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Myocardial injury in patients with SARS-CoV-2 pneumonia: Pivotal role of inflammation in COVID-19

Francesco Melillo[1] | **Antonio Napolano**[1] | **Marco Loffi**[2] | **Valentina Regazzoni**[2] | **Antonio Boccellino**[1] | **Gian Battista Danzi**[2] | **Alberto Maria Cappelletti**[3] | **Patrizia Rovere-Querini**[4,5] | **Giovanni Landoni**[5,6] | **Giacomo Ingallina**[1] | **Stefano Stella**[1] | **Francesco Ancona**[1] | **Lorenzo Dagna**[5,7] | **Paolo Scarpellini**[8] | **Marco Ripa**[8] | **Antonella Castagna**[5,8] | **Moreno Tresoldi**[9] | **Alberto Zangrillo**[5,6] | **Fabio Ciceri**[5,10] | **Eustachio Agricola**[1,5]

[1]Cardiovascular Imaging Unit, Cardiothoracic Department, San Raffaele Scientific Institute, Milan, Italy

[2]Division of Cardiology, Cremona Hospital, Cremona, Italy

[3]Cardiac Intensive Care Unit, San Raffaele Scientific Institute, Milan, Italy

[4]Internal Medicine, Diabetes and Endocrinology Unit, San Raffaele Scientific Institute, Milan, Italy

[5]Vita-Salute San Raffaele University, Milan, Italy

[6]Department of Anesthesia and Intensive Care, San Raffaele Scientific Institute, Milan, Italy

[7]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, San Raffaele Scientific Institute, Milan, Italy

[8]Department of Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy

[9]Department of Internal Medicine and Advanced Therapies, San Raffaele Scientific Institute, Milan, Italy

[10]Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Milan, Italy

Correspondence
Eustachio Agricola, Cardiothoracic Department, Cardiovascular Imaging Unit, San Raffaele Scientific Institute, Milan, Italy.
Email: agricola.eustachio@hsr.it

Abstract

Aims: Infection by SARS-CoV-2 may result in a systemic disease and a proportion of patients ranging 15%–44% experienced cardiac injury (CI) diagnosed by abnormal troponin levels. The aim of the present study was to analyse the clinical characteristics of a large series of hospitalized patients for COVID-19 in order to identify predisposing and/or protective factors of CI and the outcome.

Methods and results: This is an observational, retrospective study on patients hospitalized in two Italian centres (San Raffaele Hospital and Cremona Hospital) for COVID-19 and at least one high-sensitivity cardiac troponin (hs-cTnt) measurement during hospitalization. CI was defined if at least one hs-cTnt value was above the 99th percentile. The primary end-point was the occurrence of CI during hospitalization.

We included 750 patients (median age 67, IQR 56–77 years; 69% males), of whom 46.9% had history of hypertension, 14.7% of chronic coronary disease and 22.3% of chronic kidney disease (CKD). Abnormal troponin levels (median troponin 74, IQR 34–147 ng/l) were detected in 390 patients (52%) during the hospitalization. At multivariable analysis age, CKD, cancer, C-reactive protein (CRP) levels were independently associated with CI. Independent predictors of very high troponin levels were chronic kidney disease and CRP levels. Patients with CI showed higher rate of all-cause mortality (40.0% vs. 9.1%, $p = 0.001$) compared to those without CI.

Conclusion: This large, multicentre Italian study confirmed the high prevalence of CI and its prognostic role in hospitalized patients with COVID-19, highlighting the leading role of systemic inflammation for the occurrence of CI.

Francesco Melillo, Antonio Napolano, Shared first co-authors.

KEYWORDS
cardiac complications, COVID-19, myocardial injury, SARS-coronavirus-2, troponin

1 | INTRODUCTION

Infection by SARS-CoV-2 with its wide spectrum of clinical presentations has now been recognized to result in a systemic disease. In addition to respiratory tract infection, systemic inflammation and coagulopathy can lead to multiorgan damage, with varying degrees of cardiac involvement.[1] A proportion of patients ranging 15%–44%[2] experienced cardiac injury diagnosed by abnormal troponin levels. Although patients with pre-existing cardiovascular disease (CVD) has more predisposed to develop myocardial injury, troponin elevation may be detected also in patients without prior CVD[3] and is independently associated with worse outcome.[23] Mechanism of myocardial injury is multifactorial and not fully elucidated: SARS-CoV-2 viral cell entry is mediated by angiotensin-converting enzyme 2 (ACE-2) receptor that is expressed on epithelial cells of the respiratory tract, but also on vascular endothelium, heart and kidneys,[4] but several studies failed to detect the virus in the myocardium[5]; hypoxia, supply-demand mismatch, endothelial damage with microvascular thrombosis, inflammatory cascade and type 1 myocardial infarction may all play a role.

Moreover, cardiac magnetic resonance (CMR) studies in patients who recovered from COVID-19 showed frequent cardiac inflammatory involvement in terms of oedema and myocardial fibrosis in up to 78% of patients.[67] Although the evolution of persistent cardiac damage or ongoing perimyocarditis towards dilatative cardiomyopathy or arrhythmogenic substrate cannot yet be determined, identification of patients at risk of myocardial injury may be valuable to reserve them a tighter monitoring during hospitalization and to identify further disease progress during follow-up.

To date, predisposing factors for cardiac injury have not been identified yet and whether ongoing therapy with cardiovascular drugs may have a protective effect is still unknown. The aim of the present study was to analyse the clinical characteristics of a large series of hospitalized patients for COVID-19 in order to identify predisposing and/or protective factors of myocardial injury and the outcome.

2 | METHODS

We performed an observational, retrospective study on a large series of patients hospitalized in two centres: San Raffaele Hospital, IRCCS, Milan, and ASST Cremona Hospital, Cremona. These two single tertiary centres were involved in frontline care during COVID-19 outbreak in Italy. We included in the study all adult patients admitted to our hospitals from 27 February to 29 April 2020, with a confirmed diagnosis of SARS-CoV-2 pneumonia by chest x-ray or CT-scan and real-time PCR on nasopharyngeal swab (COPAN Diagnostic, Inc,) and at least one high-sensitivity cardiac troponin (hs-cTnt) measurement during hospitalization. Patients were excluded if a definite cause for abnormal troponin levels was diagnosed (acute coronary syndrome, acute pulmonary embolism).

The series of patients from San Raffaele Hospital is part of the COVID-19 institutional clinical-biological cohort (COVID-BioB; ClinicalTrials.gov Identifier: NCT04318366). The study complies with the Declaration of Helsinki.

The demographic characteristics, clinical data and laboratory findings were obtained from electronic medical records by two investigators (A.N. and A.B.). Follow-up was performed by either telephonic interview, direct visit or obtained from hospital records.

Myocardial injury was defined according to the recent Fourth Universal Definition of Myocardial Infarction,[8] if at least one hs-cTnt value above the 99th percentile was detected during hospitalization. Very high troponin levels were defined as troponin levels above 5 × 99th percentile and high troponin levels were defined as troponin levels above the 99th percentile but below the 5 × 99th percentile. Acute kidney injury was defined according to AKIN criteria (absolute increase in serum creatinine ≥0.3 mg/dl within 48 h or increase in serum creatinine ≥1.5 times baseline within the prior 7 days).

The primary end-point was the occurrence of myocardial injury during hospitalization. Secondary end-points were all-cause mortality and need for intensive care unit (ICU) admission.

Continuous variables were reported as median and interquartile range (IQR) or mean ± standard deviation (SD) as appropriate and compared with Student *t* test or Mann-Whitney *U* test. Categorical variables were compared with χ^2 or the Fisher exact test as appropriate. Logistic regression analysis and Cox regression analysis was performed to identify the predictors of myocardial injury and all-cause death, respectively. The clinical variables were selected a priori based on previous clinically studies on prognosis of COVID-19 patients.[9] Prognostic properties of cardiovascular chronic treatments were assessed based on the uncertainty regarding the effects

TABLE 1 Baseline characteristics of the population study

	Overall population	Myocardial injury	No myocardial injury	*p*
	***N* = 750**	***N* = 390**	***N* = 360**	**value**
Age, years	67 (56–77)	74 (64–81)	58 (50–68)	**0.001**
Sex (male), *n* (%)	531 (69%)	294 (71.3%)	237 (65%)	0.088
Smoker, *n* (%)	28 (3.6%)	15 (3.6%)	13 (3.6%)	0.97
Symptom onset to admission, days	6 (3–9)	5 (3–8)	7 (4–10)	**0.001**
PaO_2/FiO_2, mmHg	310 (248–375)	290 (228–365)	325 (276–380)	**0.001**
EF %	58 (55–63)	57 (51–62)	60 (55.25–64.00)	**0.026**
ICU length of stay, days	12 (8–25)	14 (8.75–16.25)	7 (3.00–11.75)	**0.005**
Length of stay survivors, days	16 (9–27)	21.5 (13—37.75)	12 (7–21)	**0.001**
Length of stay nonsurvivors, days	10 (6–20)	10 (5.25—20.75)	13 (8—19.5)	0.136
Comorbidities				
Hypertension	263 (46.9%)	240 (58.3%)	123 (34.1%)	**0.001**
CAD	114 (14.7%)	95 (23.1%)	19 (5.1%)	**0.001**
HF	31 (4%)	28 (6.8%)	3 (0.8%)	**0.001**
AF	76 (9.8%)	66 (16%)	10 (2.8%)	**0.001**
Prior Stroke/TIA	34 (4.4%)	26 (6.3%)	8 (2.2%)	**0.006**
Prior PTE	34 (4.4%)	18 (4.4%)	16 (4.4%)	0.96
CABG	29 (3.9%)	25 (6.1%)	4 (1.1%)	**0.001**
PCI	68 (8.8%)	59 (14.3%)	9 (2.5%)	**0.001**
AMI	62 (8.0%)	52 (12.6%)	10 (2.8%)	**0.001**
Diabetes Mellitus	129 (16.7%)	84 (20.4%)	45 (12.5%)	**0.003**
Cancer	80 (10%)	62 (15%)	18 (5%)	**0.001**
COPD	52 (6.7%)	43 (10.4%)	9 (2.5%)	**0.001**
CKD	173 (22.3%)	148 (35.9%)	25 (6.9%)	**0.001**
PAD	71 (9.2%)	57 (13.8%)	14 (3.9%)	**0.001**
Dyslipidemia	143 (18.5%)	101 (24.5%)	42 (11.6%)	**0.001**
Drugs				
ACE Inhibitor	112 (14.5%)	73 (17.7%)	39 (10.8%)	**0.006**
ARB	109 (14.1%)	74 (18%)	35 (9.7%)	**0.001**
Beta Blocker	212 (27.4%)	161 (39.1%)	51 (14.1%)	**0.001**
MRA	26 (3.3%)	25 (6.1%)	1 (0.3%)	**0.001**
CCB	113 (14.6%)	76 (18.6%)	37 (10.4%)	**0.001**
Loop Diuretic	99 (12.8%)	88 (21.4%)	11 (3.0%)	**0.001**
Thiazide	42 (5.4%)	33 (8.0%)	9 (2.5%)	**0.001**
ACE-I/ARB	222(28.7%)	148 (35.9%)	74 (20.5%)	**0.001**
ACE-I + BB	52 (6.7%)	37 (9.0%)	15 (4.2%)	**0.008**
ARB + BB	57(7.4%)	45 (10.9%)	12 (3.3%)	**0.001**
Statin	110 (14.2%)	82 (19.9%)	28 (7.8%)	**0.001**
Vitamin D	46 (5.9%)	33 (8.0%)	13 (3.6%)	**0.010**
ASA	169 (21.8%)	133 (32.3%)	36 (10.0%)	**0.001**
Clopidogrel	26 (3.3%)	21 (5.2%)	5 (1.4%)	**0.004**
Antiplatelets	191 (24.7%)	151 (36.7%)	40 (11.1%)	**0.001**
VKA	23 (2.97%)	22 (5.4%)	1 (0.3%)	**0.001**

(Continues)

TABLE 1 (Continued)

	Overall population	Myocardial injury	No myocardial injury	*p*
	***N* = 750**	***N* = 390**	***N* = 360**	**value**
DOAC	38 (4.9%)	32 (7.8%)	6 (1.7%)	**0.001**
Anticoagulants	76 (9.8%)	67 (16.3%)	9 (2.5%)	**0.001**
Laboratory findings				
CRP, mg/l	133 (65–230)	173 (94—274)	97 (40–164)	**0.001**
NT-proBNP peak, pg/ml	415 (94–1799)	1349 (502–2865.5)	87 (41–241)	**0.001**
Troponin T peak, ng/l	13 (5.5—38.02)	74 (34.3–147)	6.8 (4.7–10)	**0.001**
Serum Ferritin peak, ng/ml	1234 (623–2357)	1491 (722–2927)	976 (588–1678)	**0.001**
IL—6 peak, pg/ml	40.3 (21.2–97.8)	60 (29.4–142)	30 (10–60)	**0.001**
D-Dimer peak, mcg/ml	1.51 (0.67–4.57)	2.06 (1.3–6.19)	0.82 (0.49–1.60)	**0.001**
eGFR baseline, ml/min/1.73 m^2	66.9 (52.7–86.8)	60 (42–77.7)	89.6 (78–105.3)	**0.001**

Abbreviations: ACE-I, Angiotensin-converting enzyme inhibitor; AF, Atrial fibrillation; AKI, Acute kidney injury; AMI, Acute myocardial infarction; ARB, Angiotensin receptor blocker; BB, Beta blocker; CABG, Coronary artery bypass grafting; CAD, Coronary artery disease; CCB, Calcium channel blocker; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; CRP, C-reactive protein; CRT, cardiac resynchronization therapy; DOAC, Direct oral anticoagulant; EF, Ejection fraction; eGFR, Estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator ICU, intensive care unit; MRA, Mineralocorticoid receptor antagonist; PAD, Peripheral artery disease; PCI,Percutaneous coronary intervention; PM,Pacemaker PTE, Pulmonary thromboembolism; TIA, Transient ischaemic attack; VKA, Vitamin K Antagonist.

of ACEI, ARB and mineralocorticoid antagonist in COVID-19 patients[10] and the potentially beneficial effects of beta blockers and calcium-channel blockers on myocardial injury. Antithrombotic treatments were included in the regression as coagulopathy is a common part of the systemic inflammatory response syndrome in COVID-19 patients.[11] Multivariate regression analysis was performed including only covariates that were significantly associated with the risk of myocardial injury and cardiac death at the univariate analysis and the convention of limiting the number of independent variables to one for ten events was followed. The Hosmer-Lemeshow (H-L) goodness of fit test and c-statistic were used to confirm good calibration and discrimination of the multivariable model. Survival curves were plotted using the Kaplan-Meier method. Receiver operator curve analysis was utilized to identify the optimal cut-off for troponin level that better discriminated patients at risk for death. We utilized SPSS (version 23) software for statistical analysis.

Reporting of the study conforms to broad EQUATOR guidelines.[12]

3 | RESULTS

During the index period, 1197 patients were hospitalized for SARS-CoV-2 pneumonia in the two centres (667 pts at San Raffaele Hospital and 530 at ASST Cremona Hospital). Excluding patients with no troponin levels available ($n = 405$), acute coronary syndrome ($n = 3$) or acute pulmonary embolism ($n = 16$) and incomplete data collection ($n = 23$), the final study population consisted of 750 patients (median age 67 years, IQR 56–77 years; 69% males). The median PaO_2/FiO_2 on hospital admission was 310 mmHg (IQR 248–375 mmHg), and the median time from symptoms onset to admission was 6 days (IQR 3–9 days).

Baseline characteristics are reported in Table 1.

Two-hundred sixty-three patients (46.9%) had history of hypertension, 114 (14.7%) of chronic coronary disease, 129 (16.7%) of diabetes mellitus and 173 (22.3%) of chronic kidney disease. Medical therapy on admission is reported in Table 1. Medications were continued in all patients during hospital stay, unless not tolerated and withdrawn in case of intensive care unit (ICU) admission.

Abnormal troponin levels (median troponin 74 ng/l, IQR 34–147 ng/l) were detected in 390 patients (52%) during the hospitalization; among these, 346 patients (46.1%) showed evidence of myocardial injury within 24 h of admission. Very high troponin elevation (median 134 ng/l, IQR 95–208 ng/l) was detected in 137 (18.1%) patients. Patients with cardiac injury (CI + group,) were older and more frequently affected by cardiac comorbidities such as hypertension, coronary artery disease, heart failure, atrial fibrillation, diabetes, dyslipidaemia and chronic kidney disease. Peak values of laboratory marker of inflammation as C-reactive protein (CRP), serum ferritin, interleukine-6 (IL-6), d-dimer levels and NT-proBNP levels were significantly higher in the CI + group. A higher proportion of patients in the CI + group were taking angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor

blockers (ARBs), beta blockers, calcium-channel blockers, diuretics, antithrombotic agents and statins, compared to patients in the CI- group (Table 1).

Bedside echocardiography was performed in 122 patients and showed a reduced ejection fraction (EF<55%) in 21 patients (19.6%); of those, 16 (76%) had mild degree of EF impairment (54%–40%) and 7 (33%) were already known for cardiac dysfunction. Three patients were diagnosed with acute myocarditis according to cardiac magnetic resonance findings. De novo atrial fibrillation was detected in five patients.

Univariate predictors of myocardial injury are shown in Table 2. At multivariable analysis age, chronic kidney disease, cancer, CRP levels were independently associated with elevated serum troponin levels. Table 3 shows that independent predictors of very high troponin levels were chronic kidney disease and CRP levels.

At a median follow-up of 85 days (IQR 77–93 days), 186 patients (24.8%) died during hospitalization, 131 (17.5%) required ICU admission and 564 (75.2%) were discharged and did not experience further adverse events (Table 4). Median in-hospital stay was 8 days (IQR 1–17).

Compared to patients with no myocardial injury, CI + patients showed higher rate of all-cause mortality (40.0% vs. 9.1%, log rank test $p = 0.001$; Figure 1), ICU admission (26.0% vs. 8.3%, $p = 0.001$) and acute kidney injury (23.5% vs. 6.6%, $p = 0.001$). Patients with very high troponin levels had higher mortality rate compared to both patients with high troponin levels (54% vs. 31%, log rank test $p = 0.001$) and to those without myocardial injury (54% vs. 31%, log rank test $p = 0.001$; Figure 2).

Myocardial injury was an independent predictor of all-cause death as well as age, chronic kidney disease and CRP levels (Table 5).

TABLE 2 Predictors of myocardial injury

	Univariate		Multivariate	
	OR (95% CI)	***p* value**	**OR (95% CI)**	***p* value**
Age*	1.09 (1.07–1.01)	**<0.001**	1.05 (1.03–1.08)	**0.001**
Male Sex	1.30 (0.96–1.77)	0.09		
Smoker	1.01 (0.47–2.15)	0.97		
Hypertension	2.70 (2.01–3.62)	**<0.001**		
Heart Failure	8.70 (2.62–28.87)	**<0.001**		
CAD	5.39 (3.22–9.03)	**<0.001**		
AF	6.69 (3.39–13.23)	**<0.001**		
Prior PTE	0.98 (0.49–1.96)	0.96		
Diabetes Mellitus	1.80 (1.21–2.67)	**0.003**		
Dyslipidaemia	2.47 (1.67–3.65)	**<0.001**		
Cancer	3.38 (1.96–5.82)	**<0.001**	2.7 (1.0–6.7)	**0.018**
COPD	4.56 (2.19–9.49)	**<0.001**		
CKD	7.53 (4.79–11.86)	**<0.001**	4.2 (1.9–8.9)	**<0.001**
ACE Inhibitor	1.78 (1.17–2.70)	**0.007**		
ARB	2.04 (1.33–3.13)	**0.001**		
Beta Blocker	3.90 (2.73–5.56)	**<0.001**		
MRA	23.25 (3.13–172.51)	**0.002**		
CCB	1.98 (1.30–3.02)	**0.001**		
Antiplatelet	4.30 (2.88–6.43)	**<0.001**		
Anticoagulant	7.59 (3.73–15.47)	**<0.001**		
Statin	2.95 (1.87–4.66)	**<0.001**		
CRP peak*	1.01(1.00–1.01)	**<0.001**	1.01 (1.0 0–1.01)	**<0.001**

Note: Hosmer-Lemeshow test 0.719; C statistics 0.893.

Abbreviations: ACE-I, Angiotensin-converting enzyme inhibitor; AF, Atrial fibrillation; ARB, Angiotensin receptor blocker; CAD, Coronary artery disease; CCB, Calcium channel blocker; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; CRP, C-reactive protein; HF, Heart failure; MRA, Mineralocorticoid receptor antagonist; PTE, Pulmonary thromboembolism.

*Per 1 unit increase

TABLE 3 Predictors of very high troponin elevation

	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age*	1.04 (1.02–1.05)	**<0.001**		
Female sex	0.64 (0.41–0.96)	**0.034**		
Smoker	1.06 (0.39–22.83)	0.86		
Hypertension	2.05 (1.40–3.00)	**<0.001**		
Heart Failure	2.88 (1.33–6.26)	**0.007**		
CAD	2.66 (1.68–4.20)	**<0.001**		
AF	2.88 (1.71–4.86)	**<0.001**		
Prior PTE	1.17 (0.46–2.94)	0.731		
Diabetes Mellitus	2.2 (1.4–3.4)	**0.001**		
Dyslipidaemia	1.7 (1.11–2.69)	**0.014**		
Cancer	1.60 (0.93–2.76)	0.089		
COPD	1.63 (0.84–3.16)	0.146		
CKD	3.47 (2.33–5.16)	**<0.001**	2.52 (1.43–4.43)	**<0.001**
ACE Inhibitor	1.36 (0.83–2.33)	0.210		
ARB	2.04 (1.33–3.13)	0.620		
Beta Blocker	2.4 (1.64–3.55)	**<0.001**		
MRA	2.05 (0.87–4.81)	0.100		
CCB	1.20 (0.73–1.99)	0.459		
Antiplatelet	2.75 (1.85–4.08)	**<0.001**		
Anticoagulant	2.62 (1.55–4.43)	**<0.001**		
Statin	1.53 (0.94–2.50)	0.083		
CRP*	1.01(1.00–1.01)	**<0.001**	1.01 (1.00–1.01)	**<0.001**

Note: Hosmer-Lemeshow test 0.168; C statistics 0.811.

Abbreviations: ACE-I, Angiotensin-converting enzyme inhibitor; AF, Atrial fibrillation; ARB, Angiotensin receptor blocker; CAD, Coronary artery disease; CCB, Calcium channel blocker; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; CRP, C-reactive protein; EF, Ejection fraction; HF, Heart failure; MRA, Mineralocorticoid receptor antagonist; PTE, Pulmonary thromboembolism.

*Per 1 unit increase.

TABLE 4 Follow-up events

	Overall population	Myocardial injury	No myocardial injury	
	N = 750	*N* = 390	*N* = 360	*p* value
Death, *n* (%)	186 (24.8%)	153 (39.2%)	33 (9.2%)	**0.001**
ICU, *n* (%)	131 (17.5%)	101 (25.9%)	30 (8.3%)	**0.001**
Death + ICU, *n* (%)	261 (34.8%)	208 (53.3%)	53 (14.7%)	**0.001**
AKI, *n* (%)	121 (15.6%)	97 (34.0%)	24 (10.2%)	**0.001**
Lowest eGFR, ml/min/1.73 m^2	66.8 (40.1–88.4)	51.4 (32.1–74.6)	86.2 (70.8–104.5)	**0.001**

Abbreviations: AKI, Acute kidney injury; Egfr, Estimated glomerular filtration rate; ICU, Intensive care unit.

According to receiver operator curve analysis, the optimal cut-off of troponin level to identify patients at risk of death was 27.75 ng/L with 68% sensibility and 76% specificity.

4 | DISCUSSION

The present study represents the largest European cohort of consecutive, white patients hospitalized for COVID-19,

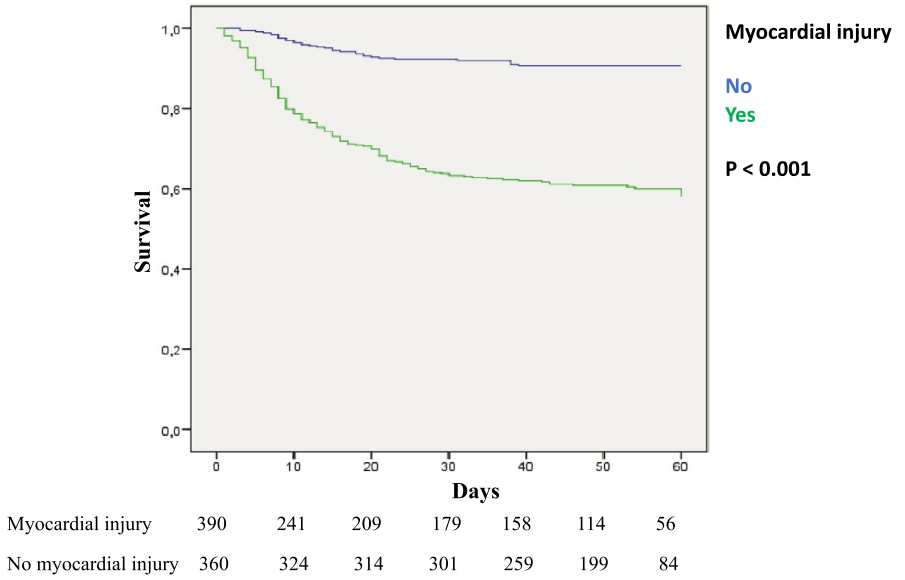

FIGURE 1 Survival curves according to occurrence of cardiac injury (log rank test)

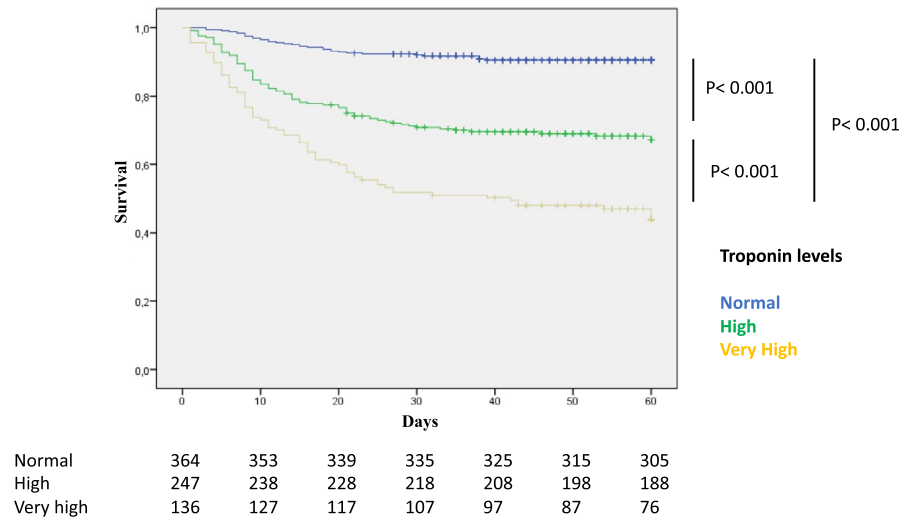

FIGURE 2 Survival curves according to troponin values (log rank test)

providing a report on the incidence of myocardial injury and its predisposing factors.

More than 50% of patients in our study had evidence of elevated troponin levels. We confirmed that patients with abnormal troponin levels were more frequently older, affected by cardiac comorbidities and with higher inflammatory markers and that myocardial injury was an independent predictor of all-cause death. In line with other studies, we showed that higher degrees of myocardial injury are associated with worse outcomes.[3]

Our study is one of the first that evaluated the occurrence of myocardial injury in COVID-19 in relation to chronic cardiovascular treatment. Indeed, we demonstrated that in patients hospitalized for pneumonia, neither chronic treatment with ACE inhibitors, ARBs, calcium-channel blockers, beta blockers, antiplatelet or antithrombotic agents has protective or negative effects against myocardial injury. Elevated CRP levels were intriguingly an independent predictor of myocardial injury, suggesting the role of systemic inflammation in the pathogenetic mechanism of cardiac damage. The prevalence of myocardial injury in our study was higher compared to studies from China[13,14] and the United States (multiethnic)[3] probably due to the higher median age and prevalence of comorbidities of the white Italian population.

We can identify at least four mechanisms underlying COVID-19-related myocardial injury: direct infection through ACE-2 receptors, myocardial oxygen supply/demand imbalance, abnormal coagulation and microcirculatory disturbance and cytokine storm.[15]

The excessive and uncontrollable cytokine and chemokine production in response to the virus invasion can lead to a 'cytokine storm' and eventually to a severe multiorgan damage, mimicking systemic inflammatory and autoimmune diseases.[16] Myocardial injury can be interpreted as a 'bystander effect' of the inflammatory response as the cytokine storm promotes cardiac inflammation by

TABLE 5 Predictors of all-cause death

	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age*	1.08 (1.07–1.09)	**0.001**	1.04 (1.01–1.06)	**0.001**
Male Sex	1.30 (0.96–1.77)	**0.09**		
Smoke	1.01 (0.47–2.15)	0.97		
Hypertension	1.80 (1.35–2.39)	**0.001**		
Heart Failure	2.10 (1.22–3.63)	**0.007**		
CAD	2.81 (2.06–3.84)	**0.001**		
AF	2.31 (1.60–3.33)	**0.001**		
PTE	0.98 (0.49–1.96)	0.96		
Stroke/TIA	2.97 (1.33–6.65)	**0.008**		
PAD	3.98 (2.18–7.27)	**<0.001**		
Diabetes Mellitus	1.66 (1.19–2.31)	**0.003**		
Dyslipidaemia	2.47 (1.67–3.65)	**<0.001**		
Cancer	3.38 (1.96–5.82)	**<0.001**	1.94 (1.01–3.71)	**0.044**
COPD	1.89 (1.20–2.97)	**0.006**		
CKD	3.10 (2.33–4.11)	**0.001**		
ACE Inhibitor	1.78 (1.17–2.70)	**0.007**		
ARB	2.04 (1.33–3.13)	**0.001**		
Beta Blocker	3.90 (2.73–5.56)	**<0.001**		
MRA	23.25 (3.13–172.51)	**0.002**		
Loop Diuretic	8.64 (4.53–16.46)	**<0.001**		
Thiazide	3.40 (1.10–7.22)	**0.001**		
CCB	1.98 (1.30–3.02)	**0.001**		
Antiplatelet	2.60 (1.96 −3.45)	**0.001**		
Anticoagulant	7.59 (3.73–15.47)	**<0.001**		
Statins	1.18 (0.81–1.74)	**0.382**		
Myocardial injury	5.31 (3.65–7.71)	**0.001**	2.45 (1.22–4.93)	**0.012**
CRP*	1.01(1.00–1.01)	**<0.001**	1.01 (1.00–1.01)	**0.001**
IL−6*	1.01 (1.00–1.01)	**0.018**		
Ferritin*	1.01(1.00–1.01)	**0.002**		
D-Dimer*	1.13 (1.07–1.19)	**<0.001**		
NT-proBNP*	1.01(1.00–1.01)	**<0.001**		

Note: Hosmer-Lemeshow test 0.645; C statistics 0.823.

Abbreviations: ACE, Angiotensin-converting enzyme; AF, Atrial fibrillation; AMI, Acute myocardial infarction; ARB, Angiotensin receptor blocker; CABG, Coronary artery bypass grafting; CAD, Coronary artery disease; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; EF, Ejection fraction; HF, Heart failure; MRA, Mineralocorticoid receptor antagonist; PAD, Peripheral artery disease; PCI, Percutaneous coronary intervention; PTE, Pulmonary thromboembolism; TIA, Transient ischemic attack.

*Per 1 unit increase

an 'indirect effect'.[17] However, little is known about the mechanisms of myocardial injury due to cytokine storm. The high serum values of pro-inflammatory cytokines, mainly IL-6, lead to increasing vessel permeability, vascular leakage and interstitial oedema, increasing oxygen consumption, increasing blood coagulability and reducing myocardium contractility.[18] Several studies have reported myocardial interstitial infiltration by mononuclear cells and lymphocytes proven by either in vivo[19,20] and post-mortem[21] pathology.

We demonstrated that patients with elevated troponin levels had higher IL-6, serum ferritin and CRP levels and

that the latter was an independent predictor of myocardial injury, confirming the role of systemic inflammation in the development of cardiac damage.

Together with chronic kidney disease, elevated CRP levels were also predictors of very high troponin elevation.

Whether the use of biological agents against IL-1 and IL-6 would reduce the burden of cardiac damage is yet to be determined: tocilizumab was not associated with a lower degree of cardiac injury[22] and canakinumab failed to improve mortality in patients hospitalized with COVID-19, myocardial injury and elevated CRP; however, there was a favourable trend among patients who received higher dose canakinumab.[23]

Colchicine, an old drug with anti-inflammatory and anti-thrombogenic properties, improved clinical outcomes in patients hospitalized with COVID-19; however, there were no significant differences in peak troponin or peak CRP levels.[24] Interestingly, there was an attenuated D-Dimer increase in patients treated with colchicine and it may be related to its anti-inflammatory and anti-thrombogenic properties.

Although ACE inhibitors or ARBs may counterbalance SARS-CoV-2-mediated renin-angiotensin system hyperactivation,[25,26] they did not prove to be protective in this setting. A large study from the United States[3] highlighted the positive effect of statins, but this was not confirmed by our data. Finally, although there is increasing evidence of coagulopathy and microvascular thrombosis,[27] neither use of antiplatelet or anticoagulant agents resulted protective against myocardial injury.

Confirming the clear association between cardiac injury and poor clinical outcome, our data support the measurement of cardiac troponin on admission and during hospitalization to identify patients at increased risk of adverse events. Consistent with the overall low values of troponin levels detected in patients with myocardial injury, we showed that most patients did not experience alteration in cardiac function or mild degree of dysfunction at bedside transthoracic echocardiography. However, as shown by CMR studies,[6,7] a relevant proportion of patients recovered from COVID-19 reveals myocardial fibrosis or oedema, highlighting the need for long-term follow-up to identify late cardiac complications in survivor patients with evidence of myocardial injury during the acute phase of the disease.

This study shows all the limitations of retrospective studies. Considering the hospital overload during the early pandemic, not all patients had available laboratory data of IL-6 and ferritin levels.

For the same reason, it was not possible to retrieve the reports of all the ECG performed during the hospitalization.

In conclusion, this large, multicentre Italian study confirmed the high prevalence of myocardial injury and its prognostic role in hospitalized patients with COVID-19, highlighting the usefulness of troponin measurement. The chronic treatment with ACE inhibitors, ARBs, calcium-channel blockers, antiplatelet or antithrombotic agents does not seem to have protective effect against the occurrence of myocardial injury, while the systemic inflammation plays a leading role.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

ORCID

Francesco Melillo https://orcid.org/0000-0003-2159-1359
Antonio Napolano https://orcid.org/0000-0002-7456-6395
Marco Ripa https://orcid.org/0000-0002-6380-0377

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