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Can creatine kinase levels be an indicator of the need for hemodialysis?

Могу ли нивои креатин киназе бити показатељ потребе за хемодијализом?

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SUMMARY

Introduction/Objective This study aimed to evaluate the relationship between changes in creatine kinase (CK) levels and the need for dialysis in patients with crush syndrome (CS).

Methods We conducted a retrospective analysis of patients with CS who were admitted to our hospital after the earthquake from February to May of 2023. We recorded demographic and laboratory data of the patients and divided them into two groups based on the change in CK levels within 48 hours. The groups were compared based on the need for dialysis and mortality rates.

Results A total of 84 patients with crush injuries participated in the study (41 males and 43 females). The average age was 33.65 ± 13.1 years. Nineteen patients received hemodialysis, and 18 patients underwent fasciotomy due to compartment syndrome. The patients were divided into two groups, Group 1 consisted of patients with more than a 50% decrease in CK levels within 48 hours, while Group 2 included patients with a decrease of less than 50% in CK levels during the same period. We compared the two groups regarding the frequency of dialysis and mortality. No statistically significant differences were found between the groups (p = 0.328 for dialysis and p = 0.89 for mortality).

Conclusion Although CK is an important enzyme for diagnosing CS and indicates ongoing muscle damage, changes in CK levels during follow-up do not reliably predict the need for dialysis or mortality risk.

Keywords: crush syndrome; creatine kinase; dialysis; mortality

САЖЕТАК

Увод/Циљ Ова студија је имала за циљ да испита однос између промена у нивоима креатин киназе (КК) и потребе за дијализом код болесника са трауматском рабдомиолизом.

Методе Спроведена је ретроспективна анализа болесника са трауматском рабдомиолизом који су примљени у нашу болницу након земљотреса у периоду од фебруара до маја 2023. године. Забележени су демографски и лабораторијски подаци болесника, који су потом подељени у две групе на основу промене у нивоима КК унутар 48 сати. Групе су упоређене у односу на потребу за дијализом и стопу морталитета.

Резултати У студији је учествовало укупно 84 болесника са повредама услед дробљења (41 мушкарац и 43 жене). Просечна старост била је 33,65 ± 13,1 година. Деветнаест пацијената је подвргнуто хемодијализи, док је 18 пацијената подвргнуто фасциотомији због синдрома компартмана. Болесници су подељени у две групе: Група 1 обухватала је болеснике код којих је дошло до смањења КК за више од 50% у року од 48 сати, док су у Групи 2 били болесници са смањењем КК мањим од 50% у истом временском периоду. Упоређивање две групе у погледу учесталости дијализе и стопе морталитета није показало статистички значајне разлике (p = 0,328 за дијализу и p = 0,89 за морталитет).

Закључак Иако је КК важан ензим за дијагнозу трауматске рабдомиолизе и указује на текуће оштећење мишића, промене у нивоима КК током праћења нису поуздан предиктор потребе за дијализом или ризика од морталитета.

Кључне речи: трауматска рабдомиолиза; креатин киназа; дијализа; морталитет

INTRODUCTION

On February 6, 2023, one of the biggest earthquake catastrophes in Turkey and Syria's history hit the southeast part of Turkey and Syria, which inhabits more than 20 million people. More than fifty thousand people lost their lives according to official numbers revealed by the Health Ministry of Turkey [1, 2, 3]. In Syria, which is a war zone, less studied and less secure zone compared to Turkey, more than 4000 people lost their lives as declared by the World Health Organization [3]. Over 160,000 buildings were demolished, and 16 hospitals collapsed following the earthquake, which blocked access to health care in the first hours of the earthquake. Most patients were transferred to the hospitals adjacent to earthquake-hit cities [1, 2, 3].

Crush syndrome (CS) could defined as trauma or compressing associated muscle injury caused by disasters, accidents, or explosions. Generally, it involves the skin, subcutaneous tissue, muscle, tendon, and bones and frequently involves the lower extremities [4]. Following muscle injury, major intracellular electrolytes such as potassium and phosphate and enzymes such as creatine kinase (CK) are released into the systemic circulation. That can cause electrolyte imbalance and might need medical treatment, sometimes resulting in renal replacement therapy [5, 6, 7].

Acute kidney injury (AKI) is one of the most serious complications of CS. According to different studies, the rate of AKI might differ between %15-50 among patients with CS [8, 9, 10]. As a treatment, it is vital to initiate fluid resuscitation therapy as soon as access to treatment is available and renal replacement therapy when necessary [11, 12]. CK is an enzyme primarily present in muscles, the brain, and visceral tissues with a small amount. It is an intracellular enzyme and very sensitive to hypoxia and injury. Following a trauma, hypoxia, or myocardial ischemia, serum CK levels can be detected elevated. Despite the sensitivity, it is not specific to any disease due to its presence in different tissues [13, 14]. Similarly, in CS patients, CK levels can measured higher than 10,000 U/L [9]. Following muscle injury, CK levels rise within 2–12 hours, peak between 24 and 72 hours, and decline by the third to fifth day. Persistently elevated CK levels or a failure to decrease as expected may indicate ongoing muscle damage, a pre-existing muscle disorder, or compartment syndrome [15].

Change in CK levels, as a sign of injury, could be theoretically a sign of ongoing nephrotoxic effects on the kidney. Therefore, in this study, we aim to determine whether the change in CK levels could be a sign of the need for renal replacement therapy or not.

METHODS

Setting and participants

We retrospectively included adult CS patients in our study. Patients admitted to our hospital following the catastrophic earthquake that occurred on February 6, 2023, in our region with a history of trauma and whose CK levels were 10,000 U/L or above were diagnosed as CS. In addition, according to the KDIGO Guidelines, among these patients, those who developed acute kidney injury were recorded [16].

Patients under 18 years of age, with end-stage renal disease, and with a history of recent surgical intervention were excluded from the study.

The institutional Clinical Research Ethics Committee approved the study protocol. All procedures followed the Turkish Medicine and Medical Devices Agency Good Clinical Practices Guidelines and the Declaration of Helsinki.

Patient characteristics and procedures

Patient data was obtained from the hospital's patient database system. Demographic characteristics such as age and gender were noted. Laboratory findings at the time of admission including white blood cell count, neutrophil, hemoglobin, hematocrit, platelets, urea, creatinine, CK, sodium, potassium, total calcium, phosphate, and C-reactive protein were recorded. The information of time passed under the rubble until the first medical intervention, length of hospital stays, the rate of fasciotomy, dialysis, and mortality were retrieved from the electronic health records of the participants. Although not optimal, since continuous renal replacement therapy (CRRT) was not an option in our clinic, conventional intermittent hemodialysis was applied to every patient requiring dialysis.

In addition to CK levels at the time of admission, CK levels after 48th hours of admission were recorded. The patients were divided into two groups the "fast responders" (decreased more than 50% within 48 hours) and the "slow responders" (decreased less than 50% within 48 hours) according to the decrease in the level of CK within 48 hours. These two groups were compared in terms of frequency of dialysis, mortality, length of hospital stay, and need for fasciotomy.

Statistical analysis

The program used for statistical analysis was Statistical Package for Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). The distribution of the data was assessed using the Kolmogorov-Smirnov test. The data with normal distribution were presented as mean ± standard deviation (SD) and skewed data were expressed as median and inter-quartile range (IQR). Categorical variables were reported as the percentage of the total. The difference between continuous, and skewed variables was compared with the Student t-test and the Mann-Whitney U test, respectively. The chi-square test was used to determine the relationship between categoric variables. Point biserial correlation was calculated to evaluate the potential correlation of CK levels with hemodialysis, fasciotomy, mortality, and length of hospital stay. P values less than 0.05 were accepted as statistically significant.

RESULTS

This study included 84 patients with a median age of 29 years (min: 18, Max:72, IQR: 15), and 51.2% (n = 43) of them were female. The demographic characteristics including age and gender, and baseline laboratory findings of participants were given in Table 1. The median CK levels of enrollees at the time of admission was 7868 U/L (IQR: 23351), and 32.1% (n = 27) of them were diagnosed with AKI. While the CK levels of patients in the "fast responders" group at the time of admission were significantly higher, the CK levels at the 48th hour were found to be similar in both fast and slow responders.

While 22.6% (n = 19) of patients received hemodialysis, 21.4% (n = 18) of patients underwent fasciotomy due to compartment syndrome. The in-hospital mortality rate was 6% (n = 5). The comparison of fast and slow responder groups in terms of the need for dialysis treatment and in-hospital mortality revealed that neither need for dialysis (11.9% *vs.* 10.7%, p = 0.328) nor in-hospital mortality rates (2.4% *vs.* 3.6%, p = 0.890) were significantly different between groups (Table 2). However, the mortality rate was significantly higher among patients who received hemodialysis (4.8% *vs.* 1.2%, p = 0.002). In addition, fasciotomy rates (8.3% *vs.* 13.1%, p = 0.701) and the length of hospital stay (12 days *vs.* 11.5 days, p = 0.553) were similar between both groups (Table 2).

While the CK levels at the time of admission and the amount of fall in the first 48 hours were significantly correlated with the need for hemodialysis (r = 0,371, p<0.001, r = 0,302, p = 0.005, respectively), we did not observe such correlation for mortality rates, fasciotomy rates or the length of hospital stay (p > 0.05 for all) (Table-3).

In our study, we examined electrolyte imbalances in all patients. The rate of patients with hyperkalemia and hypokalemia was 8.3% (n: 7) and 9.5% (n: 8), respectively. In addition, hypocalcemia and hyponatremia, which are common electrolyte disorders in patients with CS, were 41.6% (n: 35) and 30.9% (n: 26), respectively.

DISCUSSION

The CS, defined by Bywaters 60 years ago and is also known as Bywaters syndrome, is a medical condition consisting of elevated CK levels and renal failure resulting from the destruction of muscle cells following an injury or hypoxia. In its etiology, different events or diseases can play significant roles, such as trauma and injury caused by natural and unnatural disasters (earthquake, typhoon, war, mine accident), toxins, viral infection, and strenuous exercise [17,

18]. Elevated CK levels can be observed in CS and remain elevated if CS continues. Change in CK levels, as a sign of injury, could be theoretically a sign of ongoing nephrotoxic effects on the kidney. Therefore, in this study, we aim to determine whether the change in CK levels could be a sign of the need for renal replacement therapy.

In our study, comparable to previous studies, the median age was 29 (18-72). The fact that the rate of patients over the age of 65 in our study was 2.4% (n:2), and this situation was lower than the distribution of the population over the age of 65, may be related to the high mortality rate of elders at the scene [19, 20, 21]. Although the unknown age distribution of deaths at the scene makes this situation difficult, our study is comparable to the previous study of Erek et al. [22]. Tanida et al. [19] reported that in the Hanschin earthquake that occurred in Japan in 1995, the mortality rate was found 6 times higher in patients older than 80 years compared to patients younger than 50 years. This low rate may be related to previous observations that the geriatric population is more prone to earthquake-related injury but has a much higher on-the-spot mortality rate [19, 20]. In terms of mortality rate between different genders, there was no difference between the patients (male: 41, female: 43) (p.684).

AKI caused by CS is one of the severe complications observed at different levels in various studies. In a study conducted in China after the Wenchuan Earthquake, the rate of AKI was detected at 41,6% among hospitalized patients [23]. However, in one of the leading studies conducted in Turkey by Sever et al., the rate of AKI was %12 in the patients [12]. Therefore, it might be challenging to estimate the exact rate of AKI, which might be caused by different factors. In our study, the rate of acute kidney injury was 32.1%, which was compatible with other studies.

In terms of electrolyte imbalances, which can be observed in CS, hyperkalemia, hyperphosphatemia, and hypocalcemia are the most common disturbances that can be life-threatening if not treated on time. Aggressive fluid management with the control of urine output is the first-line treatment of CS. Urine alkalization and dialysis intervention to control electrolyte imbalances can be applied. Hyperkalemia is the most fatal complication and one of the leading factors of mortality observed in patients with CS [24, 25]. In the Marmara Earthquake, Erek et al. [22] reported that hyperkalemia is the most frequent electrolyte imbalance observed in cases (%42 of cases) that died from CS. And hyperkalemia is more commonly observed than hypokalemia. In our study, despite there was no statistical difference was observed ($p > 0.05$), the rate of hypokalemia was higher than hyperkalemia %9.5 (n: 8) and %8.3 (n: 7), respectively. In this regard, our data is more like the study conducted in the Wenchuan Earthquake in China

which showed that hypokalemia (18.2%) was more common than hyperkalemia (15.9%) [23]. Apart from these, hypocalcemia and hyponatremia were detected at the rate 41.6% (n: 35) and 30.9% (n: 26), respectively.

In rhabdomyolysis-associated AKI, elevated CK is an indicator of ongoing muscle damage, which may be an indicator of increased risk of kidney damage [26]. For this reason, the absence of an increase in CK level and a decrease in CK level theoretically creates less need for dialysis. In this study, we compared the patients whose CK levels decreased by more than 50% within the first 48 hours from the moment of admission of patients admitted to our hospital with crush injury and the patients who did not decrease in terms of dialysis. We could not detect any statistical difference in dialysis frequency between these two groups (p:0.328). In a study conducted by Xiao et al. [27] on 86 patients, no significant difference was detected between the CK level of the patients and the need for CRRT, and no statistically significant relationship between CK and renal function was observed in this study. In our study, patients received conventional intermittent dialysis, as our clinic did not offer the option of CRRT. This approach allowed us to monitor and assess the effectiveness of intermittent treatment. Notably, the outcomes we observed closely aligned with the findings reported by Xiao et al. [27], reinforcing the validity of our study results.

Mortality in CS can be caused by many factors, such as the duration of exposure under the rubble, the time of transfer to the patient, the moment of starting the first treatment, the presence of electrolyte imbalance, the development of acute kidney injury, the availability of dialysis, fasciotomy or trauma-related surgery. Although the overall mortality rate reaches 20% in the population with kidney damage, this rate may vary [28, 29]. This rate may be even higher in patients with multiorgan damage. In a study conducted by Erek et al. [22] in 639 patients, they found the mortality rate in patients with CS who were on dialysis and who were not on dialysis to be 17.2% and 9.3%, respectively. In our study, death occurred in five patients, and this rate was determined as 5.9%. Reasons for the lower mortality rate compared to other studies may be related to many situations, such as our low number of patients, the partial distance of our center from the epicenter of the earthquake, and the increase in treatment opportunities for CS.

Our study has several limitations. This study was performed retrospectively with patients who received medical treatment under the extreme and devastating conditions of a massive earthquake that caused power and internet outages, staff shortages, and usage of field hospitals. So, we could not retrieve the data of initial treatments applied to the patients (type, dose, duration of treatments, etc.) and information on diuresis adequately and accurately from the hospital's

patient database system. Therefore, we couldn't compare the initial treatments of responders and non-responders. Apart from this, the number of patients in our study compared to previously published studies was relatively low, which makes it hard to draw vast conclusions. The urgency of the situation was challenging and obstructed our study to be designed prospectively. Therefore, our study was retrospectively designed. These were the limitations encountered during the study.

CONCLUSION

Although CK is a significant enzyme in the diagnosis of CS and can be a sign of continuing damage of muscles, the present study revealed that the changes in CK levels during the first 48 hours have no predictive value for the need for dialysis and in-hospital mortality. However, due to the retrospective design of this study and a relatively small number of participants, future studies are warranted to confirm the current findings. Besides this, electrolyte imbalances are frequent and can be fatal in CS. Therefore, awareness of clinicians and on-time treatment is crucial.

Conflict of interest: None declared.

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Table 1. General characteristics, and baseline laboratory findings of patients

Characteristic	Total (n = 84)	Fast responders (n = 36)	Slow responders (n = 48)	p*
Age (Years), median (IQR)	29 (15)	28.5 (14)	29.5 (16)	0.238
Sex, n (%), female	43 (51.2)	20 (23.8)	23 (27.4)	0.488
WBC (10^9/L), mean (SD)	15 (6.6)	14.4 (7.2)	15.4 (6.1)	0.968
Neutrophil (10^9/L), mean (SD)	12.3 (5.9)	11.6 (6.5)	12.8 (5.5)	0.717
Hemoglobin (mmol/L), mean (SD)	7.97 (2.02)	8.24 (2.15)	7.76 (1.92)	0.119
Hematocrit, mean (SD)	0.39 (0.1)	0.4 (0.1)	0.38 (0.9)	0.148
Platelets (10^9/L), mean (SD)	232 (93.8)	237.4 (79.9)	229.3 (104.7)	0.787
Urea (mmol/L), median (IQR)	7.58 (9.32)	9.07 (8.99)	7.41 (11.49)	0.603
Creatinine (μmol/L), median (IQR)	76.91 (130.83)	79.56 (228.96)	65.42 (128.18)	0.235
CK (admission) (U/L), median (IQR)	7868 (23351)	15,823 (46808)	5326 (16,102)	0.005
CK (48th hour) (U/L), median (IQR)	5294 (13462)	5294 (13292)	5515 (13526)	0.910
Sodium (mmol/L), median (IQR)	137 (5)	137 (7)	137 (4)	0.647
Potassium (mmol/L), median (IQR)	4.26 (0.88)	4.4 (1.12)	4.09 (0.88)	0.097
Calcium (mmol/L), median (IQR)	2.15 (0.21)	2.15 (0.24)	2.16 (0.19)	0.645
Phosphorus (mmol/L), median (IQR)	1.33 (6.46)	1.33 (7.10)	1.33 (5.49)	0.927
CRP (mg/L), median (IQR)	122 (143.3)	119 (132.5)	123 (147)	0.964

IQR – inter quantile range; WBC – white blood count; CK – creatine kinase CRP – C-reactive protein;
*p-values < 0.05 were considered statistically significant

Table 2. The comparison of outcomes between slow and fast responders

Characteristic	Total (n = 84)	Fast responders (n = 36)	Slow responders (n = 48)	p*
Hemodialysis, n (%)	19 (22.6)	10 (11.9)	9 (10.7)	0.328
Fasciotomy, n (%)	18 (21.4)	7 (8.3)	11 (13.1)	0.701
Mortality, n (%)	5 (6)	2 (2.4)	3 (3.6)	0.894
Length of hospital stay (days), median (IQR)	12 (15)	12 (14)	11.5 (19)	0.553

IQR – inter quantile range;
*p-values < 0.05 were considered statistically significant

Table 3. The Point Biserial Correlation of patients' CK levels, Δ CK levels, and outcomes

Characteristic	CK (admission)		Δ CK (first 48 hours)	
	r	p*	r	p*
Hemodialysis	0.371	0.001	0.302	0.005
Fasciotomy	0.188	0.088	0.154	0.161
Mortality	0.164	0.136	0.103	0.351
Length of hospital stay (days)	0.126	0.252	0.147	0.182

CK – creatine kinase; Δ CK – the amount of fall in CK in the first 48 hours; r – Point Biserial Correlation;
*p values <0.05 were considered statistically significant

