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Cardiac Abnormalities in COVID-19 and Relationship to Outcome

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Abstract

Objective: To characterize the clinical and transthoracic echocardiographic features and 30-day outcomes of hospitalized patients with coronavirus disease 2019 (COVID-19).

Methods: Retrospective cohort study that included consecutive inpatients with COVID-19 infection who underwent clinically indicated transthoracic echocardiography at 10 sites in the Mayo Clinic Health System between March 10 and August 5, 2020. Echocardiography was performed at bedside by cardiac sonographers according to an abbreviated protocol. Echocardiographic results, demographic characteristics, laboratory findings, and clinical outcomes were analyzed.

Results: There were 179 patients, aged 59.8±16.9 years and 111 (62%) men; events within 30 days occurred in 70 (39%) patients, including prolonged hospitalization in 43 (24%) and death in 27 (15%). Echocardiographic abnormalities included left ventricular ejection fraction less than 50% in 29 (16%), regional wall motion abnormalities in 26 (15%), and right ventricular systolic pressure (RVSP) of 35 or greater mm Hg in 44 (44%) of 101 in whom it was measured. Myocardial injury, defined as the presence of significant troponin level elevation accompanied by new ventricular dysfunction or electrocardiographic abnormalities, was present in 13 (7%). Prior echocardiography was available in 36 (20%) patients and pre-existing abnormalities were seen in 28 (78%) of these. In a multivariable age-adjusted model, area under the curve of 0.81, prior cardiovascular disease, troponin level, D-dimer level, and RVSP were related to events at 30 days.

Conclusion: Bedside Doppler assessment of RVSP appears promising for short-term risk stratification in hospitalized patients with COVID-19 infection undergoing clinically indicated echocardiography. Pre-existing echocardiographic abnormalities were common; caution should be exercised in attributing such abnormalities to the COVID-19 infection in this comorbid patient population.

Coronavirus disease 2019 (COVID-19) is a rapidly evolving emergency with frequent cardiovascular involvement. A high risk for mortality has been reported among hospitalized patients with COVID-19 infection with pre-existing coronary artery disease and those who develop acute cardiac injury. However, to date, the impact of cardiac involvement on short-term outcomes in the setting of COVID-19 infection is incompletely understood.

Echocardiography is widely used in the bedside evaluation of patients with COVID-19 infection, and echocardiographic abnormalities have commonly been detected. Cardiac manifestations have included myocardial injury from acute coronary syndromes, myocarditis, and takotsubo cardiomyopathy. Adverse right ventricular (RV) remodeling and abnormal RV longitudinal strain are among the frequently described abnormalities in patients with COVID-19 infection and have been related to increased mortality. However, some of the echocardiographic findings in patients with COVID-19 infection may have been pre-existent, not unlikely in a group of patients who frequently have comorbid conditions.

To protect sonography staff and patients, cardiac imaging protocols have been abbreviated in the era of COVID-19. Bedside
Echocardiograms have been focused to assessing ventricular size and systolic function, the presence of left ventricular regional wall motion abnormalities, and the presence of hemodynamically significant valvular heart disease or pericardial effusion.\textsuperscript{8-10} However, these modifications to a standard comprehensive echocardiographic examination may limit the utility of echocardiography in clinical risk stratification.

The current study was undertaken to characterize the clinical and echocardiographic features and 30-day outcomes of hospitalized patients with COVID-19 infection in whom echocardiography was clinically indicated. We hypothesized that in addition to clinical characteristics and laboratory values, echocardiographic findings would be independently associated with short-term outcome.

METHODS
Patient Population
This study was approved by the institutional review board and conducted among consecutive inpatients with a diagnosis of COVID-19 infection who underwent clinically indicated transthoracic echocardiography (TTE) at 10 sites in the Mayo Clinic Health System between March 10 and August 5, 2020. The first available transthoracic echocardiogram performed after hospital admission for COVID-19 infection was included. Clinical information was abstracted from the medical record. Inpatient laboratory values closest to the time of the echocardiogram were recorded.

Echocardiography
Echocardiography was performed by registered cardiac sonographers at the patient’s bedside using full-sized ultrasound systems (Vivid E9, GE Healthcare; and EPIQ, Philips). An abbreviated protocol was used to minimize staff contact with the patient. The focused study was directed toward evaluating biventricular function, detecting pericardial effusion, assessing pulmonary artery systolic pressure when feasible, and screening for significant valvular stenosis or regurgitation using 2-dimensional imaging and color Doppler.\textsuperscript{11} Additional image acquisition and analysis, including measurement of global longitudinal strain (GLS), tricuspid annulus systolic excursion or tissue Doppler s’, quantification of valvular heart lesions (proximal isovelocity surface area, multiwindow Pedof transducer assessment, constriction/restriction, and left or ventricular or RV strain) were performed only when clinically relevant and feasible. Sonographer staff entered the patient’s room with contrast available in case this was necessary for assessment of ventricular function and regional wall motion.

Detailed retrospective review of the echocardiographic images, including side-by-side comparison with any echocardiogram before the diagnosis of COVID-19 infection but within 5 years, was performed by experienced level 3 echocardiographers blinded to clinical information and outcome. Right ventricular size and systolic function were assessed in multiple views and by Doppler method when available. Left ventricular volumes were traced in the apical views when feasible. In some cases, a view or measurement was missing, precluding comparison of that variable for the 2 studies; the number in which comparison was possible is indicated in the results for each measurement comparison.

Outcomes
Thirty-day outcome was obtained by retrospective review of the electronic medical record to assess patient management and events during hospitalization, including prolonged ($\geq$21 days) hospitalization\textsuperscript{12} or death. Myocardial injury was also recorded and described, defined as the presence of significant elevation in high-sensitivity cardiac troponin\textsuperscript{13} level accompanied by either new or presumed new ventricular dysfunction or electrocardiographic abnormalities consistent with myocardial injury but was not included as the outcome because echocardiographic evidence of injury was part of the definition.
TABLE 1. Clinical Characteristics by Outcome (30-day Death and Prolonged Hospitalization)

| Variable | No Event (N=109) | Event (N=70) | P  |
|----------|-----------------|--------------|----|
| Age (y), median (Q1-Q3) | 59.0 (47.0-70.0) | 63.5 (49.0-76.0) | .18 |
| Patient-identified sex, no. (%) | | | .55 |
| Male | 65 (60) | 46 (66) | | |
| Female | 43 (39) | 24 (34) | | |
| Intersex | 1 (1) | 0 (0) | | |
| Race/ethnicity, no. (%) | | | .24 |
| White | 53 (49) | 27 (39) | | |
| African American | 4 (4) | 5 (7) | | |
| Native American | 21 (19) | 11 (16) | | |
| Asian | 2 (2) | 6 (9) | | |
| Hispanic | 21 (19) | 15 (21) | | |
| Other | 8 (7) | 6 (9) | | |
| Body mass index (kg/m²), median (Q1-Q3) | 30.7 (27.1-36.3) | 28.4 (25.2-32.5) | .03 |
| COVID-19 symptoms, no. (%) | | | | |
| Dyspnea, cough | 80 (73) | 59 (84) | .09 |
| Fever, fatigue, malaise | 71 (65) | 38 (54) | .15 |
| Gastrointestinal symptoms | 37 (34) | 17 (24) | .17 |
| Anosmia, dysgeusia | 8 (7) | 1 (1) | .08 |
| Clinical characteristics, no. (%) | | | | |
| Diabetes mellitus | 37 (34) | 30 (43) | .23 |
| Hypertension | 47 (43) | 37 (53) | .20 |
| Chronic kidney disease | 10 (9) | 11 (16) | .18 |
| Dialysis | 3 (3) | 2 (3) | .97 |
| Coronary artery disease | 8 (7) | 9 (13) | .22 |
| Valvular heart disease | 5 (5) | 3 (4) | .92 |
| Cardiac transplant | 2 (2) | 2 (3) | .65 |
| Other organ transplant | 3 (3) | 3 (4) | .58 |
| Chronic obstructive pulmonary disease or asthma | 11 (10) | 12 (17) | .17 |
| Pulmonary circulation disorder | 0 (0) | 2 (3) | .08 |
| Chronic liver disease | 2 (2) | 2 (3) | .65 |
| Cancer | 3 (3) | 7 (10) | .04 |
| Stroke | 5 (5) | 9 (13) | .04 |
| Cardiovascular disease (stroke/coronary artery disease) | 13 (12) | 17 (24) | .03 |
| Current/former smoker | 32 (29) | 19 (27) | .75 |
| Laboratory values, median (Q1-Q3) | | | | |
| Hemoglobin (g/dL) [n=178] | 12.9 (11.3-14.3) | 11.1 (9.2-12.4) | <.001 |
| C-Reactive protein (mg/L) [n=169] | 72.8 (24.0-134.4) | 97.0 (32.1-187.9) | .10 |
| Ferritin (µg/L) [n=163] | 615.0 (187.0-932.0) | 726.5 (333.5-1282.5) | .05 |
| Serum creatinine (mg/dL) [n=158] | 0.9 (0.7-1.2) | 1.1 (0.8-2.2) | .003 |
| Troponin (ng/L) [n=133] | 6 (9-26) | 44 (13-86) | <.001 |
| N-terminal prohormone B-type natriuretic peptide (pg/mL) [n=113] | 188 (78-508) | 2159 (392-5030) | <.001 |
| D-Dimer (ng/mL) [n=164] | 785 (503-1267) | 1356 (933-4154) | <.001 |

COVID-19, coronavirus disease 2019; Q, quartile.

Statistical Analyses
Continuous variables were expressed as mean ± SD or median with interquartile range according to data distribution and compared using Student t test or Wilcoxon rank sum test, as appropriate. Categorical data, presented as number and percentage, were compared using χ² test. Univariate and multivariable logistic regression analyses were performed to identify clinical and
| Variable                                                                 | No Event (N=109) | Event (N=70) | P     |
|-------------------------------------------------------------------------|------------------|--------------|-------|
| Atrial fibrillation/flutter, no. (%)                                    | 7 (6)            | 8 (11)       | .24   |
| Heart rate (beats/min), mean ± SD                                       | 78±15            | 80±17        | .41   |
| Systolic blood pressure (mm Hg), mean ± SD                             | 124±18           | 119±23       | .12   |
| Diastolic blood pressure (mm Hg), mean ± SD                            | 73±13            | 67±14        | .005  |
| Ultrasound image enhancing agent, no. (%)                              | 33 (30)          | 24 (34)      | .57   |
| LV end-diastolic dimension (mm), mean ± SD                              | 46±9             | 46±11        | .88   |
| LV end-systolic dimension (mm), mean ± SD                               | 30±7             | 31±10        | .48   |
| LV end-diastolic volume (mL), mean ± SD                                 | 109±36           | 115±50       | .38   |
| LV end-systolic volume (mL), mean ± SD                                  | 45±21            | 53±41        | .13   |
| Septal wall thickness (mm), mean ± SD                                   | 10.4±2.5         | 10.9±2.0     | .16   |
| Posterior wall thickness (mm), mean ± SD                                | 9.6±2            | 10.3±1.7     | .02   |
| Increased LV wall thickness (includes visual assessment), no. (%) [n=178] | 21 (19)          | 15 (22)      | .77   |
| Relative wall thickness, mean ± SD                                      | 39±15            | 43±14        | .12   |
| LVEF, mean ± SD                                                         | 59±9             | 57±14        | .16   |
| LVEF<35%, no. (%)                                                       | 3 (3)            | 6 (9)        | .08   |
| LVEF<50%, no. (%)                                                       | 10 (9)           | 19 (27)      | .001  |
| Change in LVEF vs prior echocardiogram, mean ± SD                       | −0.8±5.7         | −0.4±7.8     | .86   |
| LV global longitudinal strain, mean ± SD [n=29]                         | −17.8±4.1        | −14.6±2.5    | .03   |
| RWMSI, mean ± SD                                                        | 1.1±0.3          | 1.2±0.4      | .02   |
| RWMSI >1, no. (%)                                                       | 10 (11)          | 16 (27)      | .01   |
| Change in regional wall motion vs prior echocardiogram, no. (%)         |                  |              | .10   |
| No change                                                               | 19 (86)          | 9 (64)       |       |
| Increased extent and severity                                           | 2 (9)            | 4 (29)       |       |
| Increased severity, same extent                                          | 0 (0)            | 1 (7)        |       |
| Improved                                                                | 1 (5)            | 0 (0)        |       |
| Mitral E/A ratio, mean ± SD                                             | 1.1±0.5          | 1.2±0.7      | .34   |
| Mitral annulus e' medial, mean ± SD                                     | 0.1±0.03         | 0.1±0.01     | .42   |
| Mitral E/e' (medial), mean ± SD                                         | 10.6±4.1         | 12.0±5.7     | .12   |
| Left atrial size (visual), no. (%) [n=166]                              |                  |              | .13   |
| Normal                                                                  | 75 (73)          | 37 (59)      |       |
| Mildly enlarged                                                          | 11 (11)          | 14 (22)      |       |
| Moderately enlarged                                                      | 10 (10)          | 9 (14)       |       |
| Severely enlarged                                                        | 7 (7)            | 3 (5)        |       |
| Change in left atrial size vs prior echocardiogram, no. (%) [n=32]       |                  |              | .15   |
| No change                                                               | 19 (90)          | 7 (64)       |       |
| Mildly increased                                                         | 1 (5)            | 3 (27)       |       |
| Moderately increased                                                    | 1 (5)            | 1 (9)        |       |
| RV size, no. (%) [n=175]                                                 |                  |              | .31   |
| Normal                                                                  | 72 (67)          | 39 (57)      |       |
| Mildly enlarged                                                          | 24 (22)          | 21 (31)      |       |
| Moderately enlarged                                                      | 9 (8)            | 8 (12)       |       |
| Severely enlarged                                                        | 2 (2)            | 0 (0)        |       |
| Change in RV size vs prior echocardiogram, no. (%) [n=34]                |                  |              | .43   |
| None                                                                    | 18 (86)          | 10 (77)      |       |
| Mildly increased                                                         | 3 (14)           | 2 (15)       |       |
| Moderately increased                                                    | 0 (0)            | 1 (8)        |       |
echocardiographic predictors of events at 30 days, including the composite of prolonged hospitalization or death. In multivariable models, missing values were imputed using median values and missing value indicator variables were added to these models to account for the imputation. Separate sensitivity analyses were conducted using imputed values from the first and third quartiles and similar results were found.

RESULTS

There were 179 inpatients with COVID-19 infection who underwent TTE during the study; 110 (61%) were managed in the intensive care unit. Mean ± SD patient age was 59.8±16.9 years and 111 (62%) were men. Indications for echocardiography included assessment of left ventricular function in 87 (49%), hypoxemia in 36 (20%), RV function in 18 (10%), arrhythmia in 14 (8%), hypotension in 13 (7%), and chest pain/suspected acute coronary syndrome in 11 (6%). An ultrasound image enhancing agent was used in 57 (32%).

Left ventricular ejection fraction was measured by biplane Simpson in 74 (41%) patients, single plane in 52 (29%), linear in 30 (17%), and visual estimation in 23 (13%). Right ventricular size and function were assessed by visual estimation, supplemented by tissue Doppler in 35 (20%), tricuspid annulus systolic excursion in 19 (11%), and free wall strain in 4 (2%) patients.

During the hospitalization, 64 (36%) patients required mechanical ventilation (44 were mechanically ventilated at the time of

| TABLE 2. Continued |
|---------------------|
| Variable | No Event (N=109) | Event (N=70) | P |
| RV function, no. (%) [n=175] | | | |
| Normal | 77 (72) | 44 (65) | .13 |
| Mildly reduced | 23 (21) | 14 (21) | |
| Moderately reduced | 4 (4) | 9 (13) | |
| Severely reduced | 3 (3) | 1 (1) | |
| Change in RV function vs prior echocardiogram, no. (%) [n=34] | | | .36 |
| No change | 19 (90) | 10 (77) | |
| Mildly reduced | 2 (10) | 2 (15) | |
| Moderately reduced | 0 (0) | 1 (8) | |
| Right atrial pressure (mm Hg), mean ± SD | 7±4 | 11±5 | <.001 |
| Change in right atrial pressure (mm Hg), mean ± SD [n=30] | 2±4 | 3±7 | .58 |
| RVSP (mm Hg), mean ± SD [n=101] | 33±10 | 40±11 | <.001 |
| RVSP ≥35 mm Hg, no. (%) | 20 (32) | 24 (62) | .004 |
| Change in RVSP vs prior echocardiogram, mean ± SD [n= 23] | 3.4±9.9 | 4.7±5.6 | .74 |
| Tricuspid valve regurgitation, no. (%) [n=172] | | | .04 |
| None or trivial | 81 (76) | 42 (64) | |
| Mild-moderate | 21 (20) | 19 (29) | |
| Moderate | 3 (3) | 3 (5) | |
| Moderate-severe | 1 (1) | 0 (0) | |
| Severe | 0 (0) | 2 (3) | |
| Change in tricuspid valve regurgitation vs prior echocardiogram, no. (%) | | >0.99 |
| None | 21 (95) | 14 (100) | |
| Mildly increased | 1 (5) | 0 (0) | |
| Pericardial effusion, no. (%) | 10 (9) | 13 (19) | .07 |
| Intracardiac mass or thrombus, no. (%) | 0 (0) | 2 (3) | .21 |

*LV, left ventricular; LVEF, left ventricular ejection fraction; RV, right ventricular; RVSP, right ventricular systolic pressure; RWMSI, regional wall motion score index.

*Number of patients for whom this comparison could be made when it was less than the total.

*21 patients with global left ventricular dysfunction and 9 in whom regional wall motion could not be accurately assessed were excluded from the comparison.
| No | Age (y) | Sex | Clinical Cardiac Diagnosis | LVEF Nadir | Wall Motion Abnormality | Peak High-Sensitivity Troponin T (ng/L) | Management, Events, Death Due to COVID-19 |
|----|---------|-----|-----------------------------|------------|------------------------|----------------------------------------|------------------------------------------|
| 1  | 49      | Male| Myocarditis                 | 47%        | Basal/mid              | 526                                    | Venovenous ECMO                           |
| 2  | 84      | Male| Status post cardiac arrest, prior coronary artery bypass grafting, presumed ischemic cardiomyopathy | 25%        | Global                 | 237                                    | Torsades de pointes cardiac arrest, shock, RRT, death |
| 3  | 53      | Male| Myocarditis                 | 31%        | Basal/mid              | 76                                     | Small pericardial effusion                |
| 4  | 61      | Female| Myocarditis/stress cardiomyopathy | 18%        | Mid/apex               | 2367                                   | Shock, RRT, pulmonary embolism           |
| 5  | 70      | Male| Stress cardiomyopathy       | 40%        | Mid/apex               | 28                                     | Shock, left ventricular thrombus, deep venous thrombosis, RRT |
| 6  | 75      | Female| Stress cardiomyopathy       | 48% (−29%) | Global                 | 47                                     | Shock, RRT, moderate pericardial effusion, death |
| 7  | 77      | Female| Stress cardiomyopathy       | 50%        | Mid/apex               | 47                                     | Diabetic ketoacidosis                    |
| 8  | 95      | Female| NSTEMI                        | 46% (−15%) | Inferior, inferoseptal | 257                                   | New atrial fibrillation, death           |
| 9  | 82      | Female| NSTEMI                        | 20%        | Mid/apex               | 292                                   | 3-vessel percutaneous coronary intervention |
| 10 | 70      | Male| NSTEMI                        | 65%        | None                   | 227                                   | 3-vessel coronary artery bypass graft    |
| 11 | 68      | Female| NSTEMI                        | 60%        | None                   | 163                                   | Death                                    |
| 12 | 78      | Male| NSTEMI                        | 38%        | Anterior, inferior, apex | 2375                                  | Shock, atrial fibrillation, right ventricular dysfunction, death |
| 13 | 47      | Male| NSTEMI                        | 62%        | None                   | 105                                   | Percutaneous coronary intervention       |

*COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; LVEF, left ventricular ejection fraction; NSTEMI, non–ST-elevation myocardial infarction; RRT, renal replacement therapy.

In parenthesis, change in left ventricular ejection fraction from most recent prior echocardiographic study.

Reference: ≤15 ng/mL.
the echocardiography) and 47 (26%) required circulatory support, which included pressors and/or mechanical circulatory support. Events within 30 days occurred in 70 (39%) patients, including prolonged hospitalization in 43 (24%) and death in 27 (15%).

Baseline clinical characteristics, presenting symptoms, and baseline laboratory values for patients with and without the 30-day end point are shown on Table 1. Other characteristics included cardiac device leads in 8 (4%) and prior congenital heart disease repair in 2 (1%).

Hemodynamic and echocardiographic characteristics according to the presence of an end point are shown in Table 2. Echocardiographic abnormalities included left ventricular ejection fraction less than 50% in 29 (16%), regional wall motion abnormalities in 26 (15%), global dysfunction in 21 (12%), left ventricular hypertrophy in 36 (20%), left atrial enlargement in 54 (33%), RV enlargement in 64 (37%), RV systolic dysfunction in 54 (31%), RV systolic pressure (RVSP) of 35 mm Hg or greater in 44 (44%), tricuspid regurgitation (TR) of mild-moderate or greater severity in 49 (27%), pericardial effusion in 23 (13%), and ventricular thrombus in 2, one in the apex of the left ventricle (accompanied by apical akinesis) and 1 in the right ventricle, adherent to the tricuspid chordal apparatus in a patient receiving venovenous extracorporeal membrane oxygenation. Left ventricular GLS was performed in 11 patients with events and 18 patients without events and was lower in those with events (−14.6±2.5 vs −17.8 ±4.1; P=.03). For the 21 patients in whom both troponin levels and GLS were available, these showed good correlation, r=0.65.

Prior echocardiography was available in 36 (20%) patients; these examinations were performed at a median of 8 (interquartile range, 3-30) months previously. Among these patients, pre-existing abnormalities were present in 28 (78%) and included left ventricular ejection fraction less than 50% in 4 (11%) and regional wall motion abnormalities in 9 (25%). Of the 29 patients with ejection fraction less than 50% after COVID-19 infection, pre-existing ejection fraction less than 50% was present in 4 of the 7 with prior studies. Additionally, 12 of the 26 patients with regional wall motion abnormalities following COVID-19 infection had undergone prior TTE; 7 of these 12 patients had new or worsened regional wall motion abnormalities and the remaining 5 showed no change from the baseline study. Echocardiographic abnormalities also included left ventricular hypertrophy in 9 (25%), left ventricular enlargement in 7 (19%), left atrial enlargement in 23 (64%), RVSP ≥35 mmHg in 8 (22%), RV enlargement in 8 (22%), RV dysfunction in 5 (14%), and moderate or greater severity valvar disease in 8 (22%; moderate aortic stenosis (AS) in 2, severe AS in 1, moderate mitral regurgitation [MR] in 2, moderate TR in 2, and both moderate MR and moderate TR in 1). The most common new echocardiographic abnormalities after COVID-19 infection were increased extent and/or severity of left ventricular regional wall motion abnormalities, increase in left atrial size, increase in RV size, decrease in RV systolic function, and increase in RVSP (Table 2).

Thirteen (7%) patients sustained acute myocardial injury; clinical features are detailed on Table 3. Clinical diagnoses included myocarditis, non-ST-elevation myocardial infarction, global ventricular dysfunction after resuscitated cardiac arrest, and stress cardiomyopathy.

Predictors of Outcome
Age- and troponin-adjusted and multivariate predictors of events are shown in Table 4. History of cardiovascular disease, highsensitivity troponin T level, D-dimer level, and RVSP were independently associated with the composite end point of prolonged hospitalization or death.

DISCUSSION
Among patients hospitalized with COVID-19 infection and requiring clinically indicated echocardiography, comorbid conditions were prevalent, including especially hypertension, diabetes mellitus, history of prior
cardiovascular disease, and history of smoking. Patients for whom echocardiograms were obtained were a sick cohort; 61% (110/179) of patients required intensive care unit management, more than one-third (36%; n = 64) required mechanical ventilation, and about a quarter (26%; n = 47) required pharmacologic or circulatory support. Echocardiographic findings in COVID-19 most often included RV enlargement and RV systolic dysfunction, present in 37% (64/175) and 31% (54/175), respectively. RVSP was elevated (≥35 mm Hg) in 44% (n = 44/101).

Adverse 30-day outcomes occurred in 70 (39%), including prolonged hospitalization in 25 (14%) and death in 27 (15%). Patients with these events were nearly 4 years older and more often had a diagnosis of cancer or known cardiovascular disease. Abnormal biomarkers of low hemoglobin or increased creatinine, ferritin, troponin, N-terminal prohormone B-type natriuretic peptide, and D-dimer levels were more prevalent among those with a 30-day clinical end point. Echocardiographic features associated with the end point in age-adjusted analysis included Doppler-derived RVSP and the presence of regional wall motion abnormalities. In a multivariable age-adjusted model, area under the curve of 0.81, cardiovascular disease, troponin level, D-dimer level, and RVSP were related to events at 30 days.

The RVSP likely reflects both the underlying severity of pulmonary involvement with COVID-19 and pulmonary venous hypertension from left heart involvement and may be an additive prognostic marker in these patients. Multiple types of lung involvement may contribute to the increase in RVSP. Pneumonia caused by COVID-19 contributed to lung disease and some patients may have had bacterial superinfection. Hypercoagulability associated with this

| Risk Factor | Age Adjusted | Age- & Troponin-Adjusted Model | Multivariable Model |
|-------------|--------------|-----------------------------|-------------------|
|             | Odds Ratio (95% CI) | P     | Odds Ratio (95% CI) | P     | Odds Ratio (95% CI) | P     |
| Age, per 5 y | 1.06 (0.97-1.16) | .20  | 0.99 (0.90-1.10) | .91  | 0.92 (0.81-1.03) | .16  |
| Nonwhite/non-Hispanic | 1.49 (0.79-2.81) | .22  | 1.29 (0.66-2.52) | .46  |                    |      |
| Cancer      | 3.74 (0.93-15.06) | .06  | 4.65 (1.10-19.48) | .04  |                    |      |
| Cardiovascular disease | 2.18 (0.95-4.99) | .07  | 1.85 (0.77-4.44) | .17  | 3.12 (1.20-8.17) | .02  |
| Atrial fibrillation/flutter [n=178] | 1.60 (0.53-4.86) | .40  | 1.53 (0.46-5.09) | .49  |                    |      |
| Creatinine, per 1 SD [n=159] | 1.77 (1.14-2.75) | .01  | 1.40 (0.89-2.19) | .14  |                    |      |
| Troponin, per 1 SD [n=133] | 2.28 (1.36-3.80) | .002 |                |      | 1.86 (1.16-2.98) | .01  |
| N-terminal prohormone B-type natriuretic peptide, per 1 SD [n=113] | 2.85 (1.71-4.76) | <.001 | 2.53 (1.46-4.39) | .001 |                    |      |
| D-Dimer, per 1 SD | 2.41 (1.60-3.65) | <.001 | 2.30 (1.52-3.49) | <.001 | 2.45 (1.59-3.76) | <.001 |
| Systolic blood pressure, per 5 mm Hg [n=178] | 0.94 (0.87-1.01) | .10  | 0.95 (0.88-1.03) | .20  |                    |      |
| Diastolic blood pressure, per 5 mm Hg [n=177] | 0.85 (0.75-0.97) | .007 | 0.85 (0.75-0.97) | .01  |                    |      |
| Ejection fraction, per 5% | 0.92 (0.80-1.05) | .23  | 0.99 (0.85,1.15) | .88  |                    |      |
| RWMSI >1 [n=154] | 2.95 (1.21-7.17) | .02  | 1.66 (0.61-4.52) | .32  |                    |      |
| RV enlargement [n=175] | 1.51 (0.81-2.84) | .20  | 1.38 (0.71-2.69) | .35  |                    |      |
| RV dysfunction [n=175] | 1.38 (0.72-2.66) | .33  | 0.95 (0.46-1.95) | .89  |                    |      |
| RVSP, per 5 units [n=101] | 1.56 (1.22-1.99) | <.001 | 1.52 (1.16-1.99) | .002 | 1.32 (1.03-1.69) | .03  |
| RVSP ≥35 mm Hg [n=101] | 4.06 (1.65-9.97) | .002 | 3.14 (1.18-8.34) | .02  |                    |      |

* RV, right ventricular; RWMSI, regional wall motion score index; RVSP, right ventricular systolic pressure.
* Troponin levels imputed using median in adjustment model. Model also includes indicator variable for imputation.
* Troponin, RVSP, and D-dimer values imputed using median in model. Model also includes indicator variables for imputation.
infection also predisposes patients to pulmonary embolism. Patients did not routinely undergo assessment for pulmonary thromboembolism and some were empirically treated with anticoagulation therapy. Ventilator therapy, positive airway pressure, and hypoxemia also contributed to elevations in RVSP. Even mild ($\geq 35$ mm Hg in 62% [24/39]) elevation in RVSP was seen at greater rates in patients meeting the end point.

Although RV size and systolic function abnormalities were the most frequently seen echocardiographic abnormalities among patients with COVID-19 infection, neither parameter was independently associated with outcome. In contrast, Kim et al observed a 2-fold increase in mortality risk associated with adverse RV remodelling using a variable that combined both an increase in RV linear dimension and peak tricuspid annular longitudinal systolic velocity. Linear RV dimension alone may not be very reliable in the assessment of RV size because of difficulty obtaining reproducible images of the right ventricle in critically ill mechanically ventilated patients. Hence, we assessed RV size in multiple views and used both subjective and objective measures for assessment of RV size. Doppler-derived RVSP may be an additive bedside prognostic marker.

The left heart was also affected, through processes clinically believed to represent ischemia/infarction, inflammatory or viral myocarditis, and stress cardiomyopathy. Left ventricular ejection fraction was more often less than 50% among individuals meeting the end point (27% [n=19] vs 9% [n=10]; $P=0.001$). Though only 5% (n=9) of patients with COVID-19 infection had a severely reduced left ventricular ejection fraction, 15% (n=26/179) demonstrated regional wall motion abnormalities. Regional wall motion score index was more likely to be abnormal (27% [n=16/60] vs 11% [n=10/94]; $P=0.01$) in those meeting the end point. Of the 36 individuals with pre—COVID-19 infection echocardiograms for comparison, 9 (25%) had baseline wall motion abnormalities and 6 of these individuals had no change or improvement in wall motion. Conversely, 7 of these 36 patients (19%) developed new or worsened wall motion abnormalities, suggesting a myopathic or ischemic effect of COVID-19. Among the 13 (7%) patients deemed to have myocardial injury during COVID-19 hospitalization, abnormalities included non—ST-elevation myocardial infarction, takotsubo cardiomyopathy, and presumed myocarditis. Reduced ejection fraction (<50%) and global or regional wall motion abnormalities were documented by echocardiography in 10 (77%) of these patients.

Prior studies in patients with COVID-19 infection have documented cardiac involvement in a broad range of patients. Puntmann et al showed a 60% rate of myocardial inflammation by cardiac magnetic resonance imaging in a population of recovered patients with COVID-19 infection with varying degrees of illness severity 2 or more months after infection. Autopsy data have documented myocarditis in 7.2%, nonmyocarditis inflammation in 12.6%, acute myocardial infarction in 4.7%, and small vessel thrombi in 10.8%. Other data have placed the rate of myocardial injury as measured by biomarker level elevation and echocardiographic wall motion or reduced ejection fraction at approximately 35%.

However, few studies have incorporated pre—COVID-19 echocardiographic data to better understand the rate of left ventricular dysfunction attributable to COVID-19 itself, rather than simply an unmasking of baseline abnormalities in a population with a high incidence of comorbid conditions. We found a high prevalence (78%; n=28) of prior echocardiographic abnormalities among 20% (n=36) of patients who had received an echocardiogram before the onset of COVID-19. Among the 29 patients with reduced ejection fraction less than 50%, pre-existing low ejection fraction was known to be present in 4 of the 7 with baseline studies. Of the 26 patients with regional wall motion abnormalities, 12 had undergone prior TTE; 7 had either new or worsened regional wall motion abnormalities and the remaining 5 had no change.

The abbreviated echocardiographic imaging protocol instead of a standard
comprehensive echocardiographic examination may have resulted in failure to recognize echocardiographic abnormalities in some patients in our cohort. Despite this and unlike prior studies, volumetric assessment of left ventricular size and systolic function was performed in 70% (n=126) of our patients. Quantitative assessment of RV function was performed in 50 (28%) patients. Only 32% (57/179) of the echocardiograms in the present series were obtained using an ultrasound image-enhancing agent; a higher prevalence of wall motion abnormalities may have been identified with more widespread use of these agents.

The study had some limitations. Data collection was retrospective and obtained through electronic health record extraction. It was therefore subject to reporting and ascertainment bias. Patient selection for echocardiographic assessment was based on clinical judgment and not performed in a systematic manner; this likely predisposes our study toward overestimating the frequency of abnormalities. Only 20% (n=36) of patients had baseline TTE studies for comparison. Interim development or resolution of echocardiographic abnormalities may have skewed our comparative assessment of these data. Measurement of biomarkers was performed according to clinical judgment rather than systematically. Incorporation of newer therapeutic agents and methods found effective in various publications during the study period may have influenced our results. The scope of this study was limited to 30-day outcomes.

The long-term impact of COVID-19 infection on cardiac outcomes remains to be prospectively investigated. Bedside Doppler assessment of RVSP appears promising for risk stratification and this variable should be measured in patients with COVID-19 infection undergoing clinically indicated echocardiography.

CONCLUSION

This study found that bedside Doppler assessment of RVSP may be a useful predictive tool for short-term risk stratification of hospitalized patients with COVID-19 infection undergoing clinically indicated echocardiography. Pre-existing echocardiographic abnormalities were common, present in 78% (n=28) of those with a baseline study; caution should be exercised in attributing such abnormalities to the COVID-19 infection in this comorbid patient population.

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SUPPLEMENTAL ONLINE MATERIAL

Video 1

Abbreviations and Acronyms: AS = aortic stenosis; COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; GLS = global longitudinal strain; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NSTEMI = non–ST-elevation myocardial infarction; Q = quartile; RRT = renal replacement therapy; RV = right ventricular; RWMSI = regional wall motion score index; RVSP = right ventricular systolic pressure; TR = tricuspid regurgitation; TTE = transthoracic echocardiography

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