RHABDOMYOLYSIS IS ASSOCIATED WITH IN-HOSPITAL MORTALITY IN PATIENTS WITH COVID-19

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ABSTRACT—**Purpose:** Rhabdomyolysis (RM) has been associated with many viral infectious diseases, and associated with poor outcomes. We aim to evaluate the clinical features and outcomes of RM in patients with coronavirus disease 2019 (COVID-19). **Method:** This was a single-center, retrospective, cohort study of 1,014 consecutive hospitalized patients with confirmed COVID-19 at the Huoshenshan Hospital in Wuhan, China, between February 17 and April 12, 2020. **Results:** The overall incidence of RM was 2.2%. Compared with patients without RM, those with RM tended to have a higher risk of deterioration. Patients with RM also constituted a greater percentage of patients admitted to the intensive care unit (90.9% vs. 5.3%, $P < 0.001$) and a greater percentage of patients undergoing mechanical ventilation (86.4% vs. 2.7% $P < 0.001$). Moreover, patients with RM had laboratory test abnormalities, including the presence of markers of inflammation, activation of coagulation, and kidney injury. Patients with RM also had a higher risk of in-hospital death ($P < 0.001$). Cox's proportional hazard regression model analysis confirmed that RM indicators, including peak creatine kinase levels > 1,000 IU/L (HR = 6.46, 95% CI: 3.02–13.86) and peak serum myoglobin concentrations > 1,000 ng/mL (HR = 9.85, 95% CI: 5.04–19.28), were independent risk factors for in-hospital death. Additionally, patients with COVID-19 that developed RM tended to have delayed viral clearance. **Conclusion:** RM might be an important contributing factor to adverse outcomes in COVID-19 patients. The early detection and effective intervention of RM may help reduce mortality among COVID-19 patients.

KEYWORDS—COVID-19, in-hospital death, rhabdomyolysis, skeletal muscle

ABBREVIATIONS—AKI—acute kidney injury; ANOVA—analysis of variance; ARDS—acute respiratory distress syndrome; AUC—area under the curve; BNP—B-brain natriuretic peptide; CK—creatine kinase; CK-MB—serum creatine kinase cardiac isoenzyme; COVID-19—coronavirus disease 2019; CRP—C-reactive protein; CysC—cystatin c; HR—hazard rate; ICU—intensive care unit; IL-6—interleukin 6; KDIGO—Kidney Disease Improving Global Outcomes; MYO—myoglobin; RM—rhabdomyolysis; SARS—severe acute respiratory syndrome; SARS-CoV-2—severe acute respiratory coronavirus 2; Scr—serum creatinine; SD—standard deviation; SKM—skeletal muscle; UCRP—ultra-sensitivity CRP

Take-home message

Rhabdomyolysis may be an important complication of COVID-19, and was correlated with adverse outcomes among COVID-19 patients.

INTRODUCTION

Although acute respiratory distress syndrome remains the leading cause of adverse outcomes for coronavirus disease 2019 (COVID-19) patients, the contribution of dysfunction

in other organs is largely unknown (1–4). Several studies have demonstrated that severe acute respiratory coronavirus 2 (SARS-CoV-2) RNA can enter the blood and accumulate in organs other than the lung, resulting in damage (5). Several recent reports have described patients with COVID-19 that developed rhabdomyolysis (RM) during hospitalization (6–13). Furthermore, an analysis of the autopsies on 26 COVID-19 patients found pigmented casts associated with high serum creatine kinase (CK) levels in three of the patients, which might be indicative of RM (14). Although the above findings suggested that RM may be an important complication of COVID-19, there are still insufficient cases to allow a comprehensive understanding of the clinic features and outcomes of RM in patients with COVID-19.

Therefore, we conducted this large cohort study of COVID-19 patients in a major designated COVID-19 hospital in Wuhan, China. We aimed to determine the prevalence of RM among patients with COVID-19 and investigate the association between RM-related indicators and in-hospital death in patients infected with COVID-19.

METHODS

Participants

A total of 1,014 COVID-19 patients admitted to Huoshenshan Hospital from February 17, 2020 to April 12, 2020 were enrolled in our study. All the patients were followed up until in-hospital death or discharge from hospital after recovery. Huoshenshan Hospital was one of the major hospitals designated specifically for COVID-19 patients in Wuhan, Hubei Province, China.

COVID-19 was diagnosed according to the guidance issued by the Chinese National Health Commission. Patients with recent evidence of myocardial infarction or stroke were excluded. The clinical outcomes (i.e., discharge, mortality, and length of hospital stay) were monitored.

Ethical approval to conduct this study was obtained from the Huoshenshan Hospital. As the collected data formed part of the infectious disease outbreak investigation, individual informed consent was waived.

Data sources

All the medical data of the enrolled in-patients were extracted from the electronic medical records. Laboratory data consisted of complete blood count; liver and renal function; serum CK, serum creatine kinase cardiac isoenzyme (CK-MB), myoglobin (MYO), C-reactive protein (CRP), ultrasensitivity CRP (UCRP), procalcitonin, lactate dehydrogenase, B-brain natriuretic peptide, and cystatin c (CysC) levels; coagulation function; and erythrocyte sedimentation rate. Serum interleukin (IL)-6 concentrations were measured by ELISA. Throat swab specimens were collected for SARS-CoV-2 nucleic acid measurement. Owing to the limited laboratory capacity, the upper limits of detection for CK and MYO, two classical markers of skeletal muscle (SKM) injury, were 1,000 IU/L and 3,000 ng/mL, respectively. All the data were reviewed by a trained team of physicians.

Diagnosis of SKM injury

SKM injury can be divided into mild SKM injury and RM. Mild SKM injury was defined as a serum CK value one to five times above the upper limit of normal (reference 24 IU/L–170 IU/L) and with a CK-MB concentration comprising less than 5% of the total CK level. RM was defined as a serum CK value five times higher than the upper limit of normal and with a serum CK-MB concentration comprising less than 5% of the total CK level (15).

Definition

The date of COVID-19 onset was defined as the day when the first symptom was noticed. Disease severity was staged according to the guidelines for the diagnosis and treatment of COVID-19 (seventh edition) published by the Chinese National Health Commission on March 3, 2020. A mild case was defined based on mild clinical symptoms and no sign of pneumonia in imaging. A moderate case was defined based on the presence of fever and respiratory

symptoms, and with signs of pneumonia in imaging. A severe case was defined based on a respiratory rate >30 breaths/min, oxygen saturation ≤93%, or a PaO$_2$/FiO$_2$ ratio ≤300 mm Hg. A critical severe case was defined based on the inclusion of one of the following criteria: shock; respiratory failure requiring mechanical ventilation; combined with the other organ failure admission to intensive care unit (ICU). According to the WHO ordinal scale for the severity of COVID-19, a mild case corresponded to a WHO score of 2; a moderate case to a WHO score of 3; a severe case to WHO scores of 4 to 5; and a critical severe case to WHO scores of 6 to 8. Acute kidney injury (AKI) was defined as an increase of ≥26.5 μmol/L in serum creatinine (Scr) levels within 48 h or a ≥50% increase in Scr levels from baseline within 7 days according to Kidney Disease: Improving Global Outcomes criteria (16). Prolonged viral RNA shedding was defined as disease duration over 15 days without SARS-CoV-2 RNA clearance (17).

Statistical analysis

Categorical variables were summarized as frequency and percentages, and continuous variables were expressed as means ± standard deviation (SD). Analysis of variance was used for continuous variables, and chi-square or Fisher exact tests were used for categorical variables as appropriate. The candidate risk factors included age, sex, COVID-19 severity, and laboratory data. Cumulative rates of in-hospital death were determined using the Kaplan–Meier method. The risk factors and corresponding hazard rates were calculated using Cox's proportional hazard regression model. Statistical analyses were performed using R software (version 3.5.1) with statistical significance set at two-sided $P < 0.05$.

RESULTS

Baseline clinical features

The average age of the 1,014 patients was 58.7 ± 14.85 years (range: 16–100), and 527 (51.97%) of the patients were males. The average time from COVID-19 onset to hospital admission was 21.6 ± 13.04 days (range: 1–63) (Additional Table 1, http://links.lww.com/SHK/B206). A total of 463 (45.7%) patients had at least one comorbidity. Hypertension (352 [43.7%]), diabetes (125 [12.3%]), cardiovascular disease (108 [10.7%]), and cerebrovascular disease (48 [4.7%]) were the most common coexisting conditions. Fever (706 [69.7%]), dry cough (637 [62.8%]), fatigue (590 [58.2%]), and myalgia (289 [28.5%]) were the most common symptoms at the onset of COVID-19 (Additional Table 1, http://links.lww.com/SHK/B206).

Incidence and characteristics of SKM injury

Among the 1,014 cases, 40 (3.9%) developed mild SKM injury (Table 1), while RM was documented in 22 (2.2%) of the patients. In most of these cases (18/22 [81.8%]), RM developed after hospital admission, and the mean interval between hospital admission and RM occurrence was 7.91 ± 7.44 days (Additional Figure 1, http://links.lww.com/SHK/B207). During hospitalization, the incidence of critical severe COVID-19 cases (WHO score 6–8) among patients with RM or mild SKM injury was significantly higher than that in patients without SKM injury (90.9% and 30.0% vs. 5.3%, respectively; $P < 0.001$) (Table 1). Compared with patients without SKM injury, a greater percentage of patients with RM were admitted to the ICU (90.9% [20/22] vs. 5.3% [50/952]; $P < 0.001$) and underwent mechanical ventilation (86.4% [19/22] vs. 2.7% [26/952]; $P < 0.001$). Patients with SKM injury tended to be older males with a greater number of underlying diseases, who also had a shorter time from COVID-19 onset to hospital admission ($P < 0.05$) (Additional Table 1, http://links.lww.com/SHK/B206).

TABLE 1. **Clinic characteristics and outcomes of patients with COVID-19 during hospitalization**

Variables	All patients (n = 1,014)	Non SKM injury (n = 952)	Mild SKM injury (n = 40)	RM (n = 22)	P value
Peak creatinine kinase > 1,000 IU/L, %	11 (1.25)	0 (0.00)	0 (0.00)	11 (50.00)	0.000
Peak serum myoglobin					
1,000–3,000 ng/mL, %	8 (1.97)	0 (0.00)	1 (2.50)	7 (31.82)	0.000
> 3,000 ng/mL, %	7 (1.72)	0 (0.00)	1 (2.50)	6 (27.3)	0.000
Peak NLR	5.46 ± 11.87	4.96 ± 8.94	16.53 ± 20.57	39.93 ± 24.85	0.000
Platelet count < 100 × 10^9/L, %	72 (8.05)	48 (5.75)	9 (24.32)	15 (68.18)	0.000
Nadir Hemoglobin, g/L	117.25 ± 26.06	118.59 ± 25.23	99.25 ± 35.60	95.05 ± 18.06	0.000
Prothrombin time > 14.5 s, %	128 (16)	93 (12.53)	17 (44.74)	18 (90.00)	0.000
Peak activated partial thromboplastin time > 42 s, %	21 (2.63)	14 (1.89)	2 (5.26)	5 (25.00)	0.000
Peak prothrombin time, s	13.64 ± 2.92	13.39 ± 2.56	15.12 ± 3.65	20.12 ± 5.18	0.000
Peak activated partial thromboplastin time, s	29.70 ± 9.61	29.08 ± 7.36	31.81 ± 10.84	48.67 ± 33.81	0.000
Nadir fibrinogen, g/L	2.91 ± 0.67	2.93 ± 0.65	2.69 ± 0.86	2.33 ± 0.82	0.000
Peak D-dimer > 1.5 mg/L, %	104 (12.98)	80 (10.72)	9 (25.71)	15 (75.00)	0.000
Peak C-reactive protein, mg/L	27.40 ± 54.51	21.97 (46.26)	70.38 ± 80.68	158.71 ± 85.06	0.000
High-sensitivity C-reactive protein ≥ 10 mg/L, %	180 (25.39)	153 (22.94)	13 (52.00)	14 (82.35)	0.000
Peak interleukin 6, pg/mL	85.48 ± 467.17	50.52 ± 290	317.26 ± 739.27	1130.48 ± 2051.64	0.000
Peak alanine aminotransferase, U/L	45.56 ± 73.84	41.70 ± 63.14	73.59 ± 140.30	151.60 ± 167.29	0.000
Peak aspartate aminotransferase, U/L	37.84 ± 70.34	31.57 ± 50.32	89.02 ± 165.33	198.95 ± 179.97	0.000
Peak total bilirubin, mmol/L	13.05 ± 24.22	11.64 ± 8.23	34.79 ± 109.63	31.16 ± 26.83	0.000
Peak lactose dehydrogenase, U/L	237.16 ± 156.56	217.38 ± 118.31	376.79 ± 245.03	718.46 ± 272.14	0.000
Peak serum potassium > 5.5 mmol/L	41 (4.58)	27 (3.23)	6 (15.79)	8 (36.36)	0.000
Acute kidney injury, %	48 (4.73)	26 (2.7)	5 (12.50)	17 (77.27)	0.000
Peak body temperature, °C	37.06 ± 0.56	37.01 ± 0.49	37.59 ± 0.90	37.98 ± 1.12	0.000
Peak pulse rate, /min	95.70 ± 13.28	94.99 ± 12.20	99.05 ± 17.05	120.18 ± 23.23	0.000
Prolonged viral RNA shedding, %	84 (8.48)	69 (7.13)	6 (15.00)	9 (40.91)	0.000
Drug use					
Disoprofol	52 (5.1)	26 (2.6)	18 (45.0)	8 (36.4)	0.000
Glucocorticoid	512 (50.5)	468 (47.2)	29 (72.5)	15 (68.2)	0.000
Nondepolarizing muscle relaxant	49 (4.8)	23 (2.3)	16 (40.0)	10 (45.5)	0.000
Midazolam	56 (5.5)	24 (2.4)	21 (52.5)	11 (50.0)	0.000
Omeprazole	291 (28.7)	259 (26.1)	19 (47.5)	13 (59.1)	0.000
Degree of COVID-19					
Mild	31 (3.1)	30 (3.2)	1 (2.5)	0 (0.0)	1
Moderate	666 (65.7)	652 (68.5)	13 (32.5)	1 (4.5)	0.000
Severe	235 (23.2)	220 (23.1)	14 (35.0)	1 (4.5)	0.000
Critical severe	82 (8.1)	50 (5.3)	12 (30.0)	20 (90.9)	0.000
Administration of mechanical ventilation	53 (5.2)	26 (2.7)	8 (20)	19 (86.4)	0.000
Admission to intensive care unit	122 (12.03)	88 (9.2)	14 (35)	20 (90.9)	0.000
In-hospital death	60 (5.92)	30 (3.2)	10 (25.00)	20 (90.91)	0.000

Data are presented as number (percentage) or mean ± SD. The severity was staged based on the guidelines for diagnosis and treatment of COVID-19 (trial seventh edition) published by the Chinese National Health Commission on March 3, 2020. Mild SKM injury was defined as the serum creatinine kinase value elevated to the level between one to five times over the upper limit of normal, with serum creatine kinase cardiac isoenzymes lower than 5% of the creatinine kinase level. RM was defined as an increase serum creatinine kinase higher than five times the upper limit of normal, with serum creatine kinase cardiac isoenzymes lower than 5% of the creatine kinase level. Prolonged viral RNA shedding was defined as disease duration over 15 days without SARS-CoV-2 RNA clearance. Acute kidney injury was defined as an increase in serum creatinine by 26.5 μmol/L within 48 h or a 50% increase in serum creatinine from the baseline within 7 days according to the Kidney. Peak value of variables represented highest value during hospitalization. Nadir value of variables represented lowest value during hospitalization.
COVID-19 indicates coronavirus disease 2019; NLR, neutrophil-to-lymphocyte ratio; RM, rhabdomyolysis; SKM, skeletal muscle.

Analysis of laboratory data revealed that differences between patients with SKM injury and those without were mainly associated with indicators of inflammation, cell damage, coagulation, and kidney function. Compared with patients without SKM injury at admission, patients with SKM injury had significantly higher baseline levels of UCRP (≥4 mg/L), CK, MYO, procalcitonin, CRP, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), Scr, URN, and CysC; a significantly higher baseline leukocyte count and neutrophil-to-lymphocyte ratio; and a lower baseline lymphocyte count (Table 2). During hospitalization, the gap between the peak (or nadir) and baseline values of the above parameters was substantially greater among patients with SKM injury, particularly those with RM (Table 1). Notably, patients who developed RM displayed more than 22-fold higher serum levels of IL-6 compared with patients without SKM injury, and nearly two-fold higher levels than patients with mild SKM injury. Patients with SKM injury were more likely to present with abnormal coagulation function, including prolonged prothrombin time and activated partial thromboplastin time, lower fibrinogen levels and platelet counts, and higher D-dimer levels (Table 2), and these effects were more pronounced after RM occurrence (Table 1). The extent of inflammation, coagulation dysfunction, and kidney injury correlated with the degree of SKM injury (Additional Table 2, http://links.lww.com/SHK/B206). Moreover, the incidence of AKI in patients with RM

TABLE 2. **Baseline laboratory data of patients with COVID-19**

Variables	All patients (n = 1,014)	Non-SKM injury (n = 952)	Mild SKM injury (n = 40)	RM (n = 22)	P value
Leukocyte count, × 10⁹/L	6.51 ± 3.44	6.48 ± 3.39	6.15 ± 2.38	9.22 ± 6.42	0.014
Lymphocyte count, × 10⁹/L	1.49 ± 0.68	1.53 ± 0.66	0.96 ± 0.64	0.59 ± 0.46	0.000
NLR, %	4.48 ± 6.91	3.85 ± 5.09	9.76 ± 13.77	19.10 ± 19.88	0.000
Hemoglobin, g/L	114.29 ± 37.58	115.99 ± 37.11	93.29 ± 45.15	111.67 ± 21.60	0.054
Platelet count, × 10⁹/L	226.22 ± 82.26	229.01 ± 80.04	205.21 ± 114.37	151.53 ± 61.87	0.001
Prothrombin time, s	13.20 ± 2.20	13.12 ± 2.13	13.56 ± 1.29	16.54 ± 4.75	0.000
Activated partial thromboplastin time, s	28.56 ± 5.87	28.24 ± 4.26	30.42 ± 4.77	43.57 ± 31.65	0.000
Fibrinogen, g/L	3.06 ± 0.73	3.06 ± 0.72	3.28 ± 0.78	2.79 ± 0.88	0.186
D-dimer, mg/L	1.14 ± 3.12	1.05 ± 3.04	1.87 ± 2.91	5.50 ± 5.47	0.000
Procalcitonin, ng/mL	0.12 ± 0.64	0.08 ± 0.16	0.12 ± 0.10	4.09 ± 6.14	0.000
High-sensitivity C-reactive protein					0.000
< 4 mg/L, %	311 (43.86)	308 (46.18)	2 (8)	1 (5.88)	0.000
4 mg/L−10 mg/L, %	67 (9.45)	67 (10.04)	0 (0)	0 (0)	/
≥10 mg/L, %	101 (14.25)	86 (12.89)	7 (28)	8 (47.06)	0.000
C-reactive protein, mg/L	16.27 ± 36.22	14.12 ± 33.35	40.28 ± 51.00	79.31 ± 66.21	0.000
Interleukin 6, pg/mL	12.17 ± 37.24	11.93 ± 37.54	22.34 ± 19.06	27.50 ± 19.17	0.759
Alanine aminotransferase, U/L	30.77 ± 33.32	30.67 ± 33.84	32.70 ± 24.61	31.52 ± 25.98	0.949
Aspartate aminotransferase, U/L	25.10 ± 19.53	23.97 ± 17.60	38.04 ± 26.59	49.75 ± 47.16	0.000
Total bilirubin, mmol/L	11.20 ± 8.58	10.86 ± 6.85	13.69 ± 14.53	22.53 ± 32.33	0.000
Lactose dehydrogenase, U/L	206.89 ± 95.31	198.39 ± 86.79	279.39 ± 103.46	403.44 ± 134.04	0.000
Serum creatinine, μmol/L	73.86 ± 73.10	72.18 ± 72.61	87.86 ± 53.75	115.59 ± 108.48	0.043
Serum urea nitrogen, mmol/L	5.32 ± 3.59	5.10 ± 3.29	6.89 ± 4.85	10.33 ± 6.45	0.000
Cystatin C, mg/L	1.04 ± 0.47	1.012 ± 0.44	1.36 ± 0.63	1.46 ± 0.88	0.000
Sodium, mmol/L	141.67 ± 3.48	141.81 ± 3.29	139.30	140.06 ± 7.20	0.000
Potassium, mmol/L	4.27 ± 0.51	4.27 ± 0.50	4.34 ± 0.77	4.21 ± 0.39	0.743
Creatinine kinase, IU/L	77.53 ± 95.14	61.40 ± 37.41	245.75 ± 92.91	357.41 ± 377.64	0.000
Serum myoglobin, ng/mL	24.90 ± 70.80	17.48 ± 51.85	145.35 ± 188.61	124.27 ± 121.91	0.000

Data are presented as number (percentage) or mean ± SD. Mild SKM injury was defined as the serum creatinine kinase value elevated to the level between one to five times over the upper limit of normal, with serum creatine kinase cardiac isoenzymes lower than 5% of the creatinine kinase level. RM was defined as an increase serum creatinine kinase higher than five times the upper limit of normal, with serum creatine kinase cardiac isoenzymes lower than 5% of the creatine kinase level. Baseline value of variables represented value at the admission.
COVID-19 indicates coronavirus disease 2019; NLR, neutrophil-to-lymphocyte ratio; RM, rhabdomyolysis; SKM, skeletal muscle.

was significantly higher than that in patients without SKM injury (77.27% [17/22] vs. 2.7% [26/952]; $P < 0.001$) (Table 1).

Etiology of SKM injury in COVID-19 patients

Table 1 and Additional Table 3, http://links.lww.com/SHK/B206 show the use of possible myotoxic drugs in patients with COVID-19. None of the RM patients in this study had used antipsychotics or statins during hospitalization. The ratios of the use of glucocorticoids, disoprofol, nondepolarizing muscle relaxant, midazolam, and omeprazole among patients with SKM injury were all significantly higher than those in patients without SKM injury ($P < 0.001$). However, considering that all these drugs were commonly administered in the ICU, we especially compared the use of these drugs between critically ill COVID-19 patients (WHO score 6–8) with SKM injury and those without SKM injury. As shown in Additional Table 4, http://links.lww.com/SHK/B206, no significant difference was observed in the use of glucocorticoids, disoprofol, nondepolarizing muscle relaxant, midazolam, or omeprazole between the two sets of patients. Additionally, two of the RM patients had not taken any of the above drugs before RM occurrence (Additional Table 3, http://links.lww.com/SHK/B206). The analysis of the pattern of viral shedding also revealed that, compared with patients without SKM injury, those with RM tended to have delayed SARS-CoV-2 clearance (40.91% [9/22] vs. 7.13% [69/968]; $P < 0.001$) (Table 3).

RM was associated with in-hospital death among COVID-19 patients

Sixty in-hospital deaths occurred among the 1,014 patients. There was a significantly higher mortality rate among patients with RM (90.9%, 20/22) than among those without RM (3.2%, 30/952) (Table 1). Kaplan−Meier analysis revealed a significantly higher in-hospital death rate among patients with SKM injury, including those with higher peak serum CK and MYO levels, and those with hyperkalemia and RM ($P < 0.001$) (Fig. 1). Univariate Cox regression analysis showed that age > 65 years, being male, and having comorbidity were significantly associated with in-hospital death. Additionally, the RM markers (i.e., CK and MYO) mentioned above were also associated with in-hospital death (Table 1). After adjusting for age, sex, and comorbidity, RM and the following parameters were all associated with in-hospital death: peak CK > 1,000 IU/L, peak serum MYO > 1,000 ng/mL, peak leukocyte count > 10×10^9/L, trough lymphocyte count < 1.1×10^9/L, trough platelet count < 100×10^9/L, peak prothrombin time > 14.5 s, peak activated partial thromboplastin time > 42 s, peak fibrinogen < 2 g/L, peak CRP ≥10 mg/L, peak high-sensitivity CRP ≥10 mg/L, peak AST > 100 U/L, and acute kidney injury (Fig. 2).

We further determined the value of using age, sex, comorbidity, and RM for predicting death among COVID-19 patients. As shown in Figure 3, the area under the curve (AUC) of the

TABLE 3. **Univariate Cox regression analysis of association between RM indicators and in-hospital death in patients with COVID-19**

Variables	HRs	95% CI		P value
Age, years				
< 40	Reference			
40−65	3.07	0.40	23.22	> 0.05
> 65	11.83	1.63	86.07	< 0.05
Sex				
Female	Reference			
Male	2.33	1.33	4.09	< 0.01
Comorbidities	3.38	1.85	6.19	< 0.001
Peak leukocyte count > 10.0×10^9/L	24.15	13.12	44.44	< 0.001
Nadir lymphocyte count < 1.1×10^9/L	27.30	10.89	68.40	< 0.001
Peak creatinine kinase > 1,000 IU/L	11.99	5.80	24.78	< 0.001
Peak serum myoglobin > 1,000 ng/mL	18.25	9.85	33.83	< 0.001
Nadir platelet count < 100×10^9/L, %	1.65	0.87	3.13	> 0.05
Peak prothrombin time > 14.5 s	14.75	2.04	106.87	< 0.01
Peak activated partial thromboplastin time > 42 s	19.85	11.14	35.39	< 0.001
Nadir fibrinogen < 2 g/L	0.40	0.23	0.69	< 0.001
Peak C-reactive protein ≥ 10 mg/L	27.19	9.80	75.45	< 0.001
Peak high-sensitivity C-reactive protein ≥ 10 mg/L	15.19	6.70	34.43	< 0.001
Peak aspartate aminotransferase > 100 U/L	17.35	10.17	29.60	< 0.001
Acute kidney injury	26.03	15.54	43.57	< 0.001
Group				
Non SKM injury	Reference			
Mild SKM injury	11.03	5.36	22.71	< 0.001
RM	35.84	20.16	63.73	< 0.001
Prolonged viral RNA shedding, %	9.67	5.45	17.17	< 0.001

Mild SKM injury was defined as the serum creatinine kinase value elevated to the level between one and five times over the upper limit of normal, with serum creatine kinase cardiac isoenzymes lower than 5% of the creatinine kinase level. RM was defined as an increase serum creatinine kinase higher than five times the upper limit of normal, with serum creatine kinase cardiac isoenzymes lower than 5% of the creatine kinase level. Prolonged viral RNA shedding was defined as disease duration over 15 days without SARS-CoV-2 RNA clearance. Acute kidney injury was defined as an increase in serum creatinine by 26.5 μmol/L within 48 h or a 50% increase in serum creatinine from the baseline within 7 days according to the Kidney. Peak value of variables represented highest value during hospitalization. Nadir value of variables represented lowest value during hospitalization.
COVID-19 indicates coronavirus disease 2019; RM, rhabdomyolysis; SKM, skeletal muscle.
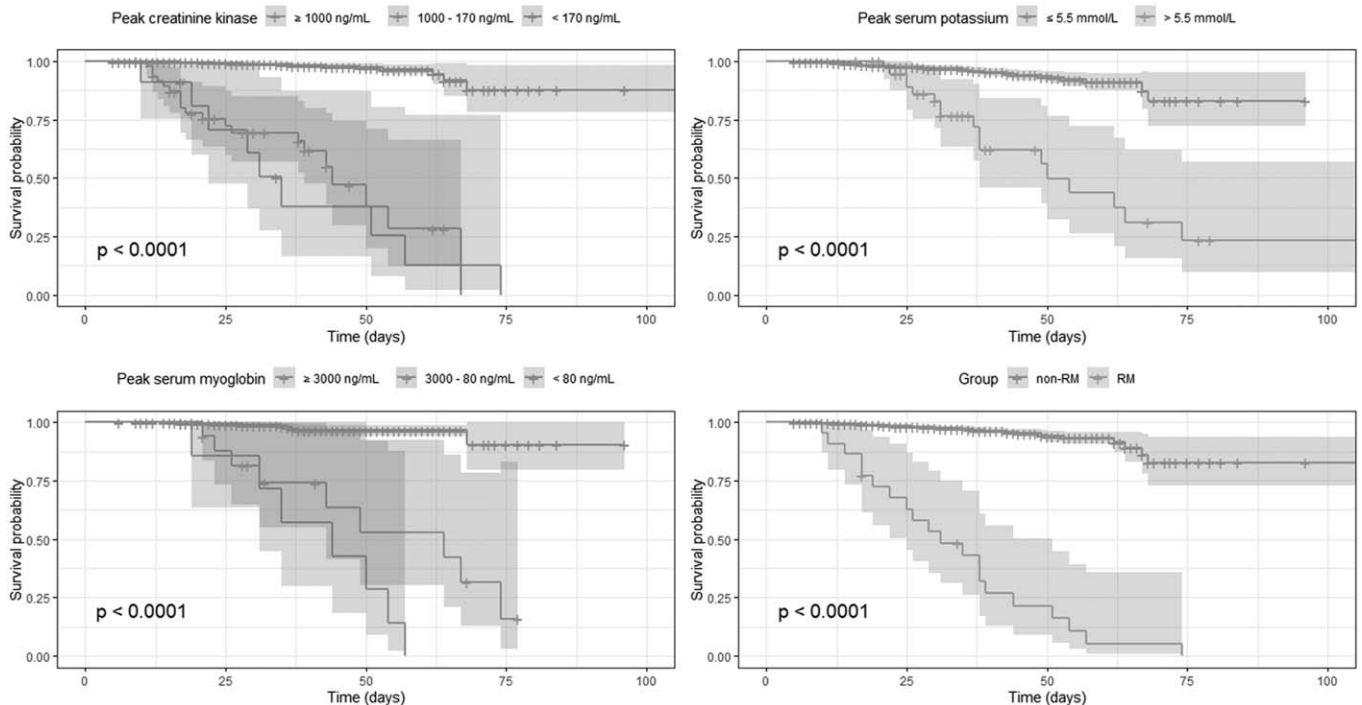
FIG. 1.   **The cumulative incidence of in-hospital deaths among patients with coronavirus disease 2019 subgrouped by skeletal muscle (SKM) injury indicators.** Shadows indicate the 95% confidence intervals of the corresponding estimates, as follows: peak serum creatine kinase, peak serum potassium, peak serum myoglobin, and rhabdomyolysis (RM). RM was defined as an increase in serum creatinine kinase concentrations greater than five times the upper limit of normal, with the serum creatine kinase cardiac isoenzyme concentration comprising less than 5% of the total creatine kinase level.

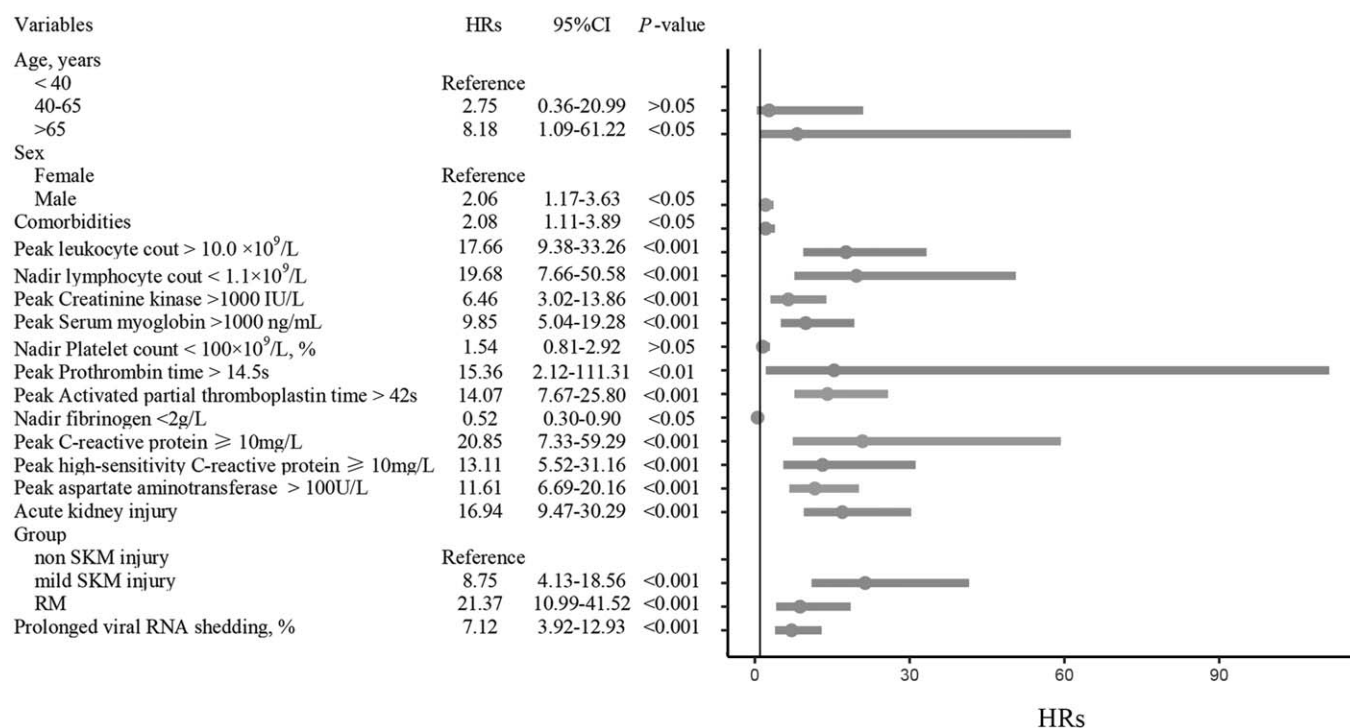| Variables	HRs	95%CI	P-value
Age, years			
< 40	Reference		
40-65	2.75	0.36-20.99	>0.05
>65	8.18	1.09-61.22	<0.05
Sex			
Female	Reference		
Male	2.06	1.17-3.63	<0.05
Comorbidities	2.08	1.11-3.89	<0.05
Peak leukocyte cout > 10.0 ×10^9/L	17.66	9.38-33.26	<0.001
Nadir lymphocyte cout < 1.1×10^9/L	19.68	7.66-50.58	<0.001
Peak Creatinine kinase >1000 IU/L	6.46	3.02-13.86	<0.001
Peak Serum myoglobin >1000 ng/mL	9.85	5.04-19.28	<0.001
Nadir Platelet count < 100×10^9/L, %	1.54	0.81-2.92	>0.05
Peak Prothrombin time > 14.5s	15.36	2.12-111.31	<0.01
Peak Activated partial thromboplastin time > 42s	14.07	7.67-25.80	<0.001
Nadir fibrinogen <2g/L	0.52	0.30-0.90	<0.05
Peak C-reactive protein ≥ 10mg/L	20.85	7.33-59.29	<0.001
Peak high-sensitivity C-reactive protein ≥ 10mg/L	13.11	5.52-31.16	<0.001
Peak aspartate aminotransferase > 100U/L	11.61	6.69-20.16	<0.001
Acute kidney injury	16.94	9.47-30.29	<0.001
Group			
non SKM injury	Reference		
mild SKM injury	8.75	4.13-18.56	<0.001
RM	21.37	10.99-41.52	<0.001
Prolonged viral RNA shedding, %	7.12	3.92-12.93	<0.001

Fig. 2. **The association between rhabdomyolysis (RM) and in-hospital death in patients with coronavirus disease 2019 (COVID-19).** The hazard ratio (HR) for each variable was obtained using separate Cox proportional hazards models after adjusting for age, sex, and any comorbidity. The severity was staged based on the guidelines for diagnosis and treatment of COVID-19 (trial seventh edition) published by the Chinese National Health Commission on March 3, 2020. Mild skeletal muscle (SKM) injury was defined as a serum creatinine kinase value one to five-fold greater than the upper limit of normal, and a serum creatine kinase cardiac isoenzyme level comprising less than 5% of the total creatinine kinase level. RM was defined as an increase in serum creatinine kinase levels greater than five times the upper limit of normal, and a serum creatine kinase cardiac isoenzyme level comprising less than 5% of the total creatine kinase level. Prolonged viral RNA shedding was defined as disease duration over 15 days without SARS-CoV-2 RNA clearance. Acute kidney injury was defined as an increase of ≥26.5 μmol/L in serum creatinine levels within 48 h or a ≥50% increase in serum creatinine levels from baseline within 7 days according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Comorbidities include hypertension, cardiovascular disease, diabetes, malignancy, cerebrovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, and HIV infection. CI indicates confidence interval.

predictive model was 0.787 (95% CI: 0.731−0.843) with a sensitivity of 73.3% and a specificity of 74.7%. After adding RM diagnosis to the model, the AUC rose to 0.867 (95% CI: 0.817−0.917), with a higher sensitivity of 85.7% and a higher specificity of 75.0%.

DISCUSSION

In the present study, we report the prevalence and clinic features of RM in hospitalized COVID-19 patients. Importantly, we found that the occurrence of RM was associated with a markedly higher in-hospital mortality rate, which has not been previously reported.

RM is a potentially lethal syndrome characterized by the breakdown of damaged muscle. Myocyte injury leads to release of intracellular contents including MYO, Scr, potassium, CK, and other muscle enzymes such as aminotransferases and LDH (18). Other laboratory features include rapidly rising serum potassium or Scr, hyperuricemia, hypo- or hypercalcemia, hyperphosphatemia, metabolic (lactic) acidosis, thrombocytopenia, and disseminated intravascular coagulation. Although determination of CK concentration in serum is the basis for the early diagnosis of rhabdomyolysis, the existence of these cocommodities may help the diagnosis of rhabdomyolysis (18). In our cohort, the incidence and extent of AKI and

coagulation dysfunction were significantly higher in patients with RM than in those without RM. Coagulation dysfunction and kidney injury have been demonstrated to be key prognostic factors for the deterioration of COVID-19 patients (5). Of note, in our study, patients with RM exhibited a marked increase in serum IL-6 concentrations. IL-6, one of the so-called myokines, can be released in large quantities when SKM is damaged (19, 20), and is known to be correlated with the deterioration of COVID-19 patients (21).

The occurrence of RM has been linked with several viruses, including influenza A virus subtype H1N1 and SARS-CoV-1 (15, 22−28). Several studies have reported that some patients with severe acute respiratory syndrome (SARS) or H1N1 infection display mild to moderate increases in serum CK concentrations (15, 22−28). Furthermore, a literature review involving 300 cases indicated that approximately 3% of patients with influenza developed RM (29), while a case series of 30 patients with SARS-CoV-1-associated pneumonia showed that 10% of them had RM (22). SARS patients with RM are also at high risk of renal failure and death (22−24). Regarding musculoskeletal complications, fatigue and myalgia are common symptoms among COVID-19 patients (5, 19, 30−32). Nevertheless, there are relatively few reports to date of COVID-19 complicated with RM (6−14). One study reported that 138 patients with COVID-19 who were admitted to ICU
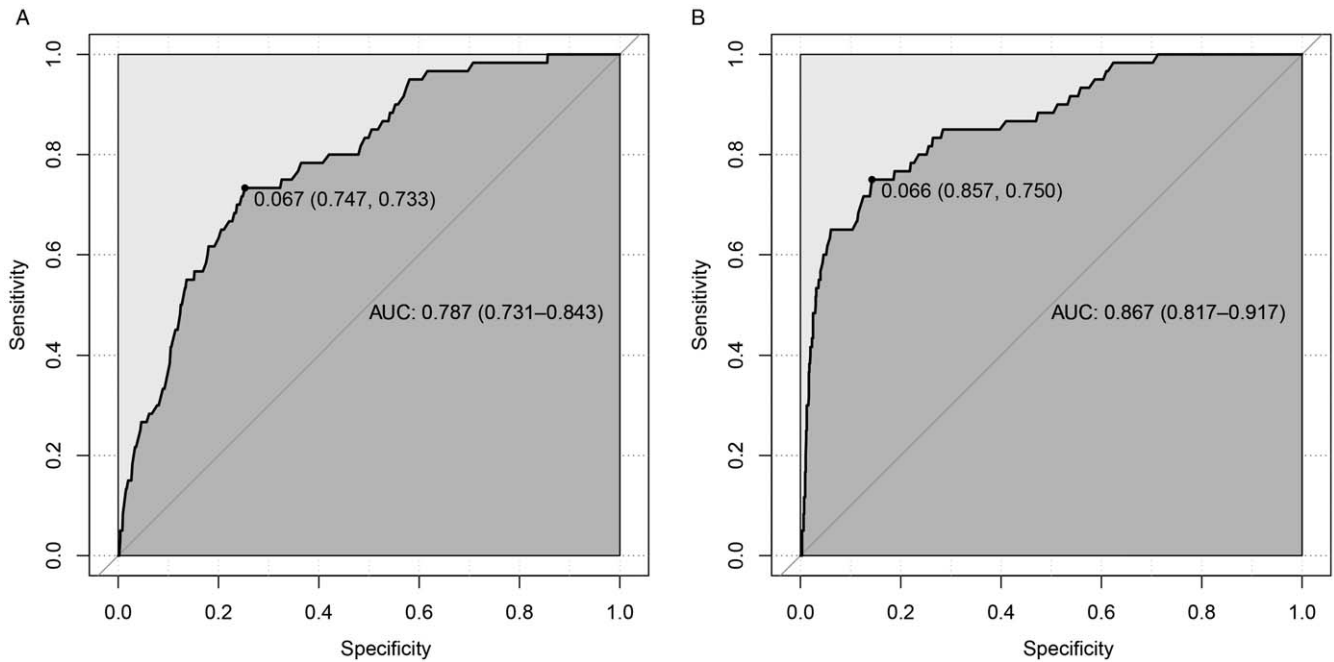
FIG. 3.   **Receiver operating characteristics (ROC) curves were generated to determine the value of predicting death by age, sex, and comorbidity (A) and age, sex, comorbidity, and RM occurrence (B).**

showed a tendency toward increased CK levels (32). In agreement with this observation, a large prospective cohort study involving 710 patients with COVID-19 revealed that those patients who presented with kidney injury also tended to have increased CK levels (2). In our cohort, there was a substantial increase in the incidence of RM after admission. Approximately 72.7% of the patients with RM displayed only mildly elevated (i.e., < 5 times the upper limit) or normal serum CK levels at admission, and most of them developed RM during hospitalization. This indicates that monitoring serum CK and MYO concentrations should be emphasized, even for patients who display only mild symptoms and normal serum CK and MYO values at admission. This is especially true for aged male patients with comorbidities.

In our cohort, patients with RM tended to have a higher risk of progressing to critical severe COVID-19 (WHO score 6–8), characterized by a higher rate of admission to the ICU and a requirement for mechanical ventilation. Exacerbation to a critical severe case is an important clinical endpoint of COVID-19. The risk factors for progression to critical severe COVID-19 included age, gender, and underlying disease (5, 19, 31, 32). Our results highlighted that indicators of RM (i.e., CK and MYO levels) were associated with a significantly higher risk of in-hospital death, even after adjusting for potential confounders. Compared with the AUC value associated with predicting death by age, sex, and underlying disease, adding RM diagnosis to the predictive model increased the AUC value, as well as the sensitivity and specificity. The larger the AUC value, the better the predictive value of the model, suggesting that RM diagnosis may be an important predictor for adverse outcomes.

The etiology of SKM injury involvement in patients with COVID-19 remains uncertain. First, the use of myotoxic drugs

was reported to be the second most common cause of RM (15, 18). Most of the patients with RM in this study had been treated with glucocorticoids, disoprofol, midazolam, and vecuronium, all of which are potential myotoxic drugs (15, 20–22). However, no significant difference in the use of the above drugs was observed between critical severe COVID-19 (WHO score 6–8) patients with or without RM. Moreover, two patients with RM had not used any of the above drugs before RM occurrence. These observations suggest that myotoxic drugs may not be the main cause of RM pathogenesis in COVID-19 patients. Second, in a study on postviral myositis, viral, and viral-like particles were detected using electron microscopy (33). Our data indicated that patients with SKM injury tended to have delayed SARS-CoV-2 clearance, and none of the patients with SKM injury had underlying SKM disease, suggesting that SARS-CoV-2 infection may exert direct cytopathic effects on SKM tissue. However, direct evidence that SARS-CoV-2 directly invades skeletal muscle cells is still lacking.

Early recognition and prompt treatment remain the most efficient approaches for treating RM. Treatment includes addressing the underlying etiology and avoiding myotoxic drugs, as well as aggressive intravenous hydration with a goal urine output of 300 mL/h, urine alkalization, and renal replacement therapy, when necessary. In one case report of a COVID-19 patient with RM who was admitted to ICU, the patient did not develop renal failure owing to early RM diagnosis and aggressive intravenous fluid treatment, and the patient survived (6). This suggests that RM indicators (i.e., CK and MYO levels) should be closely monitored in COVID-19 patients, especially those who display one or more risk factors for RM.

Our study had several limitations. First, due to the limited laboratory capacity, there were constraints regarding the upper limits of detection for both CK and MYO concentrations.

Consequently, we could not track the precise linear changes occurring with these two indicators. Second, although we attempted to adjust for relevant confounders, unmeasured or unknown confounders may have biased the results.

CONCLUSION

In conclusion, the diagnosis of RM might be important for predicting adverse outcomes in COVID-19 patients. Clinicians should increase their awareness of RM in hospitalized COVID-19 patients. The early detection and effective intervention of RM involvement may help to reduce the number of deaths among patients with COVID-19.

ACKNOWLEDGMENTS

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