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*the ECHOVID-19 study*

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# Echocardiographic abnormalities and predictors of mortality in hospitalized COVID-19 patients: the ECHOVID-19 study

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## Abstract

**Aims** The present study had two aims: (i) compare echocardiographic parameters in COVID-19 patients with matched controls and (2) assess the prognostic value of measures of left (LV) and right ventricular (RV) function in relation to COVID-19 related death.

**Methods and results** In this prospective multicentre cohort study, 214 consecutive hospitalized COVID-19 patients underwent an echocardiographic examination (by pre-determined research protocol). All participants were successfully matched 1:1 with controls from the general population on age, sex, and hypertension. Mean age of the study sample was 69 years, and 55% were male participants. LV and RV systolic function was significantly reduced in COVID-19 cases as assessed by global longitudinal strain (GLS) ( $16.4\% \pm 4.3$  vs.  $18.5\% \pm 3.0$ ,  $P < 0.001$ ), tricuspid annular plane systolic excursion (TAPSE) ( $2.0 \pm 0.4$  vs.  $2.6 \pm 0.5$ ,  $P < 0.001$ ), and RV strain ( $19.8 \pm 5.9$  vs.  $24.2 \pm 6.5$ ,  $P = 0.004$ ). All parameters remained significantly reduced after adjusting for important cardiac risk factors. During follow-up (median: 40 days), 25 COVID-19 cases died. In multivariable Cox regression reduced TAPSE [hazard ratio (HR) = 1.18, 95% confidence interval (CI) [1.07–1.31],  $P = 0.002$ , per 1 mm decrease], RV strain (HR = 1.64, 95%CI[1.02;2.66],  $P = 0.043$ , per 1% decrease) and GLS (HR = 1.20, 95%CI[1.07–1.35],  $P = 0.002$ , per 1% decrease) were significantly associated with COVID-19-related death. TAPSE and GLS remained significantly associated with the outcome after restricting the analysis to patients without prevalent heart disease.

**Conclusions** RV and LV function are significantly impaired in hospitalized COVID-19 patients compared with matched controls. Furthermore, reduced TAPSE and GLS are independently associated with COVID-19-related death.

**Keywords** COVID-19; Echocardiography; Global longitudinal strain; Right ventricular strain; SARS-CoV-2

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[Correction added on 26 December 2020 after first online publication: The middle name of the author Filip Krag Knop has been added in this version.]

## Introduction

The COVID-19 pandemic has rapidly spread around the world and resulted in a high number of hospitalizations, intensive care unit admissions, and deaths.<sup>1,2</sup> COVID-19 may affect the heart in several different ways. The right ventricle (RV) could be impacted secondarily to pulmonary pathology-induced elevation in RV afterload.<sup>3</sup> The left ventricular (LV) function may be affected secondary to RV volume and pressure overload due to ventricular interdependence.<sup>4</sup> But direct cardiac complications in COVID-19 have been reported in several case-series including acute myocardial injury,<sup>5</sup> myocarditis,<sup>6,7,8</sup> and Takotsubo cardiomyopathy.<sup>9</sup> However, a direct measure of how the heart is affected in COVID-19 compared with matched controls from the general population has not yet been reported.

Transthoracic echocardiography is a cheap, fast and widely available tool that can be used to directly quantify myocardial function in both systole and diastole. Measures such as LV ejection fraction (LVEF), pulsed-wave Doppler measurements (such as  $E/e'$ ) and RV parameters [tricuspid regurgitation velocity and tricuspid annular plane systolic excursion (TAPSE)] are widely validated measurements and reveal substantial information about cardiac function.

Global longitudinal strain (GLS) is a speckle tracking based method to angle-independently measure LV contraction.<sup>10,11,12</sup> Compared with LVEF, GLS measurements are less influenced by loading conditions, myocardial compliance, and afterload as it measures myocardial deformation directly. In this study, we investigated how echocardiographic parameters, both conventional and speckle tracking measurements, potentially differed between patients hospitalized with COVID-19 and matched controls. We hypothesized that impaired myocardial function measured by echocardiography is present in hospitalized COVID-19 patients compared with controls and that it predicts mortality.

## Methods

### Population

The ECHOVID-19 study is a prospective cohort study of hospitalized COVID-19 patients. Patients were included from all hospitals in eastern Denmark. All patients were included from 30 March 2020 to 1 June 2020. Inclusion criteria were age

≥18 years, hospitalization with a laboratory-confirmed diagnosis of COVID-19, and being capable of signing a written informed consent. All patients from the COVID-19 wards were invited to participate if able to sign a written informed consent. The investigators enrolling patients did not have any prior knowledge of the health status of the invited patients. All patients were consecutively invited to participate independently of their health status. All included participants gave written informed consent. The study was performed in accordance with the Second Declaration of Helsinki and approved by the regional ethics board. The ECHOVID-19 study is registered at Clinicaltrials.gov (NCT04377035). A power test was performed to determine the sufficient number of patients to detect echocardiographic differences (Supporting Information, *Table S1*).

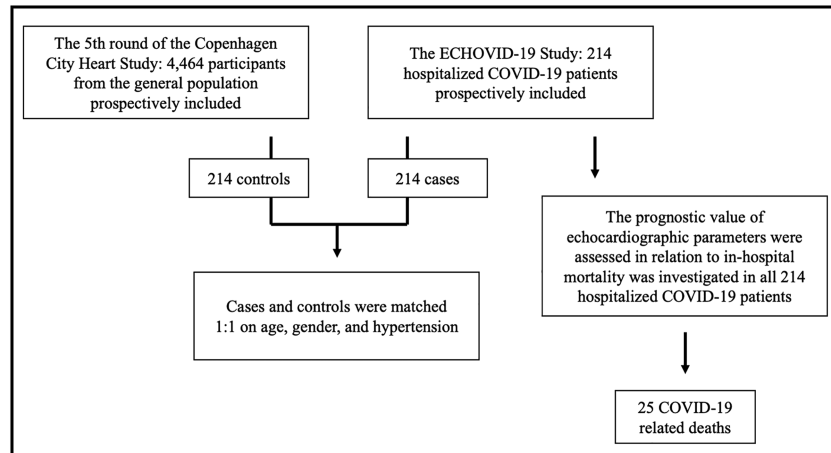
### Controls and matching

The control group comprised participants from the fifth round of the Copenhagen City Heart Study (CCHS5). The CCHS5 is a large general population study in which a random sample of 4464 participants from the greater Copenhagen area underwent an echocardiographic examination in which speckle tracking was also performed. The CCHS5 has previously been described in detail.<sup>13</sup> A total of 214 COVID-19 patients were included in the ECHOVID-19 study. Cases and controls were matched on age (5 year intervals), sex, and hypertension. On the basis of these criteria, all COVID-19 patients were matched 1:1 with controls from the CCHS5 (*Figure 1*).

### Clinical data and baseline information

All participants in the ECHOVID-19 study answered an extensive questionnaire covering family history of cardiovascular disease, smoking history, medication, physical activity, and alcohol consumption. The electronic health records were used to obtain clinical information such as early warning score parameters (of the day of the echocardiographic examination) and comorbidities. Hypertension and hyperlipidaemia were defined as use of antihypertensive/cholesterol lowering medication, self-reported information, or reported in the electronic health record. Diabetes mellitus was defined as the use of antidiabetic medication, self-reported disease, or reported in the electronic health record. Heart failure

**Figure 1** Study flow chart. Flow chart illustrating inclusion process for cases and controls for matched comparison and assessment of the prognostic value of echocardiography. BMI, body mass index.



was defined as the use of heart failure medication (beta-blockers, aldosterone antagonists, and ACE/ARB inhibitors all with an indication for heart failure), self-reported disease, or reported in the electronic health record. Previous ischemic heart disease was defined as admission due to myocardial infarction, percutaneous coronary intervention, or coronary by-pass grafting. Prevalent heart disease was defined as the composite of heart failure and previous ischemic heart disease. LV dysfunction was defined as LVEF < 40%, while RV dysfunction was defined as TAPSE < 1.6 cm).<sup>14,15</sup>

## Outcome

The outcome was death. All deaths registered during the follow-up period were related to COVID-19. The date of follow-up was 1 June 2020 on which all patients were censored.

Development of pulmonary embolisms was CT-verified. The development of acute respiratory distress syndrome was defined according to the Berlin criterium.

## Transthoracic echocardiography

The portable Vivid IQ Ultrasound System (GE Healthcare, Horten, Norway) was used for all echocardiographic examinations which were performed bedside. All examinations were performed according to a pre-determined comprehensive echo-protocol. A single trained investigator blinded to all clinical information analysed all echocardiographic examinations offline. Commercially available post-processing software (ECHOPAC Version 203, GE Vingmed Ultrasound AS) was used for all analyses.

## Conventional echocardiography

Left ventricular ejection fraction was measured using Simpson's biplane method. Pulsed-wave Doppler at the tips of the mitral leaflets in the four-chamber view was used to measure peak mitral inflow velocities: E-wave, A-wave, E/A ratio, and deceleration time of E. Left atrial volume was measured by the area-length method in the apical four-chamber and two-chamber view and indexed to body surface area to calculate left atrial volume index. Colour tissue Doppler velocities ( $e'$ ,  $a'$ , and  $s'$ ) were obtained from the apical four-chamber view at the septal and lateral wall of the mitral annulus. E-wave was indexed to  $e'$  to obtain E/ $e'$ . M-mode was used in the apical four-chamber view to measure TAPSE. All conventional measurements were made as recommended by existing guidelines.<sup>16,17</sup>

## Two-dimensional speckle tracking

All analyses were performed offline in the three apical views (four-chamber, two-chamber, and three-chamber). Projections with the highest available frame rate were used. A semi-automatic function was used to place the region of interest over the entire myocardial wall. In cases of inaccurate tracing, the region of interest could be manually adjusted. Six regions from each projection were included into a global 18-segment model of the LV. Global values were calculated as the average of all segments included. A segment could be excluded by the investigator if it was deemed untraceable. In total, 20 cases (9.3%) did not have sufficient image quality for 2DSTE analysis. Right ventricular longitudinal strain (RVLS) was measured in an apical four-chamber projection optimized for a view of the RV. The RV free wall was divided into three segments, and the septal deformation was not included in RVLS. The strain values of the three segments were averaged to obtain RVLS. GLS and RVLS were expressed as absolute values. The American Society of Echocardiography

together with the European Association of Cardiovascular Imaging have previously published normal values of conventional and 2DSTE parameters.<sup>18</sup>

**Reproducibility** To evaluate reproducibility of TAPSE and GLS in cases, intraobserver and interobserver variability (mean differences  $\pm$  1.96 standard deviation) was obtained through the Bland–Altman method. Intraobserver variability of TAPSE was  $1 \pm 3$  mm [intra-class correlation coefficient (ICC) = 0.98], while interobserver variability was  $1 \pm 4$  mm (ICC = 0.95). Intraobserver variability for GLS was  $0.1 \pm 2.2\%$  (ICC = 0.98), while interobserver variability was  $0.1 \pm 2.9\%$  (ICC = 0.96).

## Statistics

A two-tailed *P* value  $< 0.05$  was used to define statistical significance. Baseline data (Tables 1 and 2) were listed as comparisons between cases and controls. Differences in baseline characteristics between survivors and non-survivors are listed in Table S1. Histograms and Q–Q plots were used to determine the type of distribution for continuous variables. Gaussian distributed (reported as means  $\pm$  SD) variables were compared using ANOVA, non-Gaussian distributed variables [reported as medians with inter-quartile range (IQR)] were compared using Wilcoxon rank-sum test or Kruskal–Wallis test as appropriate. Categorical variables were compared using Pearson's  $\chi^2$  test, and dichotomous variables were compared using Fisher's exact test. Multivariable linear regression models were used to adjust for heart rate, prevalent heart failure, smoking status, diagnosis of chronic obstructive pulmonary disease, hyperlipidaemia, body mass index and eGFR when testing for differences in echocardiographic parameters between cases and controls

(Table 2). The prognostic value of significantly affected echocardiographic measurements was investigated using univariable and multivariable Cox proportional hazard regression models in relation to COVID-19-related death. Two multivariable Cox regression models were constructed. Model 1 was adjusted for age and sex, and Model 2 was adjusted for the same variables as Model 1 and additionally for hypertension, diabetes, body mass index, and smoking status. Secondary Cox regressions were performed with Model 2 and additionally oxygen therapy at the day of the visit, eGFR, and C-reactive protein. In the survival analysis, a sensitivity analysis was conducted in which all patients with prevalent heart disease were excluded from the analyses. Logistic restricted cubic spline models were used to visualize the association between affected echocardiographic parameters and COVID-19-related death (Figure 2). The Akaike information criterion was used to choose the number of knots for the spline models. Harrel's C-statistics were calculated for TAPSE and GLS and compared.

## Results

A total of 214 patients with COVID-19 and 214 matched COVID-19 free controls were included in the study. Baseline characteristics of cases and controls are listed in Table 1. All cases underwent an echocardiographic examination a median of 4 days IQR: [2, 8]) from the day of admission. The mean age of the two groups were 69 years, and 55% were male participants in both groups. Cases and controls differed on several parameters including cardiovascular risk factors. A larger proportion of cases suffered from diabetes, hyperlipidaemia, prevalent heart failure, and chronic obstructive pulmonary disease.

**Table 1** Baseline characteristics of cases and controls

Characteristic	Controls	Cases	<i>P</i> value
Number	214	214	
Male (%)	117 (54.7%)	117 (54.7%)	1.00
Age, years (SD)	68.6 (13.5)	68.9 (13.5)	0.80
BMI, kg/m <sup>2</sup> (SD)	27.2 (4.8)	26.8 (5.6)	0.37
Pack-years if smoking history, (IQR)	20.3 (8.6, 36.9)	25.0 (15.0, 41.0)	0.31
Smoking status, (%)			0.003
Current	27 (12.6%)	12 (6.2%)	
Former	102 (47.7%)	74 (38.5%)	
Never	85 (39.7%)	106 (55.2%)	
Hypertension (%)	122 (57.0%)	122 (57.0%)	1.00
Diabetes (%)	18 (8.4%)	52 (25.5%)	$< 0.001$
Hyperlipidaemia (%)	56 (26.2%)	86 (40.2%)	0.002
Prevalent heart failure (%)	11 (5.1%)	22 (10.3%)	0.046
Previous ischemic heart disease (%)	24 (11.2%)	34 (15.9%)	0.16
Chronic obstructive pulmonary disease (%)	14 (6.5%)	32 (15.0%)	0.005
Heart rate, beats per minute (SD)	65.8 (11.0)	81.4 (16.6)	$< 0.001$
eGFR, mL/min/1.73 m <sup>2</sup> (IQR)	81.8 (70.3, 91.9)	86.7 (63.3, 111.7)	0.060

BMI, body mass index; IQR, inter-quartile range.

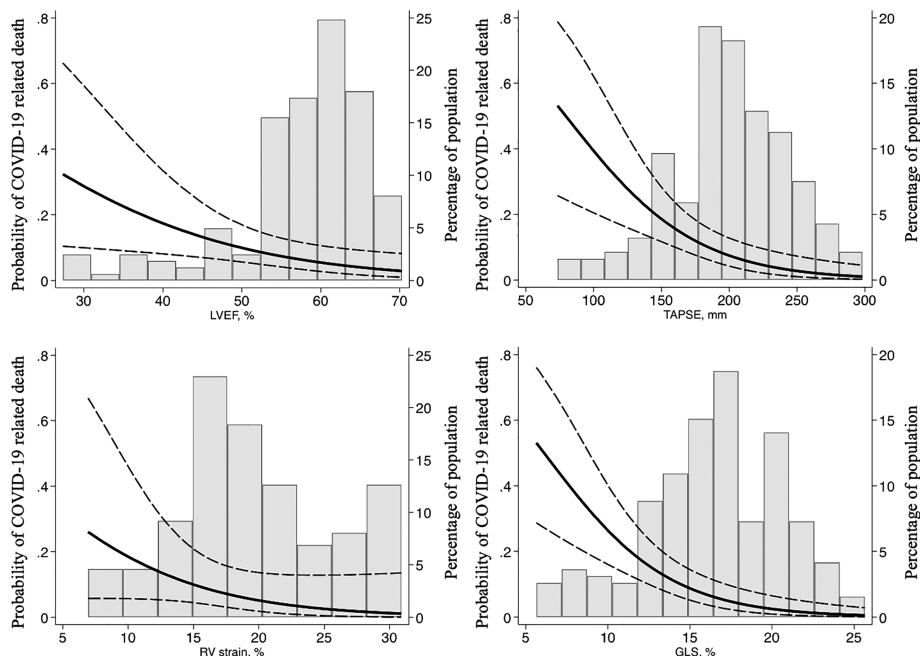
**Table 2** Differences in echocardiographic parameters between cases and controls

Variable	Controls	Cases	P value	Adjusted P value <sup>a</sup>
Number	214	214		
<b>Systolic function</b>				
Left ventricular ejection fraction, (%) mean (SD)	59.0 ± 7.2	57.6 ± 9.0	0.15	
Global longitudinal strain, (%) mean (SD)	18.5 ± 3.0	16.4 ± 4.3	<0.001	0.047
<b>Diastolic function</b>				
E/e', median (IQR)	8.5 [6.6, 10.5]	8.5 [6.8, 11.9]	0.10	
E/A ratio median (IQR)	0.9 [0.7, 1.2]	1.0 [0.8, 1.3]	0.006	0.23
E-wave deceleration time, ms (IQR)	193.4 [165.8, 228.5]	189.9 [156.4, 228.2]	0.48	
<b>Right ventricular function</b>				
TAPSE, mean (SD)	2.6 ± 0.5	2.0 ± 0.4	<0.001	<0.001
TR velocity, m/s mean (SD)	2.4 ± 0.4	2.5 ± 0.3	0.46	
Right ventricle longitudinal strain, % (SD)	24.2 ± 6.5	19.8 ± 5.9	<0.001	0.004

BMI, body mass index; IQR, inter-quartile range.

<sup>a</sup>Multivariable model adjusting for heart rate, prevalent heart failure, smoking status, hyperlipidaemia, diabetes, eGFR, COPD, and BMI.

**Figure 2** Association between RV and LV echocardiography-assessed function and COVID-19-related death. Displaying the unadjusted probability of COVID-19-related death (with 95% confidence intervals) for the population in relation to LVEF, GLS, TAPSE, and RVLS. GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; RVLS, right ventricular longitudinal strain; TAPSE, tricuspid annular plane systolic excursion.



## Echocardiographic data

Median time from admission to echocardiography was 4 days IQR: [2, 8]. Several echocardiographic parameters differed between cases and controls (Table 2). Systolic function was significantly reduced in COVID-19 patients as assessed by GLS (cases: 16.4% ± 4.3 vs. controls: 18.5% ± 3.0,  $P < 0.001$ ) and remained significantly reduced after multivariable adjustment ( $P = 0.047$ ). Of the

investigated diastolic parameters, only E/A ratio differed between the two groups (cases: 1.0 [0.8, 1.3] vs. controls: 0.9 [0.7, 1.2],  $P = 0.006$ ). However, this difference was not significant after multivariable adjustment ( $P = 0.23$ ). Right ventricular function was significantly impaired in COVID-19 cases compared with controls, (TAPSE: cases: 2.0 ± 0.4 vs. controls: 2.6 ± 0.5,  $P < 0.001$ , and RVLS: cases: 19.8 ± 5.9 vs. controls: 24.2 ± 6.5,  $P < 0.001$ ), and remained significant after multivariable adjustment (TAPSE:  $P < 0.001$ ,

RVLS:  $P = 0.004$ ). Tricuspid regurgitation velocity was similar in the two groups.

### The prognostic value of echocardiographic parameters

During the follow-up period (median 40 days IQR: [27, 52]), 25 COVID-19 cases died. Median time from the echocardiographic examination to death was 8 days IQR: [5, 18]. The cause of death was respiratory failure in 20 cases, multiple organ failure in two cases, cardiac arrest in one case, and aggravation of other diseases due to COVID-19 in two cases. Twelve cases developed pulmonary embolisms during hospitalization; however, prevalence of pulmonary embolisms was not significantly higher in patients who died [2 (8%) vs. 10 (5%),  $P = 0.58$ ]. Participants dying were older, suffered more frequently from prevalent heart disease, had a prior history of deep vein thrombosis or lung embolisms, had higher levels of C-reactive protein, NT-proBNP, troponin, and reduced kidney function as assessed by eGFR (Table S1).

Left ventricle or RV dysfunction was observed in 39 (20.0%) of cases. Troponin levels in cases with LV or RV dysfunction was median 24 ng/L (IQR: [14, 35]) (troponin T)/34 ng/L (IQR: [11, 46]) (troponin I); meanwhile in cases without LV or RV dysfunction, median troponin T was 18 ng/L (IQR: [6, 27]), and troponin I was 12 ng/L (IQR: [8, 42]). Participants with observed LV or RV dysfunction were more likely to suffer from valvular disease [12 (31%) vs. 13 (8%),  $P < 0.001$ ] and prevalent heart failure [13 (33%) vs. 8 (5%),  $P < 0.001$ ]. But patients with LV or RV dysfunction did not suffer more from pulmonary embolisms (1 (3%) vs. 4 (3%),  $P = 1.00$ ), acute respiratory distress syndrome [4 (11%) vs. 22 (14%),  $P = 0.56$ ], or pulmonary hypertension [16 (49%) vs. 53 (37%),  $P = 0.24$ ] prior to echocardiography. The prevalence of previous ischemic heart disease was not higher in the group with LV or RV dysfunction [5 (13%) vs. 13 (8%),  $P = 0.39$ ]. Cases with LV or RV dysfunction were more likely to die than cases without [8 (21%) vs. 11 (8%),  $P = 0.011$ ] but did not develop pulmonary embolism more frequently [2 (5%) vs. 10 (6%),  $P = 0.77$ ].

Univariable and multivariable Cox regression models investigating the association between reduced LV and RV parameters and COVID-19 related death are listed in Table 3. In univariable models, reduced TAPSE, LVEF, and GLS were all significantly associated with a higher risk of dying. In the multivariable Model 2, TAPSE [hazard ratio (HR) = 1.18, 95% confidence interval (CI) [1.07–1.31],  $P = 0.002$ , per 1 mm decrease], RVLS (HR = 1.64, 95%CI[1.02;2.66],  $P = 0.043$ , per 1% decrease), and GLS (HR = 1.20, 95%CI[1.07–1.35],  $P = 0.002$ , per 1% decrease) were significantly associated with COVID-19-related mortality. The measures remained statistically significant after the additional adjustment for oxygen therapy, eGFR, and CRP. When excluding all participants with

**Table 3** Prognostic value of RV and LV parameters

Parameter	Unadjusted regression			Model 1			Model 2			Sensitivity analysis <sup>a</sup>		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
RV parameters												
TAPSE, per 1 mm decrease	1.23	[1.11, 1.36]	<0.001	1.20	[1.08, 1.33]	0.001	1.18 <sup>b</sup>	[1.07, 1.31]	0.002	1.20	1.02;1.40	0.024
RV strain, per 1% decrease	1.14	[0.98, 1.34]	0.092	1.44	[1.06, 1.96]	0.018	1.64 <sup>b</sup>	[1.02, 2.66]	0.043	1.41	0.85 2.35	0.18
LV parameters												
LVEF, per 1% decrease	1.06	[1.01, 1.11]	0.010	1.04	[0.99, 1.09]	0.12	1.03	[0.98, 1.09]	0.25	1.30	1.10;1.53	0.002
GLS, per 1% decrease	1.28	[1.15, 1.42]	<0.001	1.20	[1.08, 1.33]	0.001	1.20 <sup>b</sup>	[1.07, 135]	0.002	1.30	1.10;1.53	0.002

GLS, global longitudinal strain; LV, left ventricle; LVEF, left ventricular ejection fraction; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion. Model 1 includes the variables: sex and age. Model 2 includes the variables of Model 1 along with hypertension, diabetes, body mass index, and smoking status. <sup>a</sup>All participants with prevalent disease were excluded from a multivariable Cox regression with Model 2. <sup>b</sup>Remained significant in multivariable models including model 2, CRP, oxygen therapy, and eGFR.

prevalent heart failure ( $N = 22$ ) from the analysis, only TAPSE and GLS remained significantly associated with COVID-19-related death in the fully adjusted model (Table 3). The association between RV and LV echocardiography-assessed function and the risk of COVID-19 related death is illustrated in Figure 2. Prognostic value of regarding risk of death did not differ between TAPSE and GLS when comparing Harrel's C-statistics: 0.71 vs. 0.79,  $P = 0.13$ .

## Discussion

The present report is the largest prospective echocardiographic study of COVID-19 patients and the first case-control study assessing differences in cardiac function between hospitalized COVID-19 patients and matched controls. In this prospective multicentre cohort study, we found that (i) both LV and RV systolic function were reduced in patients with COVID-19, and even after adjusting for multiple potential confounders, (ii) these reduced measures of LV and RV systolic function were independently associated with an increased risk of COVID-19 mortality.

A recently published study on 120 patients with COVID-19<sup>19</sup> found RVLS to be an important predictor of all-cause mortality, and multiple studies have reported a high prevalence of myocardial injury (defined as elevated cardiac biomarkers) in COVID-19 patients.<sup>20,21</sup> Additionally, case-series have described a number of different cardiovascular complications in COVID-19.<sup>22,9,7,23</sup> A large retrospective survey study including 1216 observations from COVID-19 patients has recently been published. The authors report high numbers of cardiac complications (55% with an abnormal echocardiography).<sup>24</sup> However, this study is based on survey data obtained from retrospectively obtained clinical echocardiograms and only includes echocardiographic findings of COVID-19 patients who clinically required an echocardiography during their hospitalization which may have resulted in an overestimation of the degree of cardiac involvement in COVID-19. It remains unknown whether SARS-CoV-2 affects the myocardium directly leading to impaired cardiac function or the cardiac impairment is related to the systemic consequences of acute COVID-19. Systemic inflammation is known to destabilize vascular plaques and increase metabolic demand leading to cardiac stress.<sup>25</sup> An alternative hypothesis is that the virus causes diffuse systemic endothelial inflammation including microvascular systems in both the heart, kidney, and intestines, which may lead to compromised local myocardial blood flow and cause ischemia-related cardiovascular complications such as myocardial infarction with non-obstructive coronary arteries (MINOCA).<sup>26</sup>

In this study, we matched hospitalized COVID-19 patients 1:1 to participants from the large general population study, the CCHS5. All participants from both CCHS5 and

ECHOVID-19 live in eastern Denmark and have many similarities such as socio-economic status and demographics. This makes matching well-balanced and useful when assessing differences in echocardiographic parameters between COVID-19 cases and COVID-19-free controls. We found that both LV and RV function were lower in COVID-19 cases compared with matched controls and also lower than normal observed values (Normal TAPSE = 2.4 mm, normal GLS = 16.7).<sup>18</sup> The reported TAPSE values were not below recommended cut-offs and as such most patients did not have significant RV pathology. However, the echocardiography was performed early in their hospital stay, and it thus seems that TAPSE already at an early stage starts to decline compared to matched controls. This is in line with what has been suggested in the studies reporting myocardial injury. However, previous studies have lacked a control group to demonstrate that the myocardial impairment could be related directly to COVID-19. It may be that patients presenting with myocardial impairment in the study may already have had un-acknowledged myocardial impairment prior to the COVID-19 infection. Unfortunately, we did not have information on myocardial performance in the patients prior to hospitalization and could thus not control for it. We adjusted for heart rate as this parameter was naturally higher in cases with COVID-19 due to the acute infection. Additionally, we adjusted for prevalent heart failure as this of course influences echocardiographic parameters. What remains unknown is whether the reduced myocardial function happens as a result of SARS-CoV-2 attacking the heart directly, happens as a secondary consequence of the systemic infection, or due to a combination of the two. Also, we cannot rule out that there may be a higher prevalence of undetected sub-clinical heart disease in COVID-19 patients requiring hospitalization compared with the general population. No matter which explanation is true, it does not change the finding that we observe a reduced systolic function of both ventricles in hospitalized COVID-19 patients. We believe that it is clinically relevant to assess cardiac function in hospitalized COVID-19 patients as we found that echocardiographic parameters were closely associated with death due to COVID-19.

Li et al<sup>19</sup> recently published a study including 120 COVID-19 patients from a single centre in which they reported prognostic findings similar to our multicentre study. They found that patients with reduced RV function as assessed by RVLS and TAPSE had a higher risk of dying than those with more preserved RV function. Their reported range of both RVLS and TAPSE is like ours underscoring the impact of COVID-19 on the RV. They did, however, not report values of GLS, and it seems that this measurement was not included as a measure in their study. We found GLS to be strongly associated with COVID-19-related death. Thus, the findings of our study further broaden the knowledge on cardiac involvement in hospitalized COVID-19 patients as we demonstrate reduced systolic function of both the RV and LV.



Furthermore, the reduced systolic function of both the RV and LV are closely associated with prognosis in COVID-19.

## Strengths and limitations

The sample size in the present study is relatively small which limits the power of the study. We included patients from all hospitals in the Copenhagen region and the Zealand region to increase sample size. This ensures that our multicentre population is representative of the general population being admitted with COVID-19 in Denmark. Another strength is that The Copenhagen City Heart Study included participants from the same region of Denmark as the ECHOVID-19 study. We cannot exclude selection bias, but all patients were asked if they wanted to participate in the study in a blinded fashion. In particular, patients were included consecutively based on name and a COVID-19 positive test. The patients were not selected for echocardiography because of a perceived increased risk or clinical worsening. All of this was done to avoid selection bias. A limitation to our study is that we did not record information on the type of oxygen therapy device which could have affected the pulmonary pressure. However, none of the patients were invasively intubated at the time of echocardiography, which is known to cause mechanical injury. Additionally, information on arterial pO<sub>2</sub>/fraction of inspired oxygen at the time of echocardiography was not recorded. Furthermore, we did not include information on chamber dimensions in this study as the aim was to assess how cardiac function and not dimensions were affected in patients with COVID-19. Another strength of the ECHOVID-19 study is the prospective design with the echocardiographic examination being performed on all patients according to a pre-determined research protocol. It would have been interesting if it had been possible to perform a computed tomography on all participants to assess the number of pulmonary embolisms. However, this was not possible. Additionally, we did not have data available on cardiac biopsies and the presence of viral genome inside heart cells, autoptic specimens nor magnetic resonance imaging, which could have revealed more about how COVID-19 affects the heart.

## References

1. Mahase E. Coronavirus covid-19 has killed more people than SARS and MERS combined, despite lower case fatality rate. *BMJ* 2020; **368**: m641.
2. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, Liu L, Shan H, Lei C-L, Hui DSC, Du B, Li L-J, Zeng G, Yuen K-Y, Chen R-C, Tang C-L, Wang T, Chen P-Y, Xiang J, Li S-Y, Wang J-L, Liang Z-J, Peng Y-X, Wei L, Liu Y, Hu Y-H, Peng P, Wang J-M, Liu J-Y, Chen Z. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; **382**: 1708–1720.
3. Chapman AR, Bularga A, Mills NL. High-sensitivity cardiac troponin can be an ally in the fight against COVID-19. *Circulation* 2020; **141**: 1733–1735.
4. Alpert JS. The effect of right ventricular dysfunction on left ventricular form and function. *Chest* 2001; **119**: 1632–1633.
5. Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, Ibrahim H, Friedman GH, Thompson C, Alviar CL, Chadow HL, Fishman GI, Reynolds HR, Keller N, Hochman JS. ST-segment elevation in patients with Covid-19—a case series. *N Engl J Med* 2020; **382**: 2478–2480.

## Conclusions

In hospitalized COVID-19 patients, RV and LV function were significantly reduced compared with matched controls from the general population. Furthermore, we demonstrate that both reduced TAPSE and GLS were independently associated with COVID-19-related death.

## Conflict of interest

T.B.S. reports receiving research grants from Sanofi Pasteur, and GE Healthcare, is a Steering Committee member of the Amgen financed GALACTIC-HF trial, on advisory boards for Sanofi Pasteur and Amgen, and speaker honorariums from Novartis and Sanofi Pasteur. The remaining authors have nothing to disclose.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Power calculation.

**Table S2.** differences in baseline characteristics between survivors and non-survivors.

6. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, Jain SS, Burkhoff D, Kumaraiah D, Rabbani L, Schwartz A, Uriel N. Coronavirus disease 2019 (COVID-19) and cardiovascular disease. *Circulation* 2020; **141**: 1648–1655
7. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J* 2020.
8. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020; **17**: 259–260.
9. Meyer P, Degrauwe S, Delden CV, Ghadri J-R, Templin C. Typical Takotsubo syndrome triggered by SARS-CoV-2 infection. *Eur Heart J* 2020; **41**: 1860.
10. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, Krakover R, Vered Z. Two-dimensional strain—a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004; **17**: 1021–1029.
11. Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. *J Am Soc Echocardiogr* 2004; **17**: 630–633.
12. Yingchoncharoen T, Agarwal S, Popović ZB, Marwick TH. Normal ranges of left ventricular strain: a meta-analysis. *J Am Soc Echocardiogr* 2013; **26**: 185–191.
13. Skaarup KG, Lassen MCH, Marott JL, Biering-Sørensen SR, Jørgensen PG, Appleyard M, Berning J, Høst N, Jensen G, Schnohr P, Søgaard P, Gislason G, Møgelvang R, Biering-Sørensen T. The impact of cardiovascular risk factors on global longitudinal strain over a decade in the general population: the Copenhagen city heart study. *Int J Cardiovasc Imaging* 2020; **36**: 1907–1916.
14. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Filippatos G, McMurray JJV, Aboyans V, Achenbach S, Agewall S, Al-Attar N, Atherton JJ, Bauersachs J, John Camm A. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J Oxford Academic* 2016; **37**: 2129–2200.
15. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; **23**: 685–713 quiz 786–788.
16. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt J-U. 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.
17. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 1321–1360.
18. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt J-U. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 233–270.
19. Li Y, Li H, Zhu S, Xie Y, Wang B, He L, Zhang D, Zhang Y, Yuan H, Wu C, Sun W, Zhang Y, Li M, Cui L, Cai Y, Wang J, Yang Y, Lv Q, Zhang L, Xie M. Prognostic value of right ventricular longitudinal strain in patients with COVID-19. *JACC Cardiovasc Imaging* 2020.
20. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet Lond Engl* 2020; **395**: 1054–1062.
21. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061–1069.
22. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. *Am J Emerg Med* 2020; **38**: 1504–1507.
23. Liu K, Fang Y-Y, Deng Y, Liu W, Wang M-F, Ma J-P, Xiao W, Wang Y-N, Zhong M-H, Li C-H, Li G-C, Liu H-G. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)* 2020; **133**: 1025–1031.
24. Dweck MR, Bularga A, Hahn RT, Bing R, Lee KK, Chapman AR, White A, Salvo GD, Sade LE, Pearce K, Newby DE, Popescu BA, Donal E, Cosyns B, Edvardsen T, Mills NL, Haugaa K. Global evaluation of echocardiography in patients with COVID-19. *Eur Heart J Cardiovasc Imaging* 2020; **21**: 949–958.
25. Davis MM, Taubert K, Benin AL, Brown DW, Mensah GA, Baddour LM, Dunbar S, Krumholz HM. Influenza vaccination as secondary prevention for cardiovascular disease: a science advisory from the American Heart Association/American College of Cardiology. *J Am Coll Cardiol* 2006; **48**: 1498–1502.
26. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet Lond Engl* 2020; **395**: 1417–1418.