

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

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Research

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Abstract

Background: Rhabdomyolysis (RM) associated acute kidney injury (AKI) is the most common systemic complication of RM. The present study aimed to assess the clinical characteristics and risk factors for intensive care unit (ICU) transfer for patients with RM-associated AKI.

Methods: We included all patients who were age ≥ 18 years old with a diagnosis of RM from September 2012 to October 2018 and divided them into RM-associated AKI group and RM without AKI group. The primary outcome was transferring to ICU treatment. Regression analysis was performed to identify factors associated with ICU treatment and recovery of renal function.

Results: Among the 149 patients with RM, 68 (45.6%) developed AKI. The percentage of patients with AKI who transferred to ICU was higher than patients without AKI (33.8% versus 12.3%, $P < 0.002$). Additionally, patients with AKI had higher percentage of undergoing dialysis (19.1% versus 2.5%, $P < 0.01$), all-cause mortality (13.2% versus 1.2%, $P < 0.01$), cost of hospitalization [10.8 1,000 yuan, IQR (5.5, 3.5) versus 5.9 1,000 yuan, IQR 5.9 (3.6, 9.9), $P = 0.03$], as well as longer length of hospital stay [8.0 (5.0, 14.0)] versus [6.0 (4.0, 11.0)], $P = 0.02$). Moreover, most patients with AKI achieved complete recovery (77.9%) at discharge. After adjusting for potential risk factors, RM-associated AKI remained an independent risk factor for ICU transfer ($OR = 3.0$, 95% CI, 1.11–8.3, $P = 0.03$). However, ICU transfer was not associated with recovery of renal function ($OR = 0.88$, 95% CI, 0.22–3.57, $P = 0.856$).

Conclusion: RM led to AKI in most patients. RM-associated AKI could cause worse clinical outcome and predict ICU transfer for patients with RM.

Background

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

RM-associated AKI is the most common systemic complication of RM and may account for 7–10% of all cases of acute renal failure [5, 6]. It is associated with poor clinical outcomes, increase of economic and survival burden for patients, which is the crucial issue to be solved. Most studies focused on the risk factors of the incidence of RM-associated AKI in the intensive care unit (ICU) [2, 7]. However, as the first-hand clinical data in the inpatient ward or emergency department, early identification of risk factors of ICU transfer for such population is of great significance for condition evaluation and intervention. Therefore, the aim of this study was to assess the clinical characteristics in the inpatient ward or emergency department and risk factors for ICU transfer for patients with RM-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. Each patient gave the written informed consent.

Inclusion criteria and Exclusion criteria

Inclusion criteria: patients age ≥ 18 years old with a diagnosis of rhabdomyolysis in the inpatient ward or emergency department.

Exclusion criteria: (1) a history of pre-existing end-stage renal disease; (2) chronic dialysis, kidney transplant or amputation patients; (3) pregnancy; (4) peak Serum creatinine (SCr) $< 53\mu\text{mol/L}$; (5) elevated CK levels were caused by myocardial infarction or acute coronary syndrome; (6) missing data to support a diagnosis of rhabdomyolysis and AKI.

Definitions

Rhabdomyolysis was defined as a serum CK concentration above the levels five times the upper limit of normal levels (>1000 U/L) accompanied by clinical symptoms such as myalgia, limb weakness, pigmenturia, and oliguria at admission [3]. According to the definition of Kidney Disease: Improving Global Outcomes (KDIGO) criteria in 2012, the definition of AKI was determined as an absolute increase in SCr $> 0.3\text{mg/dL}$ within 48 hours or 1.5 times relative increase over the baseline values within 7 days or urine volume $< 0.5\text{ml} / (\text{kg} \cdot \text{h})$ lasted for ≥ 6 hours [8]. The recovery of renal function was defined by comparing the last SCr before discharge with the baseline value: last SCr value before discharge < 1.2 times of baseline value was defined as the complete recovery of renal function; between 1.2-1.5 times was partial recovery; > 1.5 times or receiving renal replacement therapy after discharge was not recovery [9]. Baseline SCr value was checked and identified by reference 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 center.

Clinical data and observing outcomes

When a diagnosis of rhabdomyolysis has been established, experienced clinicians queried the patients on any history of trauma, hypokalemia, seizure, unusual recent physical activity, metabolic/endocrine, toxicity and diet related to categorize the main etiology. We also classified the etiology of RM as trauma and muscle compression (any cause by large area muscle injury or ischemia hypoxia injury, including natural disaster, traffic accident and electric shock, etc.), non-traumatic and exertional (energy supply of muscles is insufficient to meet the demand, including violent exercise, seizures and heat shock, etc.), and

non-exertional and non-traumatic (including infection, food and drug, intoxication, and electrolyte disorder). We also collected the demographic characteristics [age, gender, and body mass index (BMI)], clinical symptom and laboratory examinations at admission, as well as related indicators.

The primary outcome was transferring to ICU treatment. Other observing outcome variables included: recovery of renal function, in-hospital mortality, length of hospital stay, hospitalization expenses, need for renal replacement therapy during hospitalization.

Statistical methods

Statistical analysis was performed by Stata version 15 (Stata Corp LP, College Station, TX, USA). Continuous variables were described by means \pm standard deviation (SD) 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-square 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 interval (CI) were estimated by multivariable logistic regression. All statistical tests were two-tailed and statistical significance was accepted at $P < 0.05$.

Results

Characteristics of the patients

A total of 149 patients with RM aged over 18 years old were recruited [median age 36 years, IQR (22; 63); BMI 21.5, IQR (19.8,23.5); male gender $n = 117$ (78.5%)]. Of these, 68 patients with RM-associated AKI were identified, with an overall AKI percentage of 45.6%. Patients with AKI was older, and had higher level of urea nitrogen, SCr and potassium, as well as urine protein than those without AKI ($P < 0.05$). RM without AKI presented with more clinical symptoms of pigmenturia and myalgia ($P < 0.05$). The main causes of RM-associated AKI were non-exertional and non-traumatic as well as trauma and muscle compression, while RM without AKI were nontraumatic and exertional ($P = 0.003$) (Table 1).

Table 1
Baseline characteristics of rhabdomyolysis patients with and without acute kidney injury

Characteristic	Total	RM without AKI	RM associated AKI	P value
Cases	149	81	68	
Demographic				
Age, median (IQR), y	36.0 (22.0,63.0)	29.0 (21.0, 52.0)	52.5 (23.5, 67.0)	0.01
Age > 60y (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
BMI, mean (SD), kg/m ²	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				
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				
Hemoglobin, 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, 31648.1)	9000.0 (3088.0, 38404.0)	11275.5 (3539.5, 20878.5)	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
Phosphorus, median (IQR), mmol/L	1.29 (1.17, 1.52)	1.2 (1.2, 1.3)	1.4 (1.2, 2.1)	0.09
Potassium, mean (SD), mmol/L	4.3 (2.5)	3.8 (0.8)	4.8 (3.7)	0.02
AST, median (IQR), U/L	131.5 (53.1, 483.0)	115.5 (53.0, 401.0)	172.5 (52.0, 543.5)	0.58

RM, rhabdomyolysis; AKI, acute kidney injury; BMI, body mass index; CK, creatine kinase; CKMB, creatine kinase MB; AST, aspartate aminotransferase; ALT, Alanine aminotransferase; SD, standard deviation; IQR, inter-quartile range

Characteristic	Total	RM without AKI	RM associated AKI	P value
ALT, median (IQR), U/L	65 (26, 166)	61.0 (30.0, 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	71 (47.7)	31 (38.3)	40 (58.8)	0.02
Causes of rhabdomyolysis (n, %)				0.003
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)	
unknow	30 (20.1)	11 (13.6)	19 (27.9)	
RM, rhabdomyolysis; AKI, acute kidney injury; BMI, body mass index; CK, creatine kinase; CKMB, creatine kinase MB; AST, aspartate aminotransferase; ALT, Alanine aminotransferase; SD, standard deviation; IQR, inter-quartile range				

Clinical Outcomes In Patients With Rm-associated Aki

Clinical outcomes in patients with RM-associated AKI and RM without AKI are shown in Table 2. The percentage of patients with AKI who transferred to ICU was higher than patients without AKI (33.8% versus 12.3%, $P < 0.002$). Compared patients without AKI, patients with AKI had higher percentage of undergoing dialysis (19.1% versus 2.5%, $P < 0.01$), in-patient all-cause mortality (13.2% versus 1.2%, $P < 0.01$), cost of hospitalization [10.8 1,000 yuan, IQR (5.5, 3.5) versus 5.9 1,000 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 (5.0, 14.0)] versus [6.0 (4.0, 11.0)], $P = 0.02$). 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 existed no statistical difference on the recovery of renal function between ICU transfer ($P = 0.16$) (Table 3)).

Table 2
Clinical outcomes in rhabdomyolysis patients with and without acute kidney injury

Outcomes	Total (n = 149)	RM without AKI (n = 81)	RM associated AKI (n = 68)	P value
Transfer to ICU (n, %)	33 (22.1)	10 (12.3)	23 (33.8)	0.002
Dialysis during hospitalization (n, %)	15 (10.1)	2 (2.5)	13 (19.1)	< 0.01
In-hospital mortality (n, %)	10 (6.7)	1 (1.2)	9 (13.2)	< 0.01
Costs, median (IQR), 1,000 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), d	7 (5.0, 11.0)	6.0 (4.0, 11.0)	8.0 (5.0, 14.0)	0.02
RM, rhabdomyolysis; AKI, acute kidney injury; ICU, intensive care unit; IQR, inter-quartile range				

Table 3
Recovery of renal function for rhabdomyolysis patients with acute kidney injury

Recovery of renal function (n, %)	Total (n = 68)	Non-ICU transfer (n = 45)	ICU transfer (n = 23)
Complete recovery	53 (77.9)	37 (54.4)	16 (23.5)
Partial recovery	2 (2.9)	2 (2.9)	0
No recovery	13 (19.1)	6 (8.8)	7 (10.3)
ICU, intensive care unit			

Risk factors for ICU transfer and recovery of renal function

Using univariate analysis, age, limb weakness, smoking and RM-associated AKI were all associated with ICU transfer (Table 4). After adjusting for potential risk factors, RM-associated AKI remained an independent risk factor for ICU transfer ($OR = 3.0$, 95% CI, 1.11–8.3, $P = 0.03$) (Fig. 1). However, ICU transfer was not associated with recovery of renal function for patients with RM-associated AKI after adjusting for other potential risk factors ($OR = 0.88$, 95% CI, 0.22–3.57, $P = 0.856$) (Table S1).

Table 4
Univariate analysis of risk factors for predicting ICU transfer

Variables	OR	95% CI		P value
		Lower	Upper	
Age	1.05	1.03	1.08	< 0.001
Body mass index	1.12	0.97	1.29	0.114
Myalgia	0.91	0.83	1.14	0.215
Pigmenturia	0.40	0.11	1.41	0.154
Limb weakness	4.19	1.77	9.91	0.001
CK > 5000	2.05	0.85	4.94	0.109
Potassium	1.07	0.93	1.23	0.366
Smoking	3.98	1.46	10.84	0.007
Acute kidney injury	3.63	1.58	8.33	0.002
Urine protein	1.49	0.95	2.24	0.085
Gender	0.82	0.33	2.03	0.661

CK, creatine kinase; ICU, intensive care unit; OR, odds ratio; CI, confidence interval

Discussion

The present study showed RM-associated AKI developed in 45.6% of patients with RM and presented with a higher percentage of transferring to an intensive care unit, undergoing dialysis, all-cause mortality, and cost of hospitalization, as well as a longer length of hospital stay. Furthermore, RM-associated AKI predicted ICU transfer for patients with RM.

AKI constitutes a common complication after RM. However, since there is no established definition of rhabdomyolysis and lack of large prospective studies, the true incidence of RM and associated AKI is difficult to determine [10]. Base on epidemiological studies, it's reported that AKI develop in 19%-58% of patients with RM [2, 11], while could reach 81.4% for patients with severe cases in the ICU department [7]. The present study observed 45.6% of patients with RM developed AKI and most of them were older than RM without AKI. Aging process is associated with deterioration in organ functions and was considered to be the most consistent risk factor for AKI development in trauma patients [12]. Accordingly, the results indicated the occurrence of RM-associated AKI in the inpatient ward or emergency department was at a high level and should be considered, especially for the high-risk elderly patients. To note, myalgia, limb weakness, and gross pigmenturia without hematuria are the common denominator of RM [13]. However, the present study found RM patients without AKI presented with more clinical symptoms of pigmenturia

and myalgia, which suggesting the evaluation of AKI could not be neglected even though patients with RM did not present with the typical clinical symptoms. Moreover, there existed no statistical difference on the serum CK level between RM patients with and without AKI in the present study. The reason could be the link between serum CK level and the occurrence of AKI in the patients with RM was still under controversial [2, 14]. Simpson et al. [2] showed serum CK level was not an early or specific predictor of AKI in patients with RM. On the contrary, Safari et al. [14] found the value of creatine kinase (CK) had great predictive performance in the risk of rhabdomyolysis-induced AKI in crush injury cases (adjusted OR = 14.7, 95% CI = 7.63–28.52), while it was not desirable in non-traumatic cases (adjusted OR = 0.99, 95% CI = 0.92–1.06). The main causes of RM-associated AKI in the present study were non-exertional and non-traumatic as well as trauma and muscle compression, while RM without AKI were non-traumatic and exertional, which may indicate the potential association of the role of RM etiology and serum CK level.

In agreement with previous studies [7, 15, 16], we found that patients with RM developing AKI had worse in-hospital outcomes and prognosis than those without AKI. Previous showed trauma ICU patients with AKI had higher mortality than those without AKI (17.2% vs.9.7%) and was associated with increased more medical resource costs [17]. Sovik et al. [16] 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 our study, RM patients with AKI in the inpatient ward or emergency department still had a higher percentage of undergoing dialysis (19.1% versus 2.5%) and all-cause mortality (13.2% versus 1.2%), as well as increased daily cost and length of stay. In addition, few studies reported RM patients transferred to ICU from other departments, while we indicated the percentage of patients with AKI who transferred to ICU reached up to 33.8%. This finding suggested that RM with AKI increased a financial burden to families and societies, which required special medical care in the clinical practice.

Most studies had identified the risk factors for the incidence of RM-associated AKI in ICU. However, there was a paucity of data investigating patients with RM transferred to an ICU from another departments. Most noteworthy, ICU transfer could reflect severity and progression of illness shortly. Early ICU transfer is a considerable quality measure of emergency department care and delayed ICU admission was showed to be associated with increased mortality [18, 19]. It's also reported that unplanned transfers from acute care than among other intensive care admissions had higher mortality [20]. Therefore, it's essential to describe the patients with RM transferred to an ICU from another departments since RM is a potentially dangerous medical condition that needs rapid diagnosis and management. The present showed about 22.8% RM patients in present study was transferred to an ICU and RM-associated AKI remained an independent risk factor for ICU transfer. The results suggested that RM-associated AKI could be activation of a prompt response alerts and outcomes of transferring from acute care units to the ICU. Emergency and inpatient clinicians with knowledge of this condition may be beneficial for appropriate management. However, ICU transfer was not associated with recovery of renal function after adjusting for other potential risk factors. The possible reason could be most patients with AKI achieved complete recovery at discharge and no statistical difference on the recovery of renal function between ICU transfer. Moreover, due to the limitation of sample size, we could not investigate the effect of ICU transfer on mortality, which required larger well-controlled trials with available sample size to further determine.

Several limitations of our study are discussed as following. Firstly, as a single-center retrospective study, the results cannot prove causation, and should be interpreted with caution. Secondly, the study protocol has not been registered in a database of clinical studies (i.e., ClinicalTrials.gov), which it is not mandatory for retrospective observational studies. Thirdly, although consecutive patients RM-associated AKI were included and many potential risk confounders were adjusted in the multivariate analysis to limit selection bias, there still existed the possibility of residual confounders secondary to unmeasured variables. Lastly, we lacked the data on prolonged follow-up duration. Therefore, the predictive factors of RM-associated AKI to chronic kidney disease transition required further prospective studies to determine. However, the data in this study permit an initial assessment of the clinical characteristics and prediction of ICU transfer, which was of great significance for timely clinical condition evaluation and intervention for patients with RM-associated AKI.

Conclusions

The present study showed RM-associated AKI developed in 45.6% of patients with RM. The clinical outcome was worse in RM patients with AKI. RM-associated AKI predicted ICU transfer for patients with RM. These results highlight the importance of early recognition and management of RM-associated AKI.

Abbreviations

AKI, acute kidney injury; AST, aspartate aminotransferase; ALT, Alanine aminotransferase; SD, standard deviation; BMI, body mass index; CI, confidence interval; CK, creatine kinase; CKMB, creatine kinase MB; IQR, inter-quartile range; ICU, intensive care unit; OR, odds ratio; RM, rhabdomyolysis; SCr, Serum creatinine.

Declarations

Authors' contributions

The author contributions are as follows: XCZ and DCZ designed the study and revision of the manuscript; DCZ contributed to writing the manuscript. WYL and JWZ contributed to the statistical analysis of the data and preparing the article; JST, WYX and XLQ contributed to the data collection; All authors contributed to critical revision of the article and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Guangdong Provincial Hospital of Chinese Medicine.

Availability of data and materials

All authors had full access to all the data in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

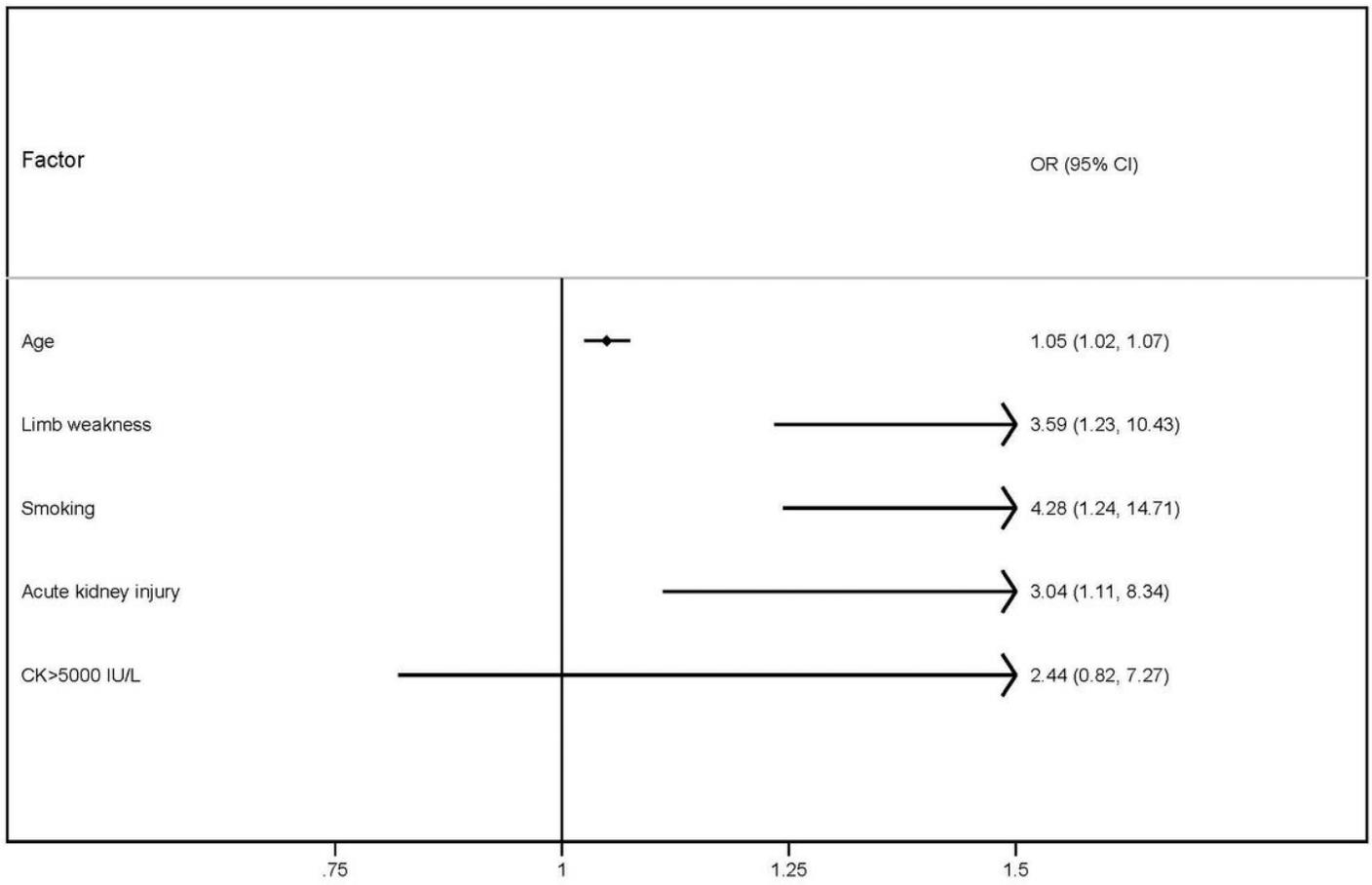


Figure 1

Risk factors for predicting ICU transfer

Supplementary Files

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