**Turk Neurosurg** 31(3):333-338, 2021

*Original Investigation*

**DOI:** 10.5137/1019-5149.JTN.29843-20.2

Received: 12.03.2020
Accepted: 19.05.2020

Published Online: 20.11.2020

# Evaluation of Blood Urea, Creatinine, and Glucose Levels as Biochemical Indicators of the Type and Severity of Traumatic Brain Injury

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## ABSTRACT

**AIM:** To investigate the effects of trauma type and survival on biochemical parameters including blood urea, creatinine, and glucose levels on patients with traumatic brain injury (TBI).

**MATERIAL and METHODS:** The medical records of 102 patients with TBIs who were admitted to the emergency department and/or hospitalized in the neurosurgery department between 2016 and 2019 were examined retrospectively.

**RESULTS:** Types of trauma included: 19 cases of subarachnoid hemorrhage, 25 cases of subdural hemorrhage, 9 cases of epidural hemorrhage, 28 cases of intracerebral hemorrhage, 4 cases of multiple hemorrhage, and 12 cases with other hemorrhages. We examined the effects of trauma type and survival on a total of 17 blood test parameters, but only three (blood urea, creatinine, and glucose) showed significance for the overall model, meaning that either trauma type or survival or an interaction between the two had significant effects on these three blood parameters.

**CONCLUSION:** Our findings imply that the risk of fatality due to TBI might be deduced from observation of the patient's blood urea and glucose levels as these two parameters differed significantly in fatal versus surviving cases. Blood urea and creatinine levels were different for different trauma types and may be useful in distinguishing the type of injury.

**KEYWORDS:** Traumatic brain injury, Fatality, Urea, Creatinine, Glucose

**ABBREVIATIONS: TBI:** Traumatic brain injury, **HBG:** Hemoglobin, **HCT:** Hematocrit, **ICPIS:** Intracranial pressure increase syndrome

## INTRODUCTION

Traumatic brain injury (TBI) occurs primarily due to head trauma and accounts for a considerable proportion of adult traumatic mortality cases. These trauma cases are among the leading cases of admission to emergency departments worldwide (1). Due to its common occurrence, TBI is also considered to be a silent epidemic (14). TBI cases are often fatal and even nonfatal TBIs carry lifelong consequences for the patient (9,20,22).

Although the neurological and neuropsychological effects of TBIs and the associated long-term cognitive and intellectual problems have been extensively investigated and widely published (7,13), case types, risk assessment, and treatment strategies in the emergency and neurosurgery rooms require further investigation (10,17). Novel findings in this area, particularly in relation to treatment strategies, would be invaluable in improving the outcomes of patients with TBIs in emergency and neurosurgery departments (3).

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We retrospectively reviewed a large array of TBIs arising from accidental traumas in order to evaluate the relative incidence, distribution, and clinical success achieved in these cases. We further aimed to examine the relationships between clinical biochemical data obtained from these patients and the outcomes of their TBIs.

## MATERIAL and METHODS

### Data Collection

Prior to initiation of the study, we obtained ethics approval from the relevant ethics committee (No: 2019-187-07). All data were obtained from the hospital automation system retrospectively. The study included patients with accidental head trauma, admitted to the emergency department between January 1, 2016 and May 30, 2019 and examined by a neurosurgeon.

### Study Population

The inclusion criteria were serious head injury and older than 18 years. All patients were examined by a neurosurgeon at the initial emergency room consultation in order to determine further treatment requirements. We gathered all the clinical data from a total of 102 cases with head trauma during the study period. This included time of the injury, demographics, clinical presentation, radiologic findings, and clinical biochemistry data. The neurological status of the patients at presentation and exit were evaluated according to the Glasgow Coma Scale (GCS) and Glasgow Recovery Scale (GRS) (20). The biochemical parameters tested included urea, creatinine, and glucose, which are routine blood tests and typically the first blood tests requested by neurosurgeons for evaluation of patients in the emergency room prior to hospitalization.

### Statistical Analyses

A general linear model was fitted to all the continuous data using two variables (i.e., survival and trauma type). The main effects of each variable and their two-way interaction were examined. SAS 9.4 software (SAS Institute, Cary, NC) was used for all the statistical analyses. A p-value of less than 0.05 was considered indicative of a statistically significant difference.

## RESULTS

### Age and Gender

We examined the medical records of 102 adult patients with serious head injuries who presented to the emergency clinic. Head imaging for each case was conducted to determine the nature of the injury. Among this cohort, 24 (23.6%) were between 19 and 39 years of age, 44 (43.1%) were between 40 and 69 years of age, and the remaining 34 cases (33.3%) were above or 70 years old. Male patients (76 [74.5%]) far outnumbered female patients (26 [25.5%]). There were 25 fatalities (24.5%) (Table I).

### Mechanism of Injury

We investigated the mechanism of injury and found that traffic accidents were the most frequent cause of head trauma in our cohort with 39 cases (38.2%). Falling was the second most common cause with 33 cases (32.4%). Collision with an object was the third most common cause of trauma, 12 cases (11.8%). Abuse accounted for 11 cases (10.8%) and in seven cases the reason was not reported (Table I).

### Time Period of the Event

We obtained and analyzed information regarding the time of injury. Dividing the day into four quarters of 6 hours each, the events occurred as often in the afternoon as they did in the evening/nighttime quarters with 36 cases (35.3%) in each of these quarters. A total of 16 events (15.7%) happened in the early morning between 00:00 and 06:00, whereas 14 events (13.7%) occurred in the morning between 06:00 and 12:00 (Table I).

### Clinical Treatment

About 65 cases (63.7%) were referred to the intensive care department, whereas 23 cases (22.6%) were referred to the brain surgery department, and five cases (4.9%) were referred to various other departments. The remaining nine cases (8.8%) were discharged directly from the emergency room (standing discharge) (Table I).

**Table I:** Summary Statistics for Patients with Serious the Head Injuries

| Parameter | Groups | n | % |
|---|---|---|---|
| Age | 19-39 | 24 | 23.6 |
| | 40-69 | 44 | 43.1 |
| | ≥70 | 34 | 33.3 |
| Gender | Female | 26 | 25.5 |
| | Male | 76 | 74.5 |
| Mechanism of the injury | Motor vehicle accident | 39 | 38.2 |
| | Collision with an object | 12 | 11.8 |
| | Fall | 33 | 32.4 |
| | Abuse | 11 | 10.8 |
| | Unknown | 7 | 6.8 |
| Time period of the event | 6:00-12:00 | 14 | 13.7 |
| | 12:01-18:00 | 36 | 35.3 |
| | 18:01-00:00 | 36 | 35.3 |
| | 00:00-6:00 | 16 | 15.7 |
| Treated clinic | Intensive Care | 65 | 63.7 |
| | Neurosurgery | 23 | 22.6 |
| | Others | 5 | 4.9 |
| | Standing discharge | 9 | 8.8 |

### Glasgow Coma Scale (GCS) and Glasgow Result Scale (GRS) Scores

The neurological status of patients at the time of initial admission to the emergency department was examined. The 38 patients with GCS scores ≤8 were regarded to have severe TBIs, whereas the 64 patients with GCS scores >8 were considered to have moderate or mild head traumas. When we examined the neurological conditions of patients at discharge, we observed that the 25 patients who died were discharged with GRS scores of 1. Six patients were discharged with GRS scores of 4, and the remaining 71 patients were discharged with GRS scores of 5. No patients had GRS scores of 2 or 3.

### Types of Hemorrhage and Trauma Localization

Head hemorrhage type was also examined, and the results revealed that there were 19 cases (18.6%) of subarachnoid hemorrhage, 25 cases (24.5%) of subdural hemorrhage, 9 cases (8.8%) of epidural hemorrhage, 28 cases (27.4%) of intracerebral hemorrhage, 4 cases (3.9%) of multiple hemorrhage, and 12 cases had other hemorrhages (e.g., scalp injuries or hematoma after head linear fractures). About 6 cases (5.9%) had no hemorrhage (Table II).

We also investigated trauma locations and found that 15 cases had frontal injuries (14.7%). Parietal injury was detected in 16 cases (15.7%). Occipital injuries were present in 5 cases (4.9%), and temporal injuries were observed in 21 cases (20.6%). There were 37 cases (36.3%) with trauma in multiple locations (Table II).

**Table II:** The Corresponding Numbers and Percentages for the Trauma Pathologies Types and the Location of Trauma in 102 Patients

| Hemorrhage Type | n | % |
|---|---|---|
| Subarachnoid hemorrhage | 19 | 18.6 |
| Subdural hemorrhage | 25 | 24.5 |
| Epidural hemorrhage | 9 | 8.8 |
| Intracerebral hemorrhage | 28 | 27.4 |
| Multiple hemorrhage | 4 | 3.9 |
| Other (scalp or head linear fracture) | 12 | 11.8 |
| Normal | 6 | 5.9 |
| **Trauma Location** | | |
| Frontal | 15 | 14.7 |
| Parietal | 16 | 15.7 |
| Occipital | 5 | 4.9 |
| Temporal | 21 | 20.6 |
| Multiple | 37 | 36.3 |
| Normal | 8 | 7.8 |

***Multiple hemorrhage:*** *developing at least two or more different types of brain bleeding.*
***Other hemorrhages:*** *scalp injuries or developing linear skull bone fracture hematoma.*

### The Overall General Linear Model for Biochemical Parameters

We investigated the effects of trauma type and survival on three blood parameters: blood urea, creatinine, and glucose. All three parameters indicated a significance ($p<0.05$) for the overall model, which means that either trauma type or survival or an interaction between the two had significant effects on these blood parameters (Table III). We estimated the significance of each parameter using the linear model for each blood parameter. Both variables (trauma type and survival) and their interactions were significant for urea ($p<0.001$).

Glucose levels differed significantly between exitus cases and survival cases, indicating that survival was significant in the glucose model. However, there was no significant difference in glucose levels among different trauma types indicating that neither trauma type nor the two-way interaction were significant in the glucose model (Table IV).

An exactly opposite pattern was evident in creatinine where survival was not significant and trauma type and two-way interaction were significant ($p<0.001$), since creatinine levels differed significantly among trauma types but were not significantly different in exitus and survival patients (Table IV).

When the average blood values of the exitus and survival groups were examined using the overall model, the blood urea (47.12 ± 31.63 mg/dL), creatinine (0.98 ± 0.47 mg/dL) and glucose (180.75 ± 67.35 mg/dL) levels of exitus patients were elevated compared to the survival group levels of 35.09 ± 13.80 mg/dL, 0.90 ± 0.29 mg/dL, and 126.56 ± 40.36 mg/dL, respectively. However, the increase was not statistically significant ($p>0.05$) for creatinine levels (Table V).

In addition, when the average blood levels of all three parameters were compared for different trauma types, blood urea and creatinine levels showed statistically significant differences, whereas increases in glucose levels were found to be insignificant (Table VI).

**Table III:** Results of the Overall General Linear Model for the Significant Parameters

| Parameter | DF | Sum of Squares | Mean Square | F Value | P>F |
|---|---|---|---|---|---|
| Urea | 16 | 20730 | 1296 | 5.36 | **<0.001** |
| Creatinine | 16 | 4.3 | 0.3 | 3.12 | **<0.001** |
| Glucose | 16 | 77895 | 4868 | 1.99 | **0.02** |

**Table IV:** Mean Squares and Significance of Effects of the Variables and Interaction Between Variables on Three Significant Parameters in the Model Based on Findings from 102 TBI Cases

| Source of Variation | DF | Urea | Creatinine | Glucose |
|---|---|---|---|---|
| Trauma type | 8 | 1738*** | 0.41*** | 2179 |
| Survival | 1 | 4125*** | 0.24 | 27743*** |
| Trauma type*Survival | 7 | 2032*** | 0.49*** | 1529 |

****p<0.001: Means of groups are different according to least significant difference method*
** interaction between trauma type and survival.*

**Table V:** Means and Standard Deviations of All Significant Parameters in the Model for Fatal and Surviving Cases

| Group | Urea (mg/dL) | Creatinine (mg/dL) | Glucose (mg/dL) |
|---|---|---|---|
| Exitus | 47.12 ± 31.63* | 0.98 ± 0.47 | 180.75 ± 67.35* |
| Survival | 35.09 ± 13.80* | 0.90 ± 0.29 | 126.56 ± 40.36* |

**p<0.05: Means of groups are different according to least significant difference method.*

**Table VI:** Means and Standard Deviations of All Significant Parameters in Model for Hemorrhage Types

| Hemorrhage Types | Urea (mg/dL) | Creatinine (mg/dL) | Glucose (mg/dL) |
|---|---|---|---|
| Subarachnoid hemorrhage | 44.95 ± 30.92* | 1.02 ± 0.46* | 134.39 ± 27.81 |
| Subdural hemorrhage | 38.95 ± 16.85 | 0.93 ± 0.3 | 148.14 ± 70.62 |
| Epidural hemorrhage | 46.25 ± 36.28* | 1.07 ± 0.55* | 146.63 ± 39.59 |
| Intracerebral hemorrhage | 31.36 ± 9.23* | 0.87 ± 0.24* | 132.79 ± 54.02 |
| Multiple hemorrhage | 39.71 ± 12.55 | 0.79 ± 0.32* | 139.65 ± 78.42 |
| Other hemorrhage | 35.01 ± 12.57 | 0.91 ± 0.28 | 141.38 ± 62.31 |
| Normal | 35.6 ± 16.04 | 0.82 ± 0.32 | 118 ± 36.41 |

**p<0.05: Means of groups are different according to least significant difference method.*

## DISCUSSION

Severe TBI is estimated to occur at an annual rate of between 7 and 20 cases per 100,000 people (3,4,8,15,16). Here, we report on 102 patients who, over a period of two years, visited the emergency department of a hospital that serves approximately 260,000 people. This corresponds to an incidence of 19.6 cases per 100,000 people. Hence our patient numbers fall within the incidence range reported by other studies (3,4,8,15,16).

A large variation in hospital fatality rates among TBI cases has been reported, and the rate of variation is dependent upon population and age groups. Although some studies have reported a steady decline in the mortality rate of TBI cases (12,25), there have been reports of a constant rate at least for the last two decades (24). Retrospective analyses over the past 150 years indicate a sharp decline from a fatality rate of 68% in the 1800s to a 34% rate in the 1990s (24). The fatality rate among our cohort of 102 patients in this study was 24.5%. This lower number could be attributed to the fact that our cohort included a relatively higher proportion of younger patients (66% were <70 years of age), which lends itself to a higher survival rate.

Higher proportions of males with head injuries have been reported in earlier studies (21,22) and in our cohort males with TBIs outnumbered females at a rate of almost three-to-one.

Our results also agreed with those of previous studies that falling and traffic accidents were the leading causes of TBIs (3,11). Given that serious head trauma can only occur in complicated events, and those events are not routine in daily life, it is unsurprising that falling, collision with an object or traffic accidents collectively caused 82.4% of all the cases.

In TBI cases, a heterogeneous pattern has been reported for the localization of trauma (5). In the present study, head injuries were located in all four areas of the skull, and subarachnoid, subdural, epidural, and intracerebral hemorrhages were observed. In addition, patients with multiple isolated brain hemorrhages (developing at least two or more different types of brain bleeding) were found among patients with scalp

injuries and those with developing linear skull bone fracture hematomas.

In addition to posing a serious life threat in patients with head injuries, we hypothesized that internal bleeding may have an effect on a number of blood parameters, resulting in potentially different values for these parameters among patients with different injury types. Blood parameter values may even differ in fatal and surviving patients. However, the general linear model indicated that among the 17 parameters tested, only three showed significant differences for survival/fatality and/or trauma types. Previously a wide range of hematological markers were tested for early detection of brain trauma, but only a few were found to show any potential (2). Although hemoglobin (HGB) and hematocrit (HCT) have been associated with the risk of subarachnoid hemorrhage (19), we did not detect such a relationship in our cohort.

The neurometabolic cascade of acute trauma is multifaceted and includes hormonal changes, abrupt neuronal depolarization, a release of excitatory neurotransmitters, disruption of ionic balance, changes in glucose metabolism, vascular trauma, altered cerebral blood flow/neurovascular coupling, and impaired axonal function (26).

The model used to analyze data in the present study showed significant increases in the blood glucose levels of patients in the exitus group compared to the survival group. However, in our cohort, these increases were not significantly related to the localization of bleeding in the brain tissue and therefore would not be effective in determining this aspect of TBIs. The increase in blood glucose is unsurprising when one considers the primary role which hormones play in many traumas including acute severe brain traumas. Hormone levels typically increase during trauma. This is especially true of hormones involved in glucose metabolism, such as cortisol and glucagon. The increase in these hormones in the blood leads to increased blood glucose levels through the triggering of a series of metabolic pathways such as lipolysis, proteolysis, glycogenolysis, and gluconeogenesis in many tissues, but particularly in the liver. Raised blood glucose levels occur in response to the increased glucose requirements of damaged brain tissue cells and therefore may be expected to increase with increasing severity of the damage (23).

Differences in urea levels between trauma types and between exitus and survival groups were found to be significant. Blood urea levels in the survival group for instance were significantly lower than those of the exitus group. The reason for these differences may be due to prerenal azotemia and underlying acute tubular necrosis pathology in higher life-threatening cases. As a result of severe brain trauma, different neuropathological complications such as ischemia, hypotension, cerebral hypoxia, cerebral edema, and intracranial pressure increase syndrome (ICPIS) occur (18). Although increased intracranial pressure in various localizations of bleeding in the brain is effective for neurological survival, the increase in the amount of urea observed in the blood of these patients can be interpreted as a reflex response by the body due to acute trauma in an attempt to decrease the raised intracranial pressure. Apart from these pathological reasons, it is possible that high urea levels may develop in patients with serious injuries as a result of multiple damage or multiple insufficiencies.

Creatinine levels in this model were significantly different among trauma types only and did not show any significant effect with regard to survival. The increase in intra-cerebral blood flow, brain edema, and ICPIS findings depend on the severity of bleeding in post-traumatic brain tissue (6). Based on these outcomes, it is possible that high creatinine levels may have developed as a secondary response to the decrease in blood flow to other organs during the acute phase.

A limitation of the present study is that alive/died based binary distribution was used in the analyses. The fact that the data was gathered from a single hospital in one province in Turkey poses another limitation. Therefore, research involving larger cohorts including patients from around the country should be conducted to establish national estimates. Despite these limitations, our results offer valuable insights into an important area that has not, as yet, been widely researched.

## CONCLUSION

Severe TBI can lead to serious life threating consequences, and the risk of fatality might be deduced by testing patient blood urea and glucose levels as these were significantly different in fatal versus surviving patients. Blood urea and creatinine levels were different for different injury types and could be utilized to distinguish these different trauma types.

## ACKNOWLEDGEMENTS

The authors would like to acknowledge the administration of the Kars Harakani State Hospital for providing access to the data. We would also like to thank Enago for providing English language editing services.

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