injury (TBI) remains a major public health issue worldwide. The annual incidence is estimated at 500/100,000 in the U.S. and Europe, resulting in over 200 per 100,000 individuals being admitted to hospitals each year in Europe (1-3). About 1.5 million people die globally from TBI, the majority in developing countries and it is the leading cause of mortality between 1-44 years of age. In addition, TBI affords a large societal and economic toll. The estimated economic cost in 2010, including direct and indirect medical costs, is estimated to be approximately $76.5 billion. Fatal TBI and TBI requiring hospitalization account for approximately 90% of the total TBI medical costs (5, 6).

Length of stay (LOS) is an important measure of health care utilization and determinant of hospitalization costs. Although there are accepted prognostic models for severe TBI, little has been published on factors influencing intensive care unit (ICU) LOS in this population. Monitoring and control of intracranial pressure (ICP) is one of the defining components of ICU management in these patients; the association of ICP with ICU LOS has not been thoroughly explored. Proper analysis ought to consider confounding factors that accompany high ICP and the fact that patients suffering refractory intracranial hypertension may have shorter ICU LOS. The aim of thiscurrent study is to explore the relationship of ICP and ICU LOS after adjusting for prognostically important clinical and radiologic featureson admission in a large cohort of severe TBI patients. The identification of factors associated with prolonged ICU stay and insight in the relationship of ICP and LOS are important in allowing clinicians to identify high-risk patients, assistwith clinical decision-making, and facilitate the appropriateallocation of hospital resources. Furthermore, and in view of the contemporary debate over the significance of monitoring and management of ICP, the relation with ICU course is a highly relevant question to answer.

**MATERIALS AND METHODS**

The study design was a database review of de-identified research data that had been collected prospectively as a part of Institutional Review Board–approved research studies.

**Patients and Management**

A total of 438 patients who were admitted to Ben Taub General Hospital in the period 1995-2005 and received critical care for severe TBI, including the standardized monitoring and management of ICP and cerebral perfusion pressure (CPP), were studied. Inclusion criteria were the following: TBI, motor component of the Glasgow Coma Scale (GCS) score ≤ 5 (either after resuscitation or after subsequent deterioration), valid ICP data collected as a part of an ongoing research protocol, and demographic and injury characteristics and neurological outcome collected as a part of an ongoing research protocol. Exclusion criteria included GCS score of 3 with fixed, dilated pupils and loss to follow-up before 3 months after injury. A standard management protocol was employed that emphasized the prevention of secondary insults and the prompt evacuation of intracranial masses. General management goals were PaO2 > 100 mm Hg, PaCO2 of 35 to 40 mm Hg, systolic blood pressure > 120 mm Hg, central venous pressure of 5 to 10 mm Hg, and urine output > 0.5 to 1 mL/kg/h. Phenytoin was given for 7 days as prophylaxis for seizures. Invasive monitoring of ICP was usually via ventriculostomy. The goals of management were ICP < 20 mm Hg and CPP > 60 mm Hg [for some patients a higher CPP was targeted based on jugular bulb oxygen saturation (Sjvo2) and/or brain partial tissue oxygenation (Pbto2) readings]. Treatment of intracranial hypertension was based on Brain Trauma Foundation guidelines for management of severe TBI and involved surgical removal of mass lesions, use of cerebrospinal fluid drainage via ventriculostomy, sedation, neuromuscular paralysis, mannitol, and mild to moderate hyperventilation. Barbiturate coma, moderate hypothermia, and decompressive craniectomy were treatment options used for refractory intracranial hypertension (7). Monitoring of ICP was continued until the ICP was < 20 mm Hg for 24 hours without treatment.

**Data Collection**

The demographic and clinical data collected included age, sex, race, mechanism of injury, GCS, pupil size/reactivity, and Injury Severity Score (ISS) score upon admission. Intracranial pressure and other physiological parameters were recorded hourly within a few hours after ICU admission and for the duration of the monitoring. The Marshall CT category (8) was used to describe the admission CT scan findings, and the results were collapsed into the following 3 groups: mild diffuse injury (diffuse injury 1 and 2), severe diffuse injury (diffuse injury 3 and 4), and mass lesions (evacuated and non-evacuated). The GCS score on admission was also classified into the following 2 categories according to the motor GCS score: motor GCS score 4-6 and 1-3. Pupil reactivity was classified as both pupils reactive, 1 unreactive pupil, or both pupils unreactive. Six month Glasgow Outcome Scale (GOS) was collected and dichotomized as favorable recovery (good recovery or moderate disability) and unfavorable recovery (severe disability, vegetative, or dead).

**Statistical Analysis**

We used joint modeling of longitudinal measurements and event time data in order to examine the relationship between ICU LOS and ICP, adjusting for important prognostic, admission factors (Age, Sex, Pupil reactivity, GCS, CT characteristics, PaCO2) (9). Since ICP measurements are repeatedly measured overtime, i.e. time dependent, we can not simply take the mean of ICP and use it as the covariate since during the ICU stay patients with higher ICP may die earlier resulting in a shorter ICU LOS. So, we consider these patients as censored cases to adjust the effect of higher ICP on ICU LOS. This is accomplished by using the joint modeling method in which ICU LOS is treated as a time to event process and simultaneously, ICP is longitudinally modeled. Specifically, *(Ming to put equations here)*

hi( tjwi ;mi( t)) = h0( t) exp[>wi + \_mi( t)]

yi( t) = mi( t) + "i( t) = x>i( t)\_ + z>i( t)b + "i( t) ; "i( t) \_ N(0 ; \_2)

where (t) is the time to event (ICU discharge), i.e. ICU LOS; mi (t) is ICP measurements for subject i at time t; wi are time independent variables for subject i; xi are fixed effects covariates and zi are random effects covariates, they can be either time dependent or independent.

**RESULTS**

**Patient Characteristics**

Demographic and injury characteristics of all 438 patients, which are summarized in Table 1, were typical for a severe TBI population. Men predominated in the group, 379 (86.5%) compared with 59 women (13.5%). The mean age for the group was 33.2 ± 14.5 years, and the mean Injury Severity Score was ?. *The mechanism of injury was motor vehicle collision in 268 (66.2%), assault in 41 (10.1%), fall/jump in 58 (14.3%), and other in 21 (5.2%). In 17 patients (4.2%), the mechanism was unknown. An admission GCS score was available for 403 of the patients. The motor component of the GCS score was 1 to 3 in 188 patients (46.4%) and 4 to 6 in 215 patients (53.1%). In 2 patients (0.5%), an admission GCS score could not be obtained because of pharmacological paralysis. A small fraction of patients (3.6%) had a motor score of 6 on their postresuscitation examination but subsequently deteriorated to , 6.* Pupils were reactive on admission in 181 patients (41.3%), 1 pupil was unreactive in 44 patients (10%), and both pupils were unreactive in 109 patients (24.9%). For 104 patients (23.7%), the pupils could not be assessed.The CT scan of the head on admission was classified as diffuse injury 1 or 2, diffuse injury 3 or 4, and mass lesion in 115 patients (26.2%), 82 patients (18.7%), and 240 patients (54.8%), respectively.

The GOS score was assessed 6 months. A total of 148 patients (33.8%) had a favorable outcome, whereas 211 patients (48.1%) had an unfavorable outcome. One hundred twenty-four patients died (28.3%). No outcome data were available in 48 patients (11%).

**Intracranial Pressure and ICU LOS**

The mean ICU LOS is ?

Joint modeling of longitudinal measurements of ICP and event time data (ICU discharge as an event) was employed. In the longitudinal model, where ICP is the outcome, the following variables were found to be statistically significant and to predict a higher ICP: Younger age, male gender, presence of CT diffuse injury 3 and 4 (Marshall classification) and lower GCS on admission. When this model is jointly analyzed with the event process analysis it can be seen that the only significant predictor of longer ICU LOS is CT classification CTM12 (presence of mass lesion, evacuated and non-evacuated). Of marginal significance is CT diffuse injury 3 and 4 (p = 0.0565). Intracranial pressure is not significantly associated with ICU LOS, nevertheless the association is in the direction of higher ICP relating to a longer LOS.

**DISCUSSION**

*-CT classification and clinical outcomes*

*-CT classification and ICU LOS*

*-ICP and ICU LOS*

**Limitations**

**CONCLUSIONS**

**ACKNOWLEDGMENTS**

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**FIGURE LEGENDS**

**TABLES**

Should get median/mean of ICU LOS, defined prolonged stay and look at outcomes of that group after controlling for confounders.

*(Maas et al. NUS 2005)* In 1991 Marshall et al. (24), after analysis of the Traumatic Coma Data Bank, proposed a CT classification for grouping patients with TBI according to multiple CT characteristics. This CT classification identifies six different groups of patients with TBI, based on the type and severity of several abnormalities on the CT scan. It differentiates between patients with and without mass lesions and permits a further discrimination of patients with diffuse injuries into four categories, taking into account signs of raised intracranial pressure (ICP; i.e., compressed or absent basal cisterns, midline shift). Since its introduction, this CT classification has become widely accepted for descriptive purposes, and is also increasingly being used as major predictor of outcome in TBI. Various studies have confirmed the predictive value of the CT classification (17, 21, 28), and the international guidelines on prognosis include the CT classification as a major CT predictor based on Class I evidence (5). Whether the Marshall CT classification is best suited for prediction or whether other combinations of CT parameters may be more appropriate for this specific purpose has not been investigated in detail.

Further, the Marshall CT classification does not permit any distinction on type of mass lesion. Many studies have shown that prognosis in patients with an EDH is much better than in those with a subdural or intracerebral hematoma (5, 10). Bricolo et al. (3) postulated that mortality should approach zero in patients with an uncomplicated EDH. As shown in Table 6, we found zero mortality in such patients (mass lesion with a prognostic score of 1). A further problem with the original CT classification is that it differentiates between patients with evacuated versus non evacuated mass lesions. Many have argued that this reflects a clinical decision and does not in itself constitute a CT parameter, and in clinical practice this has led to confusion and it has been proposed not to include this differentiation (28).

*(Witiw et al. NCC 2013)* Given the highly variable course following a hemorrhagicevent, these intensive care unit (ICU) admissionsrange from a few days to multiple weeks. At present,however, there is a paucity of information regarding earlypredictors of a prolonged critical care stay. The aim of thiscurrent study is to identify clinical and radiologic featureson admission that predict a prolonged stay in a critical careunit following aSAH in a large cohort of subjects enrolledin the Clazosentan to Overcome Neurological iSChemiaand Infarction OccUrring after Subarachnoid hemorrhage(CONSCIOUS-1) trial. The identification of such factorsmay allow clinicians to identify high-risk patients, assistwith clinical decision-making, and facilitate the appropriateallocation of hospital resources.

*(Okasha et al, NCC 2014)* LOS is an important measure of health care utilization and determinant of hospitalization costs. Although many reports in the literature are available that determine risk factors for mortality and unfavorable outcome after TBI, at present little is published on factors influencing ICU LOS. In a study of 216 subdural hemorrhage patients, hospital and ICU LOS were independently associated with poor GCS [33 ]. Kim et al. [34 ]. found that TBI patients with GCS scores ranging from 3 to 8 had a longer average hospital LOS than did those with a GCS of 13–15 (18.2 vs. 9.2 days, p < 0.01). To our knowledge, this study is the first to report the prediction of ICU LOS from admission coma scores. It is important to note that, although the type and severity of patients’ illnesses can directly affect LOS [35], there is structural and managerial factors that influence ICU LOS. However, these factors are difficult to control in predictive models [36 ].

*(Soares et al. Chest 2008)* The SOFA score at ICU admission was not associated with a worse outcome. This fact can be expected because patients with very high or very low levels of severity of organ failures will experience a shorter ICU stay. Those patients are at increased risk for dying or being discharged early in the course of ICU admission. In conclusion, 15% of critically ill patients with cancer had a prolonged ICU LOS. Their short- and long-term survival rates were similar to patients with a shorter ICU LOS, and their prognosis was better than expected a priori. In our opinion, the length of ICU admission per se should not be used in the clinical decisions regarding the continuation of treatment in these patients.

The World Health Organization (WHO) predicts that deaths from road traffic incidents (primarily due to TBI) will double between 2000 and 2020, and that this increase will come exclusively in low- and middle income countries (4). In developed, westernized societies, the group with increasing incidence of TBI is people aged over 60 years.

Generally accepted prognostic models for moderate and severe TBI take into account age, indicators of injury severity such as GCS, pupillary reactivity and CT parameters.9,10,26