Original Article

Diagnostic Competence of Creatine Kinase BB, in Mild Traumatic Brain Injury and its Prognostic Value

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Abstract

Background: Due to the very high and increasing prevalence, essential complications, and risk factors for psychiatric disorders, it is necessary to introduce screening tests for diagnosing and predicting mild traumatic brain injury (mTBI) prognosis.

Materials and Methods: After completing the consent form and recording information and examination findings of patients with mild trauma, venous blood samples were taken from these patients. The samples were measured by observing the cold chain. After 3 months from mTBI, the post concussion symptoms questionnaire (PCSQ) and the short form 36 (SF-36) questionnaire for physical and mental evaluations were performed. Statistical tests analyzed the relationship between different variables and serum Creatine kinase BB (CKBB) levels.

Results: Statistic analyses showed no relation between CKBB level of serum and age, gender, level of consciousness, PCSQ, and SF 36 scale, and the interval between trauma and arrival to the hospital. Further, there is a significant correlation between CK-BB levels and intracranial damage based on Fisher's exact test.

Conclusion: This study and following more significant considerations can introduce a serum-based biomarker panel that can accurately differentiate patients with complicated mTBI from those with uncomplicated.

Keywords: BB creatine kinase, intracranial hemorrhage, kinase, traumatic brain injuries

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Introduction

Mild traumatic brain injury (MTBI) is caused by the transfer of mechanical energy to the brain caused by a traumatic event such as a rapid change of speed, a direct blow to the head, or an explosion. MTBI is generally associated with a range of neurological, cognitive, and behavioral symptoms and can lead to increased intracranial pressure as well as a postconcussion syndrome in the long term.[1,2] However, the pathophysiology of mTBI has not been determined, and as a result, there are no appropriate identification and diagnosis methods and treatment strategies for it. Due to limitations in medical imaging techniques and incomplete diagnostic methods, researchers have begun to study mTBI at the molecular and cellular levels.[3,4] Currently, determining and predicting brain injury clinical markers include Glasgow coma scale (GCS), pupil response, and brain computed tomography (CT) scans. While these clinical markers have a proven value in estimating the severity and extent of brain damage, they have limited ability to foretell adverse and secondary brain complications since mTBI.[5,6] Diagnosis is subjective and primarily based on self-reported neurological symptoms. Hence the definitive diagnosis of mTBI may be influenced by factors such as mental thrill to conceal symptoms or exaggeration in the patient's expression of symptoms.[7]

As a creatine kinase isoenzyme, Creatine Kinase BB (CKBB) is predominantly found in the central nervous system (CNS)

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and had a half-life of 1 to 5 h. However, a small amount of it is found in the gastrointestinal tract, uterus, and vascular wall and seems to be one of the adenocarcinomas markers. It is generally assumed that due to the specificity of CK-bb in the CNS, this marker has a low sensitivity as a plasma marker of traumatic brain injury.[8,9] However, studies examining a larger community of mTBI had a better view of CK-BB changes after trauma in patients with high consciousness levels.[10,11] Since minor head trauma is widespread and its diagnosis remains one of the clinical problems that may have many complications, identifying biomarkers to diagnose this complication and managing patients, especially those at risk, is critical. Therefore, the present study investigated the correlation between serum CK-bb biomarker levels in patients with mTBI and postconcussion syndrome after 3 months in the same patients.

Materials and Methods

The present study was performed on 148 patients with mTBI in central trauma hospitals in the southwest of Iran in 2019. The inclusion criteria were 18 years old and over, clinical diagnosis of mTBI. mTBI is defined by slight confusion, loss of consciousness, posttraumatic amnesia, and/or other transient neurological abnormalities, with a GCS score of 13–15 after.[12] The exclusion criteria included over 10 h elapsed since the injury, <90 mm Hg systolic blood pressure, known neurological or mental illnesses, spinal cord injury, the existence of focal neurological disorder after trauma, patients who need resuscitation, history of alcohol or drug addiction, dissatisfaction to participating in the research project and Serum Beta hCG positive in female patients.

First, the patient's demographic information and details of head trauma, including the cause of the injury, the injury's time, the injury's location, the severity of the injury, and the patient's condition when entering the data collection checklist, are recorded. A spiral brain CT scan is performed for all patients upon arrival (within the first 10 h after the accident). According to the results, the presence or absence of intracranial damage is examined and recorded. Interpretation will be performed by radiologists who are not aware of the patient's information. Any abnormality detected in the spiral brain CT scan related to the accident is considered an intracranial injury. In this research, blood samples were taken from all eligible patients to assess serum CK-BB levels. The samples were poured into serum separator tubes and stored in a freezer at a temperature (−10%) until use. Evaluation of CK-BB biomarker was performed by enzyme-linked immunosorbent assay (ELISA) method with monoclonal antibodies. The lowest CK-bb biomarker detection in the ELISA method is 1.5 ng/ml, which is considered zero in all analyzes. Due to different articles and cut-off point levels, a cut-off point of 5.52 ng/ml was determined to interpret the present study results. After 3 months from mTBI, the postconcussion symptoms questionnaire (PCSQ) and the short form 36 (SF-36) questionnaire for physical and mental evaluations were performed.

Statistics

According to similar studies,[11] the prevalence increase of CKBB in mTBI individuals estimated to be 0.107, estimated at a significance level of 0.05 and an error of 0.05 according to the following formula.[11] $n = \frac{z^2 pq}{d^2} \cong 147$

Descriptive statistics (mean, frequencies, and proportion) were used to define the variables. The biomarker level was analyzed as a continuous variable. Differences between groups were examined using an independent sample *t*-test for continuous variables and a Chi-square test for categorical variables.

Results

This study included 148 patients who were referred to hospitals due to mTBI. Most patients (73.6%) were 18–40 years, and 107 patients (72.2%) were male. The mean time interval between the onset of trauma and referral was 2.68 h. According to additional evaluations, including imaging (spiral brain CT scan) and physical examination, seven patients (4.7%) had an intracranial injury. The percentage of people with increased CKBB levels was calculated to be 26.4%. Three months after mTBI, the SF-36 questionnaire and postconcussion syndrome questionnaire (PCSQ) symptoms were evaluated. During the study period, 26 people were excluded from the study for various reasons, and 122 people participated in the second part of the study. Demographic information of the participants with more details is shown in more detail in Table 1.

Next, the correlation between CK-BB levels and age group, gender, onset to admission interval, GCS, abnormal and normal CT scan, SF-36, and PCSQ score were evaluated. As can see in Table 2, there is a significant correlation between CK-BB levels and intracranial damage based on Fisher's exact test. Also, other variables were not significantly associated with an increased level of the biomarker. For further comparison between CT scan, which has 100% diagnostic sensitivity, and CK-BB test as a possible alternative, receiver operating characteristic (ROC) curve related to this biomarker's sensitivity and specificity was prepared. Given that the area under the ROC curve is more than 50% of the total screen area, it can be an acceptable test to diagnose cranial damage Figure 1.

Table 1: Demographic and basic data

Variables	Mean±SD/frequency (%)
Age group	
18-40	109 (73.6)
41-60	26 (17.6)
61-90	13 (8.8)
Gender	
Male	107 (72.2)
Female	41 (27.7)
Onset to admission interval (h)	2.68±1.2 (minimum: 1-maximum: 6)
Brain injury (based on CT scan)	7 (4.7)
Elevated CK-BB, cut-off 5.2	39 (26.4)

SD: Standard deviation, CT: Computed tomographic, CK-BB: Creatine kinase BB

Table 2: The relation between CK-BB levels in two groups

Variables	Frequency (%) or mean±SEM		*P*
	CK-BB levels <5.2 ng/ml	CK-BB levels >5.2 ng/ml	
Total participants	109 (73.6)	39 (26.4)	
Age group			
18-40	82 (75.2)	27 (69.2)	0.569
41-60	19 (17.4)	7 (17.9)	
61-90	8 (7.3)	5 (12.8)	
Gender			
Male	83 (76.1)	24 (61)	0.064
Female	26 (23.9)	15 (39)	
Onset to admission interval (h)	2.676±1.2499	2.718±1.2967	0.859
GCS			
15/15	98 (89.9)	33 (84.6)	0.374
14/15	11 (10.1)	6 (15.4)	
Abnormal CT scan	2 (28.6)	5 (71.4)	0.014
Normal CT scan	107 (75.9)	34 (24.1)	
SF-36 score	83±6.6	76±9.4	0.084
PCSQ score	13±4.5	18±9.3	0.123

Tests and variables using Pearson Chi-square and independent *t*-test. 5.2 ng/ml< cut-off point. The statistically significant level of $P<0.05$. CT: Computed tomographic, PCSQ: Postconcussion symptoms questionnaire, SEM: Standard error of mean, SF: Short form, GCS: Glasgow coma scale, CK-BB: Creatine kinase BB

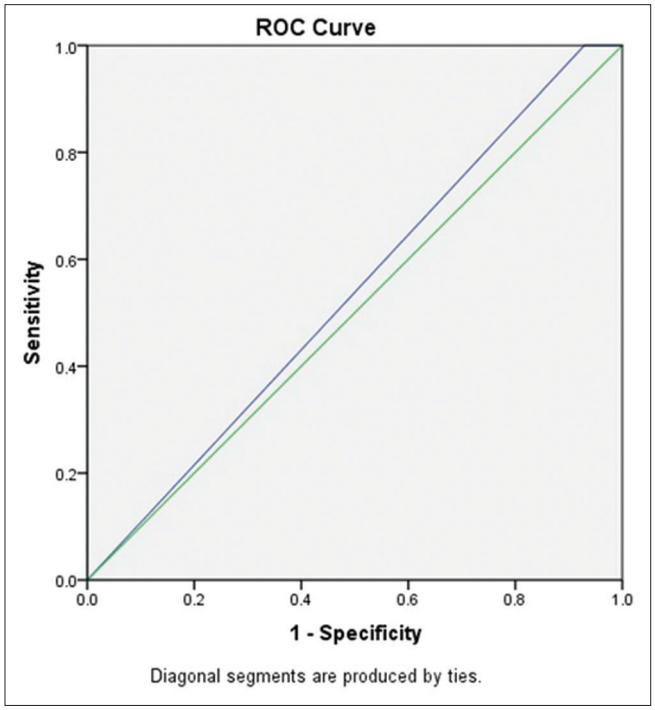

Figure 1: Receiver operating characteristic curves for CKBB to predicting the intracranial lesions. The area under the receiver operating characteristic curve is more than 50%

Based on the present study findings, rapid irritability was the most common among these signs and symptoms in the study population. After that, the degrees of fatigue, sensitivity to sound, headache, depression, boredom, and dizziness, respectively, had the most complaints after 3 months in subjects. The least common symptom in patients was diplopia, in which only one patient (0.82%) had this complication, who was also reported as very mild.

Discussion

With an estimated 54–60 million people a year, traumatic brain injury (TBI) is one of the leading global causes of long-term death and disability. Ideal biomarkers should also be cost-effective with high sensitivity and specificity. Biomarkers are used to classify the severity of injuries, report the mechanism of injury, and progression, predict trauma complications, and ultimately monitor response to treatment.[13,14] Despite the high and increasing incidence of mTBI, significant and sometimes permanent complications for patients, and the risk factor for many neurological and psychiatry diseases, the need for early adjuvant diagnosis is still evident.[15,16] One of the most important objectives of the present study was investigating the relationship between CK-BB biomarkers and intracranial injuries in the study population.

In this study, out of 148 patients, 7 had intracranial injuries (4.7%), of which five people had serum CKBB levels higher than 5.2 ng/ml. Further, out of 141 patients with a normal CT scan, 34 (24%) had CKBB levels higher than 5.2 ng/ml, which also needs further investigation. In 2017 a study with a sample size of 110 mTBI patients, 17 of whom were positive CT, showed the Matrix metalloproteinase-2, C-reactive protein, CKBB, hFABP, and granulocyte-macrophage colony-stimulating factor, MDA-LDL intracranial biomarkers were firmly able to predict lesions. Among them, the CKBB biomarker had a higher score for predicting intracranial injuries.[10] Other similar articles discuss the predictive effects of biomarkers such as glial fibrillary acidic protein

and CKBB in intracranial injuries and mild TBI.[17,18] CKBB, as an intracellular protein, catalyzes creatine phosphorylation to phosphocreatine and active as a component of cellular energy.[19] Studies conducted by Kilianski, *et al*. in 2017,[20] Ahmed, *et al*. In 2012,[21] and Sjödin *et al*. in 2010[22] were also among the studies that found a significant relationship between serum and CSF levels of CKBB biomarker with quantity and severity brain trauma. Meanwhile, Levitt *et al*. 1995,[23] Skogseid *et al*. 1992,[24] Carr *et al*. 2009,[11] and their colleagues described the link between the CKBB biomarker and head trauma as weak and insignificant. Indeed, there exist issues about the credit of CKBB as an indicator of mild brain damages. Since the blood-brain barrier's integrity and the degree to which CNS biomarkers deliver systemic circulation during brain injury can vary and Controversial. It seems that this variation exists in several studies is due to different reasons such as a variety in sample size, laboratory methods of measuring CKBB, the short half-life of CKBB biomarker, and the need to observe the cold chain for sample transfer before serum separation and freezing serum after separation up to the timing of the test, which is all hard and sensitive.

In the current experiment, the excellent efficiency recommends that cellular damage within specific brain regions is involved in the pathophysiology of mTBI. It should be noted that there are several clinical decision rules to predict the need for CT scans in mild TBI. Although these rules sometimes have a sensitivity of close to 100%, their features are not complete and sufficient, resulting in approximately 50% of CT scans of patients being reported negative.[25] However, the results of new studies suggest that low levels of many biomarkers may help reduce unnecessary CT scans in mTBI patients.

In this study, the variables of age, gender, GCS, consciousness during the preliminary examination, and onset to admission interval did not show a significant relationship with the increased level of CKBB. However, several observations make statistical comparisons and classifications based on age, time after injury, and gender virtually at the biomarkers and immunoglobulin.[26,27] In a clinical state, medicine arrangements are performed at various time points postinjury. Therefore, subsequent investigations will require intently analyzing how the biomarkers may modify as a function of time postinjury. The sample size was also of interest, mainly among the CT-positive patients. However, provided the number of subjects was suitable for the declared purposes of the current study, the clinical advantage of biomarker better to assessed applying a broad sample. It may be necessary to update these prognostic models in larger communities.

Conclusion

Appropriate biomarkers should be obtained using a minimally invasive method and can be widely measured. They can also play an important role in referring the patient to advanced imaging and identifying different blood-brain barrier injuries. As expected, the present study, show a significant relation between serums CKBB levels, mTBI, and intracranial lesions. Also, a significant relation was found between the serum level of the CKBB biomarker and the score obtained in the postconcussion syndrome signs and symptoms questionnaire. It is hoped that with subsequent studies in more extensive investigations, serum biomarkers can be used as a tool in determining the prognosis of head trauma patients.

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Conflicts of interest

There are no conflicts of interest.

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