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Short and long term multimodal characterisation of cardiac Injury in critically ill patients with COVID-19: a longitudinal study

Didac Aurenche Mateu

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UNIVERSITE DE NICE SOPHIA-ANTIPOLIS

FACULTE DE MEDECINE

THESE

**Pour l'obtention du diplôme d'état de Docteur en Médecine
Spécialité : Médecine Intensive Réanimation**

Présentée et soutenue publiquement le 8 avril 2022

Par

Didac AURENCHE MATEU, né le 03/03/1993 à Douala (Cameroun)

**Caractérisation multimodale à court et long terme de l'atteinte
cardiaque des patients COVID-19 sévères : une étude longitudinale**

**Short and long-term multimodal characterization of cardiac Injury
in critically ill patients with COVID-19 : a longitudinal study**

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‘parce qu’il n’y a pas de bonne ou de mauvaise situation mais que la vie c’est d’abord une histoire des rencontres’ (Otis)

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Résumé / Abstract

Contexte : La survenue d'une atteinte cardiaque est fréquente au cours de la COVID-19. De nombreuses anomalies ECG ou échocardiographiques ont été décrites parmi lesquelles l'atteinte du cœur droit qui prédomine à celle du cœur gauche. La présence d'anomalies ECG ou ETT évocatrices de cardiopathie gauche, notamment de coronaropathie ou de myocardite, sont aussi fréquemment rapportées. La signification de ces anomalies et l'évolution de l'ensemble des anomalies cardiaques à la phase aiguë et à distance sont mal décrites chez les patients les plus graves admis en réanimation.

But de l'étude : Déterminer l'incidence et l'évolution à court et long terme des différentes anomalies cardiaques observées au cours de la COVID-19, et préciser la cardiopathie associée aux anomalies du cœur gauche initialement observées.

Méthodologie : Il s'agit d'une étude monocentrique prospective menée dans un hôpital universitaire. Des patients consécutivement admis dans un service de réanimation pour une infection à SARS-Cov-2 et nécessitant un support respiratoire ou hémodynamique ont été inclus. Une évaluation cardiaque multimodale associant une analyse ECG, échocardiographique et de biomarqueurs cardiaques a été réalisée à plusieurs temps au cours du séjour en réanimation. Une atteinte cardiaque aiguë (ACA) était définie par l'association d'une élévation de la troponine et d'une anomalie ECG et/ou échocardiographique. La même analyse multimodale a été réalisée dans un délai de 3 à 6 mois après la sortie d'hospitalisation. Selon un algorithme décisionnel prédéfini, d'autres examens complémentaires étaient réalisés: ECG d'effort, holter ECG des 24 heures, imagerie fonctionnelle non invasive (scintigraphie ou échocardiographie de stress), coronarographie ou imagerie par résonance magnétique cardiaque.

Résultats : Sur une période de 1 an, 100 patients ont été inclus parmi lesquels 37 (37%) ont présenté une ACA. Au total, 61% des patients étaient sous ventilation mécanique, 34% sous oxygénothérapie à haut débit et 5% sous ventilation non invasive. Le risque cardiovasculaire SCORE était plus important chez les patients avec ACA que sans ACA (10% vs. 3%, $p < 0.01$). La survenue d'une ACA était précoce concernant déjà 89% des patients avec ACA à l'admission. Parmi les ACA, les anomalies les plus fréquemment retrouvées étaient: une altération du strain longitudinal global du ventricule gauche (86%) et du strain de la paroi libre du ventricule droit (78%), des signes ECG/ETT d'anomalies du ventricule gauche (73%), une dysfonction du ventricule droit (51%), une fibrillation auriculaire (30%), une dysfonction diastolique du ventricule gauche (24%), une dysfonction systolique du ventricule gauche (22%), un cœur pulmonaire (14%) et un épanchement péricardique (14%). Au long cours, l'ensemble des anomalies se sont améliorées mais persistait une altération des strains gauche et droit toujours importante (43%). Des lésions coronaires significatives ont été retrouvées chez 8 patients (10%), plus fréquemment chez les patients avec ACA que sans ACA (29% vs 4%, $p < 0.01$). Un seul diagnostic de myocardite a été confirmé (1%). L'incidence de fibrillation auriculaire au long cours était de 6% dans toute la population, et 14% chez les patients avec ACA initiale.

Conclusion : L'ACA est fréquente et précoce au cours de la COVID-19 en réanimation. Toutes les ACA se sont améliorées au cours du suivi. L'incidence de coronaropathie et de fibrillation auriculaire étaient importantes au long cours, mais celle de myocardite est restée rare. Ces résultats suggèrent qu'un dépistage de coronaropathie et de fibrillation auriculaire au long cours est à discuter chez ces patients compte tenu de la morbi-mortalité importante associée à ces pathologies.

Introduction

As of December 2019, an emerging coronavirus SARS-Cov-2 is responsible for the worldwide pandemic coronavirus disease 2019 (COVID-19) (1). Although pulmonary involvement is at the forefront of the clinical presentation, numerous cardiovascular manifestations associated with COVID-19 were described (2). Cardiac injury was found in 12% to 55% of all COVID patients (3-6), and in 33 to 70% of the most severe patients admitted to intensive care unit (ICU) (7, 8). Cardiac injury is associated with an increased risk of COVID-19 severity and mortality (4-6, 8, 9).

Right ventricular dysfunction seemed to be more frequent than left ventricular dysfunction, concerning 15% of all COVID-19 patients and up to 33% of critically ill patients (8-10). At the same time, the presence of electrocardiographic and/or echocardiographic signs suggestive of left ventricular abnormalities (i.e. coronary artery disease, myocarditis, Takotsubo syndrome or septic cardiomyopathy) are abnormalities that are also frequently reported, concerning 39% of all patients and up to 60% of critically ill patients (4, 8). Authentic coronary artery disease (11), Takotsubo syndrome (12-14) or myocarditis (15-17) have been documented. However, there are few studies to determine exactly which cardiomyopathy correspond to these abnormalities suggestive of left heart disease. Moreover, more globally, the analysis of the evolution at distance from hospitalization of all cardiac abnormalities during COVID-19 is very poorly described in critically ill patients. The only long term analyses of these patients are incomplete, either limited to ultrasound data only, without ischemic or angiographic exploration tests, without magnetic resonance imaging data, or without access to analysis of initial cardiac abnormalities in the acute phase of COVID-19 (18-23).

Our study aims prospectively and systematically to (i) characterize the cardiac injury observed in the acute phase of COVID-19 in the ICU with a repeated multimodal diagnostic approach integrating the analysis of the electrocardiogram (ECG), cardiac biomarkers, echocardiographic (TTE) data, and (ii) to follow the evolution of these abnormalities at 3 to 6 months of hospitalization with the same multimodal diagnostic approach by integrating, depending on the presentation, the performance of ischemic tests and/or coronary angiography and/or cardiac magnetic resonance imaging (MRI) in order to specify as precisely as possible the etiology and evolution of the abnormalities that may have been observed in the acute phase of COVID-19 and the long term cardiac sequelae of COVID-19.

Methods

We performed a single-center prospective observational study conducted in the medical intensive care unit and the cardiology department of the University Hospital of Nice. This study complies with the Declaration of Helsinki and was approved by our local ethics institutional review board (ClinicalTrials.gov Identifier: NCT04335162 ; IDRCB number: 2020-A01197-32). All patients or next of kin were informed about the study and consented to participate.

Study population

We included all consecutively admitted patients in the medical ICU with a confirmed diagnosis of COVID-19 by Real-Time Polymerase Chain Reaction obtained by nasal swab or lung samples. Critically ill patients with microbiologically confirmed COVID-19 who were admitted to an intensive care unit (ICU) and receiving respiratory or cardiovascular organ support were classified as having a severe disease state and were eligible for enrollment. Respiratory organ support was defined as invasive or noninvasive mechanical ventilation, including through high-flow nasal cannulae if the flow rate was more than 60 liters per minute and the fraction of inspired oxygen was more than 0.6. Exclusion criteria were (i) age <18 years, (ii) history of heart failure (congestive heart failure or left ventricular ejection fraction (LVEF) <50%) (iii) patients with care-limitation decision and (iv) poor echogenicity, defined as inability to obtain a reliable Doppler study and LVEF measurements or inability to clearly visualize the valves or 2 segments as defined by the American Society of Echocardiography (24).

ECG analyses

Besides continuous ECG monitoring to look for arrhythmia, 12-lead ECGs (or 18-lead ECGs in case of suspicion of circumflex occlusion and inferior or right ventricular (RV) infarction (25)) were performed at each TTE examination time. Continuous ECG monitoring and ECG were interpreted offline by the same experienced cardiologist blinded to clinical and paraclinical data.

Electrocardiogram (ECG) signs of right ventricular (RV) strain were defined by T waves inversion in leads V1-V4, a QR pattern in V1, a S1Q3T3 pattern, or incomplete or complete right bundle branch

(26). ECG signs of left ventricular (LV) hypertrophy were defined by (i) a Sokolow–Lyon index >35 mm, (ii) a R in aVL >11 mm, (iii) a Cornell voltage duration product >2440 mm.ms, or (iv) a Cornell voltage >28 mm in men or >20 mm in women (27).

Echocardiographic measurements

All TTE were performed by certified board operators (3 operators participated in the study) according to current guidelines (28) and analyzed offline blinded to clinical and paraclinical data on a remote station using the software EchoPAC™ (GE Healthcare, Horto, Norway).

All TTE measurements were performed with a Vivid E9 (GE Healthcare, Horto, Norway). All measurements were averaged on three consecutive end-expiratory measurements in patients with sinus rhythm and five consecutive end-expiratory measurements in patients with atrial fibrillation (29). All contours were hand-drawn.

Long-axis and short-axis parasternal views as well as apical five, four, three and two-chamber views were recorded. From the apical five- and four-chamber views, we measured: the left atrial area, the early (E) and atrial (A) peak velocities of the mitral flow with pulsed Doppler, the early diastolic (e') peak velocity of the lateral and septal mitral annulus with Tissue Doppler Imaging, the tricuspid annular plane systolic excursion, the systolic tricuspid annular velocity with Tissue Doppler Imaging, the tricuspid regurgitant jet velocity and the LV and RV end-diastolic areas (LVEDA and RVEDA). From these variables, we calculated e' averaged, the E/A, E/ e' and RVEDA/LVEDA ratios. RV dilation was defined by a RVEDA/LVEDA ratio >0.6 . The LV ejection fraction and left atrial volume were calculated by the modified Simpson's rule. The systolic pulmonary artery pressure estimation was based on the peak tricuspid regurgitation velocity taking into account right atrial pressure as described by the simplified Bernoulli equation. Right atrial pressure estimation was based on the diameter and respiratory variation in diameter of the inferior vena cava (30). The LV mass was estimated from LV linear dimensions acquired from 2D long-axis parasternal view as recommended. LV hypertrophy was defined by a LV mass >95 g/m² in women and >115 g/m² in men (28). w. Left ventricular global longitudinal strain (LVGLS) was calculated as the average of all available segments from the four, three and the two-chambers views. LVGLS was considered abnormal if $>18\%$ (28).

Right ventricular global longitudinal strain (RVGLS) and right ventricular free-wall strain (RVFWS) were calculated by analysis of VD segments from the four chambers view and were considered abnormal if $>20\%$ (28).

Cardiac injury definition

Cardiac injury was defined by an increase in high sensitivity troponin-I levels above the 99th percentile upper reference limit (25) and newly diagnosed ECG and/or TTE abnormalities (3, 5). The ECG and TTE abnormalities were considered newly diagnosed if they were unknown prior to ICU admission (patients with no or without available results of prior cardiac assessment in patients' file held by the referring physicians) or if they appeared during ICU stay.

Newly diagnosed ECG abnormalities defining cardiac injury were the following: (i) ECG signs of LV abnormalities suggestive of coronary heart disease, Takotsubo syndrome, myocarditis or septic cardiomyopathy (repolarization abnormalities involving at least two contiguous leads of the same territory (T waves inversion, ST segment depression or elevation), pathological Q waves (in at least two contiguous leads), newly diagnosed left bundle branch block, ventricular arrhythmia and severe brady-arrhythmia)) (4, 25, 31-34) and (ii) new-onset atrial arrhythmias (atrial fibrillation, atrial flutter or atrial tachycardia).

Newly diagnosed echocardiographic abnormalities defining cardiac injury were the following: (i) echocardiographic signs of LV abnormalities suggestive of coronary heart disease, Takotsubo syndrome, myocarditis or septic cardiomyopathy (wall motion abnormalities, LV systolic dysfunction ($LVEF < 50\%$)) (4, 25, 31-33, 35), (ii) abnormal LVGLS (if $> -18\%$) (24), (iii) LV relaxation impairment (i.e. LV diastolic dysfunction), with at least two of the following abnormalities: abnormal e' wave velocity ($e'_{\text{septal}} < 7\text{cm/s}$ or $e'_{\text{lateral}} < 10\text{cm/s}$), $E/e'_{\text{averaged}} > 14$ in patients with sinus rhythm or $E/e'_{\text{septal}} > 11$ in patients with atrial arrhythmia, or left atrial dilation (volume $> 34\text{ml/m}^2$), (36), (iv) cor pulmonale (right ventricular end-diastolic area/left ventricular end-diastolic area > 0.6 and flattened interventricular septum), (v) elevated systolic pulmonary artery pressures ($> 38\text{mmHg}$) (37), (vi) RV systolic dysfunction (tricuspid annular plane systolic excursion (TAPSE) $< 16\text{mm}$, or systolic tricuspid annular velocity $< 9.5\text{cm/s}$ or RV fractional area change $< 35\%$) (28), (vii)

abnormal RVGLS (>-20%) or abnormal RVFWS (>-20%) (24), (viii) any new significant valvulopathy (aortic, mitral, tricuspid and pulmonary valve disease) (38), and (ix) pericardial effusion (39).

Data collection during COVID-19 in the intensive care unit

Demographic characteristics and comorbidities of patients, clinical and biological data, results of cardiac function assessment (ECG, TTE and cardiac biomarkers, i.e. 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, renal replacement therapy) were collected and analyzed.

All biological, electrocardiographic, and echocardiographic analyses were performed at ICU admission (D0), at D3 and then weekly until ICU discharge or death with a maximum follow-up of 28 days.

Coronary angiography was performed immediately in case of (i) ST-elevation myocardial infarction (STEMI) (ii) or non-ST-elevation myocardial infarction (NSTEMI) at high risk (cardiogenic shock, recurrent/refractory chest pain despite medical treatment, life-threatening arrhythmias, cardio-respiratory arrest, mechanical complications of mitral insufficiency, refractory acute heart failure related to NSTEMI, recurrent repolarization disorders in particular ST-segment depression >1 mm in 6 leads plus ST-segment elevation aVr and/or V1) (40, 41).

Coronary angiography was considered without urgency but as soon as the patient's condition allowed it in case of (i) high cardiovascular risk, (ii) or elevation beyond 5-fold the upper reference limit of high sensitive troponin I (40, 41).

Non-invasive functional imaging (single-photon emission computed tomography, or stress echocardiography) were considered remote from the acute phase of COVID-19 in case of non-ST-elevation myocardial infarction and low to intermediate cardiovascular risk, considering that it was a type 2 myocardial infarction, i.e., more consecutive to a functional ischemia than to a real atheromatous plaque rupture (40, 41). Coronary computed tomography angiography was not

considered for local logistical reasons. In case of abnormal non-invasive functional imaging coronary angiography was performed.

If there was no culprit atherosclerotic coronary disease to explain the ECG and/or TTE abnormalities a cardiac magnetic resonance imaging (MRI) was realized to eliminate differential diagnoses (particularly myocarditis and Takotsubo syndrome).

The decision algorithm for performing non-invasive functional imaging, coronary angiography, or cardiac MRI during the acute phase of COVID-19 is presented **Figure 1**.

Data collection during long term follow-up

Within 3 to 6 months of discharge from the ICU, a consultation with an experienced cardiologist, pulmonologist and infectiologist was organized for all survivors. During this consultation, a clinical examination, standard blood tests (including investigation of lipid abnormality, fasting blood glucose, DDimer, high-sensitivity troponin I, and B-type natriuretic peptide), an ECG, and a TTE examination were systematically performed. Depending on the results of these examinations, the cardiologist decided to schedule other advanced exams : exercise ECG, a holter ECG, a non-invasive functional imaging, a coronary angiography, or a cardiac MRI. The cardiologist could also judge that no further advanced examination was necessary.

The decision algorithm for performing advanced exams during the long term follow up of COVID-19 is presented **Figure 1**

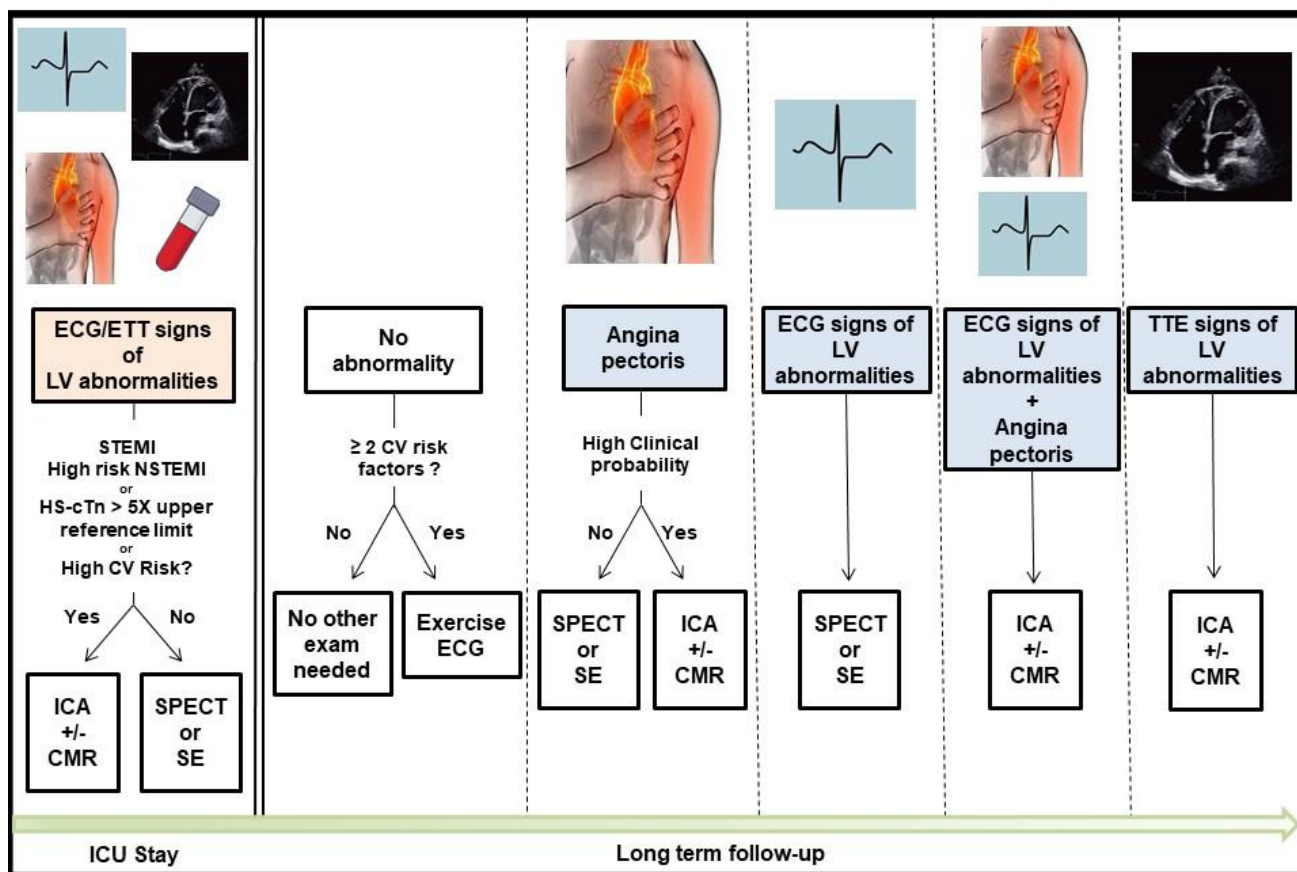


Figure 1. Decision algorithm for performing advanced exams during the acute phase of COVID-19 and during the long term follow up (31, 40, 41); ECG = electrocardiogram, TTE = transthoracic echocardiography; LV = left ventricular; STEMI = ST-elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; HS-cTn = high-sensitivity cardiac troponin I; CV = cardiovascular; ICA = invasive coronary angiography; CMR = cardiac magnetic resonance imaging; SPECT = single-photon emission computed tomography; SE = stress echocardiography; ICU = intensive care unit

A 24-hour ECG holter was programmed in case of palpitations, dizziness, syncope reported by the patient during the consultation.

Statistical analysis

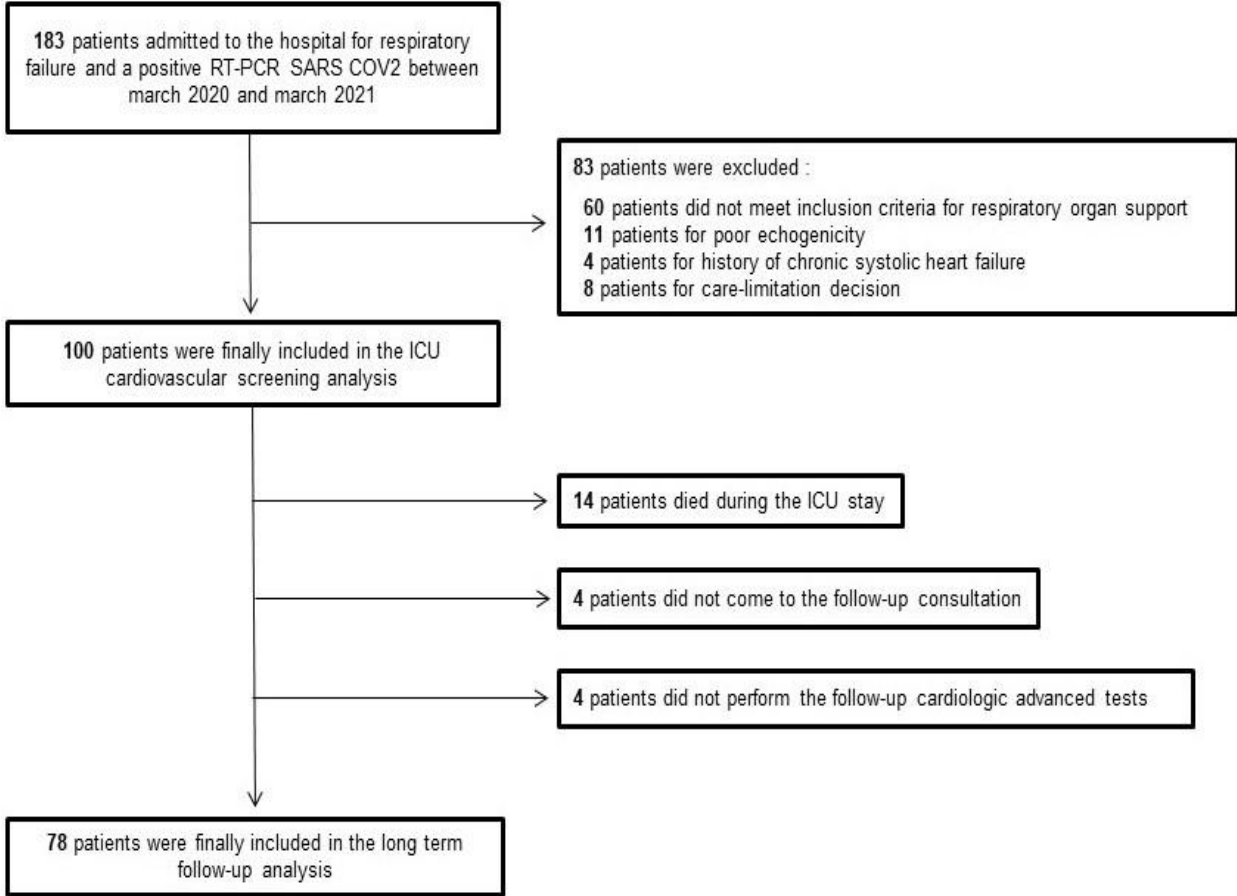
Since it was a descriptive study, no statistical sample size calculation was performed a priori. The normality of the variables was tested with the Kolmogorov-Smirnov test. Continuous variables were summarized as mean \pm standard deviation or median [interquartile range] as appropriate and categorical variables were summarized as counts and percentages. Categorical variables were compared with a Fisher exact test or a chi-2 test and continuous variables were compared with a Student-t- test or a Mann-Whitney U test. Statistical analysis was performed with SPSS (Statistical

Package for Social Science software, version 19, Chicago, Illinois, USA). A p value <0.05 was considered statistically significant.

Results

Study population during the acute phase of COVID-19

Between March 2020 and March 2021, 183 patients were admitted to the hospital for respiratory failure and a positive RT-PCR SARS Cov-2; 83 patients were excluded: 60 patients did not meet inclusion criteria for respiratory or cardiac organ support, 11 patients for poor echogenicity, 8 patients for care-limitation decision, and 4 patients for history of chronic heart failure. Finally, 100 patients were included. The flow chart of the study is presented [Figure 2](#).



[Figure 2](#). Flow chart of the study

The mean age of the population was 64 ± 11 years with a predominance of male (76%). Sixty-one patients (61%) were under mechanical ventilation, 34 patients (34%) under high-flow oxygen therapy, and 5 patients (5%) under non-invasive ventilation. Sixty patients (60%) received vasopressors. Finally, 37 patients (37%) experienced acute cardiac injury. The baseline characteristics of the population are presented [Table 1](#).

Patients with acute cardiac injury (ACI) were at higher cardiovascular risk than those without, with a higher risk SCORE (10 [10-10] vs. 3 [1-10], $p < 0.01$), higher history of hypertension and atherosclerosis (respectively 59% vs. 38% and 24% vs 8% with $p = 0.04$ and $p = 0.02$), and higher proportion of male (89% vs. 68%, $p = 0.02$). At admission, patients with ACI exhibited higher levels of inflammatory markers than patients without ACI with higher levels of procalcitonin and TNF-alpha (respectively 0.7 [0.19-3] vs. 0.16 [0.08-0.4] ng/mL, and 28 [13-44] vs. 17 [13-26] pg/mL, with $p < 0.01$ and $p = 0.01$) ([Table 1](#)).

Table 1. Baseline characteristics of patients with and without acute cardiac injury.

	Overall (N = 100)	Patients with cardiac Injury (N = 37)	Patients without cardiac Injury (N = 63)	p value
Age, years	64 ± 11	66 ± 12	62 ± 11	0.1
Sex gender, (no. (%) Male/no. (%) Female)	76 (76)/24 (24)	33 (89)/4 (11)	43 (68)/20 (32)	0.02
Simplified Acute Physiology Score II	37 ± 14	45 ± 15	33 ± 10	<0.01
SOFA score	4 [3-8]	8 [6-9]	3 [3-6]	<0.01
Percentage of affected lung parenchyma, %	50 [25-50]	50 [25-58]	50 [25-50]	0.64
Comorbidities				
Cardiovascular risk factors, no. (%)	67 (67)	32 (87)	35 (56)	<0.01
Number of cardiovascular risk factors, no.	1 [0-2]	1 [1-3]	1 [0-2]	<0.01
Score Cardiovascular Risk, (%)	8 [2-10]	10 [10-10]	3 [1-10]	<0.01
Hypertension, no. (%)	46 (46)	22 (59)	24 (38)	0.04
ACEi / Angiotensin-Receptor Blocker no. (%)	38 (38)	20 (54)	18 (28)	0.01
Diabetes, no. (%)	28 (28)	13 (35)	15 (24)	0.22
Smokers, no. (%)	18 (18)	9 (24)	9 (14)	0.2
Dyslipidemia, no. (%)	19 (19)	8 (22)	11 (18)	0.61
Atherosclerosis, no. (%)	14 (14)	9 (24)	5 (8)	0.02
Coronary heart disease, no. (%)	8 (8)	5 (14)	3 (5)	0.12
Chronic respiratory disease, no. (%)	5 (5)	2 (5)	3 (5)	0.89
Chronic renal disease, no. (%)	9 (9)	7 (19)	2 (3)	<0.01
Chronic liver disease, no. (%)	1 (1)	1 (3)	0 (0)	0.19
Malignancy, no. (%)	11 (11)	5 (14)	6 (10)	0.54
Immunodepression, no. (%)	9 (9)	5 (14)	4 (6)	0.23
Immunosuppressive treatment, no. (%)	8 (8)	4 (11)	4 (6)	0.43
Venous thromboembolism history, no (%)	8 (8)	4 (11)	4 (6)	0.43
Clinical parameters				
Body Mass Index, kg/m ²	29 ± 5	29 ± 5	29 ± 5	0.86
Norepinephrine use at admission, no. (%)	31 (31)	23 (62)	8 (13)	<0.01
Norepinephrine dosage at admission, µg/kg/min	0.08 [0-0.14]	0.1 [0-0.17]	0.05 [0-0.13]	0.52
Ventilation parameters				
Invasive Mechanical Ventilation, no. (%)	61 (61)	33 (89)	28 (44)	<0.01
PaO ₂ /FiO ₂ ratio	1.27 ± 0.57	1.5 ± 0.7	1.1 ± 0.4	0.01
PEEP, cm H ₂ O	13 ± 3	13 ± 3	13 ± 3	0.98
Tidal volume, mL/kg of predicted body weight	6.1 ± 0.5	6.1 ± 0.4	6.2 ± 0.6	0.5
Total respiratory rate, breaths/min	26 ± 4	27 ± 4	25 ± 3	0.22
Biological parameters				
HS Troponin-I, ng/L (no.=17)	19 [16-46]	52 [20-169]	17 [16-24]	<0.01
Creatine Kinase U/L (no.=190)	93 [60-217]	77 [56-336]	94 [62-162]	0.54
BNP, pg/mL (no.=17)	106 ± 132	151 ± 179	81 ± 88	0.01
Lactate, mmol/L	1 [0.9-1.4]	1.1 [0.9-1.5]	1 [0.9-1.3]	0.7
Interleukin-6, pg/mL	64.4 [19-202]	74 [23-245]	63.7 [17-170]	0.61
Interleukin-1, pg/mL	0.5 [0.3-1.3]	0.7 [0.3-6]	0.3 [0.3-1.3]	0.08
Interleukin-8, pg/mL	29 [13-88]	40 [18-135]	24 [22-78]	0.18
TNF-alpha, pg/mL	20 [13-28]	28 [13-44]	17 [13-26]	0.01
Creatinine clearance, ml/minute	92 [63-100]	60 [29-93]	95 [82-103]	<0.01
Plasma Creatinine, µmol/L	73 [61-102]	98 [72-180]	69 [57-80]	<0.01
Plasma Urea, mmol/L	7 [5-10]	10 [6-13]	6 [5-9]	<0.01
Plasma pH	7.46 ± 0.07	7.43 ± 0.09	7.47 ± 0.05	<0.01
Sodium Bicarbonate, mmol/L	24.8 ± 3.6	23.2 ± 4	26 ± 3	<0.01
Potassium, mmol/L	4 ± 0.6	4.2 ± 0.7	4 ± 0.47	0.1
SGOT, U/L	50 [36-71]	50 [39-85]	48 [34-70]	0.35
SGPT, U/L	19 [16-47]	36 [27-50]	37 [27-65]	0.59
Total Bilirubin, mmol/L	7 [5-10]	7 [5-10]	7 [6-10]	0.72
Protein C reactive, mg/L	165 ± 115	194 ± 129	148 ± 103	0.05
Procalcitonin, ng/mL	0.2 [0.1-0.82]	0.7 [0.19-3]	0.16 [0.08-0.4]	<0.01
Lactate dehydrogenase, UI/L	485 ± 232	560 ± 306	444 ± 168	0.03
Prothrombin, %	81 ± 15	79 ± 17	83 ± 15	0.29
Ratio APTT	0.99 [0.93-1.06]	1.03 [0.97-1.1]	0.96 [0.91-1.03]	0.04
Fibrinogen, g/L	6.2 ± 1.8	6.2 ± 1.8	6.3 ± 1.8	0.79
D-dimer, µg/L	927 [528-1869]	1026 [689-2903]	833 [444-1535]	0.08
White blood cells count, x10 ⁹ /L	9.4 ± 4.3	9.7 ± 5.2	9.2 ± 3.7	0.43
Neutrophils, x10 ⁹ /L	7.9 ± 3.8	8.4 ± 4.9	7.7 ± 3	0.41
Lymphocytes, x10 ⁹ /L	0.7 [0.5-0.9]	0.7 [0.5-0.8]	0.6 [0.5-0.9]	0.7
Hemoglobin, g/dL	12.9 ± 1.6	12.8 ± 1.7	13 ± 1.5	0.57
Platelets count, x10 ⁹ /L	233 [175-273]	277 [157-262]	244 [185-305]	0.1
Ferritin ng/mL	1233 ± 1230	1209 ± 1270	1242 ± 1231	0.93

Data are expressed as number (%), mean ± standard deviation or median [interquartile range], no. = number of patients; SOFA = sepsis-related organ failure assessment; ACEi = angiotensin converting enzyme inhibitors; PaO₂ = partial pressure of oxygen; FiO₂ = fraction of inspired oxygen; PEEP = positive end-expiratory pressure; HS Troponin-I = high-sensitivity troponin-I; BNP = B-type Natriuretic Peptide; TNF = tumor necrosis factor; SGOT = serum glutamoxalacetic transaminase; SGPT = serum glutamate pyruvate transaminase, APTT = activated partial thromboplastin time

Patients with ACI had poorer prognosis than patients without ACI: they required more vasopressor, mechanical ventilation, renal replacement (respectively 92% vs. 41%, 89% vs 44%, 32% vs 3%, $p<0.01$), and have higher length of ICU stay (15 [9-33 vs. 7 [4-10] days, $p<0.01$) and higher mortality (32% vs 3%, $p<0.01$) than patients without ACI. Patients with ACI received as much glucocorticoids and immunomodulating agents as patients without ACI, but they received more curative anticoagulation (40% vs. 13%, $p<0.01$). Intensity of supportive care and treatments of all patients are presented **Table 2**.

Table 2. Intensity of supportive care and treatments during ICU stay in patients with and without cardiac injury

	Overall (N = 100)	Patients with acute cardiac Injury (N = 37)	Patients without acute cardiac Injury (N=63)	p value
Vasopressor/Inotrope, no. (%)	60 (60)	34 (92)	25 (41)	<0.01
Norepinephrine, no. (%)	60 (60)	34 (92)	25 (41)	<0.01
Epinephrine, no. (%)	2 (2)	2 (5)	0 (0)	0.06
Dobutamine, no. (%)	0 (0)	1 (3)	0 (0)	0.18
Ventilation				
Invasive mechanical ventilation, no. (%)	61 (61)	33 (89)	28 (44)	<0.01
Mechanical ventilation duration, days	9 [4-23]	15 [7.5-31.5]	5 [3-11]	<0.01
Non-invasive ventilation, no. (%)	5 (5)	4 (11)	1 (2)	0.04
High-Flow oxygen therapy, no. (%)	39 (39)	4 (11)	35 (56)	<0.01
Treatments during ICU stay				
Glucocorticoids, no. (%)	98 (98)	36 (97)	62 (98)	0.7
Tocilizumab, no. (%)	40 (40)	11 (30)	29 (46)	0.1
Antibiotics, no. (%)	37 (37)	21 (57)	16 (25)	<0.01
Curative dose anticoagulation, no. (%)	23 (23)	15 (40)	8 (13)	<0.01
Intermediate dose anticoagulation, no. (%)	79 (79)	25 (68)	54 (86)	0.03
Amiodarone intravenous treatment, no. (%)	14 (14)	10 (27)	4 (6)	<0.01
Venous thromboembolism, no (%)	30 (30)	17 (46)	13 (21)	<0.01
Venovenous extracorporeal membrane oxygenation, no. (%)	1 (1)	1 (3)	0 (0)	0.19
Prone positioning, no. (%)	85 (85)	34 (92)	51 (81)	0.14
Neuromuscular-blockers use, no. (%)	50 (50)	29 (78)	21 (33)	<0.01
Inhaled nitric oxyd, no. (%)	13 (13)	4 (16)	9 (16)	0.98
Acute kidney injury, no (%)	28 (28)	223 (62)	5 (8)	<0.01
Renal replacement therapy, no. (%)	14 (14)	12 (32)	2 (3)	<0.01
Length of stay in ICU, days	9 [5-16]	15 [9-34]	7 [4-10]	<0.01
Mortality at D28, no. (%)	10 (10)	8 (22)	2 (3)	<0.01
In ICU Mortality, no. (%)	14 (14)	12 (32)	2 (3)	<0.01

Data are expressed as number (%) and median [interquartile range]. no. = number of patients; ICU = intensive care unit.

Cardiac abnormalities and characteristics of acute cardiac injury

Overall, 64% of the population presented ECG abnormalities and 98% TTE abnormalities during the ICU stay. Patients defined with ACI presented more ECG and TTE abnormalities than those without (5 [4-9] vs. 4 [2-5] ECG and TTE abnormalities per patient, $p<0.01$).

All ECG and TTE characteristics of patients with and without ACI are presented **Table 3**.

Table 3. Electrocardiographic and echocardiographic abnormalities in patients with or without cardiac injury during the 28 days of follow-up in the ICU

	Overall (N=100)	Patients with cardiac injury (N=37)	Patients without cardiac injury (N=63)	p value
ECG abnormalities, number per patient	1 [0-2]	1 [1-3]	1 [0-1]	<0.01
ECG abnormalities, no. (%)	64 (64)	30 (81)	34 (54)	<0.01
ECG signs of left ventricular abnormalities, no. (%)	48 (48)	26 (70)	22 (35)	<0.01
Repolarization abnormalities, no. (%)	42 (42)	24 (65)	18 (29)	<0.01
Inverted T waves, no. (%)	38 (38)	20 (54)	18 (29)	0.01
ST segment elevation, no. (%)	3 (3)	3 (8)	0 (0)	0.02
ST segment depression, no. (%)	18 (18)	11 (30)	7 (11)	0.02
Pathological Q waves, no. (%)	9 (9)	4 (11)	5 (8)	0.6
New left branch bundle block, no. (%)	3 (3)	2 (5)	1 (2)	0.28
Life-threatening ventricular arrhythmia, no. (%)	2 (2)	1 (3)	1 (2)	0.7
Severe bradyarrhythmia, no. (%)	3 (3)	2 (5)	1 (2)	0.28
New-onset atrial arrhythmias, no. (%)	16 (16)	11 (30)	5 (8)	<0.01
Atrial fibrillation, no. (%)	16 (16)	11 (30)	5 (8)	<0.01
Atrial flutter, no. (%)	3 (3)	3 (8)	0 (0)	0.02
Atrial tachycardia, no. (%)	0 (0)	0 (0)	0 (0)	1
Signs of right ventricular strain, no. (%)	41 (41)	17 (46)	24 (38)	0.44
Inverted T waves in leads V1-V4, no. (%)	23 (23)	12 (32)	11 (17)	0.09
QR pattern in V1, no. (%)	2 (2)	2 (5)	0 (0)	0.06
S1Q3T3 pattern, no. (%)	11 (11)	2 (5)	9 (14)	0.17
Incomplete or complete right bundle branch, no. (%)	13 (13)	5 (13)	8 (13)	0.9
TTE abnormalities number per patient, no.	3 [2-4]	4 [3-6]	3 [2-4]	<0.01
TTE abnormalities, no. (%)	98 (98)	37 (100)	61 (97)	0.27
TTE signs of left ventricular abnormalities, no. (%)	23 (23)	13 (35)	10 (16)	0.03
LV wall motion abnormalities, no. (%)	14 (14)	10 (27)	4 (6)	<0.01
LV ejection fraction (%)	61.4 ± 7.3	60.7 ± 8.3	61.8 ± 6.6	0.48
LV systolic dysfunction, no. (%)	15 (15)	8 (22)	7 (11)	0.15
Cardiac index, (L/ml/ m ²)	2.87 ± 0.79	2.82 ± 0.76	2.9 ± 0.8	0.6
LV global longitudinal, (%)	-14.8 ± 3.5	-13.9 ± 3.4	-15.3 ± 3.5	0.07
Impaired LV global longitudinal strain, no. (%)	88 (88)	32 (86)	56 (89)	0.72
LV diastolic dysfunction, no. (%)	20 (20)	9 (24)	11 (17)	0.4
E/A ratio	0.94 ± 0.27	1 ± 0.36	0.9 ± 0.2	0.04
e' lateral (cm/s)	10 [9-12]	10 [8-12]	11 [9-13]	0.03
e' septal (cm/s)	8 [7-9]	7 [6-8]	8 [7-10]	<0.01
E/e' averaged ratio	8 ± 2	9 ± 3	8 ± 2	0.04
LV filling pressure elevation, no. (%)	12 (12)	9 (24)	3 (5)	<0.01
LV mass index (g/m ²)	95 ± 37	107 ± 43	88 ± 31	0.01
LV hypertrophy, no. (%)	53 (53)	27 (73)	26 (41)	<0.01
Indexed left atrial volume, (ml/m ²)	21 ± 7	22 ± 7	21 ± 7	0.46
Left atrial dilatation, no. (%)	13 (13)	5 (13)	8 (13)	0.9
LV end-diastolic volume index, (ml/m ²)	44 ± 13	45 ± 16	44 ± 11	0.66
LV dilatation, no. (%)	5 (5)	3 (8)	2 (3)	0.27
Systolic pulmonary arterial pressure, (mm Hg)	25 [17-30]	27 [24-46]	20 [15-25]	<0.01
Pulmonary hypertension no. (%)	18 (18)	14 (38)	4 (6)	<0.01
RV dysfunction, no. (%)	30 (30)	19 (51)	11 (18)	<0.01
Tricuspid annular plane systolic excursion (mm)	22 ± 3	21 ± 3	23 ± 3	0.01
Systolic tricuspid annular velocity (cm/s)	16 ± 3	15 ± 4	16 ± 2	0.17
RV fractional area change (%)	50 ± 9	52 ± 11	49 ± 8	0.06
Longitudinal RV global strain (%)	-15 ± 4	-14 ± 4	-15 ± 4	0.47
Longitudinal RV free wall strain (%)	-16 ± 4	-16 ± 5	-16 ± 3	0.9
Impaired RV strain, no. (%)	81 (81)	29 (74)	52 (82)	0.6
Right/left ventricular end-diastolic areas ratio	0.18 [0.15-0.22]	0.18 [0.15-0.38]	0.17 [0.25-0.21]	0.17
RV dilatation, no. (%)	6 (6)	6 (16)	0 (0)	<0.01
Acute cor pulmonale, no. (%)	6 (6)	5 (14)	1 (2)	0.02
Pericardial effusion, no. (%)	11 (11)	5 (14)	6 (9)	0.54
Valvulopathy, no. (%)	0 (0)	0 (0)	0 (0)	1
ECG/TTE signs of left ventricular abnormalities	56 (56)	27 (73)	29 (46)	<0.01
ECG/TTE abnormalities, number per patient	4 [3-5]	5 [4-9]	4 [2-5]	<0.01
ECG/TTE abnormalities, no. (%)	99 (99)	37 (100)	62 (98)	0.44

Data are expressed as number (%) or mean±standard deviation. no. = number of patients; ECG = electrocardiogram; TTE = Transthoracic echography; LV= Left Ventricle; E = early peak velocity of the mitral flow with pulsed Doppler; A = atrial 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; RV = Right Ventricle.

The most frequent newly diagnosed abnormalities among patients with ACI during all ICU stay were impaired LV global longitudinal strain (86%), impaired RV free-wall strain (78%), ECG/TTE signs of LV abnormalities (73%), RV dysfunction (51%), atrial fibrillation (30%), LV diastolic dysfunction (24%), LV systolic dysfunction (22%), cor pulmonale (14%) and pericardial effusion (14%). None of the pericardial effusion was associated with tamponade. No significant valvulopathy was found. Cardiac abnormalities in patients with ACI are presented **Figure 3**.

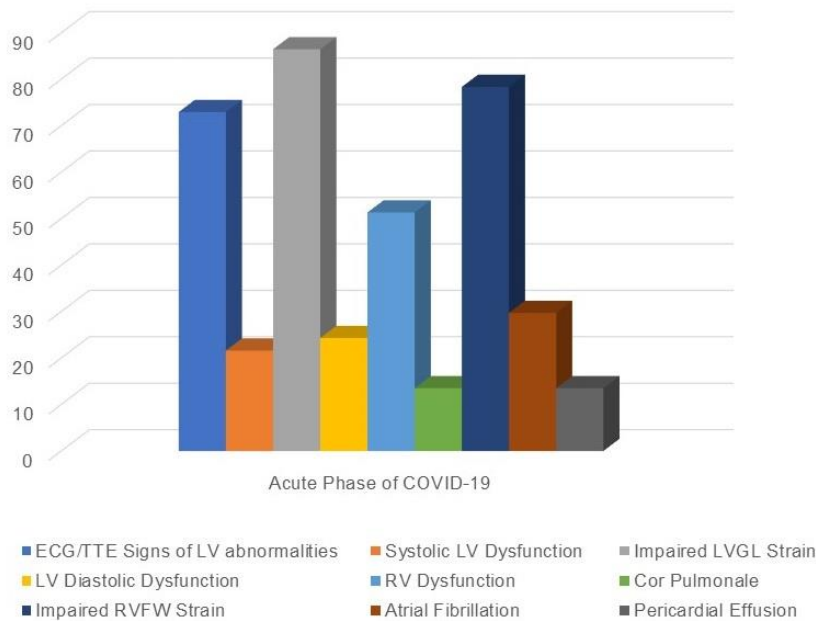


Figure 3. Incidences of different cardiac abnormalities in patients with acute cardiac injury during the 28 days follow-up in the ICU (n=37). ECG = electrocardiogram, TTE = echocardiography, LVGL = left ventricular global longitudinal, LV = left ventricular, RV = right ventricular, RVFW = right ventricular free wall

Overtime, incidence of LV systolic dysfunction, RV dysfunction, LVGL strain, RVFW strain and cor pulmonale decreased while that of atrial fibrillation and pericardial effusion increased. Conversely, incidence of ECG/TTE signs of LV abnormalities and LV diastolic dysfunction remained stable. The time course of each cardiac abnormality incidence among patients with ACI is presented **Figure 4**.

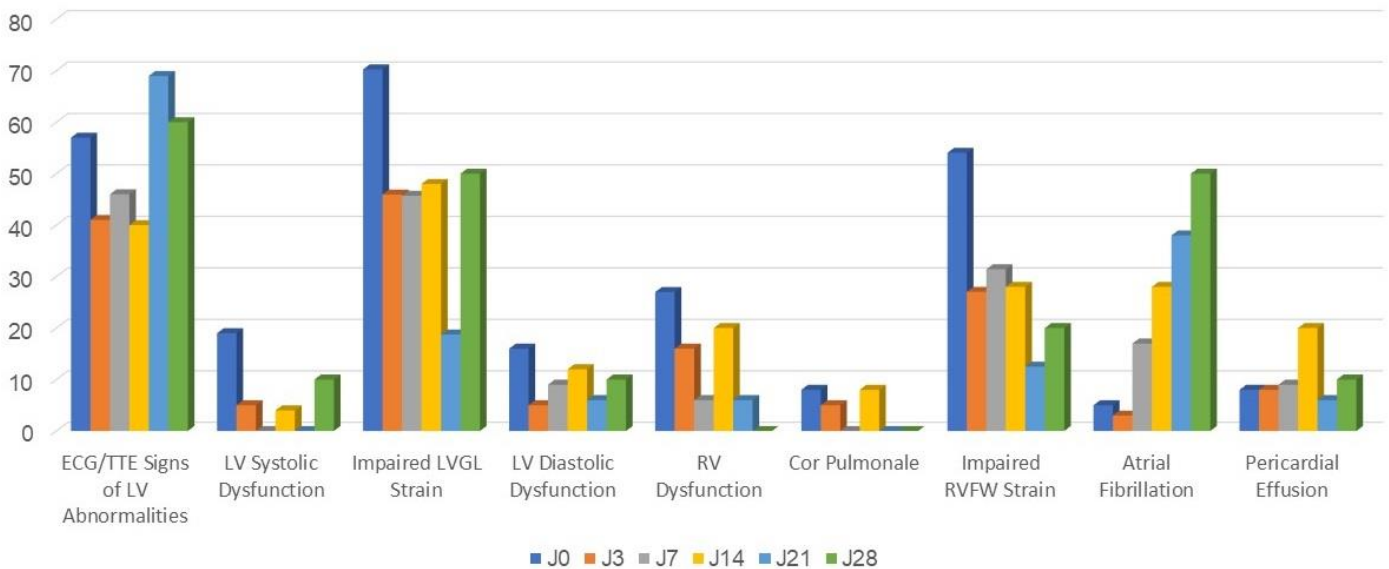


Figure 4. Time course of each cardiac abnormality incidence in patients with acute cardiac injury during the 28 days follow-up in the ICU (n=37). ECG = electrocardiogram, TTE = echocardiography, LVGL = left ventricular global longitudinal, LV = left ventricular, RV = right ventricular, RVFW = right ventricular free wall

Proportion of ACI occurring remains high during all ICU stay: 89% at D0, 68% at D3, 83% at D7, 84% at D14, 81% at D21 and 80% at D28. ACI occurrence was early concerning 33 patients at admission (89%), 3 patients at D7 (8%), and 1 patient at D14 (3%).

Patients with ACI exhibited more ECG abnormalities during the ICU stay than patients without ACI (81% vs 54%, $p < 0.01$), particularly more repolarization abnormalities and more atrial fibrillation (respectively 65% vs 29% and 30% vs 8%, $p < 0.01$ for both) (Table 3). More TTE abnormalities were also found in patients with ACI than patients without (4 [3-6] vs 3 [2-4] TTE abnormalities per patient, $p < 0.01$) (Table 2), particularly more LV wall motion abnormalities (27% vs 6%, $p < 0.01$), more left ventricular hypertrophy (73% vs 41%, $p < 0.01$), more impaired relaxation with lower septal and lateral e' velocities, higher E/e' averaged ratio (respectively 10 [8-12] vs 11 [9-13], 7 [6-8] vs 8 [7-10] and 9 ± 3 vs 8 ± 2 ; with $p = 0.03$, $p < 0.01$ and $p = 0.04$). Overall, more ECG/TTE signs of LV abnormalities were found in patients with ACI than without (73% vs 46%, $p < 0.01$). Right ventricle was also more impaired in patients with ACI than patients without ACI, showing higher systolic pulmonary arterial pressure 27 [24-46] 20 [15-25], $p < 0.01$), more right ventricular dysfunction (51% vs 18%, $p < 0.01$) and more acute cor pulmonale (13% vs 2%, $p = 0.02$) than patients without ACI.

During the ICU stay, urgent coronary angiography and cardiac MRI was indicated for 1 patient finally diagnosed with myocarditis. Two other coronary angiograms were performed soon after ICU discharge and showed significant coronary lesions. No non-invasive functional imaging (SPECT or stress echocardiography) was done soon after ICU discharge for patients with type 2 myocardial infarction due to the need for rehabilitation. No Takotsubo syndrome or septic cardiomyopathy was diagnosed.

Long term follow-up

Among the 100 patients included and analyzed during the ICU stay, 22 patients could not be included for the whole follow up analysis: 14 patients died during the ICU stay, 4 patients did not come to their consultation, and 4 patients did not perform the advanced cardiac tests. Finally, 78 patients were reviewed in consultation and performed all the advanced cardiac tests prescribed. The median delay of consultation from ICU discharge was 107 [95-162] days.

The long term biological parameters of patients with and without ACI are presented **Supplemental Table 1**. The long term ECG and TTE parameters of patients with and without ACI are presented **Supplemental Table 2**. Blood levels of troponin, BNP, Interleukin-6, triglycerids, and glycosylated hemoglobin ($p < 0.01$) remained higher at long term follow-up in patients with ACI than those without (respectively 17 [17-22.5] vs 17 [17-17] ng/L, 5.6 [2.9-7.9] vs 2.6 [1.8-5.1] pg/mL, 42 [31-58] vs 23 [14-35] pg/mL, 2.3 [1.3-3.2] vs 1.5 [0.9-1.9] g/L and 6.8 [5.4-9.2] vs 5.5 [5.2-6.3] % ; with $p < 0.01$, $p = 0.01$, $p < 0.01$ and $p < 0.01$) (**Supplemental Table 1**)

Among patients with ACI reviewed, compared to the acute phase LV systolic dysfunction, LV diastolic dysfunction, RV dysfunction and pericardial effusion nearly normalized for the majority of patients (decrease of the incidence respectively from 19% to 5%, 19% to 5%, 52% to 9%, and 14% to 5%). Similarly all cor pulmonale normalized at follow up.

LVGL and RVFW strains improved overtime but remained impaired in a large proportion of patients (decrease of the incidence respectively from 86% to 43% and from 71% to 43%). Similarly, atrial fibrillation was less frequent but still concerned a significant proportion of patients with an incidence decreasing from 24% to 14% in patients with ACI. The evolution of each cardiac abnormality

incidence in patients with ACI between acute phase of COVID-19 and long term follow-up is presented **Figure 5**.

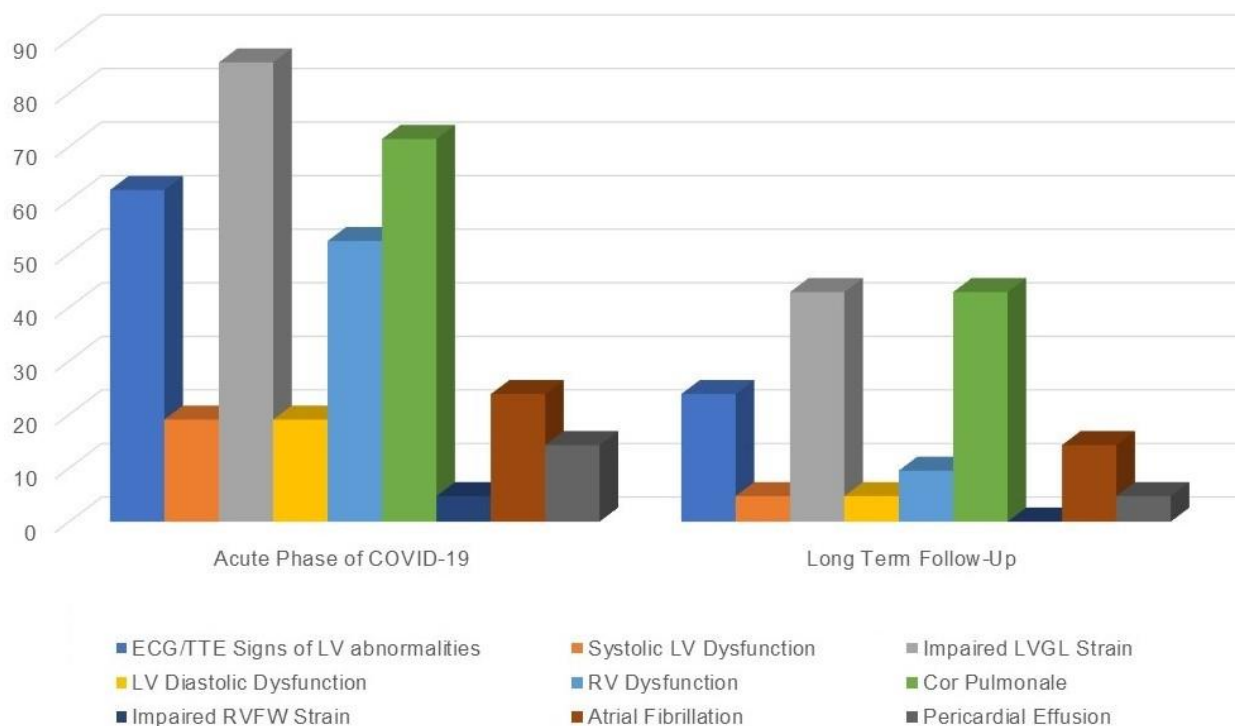


Figure 5. Evolution of each cardiac abnormality incidence in patients with ACI between acute phase of COVID-19 and long term follow-up (n=21). ECG = electrocardiogram, TTE = echocardiography, LVGL = left ventricular global longitudinal, LV = left ventricular, RV = right ventricular, RVFW = right ventricular free wall

Long term advanced cardiac tests were realized in 56% (n=44) of all 78 reviewed patients: exercise ECG was realized in 9% (n=7), SPECT in 39% (n=30), stress echocardiography in 3% (n=2), coronary angiography in 13% (n=10), cardiac MRI in 10% (n=8), and holter ECG in 9% (n=7) of all patients. Counting the examinations performed in the acute phase and after the long-term follow-up, patients with ACI performed more coronary angiography than patients without ACI (38% vs 9%, $p<0.01$). But overall they performed as many advanced cardiac tests as patients without ACI (1 [0-2] vs 1 [0-1] advanced exam per patient, $p=0.44$).

Significant coronary lesions were found in 8 patients (10%), more in patients with ACI than without (29% vs 4%, $p<0.01$). Patients with coronaropathy exhibited during COVID-19 more ECG signs of LV abnormalities than patients without coronaropathy (88% vs 39%, $p<0.01$), particularly more ST segment depression (38% vs 10%, $p=0.03$) and new left bundle branch block (25% vs 0%, $p<0.01$), more LV wall motion abnormalities (38% vs 10%, $p=0.03$), more impaired LVEF (38% vs 10%,

p=0.03), and more LV hypertrophy (88% vs 49%, p=0.04). None of RV ECG or TTE cardiac parameters was more found in patients with coronaropathy than those without.

Overall, 8 cardiac MRI (10%) were performed with a median delay of 202 days, and only 1 myocarditis (1%) was diagnosed. No sign of myocarditis was found in cardiac MRI (n=7) performed during the long term follow-up.

Advanced tests including SPECT, stress echocardiography, coronary angiography or cardiac MRI were performed in 60% of patients with ECG/TTE signs of LV abnormalities during COVID-19.

During the follow-up, atrial fibrillation was found in 5 patients (6%), more in patients with previous new onset atrial fibrillation occurring during COVID-19 than the others (33% vs 3%, p<0.01). Long term 24-hour ECG holter was performed only in 22% of patients with new onset atrial fibrillation occurring during COVID-19.

At least one year after the start of the study (march 2022), all patients, including those who did not attend their consultation, were contacted successfully by phone. Finally, apart from the deaths in the acute phase, no patient died 1 year after the beginning of follow-up.

Discussion

Cardiac injury is frequent in critically ill COVID-19 patients (7, 8) but its long term evolution is poorly or incompletely described (18-23). To our knowledge, this study is the first to longitudinally characterize with a comprehensive multimodal clinical and paraclinical strategy the short and long term cardiac abnormalities occurring in critically ill COVID-19 patients.

We confirmed that cardiac abnormalities are frequent in severe COVID-19 patients: 64% of the population presented ECG abnormalities and 98% TTE abnormalities. The incidence of cardiac injury as defined in our study (association of a newly diagnosed ECG or TTE abnormality with elevation of troponin) was 37%. This definition allowed us to better characterize patients with higher cardiovascular risk and poorer prognosis, as evidenced by the higher cardiovascular risk SCORE, the higher level of supportive care intensity and higher mortality in the population of patients with ACI.

Alteration of the LV and RV strain represented the most frequent cardiac abnormalities, with an incidence of 86% and 78%, respectively in patients with ACI. Baruch and colleagues showed in less severe COVID-19 patients an alteration of LV and RV strains in lesser proportions (33 and 23% respectively) (23). These abnormalities are very sensitive but probably too sensitive in our severe population and did not make it possible to discriminate patients with ACI from those without.

ECG/TTE signs of LV abnormalities (i.e. suggestive of coronary heart disease, Takotsubo syndrome, myocarditis or septic cardiomyopathy) were also frequent (73%) among patients with ACI and could distinguish better patients with ACI from those without, as well as new onset atrial fibrillation (30%), RV dysfunction (51%) and LV dysfunctions (22%). LVGL strain was not used in our methodology for define TTE sign of LV abnormality because LVGL strain impairment did not define yet NSTEMI or STEMI (25).

RV dysfunction was more frequent than LV dysfunction (51% vs 22%) confirming previous findings (8-10). Pulmonary vascular resistances are particularly high in COVID-19 due to parenchymal injury, increased venous thromboembolic risk and intra-thoracic pressures exerted by invasive or non-invasive ventilation in the intensive care unit (6, 8, 10, 42, 43).

Long-term follow-up showed improvement of all abnormalities. However, impaired LV and RV strains still affected a high proportion of patients with ACI confirming data from Baruch and colleagues (23).

Overall, coronary heart disease was found in 29% of patients with ACI, and 10% of the whole population. This incidence was higher than predicted by the calculated cardiovascular risk SCORE : this score predicted a long term incidence of cardiovascular events of 10% in patients with ACI and 8% in the whole population in our cohort (44). This could mean that COVID-19 could have been responsible for triggering coronary heart disease. This is not surprising since the risk of myocardial infarction increases in other viral infections: Kwong and colleagues reported a 2 in 10 increase in risk of coronary heart disease after infection with influenza virus, parainfluenzae, adenovirus, metapneumovirus, coronarivirus, enterovirus, or respiratory syncytial virus (45). Inflammation associated with COVID-19 could be responsible of atheromatous plaque rupture.

Myocarditis was found in only 1 patient representing 5% of patients with ACI and 1% of the whole population. This is less than described recently by Baruch and colleagues which reported an incidence of 9% in a cohort of 80 patients (23). Cardiac MRI was performed in 10% of our population. It was not systematically performed because we followed a defined diagnostic algorithm. Some subclinical myocarditis could have been missed. In addition, only one cardiac MRI was done in the acute phase and most of cardiac MRI were done at least within 3 months and could also missed acute signs of myocarditis. Nevertheless, our result showed at least that potential myocarditis did not leave sequela on follow-up. The true incidence of myocarditis during COVID-19 is discussed. While Daniels and colleagues showed cardiac MRI signs of myocarditis in 2.3% of a US athletes population (46), Kawakami and colleagues reported an incidence of only 4.5% of pathological myocardial evidence for SARS-Cov-2 in autopsy examinations (15) which is similar with our incidence.

Fourteen patients died (14%). One cannot exclude that these patients could also have coronary heart diseases or myocarditis especially since these were the most serious patients. Thus incidences of coronary heart disease and of myocarditis may have been underestimated.

Long term atrial fibrillation was found in a significant proportion of patients with ACI (14%) and concerned 6% of the whole population. To our knowledge, no other study have described long term atrial fibrillation occurrence after ICU discharge. Walkey and colleagues showed in a large retrospective multicentre study long term higher risk of stroke, heart failure and death in critically ill patients with new onset atrial fibrillation associated with sepsis, which suggested a possible long term recurrence of atrial fibrillation (47). Given the high morbidity associated with atrial fibrillation, our results showed that long term atrial fibrillation screening should be considered in critically ill COVID-19 patients. In addition, our recurrence rate was probably underestimated. Our study was more focused on coronary heart disease and myocarditis screening and was not designed for long term atrial fibrillation screening: only 22% of patients with new onset atrial fibrillation performed long term 24-hour long holter ECG.

Our study has other limits. First, this is a monocentric study. However, the monocentric character facilitated the application of the diagnostic algorithm of comprehensive cardiovascular screening

which was difficult to be conducted in more than one center. Furthermore the monocentric nature of our study allowed patients to be contacted several times, which explains the low rate of loss to follow-up (n=4). Second, only 60% of patients with ECG/TTE signs of LV abnormalities were screened as planned with the diagnostic algorithm which represented a high but incomplete proportion of the population. The incidence of cardiac abnormalities, especially coronary heart disease, has been further underestimated. Third, the size of our cohort is small. Our findings have to be confirmed in further cohorts.

Conclusion

Acute cardiac injury is frequent and occurred early in critically ill COVID-19 patients. RV is more impaired than LV. All abnormalities improved on long term follow-up. ECG/TTE signs of LV abnormalities resulted long term mainly in coronary heart disease and rarely in myocarditis. Atrial fibrillation prevalence was still significant on the long term follow-up. The long term significant incidence of coronary heart disease and atrial fibrillation support a long term screening for these abnormalities which are associated with high morbidity.

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Supplemental data

Supplemental Table 1. Long term biological parameters in patients with and without acute cardiac injury

	Overall (N = 75)	Patients with cardiac injury (N = 18)	Patients without cardiac injury (N = 57)	<i>p</i> value
Troponin-I, ng/L	17 [17-17]	17 [17-22,5]	17 [17-17]	<0.01
BNP, pg/mL	28 [14-39.7]	42 [31-58]	23 [14-35]	<0.01
Interleukin-6, pg/mL	2.9 [1.9-5.6]	5.6 [2.9-7.9]	2.6 [1.8-5.1]	0.01
Interleukin-1, pg/mL	0.32 [0.32-0.7]	0.34 [0.32-0.69]	0.32 [0.32-0.7]	0.86
Interleukin-8, pg/mL	23 [15.5-67.1]	40.3 [24.3-96.9]	20.9 [14.6-54]	0.09
TNF-alpha, pg/mL	14.7 ± 5.9	18.6 ± 8.6	13.9 ± 4.83	0.1
Creatinine clearance, ml/minute	80 ± 23	68 ± 28	84 ± 21	0.05
Plasma Creatinine, µmol/L	80 [64-96]	94 [73.7-120]	78 [61-88.5]	0.01
Plasma Urea, mmol/L	6 [4.9-7]	9.7 [6.9-13]	5.4 [4.6-6.6]	<0.01
Potassium, mmol/L	4 [3.8-4.3]	4.2 [3.8-4.4]	4 [3.9-4.3]	0.6
SGOT, U/L	22 [19-26]	21.5 [17.7-26]	23 [19-27]	0.38
SGPT, U/L	24 [18-31]	21 [17-30.7]	24 [18-32]	0.35
Total bilirubin, mmol/L	6 [5-7]	5 [4-7.2]	6 [5-7.5]	0.16
Protein C reactive, mg/L	1.9 [1-4.7]	2.6 [1-5.3]	1.5 [1-4]	0.42
Procalcitonin, ng/mL	0.05 [0.05-0.05]	0.05 [0.05-0.14]	0.05 [0.05-0.05]	0.13
Ratio APTT	1 [0.96-1.1]	1.1 [0.91-1.1]	1 [0.94-1.1]	0.58
Prothrombin, %	93 ± 12	86.9 ± 16.3	96 ± 5.8	<0.01
Fibrinogen, g/L	3 [2.5-3.4]	3 [2.7-3.4]	3 [2.5-3.5]	0.43
D-dimer, µg/L	405 [295-648]	406 [290-985]	398 [290-634]	0.45
White blood cells count, x10 ⁹ /L	7.0 ± 2.1	7.9 ± 2.6	6.7 ± 1.8	0.12
Neutrophils, x10 ⁹ /L	3.9 ± 1.7	4.8 ± 2.4	3.7 ± 1.3	0.1
Lymphocyt, x10 ⁹ /L	2.1 ± 0.8	2.1 ± 0.7	2.1 ± 0.8	0.67
Hemoglobin, g/dL	13.8 ± 1.4	13.2 ± 1.6	13.9 ± 1.4	0.51
Platelets count, x10 ⁹ /L	254 ± 74	245 ± 56	257 ± 79	0.2
Ferritin, ng/mL	77 [32.5-149]	62 [51.2-123.2]	94.5 [31-151]	0.99
HbA1c, %	5.7 [5.2-6.8]	6.8 [5.4-9.2]	5.5 [5.2-6.3]	<0.01
Triglycerids, g/L	1.6 [1.1-2]	2.3 [1.3-3.2]	1.5 [0.9-1.9]	<0.01
Cholesterol total, g/L	2.0 ± 0.5	2.12 ± 0.57	1.98 ± 0.4	0.03
LDL cholesterol, g/L	1.3 ± 0.5	1.5 ± 0.6	1.3 ± 0.4	0.13
HDL cholesterol, g/L	0.5 ± 0.2	0.47 ± 0.12	0.52 ± 0.15	0.4

Data are expressed as number (%), mean ± standard deviation or median [interquartile range], no. = number of patients, BNP = B-type Natriuretic Peptide, TNF = tumor necrosis factor, SGOT = serum glutamo-oxalacetic transferase, SGPT = serum glutamo-pyruvate transferase, APTT = activated partial thromboplastin time, HbA1c = glycated hemoglobin, LDL = low-density lipoprotein, HDL = high-density lipoprotein,

Supplemental Table 2. Long term ECG and echocardiographic abnormalities in patients with and without acute cardiac injury

	Overall (N=78)	Patients with cardiac injury (N=21)	Patients without cardiac injury (N=57)	p value
ECG abnormalities, number per patient	0 [0-1]	0 [0-1]	0 [0-1]	0.41
ECG abnormalities, no. (%)	27 (35)	9 (43)	18 (32)	0.35
ECG signs of left ventricular abnormalities	19 (24)	5 (24)	14 (25)	0.95
Repolarization abnormalities, no. (%)	11 (14)	2 (10)	9 (16)	0.48
Inverted T waves, no. (%)	9 (11)	2 (9)	7 (12)	0.73
ST segment elevation, no. (%)	0 (0)	0 (0)	0 (0)	1
ST segment depression, no. (%)	3 (4)	0 (0)	3 (5)	0.28
Pathological Q waves, no. (%)	4 (5)	1 (5)	3 (5)	0.93
New left branch bundle block, no. (%)	4 (5)	2 (9)	2 (4)	0.28
Life-threatening ventricular arrhythmia, no. (%)	0 (0)	0 (0)	0 (0)	1
Severe bradyarrhythmia, no. (%)	1 (1)	0 (0)	1 (2)	0.55
Atrial arrhythmias, no. (%)	5 (6)	3 (14)	2 (3)	0.08
Atrial fibrillation, no. (%)	5 (6)	3 (14)	2 (3)	0.08
Atrial flutter, no. (%)	1 (1)	1 (5)	0 (0)	0.1
Atrial tachycardia, no. (%)	0 (0)	0 (0)	0 (0)	1
Signs of right ventricular strain, no. (%)	10 (13)	4 (19)	6 (11)	0.31
Inverted T waves in leads V1-V4, no. (%)	2 (3)	1 (5)	1 (2)	0.45
QR pattern in V1, no. (%)	0 (0)	0 (0)	0 (0)	1
S1Q3T3 pattern, no. (%)	3 (4)	2 (10)	1 (2)	0.11
Incomplete or complete right bundle branch, no. (%)	7 (9)	2 (10)	5 (9)	0.91
Left ventricular hypertrophy, no. (%)	15 (20)	5 (24)	10 (18)	0.53
TTE abnormalities, number per patient	1 [0-2]	1 [0-2]	1 [0-1.5]	0.1
TTE abnormalities, no. (%)	44 (56)	14 (67)	30 (53)	0.27
TTE signs of LV abnormalities, no. (%)	2 (3)	1 (5)	1 (2)	0.46
LV wall motion abnormalities, no. (%)	2 (3)	1 (5)	1 (2)	0.46
LV ejection fraction (%)	60 [60-65]	60 [57-64]	62 [60-66]	0.12
LV systolic dysfunction, no. (%)	1 (1)	1 (5)	0 (0)	0.1
LV global longitudinal strain, no. (%)	16.8 ± 3.4	16 ± 3.6	17.1 ± 3.3	0.32
Impaired LV global longitudinal strain, no. (%)	26 (33)	9 (42)	17 (30)	0.32
LV diastolic dysfunction, no. (%)	2 (3)	1 (5)	1 (2)	0.46
E/A ratio	0.9 [0.66-1]	0.9 [0.63-1]	0.8 [0.69-1]	0.64
e' lateral (cm/s)	10.3 ± 2.7	10.5 ± 3.3	10.3 ± 2.5	0.75
e' septal (cm/s)	8.6 ± 2	8.7 ± 0.3	8.6 ± 2	0.87
E/e' averaged ratio	7.7 ± 2	7.9 ± 2.7	7.7 ± 1.7	0.67
LV filling pressure elevation, no. (%)	1 (2)	0 (0)	1 (2)	0.55
LV mass index (g/m ²)	85.6 [73-111]	91 [73-120]	85 [76-110]	0.85
LV hypertrophy, no. (%)	15 (19)	5 (24)	10 (18)	0.53
Indexed left atrial volume, (ml/m ²)	18.5 ± 6.2	18.7 ± 6.8	18.4 ± 6	0.02
Left atrial dilatation, no. (%)	1 (1)	1 (5)	0 (0)	0.1
LV dilatation, no. (%)	2 (3)	2 (14)	0 (0)	0.02
Systolic pulmonary arterial pressure, (mm Hg)	28.8 ± 6.9	29.7 ± 9	28 ± 6	0.1
Pulmonary hypertension no. (%)	1 (1)	1 (5)	0 (0)	0.1
RV dysfunction, no. (%)	4 (5)	2 (10)	2 (3)	0.28
Tricuspid annular plane systolic excursion (mm)	20 [20-24]	20 [20-24]	21 [20-23.5]	0.85
Systolic tricuspid annular velocity (cm/s)	16 [15-18]	16 [15-17]	16 [15-18]	0.47
Right/left ventricular end-diastolic areas ratio	0.17 ± 0.05	0.17 ± 0.06	0.17 ± 0.05	0.48
Longitudinal RV free wall strain, no. (%)	17 ± 4.2	17 ± 3.3	18 ± 4.6	0.47
Impaired RV strain, no. (%)	27 (35)	9 (43)	18 (32)	0.35
Pericardial Effusion, no. (%)	1 (1)	1 (5)	0 (0)	0.1
Valvulopathy, no. (%)	0 (0)	0 (0)	0 (0)	1
ECG and TTE signes of LV abnormalities, no. (%)	19 (24)	5 (24)	14 (25)	0.95
ECG and TTE abnormalities, number per patient	1 [0-2]	2 [1-3]	1 [0-2]	0.03
ECG and TTE abnormalities, no. (%)	54 (69)	19 (91)	35 (61)	0.01

Data are expressed as number (%) or mean ± standard deviation. no. = number of patients, ECG = electrocardiogram, TTE = transthoracic echocardiography, LV = Left Ventricle, E = early peak velocity of the mitral flow, A = atrial peak velocity of the mitral flow, e' = early diastolic peak velocity of the lateral and septal mitral annulus, RV= right ventricle.

SERMENT D'HIPPOCRATE

Au moment d'être admis à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me le demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré et méprisé si j'y manque.

Résumé / Abstract

Contexte : La survenue d'une atteinte cardiaque est fréquente au cours de la COVID-19. De nombreuses anomalies ECG ou échocardiographiques ont été décrites parmi lesquelles l'atteinte du cœur droit est prédominante à celle du cœur gauche. La présence d'anomalies ECG ou ETT évocatrices de cardiopathie gauche, notamment de coronaropathie ou de myocardite, sont aussi fréquemment rapportées. La signification de ces anomalies et l'évolution de l'ensemble des anomalies cardiaques à la phase aiguë et à distance sont mal décrites chez les patients les plus graves admis en réanimation.

But de l'étude : Déterminer l'incidence et l'évolution à court et long terme des différentes anomalies cardiaques observées au cours de la COVID-19, et préciser la cardiopathie associée aux anomalies du cœur gauche initialement observées.

Méthodologie : Il s'agit d'une étude monocentrique prospective menée dans un hôpital universitaire. Des patients consécutivement admis dans un service de réanimation pour une infection à SARS-Cov-2 et nécessitant un support respiratoire ou hémodynamique ont été inclus. Une évaluation cardiaque multimodale associant une analyse ECG, échocardiographique et de biomarqueurs cardiaques a été réalisée à plusieurs temps au cours du séjour en réanimation. Une atteinte cardiaque aiguë (ACA) était définie par l'association d'une élévation de la troponine et d'une anomalie ECG et/ou échocardiographique. La même analyse multimodale a été réalisée dans un délai de 3 à 6 mois après la sortie d'hospitalisation. Selon un algorithme décisionnel prédéfini, d'autres examens complémentaires étaient réalisés: ECG d'effort, holter ECG des 24 heures, imagerie fonctionnelle non invasive (scintigraphie ou échocardiographie de stress), coronarographie ou imagerie par résonance magnétique cardiaque.

Résultats : Sur une période de 1 an, 100 patients ont été inclus parmi lesquels 37 (37%) ont présenté une ACA. Au total, 61% des patients étaient sous ventilation mécanique, 34% sous oxygénothérapie à haut débit et 5% sous ventilation non invasive. Le risque cardiovasculaire SCORE était plus important chez les patients avec ACA que sans (10% vs. 3%, $p<0.01$). La survenue d'une ACA était précoce concernant déjà 89% des patients avec ACA à l'admission. Parmi les ACA, les anomalies les plus fréquemment retrouvées étaient: une altération du strain longitudinal global du ventricule gauche (86%) et du strain de la paroi libre du ventricule droit (78%), des signes ECG/ETT d'anomalies du ventricule gauche (73%), une dysfonction du ventricule droit (51%), une fibrillation auriculaire (30%), une dysfonction diastolique du ventricule gauche (24%), une dysfonction systolique du ventricule gauche (22%), un cœur pulmonaire (14%) et un épanchement péricardique (14%). Au long cours, l'ensemble des anomalies se sont améliorées mais persistait une altération des strains gauche et droit toujours importante (43%). Des lésions coronaires significatives ont été retrouvées chez 8 patients (10%), plus fréquemment chez les patients avec ACA que chez les autres (29% vs 4%, $p<0.01$). Un seul diagnostic de myocardite a été confirmé (1%). L'incidence de fibrillation auriculaire au long cours était de 6% dans toute la population, et 14% chez les patients avec ACA initiale.

Conclusion : L'ACA est fréquente et précoce au cours de la COVID-19 en réanimation. Toutes les ACA se sont améliorées au cours du suivi. L'incidence de coronaropathie et de fibrillation auriculaire étaient importantes au long cours, mais celle de myocardite est restée rare. Ces résultats suggèrent qu'un dépistage de coronaropathie et de fibrillation auriculaire au long cours est à discuter chez ces patients compte tenu de la morbi-mortalité importante associée à ces anomalies.