Research Article

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Journal of Neurology and Neuroscience
ISSN 2171-6625

2021
Vol.12 No.6:373

Incidence of Skeletal Muscle Injury with SARS-CoV-2 Infection in Tertiary Care Hospitals in Qatar

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Citation: VAli L, Khan A, Alhatou M, Elalamy O, Canibano B, et al. (2021) Incidence of Skeletal Muscle Injury with SARS-CoV-2 Infection in Tertiary Care Hospitals in Qatar. J Neurol Neurosci Vol.12 No.6:373

Abstract

Background: SARS-CoV-2 can contribute to a number of neurological manifestations. 19.3% of patients with severe COVID-19 had evidence of marked skeletal muscle injury and 13.7% of patients with COVID-19 have high CK levels.

Methodology: We retrospectively analyzed 413 COVID-19 patients. We reviewed electronic medical records and collected data. Skeletal muscle injury was defined as skeletal muscle pain and elevated serum creatine kinase level. The primary objective to determine the incidence of skeletal muscle injury in COVID-19 patients.

Results: The most common risk factors were hypertension diabetes and obesity and neurological symptoms at onset of illness were myalgia. Multi-organ systems involvement including 47.8% had skeletal muscle injury, 15.7% had rhabdomyolysis, 36.7% had acute kidney injury, 27.5% had acute liver injury, 23.9% had acute myocardial injury.

Discussion: In addition to respiratory system involvement, other extrapulmonary multiorgan systems involvement including skeletal muscle injury, acute kidney injury, acute liver injury, acute myocardial injury, rhabdomyolysis, acute heart failure, acute pancreatitis and post ICU critical illness neuromyopathy. SARS-CoV-2 may direct invade skeletal muscle, hematogenous dissemination, immune-mediated skeletal muscles injury and inflammatory response with cytokine storm may lead to pathological changes in skeletal muscle tissue including muscle fiber proteolysis and fibrosis.

Conclusion: Skeletal muscles injury with COVID-19 patient's manifest as myalgia, generalized fatigue, myositis, rhabdomyolysis, dermatomyositis-like interferonopathy 1, immune-mediated necrotizing myopathy and respiratory failure. Further studies are requiring with focus on long term outcomes of skeletal muscles injury and benefits of using post COVID rehabilitation programs.

Keywords: SARS-CoV-2; MERS; ACE2; CK; Rhabdomyolysis; Myositis

Received: May 27, 2021; **Accepted:** June 23, 2021; **Published:** June 30, 2021

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel beta-coronavirus that causes a variety of neurologic symptoms including anosmia, ageusia, seizures, stroke, confusion, encephalopathy and quadriplegia [1,2]. Up to 20% of COVID-19 patients who require intensive care unit admission are due to their neurological deficits [3]. SARS-CoV-2 virus have a high similarity to SARS-Cov1 and MERS, appears to have the capacity to injure the central and peripheral nervous systems through direct and indirect ways [4,5]. The binding of SARS-CoV-2 to angiotensin converting enzyme 2 (ACE2) receptor is a critical step in the pathophysiology [6]. The function of ACE2 in normal human physiology is to regulate blood pressure via inhibition of the angiotensin- renin-aldosterone pathways. ACE2 facilitates conversion of angiotensin II to angiotensin (1-7) [7]. Higher levels of angiotensin II are associated with vasoconstriction, kidney failure, heart disease, apoptosis, and oxidative processes [8]. This enzyme protein in the cell membranes of multiple organs to serve as the receptor for SARS-CoV-2 [9]. ACE2 has a wide distribution

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in multiple organs including the nose, lungs, kidneys, liver, blood vessels, immune system, skeletal muscles and brain [9]. After binding ACE2 in respiratory epithelial cells and then epithelial cells in blood vessels, SARS-CoV-2 triggers the formation of a cytokine storm [10]. High levels of these cytokines increase vascular permeability, edema, and widespread inflammation with consequent damage in multiple organs [11]. The cytokine storm also triggers hypercoagulation cascades. Combined hyperactivation of inflammatory markers, vascular injury, and coagulation factors contributes to ARDS, kidney failure, liver injury, heart failure, myocardial infarction as well as multiple neurological conditions. The cytokines activated by SARS-CoV-2 can also trigger vasculitis in and around nerves and muscles, with or without a molecular mimicry [12]. A direct invasion by the virus to the muscles can potentially occur [13]. Muscle injury and high levels of creatine kinase (CK) in COVID-19 patients in ICU can be attributed to critical care myopathy. The early time course of severe muscle weakness in COVID-19 patients may suggestive of myositis [14]. With regards to cardiac muscle, there is evidence that both myocarditis due to SARS-CoV-2 as well as myocardial infarction due to cytokine storm, hypercoagulability, and ischemia can happen at the same time [15] and reported that 19.3% of patients with severe COVID-19 had evidence of marked muscle injury [2].

Viral myositis is often self-limited but can be complicated by rhabdomyolysis [16]. Viral myositis and rhabdomyolysis are most commonly caused by influenza A and B. Approximately 3% of patients with influenza-induced myositis developed rhabdomyolysis per literature review of 300 cases [17,18]. In a study by Guan et al. 13.7% of patients with COVID-19 had CK levels above 200 U/L, but the CK levels did not correlate with the disease severity [19]. Coronavirus infections may be associated with myopathies. In published studies of COVID-19 in China, myalgia or fatigue affected 44-70% of hospitalized patients and increased creatine kinase (CK) was present in up to 33% of admitted patients [20]. As many as a third of patients infected with other coronavirus infections manifested with myalgias and elevated CKs and rhabdomyolysis [21,22]. This suggests that coronavirus infections may cause a viral myositis [23,24]. SARS-CoV, was not detected in skeletal muscle by postmortem examination [25,26]. Exact mechanism of skeletal muscle injury in COVID 19 patients are not fully recognize. Direct SARS-CoV-2 viral invasion of skeletal muscle through ACE2 receptor, hematogenous dissemination and immune-mediated skeletal muscles injury secondary to activation of immune cells and inflammatory response with cytokine storm syndrome may be possible mechanism of skeletal muscle injury, could lead to including muscle fiber proteolysis and fibrosis [27]. The available data at present suggest that COVID-19 associated muscle injury is most likely para-infectious and or immune-mediated and can manifest as dermatomyositis-like interferonopathy-1, myositis, or immune-mediated necrotizing myopathy [28]. Direct SARS-CoV-2 viral invasion of diaphragm muscle may contribute to diaphragm dysfunction and lead to difficulty to weaning from mechanical ventilation and respiratory failure [29].

Research Methodology

This is retrospective observational cross-sectional study. This study was done at Hamad medical cooperation (HMC), Doha, Qatar. There are designated hospitals assigned by the government to treat patients with COVID-19 with Protocol ID # MRC-01-20-523. We retrospectively analyzed 413 patients from January, 1, 2020, to January, 31, 2021, who had been diagnosed as having COVID-19. A confirmed case of COVID-19 was defined as a positive result on real-time reverse transcription polymerase chain reaction (RT-PCR) analysis of both nasopharyngeal and oropharyngeal specimens from patients were tested simultaneously. Radiologic assessments included chest x- rays and chest CT, EMG/NCS studies and all laboratory testing (CBC, CMP, PT/APPT/INR, RFT, LFT, CRP, Ferritin, LDH, D-dimer, IL-6, lactic acid, CPK, myoglobin and lumbar puncture) was performed according to the clinical care and standard clinical practice needs of the patient. Study was approved and written informed consent was waived by the Ethics Committee of HMC (MRC-01-20-523), Doha, Qatar, on June, 16, 2020, owing to the rapid emergence of the disease and the urgent need to collect data. We reviewed electronic medical records, laboratory findings, and radiologic examinations for all patients with laboratory-confirmed SARS-CoV-2 infection and collected data on age, gender, comorbidities (hypertension, diabetes, cardiac or cerebrovascular disease, malignancy, and chronic kidney disease etc.), typical symptoms from onset to hospital admission (fever, cough, anorexia, myalgia etc.), nervous system symptoms, laboratory findings and chest CT scan if available. All neurologic manifestations were reviewed and confirmed by 2 trained neurologists. Skeletal muscle injury was defined as when a patient had skeletal muscle pain and elevated serum creatine kinase level greater than 300 U/L or myoglobin >72 ng/ml and rhabdomyolysis was defined as when patients had elevated serum creatine kinase level greater than 1000 U/L. The primary objective to determine the incidence of skeletal muscle injury in COVID-19 patients and secondary objective to determine the association of skeletal muscles injury with acute myocardial injury and acute kidney injury in COVID-19 patients in tertiary care Hospitals in Qatar. The incidence of skeletal muscle injury in COVID-19 patients and to determine the association of acute myocardial injury and acute kidney injury with skeletal muscle injury in COVID-19 patients estimated and presented with 95% CI. Descriptive statistics used to summarize and determine the sample characteristics and distribution of various considered parameters related to demographic, diagnostic, clinical features, follow-up outcome measures and other related features of such patients. The normally distributed data and results reported with mean and standard deviation (SD) with corresponding 95% confidence interval (CI); the remaining results reported with median and interquartile range (IQR). Categorical data summarized using frequencies and percentages. Associations between two or more qualitative variables examined and assessed using Pearson Chi-square and Fisher Exact tests as appropriate. Unpaired t and ANOVA used to compare mean values of different quantitative parameters between two or more than two groups. Correlation between various outcomes measured evaluated

quantitatively calculated by Pearson or Spearman rank-order correlation. An appropriate regression analysis performed to assess the effects of various factors and covariates on primary outcome measures. Pictorial presentations of the key results made using appropriate statistical graphs. A two-sided P value <0.05 statistically significant. All statistical analyses done using statistical packages SPSS 24.0 (SPSS Inc. Chicago, IL) and Epi Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA).

Results

A total of 413 hospitalized patients with confirmed SARS CoV-2 infection were included in this study. Their demographic in **Table 1** and clinical characteristics are shown in **Table 2.** Their Age mean (SD-14) was 52 (range from 22 to 86 year) years, and 94% were men (389) and 6% were female (25). 57% were less than 55 years age, 43% were greater than 55 years age and 5.6% were greater than 75 years of total patients. Different nationality with majority were 20% Indian (84), 12.5% Bangladeshi (52), 10% Qatari (42), 9% Nepali (38) and 8.7% (36) Filipino and Pakistanis. Of these all patients, following underlying risk factors including 47.6% hypertension (197), 46.9% diabetes (194), 21% obesity (88), 10% newly diagnosed (42), 10% chronic kidney disease (43), 9.7% ischemic heart disease (40), 6.8% smoker (28), 3.6% asthma (15) and 2.91% malignancy (12). These are presented in **Table 3.** Neurologic manifestations were categorized into three major categories: Central nervous system (CNS), peripheral nervous system (PNS) and skeletal muscles. Skeletal muscle injury was 47.8% and rhabdomyolysis was 15.7% **(Figures 1-5).** CNS manifestations were 26.7%, PNS were 4.3%. 48.5% patients (201) had nervous system symptoms: the most common neurological symptoms at onset of illness including myalgia were 28% shown in bar chart (116), headache was 10.4% (43), dizziness was 5.8% (24), anosmia was 2.9% (12) and dysgeusia were 1.4% (6). In patients with skeletal muscle injury the most common reported symptoms including were 28% myalgia. 29% (120) patients admitted in MICU were intubated and ventilated while 16.2% (67) patients had noninvasive ventilation. 8.5% (35) patients died in MICU with COVID complication and septic shocks. 66.7% (276) patients received steroids, 21.5% (89) took convalescent plasma. Multiorgan systems involvement of COVID-19 patients **(Figures 6-9)** including 47.8% (198) had skeletal muscle injury (serum creatine kinase >300 U/L or myoglobin >72 ng/ml), 15.7% (65) had rhabdomyolysis (serum creatine kinase >1000U/L), 36.7% (152) had acute kidney injury, 27.5% (114) had acute liver injury (>200 ALT or AST levels), 23.9% (99) acute myocardial injury (high tropT hs, male>30, female>20ng/l), 11.4% (47) had acute heart failure (high proBNP >1800pg/ml), 11.1% (46) had acute pancreatitis (serum lipase >180 u/l), 5.8% (24) had previous uncontrolled blood sugar (with HbA1c>12) and 3.1% (13) had post ICU critical illness neuromyopathy supported by clinical and NCS/EMG study. 11% (46) had AKI associated with rhabdomyolysis, 9.9% (41) had cytokine storm syndrome associated with rhabdomyolysis, 9.2% (38) had acute liver injury associated with rhabdomyolysis, 6.7% (28) had acute myocardial injury associated with rhabdomyolysis. **Table 4** showed the laboratory, Echocardiography and Nerve conduction study / Electromyographic findings. Laboratory

Table 1 Demographics.

Age (Years)		
Variables	**Frequency**	**Percentage (%)**
<54	234	**56.7%**
55-64	107	**25.9**
65-74	49	11.9
75-84	21	5.1
>85	2	0.5
Gender		
Male	389	**94.**0%
Female	23	6.0
Nationality		
Afgthan	3	0.7
American	1	0.2
Bangladesh	52	12.5
Cameron	1	0.2
Egyptian	29	7.0
Filipino	36	8.7
Greek	1	0.2
Indian	84	20.3
Indonesian	2	0.5
Iranian	11	2.7
Iraqi	2	0.5
Jordanian	8	1.9
Kenyan	2	0.5
Malaysian	1	0.2
Moroccan	3	0.7
Nepalese	38	9.2
Nigerian	1	0.2
Pakistani	36	8.7
Palestinian	12	2.9
Qatari	42	10.1
Somali	1	0.2
Sri Lankan	12	2.9
Sudanese	13	3.1
Syrian	14	3.3
Thai	2	0.5
Tunisian	1	0.2
Turkish	1	0.2
Yemeni	5	1.2

Table 2 Clinical manifestations.

Symptoms		
Variables	**Frequency**	**Percentage (%)**
Fever	321	77.5
Shortness of breath	243	58.7
Cough	279	67.4
Chest pain	41	9.9
Myalgia	116	28.0
Muscle Weakness	16	3.9
Cola urine colour	1	0.2
Headache	43	10.4
Anosmia	12	2.9
Dysuria	6	1.4
Vertigo	24	5.8

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Table 3 Underlying risk factors.

Underlying risk factors		
	Frequency	Percentage (%)
Hypertension	197	47.6
Diabetes	194	46.9
Obesity	88	21
Newly diagnosed	42	10
Chronic Kidney disease	43	10
Ischemic heart disease	40	9.7
Smoker	28	6.8
Asthma	15	3.6
Malignancy	12	2.91

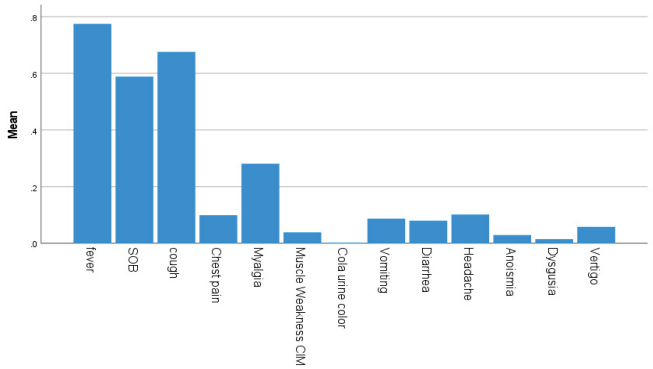

Figure 1 Mean values of the neurologic manifestations.

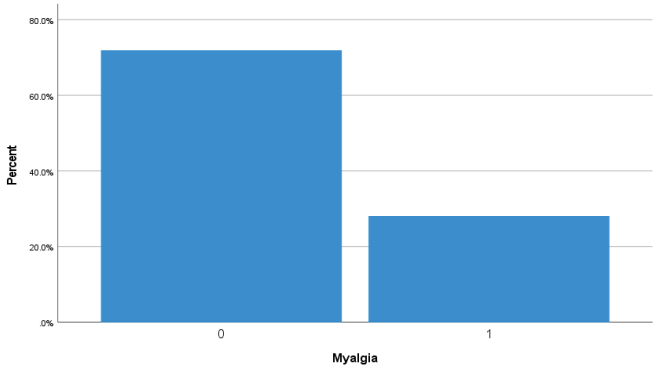

Figure 2 Percentage with respect to myalgia.

features associated with severe COVID-19 including 39.4% (163) had > 300 u/L serum creatine kinase, 35.7% (148) had serum myoglobin >72 ng/ml, 15.7% (65) had rhabdomyolysis (serum creatine kinase >1000 U/L), 71% (295) had >500 mcg/L ferritin level, 66.2% (274) had LDH >245 units/L, 61% (253) had >100 mg/l C-reactive protein levels, 53.9% (223) had >1000 ng/mL D-dimer, 37% (153) had >70 pg/m of IL-6, 22.2% (90) had >2 ng/ml procalcitonin, 6.3% (26) had >4 mmol/l lactic acid. 7.7% (32) patients had echo showed 3.4% (14) were mild low EF, 1.7% (7) were severe low EF, 0.5% (2) were moderate low EF. 2.7% (11) patients had NCS/EMG studies showed 1.7% (7) patients were CINM and 0.7% (3) patients were CIM.

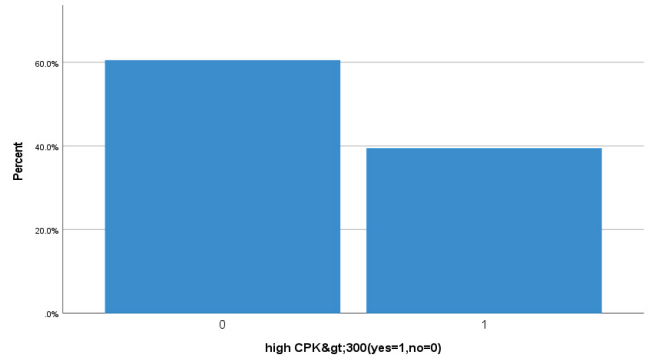

Figure 3 Percentage with respect to CPK values.

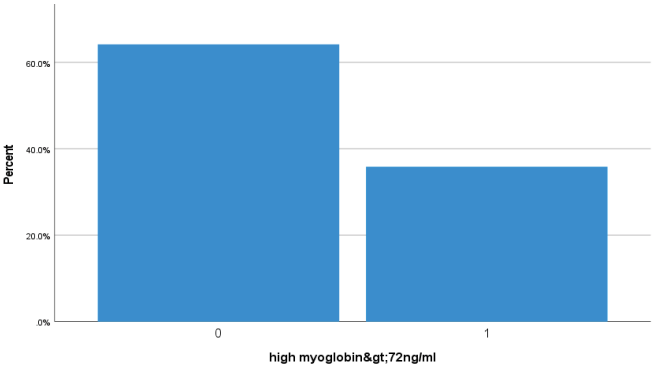

Figure 4 Percentage with respect to myoglobin.

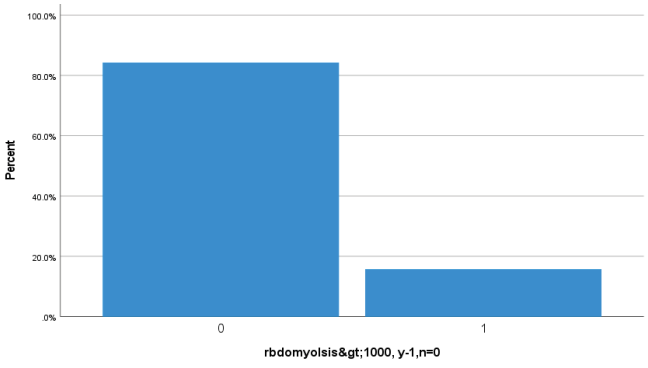

Figure 5 Percentage with respect to rhabdomyolsis.

Discussion

This is the first report on skeletal muscles injury and rhabdomyolysis of the hospitalized patients with COVID-19 from Qatar. From 1, January, 2020 to 31, January, 2021, total 413 patients were included in this study. Majority of patient were less than 55 years age (57%) with different nationality. The most common risk factors were found Hypertension, Diabetics and Obesity. Total of 413 patients, 48.5% (201) had various neurologic symptoms that involved CNS, PNS, and skeletal muscles. Most common neurological symptoms

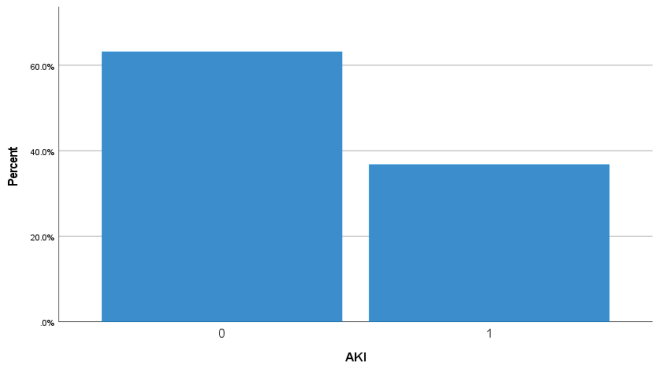

Figure 6 AKI percentage.

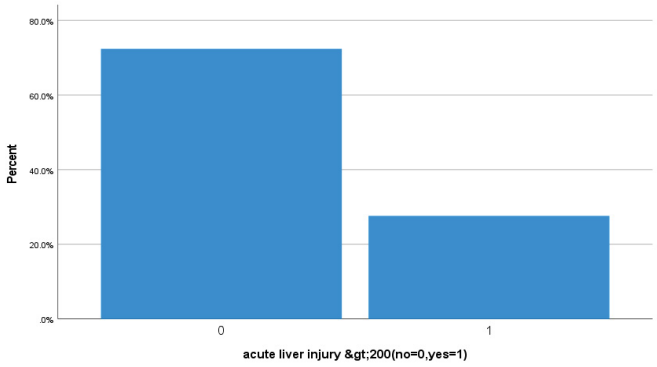

Figure 7 Percentage of acute liver injury.

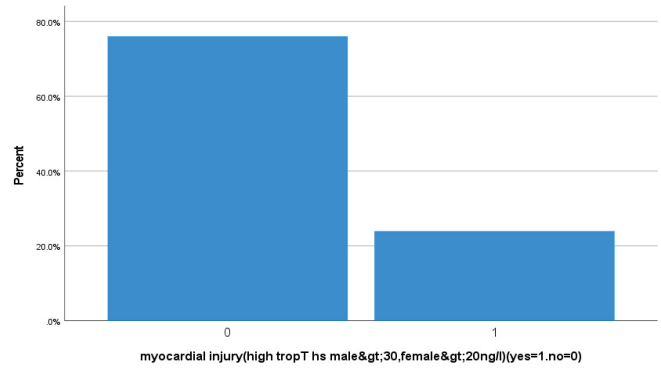

Figure 8 Percentage of myocardial injuries.

including myalgia, headache and dizziness in order of descending frequency. The most common neurological involvement was skeletal muscle injury (47.8%). In addition to respiratory system, other extra-pulmonary multiorgan systems involvement of COVID patients including skeletal muscle injury (47.8%), acute kidney injury (36.7%), acute liver injury (27.5%), acute myocardial injury (23.9%), rhabdomyolysis (15.7%), acute heart failure (11.4%), acute pancreatitis (11.1%) and post ICU critical illness neuromyopathy (3.1%) that supported by clinical and NCS/EMG study. Multiorgan system involvements association with rhabdomyolysis including AKI, cytokine storm syndrome, acute

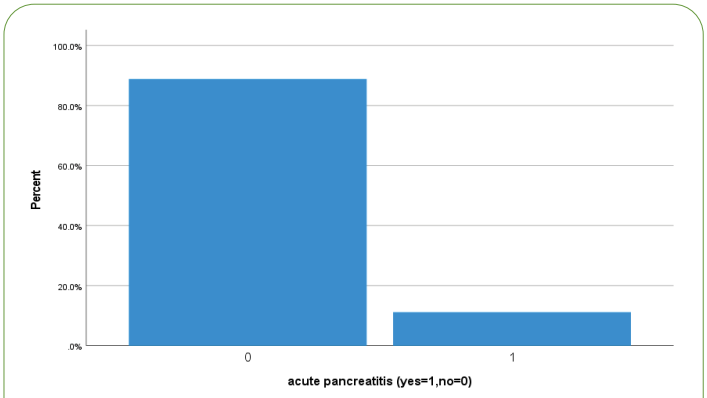

Figure 9 Percentage of acute pancreatitis.

Table 4: Laboratory, echocardiography and nerve conduction study/ electromyographic findings.

Laboratory features		
Variables	**Frequency**	**Percentage (%)**
Serum CK>300u/L	163	**39.4**
Serum myoglobin >72 ng/dl	148	**35.7**
Serum CK>1000 U/L causing Rhabdomyolysis	65	**15.7**
Serum Ferritin>500mcg/L	295	71
LDH >245 units/L	274	66.2
C-reactive protein levels	253	61
D-Dimer >1000 ng/ml	223	53.9
IL6 >70 pg/ml	153	37
Procalcitonin > 2 ng/ml	90	22.2
Lactic acid > 4 mml/l	26	6.3
Echocardiography		
Mildly low Ejection Fraction	32	**7.7**
Severely low Ejection Fraction	7	1.7
Moderately low Ejection Fraction	11	2.7
Nerve conduction/Electromyographic studies		
CINM	7	**1.7**
CIM	3	0.7

liver injury and acute myocardial injury in order of descending frequency. Exact mechanisms of skeletal muscle injury in COVID 19 patients are not fully recognize. Direct SARS-CoV-2 viral invasion of skeletal muscle including diaphragm through ACE2 receptor, hematogenous dissemination and immune-mediated skeletal muscles injury secondary to activation of immune cells and inflammatory response with cytokine storm syndrome may lead to pathological changes in skeletal muscle tissue including muscle fiber proteolysis and fibrosis. Dystrophic myopathies like Duchenne muscular dystrophy with severe COVID-19 infection are at higher risk of respiratory failure due to diaphragm dysfunction. Rhabdomyolysis have been reported in COVID-19 patients that can lead to acute kidney injury, compartment syndrome and disseminated intravascular coagulation.

Limitations

All data were retrieved from the electronic medical records retrospectively and mostly from dedicated COVID facility for male

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patients. During COVID 19 spike waves times and high admissions rate of patients infected with COVID-19, neuroimaging like CT scan or magnetic resonance imaging and diagnostic procedures such as EMG/NCS were limited to reduce the risk of cross infection. Therefore, most of neuromuscular symptoms of patients were subjective descriptions.

Conclusion

In conclusion, the most common neuromuscular manifestation of COVID-19 patients were skeletal muscle injury and followed by other multi-organ dysfunctions including renal, hepatobiliary, cardiac and venous thromboembolism. The patients with severe COVID-19 infection with concomitant dystrophic myopathies are at higher risk for severe skeletal muscle injury including diaphragm. Skeletal muscles injury with SARS-CoV-2 infection manifest as myalgia, generalized fatigue, myositis, rhabdomyolysis, dermatomyositis-like interferonopathy 1, immune-mediated necrotizing myopathy and diaphragmic or respiratory failure. Thus, we postulated that skeletal muscles injury may be peculiarly affected by SARS-CoV-2 via direct viral invasion through ACE2 receptor, immune-mediated cytokines and proinflammatory signaling molecules and hematogenous dissemination. Further studies are requiring with focus on long term outcomes of skeletal muscles and neuromuscular health of patients recovering from COVID-19 and benefits of using post COVID rehabilitation programs.

Ethical Approval

Protocol ID MRC-01-20-523 entitled "Incidence of skeletal muscle injury with SARS-CoV-2 infection in tertiary care hospitals in Qatar." has been approved by MRC.

Conflict of Interest

There is no conflict of interest.

Funding Disclosure

Nil.

Author's Contributions

Liaquat Ali: Data collection, Data analysis, Manuscript writing & Review literature.

Adnan Khan: Manuscript writing, Manuscript review.

Mohammad Alhatou; Manuscript writing & review literature.

Osama Elalamy: Data analysis, Manuscript review

Beatriz Canibano: Data analysis, Manuscript writing & review

Golam Adeli: Data analysis, Manuscript writing & review

Ahmed Mohammad: Data collection, data analysis

Khawaja H Haroon: Manuscript writing, manuscript review

Suhail H: Data analysis, manuscript writing

Suha Elmaki: Data analysis, manuscript writing

Yahya Imam: Data collection, data analysis

Ambreen Iqrar: Manuscript writing, manuscript review.

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