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Acute kidney injury following traumatic rhabdomyolysis in Kermanshah earthquake victims; A cross-sectional study

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ABSTRACT

Introduction: Rhabdomyolysis induced acute kidney injury (AKI) develops due to leakage of the potentially nephrotoxic intracellular content into the circulation. This study aimed to evaluate the prevalence and predictive factors of AKI in Kermanshah earthquake victims.
Methods: This cross-sectional study was performed on victims of 2017 Kermanshah earthquake, Iran, who were admitted in Kermanshah and Tehran Hospitals. Data of the hospitalized patients were gathered and the prevalence of rhabdomyolysis induced AKI was studied. In addition, correlations of various clinical and laboratory variables with rhabdomyolysis induced AKI were assessed.
Results: 370 hospitalized patients with the mean age of 39.24 ± 20.32 years were studied (58.6% female). 10 (2.7% of all admitted) patients were diagnosed with AKI. Time under the rubble ($p < .0001$), serum level of creatinine phosphokinase (CPK) ($p < .001$), lactate dehydrogenase (LDH) ($p < .0001$), aspartate aminotransferase (AST) ($p = .001$) and uric acid ($p = .003$) were significantly higher in patients with AKI. Area under the ROC curves of CPK, LDH, AST, and uric acid for predicting the risk of developing AKI were 0.883 (95% CI: 0.816–0.950), 0.865 (95% CI: 0.758–0.972), 0.846 (95% CI: 0.758–0.935), and 0.947 (95% CI: 0.894–0.100), respectively. The best cutoff points for CPK, LDH, AST, and uric acid in this regard were 1656 IU/L, 839.5 U/L, 46.00 IU/L, and 5.95 mg/dL.
Conclusion: The rate of traumatic rhabdomyolysis induced AKI development was estimated to be 2.7%. Time under the rubble and serum levels of CPK, LDH, AST, and uric acid were identified as the most important predictive factors of AKI development.

1. Introduction

Iran is the third earthquake prone country after China and Indonesia with around 106 earthquakes in the time interval between 1900 and 2016 [1]. This emphasizes the need for constant preparedness of the rescue and medical teams for facing natural disasters in this part of the world. Undoubtedly, experiences gained from previous disasters can help prevent financial and life burdens of similar future disasters. In this regard, we learned valuable lessons regarding management of medical complications of natural disasters from Bam 2003 earthquake, Iran [2-5].

One of the most important medical problems in those trapped under the rubble is traumatic rhabdomyolysis and crush syndrome. Prevalence of crush syndrome has been estimated to be between 2% and 5% for all those injured in the earthquake and all such victims, regardless of the severity of their injury, should be considered prone to crush syndrome [6,7]. This syndrome develops due to injury to skeletal muscles and leakage of the potentially toxic content of the cell into the blood circulation. In addition, hemoglobin excretion via urine results in acute kidney injury (AKI) in 15% to 33% of victims [8].

Therefore, crush syndrome can be associated with complications such as AKI, sepsis, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), cardiac failure, and dysrhythmia [7,9]. Various rates have been reported for prevalence of crush syndrome and AKI as its most important complication in different earthquakes. Difference in the time under rubble, the type of rubble, and the type of therapeutic interventions after being extracted out of the rubble could be among the probable reasons for the differences in the reported statistics [3,10]. Of course, the rate and type of fluid therapy as well as the time of treatment initiation are among the most important and determining variables in improvement of outcome and decrease in the number of cases with AKI and need for dialysis [11,12].

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On Sunday November 12th, 2017 an earthquake with a magnitude of 7.3 on the Richter scale shook Ozgole, Kermanshah province on the border of Iran and Iraq. This earthquake turned out as one of the bitterest disasters of the past 10 years in Iran with >10,000 injured and 600 deaths and many becoming homeless. Considering the importance of the burden of crush syndrome and its complication, the present study aimed to evaluate the prevalence and predictive factors of rhabdomyolysis induced AKI in 2017 Kermanshah earthquake victims.

2. Methods

2.1. Study design and setting

The present cross-sectional study was performed on victims of 2017 Kermanshah earthquake, Iran, who were admitted in different hospitals in Kermanshah (Imam Reza, Taleghani, Imam Khomeini, Military, and Imam Hossein Hospitals) and Tehran (Imam Hossein, Imam Khomeini, Shariati, Milad, Loghman Hakim, and Firoozgar Hospitals) cities. Data of the hospitalized patients were gathered and the prevalence of traumatic rhabdomyolysis and AKI due to it was studied. In addition, correlations of various clinical and laboratory variables with rhabdomyolysis induced AKI were assessed. This study was approved by the ethics committees of Shahid Beheshti University of Medical Sciences. (code: IR.SBMU.RETECH.REC.1396.940) and Kermanshah University of Medical Sciences (code: IR.KUMS.REC.1397.692). Throughout the study, the researchers adhered to the confidentiality of patient data and ethical principles of clinical studies according to Declaration of Helsinki.

2.2. Participants

All the patients hospitalized in various hospitals throughout cities of Kermanshah as well as some of the hospitals throughout Tehran (Imam Khomeini, Imam Hossein, Loghman, Shariati, Firouzgar, Milad), and Karaj (Madani, Bahonar) were included in the study using census method without considering any age or sex limitation. Patients without any available clinical and laboratory data, those who had died upon arrival at the hospital or had left the hospital against medical advice before completion of diagnostic and therapeutic measures were excluded from the study. In addition, victims with chronic kidney failure and neuromuscular diseases with dysfunctional muscle enzymes were identified and excluded.

2.3. Data gathering

The designed checklist used for data gathering consisted of demographic variables (age, sex, weight) history of underlying diseases, time under the rubble, type of rubble (mud-brick or concrete cement), type of injury (fracture, soft tissue injury), vital signs on admission to emergency department (blood pressure, pulse rate, respiratory rate, level of consciousness), rate and type of fluids received, laboratory findings (muscle enzymes, kidney function tests, electrolyte profile, and urinalysis), and final outcome (death, fasciotomy, amputation, sepsis, multiple organ failure, acute respiratory failure, need for dialysis). A senior internal medicine resident and 2 trained medical interns were responsible for gathering data of Kermanshah and Tehran, respectively. Considering the critical conditions at the time of earthquake, some checklists were filled out in a prospective manner and at the time of patients' admission to hospital and others were completed in a retrospective manner using the patients' medical profiles.

2.4. Definitions

In the present study, the following definitions were used for statistical analyses and reporting the results:

- Acute kidney injury (AKI): two creatinine value ≥1.6 mg/dL in the initial 3 days after admission.
- Mild rhabdomyolysis: Serum level of creatinine phosphokinase enzyme >300 IU/L and <1000 IU/L on the first day of admission.
- Moderate and severe rhabdomyolysis (crush injury): Serum level of creatinine phosphokinase enzyme equal to or >1000 IU/L on the first day of admission without any evidence of systemic complications.
- Crush syndrome: Serum level of creatinine phosphokinase enzyme equal to or >1000 IU/L on the first day of admission along with presence of systemic complications (AKI, sepsis, multiple organ failure, and acute respiratory failure).

2.5. Statistical analysis

All the filled out checklists were entered to excel software and after a final check were statistically analyzed using SPSS 21. To report the findings, mean ± standard deviation of the values or frequency (%) were used in tables and charts. In addition, to compare continuous and discrete variables, *t*-test, Chi square, and Fisher's exact tests were applied. To calculate the accuracy of creatine phosphokinase, lactate dehydrogenase, aspartate aminotransferase, and uric acid in predicting the risk of developing AKI receiver operating characteristic (ROC) curve was drawn and area under the ROC curve with 95% confidence interval (CI) and the best cut-off point were calculated. In this study, the level of significance was considered <0.05.

3. Results

3.1. Baseline characteristics of the victims

The total number of those injured in this earthquake was estimated to be 10,141 people, 8647 of whom received pre-hospital emergency care. 1494 people were referred to Kermanshah for further treatments, 225 (15.1%) of which were hospitalized and the rest were treated as outpatients. In addition, the data of 145 patients hospitalized in Tehran were also gathered. Overall, 370 hospitalized patients with the mean age of 39.24 ± 20.32 (1–90) years were evaluated (58.6% female). Mean duration of remaining under rubble in the hospitalized patients was 47.11 ± 71.92 (0–480) minutes. Table 1 depict the baseline characteristics of the studied patients. Most patients (43.5%) were in the 18 to 40 years age group. Lower extremities were the most common site for bone fracture (56.2%) and thorax was the most common site for soft tissue injuries (33.2%).

3.2. Traumatic rhabdomyolysis

Fig. 1 shows the level of creatine phosphokinase, lactate dehydrogenase, aspartate aminotransferase, and uric acid in the studied patients on the first day of hospitalization. Based on the level of creatinine phosphokinase on the first day, 143 (68.8%) patients were normal or had mild rhabdomyolysis and 65 (31.2%) showed moderate to severe rhabdomyolysis. Mean time under the rubble was 78.0 ± 116.5 min for patients with moderate to severe rhabdomyolysis and 38.5 ± 59.6 min for those with mild rhabdomyolysis ($p = .009$).

There was a significant correlation between presence of soft tissue injuries in lower extremities and probability of being affected with traumatic rhabdomyolysis ($p = .037$). There was no significant correlation between creatinine phosphokinase on the first day and sex ($p = .714$), type of rubble ($p = .859$), having underlying illnesses ($p = .582$), and presence of fracture ($p = .901$).

3.3. Acute kidney injury

12 patients had a creatinine measure ≥1.6 mg/dL at least twice in the first 3 days of hospitalization. After elimination of 2 patients with

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Table 1
Baseline characteristics of studied patients

Variables	Number (%)
Sex	
Male	151 (41.4)
Female	217 (57.6)
Age (year)	
<18	47 (12.7)
18–40	160 (43.5)
40–60	89 (24.2)
≥60	72 (19.6)
Time under the rubble (hour)	
<0.5	147 (51.4)
0.5–1	56 (19.6)
1–2	44 (15.4)
≥ 2	39 (13.6)
Type of rubble	
Mud-brick	19 (6.3)
Concrete cement	281 (93.7)
Presenting vital signs	
Unconscious	47 (13.2)
Respiratory rate ≥ 20/min	107 (32.0)
Pulse rate ≥ 100/min	32 (8.9)
Systolic BP ≤ 90	13 (3.6)
Fractures	
Head and neck	23 (9.2)
Thorax	42 (16.9)
Upper extremities	44 (17.7)
Lower extremities	140 (56.2)
Soft tissue injuries	
Head and neck	55 (24.0)
Thorax	76 (33.2)
Upper extremities	33 (14.4)
Lower extremities	65 (28.4)
Comorbid diseases	
Diabetes mellitus	17 (4.6)
Hypertension	39 (10.6)

chronic kidney failure, in the end, 10 (2.7% of all the admitted cases) patients were diagnosed with AKI. Among patients with creatinine phosphokinase levels >1000 IU/L on the first day, 10 (15.4%) patients had developed AKI (crush syndrome).

Table 2 compares the clinical and laboratory findings of patients with and without AKI. Time under the rubble ($p < .0001$), serum level of creatinine phosphokinase ($p < .001$), lactate dehydrogenase ($p < .0001$), aspartate aminotransferase ($p = .001$) and uric acid ($p = .003$) were significantly higher in patients with AKI. Area under the ROC curves of creatinine phosphokinase, lactate dehydrogenase, aspartate aminotransferase, and uric acid for predicting the risk of developing rhabdomyolysis induced AKI were 0.883 (95% CI: 0.816–0.950), 0.865 (95% CI: 0.758–0.972), 0.846 (95% CI: 0.758–0.935), and 0.947 (95% CI: 0.894–0.100), respectively (Fig. 2). The best cutoff points for creatinine phosphokinase, lactate dehydrogenase, aspartate aminotransferase, and uric acid in this regard were estimated to be 1656 IU/L, 839.5 U/L, 46.00 IU/L, and 5.95 mg/dL.

4. Discussion

Based on the findings of the present study, the rate of traumatic rhabdomyolysis induced AKI development was estimated to be 2.7%. Time under the rubble as well as serum levels creatine phosphokinase, lactate dehydrogenase, aspartate aminotransferase, and uric acid were the most important predicting factors of AKI development.

Mechanical injuries to kidney tubules due to myoglobin sedimentation, direct poisonous effect of free iron on kidney tubules, and decrease in the circulating volume are among the probable factors causing AKI following traumatic rhabdomyolysis [8,13]. Incidence and risk factors of rhabdomyolysis induced AKI have been evaluated in various studies. Based on the findings of Hatamizadeh et al. the rate of AKI development in Bam earthquake was estimated to be 6.9%. The mentioned study showed that time under the rubble, muscle enzymes, and serum level of potassium on admission were significantly higher in those with AKI [14].

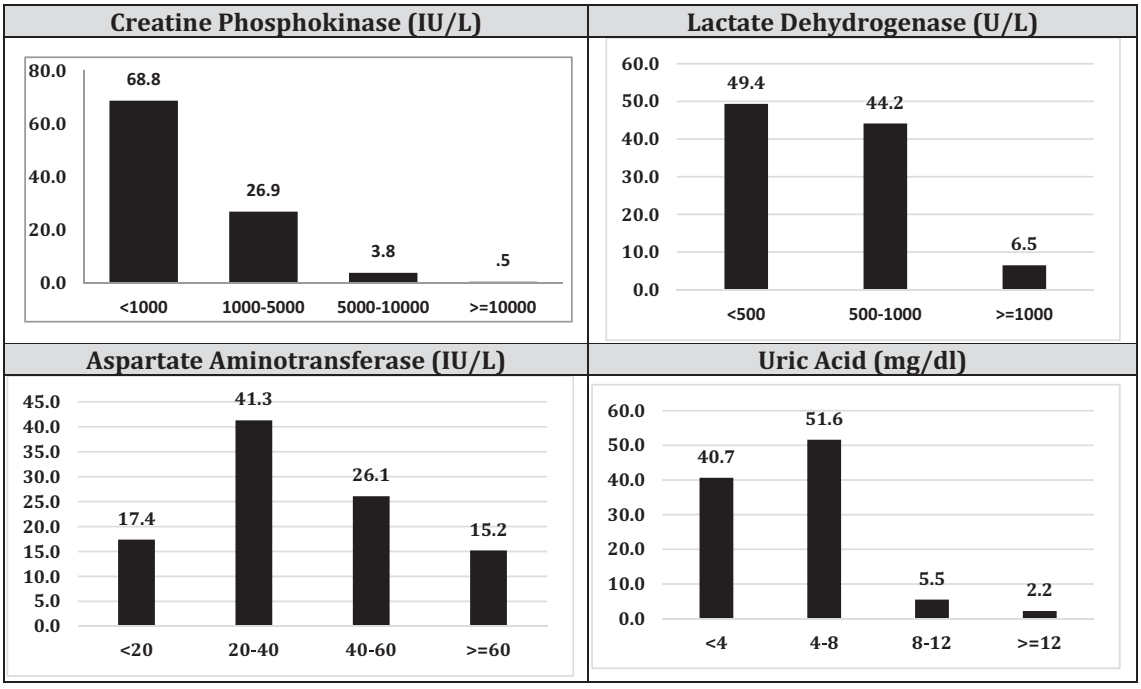

Fig. 1. The serum level of creatine phosphokinase, lactate dehydrogenase, aspartate aminotransferase, and uric acid of studied patients on admission to the hospital. Data are presented as percentage of patients in each category.

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Table 2
Comparing the baseline and laboratory characteristics of patients with and without traumatic rhabdomyolysis-induced acute kidney injury (AKI)

Variables	Non-AKI	AKI	*P* value
Sex			
Male	84 (93.3)	6 (6.7)	0.182
Female	132 (97.1)	4 (2.9)	
Age (year)			
Mean ± SD	39.5 ± 20.1	41.6 ± 24.1	0.749
Weight (kg)			
Mean ± SD	63.9 ± 17.5	73.1 ± 11.3	0.143
Type of rubble			
Mud-brick	12 (100.0)	0 (0.0)	0.466
Concrete cement	146 (93.6)	10 (6.4)	
Time under the rubble (minute)			
Mean ± SD	47.9 ± 66.2	198.9 ± 184.3	<0.001
Comorbid diseases			
Diabetes mellitus	11 (100.0)	0 (0.0)	0.599
Hypertension	24 (96.0)	1 (4.0)	0.693
Traumatic injuries			
Fracture	153 (96.8)	6 (3.2)	0.887
Soft tissue	133 (93.7)	9 (6.3)	0.049
Vital signs (presenting)			
Unconscious	24 (92.3)	2 (7.7)	0.294
Respiratory rate ≥ 20/min	62 (95.4)	3 (4.6)	0.578
Pulse rate ≥ 100/min	25 (96.2)	1 (3.8)	0.667
Systolic BP ≤ 90	10 (90.9)	1 (9.1)	0.402
Laboratory findings (day 1)			
CPK (IU/L)	1171.2 ± 1894.1	3490.5 ± 2418.3	<0.001
LDH (U/L)	554.8 ± 234.3	1204.0 ± 741.2	<0.001
AST (IU/L)	39.5 ± 35.6	82.4 ± 40.4	0.001
Uric acid (mg/dL)	4.6 ± 2.12	7.8 ± 1.3	0.003
Calcium (mg/dL)	8.222 ± 1.2218	8.050 ± 1.3435	0.846
Phosphorus (mg/dL)	2.8 ± 1.0	3.4 ± 0.0	0.603
Potassium (mEq/L)	3.9 ± 0.4	3.8 ± 0.8	0.549
Sodium (mEq/L)	137.7 ± 3.5	135.5 ± 6.7	0.103
BUN (mg/dL)	34.4 ± 23.6	85.3 ± 50.8	<0.001
Creatinine (mg/dL)	0.91 ± 0.7	1.9 ± 0.65	<0.001
Hemoglobin (g/dL)	11.9 ± 8.1	9.7 ± 1.7	0.449
Platelet (1000/mm^3)	227.7 ± 74.2	231.6 ± 103.9	0.885

Data are presented as mean ± standard deviation or number (%). CPK: Creatine phosphokinase, LDH: lactate dehydrogenase; AST: Aspartate Aminotransferase; BUN: blood urea nitrogen.

A systematic review confirmed the significant correlation between serum level of creatinine phosphokinase enzyme and increase in the risk of developing rhabdomyolysis induced AKI and showed that this role depends on the type of rhabdomyolysis. Cumulative odds ratio of creatinine phosphokinase in this regard has been estimated to be about 15 [5]. In a study titled "early detection of patients at high risk for acute kidney injury during disasters", Najafi et al. showed that by using/assessing creatinine phosphokinase, potassium, lactate dehydrogenase, and uric acid levels on the first day of admission we can estimate the probability of AKI development in patients on the third day of hospitalization with 96.6% sensitivity and 95.7% specificity [15].

The incidence rates of crush syndrome and AKI due to it were estimated as 8.2% and 3.3% in Wenchuan earthquake in 2008. In this earthquake, 41.6% of patients with crush syndrome developed AKI [16]. In addition, Sever et al. studied 5302 patients injured in Marmara earthquake, Turkey, and reported the frequency of AKI development due to crush syndrome to be about 12% [17].

Probable reasons that could explain this difference in the reported statistics regarding AKI due to crush syndrome could be differences in demographic data of the injured patients, time of earthquake, time under the rubble, type of treatment used for patients, delay in initiation of prophylactic treatments, and difference in volume and combination of fluids used for treating dehydration in patients.

For instance, in Kermanshah earthquake the higher frequency of women compared to men, shorter time under the rubble, concrete cement type of rubble, and the earthquake occurring during the daytime and the possibility of more rapid notification and care provision could be among the causes of significantly less complications in those injured in this earthquake compared to the previous earthquake in Bam, Iran. It may be that concrete cement rubble affects less muscular volume due to less destruction and consequently less pressure, which might be a reason for the significantly lower level of CPK in the victims of this earthquake compared to Bam (3490.5 ± 2418.3 in Kermanshah versus 17,400 ± 24,700 IU/L in Bam), where rubble type was mostly mud-brick [18]. Findings of Bam earthquake showed that preventing systemic complications due to rhabdomyolysis requires fluid therapy with a minimum volume of 6 l per day [11]. However, since providing this volume of fluids for a large number of victims is not possible, we should screen at risk patients.

For screening at risk patients various tools can be used. The simplest of which is screening using available factors such as: serum level of muscle enzymes, clinical examination, and time under the rubble. With longer time of direct pressure on the muscle bulks, wider surface of muscles under rubble (such as thigh in the lower extremity), and higher level of enzymes we should expect higher risk of being affected with systemic complications due to rhabdomyolysis. Urine dipstick test and screening patients with myoglobinuria is another available test in this regard [4,19,20]. It seems that victims can be screened with a relatively acceptable accuracy using a rapid and cheap dipstick test. The importance of this test becomes obvious when some of the injured patients avoid receiving treatment and start helping others immediately after being rescued from rubble if they have no broken bones or serious injuries. However, they are unaware that rhabdomyolysis is silently causing complications in their body. Using urine dipstick test on the scene of an earthquake can be very helpful in identifying this type of patients, since most of the times, especially on the first hours and days, laboratory factors cannot be checked on the scene. In addition, using clinical decision rules can also help in this regard. Najafi et al. studied Bam earthquake and designed and introduced rule of thumb and AKI rule based on multivariate regression analysis as well as area under the ROC curve of variables in prediction of AKI due to rhabdomyolysis [15].

Overall, it seems that currently, the best way to reduce the medical burden of earthquake victims, especially regarding traumatic rhabdomyolysis, is rapid screening, referral to centers with better equipment, initiating strict treatment, and constantly monitoring them until sufficient urinary output is established and muscle enzymes decrease. In Kermanshah earthquake, by nearly complete adherence to the mentioned policy, we could prevent crush related AKI to a great extent (compared to Bam earthquake).

4.1. Limitations

In Iran, like other developing countries, despite all of the planning and monitoring done for checking laboratory tests and gathering data for all patients, we still encountered a significant amount of missing data. In some cases, considering the crowding and the chaotic situation after earthquake, the adherence of treatment staff to guidelines for dealing with patients had reduced and hospitalization of the patients in various centers raises the possibility of different treatment protocols affecting the patients' outcome. However, the findings of this study can be helpful in our future encounters with similar victims.

5. Conclusion

Based on the findings of the present study, the rate of traumatic rhabdomyolysis induced AKI development was estimated to be 2.7%. Time under the rubble and serum levels of CPK, LDH, AST, and uric

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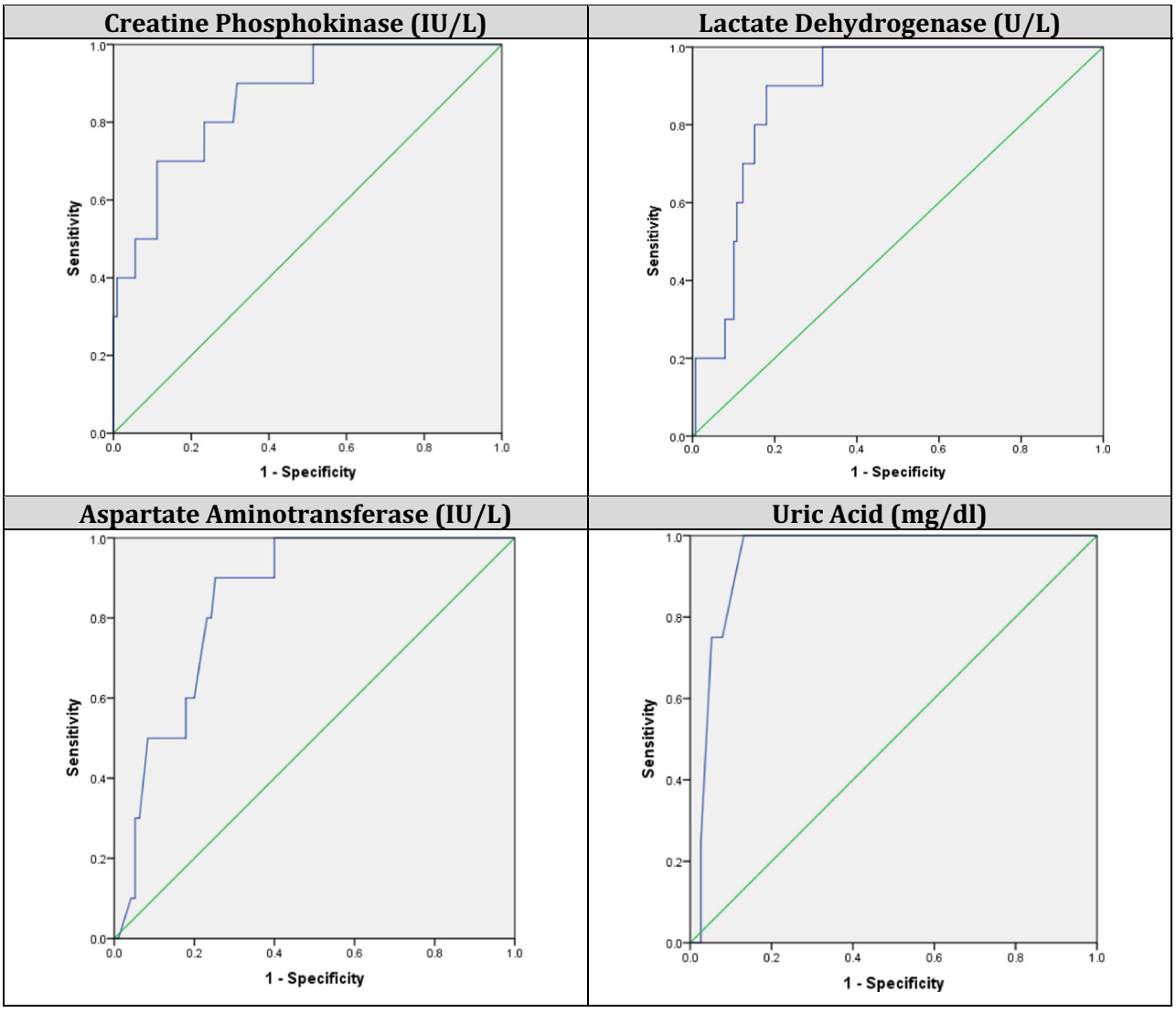

Fig. 2. Area under the receiver operating characteristic (ROC) curve of creatine phosphokinase, lactate dehydrogenase, aspartate aminotransferase, and uric acid in predicting the risk of traumatic rhabdomyolysis-induced acute kidney injury.

acid were identified as the most important predictive factors of AKI development.

Ethics approval and consent to participate

This study was approved by the ethics committees of Shahid Beheshti University of Medical Sciences (code: IR.SBMU.RETECH.REC.1396.940) and Kermanshah University of Medical Sciences (code: IR.KUMS.REC.1397.692). Throughout the study, the researchers adhered to the confidentiality of patient data and ethical principles of clinical studies according to Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and material

Author(s) guarantee that data of the study are available for at least 10 years and will be provided if anyone needs them.

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Author contribution

All authors met the four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

CRediT authorship contribution statement

Hamidreza Omrani: Conceptualization, Writing - original draft, Writing - review & editing, Supervision. **Iraj Najafi:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision. **Kiomars Bahrami:** Data curation, Writing - original draft, Writing - review & editing. **Farid Najafi:** Data curation, Writing - original draft, Writing - review & editing. **Saeed Safari:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Supervision.

Declaration of competing interest

None.

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