

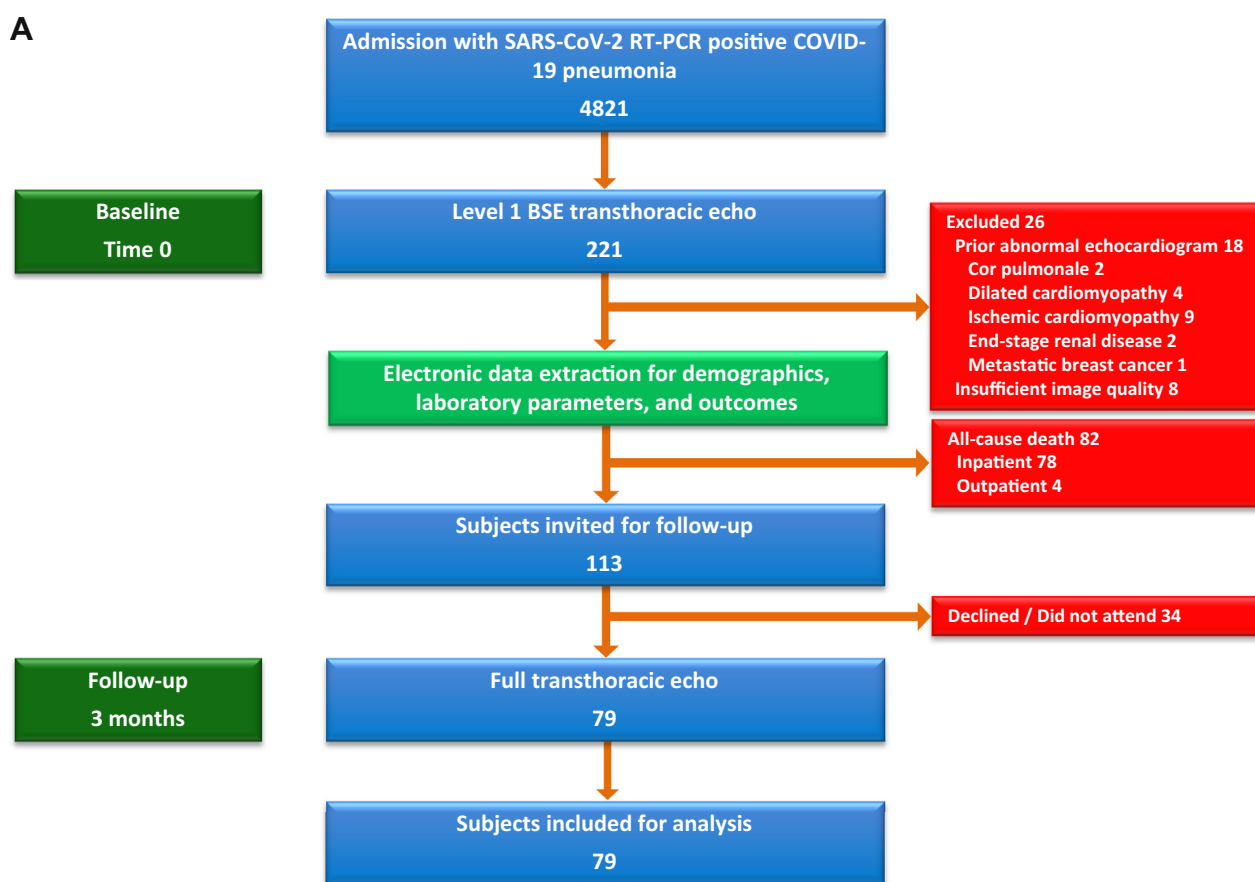
## Persisting Adverse Ventricular Remodeling in COVID-19 Survivors: A Longitudinal Echocardiographic Study



Abnormalities in cardiac structure and function are common in patients hospitalized with severe COVID-19 pneumonia who have evidence of myocardial injury based on elevated high-sensitivity cardiac troponin (HScTn).<sup>1</sup> Studies performing transthoracic echocardiography (TTE) in an acute setting have consistently demonstrated a high prevalence of right ventricular (RV) dilation and dysfunction, a finding that is associated with early mortality independent of standard clinical and biomarker risk stratification.<sup>1,2</sup> These studies have, however, been limited by their cross-sectional design; to date, there have been no

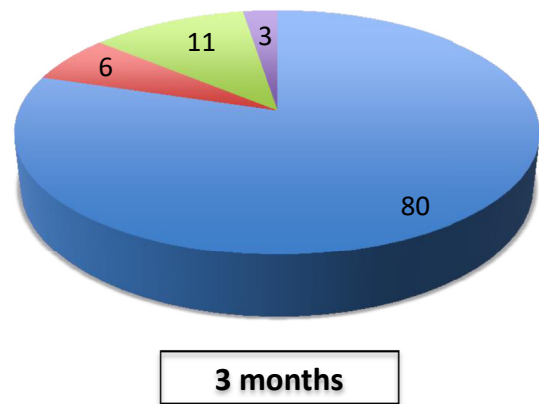
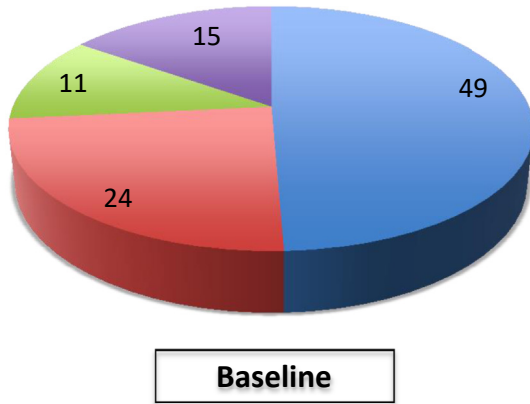
longitudinal studies aimed at determining whether adverse ventricular remodeling is transient or permanent. To address this, we elected to perform repeat echocardiographic assessment at 3 months in survivors following hospitalization for severe COVID-19 pneumonia.

This was a multicenter, prospective, observational, cohort study of adults ages  $\geq 18$  years hospitalized with COVID-19 pneumonia (study CONSORT, Figure 1A). The methodology for baseline assessment was published in a retrospective observational analysis<sup>2</sup>; survivors are included in the current study. In brief, baseline TTE followed a modified level 1 focused protocol limited to assessment of chamber size and function, valvular disease, and likelihood of pulmonary hypertension. At 3 months after the first TTE, a comprehensive departmental study was performed according to standard guidelines.<sup>3</sup> All measurements were performed retrospectively and off-line using archived images by British Society of Echocardiography



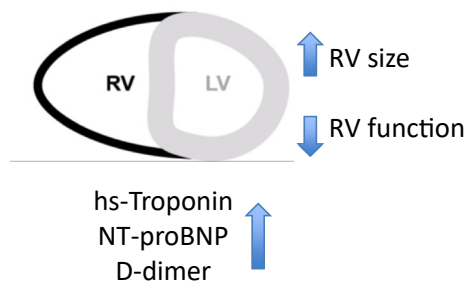
**Figure 1 (A)** Study CONSORT diagram of patient selection for follow-up echocardiography and study inclusion. **(B)** Percentage frequency of RV abnormalities at baseline and 3 months among COVID-19 survivors ( $n = 79$ ). All patients who had undergone in-patient TTE as part of routine clinical care after admission to one of six UK hospitals between March 16 and May 9, 2020, and survived to discharge were identified (the Queen Elizabeth Hospital, Birmingham and Birmingham Heartlands Hospital, University Hospitals Birmingham, Birmingham; New Cross Hospital, Wolverhampton; Glenfield Hospital, Leicester; Gloucester Royal Hospital, Gloucester; and Cheltenham General Hospital, Cheltenham). Before inclusion, all cases were confirmed as having COVID-19 pneumonia through reverse transcriptase–polymerase chain reaction (RT-PCR) assays performed on nasopharyngeal swabs and confirmation of pulmonary infiltrates on chest radiography. Patients were excluded if they had a history of heart failure, valvular heart disease, or an abnormal echocardiogram prior to admission with COVID-19 or if baseline TTE images were of insufficient quality to make objective measurements.

**B**



**Acute COVID-19 disease**

Hypoxic pulmonary vasoconstriction  
Ventilator induced lung injury  
Pulmonary thromboembolic disease  
Direct myocardial injury

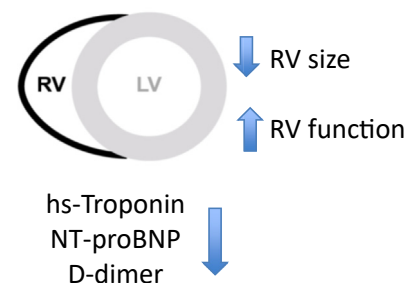


3 months



**Recovery from COVID-19**

Normalization of RV size and function



**Figure 1** (Continued)

level 2 accredited observers blinded to clinical and serological biomarker data.<sup>4</sup> At three recruiting centers, participants underwent cardiac biomarker assessment at follow-up.

Seventy-nine patients (57 ± 11 years, 74% male) were included in the analysis. Of those 46 (67%) had a baseline elevated HScTn (>99th percentile). Baseline TTE was performed at a median of 8 days (interquartile range [IQR], 2–16) after hospital admission. Of the 63 patients (80%) that required mechanical ventilation, 60 (95%) underwent baseline TTE while ventilated. The median in-hospital length of stay was 32 (IQR, 24–56) days.

The results of echocardiography performed at baseline and 3 months are detailed in Table 1. At entry, 36 (46%) patients had a normal TTE. In those with any abnormality, 32 (41%) had RV remodeling, 5 (6%) had LV remodeling, and 6 (8%) had biventricular involvement. Right ventricular dilation was present in over a third of patients (39%), a 1.5-fold higher prevalence than that of RV

dysfunction (27%). Conversely, left ventricular (LV) dilation and LV dysfunction were only found in 4% and 13% of patients, respectively. Follow-up TTE was undertaken at a median of 91 days (IQR, 92–99) after the baseline study. At 3 months, 56 (71%) patients had a normal TTE. In those with any abnormality, 16 (20%) had only RV adverse remodeling, 5 (6%) had only adverse LV remodeling, and 2 (3%) had biventricular involvement. There was reverse RV remodeling in the majority (Figure 1B), reflected by a significantly lower RV basal dimension and an augmented RV fractional area change compared with baseline. There was no significant change in peak tricuspid regurgitant velocity at follow-up compared with baseline, although most had a low echocardiographic probability of pulmonary hypertension, acknowledging that the number of patients with a measurable Doppler signal was small. There were no significant changes in LV parameters at 3 months compared with baseline. Of the 16 patients (20%) with persisting RV changes at 3 months, 7 (44%) had

**Table 1** Longitudinal echocardiographic and serological biomarker assessment

Echocardiographic parameter	Baseline (n = 79)	3 Months (n = 79)	P value
<b>Left heart:</b>			
LV size:			
Normal, n (%)	76 (96)	77 (97)	1.00
Dilated, n (%)	3 (4)	2 (3)	
LV end-diastolic dimension, mean ± SD, mm	45 ± 7	46 ± 7	.17
LV end-systolic dimension, mean ± SD, mm	31 ± 6	31 ± 7	.81
Eccentricity index, D1/D2, mean ± SD	—	0.94 ± 0.10	—
LV systolic function, n (%):			
Normal	69 (87)	72 (91)	.69
Mildly impaired	5 (6)	6 (8)	
Moderately impaired	2 (3)	0 (0)	
Severely impaired	3 (4)	1 (1)	
LV ejection fraction, median (IQR), %	60 (56-65)	60 (57-63)	.08
<b>Right heart:</b>			
RV size, n (%):			
Normal	48 (61)	72 (91)	<.001
Dilated	31 (39)	7 (9)	
RV basal diameter, mean ± SD, mm	39 ± 7	36 ± 5	.006
RV to LV basal dimension ratio, mean ± SD	0.84 ± 0.19	0.80 ± 0.12	.44
RV to LV basal dimension ratio > 1.0, n (%)	19 (24)	8 (10)	.035
RV systolic function			
FAC, mean ± SD, %	40 ± 10	46 ± 10	.001
TAPSE, mean ± SD, mm	20 ± 5	20 ± 6	.75
RV S', cm/sec	—	14.3 ± 2.9	—
RV systolic function (TAPSE < 17 mm or FAC < 35%):			
Normal, n (%)	58 (73)	68 (86)	.048
Abnormal, n (%)	21 (27)	11 (14)	
FAC < 35%, n (%)	21 (27)	7 (9)	.004
TAPSE < 17 mm, n (%)	9 (11)	11 (14)	.63
RV S' < 9.5 cm/sec, n (%)	—	2 (3)	—
RVOT acceleration time, mean ± SD, msec	—	109 ± 27	—
IVC size, mean ± SD, mm	20 ± 3	17 ± 3	.031
Right atrial area, mean ± SD, cm <sup>2</sup>	15 ± 5	14 ± 4	.32
Main pulmonary artery diameter, mean ± SD, mm	20 ± 7	21 ± 9	.80
Pulmonary hypertension, n (%):			
Low probability	12 (15)	57 (72)	.002
Intermediate probability	5 (6)	4 (5)	
High probability	3 (4)	0 (0)	
Unable to estimate*	59 (49)	18 (22)	<.001
Peak tricuspid regurgitation velocity, mean ± SD <sup>†</sup>	2.4 ± 0.7	2.2 ± 0.7	.34
Pericardial effusion, n (%)	4 (5)	3 (4)	1.00
<b>Serum biomarker</b>			
	Baseline (n = 45)	3 Months (n = 45)	P value
HScTn, median (IQR), ng/L	27 (9-129)	2 (0-5)	<.001
HScTn above the 99% percentile, n (%)	27 (60)	0 (0)	<.001
HScTn ≥ 5 ng/L, n (%)	44 (98)	11 (24)	<.001
NT-proBNP, median (IQR), ng/L	—	76 (20-246)	—

(Continued)

**Table 1** (Continued)

Serum biomarker	Baseline (n = 45)	3 Months (n = 45)	P value
NT-proBNP > 450 ng/L, n (%)	—	8 (18)	—
D-dimer, peak admission, median (IQR), ng/mL	7,321 (4,900-12,400)	293 (175-700)	<.001
D-dimer > 500 ng/mL fibrinogen equivalent units	39 (87)	9 (20)	<.001

FAC, Fractional area change; IVC, inferior vena cava; NT-proBNP, N-terminal pro b-type natriuretic peptide; RVOT, RV outflow tract; TAPSE, tricuspid annular plane systolic excursion.

The normality of distribution for continuous variables was determined using the Kolmogorov-Smirnov test. Continuous data were analyzed using an independent samples Student's *t* test if normally distributed or a Mann-Whitney *U* test for if not normally distributed. Categorical data were analyzed using  $\chi^2$  or, where appropriate, Fisher's exact tests.

\*Due to an incomplete tricuspid regurgitation continuous-wave Doppler signal.

†There were 18 patients with baseline and follow-up measurable tricuspid regurgitation continuous-wave Doppler signal.

pulmonary embolism diagnosed on computed tomography pulmonary angiography during hospital admission. There was no effect of gender (male 25% vs female 26%;  $P = .95$ ) or ethnicity (nonwhite 35% vs white 33%,  $P = .89$ ) on the frequency of patients with abnormal RV size and/or function at follow-up. In 45 subjects with paired biomarker data, there were significant reductions in HScTn and D-dimer (Table 1). Despite persistent LV and/or RV abnormalities in 11 (24%) patients, no patient at 3 months had a HScTn above the 99th percentile for age and sex.

We found a higher rate of abnormal ventricular dilation or dysfunction than cross-sectional cardiac magnetic resonance studies performed at approximately 10 weeks, although these included a majority of patients cared for at home and few who were ventilated.<sup>5,6</sup> Our results also differed from a smaller TTE study that enrolled predominantly HScTn-negative patients in whom both TTE abnormalities and cardiac biomarkers resolved within a median 41 days.<sup>7</sup> This difference is likely explained by the severity of COVID-19 pneumonia in our population. The high frequency of adverse RV remodeling at baseline may in part relate to acute effects from mechanical ventilation. Nonetheless, the prevalence of isolated RV dysfunction did not change at follow-up, which implicates other factors such as direct myocardial injury and thromboembolic disease.

While our cohort is modest in size and is highly selected, this is the largest echocardiographic follow-up study to date in COVID-19 and included a cohort at the highest risk of adverse outcomes. Our patients were referred for echocardiography on clinical grounds, most had elevated HScTn on admission and required ventilation, and those with previous abnormalities on echocardiography were excluded. These results are not, therefore, generalizable to all patients hospitalized with COVID-19 or to those not requiring admission.

In summary, although acute abnormalities in ventricular size or function among hospitalized patients with COVID-19 pneumonia resolved in most patients after 3 months, there was persistent evidence of adverse ventricular remodeling in nearly one-third (29%). Furthermore, repeat TTE appears necessary for surveillance because a significant proportion in whom biomarkers normalized continued to demonstrate ventricular abnormalities.

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