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C-Reactive Protein and D-dimer as Prognostic Markers for Clinical Outcomes in Patients with Mild Traumatic Brain Injury: A Cross-Sectional Study

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ABSTRACT

Objective: To investigate the use of prognostic markers such as C-reactive protein (CRP) and D-dimer for clinical outcomes in patients with mild traumatic brain injury (TBI).
Methods: This cross-sectional study was conducted on patients with mild head trauma who were admitted to the Emergency Department of Imam Khomeini Hospital (Sari, Iran). Data were collected from 2018 to 2019. Age, sex, the time of injury hospitalization, length of hospitalization, length of unconsciousness, blood pressure, heart rate, respiratory rate, and concomitant symptoms were all recorded using a pre-designed checklist. The patient's Glasgow Coma Scale (GCS), CRP, and D-dimer were also measured. Moreover, all patients underwent CT scan.
Results: This study included 74 patients with TBI. The mean age of the participants was 36.92±3.54. The mean CRP and D-dimer values were 5.69±0.77 and 0.58±0.11 in these patients, respectively. At the cut-off point of 11.50 for CRP, the sensitivity and specificity to detect the pathological lesions in CT scan were 75% and 95.50%, respectively (p<0.001). Additionally, with a D-dimer cut-off point of 0.90, the sensitivity and specificity for diagnosing pathological lesions in CT scan were 100% and 98.50%, respectively (p<0.001).
Conclusion: In general, the CRP and D-dimer levels of patients with mild TBI (GCS≥13) can be assessed to protect against CT-induced radiation exposure and subsequent disorders; if they do not exhibit clinical signs to increase the risk of adverse brain damage, such as reduced level of consciousness, drowsiness, and prolonged periods of unconsciousness.

Keywords: C-reactive protein; D-dimer; Head trauma; Head injury.

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Introduction

Traumatic injuries are recognized as a major public health issue all over the world [1]. Traumatic brain injury (TBI) may be developed as a result of anatomical changes in the scalp, brain, or blood vessels following a traumatic head injury. Although everyone is susceptible to TBI, middle-aged and older adults are particularly vulnerable [2]. TBI accounts for 30-50% of trauma-associated deaths and is the leading cause of trauma-related disability in people under the age of 40 [3]. It is estimated that 69 million people suffer from TBI every year [4]. In the United States, the death rate due to TBI reaches 52,000 million people annually [5]. Although some countries regarded falls as the most prevalent cause of TBI, and others considered traffic accidents as the most common cause; a published report from Iran indicated that the incidence of TBI was lower than other countries [6].

Following an external hit to the head, inflammatory, metabolic, and neurochemical processes begin, and symptoms may be delayed for hours or days depending on the severity of the injury [5]. TBI is typically divided into three categories: mild, moderate, and severe [7]. Glasgow Coma Scale (GCS) score is used to categorize the clinical severity of TBI into three categories: mild (GCS: 14-15), moderate (GCS: 9-13), and severe (GCS: 3-8) [8]. According to the findings of a previous study, approximately 75% of TBI patients should be classified as having mild TBI [9]. Patients with mild TBI frequently experience symptoms such as vestibular or oculomotor disorders, headache, sleep disturbance, post-traumatic stress disorder, and cognitive dysfunction [10]. Therefore, many cases of mild TBI go unrecognized [3].

To diagnose the intracranial pathology, standard method is computed tomography (CT) scan, although it is associated with the risk of radiation-induced malignancy [11]. In such circumstances, several blood biomarkers can be used to determine the need of CT scans for the definitive diagnosis of mild TBI [12]. Due to the massive release of thromboplastin after trauma, patients with TBI are at risk of developing coagulopathy, which adversely affects their prognosis. In this regard, Subedi *et al*., [13] indicated that D-dimer levels increased in TBI patients. Furthermore, previous research showed that acute inflammatory reactions occurred following a head injury. Due to its short response time, C-reactive protein (CRP) level measurement has been used to identify and monitor inflammation [14]. Su *et al*., [15] found that the level of CRP increased in mild TBI patients, and this elevated level was associated with an increasing in unfavorable outcomes.

The relationship between TBI and biomarkers such as CRP and D-dimer was previously established. However, few studies [need at least 2 references] were conducted to evaluate them as screening tests. It seems necessary to perform screening tests by considering the carcinogenicity, high expense, and restricted access to CT. Therefore, the objective of this study is to investigate the use of CRP and D-dimer as prognostic markers for clinical outcomes in patients with mild TBI.

Materials and Methods

This cross-sectional study was conducted on patients with mild head trauma who were admitted to the emergency department of Imam Khomeini hospital (Sari, Iran), from 2018 to 2019. The inclusion criteria for this study were mild head trauma with a GCS score of 14 and 15. The exclusion criteria were moderate and severe head trauma, underlying coagulation disorders, receiving blood products, and surgical interventions. The study protocol was approved by the ethics committee of the Mazandaran University of Medical Sciences (IR.MAZUMS.REC.94-1909).

The following formula was used to estimate the required sample size for evaluating the use of CRP and D-dimer as prognostic markers for clinical outcomes in patients with mild TBI. Based on the following formula, with d=10%, p (prevalence of head trauma)=30%, q (prevalence of TBI)=10%, z=1.96, and a potential 10% attrition rate, a sample size of 74 was calculated.

$$N = \frac{\frac{z^2 pq}{d^2}}{1 + \frac{1}{N}\left(\frac{z^2 pq}{d^2} - 1\right)}$$

The participants were informed about the research goals, and verbal informed consent was obtained of the patients before participation. A pre-designed checklist was used to gather information such as age, sex, time of the injury to hospitalization, length of hospitalization, length of unconsciousness, blood pressure, heart rate, respiratory rate, and concomitant symptoms. The patient's GCS, CRP, and D-dimer levels were also measured. Moreover, all patients underwent CT scan.

The GCS is used to determine the level of consciousness in all types of acute illnesses and trauma patients. The scale rates patients based on their verbal, motor, and eye-opening responses. A person with a score of 3 is considered as a brain dead or in a severe coma. The maximum value of 15 denotes a fully conscious patient [16].

CRP and D-dimer levels were determined using the Enzyme-linked immunosorbent assay (ELISA) method. A normal value for CRP was considered to be less than 10 mg/L, and anything higher was considered positive. D-dimer levels over the accepted upper limit of 0.5 mg/L or 500 ng/mL were considered abnormal.

The data were analyzed using SPSS software,

version 16.0 (SPSS Inc., Chicago, IL, USA). The Fisher exact test was used to compare concomitant symptoms in two groups of presence and absence of lesions in CT scan. Besides, the independent sample T-test and Mann-whitney test were used to compare the mean and median of demographic variables between the two groups. Pearson's correlation coefficient was also used to evaluate the relationship between biomarkers and level of consciousness. The receiver operating characteristic curve (ROC) was used to calculate the prediction and determination of the cut-off point for CRP and D-dimer. $P<0.05$ was considered statistically significant.

Results

Table 1 shows that 74 patients with TBI were participated in this study. The mean age of the participants was 36.92±3.54 (IQR=36.0058). Eleven percent of the participants were men. The presence of lesions in the CT scan was negative in 75.68% of the patients. The mean time from injury to hospitalization (hour) was 0.99±0.20 (IQR=0.50), the duration of hospitalization (hour) was 4.67±0.28 (IQR=1.56), and the duration of unconsciousness (seconds) was 7.56±2.80. Additionally, the patients' mean systolic blood pressure (mm/hg) was 123.72±3.07 (IQR=20.00), and diastolic blood pressure (mm/hg) was 73.89±1.75 (IQR=10.00). These patients' median heart rate was 72.54±1.24 (IQR=17.00), respiratory rate was 14±2 (IQR=6.00), and GCS was 15.00. Furthermore, these patients' mean CRP and D-dimer values were 5.69±0.77 and 0.58±0.11, respectively.

As shown in Table 1, there was a significant difference in the duration of unconsciousness ($p<0.001$), CRP ($p<0.001$), D-dimer ($p<0.001$), reduced level of consciousness ($p<0.001$), stupor and drowsiness ($p=0.02$), and headache ($p=0.009$) between the two groups of patients with the presence or absence of a lesion in their CT scan.

Additionally, as indicated in Table 2, there was a significant positive relationship between the length of unconsciousness and CRP (r=0.400, $p<0.01$), length of unconsciousness and D-dimer (r=0.404, $p<0.01$), and CRP and D-dimer (r=0.427, $p<0.01$). Besides, there was a significant negative correlation between GCS and length of unconsciousness (r=-0.515, $p<0.01$), GCS and CRP (r=-0.607, $p<0.01$), and GCS and D-dimer (r=-0.641, $p<0.01$).

According to Figure 1, the sensitivity and specificity to detect pathological lesions in CT scan were 75.00 and 95.50%, respectively ($p<0.001$) at the cut-off

Table 1. Patient characteristics and their relationship with the presence of lesions in computed tomography (CT) scan.

Variable		Total (N=74)	IQR[a]	Presence of lesions in CT[g] scan				*P*-value
				Yes (N=18)	IQR[a]	No (N=56)	IQR[a]	
Age		36.92±3.54	36.00	44.37±6.78	35.75	34.52±2.50	35.25	0.21[d]
Sex	Male	43 (58.11)		5 (11.63)		38 (88.37)		≥0.999[f]
	Female	31 (41.89)		3 (9.68)		28 (90.32)		
Time of injury to hospitalization (Hours)		0.99±0.20	0.50	0.84±0.12	0.50	1.04±0.22	0.50	0.74 [d]
Duration of hospitalization (Hours)		4.67±0.28	1.56	5.28±.48	2.81	4.47±0.21	1.50	0.20 [d]
Duration of unconsciousness (Seconds)		7.56±2.80	0	28.75±9.19	56.25	0.75±0.75	0	<0.001 [d]
Systolic blood pressure (mm/Hg)		123.72±3.07	20.00	127.50±5.17	21.25	122.50±2.39	16.25	0.48 [d]
Diastolic blood pressure (mm/Hg)		73.89±1.75	10.00	76.87±2.48	12.5	72.93±1.52	10.00	0.38 [d]
Heart rate (b/min)		72.54±1.24	17.00	68.00±2.00	15.00	74.00±1.00	17.00	0.17[e]
Respiratory rate (/min)		14±2	6.00	15.00±2	5.00	13.00±4	6.00	0.73[e]
GCS[b]		15.00	0	15.00	0	15.00	0	0.681[e]
CRP[c]		5.69±0.77	3.25	11.12±1.96	9.00	3.94±0.39	3.00	<0.001 [d]
D-dimer		0.58±0.11	0	2.21±0.37	1.73	0.06±0.03	0	<0.001 [d]
Concomitant symptoms	Vomiting	37 (50.00)		6 (16.22)		31 (83.78)		0.26e
	Reduced level of consciousness	6 (8.11)		5 (83.33)		1 (16.67)		<0.001[f]
	Stupor and drowsiness	12 (16.22)		4 (33.33)		8 (66.67)		0.02[f]
	Headache	42 (56.76)		8 (19.05)		34 (80.95)		0.009[f]

[a]IQR: Interquartile Range (for continuous variables); [b]GCS: Glasgow coma scale; [c]CRP: C reactive protein; [d]*p*-value was obtained with an independent T-test; [e]*p*-value was obtained with a Mann-Whitney test; [f]*p*-value was obtained with a Fisher exact test; [g]CT: Computed Tomography. Data are presented as a number (percentage) for categorical variables and mean±SD and IQR for continuous variables.

Table 2. The relationship between biomarkers and level of consciousness in traumatic brain injury (TBI) patients.

Variable	Age	GCS[a]	Duration of unconsciousness	CRP[b]	D-dimer
Age	1				
GCS[a]	-0.113	1			
Duration of unconsciousness	0.080	-0.515*	1		
CRP[b]	0.153	-0.607[c]	0.400 [c]	1	
D-dimer	0.132	-0.641 [c]	0.404 [c]	0.427 [c]	1

[a]GCS: Glasgow coma scale; [b]CRP: C reactive protein; [c]*p*-value was obtained with the Pearson correlation coefficient test ($p<0.01$).

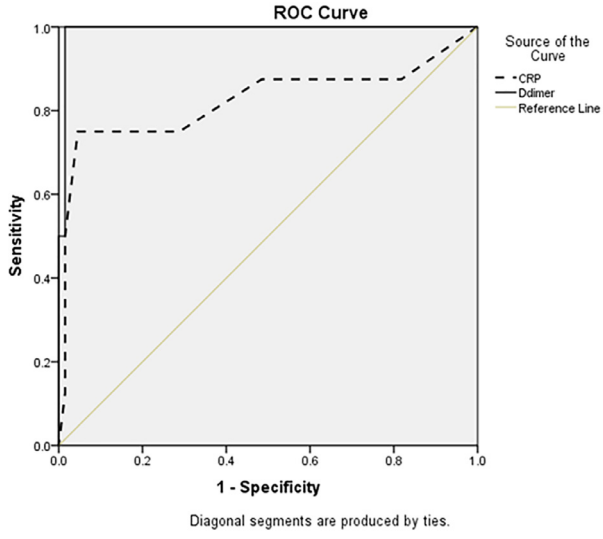

Fig. 1. Characteristics of C - reactive protein (CRP) and D-dimer curves in computed tomography (CT) scan brain lesions.

point of 11.50 for CRP. Furthermore, the sensitivity and specificity for diagnosing pathological lesions in CT scan were 100 and 98.50%, respectively (p<0.001) at the cut-off point of 0.90 for D-dimer.

Discussion

TBI is a worldwide public health issue and causes death and disability [17]. The majority of TBI patients are in the mild class (GCS>13), which may not be diagnosed, since no lesions are visible on their CT scan on the day of the injury [18]. According to the findings of previous research, approximately 7 to 20% of individuals with mild TBI had abnormalities such as hemorrhage, hematoma, and swelling in the CT scan within the first 24 hours [19]. In the present study, CT scan was used to make the final diagnosis of mild TBI, and lesions were seen in only one-quarter of the cases. Those patients who revealed the presence of lesions with CT scan had a lower GCS score than other patients. Previous research found that abnormal GCS was associated with a reduced level of consciousness, which was indicative of brain injury [20]. According to the findings of the present study, patients who identified lesions in the CT had clinical symptoms of brain injury such as decreased levels of consciousness, prolonged durations of unconsciousness, stupor, drowsiness, and headaches. In such circumstances, blood biomarkers could be efficient in determining the necessity for CT scan [12].

One of the biomarkers that investigated in the present study was D-dimer. Since the early 1980s, it has been recognized that TBI can result in coagulation disorders [21]. Previous studies [22, 23] showed that elevated D-dimer levels were associated with poor TBI outcomes. In this regard, the present study showed that patients with higher levels of D-dimer had lower GCS scores, and there was a significant positive correlation between D-dimer and the length of unconsciousness. In this regard, Subedi *et al*., [13] indicated that D-dimer increase in TBI patients was correlated with a lower GCS score. Furthermore, in this study, it was found that patients with abnormal CT had higher D-dimer levels. In line with the findings of the present study, Swanson *et al*., [24] reported that a higher serum D-dimer concentration was associated with the presence of lesions in CT. In the present research, CRP was also measured as a blood biomarker. After TBI, inflammation is rapidly generated by endogenous brain cells and circulating inflammatory cells. In such circumstances, the concentration of CRP which is an acute phase protein, increases as a result of increased synthesis by the liver in response to systemic inflammation [25]. Our findings showed that CRP level was significantly higher in TBI patients with abnormal CT, which was consistent with the findings of previous studies [15-26]. Furthermore, patients with higher serum levels of CRP had a lower GCS status, which was associated with a longer period of unconsciousness. Similarly, *Su et al*., [15] demonstrated that CRP was correlated with unfavorable outcomes in TBI patients. Therefore, it can be expected that health policymakers will prioritize the evaluation of such biomarkers to determine the necessity of performing a CT scan for a definitive diagnosis.

In the present study, the evaluations showed the high specificity and sensitivity of CRP and D-dimer tests to predict the absence of CT lesions in patients with mild TBI. Although studies conducted in Iran and South Korea achieved high levels of sensitivity and specificity for D-dimer and CRP tests, they stated that merely these tests cannot be used for screening by considering the dangerous consequences of brain injury [26, 27], which was similar to the findings of the present study. However, due to their high specificity, these tests may limit the use of CT scan in patients with mild TBI.

This study had several limitations. First, it just included patients with mild TBI. It is recommended to compare the diagnostic power of these tests in all categories of TBI by considering that biomarkers are highly variable under the influence of injury severity. Another limitation of this study was the small sample size, which may lead to bias in the estimates.

Therefore, multicenter studies are recommended with a larger sample size including all categories of TBI patients. It is also suggested that researchers design well-designed randomized controlled trials in the future to examine the hypotheses of this study.

In general, the CRP and D-dimer levels of patients with mild TBI (GCS≥13) can be assessed to protect against CT-induced radiation exposure and subsequent disorders; if they do not exhibit clinical signs that increase the risk of adverse brain damage, such as reduced level of consciousness, drowsiness, and prolonged periods of unconsciousness.

Declaration

Ethics approval and consent to participate: The present research was approved by the ethics committee of Mazandaran University of Medical Sciences, Iran (IR.MAZUMS.REC.94-1909). After obtaining permission from the hospital administration, the researchers visited the hospital. Verbal informed consent was obtained from the participants.

Consent for publication: All authors read and approved the final manuscript to be published and agreed to be accountable for all aspects of the work in terms of the accuracy and integrity of any of its parts.

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