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Relationship between growth differentiation factor 15 and functional prognosis and severity in traumatic brain injury

Hiroshi Ito, Takeshi Ebihara✉, Hisatake Matsumoto & Jun Oda

Circulating growth differentiation factor 15 (GDF-15) increases in response to inflammation and tissue damage. Its association with functional prognosis in cerebral infarction and subarachnoid hemorrhage is established; however, its role in traumatic brain injury (TBI) and its relationship with Sequential Organ Failure Assessment (SOFA) score, an indicator of systemic organ damage in TBI, remains unclear. This study aimed to explore the correlation between GDF-15 and functional outcomes at discharge in patients with TBI and stroke, including its association with SOFA scores in TBI. Patients with cerebral infarction, subarachnoid hemorrhage, and TBI transported within 24 h from July 2020 to August 2022 were included. Multivariable logistic regression analyzed the relationship between GDF-15 levels at admission and functional outcomes at discharge, with age and sex as covariates. Additionally, correlations between GDF-15 levels and SOFA scores were assessed. Multivariable logistic regression showed a relationship between GDF-15 levels at admission and functional outcomes at discharge in cerebral infarction and subarachnoid hemorrhage but not in TBI. In TBI cases, GDF-15 correlated with SOFA scores, indicating its potential as a TBI severity marker. Although functional prognosis at discharge was evaluated, long-term outcomes were not clear, and this will be addressed in future research.

Keywords Growth differentiation factor 15, Traumatic brain injury, Sequential organ failure assessment score

Growth differentiation factor 15 (GDF-15) is a member of the transforming growth factor cytokine superfamily[1] and is generally produced at low levels in most human tissues except the placenta[2]. Previous studies have found that circulating blood GDF-15 levels are associated with cardiovascular risk factors such as age, smoking, and diabetes[3] and that GDF-15 expression substantially increases under pathological conditions such as oxidative stress, hypoxia, inflammation, and tissue damage[4]. In sepsis and burns, GDF-15 levels are associated with the Sequential Organ Failure Assessment (SOFA) score, which indicates organ damage, and GDF-15 is also considered an indicator of systemic severity. GDF-15 has also been reported to be associated not only with systemic severity but also with death[5,6].

GDF-15 has also been linked to central nervous system (CNS) diseases. In animal models of cerebral ischemia, GDF-15 was upregulated in ischemic brain lesions[7], and its level in the circulating blood was also elevated[8]. In the CNS, GDF-15 in the blood acts on GDF-15 receptors to regulate food intake and body weight[9]. The relationship between GDF-15 levels in plasma after onset and functional prognosis has been reported in cerebral infarction and subarachnoid hemorrhage with CNS damage[10–12]. As vascular stress, such as hypertension, is considered to be one of the factors that increase the risk of stroke and subarachnoid hemorrhage[13], GDF-15 is thought to reflect vascular stress before disease onset. It has also been suggested that GDF-15 levels reflect oxidative stress following brain damage and disease onset. Measuring GDF-15 levels at the time of hospital admission is considered useful in predicting prognosis.

Therefore, GDF-15 is considered a critical indicator of various diseases. However, this has not yet been reported in trauma. The pathogenesis of trauma varies; therefore, we considered that GDF-15 may similarly be associated with functional prognosis in traumatic brain injuries (TBIs) with damage to the CNS, as it is associated with prognosis in stroke. We also considered that GDF-15 may be associated with SOFA scores, which is also an indicator of severity, head trauma, sepsis, and burns. It is crucial to recognize not only the functional prognosis

Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine, 2- 15 Yamada-oka, Osaka 565-0871, Japan. ✉email: ebihara.830@hp-emerg.med.osaka-u.ac.jp

but also the overall injury severity before proceeding with TBI treatment. To date, the relationship between GDF-15 levels, functional prognosis, and SOFA score has not been investigated in head trauma. Understanding these relationships could improve the recognition of functional prognosis and severity in patients with TBIs. The primary endpoint of this study was to compare TBI, cerebral infarction, and subarachnoid hemorrhage and to determine the association between GDF-15 levels and functional prognosis at discharge in TBI. The secondary endpoint was to determine the correlation between GDF-15 and SOFA scores in TBI.

Methods

The study protocol complied with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Osaka University Hospital (Permit Number: 885 [Osaka University Critical Care Consortium Novel Omix Project; Occonomix Project]). Written informed consent was obtained from the patients or their relatives and healthy volunteers to collect blood samples. The study included patients with cerebral infarction, subarachnoid hemorrhage, or TBI who were admitted within 24 h of onset to our emergency center between July 2020 and August 2022. Only cases where residual plasma specimens collected for blood tests on the day of admission were preserved were included. The definitions of cerebral infarction, subarachnoid hemorrhage, and TBI were as follows. Cerebral infarction diagnosis was based on the presence of neuroimaging findings such as high-signal intensity diffusion-weighted image on magnetic resonance imaging or vascular occlusion on contrast-enhanced computed tomography (CT) and the presence of acute focal neurologic deficit. Subarachnoid hemorrhage diagnosis was made based on CT of the subarachnoid space. TBI was defined as acute intracranial hemorrhage due to traumatic injury and an Abbreviated Injury Scale (AIS) < 3 other than head injury. The healthy control population was comprised of healthy individuals recruited through a public poster. Data collected from electronic medical records by the investigators included age; sex; comorbidities (hypertension, coronary artery disease, diabetes, chronic renal failure); Glasgow Coma Scale (GCS) on admission; systolic and diastolic blood pressure on admission; blood draw data on days 1, 3, and 7; SOFA scores on days 1, 3, and 7; National Institutes of Health Stroke Scale; World Federation of Neurosurgical Societies classification; head AIS score; type of traumatic intracranial hemorrhage; neurosurgical surgery performed; modified Rankin Scale (mRS) at discharge; and Glasgow Outcome Scale (GOS) at discharge. In this study, good functional prognosis was defined as mRS 0–3 at discharge for cerebral infarction and subarachnoid hemorrhage and GOS 4–5 at discharge for TBI. Neurosurgical procedures were defined as coil embolization, clipping, craniotomy, decompressive craniectomy, or trepanation.

Samples were plasma residuals from blood draws performed on days 1, 3, and 7 (maximum of three-time points/case). Samples were also collected from volunteers on days without any physical problems. Samples were stored at -30 °C until analysis, and GDF-15 was assayed by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA) to determine plasma levels. Absorbance was measured using a microplate reader (SH-9000Lab; Corona Electric Co., Japan).

Summary data were presented as medians (interquartile ranges) for continuous variables and numbers (%) for categorical variables. The Mann–Whitney U test was used to detect differences between the two groups for items with continuous variables, and the chi-square test or Fisher's exact test for items with categorical variables. Univariable and multivariable logistic regression analyses were performed to determine the effect of GDF-15 level on functional prognosis, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The objective variable was poor functional prognosis, the explanatory variable was GDF-15 level (day 1). For cerebral infarction and subarachnoid hemorrhage, age was used as the adjustment factor, whereas for TBI, age and sex were used as adjustment factors[14–17]. Scatter plots were drawn for GDF-15 and SOFA scores for TBI cases on days 1, 3, and 7. The total SOFA score was treated as a continuous variable, whereas the SOFA subscore for each organ was treated as an ordinal variable, given that the intervals between each point were not necessarily equivalent. Correlation coefficients and P-values were calculated. A similar analysis was also performed for each day of the study. In addition, as part of a sensitivity analysis, correlation coefficients and P-values for GDF-15 were recalculated when the total SOFA score was treated as an ordinal variable or when it was stratified by hematoma morphology.

Correlation coefficients and P-values were evaluated for the GDF-15 and SOFA scores for each organ subscore for all days of the study (days 1, 3, and 7). The same analysis was also performed for each hospital day. Statistical analysis was performed using commercially available statistical analysis software (JMP pro 16 software, SAS Institute Inc. Cary, NC, USA). P-values < 0.05 were considered statistically significant.

Results

Patient background and GDF-15 by disease

A total of 129 patients with cerebral infarction, 36 patients with subarachnoid hemorrhage, and 69 patients with TBI were admitted to the hospital during the study period. Among these, 17 cerebral infarction cases, 19 subarachnoid hemorrhage cases, and 37 TBI cases had plasma stored from their blood samples on the day of admission and were included in the study. Twenty healthy controls participated in this study.

The median age and the number and percentage of males in the analyzed cases were as follows: 78.0 years and 9 (52.9%) for cerebral infarction cases, 61.0 years and 6 (31.6%) for subarachnoid hemorrhage cases, 62.0 years and 22 (59.5%) for patients with TBI, and 70.5 years and 13 (65.0%) for healthy controls, respectively. The median GDF-15 level on the day of admission was 589.7 pg/mL for cerebral infarction, 602.2 pg/mL for subarachnoid hemorrhage, and 908.0 pg/mL for patients with TBI, which was significantly higher in patients with TBI than in healthy controls. GDF-15 levels were significantly increased in patients with subarachnoid hemorrhage and TBI on days 3 and 7 compared to healthy controls (Table 1). Note that GDF-15 levels were not measured on day 7 for all cerebral infarction cases, as day 7 specimens were not stored. Among patients with

Characteristic	Cerebral infarction (*n* = 17)	*P*-value	Subarachnoid hemorrhage (*n* = 19)	*P*-value	Traumatic brain injury (*n* = 37)	*P*-value	Healthy control (*n* = 20)
Age*, median (IQR), years	78.0 (69.0–88.5)	0.02	61.0 (49.0–66.0)	0.03	62.0 (40.0–78.5)	0.29	70.5 (60.0–76.0)
Male sex*, n (%)	9 (52.9)	0.46	6 (31.6)	0.04	22 (59.5)	0.68	13 (65.0)
Comorbidities							
Hypertension, n (%)	11 (64.7)		7 (36.8)		13 (35.1)		0 (0.0)
Coronary artery disease, n (%)	0 (0.0)		0 (0.0)		2 (5.4)		0 (0.0)
Diabetes mellitus, n (%)	4 (23.5)		0 (0.0)		1 (2.7)		0 (0.0)
Chronic kidney disease, n (%)	1 (5.9)		1 (5.2)		2 (5.4)		0 (0.0)
Admission GCS, median (IQR)	10 (6–14)		6 (4–14)		8 (6–13.5)		-
Admission GCS ≦ 8, n (%)	7 (41.2)		10 (52.6)		20 (54.1)		-
Admission GCS ≧ 9, ≦12, n (%)	3 (17.6)		3 (15.8)		5 (13.5)		-
Admission GCS ≧ 13, ≦15, n (%)	7 (41.2)		6 (31.6)		12 (32.4)		-
Admission systolic blood pressure, median (IQR), mmHg	164 (150.5- 188.5)		165 (139–192)		148 (133.5–168)		-
Admission diastolic blood pressure, median (IQR), mmHg	96 (85.0–110.5)		98 (86–131)		91 (76–104)		-
SOFA score (day 1), median (IQR)	6 (2–4)		4 (2–5)		3 (2–5)		-
WFNS grade	-				-		-
Grade I, n (%)	-		4 (21.1)		-		-
Grade II, n (%)	-		1 (5.3)		-		-
Grade III, n (%)	-		1 (5.3)		-		-
Grade IV, n (%)	-		3 (15.8)		-		-
Grade V, n (%)	-		10 (52.6)		-		-
NIHSS, median (IQR)	21 (5–28.5)		-		-		-
AIS - head, median (IQR)	-		-		4 (2–5)		-
Type of traumatic intracranial hemorrhage, n (%)	-		-				
ASDH	-		-		18 (48.6)		-
AEDH	-		-		5 (13.5)		-
Contusion	-		-		4 (10.8)		-
tSAH	-		-		10 (27.0)		-
Type of neurosurgery, n (%)	0 (0.0)		18 (94.7)		26 (70.3)		-
Coil embolization	0 (0.0)		16 (84.2)		-		-
Clipping	0 (0.0)		3 (15.8)		-		-
Craniotomy	0 (0.0)		-		10 (27.0)		-
Decompressive craniectomy	0 (0.0)		-		8 (21.6)		-
Trepanation	0 (0.0)		-		8 (21.6)		-
GDF-15 (day 1)*, median (IQR), pg/mL	589.7 (394.9–782.4)	0.52	602.2 (411.3–811.0)	0.34	908.0 (473.1–1722.7)	**0.005**	505.8 (344.6–654.8)
GDF-15 (day 3)*, median (IQR), pg/mL	729.3 (494.5–1095.5)	0.08	773.0 (534.3–996.2)	**0.02**	958.4 (693.1–1561.9)	**< 0.001**	-
GDF-15 (day 7)*, median (IQR), pg/mL	-		751.2 (621.3–899.0)	**0.02**	1185.6 (796.5–2073.4)	**< 0.001**	-
Unfavorable functional outcome at discharge, n (%)	12 (70.6)		10 (52.6)		24 (64.9)		-
GOS at discharge, median (IQR)	-		-		3 (2–4)		-
mRS at discharge, median (IQR)	4 (3–5)		4 (0–5)		-		-
In-hospital mortality, n (%)	1 (5.9)		0 (0.0)		5 (13.5)		-

Table 1. Patient characteristics and comparison with healthy control. IQR: interquartile range, GCS: Glasgow coma scale, SOFA score: sequential organ failure assessment score, NIHSS: national institutes of health stroke scale, WFNS grade: world federation of neurosurgical societies grade, AIS: abbreviated injury scale, ASDH: acute subdural hematoma, AEDH: acute epidural hematoma, tSAH: traumatic subarachnoid hemorrhage, GDF-15: growth differentiation factor 15, GOS: Glasgow outcome scale, mRS: modified rankin scale. *Comparison with healthy control.

TBI, 20 (54.1%) had severe TBI (GCS ≤ 8), 5 (13.5%) had moderate TBI (GCS ≥ 9, ≤12), and 12 (32.4%) had mild TBI (GCS ≥ 13, ≤15) (Table 1). In addition, the GDF-15 value on day 1 for each hematoma morphology in TBI was highest for contusion (1653.0 pg/mL) (Table S1).

Relationship between GDF-15 and functional prognosis

The number and percentage of patients with poor functional prognosis at discharge from the hospital were 12 (70.6%) for cerebral infarction, 10 (52.6%) for subarachnoid hemorrhage, and 24 (64.9%) for patients with TBI, respectively (Table 1). The background factors of patients with good functional prognoses at discharge and those with poor prognoses were compared between the two groups (Table 2). Significant differences in SOFA score (day 1) were observed between the good and poor functional outcome groups in cerebral infarction, subarachnoid hemorrhage, and TBI. In patients with cerebral infarction and subarachnoid hemorrhage, there were differences in GDF-15 levels on day 1, but no significant differences were observed on days 3 and 7 between the good and poor functional outcome groups. In TBI, there was no difference in GDF-15 levels on days 1, 3, and 7. Patients with TBI had good prognoses, and those with poor prognoses showed differences in SOFA scores on days 3 and 7 (Table S2).

Logistic regression analysis was performed to evaluate the effect of day 1 GDF-15 levels on poor functional prognosis at discharge. For cerebral infarction, the adjusted OR for GDF-15 (day 1) was 1.02 (95% CI: 0.98–1.07, $P = 0.01$). For subarachnoid hemorrhage, the adjusted OR for GDF-15 (day 1) was 1.00 (95% CI: 1.00–1.01, $P = 0.02$). For TBI, the adjusted OR for GDF-15 (day 1) was 1.00 (95% CI: 1.00–1.00, $P = 0.57$) (Table 3).

Relationship between GDF-15 and SOFA score in head injury

In TBI, GDF-15 levels were higher than those in healthy controls, although no difference was found between good and poor prognosis on hospital days 1, 3, and 7. We hypothesized that GDF-15 levels are elevated post-TBI because of post-injury stress. Therefore, we evaluated its association with SOFA scores. We analyzed the correlation between all GDF-15 values measured on days 1, 3, and 7 after hospital admission and the SOFA score on each hospital day and found a correlation ($r = 0.25$, $P = 0.02$) (Fig. 1). When each hospital day was evaluated in the same manner, no correlation was observed for day 1 ($r = 0.33$, $P = 0.05$), day 3 ($r = 0.23$, $P = 0.2$), or day 7 ($r = 0.25$, $P = 0.26$) (Fig. 2). In the sensitivity analysis, when the SOFA score was analyzed as an ordinal variable, a correlation was observed between GDF-15 and the SOFA score. However, no correlation was observed when hematoma morphology was categorized (Tables S3 and S4).

To evaluate which organ disorders comprising the SOFA score were most associated with GDF-15, we assessed the correlation coefficient and P-value between GDF-15 and each organ sub-score of the SOFA score on days 1, 3, and 7. A correlation was observed between cardiovascular ($r = 0.21$, $P = 0.04$) and renal functions ($r = 0.42$, $P < 0.01$). The same evaluation on days 1 and 3 showed an association with renal function: day 1 ($r = 0.38$, $P = 0.02$) and day 3 ($r = 0.50$, $P < 0.01$), with all correlations linking to renal function (Table 4).

Discussion

GDF-15 expression is considered to be related to two factors: the possibility that GDF-15 is expressed owing to oxidative stress in blood vessels before stroke onset and the possibility that its expression increases because of pathological stress after stroke onset[18]. The elevated GDF-15 levels in patients with stroke on days 3 and 7 after hospitalization compared to that in healthy controls suggests that GDF-15 production is low immediately after stroke onset but increases over time owing to post-onset pathological stress. In TBI, GDF-15 levels were elevated immediately after injury, indicating that stress before or immediately after TBI has a similar effect on GDF-15.

For cerebral infarction and subarachnoid hemorrhage, GDF-15 levels on admission day have been reported to be associated with mRS at 90 days[10–12]. In the present cohort, we evaluated cerebral infarction and subarachnoid hemorrhage cases and found significant differences in admission-day GDF-15 values between patients with good and poor functional prognoses at discharge. Similar results were obtained when GDF-15 levels and functional prognosis at discharge were evaluated separately for cerebral infarction and subarachnoid hemorrhage. When the data were adjusted for age and sex as factors potentially associated with functional prognosis before the onset of cerebral infarction and subarachnoid hemorrhage, an association was found between GDF-15 levels on admission day and functional prognosis at discharge, confirming a trend similar to that reported previously. However, the relationship between admission day GDF-15 levels and functional prognosis has not been reported for TBI. In the present study, we examined the relationship between GDF-15 and functional prognosis and found no significant difference in admission-day GDF-15 levels between good and poor functional prognoses at discharge in patients with TBI. Multivariate analysis of the association between GDF-15 levels on admission and functional outcomes at discharge, the primary endpoint, confirmed no association between GDF-15 levels on admission and functional outcomes at discharge. GDF-15 may be associated with a different pathophysiology than the functional prognosis in TBI.

Although an association between GDF-15 and SOFA scores has been reported in sepsis and burn injuries[5,6], the relationship between GDF-15 and SOFA scores in TBI has not been clarified. Therefore, we determined the correlation between GDF-15 and SOFA scores in TBI as a secondary endpoint.

First, we found a correlation between the SOFA score and GDF-15 level when all hospital days (days 1, 3, and 7) were evaluated together. The correlation coefficients and P-values of GDF-15 with the subscores of each of the six organ damage components of the SOFA score were evaluated. GDF-15 was significantly correlated with renal function on all hospital days (days 1, 3, and 7), as well as specifically on days 1 and 3. Although assessing the estimated GCS was challenging in some cases owing to sedation, no significant differences were observed in the CNS on any hospital day[19]. These results suggest that GDF-15 is most related to renal function among SOFA scores, while it is less related to the CNS, which is directly injured. This may be one finding that in TBI, GDF-15 is unlikely to be an indicator of head-limited pathological stress and that GDF-15 is not associated with

Characteristic	Cerebral infarction			Subarachnoid hemorrhage			Traumatic brain injury		
	Good functional outcome (*n* = 5)	Poor functional outcome (*n* = 12)	*P*-value	Good functional outcome (*n* = 9)	Poor functional outcome (*n* = 10)	*P*-value	Good functional outcome (*n* = 13)	Poor functional outcome (*n* = 24)	*P*-value
Age, median (IQR), years	72 (49–77.5)	84 (70.8–89)	**0.04**	57 (41–64.5)	64.5 (50.5–69)	0.19	43 (30–59)	69.5 (50.8–79)	**0.01**
Male sex, n (%)	3 (60.0)	6 (50.0)	1.00	3 (33.3)	3 (30.0)	1.00	8 (61.5)	14 (58.3)	1.00
Comorbidities									
Hypertension, n (%)	3 (60.0)	8 (66.7)		3 (33.3)	4 (40.0)		1 (7.7)	12 (50.0)	
Coronary artery disease, n (%)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	2 (8.3)	
Diabetes mellitus, n (%)	0 (0.0)	4 (33.3)		0 (0.0)	0 (0.0)		0 (0.0)	1 (4.2)	
Chronic kidney disease, n (%)	0 (0.0)	1 (8.3)		0 (0.0)	1 (10.0)		0 (0.0)	2 (8.3)	
Admission GCS, median (IQR)	15 (11.5–15)	7 (5.3–12.8)	**0.02**	14 (3.5–15)	6 (4–9.3)	0.30	13 (9–14.5)	7 (3.8–10.8)	**0.04**
Admission GCS ≦ 8, n (%)	0 (0.0)	7 (58.3)	**0.04**	3 (33.3)	7 (70.0)	0.18	3 (23.1)	17 (70.8)	**< 0.01**
Admission GCS ≧ 9, ≦12, n (%)	1 (20.0)	2(16.7)	1.00	1 (11.1)	2 (20.0)	1.00	3 (23.1)	2 (8.33)	0.32
Admission GCS ≧ 13, ≦15, n (%)	4 (80.0)	3 (25.0)	0.10	5 (55.6)	1 (10.0)	0.06	7 (53.9)	5 (20.8)	0.07
Admission systolic blood pressure, median (IQR), mmHg	160 (131–195.5)	167 (151.8–181.8)	0.83	151 (132–164)	184 (158.5–223.5)	**0.04**	139 (132–149)	157.5 (136.5–177.8)	0.09
Admission diastolic blood pressure, median (IQR), mmHg	98 (84.5–113)	94.5 (84.5–110.8)	0.79	86 (82–111)	102.5 (97.3–134.5)	**0.03**	91 (77.5–102)	91 (75.3–112.5)	0.95
SOFA score (day 1), median (IQR)	1 (0–4)	5 (3.25–6)	**0.02**	2 (0.5–4.5)	4 (3–7)	**0.10**	2 (1–3.5)	4 (3–5)	**0.01**
WFNS grade	-	-				0.08	-	-	
Grade I, n (%)	-	-		3 (33.3)	1 (10.0)		-	-	
Grade II, n (%)	-	-		1 (11.1)	2 (20.0)		-	-	
Grade III, n (%)	-	-		1 (11.1)	0 (0.0)		-	-	
Grade IV, n (%)	-	-		1 (11.1)	0 (0.0)		-	-	
Grade V, n (%)	-	-		3 (33.3)	7 (70.0)		-	-	
NIHSS, median (IQR)	5 (1–16)	25.5 (9–30.5)	**0.04**	-	-		-	-	
AIS - head, median (IQR)	-	-		-	-		3 (2–4.5)	5 (4–5)	**0.02**
Type of traumatic intracranial hemorrhage, n (%)	-	-		-	-				**< 0.01**
ASDH	-	-		-	-		2 (15.4)	16 (66.7)	
AEDH	-	-		-	-		4 (30.8)	1 (4.17)	
Contusion	-	-		-	-		2 (15.4)	2 (8.33)	
tSAH	-	-		-	-		5 (38.5)	5 (20.8)	
neurosurgery, n (%)	0 (0.0)	0 (0.0)		8 (88.9)	10 (100.0)	0.47	7 (53.9)	19 (79.2)	0.14
Type of neurosurgery, n (%)	-	-				0.58			0.08
Coil embolization	-	-		7 (77.8)	9 (90.0)		-	-	
Clipping	-	-		1 (11.1)	1 (10.0)		-	-	
Craniotomy	-	-		-	-		3 (23.1)	7 (29.2)	
Decompressive craniectomy	-	-		-	-		0 (0.0)	8 (33.3)	
Trepanation	-	-		-	-		4 (30.8)	4 (16.7)	
GDF-15 (day 1), median (IQR), pg/mL	395.6 (324.0–415.2)	663.9(513.7–922.3)	**0.01**	510.7 (377.1–604.4)	768.7 (519.7–960.3)	**0.03**	863.2 (473.1–1530.9)	1217.9 (456.4–1815.3)	0.39
GDF-15 (day 3), median (IQR), pg/mL	204.3(204.3–204.3)	842.7(513–1194.0)	0.11	866.0 (577.8–1030.2)	691.2 (512.7–963.9)	0.44	765.9 (686.9–993.9)	1452.9 (611.4–1914.5)	0.07
GDF-15 (day 7), median (IQR), pg/mL	-	-		773.0 (433.1–899.0)	720.5 (626.4–1193.0)	0.82	883.6 (602.3–1197.0)	1329.0 (892.4–2312.3)	0.07

Table 2. Comparison of patient background on prognosis at discharge. IQR: interquartile range, GCS: Glasgow coma scale, SOFA score: sequential organ failure assessment score, NIHSS: national institutes of health stroke scale, WFNS grade: world federation of neurosurgical societies grade, AIS: abbreviated injury scale, ASDH: acute subdural hematoma, AEDH: acute epidural hematoma, tSAH: traumatic subarachnoid hemorrhage, GDF-15: growth differentiation factor 15.

functional prognosis. In addition, as GDF-15 has been reported to be elevated in patients with renal failure[20], it is possible that GDF-15 was similarly elevated in TBI owing to impaired renal function.

Similar to previous studies on sepsis and burns[5,6], GDF-15 level was similarly associated with the SOFA score in the present study. The APACHE II score, which measures the illness severity in critically ill patients, includes pre-injury factors such as age and medical history. In contrast, the SOFA score does not include pre-injury factors such as age and medical history but reflects organ damage at the time of scoring after injury. This suggests that in post-TBI, GDF-15 is related to post-injury pathophysiology.

1. Cerebral infarction						
	Univariable analysis			Multivariable analysis		
Variables	OR	95% CI	P-value	OR	95% CI	P-value
GDF-15 (day 1)	1.23	0.99–1.07	< 0.01	1.02	0.98–1.07	**0.01**
Age	1.11	1.00–1.25	0.02	1.04	0.87–1.23	0.69
II. Subarachnoid hemorrhage						
	Univariable analysis			Multivariable analysis		
Variables	OR	95% CI	P-value	OR	95% CI	P-value
GDF-15 (day 1)	1.01	1.00–1.01	0.01	1.00	1.00–1.01	**0.02**
Age	1.05	0.97–1.14	0.21	1.03	0.94–1.13	0.52
III. Traumatic brain injury						
	Univariable analysis			Multivariable analysis		
Variables	OR	95% CI	P-value	OR	95% CI	P-value
GDF-15 (day 1)	1.00	1.00–1.00	0.17	1.00	1.00–1.00	0.57
Age	1.05	1.01–1.09	< 0.01	1.05	1.01–1.09	**0.01**
Sex	1.14	0.29–4.55	0.85	1.29	0.15–3.97	0.76

Table 3. Results of univariable and multivariable logistic regression analyses assessing the impact of clinical parameters, including GDF-15, on unfavorable functional outcomes at discharge.

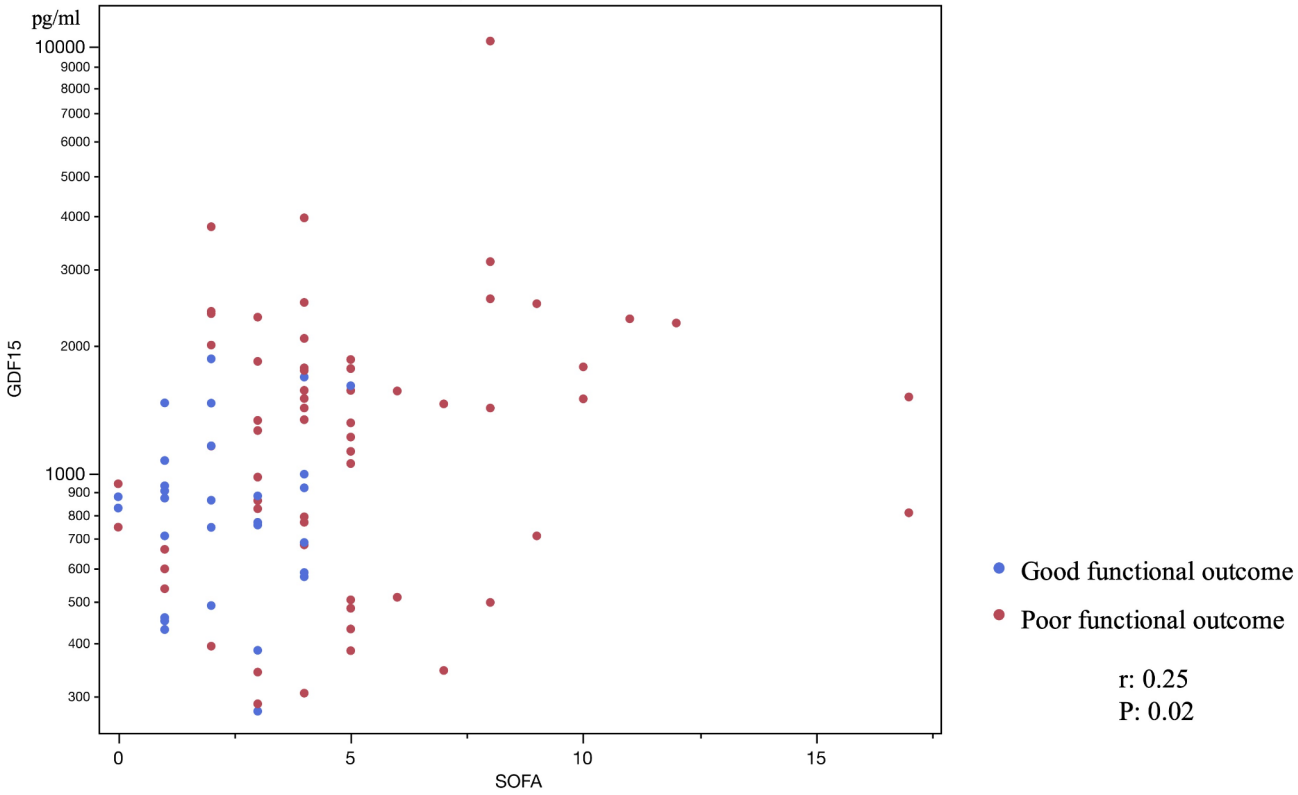

Fig. 1. Scatterplot of GDF-15 and SOFA scores in traumatic brain injury. GDF-15 levels and SOFA scores were correlated. GDF-15 levels and functional outcomes were not correlated. GDF-15, growth differentiation factor 15; SOFA, Sequential Organ Failure Assessment.

The significance of measuring GDF-15 post-TBI lies in its potential use as a parameter to assess the systematic severity of the injury rather than solely for predicting functional prognosis. Severe TBI often requires intensive care with ventilators and multiple medications, and the patient's medical treatment is decided based on a comprehensive assessment of various parameters. Therefore, GDF-15 may be utilized as a new parameter for evaluating the severity of the overall condition in the treatment of TBI.

Although there are various reports on the role of GDF-15 in the body and its pathological significance, such as its bioprotective effect, there are many unknowns[21]. It has been shown that when the cerebral cortex undergoes

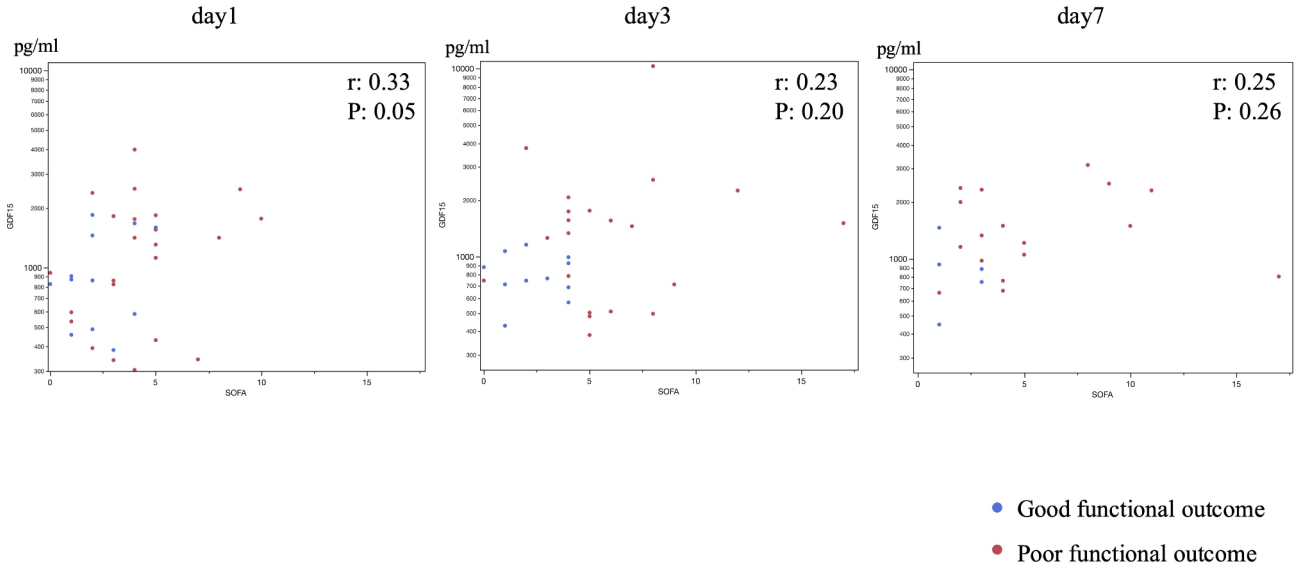

Fig. 2. Scatterplot of GDF-15 levels and SOFA scores by hospitalization day in traumatic brain injury. GDF-15 levels and SOFA scores were correlated on day 1 but not on days 3 and 7. GDF-15 and functional outcomes were not correlated on days 1, 3, and 7. GDF-15, growth differentiation factor 15; SOFA, Sequential Organ Failure Assessment.

		Respiratory	Coagulation	Hepatic	Cardiovascular	Neurological	Renal
Total (day 1, 3, 7)	r	0.13	0.16	-0.03	0.21	0.16	0.42
	P-value	0.22	0.13	0.81	**0.04**	0.13	**< 0.01**
Day 1	r	0.12	0.08	0.07	0.17	0.08	0.38
	P-value	0.49	0.62	0.69	0.31	0.63	**0.02**
Day 3	r	0.23	0.10	-0.13	0.29	0.12	0.50
	P-value	0.21	0.60	0.49	0.11	0.52	**< 0.01**
Day 7	r	0.04	0.25	-0.06	0.16	0.30	0.37
	P-value	0.87	0.26	0.78	0.49	0.18	0.09

Table 4. SOFA subscores for each organ and correlation coefficient with GDF-15 of TBI patients. SOFA score: sequential organ failure assessment score, GDF-15: growth differentiation factor 15, TBI: traumatic brain injury.

a freezing injury, GDF-15 mRNA levels significantly increase in several neurons[22]. In addition, GDF-15 exerts a neurotrophic effect on nerve cells and promotes the proliferation and differentiation of neural stem cells in the hippocampus region[23]. Thus, it is possible that GDF-15 in the serum is produced as a defense mechanism in response to TBI-induced brain damage.

This study provides a platform for further elucidation of the role and significance of GDF-15 in various CNS disorders.

Limitations

This was a single-center, prospective, observational study based on medical records. The small sample size limited the ability to perform a detailed analysis. Additionally, no correlation was observed between hematoma morphology and the relationship between the SOFA score and GDF-15 in the sensitivity analysis. Further verification with a larger sample size is needed.

Patients whose residual plasma from blood collection was not preserved on the day of admission were excluded, which could have resulted in selection bias. The reason for this was the possibility that the plasma was used for all routine tests or was not stored because the patient was admitted on the weekend. The functional prognosis at discharge was evaluated; however, the long-term prognosis was not assessed. The relationship between GDF-15 levels and long-term prognosis thus remains an area for future research.

Conclusions

In stroke, admission day GDF-15 level was associated with functional outcomes at discharge but not with TBI. In TBIs, GDF-15 levels were correlated with SOFA scores. Therefore, GDF-15 should be utilized as a new parameter for evaluating the severity of TBI.

Data availability
All data generated or analyzed during this study are included in this published article.

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References
1. Song, L., Söderholm, M., Svensson, E. H., Borné, Y. & Engström, G. Circulating growth differentiation factor 15 levels are associated with risk of both intracerebral and subarachnoid hemorrhage. *Front. Neurol.* **12**, 664010 (2021).
2. Hromas, R. et al. PLAB, a novel placental bone morphogenetic protein. *Biochim. Biophys. Acta* **1354**, 40–44 (1997).
3. Wollert, K. C., Kempf, T. & Wallentin, L. Growth differentiation factor 15 as a biomarker in cardiovascular disease. *Clin. Chem.* **63**, 140–151 (2017).
4. Corre, J., Hébraud, B. & Bourin, P. Concise review: Growth differentiation factor 15 in pathology: A clinical role? *Stem Cells Transl Med.* **2**, 946–952 (2013).
5. Buendgens, L. et al. Growth differentiation factor-15 is a predictor of mortality in critically ill patients with sepsis. *Dis. Mark.* 5271203 (2017). (2017).
6. Onishi, S. et al. Growth differentiation factor-15 correlates with mortality and severity in severe burns. *Shock* **57**, 211–217 (2022).
7. Schindowski, K. et al. Regulation of GDF-15, a distant TGF-β superfamily member, in a mouse model of cerebral ischemia. *Cell. Tissue Res.* **343**, 399–409 (2011).
8. Meloux, A. et al. Ischemic stroke increases heart vulnerability to ischemia-reperfusion and alters myocardial cardioprotective pathways. *Stroke* **49**, 2752–2760 (2018).
9. Hsu, J. Y. et al. Non-homeostatic body weight regulation through a brainstem-restricted receptor for GDF15. *Nature* **550**, 255–259 (2017).
10. Worthmann, H. et al. Growth differentiation factor 15 plasma levels and outcome after ischemic stroke. *Cerebrovasc. Dis.* **32**, 72–78 (2011).
11. Gröschel, K. et al. Growth-differentiation factor-15 and functional outcome after acute ischemic stroke. *J. Neurol.* **259**, 1574–1579 (2012).
12. Csecsei, P. et al. Different kinetics of serum ADAMTS13, GDF-15, and neutrophil gelatinase-associated lipocalin in the early phase of aneurysmal subarachnoid hemorrhage. *Int. J. Mol. Sci.* **24**, 11005 (2023).
13. Kitagawa, K. et al. Effect of standard vs intensive blood pressure control on the risk of recurrent stroke: A randomized clinical trial and meta-analysis. *JAMA Neurol.* **76**, 1309–1318 (2019).
14. Kammersgaard, L. P. et al. Short- and long-term prognosis for very old stroke patients. The Copenhagen stroke study. *Age Ageing* **33**, 149–154 (2004).
15. Roy-O'Reilly, M. & McCullough, L. D. Age and sex are critical factors in ischemic stroke pathology. *Endocrinology* **159**, 3120–3131 (2018).
16. Giordano, K. R., Rojas-Valencia, L. M., Bhargava, V. & Lifshitz, J. Beyond binary: Influence of sex and gender on outcome after traumatic brain injury. *J. Neurotrauma* **37**, 2454–2459 (2020).
17. Lingsma, H. F., Roozenbeek, B., Steyerberg, E. W., Murray, G. D. & Maas, A. I. R. Early prognosis in traumatic brain injury: From prophecies to predictions. *Lancet Neurol.* **9**, 543–554 (2010).
18. Brenière, C. et al. Growth differentiation factor-15 (GDF-15) is associated with mortality in ischemic stroke patients treated with acute revascularization therapy. *Front. Neurol.* **10**, 611 (2019).
19. Tamoto, M. et al. Survey of Glasgow Coma Scale and PaO_2/FIO_2 ratio assessment methods for the sequential organ failure Assessment score in Japanese intensive care units. *Acute Med. Surg.* **9**, e785 (2022).
20. Zhou, Z. et al. Circulating GDF-15 in relation to the progression and prognosis of chronic kidney disease: A systematic review and dose–response meta-analysis. *Eur. J. Intern. Med.* **110**, 77–85 (2023).
21. Luan, H. H. et al. GDF15 is an inflammation-induced central mediator of tissue tolerance. *Cell* **178**, 1231–1244e11 (2019).
22. Schober, A. et al. Expression of growth differentiation factor-15/ macrophage inhibitory cytokine-1 (GDF-15/MIC-1) in the perinatal, adult, and injured rat brain. *J. Comp. Neurol.* **439**, 32–45 (2001).
23. Kim, D. H. et al. GDF-15 secreted from human umbilical cord blood mesenchymal stem cells delivered through the cerebrospinal fluid promotes hippocampal neurogenesis and synaptic activity in an Alzheimer's disease model. *Stem Cells Dev.* **24**, 2378–2390 (2015).

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Author contributions
H.I., T.E., and H.M. participated in the study design, data collection, data analysis, data interpretation, and drafted the manuscript. H.I., T.E., H.M., and J.O. contributed to the discussion and managed the study. All authors have read the draft and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical guidelines and approvals
We confirm that this study complies with the ethical standards as outlined in the Declaration of Helsinki. The study was reviewed and approved by the Ethics Committee of our hospital (Approval No. 885) and was

anonymized according to the Act on the Protection of Personal Information.

Additional information

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Correspondence and requests for materials should be addressed to T.E.

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