CORRESPONDENCE

Characterization and outcomes of acute myocardial injury in COVID-19 intensive care patients

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Abbreviations

cTn	Cardiac troponin
BNP	B-type natriuretic peptide
COVID-19	Coronavirus Disease 2019
ECG	Electrocardiography
Hs-cTnI	High sensitivity cardiac troponin I
ICU	Intensive care unit
MI	Myocardial injury
TTE	Two-dimensional transthoracic echocardiography

Acute myocardial injury (MI), defined by an increase in cardiac troponin (cTn), is common in patients hospitalized with COVID-19. MI has been associated with mortality in series mostly retrospective, including heterogeneous COVID-19 patients presenting with mild to critically ill conditions [1, 2]. Measurements of cardiac troponin (cTn) were often obtained only at baseline and requested based on clinical judgment. Thus, the prevalence of MI in the intensive care unit (ICU) patients evaluated by systematic serial cTn assessments is unknown. In addition, information for comprehension of the potential underlying mechanism leading to MI is still lacking. In this series of consecutive ICU COVID-19 patients, MI was assessed by a comprehensive workup including sequential cTn dosages, electrocardiography (ECG), and two-dimensional transthoracic echocardiography (TTE) to address the question of its prevalence, characterization, and prognostic value in the ICU setting.

All the consecutive patients with laboratory-confirmed SARS-CoV-2 infection admitted to our dedicated COVID-19 ICU between February 22 and April 31, 2020, were analysed. Laboratory confirmation of SARS-CoV-2 was defined as a positive result of real-time RT-PCR assay of nasal and pharyngeal swabs. The study was approved by the local Institutional Ethical Board (Sorbonne University, CER-2020-14). Cardiac investigations were systematically collected including daily dosage of High sensitivity cardiac troponin I (Hs-cTnI) during the first week of ICU stay, and B-type natriuretic peptide (BNP), ECG, and a TTE on ICU admission. The presence of MI was defined by the highest Hs-cTnI value above the 99th percentile upper reference limit and a change in values of $\geq 20\%$ within the first 48 h (Hs-cTnI initial value) [3]. Studied outcomes were the

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Table 1 Characteristics, management, and outcome at day 28 of patients with COVID-19

	Total, $n = 92$[a]	No acute myocardial injury, $n = 39$	Acute Myocardial injury, $n = 53$	p
Baseline characteristics				
Age, median (IQR), years	62 (53–69)	60 (52–65)	63 (55–71)	0.07
Male, No. (%)	72 (78.3)	29 (74.4)	43 (81.1)	0.45
Body mass index, median (IQR), kg/m^2	28 (24–31)	28 (24–31)	27 (25–31)	0.72
Time to ICU admission from symptoms onset, median (IQR), days	8 (6–11)	8 (6–13)	8 (5–10)	0.14
Direct ICU admission (from home or ED), No. (%)	49 (53.3)	17 (43.6)	32 (60.4)	0.14
Active smoking, No. (%)	6 (6.5)	3 (7.7)	3 (5.7)	0.69
Diabetes mellitus, No. (%)	24 (26.1)	12 (30.8)	12 (22.6)	0.47
Arterial hypertension, No. (%)	58 (63.0)	18 (46.2)	40 (75.5)	0.005
Coronary artery disease, No. (%)	16 (17.4)	4 (10.3)	12 (22.6)	0.17
Coronary revascularization[b], No. (%)	10 (10.9)	3 (7.7)	7 (13.2)	0.51
Congestive heart disease, No. (%)	8 (8.7)	2 (5.1)	6 (11.3)	0.46
Left-sided significant valve disease, No. (%)	3 (3.3)	0 (0)	3 (5.7)	0.26
ACEI/ARB, No. (%)	42 (45.7)	12 (30.8)	30 (56.6)	0.02
Acute myocardial injury characteristics				
Electrocardiography on ICU admission				
Heart rate, median (IQR), beats/min	87 (75–100)	90 (77–100)	81 (75–100)	0.40
ST segment elevation, No. (%)	1 (1.1)	0 (0.0)	1 (1.9)	1.00
ST segment depression, No. (%)	3 (3.3)	1 (2.6)	2 (3.8)	1.00
T wave inversion, No. (%)	14 (15.4)	1 (2.6)	13 (24.5)	0.01
Laboratory findings on ICU admission, median (IQR)[c]				
Hs-cTnI[d], pg/mL	33 (15–119)	12 (7–18)	112 (54–260)	< 0.001
BNP, pg/mL	37 (18–116)	20 (13–59)	78 (25–188)	< 0.001
Creatinine, micromol/L	80 (67–128)	74 (60–82)	102 (70–199)	< 0.001
C-reactive protein, mg/L	190 (117–271)	180 (116–249)	192 (121–275)	0.70
Leukocytes, G/L^{-1}	8.43 (6.06 11.06)	8.80 (5.97–12.79)	8.16 (6.65–10.34)	0.25
Initial transthoracic echocardiography[e], No. (%)				
Left ventricular ejection fraction, median (IQR), %	60 (50–60)	60 (55–60)	55 (50–60)	0.02
Normal (LVEF ≥ 50%), No. (%)	74 (87.1)	33 (94.3)	41 (82)	0.11
Mildly to Moderately impaired (LVEF 49–31%), No. (%)	7 (8.2)	2 (5.7)	5 (10)	0.69
Severely impaired (≤ 30%), No. (%)	4 (4.7)	0	4 (8)	0.14
Right ventricular severe dilatation, No. (%) [f]	2 (2.4)	0 (0.0)	2 (4.1)	0.51
Pericardial effusion, No. (%) [g]	16 (20.0)	4 (11.4)	12 (26.7)	0.16
Initial severity and organ failure management				
SAPS II score, median (IQR)	40 (34–49)	37 (28–41)	45 (37–54)	< 0.001
SOFA score, median (IQR)	7 (4–8)	5 (3–7)	8 (6–10)	< 0.001
Catecholamine, No. (%)	59 (64.1)	20 (51.3)	39 (73.6)	0.05
Invasive mechanical ventilation, No. (%)	83 (90.2)	31 (79.5)	52 (98.1)	0.004
Renal replacement therapy, No. (%)	23 (25.0)	5 (12.8)	18 (34.0)	0.03
ECMO[h], No. (%)	6 (6.5)	2 (5.1)	4 (7.5)	1.00
Outcomes at day-28				
Cardio-vascular event, No. (%)	23 (25.0)	4 (10.3)	19 (35.8)	0.01
Death from any cause, No. (%)	18 (19.6)	4 (10.3)	14 (26.4)	0.07
Cardiac arrest from cardiogenic origin, No. (%)	1 (1.1)	0 (0.0)	1 (1.9)	1.00
Cardiogenic shock[i], No. (%)	4 (4.3)	0 (0.0)	4 (7.5)	0.13
Arterial thrombotic event[j], No. (%)	4 (4.3)	0 (0.0)	4 (7.5)	0.13
ICU-free days[k], median (IQR), days	0 (0–15)	5 (0–20)	0 (0–8)	0.03

Characteristics of patients are compared with Mann–Whitney–Wilcoxon tests for quantitative variables and Fisher's exact test for categorical variables, according to acute myocardial injury

Table 1 (continued)

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BNP* binding natriuretic protein, *ED* emergency department, *Hs-cTnI* high sensitivity cardiac troponin I, *ICU* intensive care unit, *LVEF* left ventricular ejection fraction, *SAPS* Simplified Acute Physiology Score, *SOFA* Sepsis-related Organ Failure Assessment, *Vv/Va-ECMO* venovenous/venoarterial extracorporeal membrane oxygenation;

[a]Missing data: Time to ICU admission from symptoms onset for 1 patient, Electrocardiography for 1 patient, B-type natriuretic peptide for 4 patients, left ventricular systolic ejection fraction for 7 patients, right ventricular dilatation for 8 patients, pericardial effusion for 12 patients

[b]Percutaneous coronary intervention, $n=9$; Coronary Artery Bypass Graft Surgery, $n=3$

[c]Highest values during the first 48 h from intensive care unit admission;

[d]Measured with the Abbott Architect Method (Abbott, Lake Forest, IL 60,045, USA) wherein the 99th percentile for a normal population is 26 ng/ml [3]

[e]Median (IQR) time from ICU admission: 0 (0–1) day; performed by trained operators with competence in advanced critical care TTE

[f]Right ventricular severe dilatation: end-diastolic area ratio ≥ 1; paradoxical interventricular septum, $n=0$

[g]Pericardial tamponade, $n=0$

[h]Vv-ECMO, $n=5$; Va-ECMO, $n=1$ (in the acute myocardial injury group)

[i]Patients fulfilled the following criteria: mean atrial pressure <65 mm Hg without a vasopressor agent or need for vasopressor therapy to correct hypotension, low cardiac output, left ventricular systolic dysfunction without inotrope support; elevation of left heart pressures, at least one evidence of tissue hypo-perfusion

[j]Ischaemic stroke, $n=3$; non-cerebrovascular thromboembolism, $n=1$

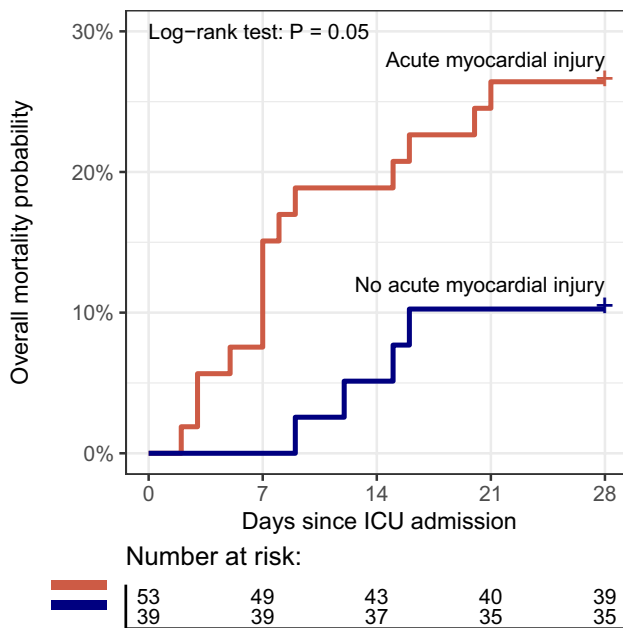[k]Calculated as 28 minus the length of ICU stay

Fig. 1 Kaplan–Meier curves for overall mortality at day 28 as a function of the presence of an acute myocardial injury (log-rank test: $p=0.05$). ICU, intensive care unit

Fig. 2 Probability of overall mortality at day 28 as a function of High sensitivity cardiac Troponin-I initial[a] values. *Hs-cTnI* high sensitivity cardiac troponin I, *ICU* intensive care unit. The bars represent the proportions of patients who died up to day 28 with their 95% confidence interval, according to their Hs-cTnI on ICU admission. Patient count in each Hs-cTnI class is reported above bars. [a]Highest values during the first 48 h of ICU admission

overall mortality at day-28 and the incidence of cardiovascular events (a composite of death, cardiac-arrest, cardiogenic shock, and arterial thrombotic event) at day 28. The association between MI and outcomes was estimated by logistic regression.

Overall, 92 patients (78.3% men; age 62 [53–69] years) were analysed (Table 1). COVID-19 was diagnosed in ambulant setting, 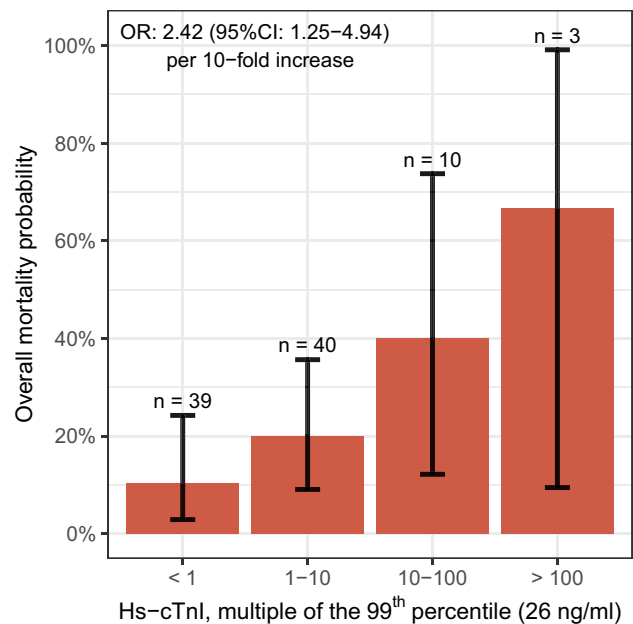hospital (emergency department or conventional wards), and ICU in respectively 4 (4.3%), 70 (76.1%), and 18 (19.6%) patients. MI was diagnosed in 53 patients (57.6%; 95% confidence interval[CI], 46.8–67.9%) with a Hs-cTnI initial value of 112 (54–260) pg/ml. Among patient with MI, 13 (24.5%) presented ECG abnormalities including 1 (1.9%)

ST-segment elevation, 2 (3.8%) ST-segment depression and 13 (24.5%) T wave inversion. Patients with MI had higher BNP levels (78 [20–188] vs. 20 [13–59], $p < 0.001$) and a lower left ventricular ejection fraction (55 [50–60] vs. 60 [55–60], $p = 0.02$) than patients without MI. A greater proportion of patients with MI required catecholamine, invasive mechanical ventilation, and renal replacement therapy. Cardiovascular events occurred in 23 (25%) patients, including cardiac arrest ($n = 1$, 1.1%), cardiogenic shock ($n = 4$, 4.3%), arterial thrombotic event ($n = 4$, 4.3%), and death ($n = 18$; 19.6%). Figure 1 illustrates the association of mortality with MI (Kaplan–Meier survival curves, log-rank test $p = 0.05$). At day 28, the Odds Ratio (OR) for death and cardiovascular events in patients with *versus* without MI were 3.14 (95% CI 1.02–11.89) and 4.22 (95%CI 1.43–12.40), respectively. When adjusting on sepsis-related organ failure assessment, these associations were not significant (OR 1.74, 95%CI 0.49–7.09 and OR 2.01, 95%CI 0.56–8.31, respectively). The magnitude of the Hs-cTnI initial values was associated with overall mortality (crude [OR] 2.42; 95%CI 1.25–4.94 per tenfold increase; Fig. 2). Median daily Hs-cTnI values during the first week of ICU admission remained higher in non-survivors, as compared with survivors (see Figure E1 in the online supplement data).

In this cohort of consecutive critically ill COVID-19 patients, the prevalence of MI was higher than that reported in non-ICU patients, suggesting that MI is related to an overall severity and a poor prognosis [1, 2]. Despite its association with an increased BNP level and a decreased left ventricular ejection fraction, MI rarely induced severe left ventricular systolic dysfunction. Severe right ventricular dilatation was also rarely diagnosed in our cohort, despite severe acute respiratory disease requiring mechanical ventilation. In line with our results, an international survey in COVID 19 patients reported left and right ventricular severe impairment in only 9% and 6% of cases [4]. As suggested by the absence of ECG abnormalities in most of our patients, MI may be mediated through non-ischemic mechanisms, such as cytokine storm or direct entry of SARS-CoV-2 into myocardial cells [5]. However, coronary mechanisms like microvascular damage, supply–demand inequity, or destabilization of atheroma cannot be excluded [2, 5].

To summarize, acute myocardial injury is very frequent in critically ill COVID-19 patients and is associated with severity.

Compliance with ethical standards

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