Rhabdomyolysis is Associated with Hospital Mortality in Patients with COVID-19

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Abstract

Purpose: To evaluate the clinical features and outcomes of rhabdomyolysis (RM) in patients with COVID-19.

Method: 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%. Comparing with patients without RM, patients with RM tended to have a higher risk of deterioration, representing by higher ratio to be admitted to the intensive care unit (ICU) (90.9 % vs 5.3%, $P<0.001$), and to undergo mechanical ventilation (86.4 % vs 2.7% $P<0.001$). Compared with patients without RM, patients with RM had laboratory test abnormalities, including indicators of inflammation, coagulation activation and kidney injury. Patients with RM had a higher risk of hospital death ($P<0.001$). Cox proportional hazard regression model confirmed that RM indicators, including peak creatine kinase (CK) >1000 IU/L (HR=6.46, 95% CI: 3.02-13.86), peak serum myoglobin (MYO) >1000 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 a delayed virus clearance.

Conclusion: RM might be an important factor contributing to adverse outcomes of patients with COVID-19. Early detection and effective intervention of RM may help reduce deaths of patients with COVID-19.

Introduction

Although acute respiratory distress syndrome (ARDS) was the leading cause of adverse outcome of coronavirus disease 2019 (COVID-19) patients, the contribution of other organs dysfunction had remained largely unknown (1, 2). Some studies have demonstrated that COVID-19 RNA could enter the blood, accumulate in other organs, and result in damages (3). Recently, a few case reports described patients with COVID-19 that developed rhabdomyolysis (RM) during hospitalization (4–11). Furthermore, an analysis of autopsies on 26 patients with COVID-19 revealed that pigmented casts associated with high serum CK levels could be found in 3 patients, which might represent RM (12). Although the above findings indicated that RM maybe an important complication of COVID-19, the present studies still lacking enough cases to comprehensively understand the clinic features and outcomes of RM in patients with COVID-19.

We thus conducted this large cohort study of COVID-19 patients in a major designated hospital for COVID-19 infection in Wuhan, China. We aimed to determine the prevalence of RM among patients with COVID-19 and to 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 to April 12, 2020 were enrolled in our cohort, all the patients were followed up till in-hospital death or being discharged from the hospital after recovery. Huoshenshan Hospital was one of the major designated hospitals specifically against COVID-19 infection in Wuhan, Hubei Province.

All the patients were diagnosed as COVID-19 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., discharges, mortality, and length of hospital stay) were monitored.

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

Data Sources

All of the medical data of inpatients enrolled in this hospital were extracted from the electronic medical records. Laboratory data consisted of complete blood count, liver and renal function, serum creatine kinase (CK), serum creatine kinase cardiac isoenzymes (CK-MB), myoglobin (MYO), coagulation function, C-reactive protein (CRP), ultra-sensitivity CRP (UCRP), procalcitonin, erythrocyte sedimentation rate, lactate dehydrogenase, B-brain natriuretic peptide (BNP) and cystatin c (CysC). Serum interleukin 6 (IL-6) concentration was detected by ELISA assay. Throat swab specimens were collected for severe acute respiratory coronavirus 2 (SARS-CoV-2) nucleic acid measurement. Due to the limited laboratory capacity, the detection upper limits of CK and MYO, two classical indicators of skeletal muscle (SKM) injury, were 1000 IU/L and 3000 ng/mL, respectively. All of 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 the serum CK value elevated to the level between 1–5 times over the upper limit of normal (reference 24–170 IU/L), with CK-MB lower than 5% of the CK level. RM was defined as an increase serum CK higher than 5 times the upper limit of normal, with serum CK-MB lower than 5% of the CK level (13).

Definition

The date of COVID-19 onset was defined as the day when the symptom was noticed. Severity of the disease was staged according to the guidelines for diagnosis and treatment of COVID-19 (the seventh edition) published by Chinese National Health Commission on March 3, 2020. Mild case was defined as: (i) mild clinical symptoms, and (ii) without signs of pneumonia in imaging. Moderate case was defined as: (i) has fever and respiratory symptoms, and (ii) with signs of pneumonia in imaging. Severe case was defined as either: (i) respiratory rate $> 30/\text{min}$, or (ii) oxygen saturation $\leq 93\%$, or (iii) $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 300 mmHg. Critical severe case was defined as including one criterion as follow: shock; respiratory failure requiring mechanical ventilation; combined with the other organ failure admission to intensive care unit

(ICU). In corresponding to WHO ordinal scale for the severity of COVID-19, mild case equal to 2 WHO score; moderate case equal to 3 WHO score; severe case equal to 4 to 5 WHO scores; critical severe case equal to 6 to 8 WHO scores. Acute kidney injury (AKI) was defined as an increase in serum creatinine (Scr) by 26.5 $\mu\text{mol/L}$ within 48 hours or a 50% increase in Scr from the baseline within 7 days according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (14). Prolonged viral RNA shedding was defined as disease duration over 15 days without SARS-CoV-2 RNA clearance (15).

Statistical Analysis

Categorical variables were summarized as frequency and percentages, and continuous variables were expressed as the mean $\pm$ standard deviation (SD). Analysis of variance (ANOVA) was used for continuous variables, and Chi-square tests or Fisher's exact tests were used for categorical variables as appropriate. The candidate risk factors included age, sex, severity of COVID-19, and laboratory data. Cumulative rates of in-hospital death were determined using the Kaplan–Meier method. The risk factors and corresponding hazard rates (HRs) were calculated using the Cox proportional hazard regression model. Statistical analyses were performed using R software (version 3.5.1) with statistical significance set at 2-sided $P < 0.05$.

Results

Baseline clinical features

Of the 1,014 patients, the average age was 58.7 ± 14.85 (range: 16–100) years, and 527 (51.97%) were males. The average time span from COVID-19 onset to hospital admission was 21.6 ± 13.04 (range: 1–63) days (see additional table file [Additional file 1]). 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 (see additional table file [Additional file 1]).

Incidence and characteristics of SKM injury

Among the 1,014 cases, 40 (3.9%) developed mild SKM injury (Table 1), and RM was documented in 22 (22/1,014 [2.2%]) patients. In most cases, RM occurred after hospital admission (18/22 [81.8%]), the mean interval between hospital admission and RM occurrence was 7.91 ± 7.44 days (see additional figure file [Additional file 6]). During hospitalization, the incidence of critical severe cases (WHO score 6–8) in patients with RM or mild SKM injury was significantly higher than that in non SKM injury patients (90.9% or 30.0% vs 5.3%, respectively, $P < 0.001$) (Table 1). In comparison with non SKM injury patients, patients with RM had a higher ratio to be admitted to the ICU (90.9% [20/22] vs 5.3% [50/952], $P < 0.001$), and to undergo mechanical ventilation (86.4% [19/22] vs 2.7% [26/952], $P < 0.001$). Patients with SKM injury tended to be males, older, have more underlying diseases, and have a shorter time span from COVID-19 onset to hospital admission ($P < 0.05$) (see additional table file [Additional file 1]).

Table 1
Clinic characteristics and outcomes of patients with COVID-19 during hospitalization

variables	all patients (n = 1014)	non SKM injury (n = 952)	mild SKM injury (n = 40)	RM (n = 22)	P-value
Peak creatinine kinase > 1000 IU/L, %	11 (1.25)	0 (0.00)	0 (0.00)	11 (50.00)	0.000
Peak serum myoglobin					
1000–3000 ng/mL, %	8 (1.97)	0 (0.00)	1 (2.50)	7 (31.82)	0.000
>3000 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

variables	all patients (n = 1014)	non SKM injury (n = 952)	mild SKM injury (n = 40)	RM (n = 22)	P-value
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

variables	all patients (n = 1014)	non SKM injury (n = 952)	mild SKM injury (n = 40)	RM (n = 22)	P-value
COVID-19, coronavirus disease 2019; SKM, skeletal muscle; RM, rhabdomyolysis; NLR, neutrophil-to-lymphocyte ratio.					
Data are presented as number (percentage) or mean $\pm$ 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 1–5 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 5 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.					

As per laboratory data revealed, the difference between patients with SKM injury and those without mainly focus on inflammation, cell damage, coagulation and kidney function indicators. Compared with patients without SKM injury at the admission, patients with SKM injury had significantly higher baseline percentage of UCRP ≥ 4 mg/L, higher baseline level of CK, MYO, leukocyte count, neutrophil-to-lymphocyte ratio (NLR), procalcitonin, CRP, aspartate aminotransferase (AST), lactose dehydrogenase (LDH), Scr, URN, CysC, and had lower baseline lymphocyte count (see additional table file [Additional file 2]). During hospitalization, the gap between peak (or nadir) and baseline value of the above parameters was much greater among patients with SKM injury, particularly in patients with RM (Table 1). Of notes, the elevated level of serum IL-6 was more pronounced after RM occurrence, with more than 22 times over patients without SKM injury, and nearly 2 times over patients with mild SKM injury. The abnormal coagulation function, including prolonged prothrombin time, activated partial thromboplastin time, lower fibrinogen and platelet count, and higher D-dimer, were more likely to present in patients with SKM injury (see additional table file [Additional file 2]), and were more pronounced after the occurrence of RM (Table 1). The extent of inflammation, coagulation dysfunction and kidney injury correlated with the degree of SKM injury in patients with SKM injury (see additional table file [Additional file 3]). Moreover, the incidence of AKI in patients with RM 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 file (Additional file 4) show the use of possible myotoxic drugs in patients with COVID-19. None of the patients with RM in this study had used antipsychotics or statins during hospitalization. The ratio of the use of glucocorticoid, disoprofol, nondepolarizing muscle relaxant, midazolam and omeprazole in patients with SKM injury were all significantly higher than that in non SKM injury patients ($P < 0.001$). However, considering that all these drugs were common medicines in ICU, we specially compared the use of these drugs in critical ill patients (WHO score 6–8) with SKM injury and critical ill patients without SKM injury. As shown in additional table file (Additional file 5), no significant difference was observed in the use of glucocorticoid, disoprofol, nondepolarizing muscle relaxant,

midazolam and omeprazole drugs between critical ill patients with SKM injury and patients without. In addition, two of the RM patients didn't have use any of the above drugs before RM occurrence (see additional table file [Additional file 4]). Besides, the analysis of the pattern of viral shedding revealed that, compared with non SKM injury patients, patients with RM tended to have a delayed SARS-CoV-2 virus clearance (40.91% [9/22] *vs* 7.13% [69/968], $P < 0.001$) (Table 2).

Table 2
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 > $10.0 \times 10^9/L$	24.15	13.12	44.44	< 0.001
Nadir lymphocyte count < $1.1 \times 10^9/L$	27.30	10.89	68.40	< 0.001
Peak Creatinine kinase > 1000 IU/L	11.99	5.80	24.78	< 0.001
Peak Serum myoglobin > 1000 ng/mL	18.25	9.85	33.83	< 0.001
Nadir Platelet count < $100 \times 10^9/L$, %	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

Variables	HRs	95%CI	P-value
<p>COVID-19, coronavirus disease 2019; SKM, skeletal muscle; RM, rhabdomyolysis.</p> <p>Mild SKM injury was defined as the serum creatinine kinase value elevated to the level between 1–5 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 5 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 $\mu\text{mol/L}$ within 48 hours or a 50% increase in serum creatinine from the baseline within 7 days according to the Kidney.</p>			

RM associated with in-hospital death of COVID-19 patients

Out of the 1,014 patients, 60 in-hospital deaths were observed. We observed a significantly higher fatality rate among patients with RM (90.9%, 20/22) than those without (3.2%, 30/952) (Table 1). Kaplan-Meier analysis revealed a significantly higher in-hospital death rate for patients with SKM injury, including peak serum CK, MYO, hyperkalemia and RM ($P < 0.001$) (Fig. 1). Univariate Cox regression analysis showed that older than 65 years, male and commodity were significantly associated with in-hospital death. In addition, the RM indicators mentioned above were also associated with in-hospital death (Table 1). After adjusted for age, sex, and commodity, RM and the following were all associated with in-hospital death: peak CK > 1000 IU/L, peak serum MYO > 1000 ng/mL, peak leukocyte count $> 10.0 \times 10^9/\text{L}$, bottom lymphocyte count $< 1.1 \times 10^9/\text{L}$, bottom platelet count $< 100 \times 10^9/\text{L}$, peak prothrombin time > 14.5 s, peak activated partial thromboplastin time > 42 s, nadir fibrinogen < 2 g/L, peak C-reactive protein ≥ 10 mg/L, peak high-sensitivity C-reactive protein ≥ 10 mg/L, peak AST > 100 U/L, and acute kidney injury (Fig. 2).

We further used age, sex, comorbidity and RM to determine the value of the predicting death of patients with COVID-19. As shown in Fig. 3, the area under the curve (AUC) of the predicting model was 0.787 (95% CI: 0.731, 0.843) with the sensitivity of 73.3% and the specificity of 74.7%. After adding the diagnosis of RM in the predicting model, the AUC rise to 0.867 (95% CI: 0.817, 0.917) with a higher sensitivity of 85.7% and a higher specificity of 75.0%.

Discussion

The present study reports the prevalence and clinic features of RM in hospitalized patients with COVID-19. More importantly, the presence of RM was associated with a strikingly higher in-hospital mortality rate, which has not been reported previously.

RM is a potentially lethal syndrome, which is defined by the breakdown of damaged muscle and release of intracellular muscle content, including MYO, CK, LDH, and electrolytes (16). The disease progresses from asymptomatic with mild CK elevation to a life-threatening condition with renal failure, severe electrolyte derangements, and disseminated intravascular coagulation (DIC) (16). In this cohort, the

incidences and extents of AKI and coagulation dysfunction in patients with RM were significantly higher than those in patients without RM. Coagulation dysfunction and kidney injury were all had been demonstrated to be the key prognostic factors for deterioration of patients with COVID-19 (5). Of notes, patient with RM exhibited an extraordinary elevation of serum IL-6 concentration in our study. As one of the so calls myokines, IL-6 can be released in large quantities when SKM is damaged (30, 31). It had been well documented that IL-6 correlated with the deterioration of patients with COVID-19 (32).

The occurrence of RM has been linked with a few viruses, including influenza A virus subtype H1N1 and SARS-CoV-1 (13, 17–23). As per reports, some of the patients with severe acute respiratory syndrome (SARS) or H1N1 had mild to moderate elevations of serum CK (13, 17–23). Approximately 3% of patients with influenza developed RM per literature review of 300 cases (24). A case series of 30 patients with SARS-CoV-1 pneumonia showed 10% had RM (17). SARS patients with RM had a high risk of renal failure and death (17–19). Regarding musculoskeletal complications, fatigue and myalgia were common symptoms (3, 25–28), but COVID-19 complicated with RM has only rarely been reported so far (4–12). In fact, 138 patients with COVID-19, who were admitted to ICU, showed a tendency toward increased CK levels (27). In keeping with this observation, an large prospective cohort study for 710 patients with COVID-19 has revealed that the patients with kidney injury tended to have increased CK levels as well (2). In this cohort, we observed a substantial increase in the incidence of RM after admission. About 72.7% patients with RM only had mild elevated (i.e., with $< 5 \times$ upper limit) or normal test results of serum CK at admission, and most of them developed RM during hospitalization. Thus, monitoring serum CK and MYO should be emphasized even in patients only have mild symptoms and normal serum CK and MYO at admission, especially for the patients that were aged male, and with comorbidities.

In this cohort, patients with RM tend to have a higher risk of progressing to critical severe COVID-19 (WHO score 6–8), representing by higher ratio to be admitted to the ICU, and to undergo mechanical ventilation. Exacerbation to critical severe case is an important clinical end point of COVID-19. In previous studies, the risk factors of critical severe COVID-19 included age, gender, and underlying disease (3, 26–28). This report highlights the indicators of RM (i.e. CK and MYO) were associated with a significantly higher odds of in-hospital death even after adjustment for potential confounders. Comparing with the AUC value of the predicting death by age, sex and underlying disease, adding the diagnosis of RM in the predicting model exhibited higher AUC value, as well as higher sensitivity and specificity. The larger the AUC value, the better the predictive value of the model, thus, the diagnosis of RM might be important for predicting the adverse outcomes.

The etiology of SKM injury involvement in patients with COVID-19 remain uncertain. First, myotoxic drugs usage was the second most common cause of RM (13, 16). Most of patients with RM in this study had accepted treatments of glucocorticoids, disoprofol, midazolam, and vecuronium, which were all potential myotoxic drugs (13, 17, 29, 30). However, no significantly 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, there were 2 patients with RM that didn't use any of the above drugs before RM occurrence. Thus, myotoxic drugs may not be the main cause of the pathogenesis of RM in patients with COVID-19. Second, Viral and

viral-like particles have been described on electron microscopy in the study of postviral myositis (31). According to our data, patients with SKM injury tend to have a delayed SARS-CoV-2 virus clearance, and none of patients with SKM injury had underlying SKM disease, suggesting that SARS-CoV-2 infection may exert direct cytopathic effects on SKM tissue. However, there still lacking of direct evidence for the invasion of SARS-CoV-2 to skeletal muscle cell.

Early recognition, and thus began prompt treatment is the efficient approach against RM. Treatment includes addressing the underlying etiology, avoidance of 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 for an ICU admitting patient with COVID-19 that developed RM, owing to early diagnose of RM and aggressive intravenous fluids treatment, the patient didn't develop renal failure, and finally survived from COVID-19 (4). Thus, it is suggested to closely monitor RM indicators (i.e., CK and MYO) in patients with COVID-19, especially for the patients that had one or more risk factors for RM.

This study has several limitations. First, due to the limitation of the laboratory capacity, there were the detection upper limits existed in both of the CK and MYO indicators. Thus, we could not track the precise linear change of these two indicators. Second, although we attempted to adjust for many confounders, other unmeasured or unknown confounders might have played a role.

Conclusion

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

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 isoenzymes; coronavirus disease 2019, COVID-19; 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.

Declarations

Take-home message

Rhabdomyolysis maybe an important complication of COVID-19, which correlated with the adverse outcomes of the patients with COVID-19.

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Conflicts of interest

All the authors declared no competing interests.

Ethics approval

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

Consent to participate and publication

All authors reviewed and approved the final version.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and material

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Authors' contributions

YG, Y D, NP and TY collected the clinical data. SZ and HL processed statistical data. YG drafted the manuscript. FW, QM, HL and LS revised the final manuscript. All authors contributed to data acquisition, data analysis, or data interpretation.

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Figures

Figure 1

Cumulative incidence for in-hospital death of patients with coronavirus disease 2019 subgrouped by skeletal muscle (SKM) injury indicators. Shadows indicate the 95% confidence intervals of the corresponding estimates: (a) peak serum creatine kinase, (b) peak serum potassium, (c) peak serum myoglobin, (d) rhabdomyolysis (RM). RM was defined as an increase serum creatinine kinase higher than 5 times the upper limit of normal, with serum creatine kinase cardiac isoenzymes lower than 5% of the creatine kinase level.

Figure 2

Association of RM with in-hospital death in patients with coronavirus disease 2019 (COVID-19). Hazard ratios (HRs) of each variable were obtained using separate proportional hazard Cox models after adjustment 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 SKM injury was defined as the serum creatinine kinase value elevated to the level between 1-5 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 5 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 μ mol/L within 48 hours or a 50% increase in serum creatinine from the baseline within 7 days according to the Kidney. Comorbidities include hypertension, cardiovascular disease, diabetes, malignancy, cerebrovascular disease, COPD, chronic kidney disease, chronic liver disease, and HIV infection. 95% CI, 95% confidence interval.

Figure 3

Receiver operating characteristics (ROC) curves were conducted to determine the value of the predicting death by age, sex and comorbidity (A) and age, sex, comorbidity and RM (B).

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