# Right Ventricular Dysfunction and Its Association With Mortality in Coronavirus Disease 2019 Acute Respiratory Distress Syndrome*

Minesh Chotalia, BMBCh[1,2]
Muzzammil Ali, MRCP[2]
Joseph E. Alderman, MBChB[1,2]
Manish Kalla, DPhil[3]
Dhruv Parekh, PhD[1,2]
Mansoor N. Bangash, PhD[1,2]
Jaimin M. Patel, PhD[1,2]

**OBJECTIVES:** To assess whether right ventricular dilation or systolic impairment is associated with mortality and/or disease severity in invasively ventilated patients with coronavirus disease 2019 acute respiratory distress syndrome.

**DESIGN:** Retrospective cohort study.

**SETTING:** Single-center U.K. ICU.

**PATIENTS:** Patients with coronavirus disease 2019 acute respiratory distress syndrome undergoing invasive mechanical ventilation that received a transthoracic echocardiogram between March and December 2020.

**INTERVENTION:** None.

**MEASUREMENTS AND MAIN RESULTS:** Right ventricular dilation was defined as right ventricular:left ventricular end-diastolic area greater than 0.6, right ventricular systolic impairment as fractional area change less than 35%, or tricuspid annular plane systolic excursion less than 17 mm. One hundred seventy-two patients were included, 59 years old (interquartile range, 49–67), with mostly moderate acute respiratory distress syndrome ($n = 101$; 59%). Ninety-day mortality was 41% ($n = 70$): 49% in patients with right ventricular dilation, 53% in right ventricular systolic impairment, and 72% in right ventricular dilation with systolic impairment. The right ventricular dilation with systolic impairment phenotype was independently associated with mortality (odds ratio, 3.11 [95% CI, 1.15–7.60]), but either disease state alone was not. Right ventricular fractional area change correlated with $Pao_2$:$Fio_2$ ratio, $Paco_2$, chest radiograph opacification, and dynamic compliance, whereas right ventricular:left ventricle end-diastolic area correlated negatively with urine output.

**CONCLUSIONS:** Right ventricular systolic impairment correlated with pulmonary pathophysiology, whereas right ventricular dilation correlated with renal dysfunction. Right ventricular dilation with systolic impairment was the only right ventricular phenotype that was independently associated with mortality.

**KEY WORDS:** acute respiratory distress syndrome; coronavirus disease 2019; right ventricular dilation; right ventricular dysfunction; right ventricular failure

Right ventricular dysfunction (RVD) is common in patients with acute respiratory distress syndrome (ARDS) (1) and develops due to acute pulmonary hypertension. It can lead to end-organ venous congestion and, when severe, inadequate delivery of blood to the left ventricle (LV), precipitating left ventricular (LV) failure, systemic hypoperfusion and death (2). RVD in ARDS is modifiable through alteration of patient positioning, ventilator pressures, and $Paco_2$ levels (3).

Critically ill patients with coronavirus disease 2019 (COVID-19) have a high prevalence of ARDS (4) and cardiovascular instability (5). Pulmonary vascular dysfunction has been implicated in their pathophysiology (6, 7), and myocardial

*See also p. 1832.



DOI: 10.1097/CCM.0000000000005167

injury is a poor prognostic sign (8, 9). However, few studies have reported on right heart function in these patients and those that have tend to look at mixed cohorts of illness severity rather those mechanically ventilated with ARDS (10–12).

RVD is difficult to define in the critical care population. Most studies use RV dilation (RV:LV end-diastolic area [RV:LVEDA] greater than 0.6) with or without septal dyskinesia to delineate RVD (1, 13–16). A recent consensus definition characterizes RVD as "RV dilation with evidence of systemic congestion" (17). In contrast, the American Society of Echocardiography proposes using markers of RV systolic impairment to define RVD (e.g., Tricuspid annular plane systolic excursion [TAPSE] less than 17mm and RV-fractional area change [RVFAC] less than 35%) (18). It is unknown which of the two (dilation or systolic impairment) most closely associates with mortality or disease severity in ARDS, including those with COVID-19. It is also unknown whether the presence of both dilation and systolic impairment is associated with a worse outcome.

Detection of RVD in patients with COVID-19 ARDS might allow early intervention with RV protective measures aimed at ameliorating the dysfunction and improving patients' outcomes (19). This requires identification of RV phenotypes associated with mortality to provide prognostic enrichment for medical intervention. The aim of this study was to assess whether RV dilation or systolic impairment associated with mortality and/or disease severity in patients with COVID-19 ARDS. Whether RV dilation with systolic impairment conveyed an additional pathophysiological burden compared with either disease state alone was also investigated.

## MATERIALS AND METHODS

This study was a retrospective service evaluation of routinely collected, anonymized data, as defined by the U.K. NHS Health Research Authority (http://www.hra.nhs.uk). This work uses data provided by patients and collected by the NHS as part of their care and support at University Hospitals Birmingham (UHB) NHS Foundation trust. It has been approved by the UHB NHS Foundation Trust, Clinical Audit Registration and Management System (CARMS), and the COVID-19 research facilitation group under application reference CARMS-16778.

### Study Design, Patient Population, and Data Collection

This was a retrospective, single-center cohort study of patients with COVID-19 ARDS that underwent invasive ventilation and transthoracic echocardiography (TTE) examination in the ICU at Queen Elizabeth Hospital, Birmingham, United Kingdom, between March 3, 2020, and December 11, 2020. All patients had severe acute respiratory syndrome coronavirus-2 infection detected via polymerase chain reaction of nasal swabs/sputum. Patient management was protocolized (**s-Table 1**, http://links.lww.com/CCM/G568) and adhered closely to lung protective ventilation strategies: a target tidal volume (TV) of 6–8 mls/kg/predicted body weight. Positive end-expiratory pressure (PEEP) was titrated to $F_{IO_2}$ (s-Table 1, http://links.lww.com/CCM/G568) rather than being individualized given the high volume of redeployed staff, although senior clinical review to titrate PEEP was sought at high $F_{IO_2}$ requirements (greater than 70%). Patients who had preexisting abnormal TTE findings, did not meet Berlin criteria for ARDS (20), were not undergoing invasive positive pressure ventilation, or who received venovenous extracorporeal membrane oxygenation were excluded with the aim of delineating TTE abnormalities due to COVID-19 ARDS in a generalizable ICU population. The primary end point was the 90-day mortality rate of patients with RV dilation, RV systolic impairment, and RV dilation with systolic impairment on TTE. Secondary end points included the association between TTE measurements of RV size and function and clinical parameters. All statistical analysis was decided a priori.

Data were retrieved retrospectively from the hospital's electronic patient records. All clinical parameters were recorded at the time of the TTE. Dynamic compliance ($C_{dyn}$) was calculated using the following equation ($C_{dyn}$ = TV/[peak inspiratory airway pressure ($P_{peak}$) – PEEP]) (21). Dead space fraction was calculated, as described by Beitler et al (22). Mean urine output from 3 hours before and after TTE was calculated in mL/kg/hr. Patients that received furosemide within that window were excluded from that analysis. Vasopressor dose was calculated by summing the norepinephrine equivalent infusion rates of all vasopressor and inotropic medication being administered (23). The chest radiograph performed closest in time to TTE was graded for severity of opacification using

a semiquantitative scoring system ranging from 0 to 16 (24). The Berlin definition for ARDS was used to classify its severity (20). Frailty scoring was recorded on hospital admission using the Rockwood Clinical Frailty Scale (25). Blood gas and ventilatory parameters were recorded immediately before and 6 hours after the institution of prone ventilation.

### Transthoracic Echocardiography

Patients were referred for TTE at the treating clinician's discretion. All TTE requests were confirmed as appropriate by an imaging consultant cardiologist after documentation of an elevated high-sensitivity Troponin I (greater than 14 ng/L). TTE was performed by level 2 accredited echocardiographers (British Society of Echocardiography [BSE]) using the Sparq 795090CC ultrasound system (Philips Healthcare, Amsterdam, the Netherlands) with an S5 phased array probe. A modified level 1–focused protocol was performed, with assessment of chamber size and function, valvular disease, and likelihood of pulmonary hypertension (26). Retrospective measurements recorded RVEDA, RV end-systolic area (RVESA), and LVEDA in triplicate by two independent observers accredited in critical care echocardiography (M.C. and M.A.) blinded to the clinical data. RV dilation was defined as RV:LVEDA greater than 0.6, RV systolic impairment as RVFAC less than 35% or TAPSE less than 17 mm, and RV dilation with systolic impairment if both criteria were met. LV eccentricity index (LVEI) was measured at end-systole and end-diastole as per BSE guidelines, and values greater than 1.1 were considered abnormal (27). The TTE probability of pulmonary hypertension was assessed in accordance with international guidelines (28). LV systolic function was assessed visually by the echocardiographers, as per BSE level 1 guidance.

### Statistical Analysis

Statistical analysis was performed using GraphPad Prism Version 8.0 (GraphPad Software Inc., San Diego, CA). Categorical data are presented as *n* (%) and compared using a chi-square test. Continuous data were tested for normality using Shapiro-Wilk test and are presented as median (interquartile range [IQR]) and compared using a Mann-Whitney *U* test. Correlation between TTE and clinical parameters was assessed using a Spearman correlation test. Simple linear regression generated a line of best fit through all data points with 95% CIs. This was a pragmatic study, and post hoc power calculations to determine study size were not performed. Intra- and interobserver variation of TTE measurements was assessed using the coefficient of variation (CV; SD/mean × 100). A *p* value of less than 0.05 was considered statistically significant, and all tests performed were two-sided.

A univariate analysis was performed, and all variables that associated with mortality with a *p* value of less than 0.05 were included in a multivariate model. Vasopressor doses were multiplied by 10 so that the unit increment for the odds ratio output was 0.1 μg/kg/min of vasopressor dose. The day of TTE post-ICU admission was also included as a variable. A *p* value of greater than 0.05 on the Hosmer-Lemeshow test indicated goodness of fit.

## RESULTS

### Baseline Demographics

Two hundred sixty-seven patients were admitted with COVID-19 ARDS and met inclusion criteria, of whom 172 (65%) received TTE (**Fig. 1**). Patient demographics are outlined in **Table 1** and **s-Table 2** (http://links.lww.com/CCM/G569). Patients had a median age of 59 years (IQR, 49–67), and the majority were male (*n* = 132; 77%) with moderate ARDS (*n* = 101; 59%). In our cohort, 15 computerized tomography pulmonary angiograms were performed and six patients had evidence of pulmonary embolism. The 90-day mortality was 41% (*n* = 70). Eighty-nine patients (33%) did not receive TTE despite meeting inclusion criteria.

### Right Ventricular Function

TTE was performed on median day 6 (3–10) of ICU and was most commonly requested for hemodynamic instability (*n* = 67; 39%) or elevated troponin-I/D-dimer levels (*n* = 60; 35%). Intraobserver variability (CV) in RVEDA, RVESA, and LVEDA was 1.6%, 2.1%, and 0.9%, respectively. Interobserver variability (CV) in the same TTE parameters was 2.5%, 2.7%, and 2.0%, respectively.

Most patients (77%; *n* = 132) had some evidence of RVD: RV dilation in 49% (*n* = 84), RV systolic impairment in 51% (*n* = 87), and both in 23% (*n* = 39). Severe dilation (RV:LVEDA greater than 1.0) was present in

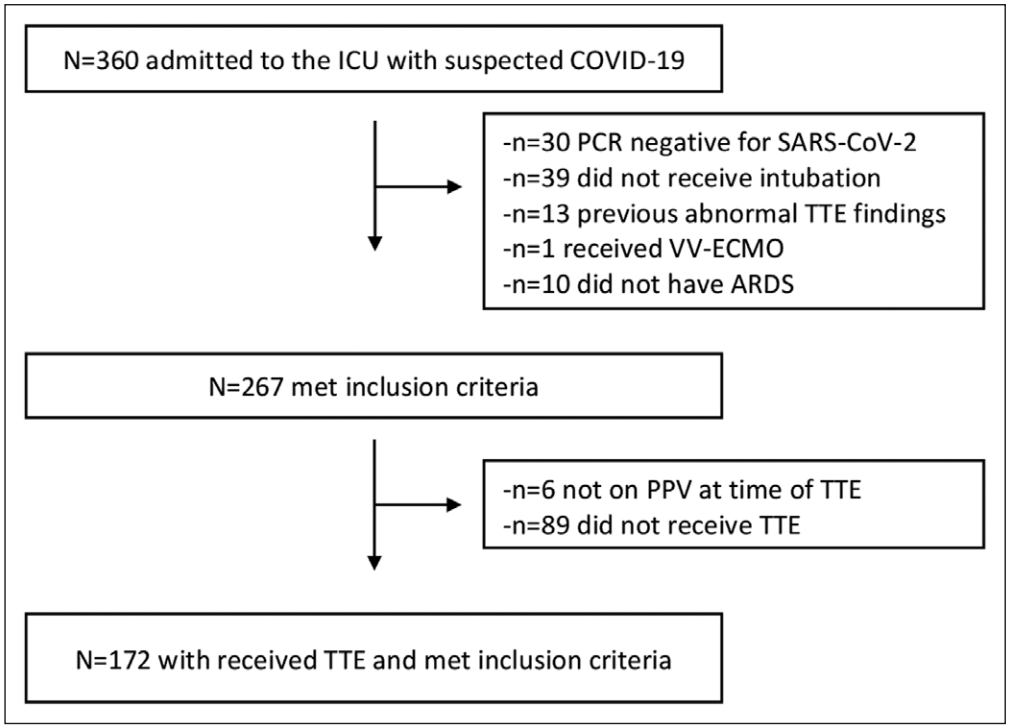


**Figure 1.** Flowchart for the identification of patients included in the study. ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, N = number, PCR = polymerase chain reaction, PPV = positive pressure ventilation, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2, TTE = transthoracic echocardiography, VV-ECMO = venovenous extracorporeal membrane oxygenation.

5% ($n$ = 9). TAPSE was normal in 81% ($n$ = 70/87) of patients with RV systolic impairment defined by RVFAC less than 35%. No patients had RV systolic impairment defined by a low TAPSE but normal RVFAC. Left ventricular function was most commonly normal ($n$ = 91; 52%) or hyperdynamic ($n$ = 65; 37%) (Table 1).

## Correlation With Clinical Parameters

Although RV:LVEDA and TAPSE negatively correlated with each other, no relationship with RVFAC was found (**s-Fig. 1**, http://links.lww.com/CCM/G570; **legend**, http://links.lww.com/CCM/G573). RVFAC correlated with $Pao_2$:$FIO_2$ (P/F) ratio, $PaCO_2$, peak airway pressure, dynamic compliance, and chest radiograph opacification (**s-Fig. 2**, http://links.lww.com/CCM/G571; legend, http://links.lww.com/CCM/G573) but not with PEEP, dead space fraction, pH, vasopressor dose, or urine output (data not shown). RV:LVEDA negatively correlated with urine output and positively correlated with vasopressor dose (s-Fig. 2, http://links.lww.com/CCM/G571; legend, http://links.lww.com/CCM/G573) but not with ventilatory or blood gas parameters (data not shown). TAPSE negatively correlated with vasopressor dose (s-Fig. 2, http://links.lww.com/CCM/G571; legend, http://links.lww.com/CCM/G573) but not with other clinical variables (data not shown). TTE parameters did not correlate with alanine transaminase or alkaline phosphatase (data not shown), and there were no differences in these liver function tests between RV phenotypes (**Table 2**). TTE parameters also did not correlate with LVEI in end-systole/end-diastole (data not shown).

## RV Phenotype and Effect on Mortality

Patients with RV dilation had an increased mortality compared with patients without (49% [41/84] vs 33% [29/88]; $p$ = 0.049) (**Fig. 2*A***) as did those with RV systolic impairment (53% [46/87] vs 28% [24/85]; $p$ = 0.0017) (**Fig. 2*B***). A further increase was observed in those with RV dilation with systolic impairment (72% [28/39] vs 32% [42/133]; $p < 0.0001$) (**Fig. 2*C***). Isolated RV systolic impairment or dilation had no difference in mortality compared with normal RV function (Fig. 2*C* and Table 2). Following multivariate logistic regression analysis, RV dilation/RV systolic impairment did not independently associate with mortality (**Fig. 3**). However, the RV dilation with systolic impairment phenotype did (odds ratio, 3.11 [95% CI, 1.15–7.60]).

In this RV phenotype, vasopressor dose, chest radiograph opacification, and dynamic compliance were higher, and urine output was lower than other RV phenotypes (Table 2). There was a higher prevalence of renal replacement therapy (RRT) in patients with RV dilation with impairment compared with those without (64% [25/39] vs 41% [55/133]; $p$ = 0.011). Although rates of septal dyskinesia were low and not significantly different, a greater proportion of this RV

## TABLE 1.
## Comparison of Clinical and Echocardiographic Parameters in Survivors and Nonsurvivors

| Cohort | All ($n = 172$) | Died ($n = 70$) | Survived ($n = 102$) | $p$ |
|---|---|---|---|---|
| Age (yr) | 59 (49–67) | 63 (53–71) | 55 (47–62) | 0.0007 |
| Sex, male, *n* (%) | 132 (76.7) | 50 (71.4) | 82 (80.4) | 0.054 |
| Day of transthoracic echocardiography | 6 (3–10) | 7 (4–11) | 6 (3–9) | 0.461 |
| Right ventricle | | | | |
| RV:left ventricular end-diastolic area | 0.60 (0.50–0.73) | 0.66 (0.51–0.81) | 0.59 (0.46–0.67) | 0.0049 |
| RV fractional area change (%) | 35 (27–43) | 30 (24–37) | 39 (28–45) | < 0.0001 |
| Tricuspid annular plane systolic excursion (mm) | 21 (18–25) | 21 (17–25) | 21 (19–25) | 0.420 |
| Septal dyskinesia, *n* (%) | 37 (21.5) | 16 (22.9) | 21 (20.6) | 0.867 |
| Abnormal end-diastolic LVEI, *n* (%) ($n = 124$) | 38/124 (30.4) | 16/49 (32.7) | 22/75 (29.3) | 0.695 |
| Abnormal end-systolic LVEI, *n* (%) ($n = 124$) | 36/124 (29.0) | 15/49 (30.6) | 21/75 (28.0) | 0.754 |
| Peak tricuspid regurgitation velocity (m $s^{-1}$)[a] | 2.7 (2.3–3.1) | 2.9 (2.7–3.2) | 2.4 (2.2–2.9) | 0.0020 |
| Normal RV, *n* (%) | 40 (23.3) | 11 (15.7) | 29 (28.4) | 0.079 |
| RV dilation, *n* (%) | 84 (48.8) | 41 (58.6) | 43 (42.2) | 0.050 |
| RV systolic impairment, *n* (%) | 87 (50.6) | 46 (65.7) | 41 (40.2) | 0.0017 |
| RV phenotype | | | | |
| RV dilation with normal systolic function, *n* (%) | 45 (26.2) | 13 (18.6) | 32 (31.3) | 0.089 |
| RV systolic impairment with normal size, *n* (%) | 48 (27.9) | 18 (25.7) | 30 (29.4) | 0.720 |
| RV dilation with systolic impairment, *n* (%) | 39 (22.7) | 28 (40.0) | 11 (10.7) | < 0.0001 |
| Probability of pulmonary hypertension | | | | |
| Low | 15 (8.7) | 5 (7.1) | 19 (18.6) | 0.071 |
| Intermediate | 25 (14.5) | 10 (14.3) | 15 (14.7) | |
| High | 24 (14.0) | 14 (20.0) | 10 (9.8) | |
| Unable to determine[b] | 99 (57.6) | 41 (58.6) | 58 (56.9) | |
| Left ventricle | | | | |
| Left ventricular ejection fraction, *n* (%) | | | | |
| Normal (55–70) | 91 (54.1) | 33 (47.1) | 58 (56.8) | 0.215 |
| Hyperdynamic (> 70) | 65 (36.6) | 32 (45.7) | 33 (32.3) | |
| Depressed (< 55) | 16 (9.3) | 5 (7.1) | 11 (10.8) | |
| ICU management | | | | |
| Prone ventilation (%) | 115 (66.9) | 54 (77.1) | 61 (59.8) | 0.027 |
| Paralysis use, *n* (%) | 147 (85.5) | 65 (92.9) | 82 (80.4) | 0.040 |
| Vasopressor use, *n* (%) | 155 (90.1) | 69 (98.6) | 86 (84.3) | 0.0048 |
| Renal replacement therapy administered, *n* (%) | 80 (46.5) | 47 (67.1) | 33 (32.4) | < 0.0001 |

LVEI = left ventricular eccentricity index, RV = right ventricular.

[a]In 73 patients with measurable tricuspid regurgitation continuous-wave Doppler signal.

[b]Due to incomplete tricuspid regurgitation continuous-wave Doppler signal.

Data are presented as *n* (%) or median (IQR).

Categorical data are compared using a $\chi^2$. Continuous data are compared using a Mann-Whitney *U* test.

## TABLE 2.
### Comparison of Clinical and Echocardiographic Parameters in Right Ventricular Phenotypes

| RV Phenotype | Normal ($n = 40$) | RV Dilation With Normal Systolic Function ($n = 45$) | RV Systolic Impairment With Normal Size ($n = 48$) | RV Dilation With Systolic Impairment ($n = 39$) | $p$ |
|---|---|---|---|---|---|
| Age (yr) | 55 (49–68) | 59 (46–69) | 54 (46–63) | 60 (55–71) | 0.063 |
| Sex, male, *n* (%) | 35 (87.5) | 32 (71.1) | 32 (66.7) | 33 (84.6) | 0.058 |
| Day of TTE | 6 (3–9) | 6 (3–10) | 6 (4–10) | 6 (3–9) | 0.682 |
| Sequential Organ Failure Assessment score | 6 (3–9) | 7 (3–9) | 7 (4–9) | 9 (6–11) | 0.059 |
| TTE parameters | | | | | |
| Right ventricular end-diastolic area ($cm^2/m^2$) | 8 (6–10) | 11 (9–12) | 8 (6–9) | 11 (10–14) | < 0.0001 |
| Right ventricle end-systolic area ($cm^2/m^2$) | 5 (4–6) | 6 (5–8) | 6 (5–7) | 8 (7–10) | < 0.0001 |
| RV:LVEDA | 0.5 (0.40–0.57) | 0.73 (0.65–0.8) | 0.5 (0.43–0.55) | 0.74 (0.6–0.91) | < 0.0001 |
| RV fractional area change (%) | 43 (39–47) | 42 (38–49) | 27 (23–29) | 27 (21–32) | < 0.0001 |
| Tricuspid annular plane systolic excursion (mm) | 22 (20–26) | 20 (19–23) | 22 (19–26) | 18 (14–23) | < 0.0001 |
| Septal dyskinesia, *n* (%) | 5 (12.5) | 9 (20.0) | 11 (22.9) | 12 (30.8) | 0.259 |
| Abnormal LV eccentricity index in diastole | 3/25 (12.0) | 12/33 (36.4) | 11/38 (28.9) | 13/28 (46.4) | 0.051 |
| Abnormal LV eccentricity index in systole | 2/25 (8.0) | 7/33 (21.2) | 11/38 (28.9) | 15/28 (53.6) | 0.0021 |
| Left ventricular ejection fraction (%) | 65 (60–75) | 65 (60–75) | 65 (60–75) | 65 (60–75) | 0.446 |
| LVEDA ($cm^2/m^2$) | 17 (15–19) | 15 (14–17) | 16 (14–19) | 15 (13–16) | 0.00021 |
| Pulmonary hypertension probability | | | | | |
| Low | 1 (2.5) | 8 (17.8) | 11 (22.9) | 4 (10.3) | 0.021 |
| Intermediate | 7 (17.5) | 8 (17.8) | 3 (6.3) | 7 (18.0) | |
| High | 1 (2.5) | 5 (11.1) | 8 (16.7) | 8 (20.5) | |
| Unable to determine[a] | 31 (77.5) | 24 (53.3) | 26 (54.2) | 20 (51.3) | |
| Clinical parameters | | | | | |
| $Pao_2$:$FIo_2$ ratio | 23 (19–26) | 20 (14–26) | 18 (16–23) | 16 (11–20) | 0.0004 |
| $Paco_2$ (kPa) | 7.3 (6.5–8.9) | 7.3 (6.1–9) | 8.3 (6.5–9.4) | 8.6 (6.7–10.1) | 0.155 |
| pH | 7.34 (7.28–7.38) | 7.32 (7.27–7.42) | 7.31 (7.28–7.38) | 7.28 (7.20–7.35) | 0.136 |
| Alanine transaminase ($IU\ L^{-1}$) | 45 (26–88) | 39 (22–74) | 38 (20–62) | 36 (25–58) | 0.587 |
| Alkaline phosphatase ($IU\ L^{-1}$) | 85 (62–119) | 103 (67–146) | 100 (76–126) | 89 (69–126) | 0.661 |
| Mean tidal volume (mLs $kg^{-1}$ predicted body weight) | 7.3 (6.5–7.6) | 6.9 (6.5–7.6) | 7.3 (6.9–7.6) | 7.3 (7.0–7.7) | 0.313 |
| Vasopressor dose ($\mu g\ kg^{-1}\ min^{-1}$) | 0.04 (0–0.14) | 0.07 (0–0.15) | 0.01 (0–0.11) | 0.1 (0.05–0.31) | 0.0020 |
| Chest radiograph opacification score (0–16) | 6 (6–8) | 6 (4–8) | 8 (3–8) | 8 (8–10) | < 0.0001 |
| Dead space fraction | 0.67 (0.6–0.72) | 0.65 (0.6–0.75) | 0.68 (0.6–0.76) | 0.74 (0.65–0.8) | 0.137 |
| Dynamic compliance (mLs cm $H_2O^{-1}$) | 32 (23–37) | 28 (23–36) | 24 (19–31) | 24 (21–31) | 0.00070 |
| Peak inspiratory airway pressure (cm $H_2O$) | 25 (20–28) | 26 (20–30) | 28 (24–30) | 29 (26–32) | 0.00060 |
| Positive end-expiratory pressure (cm $H_2O$) | 8 (5–10) | 10 (5–10) | 8 (6–10) | 10 (8–12) | 0.044 |
| Urine output (mLs $kg^{-1}\ hr^{-1}$) | 0.90 (0.54–1.18) | 0.75 (0.31–0.94) | 0.85 (0.67–1.19) | 0.41 (0.24–0.68) | 0.00090 |

(*Continued*)

**TABLE 2. (*Continued*).**
**Comparison of Clinical and Echocardiographic Parameters in Right Ventricular Phenotypes**

| RV Phenotype | Normal ($n = 40$) | RV Dilation With Normal Systolic Function ($n = 45$) | RV Systolic Impairment With Normal Size ($n = 48$) | RV Dilation With Systolic Impairment ($n = 39$) | *p* |
|---|---|---|---|---|---|
| Management | | | | | |
| Prone ventilation, *n* (%) | 25 (62.5) | 29 (64.4) | 30 (62.5) | 31 (79.5) | 0.298 |
| Neuromuscular blockade, *n* (%) | 32 (80.0) | 39 (86.7) | 40 (83.3) | 36 (92.3) | 0.447 |
| Renal replacement therapy *n* (%) | 18 (45.0) | 20 (44.4) | 17 (35.4) | 25 (64.1) | 0.062 |
| 90-d mortality, *n* (%) | 11 (27.5) | 13 (28.9) | 18 (37.5) | 28 (71.8) | 0.00090 |

IU = international units, LV = left ventricle, LVEDA = left ventricular end-diastolic area, RV = right ventricular, TTE = transthoracic echocardiography.
[a]Due to incomplete tricuspid regurgitation continuous wave Doppler signal.
Data are presented as *n* (%) or median (interquartile range).
Categorical data are compared with a $\chi^2$. Continuous data are compared using a Kruskal-Wallis test.

phenotype had abnormal end-systolic LVEI, with a similar, albeit nonsignificant trend observed in end-diastolic LVEI (Table 2).

Furthermore, in 51 patients that underwent prone positioning within 24 hours of TTE, those with RV dilation with systolic impairment had a greater percentage reduction in $Paco_2$ and dead space fraction in response to prone ventilation compared with those without (**s-Fig. 3**, http://links.lww.com/CCM/G572; legend, http://links.lww.com/CCM/G573).

## DISCUSSION

The main finding of this study is that RV dilation with systolic impairment was independently associated with mortality, whereas either disease state alone was not. Therefore, combining the European and American definitions of RVD (17, 18) identified the RV phenotype with the strongest association with mortality. This may be because it combines pulmonary pathology (associated with RV systolic impairment) with renal dysfunction (associated with RV dilation).

In over 700 patients with non-COVID-19 ARDS, Mekontso Dessap (1) identified severe RV dilation (RV:LVEDA greater than 1, with an evidence of septal dyskinesia) independently associated with mortality. However, they found, just as we did, that RV dilation (albeit with septal dyskinesia)—termed acute cor pulmonale—did not (1). This may be because a substantial proportion of this cohort had preserved RV systolic function. RV size negatively correlated with urine output, in keeping with studies associating markers of ventricular stretch with acute kidney injury (AKI) development (29). However, patients with isolated RV dilation (with normal RV systolic function) did not have an increased need for RRT, whereas those with RV dilation with systolic impairment did. This may be because acute RV dilation concomitantly increases stroke volume (as predicted by the Frank-Starling mechanism), somewhat preserving RV systolic function but at the expense of renal venous congestion. Patients with RV dilation with systolic impairment may have exhausted this compensatory response and are unable to preserve RV forward flow, contributing to an increased need for RRT and mortality. This mechanism of organ dysfunction with RV determined alterations in systemic blood flow is supported by ultrasound studies, demonstrating disrupted renal blood flow in accordance with AKI severity in COVID-19 (30). The increased prevalence of RV pressure overload and trend toward increased prevalence of RV volume overload (as estimated by the LVEI) in this RV phenotype may also contribute to its strong association with mortality.

The prognostic implication of RV systolic impairment in ARDS has not been studied in detail (31) as most studies focus on RV size instead (1, 15, 16, 32). RV systolic impairment did not independently associate with mortality.

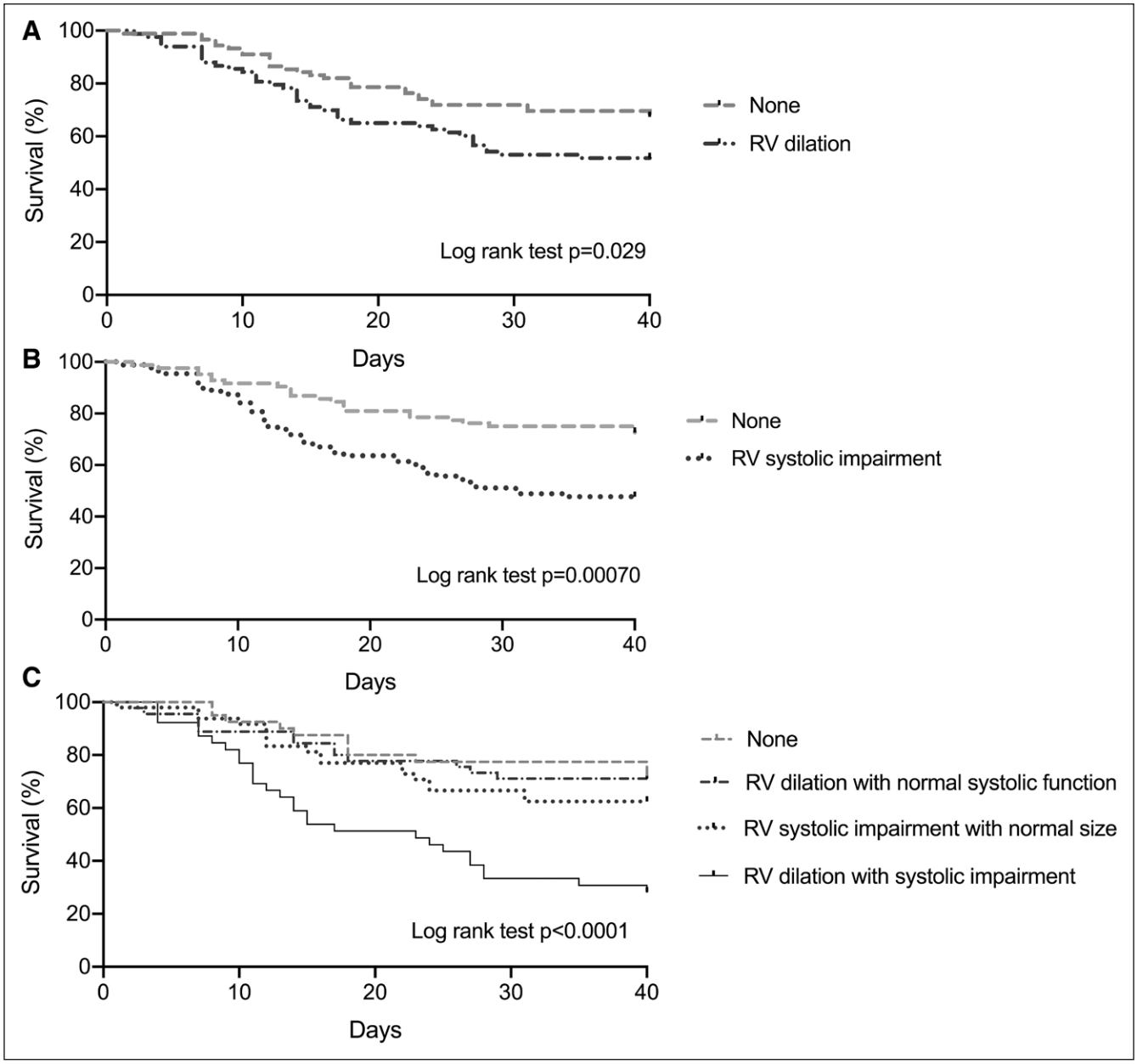


**Figure 2.** Kaplan-Meier curves of right ventricular (RV) phenotypes. Kaplan-Meier curves with log rank test. **A**, Patients with RV dilation. **B**, Patients with RV systolic impairment. **C**, Patients with RV dilation with normal systolic function, RV systolic impairment with normal size, and RV dilation with systolic impairment.

This may be because patients with isolated RV systolic impairment (with normal RV size) had a similar mortality to the normal RV phenotype. This cohort had small RV size that may have resulted in RVFAC underestimating their RV systolic efficiency. Alternatively, RV dilation with impairment could convey an added pathophysiological burden. Although there are different definitions of RVD in the literature, either using dilation (17) or systolic impairment (18), combining both markers identified the phenotype that independently associated with mortality.

RVD in ARDS may develop due to increased pulmonary vascular tone resulting from endothelial injury, micro- or macrothrombosis, hypoxic pulmonary vasoconstriction, hypercapnia, acidosis, and mechanical ventilation increasing transpulmonary pressure (TPP) (2). We and others demonstrate that RV systolic impairment correlates with many of these factors in COVID-19 ARDS, including hypoxia/hypercapnia (when measured at the time of TTE, but not when values are averaged over the entire day

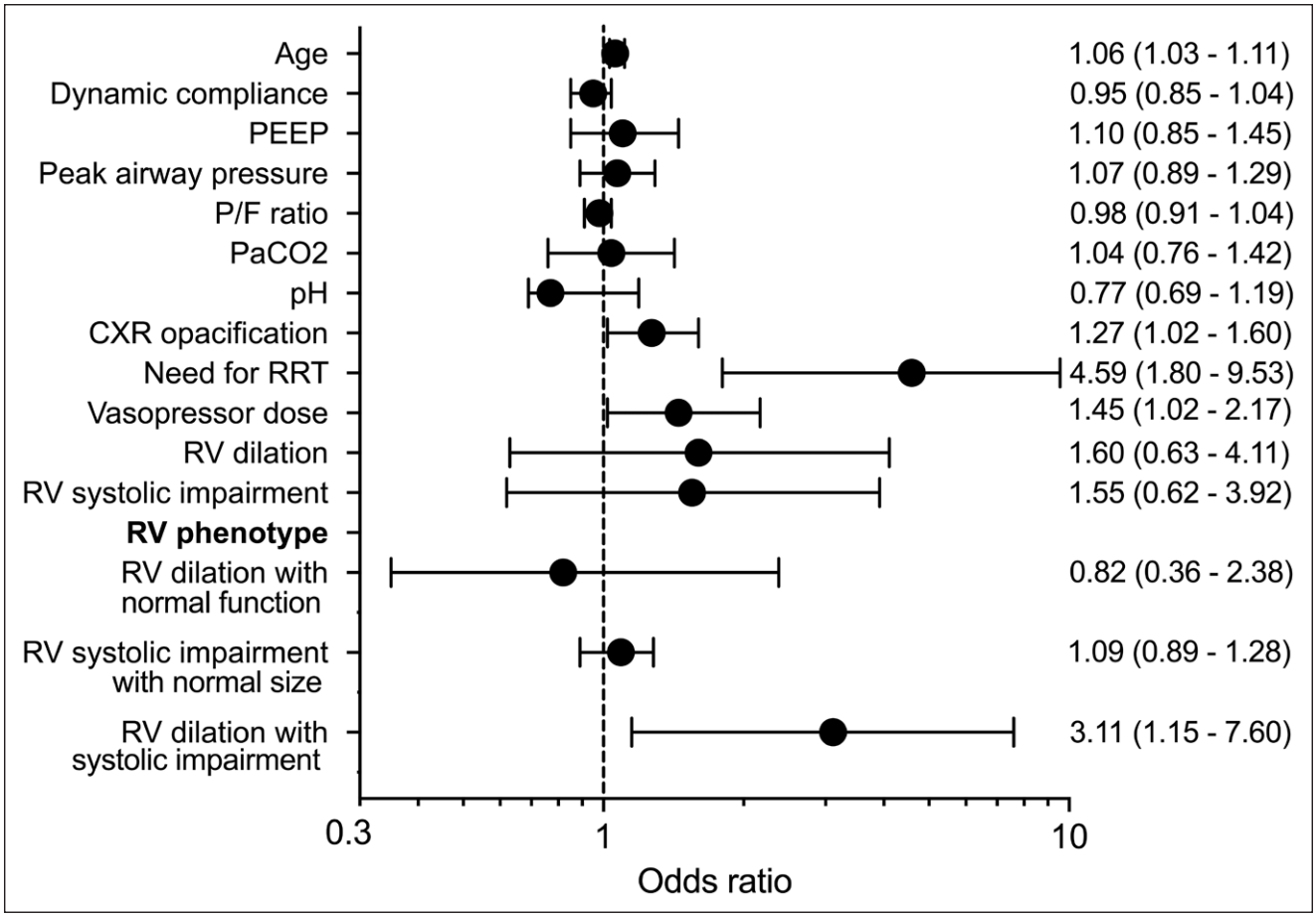


**Figure 3.** Odds ratio for 90-d mortality after multivariate logistic regression analysis. Numbers outline odds ratio with 95% CIs following multivariate logistic regression analysis. CXR = chest radiograph, P/F = $Pao_2$:$Fio_2$ ratio, PEEP = positive end-expiratory pressure, RRT = renal replacement therapy, RV = right ventricular.

[12]), lung inflammation (chest radiograph opacification and C-reactive protein [12, 26]), and factors influencing TPP ($P_{peak}/C_{dyn}$). However, these observational data are unable to conclude whether RV systolic impairment exacerbates these perturbed parameters or is merely a bystander of disease severity. Some studies suggest that troponin release and myocardial dysfunction are better explained by immune-mediated cell death processes in the context of hyperinflammation (33, 34). These processes have been found to occur in the lungs in ARDS (35), in the heart in ischemia-reperfusion injury (36), and in the kidney in AKI (37). Thus, RVD (and extrapulmonary organ) may mirror the enormous burden of pulmonary cell stress and systemic microvascular dysfunction in COVID-19 (38, 39) but also where the dysfunctional RV further contributes to remote organ dysfunction through harmful reductions in organ blood flow.

Prone ventilation recruits collapsed dorsal lung parenchyma, reduces ventilation:perfusion (VQ) mismatch, lowers pulmonary vascular resistance, and improves RV three-dimensional (3-D) geometry, thereby improving RV function (3). Although there was no difference in the P/F ratio response, patients with RV dilation with systolic impairment had a greater reduction in $Paco_2$ with prone ventilation than those without, with the latter better predicting survival from ARDS (40). This appeared independent of lung recruitment as no difference in the change in lung compliance was observed. Instead, improved VQ matching or optimized RV forward flow through alteration of its 3-D geometry (resulting in greater reductions in dead space fraction) may occur in patients with RVD. We were unable to measure post-prone RV function to confirm this hypothesis (41).

TAPSE poorly delineated the extent of RV systolic impairment, and RVFAC may be a superior measure of RV function in COVID-19 ARDS, with numerous

studies reporting isolated RV radial impairment with preserved longitudinal function not described in non-COVID ARDS (12, 42, 43). Similarly, septal dyskinesia was uncommon and inadequately represented the extent of RVD. This validates newer definitions of RVD that no longer include this parameter (17). Although case reports of LV impairment in the context of myocarditis were initially described (44, 45), we and others have reported mostly normal/hyperdynamic LV function in COVID-19 patients (10, 12, 26).

To the best of our knowledge, this is the largest analysis to date of TTE performed in mechanically ventilated COVID-19 ARDS patients. The cohort was homogenous and generalizable (all receiving positive pressure ventilation with excellent adherence to lung protective ventilation). TTE requests were screened (limited to those with evidence of myocardial injury), the majority (greater than 80%) were performed within 7 days of ICU admission by experienced echocardiographers using a standardized protocol, with detailed clinical parameters recorded at the time of the study.

Nonetheless, this study has important limitations. The findings are subject to selection bias as not all patients with COVID-19 ARDS received TTE and we cannot comment on the overall prevalence of RVD in our cohort. However, approximately 65% of our cohort (172/267) did receive TTE. It was not possible to standardize the day after ICU admission that the TTE was performed or assess longitudinal changes in RV function. Nonetheless, these limitations demonstrate the real-world applicability of our findings, where ICU physicians must interpret TTE findings requested at a time of clinical need. The measurement of RV global longitudinal strain or RV free-wall strain, which have previously been demonstrated to be superior to RVFAC/TAPSE in assessment of RVD (46), was also not possible. Measurement of LVEI was not possible in every patient due to inadequate views. Pulmonary hypertension estimation using TTE in critically ill patients is challenging; however, we adhered to guideline recommendations (29). Although we demonstrate that RV systolic function correlated with numerous ventilatory parameters, the strength of the correlations was occasionally weak leaving the clinical significance of some of the comparisons potentially suspect. Finally, although to the best of our knowledge this is the largest TTE analysis in COVID-19 ARDS, the sample size is still small.

The finding that an RV phenotype (dilation with systolic impairment) is independently associated with mortality requires prospective validation in larger COVID-19 and non-COVID 19 ARDS cohorts, through serial assessment of RV function at fixed time intervals, such as every 72-hour postintubation. Evaluation of potential RV protective measures, such as personalized ventilation strategies, including targeted use of prone ventilation, inhaled nitric oxide, and inotrope therapy in this prognostically enriched phenotype, could then be undertaken. Longitudinal analysis of whether RV protective measures reduce transition to this phenotype should also be performed.

## CONCLUSIONS

In patients with COVID-19 ARDS who underwent TTE, RV systolic function correlated with pulmonary pathophysiology, whereas RV dilation was associated with renal dysfunction. The combination of RV dilation with systolic impairment was associated with the greatest risk of death, compared with the presence of either disease state in isolation.

## ACKNOWLEDGMENTS:

We thank Dr. Peter Nightingale, University of Birmingham, for help with the statistical analysis.

1 *Birmingham Acute Care Research Group, University of Birmingham, Birmingham, United Kingdom*

2 *Department of Anaesthetics and Critical Care, Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom.*

3 *Department of Cardiology, Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom.*

*Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).*

*Drs. Parekh and Patel received support for article research from Research Councils UK. Dr. Parekh received support for article research from the National Institute for Health Research. Dr. Bangash received funding from the Intensive Care Society. The remaining authors have disclosed that they do not have any potential conflicts of interest.*

*For information regarding this article, E-mail: minesh.chotalia@nhs.net*

## REFERENCES


1. Mekontso Dessap A, Boissier F, Charron C, et al: Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: Prevalence, predictors, and clinical impact. *Intensive Care Med* 2016; 42:862–870
2. Zochios V, Parhar K, Tunnicliffe W, et al: The right ventricle in ARDS. *Chest* 2017; 152:181–193
3. Vieillard-Baron A, Charron C, Caille V, et al: Prone positioning unloads the right ventricle in severe ARDS. *Chest* 2007; 132:1440–1446
4. Grasselli G, Tonetti T, Protti A, et al; Collaborators: Pathophysiology of COVID-19-associated acute respiratory distress syndrome: A multicentre prospective observational study. *Lancet Respir Med* 2020; 8:1201–1208
5. Michard F, Vieillard-Baron A: Critically ill patients with COVID-19: Are they hemodynamically unstable and do we know why? *Intensive Care Med* 2021; 47:254–255
6. Patel BV, Arachchillage DJ, Ridge CA, et al: Pulmonary angiopathy in severe COVID-19: Physiologic, imaging, and hematologic observations. *Am J Respir Crit Care Med* 2020; 202:690–699
7. Ackermann M, Verleden SE, Kuehnel M, et al: Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020; 383:120–128
8. Akhmerov A, Marbán E: COVID-19 and the heart. *Circ Res* 2020; 126:1443–1455
9. Li Y, Li H, Zhu S, et al: Prognostic value of right ventricular longitudinal strain in patients with COVID-19. *JACC Cardiovasc Imaging* 2020; 13:2287–2299
10. D'Alto M, Marra AM, Severino S, et al: Right ventricular-arterial uncoupling independently predicts survival in COVID-19 ARDS. *Crit Care* 2020; 24:670
11. Vieillard-Baron A, Charron C, Tran S, et al: Echocardiographic patterns in critically ill COVID-19 patients. 2020. Available at: https://doi.org/10.21203/rs.3.rs-52431/v1. Accessed June 11, 2021
12. Bleakley C, Singh S, Garfield B, et al: Right ventricular dysfunction in critically ill COVID-19 ARDS. *Int J Cardiol* 2020; 327:251–258
13. Vieillard-Baron A, Prigent A, Repessé X, et al: Right ventricular failure in septic shock: Characterization, incidence and impact on fluid responsiveness. *Crit Care* 2020; 24:630
14. Vieillard-Baron A, Price LC, Matthay MA: Acute cor pulmonale in ARDS. *Intensive Care Med* 2013; 39:1836–1838
15. Repessé X, Charron C, Vieillard-Baron A: Right ventricular failure in acute lung injury and acute respiratory distress syndrome. *Minerva Anestesiol* 2012; 78:941–948
16. Vieillard-Baron A, Bouferrache K, Charron C: Right ventricular function evaluation in acute respiratory distress syndrome: Back to the future. *Crit Care Med* 2010; 38:1909–1910
17. Vieillard-Baron A, Naeije R, Haddad F, et al: Diagnostic workup, etiologies and management of acute right ventricle failure: A state-of-the-art paper. *Intensive Care Med* 2018; 44:774–790
18. Rudski LG, Lai WW, Afilalo J, et al: Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; 23:685–713
19. Zochios V, Parhar K, Vieillard-Baron A: Protecting the right ventricle in ARDS: The role of prone ventilation. *J Cardiothorac Vasc Anesth* 2018; 32:2248–2251
20. Ferguson ND, Fan E, Camporota L, et al: The Berlin definition of ARDS: An expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012; 38:1573–1582
21. Stahl CA, Möller K, Schumann S, et al: Dynamic versus static respiratory mechanics in acute lung injury and acute respiratory distress syndrome. *Crit Care Med* 2006; 34:2090–2098
22. Beitler JR, Thompson BT, Matthay MA, et al: Estimating dead-space fraction for secondary analyses of acute respiratory distress syndrome clinical trials. *Crit Care Med* 2015; 43:1026–1035
23. Khanna A, English SW, Wang XS, et al; ATHOS-3 Investigators: Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med* 2017; 377:419–430
24. Mason SE, Dieffenbach PB, Englert JA, et al: Semi-quantitative visual assessment of chest radiography is associated with clinical outcomes in critically ill patients. *Respir Res* 2019; 20:218
25. Afilalo J: The clinical frailty scale: Upgrade your eyeball test. *Circulation* 2017; 135:2025–2027
26. Mahmoud-Elsayed HM, Moody WE, Bradlow WM, et al: Echocardiographic findings in patients with COVID-19 pneumonia. *Can J Cardiol* 2020; 36:1203–1207
27. Zaidi A, Knight DS, Augustine DX, et al; Education Committee of the British Society of Echocardiography: Echocardiographic assessment of the right heart in adults: A practical guideline from the British Society of Echocardiography. *Echo Res Pract* 2020; 7:G19–G41
28. Galiè N, Humbert M, Vachiery JL, et al; ESC Scientific Document Group: 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016; 37:67–119
29. Haines R, Crichton S, Wilson J, et al: Cardiac biomarkers are associated with maximum stage of acute kidney injury in critically ill patients: A prospective analysis. *Crit Care* 2017; 21:88
30. Renberg M, Jonmarker O, Kilhamn N, et al: Renal resistive index is associated with acute kidney injury in COVID-19 patients treated in the intensive care unit. *Ultrasound J* 2021; 13:3
31. Shah TG, Wadia SK, Kovach J, et al: Echocardiographic parameters of right ventricular function predict mortality in acute respiratory distress syndrome: A pilot study. *Pulm Circ* 2016; 6:155–160
32. Vieillard-Baron A, Schmitt JM, Augarde R, et al: Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: Incidence, clinical implications, and prognosis. *Crit Care Med* 2001; 29:1551–1555
33. Amgalan D, Pekson R, Kitsis RN: Troponin release following brief myocardial ischemia: Apoptosis versus necrosis. *JACC Basic Transl Sci* 2017; 2:118–121

34. King KR, Aguirre AD, Ye YX, et al: IRF3 and type I interferons fuel a fatal response to myocardial infarction. *Nat Med* 2017; 23:1481–1487
35. Cheng KT, Xiong S, Ye Z, et al: Caspase-11-mediated endothelial pyroptosis underlies endotoxemia-induced lung injury. *J Clin Invest* 2017; 127:4124–4135
36. Toldo S, Mauro AG, Cutter Z, et al: Inflammasome, pyroptosis, and cytokines in myocardial ischemia-reperfusion injury. *Am J Physiol Heart Circ Physiol* 2018; 315:H1553–H1568
37. Miao N, Yin F, Xie H, et al: The cleavage of gasdermin D by caspase-11 promotes tubular epithelial cell pyroptosis and urinary IL-18 excretion in acute kidney injury. *Kidney Int* 2019; 96:1105–1120
38. Favaron E, Ince C, Hilty MP, et al: Capillary leukocytes, microaggregates, and the response to hypoxemia in the microcirculation of coronavirus disease 2019 patients. *Crit Care Med* 2021; 49:661–670
39. Metkus TS, Guallar E, Sokoll L, et al: Prevalence and prognostic association of circulating troponin in the acute respiratory distress syndrome. *Crit Care Med* 2017; 45:1709–1717
40. Gattinoni L, Vagginelli F, Carlesso E, et al; Prone-Supine Study Group: Decrease in $PaCO_2$ with prone position is predictive of improved outcome in acute respiratory distress syndrome. *Crit Care Med* 2003; 31:2727–2733
41. Giustiniano E, Fazzari F, Bragato RM, et al: Trans-thoracic echocardiography in prone positioning COVID-19 patients: A small case series. *SN Compr Clin Med* 2020 Sep 15. [online ahead of print]
42. Pagnesi M, Baldetti L, Beneduce A, et al: Pulmonary hypertension and right ventricular involvement in hospitalised patients with COVID-19. *Heart* 2020; 106:1324–1331
43. D'Andrea A, Scarafile R, Riegler L, et al: Right ventricular function and pulmonary pressures as independent predictors of survival in patients with COVID-19 pneumonia. *JACC Cardiovasc Imaging* 2020; 13:2467–2468
44. Zeng JH, Liu YX, Yuan J, et al: First case of COVID-19 complicated with fulminant myocarditis: A case report and insights. *Infection* 2020; 48:773–777
45. Sawalha K, Abozenah M, Kadado AJ, et al: Systematic review of COVID-19 related myocarditis: Insights on management and outcome. *Cardiovasc Revasc Med* 2021; 23:107–113
46. Lu KJ, Chen JX, Profitis K, et al: Right ventricular global longitudinal strain is an independent predictor of right ventricular function: A multimodality study of cardiac magnetic resonance imaging, real time three-dimensional echocardiography and speckle tracking echocardiography. *Echocardiography* 2015; 32:966–974