Rhabdomyolysis-associated acute kidney injury: clinical characteristics and intensive care unit transfer analysis

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Key words
acute kidney injury, rhabdomyolysis, intensive care unit, emergency department.

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Abstract

Background: Information on rhabdomyolysis-associated acute kidney injury (AKI) in the emergency department or general ward is limited.

Aim: To assess the risk factors, outcomes and clinical correlates with intensive care unit (ICU) transfer of patients with rhabdomyolysis-associated AKI.

Methods: Patients with rhabdomyolysis were divided into the rhabdomyolysis-associated AKI group and the rhabdomyolysis without AKI group. Inhospital outcomes, including ICU transfer, mortality, length of stay, daily cost and renal recovery were analysed. Multivariate regression analysis was performed to identify the association between rhabdomyolysis-associated AKI and ICU transfer.

Results: Among 149 patients with rhabdomyolysis, 68 (45.6%) developed AKI. Age and urine protein were important risk factors for incidence of rhabdomyolysis-associated AKI. Patients with rhabdomyolysis-associated AKI had higher levels of undergoing dialysis (19.1% vs 2.5%; \( P < 0.01 \)), all-cause mortality (13.2% vs 1.2%; \( P < 0.01 \)), cost of hospitalisation (10.8 1000 yuan, IQR 5.5, 3.5) vs 5.9 1000 yuan, IQR 3.6, 9.9; \( P = 0.03 \)), as well as longer length of hospital stay (8.0 days (5.0, 14.0)) versus (6.0 days (4.0, 11.0); \( P = 0.02 \)). Additionally, the percentage of patients with AKI who transferred to ICU was higher than patients without AKI (33.8% vs 12.3%; \( P < 0.002 \)) and rhabdomyolysis-associated AKI was an independent risk factor for ICU transfer (adjusted odds ratio = 2.58; 95% confidence interval, 1.12–6.8, \( P = 0.03 \)).

Conclusion: Rhabdomyolysis-associated AKI was common in the emergency department or general ward and led to more severe outcomes. It was also associated with an increased risk of ICU transfer.

Introduction

Rhabdomyolysis is an acute and potentially fatal syndrome. It is characterised by striated muscle breakdown and subsequent leakage of muscle cell contents (e.g. myoglobin, creatine kinase (CK) and electrolytes) into the circulation when muscles are injured by trauma, inflammation, ischaemia, systemic toxic or genetic.\(^1,2\) Rhabdomyolysis can often occur in excessive physical activity, military training and man-made and natural disasters.\(^3,4\) Severe complications secondary to rhabdomyolysis, including electrolyte derangements, acute kidney injury (AKI), shock and disseminated intravascular coagulation,\(^5\) can be life-threatening and cause mortality rates to reach up to 37% of severe patients.\(^2\)

Rhabdomyolysis-associated AKI is the most common systemic complication of rhabdomyolysis and may account for 7–10% of all cases of acute renal failure.\(^5,6\) It is associated with poor clinical outcomes, and an increase in economic and survival burden for patients, which is the crucial issue to be solved. Most studies have focussed on the risk factors of the incidence of rhabdomyolysis-associated AKI in the intensive care unit (ICU).\(^2,7\) However, from first-hand clinical data in the emergency department or general ward, it is of great significance to identify early the risk factors of ICU transfer.
for such a population. Therefore, the present study sought to evaluate the risk factors, inhospital outcomes and clinical correlates of ICU transfer for patients with rhabdomyolysis-associated AKI.

**Methods**

**Study population**

Patients with a diagnosis of rhabdomyolysis in the inpatient ward or emergency of Guangdong Provincial Hospital of Chinese Medicine from September 2012 to October 2018 were enrolled in this retrospective observational study. The study adhered to the Principles of Helsinki Declaration and was approved by the Ethics Management Committee of Guangdong Provincial Hospital of Chinese Medicine. Requirements for written informed consent were waived because all personal data were de-identified before the analyses.

**Inclusion criteria and exclusion criteria**

Inclusion criteria: patients aged ≥18 years with a diagnosis of rhabdomyolysis in the emergency department or general ward.

Exclusion criteria: (i) patients with a history of pre-existing end-stage renal disease, chronic dialysis or kidney transplant; (ii) pregnancy; (iii) peak serum creatinine (SCr) <53 μmol/L; (iv) elevated CK levels caused by myocardial infarction or acute coronary syndrome; or (v) missing data to support a diagnosis of rhabdomyolysis and AKI. We also excluded patients who were directly transferred to the ICU without initially monitoring in the emergency department or general ward (Supporting Information Fig. S1).

**Definitions**

Rhabdomyolysis was defined as a marked elevation of serum CK concentration five times above the upper limit of normal levels (>1000 U/L) accompanied by clinical symptoms such as myalgia, limb weakness, pigmentation and oliguria at admission. According to the definition of kidney disease from the Improving Global Outcomes (KDIGO) criteria in 2012, the definition of AKI was determined as an absolute increase in SCr >0.3 mg/dL within 48 h or 1.5 times relative increase over the baseline values within 7 days or urine volume <0.5 mL/(kg·h) lasting for ≥6 h. Baseline SCr value was checked and identified by referring to SCr results from previous admission, clinical outpatient records or whether SCr returned to within normal limits at least 3 months before the rhabdomyolysis episode, either in the relevant basic health area or our centre. Multiple-organ dysfunction syndrome was diagnosed if the presence of altered organ dysfunction involved two or more major organ systems. The ICD for discharge-diagnosis of multiple-organ dysfunction syndrome is ICD-10: R65.301.

**Clinical data and observing outcomes**

When a diagnosis of rhabdomyolysis was established, experienced clinicians queried the patients on any history of trauma, hypokalaemia, seizure, unusual recent physical activity, metabolic/endocrine, toxicity and diet to categorise the main aetiology. We classified the aetiology of rhabdomyolysis as trauma and muscle compression (any cause by large area muscle injury or ischaemia hypoxia injury, including natural disaster, traffic accident and electric shock), non-traumatic and exertional (energy supply of muscles is insufficient to meet the demand, including violent exercise, seizures and heat shock), and non-exertional and non-traumatic (including infection, food and drug, intoxication and electrolyte disorder). We also collected demographic characteristics (age, gender and body mass index), clinical symptoms and laboratory examinations at admission.

The primary outcome was transferring to ICU treatment because of deteriorating clinical condition. The decision to transfer patients to the ICU was made by the treating ICU physician. Other observing outcome variables included inhospital mortality, length of hospital stay, hospitalisation expenses, recovery of renal function, and renal replacement therapy during hospitalisation.

**Statistical methods**

Statistical analysis was performed using Stata version 15 (Stata Corp LP, College Station, TX, USA). Continuous variables were described by means ± standard deviation or medians (25th, 75th percentile). Student’s t-test and Mann–Whitney U-test (if not normally distributed) were used for the comparison. Categorical variables were given as percentages and compared using the Chi-squared test or Fisher exact test. Variables that were significant in the univariate analysis or clinically important were included in the multivariable models. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated using multivariable logistic regression. All statistical tests were two-tailed and statistical significance was accepted at $P < 0.05$. 

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Results

Characteristics of the patients

A total of 149 patients with rhabdomyolysis aged over 18 years were recruited (median age 36.0 years, IQR (22.0; 63.0); body mass index 21.5 kg/m², IQR (19.8, 23.5); male gender n = 117 (78.5%)). Of these, 68 patients with rhabdomyolysis-associated AKI were identified, with an overall AKI percentage of 45.6%. Patients with AKI were older and had higher levels of urea nitrogen, SCr and potassium, as well as urine protein, than those without AKI ($P < 0.05$). Rhabdomyolysis without AKI presented with more clinical symptoms of pigmenturia and myalgia ($P < 0.05$). The main causes of rhabdomyolysis-associated AKI were non-exertional and non-traumatic as well as trauma and muscle compression, while for rhabdomyolysis without AKI the causes were non-traumatic and exertional ($P = 0.003$; Table 1).

Risk factors for rhabdomyolysis-associated AKI

After adjusting for other potential risk factors, age (adjusted OR = 1.01; 95% CI, 1.00–1.03; $P = 0.05$) and urine protein (adjusted OR = 1.67; 95% CI, 1.10–2.56; $P = 0.017$) was important risk factors of the incidence of rhabdomyolysis-associated AKI (Fig. 1).

Clinical outcomes in patients with rhabdomyolysis-associated AKI

The percentage of ICU transfer was higher in patients with AKI than those without AKI (33.8% vs 12.3%; $P < 0.002$). Compared with patients without AKI, patients with AKI had higher percentage of undergoing dialysis (19.1% vs 2.5%; $P < 0.01$), multiple-organ dysfunction syndrome (16.2% vs 4.9%; $P = 0.023$), inhospital all-cause mortality (13.2% vs 1.2%; $P < 0.01$), cost of hospitalisation (10.8 1000 yuan, IQR (5.5, 13.5) vs 5.9 1000 yuan, IQR 5.9 (3.6, 9.9); $P = 0.03$). In addition, patients with AKI also had longer length of hospital stay (8.0 days (5.0, 14.0) vs 6.0 days (4.0, 11.0); $P = 0.02$; Table 2). Moreover, the proportion of patients with AKI who achieved complete recovery and partial recovery of renal function were 77.9% and 2.9%, while no recovery was 19.1%. However, there was no statistical difference in the recovery of renal function between ICU transfer ($P = 0.16$).

Relationship between rhabdomyolysis-associated AKI and ICU transfer

Using univariate regression analysis, age, limb weakness, multiple-organ dysfunction syndrome and rhabdomyolysis-associated AKI were all associated with ICU transfer. After adjusting for potential risk factors, rhabdomyolysis-associated AKI remained related to the increased risk of ICU transfer (adjusted OR = 2.58; 95% CI, 1.12–6.80; $P = 0.03$; Table 3).

Discussion

The present study showed rhabdomyolysis-associated AKI developed in 45.6% of patients with rhabdomyolysis and had a higher percentage of transferring to an ICU, undergoing dialysis, all-cause mortality, and cost of hospitalisation, as well as a longer length of hospital stay, than those without AKI. Furthermore, rhabdomyolysis-associated AKI was related to the risk of ICU transfer.

AKI constitutes a common complication after rhabdomyolysis. However, since there is no established definition of rhabdomyolysis and lack of large prospective studies, the true incidence of rhabdomyolysis and associated AKI is difficult to determine. Based on epidemiological studies, it is reported that AKI develops in 19–58% of patients with rhabdomyolysis, but could reach 81.4% for severe cases in the ICU department. The present study observed 45.6% of patients with rhabdomyolysis developed AKI and most of them were older than rhabdomyolysis without AKI. The ageing process is associated with deterioration in organ functions and was considered to be one of the most consistent risk factors for AKI development in trauma patients. Accordingly, the results indicated the occurrence of rhabdomyolysis-associated AKI in the emergency department or general ward was at a high level and raised concern, especially for high-risk elderly patients. Of note, myalgia, limb weakness and gross pigmenturia without haematuria are the common denominators of rhabdomyolysis. However, the present study found rhabdomyolysis patients without AKI presented with more clinical symptoms of pigmenturia and myalgia, suggesting the evaluation of AKI could not be neglected even though patients with rhabdomyolysis did not present with the typical clinical symptoms. Moreover, there was no statistical difference in the serum CK levels between rhabdomyolysis patients with and without AKI in the present study. The reason could be that the link between serum CK levels and the occurrence of AKI in the patients with rhabdomyolysis is still controversial. Simpson et al. showed serum CK levels was not an early or specific predictor of AKI in patients with rhabdomyolysis. In contrast, Safari et al. showed...
found the value of CK had great predictive performance in the risk of rhabdomyolysis-associated AKI in crush injury cases (adjusted OR = 14.7; 95% CI = 7.6–28.5), while the predictive performance was not desirable in non-traumatic cases (adjusted OR = 0.99; 95% CI = 0.92–1.06). The main causes of rhabdomyolysis-associated AKI in the present study were non-exertional and non-traumatic, as well as trauma and muscle compression, while the causes of rhabdomyolysis without AKI were non-traumatic and exertional, which might also indicate the potential association between the role of rhabdomyolysis aetiology and serum CK levels.

In agreement with previous studies, we found that patients with rhabdomyolysis-associated AKI had worse inhospital outcomes and prognosis than those without AKI. Previous studies showed trauma ICU patients with AKI had higher mortality than those without AKI (17.2% vs 9.7%) and was associated with increased medical resource costs. Sovik et al. found that renal replacement therapy was required for 2% of all trauma ICU admissions and 10% of trauma patients with AKI in ICU department. In the present study, rhabdomyolysis patients with AKI in the emergency department or general ward still had a higher percentage of undergoing dialysis (19.1% vs 2.5%) and all-cause mortality (13.2% vs 1.2%), as well as medical expense and duration of hospital stay. In addition, few studies reported rhabdomyolysis patients transferred to the ICU from other departments. The present study indicated that the percentage of patients with AKI who transferred to the ICU reached up to 33.8%. This finding suggests that rhabdomyolysis-associated AKI increases the financial burden on families and societies when special medical care is required in clinical practice.

There was a paucity of data investigating patients with rhabdomyolysis transferred to an ICU from other departments. Most noteworthy, ICU transfer could reflect severity and progression of illness quickly. Early ICU

| Characteristic | Total | Rhabdomyolysis without AKI | Rhabdomyolysis-associated AKI | P-value |
|---------------|-------|---------------------------|-------------------------------|---------|
| Cases         | 149   | 81                        | 68                            |         |

Demographic

| Age, median (IQR) (years) | 36.0 (22.0, 63.0) | 29.0 (21.0, 52.0) | 52.5 (23.5, 67.0) | 0.01 |
| Age >60 years, n (%)      | 45 (30.2)         | 18 (22.2)         | 27 (39.7)         | 0.02 |
| Man gender, n (%)         | 117 (78.5)        | 62 (76.5)         | 55 (80.9)         | 0.52 |
| Body mass index, mean (SD) (kg/m²) | 21.5 (19.8, 23.5) | 22.1 (4.4)       | 22.1 (3.3)        | 0.98 |
| Smoking, n (%)            | 19 (12.8)         | 11 (13.6)         | 8 (11.8)          | 0.74 |

Characteristics at the admission

| Hypertension, n (%)       | 31 (20.8)         | 13 (16.0)         | 18 (26.5)         | 0.12 |
| Diabetes, n (%)           | 13 (8.7)          | 5 (6.2)           | 8 (11.7)          | 0.23 |

Clinical symptoms, n (%)  

| Pigmenturia              | 27 (18.1)         | 20 (24.7)         | 7 (10.3)          | 0.03 |
| Myalgia                  | 96 (64.4)         | 61 (75.3)         | 35 (51.5)         | <0.01 |
| Limb weakness            | 32 (21.5)         | 16 (19.8)         | 16 (23.5)         | 0.51 |

Laboratory tests

| Haemoglobin, mean (SD) (g/L) | 131.6 (22.4) | 135.2 (20.1) | 127.3 (24.5) | 0.05 |
| CK, median (IQR) (IU/L)      | 9861.0 (2383.0, 31 648.1) | 9000.0 (3088.0, 38 404.0) | 11 275.5 (3539.5, 20 878.5) | 0.36 |
| CKMB, median (IQR) (IU/L)    | 102.5 (38.2, 333.4) | 90.2 (38.0, 332.0) | 126.0 (38.0, 334.0) | 0.83 |
| Myoglobin, median (IQR) (ng/mL) | 306.2 (123.9, 1000.0) | 696.7 (156.2, 1084.0) | 147.5 (101.5, 696.0) | 0.08 |
| Potassium, mean (SD) (mmol/L) | 4.3 (2.5)       | 3.8 (0.8)        | 4.8 (3.7)        | 0.02 |
| AST, median (IQR) (UL)      | 131.5 (53.1, 483.0) | 115.5 (53.0, 401.0) | 172.5 (52.0, 543.5) | 0.58 |
| ALT, median (IQR) (UL)      | 65 (26, 166)      | 61.0 (50.0, 162.0) | 68.5 (26.0, 179.0) | 0.93 |
| Creatinine, median (IQR) (mmol/L) | 104.2 (74.1, 239.0) | 77.0 (70.0, 95.0) | 219.0 (156.0, 356.0) | <0.01 |
| Urea nitrogen, mean (SD) (mg/dL) | 8.6 (8.4)      | 5.0 (5.1)        | 13.0 (9.6)       | <0.01 |
| Positive urine protein, n (%) | 71 (47.7)       | 31 (38.3)        | 40 (58.8)        | 0.02 |

Causes of rhabdomyolysis, n (%)

| Non-exertional and non-traumatic | 31 (20.8) | 13 (16.0) | 18 (26.5) |
| Non-traumatic and exertional    | 75 (50.3) | 52 (64.2) | 23 (33.8) |
| Trauma and muscle compression   | 13 (8.7)  | 5 (6.2)   | 8 (11.8)  |
| Unknown                         | 30 (20.1) | 11 (13.6) | 19 (27.9) |

AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CKMB, creatine kinase MB; IQR, interquartile range; SD, standard deviation.
transfer is a considerable quality measure of emergency department care and delayed ICU admission was shown to be associated with increased mortality.\textsuperscript{17,18} It is also reported that unplanned transfers from acute care than other intensive care admissions had higher mortality.\textsuperscript{19} Therefore, it is essential to describe the ICU transfer for

### Table 2  Clinical outcomes in rhabdomyolysis patients with and without AKI

| Outcome                                | Total (n = 149) | Rhabdomyolysis without AKI (n = 81) | Rhabdomyolysis-associated AKI (n = 68) | P value |
|----------------------------------------|----------------|-------------------------------------|--------------------------------------|---------|
| ICU transfer, n (%)                    | 33 (22.1)      | 10 (12.3)                           | 23 (33.8)                           | 0.002   |
| Dialysis during hospitalisation, n (%) | 15 (10.1)      | 2 (2.5)                             | 13 (19.1)                           | <0.01   |
| Multiple-organ dysfunction syndrome, n (%) | 15 (10.1)    | 4 (4.9)                             | 11 (16.2)                           | 0.023   |
| In-hospital all-cause mortality, n (%) | 10 (6.7)       | 1 (1.2)                             | 9 (13.2)                            | <0.01   |
| Cost, median (IQR) (1000 yuan)         | 7.4 (4.6, 19.4)| 5.9 (3.6, 9.9)                      | 10.8 (5.5, 3.5)                     | 0.03    |
| Length of hospital stay, median (IQR) (days) | 7 (5.0, 11.0)| 6.0 (4.0, 11.0)                     | 8.0 (5.0, 14.0)                     | 0.02    |

AKI, acute kidney injury; ICU, intensive care unit; IQR, interquartile range.

### Table 3  Association between rhabdomyolysis-associated AKI and ICU transfer by multivariate regression analysis

| Variable                                | Univariate analysis | Multivariate analysis |
|-----------------------------------------|---------------------|-----------------------|
|                                        | OR      | 95% CI   | P-value | OR      | 95% CI   | P-value |
| Age                                     | 1.05    | 1.03–1.08 | <0.001  | 1.05    | 1.03–1.08 | <0.001  |
| Body mass index                         | 1.12    | 0.97–1.29 | 0.11    | —       | —       | —       |
| Myalgia                                 | 0.91    | 0.83–1.14 | 0.22    | —       | —       | —       |
| Pigmenturia                             | 0.40    | 0.11–1.41 | 0.15    | —       | —       | —       |
| Limb weakness                           | 4.19    | 1.77–9.91 | 0.001   | 1.18    | 0.31–4.44 | 0.81   |
| CK > 5000                               | 2.05    | 0.85–4.94 | 0.11    | 2.97    | 1.00–8.78 | 0.05   |
| Potassium                               | 1.07    | 0.93–1.23 | 0.37    | —       | —       | —       |
| AKI                                     | 3.63    | 1.58–8.33 | 0.002   | 2.58    | 1.12–6.80 | 0.03   |
| Urine protein                           | 1.49    | 0.95–2.24 | 0.09    | —       | —       | —       |
| Gender                                  | 0.82    | 0.33–2.03 | 0.66    | —       | —       | —       |
| Multiple organ dysfunction syndrome     | 2.64    | 1.38–8.06 | 0.028   | 2.21    | 1.08–7.11 | 0.041  |

AKI, acute kidney injury; CI, confidence interval; CK, creatine kinase; ICU, intensive care unit; OR, odds ratio.
patients with rhabdomyolysis from other departments as rhabdomyolysis is a potentially dangerous medical condition that needs rapid diagnosis and management. The present study showed that 22.8% rhabdomyolysis patients were transferred to an ICU and rhabdomyolysis-associated AKI remained an independent risk factor for ICU transfer. The results suggest that rhabdomyolysis-associated AKI could be activation of prompt response alerts and outcomes of transferring from acute care units to the ICU. It might be beneficial for medical staff in the emergency department to have knowledge of this condition for appropriate management.

Several limitations of the study are discussed as follows. First, as a single-centre retrospective study the results cannot prove causation and should be interpreted with caution. Second, although consecutive patients with rhabdomyolysis-associated AKI were included and many potential risk confounders were adjusted in the multivariate analysis to control the selection bias, there still existed the possibility of residual confounders secondary to unmeasured variables. Third, due to the limitation of sample size, we could not investigate the effect of ICU transfer on mortality. Last, we lacked data on prolonged follow-up duration. Therefore, the predictive factors of rhabdomyolysis-associated AKI progressing to chronic kidney disease transition require further prospective studies to determine. However, the present study raised awareness of rhabdomyolysis-associated AKI in the prediction of ICU transfer, which is of great significance for timely clinical condition evaluation and intervention for such patients.

Conclusion

The present study showed rhabdomyolysis-associated AKI developed in 45.6% of patients with rhabdomyolysis. Patients with rhabdomyolysis-associated AKI had a worse clinical outcome compared with those without AKI and were related to increased risk of ICU transfer. These results highlight the importance of early recognition and management of rhabdomyolysis-associated AKI in the emergency department or general ward.

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**Supporting Information**

Additional supporting information may be found in the online version of this article at the publisher’s web-site:

**Fig. S1** Flow chart of the study population selection.