# Cardiac Biomarkers and Right Ventricular Dysfunction Are Associated Independently With 1-Year Mortality in Patients With COVID-19 Receiving Mechanical Ventilation

## A Prospective Cohort Study

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**BACKGROUND:** The cardiac biomarkers N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin frequently are raised in patients with acute COVID-19. As a secondary analysis of the Right Ventricular Dysfunction in Ventilated Patients With COVID-19 study, we sought to determine the association between raised cardiac biomarkers and 1-year mortality in patients with COVID-19 receiving invasive mechanical ventilation (IMV). As an exploratory investigation, we combined point-of-care echocardiography and cardiac biomarker analyses to determine whether the biomarker signal represented a global or regional cardiac injury.

**STUDY QUESTION:** Are abnormal cardiac biomarker levels associated with 1-year mortality in patients with COVID-19 requiring IMV?

**STUDY DESIGN AND METHODS:** In this prospective cardiac biomarker and echocardiography study in patients with COVID-19 across 10 ICUs in the west of Scotland, patients underwent contemporaneous cardiac biomarker testing with point-of-care echocardiography between days 2 and 14 after intubation. Survival analyses was performed using univariable log-rank and multivariable Cox regression.

**RESULTS:** One hundred twenty-one patients were recruited between September 2, 2020, and March 22, 2021. At 1 year, 57.6% of patients (68 of 118) had died. Patients with abnormal NT-proBNP levels and patients with abnormal troponin levels showed a 1-year mortality incidence of 71.4% (50 of 70) and 80.4% (45 of 56), respectively. Both abnormal NT-proBNP and abnormal troponin levels were associated with 1-year mortality ($P < .001$ for both). Abnormal troponin level was associated with subjective right ventricular dysfunction (RVD; $P = .003$), and no association with subjective left ventricular dysfunction was found ($P = .342$). On multivariable analysis, abnormal NT-proBNP level, abnormal troponin level, and subjective RVD were associated independently with 1-year mortality (hazard ratios, 2.82 [95% CI, 1.19-6.67], 2.84 [95% CI, 1.44-5.62], and 2.09 [95% CI, 1.07-4.07], respectively).

**INTERPRETATION:** Abnormal NT-proBNP level, abnormal troponin level, and subjective RVD are associated independently with 1-year mortality in patients with COVID-19 receiving IMV. Cardiac biomarker testing and point-of-care echocardiography are available readily during ICU admission and may identify a group of patients who are at very high risk of poor outcomes.

**TRIAL REGISTRY:** ClinicalTrials.gov; No.: NCT04764032; URL: www.clinicaltrials.gov

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**KEY WORDS:** ARDS; cardiac biomarkers; COVID-19; echocardiography; intensive care; right ventricle

## Take-home Points

**Study Question:** Are abnormal levels of cardiac biomarkers (N-terminal pro-brain natriuretic peptide and troponin) associated with long-term outcomes in mechanically ventilated patients with COVID-19, and as an exploratory investigation, can the use of point-of-care echocardiography localize where in the heart this biomarker signal is coming from?

**Results:** Abnormal N-terminal pro-brain natriuretic peptide level, abnormal troponin level, and subjective right ventricular dysfunction are associated independently with 1-year mortality in mechanically ventilated patients with COVID-19. When all three were present, the mortality rate was 92.3%.

**Interpretation:** Cardiac biomarker testing and point-of-care echocardiography are available readily during intensive care admission and may help to identify patients at risk of very poor outcomes.

As the COVID-19 pandemic enters its fourth year, focus has shifted toward investigating the longer-term outcomes of the disease. Cardiac biomarker assessment has received much attention during the COVID-19 pandemic. Biomarker measures of hemodynamic cardiac stress and myocardial injury, N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin, respectively, were investigated extensively before the COVID-19 pandemic as prognostic indicators. Raised NT-proBNP and troponin levels have been shown to be associated with mortality in patients with sepsis,[1,2] pulmonary thromboembolism (PTE),[3,4] and non-COVID-19 ARDS.[5,6] In patients with COVID-19, NT-proBNP and troponin levels have been shown to be raised and are associated with early and late mortality in mixed populations of patients requiring and not requiring invasive mechanical ventilation (IMV).[7-10] The association between cardiac biomarkers and late mortality has not been described in a patient population receiving IMV. As a secondary analysis of the Right Ventricular Dysfunction in Ventilated Patients With COVID-19 (COVID-RV) study (a prospective multicenter ICU clinician-led cardiac biomarker and echocardiography study in patients with COVID-19[11]), we sought to examine the association between raised cardiac biomarker levels and 1-year mortality in a population of patients with COVID-19, all of whom received IMV.

It is unclear whether the increase in cardiac biomarkers observed in patients with COVID-19 represents global hemodynamic cardiac stress or cardiac injury, or if this is a phenomenon localized to either cardiac ventricle. Point-of-care echocardiography in the ICU is finding increased clinical usefulness and may aid identification of the anatomic site of the cardiac biomarker signal. An important aspect of point-of-care echocardiography underpinning its pragmatic usefulness is the subjective assessment of right ventricular (RV) and left ventricular (LV) function,[12,13] with a global survey demonstrating that subjective RV dysfunction (RVD) is the most common measure used clinically (more so than conventional quantitative measures).[14] As an exploratory investigation, we sought to determine whether the cardiac biomarker signal represented a global or regional cardiac injury by combining subjective echocardiography assessment of RV and LV function with NT-proBNP and troponin analyses. Cardiac biomarkers and point-of-care echocardiography are highly clinically relevant measurements, often obtained at ICU admission. We hypothesized that their combined use may be able to identify patients at risk of poor outcomes in the ICU and beyond.

## Study Design and Methods

The study methods have been reported previously.[15] Briefly, the COVID-RV study was a prospective observational cohort study of cardiac biomarkers and echocardiography conducted across 10 ICUs in NHS Scotland. Ethical approval was obtained from Scotland A Research Ethics Committee (Identifier: 20/SS/0059) on June 5, 2020. Procedures during this study were in accordance with the ethical

**ABBREVIATIONS:** BSE = British Society of Echocardiography; COVID-RV = Right Ventricular Dysfunction in Ventilated Patients With COVID-19; CVP = central venous pressure; FICE = focused intensive care echocardiography; IMV = invasive mechanical ventilation; LV = left ventricular; LVD = left ventricular dysfunction; NT-proBNP = N-terminal pro-brain natriuretic peptide; PEEP = positive end-expiratory pressure; PTE = pulmonary thromboembolism; RV = right ventricular; RVD = right ventricular dysfunction

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standards of this committee and the tenets of the Declaration of Helsinki of 1975. A legal representative provided informed consent for all patients. The COVID-RV study was registered at ClinicalTrials.gov (Identifier: NCT04764032). We included patients older than 16 years with confirmed COVID-19 infection with severe acute respiratory failure requiring invasive positive pressure ventilation. Exclusion criteria included: pregnancy, ongoing participation in investigational research that may undermine the scientific basis of the study, previous participation in the COVID-RV study, requirement for extracorporeal membrane oxygenation, and end-of-life care (where the patient was not expected to survive > 24 h). Study data were collected and stored electronically on Research Electronic Data Capture software (Vanderbilt University), hosted by the University of Glasgow. All data were collected prospectively. These included baseline demographics, chronic comorbidities, acute comorbidities since hospital admission, severity of COVID-19 illness, clinical data relating to putative mechanisms for RVD, and follow-up data. One-year survival was assessed by accessing patient electronic records at 1 year after enrolment. On the day of echocardiography, blood samples were obtained from patients for measurement of high-sensitivity troponin (T or I, subject to the assay used at each site) and NT-proBNP levels. Abnormal values were defined for troponin (high-sensitivity troponin T ≥ 15 ng/L or high-sensitivity troponin I ≥ 34 ng/L for male patients; and high-sensitivity troponin I ≥ 16 ng/L for female patients) and for NT-proBNP (> 300 ng/L).[16-18]

Participants underwent a single transthoracic echocardiography study between day 2 and day 14 after intubation. To reflect the clinical practice of point-of-care echocardiography in the ICU, imaging was in keeping with the protocol for a focused intensive care echocardiography (FICE) scan.[19] A FICE scan rapidly assesses for significant cardiac pathologic features in patients receiving intensive care. The image set includes parasternal short-axis, parasternal long-axis, apical four-chamber, and subcostal views. Subjective RVD and subjective LV dysfunction (LVD) were assessed at the bedside by so-called eyeballing of ventricular function (a commonly used method in clinical practice).[20,21] Severe RV dilation was assessed visually by the echocardiographer from the apical four-chamber view at end-diastole and was present when the RV to LV area ratio was deemed to be > 1. Interventricular septal flattening was determined from the parasternal short-axis view. Echocardiographers were not masked to the clinical status of patients in all cases. The accreditation status of echocardiographers was recorded, including: none, FICE or FICE mentor (50-scan logbook for accreditation),[19] and British Society of Echocardiography (BSE) critical care or BSE full accreditation (250-scan logbook for accreditation).[22] Echocardiography experience was split into nonexperts (no accreditation, FICE, and FICE mentors) and expert echocardiographers (BSE critical care and full BSE).

The primary outcome of this secondary analysis was the prevalence of abnormal levels of cardiac biomarkers (NT-proBNP and troponin) during ICU admission and their association with 1-year mortality. Exploratory outcomes included the prevalence of subjective RVD and subjective LVD and their association with 1-year mortality. Given that this study was a secondary analysis primarily investigating cardiac biomarkers, no power calculation was performed.

We analyzed the association of abnormal cardiac biomarkers with 1-year mortality using the Pearson $\chi^2$ test and Fisher exact test as appropriate. For survival analyses, the Kaplan-Meier plot with log-rank univariable analysis was used, followed by multivariable Cox regression analysis predicting 1-year mortality from the presence or absence of abnormal cardiac biomarker levels and the presence or absence of subjective ventricular dysfunction. An a priori plan to adjust for baseline characteristics (age, sex, and ethnicity), phase of disease (time from intubation to echocardiography), and baseline severity of illness (Acute Physiology and Chronic Health Evaluation II score) during multivariable analysis was implemented.[15,23] Variables in the Cox regression analysis were assessed for an interaction between time variable and covariate to establish that the proportional hazard's function assumption was met. Variables in the multivariable model were analyzed for multicollinearity using the variance inflation factor. A variance inflation factor of > 5 for a variable was considered to demonstrate multicollinearity. Ordinal and categorical data are presented as number (proportion). Between-group differences were assessed using the Student *t* test or Mann-Whitney *U* test for continuous variables. No correction was performed for multiple hypothesis testing. Statistical analyses were performed using SPSS version 28.0.0.0 software (IBM).

## Results

One hundred twenty-one patients were recruited to the COVID-RV study between September 2, 2020, and March 22, 2021, representing 24% of patients with COVID-19 admitted to participating study centers over this period. Of these 121 patients, NT-proBNP was measured in 106 patients and troponin was measured in 116 patients. Seventy of 116 patients (66.0%) showed abnormal NT-proBNP levels, and 56 of 116 patients (48.3%) showed abnormal troponin levels (Table 1). One hundred eighteen patients underwent echocardiography (Table 2).

The overall 1-year mortality incidence was 57.6% (68 of 118 patients) (e-Table 1). Patients with abnormal NT-proBNP levels showed a 1-year mortality incidence of 71.4% (50 of 70 patients), compared with 25% (9 of 36 patients) in patients with normal NT-proBNP levels. Patients with abnormal troponin levels also showed a higher incidence of 1-year mortality of 80.4% (45 of 56 patients), compared with 36.7% (22 of 60 patients) in patients with normal troponin. On univariate analysis, abnormal NT-proBNP and abnormal troponin levels were associated with 1-year mortality ($P < .001$ for both) (Fig 1, e-Table 1).

Patients with abnormal NT-proBNP levels were older, showed higher Acute Physiology and Chronic Health Evaluation II scores, showed higher Coronavirus Clinical Characterization Consortium scores, and were more likely to be receiving renal replacement therapy ($P \leq .033$ for all) (Table 1).[24] A trend was found between patients with abnormal NT-proBNP levels and those not having received IV corticosteroids ($P = .052$). Of the clinical parameters on the day of cardiac biomarker testing, abnormal NT-proBNP level was associated with higher C-reactive protein level, higher central venous pressure (CVP), increased levels of

**TABLE 1** ] Patient Characteristics From Hospital Admission to Day of Echocardiography

| Characteristic | All (N = 118) | NT-proBNP Level | | | Troponin Level | | |
|---|---|---|---|---|---|---|---|
| | | Normal (n = 36) | Abnormal (n=70) | *P* Value | Normal (n = 60) | Abnormal (n = 56) | *P* Value |
| Age, y | 60 (53-68) | 58 (49-63) | 62 (53.8-69) | .033[a] | 58.5 (49.3-66) | 64 (54.5-68) | .052[a] |
| Male sex | 78 (66.1%) | 27 (75%) | 44 (62.9%) | .208[b] | 40 (66.7%) | 37 (66.1%) | .946[b] |
| BMI, kg/m$^2$ | | | | .989[a] | | | .408[a] |
| No. (No. missing) | 115 (3) | 35 (1) | 68 (2) | | 58 (2) | 55 (1) | |
| Median (IQR) | 31.6 (25.3-35.8) | 32.1 (28.4-37.7) | 31.6 (28.5-35.8) | | 32.2 (28.6-37.2) | 31.0 (28.0-33.8) | |
| Ethnicity | | | | .500[c] | | | .126[b] |
| No. (No. missing) | 117 (1) | 35 (1) | 70 (0) | | 59 (1) | 56 (0) | |
| White | 105 (89%) | 30 (85.7%) | 64 (91.4%) | | 50 (84.7%) | 53 (94.6%) | |
| Non-White[d] | 12 (10.2%) | 5 (14.3%) | 6 (8.6%) | | 9 (15.3%) | 3 (5.4%) | |
| Clinical frailty score | | | | .273[a] | | | .927[a] |
| No. (No. missing) | 117 (1) | 36 (0) | 70 (0) | | 60 (0) | 56 (0) | |
| Median (IQR) | 2 (2-3) | 2 (2-3) | 2 (2-3) | | 2 (2-3) | 2 (2-3) | |
| APACHE II score | | | | .005[a] | | | .018[a] |
| No. (No. missing) | 113 (5) | 34 (2) | 69 (1) | | 59 (1) | 53 (3) | |
| Median (IQR) | 16 (13-19) | 15 (12.8-16) | 17 (13-21.5) | | 15 (13-17) | 17 (14-22) | |
| CCCC | | | | .004[e] | | | .198[e] |
| No. (No. missing) | 108 (10) | 34 (2) | 64 (6) | | 56 (4) | 50 (6) | |
| Mean ± SD | 10.2 ±2.8 | 9.1 ±2.5 | 0.8 ±2.8 | | 9.9 ±2.8 | 10.6 ±2.8 | |
| Comorbidities | | | | | | | |
| Hypertension | 40 (33.9%) | 11 (30.6%) | 21 (30.0%) | .953[b] | 18 (30.0%) | 22 (39.3%) | .293[b] |
| Coronary artery disease | 11 (9.3%) | 4 (11.1%) | 6 (8.6%) | .824[c] | 4 (6.7%) | 7 (12.5%) | .274[c] |
| Diabetes | 34 (28.8%) | 8 (22.2%) | 23 (32.9%) | .254[b] | 12 (20.0%) | 21 (37.5%) | .037[b] |
| Asthma | 17 (14.4%) | 5 (13.9%) | 11 (15.7%) | .804[b] | 7 (11.7%) | 9 (16.1%) | .492[b] |
| COPD | 10 (8.5%) | 1 (2.8%) | 8 (11.4%) | .130[c] | 7 (11.7%) | 3 (5.4%) | .325[c] |
| Treatments before intubation | | | | | | | |
| IV corticosteroids | 75 (63.6%) | 27 (75%) | 39 (55.7%) | .052[b] | 44 (73.3%) | 31 (55.4%) | .043[b] |
| Noninvasive ventilation | 81 (68.6%) | 26 (72.2%) | 48 (68.5%) | .698[b] | 42 (70.0%) | 38 (67.9%) | .803[b] |
| High-flow nasal oxygen | 69 (58.5%) | 23 (63.9%) | 41 (58.6%) | .596[b] | 35 (58.3%) | 34 (60.7%) | .794[b] |
| Awake self-proning | 58 (49.2%) | 18 (50%) | 35 (50%) | > .999[b] | 31 (51.7%) | 27 (48.2%) | .710[b] |

*(Continued)*

**TABLE 1** ] *(Continued)*

| Characteristic | All (N = 118) | NT-proBNP Level | | | Troponin Level | | |
|---|---|---|---|---|---|---|---|
| | | Normal (n = 36) | Abnormal (n=70) | *P* Value | Normal (n = 60) | Abnormal (n = 56) | *P* Value |
| Acute comorbidities (acquired since hospital admission) | | | | | | | |
| New arrhythmias | 18 (15.3%) | 4 (11.1%) | 12 (17.1%) | .715[c] | 7 (11.7%) | 10 (17.9%) | .362[c] |
| Confirmed or suspected PTE | | | | .189[c] | | | .045[c] |
| Radiologically confirmed | 5 (4.2%) | 0 (0%) | 5 (7.1%) | | 0 (0%) | 5 (8.9%) | |
| Clinically suspected | 5 (4.2%) | 0 (0%) | 3 (4.3%) | | 2 (3.3%) | 3 (5.4%) | |
| No | 106 (89.8%) | 36 (100%) | 61 (87.1%) | | 58 (96.7%) | 47 (83.9%) | |
| Unknown | 2 (1.7%) | 0 (0%) | 1 (1.4%) | | 0 (0%) | 1 (1.8%) | |
| Acute coronary syndrome | 6 (5.1%) | 0 (0%) | 4 (5.7%) | .297[c] | 0 (0%) | 6 (10.7%) | .011[c] |
| Requirement for RRT | 20 (16.9%) | 1 (2.8%) | 17 (24.3%) | .005[c] | 7 (11.7%) | 13 (23.2%) | .111[c] |
| Requirement for prone invasive ventilation | 82 (69.5%) | 25 (69.4%) | 51 (72.9%) | .917[c] | 38 (63.3%) | 42 (75%) | .204[c] |
| Clinical parameters on day of cardiac biomarker testing or echocardiography | | | | | | | |
| $Pa_{O_2}$, kPa | | | | .837[a] | | | .942[a] |
| No. (No. missing) | 117 (1) | 36 (0) | 69 (1) | | 60 (0) | 55 (1) | |
| Median (IQR) | 9.1 (8.5-10.0) | 9.1 (8.1-11.0) | 9.0 (8.6-9.9) | | 9.2 (8.3-10.2) | 9.0 (8.5-10.0) | |
| $Pa_{O_2}$ to $F_{IO_2}$ ratio | | | | .073[a] | | | .030[a] |
| No. (No. missing) | 116 (2) | 35 (1) | 69 (1) | | 60 (0) | 54 (2) | |
| Median (IQR) | 17.0 (13.3-21.7) | 17.8 (14.0-23.1) | 15.8 (12.6-21.0) | | 17.8 (14.4-22.7) | 15.8 (12.1-20.2) | |
| CRP, mg/L | 61.5 (11.8-157.5) | 22.0 (6.0-91.0) | 71.0 (14.8-178.5) | .010[a] | 35.0 (7.3-100.8) | 82 (12.5-237.0) | .015[a] |
| Neutrophils, $\times 10^9$/L | | | | .658[a] | | | .136[a] |
| No. (No. missing) | 117 (1) | 36 (0) | 69 (1) | | 60 (0) | 55 (1) | |
| Median (IQR) | 10.5 (8.6-16.1) | 10.4 (8.5-13.8 | 10.5 (8.0-22.4) | | 10.4 (7.5-14.0) | 10.5 (9.4-17.5) | |
| MAP, mm Hg | | | | .355[a] | | | .345[a] |
| No. (No. missing) | 111 (7) | 33 (3) | 66 (4) | | 58 (2) | 51 (5) | |
| Median (IQR) | 79.0 (71.0-88.0) | 80.0 (73.0-92.5) | 78.0 (71.0-87.0) | | 80 (71.8-92.5) | 78.0 (70.0-86.0) | |

*(Continued)*

**TABLE 1** ] *(Continued)*

| Characteristic | All (N = 118) | NT-proBNP Level | | | Troponin Level | | |
|---|---|---|---|---|---|---|---|
| | | Normal (n = 36) | Abnormal (n=70) | *P* Value | Normal (n = 60) | Abnormal (n = 56) | *P* Value |
| Vasopressor use | 70 (59.3%) | 22 (61.1%) | 39 (55.7%) | .594[b] | 40 (66.7%) | 28 (50%) | .069[b] |
| CVP, mm Hg | | | | < .001[a] | | | .078[a] |
| No. (No. missing) | 78 (40) | 21 (15) | 48 (22) | | 41 (19) | 35 (21) | |
| Median (IQR) | 7.5 (4.0-12.0) | 4.0 (2.0-6.5) | 9.5 (6.25-14.0) | | 7.0 (3.5-11.0) | 9.0 (6.0-14.0) | |
| PEEP, cm $H_2O$ | | | | .048[a] | | | .527[a] |
| No. (No. missing) | 117 (1) | 35 (1) | 70 (0) | | 59 (1) | 56 (0) | |
| Median (IQR) | 10.0 (8.0-12.0) | 10.0 (7.0-10.0) | 12.0 (10.0-14.0) | | 10.0 (8.0-12.0) | 10.0 (8.0-12.0) | |
| Plateau pressure, cm $H_2O$ | | | | .421[a] | | | .083[a] |
| No. (No. missing) | 62 (56) | 13 (23) | 42 (28) | | 28 (32) | 33 (23) | |
| Median (IQR) | 24.0 (22-29) | 24.0 (22.5-25.5) | 25.5 (21.8-30.0) | | 24.0 (21.3-26.0) | 26.0 (23.0-29.5) | |
| Murray lung injury score | | | | .017[a] | | | .072[a] |
| No. (No. missing) | 104 (114) | 29 (7) | 64 (6) | | 55 (5) | 47 (9) | |
| Median (IQR) | 2.8 (2.3-3.0) | 2.5 (1.8-3.0) | 2.8 (2.5-3.3) | | 2.8 (2.0-3.0) | 2.8 (2.5-3.3) | |

Data are presented as No. (%), mean ± SD, or median (IQR), unless otherwise indicated. Data are complete unless indicated by No. (No. missing). APACHE = Acute Physiology and Chronic Health Evaluation; CCCC = Coronavirus Clinical Characterization Consortium; CRP = C-reactive protein; CVP = central venous pressure; IQR = interquartile range; MAP = mean airway pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; PEEP = positive end-expiratory pressure; PEEP = positive end-expiratory pressure; PTE = pulmonary thromboembolism; RRT = renal replacement therapy.

[a]Between-group differences assessed using Mann-Whitney *U* test.

[b]Between-group differences assessed using Pearson $\chi^2$ test.

[c]Between-group differences assessed using the Fisher exact test.

[d]Non-White ethnicity included Black (including Black African and Black Caribbean), Asian, and other (including mixed race).

[e]Between-group differences assessed using the Student *t* test.

**TABLE 2** ] Echocardiography Parameters

| Echocardiography parameter | All (N=118) | NT-proBNP Level | | | Troponin Level | | |
|---|---|---|---|---|---|---|---|
| | | Normal (n = 36) | Abnormal(n = 70) | *P* Value | Normal (n = 60) | Abnormal (n = 56) | *P* Value |
| Time from symptom onset to echocardiography, d | | | | 0.906[a] | | | 0.513[a] |
| No. (No. missing) | 117 (1) | 36 (0) | 69 (1) | | 60 (0) | 55 (1) | |
| Median (IQR) | 18 (13-22) | 17.5 (13-22) | 18 (13-22) | | 17 (13-21.8) | 18 (13-22) | |
| Time from intubation to echocardiography, d | 5 (4-8) | 5 (4-9) | 5 (4-7.3) | 0.755[a] | 5 (4-8.8) | 5.5 (4-7.8) | 0.973[a] |
| Severe RV dilation, RV:LV > 1:1 | | | | 0.785[b] | | | 0.408[b] |
| No. (No. missing) | 110 (8) | 34 (2) | 64 (6) | | 59 (1) | 49 (7) | |
| No. (%) | 31 (28.2%) | 11 (32.4%) | 19 (29.7%) | | 15 (25.4%) | 16 (32.7%) | |
| Interventricular septal flattening | | | | 0.156[c] | | | 0.075[c] |
| No. (No. missing) | 109 (9) | 34 (2) | 64 (6) | | 59 (1) | 48 (8) | |
| No. (%) | 9 (8.3%) | 1 (2.9%) | 8 (12.5%) | | 2 (3.4%) | 7 (14.6%) | |
| Subjective RV dysfunction | | | | 0.291[b] | | | 0.003[b] |
| No. (No. missing) | 113 (5) | 35 (1) | 66 (4) | | 60 (0) | 51 (5) | |
| No. (%) | 18 (15.9%) | 4 (11.4%) | 13 (19.7%) | | 4 (6.7%) | 14 (27.5%) | |
| LV dilation | | | | > 0.999[c] | | | 0.434[c] |
| No. (No. missing) | 108 (10) | 35 (1) | 63 (7) | | 60 (0) | 46 (10) | |
| No. (%) | 1 (0.9%) | 0 (0%) | 1 (1.6%) | | 0 (0%) | 1 (2.2%) | |
| Subjective LV dysfunction | | | | 0.735[c] | | | 0.342[b] |
| No. (No. missing) | 112 (6) | 35 (1) | 66 (4) | | 60 (0) | 50 (6) | |
| No. (%) | 12 (10.7%) | 4 (11.4%) | 6 (9.1%) | | 5 (8.3%) | 7 (14.0%) | |

Data are presented as No. (%) or median (interquartile range), unless otherwise indicated. Data are complete unless indicated by No. (No. missing). IQR = interquartile range; LV = left ventricular; NT-proBNP = N-terminal pro-brain natriuretic peptide; RV = right ventricular.

[a]Between-group differences were assessed using Mann-Whitney *U* test.

[b]Between-group differences were assessed using Pearson $\chi^2$ test.

[c]Between-group differences were assessed using the Fisher exact test.

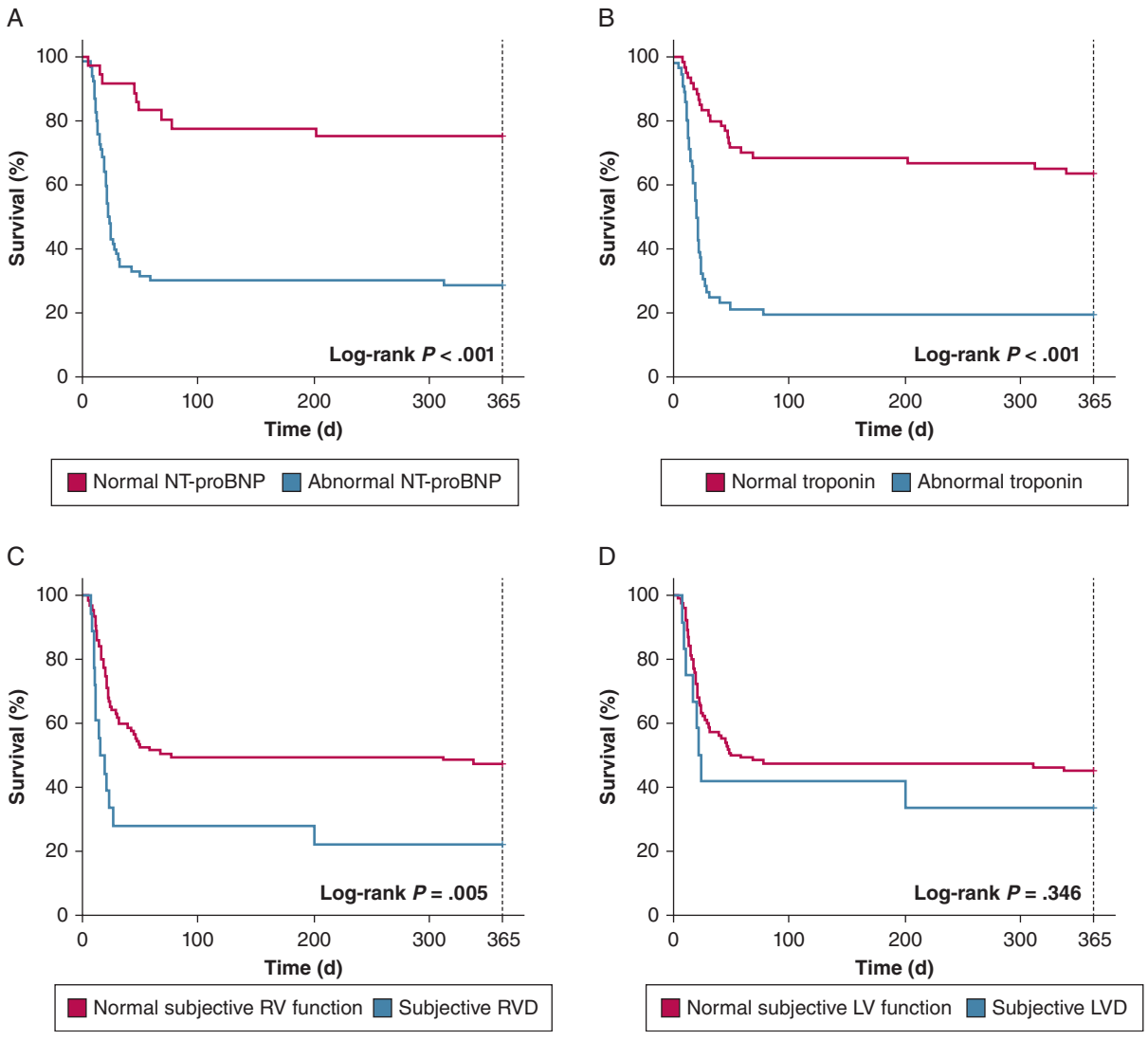


Figure 1 – *A-D, Kaplan-Meier plots showing log-rank univariate survival analysis of cardiac biomarkers and subjective right and left ventricular function for patients with abnormal NT-proBNP levels (A), abnormal troponin levels (B), subjective right ventricular dysfunction (C), and subjective left ventricular dysfunction (D). LV = left ventricular; LVD = left ventricular dysfunction; NT-proBNP = N-terminal pro-brain natriuretic peptide; RV = right ventricular; RVD = right ventricular dysfunction.*

positive end-expiratory pressure (PEEP), and worse Murray lung injury score ($P \leq .048$ for all).[25] Patients with abnormal troponin levels showed higher Acute Physiology and Chronic Health Evaluation II scores, more frequently had a diagnosis of diabetes mellitus, and were less likely to have received IV corticosteroids ($P \leq .043$ for all) (Table 1). An association was found among abnormal troponin level, a new diagnosis of PTE, a new diagnosis of acute coronary syndrome, and higher C-reactive protein ($P \leq .045$ for all).

Of the 118 echocardiography scans obtained, ICU clinicians performed 93 of 118 scans (78.8%). Echocardiography images were of adequate quality to assess for subjective RVD in 113 patients, with subjective RVD being present in 18 patients (15.9%). Subjective LVD was present in 12 of 112 scans (10.7%). Echocardiography was performed by echocardiographers with a range of experience (e-Table 2). No significant difference was found in reported measures of RV and LV function between patients with normal and abnormal NT-proBNP levels (Table 2). An association was found between abnormal troponin level and presence of subjective RVD ($P = .003$). No other significant associations were found between troponin levels and echocardiography parameters. Subjective RVD was associated with 1-year mortality ($P = .005$) (Fig 1), and no association was observed between

subjective LVD and mortality ($P = .346$). The association between subjective RVD and 1-year mortality remained when subjective RVD was diagnosed by both expert and nonexpert echocardiographers alike ($P = .035$ and $P = .003$, respectively) (e-Fig 1).

On multivariable analysis, abnormal NT-proBNP level (hazard ratio, 2.82; 95% CI, 1.19-6.67; $P = .018$), abnormal troponin level (hazard ratio, 2.84; 95% CI, 1.44-5.62; $P = .003$), and subjective RVD (hazard ratio, 2.09; 95% CI, 1.07-4.07; $P = .030$) were found to be associated independently with 1-year mortality (Table 3). The variance inflation factor for this model was < 5 for all variables, suggesting that multicollinearity was not present. These associations remained true after sensitivity analysis to adjust for the use of renal replacement therapy, administration of IV corticosteroids, $Pao_2$ to $Fio_2$ ratio, and level of PEEP ($P < .37$ for all) (e-Tables 3-6). When adjusting for severity of ARDS (using Murray lung injury score), the associations between abnormal NT-proBNP and abnormal troponin levels with 1-year mortality remained ($P = .031$ and $P = .013$) (e-Table 7), with a trend demonstrated between subjective RVD and 1-year mortality ($P = .058$). When the multivariable analysis was adjusted for diagnosis of PTE, the association of abnormal NT-proBNP and abnormal troponin levels with 1-year mortality remained ($P = .027$ and $P = .003$) (e-Table 8); however, the association between subjective RVD and 1-year mortality no longer was significant ($P = .262$). When patients were divided into groups showing normal NT-proBNP level, normal troponin level, normal subjective RV function, one abnormal variable, two abnormal variables, or three abnormal variables, a stepwise increase in mortality was observed in which each increment of an abnormal variable increased the incidence of 1-year mortality ($P < .001$) (Fig 2). Patients with a combination of abnormal NT-proBNP level, abnormal troponin level, and subjective RVD showed the highest incidence of 1-year mortality of 92.3% (12 of 13) compared with the lowest incidence of 20% (5 of 25) mortality when normal NT-proBNP level, normal troponin level, and normal subjective RV function were present.

## Discussion

We report the novel finding that abnormal NT-proBNP level, abnormal troponin level, and subjective RVD are associated independently with 1-year mortality in patients with COVID-19 requiring IMV. We observed an incidence of 1-year mortality of 57.6% in patients with COVID-19 requiring IMV, which is broadly similar to previous reports in this population at 1 year (47.4%-49.4%).[26,27]

Cardiac biomarkers commonly are raised in patients with COVID-19, with a reported prevalence of abnormal NT-proBNP level of 48.5% to 81.3% and abnormal troponin level of 39.0% to 78.4%.[28,29] We found an abnormal NT-proBNP prevalence of 66.0% and abnormal troponin prevalence of 48.3%, similar to previous reports. NT-proBNP and troponin levels previously were shown to be associated with short-term mortality,[7,28,30,31] with a single study identifying an association with 1-year mortality in a mixed population of patients with COVID-19 both in the ICU and not in the ICU.[8] The current study demonstrated a strong association between both cardiac biomarkers and 1-year mortality; mortality was 71.4% in those with abnormal NT-proBNP levels and 80.4% in those with abnormal troponin levels ($P < .001$). The associations between abnormal cardiac biomarkers and the very high 1-year mortality have not been reported previously in a cohort of patients with

**TABLE 3** ] Multivariable Cox Regression for 1-Year Mortality From ICU Admission (n = 97)

| Variable | HR (95% CI) | *P* Value |
|---|---|---|
| Abnormal NT-proBNP level | 2.82 (1.19-6.67) | .018 |
| Abnormal troponin level | 2.84 (1.44-5.62) | .003 |
| Subjective RVD | 2.09 (1.07-4.07) | .030 |
| Age, per 1-y increase, y | 1.04 (1.00-1.07) | .033 |
| Female sex | 0.73 (0.39-1.36) | .319 |
| Non-White ethnicity[a] | 1.38 (0.50-3.80) | .537 |
| APACHE II score on admission to ICU (per 1-score increase) | 1.02 (0.98-1.07) | .349 |
| Time from intubation to date of echocardiography, per 1-d increase, d | 1.01 (0.93-1.11) | .766 |

APACHE = Acute Physiology and Chronic Health Evaluation; HR = hazard ratio; NT-proBNP = N-terminal pro-brain natriuretic peptide; RVD = right ventricular dysfunction.
[a]Non-White ethnicity included Black (including Black African and Black Caribbean), Asian, and other (including mixed race).

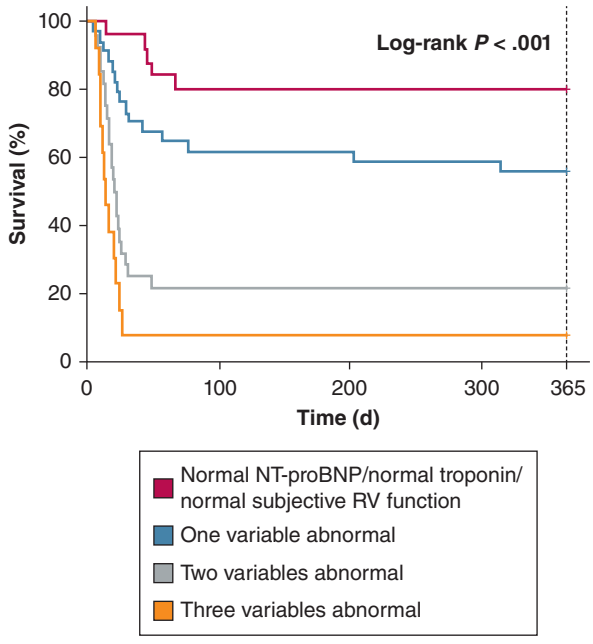


Figure 2 – *Kaplan-Meier plot of log-rank analysis showing incidence of 1-year mortality comparing groups with normal NT-proBNP levels, normal troponin levels, and normal subjective RV function with groups with abnormal variables for one, two, and all three features. Incidences of 1-year mortality: normal NT-proBNP level, normal troponin level, and normal RV function, 20.0% (20 of 25); one variable abnormal, 44.1% (15/34); two variables abnormal, 78.6% (22 of 28); and three variables abnormal, 92.3% (12/13). Total n = 100. NT-proBNP = N-terminal pro-brain natriuretic peptide; RV = right ventricular.*

COVID-19 all of whom received mechanical ventilation. The independent associations of NT-proBNP and troponin levels with mortality indicate that these biomarkers may be identifying different aspects of COVID-19 disease that impact on survival.

This study demonstrated that abnormal NT-proBNP level was associated strongly with higher CVP ($P <$ .001), with a weaker trend also observed between abnormal troponin level and CVP ($P = .078$). Using CVP as a surrogate for right atrial and RV filling pressures (noting that CVP also may be influenced by airway pressures),[32] this may suggest that RV hemodynamic cardiac stress may represented better by NT-proBNP release, rather than troponin release. NT-proBNP level as a measure of RV hemodynamic cardiac stress (relating to RV volume and pressure overload) has been well documented.[33,34] Additionally, higher levels of PEEP and more severe ARDS (as measured by Murray lung injury score) were associated with abnormal NT-proBNP levels ($P = .048$ and $P = .017$, respectively), whereas no association was observed between PEEP and abnormal troponin levels ($P = .527$) and a modest trend was observed between Murray lung injury score and abnormal troponin levels ($P = .072$). Higher PEEP and more severe ARDS are clinical parameters that can increase pulmonary vascular resistance[35,36] and RV hemodynamic cardiac stress, again indicating that NT-proBNP level may be a measure of hemodynamic cardiac stress that is not detected by measurement of troponin level. Acute coronary syndrome was associated with abnormal troponin level ($P = .011$), but not abnormal NT-proBNP level ($P = .297$), suggesting that troponin may be a better marker for detecting myocardial ischemia. Acute PTE was associated with abnormal troponin level ($P = .045$), but not abnormal NT-proBNP level ($P = .189$); however, we did not screen systematically for acute PTE and therefore are at risk of having missed an association between acute PTE and abnormal NT-proBNP level. Both abnormal NT-proBNP and abnormal troponin levels were associated with not receiving IV corticosteroids ($P = .052$ and $P = .043$, respectively) and with higher C-reactive protein level ($P = .010$ and $P = .015$, respectively), suggesting that inflammation may be implicated in the release of these cardiac biomarkers. Therefore based on our study results, it may be reasonable to conclude that measurement of NT-proBNP level may detect patients who are experiencing hemodynamic cardiac stress, that measurement of troponin level may identify patients with cardiac ischemia, and that both NT-proBNP and troponin levels are raised in inflammatory states, and that these different pathologic phenotypes may influence survival.

In the present study, echocardiography-diagnosed subjective RVD showed a prevalence of 15.9% and subjective LVD showed a prevalence of 10.7%. An RVD prevalence of 6.25% to 76.2% previously was demonstrated in populations with COVID-19 receiving IMV in the ICU,[11,37,38] varying considerably depending on the measure and definition of RV function used. No association was found between abnormal cardiac biomarkers and subjective LVD. However, a significant association was identified between abnormal troponin level and subjective RVD ($P = .003$), and this association might suggest that the site of troponin release is predominantly from the dysfunctional right ventricle, rather than the left ventricle. RVD has been shown to be associated independently with short-term and intermediate-term mortality in patients with COVID-19 receiving IMV,[39,40] although long-term outcomes have not been reported. The present study demonstrated that subjective RVD, but not subjective LVD, was associated with 1-year mortality.

Previous studies using transthoracic and transesophageal echocardiography showed that subjective RV function assessment is highly sensitive in diagnosing severe RVD; however, more advanced training is required to diagnose subtle RVD.[20,21,41] Orde et al[20] conclude that "it seems prudent to avoid subjective RV assessment in isolation," and we agree with this statement, with our results demonstrating that a combination of subjective RV assessment, NT-proBNP analyses, and troponin analyses identifies a group of patients with COVID-19 at very high risk of mortality. In the present study, when subjective RVD, abnormal NT-proBNP level, and abnormal troponin level were present, 92.3% of patients had died at 1 year, compared with 20% mortality in patients with normal subjective RV function, normal NT-proBNP level, and normal troponin level. We suggest that these three measurements may provide useful information during ICU admission to identify patients with COVID-19 (or possibly other ARDS groups) at risk of a very poor outcome. A recent editorial states that "despite increasing use . . . the prognostic and therapeutic significance of many echocardiographic findings in critically ill patient populations, such as those with ARDS, remains uncertain in practice . . . [and] novel approaches to interpreting echocardiography, at a population level, may be needed."[42] We propose that the use of cardiac biomarkers may be the novel approach required. Cardiac biomarker analysis may contribute key information, providing a context for the interpretation of echocardiography findings, and may aid clinicians in identifying patients with a poor prognosis.

A limitation of our study is that given the lack of cardiac biomarker measurements before admission, we were unable to report baseline NT-proBNP or troponin levels. Additionally, with the absence of prior echocardiography imaging, we were unable to report pre-existing RVD or LVD. A second limitation is that we were unable to report echocardiography surrogate measures of pulmonary afterload, and therefore have been unable to comment on pulmonary artery-RV coupling. However, this would have required an advanced echocardiography image set beyond our deliberately pragmatic FICE scan protocol. Finally, any associations identified between abnormal cardiac biomarker levels and potential drivers of the cardiac biomarker signal are at risk of type I error and therefore are exploratory only.

Strengths of the study include that ICU clinicians performed echocardiography in most patients (78.8%), highlighting the clinical usefulness of subjective RVD in identifying patients at high risk of mortality. We used a study design that easily translates to clinical practice: cardiac biomarker measurements and point-of-care echocardiography are easily obtained during ICU admission and could be used to identify patients at high risk of poor outcomes earlier in the clinical course. Our study was designed prospectively with a prepublished protocol and recruited a high proportion of patients with COVID-19 admitted to the ICU over the study period.

## Interpretation

We report the unique finding that abnormal NT-proBNP level, abnormal troponin level, and subjective RVD are associated independently with 1-year term mortality in mechanically ventilated patients with COVID-19. These investigations are available readily for patients during ICU admission, and their combined use can identify those at significantly higher risk of death at 1 year.


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None declared.

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