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"BIOMARKERS IN THE PREDICTION OF PROGNOSIS IN TRAUMATIC HEAD INJURY PATIENTS AT OUR TERTIARY CARE HOSPITAL": A PROSPECTIVE FOLLOW-UP STUDY

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ABSTRACT

Introduction: Traumatic brain injury (TBI) occurs when a sudden trauma, often a blow of jolt to the head causes damage to brain. Traumatic brain injury is the leading cause of morbidity and mortality across the globe from developing to developed nations. There is increase in the inflammatory reaction in Traumatic brain injury patients evidenced by raise in the levels of inflammatory cytokines, chemokines and acute phase reactants in serum as well in cerebrospinal fluid (CSF). Measuring these acute phase reactants in the blood sample will aid in understanding the progression of pathogenesis resulting from TBI thus the prognosis and outcomes can be predicted. Objectives of the study: to determine the levels of acute phase reactants (albumin, CRP, Prothrombin, ESR, thrombocytes, fibrinogen, transferrin) within 24 hours of admission and to find out the correlation of baseline values of Acute Phase Reactants with respect to mortality and clinical outcomes at admission and follow-ups. Methodology: At the time of admission the severity of traumatic brain injury was assessed using Glasgow Coma Scale (GCS). All the patients underwent detailed clinical evaluation including GCS score, based on GCS score they were categorized as mild, moderate and severe traumatic brain injury. Subsequent relevant laboratory investigations were carried out which include acute phase reactant biomarkers albumin, c reactive protein (CRP), prothrombin, fibrinogen and transferrin levels along with routine laboratory investigations (hemoglobin, complete hemogram, arterial blood gas analysis) within 24 hours of day of admission. GOS scoring was done in all the patients at the time of discharge and follow-ups at one month and third month. Statistical analysis: Categorically data was presented as frequency and percentage (%), and measurement data with normal distribution were presented as mean ± S.D. The independent predictors of head injury were determined by univariate and multivariate logistic regression analysis odds ratio (OR) and 95% of confidence of interval (CI) was calculated. Conclusion: In our study we found that, the traumatic brain injury patients had decreased albumin level and transferrin level while the levels CRP, prothrombin, ESR, thrombocytes and plasma fibrinogen were increased at the time of admission. Most of the patients had severe GCS score at the time of admission. The levels of acute phase reactants (serum albumin, CRP, prothrombin, ESR, thrombocytes, plasma fibrinogen and transferrin) had highly significant association with the severity of head injury (GCS score) at the time of admission. The association between severity of head injury (according to GCS score) at the time of admission and severity of head injury (according to GCS score) at the time of discharge and after one month of discharge are highly significant. In the present study we conclude that levels of plasma fibrinogen, serum transferrin and GCS score at the time of admission had statistically highly significant impact on the outcomes of head injury patients at the time of discharge, one month follow-up, and three months follow-ups respectively. Thus, measurement of these biomarkers at the time of admission in patients with head injury will be highly helpful in predicting the prognosis. Further, our Research study also adds the significant values for

future planning of usage of anti-inflammatory drugs to manage head injury patients for the better outcome.

Key-words: traumatic brain injury, c reactive protein, prothrombin, fibrinogen and albumin

INTRODUCTION

Traumatic brain injury occurs when a sudden trauma, often a blow of jolt to the head causes damage to brain. The severity Traumatic brain injury is the leading cause of morbidity and mortality[1] across the globe from developing to developed nations. The worldwide incidence rate of traumatic brain injury is 295 cases per 100000[2]. India has highest rate of head injury in the world accounting for death of almost 100000 per year and over one million suffering from serious head injuries and 60% of all traumatic brain injury are caused by road traffic accidents in the age group 20-40 years and the severity of traumatic brain injury can range from mild to severe.[3] A Traumatic brain injury (TBI) occurs when an external force or blow to the head disrupts brain function, which can result in a decreased level of consciousness, memory loss before or after injury, alteration of mental status, neurologic deficits, or intracranial lesions.[4] There is gender prevalence of traumatic brain injury, i.e. males are four times more likely to experience TBI and they are at higher risk of TBI related hospitalization compared to females across all mechanisms of injury.[5,6] TBI injuries are classified as focal and diffuse injuries. Focal injuries include lacerations, skull fractures, contusions, and intracranial haemorrhage. Diffuse injuries examples include ischemic injury, diffuse axonal injury, and cerebral oedema.[7] Even minor traumatic brain injuries can have long-term effects on brain functioning such as pain, insomnia, and cognitive decline which is a major concern.[8] Unfortunately mild traumatic brain injury (MTBI), chronic traumatic encephalopathy, and concussion syndrome are often overlooked and patients are usually just given medication for pain relief and sleep disorders. However, patients with MTBI can suffer from both physical, emotional, and cognitive impairments, while most symptoms of MTBI disappear within 3-6 months, it's important to recognize and address them properly.[9,10]

There is increase in the inflammation reaction in Head injury/Traumatic brain injury patients evidenced by raise in the inflammatory cytokines, chemokines and acute phase reactants in serum as well in cerebrospinal fluid (CSF).[11] Measuring these acute phase reactants in the blood sample will aid in understanding the progression of pathogenesis resulting from TBI thus the prognosis and outcomes can be predicted.[12]

There are limited biomarkers that can indicate the severity of head injury, it is very crucial to determine the levels of these biomarkers in serum concerning and predicting neurological outcomes. In the present study we measured acute phase reactants biomarkers namely albumin, c reactive protein (CRP), prothrombin, fibrinogen and transferrin levels in traumatic brain injury patients at the time of admission to our tertiary care hospital in trauma unit.

AIM AND OBJECTIVES OF THE STUDY

Aim: to study the role of acute phase reactants response in the prognosis of traumatic brain injury.

Objectives: the objectives of the study include

1. To determine the levels of acute phase reactants (albumin, CRP, Prothrombin, ESR, thrombocytes, fibrinogen, transferrin) within 24 hours of admission.
2. To find out the correlation of baseline values of Acute Phase Reactants with respect to mortality and clinical outcomes at admission and follow-ups.

RESULTS

The present study included a total of 435 clinically diagnosed traumatic brain injury patients of both the genders. Males were 355 (81.6%) and females were 80 (18.4%) respectively. The mean age in female patients were 41.9±15.2 and 33.2 ± 12.2 years respectively. At the time of admission, the GCS

scores were evaluated by the clinician, the relationship between GCS score and outcome is the basis for common classification of acute traumatic brain injury. Severity ranges from mild (GCS 13-15), moderate (GCS 9-12) and severe (GCS 3-8). The distribution of traumatic head injury patients in the present study reveals that, none of them had mild injury, 162 (37.2%) had moderate injury and 273 (62.8%) had severe injury at the time of admission.

Table 1: Distribution of traumatic brain injury patients based on age, gender and GCS scores at the time of admission

	Number	Percentage
Gender		
Males	355	81.6
Females	80	18.4
Total	435	100
Age (mean ± SD)		
Males	33.2 ± 12.2	
Females	41.9±15.2	
GCS scores at the time of admission		
Mild	0	0
Moderate	162	37.2
Severe	273	273
total	435	100

Table 2: Shows the Mean ±SD values of acute phase reactants in traumatic brain injury patients according to GCS score at the time of admission, GOS score at the time of discharge and GOS score at one month follow-up

	GCS score at the time of admission		GOS score at the time of discharge			GOS score at one month of follow-up		
Mean ± SD (Parameters)	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Albumin (g/dL)	3.6±0.7	3±0.6*	4.4±0.6	3.5±0.7	2.8±0.6*	3.7±0.7	3.2±0.7	2.7±0.5*
CRP (mg/dL)	1.9±1.4	3.8±4.5*	3±2.1	2.1±1.7	4.4±5.2*	1.9±1.5	2.9±3.1	4.7±5.8*
Prothrombin (mg/dL)	14.9±2.7	17.1±4.1*	16±1.8	15.1±2.8	17.9±4.5*	14.8±2.5	16.1±3.4	18.2±4.8*
ESR (mm/h)	24.4±8.2	30±8.1*	20.2±5.8	25.3±8.2	32±7.3*	24.1±7.3	27.4±8.6	33.3±7*
Thrombocytes (10^3/µL)	241.4±113.2	364.5±132.3*	171.5±36.5	264.1±122.3	401.3±119.7*	245±112.6	306.1±136.9	428±98.4*
Fibrinogen (g/L)	2.8±0.5	1.9±0.8*	2.9±0.6	2.7±0.6	1.6±0.7*	2.8±0.5	2.3±0.8	1.5±0.7*
Transferrin (mg/dL)	221.7±47	179.2±57.8*	202.9±46.5	217.9±50.2	162.2±52.3*	221.9±45.8	203.2±55.8	147.8±45.1*

Table 2 presents the levels of prognostic predictor biomarkers albumin, c reactive protein, prothrombin, ESR, fibrinogen and transferrin levels in patients with mild, moderate and severe traumatic brain injury at the time of admission, at the time of discharge and at one follow-up. The mean and SD values of albumin, fibrinogen and transferrin were significantly decreased in TBI patients with severe GCS compared to patients with mild and moderate GCS and GOS scores respectively at the time of admission, at the time of discharge and at one month follow-up. Similarly, the levels of CRP, Prothrombin, ESR and thrombocytes were elevated in patients with severe GCS and GOS scores at the time of admission, at the time of discharge and at one month follow-ups compared to the patients with mild and moderate GCS score at the time of admission, at the time of discharge and at one month follow-up.

Table 3: Shows the association between GCS score at the time of admission and GOS score at one month follow-up					
GCS score at the time of Admission	**GOS score at one month follow-up**			**Grand Total**	**p-value & Statistical Significance**
	Mild	**Moderate**	**Severe**		
Moderate (no =162)	106(24.4%)	55(12.6%)	1(0.2%)	162(37.2%)	**p=0.02 Significant**
Severe (no=273)	12(2.8%)	158(36.3%)	103(23.7%)	273(62.8%)	
Grand Total	118(27.1%)	213(49%)	104(23.9%)	435(100%)	

Table 3 shows the association between GCS score at the time of admission and at one month discharge. Out of 435 traumatic brain injury patients 162(37.2%) patients had moderate score at the time of admission but at one month follow-up 106(24.4%) patients had mild GOS score, 55 (12.6%) patients had moderate GOS score and one patient had severe GOS score. Out of 435 traumatic brain injury patients 273(62.8%) had severe GCS score at the time of admission and at one month follow-up 12 (2.8%) had mild GOS score, 158 (36.3%) had moderate GOS score and 103 (23.7%) had severe GOS score. In this table, it is very evident that patients who had moderate GCS score at the time of admission had better outcomes as compared to the patients who had severe GCS score at the time of admission. Thus, the association of GCS score at the time of admission and at one month follow-up was statistically significant p= 0.02 (table 3).

Table 4: Shows the mortality and other outcomes after discharge		
Outcome	**Outcome after one month of discharge**	**Outcome after three months of discharge**
Mortality (GOS 1)	13(3%)	17(3.9%)
Vegetative state with an inability to live (GOS 2)	22(5.1%)	0(0%)
Severe Disability with an inability to live (GOS 3)	147(33.8%)	23(5.3%)
Moderate Disability (GOS 4)	240(55.2%)	114(26.2%)
Good recovery (GOS 5)	13(3%)	281(64.6%)
Grand Total	435(100%)	435(100%)
Unfavourable outcome	182(41.8%)	40(9.2%)
Favourable outcome	253(58.2%)	395(90.8%)

The data represented in table 4 indicates that out of 435 patients 182 (41.8%) had unfavourable outcome and 253 (58.2%) had favourable outcome after one month follow-up. Similarly, 40 (9.2%) had unfavourable outcome and 395 (90.8%) had favourable outcome at 3 months follow-up. The unfavourable outcomes include mortality and vegetative state with an inability to live. At one month follow-up 13 (3%) had mortality and 22 (5.1%) were in vegetative state with inability to live. Similarly at 3 months follow-up, 17 (3.9%) had mortality and none of them were in vegetative state with inability to live.

Table 5: Multivariate logistic regression assessing the risk of unfavourable outcome at one month and three month follow-up				
	One month follow-up		Three months follow-up	
Depending Parameter	Odd Ratio (OR)	p-value	Odd ratio (OR)	P value
Albumin Level (0-3.5)	1.6	0.289	4.4	0.217
CRP Level (≤1)	0.8	0.570	2.4	0.212
Prothrombin Level (<10)	0.0	0.999	0.8	1.000
Prothrombin Level (10-15)	0.6	0.136	0.4	0.060
ESR Level (<20)	1.8	0.212	1.1	0.960
Thrombocytes Level (<150)	0.3	0.071	0.6	0.682
Thrombocytes Level (150-200)	0.5	0.068	0.7	0.632
Fibrinogen Level (<2)	3.9	0.0001*	4.9	0.032*
Transferrin Level (<200)	9.7	0.001*	1.8	0.0408*
Transferrin Level (200-300)	1.5	0.598	0.0	0.995
GCS Score (3-8) (at the time of admission)	27.0	0.0001*	0.0	0.995
Constant	0.0	0.0001*	0.0	0.994

Table 5 presents multivariate regression analysis between outcomes at one month follow-up as dependent variable and prognosis predictor biomarkers (albumin, CRP, prothrombin, ESR, thrombocytes, plasma fibrinogen and transferrin) with the GCS score as independent variables clearly indicates that Fibrinogen, Transferrin and GCS score at the time of admission have significant impact on the one-month outcome of traumatic brain injury patients ($p < 0.05$). Patients with fibrinogen level <2 were 3.9 times and 4.9 times more likely to develop unfavourable outcomes at one month and 3rd month respectively compared to patients with fibrinogen >2. Patients with transferrin level <200 were 9.7 times odds and 1.8 times odds to progress to unfavourable outcomes at one month and 3rd month respectively compared to patients with transferrin levels >200. Patients with GCS score 3-8 were 27 times odds of progressing to unfavourable outcomes at one month and 3rd month respectively compared to patients with GCS score >8 (table 5).

DISCUSSION

The present study has shown that the prognostic predictor biomarkers (acute phase reactants) have considerable impact on the prediction of prognosis in patients with traumatic brain injury.

All the biomarkers (albumin, CRP, prothrombin, ESR, thrombocytes, fibrinogen and transferrin) were measured within 24 hours of admission to our tertiary care hospital.

Albumin is an negative acute phase reactant, synthesised by the liver, the normal level in healthy individual ranges from 3.5 to 5.5 gm/dL. In the present study it is seen that patients with severe TBI had significantly decreased albumin levels compared to moderate TBI and these patients with reduced albumin levels had poor outcomes.

Chen et al [24] in their study, found that the serum albumin levels within 24 hours after admission may predict poor outcomes with GOS: 1–2 in severe head injury patients. They concluded that hypoalbuminemia occurs in head injury patients, it may be due to suppression of synthesis of albumin by the liver, increased consumption of albumin during stressful conditions, or loss of albumin during massive haemorrhage. There was significant decrease in serum albumin levels in patients with severe GCS score compared to the moderate GCS score.

It is suggested that serum albumin levels significantly improve blood flow and re-establish the balance between oxygen supply and demand. It was also observed that serum Albumin levels are favourable therapeutic time window allowing administration within a clinically feasible delay. This is in accordance with Belayev L, Liu Y, Zhao W, et al [25]

In the present study we found that the head injury patients with severe head injury had increase CRP level and mortality was higher. It is very evident in the present study that the patients who had moderate GCS score at the time of discharge had better outcome as compare to the patients who had severe GCS score at the time of admission. Thus, the association of GCS score at the time of admission and at time of discharge was statistically significant p value <0.05.

Felger et al.[26] in their study found that the CRP concentration may impact on CNS function by accessing the CNS. CRP levels was increased in both periphery and CSF in depressed patients. This study suggested that CRP was a better marker for both peripheral and central inflammation.

An acute brain injury triggers an immediate and robust inflammatory response known as acute phase response. CRP is an acute-phase reactant that synthesize in liver. CRP significantly increases during this acute phase response in inflammation. Increased CRP level during inflammation is due to a reaction to the tissue damage and has proven as a predictor of poor outcome in head injury patients whereas higher CRP indicate more severe Head trauma. It has been clinically experimented and documented previously in patients with head injuries in accordance with Cederberg D et al.[27]

Lee DG et al.,[28] CRP has been recently considered not only as a biochemical marker of inflammation but also as a predictor of prognosis and outcome in head injury. The correlation of CRP levels was evaluated with outcome and mortality after ICU admission in a head trauma group of ICU patients.

According to another investigation in a heterogeneous ICU population, elevated concentrations of serum CRP on ICU admission were correlated with an increased risk of death. Patients with high CRP levels at ICU admission had higher mortality rates than patients with normal ICU admission CRP levels.[29]

Wang et al.,[30] performed a study comprising 368 patients and a systematic review of 18 studies involving 15,238 patients. They determined that CRP was not associated with poor outcomes in patients with infection.

In the present study, we investigated the critical role of plasma prothrombin concentration in head injury patients and prediction of outcome in head trauma patients. American College of Chest Physicians recommendations, PCC is used as the first-line drug in the reversal of anticoagulation therapy and in patients with life-threatening bleeding and an increased INR.[31]

Balendran et al.,[32] From this prospective observational cohort study concluded that low prothrombin concentration with a cut-off in the range of 50–70 IU/dL (corresponding to approximately 50–70% of normal prothrombin concentration) together with low fibrinogen level was a role as rate-limiting for coagulation in bleeding head trauma patients. They found the association role of low prothrombin concentration with low fibrinogen levels an increased risk for massive transfusion and mortality and clinical outcome. It is currently considered as the best index of coagulation biomarkers as surrogates for detecting critically low plasma prothrombin levels. Admission time prothrombin plasma concentration can be predicting increased survival and a lower transfusion demand within the first 24 h admitted head injury patients and that a cut-off in the range of 50–70 IU/dL at admission is associated with a worse outcome.[33]

We found statistically significant association between GCS score and ESR level. It is very evident that patients who had moderate GCS score at the time of discharge had better outcome as compare to the patients who had severe GCS score at the time of admission. Thus, the association of GCS score at the time of admission and at time of discharge was statistically significant p value <0.05.

Natakusuma et al., (2021)[34] Concluded a study on “Role of Monocyte-to-lymphocyte Ratio, Mean Platelet Volume-to-Platelet Count Ratio, C-Reactive Protein and Erythrocyte Sedimentation Rate as Predictor of Severity in Secondary Traumatic Brain Injury”. Increased monocyte count and platelet volume followed by decreased lymphocyte and PCR were a reflection of neuroinflammation severity in head injury patients. Increased levels of CRP and high ESR were also indicators of inflammation severity in head injury patients. They also conclude the level of MLR, MPV-PCR, CRP, and ESR could be predictors of severity in secondary head injury patients.

In a study by **Bray C et al, [35]** the mean ESR levels in head injury patients were within the normal range, and only 28.2% of them had elevated ESR levels (ESR >20 mm/h). These results could occur because the ESR examinations were carried out on the 1st-day post-injury, where the ESR levels did not change rapidly at the beginning of the inflammatory process and would return to normal range in a longer time than other acute phase reactants.

In the present study we found that patients with severe head injury (GCS score 3-8) had mildly increased Thrombocytes and the mortality was higher.

Similarly studied by **Carrick et al., (2005)**,[36] Platelet count was low in head injury patients at admission time, and reduced on 3rd day. They suggest further study needed. Platelets count in head injury patients was within the normal range, and none of them had thrombocytosis. Few head injury patients had thrombocytopenia instead. These results supported several previous studies, which also found that the platelet count in head injury patients was still within the normal range.[37,38] The decreased platelets count in TBI patients can occur due to the increased platelet consumption (consumption coagulopathy), where the coagulation system was activated when the blood passes through the injured brain tissue post-brain injury.

Our study also found a significant correlation between thrombocyte level at the time of admission and GCS score at the time of discharge. During inflammation process, thrombocytes increased and also predict the severity of head injury.

We found statistically significant the association between GCS score and low level of fibrinogen. It is very evident that patients who had mild and moderate GCS score at the time of discharge had better outcome as compare to the patients who had severe GCS score at the time of admission. Thus, the association of GCS score at the time of admission and at time of discharge was statistically significant $p<0.05$.

The newer study showed that the relationship between fibrinogen levels at the time of admission and the probability of favorable outcome and mortality was not nonlinear but rather curvilinear. When fibrinogen was < 2.0 g/L, these levels were an independent prognostic factor for 3-month mortality. However, for patients with fibrinogen levels < 2.5 g/L, multivariate analyses showed that the levels were instead an independent prognostic factor for 3-month favorable outcomes, with the likelihood of a favorable outcome increasing in association with an increase in level. This is an accordance with **Ke Lv et al.[39]**

Our data demonstrate to associated correlation between head injury patients with hypofibrinogenemia during acute head trauma. Poor level of fibrinogen in head injury patients at the time of admission is strongly related the to an increased rate of mortality. Our outcome suggested maintaining fibrinogen level may the best way to improve prognosis.

We found statistically significant association between GCS score and transferrin level (< 0.05).

The association between transferrin level at the time of admission and GCS score at the time of discharge were out of 435 head injury patients 252(57.9%) patients had moderate score at the time of admission but at the time of discharge 143(32.9%) patients had moderate GCS score, and 6(1.4%) patients had mild GCS score at the time of admission but at the time of discharge 2(0.5%) patients had mild GCS score, and 177(40.7%) had severe GCS score at the time of admission and at the time of discharge 151(34.7%) had severe GCS score.

it is very evident that patients who had moderate GCS score at the time of discharge had better outcome as compare to the patients who had severe GCS score at the time of admission. Thus, the association of GCS score at the time of admission and at time of discharge was statistically significant p value <0.05.

In the present study we found that patient with severe head injury (GCS score 3-8) had decrease transferrin level and mortality was higher.

A study on Intracerebral hemorrhage patients serum iron level measured with acute hemorrhagic stroke using atomic absorption spectrophotometry as an indicator. Transferrin is unique in chelating iron with very high affinity. It was reported that Tf concentration was significant, compared with the

controls, serum iron levels were significantly lower in patients with ICH, instead found higher in patients with acute hemorrhagic stroke. This is an accordance with **Karadas S. et al.**[40]

Yang et al., (2016)[41] study investigated the changes of serum iron and Tf in patients with ICH and demonstrated first both serum iron and Tf levels at day one (admission) in patients with poor outcome were significantly lower than those in the patients with good outcome as well as in the control. Increased serum ferritin level, low serum iron, and Tf was associated with functional outcome patients with Intracerebral hemorrhage (ICH). This is in accordance with **Yang et al.**[41]

This study demonstrate that the level of albumin, transferrin and fibrinogen level were decreased with severe GCS score at the time of admission. the mean value of CRP, Prothrombin, ESR and Thrombocytes were increased with severe GCS score.

We found that serum albumin level, serum Transferrin and plasma fibrinogen at the time of admission were significantly decreased with severe GCS score (3-8) after one month of discharge than the GCS score moderate (9-12) and mild GCS score (13-15) after one month of discharge.

The concentration of CRP, Prothrombin, ESR and Thrombocytes at the time of admission were increased with severe GCS score (3-8) in head injury patients than the GCS score moderate (9-12) and mild GCS (13-15) after one month of discharge.

It is evident from outcome scale was important in serum albumin level in patients which GOS-1 to GOS-5 respectively, which was statistically significant (p=0.01), and It is was important in serum CRP level in patients which GOS-1 to GOS-5 respectively, which was statistically significant (p=0.01).

Outcome score was important in Prothrombin level in patients which GOS-1 to GOS-5 respectively, which was statistically significant (p=0.005), and in ESR level in patients which GOS-1 to GOS-5 respectively, which was statistically significant (p=0.009).

We found that Thrombocytes level in patients which GOS-1 to GOS-5 respectively, which was statistically significant (p=0.04), and important in Fibrinogen level in patients which GOS-1 to GOS-5 respectively, which was statistically significant (p=0.03), and Transferrin level in patients which GOS-1 to GOS-5 respectively, which was statistically significant (p=0.006).

CONCLUSION

In our study we found that, the traumatic brain injury patients had decreased albumin level and transferrin level while the levels CRP, prothrombin, ESR, thrombocytes and plasma fibrinogen were increased at the time of admission. Most of the patients had severe GCS score at the time of admission. The levels of all acute phase reactants (serum albumin, CRP, prothrombin, ESR, thrombocytes, plasma fibrinogen and transferrin) had highly significant association with the severity of head injury (GCS score) at the time of admission. The association between severity of head injury (according to GCS score) at the time of admission and severity of head injury (according to GCS score) at the time of discharge and after one month of discharge are highly significant. In the present study we conclude that levels of plasma fibrinogen, serum transferrin and GCS score at the time of admission had statistically highly significant impact on the outcomes of head injury patients at the time of discharge, one month follow-up, and three months follow-ups respectively. Thus, measurement of these biomarkers at the time of admission in patients with head injury will be highly helpful in predicting the prognosis. Further, our Research study also adds the significant values for future planning of usage of anti-inflammatory drugs to manage head injury patients for the better outcome.

MATERIALS AND METHODS

The prospective follow-up study with 435 clinically diagnosed traumatic brain injury patients admitted in the department of neurosurgery at our tertiary care trauma center from 2021 to 2022 were enrolled in the study. The study was conducted by department of Biochemistry in collaboration with department of Neurosurgery National Institute of Medical Sciences and Research, Jaipur after taking institutional ethical committee approval **NIMSUR/URC/2022/006-4** in accordance with relevant

guidelines and regulations. An voluntary informed consent was obtained from all the subjects/guardians included in the study.
Study design: Prospective
Sample Size: sample size was calculated using the formula as per directions of statistician,
Sample size calculation

$$= \frac{Z^2 * p * (1-p)}{e^2}$$

Where:
z= 1.96: inverse normal value at 5% level of significance
p = 0.386: proportional rate
e=5% =0.05: margin of error
n= $\frac{1.96^2 * 0.386 * 0.614}{0.05^2}$ = 362.3 +20% dropout =435
Inclusion criteria: We included the patients with traumatic brain injury both males and females in the age group 18-70 years admitted within 24 hours, whose attendants willing to participate in the study and during follow-up.
Exclusion criteria: we excluded the patients with solid organ damage, chronic diseases such as tuberculosis and chronic renal disease, patients on anticoagulant therapy, pre-trauma fever, hemolytic disorders, HIV infections, pre-existing hepatic disease/insufficiency, pregnancy and lactating women. At the time of admission the severity of traumatic brain injury was assessed using Glasgow Coma Scale (GCS).[13-15] All the patients underwent detailed clinical evaluation including GCS score, based on GCS score they were categorized as mild, moderate and severe traumatic brain injury. Subsequent relevant laboratory investigations were carried out which include acute phase reactant biomarkers albumin, c reactive protein (CRP), prothrombin, fibrinogen and transferrin levels along with routine laboratory investigations (hemoglobin, complete hemogram, arterial blood gas analysis) within 24 hours of day of admission. Serum albumin was measured by BCG method[16] in fully automated biochemistry analyzer, CRP levels were measured by sandwich chemiluminescence method[17], PT concentration in plasma was measured by coagulation method on STA® analyser[18], complete blood counts were measured by using a five-part differential system[19] automated blood cell counter Elite 580, plasma Fibrinogen was estimated by the immunoturbidimetric method[20], Serum transferrin level by using plain vacutainer was estimated on CS-T180 fully automated Biochemistry analyser by the immunoturbidimetric method.[21,22] Severe head injury is associated with considerable morbidity and mortality. Glasgow outcome scale scoring[23] is one of the tool used for measuring the outcome after the traumatic brain injury. GOS scoring was done in all the patients at the time of discharge and follow-ups at one month and third month.
Statistical analysis: Categorically data was presented as frequency and percentage (%), and measurement data with normal distribution were presented as mean ± S.D. The independent predictors of head injury were determined by univariate and multivariate logistic regression analysis odds ratio (OR) and 95% of confidence of interval (CI) was calculated.

Declarations

Ethical Approval

The study was approved by NIMS University Institutional ethical committee with proposal number **NIMSUR/URC/2022/006-4 as** per the guidelines. Informed consent was obtained from all the subjects participated in the study and the consent was obtained for publication.

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Declarations
Ethical considerations
Ethical clearance was obtained from Institutional Ethical Committee NIMS University for the study and the informed consent was obtained from all the subjects who participated in the study on voluntary basis.

Consent for publication
As our manuscript does not contain any individual persons data, this section is “Not applicable”.

Availability of data and materials
The data for the current study included patients admitted in Emergency Department and Neurosurgery department. Excel data is presented in the last page of this manuscript itself.