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Original Article

Study of certain easily available biochemical markers in prognostication in severe traumatic brain injury requiring surgery

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ABSTRACT

Background: This study aimed to identify easily available prognostic factors in severe traumatic brain injury (TBI) patients undergoing craniotomy.

Methods: We retrospectively analyzed the clinical characteristics (age, sex, Glasgow coma scale score, cause of TBI, and oral antithrombotic drug use), laboratory parameters (hemoglobin, sodium, C-reactive protein, D-dimer, activated partial thromboplastin time, prothrombin time-international normalized ratio, and glucose-potassium [GP] ratio), and neuroradiological findings of 132 patients who underwent craniotomy for severe TBI in our hospital between January 2015 and December 2021. The patients were divided into two groups: Those with fatal clinical outcomes and those with non-fatal clinical outcomes, and compared between the two groups.

Results: The patients comprised 79 (59.8%) male and 53 (40.2%) female patients. Their mean age was 67 ± 17 years (range, 16–94 years). Computed tomography revealed acute subdural hematoma in 108 (81.8%) patients, acute epidural hematoma in 31 (23.5%), traumatic brain contusion in 39 (29.5%), and traumatic subarachnoid hemorrhage in 62 (47.0%). All 132 patients underwent craniotomy, and 41 eventually died. There were significant differences in the D-dimer, GP ratio, and optic nerve sheath diameter between the groups (all $P < 0.01$). Multivariate logistic regression analysis showed elevated GP ratio and D-dimer were associated with the death group ($P < 0.01$, $P < 0.01$, respectively). A GP ratio of >42 was the optimal cutoff value for the prediction of a fatal outcome of TBI (sensitivity, 85.4%; specificity, 51.1%).

Conclusion: The GP ratio and D-dimer were significantly associated with poor outcomes of TBI. A GP ratio of >42 could be a predictor of a fatal outcome of TBI.

Keywords: Neurosurgery, Prognostic factors, Traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) remains a common cause of death and disability worldwide.[5] In severe cases, it is important to assess the severity in the initial emergency setting due to the need for treatment in the acute phase. Recently, S100B, glial fibrillary acid protein (GFAP), neuron-specific enolase, and ubiquitin C-terminal hydrolase-L1 (UCH-L1) have become available for evaluation of the severity of TBI and proven to be effective as prognostic factors.[2,3,13] However, these tests are costly and available in only a few facilities. There are some well-known and easy-to-use classical biomarkers for TBI, including age, the Glasgow coma scale (GCS) score, pupil size, and D-dimer level.[9,16,19] International mission for prognosis and clinical trials (IMPACT) in TBI, corticosteroid randomization after significant head (CRASH) injury, GCS pupils age (GCS-PA), and Madras Head Injury Prognostic Scale (MHIPS) are also very useful systems for predicting TBI prognosis.[12,15-17] Patient age, GCS, pupil reaction to light, computed tomography (CT) findings, oculocephalic reflex, and systemic injuries are listed as risks in these scales. This study aimed to identify other prognostic biochemical factors that are readily accessible in the general emergency care setting and can be used to predict the survival outcome in patients with severe TBI who undergo craniotomy.

MATERIALS AND METHODS

Study design and patient selection

The study had a retrospective and observational single-center design and included 153 patients with TBI who underwent open surgery between January 2015 and December 2021. Patients with multiple trauma (moderate or severe trauma with an abbreviated injury scale score >3 at sites other than the brain, $n = 15$) and those who died from systemic disease ($n = 6$) were excluded from the study. Finally, 132 patients were enrolled [Figure 1]. The study was approved by the Committee on Human Research at Saitama International Medical Center (approval number 2022–051). The requirement for informed consent was waived due to the retrospective nature of the study.

Data collection and diagnostic modalities

We collected the following patient data on arrival in the emergency room: age, sex, GCS score, cause of TBI, oral antithrombotic drug use, blood tests including hemoglobin (g/dL), sodium (mEq/L), C-reactive protein (mg/dL), D-dimer (mg/dL), activated partial thromboplastin time(s), prothrombin time-international normalized ratio, and glucose and potassium. The specific glucose-potassium (GP) ratio is calculated in peripheral blood measurements and has been reported to be a useful biomarker of subarachnoid hemorrhage.[4,14]

Findings on CT were reviewed for patients who had scans before, immediately after, and one-day post-surgery. We confirmed the diagnosis of TBI and assessed the CT images for the occurrence of injury-related cerebral infarction. Most cases of injury-related cerebral infarction could not be detected by preoperative CT alone and required confirmation on postsurgical CT images. Optic nerve sheath diameter (ONSD) was measured on the preoperative CT images. ONSD is easily obtained in the initial emergency care setting, and it has been reported that a diameter wider than 5 mm indicates increasing intracranial pressure (ICP).[8] ONSD was defined as the diameter of the optic nerve sheath. We measured ONSD 3 mm posterior to the eyeball on CT axial images depicting the center of the eyeball [Figure 2].[8]

Surgical procedures

The indication for surgery was based on the Japanese Neurotrauma Society guidelines.[21] Hematoma evacuation was performed in 52 patients (39.4%), and additional decompressive craniectomy in 80 (60.6%). An ICP monitor was inserted depending on the case.

Statistical analysis

Quantitative variables were expressed as the mean ± standard deviation or the median (range) as appropriate. Normally distributed variables were compared using the Student's *t*-test, and non-normally distributed variables using the Mann–Whitney U-test. Multivariable logistic regression analysis was performed on factors that showed a significant between-group difference in univariate analysis. $P < 0.05$

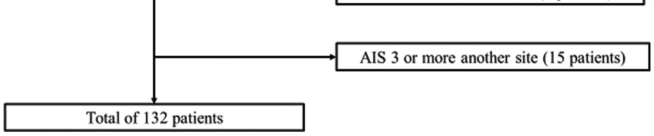

Figure 1: Findings in 153 patients with traumatic brain injury in whom craniotomy was

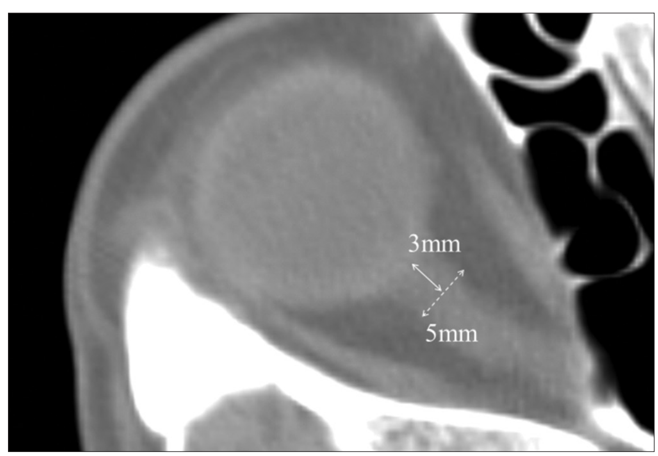

Figure 2: Method used to calculate optic nerve sheath diameter.

was considered statistically significant. The optimal cutoff value on the receiver-operating characteristic (ROC) curve was determined based on the Youden index. All statistical analyses were performed with Easy R (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[7]

RESULTS

The clinical characteristics of the 132 patients are shown in Table 1. The average patient age was 67 ± 17 years (range, 16–94); 79 patients (59.8%) were male and 53 (40.2%) were female. The GCS score was 13–15 in 35 patients, 8–12 in 17, and 3–8 in 77, and was not recorded in three patients. Forty-one patients used antithrombotic agents, which consisted of antiplatelet agents in 22 (16.7%), warfarin in 15 (11.4%), and direct oral anticoagulants in four (3%). The most common mechanism of injury was a fall from standing height (36%). Other causes included road traffic injury (24%), a fall from height (17%), and an unknown cause due to no witnesses (23%) [Figure 3].

CT revealed acute subdural hematoma (ASDH) in 108 patients (81.8%), acute epidural hematoma (AEDH) in 31 (23.5%), traumatic brain contusion in 39 (29.5%), and traumatic subarachnoid hemorrhage in 62 (47%). ASDH complicated other TBI in 56% of cases, as AEDH complicated in 68% of cases [Figure 4]. Some patients had multiple CT findings, so the total percentage of CT findings exceeds 100%. All 132 patients underwent craniotomy, and 41 eventually died. The preoperative CT findings revealed a significantly higher incidence of injury-related cerebral infarction and a significantly greater likelihood of concomitant cerebral contusion in the group with a fatal outcome, whether ASDH or AEDH ($P < 0.01$) [Table 2]. There were significant between-group differences in the D-dimer level, GP ratio, and ONSD (all $P < 0.01$ [Table 3]). Multivariate logistic regression analysis showed that a fatal outcome was associated with the GP ratio (odds ratio [OR] 1.03; 95% confidence interval [CI] 1.010–1.060, $P < 0.01$) and D-dimer level (OR 1.01; 95% CI 1.010–1.020, $P < 0.01$) [Table 4]. ROC curve analysis revealed that a GP level of 42 (area under the curve [AUC] 0.701, 95% CI 0.602–0.799) was the cutoff value for a fatal outcome (sensitivity, 85.4%; specificity, 51.1%) [Figure 5]. At a cutoff value of 55 (AUC 0.711, 95% CI 0.619–0.803), the GP ratio had a sensitivity of 54.2% and a specificity of 81.5% for injury-related cerebral infarction [Figure 6]. ROC curve analysis also revealed that a D-dimer level of 53 (AUC 0.742, 95% CI 0.641–0.844) was the cutoff value for a fatal outcome (sensitivity, 65%; specificity, 80.5%).

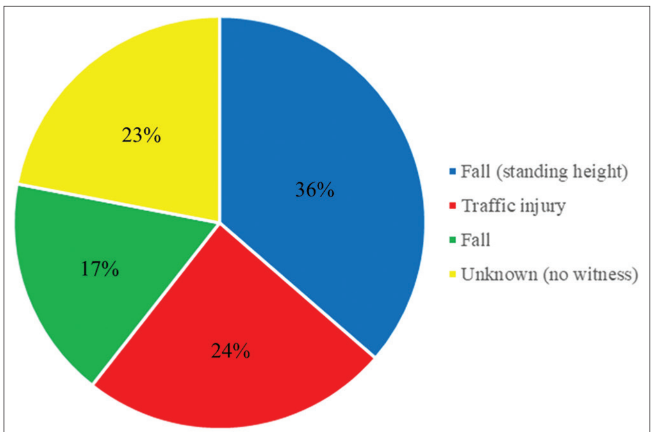

Figure 3: Mechanisms of injury.

Table 1: Characteristics of 132 patients with severe traumatic injury in whom craniotomy was required.

Variables	Patients (*n*=132)
Age in years	67±17
Male sex	79 (59.8)
Antiplatelet of anticoagulant drug	
Warfarin	15 (11.4%)
Antiplatelet drug	22 (16.7%)
Direct oral anticoagulant	4 (3%)
Glasgow coma scale 13-15	35 (26.5%)
8-12	17 (12.9%)
3-8	77 (58.3%)
No records	3 (2.3%)

DISCUSSION

There have been several studies of prognostic factors and scales for TBI, but none have identified any factors that definitely predict the prognosis. In this study, we focused on clinical biochemical data, which can be collected easily from a peripheral blood sample or on CT scans other than prognostic factors in several scales.[12,15-17] Our data indicate that the GP ratio was a significant prognostic factor in terms of the survival outcome in patients with TBI. We also found a relationship between the GP ratio and injury-related cerebral infarction.

Epinephrine is well known to be released under stressful conditions, including TBI, and induces an increase in potassium and glucose.[10] Several studies have reported that the GP ratio is a useful prognostic factor in patients with intracerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage due to ruptured aneurysm, and TBI.[4,14,11,18,20,22] Shibata *et al.*[18] reported that a GP ratio of ≥50 was associated

Table 2: Findings on computed tomography identified to be statistically significant by the Chi-squared test.

	Death *n*=41	Non-death *n*=91	*P* value
Concomitant cerebral contusion	19 (46%)	20 (22%)	<0.01
Appearance of new postoperative brain infarction	32 (78%)	16 (18%)	<0.01

Table 3: Univariate analysis of prognostic factors in patients with traumatic brain injury who had a fatal outcome.

Variable	Death *n*=41	Non-death *n*=91	*P* value
Blood examination			
Hemoglobin	12.1±2.5	12.3±2.4	0.913
Sodium	139.1±3.8	137.9±5.0	0.313
C-reactive protein	1.04±2.5	1.2±2.5	0.463
D-dimer	98.5±80.9	35.4±48.7	<0.01
Activated partial thromboplastin time	34.5±11.7	31.3±9.3	0.115
Prothrombin time-international normalized ratio	1.5±1.1	1.31±0.84	0.0581
Glucose potassium ratio	57.5±19.7	45.3±16.4	<0.01
Computed tomography findings			
Optic nerve sheath diameter	6.0±0.9	5.6±0.8	<0.01

Table 4: Prognostic factors in patients with traumatic brain injury identified to be significant in a multivariate logistic regression model.

Variable	Odds ratio	95% Confidence interval	*P* value
Glucose potassium ratio	1.03	1.010-1.060	0.0102
D-dimer	1.01	1.010-1.020	0.00012
ONSD	1.68	0.985-2.860	0.0569

ONSD: Optic nerve sheath diameter

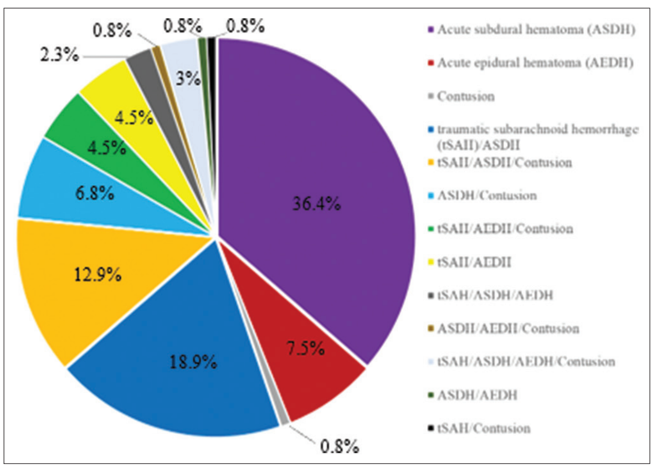

Figure 4: Diagnosis of traumatic brain injury.

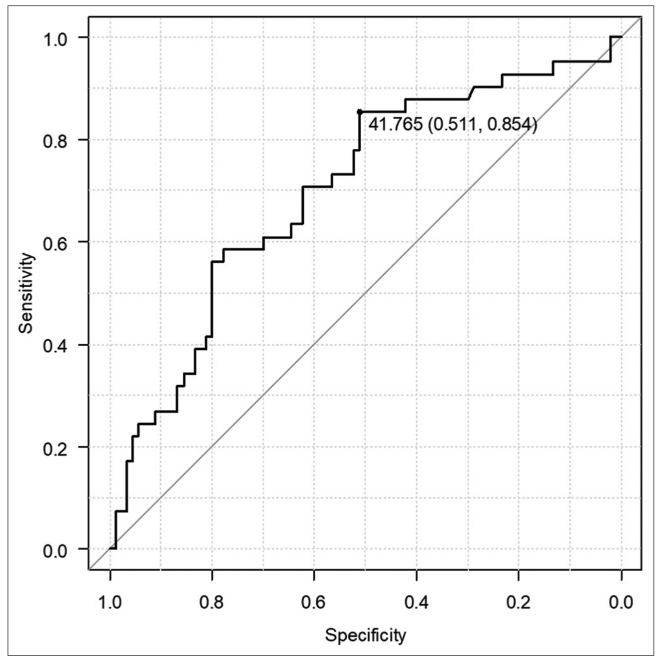

Figure 5: Prognostic factors identified by receiver-operating characteristic curve analysis to be significant in patients with a fatal outcome after traumatic brain injury.

with a poor prognosis in patients with TBI. Similarly, in our study, the GP ratio could predict the survival outcome in patients with severe TBI requiring open neurosurgery. Furthermore, ROC curve analysis showed that a GP ratio >42 could predict a fatal outcome. The GP ratio may be an important prognostic factor in patients with TBI before open neurosurgery is performed.

We also identified a relationship between the GP ratio and injury-related cerebral infarction. A GP ratio of 55 was the cutoff value for injury-related cerebral infarction. S100B, GFAP, neuron-specific enolase, and UCH-L1 have been reported to be specific biomarkers after TBI. Joseph *et al.*[6] found a relationship between the S100B level and secondary ischemic lesions after TBI. GFAP was also reported to be useful for predicting CT abnormalities in patients with TBI.[13] However, the use of these biomarkers poses several difficulties,[1] including being costly and time-consuming. The GP ratio is a biomarker that is inexpensive and can be calculated in the routine emergency care setting. In our study, the GP ratio was also useful for confirmation of injury-related cerebral infarction due to its high specificity (81.5%). Still, GP ratio cannot be a universal predictor by itself. GP is just a biochemical marker and must be judged comprehensively using physical examination, level of consciousness, neuroradiological findings, and useful prognostic scales such as IMPACT, CRASH, GCS-PA, and MHIPS.[12,15-17]

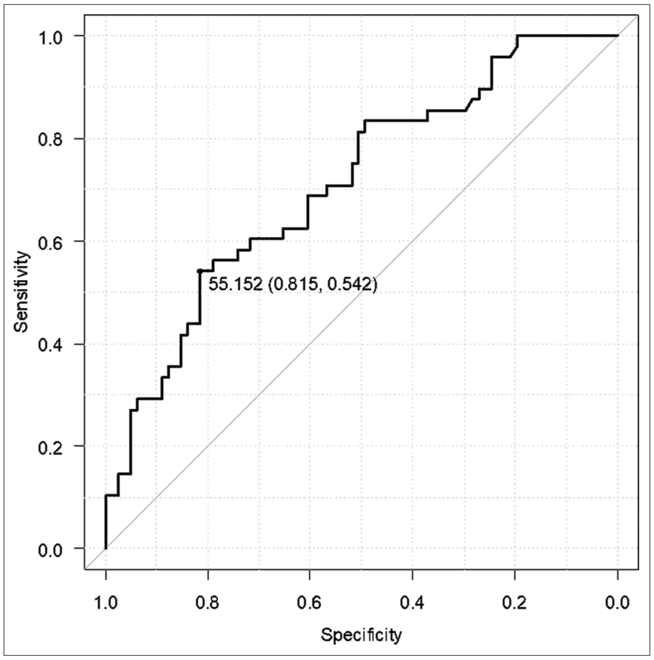

Figure 6: Receiver-operating characteristic curve analysis of the postoperative appearance of new postoperative brain infarction.

As previously reported,[19] we found that the D-dimer level was related to the survival outcome after TBI. However, although optic ONSD is known to be correlated with elevation of ICP, it was not correlated with the survival outcome after TBI in this study. A possible explanation for this finding is that ONSD reflects monophasic rather than progressive elevation of ICP.[8]

This study has several limitations. First, it only included Japanese patients who underwent open neurosurgery at a single center. Second, the analyzed data were obtained from patients undergoing open neurosurgery that several neurosurgeons performed. The guidelines were followed regarding surgical indications, but it was left to the individual surgeon whether to perform external decompression or ICP sensor insertion, which might have affected the outcome. Third, the results in terms of the GP ratio might have been affected by the inclusion of patients with diabetes and chronic renal impairment, both of which affect potassium and glucose levels.

CONCLUSION

In this study, there was a significant relationship between the GP ratio and D-dimer level and the survival outcome in patients with TBI. For the GP ratio, the cutoff value was 42 for the prediction of death and 55 for the prediction of injury-related cerebral infarction. Our findings suggest that the GP ratio should be measured in patients with TBI requiring open neurosurgery.

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Ethical approval

The author(s) declare that they have taken the ethical approval from the IEC (approval number 2022–051).

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

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