Platelet count as an independent risk factor for acute kidney injury induced by rhabdomyolysis

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Rhabdomyolysis is a severe clinical syndrome that occurs when damaged striated muscles break down and intracellular muscle components leak into the blood. Acute kidney injury (AKI) is the most common complication of rhabdomyolysis. Rhabdomyolysis patients with AKI have been shown to exhibit a higher mortality rate than those without AKI. Moreover, AKI has been reported to be an independent predictor of mortality in rhabdomyolysis.[1] Therefore, early identification of rhabdomyolysis patients with AKI or those at a high risk of developing AKI is necessary to initiate aggressive therapeutic interventions.

Proinflammatory cytokines and activated Toll-like receptor 4/nuclear factor-kappa B (TLR4/NF-κB) signaling pathway play important roles in rhabdomyolysis-induced AKI.[2] Proinflammatory cytokines activate platelets, which leads to platelet-leukocyte interactions, finally causing platelet destruction and consumption.[3] Platelet activation and elevated inflammatory factor levels play critical roles in AKI during sepsis.[4] Therefore, we hypothesize that changes in platelet counts might be correlated with AKI in rhabdomyolysis. In this study, we aimed at determining whether platelet count is an independent risk factor for AKI in rhabdomyolysis.

This was a retrospective review of rhabdomyolysis patients in a university-affiliated teaching hospital between January 2017 and August 2020. This study was ethically approved before admission. The inclusion criteria were rhabdomyolysis diagnosis with serum creatine kinase (CK) levels above 1000 U/L within the first 72 h of admission and aged at least 18 years. The exclusion criteria were simultaneous onsets of acute myocardial infarction, pre-existence of end-stage renal disease, and receipt of renal replacement therapy at least 24 h.

Demographic, clinical, and laboratory data of recruited patients were abstracted from our hospital’s electronic medical records. Demographic data included gender, age, and admission data. Clinical data included etiology, previous medical history, date of symptomatic onset, as well as Acute Physiology and Chronic Health Evaluation scores (APACHE-II) on admission. Laboratory data on admission included serum levels of CK, CK-myocardial band, myoglobin, alanine transaminase, aspartate transaminase, creatinine, and blood urea nitrogen (BUN). Moreover, they included blood levels of prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, D-dimer, platelet counts, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT). If platelet counts were determined several times within the first 24 h after admission, the first platelet count was recorded.

The outcome was AKI, which was diagnosed by serum creatinine according to the 2012 Kidney Disease Improving Global Outcomes guidelines. Urine output data were not used to define AKI, given that these data were not available for all recruited patients. Baseline creatinine levels referred to serum creatinine levels upon admission or the last available serum creatinine level within 3 months before admission.

Demographic and clinical data were presented as frequency, or median (range), as appropriate. Non-normal distribution continuous variable data were compared by Mann-Whitney U test, while categorical variables were compared by χ² test. Univariate logistic regression analysis was used to preliminarily establish the potential risk factors for rhabdomyolysis-induced AKI. Age, gender, and significant variables (P < 0.100) from the univariate logistic regression analysis were included in the multivari-
Table 1: Clinical variables on the admission of rhabdomyolysis patients by AKI status.

| Variables                  | Total (N = 162) | AKI (N = 70) | Non-AKI (N = 92) | P value |
|----------------------------|-----------------|--------------|------------------|---------|
| Age (years)                | 52.50 (32.00–70.25) | 56.50 (38.00–71.00) | 42.50 (26.25–70.00) | 0.058   |
| Gender (male)              | 117 (72.22)     | 54 (77.14)   | 63 (68.48)       | 0.223   |
| Etiologies                 |                 |              |                  | <0.001  |
| Seizures                   | 12 (7.41)       | 6 (8.57)     | 6 (6.52)         |         |
| Trauma or muscle hypoxia   | 23 (14.20)      | 15 (21.43)   | 8 (8.70)         |         |
| Temperature extremes       | 5 (3.09)        | 2 (2.86)     | 3 (3.26)         |         |
| Infections                 | 53 (32.72)      | 34 (48.57)   | 19 (20.65)       |         |
| Metabolic or electrolyte disorders | 14 (8.64)   | 4 (5.71)     | 10 (10.87)       |         |
| Drugs or toxins            | 20 (12.33)      | 6 (8.57)     | 14 (15.22)       |         |
| Exercise                   | 24 (14.81)      | 2 (2.86)     | 22 (23.91)       |         |
| Inflammatory myopathy      | 8 (4.94)        | 0 (0)        | 8 (8.70)         |         |
| Idiopathic                 | 3 (1.85)        | 1 (1.43)     | 2 (2.17)         |         |
| Blood tests                |                 |              |                  |         |
| CK (U/L)                   | 5591.50 (2439.43–16,056.75) | 3845.00 (1779.50–10,105.75) | 6917.00 (3038.75–21,570.00) | 0.006   |
| CK-MB (U/L)                | 113.50 (49.90–319.00) | 113.50 (48.18–220.00) | 111.90 (50.00–433.38) | 0.635   |
| Myoglobin (ng/mL)          | 1560.50 (617.78–3943.18) | 3243.46 (982.45–7834.00) | 973.75 (509.38–1934.25) | <0.001  |
| ALT (U/L)                  | 86.90 (45.55–259.78) | 80.15 (38.35–344.25) | 92.35 (48.48–232.25) | 0.756   |
| AST (U/L)                  | 208.50 (91.68–641.75) | 198.95 (84.38–567.28) | 228.90 (99.88–649.25) | 0.620   |
| Creatinine (μmol/L)        | 106.30 (59.50–211.00) | 226.50 (153.00–356.50) | 63.00 (49.58–86.75) | <0.001  |
| BUN (mmol/L)               | 8.81 (4.68–17.63) | 18.72 (12.38–27.42) | 5.20 (3.32–8.24) | <0.001  |
| PT (s)                     | 13.84 (12.40–15.93) | 15.95 (13.98–21.35) | 13.05 (12.20–14.00) | <0.001  |
| APTT (s)                   | 37.75 (32.35–46.23) | 44.00 (34.80–55.43) | 36.00 (31.13–40.38) | <0.001  |
| Fibrinogen (g/L)           | 3.73 (2.61–4.98) | 4.15 (2.10–5.62) | 3.63 (2.80–4.66) | 0.795   |
| D-dimer (mg/L)             | 2.30 (0.63–6.39) | 5.35 (1.83–14.32) | 1.26 (0.43–2.88) | <0.001  |
| Platelet counts (10^9/L)   | 160.50 (90.73–231.25) | 89.00 (60.50–140.00) | 194.50 (157.25–256.75) | <0.001  |
| MPV (IL)                   | 10.60 (7.90–11.90) | 11.30 (10.10–13.03) | 10.40 (9.60–11.28) | <0.001  |
| PDW (IL)                   | 16.20 (14.93–16.90) | 16.70 (16.20–17.70) | 15.90 (13.20–16.45) | <0.001  |
| PCT (%)                    | 0.17 (0.11–0.23) | 0.11 (0.07–0.15) | 0.21 (0.16–0.27) | <0.001  |
| APACHE-II score            | 18.00 (15.00–20.00) | 19.00 (16.00–23.00) | 17.00 (15.00–19.00) | <0.001  |

Data are shown as medians (interquartile range) or n (%). AKI: Acute kidney injury; ALT: Alanine transaminase; APACHE-II: Acute physiology and chronic health evaluation score; APTT: Activated partial thromboplastin time; AST: Aspartate transaminase; BUN: Blood urea nitrogen; CK: Creatine kinase; CK-MB: Creatine kinase myocardial band; MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; PT: Prothrombin time.

A stepwise logistic regression analysis. A stepwise regression method in multivariate logistic regression was simultaneously used to exclude variable multicollinearity and ultimately identify independent risk factors with (odds ratio [OR] and 95% confidence interval [CI] levels [95% CI]). Predictive abilities of independent risk factors for rhabdomyolysis-induced AKI were assessed using the area under the receiver operating characteristics (AUROC) curve method. The optimal cutoff value was determined using the Youden index. All tests were two-sided and P ≤ 0.050 was considered statistically significant. Statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA).

A total of 162 rhabdomyolysis patients were included in this study. Baseline demographic characteristics and clinical variables on admission are shown in Table 1. Patient ages ranged from 18 years to 96 years, and 117 (72.22%) patients were male. The most common etiology for rhabdomyolysis was infections in 53 (32.72%) cases followed by exercise in 24 (14.81%) cases, trauma or muscle hypoxia in 23 (14.20%) cases, drugs or toxins in 20 (12.35%) cases, metabolic or electrolyte disorders in 14 (8.64%) cases, seizures in 12 (7.41%) cases, inflammatory myopathy in 8 (4.94%) cases, temperature extremes in 5 (3.09%) cases, and idiopathy in 3 (1.85%) cases. Patients were allocated into the AKI and the non-AKI groups. Levels of myoglobin, creatinine, BUN, PT, APTT, D-dimer, MPV, PDW, and APACHE-II scores were found to be higher in the AKI group than those in the non-AKI group (P < 0.010). Levels of CK, platelet counts, and PCT were found to be lower in the AKI group than those in the non-AKI group (P < 0.010).

Univariate analysis revealed that etiologies, CK, myoglobin, creatinine, BUN, PT, APTT, D-dimer, MPV, PDW, and APACHE-II scores were significantly associated with an increased risk for rhabdomyolysis-induced AKI. Multivariate logistic regression analysis revealed the following variables to be independent risk factors for rhabdomyolysis-induced AKI: myoglobin (OR = 1.001, 95% CI = 1.000–1.001, P = 0.043), creatinine (OR = 1.136, 95% CI = 1.033–1.250, P = 0.009), and platelet counts (OR = 0.972, 95% CI = 0.946–0.999, P = 0.042).

From the receiver operating characteristic curve, platelet counts and myoglobin were found to be significant predictors of rhabdomyolysis-induced AKI with AUROC of 0.857 (95% CI = 0.798–0.916, P < 0.001) and 0.741
(95% CI = 0.662–0.819, P < 0.001), respectively [Supplementary Figure S1, http://links.lww.com/CM9/A689]. The optimal cutoff point of platelet counts was ≤126 (×10³/L) with a specificity of 0.913 and a sensitivity of 0.686. The optimal cutoff point of myoglobin was ≥2181 (ng/mL) with a specificity of 0.804 and a sensitivity of 0.614.

This study is to investigate the association between platelet counts and AKI in rhabdomyolysis. We found that platelet counts and myoglobin were independent risk factors for rhabdomyolysis-induced AKI, and platelet counts had a better predictive value than myoglobin.

The mechanisms underlying the association between suppressed platelet counts and AKI in rhabdomyolysis may involve inflammatory responses, platelet activation and consumption, formation of macrophage extracellular traps, as well as kidney tubular damage. Proinflammatory responses play a critical role in rhabdomyolysis-induced AKI. In rhabdomyolysis, plasma proinflammatory cytokine levels including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α are elevated. Inhibition of TLR4/NF-κB suppresses proinflammatory cytokine production and macrophage infiltration in the kidneys, thereby alleviating rhabdomyolysis-induced AKI.[2] After being activated by proinflammatory cytokines, platelets promote inflammatory responses by triggering the complement system, mediating endothelial cell inflammation, and interacting with leukocytes, which enhances AKI progression. In addition, heme from myoglobin activates platelets in vessels; subsequently, activated platelets interact with resident macrophages and recruited monocytes, leading to the formation of macrophage extracellular traps in renal tubules and, finally, causing kidney tubular damage.[3] During infection, activated platelets interact with circulating monocytes, which triggers the depletion of platelets in circulation, indicating the association between platelet activation and suppressed platelet counts.[3] However, the specific mechanism through which platelets are depleted in rhabdomyolysis has not been established.

This study has some limitations. First, it is a single-center study involving a small sample size and with a selection bias. Second, we did not establish a causal relationship between AKI and suppressed platelet counts. Finally, we did not evaluate the administered treatment options, such as early fluid therapy or bicarbonate therapy, upon admission and at pre-admission leading to some bias in analyzing the risk factors for rhabdomyolysis-induced AKI. More studies should aim at determining whether an intervention to raise platelet counts can reduce AKI incidences and improve the prognosis of rhabdomyolysis.

**Conflicts of interest**

None.

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