

Acute cardiac injury is associated with adverse outcomes, including mortality in COVID-19 patients

A single-center experience

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ABSTRACT

الأهداف: تقييم إصابة القلب الحادة لدى مرضى COVID-19 وارتباطها بالنتائج السلبية بما في ذلك الوفيات في سكان الإمارات العربية المتحدة.

المنهجية: أجريت دراسة بأثر رجعي أجريت بين فبراير ويونيو 2020م في دبي، الإمارات العربية المتحدة، لجميع مرضى فيروس كورونا 19 المؤكدة مخبرياً. قارنا النتائج الديموغرافية والسريية والمختبرية والإشعاعية والسريية بين المرضى الذين يعانون من إصابة قلبية حادة وغير مصابين.

النتائج: خلال فترة الدراسة، اشتملت الدراسة على 203 مريضاً، من بينهم 44 (21.7%) لديهم دليل على إصابات القلب الحادة. بالمقارنة مع المرضى الذين لا يعانون من إصابات قلبية حادة، كان المرضى الذين يعانون من إصابات قلبية حادة: كبار السن، يعانون من ضيق أكثر في التنفس، ومرض السكري، وارتفاع ضغط الدم، وارتفاع التظليل الثنائي في التصوير الشعاعي للصدر. كان لدى هؤلاء المرضى أيضاً عدد أعلى من العدلات، والبروتين التفاعلي C، والبروكالسيتونين، والفيريتين، والدايمرز ونازعة هيدروجين اللاكتات وانخفاض في عدد الخلايا الليمفاوية. فيما يتعلق بالنتائج، هؤلاء المرضى ارتفع دخولهم إلى العناية المركزة، وارتفعت معدل المضاعفات بما في ذلك إصابات الكلى والكبد الحادة، والحماض، والصدمة الإنتانية، ومتلازمة الضائقة التنفسية الحادة، والحاجة إلى مزيد من التهوية الميكانيكية، وخطر الوفاة لديهم أعلى بشكل ملحوظ.

الخلاصة: إصابة القلب الحادة شائعة بين مرضى فيروس كورونا 19. هؤلاء المرضى يعانون من أمراض مصاحبة أعلى، ولديهم علامات التهابية عالية ومخاطر أكثر لتلف الأعضاء المتعدد داخل المستشفى، والحاجة إلى التهوية الميكانيكية، والموت. يوصى بالتقييم والتدخل الكامل الفوري.

Objectives: To evaluate acute cardiac injury in COVID-19 patients and its association with adverse outcomes including mortality in the United Arab Emirates (UAE) population.

Methods: A retrospective study conducted between February and June 2020 in Dubai, UAE, for all laboratory-confirmed Coronavirus disease-19 patients. Demographic, clinical, laboratory, radiological, and clinical outcomes were compared between patients with and without acute cardiac injury.

Results: During the study period, 203 patients were included, of which, 44 (21.7%) had evidence of

acute cardiac injury. Compared with patients without acute cardiac injury, patients with acute cardiac injury were: older, had more shortness of breath, diabetes, hypertension, and more bilateral airspace shadowing on admission chest radiography. These patients also had a higher neutrophil count, C-reactive protein, procalcitonin, ferritin, D-dimers and lactate dehydrogenase but lower lymphocyte count. Regarding outcomes, these patients had higher intensive care admissions; a higher rate of complications including acute kidney and liver injury, acidosis, septic shock, acute respiratory distress syndrome, needed more mechanical ventilation, and had a significantly higher risk of death.

Conclusion: Acute cardiac injury is common among Coronavirus disease-19 patients. These patients present with higher comorbidities, have high inflammatory markers and have greater risk for in-hospital multi-organ damage, need for mechanical ventilation, and death. Prompt full assessment and intervention are recommended.

Keywords: cardiac injury, Corona virus, COVID-19, acute respiratory distress syndrome, mortality

*Saudi Med J 2020; Vol. 41 (11): 1204-1210
doi: 10.15537/smj.2020.11.25466*

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Received 12th August 2020. Accepted 6th October 2020.

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Corona virus disease-2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), resulted in the COVID-19 pandemic and healthcare challenge to almost all countries in the world. Corona virus disease-2019 was first reported in Wuhan, China in December 2019.¹ As of June 29, 2020, the total number of confirmed cases worldwide were 10,199,798, with 502,946 confirmed deaths, whereas, United Arab Emirates (UAE) had 47,797 confirmed cases with 313 deaths.²

Although respiratory failure has been the major concern in Covid-19 infection, cardiac injury manifested by a rise in high-sensitivity troponin has gained considerable attention due to its reported association with mortality.^{3,4} Subsequently, the American College of Cardiology clinical bulletin released in February 2020 has highlighted the incidence of acute onset heart failure, myocardial infarction, myocarditis and cardiac arrest in Covid-19 as higher cardiometabolic demand in acute illness can precipitate cardiac complications.⁵ Although the exact pathophysiology remains unclear, several mechanisms have been proposed. Cytokine release syndrome⁶ with high levels of interleukin-6, interferon-gamma, interferon-inducible protein-10, and monocyte chemoattractant protein-1, angiotensin-converting enzyme 2-related signaling pathways, and intractable hypoxemia due to acute respiratory distress syndrome have all been suggested.⁷

Data is scarce from the Middle East region in this regard. Hence, we conducted this study in confirmed Covid-19 patients admitted to main Ministry of Health Hospital in Dubai, UAE and compared the clinical characteristics, laboratory parameters, and clinical outcomes in patients with- and without cardiac injury.

Methods. This study was conducted at Al Kuwait Hospital, Dubai, UAE, between February 21, 2020, and June 24, 2020. We only included patients who were admitted to the hospital after a positive COVID-19 RNA polymerase chain reaction (PCR) test. The Sacace real-time reverse transcription polymerase chain reaction (RT-PCR) test was performed on patients' nasopharyngeal swabs. RNA was extracted using SaMag

Viral Nucleic Acid Extraction system and the extracted RNA was amplified using BGI- real-time fluorescent RT-PCR kit for the detection of COVID-19.

All symptomatic COVID-19 patients aged 18 years or more who tested positive with laboratory RNA PCR test were included. Any suspected COVID-19 patient without laboratory confirmation was excluded.

The study was approved by the Scientific Research Committee MOHAP/DXB-REC/MMM/NO.44/2020 and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments ethical standards.

Data included basic demographics (age, gender), clinical data (symptoms, comorbidities), laboratory parameters (complete blood count, coagulation tests, inflammatory markers, renal function tests, and liver enzymes), admission chest radiography results, in-hospital complications (acute respiratory distress syndrome, acute liver injury, acute kidney injury, acidosis, septic shock, mechanical ventilation, and death). High-sensitivity troponin-I were measured on admission and serially after admission once the cardiac injury was suspected. Data were collected in an excel sheet which was continuously rechecked by 2 researchers. Proper data collection was assured by regular involvement of an epidemiologist.

We categorized patients into 2 groups: those with an acute cardiac injury (ACI) who had at least one documented elevated high-sensitivity troponin-I, and those without cardiac injury who had normal troponin results. The cut-off for the upper limit of normal troponin was taken as 60 ng/L, which is the upper value of the normal range used by our laboratory. We then compared the 2 groups in clinical characteristics and outcomes. Among patients with cardiac injury, we further compared patients with a moderate rise (≤ 500 ng/L) and a severe rise in troponin (> 500 ng/L) in terms of clinical outcomes (cut-off 500 ng/L was chosen as an arbitrary number, based on local experience).

The acute cardiac injury was defined as the presence of raised high-sensitivity troponin-I level, with new electrocardiography or echocardiography abnormalities.⁸ Septic shock was defined as the presence of sepsis that is accompanied with persistent hypotension that needs vasopressors to keep mean arterial pressure ≥ 65 mm Hg along with high serum lactate level > 2 mmol/L (18 mg/dL) despite volume resuscitation.⁹ Acute respiratory distress syndrome was defined according to the Berlin definition that includes the presence of bilateral lung opacities accompanied by respiratory failure not fully explained by cardiac failure

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company. Dr. Fahda Alokaily is a member of the Editorial Team, and was therefore excluded from any final editorial decisions regarding this paper.

or fluid overload and low partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2), within one week of symptom onset.¹⁰ Acute kidney injury was defined as the presence of either an increase in serum creatinine ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/L}$) within 48 hours/ ≥ 1.5 times baseline, or oliguria with urine output < 0.5 ml/kg/hour for 6 hours.¹¹ Acute liver injury was defined as the presence of raised liver enzymes: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) more than 5 times the upper normal limit. The disease severity was classified into mild to moderate (up to mild pneumonia), severe (shortness of breath, high respiratory rate ≥ 30 /min, blood oxygen saturation $\leq 93\%$, the ratio of the PaO_2 to a $\text{FiO}_2 < 300$, lung infiltrates $> 50\%$ within 24-48 hours), and critical (respiratory failure, septic shock, multi-organ dysfunction/failure).¹²

Statistical analysis. Categorical variables are expressed as proportions, while continuous data are reported as mean \pm standard deviation. Proportions for categorical variables were compared using the Chi-squared test and Fisher exact test when data were limited. The means for continuous variables were compared using the independent t-tests when the data were normally distributed; otherwise, the Mann-Whitney test was used. Data were analyzed using Statistical Package for Social Sciences version 25.0 (IBM, New York, USA). A p-value of less than 0.05 was considered statistically significant.

Results. Figure 1 shows the flowchart for patient selection. A total of 250 patients were screened who were

hospitalized with laboratory-confirmed COVID-19 disease between February 21, 2020, and June 24, 2020. Forty-seven cases were excluded as the troponin test result was not performed at admission. Therefore, 203 cases were included in the final analysis; 44 (21.7%) with cardiac injury and 159 (78.3%) without cardiac injury. Overall, the mean age was 48 years (range 13-84 years, SD 14.68), and 151 (74%) were males. Common symptoms reported were fever (6.5%), cough (55.6%), and shortness of breath (40.4%).

Demographics, laboratory results, imaging findings, and in-patient treatment were compared between the 2 groups (Table 1). Compared with patients without cardiac injury, patients with acute cardiac injury were older (mean age 55 years versus 46 years, $p < 0.05$) and predominantly males (91% versus 70.5%, $p = 0.005$). They also presented with higher percentage of shortness of breath (62% versus 35%, $p = 0.001$); had more diabetes (62% versus 27%, $p = 0.000$) and hypertension (55% versus 32%, $p = 0.004$). More patients with cardiac injury showed bilateral airspace shadowing on admission chest radiography compared with patients without cardiac injury, (75% versus 46%, $p = 0.001$).

Laboratory tests showed that patients with cardiac injury had lower mean hemoglobin ($p < 0.05$), higher neutrophil count ($p < 0.05$), lower lymphocyte count ($p < 0.05$), higher C-reactive protein ($p < 0.05$), higher procalcitonin ($p < 0.05$), higher ferritin ($p < 0.05$), higher D-dimers ($p < 0.05$), higher lactate dehydrogenase ($p < 0.05$) and lower estimated-glomerular filtration rate ($p < 0.05$). There was no statistical difference in platelet

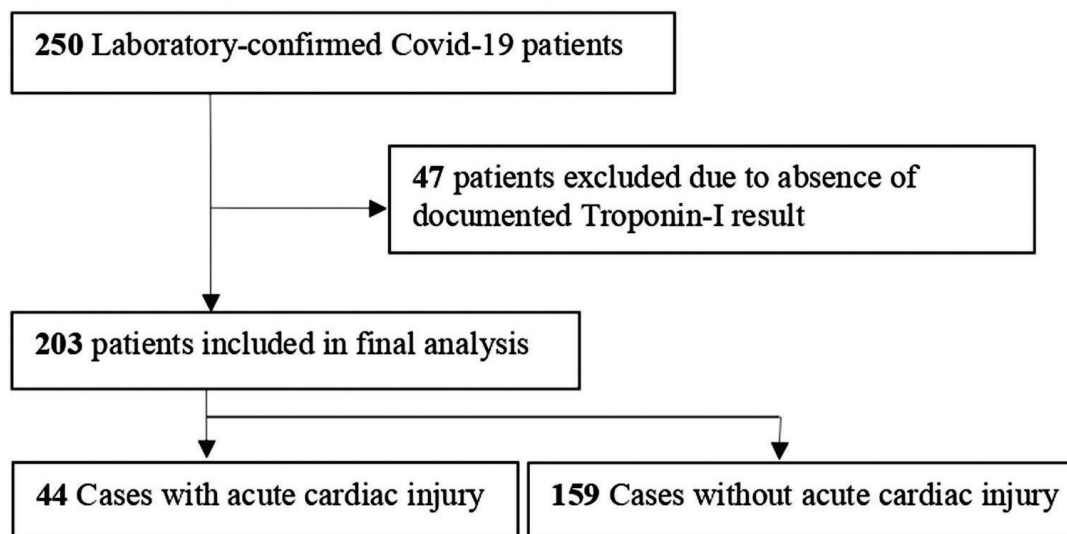


Figure 1 - Flow chart of patient's selection.

Table 1 - Clinical characteristics (demographics, laboratory, imaging and treatment) of 203 Covid-19 patients; with- and without cardiac injury.

Clinical characteristics	Acute cardiac injury		
	With (n=44)	Without (n=159)	P-value
Age, mean (±SD), years	55 ± 14	46 ± 14	<0.05
Male gender, no. (%)	41 (91.0)	110 (70.5)	0.005
Symptoms, n (%)			
Fever	31 (69.0)	103 (66.0)	0.719
Cough	25 (55.5)	87 (55.7)	0.97
Shortness of breath	28 (62.0)	55 (35.0)	0.001
Co-morbidities, n (%)			
Diabetes	28 (62.0)	42 (27.0)	0.000
Hypertension	25 (55.5)	50 (32.0)	0.004
Cardiovascular disease	4 (9.0)	5 (3.2)	0.104
Laboratory findings at admission			
Hemoglobin, g/dL, mean ±SD	12.6 ± 1.6	13.3 ± 1.9	<0.05
Neutrophil count, absolute, x10 ³ /mL, mean ±SD	10.5 ± 5.0	5.6 ± 3.4	<0.05
Neutrophil count >14 x10 ³ /mL (%)	19 (42.2)	11 (7.0)	<0.001
Lymphocyte count, absolute, x10 ³ /mL, mean ±SD	1.0 ± 0.5	1.5 ± 0.7	<0.05
Lymphocyte count <1 x10 ³ /mL (%)	24 (53.3)	44 (28.2)	0.002
Platelets, x10 ³ /mL (mean ±SD)	252 ± 86.7	245 ± 93.2	0.560
Prothrombin time, seconds, (mean ±SD)	13 ± 1.7	12 ± 1.7	0.542
International normalized ratio, (mean±SD)	1.1 ± 0.1	1.05 ± 0.1	0.652
C-reactive protein, mg/L (mean±SD)	138.5 ± 108	59 ± 75	<0.05
C-reactive protein >3 mg/L (%)	43 (95.5)	128 (82.0)	0.08
Procalcitonin, ug/L (mean ±SD)	3.4 ± 8.9	0.3 ± 1.2	<0.05
Procalcitonin >0.1 ug/L (%)	35 (77.8)	41 (26.3)	0.000
Ferritin, mcg/L (mean±SD)	1963 ± 2840	870 ± 1229	<0.05
Ferritin >388 mcg/L (%)	37 (82.2)	69 (44.2)	0.000
D-dimers, mg/dL (mean±SD)	6.4 ± 9.8	1.7 ± 4.1	<0.05
D-dimers >0.5 mg/dL (%)	34 (75.5)	75 (48.0)	0.001
Lactate dehydrogenase, IU/L (mean ±SD)	614 ± 686	314 ± 197	<0.05
Lactate dehydrogenase >227 IU/L (%)	39 (86.0)	101 (64.0)	0.017
Creatinine, umol/L (mean±SD)	184 ± 342	93 ± 73	<0.05
e-GFR, ml/min (mean±SD)	66.5 ± 31	94 ± 27	<0.05

Table 1 - Clinical characteristics (demographics, laboratory, imaging and treatment) of 203 Covid-19 patients; with- and without cardiac injury (continued).

Clinical characteristics	Acute cardiac injury		
	With (n=44)	Without (n=159)	P-value
Alanine aminotransferase, IU/L (mean±SD)	49 ± 28.3	72 ± 174	NS
Aspartate aminotransferase, IU/L (mean±SD)	60 ± 47	50 ± 75	NS
Albumin, gm/l (mean±SD)	25.7 ± 6.5	32 ± 6.5	<0.05
Chest radiography at admission n (%)			
Bilateral opacities	34 (75.5)	72 (46.0)	0.001
Treatment, n (%)			
Chloroquine/hydroxychloroquine	43 (97.0)	150 (96.0)	0.155
Lopinavir-ritonavir	41 (91.0)	128 (82.0)	0.14
Favipiravir	12 (27.0)	28 (18.0)	0.19
Intravenous antibiotics	41 (91.0)	88 (56.4)	<0.001
Intravenous steroids	34 (75.5)	56 (35.9)	<0.001
Interferon	2 (4.0)	12 (7.7)	0.45
Tocilizumab	21 (46.7)	19 (12.0)	<0.001
Antifungals	10 (22.0)	7 (4.5)	<0.001

eGFR: estimated glomerular filtration rate.

Data is expressed as mean (± standard deviation) for continuous variables and counts (percentages) for categorical variables. P value less than 0.05 is considered statistically significant

counts, coagulation parameters, and liver enzymes between the 2 groups.

The severity of disease and in-hospital complications were also compared between the 2 groups (Table 2). More patients with cardiac injury had a critical disease, while more patients without cardiac injury had mild to moderate disease (84.4% versus 18%, $p=0.00$). Regarding the outcomes and complications, patients with cardiac injury had higher intensive care admissions (82% versus 18.5%, $p=0.00$) and complications including acute kidney injury (75% versus 9.6%, $p=0.00$), acidosis (75.5% versus 8.3%, $p=0.00$), septic shock (66.7% versus 2.6%, $p=0.00$), acute respiratory distress syndrome (84% versus 17%, $p=0.00$). As well, despite there were no difference in LFTs between the 2 groups was found in the laboratory carried out on admission, whereas, we diagnosed acute liver injury in patients who developed a rise of ALT/AST >5 times the upper normal limit during the course of in-hospital

Table 2 - Comparison of clinical outcomes of 203 Covid-19 patients; with- and without cardiac injury.

Characteristic	Acute cardiac injury		
	With n=44	Without n=159	P-value
Severity of disease			
Mild to moderate	4 (9.0)	74 (48.0)	
Severe	3 (6.7)	53 (34.2)	<0.001
Critical	38 (84.4)	28 (18.0)	
Outcomes			
Admission to intensive care unit	36 (82.0)	29 (18.5)	<0.001
Acute respiratory distress syndrome	38 (84.4)	26 (16.7)	<0.001
Acute kidney injury	33 (75.0)	15 (9.6)	<0.001
Acute liver injury	13 (29.0)	16 (10.2)	0.002
Acidosis	34 (75.5)	13 (8.3)	<0.001
Septic shock	30 (66.7)	4 (2.6)	<0.001
Mechanical ventilation	32 (71.0)	9 (5.8)	<0.001
Death	31 (68.9)	8 (5.1)	<0.001

Values are expressed as number and percentage (%)

stay. Therefore, although there was no difference in liver enzymes upon admission, the patient with cardiac injury developed more acute liver injury than the other during the hospital stay with acute liver injury (29% versus 10%, $p=0.002$). Patients with cardiac injury needed more mechanical ventilation (71% versus 6%, $p=0.00$) and had a significantly higher risk of death (69% versus 5%, $p=0.00$).

We also compared the outcomes in patients with moderate rise in peak troponin level (≤ 500 ng/L) and those with high peak troponin levels (> 500 ng/L) (Table 3). There was no statistical difference between the 2 groups regarding admission to the intensive care ($p=0.550$), acute respiratory distress syndrome ($p=0.826$), acute kidney injury ($p=0.787$), acute liver injury ($p=0.173$), acidosis ($p=0.430$), septic shock ($p=0.204$), mechanical ventilation ($p=0.964$) and death ($p=0.787$).

Discussion. This study aimed to provide an insight into the association between acute cardiac injury and clinical outcomes, including death in laboratory-confirmed Covid-19 patients. We compared clinical characteristics between patients with acute cardiac injury and those without cardiac injury. Acute cardiac injury (ACI) was present in more than fifth

Table 3 - Comparison of outcomes in patients with acute cardiac injury according to the level of troponin rise (N=44).

Outcomes	Peak high-sensitivity troponin I value		
	≤ 500 ng/L (n=20)	> 500 ng/L (n=24)	P-value
Admission to intensive care unit	16 (80)	20 (83.0)	0.550
Acute respiratory distress syndrome	18 (90)	20 (83.0)	0.826
Acute kidney injury	15 (75)	18 (75.0)	0.787
Acute liver injury	4 (20)	9 (37.5)	0.173
Acidosis	17 (85)	17 (71.0)	0.430
Septic shock	12 (60)	18 (75.0)	0.204
Mechanical ventilation	15 (75)	17 (71.0)	0.964
Death	15 (75)	18 (75.0)	0.787

Values are expressed as number and percentage (%)

of COVID-19 patients. We found that the majority were male and older in age and had worse clinical presentation, comorbidities, laboratory parameters, and clinical outcomes.

We report an incidence of acute cardiac injury to be 21.7% (44/203). This is high compared to what Huang et al³ reported (12%). Also, a study of 138 Covid-19 patients admitted to the hospital reports an incidence of 7.2% for acute myocardial injury while 16.7% had arrhythmias.³ Our high reported incidence is likely related to the high prevalence of diabetes and hypertension in the region. We noted in our study that more patients in the cardiac injury group were diabetics and hypertensives, rendering them prone to cardiac injury.

Several laboratory parameters have been identified to predict adverse outcomes in COVID-19 patients. Wu et al¹³ detected the presence of low lymphocytes, high C-reactive protein, ferritin, and lactate dehydrogenase in these patients and further found these to be associated with the development of acute respiratory distress syndrome, need for intensive care, and even high mortality. In the present study, patients with acute cardiac injury have a high prevalence of hematologic abnormalities like neutrophilia and lymphopenia. These patients were also found to have higher inflammatory markers like C-reactive protein, procalcitonin, ferritin, D-dimers, and lactate dehydrogenase compared to the non-cardiac injury group. This suggests the association of severe inflammation to the risk of developing cardiac injury and the need for close monitoring of these patients. We also found that patients who develop

critical disease were more likely to develop acute cardiac injury. High troponin levels have been reported to be associated with adverse clinical outcomes. A study of 191 COVID-19 patients revealed the odds ratio for death when high-sensitivity Troponin-I concentrations were high to be 80.1 (95% confidence interval 10.3 to 620.4, $p < 0.0001$).¹⁴ Similarly, another study of 416 Covid-19 reported that patients who developed high cardiac troponin levels were more at risk to develop acute respiratory distress syndrome or acute kidney injury, require invasive or non-invasive ventilation, and a 10-fold increase in mortality.¹⁵ In concordance to the existing literature, we also found a significant association in our study between acute cardiac injury and several adverse outcome measures. Our patients with acute cardiac injury developed more multi-organ dysfunction, required intensive care and mechanical ventilation with high mortality. No cut-off for the level of troponin rise has been reported in the literature for the development of adverse outcomes. We compared patients with a moderate rise in troponin (≤ 500 ng/L) to severe rise (> 500 ng/L) and found that the risk of having adverse outcomes was similar. This highlights the fact that even low degrees of troponin leak is associated with serious outcomes and need to be monitored closely. Only few case reports suggest the successful treatment of Covid-19 related to myocarditis (high troponin levels) with methylprednisolone, immunoglobulin, inotropes, and ventilatory support.^{16,17} The European Society of Cardiology position statement¹⁸ recommends treating patients with acute myocarditis and cardiogenic shock with inotropes/vasopressors and mechanical ventilation. Additionally, extracorporeal membrane oxygenation (ECMO) and ventricular assist devices are recommended for patients that require longer-term support.

Study limitations. Firstly, this is a single center study with analysis of a small cohort of patients. Secondly, the data does not include information on echocardiography, electrocardiography (ECG), and cytokine level measurements, hence the inability to determine the potential mechanisms of cardiac injury. We understand that such data needs to be cautiously interpreted and provides a basic understanding of high-risk patient cohort.

This study represents rare data from the Middle East region. It adds to the existing scientific knowledge in this aspect from other parts of the world and explores the association of acute cardiac injury with clinical outcomes in a diverse population in UAE. The study highlights implications for future research in the management of these patients in the form of aggressive

cardiovascular support and tertiary center care.

In conclusion, acute cardiac injury is common in patients hospitalized for laboratory-confirmed COVID-19 disease in the Middle East with high prevalence of non-communicable diseases such as obesity, diabetes, and hypertension. These patients present with worse clinical presentations and laboratory abnormalities including high neutrophils, low lymphocytes, high inflammatory markers, and bilateral air space opacification on chest radiography. The risk of in-hospital multi-organ damage, need for mechanical ventilation, and death is significantly higher in patients with an acute cardiac injury. This high risk appears to be the same in patients with a moderate or high rise in peak troponin levels. Hence, early recognition with prompt management would be the best clinical practice approach with multidisciplinary team involvement.

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