Cardiac Dysfunction in Critically Ill patients with COVID-19 – A Multicentre Observational Study

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Research

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Abstract

Introduction: The importance of cardiac dysfunction in critically ill patients with COVID-19 is not well studied. The aim of the study was to assess the incidence, clinical risk factors, and prognosis of cardiac dysfunction in critical illness caused by COVID-19, and to evaluate if cardiac biomarkers can detect this condition.

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 hours from admission to the ICU and again after four to seven days. Cardiac biomarkers and clinical data were collected at the time of echocardiography. Cardiac dysfunction was defined as either left ventricular (LV) dysfunction (having an ejection fraction < 50% and/or regional hypokinesia) or right ventricular (RV) dysfunction (having a tricuspid annular plane systolic excursion (TAPSE) < 17mm or a moderate/severe RV dysfunction assessed visually).

Results: We included 132 patients of whom 94 (71%) were included prospectively. The vast majority were intubated (n=127). At the time of admission to ICU, 35 (27%) patients had cardiac dysfunction and 7 patients (5%) had cardiac dysfunction detected later in the ICU-period. LV dysfunction was found in 18 patients and RV dysfunction in 17 patients, 7 patients had both RV and LV dysfunction. Noradrenaline > 0.20µg/kg/min was the only clinical variable associated with a higher risk of cardiac dysfunction. RV dysfunction was associated with an increased risk of death in a risk-adjusted model (OR 3.98, $p = 0.013$). Troponin and N-terminal pro b-type natriuretic peptide (NTproBNP) had moderate values in detecting cardiac dysfunction (AUC 0.729 and AUC 0.744, respectively). A combination of troponin < 1.44 times the upper reference limit and NTproBNP < 857ng/L had 85% probability of excluding cardiac dysfunction.

Conclusions: Cardiac dysfunction is common in critically ill patients with COVID-19. Although not easily detected with clinical variables, cardiac biomarkers might be helpful. RV dysfunction is associated with an increased risk of death, these patients might benefit from further investigation or treatments.

Trial registration: Registered on 24 Aug 2020 at Clinicaltrials.gov; registration number NCT04524234.

Background

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of 21 December 2020, more than 70 million cases have been diagnosed worldwide and 1.6 million people have died from the disease [1]. The clinical characteristics of COVID-19 range from asymptomatic to critical infection (respiratory failure, shock, or multiorgan dysfunction), affecting around 5% of cases [2, 3]. Acute respiratory distress syndrome (ARDS) is the main complication. Other major complications in patients requiring intensive care and mechanical ventilation are cardiac injury and arrhythmias [4].

Myocardial injury with elevated troponin or creatine kinase is reported in 12–38% of hospitalized patients with COVID-19 [5, 6] and in 59% of patients treated in ICUs [7]. Cardiac complications, on a case report basis, include myocarditis [8–10], COVID-19 associated Takotsubo cardiomyopathy [11, 12], and myocardial infarction [12]. Several studies have reported abnormalities in left and right ventricular function in a large proportion of patients with COVID-19 undergoing echocardiography [12–15]. Studies have also shown that left and right ventricular dysfunction are independently correlated to increased mortality in patients with COVID-19 [14, 16]. Few prospective studies of critically ill patients with COVID-19 undergoing echocardiography exist and are limited in scope [13, 17, 18]. Thus, the clinical importance of cardiac dysfunction in critical illness caused by COVID-19 is not yet established. In addition, studies linking echocardiographic findings with clinical data, cardiac biomarkers, and mortality are lacking.

The aim of the present study was to describe the incidence, risk factors, and mortality related to cardiac dysfunction in critical illness caused by COVID-19, and to assess the value of biomarkers for the detection of this condition.

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).

Study design and inclusion

The study was performed at five ICUs in Sweden from 20 April to 30 August 2020 (details of each participating ICU, the ICU settings, and principles of patient treatment are described under Supplemental data). Most patients were included prospectively ($n = 94$, 71%), however 30 patients were included retrospectively from one of the five study sites. In addition, nine patients who had followed the study protocol before the ethics review was approved were included retrospectively from the other four centres.

All patients ≥ 18 years of age who were admitted to a participating ICU with verified COVID-19 were eligible for inclusion. Entering patients had an echocardiogram performed within 72 hours from admission to the ICU. Echocardiography was repeated in four to seven days as study resources became available or if there was evidence of clinical deterioration. Cardiac biomarkers, routine laboratory tests, and clinical data were recorded at each exam. Consent to be included in the study was obtained from the patient or patient's next of kin whenever possible. Retrospective inclusion of patients who had followed the study protocol was approved by the ethics review authority, and for these patients consent was waived.

Echocardiography, definitions, recordings, and measurements

Echocardiography was performed according to standard protocol (see Supplemental data) for assessment of left ventricular (LV) or right ventricular (RV) dysfunction and estimation of pulmonary artery pressure (PAP). Tissue Doppler was not available in all centres and this modality was not further investigated. Cardiac dysfunction was defined as having either LV or RV dysfunction. LV dysfunction was defined as ejection fraction < 50% with or without regional hypokinesia assessed with eyeballing. RV dysfunction was defined as having a tricuspid annular plane systolic excursion (TAPSE) < 17 mm or a moderately or severely depressed RV dysfunction qualitatively judged visually. Elevated PAP was defined as jet velocity of a tricuspid regurgitation > 2.9 m/s (TR Vmax), or, in patients with no tricuspid regurgitation present, having indirect signs of elevated PAP such as RV dilation and a pulmonary acceleration time < 100 ms [19, 20]. 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. Examinations were recorded and, reviewed by a physician certified in echocardiography, if performed by a non-certified intensivist.

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 was recorded. Four sites used highly sensitive troponin T and one site used troponin I. The levels are presented as times above upper limit of normal. The following clinical data was recorded on admission: age, sex, medical history, and Simplified Acute Physiology Score 3 (SAPS 3) [21]. Along with each echocardiography we also recorded systolic blood pressure, mean arterial pressure, diastolic blood pressure, noradrenaline dosage, lactate levels, respiratory settings, and PaO₂/FiO₂-ratio. Routine laboratory tests, including C-reactive protein (CRP), leukocyte count, creatinine levels, and d-dimer, were obtained on the same day as echocardiography. Mortality at 30 days and death occurring within 90 days of admission were registered.

Pre-defined outcomes

The pre-defined primary outcome was 30-day mortality in patients with, versus those without, cardiac dysfunction on admission. Sub-group analysis was performed for LV and RV dysfunction. Pre-defined secondary outcomes were a) incidence 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, as opposed to without cardiac dysfunction. Other analyses were not pre-defined at the initiation of the study and are considered exploratory.

Statistics

A statistical analysis plan was written before the analyses were performed. Continuous variables were checked for normality. 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. A generalized estimating equation was used for identification of clinical variables associated with an increased risk of experiencing cardiac dysfunction

at any time in the ICU. 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 were used to compare incidences over time. Receiver operating characteristics (ROC) analyses were used for estimation of sensitivity and specificity of troponin and NTproBNP for detection of cardiac dysfunction. IBM SPSS Statistics Version 26 were used for the statistical analyses.

No power analysis was performed, as little data of the study population was available when the study was initiated but we aimed for an inclusion of at least 100 patients.

Results

Out of 344 patients admitted to the participating ICUs during the study period, 137 were included in the study. Inclusion failure was mainly because no investigator involved in the study was available for an inclusion or echocardiographic examination. In a sensitivity analysis regarding SAPS score and age, the study population was representative of each ICU's patient population [22]. Two patients were excluded due to their echocardiography being performed > 72 hours from admission. An additional three patients were excluded as a result of poor echocardiographic image quality. Thus, a total of 132 patients included in the final analysis (Fig. 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). Seventeen patients (13%) had a history of cardiac disease and 74 others (56%) had a risk factor for cardiovascular disease. A history of coronary artery disease, valvular disease, or 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 given low-molecular weight heparine (LMWH) in doses corresponding to 0.77 (IQR 0.61–0.95) times the treatment dose for acute thrombotic disease.

Table 1
Background data

Category	Variable	All patients (n = 132)	Cardiac function		
			Normal function (n = 90)	Cardiac dysfunction (n = 42)	p- value
Demographics	Age, years	63 (53–70)	64 (53–70)	61 (52–68)	0.767
	Women, n (%)	34 (26)	27 (30)	7 (17)	0.135
	BMI	30 (25–33)	30 (26–33)	28 (25–34)	0.577
	SAPS3	51 ± 9	51 ± 9	53 ± 10	0.285
Medical	Any cardiac disease, n (%)	17 (13)	8 (9)	9 (21)	0.055
history	Heart failure, n (%)	0 (0)	0 (0)	0 (0)	-
	Coronary artery disease, n (%)	15 (11)	8 (9)	7 (17)	0.240
	Atrial fibrillation, n (%)	5 (4)	2 (2)	3 (7)	0.326
	Valvular disease, n (%)	2 (2)	0 (0)	2 (5)	0.100
	Other cardiac disease, n (%)	1 (1)	0 (0)	1 (2)	0.318
	Cerebrovascular disease, n (%)	10 (8)	5 (6)	5 (12)	0.288
	COPD or asthma, n (%)	13 (10)	9 (10)	4 (10)	> 0.999
	Renal failure, n (%)	7 (5)	4 (4)	3 (7)	0.679
	Any risk factor of CVD, n (%)	74 (56)	44 (49)	30 (71)	0.023
	Diabetes, n (%)	29 (22)	19 (21)	10 (24)	0.822
	Hypertension, n (%)	58 (44)	32 (36)	26 (62)	0.005
	Hyperlipidemia, n (%)	25 (19)	13 (14)	12 (29)	0.061
	Thrombotic disease, n (%)	6 (5)	4 (4)	2 (5)	> 0.999

BMI = body mass index, SAPS3 = simplified acute physiology score 3, COPD = chronic obstructive pulmonary disease, RAAS-blockers = renin angiotensin aldosterone system blockers

Category	Variable	All patients (n = 132)	Cardiac function		
			Normal function (n = 90)	Cardiac dysfunction (n = 42)	p- value
	Other, n (%)	28 (21)	18 (20)	10 (24)	0.651
Medications	RAAS-blockers, n (%)	40 (30)	23 (26)	17 (40)	0.104
	Betablockers, n (%)	31 (23)	20 (22)	11 (26)	0.662
	Platelet inhibitors, n (%)	24 (18)	13 (14)	11 (26)	0.145
	Other anticoagulants, n (%)	5 (4)	3 (3)	2 (5)	0.653
	Other antihypertensives, n (%)	32 (24)	20 (22)	12 (29)	0.514
	Anti-diabetics, n (%)	20 (15)	12 (13)	8 (19)	0.439
	Other medications, n (%)	63 (47)	42 (32)	21 (50)	0.700
BMI = body mass index, SAPS3 = simplified acute physiology score 3, COPD = chronic obstructive pulmonary disease, RAAS-blockers = renin angiotensin aldosterone system blockers					

Cardiac dysfunction and echocardiographic data

Median time to first echocardiography was one day (IQR 1–2); median time to second echocardiography was seven days (IQR 4–9). Thirty-five patients (26%) had cardiac dysfunction upon admission to the ICU, of whom 17 (14%) had LV dysfunction, 16 (12%) had RV dysfunction and 2 had both RV and LV dysfunction. Follow-up echocardiography was available for 89 patients (67%). Another six patients had new onset of LV dysfunction at follow-up while eleven had normalized their LV function. In six patients, a new onset of RV dysfunction was found and thirteen others had normalized the RV function. Thus, a total of 42 patients (32%) had any cardiac dysfunction of whom 18 (14%) had LV dysfunction, 17 (13%) had RV dysfunction, and 7 (5%) had both LV and RV dysfunction detected during their stay in the ICU (Fig. 1). Eight patients (6%) patients with LV dysfunction had LV 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. Two patients had suspected COVID-19 myocarditis, and one had the diagnosis verified with cardiac magnetic resonance imaging (MRI). An 18-year-old patient with global LV hypokinesia was diagnosed with paediatric multisystem inflammatory syndrome (PIMS-TS). A cardiac MRI after three months showed mild cardiac fibrosis, consistent with recent myocarditis.

Patients with LV dysfunction had a larger LV diameter and lower ejection fraction, stroke volume, and cardiac index compared to patients with normal LV function (Table 2). Of the 24 patients with RV dysfunction, 22 had low TAPSE with or without depressed RV function assessed visually, while 2 patients had moderately to severely depressed function assessed visually with preserved TAPSE. Patients with RV dysfunction had more often a tricuspid regurgitation. Elevated PAP was found in 34 patients (26%). This was diagnosed with a TR Vmax > 2.9 in 32 patients and indirect criteria in 2 patients. Elevated PAP was more common in patients with RV dysfunction, as compared to patients with normal cardiac function (58% vs 22%; $p < 0.001$).

Table 2
Echocardiographic data of the 132 participants.

Variable	Normal cardiac function, n = 90	Cardiac dysfunction	
		LV dysfunction, n = 25	RV dysfunction, n = 24
LV diameter, mm	48 ± 4	52 ± 6*	49 ± 5
LV dysfunction, n (%)	-	25 (100)*	7 (29)*
LV ejection fraction, %	59 ± 5	43 ± 6*	57 ± 11
Stroke volume indexed	40 ± 12	30 ± 9*	37 ± 11
Cardiac index	3,1 ± 0,9	2.4 ± 1*	3.0 ± 1
Regional hypokinesia, n (%)	-	8 (32)*	0 (0)
RV dysfunction, n (%)	-	6 (24)*	24 (100)*
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)*
TR Vmax is reported from patients with a TR present. LV = left ventricle, RV = right ventricle, TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation, TR Vmax = maximal tricuspid regurgitation velocity, PAP = pulmonary arterial pressure. * p-value < 0.05 vs group normal cardiac function. In group normal cardiac function, data is reported for first echo. In group LV or RV dysfunction, data is reported for first echo with dysfunction.			

Clinical characteristics and routine laboratory data

Clinical characteristics did not differ between those patients with and those without cardiac dysfunction at the time of the first echocardiography, except that patients with cardiac dysfunction more often had a high dose of noradrenaline ($> 0.20 \mu\text{g/kg/min}$). In a generalized regression analysis, taking repeated examinations into consideration, a dose of noradrenaline $> 0.20 \mu\text{g/kg/min}$ was the only clinical variable associated with an increased risk of cardiac dysfunction (see Supplemental data). Levels of d-dimer were slightly higher (2.0 mg/L vs 1.6 mg/L , $p = 0.006$) in patients with cardiac dysfunction, but there were no differences in other routine laboratory data (Table 3).

Table 3
Hemodynamic, ventilatory data and routine lab at time of first echo

Category	Variable	Cardiac function		p-value
		Normal function (n = 97)	Cardiac dysfunction (n = 35)	
Hemodynamic	Systolic blood pressure, mmHg	126 ± 18	124 ± 19	0.707
	Mean arterial pressure, mmHg	79 ± 10	78 ± 12	0.602
	Heart rate, bpm	78 ± 15	83 ± 21	0.138
	Noradrenaline > 0.20 µg/kg/min, n (%)	7 (7)	8 (23)	0.025
Ventilatory	FiO2, %	50 (40–65)	50 (45–70)	0.287
	PaO2/FiO2	19 (14.6–25.2)	20.6 (16.2–24.7)	0.624
	Mechanical ventilation, n (%)	83 (86)	31 (89)	0.780
	Ventilation mode			0.337
	PCV-VG, n (%)	43 (44)	14 (40)	
	PSV, n (%)	22 (23)	5 (14)	
	PCV, n (%)	9 (9)	8 (23)	
	APRV, n (%)	9 (9)	4 (11)	
	High flow oxygen, n (%)	9 (9)	3 (9)	
	NIV, n (%)	4 (4)	0 (0)	
	Oxygen mask, n (%)	1 (1)	1 (3)	
	Prone position within 24 hours, n (%)	36 (37)	9 (26)	0.299
Routine lab	Hemoglobin, g/l	113 (105–127)	116 (101–122)	0.473
	CRP, mg/L	230 (140–290)	230 (190–310)	0.196
	Leukocyte count, per liter	9.1 (7.2–12.2)	9.8 (6–13.4)	0.897
	Creatinine, µmol/L	81 (56–108)	93 (66–127)	0.106

FiO2 = fraction of inspired oxygen, PaO2 = partial pressure of oxygen, PEEP = positive end-expiratory pressure, PCV-VG = pressure controlled ventilation – volume guaranteed, PSV = pressure support ventilation, PCV = pressure controlled ventilation, APRV = airway pressure release ventilation, NIV = non-invasive ventilation, CRP = C-reactive protein.

Category	Variable	Cardiac function		p-value
		Normal function (n = 97)	Cardiac dysfunction (n = 35)	
	Fibrinogen, g/L	6.6 (5.3–7.6)	6.9 (5.7–8)	0.557
	D-dimer , mg/L	1.4 (0.82–2.85)	2 (1.5–13)	0.006
	Lactate levels, µg/l	1.3 (1–1.7)	1.4 (1.1–1.8)	0.325
FiO2 = fraction of inspired oxygen, PaO2 = partial pressure of oxygen, PEEP = positive end-expiratory pressure, PCV-VG = pressure controlled ventilation – volume guaranteed, PSV = pressure support ventilation, PCV = pressure controlled ventilation, APRV = airway pressure release ventilation, NIV = non-invasive ventilation, CRP = C-reactive protein.				

Mortality and clinical course

In total, 24 patients (18%) died within 30 days of admission to the ICU. Thirty-day mortality was the same in patients with cardiac dysfunction ($n = 10$, 24%) as in those with normal cardiac function ($n = 14$, 16%, $p = 0.332$). There was no increased risk of death at 30 days in patients with as opposed to without cardiac dysfunction in a risk-adjusted model (Odds ratio [OR] 1.56, $p = 0.391$). RV dysfunction on admission (risk-adjusted OR 7.03, $p = 0.002$), or detected while in the ICU (risk-adjusted OR 3.98, $p = 0.013$), was associated with an increased risk of death at 30 days. LV dysfunction was not associated with any increased risk of death at 30 days. Elevated PAP detected while in the ICU was associated with an increased risk of death at 30 days (risk-adjusted OR 3.88, $p = 0.007$) (Table 4). There was also an increased risk of death during the first 90 days from admission in patients with RV dysfunction or elevated PAP (Fig. 2).

Table 4
Mortality analysis

Presentation of cardiac dysfunction	Variable	Crude risk of death			Adjusted risk of death*		
		OR	95% CI for OR	p-value	OR	95% CI for OR	p-value
On admission	Cardiac dysfunction	1.89	0.74–4.83	0.182	1.56	0.56–4.33	0.391
	LV dysfunction	0.49	0.11–2.26	0.358	0.22	0.04–1.38	0.106
	RV dysfunction	4.90	1.68–14.3	0.004	7.03	2.08–23.8	0.002
	Elevated PAP	2.49	0.96–6.45	0.061	2.34	0.84–6.51	0.103
At any time	Cardiac dysfunction	1.70	0.68–4.22	0.255	1.43	0.53–3.83	0.476
in ICU	LV dysfunction	0.56	0.15–2.04	0.379	0.29	0.06–1.34	0.113
	RV dysfunction	3.72	1.38–10.0	0.009	3.98	1.34–11.8	0.013
	Elevated PAP	3.92	1.57–9.84	0.004	3.88	1.45–10.4	0.007
Cardiac dysfunction refers to left or right ventricular dysfunction. CI = confidence interval, OR = odds ratio, LV = left ventricle, RV = right ventricle, PAP = pulmonary arterial pressure, ICU = intensive care unit							
* Adjusted for SAPS 3 score							

Patients with cardiac dysfunction more often needed continuous renal replacement therapy ($n = 16$, 38%) as compared to patients with normal cardiac function ($n = 16$, 18%, $p = 0.016$). Patients with cardiac dysfunction had less days alive outside ICU, as compared to patients with normal cardiac function (median 0 [IQR 0–10] versus 13 days [IQR 0–20], $p = 0.042$). Length of hospital stay did not differ between the two groups (see Supplemental data).

Cardiac biomarkers

Troponin levels were higher in patients with cardiac dysfunction (2.04 times the upper reference levels [IQR 1.06–7.71]) as compared to patients with normal cardiac function (median 0.81 [IQR 0.51–1.64], $p < 0.001$). Levels of NTproBNP were also higher in patients with cardiac dysfunction (1220 ng/l [IQR 336–3540]), as compared to patients with normal cardiac function (267 ng/l [IQR 139–504], $p < 0.001$, Supplemental data). Area under the curve (AUC) of troponin for detection of cardiac dysfunction was 0.729, and the best cut-off value using Youden's index was troponin > 1.44 times over the upper reference

limit. Detection of cardiac dysfunction with NTproBNP had an AUC of 0.744, with a best cut-off value of a NTproBNP > 857 ng/l. Using a combination of troponin > 1.44 times the upper reference limit *and* NTproBNP > 857 ng/l had a positive predictive value (PPV) of 81% for detection of cardiac dysfunction. Troponin < 1.44 times the upper reference limit *and* NTproBNP < 857 ng/l had 85% probability of excluding cardiac dysfunction. (Table 5).

Table 5
Troponin and NTproBNP for detection of cardiac dysfunction

Test	Variable cut-off	AUC	Sensitivity	Specificity	PPV	NPV
Detection of cardiac dysfunction	Troponin > 1.44 times upper ref	0.729	69%	72%	55%	82%
	NTproBNP > 857 ng/l	0.744	56%	89%	71%	80%
	Troponin > 1.44 times upper ref <i>and</i> NTproBNP > 857 ng/l		54%	94%	81%	80%
Exclusion of cardiac dysfunction	Troponin < 1.44 times upper ref <i>and</i> NTproBNP < 857 ng/l		66%	76%	85%	53%
Cardiac biomarkers obtained from echocardiography at first presentation of cardiac dysfunction. In patients with normal echoes, cardiac biomarkers used were also obtained at first echocardiography. AUC = area under curve, PPV = positive predictive value, NPV = negative predictive value, NTproBNP = N-terminal pro b-type natriuretic peptide						

Discussion

The main findings of this study are that (1) cardiac dysfunction commonly occurs in critical illness caused by COVID-19; (2) RV dysfunction, defined as a TAPSE < 17 mm or moderately to severely depressed function assessed visually, was associated with an increased risk of death; (3) cardiac dysfunction is not easily recognized by clinical variables; and that (4) cardiac biomarkers have a moderate value in detecting cardiac dysfunction in patients critically ill with COVID-19.

We found that 32% of the patients had LV or RV dysfunction at some time during their stay in the ICU. Cardiac dysfunction was more common at the time of admission to the ICU than later in the ICU-period. The incidence of cardiac dysfunction was in line with other studies of patients hospitalized, whose COVID-19 disease severities ranged from mild to severe, and where LV dysfunction was found in 10 to 42% and RV dysfunction in 14 to 39% [15, 23, 24]. One reason for the relatively low incidence of RV dysfunction may have been the liberal use of thromboprophylaxis that was introduced early in the study period [25], leading to less pulmonary embolism than in many earlier studies [15, 26]. We did not assess patients with tissue doppler or strain analysis, modalities that are more sensitive for the detection of ventricular dysfunction, which could explain a comparative low incidence of cardiac dysfunction in our study.

We found a number of different types of LV dysfunction. Two patients had suspected COVID-19 myocarditis; the diagnosis was verified in one patient. Knowledge of COVID-19 myocarditis is still very limited. Patients are reported to present in various ways and they may have either global or regional hypokinesia, with or without preserved ejection fraction, and their recovery time may be brief or prolonged [27, 28]. There are no strict criteria for COVID-19 myocarditis. In the present study we can neither confirm nor exclude additional cases within our cohort. Five patients presented with a clinical presentation of the Takotsubo syndrome. Severe respiratory distress is an established trigger of Takotsubo, and the incidence we found is in agreement with other studies of Takotsubo syndrome in critically ill patients [29]. Moreover, Takotsubo has also been reported in several case studies of patients with COVID-19 [11, 12]. One patient was diagnosed with PIMS-TS, a condition associated with cardiac dysfunction in COVID-19 [30]. Other plausible causes of LV dysfunction are secondary effects due to hypoxia, hypotension, or a toxic effect due to the inflammatory state [31]. RV dysfunction was seen in 18% of participants, and there was a close correlation between elevated PAP and RV dysfunction. Thus, RV dysfunction in most cases is probably attributable to an increased RV afterload. Elevated PAP was common in our study population, having been seen in nearly one-third of all patients. Both pulmonary embolism and pulmonary microangiopathy with microthrombosis are common in severe cases of COVID-19 and are known causes of elevated PAP [32, 33]. Pulmonary hypoxia with hypoxic vasoconstriction was another likely cause of elevated PAP among our study patients [34]. Increased right chamber afterload due to mechanical ventilation is of course a common cause of elevated PAP in ICU patients in general.

Cardiac dysfunction was not associated with an increased risk of death in our study. However, patients with cardiac dysfunction had a more complex course of disease with a greater need for renal replacement therapy and less ICU-free days. It is unclear if this is a causal relationship, or if cardiac dysfunction is a marker for more severe disease. In a sub-group analysis, RV dysfunction and elevated PAP were independently associated with an increased risk of death. This is consistent with findings from other studies of patients with ARDS and hospitalized patients with COVID-19 [13, 14]. Regrettably, the main cause of death was not registered in the present study, and patients were not systematically assessed for pulmonary embolism. It is, therefore, unclear if RV dysfunction and elevated PAP are only markers of more severe pulmonary disease, with a subsequent risk of pulmonary collapse and respiratory death, or if there are other direct causes as well. It seems reasonable to assume that patients with RV dysfunction, elevated PAP, or both will benefit from further investigation 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 [35]. In severe cases of COVID-19, RV dysfunction could be supportive in a decision to prepare for, or initiate, extracorporeal membrane oxygenation (ECMO).

Cardiac dysfunction was not easily detected by clinical characteristics. Our hypothesis was that cardiac dysfunction would be associated with a more severe clinical picture, such as higher levels of oxygen, respiratory support, or elevated lactate levels. The only variable associated with an increased risk of having cardiac dysfunction was a high dose of noradrenaline. It is likely because that critical illness from COVID-19 is such a severe respiratory disease, the contribution of cardiac dysfunction is not detectable by

clinical variables in such a patient population. However, high doses of noradrenaline should be considered a marker for a more severe cardiovascular deterioration. In patients requiring noradrenaline > 0.20 µg/kg/min, cardiac dysfunction should be suspected and echocardiography ought to be performed.

The cardiac biomarkers troponin and NTproBNP only showed a moderate ability to detect cardiac dysfunction. However, a combination of troponin at less than 1.44 times its upper reference limit and NTproBNP < 857 ng/l had a negative predictive value of 85% of excluding cardiac dysfunction and might be used as a tool to rule out the need of echocardiography. This could be important in ICUs treating patients with COVID-19, where there is a need to conserve personal protective equipment and minimize the number of individuals interacting with contagious patients. On the other hand, levels above these limits had a predictive value of 81% for detection of cardiac dysfunction, suggesting that echocardiography should be performed.

Our study has some limitations. Inclusion rates were relatively low, as only 40% of the potential study population was included, mostly due to a lack of study resources. Moreover, a number of patients were retrospectively included. Nevertheless, a sensitivity analysis showed the study population was a representative sample of each site's total population. The main strength of the study is the multi-centre design. Although the sample size is relatively low in absolute numbers, it is the largest study to date with echocardiographic evaluation, cardiac biomarkers, and clinical data carried out among COVID-19 patients in an ICU-setting.

Conclusions

Cardiac dysfunction is common in critical illness caused by COVID-19, but it is not easily detected on the basis of clinical characteristics. Cardiac biomarkers here prove be helpful. The ominous sign of RV dysfunction benefit from further investigation and treatment with pulmonary vasodilators or initiation of ECMO.

Abbreviations

APRV

airway pressure release ventilation

ARDS

acute respiratory distress syndrome

AUC

area under curve

BMI

body mass index

COPD

chronic, obstructive pulmonary disease

CRP

C-reactive protein
CRRT
continuous renal replacement therapy
ECMO
extracorporeal membrane oxygenation
ICU
intensive care unit
IQR
interquartile range
LMWH
low molecular weight heparine
LV
left ventricular
LVOT
area of LV outflow tract
MRI
magnetic resonance imaging
NIV
non-invasive ventilation,
NTproBNP
N-terminal pro b-type natriuretic peptide
OR
odds ratio
PAP
pulmonary artery pressure
PEEP
positive end-expiratory pressure
PCV
pressure controlled ventilation
PCV-VG
pressure controlled ventilation – volume guaranteed
PIMS-TS
paediatric multisystem inflammatory syndrome
PPV
positive predictive value
PSV
pressure support ventilation
RAAS-blockers
renin angiotensin aldosterone system blockers
ROC

receiver operating characteristics
RV
right ventricular
SAPS 3
simplified acute physiology score 3
SARS-CoV-2
severe acute respiratory syndrome coronavirus 2
TAPSE
tricuspid annular plane systolic excursion
TR
tricuspid regurgitation
TR Vmax
jet velocity of a tricuspid regurgitation
VTI
velocity time integral
95% CI
95% confidence interval

Declarations

Ethics approval and consent to participate

This study was approved by the Swedish Ethics Review Authority Sweden (approval number 036-18, 2020-01684 and 2020-03815). Consent to be included in the study was obtained from the patient or patient's next of kin whenever possible. For patients retrospectively included, patients consent was waived.

Consent for publication

No individual data was reported in the study.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

JO and BR received funding from the Swedish Heart-Lung foundation for the conduct of this study. The other authors declare that they have no competing interests.

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Authors' contributions

JH initiation of the study, conceptualization and study design, drafting and revising the manuscript, echocardiographic examinations, data acquisition and interpretation. JBF study design, inclusion of patients, data acquisition, compilation and interpretation, drafting and revising the manuscript. CJ study design, echocardiographic examinations, data acquisition. KD, NN echocardiographic examinations, data acquisition. SM, JC data acquisition. ERW data acquisition and compilation. OC reviewing echocardiographic examinations, data acquisition. AY, study design, substantively revised the manuscript. MC data acquisition, substantively revised the manuscript. BR study design and conceptualization, statistical analyses, funding. JO initiation of the study, conceptualization and study design, echocardiographic examinations, data acquisition and interpretation, statistical analyses, funding, drafting and revising the manuscript. All authors read and revised the paper. All authors have agreed to be accountable for all aspects of the work. All authors approved the final version of the manuscript.

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Figures

Figure 1

LV = left ventricle, RV = right ventricle

Figure 2

Kaplan-Meier survival curves for patients with versus without cardiac dysfunction (A), LV dysfunction (B), RV dysfunction (C) and elevated PAP (D). The time is calculated from first echo, or in patients with presentation of dysfunction later in the ICU period, the time of second echo. LV = left ventricle, RV = right ventricle

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