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Role of substance P in cerebral edema and association with an estimated specific gravity of the brain and an outcome prediction in post-traumatic cerebral edema

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ABSTRACT

Purpose: The study aims to evaluate the role of substance P in cerebral edema and outcomes associated with acute TBI.

Method: Patients with acute TBI who presented within 6 h and a CT scan showed predominantly cerebral edema were included in the study. Substance P level was assessed from a serum sample collected within 6 h of trauma. We also evaluated the brain-specific gravity using the Brain View software.

Result: A total of 160 (128 male) patients were recruited. The median serum substance P concentration was 167.89 (IQR: 101.09–238.2). Substance P concentration was high in the early hours after trauma ($p = 0.001$). The median specific gravity of the entire brain was 1.04. Patients with a low Glasgow coma scale (GCS) at admission had a high concentration of the substance P. *In* the univariate analysis, low GCS, elevated serum concentrations of substance P level, high Rotterdam grade, high cerebral edema grade, a high international normalized ratio value, and high blood sugar levels were associated with poor outcomes at six months. In logistic regression analysis, low GCS at admission, high cerebral edema grade, and elevated blood sugar level were strongly associated with poor outcomes at six months. The area under the receiver operating characteristic curve was 0.884 (0.826–0.941).

Conclusion: Serum substance P is strongly associated with the severity of cerebral edema after TBI. However, brain-specific gravity does not directly correlate with posttraumatic cerebral edema severity. Serum substance P does not influence the clinical outcome of traumatic brain injury.

1. Introduction

Neurogenic inflammation is secondary brain injury following traumatic brain injury (TBI). Neurogenic inflammation results in vasodilatation, increased blood–brain barrier (BBB) permeability, and cerebral edema.[1,2] The mechanism of brain edema is complex and still unknown. Neurogenic inflammation is one of the mechanisms, and it increases the permeability of the BBB, leading to vasogenic edema. Various substances are released in blood from the primary sensory nerves after brain injury and propagate the primary injury.[3] Substance P is one of the neuropeptides and densely presents around the cerebral microvasculature in sensory C fibre and contributes to severe brain edema formation.[4,5] Substance P is also involved in neurogenic inflammation.[2] Cerebral edema independently predicts increased mortality and morbidity after traumatic head injury.[6] So, the role of inflammatory markers in posttraumatic cerebral edema needs to be investigated in detail. The relationship between Brain-specific gravity and traumatic brain injury is well established.[18] As radiological density is linearly correlated with brain-specific gravity, computer tomography (CT) images are useful in measuring brain-specific gravity.[17] Brain-specific

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gravity is a helpful tool to predict traumatic brain injury.[18]

The study aims to evaluate the role of substance P in cerebral edema associated with acute TBI, correlate the serum substance P level and brain-specific gravity in posttraumatic cerebral edema in acute TBI, and correlate the serum substance P level, brain-specific gravity, and neurological outcome at six months.

2. Methods and materials

It is a prospective, non-randomized clinical study conducted at the National Institute of Mental Health and Neurosciences, Bangalore, India, from 2018 to 2021. Prior approval from the institute's ethics committee was obtained. Patients with acute TBI who reached the emergency department within 6 h and a CT scan showed predominantly cerebral edema were included in the study. Patients under 18 years and those with severe extracranial injury were excluded from the study as the serum substance P level can be influenced due to severe extracranial injury. Hence excluded from the study. Patients who underwent surgery for acute subdural hematoma, contusion, and extradural hematoma were excluded from the study. The standard clinical, imaging, and laboratory parameters relevant to TBI were collected.

2.1. CT scan evaluation

Cerebral edema assessment was done on admission CT scans. Cerebral edema confined to surrounding pathology or focal was considered as grade 1, cerebral edema involving one hemisphere was considered as grade 2, and cerebral edema involving both hemispheres was considered as grade 3 (Fig. 1). Marshall and Rotterdam grading was used to grade the severity of TBI on CT scan.

2.2. Brain-specific gravity measurement

Brain-specific gravity was assessed using Brain View software developed by one of the investigators [11]. Each scan was segmented, and the specific gravity of both hemispheres was assessed after fixing the specific region of interest (ROI). The area of interest excluded intracranial hematoma, contusion, extradural hematoma, and peri-contusion area. For each area, numbers of voxels, weight, and specific gravity were computed utilizing the following equations[7]

(1) Volume of the voxel (mL) = Surface (mm^2) x Section thickness (mm)

(2) Weight of the voxel (g) = (1 +CT/1000) x Volume of the voxel (mL) where CT is the attenuation coefficient (expressed in Hounsfield unit)

(3) Volume of the compartment = Number of voxels x Volume of the voxel

(4) Weight of the compartment (g) = summation of the weight of each voxel included in the compartment

(5) Estimated specific gravity (eSG) of the compartment (g/mL) = Weight of the compartment (g)/Volume of the compartment (mL)

The estimated specific gravity (eSG) is expressed as a physical density in grams per Millilitre. In our study, we selected 1 cm lateral from the midline at the centrum semiovale.

2.3. Substance P assay

Substance P Parameter Assay ELISA kit (Catalogue #: KGE007, R&D Systems, Inc., Minneapolis, MN) was used to quantify substance P in serum samples. 5 ml of blood was collected from the recruited patients to measure the serum substance P level. Aprotinin was added within 5 min of sample collection. The serum samples, reagents, and standards were prepared according to the manufacturer's instructions. Serum samples were diluted twofold. Initially, 50 μl of serum or standards were added to the microtiter plate, 50 μl of primary antibodies, and 50 μl substance P conjugate, then incubated for 3 h at RT on a horizontal shaker. Then, 200 μl of substrate solution was added and incubated at RT for 30 min (protected from light) after a washing step. Finally, 50 μl of stop solution was added, and the reading was taken at 450 nm immediately. The four-parameter logistic curve (4-PL) fit was used to generate the standard curve, and each sample's substance P concentration was calculated using the standard curve.

2.4. Outcome assessment

The Glasgow outcome scale (GOS) was used to assess the outcome at either physical or telephonic at six months. The GOS scores 4 and 5 (moderate disability and good recovery) were considered a good outcome, and GOS 1, 2, and 3 (death, vegetative state, and severe disability) were considered bad outcomes. The serum sodium level, haemoglobin level, INR, and blood glucose level are not directly related to substance P level or Brain-specific gravity. Still, they are independent prognostic factors for the outcome of acute TBI. Hence, they are included in the univariate and prediction model analysis.

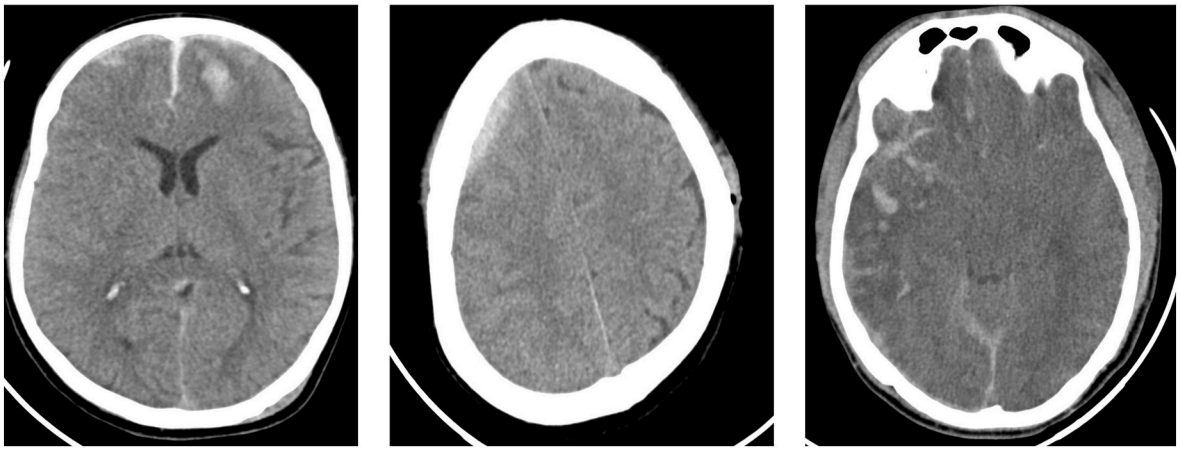

Fig. 1. A: CT Head (axial) shows Grade:1 cerebral edema and serum substance P level:72.21 pg/ml. B: CT Head (axial) shows Grade: 2 cerebral edema and serum substance P level:170.23 pg/ml. C: CT Head (axial) shows Grade:3 cerebral edema and serum substance P level:254.92 pg/ml.

2.5. Statistical analysis

Analysis was conducted using R version 4.1.2. Interval and ordinal scale data are described as the median and interquartile range (IQR), while nominal data are expressed as frequencies and percentages. Between-group analysis for dichotomized GOS was conducted using the Mann–Whitney *U* test for interval and ordinal scale variables, while the Chi-square test was used for nominal variables. Univariate association with Substance P concentration was tested using linear regression. Variables used for the final Model were chosen based on statistically significant association with GOS outcome variables. The predictive Model for GOS was created using stepwise multiple logistic regression optimized using a minimum Akaike Information Criterion (AIC). Predicted probabilities for discrimination of good vs. poor GOS at six months were used to construct a receiver operating characteristic curve. A *p*-value less than 0.05 was chosen as statistically significant.

3. Results

A total of 160 consecutive patients (128 males) were recruited in the study. The median age was 35 years (IQR: 26–46.25). The most familiar mechanism of trauma was road traffic injuries (76.25%), followed by a fall (20.62%) and assault (3.75%). The most ordinary presentation was the loss of consciousness (76.88%), followed by vomiting (33.12%) and seizures (3.75%). The median GCS at admission was 11 (IQR:7–15). Thirteen (8.12%) patients had dilation of both pupils at admission, sixteen (10%) patients had pupillary asymmetry, and ten (6.25%) patients had motor weakness. Six patients had an extracranial injury, and four had a spine injury (2.5%)—one patient presented with a cerebrospinal fluid (CSF) leak at admission. The median values of laboratory parameters were as the following: hemoglobin 14.1 gm% (12.68–15.83), international normalized ratio (INR) 1.22 (1.1–1.34), serum sodium 138 mEq/l (135–140), and blood glucose 138.5 mg% (120.75–184.5) (Table 1). Fifty-six patients (35%) with diffuse cerebral edema with midline shift or signs of herniation underwent surgery. Eighty (50%) patients had left-sided pathology, 77 patients (48.12%) had right-sided, and three patients had a bilateral injury (1.88%). The median Marshall grade was three (IQR:2–5), and the median Rotterdam grade was three (IQR:2–4). The frequency of cerebral edema was grade 1 (35%), grade 2 (36.3%), and grade 3 (28.7%). The median specific gravity of the entire brain was 1.04. The median specific gravity of the right cerebral hemisphere was 1.04, and the left hemisphere was 1.04 **(Table 2).**

Table 1
Clinical and laboratory parameters.

Variables	Values
Sample collection duration (hours), Median (IQR)	3 (2.38–4)
Age, Median (IQR)	35 (26–46.25)
Gender (male: female)	128 (80%): 32 (20%)
Mode of injury	
• Road traffic injuries	122 (76.25%)
• Fall	33 (20.62%)
• Assault	6 (3.75%)
Presenting symptoms and signs	
• Loss of consciousness	123 (76.88%)
• Seizure	6 (3.75%)
• Vomiting	53 (33.12%)
• Mydriasis	13 (8.12%)
• Asymmetric pupillary reaction	16 (10%)
• Extracranial injuries	6 (3.75%)
• Spine injury	4 (2.5%)
• CSF leak	1 (0.62%)
• GCS at admission, Median (IQR)	11 (7–15)
Laboratory parameters	
• Substance P (pmol/L), Median (IQR)	167.89 (101.09–238.2)
• Hemoglobin (g/dL)	14.1 (12.68–15.83)
• INR	1.22 (1.1–1.34)
• Serum sodium (mEq/L)	138 (135–140)
• Blood glucose (mg/dL)	138.5 (120.75–184.5)
Outcome (n=156)	
• GOS-5	83(51.9%)
• GOS-4	19(11.9%)
• GOS-3	21(13.1%)
• GOS-1	33(20.6%)

IQR – interquartile range, CSF – cerebrospinal fluid, INR – international normalized ratio, GOS – Glasgow outcome scale.

The median serum substance P concentration was 167.89 (IQR: 101.09–238.2). A linear regression analysis was done to examine the association of substance P with other parameters. Substance P concentration was high in patients presented in the early hours of trauma ($p = 0.001$). Patients with low GCS at admission had a high concentration of P. Higher Rotterdam grade on CT scans was associated with higher substance P levels **(Table 3)**. Patients with grade three cerebral edema grade had a high concentration of substance P (Fig. 2). The patients who were presented with loss of consciousness (LOC) had an elevated serum substance P level. On the contrary, patients presenting with vomiting had lower substance P levels **(Table 4)**. Although, no strong association was found between serum substance P level and brain-specific gravity (Fig. 2).

3.1. Predictors of outcome

A univariate analysis examined the variable predictors' association with the outcome at six months **(Table 4)**. A low GCS, high serum concentrations of substance P level, high Marshall grade and Rotterdam grade, cerebral edema grade, a high value of INR, and blood glucose were associated with poor outcomes at six months. Presentation with LOC, mydriasis, and asymmetry of pupils was strongly associated with poor results. A logistic regression analysis was done using the variables with a *p*-value <0.05 in univariate analysis **(Table 5)**. A low GCS at admission, high cerebral edema grade, and elevated serum blood glucose levels were strongly associated with poor outcomes at six months. Patients with high serum substance P levels had a poor outcome at six months, but it was not statistically significant. A receiver operating characteristic curve was obtained to determine the Model's accuracy. The area under the curve (AUC) was 0.884 (0.826–0.941) (Fig. 3).

4. Discussion

Substance P is a pro-inflammatory neuropeptide that facilitates secondary brain injury.[8] Several animal studies showed the role of substance P in secondary brain injury after acute TBI through neurogenic inflammation. Lorente et al.[4] reported that a high serum level of substance P was related to increased mortality. After TBI, there is evidence of increased expression of the neurokinin one receptor, and substance P acts through this receptor and activates astrocytic cells.[9] Activation of the astrocytic cell leads to more pro-inflammatory

Table 2
CT scan parameters.

Side of brain affected	
• Left	80 (50%)
• Right	77 (48.12%)
• Bilateral	3 (1.88%)
CT scan grade	
• Marshall, Median (IQR)	3 (2–5)
• Rotterdam, Median (IQR)	3 (2–4)
Edema grade	
• Grade 1	56 (35%)
• Grade 2	58 (36.3%)
• Grade 3	46 (28.8%)
Specific gravity	
• Right hemisphere, Median (IQR)	1.037 (1.03–1.04)
• Left hemisphere, Median (IQR)	1.038 (1.03–1.04)
• Average, Median (IQR)	1.036 (1.03–1.04)

IQR – interquartile range.

Table 3
Linear regression output for association of Substance P concentration with all variables.

Variables	Levels	Estimate (SE)	*p*-value
Duration	–	−17.3 (5.3)	**0.001**
Age	–	−0.3 (0.5)	0.571
Gender	Male (Ref = Female)	7.5 (17.2)	0.663
RTI	Yes (Ref = No)	−8.9 (16.2)	0.581
Fall	Yes (Ref = No)	9.7 (17)	0.568
Assault	Yes (Ref = No)	9.4 (36.2)	0.796
LOC	Yes (Ref = No)	40.8 (16)	**0.012**
Seizure	Yes (Ref = No)	−0.4 (36.2)	0.991
Vomiting	Yes (Ref = No)	−30.5 (14.4)	**0.036**
GCS	–	−4.3 (1.7)	**0.01**
Mydriasis	Yes (Ref = No)	44.2 (25)	0.078
Asymmetric Pupil	Yes (Ref = No)	31.3 (22.8)	0.172
Motor weakness	Yes (Ref = No)	56.4 (28.1)	**0.046**
Extracranial injury	Yes (Ref = No)	−10.4 (36.2)	0.774
CSF leak	Yes (Ref = No)	7.1 (87.4)	0.935
Spine injury	Yes (Ref = No)	69.1 (43.8)	0.116
Side of pathology	Left (Ref = Bilateral)	9.8 (51.3)	0.849
	Right (Ref = Bilateral)	19.2 (51.3)	0.709
Marshall grade	–	8.8 (5.2)	0.094
Rotterdam grade	–	12.1 (5.5)	**0.029**
Edema grade	–	28.9 (8.3)	**0.001**
SG - right	–	−12.7 (9.7)	0.191
SG - left	–	−2291.3 (1827.5)	0.212
SG - average	–	−25.5 (19.3)	0.189
Hemoglobin	–	2.4 (3)	0.423
INR	–	38.9 (21.2)	0.068
Serum sodium	–	−2.5 (1.6)	0.107
Blood glucose	–	0.1 (0.1)	0.546
Surgical intervention	Yes (Ref = No)	−18.2 (14.4)	0.208

RTI – road traffic injury, LOC – loss of consciousness, GCS – Glasgow coma scale, SG – specific gravity, INR – international normalized ratio.

mediators and increased blood–brain barrier permeability. Donkin et al found that the concentration of substance P rises 5 h after TBI and persists up to 24 h after trauma, mainly in the perivascular space.[10]

4.1. Substance P and cerebral edema

Cerebral edema following TBI occurs due to vasogenic and cytotoxic edema. Vasogenic edema starts in the early hours following trauma, and cytotoxic continues for up to two weeks[11] Various animal and human studies established that the increased presence of substance P in the perivascular region in the early hours leads to increased permeability of BBB. Thus, the substance P plays a significant role in vasogenic edema. Substance P also induces neuroinflammation by directly initiating the inflammatory pathway and mediators (IL-6, TNF-alfa) and indirectly activating astrocyte or microglial cells to produce inflammatory factors. Thus, substance P also participates in cytotoxic edema.[8] Cerebral edema also contributes to the significant rise in intracranial pressure (ICP) and increased mortality and morbidity after TBI. Jha et al published that cerebral edema is present in more than 60 % of TBI patients along with other mass lesions (like contusion and acute subdural) and 15 % as the sole cerebral edema.[12] Lietke et al published data on a strong correlation between cerebral edema grade and high ICP ($p < 0.0001$). They also showed that the CT grade of cerebral edema strongly correlated with the outcome.[13] Substance P works through the NK receptor pathway (NK1). The NK1 antagonist, NAT, reduces the BBB permeability of albumin and, in 80% of cases, decreases cerebral edema within 24 h.[6] In an ischemic animal study, Turner et al found that NK1 antagonist NAT reduced cerebral edema 24 h after being administered 4 h after stroke.[14] Thus, substance P antagonist plays a significant role in controlling cerebral edema and ICP.[15,16] Our current study found a high concentration of substance P level in higher grades of edema, which was statistically significant ($p = 0.001$). Higher-grade edema was strongly associated with poor outcomes after TBI (OR:1.86, $p = 0.04$).

4.2. Relationship with brain-specific gravity

Several studies established that brain-specific gravity based on CT scans and cerebral edema had a good correlation.[7,17,18] Degos et al published a study of brain-specific gravity in TBI and found that high brain-specific gravity was associated with poor outcomes at six months follow-up.[18] However, our research discovered that brain-specific gravity was slightly increased in patients with poor results (1.0347) compared to patients with good outcomes (1.0341). Still, it was not statistically significant ($p = 0.33$). Our present study was the first to correlate substance P levels with brain-specific gravity. However, we did not find a statistically significant association of substance P with

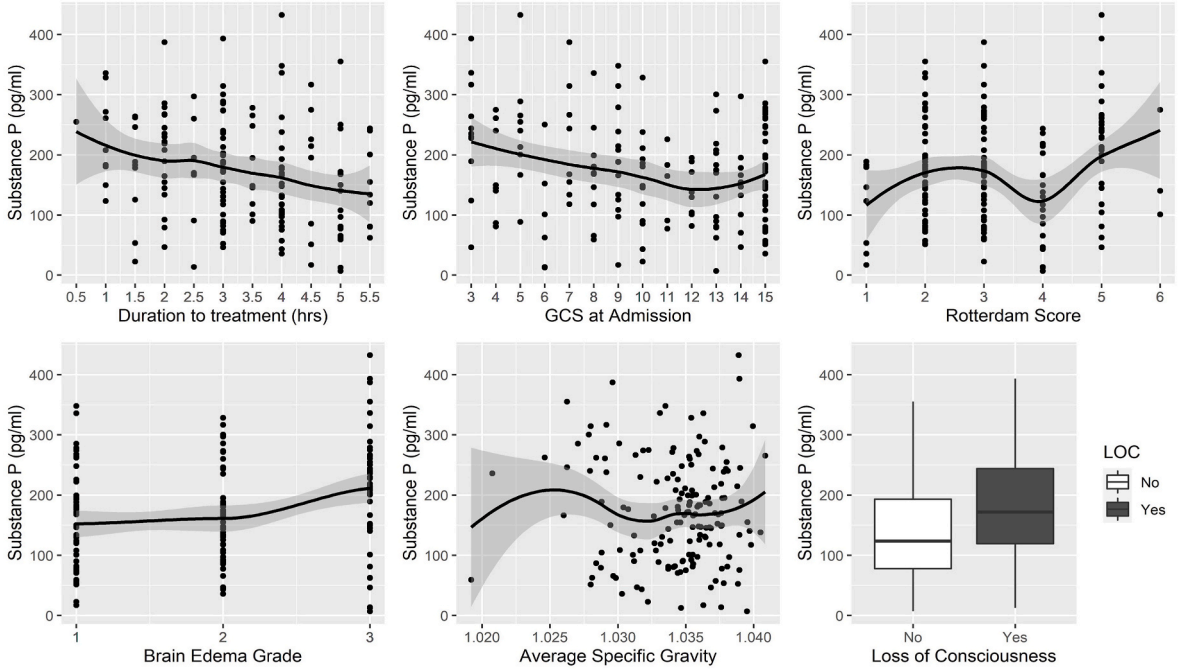

Fig. 2. shows serum substance P's relationship with traumatic brain injury-related factors.

Table 4
Univariate analysis: predictors of outcome at 6 months.

	Levels	Good	Poor	*p*-value
Duration since injury, Median (IQR)	–	3 (2.5–4)	3 (2–4)	1.000
Age, Median (IQR)	–	34.5 (25.25–42)	36 (27.5–50)	0.233
GCS, Median (IQR)	–	13 (10–15)	6 (4–9)	**<0.001**
Substance P in pmol/L, Median (IQR)	–	154.82 (97.03–198.39)	212.04 (126.79–261.65)	0.011
Marshall grade, Median (IQR)	–	3 (2–3)	5 (3–5)	**<0.001**
Rotterdam grade, Median (IQR)	–	3 (2–3)	4.5 (3–5)	**<0.001**
Edema grade, Median (IQR)	–	2 (1–2)	3 (2–3)	**<0.001**
SG – right, Median (IQR)	–	1.04 (1.03–1.04)	1.04 (1.03–1.04)	0.319
SG – left, Median (IQR)	–	1.03 (1.03–1.04)	1.04 (1.03–1.04)	0.442
SG – average, Median (IQR)	–	1.04 (1.03–1.04)	1.04 (1.03–1.04)	0.333
Hemoglobin (g/dL)	–	14.25 (12.7–15.88)	13.6 (12.53–16.03)	0.306
INR	–	1.19 (1.08–1.26)	1.28 (1.16–1.56)	0.005
Serum sodium (mEq/L)	–	138 (135–139)	138 (136.25–140)	0.295
Blood glucose (mg/dL)	–	132 (115.25–155)	183 (129.25–220.75)	**<0.001**
Gender	Female	21 (20.59%)	11 (20.37%)	1.000
	Male	81 (79.41%)	43 (79.63%)	
RTI	No	25 (24.51%)	13 (24.07%)	1.000
	Yes	77 (75.49%)	41 (75.93%)	
Fall	No	80 (78.43%)	43 (79.63%)	0.984
	Yes	22 (21.57%)	11 (20.37%)	
Assault	No	98 (96.08%)	52 (96.3%)	1.000
	Yes	4 (3.92%)	2 (3.7%)	
LOC	No	32 (31.37%)	4 (7.41%)	**0.003**
	Yes	70 (68.63%)	50 (92.59%)	
Seizure	No	98 (96.08%)	52 (96.3%)	1.000
	Yes	4 (3.92%)	2 (3.7%)	
Vomiting	No	65 (63.73%)	40 (74.07%)	0.283
	Yes	37 (36.27%)	14 (25.93%)	
Mydriasis	No	98 (96.08%)	45 (83.33%)	**0.017**
	Yes	4 (3.92%)	9 (16.67%)	
Asymmetric Pupil	No	97 (95.1%)	43 (79.63%)	**0.007**
	Yes	5 (4.9%)	11 (20.37%)	
Motor weakness	No	96 (94.12%)	50 (92.59%)	1.000
	Yes	6 (5.88%)	4 (7.41%)	
Extracranial injuries	No	97 (95.1%)	53 (98.15%)	1.000
	Yes	5 (4.9%)	1 (1.85%)	
CSF leak	No	101 (99.02%)	54 (100%)	1.000
	Yes	1 (0.98%)	0 (0%)	
Spine injury	No	100 (98.04%)	52 (96.3%)	0.915
	Yes	2 (1.96%)	2 (3.7%)	
Side of pathology	BL	2 (1.96%)	1 (1.85%)	0.946
	Left	52 (50.98%)	27 (50%)	
	Right	48 (47.06%)	26 (48.15%)	
Surgical intervention	No	71 (69.61%)	30 (55.56%)	0.089
	Yes	31 (30.39%)	24 (44.44%)	

IQR – interquartile range, RTI – road traffic injury, LOC – loss of consciousness, GCS – Glasgow coma scale, SG – specific gravity, INR – international normalized ratio, CSF – cerebrospinal fluid BL – bilateral.

brain-specific gravity level($p = 0.18$).

4.3. Inflammation as a predictor of the outcome of TBI

The outcome of TBI depends on various factors,[19] and neuroinflammation plays a significant role in determining the outcome. Neuroinflammation activates microglia and astrocytes, resulting in the release of inflammatory mediators. It also recruits the peripheral leukocytes to augment the immune response.[3] Yan Yang et al showed that serum calprotectin is involved in inflammation after trauma and strongly related to poor outcomes after TBI.[20] Raheja et al published a randomized controlled trial and found that serum IL-6 level above 71.26 pg/ml on day seven predicted poor results in one year.[21] Leonardo Lorente et al published a multicentric study and showed day one high serum substance P levels in non-survivors($p = 0.002$). They found that APACHE II score, age, and high Marshall grade were associated with poor outcomes.[4] Lorente L et al found that even the substance P level was high for one week after TBI in non-survivors.[22] Ying Zhou et al published a study of serum substance P level and its relationship with the outcome of TBI in children. They found that substance P levels were low compared to adults, but substance P was higher in non-survivors. The serum P concentration level was an independent predictor of mortality after TBI (OR>1,p=<0.01).[23] In our study, GCS at admission, edema grade, and blood sugar level were strongly associated with poor outcomes after six months. Serum substance P was a strong predictor of poor outcome in univariate analysis ($p = 0.01$), but in regression analysis, it was not statistically significant($p = 0.09$). We validated that cerebral edema is a predictor of poor outcomes. We also showed that the high cerebral edema grade was associated with higher substance P levels.

Table 5
Final model for predicting poor outcome at 6 months after stepwise AIC based selection.

	OR	ORCILo	ORCIHi	*p* value
(Intercept)	0.47	0.046	4.756	0.521
GCS	0.712	0.618	0.807	**<0.001**
Substance P levels	1.004	0.999	1.01	0.099
Edema grade	1.865	1.005	3.516	**0.049**
Blood glucose	1.008	1.002	1.015	**0.016**

AIC – Akaike Information Criterion, OR – Odds ratio, ORCILo – Odds ratio confidence interval low, ORCIHi – Odds ratio confidence interval high, GCS – Glasgow coma scale.

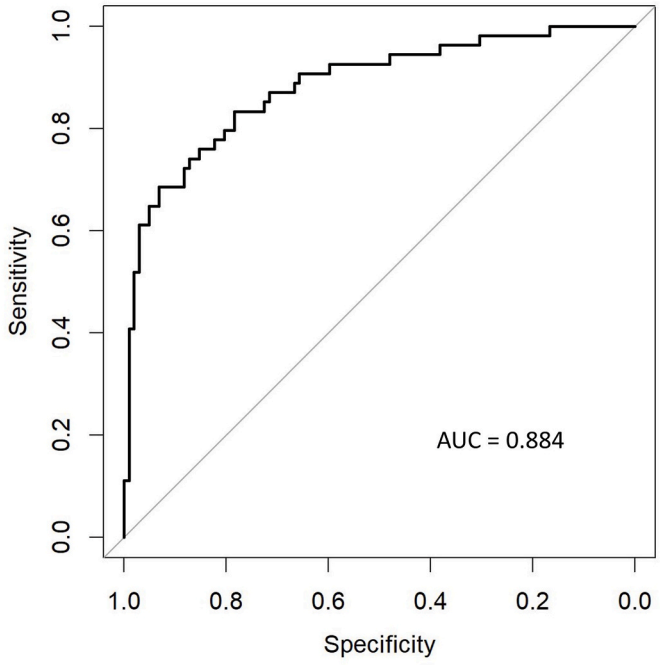

Fig. 3. shows the ROC curve of the prediction model.

4.4. Limitation

In the present study, serum substance P level at day 1 had a trend ($p = 0.09$) to predict poor outcomes. A more significant number of patients may establish the relationship better. However, substance P level strongly correlated with the cerebral edema grade. The impact of trauma was not measured in the present study, and the etiology was also different. So, the present study cannot rule out the peripheral cause of the rise of serum substance p level. CSF substance P will be ideal as an independent predictive factor of the outcome of traumatic brain injury.

5. Conclusion

Serum substance P is strongly associated with the severity of cerebral edema after TBI. However, brain-specific gravity does not directly correlate with the severity of posttraumatic cerebral edema. Serum substance P does not einfluence the clinical outcome of traumatic brain injury.

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CRediT authorship contribution statement

Subhas Konar: Writing – review & editing, Writing – original draft, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Dhaval Shukla:** Writing – review & editing, Validation, Supervision, Methodology. **B. Indira Devi:** Writing – review & editing, Supervision. **Rita Christopher:** Writing – review & editing, Supervision. **Nishanth S:** Writing – review & editing, Supervision. **Louis Puybasset:** Writing – review & editing, Supervision, Software. **Dhritiman Chakrabarti:** Formal analysis. **P. Sundaravadivel:** Investigation. **Shubham Nirmal:** Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviation

GOS: Glasgow outcome scale
GCS: Glasgow coma scale
INR: International normalised ratio
CT: Computer tomography
MRI: Magnetic resonance imaging
eSG: estimated specific gravity
IQR: Interquartile range
LOC: Loss of consciousness
BBB: Blood brain barrier