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Acute Kidney Injury Following Rhabdomyolysis in Critically Ill Patients

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Abstract

Introduction: Rhabdomyolysis, which resulted from the rapid breakdown of damaged skeletal muscle, potentially leads to acute kidney injury. **Aim**: To determine the incidence and associated risk of kidney injury following rhabdomyolysis in critically ill patients. **Methods**: All critically ill patients admitted from January 2016 to December 2017 were screened. A creatinine kinase level of > 5 times the upper limit of normal (> 1000 U/L) was defined as rhabdomyolysis, and kidney injury was determined based on the Kidney Disease Improving Global Outcome (KDIGO) score. In addition, trauma, prolonged surgery, sepsis, antipsychotic drugs, hyperthermia were included as risk factors for kidney injury. **Results**: Out of 1620 admissions, 149 (9.2%) were identified as having rhabdomyolysis and 54 (36.2%) developed kidney injury. Acute kidney injury, by and large, was related to rhabdomyolysis followed a prolonged surgery (18.7%), sepsis (50.0%) or trauma (31.5%). The reduction in the creatinine kinase levels following hydration treatment was statistically significant in the non- kidney injury group (Z= -3.948, p<0.05) compared to the kidney injury group (Z= -0.623, p=0.534). Significantly, odds of developing acute kidney injury were 1.040 (p<0.001) for mean BW >50kg, 1.372(p<0.001) for SOFA Score >2, 5.333 (p<0.001) for sepsis and the multivariate regression analysis showed that SOFA scores >2 (p<0.001), BW >50kg (p=0.016) and sepsis (p<0.05) were independent risk factors. The overall mortality due to rhabdomyolysis was 15.4% (23/149), with significantly higher incidences of mortality in the kidney injury group (35.2%) vs the non- kidney injury (3.5%) [p<0.001]. **Conclusions**: One-third of rhabdomyolysis patients developed acute kidney injury with a significantly high mortality rate. Sepsis was a prominent cause of acute kidney injury. Both sepsis and a SOFA score >2 were significant independent risk factors.

Keywords: acute kidney injury, creatinine, critically ill, dialysis, rhabdomyolysis

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Introduction

On admission to an intensive care unit, critically ill patients frequently present with many *comorbidities and* are prone to develop various complications, including rhabdomyolysis.

Rhabdomyolysis is a syndrome that involves damage and breakdown of skeletal muscle, causing myoglobin, electrolytes and other intracellular protein to leak into the blood circulation [1]. The aetiology of rhabdomyolysis can be hereditary, such as metabolic myopathies caused by the disorder of fatty acid oxidation and mitochondrial oxidation. Acquired causes are trauma, crush injuries, surgery, extreme physical activity, extreme temperature, metabolic disorder of water and salts, vascular ischemia, drugs, sepsis and prolonged immobilization [2].

In one study, the incidence of rhabdomyolysis was as high as 8.58% in surgical patients admitted to intensive care units. [2] Acute kidney injury associated with rhabdomyolysis was thought to result from vasoconstriction with decreased renal perfusion and intraluminal deposits of myoglobin, or its breakdown products and of uric acid, which causes obstruction and tubular damage [3].

The factors associated were reduced glomerular filtration rate, metabolic acidosis, high creatinine kinase levels, and the presence of myoglobin in the urine. [3]

The common challenges faced by the clinicians in diagnosing rhabdomyolysis include the variety of presentations and the limited ability to test for the condition. In one study, the clinical presentation varies tremendously, ranging from relatively asymptomatic patients to those with severe muscle pain and reddish-brown urine [4]. The syndrome typically represents as high-

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intensity muscular pain, weakness and myoglobinuria [5].

The meta-analysis by Chavez et al. (2016) suggests serum creatinine kinase more than five times the upper limit of the normal range as diagnosing criteria [6]. Serum creatinine kinase usually rises within 2 to 12 hours following the onset of muscle injury and reaches a maximum within 24 to 72 hours [4]. Besides creatinine kinase, urine myoglobin also can be used to diagnose rhabdomyolysis; however, it poses some limitations as its level rises and falls much rapidly, therefore has a low negative predictive value and cannot be used as a ruling out test [7].

The syndrome may also present with several complications such as arrhythmias, electrolyte abnormalities, metabolic acidosis, volume depletion, compartment syndrome and disseminated intravascular coagulation [7]. Acute kidney injury remains a significant outcome contributing to 59 % mortality [4]. Despite being one of the dangerous outcomes, acute kidney injury is preventable [8]. The focus of treatment is to prevent myoglobin induced acute kidney injury, which includes early and aggressive use of a crystalloid solution to maintain urinary output, administration of bicarbonate to promote alkalinization of the urine to reduce precipitation of myoglobin and use of diuretics and mannitol [4,9]. The average fluid volume used ranged from 3 to 8 litres per day [6]. The outcome of patients presenting with rhabdomyolysis differs between patients depending on age, comorbidities and causes [10]

The objective of this study was to determine the incidence and associated risk factors of acute kidney injury following rhabdomyolysis in critically ill patients.

Methods

This retrospective study was conducted following approval from the Dissertation Committee of the Department Anesthesiology and Intensive Care Universiti Kebangsaan Malaysia Medical Centre (UKMMC) and UKMMC Medical Research and Ethics Committee (UKM FF-2018-385).

Laboratory data of all patients admitted to the general intensive care unit of the UKMMC from January 2016 to December 2017 were extracted from the UKMMC Order Management System (OMS) and screened.

Inclusion criteria: All patients whose data showed serum creatinine kinase levels of more than five times the upper limit of normal (> 1000 U/L).

Exclusion criteria: Patients with elevated serum creatinine kinase due to myocardial infarction and pre-existing renal failure with glomerular filtration rate (GFR) of less than 60 ml/min/1.73m$^{2.}$

Patients who were already on renal replacement therapy (RRT) before the study.

Demographics and relevant clinical data such as medical history, duration of high serum creatinine kinase levels to highest level during GICU stay, Sequential Organ Failure Assessment (SOFA) score during peak serum creatinine kinase levels and length of stay in the intensive care unit, was extracted from their records.

Risk factors for developing kidney injury in rhabdomyolysis was determined based on previous literature reviews such as trauma, prolonged surgery, sepsis, antipsychotic drugs induced, hyperthermia with a temperature more than 40^{0}C, secondary to malignant hyperthermia or neuroleptic malignant syndrome that does not include organ dysfunction and SOFA score less than 2.

The patent's renal profile was recorded to diagnose kidney injury, as were creatinine kinase levels after a diagnosis of rhabdomyolysis and at 72 hours after hydration therapy.

Acute kidney injury was defined as an increase in serum creatinine by 26.5 µmol/l within 48 hours or an increase in serum creatinine greater than 1.5 times baseline or a urine volume <0.5 ml/kg/h for six hours, using the Kidney Disease Improving Global Outcome score.

Whether patients developed acute kidney injury or not was recorded

Those in the acute kidney injury group were subanalyzed if their condition needed either short term or long-term dialysis of more than three months after discharge.

The sample size was calculated using Epi Info 7 ™, based on a minimum of 800 GICU admissions per year and previous incidence of rhabdomyolysis of 8.58% as recommended by Kuzmanovska (2016) [2]. The estimated minimum sample size of 104 patients was needed to meet an 80% power of study with a 95% confidence level.

The descriptive analyses included the observed frequencies calculation with the respective percentages for each categorical variable, while mean (SD) or median [interquartile range] were computed for continuous variables where appropriate.

The Chi-Square or Fisher's Exact Test and ANOVA were employed to compare qualitative variables. In addition, a multiple logistic regression model was used for multivariable analysis to identify those variables independently associated with acute kidney injury post rhabdomyolysis during the stay in the ICU. The significance level was set at an alpha value, 0.05. All data were analyzed using IBM SPSS Statistics version 23.0 (IBM, Armonk, NY, USA).

Results

A total of 1620 patients' data were screened during the study period, and there were 149 patients diagnosed as having rhabdomyolysis. The overall incidence of rhabdomyolysis was 9.2%. Out of those, 54 (36.2%) patients developed acute kidney injury and 50 (92.6%) of the patients that develop acute kidney injury required haemodialysis; two of these patients needed long term dialysis.

There were no significant differences in the demography of the patients (Table 1).

The present study findings showed that patients with rhabdomyolysis that developed acute kidney injury had significantly higher mean body weight and SOFA score. In addition, the patients in the non-acute kidney injury group had higher median creatinine kinase levels upon diagnosis of rhabdomyolysis (Table 1), and the median creatinine kinase level for post hydration treatment was shown to be significantly higher in the acute kidney injury group. An analysis using Wilcoxon signed-rank test showed that following the treatment with hydration, the reduction in the creatinine kinase level ($Z = -3.948$, $p < 0.05$) in the non-acute kidney in-

Table1. Patient's demographic data, length of stay, SOFA Score, comorbid and serum creatinine kinase levels. Values are shown as mean (SD) or median (interquartile range) and number (percentage).

	Non-acute kidney injury (n=95)	Acute kidney injury (n=54)	p-value
Gender			
Male	74(77.9%)	41(75.9%)	0.783
Female	21(22.1%)	13(24.1%)	
Ethnicity			
Malay	54(56.8%)	26(48.1%)	
Chinese	19(20.9%)	14(25.9%)	0.859
Indian	14(14.7%)	9(16.7%)	
Others	8(8.4%)	5(9.3%)	
Age, Mean (SD) years	43.3(18.6)	46.8(15.5)	
<40	45(47.4%)	20(37.0%)	0.238
41-60	31(32.6%)	22(40.7%)	
>61	19(20.0%)	12(22.2%)	
Weight, kg	70[63-80]	80[70-86.8]	
<50	10(10.5%)	0	<0.001*
51-70	25(26.3%)	12(22.5%)	
>71	60(63.2%)	42(77.8%)	
Length of Stay in ICU (days)	5[2-8]	5[3-11.25]	0.210
SOFA score, Mean (SD)	5.8(3.7)	10.7(4.3)	
≤2	18(18.9%)	2(3.7%)	<0.001*
>2	77(81.1%)	52(96.3%)	
Comorbidities			
Diabetes	17(17.9%)	17(31.5%)	0.057
Asthma	7(7.4%)	3(5.6%)	0.748
Hypertension	21(22.1%)	19(35.2%)	0.083
Creatinine kinase level on upon diagnosis of rhabdomyolysis	2179[1246-4742]	2065[796-7741]	0.435
Creatinine kinase level post-treatment	1578[661-2374]	2030[764-5548]	0.048*
Time taken to reach the highest creatinine kinase (days)	2[1-2]	2[1-3]	0.260
Mortality	4(4.2%)	19(35.2%)	<0.001*

*p less than 0.05 is significant

jury group were statistically significant compared to the acute kidney injury group (Z = -0.623, $p = 0.534$).

The risk factors of developing acute kidney injury following rhabdomyolysis, shown in this study, included prolonged surgery (14.7%), sepsis (50%), trauma (31.5%), antipsychotic drug usage (1.9%) and hyperthermia (1.9%) (Table 2). Following univariate analyses, the risks of patients with rhabdomyolysis who developed acute kidney injury were mean body weight > 50kg with odds of 1.040 ($p < 0.001$), SOFA Score > 2 with odds of 1.372($p < 0.001$) and were admitted to GICU for sepsis with odds of 5.333 ($p < 0.001$). Subsequent multivariate logistic regression analysis showed that these three factors were independent risk factors for rhabdomyolysis patients to develop acute kidney injury (Table 3). The overall GICU mortality rate secondary to rhabdomyolysis in this study was 15.4% (23/149), where 16 of these patients had sepsis, and another seven had trauma. Thus, the mortality rate among patients who develop acute kidney injury was 35.2%, whereas the mortality rate in non-acute kidney injury patients was 3.5% ($p < 0.001$).

Discussion

The incidence of rhabdomyolysis in the ICU during the study was 9.2 %. This incidence is similar to a report by Kuzmanovska et al. (2016)[2]. Rhabdomyolysis is a life-threatening condition that can lead to morbidity and mortality if it is not detected and managed early. One-third of the present patient who had rhabdomyolysis went on to develop acute kidney injury. In one multicentre analysis involving 387 patients, the incidence of acute kidney injury was 81.4%, with 26.6% requiring renal replacement therapy [13]. Another study by Simpson (2016) quoted an incident of 19%, with 12.5% requiring RRT [14], comparatively lower than the current ICU incidence.

A mean body weight greater than 50 kg, a SOFA score of more than 2 and sepsis as the independent predisposing factors of developing acute kidney injury among our patients with rhabdomyolysis was identified in the study. Thus, increased weight in patients with rhabdomyolysis seems to predispose ICU patients to develop acute kidney injury significantly.

A higher creatinine kinase level is also found in patients with a body mass index greater than 25 [12]. In a study by Vasquez (2020) , serum creatinine kinase correlated with the body mass index; patients with higher body mass index were found to have higher creatinine kinase levels [15]. Chan et al. (2014) also found higher creatinine kinase levels in patients with a body mass index greater than 25 [12].

There were three cases with malignant neuroleptic syndrome that were diagnosed with rhabdomyolysis. All of these patients were on antipsychotic medications.

There was one patient diagnosed with rhabdomyolysis where the only predisposing cause was hyperthermia. The patient did not demonstrate any infectious

Table 2. Bivariate analysis of associated risk factors in Acute Kidney Injury development expressed as mean (SD), number (%), median [IQR] as appropriate.

Risk factors	Non-acute kidney injury (n=95)	Acute kidney injury (n=54)	Odds ratio	95% CI		p-value
				Lower	Upper	
Weight >50 kg			1.040	1.016	1.064	<0.001*
SOFA score (>2)			1.372	1.223	1.539	<0.001*
Antipsychotics	2 (2.1%)	1 (1.9%)				0.702
Sepsis	15 (15.8%)	27 (50%)	5.333	2.476	11.487	<0.001*
Prolonged Surgery	17 (17.9%)	8 (14.7%)				0.658
Trauma	46 (48.4%)	17 (31.5%)	0.489	0.243	0.987	0.046
Hyperthermia	0	1 (1.9%)				0.362

*p less than 0.05 is significant

Table 3. Multivariate logistic regression of risk factors developing Acute Kidney Injury in rhabdomyolysis patients.

Variable	Odds ratio	95% CI		p-value
		Lower	Upper	
Weight (>50 kg)	1.034	1.006	1.063	0.016*
Sofa Score (>2)	1.299	1.151	1.467	<0.001*
Sepsis	2.475	0.978	6.261	<0.05*

*p less than 0.05 is significant

cause at the time of rhabdomyolysis diagnosis was made. As this was retrospective data, there were limited details on the patient.

Patients with SOFA score more than 2, and septic patients may have other uncontrolled comorbidities such as diabetes and hypertension, making them resistant to conventional treatment of rhabdomyolysis by hydration. In addition, up to 50% of acute kidney injuries are associated with sepsis, and of patients with sepsis, up to 60% have acute kidney injury [16].

In this retrospective study, it was found that not all rhabdomyolysis patient needs dialysis. Initiation of hydration as a mode of treatment can reduce the incidence of acute kidney injury. This study shows that patients in the acute kidney injury group have higher creatinine kinase levels post hydration.

The mortality rate is significantly higher in the acute kidney injury group (4.21%) than in the non-acute kidney injury group (35.2%). This illustrated the need to recognize and treat rhabdomyolysis early.

Conclusions

A third of the rhabdomyolysis patients developed acute kidney injury with a significantly high mortality rate. Sepsis was an important cause, and a SOFA score >2 a significant independent risk.

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Conflict of interest

None to declare.

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