Title: Serum glucose-to-potassium ratio as a prognostic predictor of severe traumatic brain injury

Running title: glucose-to-potassium ratio in severe TBI

Ami Shibata, MD
Fumihiro Matano, MD, PhD
Nobuyuki Saito, MD, PhD
Yu Fujiki, MD, PhD
Hisashi Matsumoto, MD, PhD
Takayuki Mizunari, MD, PhD
Akio Morita, MD, PhD

1Department of Emergency and Critical Care Medicine, Nippon Medical School Tama Nagayama Hospital
2Department of Neurosurgical Surgery, Nippon Medical School
3Department of Emergency and Critical Care Medicine, Chiba Hokusoh Hospital
4Department of Emergency and Critical Care Medicine, Nippon Medical School
5Department of Neurosurgery, Chiba Hokusoh Hospital

Corresponding Author: Ami Shibata

Ami Shibata, MD
Department of Emergency and Critical Care Medicine, Nippon Medical School Tama Nagayama Hospital

1-7-1 Nagayama, Tama, Tokyo, 206-0025, Japan

Telephone: +81-42-371-2111

FAX: +81-42-372-7375

Email: 068m1044@nms.ac.jp
ABSTRACT

Background:
Initial management of severe traumatic brain injury (TBI) is important, and includes treatment decision-making and prediction of prognosis. We examined whether biomarkers at admission could be useful prognostic predictors. We focused on electrolytes and blood glucose, which can be measured easily at any facility and for which the results can be obtained promptly before those of other biomarkers, such as D-dimer.

Methods:
All trauma patients with head injury treated at Chiba Hokusoh Hospital between 2014 and 2017 were investigated. Multiple trauma cases accompanied by fatal trauma, hemorrhagic shock, and cardiopulmonary arrest, and pediatric cases were excluded from this study. The blood gas data at the initial hospital visit were reviewed retrospectively. Cases in which the patients died or were in a vegetative state due to a head injury during hospitalization were defined as having a poor outcome. Factors related to poor outcome were analyzed.

Results:
Of 185 male and 79 female patients enrolled in the study, 34 had a poor outcome. Poor outcome was correlated significantly with potassium ($P = 0.003$), glucose ($P < 0.001$), and the glucose-to-potassium ratio ($P < 0.001$) at arrival. In particular, the odds ratio for a glucose-to-potassium ratio of $\geq 50$ was 4.079.
Conclusions:

We evaluated blood gas data at initial hospital visit as these results can be obtained more quickly than those of other biomarkers assessed previously. Serum glucose-to-potassium ratio at admission may be a potential predictor of prognosis for severe TBI.

Keywords:

head injury, prognostic predictor, traumatic brain injury, glucose-to-potassium ratio
Introduction:

Severe traumatic brain injury (TBI) remains a major healthcare problem worldwide. Many TBI survivors live with severe disabilities. TBI rates are the highest in the very young (age group, 0–4 years) and in adolescents and young adults (15– years). The enormous economic burdens resulting from severe TBI affect the patients’ families and countries. Thus, initial management of severe TBI is extremely important, and includes decision-making to establish treatment strategy, timing of surgery, and determination of prognosis.

During the early phases after TBI, the incidence of coagulation abnormalities is high. These coagulation abnormalities are considered independent predictors of mortality even in the presence of other risk factors. In previous reports, D-dimer was identified as a prognostic factor for TBI. The issue with using coagulation byproducts, such as D-dimer, as prognostic factors is that results cannot be obtained immediately. This is very disadvantageous for severe TBI cases, in which physicians must make treatment decisions quickly. Few studies have evaluated the use of biomarkers other than coagulation factors at hospital admission as prognostic factors for severe TBI.

Therefore, biomarkers measured in arterial blood gas tests of patients with head injury at admission to Chiba Hokusoh Hospital were investigated retrospectively, and their use as prognostic predictors was evaluated. Blood glucose and potassium levels were identified previously as prognostic factors in cases of subarachnoid hemorrhage. Thus, we speculated that such prognostic factors also could be applied to TBI cases. Electrolytes and blood glucose are measured via arterial blood gas tests at admission and can be measured easily at any facility. The corresponding test results can be obtained more promptly than those of other biomarkers, such as D-dimer.
Materials and Methods

Our study was based on the criteria of the Strengthening the Reporting of Observational Studies in Epidemiology statement and was approved (No. 661) by the Chiba Hokusoh Hospital research ethics committee. The number of inpatients at the Chiba Hokusoh Hospital critical care center is approximately 1000 per year. The hospital also provides a doctor helicopter and a doctor car business. Approximately 80% of inpatients are trauma cases, so the facility is one of the leading trauma centers in Japan. There are approximately 250 severe trauma cases (injury severity score \([\text{ISS}] \geq 15\)) per year.

All trauma patients with TBI treated at Chiba Hokusoh Hospital between January 2014 and December 2017 were assessed regardless of the severity and mechanism of injury, and the discharge summaries for all inpatients were checked. We selected patients whose final diagnosis included head trauma (acute subdural or epidural hematoma, cerebral contusion, traumatic subarachnoid hemorrhage, skull fracture, and skull base fracture). Cases of multiple trauma, except for TBI, accompanied by fatal trauma (abbreviated injury score \([\text{AIS}] > 3\)), hemorrhagic shock, and cardiopulmonary arrest, and pediatric (<18 years) cases were excluded from this study. Patient records, including admission data, were reviewed retrospectively. Patients who died or were in a vegetative state (Glasgow Outcome Scale \([\text{GOS}] = 1, 2\)) secondary to TBI during hospitalization were defined as having a poor outcome.

Arterial blood gas samples were obtained from all trauma patients transported to our hospital. There was one stand-alone blood gas measuring device in the emergency department, and results were obtained within approximately 60 seconds. Electrolytes and blood glucose levels in the arterial blood gas test at admission and results of laboratory tests, such as coagulation factors, vital signs, and so forth, were reviewed from clinical records. The factors related to poor outcomes were analyzed.

Treatment

At Chiba Hokusoh Hospital, trauma patients are treated according to the Japan Advanced Trauma Evaluation and Care guidelines,\(^7\) which corresponds to the Advanced Trauma Life Support guidelines and provides a standardized protocol provided by the guidelines for treatment and management of severe TBI in Japan, and
overseas guidelines.8,9

Statistical Analysis

Statistical analysis was performed using SPSS for Mac (V.21.0; SPSS, Armonk, NY, USA). Variables are expressed as mean ± standard deviation, median (interquartile range, 25–75 percentile) or number of patients (%) where appropriate. The relationship between poor outcome and biomarkers at admission was investigated. Normally distributed continuous variables were compared using Student’s t-test, and nonnormally distributed variables were compared using the Mann–Whitney U test. P < 0.05 was considered statistically significant.
Results:

Patient Characteristics

Of 565 patients with TBI hospitalized within the study period (Fig. 1), 71 with hemorrhagic shock, 81 with cardiopulmonary arrest, 75 with multiple trauma accompanied with fatal trauma except for head injury, and 74 pediatric cases were excluded. Thus, we included and analyzed 264 patients (185 males, 79 females; mean age, 59.4 years; range 18–97 years).

Patient characteristics, mechanism of injury, whether patients underwent surgery, and surgical outcomes are presented in Table 1. The mechanisms of injury were traffic accident (61.7%), fall (35.2%), and others (3.0%). Procedures, such as intracranial pressure sensor insertion, decompressive craniotomy, removal of hematoma, and hematoma irrigation with trephination therapy, were performed in 35 cases (13.3%). Seven patients underwent trephination alone and 28 required craniotomy. After stratifying patients by outcome, 34 patients (12.9%) were classified into the poor outcome group (P group; GOS = 1, 2).

Patient characteristics were compared between the P and good outcome (G) groups (Table 1). Mean patient ages were 66.7 and 58.3 years, respectively; and this difference was statistically significant ($P = 0.021$). Surgical procedures were performed in 67.6% and 5.2% of patients, respectively. Poor outcome was significantly correlated with surgical procedure ($P < 0.001$). There were no statistically significant differences in sex or mechanism of injury between the two groups.

We also investigated the vital signs at admission between the two groups. Median Glasgow coma scale (GCS) at admission in the P and G groups was 4 (range, 3–13) and 14 (range, 3–15) points, respectively. Thus, a poor outcome was significantly correlated with GCS at admission ($P < 0.001$). There was a statistically significant difference in heart rate (101 and 83, respectively, $P < 0.001$), but there were no statistically significant differences in systolic blood pressure (159 and 149, respectively, $P = 0.062$), respiratory rate (23 and 21, respectively, $P = 0.205$), and blood temperature (35.8 and 36.2, respectively, $P = 0.009$) at admission between the two groups.

Arterial blood gases at admission were compared between the two groups (Table 2). Poor outcomes were correlated significantly with potassium ($P = 0.003$), glucose ($P < 0.001$), lactic acid ($P < 0.001$), hemoglobin
(P = 0.011), and base excess (P < 0.001). Mean potassium level in the P and G groups was 3.45 ± 0.42 and 3.72 ± 0.50, respectively. Mean glucose level was 197 ± 55.7 and 149 ± 45.1, respectively. The calculated blood glucose-to-potassium ratio was 57.4 ± 16.1 and 40.8 ± 13.4, respectively. There was a statistically significant difference between the groups (P < 0.001).

We also investigated the coagulation system at admission between the two groups. Poor outcomes were correlated significantly with prothrombin time and international normalized ratio (PT-INR; 1.16 in the P and 1.02 in the G groups; P < 0.001), activated partial thromboplastin time (APTT; 34.3 and 27.2, respectively; P < 0.001), fibrinogen (116 and 239, respectively; P < 0.001), fibrin degradation product (FDP; 382.3 and 47.8, respectively; P < 0.001), D-dimer (189 and 27.5, respectively; P < 0.001), and platelets (17.2 and 21.2, respectively; P < 0.001).

The multivariate logistic regression analysis of arterial blood gas tests at admission between the two groups is shown in Table 2. Multivariate analysis was performed because patients with diabetes originally were considered to have high blood glucose levels. In particular, the odds ratio for a glucose-to-potassium ratio of ≥50 was 4.079 (P = 0.030). Blood glucose ≥ 200 mg/dL is used as a diagnostic criterion for diabetes and hypokalemia is defined as K ≤ 3.5. The ratio of these values is 57.1. We defined a cutoff value as 50, which is close to 57.1 and easy to calculate.
Discussion

We demonstrated a strong correlation between poor TBI outcome (GOS = 1, 2) and glucose-to-potassium ratio at hospital admission. In particular, for cases with a glucose-to-potassium ratio of ≥50, the odds ratio was 4.079. Therefore, glucose-to-potassium ratio at admission was a potential prognostic biomarker for severe TBI.

Hypoglycemia and hypokalemia often are observed not only in cases of head injuries, but also in those with subarachnoid hemorrhages due to aneurysm rupture.\(^\text{10,11}\) Fujiki et al.\(^\text{6}\) reported that hyperglycemia and hypokalemia were more useful as prognostic factors for subarachnoid hemorrhage if the glucose-to-potassium ratio was calculated rather than values of glucose and potassium alone. Therefore, we examined whether the glucose-to-potassium ratio could be a useful prognostic predictor in TBI. Indeed, this ratio also was a prognostic predictor for severe TBI.

A blood glucose level of ≥200 is a diagnostic criterion for diabetes. If the blood potassium is ≤3.5, then hypokalemia is diagnosed. In this retrospective study, the glucose-to-potassium ratio was 57.14. We used the number 50 as a cutoff value, which was close to 57.14 and was easy to calculate.

Several studies have reported the prognostic value of coagulation indicators in patients with severe TBI.\(^\text{4,12,13}\) However, few reports have focused on the prognostic value of other factors, such as electrolytes and vital signs, at hospital admission in cases of TBI. Hypokalemia is a known independent prognostic factor for TBI.\(^\text{14-16}\) Previously, Ookuma et al.\(^\text{17}\) reported that trauma patients with hypokalemia at hospital admission are likely to present with severe TBI, and require decompression craniotomy. Brown et al.\(^\text{18}\) reported on the mechanism by which hypokalemia occurred. They reported that trauma causes an epinephrine surge, which stimulates the beta receptor of adrenaline. The sodium–potassium pump subsequently is activated and transports potassium into the cell, which leads to a decrease in the blood potassium level.

Conversely, several reports have assessed the relationship between TBI and hyperglycemia in children,\(^\text{19,20}\) but not in adults. In pediatric head injuries, hyperglycemia is known to be an independent prognostic factor.\(^\text{21,22}\) Regarding the mechanism by which hyperglycemia occurs in trauma, Rolih et al.\(^\text{23}\) reported that stress hormones, such as glucocorticoid, growth hormone, glucagon, and epinephrine, are activated as a normal response to the stress caused by trauma. As a result, gluconeogenesis and glycogen degradation pathways are believed to be
activated, causing hyperglycemia. According to this mechanism, hyperglycemia presumably may follow trauma, not only in children but also in adults. If hyperglycemia occurs after a TBI, levels of toxic metabolites, such as lactate, increase, leading to cerebral metabolic acidosis and brain damage secondary to ischemia.24

This study had several limitations. First, this was a retrospective study conducted at a single facility. Second, the medical history and any internal medication that could have led to hypokalemia were not examined. Third, except for TBI, fatal trauma cases (AIS > 3) were excluded, but the influence of other traumas in patients presenting with multiple injuries was not considered. Considering these limitations, further research may be required to support our claim.

We demonstrated that the glucose-to-potassium ratio was a prognostic factor for severe TBI. We assessed biochemical parameters in the arterial blood gas test data at initial hospital admission, which can be obtained more quickly than previous biomarkers, and we identified a new biomarker.

Serum glucose-to-potassium ratio ≥50 at admission may be a potential new biomarker for the prognosis of severe TBI. Use of this new biomarker can possibly predict the prognosis of severe TBI earlier and may be useful for physicians to make treatment decisions quickly.
Conflicts of Interest
None of the authors have any conflicts of interest.
References:


Fig. 1 Flow Diagram of patient selection.

565 cases all trauma patients with head injury during 4 years from 2014 to 2017

71 cases hemorrhagic shock

81 cases cardiopulmonary arrest

75 cases multiple trauma accompanied with fatal trauma (AIS>3) except for head trauma

74 cases pediatric (<18)

264 cases included
Fig. 1

Flow diagram of patient selection. We assessed all trauma patients with head injury during 4 years from 2014 to 2017. Cases of hemorrhagic shock, cardiopulmonary arrest, multiple trauma accompanied with fatal trauma (AIS > 3) except for head trauma, and pediatric (< 18 years) were excluded from this study. Thus, we included and analyzed 264 cases.
### Table 1  Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>TBI patients</th>
<th>poor outcome (GOS = 1, 2)</th>
<th>good outcome (GOS = 3 - 5)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. (%)</td>
<td>264</td>
<td>34 (12.9)</td>
<td>230 (87.1)</td>
<td></td>
</tr>
<tr>
<td>age -yr. (range)</td>
<td>59.4 (18-97)</td>
<td>66.7 (20-89)</td>
<td>58.3 (18-97)</td>
<td>0.021</td>
</tr>
<tr>
<td>male sex -no. (%)</td>
<td>185 (70.1)</td>
<td>24 (70.6)</td>
<td>161 (70.7)</td>
<td>0.944</td>
</tr>
<tr>
<td>Mechanism of injury -no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>traffic accident</td>
<td>163 (61.7)</td>
<td>17 (50.0)</td>
<td>146 (63.5)</td>
<td>0.089</td>
</tr>
<tr>
<td>fall</td>
<td>93 (35.2)</td>
<td>14 (41.2)</td>
<td>79 (34.3)</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>8 (3.0)</td>
<td>3 (8.8)</td>
<td>5 (2.2)</td>
<td></td>
</tr>
<tr>
<td>operation -no. (%)</td>
<td>35 (13.3)</td>
<td>23 (67.6)</td>
<td>12 (5.2)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Operations = **Intra Cranial Pressure** [ICP] sensor insertion, decompressive craniotomy, removal of hematoma, and hematoma irrigation with trephination therapy.
Table 2  Comparison between poor and good outcomes by arterial blood gas parameters

<table>
<thead>
<tr>
<th></th>
<th>poor outcome (n=34)</th>
<th>good outcome (n=230)</th>
<th>Odds ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (SD) (mEq/L)</td>
<td>139 (2.84)</td>
<td>140 (2.95)</td>
<td></td>
<td>0.828</td>
</tr>
<tr>
<td>K (SD) (mEq/L)</td>
<td>3.45 (0.42)</td>
<td>3.72 (0.50)</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Glu (SD) (mg/dL)</td>
<td>197 (55.7)</td>
<td>149 (45.1)</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Glu / K (SD)</td>
<td>57.4 (16.1)</td>
<td>40.8 (13.4)</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lac (SD) (mmol/L)</td>
<td>3 (2.0)</td>
<td>1.9 (0.98)</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hb (SD) (g/dL)</td>
<td>12.9 (2.46)</td>
<td>13.8 (1.83)</td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td>BE (± SD) (mEq/L)</td>
<td>-0.9 (4.1)</td>
<td>1.4 (2.8)</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Glu / K ≥ 50</td>
<td></td>
<td>4.079</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>age</td>
<td></td>
<td>1.058</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td></td>
<td>0.555</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td></td>
<td>1.676</td>
<td>0.576</td>
<td></td>
</tr>
</tbody>
</table>

Glu:glucose  Lac:lactate  Hb:hemoglobin  BE:base excess  GCS:glasgow coma scale  DM:diabetes mellitus