Prevalence and Predictive Factors of Rhabdomyolysis in COVID-19 Patients: A Cross-sectional Study

Abstract

Introduction: The aim of the present prospective observational study was to demonstrate the prevalence and predictive factors of rhabdomyolysis in coronavirus disease 2019 (COVID-19) patients. **Methods:** The study was performed on reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed COVID-19 patients admitted to the emergency department between March 2020 and March 2021. Peak creatinine phosphokinase (CPK) levels were used to define rhabdomyolysis. A CPK level equal to or more than 1000 IU/L was defined as the presence of moderate to severe rhabdomyolysis. We developed a COVID-19–related Rhabdomyolysis Prognostic rule (CORP rule) using the independent predictors of rhabdomyolysis in COVID-19 patients. **Results:** Five hundred and six confirmed COVID-19 patients (mean age 58.36 ± 17.83 years, 56.32% male) were studied. Rhabdomyolysis occurred in 44 (8.69%) cases throughout their hospitalization. Male gender (odds ratio [OR] = 2.78, 95% confidence interval [CI]: 1.28, 6.00), hyponatremia (OR = 2.46, 95% CI: 1.08, 5.59), myalgia (OR = 3.04, 95% CI: 1.41, 6.61), D-dimer >1000 (OR = 2.84, 95% CI: 1.27, 6.37), and elevated aspartate aminotransferase level (three times higher than normal range) (OR = 3.14, 95% CI: 1.52, 6.47) were the significant preliminary predictors of rhabdomyolysis. The area under the curve of the CORP rule was 0.75 (95% CI: 0.69, 0.81), indicating the fair performance of it in the prognosis of rhabdomyolysis following COVID-19 infection. The best cutoff of the CORP rule was 3, which had a sensitivity of 72.9% and a specificity of 72.7%. **Conclusion:** This prospective study showed that 8.69% of patients developed rhabdomyolysis following COVID-19 infection. The CORP rule with optimal cutoff can correctly classify 72.8% of COVID-19 patients at risk of developing rhabdomyolysis.

Keywords: COVID-19, prediction, rhabdomyolysis, risk factor

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Introduction

As we enter the third year of the coronavirus disease 2019 (COVID-19) pandemic, severe acute respiratory syndrome coronavirus 2 (SAR CoV 2) still poses major health problems worldwide. Considering the growing fully vaccinated population and the development of improved patient management protocols, researchers have shifted their attention from the management of the acute respiratory symptoms to other complications of the disease.[1-3] Recent studies indicate that these multiorgan and/or extrapulmonary complications are associated with a significantly higher risk of mortality.[4-6]

Rhabdomyolysis is caused by muscle necrosis and the subsequent dissolution of intracellular components into the bloodstream.[7] Although rhabdomyolysis is most often caused by direct injuries to the muscles, compartment syndrome, exertion or prolonged immobilization, the condition can also be the result of infections. Association of rhabdomyolysis with viral infections such as influenza A, influenza B, human immunodeficiency virus (HIV), and herpes has been previously demonstrated.[8,9] The severity of the condition varies from an asymptomatic illness to a severe condition involving life-threatening elevation in serum creatinine, disseminated intravascular coagulation, and renal failure.[10]

The SARS-CoV-2 that is responsible for COVID-19 has also been reported to cause rhabdomyolysis.[11] Although it was previously reported that rhabdomyolysis mostly occurred in severe cases of COVID-19 patients with older age and

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comorbidities (e.g., cardiovascular disease), there are recent reports of rhabdomyolysis developing in younger patients with less-severe forms of COVID-19.[12-14] Therefore, the present prospective observational study aimed to demonstrate the prevalence and predictive factors of rhabdomyolysis in COVID-19 patients.

Materials and Methods

The present observational study was performed on patients who were admitted to the emergency department (ED) of Shohadaye Tajrish Hospital in Tehran, Iran, between March 2020 and March 2021. The study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (ethics code: IR.SBMU.MSP.REC.1400.099), and the researchers adhered to the principles of the Helsinki Convention.

Patients confirmed with COIVD-19 and an established creatinine phosphokinase (CPK) level upon admission to the ED were included in this study. The diagnosis of COVID-19 was made with a positive reverse transcriptase-polymerase chain reaction (RT-PCR) for SAR-CoV-2 from a nasopharyngeal specimen and/or pulmonary complications identified by computed tomography scan. Patients without a CPK level, pregnant women, polytraumatic cases, and bedridden patients before the diagnosis of COVID-19 were all excluded.

Demographic data (age and gender), patients' symptoms (cough, dyspnea, myalgia, headache, chest pain), vital signs, venous blood gas parameters, hematologic and blood biochemistry parameters, and data on urine analysis were collected from patients' profile using a predesigned checklist. Peak CPK levels were used to define rhabdomyolysis. Like our previous study, a CPK level equal to or more than 1000 IU/L was defined as the presence of moderate to severe rhabdomyolysis. An emergency medicine resident under the direct supervision of an emergency medicine specialist was responsible for data gathering.

We examined normality assumption by checking kurtosis, skewness, box plot, and Q–Q plot. *t*-Test and Mann–Whitney U test were used for comparisons of continuous variables in alive and dead patients. Apart from evaluating the association between categorical variables, the Chi-square test and Fisher's exact test were used. In addition, a multivariate logistic regression model was performed for investigating the independent predictive factors of COVID-19–related rhabdomyolysis. The findings were reported as odds ratio (OR) and 95% confidence interval (95% CI). *P* value less than 0.05 was considered statistically significant. We developed a prognostic rule using the independent predictors of rhabdomyolysis in COVID-19 patients. Accordingly, each independent variable received a score equal to 1. The receiver operating characteristic (ROC) curve, sensitivity, specificity, and likelihood ratio were calculated to assess the prognostic performance of the rule. All analyses were done using the STATA 14.0 statistical software.

Results

Five hundred and six confirmed COVID-19 patients with a mean age of 58.36 ± 17.83 years were studied (56.32% male). The demographic characteristics and laboratory findings of studied cases at baseline are presented in Tables 1 and 2, respectively. Rhabdomyolysis occurred in 44 (8.69%) cases throughout their hospitalization. The mean age of rhabdomyolysis cases was 58.58 ± 17.78 years compared to 56.11 ± 18.36 years of non-rhabdomyolysis cases (*P* = 0.3816). Patients with rhabdomyolysis were significantly more likely to be male (75.0% vs. 54.55%, *P* = 0.009).

Dyspnea was found to be significantly more prevalent in the rhabdomyolysis group (63.42% vs. 47.62%, *P* = 0.043). Additionally, patients with rhabdomyolysis had significantly lower mean systolic blood pressure than patients without rhabdomyolysis (112.88 ± 21.26 vs. 120.16 ± 18.04 mmHg, *P* = 0.013).

The analysis of laboratory data during hospitalization revealed that venous blood bicarbonate levels were higher in patients with rhabdomyolysis (28.44 ± 32.56 vs. 24.17 ± 4.78, *P* = 0.013), which was probably due to adding bicarbonate to the intravenous (IV) solutions for urine alkalization in rhabdomyolysis cases. Also, the mean platelet count was significantly lower in rhabdomyolysis cases (177.83 ± 65.75 vs. 208.86 ± 92.38, *P* = 0.036). A significant difference was also observed between the groups regarding blood urea nitrogen (BUN; *P* = 0.0002), aspartate transaminase (AST; *P* = 0.0001), alanine transaminase (ALT; *P* = 0.0009), Na (*P* = 0.013), and D-dimer (*P* = 0.033), which is presented in Table 2.

Independent predictors of rhabdomyolysis

Applying a multivariate logistic regression model and utilizing a univariate analysis revealed that male gender (OR = 2.78, 95% CI: 1.28, 6.00), hyponatremia (OR = 2.46, 95% CI: 1.08, 5.59), myalgia (OR = 3.04, 95% CI: 1.41, 6.61),
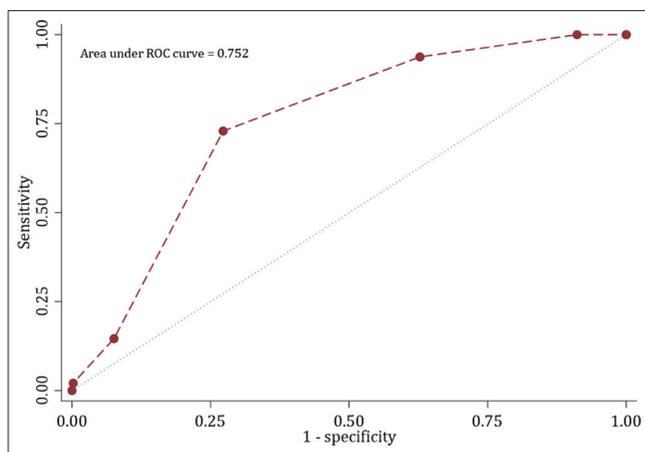
D-dimer >1000 (OR = 2.84, 95% CI: 1.27, 6.37), and elevated AST level (three times higher than the normal range) (OR = 3.14, 95% CI: 1.52, 6.47) were the significant preliminary predictors of rhabdomyolysis [Table 3].

A prognostic rule was developed using the independent predictors of rhabdomyolysis in COVID-19 patients. The COVID-19–related Rhabdomyolysis Prognostic rule (CORP rule) score ranged from zero to 5, indicating the lowest risk to the highest risk of developing rhabdomyolysis following COVID-19 infection. The area under the curve of the CORP rule was 0.75 (95% CI: 0.69, 0.81), indicating its fair performance in the prognosis of rhabdomyolysis following COVID-19 infections [Figure 1]. The best cutoff of the CORP rule was 3, with a sensitivity of 72.9% and a specificity of 72.7% [Table 4]. In this cutoff, there were 336 true-negative, 35 true-positive, 126 false-positive, and 13 false-negative cases. The CORP rule is presented in Figure 2.

Discussion

We found evidence of rhabdomyolysis in 8.69% of patients following COVID-19 infection. Male gender, hyponatremia, myalgia, elevated D-dimer, and elevated AST levels were independent predictive factors of rhabdomyolysis.

Rhabdomyolysis is a condition in which there is injury or death to muscle cells, which results in the release of cellular components into the bloodstream.[15] In addition to the symptoms caused by the general reaction of tissue death, muscle cells contain specific components like myoglobin which can lead to rhabdomyolysis. Myoglobulin is toxic to the kidneys and its association with acute kidney injury is well known.[16] COVID-19 can injure the muscle cells by direct invasion in conjunction with a wide spectrum of pulmonary and extrapulmonary manifestations such as rhabdomyolysis with hypovolemia, fever, acidosis, bacterial superinfection, and so on.[17-19] For instance, COVID-19 can cause excessive fluid depletion due to fever, gastrointestinal loss, tachypnea, possible cardiovascular injuries, and decreased intake of fluids.[20,21] The following hypovolemia could be a cause of damage to the muscle tissue. Additionally, the drop in arterial oxygen saturation in severe forms of COVID-19 is also another contributing factor to muscle injury secondary to tissue hypoxia. Moreover, COVID-19 can cause coagulopathies with elevated D-dimer

Table 1: Baseline characteristics of included COVID-19 patients

Variable	Rhabdomyolysis		Total (*n*=506)	*P*
	No (*n*=462)	Yes (*n*=44)		
Age (years)				
Mean±SD	58.58±17.78	56.11±18.36	58.36±17.83	0.3816
Gender				
Male	252 (54.55)	33 (75)	285 (56.32)	0.009
Female	210 (45.45)	11 (25)	221 (43.68)	
Symptoms				
Fever	39 (51.73)	20 (47.62)	259 (51.39)	0.610
Cough	233 (50.54)	17 (39.53)	250 (49.60)	0.167
Dyspnea	293 (63.42)	20 (47.62)	313 (62.10)	0.043
Myalgia	90 (19.48)	13 (30.23)	103 (20.40)	0.094
Headache	42 (9.09)	5 (11.63)	47 (9.31)	0.584
Chest pain	58 (12.55)	4 (9.3)	62 (12.28)	0.534
Vital signs				
SBP (mmHg)	120.16±18.04	112.88±21.26	119.53±18.42	0.013
DBP (mmHg)	74.78±11.98	72.83±12.83	74.62±12.06	0.311
MAP (mmHg)	89.91±12.78	86.18±14.48	89.59±12.96	0.072
PR (/min)	86.67±14.40	88±14.79	86.79±14.43	0.565
RR (/min)	18.66±4.16	18.84±3.8	18.68±4.12	0.791
T (°C)	37.13±0.69	37.18±0.65	37.13±0.69	0.658
O_2sat (%)				
Mean±SD	69.76±24.39	64.24±24.27	69.29±24.40	0.166
≥95	76 (16.45)	13 (27.08)	89 (17.45)	0.004
90–95	94 (20.35)	0 (0.00)	94 (18.43)	
85–89.9	35 (7.58)	5 (10.42)	40 (7.84)	
<85	257 (5.63)	30 (62.50)	287 (56.27)	

COVID-19=coronavirus disease 2019, DBP=diastolic blood pressure, MAP=mean arterial pressure, O_2sat=O_2 saturation, PR=pulse rate, RR=respiratory rate, SBP=systolic blood pressure, SD=standard deviation, T=body temperature. Data are presented as mean±SD or frequency (%)

Figure 1: Area under the ROC curve of the CORP rule in the classification of high-risk COVID-19 patients for rhabdomyolysis CORP rule = coronavirus disease 2019-related Rhabdomyolysis Prognostic rule, COVID-19 = coronavirus disease 2019, ROC = receiver operating characteristic.

The COVID-19-related Rhabdomyolysis Prognostic rule (CORP rule)*

Male gender	No (0)	Yes (+1)
Hyponatremia	No (0)	Yes (+1)
Myalgia	No (0)	Yes (+1)
D-dimer > 1000 (ng/mL)	No (0)	Yes (+1)
Abnormal AST (3 times higher than normal)	No (0)	Yes (+1)

*If any of the criteria are present, the patient can be stratified as a high-risk patient for developing rhabdomyolysis.

Figure 2: The COVID-19 related Rhabdomyolysis Prognostic rule (CORP rule). AST=aspartate transaminase.

Table 2: Baseline laboratory findings of included COVID-19 patients

Variables	Rhabdomyolysis		Total (*n*=506)	*P*
	No (*n*=462)	Yes (*n*=44)		
Venus blood gas analysis				
pH	7.343±0.063	7.338±0.077	7.343±0.064	0.602
PCO_2 (mmHg)	45.58±10.13	45.42±12.46	45.57±10.33	0.921
PO_2 (mmHg)	36.75±30.73	39.63±25.39	36.99±30.30	0.560
HCO_3 (mmol/L)	24.17±4.78	28.44±32.56	24.53±10.51	0.013
Complete blood counts				
WBC (×10⁹ cells/L)	8.35±4.93	9.06±5.48	8.41±4.97	0.380
PMN (%)	79.36±29.67	79.66±10.70	79.38±28.59	0.419
Lymph (%)	19.39±10.58	18.19±9.97	19.29±10.52	0.487
Hb (g/dL)	12.25±2.82	11.88±2.42	12.22±2.79	0.419
Platelets (×10³/L)	208.86±92.38	177.83±65.75	206.33±90.85	0.036
Coagulation profile				
PT (s)	13.76±1.77	13.95±1.76	13.77±1.77	0.547
PTT (s)	37.26±10.81	37.12±8.71	37±10.64	0.941
INR	1.10±0.24	1.14±0.24	1.10±0.24	0.322
Urine analysis				
RBC	22 (7.24)	3 (13.64)	25 (7.67)	0.276
Other parameters				
CRP (mg/L)	28.01±25.85	27.13±25.92	27.95±25.92	0.855
BUN (mg/dL)	26.61±22.27	42.63±52.86	27.94±26.48	0.0002
Creatinine (mg/dL)	1.91±9.21	1.60±1.25	1.88±8.82	0.828
AST (U/L)	56.28±88.21	275.38±1035.73	72.63±296.82	0.0001
ALT (U/L)	45.33±83.78	157.99±586.02	53.70±179.12	0.0009
ALP (U/L)	275.41±240.01	339.8±333.80	280.29±248.40	0.173
Na (mEq/L)	137.74±5.82	135.36±5.98	137.48±5.88	0.028
K (mEq/L)	4.55±9.49	4.03±0.65	4.49±8.96	0.753
Ca (mg/dL)	8.93±1.00	8.62±0.22	8.90±1.00	0.152
Troponin (ng/mL)	0.40±2.52	0.55±0.83	0.41±2.44	0.729
D-dimer (ng/mL)	947.62±2226.18	2483±4861.82	1015.22±2408.82	0.033
CPK (IU/L)	155.16±182.03	2338.32±1509.71	254.39±581.33	<0.0001

ALP=alkaline phosphatase, ALT=alanine transaminase, AST=aspartate transaminase, BUN=blood urea nitrogen, COVID-19=coronavirus disease 2019, CPK=creatinine phosphokinase, CRP=C-reactive protein, Hb=hemoglobin, lymph=lymphocyte leukocytes percentage, PCO_2=partial pressure of carbon dioxide, PMN=polymorphonuclear leukocytes percentage, PO_2=partial pressure of oxygen, RBC=red blood cell count, SD=standard deviation, WBC=white blood cell count. Microscopic hematuria: presence of more than three RBCs per high-power field on microscopic evaluation of urine sediment. Data are presented as mean±SD or frequency (%), PT: Prothrombin Time, PTT: Partial Thromboplastin Time, INR: International Normalized Ratio, HCO_3: Bicarbonate, Na: Sodium, K: potassium, Ca: calcium.

Table 3: Independent predictors of rhabdomyolysis in COVID-19 patients

Predictors	Coefficient (95% CI)	OR (95% CI)	*P*	Weight[a]
Male gender	1.02 (0.25, 1.79)	2.78 (1.28, 6.00)	0.009	1
Dyspnea	−0.58 (−1.26, 0.10)	0.56 (0.28, 1.11)	0.095	0
Hyponatremia	1.04 (0.24, 1.85)	2.84 (1.27, 6.37)	0.011	1
Myalgia	1.09 (0.32, 1.86)	3.04 (1.41, 6.61)	0.005	1
D-dimer >1000 (ng/mL)	1.13 (0.33, 1.94)	3.11 (1.40, 6.94)	0.006	1
AST three times higher than normal	1.14 (0.42, 1.87)	3.14 (1.52, 6.47)	0.002	1
Platelet >450,000 (cells/L)	1.54 (−0.04, 3.11)	4.65 (0.96, 22.37)	0.055	0

AST=aspartate transaminase, CI=confidence interval, COVID-19=coronavirus disease 2019, OR=odds ratio. [a]Weight of variable in the prognostic rule

and alterations in other laboratory findings descriptive of the coagulopathic state. Coagulopathies are a well-known etiology of muscular tissue death, further contributing to the development of rhabdomyolysis.[22,23]

For the first time, we tried to provide a prognostic rule for predicting developing rhabdomyolysis following COVID-19 infection. Male gender, hyponatremia, myalgia, elevated D-dimer, and elevated AST levels were included

Table 4: Discriminatory performance of CORP rule in prediction of rhabdomyolysis in COVID-19 patients

Cutoff point	Sensitivity (%)	Specificity (%)	LR+	LR−
≥0	100.00	0.00	1	
≥1	100.00	8.87	1.0974	0
≥2	93.75	37.23	1.4935	0.1679
≥3	72.92	72.73	2.6736	0.3724
≥4	14.58	92.42	1.925	0.9242
≥5	2.08	99.78	9.6252	0.9813

CORP rule=coronavirus disease 2019-related Rhabdomyolysis Prognostic rule, COVID-19=coronavirus disease 2019, LR=likelihood ratio

to calculate the rule. It appears that the CORP rule could correctly classify 72.8% of COVID-19 patients for their risk of developing rhabdomyolysis.

This study has a number of limitations. Since COVID-19 can cause myalgia and coagulopathies in the absence of rhabdomyolysis, the laboratory and clinical findings could be due to COVID-19 itself and are not specifically indicative of rhabdomyolysis. In addition, we included the admission time laboratory findings to develop the prognostic rule, and if the serial values of these variables were used in the decision rule, its predictive value might have increased. The CORP score was developed based on the available data of COVID-19 patients, and some variables such as inotropic requirement and serum phosphorus were not always available.

Conclusion

This prospective study showed that 8.69% of patients developed rhabdomyolysis following COVID-19 infection. Male gender, hyponatremia, myalgia, elevated D-dimer, and elevated AST levels were independent predictive factors of rhabdomyolysis. The CORP rule with optimal cutoff can correctly classify 72.8% of COVID-19 patients for their risk of developing rhabdomyolysis.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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