

# Subclinical myocardial dysfunction in patients recovered from COVID-19

Leonardo Italia MD<sup>1</sup> | Giacomo Ingallina MD<sup>1</sup> | Antonio Napolano MD<sup>1</sup> |  
Antonio Boccellino MD<sup>1</sup> | Martina Belli MD<sup>1</sup> | Francesco Cannata MD<sup>1</sup>  |  
Marco Rolando MD<sup>1</sup> | Francesco Ancona MD<sup>1</sup> | Francesco Melillo MD<sup>1</sup> |  
Stefano Stella MD<sup>1</sup> | Marco Ripa MD<sup>2</sup> | Paolo Scarpellini MD<sup>2</sup> |  
Moreno Tresoldi MD<sup>3</sup> | Alessandro Ortalda MD<sup>4</sup> | Beatrice Righetti MD<sup>4</sup> |  
Francesco De Cobelli MD<sup>5,6</sup> | Antonio Esposito MD<sup>5,6</sup> | Fabio Ciceri MD<sup>5,7</sup> |  
Antonella Castagna MD<sup>2,5</sup> | Patrizia Querini Rovere MD<sup>5,8</sup> | Gabriele Fragasso MD<sup>9</sup> |  
Eustachio Agricola MD<sup>1,5</sup> 

<sup>1</sup> Cardiovascular Imaging Unit, San Raffaele Scientific Institute, Milan, Italy

<sup>2</sup> Department of Infectious Disease, San Raffaele Scientific Institute, Milan, Italy

<sup>3</sup> Department of General Medicine and Advanced Care, San Raffaele Scientific Institute, Milan, Italy

<sup>4</sup> Department of Anesthesia and Intensive Care, San Raffaele Scientific Institute, Milan, Italy

<sup>5</sup> Vita-Salute San Raffaele University, Milan, Italy

<sup>6</sup> Experimental Imaging Center, Radiology Department, San Raffaele Scientific Institute, Milan, Italy

<sup>7</sup> Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Milan, Italy

<sup>8</sup> Internal Medicine, Diabetes and Endocrinology Unit, San Raffaele Scientific Institute, Milan, Italy

<sup>9</sup> Heart Failure Clinic, Clinical Cardiology, San Raffaele Scientific Institute, Milan, Italy

## Correspondence

Eustachio Agricola MD, Head of Cardiovascular Imaging Unit, Cardio-Thoracic-Vascular Department, Vita-Salute University, San Raffaele Hospital, Via Olgettina 60, Milan 20132, Italy.

Email: [agricola.eustachio@hsr.it](mailto:agricola.eustachio@hsr.it)

Leonardo Italia and Giacomo Ingallina contributed equally as first authors of this manuscript.

## Abstract

**Background:** Myocardial injury (MI) can be detected during the acute phase of Coronavirus disease 19 (COVID-19) and is associated with a dismal prognosis. Recent imaging studies described the persistence of cardiac abnormalities after the recovery. The aim of the study was to investigate the spectrum of cardiac abnormalities at mid-term follow-up in patients recovered from COVID-19 using clinical assessment, laboratory tests, and imaging evaluation with comprehensive echocardiography.

**Methods:** This is an observational, cross-sectional study assessing an unselected cohort of consecutive patients recovered from COVID-19. MI was defined by elevated plasma levels of high sensitive troponin T (hsTnT). At the follow-up, a complete examination including echocardiography was performed.

**Results:** The 123 patients included were divided into two groups according to the presence of MI during hospitalization: group A (without MI) and group B (with MI). After a median of 85 days, group B patients were more frequently symptomatic for dyspnea and had significantly higher values of hsTnT and N-Terminal prohormone of Brain Natriuretic Peptide (NT-proBNP), compared to Group A. No differences between the

two groups in left nor right ventricle dimension and ejection fraction were found. However, in group B a significant reduction of mean left ventricle global longitudinal strain was observed ( $-15.7 \pm .7$  vs  $-18.1 \pm .3$  in group A,  $p < 0.001$ ), together with higher frequency of impaired diastolic function and higher values of pulmonary pressure.

**Conclusions:** In patients recovered from COVID-19, echocardiography with speckle-tracking analysis may be an useful imaging tool to identify subclinical myocardial dysfunction and potentially guide management strategies.

#### KEYWORDS

COVID-19, echocardiography, heart failure, myocarditis, strain

## 1 | INTRODUCTION

Myocardial injury (MI), defined as mild increase of serum troponin, can be detected in 7–40% of patients hospitalized for Coronavirus Disease-2019 (COVID-19)<sup>1–4</sup> and is associated with a dismal prognosis.<sup>5,6</sup>

Cardiac involvement during the acute phase of COVID-19 can be primary and secondary. In secondary cardiac involvement, MI may be related to myocardial inflammation due to systemic inflammatory response with cytokine mediated damage, oxygen supply-demand imbalance ischemia, and damage from microvascular thrombi formation.<sup>7,8</sup> Patients with pre-existing cardiovascular comorbidities are particularly vulnerable to systemic inflammatory response.<sup>9,10</sup> In primary cardiac involvement, which is considered to be less common, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causes a direct viral injury on cardiomyocytes through the membrane protein angiotensin-converting enzyme 2.<sup>7</sup>

Recent imaging studies described the persistence of cardiac abnormalities after the recovery with pericardial involvement and subtle changes in ventricular structure and function<sup>11–14</sup>; the meaning of these findings are currently unknown. Follow-up clinical studies are starting to report the long-term COVID-19 consequences with many people still suffering from fatigue and distress 3–6 months after the recovery from acute infection.<sup>15–17</sup>

With millions of people affected is essential to find the best follow-up protocol for COVID-19 infection. The identification of patients with cardiac abnormalities is of pivotal importance as they may benefit from cardioprotective therapy and need different follow-up strategies.

Our study aimed to investigate the spectrum of cardiac abnormalities at mid-term follow-up in patients recovered from COVID-19 using clinical assessment, laboratory tests, and imaging evaluation with comprehensive echocardiography.

## 2 | METHODS

### 2.1 | Study design and population

This is an observational, cross-sectional study conducted at a large tertiary center (San Raffaele Scientific Institute) in Milan, Italy, including an unselected cohort of consecutive patients recovered from SARS-

CoV-2 infection. The cohort of patients is part of the COVID-19 institutional clinical-biological study (COVID-BioB; ClinicalTrials.gov identifier: NCT04318366) approved by the Hospital Ethics Committee (protocol n. 34/int/2020).

All the patients were hospitalized between March 3, 2020, and May 13, 2020. COVID-19 diagnosis was confirmed by reverse transcription-polymerase chain reaction on swab test of the upper respiratory tract. Exclusion criteria were the presence of acute coronary syndrome (ACS), reduced kidney function (Creatinine Clearance less than 50 ml/min), atrial fibrillation and history of heart failure (Figure 1). Patients affected by these conditions were excluded because these disorders can cause an increase of troponin serum levels that is potentially unrelated to COVID-19 infection.<sup>18</sup> Clinical, laboratory and biological data on all hospitalized patients were collected and included an electrocardiogram (ECG), high sensitivity troponin T (hsTnT), hematocrit, serum creatinine, C-reactive protein levels N-Terminal prohormone of Brain Natriuretic Peptide (NT-proBNP) serum levels.

Myocardial injury was defined by plasma levels of hsTnT greater than 13.9 ng/L, representing the 99th upper reference limit of the Cobas 8000 assay (Roche, Switzerland).<sup>19</sup> ACS was excluded evaluating clinical symptoms, ECG and serum troponin values, according to the current guidelines.<sup>20</sup>

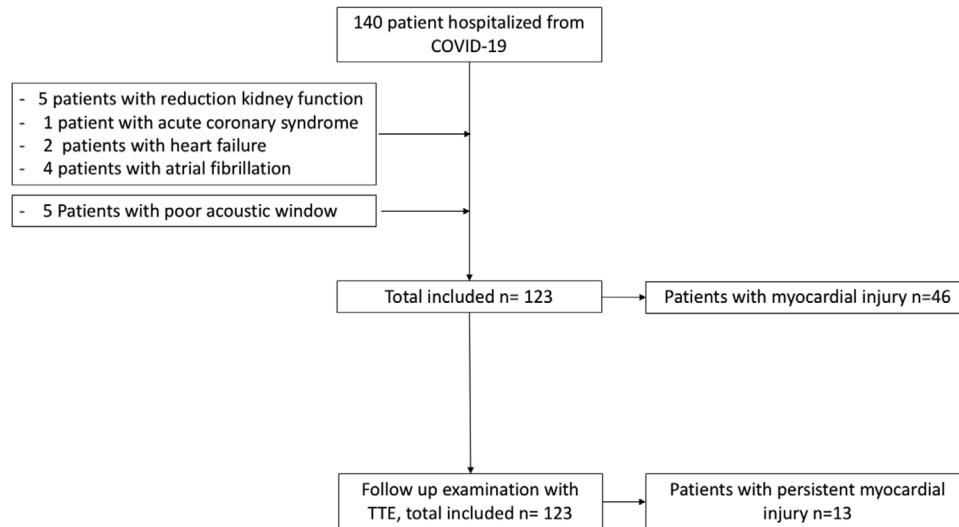
Following an appropriate period after the recovery, a complete examination including medical history, physical examination and a comprehensive echocardiography was performed. Moreover, blood test including hsTnT, hematocrit, C-reactive protein levels, and NT-proBNP serum levels were collected.

### 2.2 | Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

### 2.3 | Data collection

Transthoracic echocardiographic exams (TTE) were performed using the Vivid E95 ultrasound system equipped with a 4Vc-D 4D Matrix Cardiac transducer (GE Vingmed Ultrasound, Horten, Norway). The



**FIGURE 1** Study Flowchart

echocardiographic dataset was acquired in accordance to American Society of Echocardiography /European Association of Cardiovascular Imaging recommendations<sup>21</sup> and included 3-Dimensional (3D) volumes and ejection fraction of left and right ventricle. 3D datasets were acquired with the highest possible frame rate with a minimum setting of 12 frames per second. Left ventricular diastolic function was evaluated according to current guidelines.<sup>22</sup> Patients with poor acoustic windows at TTE were excluded.

Images within optimal frame rate intervals (> 60 F/s) were used for two-dimensional speckle tracking analysis. RV longitudinal strain (RV LS) was defined as the mean peak longitudinal strain of the three segments of the lateral wall of the RV measured in the apical four-chamber view optimized for RV visualization. Global longitudinal strain (GLS) was calculated as the mean peak systolic strain values of the 17 segments model of the LV obtained from the apical four-chamber, two-chamber, and three-chamber views. A value of LV GLS less negative than -17% was regarded as pathological.<sup>21</sup>

All the echocardiographic exams were performed by three operators: F. C., A. N., M. R.. Analysis and measurements on the acquired data were performed off-line with a dedicate workstation by a single operator (A.N.) with EchoPAC Version v201 (GE, Vingmed Ultrasound AS). To determine the intra-observer agreement measurements the left ventricular strain analysis was repeated by the same operator off-line with the same workstation in 10 patients.

## 2.4 | Statistics

Categorical data are showed as numbers and percentages; continuous variables as means  $\pm$  standard deviation or medians with inter-quartile ranges (IQRs) when appropriate.

Normality of distributions across different groups were tested using Shapiro-Wilk test. Comparisons between two independent groups were made using t tests for normally distributed variables and Mann-

Whitney test for non-normal distribution of data. Categorical variables were compared using  $\chi^2$  test when the expected value for each cell was greater than four, otherwise Fisher exact test was used.

The reproducibility was assessed by intra-class correlation coefficient (ICCs) and concordance using the Bland-Altman analysis. An excellent agreement was defined as ICC > .80. Statistical significance  $\leq .05$  was used for all the test. The analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism version 6.00 (GraphPad Software, La Jolla, CA, USA, [www.graphpad.com](http://www.graphpad.com)).

## 3 | RESULTS

An unselected cohort of 140 consecutive patients who recovered from COVID-19 infection was evaluated; 17 patients met the exclusion criteria, therefore a total of 123 patients were included in the final analysis (Figure 1).

Patients were divided into two groups according to the presence of MI during hospitalization: group A included 77 patients without MI (MI-) and group B 46 patients with MI (MI+).

### 3.1 | Hospitalization

Baseline characteristics of the overall population and the two groups are provided in Table 1.

In the overall population, 31 patients (24%) underwent noninvasive ventilation with positive airway pressure and one patient required invasive mechanical ventilation. In addition to respiratory support, patients received antiviral (51%), hydroxychloroquine (57%), tocilizumab (4%), antibiotic (56%), heparin (52%), and steroid (14%) therapy.

All patients were in sinus rhythm at the time of the admission; 42% of them presented nonspecific ventricular repolarization

**TABLE 1** Characteristics of the study population during hospitalization

	Overall (n = 123)	Group A (MI-, n = 77)	Group B (MI+, n = 46)	p
Age (years, $\pm$ SD)	62.1 $\pm$ 12.9	58.3 $\pm$ 1.3	67.8 $\pm$ 2	< 0.001
Male (n, %)	84/123 (68)	49/77 (63)	35/46 (76)	0.15
Weight (kg, $\pm$ SD)	77.5 $\pm$ 15.9	77.4 $\pm$ 1.9	78.3 $\pm$ 2.8	0.63
Height (m, $\pm$ SD)	1.7 $\pm$ .2	1.7 $\pm$ .1	1.7 $\pm$ .1	0.37
Body mass index (Kg/m <sup>2</sup> , $\pm$ SD)	26.3 $\pm$ 5.1	26.7 $\pm$ .5	25.9 $\pm$ 1.1	0.43
<b>COMORBIDITIES</b>				
Hypertension (n, %)	43 (35)	23 (29)	20 (43)	0.12
Coronary artery disease (n, %)	10 (8)	3 (4)	7 (15)	0.02
Chronic obstructive pulmonary disease (n, %)	7 (6)	1 (1)	6 (13)	0.006
Diabetes (n, %)	2 (2)	2 (3)	0	0.86
Malignant neoplasm (n, %)	12 (10)	5 (6)	7 (15)	0.11
<b>VITAL SIGNS ON ADMISSION</b>				
Heart rate on admission (beats per min, $\pm$ SD)	92 $\pm$ 16	93 $\pm$ 2	90 $\pm$ 3	0.36
Systolic blood pressure on admission (mm Hg, IQRs)	130 [115–140]	130 [115–140]	133 [112.5–140]	0.67
Body temperature on admission ( $^{\circ}$ C, IQRs)	37.8 [36.9–38.4]	37.65 [36.9–38.1]	38 [36.6–38.5]	0.61
Oxygen saturation (% , IQRs)	95 [91.5–97]	94 [92–97]	95 [90–97]	0.59
<b>ELECTROCARDIOGRAM ON ADMISSION</b>				
Sinus rhythm	123 (100)	77 (100)	46 (100)	–
Inferior Q wave	1 (1)	1 (1)	0	–
Right bundle branch block	9 (6)	6 (8)	3 (6)	0.65
Left anterior fascicular block	12 (10)	8 (10)	4 (9)	0.76
Nonspecific intra-ventricular delay	27 (22)	15 (19)	12 (26)	0.5
Nonspecific ventricular repolarization abnormalities	52 (42)	32 (41)	20 (43)	0.98
<b>BLOOD TEST DURING HOSPITALIZATION (WORST VALUES)</b>				
Worst hemoglobin (g/dl $\pm$ SD)	11.1 $\pm$ 2.1	11.7 $\pm$ .2	10.3 $\pm$ .3	<0.001
White blood cell maximum value, $\times 10^9$ /L (IQRs)	9.5 [7.1–14.4]	7.7 [6.1–10.9]	12.8 [8.4–18.4]	<0.001
C-Reactive protein maximum value (mg/L) (IQR)	122.3 [54.2–203.9]	90.8 [41.4–178.3]	167.9 [93.6– 248]	0.001
Serum creatinine maximum value (mg/dl) [IQR]	1.1 [.9–1.6]	1 [.8–1.2]	1.4 [1.1–1.9]	<0.001
Nt-proBNP maximum value, $\mu$ g/ml [IQR]	164.5 [59.2–465.8]	94 [44.7–193]	425 [169–1142]	<0.001
<b>COMPLICATIONS AFTER DIAGNOSIS OF COVID-19</b>				
Need of oxygen feeding (n, %)	40 (32)	28 (36)	12 (26)	0.23
Non-invasive ventilation (n, %)	31 (25)	18 (23)	13 (28)	0.36
Invasive ventilation (n, %)	1 (1)	0	1 (2)	–
Intensive care unit need (n, %)	20 (16)	7 (9)	13 (28)	0.005
Acute respiratory distress syndrome (n, %)	2 (2)	0	2 (4)	0.28
Acute kidney injury (n, %)	5 (4)	2 (2)	3 (6)	0.29
Pulmonary embolism	2 (2)	2 (2)	0	0.71

The values are expressed as mean  $\pm$  standard deviation, median (inter-quartile ranges) or number (percentages) as appropriate.

abnormalities without any other ACS criteria. No other significant ECG abnormalities associated with ACS were observed. Other ECG abnormalities observed are reported in Table 1.

Group B patients (MI+) compared to group A (MI-) were significantly older, had more frequently a history of Coronary Artery Disease (CAD) or Chronic Obstructive Pulmonary Disease (COPD) and more frequently required care in the Intensive Care Unit.

Laboratory exams of group B (MI+) showed significantly higher values of C-Reactive protein, NT-proBNP, creatinine and white blood cells.

### 3.2 | Follow-up

The median time from hospital admission to the follow-up examination was 85 days (IQR 70.2–102.8).

**TABLE 2** New York Heart Association (NYHA) class at follow-up evaluation

NYHA CLASS	Group A (MI-) (n = 77)	Group B (MI+) (n = 46)	p
I	58	23	0.005
II	14	12	
III	5	11	
IV	0	0	

The values are expressed as number of patients.

In the overall population, 16 patients reported dyspnea even during less-than-ordinary activity, for example, walking short distances (New York Heart Association class III).

Group B patients (MI+) were more frequently symptomatic for dyspnea (Table 2 and Figure 2).

Median hsTnT, NT-proBNP, and C-reactive protein values were 8 ng/L (5.2–12.9), 64.5  $\mu$ g/ml (29–165.8) and 2 mg/L (.7–3.7), respectively. Group B patients had significantly higher values of hsTnT and NT-proBNP as compared to Group A patients (14.2 [6.6–18.1] vs 7.2 [5–9.2] ng/L,  $p = 0.0004$ ; 137 [51.2–305] vs 44 [23.8–86]  $\mu$ g/ml,  $p = 0.0007$ , respectively), whereas no differences were found in

C-Reactive protein levels between the two groups (2 [.7–4] in group B vs 1.6 [.7–3.1] mg/L,  $p = 0.4$ ).

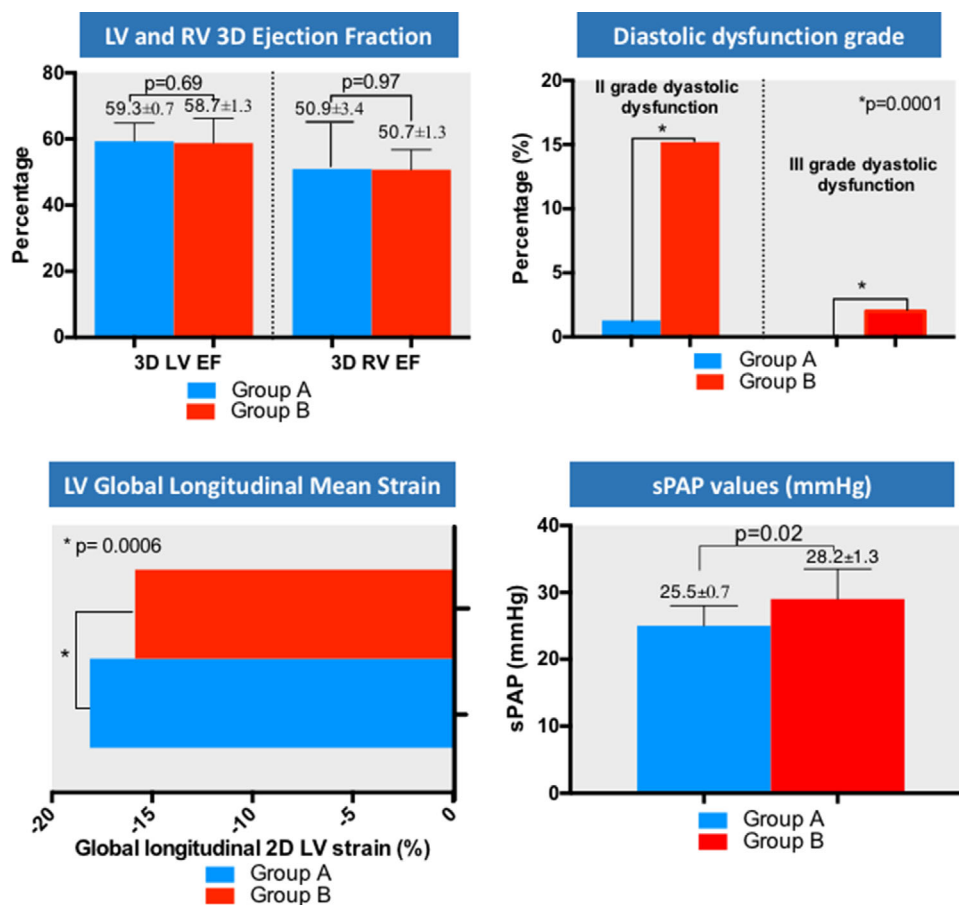
All the echocardiographic measurements are reported in Table 3.

No differences between the two groups in 3D left and right ventricle volumes and ejection fraction were found (Table 3) (Figure 2). However, 32 patients showed significant reduction of LV GLS: 14 (18%) in group A and 18 (39%) in group B ( $p = 0.01$ ) (Figure 2).

In group B patients (MI+), a significant reduction in mean LV GLS was observed as compared to group A (MI-) ( $-15.7 \pm .7$  vs  $-18.1 \pm .3$ ,  $p < 0.001$ ) (Figure 2). In addition, group B patients (MI+) presented significantly higher frequency of impaired diastolic function, larger left atrial size, and higher values of pulmonary artery pressure (Table 3 and Figure 2).

### 3.3 | Subgroup analysis

HsTnT values were persistently elevated at follow-up examination in 13 patients (11%). No patient without MI during hospitalization presented elevated hsTnT values at follow-up. A subgroup analysis was performed dividing patients in three groups. Group I included patients without MI during hospitalization ( $n = 77$ , this group is identical to the group A (MI-)), group II included patients with MI



**FIGURE 2** Main echocardiographic differences in patients recovered from COVID-19 with and without myocardial injury during hospitalization

**TABLE 3** Echocardiographic parameters at follow-up stratified by the presence of myocardial injury

	Group A (MI-) (n = 77)	Group B (MI+) (n = 46)	p
Diastolic inter-ventricular septum thickness (mm)	10 ± 1	10 ± 1	0.93
Left ventricle end diastolic Diameter (mm)	44 ± 1	45 ± 1	0.31
Diastolic posterior wall thickness (mm)	9 ± 1	10 ± 1	0.09
Left atrium volume (ml)	45 ± 2	53 ± 2	0.002
LV four-chamber 2D longitudinal strain (%)	-18.1 ± .3	-16.6 ± .5	0.009
LV two-chamber 2D longitudinal strain (%)	-17.7 ± .3	-16.5 ± .5	0.01
LV three-chamber 2d longitudinal strain (%)	-18.1 ± .3	-15.6 ± .4	0.029
LV mean global 2d longitudinal strain (%)	-18.1 ± .3	-15.7 ± .7	<0.001
LV mean GLS < 17% (n, %)	14 (18)	18 (39)	0.01
3D end diastolic volume (ml)	103 ± 3	102 ± 4	0.89
3D end systolic volume (ml)	43 ± 2	43 ± 2	0.97
3D ejection fraction (%)	59 ± 1	59 ± 1	0.69
E wave velocity (m/s)	.6 ± .1	.7 ± .1	0.27
A wave velocity (m/s)	.7 ± .1	.9 ± .1	<0.001
E/A ratio	1 ± .1	.8 ± .1	0.12
E wave DecT (msec)	213 ± 6	222 ± 10	0.38
E' lateral velocity (cm/s)	11 ± 1	9 ± 1	0.003
Diastolic dysfunction grade	0: 23/77 1: 53/77 2: 1/77 3: 0/77	0: 3/46 1: 35/46 2: 7/46 3: 1/46	<0.001
E/E' ratio	6 ± 1	8 ± 1	0.001
RV end diastolic basal diameter (mm)	35 ± 1	35 ± 1	0.87
RV end diastolic mid diameter (mm)	25 ± 1	26 ± 1	0.15
Tricuspid annular plane systolic excursion (mm)	23 ± 1	22 ± 1	0.018
RV S' TDI (cm/s)	13 ± 1	12 ± 1	0.26
Systolic Pulmonary Artery Pressure (mm Hg)	25 ± 1	28 ± 1	0.02
Right atrium volume (ml)	34 ± 1	38 ± 2	0.04
Inferior vena cava diameter (mm)	13 ± 1	12 ± 1	0.8
Central Venous Pressure (mm Hg)	4 ± 1	4 ± 1	0.51
Pulmonary artery diameter (mm)	21 ± 1	21 ± 1	0.82
RV end diastolic area (cm <sup>2</sup> )	21 ± 1	21 ± 1	0.33
RV end systolic area (cm <sup>2</sup> )	11 ± 1	11 ± 1	0.21
RV rational Area Change (%)	47 ± 1	45 ± 1	0.23
RV- free wall longitudinal strain (%)	-22 ± 1	-22 ± 1	0.51
3D RV end diastolic volume (ml)	80 ± 4	82 ± 5	0.76
3D RV end systolic volume (ml)	39 ± 2	41 ± 3	0.59
3D RV ejection fraction (%)	51 ± 3	51 ± 1	0.97

The values are expressed as mean ± standard deviation, median (inter-quartile ranges) or number (percentages) as appropriate.

Abbreviations: LV, Left Ventricle; GLS, global longitudinal strain; DecT, deceleration time; RV, right ventricle; TDI, Tissue Doppler imaging.

during hospitalization but normal hsTnT level at the follow-up examination (normalized troponin level,  $n = 33$ ), and group III included patients with MI both during hospitalization and at follow-up examinations (persistently elevated troponin level,  $n = 13$ ). The results did not show any significant difference in 3D left

ventricle volumes and ejection fraction, right ventricular function parameters, LV GLS, diastolic function and RV function parameters between group II and group III. LV GLS was significantly reduced in both group II and group III as compared to group I patients (Table 4).

**TABLE 4** Main echocardiographic parameters in patients with persistently elevated troponin at follow-up and in patients with normalized troponin values at follow-up and patients with normal troponin values at baseline

	Group I (MI-, n = 77)	Group II (normalized troponin level, n = 33)	Group III (persistently elevated troponin levels, n = 13)	p value group I versus group II	p value group I versus group II	p value group II versus group III
Ejection Fraction (%)	61 ± 1	58 ± 2	59 ± 1	0.11	0.36	0.73
LV mean global 2D longitudinal strain (%)	-18.1 ± .3	-15.6 ± 1	-15.7 ± .5	0.002	0.001	0.96
3D LV Ejection Fraction (%)	59 ± 1	59 ± 1	59 ± 2	0.64	0.9	0.86
Diastolic dysfunction grade	0: 23/77 1: 53/77 2: 1/77 3: 0/77	0: 3/33 1: 26/33 2: 4/33 3: 0/33	0: 3/33 1: 9/13 2: 3/13 3: 1/13	0.005	0.001	0.64
E/E' ratio	6 ± 1	7 ± 1	8 ± 1	0.014	0.005	0.42
RV S' TDI velocity (cm/s)	13 ± 1	12 ± 1	11 ± 1	0.86	0.08	0.11
Systolic pulmonary artery pressure (mm Hg)	25 ± .7	28 ± 1.3	28 ± 3	0.03	0.1	0.58
RV fractional area change (%)	47 ± 1	46 ± 2	45 ± 2	0.42	0.15	0.72
RV-free wall longitudinal strain (%)	-22 ± 1	-22 ± 1	-20 ± 1	0.9	0.08	0.18
3D RV ejection fraction (%)	51 ± 3	50 ± 2	53 ± 2	0.83	0.82	0.44

The values are expressed as mean ± standard deviation, median (inter-quartile ranges) or number (percentages) as appropriate.

Abbreviations: LV, Left Ventricle; GLS, global longitudinal strain; RV, right ventricle; TDI, Tissue Doppler Imaging.

**TABLE 5** Intra-observer agreement in the left ventricular strain analysis (LV GLS)

	Intra-observer
LV GLS	ICC*: .98 Bias: -.1 (-1 to 0.8)

\* $p < 0.001$ .

Abbreviations: LV GLS, Left Ventricle mean Global Longitudinal Strain; ICC, intra-class correlation coefficient.

### 3.4 | Intra-observer variability

Intra-observer agreement was excellent for global longitudinal 2D strain (Table 5).

## 4 | DISCUSSION

Our study represents an attempt to systematically characterize the spectrum of cardiac abnormalities at mid-term follow-up among hospitalized patients recovered from COVID-19.

The main findings of our study are: (1) patients with acute subclinical MI are more frequently symptomatic for exertional dyspnea at follow-up; (2) 3D dimensions and function of left and right ventricle are similar in patients with or without MI during hospitalization; (3) patients with MI during hospitalization for COVID-19 may present a subclinical LV myocardial dysfunction after COVID-19 recovery as assessed by

GLS; (4) higher grades of diastolic dysfunction with larger left atrial volumes and higher values of pulmonary artery pressure at follow-up may be found in patients with MI during hospitalization for COVID-19; (5) a persistence of elevated values of hsTnT may be found at mid-term follow-up; and (6) among patients with MI during hospitalization, the reduction in LV GLS values is similar in both patients with persistently hsTnT elevation and normal hsTnT at follow-up.

Subclinical MI during the acute phase of the infection has emerged as a relatively frequent complication with dismal prognostic consequences.<sup>6</sup> Our findings confirm that subclinical evidence of MI is frequent during COVID-19 acute phase with a prevalence of 37% in our population.<sup>4,8</sup> Patients with MI during hospitalization, as described in other studies,<sup>12,15</sup> were more frequently symptomatic for exertional dyspnea at follow-up evaluation.

Concerns were raised for a subacute and chronic phase of the inflammatory process in COVID-19, since the persistence of cardiac abnormalities early after the recovery have already been described.<sup>11-13,23</sup> Brito et al., assessing athletes who returned to university campus after uncomplicated COVID-19, have shown that 56% of them presented pericardial enhancement assessed by CMR and 12% had reduced GLS assessed by TTE or increased native T1 assessed with CMR.<sup>13</sup> A Turkish study in patients hospitalized for COVID-19 described, after 1-month follow-up, abnormal LV GLS values by TTE in 38% patients with a higher prevalence among those with MI during hospitalization.<sup>23</sup> In a study with a mid-term follow-up (71 days after COVID-19 diagnosis) Putmann et al. have found that up to 80% of patients recovered from COVID 19 have abnormal CMR findings:

primarily myocardial inflammation, regional scar and pericardial enhancement. Finally, Weckbach et al. described reduced LV GLS values after a median of 52 days, but improved as compared to the values observed during the acute phase of the infection.<sup>14</sup> Our results, assessed by TTE, confirm the presence of cardiac abnormalities at a longer follow-up (median 85 days after hospital admission). Their clinical relevance remains unknown.

Clinical presentation of the chronic myocarditis with other etiology is highly variable and the prognosis might be good for the majority of the patients; however, it can be impaired if the healing of myocarditis is incomplete<sup>24,25</sup> and patients may subsequently develop heart failure.<sup>24,26</sup> In this setting, the early identification of unhealed myocarditis could be helpful to guide the beginning of cardioprotective therapy. GLS has been previously suggested as an alternative to CMR in the diagnosis of chronic myocardial inflammatory disease.<sup>27,28</sup> LV GLS is recommended for clinical use to detect slight MI in heart failure, chemotherapy-related cardiotoxicity, and infiltrative diseases.<sup>29,30</sup> In addition, strain imaging with regional speckle-tracking assessment has been proposed as a potential surrogate for CMR late gadolinium enhancement (LGE) imaging.<sup>31</sup> Finally an abnormal LV GLS by TTE has demonstrated an adequate diagnostic performance, compared to CMR, to detect chronic myocarditis in patients with LV normal EF with 82% sensitivity, 70% specificity, and 76% accuracy.<sup>28</sup>

In the setting of COVID-19, LV GLS proved to be an independent predictor of in-hospital mortality.<sup>32</sup> Although the long-term effects of LV GLS decrease cannot be determined in COVID-19, it has been related to worse outcomes in chronic myocarditis of other etiologies.<sup>33,34</sup>

Moreover, patients with MI presented at follow-up higher frequency of impaired left ventricular diastolic function with larger left atrial volumes and higher values of pulmonary artery pressure. Those data are concerning, since in the scenario of chronic myocardial inflammatory process, the evolution to heart failure with preserved EF has been already described.<sup>24</sup>

The data of the present study suggest that: (1) despite 3D dimensions and function of left and right ventricle are similar in patients with or without MI during hospitalization, GLS may be useful for detecting subclinical myocardial dysfunction; (2) in patient with acute MI a close clinical follow-up with a comprehensive echocardiographic evaluation including LV GLS analysis should be performed; (3) LV GLS may be useful as a "gate" to further imaging investigations: patients with reduced GLS could start a follow-up with a multimodality imaging approach including CMR and TTE to assess the evolution of the inflammatory process; and (4) the early identification of patients with cardiac imaging abnormalities may allow the beginning of cardioprotective therapy.

## 5 | LIMITATIONS

Our study has some potential limitations. First, there was no assessment of echocardiographic data during hospitalization. Second, we did not include CMR and cardiac computed tomography imaging data.

Moreover, NYHA class assessment in patients with previous COVID-19 pneumonia may be affected by a lung damage.

## 6 | CONCLUSIONS

The results of this study suggest that patients with MI during the acute phase of COVID-19 may present mid-term subclinical myocardial dysfunction that can be assessed by LV GLS analysis and may show higher grades of diastolic impairment.

Long-term follow-up is needed in order to evaluate the prognostic and clinical implications of these findings. In patients recovered from COVID-19, TTE with speckle-tracking analysis could be a useful imaging tool to identify patients with subclinical MI and potentially guide management strategies.

### ORCID

Francesco Cannata MD  <https://orcid.org/0000-0002-5842-5293>

Eustachio Agricola MD  <https://orcid.org/0000-0002-4834-2187>

### REFERENCES

- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet Lond Engl*. 2020;395(10223):497-506.
- Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091. <https://doi.org/10.1136/bmj.m1091>
- Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481.
- Wang D, Hu Bo, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069.
- Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5(7):802-810. <https://doi.org/10.1001/jamacardio.2020.0950>
- Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(7):811-818. <https://doi.org/10.1001/jamacardio.2020.1017>
- Giustino G, Pinney SP, Lala A, et al. Coronavirus and cardiovascular disease, myocardial injury, and arrhythmia. *J Am Coll Cardiol*. 2020;76(17):2011-2023.
- Tomasoni D, Italia L, Adamo M, et al. COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease. *Eur J Heart Fail*. 2020;22(6):957-966.
- Bavishi C, Bonow RO, Trivedi V, Abbott JD, Messerli FH, Bhatt DL. Special article—acute myocardial injury in patients hospitalized with COVID-19 infection: a review. *Prog Cardiovasc Dis*. 2020;63(5):682-689.
- Agricola E, Beneduce A, Esposito A, et al. Heart and lung multimodality imaging in COVID-19. *Jacc Cardiovasc Imag*. 2020;13(8):1792-1808.
- Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(11):1265-1273. <https://doi.org/10.1001/jamacardio.2020.3557>



12. Huang Lu, Zhao P, Tang D, et al. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. *JACC Cardiovasc Imaging*. 2020;13(11):2330-2339.
13. Brito D, Meester S, Yanamala N, et al. High prevalence of pericardial involvement in college student athletes recovering from COVID-19. *Jacc Cardiovasc Imag*. 2021;14(3):541-555.
14. Weckbach LT, Curta A, Bieber S, et al. Myocardial inflammation and dysfunction in COVID-19-associated myocardial injury. *Circ Cardiovasc Imag*. 2021;14(1):e012220.
15. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet Lond Engl*. 2021;397(10270):220-232.
16. Townsend L, Dyer AH, Jones K, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One*. 2020;15(11):e0240784.
17. van den Borst B, Peters JB, Brink M, et al. Comprehensive health assessment three months after recovery from acute COVID-19. *Clin Infect Dis*. 2021;73(5):e1089-e1098. <https://doi.org/10.1093/cid/ciaa1750>
18. Kraus D, Von Jeinsen B, Tzikas S, et al. Cardiac troponins for the diagnosis of acute myocardial infarction in chronic kidney disease. *J Am Heart Assoc*. 2018;7(19):e008032. <https://doi.org/10.1161/JAHA.117.008032>
19. Bagai A, Alexander KP, Berger JS, et al. Use of troponin assay 99th percentile as the decision level for myocardial infarction diagnosis. *Am Heart J*. 2017;190:135-139.
20. Collet J-P, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289-1367.
21. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233-270.
22. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277-314.
23. Özer S, Candan L, Özyıldız AG, Turan OE. Evaluation of left ventricular global functions with speckle tracking echocardiography in patients recovered from COVID-19. *Int J Cardiovasc Imag*. 2021.
24. Escher F, Westermann D, Gaub R, et al. Development of diastolic heart failure in a 6-year follow-up study in patients after acute myocarditis. *Heart Br Card Soc*. 2011;97(9):709-714.
25. Escher F, Kühl U, Lassner D, et al. Long-term outcome of patients with virus-negative chronic myocarditis or inflammatory cardiomyopathy after immunosuppressive therapy. *Clin Res Cardiol Off J Ger Card Soc*. 2016;105(12):1011-1020.
26. Tschöpe C, Ammirati E, Bozkurt B, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol*. 2021;18(3):169-193.
27. Caspar T, Fichot M, Ohana M, et al. Late detection of left ventricular dysfunction using two-dimensional and three-dimensional speckle-tracking echocardiography in patients with history of nonsevere acute myocarditis. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2017;30(8):756-762.
28. Kasner M, Aleksandrov A, Escher F, et al. Multimodality imaging approach in the diagnosis of chronic myocarditis with preserved left ventricular ejection fraction (MCpEF): the role of 2D speckle-tracking echocardiography. *Int J Cardiol*. 2017;243:374-378.
29. Plana JC, Galderisi M, Barac A, Ewer MS, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2014;27(9):911-939.
30. Murtagh G, Laffin LJ, Patel KV, et al. Improved detection of myocardial damage in sarcoidosis using longitudinal strain in patients with preserved left ventricular ejection fraction. *Echocardiogr Mt Kisco N*. 2016;33(9):1344-1352.
31. Altiok E, Tiemann S, Becker M, et al. Myocardial deformation imaging by two-dimensional speckle-tracking echocardiography for prediction of global and segmental functional changes after acute myocardial infarction: a comparison with late gadolinium enhancement cardiac magnetic resonance. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2014;27(3):249-257.
32. Baycan OF, Barman HA, Atici A, et al. Evaluation of biventricular function in patients with COVID-19 using speckle tracking echocardiography. *Int J Cardiovasc Imaging*. 2020;15:1-10.
33. Kostakou PM, Kostopoulos VS, Tryfou ES, et al. Subclinical left ventricular dysfunction and correlation with regional strain analysis in myocarditis with normal ejection fraction. A new diagnostic criterion. *Int J Cardiol*. 2018;259:116-121.
34. Awadalla M, Mahmood SS, Groarke JD, et al. Global longitudinal strain and cardiac events in patients with immune checkpoint inhibitor-related myocarditis. *J Am Coll Cardiol*. 2020;75(5):467-478.

**How to cite this article:** Italia L, Ingallina G, Napolano A, et al. Subclinical myocardial dysfunction in patients recovered from COVID-19. *Echocardiography*. 2021;38:1778-1786. <https://doi.org/10.1111/echo.15215>