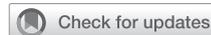


Characteristics of Cardiac Injury in Critically Ill Patients With Coronavirus Disease 2019



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BACKGROUND: Cardiac injury has been reported in up to 30% of coronavirus disease 2019 (COVID-19) patients. However, cardiac injury is defined mainly by troponin elevation without description of associated structural abnormalities and its time course has not been studied.

RESEARCH QUESTION: What are the ECG and echocardiographic abnormalities as well as their time course in critically ill COVID-19 patients?

STUDY DESIGN AND METHODS: The cardiac function of 43 consecutive COVID-19 patients admitted to two ICUs was assessed prospectively and repeatedly, combining ECG, cardiac biomarker, and transthoracic echocardiographic analyses from ICU admission to ICU discharge or death or to a maximum follow-up of 14 days. Cardiac injury was defined by troponin elevation and newly diagnosed ECG or echocardiographic abnormalities, or both.

RESULTS: At baseline, 49% of patients demonstrated a cardiac injury, and 70% of patients experienced cardiac injury within the first 14 days of ICU stay, with a median time of occurrence of 3 days (range, 0-7 days). The most frequent abnormalities were ECG or echocardiographic signs, or both, of left ventricular (LV) abnormalities (87% of patients with cardiac injury), right ventricular (RV) systolic dysfunction (47%), pericardial effusion (43%), new-onset atrial arrhythmias (33%), LV relaxation impairment (33%), and LV systolic dysfunction (13%). Between baseline and day 14, the incidence of pericardial effusion and of new-onset atrial arrhythmias increased and the incidence of ECG or echocardiographic signs, or both, of LV abnormalities as well as the incidence of LV relaxation impairment remained stable, whereas the incidence of RV and LV systolic dysfunction decreased.

INTERPRETATION: Cardiac injury is common and early in critically ill COVID-19 patients. ECG or echocardiographic signs, or both, of LV abnormalities were the most frequent abnormalities, and patients with cardiac injury experienced more RV than LV systolic dysfunction.

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KEY WORDS: cardiac injury; COVID-19; echocardiography; ECG; ICU

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ABBREVIATIONS: COVID-19 = coronavirus disease 2019; LV = left ventricular; RV = right ventricular; TTE = transthoracic echocardiography

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Take-home Point

In this French prospective cohort of critically ill patients with COVID-19, cardiac injury was common and occurred early within the first 14 days of ICU stay. The most frequent newly diagnosed abnormalities were ECG or echocardiographic signs, or both, of LV abnormalities, and patients with cardiac injury experienced more RV than LV systolic dysfunction.

Beginning in December 2019, a worldwide pandemic with an emergent coronavirus, severe acute respiratory syndrome coronavirus 2, has been responsible for coronavirus disease 2019 (COVID-19).¹ Among COVID-19 patients admitted to an ICU, from 12% to 30% of them experienced cardiac injury.²⁻⁵ These patients were more likely to have underlying

cardiovascular diseases, and cardiac injury was associated with in-hospital mortality.^{5,6}

In most studies, cardiac injury was defined by troponin elevation, regardless of new abnormalities in ECG or echocardiography results.^{5,6} Moreover in studies also considering ECG or echocardiographic abnormalities, or both, to define cardiac injury, the latter were not described, were limited to assessment of left ventricular (LV) systolic function,^{2,4,7} or were described in non-critically ill patients.⁸ Finally, no study has described the time course of cardiac injury during COVID-19.

This study aimed to characterize cardiac injury and its time course in critically ill COVID-19 patients prospectively with multimodal assessment of cardiac function combining ECG, cardiac biomarkers, and transthoracic echocardiography (TTE) analyses.

Methods

This prospective, observational study was conducted in two ICUs of university hospitals. This study was approved by our institutional review board (Numéro d'Identification - Recherches et Collections Biologiques [IDRCB] Identifier: 2020-A01197-32), and all patients or next of kin were informed about the study and consented to participate.

Patients

We included all consecutive patients with COVID-19 confirmed by real-time reverse-transcriptase polymerase chain reaction assay of nasal swabs or pulmonary samples. Exclusion criteria were (1) patients younger than 18 years, (2) patients with a care-limitation decision, and (3) patients with poor echogenicity, defined as the inability to obtain reliable Doppler and accurate LV ejection fraction measurements.

ECG Analyses and Echocardiographic Measurements

Besides continuous ECG monitoring to look for arrhythmia, 12- or 18-lead ECGs in case of suspicion of circumflex occlusion and inferior or right ventricular (RV) infarction⁹ were performed at each TTE examination time. All ECG results were interpreted offline by the same experienced cardiologist blinded to patients' identities. All TTE measurements were performed by experienced board-certified operators according to the current recommendations¹⁰ and were analyzed offline blinded to patients' identities. All ECG and TTE measurements are detailed in [e-Appendix 1](#).

Cardiac Injury Definition

Cardiac injury was defined by an increase in high-sensitivity troponin T or troponin I levels more than the 99th percentile upper reference limit⁹ and newly diagnosed ECG or TTE abnormalities, or both.^{2,7} The ECG and TTE abnormalities were considered newly diagnosed if they were unknown before ICU admission (patients with no or without available results of prior cardiac assessment in patients' files held by the referring physicians) or if they emerged during ICU stay.

Newly diagnosed ECG abnormalities defining cardiac injury were the following: (1) ECG signs of LV abnormalities suggestive of coronary

heart disease, Takotsubo syndrome, myocarditis or septal cardiomyopathy (repolarization abnormalities involving at least two contiguous leads of the same territory [T-wave inversion, ST-segment depression or elevation], pathologic Q waves [in at least two contiguous leads], newly diagnosed left bundle branch block, ventricular arrhythmia, and severe brady-arrhythmia)^{9,11-15} and (2) new-onset atrial arrhythmias (atrial fibrillation, atrial flutter, or atrial tachycardia).

Newly diagnosed echocardiographic abnormalities defining cardiac injury were the following: (1) echocardiographic signs of LV abnormalities suggestive of coronary heart disease, Takotsubo syndrome, myocarditis, or septal cardiomyopathy (mild, moderate, or severe LV systolic dysfunction or wall motion abnormalities)^{9,11-15}; (2) LV relaxation impairment (ie, LV diastolic dysfunction) with at least two of the following abnormalities: abnormal e' -wave velocity ($e'_{\text{septal}} < 7$ cm/s or $e'_{\text{lateral}} < 10$ cm/s), E/e'_{averaged} ratio > 14 in patients with sinus rhythm, E/e'_{septal} ratio > 11 in patients with atrial arrhythmia, or left atrial dilation (volume > 34 mL/m²)¹⁶; (3) cor pulmonale (RV end-diastolic area-to-LV end-diastolic area > 0.6 and flattened interventricular septum); (4) RV systolic dysfunction (tricuspid annular plane systolic excursion < 16 mm, or systolic tricuspid annular velocity < 9.5 cm/s or RV fractional area change $< 35\%$)¹⁰; (5) any new significant valvulopathy (aortic, mitral, tricuspid, and pulmonary valve disease)¹⁷; and (6) pericardial effusion.

Data Collection and Study Design

Demographic characteristics and comorbidities of patients, clinical and biological data, results of cardiac function assessment (ECG, TTE, and cardiac biomarkers, ie, high-sensitivity troponin T or troponin I and B-type or N-terminal pro-B-type natriuretic peptide), therapeutics, and ICU clinical outcomes (mortality, use of vasopressors, mechanical ventilation, and renal replacement therapy) were collected and analyzed. All biological, ECG, and echocardiographic analyses were performed at ICU admission (baseline), at day 3, and then weekly until ICU discharge or death, with a maximum follow-up of 14 days.

Statistical Analysis

Because this was a descriptive study, no statistical sample size calculation was performed a priori. The normality of the variables was tested with the Kolmogorov-Smirnov test. Continuous variables were summarized as mean \pm SD or median (interquartile range) as appropriate, and categorical variables were summarized as counts and percentages. At baseline, categorical variables were compared with a Fisher exact test or a χ^2 test, and continuous variables were compared with a Student *t* test or a Mann-Whitney *U* test.

Results

Study Population

Between March and May 2020, 53 patients with COVID-19 were admitted in the two ICUs. Among them, 10 were excluded: six for poor echogenicity and four because of transfer in other French ICUs within the first 48 h of their ICU stay for the management of the COVID-19 epidemic. In the remaining 43 patients, 41 (95%) were mechanically ventilated in the volume assist-controlled mode, 14 (33%) demonstrated chronic hypertension, 23 (54%) received vasopressors, and 21 (49%) received specific treatments for COVID-19 (hydroxychloroquine, *n* = 14; lopinavir plus ritonavir, *n* = 5; Remdesivir [Gilead Sciences], *n* = 6; and corticosteroids, *n* = 17) at baseline. The other baseline characteristics of patients are shown in [Table 1](#). Twenty-one patients (49%) demonstrated a cardiac injury at baseline and 30 patients (70%) experienced cardiac injury within the first 14 days of ICU stay ([e-Fig 1A](#)). The day 14 mortality rate was 9%, and all deceased patients experienced cardiac injury. Causes of death were multiple-organ failure (*n* = 1), refractory hypoxemia (*n* = 2), and refractory septic shock (*n* = 1).

Characteristics of Patients With Cardiac Injury

At baseline, patients with cardiac injury showed a lower clearance of creatinine (71 ± 40 mL/min vs 105 ± 40 mL/min; *P* = .01), higher plasma levels of cardiac biomarkers, a lower tricuspid annular plane systolic excursion (19 ± 5 mm vs 23 ± 3 mm; *P* = .01), and a lower systolic tricuspid annular velocity (13 ± 3 cm/s vs 15 ± 4 cm/s; *P* = .04) than patients without cardiac injury ([Tables 1 and 2](#)). The positive end-expiratory pressure level was similar between patients with cardiac injury and those without (13 ± 3 cm H₂O vs 13 ± 2 cm H₂O; *P* = .80), as well as the proportion of patients with LV hypertrophy (40% vs 30%; *P* = .50) and the proportion of patients receiving specific treatments for COVID-19 (47% vs 53%; *P* = .67).

Longitudinal analyses were performed with a generalized linear mixed model. Because noninformative censoring could not be applied in ICU context (cardiac injury is a competing event with death without cardiac injury or discharge alive from ICU), we plotted cumulative incidence function to illustrate time-to-event analysis. Statistical analysis was performed with MedCalc version 11.6.0 software (MedCalc) and XLSTAT version 2020.1 software (Excel, Microsoft Corp.). A *P* value < .05 was considered statistically significant.

Within the first 14 days of ICU stay, patients with cardiac injury required more frequently vasopressors or inotropes administration, invasive mechanical ventilation, prone positioning, and renal replacement therapy than patients without cardiac injury ([Table 3](#)). Similarly, patients with new-onset atrial arrhythmias required more frequent vasopressor administration than those without (100% vs 66%; *P* = .02). The time course of inflammatory parameters levels ([Fig 1A](#)), LV function parameters ([Fig 1B](#)), and RV systolic function parameters ([Fig 1C](#)) did not differ between patients with cardiac injury and those without.

Characteristics and Time Course of Cardiac Injury

Cardiac injury occurred in the 30 patients with a median delay of 3 days (interquartile range, 0-7 days) after ICU admission and 10 days (interquartile range, 5-14 days) after the onset of symptoms. The onset of cardiac injury was at baseline in 21 patients (70%), on day 3 in three patients (10%), on day 7 in five patients (17%), and on day 14 in one patient (3%).

The time of occurrence and the time course of the different ECG and echocardiographic abnormalities involved in cardiac injury are summarized in [Tables 4 and 5](#), in [Figure 2](#), and in [e-Figure 1B-G](#). The most frequent ECG and echocardiographic abnormalities were ECG or TTE signs, or both, of LV abnormalities (87% of patients with cardiac injury), RV systolic dysfunction (47%), pericardial effusion (43%), new-onset atrial arrhythmias (33%; ECG and TTE of patient 31) ([e-Fig 2, Video 1](#)), and LV relaxation impairment (33%) ([Table 5, Fig 2](#)). Eight patients (27%) with cardiac injury showed ECG signs of RV strain, 11 patients (37%) exhibited RV dilation or cor pulmonale (ECG and TTE of patient 8) ([e-Fig 3, Video 2](#)), and patients with cardiac injury experienced more RV (47%) than LV (13%) systolic dysfunction, with no patient experiencing LV systolic dysfunction after day 7 ([Table 5](#)). All pericardial effusions were mild (< 10 mm) without hemodynamic impairment, and no patient experienced tamponade. No new significant valvulopathy was found. Two patients experienced severe bradyarrhythmia: one second-degree and one third-degree atrioventricular block.

TABLE 1] Baseline Characteristics of Patients With and Without Cardiac Injury

Variable	Overall (N = 43)	Patients With Cardiac Injury (n = 30)	Patients Without Cardiac Injury (n = 13)	P Value
Age, y	60 ± 13	61 ± 13	56 ± 12	.17
Sex, male / female	36 (84) / 7 (16)	25 (83) / 5 (17)	11 (85) / 2 (15)	.92
Simplified Acute Physiology Score II	57 ± 21	61 ± 19	47 ± 23	.04
Mortality at day 14, %	4 (9)	4 (13)	0 (0)	.17
Comorbidities
Cardiovascular risk factors	29 (67)	19 (63)	10 (77)	.38
Hypertension	14 (33)	12 (40)	2 (14)	.11
Diabetes	12 (28)	9 (30)	3 (23)	.64
Smokers	12 (28)	7 (23)	5 (39)	.31
Dyslipidemia	10 (23)	6 (20)	4 (31)	.44
Atherosclerosis	7 (16)	6 (20)	1 (8)	.44
Coronary heart disease	2 (5)	2 (7)	0 (0)	.34
Others ^a	6 (14)	6 (20)	0 (0)	.08
Chronic heart failure	1 (2)	1 (3)	0 (0)	.51
Chronic respiratory disease	7 (16)	3 (10.0)	4 (31)	.09
Chronic renal disease	6 (14)	6 (20)	0 (0)	.08
Chronic liver disease	2 (5)	1 (3)	1 (8)	.53
Malignancy	6 (14)	4 (13)	2 (15)	.86
Immunodepression	8 (19)	6 (20)	2 (15)	.72
Clinical parameters
BMI, kg/m ²	29 ± 5	29 ± 5	29 ± 4	.74
Norepinephrine use	23 (54)	17 (59)	6 (46)	.45
Norepinephrine dosage, μg/kg/min	0.05 (0.00-0.27)	0.09 (0.00-0.28)	0.00 (0.00-0.16)	.36
Systolic arterial pressure, mm Hg	118 ± 21	118 ± 22	118 ± 19	.94
Diastolic arterial pressure, mm Hg	63 ± 14	61 ± 14	67 ± 11	.21
Mean arterial pressure, mm Hg	82 ± 16	80 ± 17	85 ± 14	.42
Heart rate, beats per min	85 ± 21	87 ± 24	82 ± 12	.50
Ventilation parameters
Invasive mechanical ventilation	41 (95)	30 (100)	11 (85)	.03
PaO ₂ :FiO ₂ ratio	187 ± 71	181 ± 70	202 ± 74	.38
PEEP, cm H ₂ O	13 ± 3	13 ± 3	13 ± 2	.80
Tidal volume, mL/kg of PBW	5.9 ± 0.6	6.0 ± 0.5	5.7 ± 0.7	.13
Total respiratory rate, breaths/min	27 ± 4	27 ± 4	27 ± 5	.81
Respiratory compliance, mL/cm H ₂ O	34 ± 10	33 ± 11	36 ± 8	.47
Biological parameters
HS troponin I (n = 17), ng/L	29 (16-366)	274 (27-491)	16 (16-28)	.01
HS troponin T (n = 26), ng/L	23 (14-69)	28 (17-88)	13 (13-35)	.08
BNP (n = 17), pg/mL	72 (28-168)	124 (67-187)	25 (16-85)	.04
NT-proBNP (n = 26), pg/mL	245 (102-1227)	277 (129-2540)	107 (52-247)	.04
Lactate, mM	1.1 ± 0.3	1.1 ± 0.3	1.0 ± 0.4	.49
IL-6, pg/mL	158 (58-297)	202 (54-1051)	97 (66-216)	.32

(Continued)

TABLE 1] (Continued)

Variable	Overall (N = 43)	Patients With Cardiac Injury (n = 30)	Patients Without Cardiac Injury (n = 13)	P Value
Creatinine clearance, mL/min	81 ± 43	71 ± 40	105 ± 40	.01
Plasma creatinine, μM	88 (67-138)	92 (70-192)	78 (57-115)	.19
Plasma urea, mM	6.8 (4.7-10.7)	8.6 (5.1-12.1)	5.6 (4.0-8.2)	.07
Sodium bicarbonate, mM	24 ± 4	23 ± 3	25 ± 4	.03
Potassium, mM	4 ± 1	4 ± 1	4 ± 1	.96
SGOT, U/L	61 ± 29	63 ± 32	58 ± 22	.63
SGPT, U/L	47 ± 30	47 ± 35	48 ± 14	.89
Total bilirubin, mM	11 ± 8	10 ± 7	13 ± 9	.34
Protein C reactive, mg/L	181 ± 110	194 ± 115	152 ± 96	.26
Procalcitonin, ng/mL	0.58 (0.27-1.67)	0.68 (0.26-2.71)	0.57 (0.37-1.06)	.61
Lactate dehydrogenase, UI/L	634 ± 264	627 ± 283	653 ± 220	.79
Prothrombin, %	76 ± 15	75 ± 15	78 ± 13	.47
Fibrinogen, g/L	6.4 ± 1.9	6.2 ± 1.8	6.8 ± 2.0	.37
D-dimer, μg/L	2,231 (984-7762)	1,921 (1081-6326)	6,403 (767-10000)	.48
WBC count, × 10 ⁹ /L	9.19 ± 4.01	9.87 ± 4.32	7.63 ± 2.71	.09
Neutrophils, × 10 ⁹ /L	7.83 ± 3.87	8.56 ± 4.18	6.13 ± 2.38	.06
Lymphocytes, × 10 ⁹ /L	0.82 ± 0.52	0.76 ± 0.58	0.95 ± 0.33	.27
Hemoglobin, g/dL	12.1 ± 1.9	11.9 ± 2.0	12.7 ± 1.8	.18
Platelet count, × 10 ⁹ /L	239 ± 89	233 ± 81	254 ± 109	.49

Data are presented as No. (%), mean ± SD, or median (interquartile range), unless otherwise indicated. BNP = B-type natriuretic peptide; HS = high-sensitivity; NT-proBNP = N-terminal pro B-type natriuretic peptide; PBW = predicted body weight; PEEP = positive end-expiratory pressure; SGOT = serum glutamo-oxalacetic transaminase; SGPT = serum glutamo-pyruvate transferase.

^aPresence of cerebrovascular disease, or aortic aneurysm, or extracranial carotid and vertebral artery disease, or lower extremity artery disease.

No patient experienced life-threatening ventricular arrhythmia.

Inverted T waves and ST-segment depression and wall motion abnormalities represented the most frequent ECG and TTE signs of LV abnormalities at baseline and within the first 14 days of ICU stay (Tables 2 and 5). Coronary angiography was performed in four patients (13%) and confirmed acute coronary syndrome in three of them: two patients showed a significant lesion of the left anterior descending artery and one patient showed a significant lesion of the circumflex artery (ECG and TTE of patient 9) (e-Fig 4, Video 3). Cardiac MRI was performed in one patient without coronary lesion on coronary angiography and confirmed the diagnosis of myocarditis.

Discussion

In our cohort of critically ill COVID-19 patients, 49% of patients demonstrated a cardiac injury at ICU admission and 70% of patients experienced cardiac injury within the first 14 days of ICU stay. The most frequent abnormalities were ECG or TTE signs, or both, of LV

abnormalities, and patients with cardiac injury experienced more RV than LV systolic dysfunction. Four different patterns of cardiac injury were identified over time: between baseline and day 14, the incidence of pericardial effusion and of new-onset atrial arrhythmias increased, the incidence of ECG or TTE signs, or both, of LV abnormalities as well as the incidence of LV relaxation impairment remained stable, whereas the incidence of RV and LV dysfunction decreased, with no patient experiencing LV systolic dysfunction after day 7.

To our knowledge, this is the first study providing the incidence and a multimodal description of associated structural abnormalities, as well as the time course, of cardiac injury in critically ill COVID-19 patients, combining ECG, cardiac biomarkers, and TTE analyses. Most previous studies have defined cardiac injury by troponin elevation only.^{5,18} Although this latter seems to be an interesting tool for risk stratifying in COVID-19 patients,^{5,18} troponin elevation does not necessarily reflect cardiac injury and is likely to be multifactorial.¹⁹ Thus, it is crucial also to consider ECG and TTE to characterize cardiac injury related to

TABLE 2] Baseline ECG Abnormalities and Echocardiographic Parameters in Patients With and Without Cardiac Injury

Variable	Overall (N = 43)	Patients With Cardiac Injury (n = 30)	Patients Without Cardiac Injury (n = 13)	P Value
ECG abnormalities	11 (26)	10 (33)	1 (8)	.08
ECG signs of left ventricular abnormalities	11 (26)	10 (33)	1 (8)	.08
Inverted T waves	9 (21)	8 (27)	1 (8)	.16
ST-segment elevation	1 (3)	1 (3)	0 (0)	.51
ST-segment depression	4 (13)	4 (13)	0 (0)	.17
Pathologic Q waves	2 (7)	2 (7)	0 (0)	.34
Localization of repolarization abnormalities and Q waves
Anterior	4 (13)	3 (10)	1 (8)	.81
Lateral	2 (7)	2 (7)	0 (0)	.34
Inferior	2 (7)	2 (7)	0 (0)	.34
Inferolateral	2 (7)	2 (7)	0 (0)	.34
Diffuse	2 (7)	2 (7)	0 (0)	.34
New left branch bundle block	2 (7)	2 (7)	0 (0)	.34
Life-threatening ventricular arrhythmia	0 (0)	0 (0)	0 (0)	1.00
Severe bradyarrhythmia	0 (0)	0 (0)	0 (0)	1.00
New-onset atrial arrhythmias
Atrial fibrillation	1 (3)	1 (3)	0 (0)	.50
Atrial flutter	0 (0)	0 (0)	0 (0)	1.00
Atrial tachycardia	0 (0)	0 (0)	0 (0)	1.00
Signs of right ventricular strain	5 (12)	4 (13)	1 (8)	.59
Inverted T waves in leads V1-V4	3 (7)	2 (7)	1 (8)	.90
QR pattern in V1 ^a	1 (3)	1 (3)	0 (0)	.51
S1Q3T3 pattern ^b	1 (3)	1 (3)	0 (0)	.51
Incomplete or complete right bundle branch	1 (3)	1 (3)	0 (0)	.51
Left ventricular hypertrophy	4 (13)	4 (13)	0 (0)	.17
Echocardiographic parameters
Left ventricular ejection fraction, %	64 ± 10	62 ± 10	68 ± 7	.09
E/A ratio	1.1 ± 0.3	1.1 ± 0.3	1.0 ± 0.3	.40
e' _{lateral} , cm/s	10 ± 3	9 ± 3	10 ± 3	.48
e' _{septal} , cm/s	8 ± 2	8 ± 2	8 ± 2	.43
E/e' _{averaged} ratio	8 ± 3	8 ± 3	8 ± 2	.62
Indexed left atrial volume, mL/m ²	24 ± 11	26 ± 12	21 ± 8	.21
Systolic pulmonary arterial pressure, mm Hg	26 ± 10	27 ± 9	22 ± 11	.33
Tricuspid annular plane systolic excursion, mm	20 ± 5	19 ± 5	23 ± 3	.01
Systolic tricuspid annular velocity, cm/s	13 ± 3	13 ± 3	15 ± 4	.04
RV fractional area change, %	50 ± 13	48 ± 13	53 ± 11	.24
RV:LV end-diastolic areas ratio	0.51 ± 0.16	0.52 ± 0.15	0.46 ± 0.19	.26

Data are expressed as No. (%) or mean ± SD. A = atrial peak velocity of the mitral flow with pulsed Doppler; E = early peak velocity of the mitral flow with pulsed Doppler; e' = early diastolic peak velocity of the lateral and septal mitral annulus with tissue Doppler imaging; LV = left ventricular; RV = right ventricular.

^aThe criteria for the diagnosis of QR pattern in V1 were the presence of a prominent Q wave of ≥0.2 mV and a ventricular depolarization <120 ms in lead V1.

^bThe criteria for the diagnosis of S1Q3T3 pattern were the presence of an S wave in lead I, a Q wave in lead III and a T inversion in lead III.

TABLE 3] Intensity of Supportive Care During ICU Stay in Patients With and Without Cardiac Injury

Variable	Patients With Cardiac Injury (n = 30)	Patients Without Cardiac Injury (n = 13)	P Value
Vasopressor/inotrope use	26 (87)	7 (54)	.02
Norepinephrine	26 (87)	7 (54)	.02
Epinephrine	1 (3)	0 (0)	.54
Maximum norepinephrine dosage, µg/kg/min	0.50 (0.20-1.40)	0.15 (0.00-0.70)	.09
Ventilation ^a
Invasive mechanical ventilation	30 (100)	11 (85)	.03
Noninvasive ventilation	2 (7)	2 (1)	.37
High-flow oxygen therapy	1 (3)	2 (15)	.15
Veno-venous extracorporeal membrane oxygenation	3 (10)	0 (0)	.28
Prone positioning	23 (77)	5 (39)	.02
Neuromuscular blocker use	23 (77)	7 (54)	.14
Sedation use	30 (100)	11 (85)	.03
Renal replacement therapy	13 (43)	0 (0)	< .01

Data are presented as No. (%) or median (interquartile range), unless otherwise indicated.

^aNoninvasive mechanical ventilation and high-flow oxygen therapy could have been performed before or after invasive mechanical ventilation.

COVID-19 adequately and more precisely. Using a multimodal assessment of cardiac function, we found that 49% of patients harbored a cardiac injury at ICU admission and that 70% of patients experienced cardiac injury within the first 14 days of ICU stay, which is higher than the incidence of between 12% and 30% found in previous studies.^{2-5,7,18} This higher incidence could be explained either by the higher severity of COVID-19 of the patients included in our cohort, as attested by the higher proportion of patients requiring supportive care compared with previous studies^{2,3,5} or by the fact that RV systolic function was not taken into account to define cardiac injury,^{2,4,7} whereas we and others⁸ found that patients with cardiac injury experienced more RV than LV systolic dysfunction. Finally, the higher incidence of cardiac injury that we found could be explained by the potential ascertainment bias of prior cohort studies, related to a nonlongitudinal cardiac assessment. Thus, it cannot be excluded that the prevalence we found is more indicative of the true prevalence of cardiac injury in critically ill COVID-19 patients.

Patients with COVID-19 seemed to experience as much newly diagnosed cardiac abnormalities as non-COVID-19 critically ill patients,²⁰ suggesting that these different cardiac abnormalities may not be totally specific to COVID-19, but also may reflect the severity of the disease and may be an epiphenomenon of critical illness.²¹⁻²⁴ The most frequent abnormalities at

ICU admission and within the first 14 days of ICU stay were ECG or TTE signs, or both, of LV abnormalities. Inverted T waves and ST-segment depression represented the most frequent ECG signs of LV abnormalities, whereas ST-segment elevation was rare, confirming findings in noncritically ill COVID-19 patients.^{25,26} Similarly, wall motion abnormalities were the most frequent TTE signs of LV abnormalities, with an incidence of 30%, higher than the 12% incidence reported in non-COVID-19 patients.²⁰ Considering ECG or TTE, or both, of LV abnormalities makes it possible to group together four different cardiomyopathies: coronary heart disease (chronic or acute), myocarditis, Takotsubo syndrome, and septic cardiomyopathy.^{9,11-15} Using this classification, Dweck and colleagues¹⁵ recently reported in a global echocardiographic survey a 39% incidence of LV abnormalities, including 8% of new myocardial infarction, myocarditis, and Takotsubo syndrome in a population of critically and noncritically ill COVID-19 patients, confirming that Takotsubo syndrome²⁷⁻²⁹ and myocarditis³⁰ seemed to be rare in these patients as well as in non-COVID-19 patients.³¹ Mechanisms of cardiac injury in COVID-19 patients remain unclear and are probably multifactorial.³²⁻³⁴ First, inflammation could induce obstructive cardiac ischemia by plaque disruption or nonobstructive cardiac ischemia because of a mismatch between oxygen supply and demand.^{32,33,35} We performed coronary angiography in four patients and found a significant coronary artery

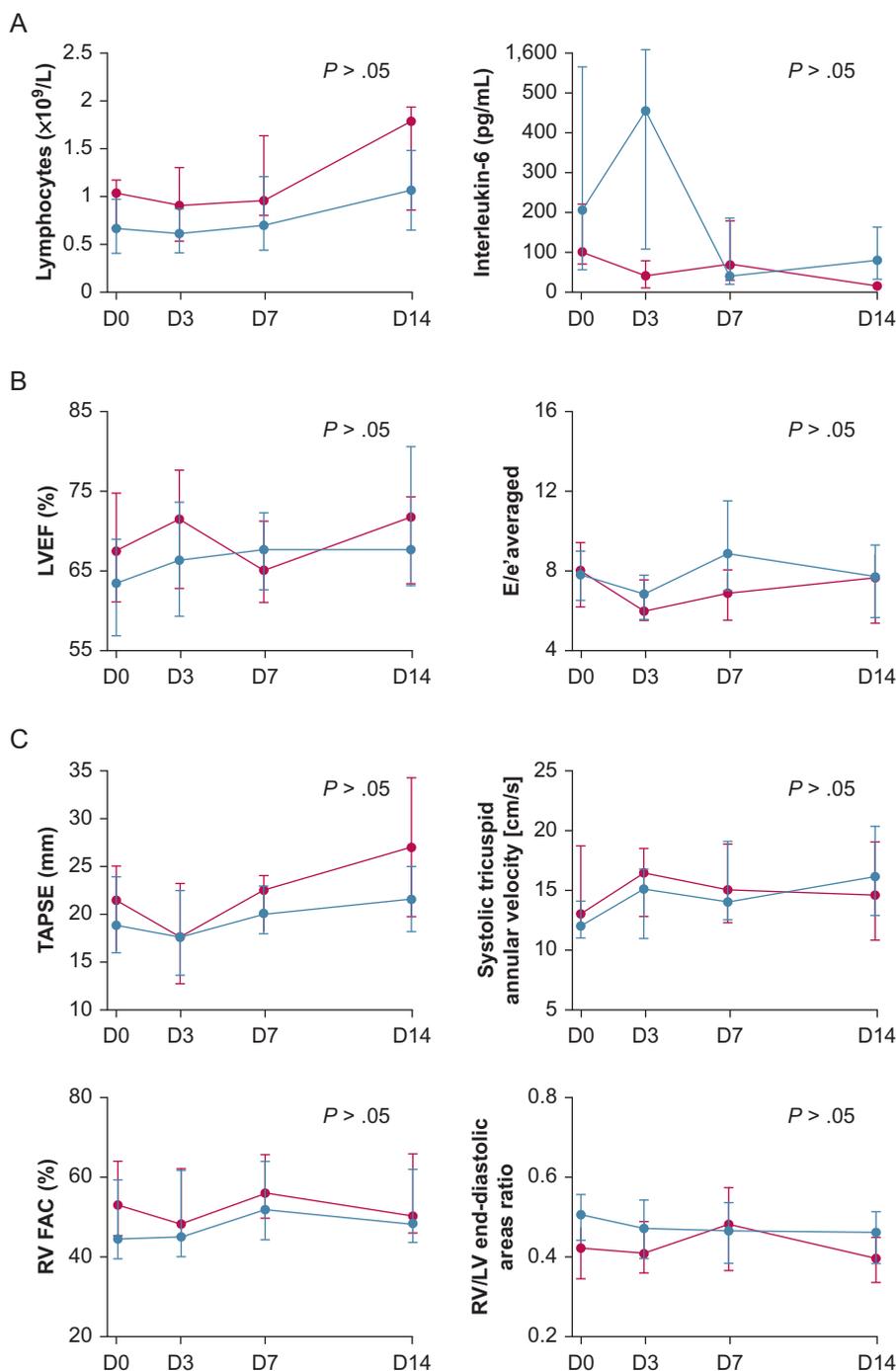


Figure 1 – Line graphs showing the time course within the first 14 days of ICU stay of inflammatory parameters (A), of left ventricular function echocardiographic parameters (B), and of right ventricular systolic function echocardiographic parameters (C) in patients with and without cardiac injury. Data are expressed as median and interquartile range. Blue circles represent patients with cardiac injury (n = 30). Red circles represent patients without cardiac injury (n = 13). D = day; E = early peak velocity of the mitral flow with pulsed Doppler; e' = early diastolic peak velocity of the mitral annulus with tissue Doppler imaging; FAC = fractional area change; LV = left ventricular; LVEF = left ventricular ejection fraction; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TTE = transthoracic echocardiography.

TABLE 4] Time of Occurrence of the Different ECG and Echocardiographic Abnormalities in the 30 Patients With Cardiac Injury Within the First 14 Days of ICU Stay

Variable	Cardiac Injury	ECG and/or TTE Signs of LV Abnormalities	LV Relaxation Impairment	Cor Pulmonale	RV Systolic Dysfunction	Pericardial Effusion	New-Onset Atrial Arrhythmias
Time of occurrence (d)	3 (0-7)	0 (0-7)	3 (0-7)	0 (0-10.5)	0 (0-3)	3 (0-14)	7 (6-14)

Data are presented as median (interquartile range). LV = left ventricular; RV = right ventricular; TTE = transthoracic echocardiography.

TABLE 5] Time Course of the Different ECG and Echocardiographic Abnormalities in the 30 Patients With Cardiac Injury Within the First 14 Days of ICU Stay

Variable	Overall (N = 30)	Day 0 (n = 21)	Day 3 (n = 20)	Day 7 (n = 17)	Day 14 (n = 18)	P Value ^a
ECG abnormalities						
ECG signs of LV abnormalities	18 (60)	10 (47)	13 (65)	10 (59)	12 (67)	.03
Inverted T waves	16 (54)	8 (38)	11 (55)	9 (53)	10 (57)	.03
ST-segment elevation	2 (7)	1 (5)	2 (10)	2 (12)	1 (6)	.07
ST-segment depression	6 (20)	4 (19)	5 (25)	3 (18)	5 (28)	.75
Pathologic Q waves	2 (7)	2 (10)	1 (5)	0 (0)	0 (0)	.84
New left branch bundle block	2 (7)	2 (10)	2 (10)	2 (12)	2 (11)	.91
Severe bradyarrhythmia	2 (7)	0 (0)	0 (0)	2 (12)	0 (0)	.83
New-onset of atrial arrhythmias	10 (33)	1 (5)	3 (15)	4 (24)	6 (33)	.02
Signs of right ventricular strain	8 (27)	5 (24)	2 (10)	2 (12)	0 (0)	.04
Echocardiographic abnormalities						
Echocardiographic signs of LV abnormalities	9 (30)	7 (33)	6 (30)	6 (35)	3 (17)	.82
LV wall motion abnormalities	9 (30)	5 (24)	5 (24)	6 (35)	3 (17)	.49
LV systolic dysfunction	4 (13)	2 (10)	2 (10)	0 (0)	0 (0)	.16
LV relaxation impairment	10 (33)	4 (19)	5 (25)	6 (35)	4 (22)	.35
Cor pulmonale	9 (30)	6 (29)	3 (15)	0 (0)	2 (11)	.22
RV dilation or cor pulmonale	11 (37)	6 (29)	4 (20)	0 (0)	3 (17)	.40
RV systolic dysfunction	14 (47)	8 (38)	5 (25)	3 (18)	2 (11)	.07
Pericardial effusion	13 (43)	6 (29)	6 (30)	7 (41)	11 (61)	.01
ECG or echocardiographic signs of LV abnormalities	26 (87)	14 (67)	13 (65)	14 (82)	12 (67)	.50
ECG and echocardiographic signs of LV abnormalities	3 (10)	4 (19)	4 (20)	2 (12)	2 (11)	.91

Data are presented as No. (%), unless otherwise indicated. LV = left ventricular; RV = right ventricular.

^aFor the generalized linear mixed model.

lesion in three of them, confirming findings from Bangalore and colleagues.³⁶ Second, myocardial inflammation could induce myocarditis or septic cardiomyopathy.^{12,32,33,35} Further cardiovascular

explorations (coronary angiography or cardiac MRI) would be required to characterize ECG or TTE signs, or both, of LV abnormalities better in COVID-19 patients.

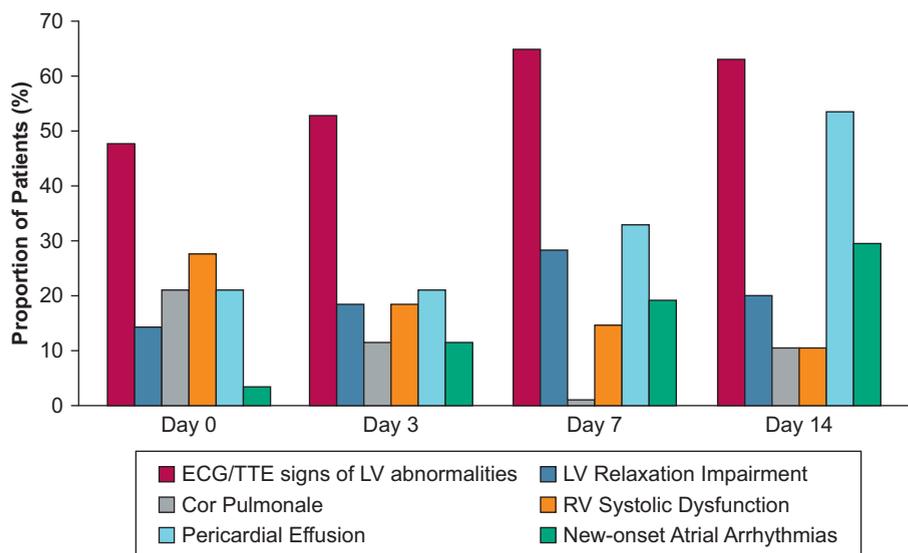


Figure 2 – Bar graph showing the time course of ECG and echocardiographic abnormalities in the 30 patients with cardiac injury within the first 14 days of an ICU stay. LV = left ventricular; RV = right ventricular; TTE = transthoracic echocardiography.

Patients with cardiac injury experienced more RV than LV systolic dysfunction, as evidenced by the higher proportion of patients with at least one impaired parameter of RV systolic function than with impaired LV ejection fraction within the first 14 days of ICU stay (47% vs 13%). Similar findings were found in patients with ARDS not related to COVID-19.²² Interestingly, previous studies showed that COVID-19 patients experienced RV systolic dysfunction without significant changes in LV systolic function^{8,37} and that RV systolic longitudinal strain³⁷ as well as increased RV end-diastolic area^{8,38} were reliable prognosis factors in these patients. Overall, this highlights the importance of early and repeated assessment of RV systolic function in COVID-19 patients, which makes sense physiologically, given the high proportion of patients with ARDS, pulmonary embolism, or both.^{39,40}

One-third of patients with cardiac injury experienced LV relaxation impairment, an incidence similar to that reported in critically ill patients with sepsis not related to COVID-19.^{24,41} It confirms that COVID-19 patients experienced more LV diastolic than systolic dysfunction.⁸ This could be explained by the high proportion of patients in our cohort with LV hypertrophy and with a medical history of arterial hypertension.^{16,42} Nevertheless, it must be kept in mind that echocardiographic parameters used to assess LV relaxation are dependent on loading conditions and that echocardiographic abnormalities suggestive of LV relaxation impairment may reflect fluid or vasopressor overload rather than an intrinsic LV diastolic dysfunction.

Besides these echocardiographic abnormalities, 33% of patients with cardiac injury also experienced arrhythmias. New-onset atrial arrhythmias were the most frequent arrhythmias, and no patient experienced sustained ventricular tachycardia, ventricular fibrillation, or cardiac arrest. Our incidence of arrhythmia is similar to that reported in the literature for COVID-19^{7,32,43} and for previous viral outbreaks,⁴⁴ as well as to that reported in non-COVID-19 critically ill patients with sepsis.⁴⁵ Arrhythmia may be driven by myocardial damage, but also by nonmyocardial factors such as metabolic abnormalities, hypoxemia, or systemic inflammation,⁴³ because some patients without cardiac injury also

experienced arrhythmias such as atrial fibrillation during their ICU stay. Interestingly, patients with new-onset atrial arrhythmias required more frequent vasopressor administration than those without, suggesting that vasopressor use may be the trigger for atrial arrhythmias through the activation of β -receptors. Nevertheless, it cannot be excluded that the need for vasopressors is a consequence of the potential hemodynamic impairment induced by atrial arrhythmias.

We acknowledge some limitations to our study. First, we included a relatively small number of patients, but no new COVID-19 patients were admitted to our ICUs after May. Nevertheless, to our knowledge this is the first study providing the frequency and a multimodal description of cardiac injury over time in critically ill COVID-19 patients. Second, it was not possible for obvious reasons in the context of a pandemic to perform coronary angiography or cardiac MRI easily in all patients with ECG or TTE signs, or both, of LV abnormalities. Third, 11% of COVID-19 patients were not included because of poor echogenicity, mainly as a result of obesity and mechanical ventilation with high positive end-expiratory pressure level. However, this proportion is similar to that reported in non-COVID-19 critically ill patients.⁴⁶ Fourth, because some patients did not have prior or had no available results of prior cardiac assessment, the potential chronicity of some newly diagnosed ECG or TTE abnormalities, or both, could not be ruled out with certainty. Fifth, we considered a maximum follow-up of 14 days to focus only on cardiac injury and to prevent the observed cardiac abnormalities from being related more to ICU stay complications than to COVID-19. Long-term follow-up with complete cardiovascular examination in COVID-19 patients deserves further study.

Interpretation

Cardiac injury was common and occurred early in critically ill COVID-19 patients. The most frequent newly diagnosed abnormalities were ECG or echocardiographic signs, or both, of LV abnormalities, and patients with cardiac injury experienced more RV than LV systolic dysfunction. Further studies are needed to characterize the potential chronic cardiac injury in COVID-19 patients.

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Author contributions: D. D. and M. J. take responsibility for the content of the manuscript, including the data and analysis. D. D., G. B., A. C., J.-P. M., J. D., and M. J. conceived the study. D. D., P. D., E. F., and M. J. recorded the data. D. D., P. D., L. M., E. F., C. S., M. B., H. H., E. F., M. J., and M. J. analyzed data. All authors contributed to the interpretation of data. D. D. and M. J. drafted the first version of the manuscript. All authors contributed drafting the manuscript, and all authors approved the final version of the manuscript.

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Additional information: The e-Appendix, e-Figures, and Videos can be found in the Supplemental Materials section of the online article.

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