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Original article

Prognostic implications of myocardial injury in patients with and without COVID-19 infection treated in a university hospital

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ABSTRACT

Introduction and objectives: Cardiac troponin, a marker of myocardial injury, is frequently observed in patients with COVID-19 infection. Our objective was to analyze myocardial injury and its prognostic implications in patients with and without COVID-19 infection treated in the same period of time.
Methods: The present study included patients treated in a university hospital with cardiac troponin I measurements and with suspected COVID-19 infection, confirmed or ruled out by polymerase chain reaction analysis. The impact was analyzed of cardiac troponin I positivity on 30-day mortality.
Results: In total, 433 patients were distributed among the following groups: confirmed COVID-19 (n = 186), 22% with myocardial injury (n = 41); and ruled out COVID-19 (n = 247), 21.5% with myocardial injury (n = 52). The confirmed and ruled out COVID-19 groups had a similar age, sex, and cardiovascular history. Mortality was significantly higher in the confirmed COVID-19 group than in the ruled out group (19.9% vs 5.3%, $P < .001$). In Cox multivariate regression analysis, cardiac troponin I was a predictor of mortality in both groups (confirmed COVID-19 group: HR, 3.54; 95%CI, 1.70-7.34; $P = .001$; ruled out COVID-19 group: HR, 5.57; 95%CI, 1.70-18.20; $P = .004$). The predictive model analyzed by ROC curves was similar in the 2 groups ($P = .701$), with AUCs of 0.808 in the confirmed COVID-19 group (0.750-0.865) and 0.812 in the ruled out COVID-19 group (0.760-0.864).
Conclusions: Myocardial injury is detected in 1 in every 5 patients with confirmed or ruled out COVID-19 and predicts 30-day mortality to a similar extent in both circumstances.

Implicaciones pronósticas del daño miocárdico en pacientes con y sin diagnóstico confirmado de COVID-19 atendidos en un hospital universitario

Palabras clave:
Daño miocárdico
Troponina
COVID-19

RESUMEN

Introducción y objetivos: La elevación de la troponina cardiaca como marcador de daño miocárdico es un predictor pronóstico en pacientes con COVID-19. Sin embargo, se desconoce su rendimiento en pacientes coetáneos con sospecha de COVID-19 pero con prueba de reacción en cadena de la polimerasa negativa.
Métodos: Estudio de cohortes retrospectivo que incluyó a todos los pacientes consecutivos atendidos en un hospital universitario con sospecha de COVID-19, confirmada o descartada mediante prueba de reacción en cadena de la polimerasa, todos ellos con determinaciones de troponina cardiaca I. Se analizó el impacto de la positividad de la troponina cardiaca I en la mortalidad a 30 días.
Resultados: Un total de 433 pacientes quedaron distribuidos en los siguientes grupos: COVID-19 confirmada (n = 186), el 22% de ellos con daño miocárdico (n = 41), y COVID-19 descartada (n = 247), el 21,5% de ellos con daño miocárdico (n = 52). Los grupos de COVID-19 confirmada y descartada tuvieron similares edad, sexo y antecedentes cardiovasculares. La mortalidad en el grupo de COVID-19 confirmada frente al de descartada fue significativamente superior (el 19,9 frente al 5,3%; p < 0,001). En ambos grupos, el daño miocárdico fue predictor de mortalidad en el análisis multivariado de regresión de

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Cox (grupo de COVID-19 confirmada, HR = 3,54; IC95%, 1,70-7,34; p = 0,001; grupo de COVID-19 descartada, HR = 5,57; IC95%, 1,70-18,20; p = 0,004). El modelo predictivo analizado por curvas ROC fue similar en ambos grupos: COVID-19 confirmada, AUC = 0,808 (0,750-0,865); COVID-19 descartada, AUC = 0,812 (0,760-0,864) (p = 0,701).

Conclusiones: Se detecta daño miocárdico en 1 de cada 5 pacientes con infección por COVID-19 confirmada o descartada. En ambas circunstancias, el daño miocárdico es predictor de mortalidad a 30 días en similar grado.

Abbreviations

cTn: cardiac troponin
cTnI: cardiac troponin I
PCR: polymerase chain reaction

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the new coronavirus SARS-CoV-2 and has produced a global pandemic with colossal impact. The disease has a wide spectrum of clinical manifestations, ranging from asymptomatic or minimally symptomatic episodes to severe respiratory failure requiring mechanical ventilation and death.[1] A number of prognostic markers have been identified that could facilitate early risk stratification in COVID-19 patients. These markers include advanced age and comorbidities such as cardiovascular disease, chronic lung disease, hypertension, and cancer,[2,3] as well as several biochemical markers, including ferritin, leukopenia, and D dimer.[4]

COVID-19 has major cardiovascular repercussions and causes myocardial injury that can manifest as an increase in cardiac troponins (cTn).[5] Several studies have indicated that elevated cTn could be another marker of poor prognosis, and therefore useful for identifying patients at high risk. The implication of cTn is unsurprising because myocardial injury in the absence of type 1 myocardial infarction is a general risk marker present in many clinical processes associated with possible cardiac involvement.[6] To date, published studies of myocardial injury and COVID-19 have been conducted in regions where health care systems have been under immense strain due to the pandemic, with hospitals dedicated almost exclusively to the care of COVID-19 patients.[7–11] The association between myocardial injury and COVID-19 prognosis has not been tested in regions where the health care burden has been lower and the care of COVID-19 patients has coexisted alongside that of patients with other diagnoses, often with an infectious etiology

METHODS

Study population

A retrospective observational study was conducted of all consecutive patients treated for suspected SARS-CoV-2 infection at a university hospital between March 16 and April 16 2020 and who had at least 1 available cardiac troponin I (cTnI) measurement. cTnI assay was included in the emergency department analytical protocol for patients with suspected COVID-19. Almost all patients were initially treated in the emergency department, and only those with extremely severe symptoms were transferred to the intensive care unit (ICU). Patients with mild clinical symptoms and normal chest X-ray were discharged immediately, without a blood analysis.

Patients were identified for inclusion in the study by examining SARS-CoV-2 polymerase chain reaction (PCR) results and cTnI values for the same patients, determined in the hospital laboratory. When a patient had several cTnI determinations, the highest value was selected. Strong clinical suspicion of COVID-19 was confirmed or ruled out by further tests for SARS-CoV-2 antigens or antibodies.

Analyzed variables

Patient variables included demographic data, cardiovascular medical history and associated risk factors, the reason for attending the emergency department, clinical and analytical variables, electrocardiograms, imaging data (chest X-ray), and data from any other examinations performed. For hospitalized patients, additional variables were the need for ICU admission, the length of stay in the unit, and the need for mechanical ventilation. Clinical data for patients with elevated cTnI were assessed for imbalance between myocardial oxygen supply and demand (increased demand, especially tachycardia, or reduced supply, especially severe hypoxemia or hypotension); patients showing an oxygen imblance were categorized as having type 2 myocardial infarction according to established criteria.[12] The study population was distributed into 4 groups according to the confirmation or exclusion of COVID-19 diagnosis and the positive or negative outcome of the cTnI assay.

The main outcome variable was 30-day mortality. Patients were followed up by accessing electronic medical records.

Laboratory assays

SARS-CoV-2 PCR assay

Viral RNA was purified with the RNeasy Mini Kit in a Qiacube Connect analyzer (QIAGEN, Germany). Reverse transcription PCR (RT-PCR) was performed in a CFX96 Touch System thermocycler (Bio-Rad Laboratories Inc, Hercules, United States) using a commercial kit that amplifies SARS-CoV-2 genes *E*, *N*, and *RdRP* (Allplex 2019-nCoV Assay, Seegene Inc, South Korea).

Antigen assay

SARS-CoV-2 antigens were detected by immunochromatography assay (Fluorescence Ag Rapid Test, BIOEASY Biotechnology Co, Ltd, China).

Antibody assay

Antibodies to SARS-CoV-2 were detected by immunochemiluminescence assay (COVID-19 VIRCLIA Monotest, Vircell SL, Spain).

Cardiac troponin I

cTnI was determined with a high-sensitivity troponin I immunoassay kit (Siemens, Advia Centaur, United States). The lower and upper detection limits were 2.5 and 25 000 ng/L, respectively, as established by the manufacturer. Determinations below the lower detection limit were assigned a value of 0 ng/L, and determinations above the upper limit were assigned a value of 25 000 ng/L. The reference limit for a positive cTnI determination was > 47 ng/L, which corresponds to the 99th percentile with a total analytical imprecision < 10% as expressed by the coefficient of variation.

Statistical analysis

Categorical variables are presented as number (%) and continuous variables as median [interquartile range]. Comparisons between categorical variables were made by chi-square test or the Fisher exact test, as appropriate. Continuous variables were compared by the Mann-Whitney *U* test. Survival was analyzed with the Kaplan-Meier method, and between-group comparisons were made using the log-rank test. To determine the association between myocardial injury and mortality, the groups with and without COVID-19 were analyzed by univariate and multivariate Cox regression. The adjusted model included variables showing significance in the univariate analysis or other clinically relevant variables. To prevent overadjustment, the model was restricted to 6 variables: age, history of hypertension, history of myocardial infarction, history of chronic lung disease, glomerular filtration rate on admission, and the presence of elevated cTnI. Univariate and multivariate Cox regression analyses were also conducted to assess the interaction between COVID-19 and elevated cTnI in the entire cohort. The proportionality assumption was verified using Schoenfeld residuals. The ability of cTnI to improve mortality prediction in the confirmed or ruled out COVID-19 groups was assessed using a specially designed simple clinical model comprising age, history of hypertension, and glomerular filtration rate on admission. The predictive ability of this model was tested before and after adding cTnI by analysis of the ROC curve, the net reclassification improvement index, and the integrated discrimination improvement index. Finally, the ROC curve method was used to compare the predictive model between the 2 groups. All statistical analyses were performed using the STATA 14.2 statistical program (StatCorp, College Station, United States). Differences were considered statistically significant at $P < .05$.

This study forms part of a large research project investigating myocardial injury detected in patients treated in the emergency department and has local Ethics Committee approval.

RESULTS

During the study period, 2447 SARS-CoV-2 PCR tests were performed on samples from 1795 patients. A large number of these tests were on outpatients or patients from other catchment populations. In total, 26% of the samples were from patients treated at our hospital and who had at least one cTnI measurement. Patients with incomplete clinical or analytical data were excluded, as were those with a diagnosis of type 1 myocardial infarction, no suspicion of COVID-19, or a negative PCR assay. The final sample included 433 patients, of whom 186 (43%) had a confirmed COVID-19 diagnosis; 29 of these patients had a negative SARS-CoV-2 PCR assay but a positive serological antigen or antibody assay. COVID-19 infection was ruled out in the remaining 247 patients (57%). Elevated cTnI was detected in 41 patients (22%) in the confirmed COVID-19 group and in 52 patients (21%) in the ruled out COVID-19 group (figure 1).

Demographic data, cardiovascular risk factors, and cardiovascular disease histories are shown for the confirmed and ruled out COVID-19 patient groups in table 1. Differences between patients with and without myocardial injury are shown in the table 1of the supplementary data and the table 2 of the supplementary data. Baseline patient characteristics categorized by 30-day survival for the whole cohort (confirmed and ruled out COVID-19 infection) are shown in the table 3 of the supplementary data. The variables showing an association with myocardial injury were similar in both patient groups: age, hypertension, dyslipidemia, a history of

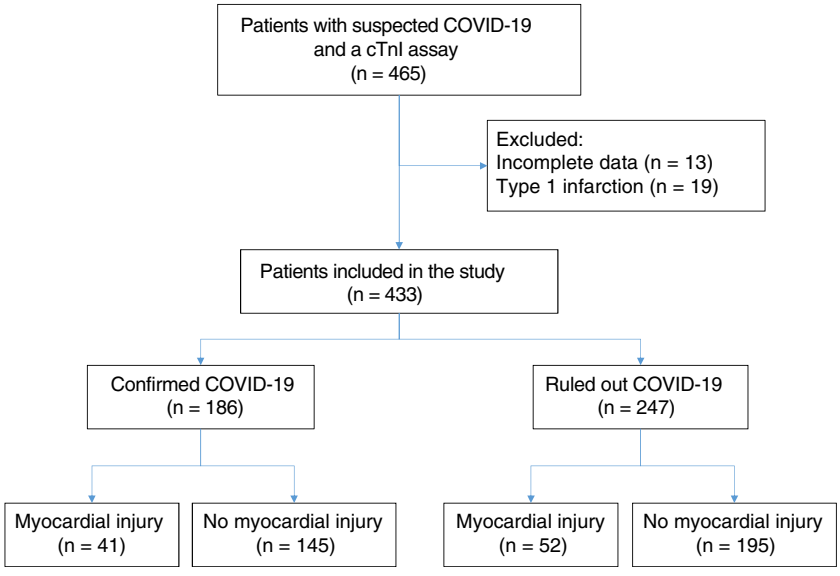

Figure 1. Patient flow chart. cTnI, cardiac troponin I.

Table 1
Baseline characteristics of patients in the confirmed and ruled out COVID-19 groups

	Confirmed COVID-19 n = 186	Ruled out COVID-19 n = 247	*P*
Demographic variables			
Age, y	67.5 [52.5-77.5]	68.5 [51.5-76.5]	.942
Men	111 (59.7)	137 (55.5)	.380
Cardiovascular risk factors			
Hypertension	80 (43.0)	122 (49.4)	.188
Diabetes mellitus	43 (23.1)	63 (25.5)	.567
Dyslipidemia	48 (25.8)	67 (27.1)	.758
Smoking	40 (21.5)	60 (24.3)	.496
History of cardiovascular disease			
Myocardial infarction	20 (10.8)	28 (11.3)	.848
Heart failure	14 (7.5)	27 (10.9)	.231
Peripheral artery disease	13 (7.0)	14 (5.7)	.574
Cerebrovascular disease	14 (7.5)	17 (6.9)	.797
Chronic kidney disease	22 (11.8)	30 (12.2)	.920
Chronic lung disease	31 (16.7)	58 (23.5)	.082

Data are expressed as No. (%) or median [interquartile range].

myocardial infarction, and a history of kidney disease. The main diagnoses among patients who tested negative for COVID-19 were respiratory infection (48%), other infections (12.2%), heart failure (8.1%), gastrointestinal disease (3.4%), neurological disorders (3.6%), and various other diagnoses.

Patients with confirmed COVID-19 more frequently presented with dyspnea, fever, and diarrhea, but the rates of coughing and muscle pain were similar to those in patients without COVID-19 (table 2 and the tables 4–6 of the supplementary data). The initial vital signs of confirmed COVID-19 patients showed small but significant differences from those of patients without COVID-19 (lower heart rate, lower systolic blood pressure, and lower oxygen saturation). Chest X-rays revealed a pattern of bilateral infiltration in almost 2 out of every 3 confirmed COVID-19 patients. Patients with and without COVID-19 showed no differences in baseline blood glucose, glomerular filtration rate, or hemoglobin. However, the 2 patient groups differed in the remaining analytical parameters. Confirmed COVID-19 patients had lower leukocyte, lymphocyte, and platelet counts, and while D dimer values were similar in the 2 groups, confirmed COVID-19 patients had higher levels of serum lactate dehydrogenase and C-reactive protein.

Patients with a confirmed COVID-19 diagnosis had a higher rate of hospitalization and ICU admission (mean admission time, 17 days). Confirmed COVID-19 patients also more frequently required mechanical ventilation (table 3 and table 7 of the supplementary data and table 8 of the supplementary data). Patients with and without COVID-19 showed no differences in the rate of pulmonary thromboembolism (0.5% and 1.2%, respectively) or the diagnosis of type 2 myocardial infarction (12.9% and 8.1%).

Treatments differed significantly between the 2 groups. Antibiotics were administered to 73% of confirmed COVID-19 patients, and two thirds of these patients were treated with hydroxychloroquine, almost half with lopinavir-ritonavir, one third with azithromycin, and a handful with corticosteroids (table 3). In-hospital mortality in the confirmed COVID-19 group was 18.8%, and 53.7% of these deceased patients had myocardial injury. In-hospital mortality among patients without COVID-19 was 4.1%, with myocardial injury detected in 13.5% of these patients (figure 2). The variables showing a statistical association with 30-day mortality among confirmed COVID-19 patients in the multivariate Cox logistic regression analysis were a history of chronic lung disease, glomerular filtration rate on admission, and a positive cTnI assay; for the ruled out COVID-19 group, the statistically associated variables were age, a history of myocardial infarction, and a positive cTnI assay (table 4). As these observations indicate, COVID-19 infection and a positive cTnI assay showed no interaction in 30-day mortality.

Predictive ability of cardiac troponin I

For the confirmed COVID-19 group, ROC curve analysis of 30-day mortality in the clinical predictive model revealed an area under the curve (AUC) = 0.775 (95% confidence interval [95%CI], 0.716-0.835). The addition of cTnI increased the AUC to 0.808 (95%CI, 0.750-0.865), and the difference was statistically significant ($P = .024$). Adding cTnI to the clinical model also increased net reclassification improvement by 0.632 (0.285-0.979; $P < .001$) and integrated discrimination improvement by 0.039 (0.005-0.073; $P = .013$).

For the ruled out COVID-19 group, ROC curve analysis of 30-day mortality in the clinical predictive model yielded an AUC = 0.770 (95%CI, 0.713-0.826), and adding cTnI increased the AUC to 0.812 (95%CI, 0.760-0.864; $P = .023$). Adding cTnI to the clinical model increased net reclassification improvement by 1.058 (0.519-1.597; $P < .001$) and integrated discrimination improvement by 0.068 (0.032-0.103; $P < .001$).

The ROC curves for the predictive model including cTnI did not differ significantly between the confirmed and ruled out COVID-19 groups ($P = .701$) (figure 3).

DISCUSSION

Main findings

Our study shows that in a consecutive cohort with suspected COVID-19, patients with positive and negative SARS-CoV-2 PCR results had a similar degree of myocardial injury assessed by cTnI assay. The predictive ability of elevated cTnI to identify 30-day mortality risk was similar in the 2 patient groups. The higher

Table 2
Clinical characteristics of patients in the confirmed and ruled out COVID-19 groups

	Confirmed COVID-19 n = 186	Ruled out COVID-19 n = 247	*P*
Symptoms			
Dyspnea	110 (59.1)	116 (47.0)	.012
Fever	133 (72.3)	108 (44.3)	< .001
Cough	94 (51.1)	104 (42.6)	.082
Myalgia	11 (6.0)	8 (3.3)	.178
Diarrhea	29 (15.9)	14 (5.8)	.001
Chest pain	15 (8.1)	23 (9.3)	.650
Other	87 (46.8)	121 (49.2)	.619
Symptom duration, d	4 [2-7]	3 [0-7]	.011
Vital signs			
Heart rate, bpm	86 [74-104]	90 [79-106]	.030
SBP, mmHg	124 [109-138]	126 [118–140]	.042
Oxygen saturation, %	96 [92-99]	98 [95-99]	< .001
Electrocardiogram			
Atrial fibrillation	19 (11.3)	32 (16.3)	.169
RBBB or LBBB	8 (4.8)	15 (7.7)	.253
Radiological findings			
Consolidation	40 (21.5)	38 (15.6)	.114
Ground glass opacities	18 (9.7)	5 (2.1)	< .001
Bilateral infiltrates	115 (62.2)	39 (16.0)	< .001
Laboratory tests			
Blood glucose, mg/dL	105 [91-140]	108 [94-143]	.149
GFR, mL/min/1.73 m^2	89 [59-103]	83 [57-99]	.080
Hemoglobin, g/dL	12.6 [11.3-13.9]	12.8 [11.0-14.0]	.821
Leukocytes, $\times 10^9$/L	6.4 [4.7–9.0]	8.8 [6.6-12.3]	< .001
Lymphocytes, $\times 10^9$/L	0.9 [0.5-1.4]	1.0 [0.5-1.9]	.013
Platelets, $\times 10^9$/L	208 [157-282]	227 [182-297]	.030
D dimer, ng/mL	724 [445-1.825]	713 [380-1.584]	.392
LDH, U/L	276 [216-385]	217 [172-267]	< .001
C-reactive protein, mg/dL	8 [3-17]	3 [1-10]	< .001
Maximum cTnI, ng/L	14 [4-37]	10 [3-38]	.235
Elevated cTnI	41 (22)	52 (21.0)	.898

cTnI, cardiac troponin I; GFR, glomerular filtration rate; LBBB, left bundle branch block; LDH, lactate dehydrogenase; RBBB, right bundle branch block; SBP, systolic blood pressure.
Data are expressed as No. (%) or median [interquartile range].

mortality in the confirmed COVID-19 group must therefore be due to mechanisms independent of cardiac involvement.

Myocardial injury in patients with confirmed COVID-19

Mortality is high among COVID-19 patients requiring hospitalization and is even higher among those who are elderly or have a history of underlying cardiovascular disease.[13] An association between SARS-CoV-2 infection and myocardial injury was first reported in a small series of 41 hospitalized COVID-19 patients, 5 of whom had elevated cTnI.[7] Elevated cTnI in COVID-19 patients was later also reported in several other small studies of Chinese populations.[7–11] In a cohort of 191 patients with confirmed COVID-19, univariate analysis indicated that the risk of death was higher when the cTnI concentration exceeded the 99th percentile upper reference limit (odds ratio [OR] = 80.15; 95%CI, 10.3-620.4; $P < .0001$).[3] These patients had a higher requirement for invasive and noninvasive ventilation (22% vs 4% and 46% vs 4%, respectively), as well as higher rates of acute respiratory distress syndrome (59% vs 15%) and acute kidney failure (9% vs 0%) ($P < .001$ in all cases). Mortality was 10 times higher among patients with myocardial injury at presentation (51% vs 5%; hazard ratio [HR] = 3.41; 95%CI, 1.62-7.16). With the global spread of COVID-19 from China, an association with myocardial injury has also been described in other countries, including Italy[14] and the United States.[15] Possible mechanisms of myocardial injury and related cardiac phenotypes in COVID-19 include a direct action of the virus on the myocardium, coronary microvascular ischemia mediated by the binding of SARS-CoV-2 to endothelial angiotensin II converting enzyme II (ACE2), stress cardiomyopathy, and tachycardia due to exogenous adrenergic stimulation.[16]

Studies published to date may have overestimated the prevalence of myocardial injury among COVID-19 patients. cTnI values were available for 145 of 191 patients (75%) included in a series of 813 consecutive adults admitted to Jinyintan Hospital or Wuhan Pulmonary Hospital[3] and for 416 of 645 consecutive patients (64%) admitted to Renmin Hospital of Wuhan University.[10] These rates suggest that cTnI was likely measured only in patients with suspected cardiac involvement (myocardial ischemia

Table 3
Clinical management, treatment, and mortality among patients in the confirmed and ruled out COVID-19 groups

	Confirmed COVID-19 n = 186	Ruled out COVID-19 n = 247	*P*
Clinical management			
Hospital admission	156 (83.9)	123 (49.8)	< .001
ICU transfer	33 (17.7)	18 (7.3)	.001
Days in ICU	17 [6-34]	5 [3-8]	.007
Mechanical ventilation	28 (15.1)	9 (3.7)	< .001
PTE	1 (0.5)	3 (1.2)	.638
Type 2 myocardial infarction	24 (12.9)	21 (8.5)	.137
Treatment			
Antibiotics*	136 (73.5)	127 (51.8)	< .001
Hydroxychloroquine	117 (63.6)	13 (5.3)	< .001
Lopinavir-ritonavir	86 (47.0)	3 (1.2)	< .001
Azithromycin	68 (37.2)	37 (15.1)	< .001
Corticosteroids	16 (8.7)	19 (7.8)	.725
ACEI or ARB	20 (10.8)	53 (21.5)	.003
Mortality			
In-hospital mortality	35 (18.8)	10 (4.1)	< .001
30-d mortality	37 (19.9)	13 (5.3)	< .001

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICU, intensive care unit; PTE, pulmonary thromboembolism.
Data are expressed as No. (%) or median [interquartile range].
* Excluding azithromycin.

or ventricular dysfunction). However, although cTnI was measured systematically in all patients in our series, the proportion of patients with elevated cTnI was similar to that reported in the Chinese studies, indicating similar rates of myocardial injury. Moreover, although no instances were detected in our series, elevated cTnI is sometimes associated with type 1 myocardial infarction due to atherothrombosis triggered by the proinflammatory and prothrombotic state, as described in previous influenza epidemics[17] and other inflammatory situations.[18] Among patients with severe hypoxemia, hypotension, or prolonged tachycardia, type 2 myocardial infarction is more common. In our series, more than half of the confirmed COVID-19 patients met the criteria for type 2 myocardial infarction, a finding not reported in previous studies.

Cardiovascular risk factors and comorbidities are prevalent in COVID-19 patients,[19] and while these conditions do not appear to enhance SARS-CoV-2 infectiousness, they may increase disease severity. An important goal of cardiovascular therapy is to reduce the concentration or activity of angiotensin II, which is involved in inflammatory mechanisms and endothelial dysfunction. It will be important to clarify whether treatment-induced tissue overexpression of ACE2 enhances SARS-CoV-2 infection or overcomes the ACE2 deficit to reduce inflammation and vasoconstriction in the heart, lungs, and kidneys. Likewise, studies should address the regulation of serum ACE2 concentration and its ability to reduce the affinity of SARS-CoV-2 for tissue ACE2 and thereby reduce infection. A study of 18 422 patients tested for COVID-19 (24.5% positive; 9.3% requiring hospitalization) observed no association between treatment with ACE inhibitors or angiotensin II receptor antagonists and a positive SARS-CoV-2 test result.[20]

It is unclear if the presumably acute myocardial injury detected in COVID-19 patients will cause future chronic myocardial injury and structural coronary disease. However, a study of 25 survivors of the previous SARS coronavirus epidemic 12 years after their

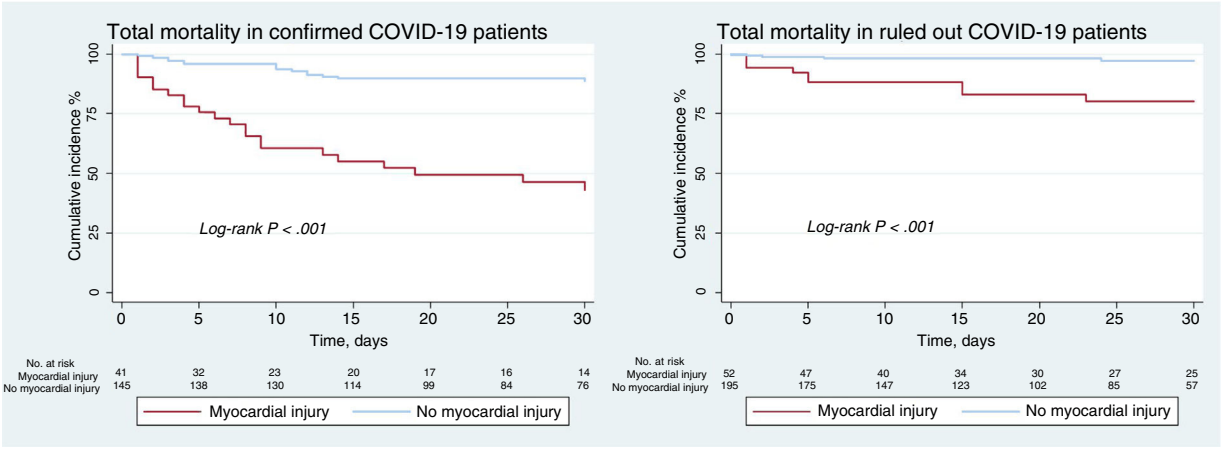

Figure 2. Kaplan-Meier curves for 30-day mortality in the confirmed and ruled out COVID-19 patient groups as a function of the presence or absence of myocardial injury.

Table 4
Univariate and multivariate analyses of 30-day mortality in the whole cohort and in the confirmed and ruled out COVID-19 patient groups

	Confirmed COVID-19 and ruled out COVID-19			
	Univariate Cox regression		Multivariate Cox regression	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age	1.05 (1.03-1.08)	<.001	1.03 (1.01-1.05)	.041
Hypertension	3.13 (1.69-5.80)	<.001	-	-
History of AMI	3.15 (1.67-5.93)	<.001	-	-
History of CLD	1.87 (1.03-3.38)	.040	1.85 (1.01-3.41)	.047
GFR on admission*	1.03 (1.02-1.04)	<.001	1.02 (1.01-1.03)	<.001
COVID-19	3.53 (1.87-6.64)	<.001	3.59 (1.62-7.93)	.002
Myocardial injury	6.50 (3.67-11.51)	<.001	4.27 (1.28-14.22)	.018
Interaction between myocardial injury and COVID-19	4.43 (1.47-13.34)	.008	1.45 (0.37-5.65)	.590
	Confirmed COVID-19			
	Univariate Cox regression		Multivariate Cox regression	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age	1.05 (1.02-1.07)	<.001	-	-
Hypertension	2.93 (1.47-5.83)	.002	-	-
History of AMI	2.69 (1.23-5.89)	.013	-	-
History of CLD	3.03 (1.54-5.95)	.001	2.57 (1.30-5.09)	.007
GFR on admission*	1.03 (1.02-1.04)	<.001	1.02 (1.01-1.03)	<.001
Myocardial injury	6.80 (3.52-13.13)	<.001	3.54 (1.70-7.34)	.001
	Ruled out COVID-19			
	Univariate Cox regression		Multivariate Cox regression	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age	1.07 (1.02-1.12)	.003	1.06 (1.01-1.12)	.021
Hypertension	6.00 (1.33-27.09)	.020	-	-
History of AMI	5.08 (1.66-15.53)	.004	3.09 (1.01-9.51)	.049
History of CLD	0.94 (0.26-3.42)	.930	-	-
GFR on admission*	1.02 (1.01-1.04)	.003	-	-
Myocardial injury	8.19 (2.52-26.62)	<.001	5.57 (1.70-18.20)	.004

95%CI, 95% confidence interval; AMI, acute myocardial infarction; CLD, chronic lung disease; GFR, glomerular filtration rate; HR, hazard ratio.
* Risk per point reduction in GFR.

clinical recovery found that 64% had hyperlipidemia, 44% cardiovascular abnormalities, and 60% glucose metabolism alterations; a metabolomic analysis of these patients revealed dysregulation of lipid metabolism.[21]

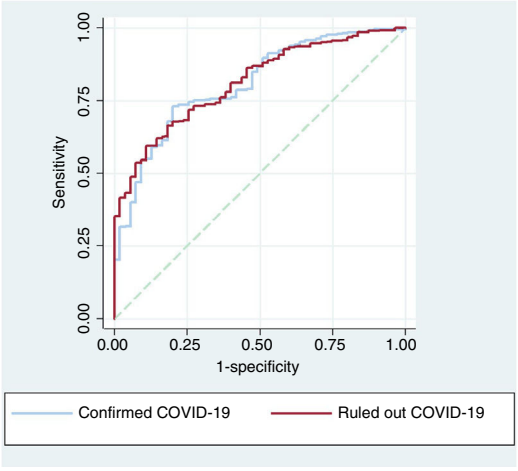

Figure 3. ROC curves for a predictive model of mortality in the confirmed COVID-19 and ruled out COVID-19 patient groups, including clinical variables and cardiac troponin.

The detection of myocardial injury could facilitate appropriate decision making about transfer to the ICU, improve understanding of the systemic consequences of COVID-19, and guide medication with drugs such as inotropes, vasopressors, and diuretics for patients with significant cardiac dysfunction. Furthermore, additional examination by echocardiography or cardiac magnetic resonance could help to identify and guide therapy for COVID-19 survivors with a clearly defined cardiac phenotype.

Myocardial injury in patients without COVID-19

The most remarkable findings of our study are likely the high frequency of myocardial injury in conditions not caused by COVID-19 and the similar predictive ability of cTnI in patients with and without COVID-19. This is not surprising, since a previous study found a similar incidence of myocardial injury in patients without type 1 myocardial infarction to that reported here.[6] It is important to define the pathophysiological diagnosis of these patients according to the fourth universal definition of myocardial infarction[22] as type 2 myocardial infarction[12] or as acute or chronic nonischemic myocardial injury.[23] Whatever the cause of hospitalization, admitted patients often have an imbalance in oxygen supply and demand, and this is especially common among patients in a critical condition. This oxygen deficit is not limited to the myocardium and likely occurs in the cells of most organs.

However, the sensitivity of cTnI assays ensures that cTnI is one of the earliest detected and most accurate biomarkers of organ dysfunction. In this context, cTnI testing could provide the basis for the early initiation of treatments to improve general tissue oxygenation and perfusion.

In recently published preliminary guidelines on the use of biomarkers in COVID-19 patients, the American College of Cardiology recommends cTnI measurement only in patients with suspected myocardial infarction.[24] However, understanding the effect of COVID-19 on the cardiovascular system is essential to provide appropriate and comprehensive treatment to patients with and without a history of heart disease. Accurate estimates of the prevalence of myocardial injury in COVID-19 can be obtained only through the systematic testing of asymptomatic and symptomatic individuals infected with SARS-CoV-2.[25]

Limitations

Our study has some limitations. First, in most patients, cTnI was determined on or within 24 hours of admission, with no repeat measurements over the course of the disease. However, changes in cTnI values have been reported during the hospitalization of COVID-19 patients.[3] A second limitation is that echocardiography was performed only sporadically, and we therefore lack information about the possible repercussions of myocardial injury on ventricular function in these patients. Third, COVID-19 was diagnosed based on PCR and serological test results. Although these tests are highly sensitive and specific, we cannot exclude the possibility of false-positive and false-negative results in our study population. However, this possibility seems unlikely given that all patients were followed up for at least 1 month. Finally, the ruled out COVID-19 group was relatively heterogeneous, although infectious disease predominated, especially affecting the respiratory system.

CONCLUSIONS

A number of questions remain regarding the myocardial injury detected in COVID-19. Areas of uncertainty include the mechanism linking SARS-CoV-2 to myocardial injury, how myocardial injury in COVID-19 patients differs from that detected in other populations, and what specific therapeutic options are available for myocardial injury in COVID-19.[26] Our study makes an important contribution to answering one of these questions; myocardial injury in COVID-19 patients is unlikely to differ significantly from that present in multiple acute processes, whether infectious or sterile, and the impact on prognosis is also likely similar. Future efforts should therefore be directed at defining the mechanisms of myocardial injury in patients with acute conditions and advancing the development of strategies to mitigate the associated poor prognosis.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

WHAT IS KNOWN ABOUT THE TOPIC?

- COVID-19 mainly affects the respiratory system, manifesting as pneumonia. However, this disease has a broad spectrum of clinical manifestations, ranging from asymptomatic or mildly symptomatic to extremely severe episodes. Myocardial injury detected as an increase in cTn is one of the main factors associated with mortality in this disease.

WHAT DOES THIS STUDY ADD?

- The frequency of myocardial injury assessed by elevated cTnI was similar in patients with confirmed COVID-19 to that in patients with exclusion of suspected COVID-19 and who were treated at the same hospital and in the same period. In both patient groups, myocardial injury was an important predictor of in-hospital mortality. A model including clinical variables and cardiac troponin showed a similar ability to predict in-hospital mortality in both patient groups.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2020.08.027

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