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# Serum Glucose-To-Potassium Ratio as a Prognostic Predictor for Severe Traumatic Brain Injury

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**Background:** Initial management of severe traumatic brain injury 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 results can be obtained promptly, before those of other biomarkers, such as D-dimer.

**Methods:** All trauma patients with head injuries treated at Chiba Hokusoh Hospital between 2014 and 2017 were investigated. Cases of multiple trauma accompanied by fatal trauma, hemorrhagic shock, or cardiopulmonary arrest, and pediatric cases, were excluded from this study. Blood gas data at the initial hospital visit were reviewed retrospectively. A poor outcome was defined as death during hospitalization or a vegetative state due to head injury. Factors related to poor outcomes were analyzed.

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

**Conclusions:** We evaluated blood gas data at the 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 traumatic brain injury.

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**Key words:** head injury, prognostic predictor, traumatic brain injury, glucose-to-potassium ratio

## Introduction

Severe traumatic brain injury (TBI) is a major healthcare concern worldwide[1]. Many TBI survivors live with severe disabilities. TBI rates are highest in the very young (age 0–4 years) and in adolescents and young adults (age ≥ 15 years)[2]. The enormous economic burdens resulting from severe TBI affect 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. Coagulation abnormalities are independent predictors of mortality, even in the presence of other risk factors[3]. In previous reports, D-dimer was identified as a prognostic factor for TBI[4,5]. The concern with using coagulation byproducts, such as D-dimer, as prognostic factors is that the results cannot be obtained immediately. This is disadvantageous for severe TBI patients, for whom physicians must make quick

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treatment decisions. 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 previously identified as prognostic factors in cases of subarachnoid hemorrhage[6]. 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 for other biomarkers, such as D-dimer.

## Materials and Methods

This 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 1,000 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 cases of severe trauma (injury severity score [ISS] $\geq$15) per year.

All patients with TBI treated at Chiba Hokusoh Hospital between January 2014 and December 2017 were assessed regardless of injury severity or cause, 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 [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 [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 and vital signs, among others, were reviewed from clinical records. 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 correspond to the Advanced Trauma Life Support guidelines. These guidelines provide a standardized protocol for treatment and management of severe TBI in Japan and are similar to guidelines used in other countries[8,9].

### Statistical Analysis

Statistical analysis was performed using SPSS for Mac (V.21.0; SPSS, Armonk, NY, USA). Variables are expressed as mean ± SD, median (interquartile range, 25th-75th percentiles), or number of patients (%), as appropriate. Associations of poor outcome with biomarkers at admission were investigated. Normally distributed continuous variables were compared with the Student t-test, and nonnormally distributed variables were compared with the Mann-Whitney U test. $P < 0.05$ was considered statistically significant.

## Results

### Patient Characteristics

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

Patient characteristics, cause of injury, surgical status, and surgical outcomes are presented in **Table 1**. The cause of injury was traffic accident (61.7%), fall (35.2%), and other causes (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 as having poor outcomes (P group; GOS = 1, 2).

Patient characteristics were compared between the P and good outcome (G) groups (**Table 1**). Mean patient age was 66.7 and 58.3 years, respectively, and the difference was significant ($P = 0.021$). Surgical procedures were performed in 67.6% and 5.2% of patients, respectively.

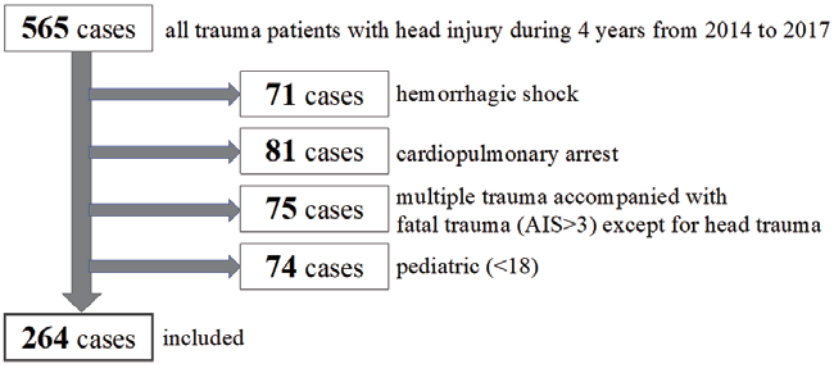


Fig. 1 Flow Diagram of patient selection.
Flow diagram of patient selection. We assessed all trauma patients with head injuries during the 4 years from 2014 through 2017. Cases of hemorrhagic shock, cardiopulmonary arrest, and multiple trauma accompanied by fatal trauma (AIS>3) except for head trauma, and all pediatric (<18 years) cases, were excluded. Thus, 264 cases were included and analyzed.

Table 1 Patient characteristics

| | | All TBI patients | Poor outcome (GOS = 1, 2) | Good outcome (GOS = 3 - 5) | P value |
|---|---|---|---|---|---|
| No. (%) | | 264 | 34 (12.9) | 230 (87.1) | |
| Age, yr. (range) | | 59.4 (18-97) | 66.7 (20-89) | 58.3 (18-97) | 0.021 |
| Male sex, no. (%) | | 185 (70.1) | 24 (70.6) | 161 (70.7) | 0.944 |
| Cause of injury, no. (%) | Traffic accident | 163 (61.7) | 17 (50.0) | 146 (63.5) | 0.089 |
| | Fall | 93 (35.2) | 14 (41.2) | 79 (34.3) | |
| | Other | 8 (3.0) | 3 (8.8) | 5 (2.2) | |
| Operation, no. (%) | | 35 (13.3) | 23 (67.6) | 12 (5.2) | <0.001 |

Operations = Intracranial Pressure (ICP): sensor insertion, decompressive craniotomy, removal of hematoma, and hematoma irrigation with trephination therapy

Poor outcome was significantly correlated with surgical procedure ($P < 0.001$). There was no significant difference in sex or cause of injury between the two groups.

We compared 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. Poor outcome was significantly correlated with GCS at admission ($P < 0.001$). There was a significant difference in heart rate (101 and 83, respectively, $P < 0.001$) but no significant difference in systolic blood pressure (159 and 149, respectively, $P = 0.062$), respiratory rate (23 and 21, respectively, $P = 0.205$), or blood temperature (35.8°C and 36.2°C, respectively, $P = 0.009$) at admission between the two groups.

Arterial blood gases at admission were compared between the two groups (**Table 2**). Poor outcome was significantly correlated 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 significant difference between groups ($P < 0.001$).

We investigated the coagulation system at admission in the two groups. Poor outcome was significantly correlated 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 results of multivariate logistic regression analysis of arterial blood gas test findings in the two groups are shown in **Table 2**. Multivariate analysis was performed

Table 2 Patient outcomes in relation to arterial blood gas variables

| | Poor outcome (n=34) | Good outcome (n=230) | Odds ratio | P value |
|---|---|---|---|---|
| Na (SD) (mEq/L) | 139 (2.84) | 140 (2.95) | | 0.828 |
| K (SD) (mEq/L) | 3.45 (0.42) | 3.72 (0.50) | | 0.003 |
| Glu (SD) (mg/dL) | 197 (55.7) | 149 (45.1) | | <0.001 |
| Glu/K (SD) | 57.4 (16.1) | 40.8 (13.4) | | <0.001 |
| Lac (SD) (mmol/L) | 3 (2.0) | 1.9 (0.98) | | <0.001 |
| Hb (SD) (g/dL) | 12.9 (2.46) | 13.8 (1.83) | | 0.011 |
| BE (± SD) (mEq/L) | –0.9 (4.1) | 1.4 (2.8) | | <0.001 |
| Glu/K ≧50 | | | 4.079 | 0.030 |
| Age | | | 1.058 | 0.005 |
| GCS | | | 0.555 | <0.001 |
| DM | | | 1.676 | 0.576 |

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

because patients with diabetes likely had high blood glucose levels. The odds ratio for a glucose-to-potassium ratio of ≥50 was 4.079 ($P$ = 0.030). A blood glucose of ≥ 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 the cutoff value as 50, which is close to 57.1 and easy to calculate.

## Discussion

We observed a strong correlation between poor TBI outcome (GOS = 1, 2) and a high 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 is a potential prognostic biomarker for severe TBI.

Hypoglycemia and hypokalemia are often observed in persons with head injuries and in those with subarachnoid hemorrhage due to aneurysm rupture[10,11]. Fujiki et al.[6] reported that hyperglycemia and hypokalemia were more useful as prognostic factors for subarachnoid hemorrhage when glucose-to-potassium ratio was calculated, as compared with glucose and potassium values alone. Therefore, we examined whether the glucose-to-potassium ratio was a useful prognostic predictor in TBI. Indeed, this ratio was a prognostic predictor for severe TBI. A blood glucose level of ≥200 is a diagnostic criterion for diabetes. If blood potassium is ≤3.5, then hypokalemia is diagnosed. In this retrospective study, the glucose-to-potassium ratio was 57.14. We used 50 as a cutoff value because it is close to 57.14 and easy to calculate.

Several studies have reported the prognostic value of coagulation indicators in patients with severe TBI[4,12,13]. However, few 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[14–16]. Ookuma et al.[17] reported that trauma patients with hypokalemia at hospital admission were likely to present with severe TBI and require decompression craniotomy. Brown et al.[18] described the mechanism by which hypokalemia occurred and reported that trauma causes an epinephrine surge that stimulates the beta receptor of adrenaline. The sodium–potassium pump is subsequently activated and transports potassium into the cell, which leads to a decrease in the blood potassium level.

Several studies assessed the association between TBI and hyperglycemia in children[19,20] but not in adults. In pediatric head injuries, hyperglycemia is an independent prognostic factor[21,22]. Regarding the mechanism by which hyperglycemia occurs in trauma, Rolih et al.[23] reported that stress hormones such as glucocorticoid, growth hormone, glucagon, and epinephrine are activated as a normal response to 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 follows trauma, in both children and 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, it is a retrospective study conducted at a single center. Second, the medical history and any internal medication that could have led to hypokalemia were not examined. Third, cases of fatal trauma (AIS > 3) other than TBI were excluded,

but the effects of other traumas in patients presenting with multiple injuries were not considered. Because of these limitations, our claims will need to be confirmed in future studies.

Glucose-to-potassium ratio was a prognostic factor for severe TBI. We assessed biochemical variables in arterial blood gas test data at initial hospital admission, which can be obtained more quickly than previous biomarkers, and we identified a new biomarker. A serum glucose-to-potassium ratio of $\geq$50 at admission may be a new biomarker of prognosis for severe TBI. Use of this new biomarker might lead to earlier prediction of prognosis for severe TBI and might be useful when rapid decision-making is required by physicians.

**Conflict of Interest:** The authors declare no conflicts of interest.

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