Cardiac dysfunction and mortality in critically ill patients with COVID-19: A Swedish multicentre observational study

Jacob Holmqvist1,2 | Josefine Beck-Friis3,4 | Carl Jensen5 | Keti Dalla1,6 | Simon Mårdstam7,8 | Jens Christensen7,8 | Nina Nordén1,6 | Hannes Widing1,9 | Elin Rosén-Wetterholm1 | Oscar Cavefors1,2 | Aylin Yilmaz3,4 | Maria Cronhjort7,8 | Björn Redfors10,11 | Jonatan Oras1,2

1Department of Anesthesiology and Intensive Care Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
2Department of Anesthesiology and Intensive Care Medicine, Sahlgrenska University Hospital/Sahlgrenska, Gothenburg, Sweden
3Department of Infectious Diseases, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
4Department of Infectious Diseases, Sahlgrenska University Hospital, Gothenburg, Sweden
5Department of Anesthesiology and Intensive Care Medicine, NU Hospital Group, Trollhättan, Sweden
6Department of Anesthesiology and Intensive Care Medicine, Sahlgrenska University Hospital/Mölndal, Gothenburg, Sweden
7Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden
8Department of Anaesthesia and Intensive Care, Södersjukhuset, Stockholm, Sweden
9Department of Anesthesiology and Intensive Care Medicine, Sahlgrenska University Hospital/Östra, Gothenburg, Sweden
10Department of Cardiology, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
11Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden

Correspondence
Jonatan Oras, Blå Stråket 5, våning 5, Anestesiexpeditionen. 41345 Gothenburg, Sweden.
Email: jonatan.oras@vgregion.se

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Abstract
Background: The prevalence and importance of cardiac dysfunction in critically ill patients with COVID-19 in Sweden is not yet established. The aim of the study was to assess the prevalence of cardiac dysfunction and elevated pulmonary artery pressure (PAP), and its influence on mortality in patients with COVID-19 in intensive care in Sweden.

Methods: This was a multicentre observational study performed in five intensive care units (ICUs) in Sweden. Patients admitted to participating ICU with COVID-19 were examined with echocardiography within 72 h from admission and again after 4 to 7 days. Cardiac dysfunction was defined as left ventricular (LV) dysfunction (ejection fraction <50% and/or regional hypokinesia) or right ventricular (RV) dysfunction (defined as TAPSE <17 mm or visually assessed moderate/severe RV dysfunction).

Results: We included 132 patients, of whom 127 (96%) were intubated. Cardiac dysfunction was found in 42 (32%) patients. Most patients had cardiac dysfunction at the first assessment (n = 35) while a few developed cardiac dysfunction later (n = 7) and some changed type of dysfunction (n = 3). LV dysfunction was found in 21 and...
Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The clinical characteristics of COVID-19 range from asymptomatic infection to critical illness with acute respiratory distress syndrome, shock or multiorgan dysfunction, affecting around 5% of symptomatic cases. 1,2 Cardiac and thrombotic complications are common in patients with COVID-19 and are associated with a higher mortality and more complicated disease course. 3 Myocardial injury with elevated troponin or creatine kinase is reported in 12 to 38% of hospitalised patients with COVID-19 4,5 and in approximately 50% of patients treated in intensive care units (ICU). 5,6 Other cardiac manifestations include myocarditis, 7 Takotsubo cardiomyopathy, 8 and cardiac dysfunction related to multisystem inflammatory syndrome in children and adults (MIS-C/A). 11,12 Several studies have reported abnormalities in heart function in a large proportion of patients with COVID-19 undergoing echocardiography 10,13,14 and both left- and right ventricular dysfunction seem to be independently correlated to mortality in patients with COVID-19. 15,17 However, incidence and influence on mortality of cardiac complications in critically ill patients with COVID-19 in Sweden are not sufficiently studied.

The aim of the present study was to assess the incidence of COVID-19-associated cardiac dysfunction and its influence on mortality in critically ill patients with COVID-19 in Sweden.

RV dysfunction in 19 patients, while 5 patients had combined dysfunction. Elevated PAP was found in 34 patients (26%) and was more common in patients with RV dysfunction. RV dysfunction and elevated PAP were independently associated with an increased risk of death (OR 3.98, \( p = .013 \) and OR 3.88, \( p = .007 \), respectively).

Conclusions: Cardiac dysfunction occurs commonly in critically ill patients with COVID-19 in Sweden. RV dysfunction and elevated PAP are associated with an increased risk of death.

KEYWORDS
cardiac biomarkers, cardiac dysfunction, COVID-19, echocardiography, intensive care unit

Editorial Comment
Cardiac dysfunction in COVID-19 patients has been reported widely. Here, the authors show that incidence in a Swedish population is comparable to previously reported non-Scandinavian incidences. Especially elevated pulmonary artery pressure and right heart dysfunction showed elevated mortality, while left ventricular dysfunction did not.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The clinical characteristics of COVID-19 range from asymptomatic infection to critical illness with acute respiratory distress syndrome, shock or multiorgan dysfunction, affecting around 5% of symptomatic cases. 1,2

Cardiac and thrombotic complications are common in patients with COVID-19 and are associated with a higher mortality and more complicated disease course. 3 Myocardial injury with elevated troponin or creatine kinase is reported in 12 to 38% of hospitalised patients with COVID-19 4,5 and in approximately 50% of patients treated in intensive care units (ICU). 5,6 Other cardiac manifestations include myocarditis, 7 Takotsubo cardiomyopathy, 8 and cardiac dysfunction related to multisystem inflammatory syndrome in children and adults (MIS-C/A). 11,12 Several studies have reported abnormalities in heart function in a large proportion of patients with COVID-19 undergoing echocardiography 10,13,14 and both left- and right ventricular dysfunction seem to be independently correlated to mortality in patients with COVID-19. 15,17 However, incidence and influence on mortality of cardiac complications in critically ill patients with COVID-19 in Sweden are not sufficiently studied.

The aim of the present study was to assess the incidence of COVID-19-associated cardiac dysfunction and its influence on mortality in critically ill patients with COVID-19 in Sweden.

2 | METHODS

This was a multicentre observational study. It was approved by the Swedish Ethics Review Authority Sweden (approval number 036–18, 2020–01684 and 2020–03815) and registered in the international database at Clinicaltrials.gov (registration number NCT04524234).

2.1 | Study design and inclusion

The study was performed in five ICUs in Sweden from 20 April to 30 August 2020. Most patients were included prospectively (\( n = 98, 72\% \)), but 30 patients were included retrospectively from one of the five study sites. This site followed the study protocol as to both examination with echocardiography and collection of laboratory data on clinical grounds but were not formally participating in the study until after the third ethical approval. Another nine patients were retrospectively included from the other centres, where the study protocol was initiated on clinical grounds before the ethical approval. Details of each participating ICU are described under Data S1.

All patients ≥18 years of age who were admitted to a participating ICU with verified COVID-19 were eligible for inclusion. Patients were included consecutively when study personnel and resources were available. Echocardiography was performed within 72 h from admission to the ICU and repeated in 4 to 7 days or at clinical deterioration. Cardiac biomarkers, routine laboratory tests and clinical data were recorded at each examination. Consent to study inclusion was obtained from the patient or patient’s next of kin whenever possible but waived for those included retrospectively.

2.2 | Echocardiography, definitions, recordings and measurements

Transthoracic echocardiography was performed according to a standardised protocol (see Data S1) for assessment of left
ventricular (LV) or right ventricular (RV) dysfunction and estimation of pulmonary artery pressure (PAP). LV dysfunction was defined as ejection fraction <50% with or without regional hypokinesia. LV ejection fraction (EF) was assessed with Simpson biplane or with eyeballing. Regional wall motion abnormalities (RWMA) were assessed using the standard 17-segment model. RV dysfunction was defined as a tricuspid annular plane systolic excursion (TAPSE) <17 mm, or visually assessed at least moderately depressed RV dysfunction. In patients with a tricuspid regurgitation (TR), elevated PAP was defined as TR jet velocity >2.9 m/s (TR Vmax). In patients with no tricuspid regurgitation, we defined elevated PAP through indirect criteria combining the following two findings: (1) A high RV load detected through ventricular dilation or flattening of the septum; (2) a high pulmonary afterload with a pulmonary acceleration time <100 ms. Velocity Time Integral (VTI), area of LV outflow tract (LVOT) with calculation of stroke volumes and cardiac output were assessed wherever image quality was acceptable. Highly experienced operators performed all examinations. These were recorded and later reviewed off-line by certified echocardiographists. Details of the echocardiographic examinations at each site are presented in Data S1.

At the time of echocardiography, blood samples for measurement of the cardiac biomarkers troponin and N-terminal pro b-type natriuretic peptide (NTproBNP) were obtained and clinical data were recorded. Four sites used highly sensitive troponin T and one site used troponin I. To present a comparable value, the troponin levels were divided by the upper limit of normal. Age, sex, medical history and Simplified Acute Physiology Score 3 (SAPS 3) were documented. Systolic blood pressure, mean arterial pressure, diastolic blood pressure, vasopressor dosage, lactate levels, ventilator settings and PaO2/FiO2-ratio were recorded when echocardiography was performed. Mortality at 30 days and death occurring within 90 days of admission to the ICU were registered.

2.3 | Predefined outcomes

The predefined primary outcome was 30-day mortality in patients with versus without cardiac dysfunction on admission to the ICU. Subgroup analysis was performed for LV and RV dysfunction. Predefined secondary outcomes were (a) prevalence of LV and RV dysfunction within 72 hours of admission and during ICU stay; (b) clinical risk factors associated with cardiac dysfunction and (c) levels of the cardiac biomarkers troponin and NTproBNP in patients with and without cardiac dysfunction. Other analyses were not predefined at the initiation of the study and are considered exploratory.

2.4 | Statistics

A statistical analysis plan was written before the analyses were performed (Data S1). Normally distributed variables are presented as mean ± standard deviation; non-normally distributed variables are presented as median and interquartile range (IQR). Student’s t-test was used to compare means of normally distributed variables and the Mann–Whitney U test was used for comparison of distributions of non-normally distributed variables. Fisher’s exact test was used for comparison of binary outcomes between two groups. Logistic regression was used to evaluate mortality at 30 days between patients with or without cardiac dysfunction in a non-adjusted and a risk-adjusted analysis (primary outcome). Kaplan–Meier methodology with a log rank test was used to compare incidences over time. IBM SPSS Statistics Version 26 was used for the statistical analyses. No power analysis was performed, as insufficient data of the study population were available when the study was initiated, but we aimed for inclusion of at least 100 patients.

3 | RESULTS

In total, 234 patients were admitted to each participating centre during their study periods, of whom 137 were included in the study. Inclusion failure occurred when no investigator involved in the study was available for including patients or performing echocardiographic examination. In a sensitivity analysis regarding SAPS score, age and 30-days mortality, the study population was representative of each ICU’s patient population. Two patients were excluded due to their echocardiography being performed >72 h from admission. An additional three patients were excluded because of poor echocardiographic image quality. Thus, a total of 132 patients included in the final analysis (Figure 1).

3.1 | Study population

The median age of the cohort was 63 years (IQR 53–70); 34 (26%) were women. Median body mass index (BMI) was 30 (IQR 25–33).
| Category           | Variable                                      | All patients \(n = 132\) | Cardiac function | p-value |
|--------------------|-----------------------------------------------|-----------------------------|-------------------|---------|
|                    |                                               |                             | Normal function \(n = 90\) | Cardiac dysfunction \(n = 42\) |         |
| Demographics       | Age, years                                    | 63 (53–70)                  | 64 (53–70)        | 61 (52–68) | .767    |
|                    | Women, \(n\) (%)                              | 34 (26)                     | 27 (30)           | 7 (17)    | .135    |
|                    | BMI                                           | 30 (25–33)                  | 30 (26–33)        | 28 (25–34) | .577    |
| Risk score         | SAPS3                                         | 51 ± 9                      | 51 ± 9            | 53 ± 10   | .285    |
| Medical history    | Any cardiac disease, \(n\) (%)               | 17 (13)                     | 8 (9)             | 9 (21)    | .055    |
|                    | Heart failure, \(n\) (%)                     | 0 (0)                       | 0 (0)             | 0 (0)     |         |
|                    | Coronary artery disease, \(n\) (%)           | 15 (11)                     | 8 (9)             | 7 (17)    | .240    |
|                    | Atrial fibrillation, \(n\) (%)               | 5 (4)                       | 2 (2)             | 3 (7)     | .326    |
|                    | Valvular disease, \(n\) (%)                  | 2 (2)                       | 0 (0)             | 2 (5)     | .100    |
|                    | Other cardiac disease, \(n\) (%)             | 1 (1)                       | 0 (0)             | 1 (2)     | .318    |
|                    | Cerebrovascular disease, \(n\) (%)           | 10 (8)                      | 5 (6)             | 5 (12)    | .288    |
|                    | COPD or asthma, \(n\) (%)                    | 13 (10)                     | 9 (10)            | 4 (10)    | >.999   |
|                    | Renal failure, \(n\) (%)                     | 7 (5)                       | 4 (4)             | 3 (7)     | .679    |
|                    | Any risk factor of CVD, \(n\) (%)            | 74 (56)                     | 44 (49)           | 30 (71)   | .023    |
|                    | Diabetes, \(n\) (%)                           | 29 (22)                     | 19 (21)           | 10 (24)   | .822    |
|                    | Hypertension, \(n\) (%)                      | 58 (44)                     | 32 (36)           | 26 (62)   | .005    |
|                    | Hyperlipidaemia, \(n\) (%)                   | 25 (19)                     | 13 (14)           | 12 (29)   | .061    |
|                    | Thrombotic disease, \(n\) (%)                | 6 (5)                       | 4 (4)             | 2 (5)     | >.999   |
|                    | Other, \(n\) (%)                              | 28 (21)                     | 18 (20)           | 10 (24)   | .651    |
| Haemodynamic       | Systolic blood pressure, mmHg                 | 125 ± 18                    | 126 ± 18          | 124 ± 19  | .707    |
|                    | Mean arterial pressure, mmHg                  | 79 ± 11                     | 79 ± 10           | 78 ± 12   | .602    |
|                    | Heart rate, bpm                               | 79 ± 17                     | 78 ± 15           | 83 ± 21   | .138    |
|                    | Noradrenaline >0.20 \(\mu\)g/kg/min, \(n\) (%)| 15 (11)                     | 7 (7)             | 8 (23)    | .025    |
| Ventilatory        | FiO2, %                                       | 50 (40–65)                  | 50 (40–65)        | 50 (45–70) | .287    |
|                    | PaO2/FiO2                                     | 19.7 (15.6–24.7)            | 19.0 (14.6–25.2)  | 20.6 (16.2–24.7) | .624    |
|                    | Mechanical ventilation, \(n\) (%)            | 114 (86)                    | 83 (86)           | 31 (89)   | .780    |
|                    | Ventilation mode                              |                             |                   |          | .337    |
|                    | PCV-VG, \(n\) (%)                             | 57 (43)                     | 43 (44)           | 14 (40)   |         |
|                    | PSV, \(n\) (%)                                | 27 (20)                     | 22 (23)           | 5 (14)    |         |
|                    | PCV, \(n\) (%)                                | 17 (13)                     | 9 (9)             | 8 (23)    |         |
|                    | APRV, \(n\) (%)                               | 13 (10)                     | 9 (9)             | 4 (11)    |         |
|                    | High flow oxygen, \(n\) (%)                  | 12 (9)                      | 9 (9)             | 3 (9)     |         |
|                    | NIV, \(n\) (%)                                | 4 (3)                       | 4 (4)             | 0 (0)     |         |
|                    | Oxygen mask, \(n\)                           | 2 (2)                       | 1 (1)             | 1 (3)     |         |
|                    | PEEP, cmH2O                                   | 14 (12–15)                  | 14 (11–15)        | 14 (12–15) | .697    |
|                    | Tidal volumes, ml/IBW adjusted kg             | 7.1 (6.3–7.9)               | 7.1 (6.4–8.1)     | 7.0 (6.3–7.8) | .473    |
|                    | Peak pressures, cmH2O                         | 26 (22–28)                  | 26 (22–29)        | 25 (23–27) | .983    |
|                    | Dynamic compliance, ml/cmH2O                  | 19 (17–23)                  | 19 (17–23)        | 18 (17–22) | .835    |
|                    | Prone position within 24 h, \(n\) (%)        | 45 (34)                     | 36 (37)           | 9 (26)    | .299    |

Note Haemodynamic and ventilatory data are obtained from time of first echo.

Abbreviations: APRV, airway pressure release ventilation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; FiO2, fraction of inspired oxygen; NIV, non-invasive ventilation; PaO2, partial pressure of oxygen; PCV, pressure controlled ventilation; PCV-VG, pressure controlled ventilation - volume guaranteed; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation; SAPS3, simplified acute physiology score 3.
Seventeen patients (13%) had a history of cardiac disease, 74 others (56%) had a risk factor for cardiovascular disease, while no patients were diagnosed with heart failure. A history of hypertension was more common in patients with cardiac dysfunction. The mean SAPS score was 52 ± 9 points (Table 1). A total of 127 patients (96%) were intubated during their ICU stay. Patients were treated with low-molecular weight heparin (LMWH) in doses corresponding to 0.77 (IQR 0.61–0.95) times the treatment dose for acute thrombotic disease. More patients with cardiac dysfunction had a high dose of noradrenaline (>0.20 µg/kg/min) compared with patients with normal cardiac function. None of the other haemodynamic or respiratory variables differed between these groups (Table 1).

## 3.2 | Cardiac dysfunction and echocardiographic data

Median time to first echocardiography was 1 day (IQR 1–2); median time to second examination was 7 days (IQR 4–9). Follow-up echocardiography was available for 89 patients (67%). Of those with no follow-up available, 19 patients were discharged, four patients died, while 20 patients were not examined due to that no study personal was available. Most patients had cardiac dysfunction at the first assessment (n = 35) and a majority of them had normalised their cardiac function at the second examination (n = 21). A smaller number of patients had developed cardiac dysfunction at the second examination (n = 7), while a few had changed type of dysfunction (n = 3). Five patients had unchanged cardiac dysfunction. In total, 42 patients (32%) had any cardiac dysfunction of whom 21 patients (15%) had LV dysfunction, 19 patients (14%) had RV dysfunction and 5 patients (5%) had combined dysfunction at any of the examinations (Figure 2). Eight (6%) patients with LV dysfunction displayed a pattern of regional hypokinesia. In two of them, this was attributed to a known history of cardiac disease. Five patients (4%) had a typical pattern of Takotsubo syndrome with reversible apical and/or midventricular akinesia and no history of cardiac disease. One patient had suspected COVID-19 myocarditis, and one other had the diagnosis verified with magnetic resonance imaging (MRI). An 18-year-old patient with global LV hypokinesia was diagnosed with MIS-C.

Patients with LV dysfunction had larger LV diameters and lower ejection fractions, stroke volumes and cardiac index compared with patients with normal LV function (Table 2). Of the 24 patients with RV dysfunction, TAPSE was depressed in 22, while two had preserved TAPSE but visually assessed moderately afflicted function. Tricuspid regurgitation was more common in patients with RV dysfunction. Elevated PAP was found in 34 patients (26%). This was diagnosed with a TR Vmax >2.9 in 32 patients and indirect criteria in two patients. Elevated PAP was more common in patients with RV dysfunction, as compared with patients with normal cardiac function (58% vs 22%; p < .001). Levels of troponin and NTproBNP were higher in patients with cardiac dysfunction compared with patients with normal cardiac function (Data S1).

## 3.3 | Mortality and clinical course

In total, 24 patients (18%) died within 30 days of admission to the ICU. The difference in 30-day mortality between patients with cardiac dysfunction (n = 10, 24%) and with normal cardiac function (n = 14, 16%) was not significant (p = .332). There was no increased risk of death at 30 days in patients with as opposed to without cardiac dysfunction in a risk-adjusted model (OR 1.89, p = .071). Right ventricular dysfunction on admission (risk-adjusted OR 7.03, p = .002), or detected at any time in the ICU (risk-adjusted OR 3.98, p = .013), was associated with an increased risk of death at 30 days. Left ventricular dysfunction was not associated with any increased risk of death at 30 days. Elevated PAP was associated with an increased risk of death at 30 days (risk-adjusted OR 3.88, p = .007) (Table 3). There was also an increased risk of death during the first 90 days from admission in both these groups (Figure 3). More patients with cardiac dysfunction needed continuous renal replacement therapy (CRRT) (n = 16, 38%) compared with patients with normal cardiac function (n=16, 18%, p = .016). The group with cardiac dysfunction had less days alive outside the ICU during the first 30 days from admission, as compared with the group with normal cardiac function (median 0[IQR 0–10] versus 13 days [IQR 0–20], p = .042). Length of hospital stay did not differ between the two groups (Data S1).

### FIGURE 2 Findings of cardiac function at each echocardiographic examination. The circles to the left represent the number of patients with different types of ventricular function/dysfunction at the first examination, and to the right at the second examination

4 | DISCUSSION

The main findings of this study are that (1) cardiac dysfunction occurs frequently in critical illness caused by COVID-19 in Sweden and that (2) RV dysfunction and elevated PAP are associated with an increased risk of death.

The present study has several limitations that needs be taken in consideration when interpreting the results. First, we used a limited echocardiography protocol oriented towards basic assessment of cardiac and haemodynamic status. Using this protocol, we missed...
evaluation of potentially important variables including diastolic dysfunction and strain analysis. Visual estimation was used for evaluation of radial RV dysfunction. This is not an objective method and using e.g. fractional area change would yield a higher reproducibility and possibly identification of more RV pathology. In addition, not all centres calculated Simpson biplane routinely. Furthermore, we did not register fluid balance which is a potential confounder in the assessment of RV and LV function. Other limitations are that not all eligible patients were included due to a lack of study resources, that not all patients had a follow-up echocardiography and that the time frames for this follow-up were wider than desired. However, patients were included systematically when resources were available, and a sensitivity analysis shows that the study population was a representative sample of each site’s total COVID-19 population. The main strengths of the study are the multi-centre design, giving a presumably high generalisability of severe COVID-19 in Sweden, and that echocardiographic follow-up was performed in a majority of patients, which is not performed in most studies of COVID-19 associated cardiac dysfunction.

In our study, 32% of the patients had cardiac dysfunction detected at any time in the ICU. A recent systematic review and meta-analysis has reported a prevalence of RV dysfunction of 20% in hospitalised COVID-19 patients. Studies focusing on patients in...

**TABLE 2** Echocardiographic data of the 132 participants

| Variable                  | Normal cardiac function, n = 90 | Cardiac dysfunction | RV dysfunction, n = 24
|---------------------------|---------------------------------|---------------------|-----------------------|
| LV diameter, mm           | 48 ± 4                          | 52 ± 6              | 49 ± 5                |
| LV ejection fraction, %   | 59 ± 5                          | 43 ± 6              | 57 ± 11               |
| Stroke volume indexed, ml/m² | 40 ± 12                        | 30 ± 9              | 37 ± 11               |
| Cardiac index, L/min/m²   | 3.1 ± 0.9                       | 2.4 ± 1             | 3.0 ± 1               |
| Regional hypokinesia, n (%)| –                               | 8 (32)              | 0 (0)                 |
| TAPSE, mm                 | 20 (19–23)                      | 20 (17–22)          | 15 (12–16)            |
| TAPSE <17, n (%)          | –                               | 3 (12)              | 22 (92)               |
| Moderate or severe RV failure, n (%) | –                           | 1 (4)               | 8 (33)                |
| TR present, n (%)         | 41 (46)                         | 15 (60)             | 19 (79)               |
| TR Vmax, m/s              | 3.1 (2.4–4.0)                   | 2.7 (2.2–3.5)       | 3.5 (2.7–4.5)         |
| Elevated PAP, n (%)       | 20 (22)                         | 6 (24)              | 14 (58)               |

Note TR Vmax is reported from patients with a TR present. In the group normal cardiac function, data are reported for first echo. In the groups LV or RV dysfunction, data are reported from the first echo when dysfunction is detected.

Abbreviations: LV, left ventricle; PAP, pulmonary arterial pressure; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TR Vmax, maximal tricuspid regurgitation velocity.

In the group normal cardiac function, data are reported for first echo. In the groups LV or RV dysfunction, data are reported from the first echo when dysfunction is detected.

Abbreviations: LV, left ventricle; PAP, pulmonary arterial pressure; RV, right ventricle.

*Includes patients with combined dysfunction.

*Note TR Vmax is reported from patients with a TR present. In the group normal cardiac function, data are reported for first echo. In the groups LV or RV dysfunction, data are reported from the first echo when dysfunction is detected.

Abbreviations: LV, left ventricle; PAP, pulmonary arterial pressure; RV, right ventricle.

**TABLE 3** Mortality analysis

| Presentation of cardiac dysfunction | Crude risk of death | Adjusted risk of death\* |
|------------------------------------|---------------------|--------------------------|
|                                    | OR 95% CI for OR    | OR 95% CI for OR         |
| On admission                        |                     |                          |
| Cardiac dysfunction                | 1.89 (0.74–4.83)    | 1.56 (0.56–4.33)         |
| LV dysfunction\b                   | 0.49 (0.11–2.26)    | 0.22 (0.04–1.38)         |
| RV dysfunction\b                   | 4.90 (1.68–14.3)    | 7.03 (2.08–23.8)         |
| Elevated PAP\b                     | 2.49 (0.96–6.45)    | 2.34 (0.84–6.51)         |

Note Cardiac dysfunction refers to having left, right or combined ventricular dysfunction. At any time in the ICU refers to having cardiac dysfunction or elevated PAP at the first or second echocardiographic examination.

Abbreviations: CI, confidence interval; ICU, intensive care unit; LV, left ventricle; OR, odds ratio; PAP, pulmonary arterial pressure; RV, right ventricle.

*Adjusted for SAPS 3 score.

\*Includes patients with combined dysfunction.
FIGURE 3 Kaplan–Meier survival curves for patients with versus without cardiac dysfunction (A), isolated LV dysfunction vs normal cardiac function (B), isolated RV dysfunction vs normal cardiac function (C), combined RV and LV dysfunction vs normal cardiac function, (D) and elevated PAP vs normal PAP (E). Time is calculated from when the cardiac abnormality was detected. In patients with normal cardiac function time is calculated from the first echo. LV, left ventricle; PAP, pulmonary artery pressure; RV, right ventricle.
the ICU, or with a high proportion of intubated patients, report an incidence of LV dysfunction of 11–21% and RV dysfunction of 19–33%.17,23,25,26 In one previous study of Scandinavian COVID-19 patients in the ICU, the prevalence of LV and RV dysfunction was 21% and 32%, respectively.27 Our results are in line with these studies, although comparisons are uncertain due to heterogeneities in the study population and the definitions and measurements used.

Cardiac dysfunction was more common at the time of admission to the ICU than later in the ICU period, and most patients with cardiac dysfunction upon admission normalised their cardiac function within the first week. As most patients with cardiac dysfunction had a dynamic evolvement of cardiac function, it seems like most of these cases were COVID-19-associated cardiac dysfunction and to a lesser extent related to a chronic cardiac disease. In fact, only five patients with cardiac dysfunction had the same pathology on admission and follow-up. Furthermore, no patient had a known history of heart failure and only a minority of patients had a history of coronary artery disease, reflecting the selection of patients admitted to the ICU with COVID-19.

One of the main findings in this study was the high prevalence of elevated PAP, which was seen in almost one-third of all patients, correlating closely with RV dysfunction. Both pulmonary embolism and pulmonary microangiopathy with microthrombosis are common in severe cases of COVID-19 and are known causes of elevated PAP.28–30 Furthermore, RV failure is a complication to ARDS, which has been recognised since before SARS-CoV-2 emerged.31 Both RV dysfunction and elevated PAP were associated with an increased risk of death. This is consistent with several previous publications of COVID-patients, including two meta-analyses and one Scandinavian study.15,24,27 It is likely that RV dysfunction is secondary to elevated PAP in most cases and that this reflects a higher degree of pulmonary disease. It could therefore be of value to investigate patients with RV dysfunction or elevated PAP further by computer tomography for diagnosis of pulmonary embolism, worsening of ARDS, COVID-19 typical infiltrates or secondary bacterial infection. Furthermore, pulmonary vasodilators could be tried to see if there is improvement in RV function or decreased PAP.32

Notably, LV dysfunction was not associated with an increased risk of death. We identified a number of different types and causes of LV dysfunction including COVID-19 myocarditis, Takotsubo syndrome and MIS-C, all described previously in COVID-19.9,10,33 In most cases, we were not able to classify the cause of LV dysfunction but other plausible causes of LV dysfunction are secondary effects due to hypoxia, hypotension or a toxic effect due to the inflammatory state.34 Previous studies have shown conflicting results regarding LV dysfunction and death, and it is likely that LV dysfunction is of less importance compared with RV dysfunction in severe COVID-19.25,35

In conclusion, cardiac dysfunction is common in critically ill Swedish patients with COVID-19 on admission to ICU, and RV dysfunction and elevated PAP are associated with an increased risk of death. We suggest that echocardiography, with focus on RV function and PAP, should be performed in COVID-19 patients on admission to the ICU. However, further research is needed to assess and establish a causal relationship between RV dysfunction and death and how to best treat this condition.

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CONFLICTS OF INTEREST
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ORCID
Josefine Beck-Fris ⏤ https://orcid.org/0000-0003-2400-4092
Keti Dalla ⏤ https://orcid.org/0000-0001-7367-2500
Jonatan Oras ⏤ https://orcid.org/0000-0001-8890-6752

REFERENCES
1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA. 2020;323:1239-1242.
2. Goran DP, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 infection: a narrative review. Ann Intern Med. 2020;173:362-367.
3. Helms J, Combes A, Aissaoui N. Cardiac injury in COVID-19. Intensive Care Med. 2022;48(1):111-113.
4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
5. Cheng MP, Cau A, Lee TC, et al. I oboARBCCSC. Acute cardiac injury in coronavirus disease 2019 and other viral infections—A systematic review and meta-analysis. Crit Care Med. 2021;49:1558-1566.
6. Xie J, Wu W, Li S, et al. Clinical characteristics and outcomes of critically ill patients with novel coronavirus infectious disease (COVID-19) in China: a retrospective multicenter study. Intensive Care Med. 2020;46:1863-1872.
7. Inciardi RM, Lupi L, Zaccone G, et al. cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5:819-824.
8. Deng Q, Hu B, Zhang Y, et al. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. Int J Cardiol. 2020;311:116-121.
9. Meyer P, Degrawue S, Van Delden C, Ghadri JR, Temp lin C. Typical takotsubo syndrome triggered by SARS-CoV-2 infection. Eur Heart J. 2020;41:1860.
10. Dweck MR, Bularga A, Hahn RT, et al. Global evaluation of echocardiography in patients with COVID-19. Eur Heart J Cardiovasc Imaging. 2020;21:949-958.
11. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020;383:334-346.
12. Patel P, DeCuir J, Abrams J, Campbell AP, Godfred-Cato S, Belay ED. Clinical characteristics of multisystem inflammatory syndrome in adults: a systematic review. JAMA Netw Open. 2021;4:e2126456.
13. Lassen MCH, Skaarup KG, Lind JN, et al. Echocardiographic abnormalities and predictors of mortality in hospitalized COVID-19 patients: the ECHOVID-19 study. ESC Heart Fail. 2020;7(6): 4189-4197.
14. Szekely Y, Lichter Y, Taieb P, et al. Spectrum of cardiac manifestations in COVID-19: a systematic echocardiographic study. Circulation. 2020;142:342-353.
15. Díaz-Arocultpa C, Saucedo-Chinchay J, Argulian E. Association between right ventricular dysfunction and mortality in COVID-19 patients: A systematic review and meta-analysis. Clin Cardiol. 2021;44:1360-1370.
16. Bagate F, Masi P, d’Humieres T, et al. Advanced echocardiographic phenotyping of critically ill patients with coronavirus-19 sepsis: a prospective cohort study. J Intensive Care. 2021;9:12.

17. Gonzalez-Fernandez O, Ponz de Antonio I, Rosillo Rodriguez SO, Ruiz Cantador J, Figueira Iglesias JC, Lopez-Sendon Hentschel JL. D-dimer and right ventricular abnormalities as prognostic factors in critically ill COVID-19 patients. Rev Esp Cardiol (Engl Ed). 2020;73:966-968.

18. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1–39):e14.

19. Galiè N, Humbert M, Vachiery JL, et al. 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. 2015;37:67-119.

20. Parasuraman S, Walker S, Loudon BL, et al. Assessment of pulmonary artery pressure by echocardiography-A comprehensive review. IJC Heart and Vasculature. 2016;12:45-51.

21. Metnitz PG, Moreno RP, Almeida E, et al. SAPS 3–From evaluation of the patient to evaluation of the intensive care unit. Part 1: objectives, methods and cohort description. Intensive Care Med. 2005;31:1336-1344.

22. Swedish Intensive Care Registry. (2020, April 1) Data portal for The Swedish Intensive Care Registry. [www document] http://portal.icuregswe.org/utdata/en/home

23. Bleakley C, Singh S, Garfield B, et al. Right ventricular dysfunction in critically ill COVID-19 ARDS. Int J Cardiol. 2021;327:251-258.

24. Corica B, Marra AM, Basili S, et al. Prevalence of right ventricular dysfunction and impact on all-cause death in hospitalized patients with COVID-19: a systematic review and meta-analysis. Sci Rep. 2021;11:17774.

25. Mahmoud-Elsayed HM, Moody WE, Bradlow WM, et al. Echocardiographic Findings in Patients With COVID-19 Pneumonia. Can J Cardiol. 2020;36:1203-1207.

26. Moody WE, Mahmoud-Elsayed HM, Senior J, et al. Impact of right ventricular dysfunction on mortality in patients hospitalized with COVID-19, according to race. CJC Open. 2021;3:91-100.

27. Norderfeldt J, Liliequist A, Frostell C, et al. Acute pulmonary hypertension and short-term outcomes in severe Covid-19 patients needing intensive care. Acta Anaesthesiol Scand. 2021;65(6):761-769.

28. 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.

29. Roncon L, Zuin M, Barco S, et al. Incidence of acute pulmonary embolism in COVID-19 patients: systematic review and meta-analysis. Eur J Intern Med. 2020;82:29-37.

30. Jonmarker S, Hollenberg J, Dahlberg M, et al. Dosing of thromboprophylaxis and mortality in critically ill COVID-19 patients. Crit Care. 2020;24:653.

31. Vieillard-Baron A, Price LC, Matthay MA. Acute cor pulmonale in ARDS. Intensive Care Med. 2013;39:1836-1838.

32. Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. Critical Care (London, England). 2010;14:R169-R269.

33. Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020;20:e276-e288.

34. Puntmann VO, Carej ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiology. 2020;5:1265-1273.

35. Liu Y, Xie J, Gao P, et al. Swollen heart in COVID-19 patients who progress to critical illness: a perspective from echo-cardiologists. ESC Heart Fail. 2020;7(6):3621-3632.

SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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