Article published online: 2024-10-03

Original Article

Predicting Progressive Hemorrhagic Injury Following Traumatic Brain Injury by the Evaluation of D-Dimer/Fibrinogen Ratio

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Indian J Neurotrauma

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Abstract

Background Prognosis of traumatic brain injury (TBI) significantly depends on the incidence of progressive hemorrhagic injury (PHI). The present study was conducted to assess whether D-dimer/fibrinogen ratio can predict PHI among the patients with TBI.

Materials and Methods A total of 150 patients were included in this retrospective study; among them 72 had PHI and 78 did not have PHI. Demographic, clinical, radiological, and laboratory parameters including plasma D-dimer and plasma fibrinogen levels and subsequently D-dimer/fibrinogen ratio were evaluated. Independent *t*-test, Mann–Whitney *U* test, chi-square test, Fisher's exact test, and multivariate logistic regression were used for statistical analysis.

Results Age, injury time, first computed tomography time, Glasgow Coma Scale scores, unreactive pupils, abnormal cisterns, midline shift above 5 mm, skull base fracture, epidural hematoma, subdural hematoma, intraventricular hemorrhage, cerebral hematoma, brain contusion, plasma D-dimer concentration, plasma fibrinogen concentration, and D-dimer/fibrinogen ratio vary significantly between PHI and non-PHI groups ($p < 0.05$). Multivariate logistic regression showed that the Glasgow Coma Scale score (odds ratio [OR], 0.531; 95% confidence interval [CI], 0.436–0.648; $p = 0.004$) and D-dimer/fibrinogen ratio (OR, 3.784; 95% CI, 2.086–6.867; $p = 0.027$) were the two independent predictors for PHI.

Conclusion D-dimer/fibrinogen ratio is a useful parameter in predicting the incidence of PHI among the patients with TBI.

Keywords
- D-dimer/fibrinogen ratio
- Glasgow Coma Scale
- plasma fibrinogen
- traumatic brain injury
- progressive hemorrhagic injury

Introduction

Despite advancements in prevention and treatment, traumatic brain injury (TBI), a serious public health issue, remains a leading cause of disability and mortality in every part of the world. It has surpassed several diseases as the leading cause of death and disability due to its increasing incidence around the globe.[1] One-third to one-half of all trauma-related deaths are attributable to TBI.[2–4] One million people die and around 1.5 to 2.0 million people are reportedly injured each year in India.[5]

The imbalance between procoagulant and anticoagulant factors, platelets, endothelial function, and fibrinolysis has been documented to cause acquired coagulation disorders in TBI.[6] It has been found that aberrant coagulation factors, such as a high prothrombin time and a low platelet (PLT) count, can predict the outcome of a TBI.[7] The function of D-dimer, a byproduct of fibrinogen (Fg) breakdown, in TBI attracted a lot

DOI https://doi.org/10.1055/s-0044-1780494.
ISSN 0973-0508.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

of attention in recent times. An abnormal D-dimer level may indicate an imbalance in the coagulation and fibrinolytic systems, which could change how TBI patients respond to treatment.[8] Researchers found that a greater D-dimer level was linked to a higher risk of progressive hemorrhagic injury (PHI); however, according to other experts the relationship was not statistically significant.[9–12]

The present study aimed to investigate whether D-dimer/Fg ratio (D/F ratio) can predict PHI among the patients with TBI.

Materials and Methods

Study Population

After obtaining the approval from the institutional ethical committee, records of patients with TBI from January 2018 to December 2022 were assessed in a tertiary care hospital in North India. Patients who were admitted within 6 hours after trauma with a highest abbreviated injury score of 3 or less and at least two computed tomography (CT) scans within 24 hours of admission were included in the study. Patients with known coagulation disorders, such as deep venous thrombosis, pulmonary embolism (PE), and myocardial infarction, or under anticoagulant therapies and previous medical history of malignancy, uremia, and liver cirrhosis were excluded from the study. Initially, 186 patients were selected for the study but after excluding 36 patients as per the exclusion criteria, finally 150 patients were included in the study and their data were analyzed. Among them 72 had PHI and 78 did not have PHI.

Methodology

Patients with TBI had their records examined. Demographic parameters like age, sex, habit of smoking, and alcoholism, comorbidities like hypertension and diabetes mellitus, and cause and duration of the injury were noted. During the clinical examination, light reflex of pupils, time from injury to first CT scan, time from first to second CT scan, and trauma-related positive radiological appearances (abnormal cisterns, midline shift, skull-cap fracture, skull base fracture, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, intraventricular hemorrhage, cerebral hematoma, brain contusion, and pneumocephalus) and Glasgow Coma Scale (GCS) score were noted. PHI was defined as the development of additional lesions or a noticeably larger hemorrhagic lesion(s) compared to the initial postinjury CT scan, with a minimum increase of 25% and a maximum increase of 50%.[13] Following laboratory data were also collected: plasma D-dimer concentration and plasma Fg concentration at time of admission. The D/F ratio was calculated as plasma D-dimer concentration (mg/L) divided by plasma Fg concentration (g/L).

Statistical Analysis

Data were tabulated in Microsoft Excel and analyzed using the SPSS (SPSS, Inc., Chicago, Illinois, United States) software. Normality of the data was assessed using Kolmogorov–Smirnov and Shapiro–Wilk test. The continuous variables which were found to be normally distributed have been presented with mean and standard deviation and compared using the independent *t*-test. The continuous variables which were not found to be normally distributed have been presented with median with quartile range (25th, 75th) and compared using the Mann–Whitney *U* test. The categorical variables have been presented with frequency and percentage and compared using the Pearson chi-square test or Fisher's exact test. A binary logistic regression model was applied to determine the predictors for PHI. A *p*-value of 0.05 or less was considered as statistically significant.

Results

►**Table 1** shows the details of the demographic, clinical, radiological, and laboratory parameters of PHI and non-PHI groups. Among the demographic parameters, only the age of the patients in the PHI group significantly vary from the non-PHI group ($p = 0.041$). Among the clinical parameters, injury time, first CT time, and GCS score were significantly lower (►**Fig. 1**) and the incidence of unreactive pupils was significantly higher among the PHI group ($p = 0.008$, $p = 0.019$, $p < 0.001$, and $p < 0.001$, respectively). Among the radiological findings, incidences of abnormal cisterns, midline shift above 5 mm, epidural hematoma, subdural hematoma, cerebral hematoma, and brain contusion were significantly higher among the PHI group ($p < 0.001$, $p < 0.001$, $p = 0.031$, $p = 0.044$, $p = 0.015$, and $p = 0.027$, respectively).

Therefore, the factors associated with PHI were found to be age, injury time, first CT time, GCS scores, unreactive pupils, abnormal cisterns, midline shift above 5 mm, skull base fracture, epidural hematoma, subdural hematoma, intraventricular hemorrhage, cerebral hematoma, brain contusion, plasma D-dimer concentration, plasma Fg concentration, and D/F ratio. ►**Table 2** shows the results of multivariate analysis where the aforementioned variables were analyzed which indicates that the GCS score and D/F ratio were independent risk factors for the incidence of PHI.

Discussion

With high prevalence and mortality, the importance of timely diagnosis of PHI with good sensitivity and specificity is important. Several factors, such as older age, male gender, poor GCS, and the presence of spot sign on CT angiography and coagulopathy, have been implicated as impact factors of intracranial hemorrhage progression.[10,13–20] Repeat CT scan is time-consuming and costly, addressing the associations between the abnormal blood tests and PHI would be of great value for which these laboratory test become meaningful; these parameters carry the most important weight for predicting PHI.

Blood clotting happens physiologically when Fg is converted into fibrin, which binds to trapped cellular components. D-dimer, a breakdown product of cross-linked fibrin in the plasma, is produced as a result of thrombin activation and the hybrid impact of plasmin. In response to increased coagulation activity, fibrinolysis is upregulated, which raises the level of D-dimer. D-dimer has been demonstrated to rise in peripheral blood from patients with

Table 1 Comparison of demographic, clinical, radiological, and laboratory parameters between PHI and non-PHI groups

Parameters	All patients (150)	PHI (72)	Non-PHI (78)	*p*-Value
Gender (male/female)	79/71	38/34	41/37	NS
Age (y)	37.2 ± 8.5	41.6 ± 7.9	35.3 ± 7.4	0.041
Cigarette smoking	65 (43.6%)	26 (36.7%)	35 (45.2%)	NS
Alcohol consumption	75 (49.8%)	37 (50.7%)	38 (49.2%)	NS
Hypertension	19 (12.9%)	10 (13.5%)	10 (12.3%)	NS
Diabetes mellitus	15 (9.7%)	6 (8.8%)	7 (9.6%)	NS
Injury time (h)	2.79 (2.14–3.26)	2.23 (1.67–3.07)	3.07 (2.14–3.53)	0.008
First CT time (h)	3.53 (2.75–4.19)	2.98 (2.33–3.63)	3.63 (2.88–4.37)	0.019
Second CT time (h)	8.28 (6.63–9.86)	7.81 (6.79–9.58)	8.28 (6.98–10.14)	NS
Glasgow Coma Scale scores	9 (6–12)	9 (3–7)	12 (8–13)	< 0.001
Traumatic causes				NS
Automobile/motorcycle	85	22	63	
Fall/jump	73	12	61	
Others	16	3	13	
Unreactive pupils	54 (35.8%)	57 (78.6%)	18 (23.1%)	< 0.001
Positive radiological appearances				
Abnormal cisterns	59 (39.1%)	60 (83.3%)	20 (25.7%)	< 0.001
Midline shift above 5 mm	52 (34.7%)	52 (71.6%)	18 (23.7%)	< 0.001
Skull-cap fracture	93 (61.8%)	48 (67.0%)	47 (60.0%)	NS
Skull base fracture	72 (47.7%)	43 (60.0%)	34 (43.9%)	NS
Epidural hematoma	63 (42.0%)	42 (57.7%)	29 (37.1%)	0.031
Subdural hematoma	82 (55.0%)	50 (69.3%)	39 (50.5%)	0.044
Subarachnoid hemorrhage	100 (67.0%)	55 (76.3%)	50 (64.0%)	NS
Intraventricular hemorrhage	5 (3.5%)	8 (11.2%)	1 (0.9%)	NS
Cerebral hematoma	60 (39.9%)	40 (55.3%)	27 (35.1%)	0.015
Brain contusion	84 (56.2%)	52 (71.6%)	40 (51.9%)	0.027
Pneumocephalus	37 (24.8%)	21 (29.8%)	18 (23.1%)	NS
Plasma D-dimer (mg/L)	3.99 (3.21–5.11)	4.55 (4.01–6.39)	3.74 (3.05–4.76)	< 0.001
Plasma fibrinogen (g/L)	2.55 (1.80–3.13)	2.08 (1.63–2.69)	2.64 (1.86–3.21)	0.003
D-dimer/fibrinogen ratio	1.57 (1.16–2.30)	2.48 (1.94–3.45)	1.40 (1.07–2.06)	< 0.001

Abbreviations: CT, computed tomography; NS, not significant; PHI, progressive hemorrhagic injury.

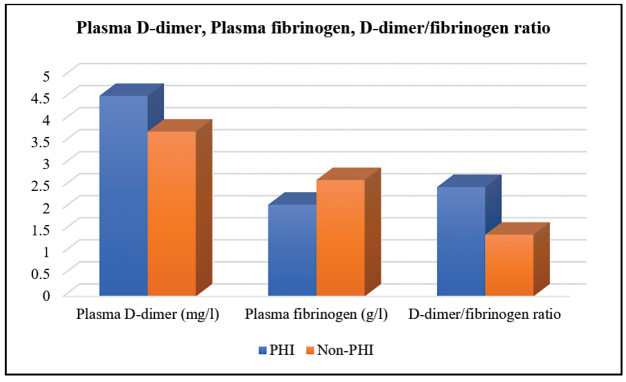

Fig. 1 Plasma D-dimer, plasma fibrinogen, and D-dimer/fibrinogen ratio between progressive hemorrhagic injury (PHI) and non-PHI groups.

disorders that affect the central nervous system, such as subarachnoid hemorrhage, ischemic stroke, and intracerebral hemorrhage.[21–23] This increase causes the coagulation system to become activated. Elevated D-dimer level is seen with coagulation disorder and is a poor prognostic factor. High D-dimer level is associated with severe grade of head injury.[19,20]

Systemic activation of coagulation leads to widespread intravascular fibrin deposition and consumption of PLTs and coagulation factors. So, we found in our study that the PLT count and Fg level degraded, and thrombocytopenia and low Fg level could to be predictors of PHI.

An increased D-dimer level is associated with poor clinical outcome of subarachnoid hemorrhage, ischemic stroke, and trauma.[21–23] Moreover, D-dimer level shows plasmin activity not only in blood but also during tissue degradation and

Table 2 Logistic regression analysis to evaluate the risk factors for PHI

Parameters	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p*-Value	Odds ratio (95% CI)	*p*-Value
Gender (male/female)	0.689 (0.348–1.365)	NS		
Age (y)	0.964 (0.941–0.987)	0.046	0.933 (0.878–0.994)	NS
Cigarette smoking	0.640 (0.321–1.277)	NS		
Alcohol consumption	0.958 (0.485–1.891)	NS		
Hypertension	0.952 (0.380–2.389)	NS		
Diabetes mellitus	0.798 (0.281–2.267)	NS		
Injury time (h)	0.541 (0.380–0.769)	0.001	0.444 (0.080–2.467)	NS
First CT time (h)	0.617 (0.454–0.837)	0.005	0.733 (0.175–3.074)	NS
Second CT time (h)	0.901 (0.809–1.003)	NS		
Glasgow Coma Scale scores	0.585 (0.502–0.681)	< 0.001	0.531 (0.436–0.648)	0.004
Traumatic causes				
Automobile/motorcycle	Reference			
Fall/jump	1.145 (0.381–3.442)	NS		
Others	0.688 (0.217–2.179)	NS		
Unreactive pupils	11.207 (4.793–26.200)	< 0.001	2.921 (0.492–17.341)	NS
Positive radiological appearances				
Abnormal cisterns	13.833 (5.449–35.117)	< 0.001	6.363 (0.549–73.683)	NS
Midline shift above 5 mm	7.203 (3.323–15.614)	< 0.001	1.136 (0.242–5.331)	NS
Skull-cap fracture	1.233 (0.593–2.562)	NS		
Skull base fracture	1.743 (0.868–3.499)	NS	2.337 (0.816–6.696.)	NS
Epidural hematoma	2.074 (1.037–4.147)	0.033	1.338 (0.355–5.025)	NS
Subdural hematoma	1.828 (0.871–3.836)	NS	2.755 (0.695–10.921)	NS
Subarachnoid hemorrhage	1.687 (0.750–3.798)	NS		
Intraventricular hemorrhage	2.372 (0.793–7.086)	NS	1.556 (0.355–6.812)	NS
Cerebral hematoma	2.048 (1.027–4.082)	0.018	1.108 (0.449–2.730)	NS
Brain contusion	2.174 (1.020–4.638)	0.025	2.075 (0.639–5.683)	NS
Pneumocephalus	1.237 (0.594–2.576)	NS		
Plasma D-dimer levels (mg/L)	1.513 (1.229–1.863)	< 0.001	1.299 (0.209–8.088)	NS
Plasma fibrinogen levels (g/L)	0.544 (0.361–0.822)	0.002	0.481 (0.163–1.425)	NS
D-dimer/fibrinogen ratio	2.819 (1.876–5.177)	< 0.001	3.784 (2.086–6.867)	0.027

Abbreviations: CI, confidence interval; CT, computed tomography; NS, not significant; OR, odds ratio; PHI, progressive hemorrhagic injury.

remodeling. In addition to aiding in the diagnosis of disseminated intravascular coagulation, it is also of clinical use when a suspicion of deep vein thrombosis or PE exists; it is promising as an exclusion test for PE if the results are negative, while positive results are quite nonspecific.[24,25] Nevertheless, whether D-dimer levels correlate with the incidence of posttraumatic cerebral infarction, which often develops in patients with moderate or severe TBI, has not been previously reported[26]

Routine D-dimer laboratory testing is supposed to be a useful clinical test to evaluate the severity of head injury. Monitoring of D-dimer level may be helpful in estimating prognosis in patients who are hospitalized early after injury and who may develop PHI and may worsen there clinical condition. Sometimes, patients with mild head injury who are under observation may deteriorate neurologically. Therefore, the blood D-dimer level can provide useful prognostic marker for physicians concerning whether to transfer patients to a facilitated hospital.

Although we found D-dimer level to be associated with PHI, the mechanisms that explain the association between D-dimer and PHI are not understood fully. D-dimer, a marker of fibrin turnover, reflects an impaired coagulation and fibrinolysis pathways. In TBI patients, this abnormal function may lead to greater intracranial hematoma volume and early hemorrhagic growth, as we observed. However, D-dimer is one of the markers of hemostatic function which are acute-phase reactants. Hence, it is possible that elevated D-dimer

levels in patients with progressing hemorrhage are simply a marker of a more severe lesion, as part of a reactant inflammatory process. In addition, a rise in plasma D-dimer concentration was independently associated to the incidence of posttraumatic PHI.[27,28] D/F ratio, as opposed to plasma D-dimer concentrations and plasma Fg concentration, emerged as a predictive factor which is independent in the current investigation, indicating that it is more likely to predict the incidence of PHI.

The finding that severely ill patients had a higher D-dimer level is fascinating. Proinflammatory states in critically ill hospitalized patients had elevated D-dimer levels via cytokine activation of the coagulation cascade.[29] When the blood is clotting, thrombin and other intermediate products are produced. Some of these products, and in particular thrombin, can activate the inflammatory cascade.[30] D-dimer as an end product of both coagulation and fibrinolysis may trigger some detrimental actions directly. D-dimer itself may stimulate monocyte synthesis and release of proinflammatory cytokines such as interleukin-6,[31] which causes both development of edema and hematoma progression. Thus, activated inflammation and activated blood coagulation are possibly related and both contribute to the occurrence of PHI. Additionally, severe head-injured patients with high D-dimer concentration may be associated with organ failure resulting from microthrombosis. Liver failure induce the reduction of blood coagulation factor generation and further bleeding and hematoma progression may result.[32]

Two studies[15] (Sun et al 2011[33])probed the potential effect of D-dimer. The retrospective study of isolated TBI with extended coagulation profiling of 598 patients shows patients with international normalized ratio (INR) greater than 1.2 had presented more with shock and lower GCS score at the time of presentation and had PIH more frequently on repeat CT compared to INR less than 1.2.

Zhang et al meta-analysis of coagulation parameter and risk of PHI after TBI shows increased D-dimer with PHI in three studies and decreased Fg with PHI in three studies.

Our findings implied that abnormal D/F ratio might indicate occurrence of PHI, which might lead to focused monitoring among TBI patients, and thus save plenty of medical resources. Our interpretation form the basis for further studies exploring whether correcting these values would prevent PHI and moreover make for subsequent operation. However, there is no strong evidence that correcting laboratorial tests in this situation actually improves outcome.

The probability of PHI after TBI is highly associated with the GCS score, a traditional sign of a bad outcome following brain injury. Additionally, it is utilized to support clinical prediction of TBI.

Conclusion

We can conclude that D/F ratio can be used to predict the incidence of PHI within hours of TBI. Therefore, the patients with TBI who have a high D/F ratio should be further evaluated to rule out the possibility of PHI and prompt intervention can be initiated to avoid unwanted outcomes.

Conflict of Interest
None declared.

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