BMJ Open

Predictors of in-hospital mortality in critically ill patients with COVID-19: a large dual tertiary centre study

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To cite: Cirillo C, Nakou E, Georgiopoulos G, *et al*. Predictors of in-hospital mortality in critically ill patients with COVID-19: a large dual tertiary centre study. *BMJ Open* 2022;**12**:e059358. doi:10.1136/bmjopen-2021-059358

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-059358).

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Received 17 November 2021
Accepted 07 September 2022

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ABSTRACT

Objectives The aim of this study was to investigate the relationship of echocardiographic parameters, laboratory findings and clinical characteristics with in-hospital mortality in adult patients with COVID-19 admitted to the intensive care units (ICU) in two large collaborating tertiary UK centres.

Design Observational retrospective study.

Setting The study was conducted in patients admitted to the ICU in two large tertiary centres in London, UK.

Participants Inclusion criteria were: (1) patients admitted to the ICU with a COVID-19 diagnosis over a period of 16 weeks. and (2) underwent a transthoracic echocardiogram on the first day of ICU admission as clinically indicated. No exclusion criteria applied.
Three hundred patients were enrolled and completed the follow-up.

Primary and secondary outcome measures The outcome measure in this study was in-hospital mortality in patients admitted to the ICU with COVID-19 infection.

Results Older age (HR: 1.027, 95% CI 1.007 to 1.047; p=0.008), left ventricular (LV) ejection fraction<35% (HR: 5.908, 95% CI 2.609 to 13.376; p<0.001), and peak C reactive protein (CRP) (HR: 1.002, 95% CI 1.001 to 1.004, p=0.001) were independently correlated with mortality in a multivariable Cox regression model. Following multiple imputation of variables with more than 5% missing values, random forest analysis was applied to the imputed data. Right ventricular (RV) basal diameter (RVD1), RV mid-cavity diameter (RVD2), tricuspid annular plane systolic excursion, RV systolic pressure, hypertension, RV dysfunction, troponin level on admission, peak CRP, creatinine level on ICU admission, body mass index and age were found to have a high relative importance (> 0.7).

Conclusions In patients with COVID-19 in the ICU, both severely impaired LV function and impaired RV function may have adverse prognostic implications, but older age and inflammatory markers appear to have a greater impact. A combination of echocardiographic and laboratory investigations as well as demographic and clinical characteristics appears appropriate for risk stratification in patients with COVID-19 who are admitted to the ICU.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Data are presented from a large dual tertiary centre study on critically-ill patients with COVID-19.
⇒ A wide range of parameters including echocardiographic, laboratory and clinical data were investigated in relation with in-hospital mortality.
⇒ Some echocardiographic data and measurements were missing which may have impacted on the results.
⇒ The results refer to patients with COVID-19 nursed in the intensive care unit and may not be applicable to patients with mild or moderate disease.

INTRODUCTION

The clinical course of COVID-19 infection is mostly characterised by respiratory tract symptoms.[1] However, data regarding cardiovascular involvement have emerged, as well as the role of echocardiography in patients with COVID-19.[2–9]

Four single-centre studies reported descriptive data on echocardiographic findings in hospitalised patients with COVID-19 being nursed in wards or intensive care units (ICU).[2–5] Right ventricular (RV) dilatation and dysfunction have been reported in patients with COVID-19,[6 7] as well as several degrees of left ventricular (LV) dysfunction.[2 5]

The aim of this study was to investigate the relationship between echocardiographic parameters, laboratory findings and clinical characteristics with in-hospital mortality in adult patients with COVID-19 admitted to the ICU in two large collaborating tertiary UK centres.

METHODS

All patients admitted to the ICU with a COVID-19 diagnosis at King's Health Partners Hospitals (Guys' and St Thomas' NHS Foundation Trust and King's College Hospital

NHS Foundation Trust) over a period of 16 weeks were screened. The patients who underwent a transthoracic echocardiogram (TTE) on the first day of ICU admission as clinically indicated, were included. The diagnosis of COVID-19 was confirmed through reverse-transcriptase PCR assays performed on nasopharyngeal swabs or typical for COVID-19 symptoms and chest CT findings.

Data collection

Clinical, laboratory, echocardiographic and demographic data were recorded from electronic patient records. For the C reactive protein (CRP) and troponin, the peak value of serial measurements as well as the value on day of admission to the ICU were documented, though the latter was not available in all patients. The medical history was recorded according to available data on electronic patient records. The Sepsis-related Organ Failure Assessment (SOFA score) was calculated based on current guidelines.[10] The medial follow-up was 38 days (IQR: 16–50 days) and did not coincide with hospital discharge for all patients.

Echocardiography

A modified British Society of Echocardiography (BSE) Level 1 TTE was performed on the day of ICU admission as clinically appropriate.[11] All echocardiographic studies were performed at bedside in the ICU using the GE E9, E95, and S70 ultrasound machines with a M5SC-D probe (GE Healthcare, Amersham, UK) or the Philips CX50, Affinity and CVx ultrasound machines with an S5-1 or X5-1 probe (Philips Healthcare, Andover, Massachusetts, USA). The echocardiograms were performed as part of clinical assessment for dynamic ECG changes, increasing inotropic/vasopressor support requirements, failure to wean, suspected pulmonary emboli, and haemodynamic instability or for research purposes under ethical approval granted by the NHS Health Research Authority (REC20/EE/0131). All studies were performed by operators with at least Level 1 BSE accreditation or European Association of Cardiovascular Imaging (EACVI) TTE certification. The analysis of the echocardiograms was performed by four BSE or EACVI TTE accredited operators, who were blinded to the cohort database. The echocardiograms were reviewed by two operators and the recorded findings reflect the consensus of the operators. When there was discrepancy among them, a third reviewer was involved. The analysis included visual assessment of the LV and RV systolic function, linear dimension measurements of the LV and RV, Doppler analysis and measurements, and in a proportion of patients, the global longitudinal strain (GLS) of the LV and/or RV was calculated. The left ventricular ejection fraction (LVEF) was graded in line with the updated BSE guidelines[12] and the remaining echocardiographic analysis including GLS assessment was performed according to the joint American Society of Echocardiography and EACVI guidance.[13]

Patient and public involvement

Given the nature of the study in ICU mechanically ventilated patients, it was practically impossible to involve patients. Similarly, the tremendous clinical workload, the urgency of data to be collected and processed and the restrictions of social distancing prevented adequate engagement with the public.

Statistical analysis

Continuous variables were tested for normal distribution based on histograms and are presented as mean±SD. Continuous variables with normal distribution were compared with the independent samples Student's t-test and those with non-normal distribution with the Mann-Whitney U test. The categorical variables were tested with the χ^2 test or Fisher's exact test as appropriate and are presented as absolute numbers and percentages. The association of clinical and echocardiographic variables with in-hospital mortality was further explored using: (a) Cox regression and (b) random forest analysis. In detail, the variables which were considered to have a plausible correlation with mortality were tested in a univariable Cox regression model.

In order to identify variables which might have correlation with in-hospital mortality but were not included or were not shown to have significant correlation in the Cox-regression model, random forests analysis with classification decision trees for deceased and survivors during admission was implemented. For a prespecified set of 23 independent variables of interest, 350 trees (ie, iterations) were used and the number of variables was set to randomly investigate equal to 4, after tuning models' parameters to minimise out-of-bag and validation error. The number of trees was tuned visually by assessing the out-of-bag error and validation error against the number of available iterations. We selected the number of iterations above which the out-of-bag and validation error stabilised at the lowest possible value. Entropy was used as splitting criterion in the random forest classification algorithm. The minimum number of observations to include at each leaf node was set at the default value of 1 and bootstrap aggregating was applied with maximum (ie, unlimited) depth of the random forest model. Variable importance plots were used to visualise and prioritise the most important variables in classifying deceased and alive patients. Variable importance plots were based on changes in prediction accuracy in the out-of-bag sample following removal (by random shuffling values) of each specific variable. The relative importance was used when building these plots (importance for each variable was divided by the highest variable importance) and values were bounded between 0 and 1.

Days from admission until occurrence of death or censoring of subjects were considered and Cox regression models were applied. Variables with $p<0.1$

in univariable models, along with high relative importance (>0.8) variables in random forest analysis and other variables of biological plausibility were included in a multivariable Cox model. From the SOFA score variables, only creatinine was tested independently. The proportionality of hazards assumption was assessed with the Schoenfeld test, and the assumption was met.

The main analysis was repeated after imputing variables presenting more than 5% missing values. The number of missing values per variable are reflected in table 1 (column 'N(%)'). To that end, multiple imputation was used with the Monte Carlo Markov Chain method and 10 datasets were added after 10 additional iterations for the burn-in period.[14]

To explore the interobserver variability for quantitative measurements, 25 randomly selected echocardiograms were analysed by a second operator who was blinded to first operator's interpretation. The variability was tested with the intraclass correlation coefficient (ICC) for absolute agreement in a two-way mixed model.

Data were analysed with IBM SPSS, V.25.0.0 (IBM Corporation Software Group), whereas STATA V.15.0 (Stata Corp) was used only for the random forests analysis and multiple imputation. Statistical significance was considered for a two-tailed p value<0.05.

RESULTS

Demographics and clinical characteristics

The baseline and clinical characteristics, laboratory findings and echocardiographic parameters are shown in table 1. The mean age was 54.4±13.1 years and 69% were male. Two hundred seventy-seven patients (92.3%) required invasive ventilation and 40 (13.3%) were treated with extra corporeal membrane oxygenator (ECMO), while vasopressors and inotropes were used in 212 (70.7%) and 20 (6.7%) patients, respectively. SOFA score was high in our cohort (8.5±4.6) and 164 patients (54.6%) were still hospitalised at the time of the analysis.

Echocardiographic parameters

TheLVEF was preserved (LVEF≥50%) in 256 (84.7%) patients, mild to moderately impaired (LVEF=36%–49%) in 22 (7.3%) and severely impaired (LVEF≤35%) in 11 (3.7%) patients (table 1). From the 11 patients with severely impaired LVEF, 5 were known to have LV dysfunction. LV GLS was available only in 51 patients from one centre (−20.5%±3.3%). Eighty-five (28.3%) patients had dilated RV as measured by the basal RV diameter (RVD1>43 mm) and/or the mid RV diameter (RVD2>35 mm), while 65 patients (21.7%) were found to have impaired RV systolic function as assessed visually. The average RV systolic pressure was found to be mildly increased (33.8±13.2 mm Hg). Pericardial effusion was noted in 43 (14.3%) patients.

The ICC and 95% CI for RVD1 was 0.990 (95% CI 0.977 to 0.996, p<0.001); for RVD2 0.957 (95% CI 0.906 to 0.981, p<0.001), for RVD3 0.926 (95% CI 0.841 to 0.966, p<0.001), for TAPSE 0.979 (95% CI 0.953 to 0.991, p<0.001), and for LV GLS 0.941 (95% CI 0.870 to 0.973; p<0.001).

Cardiovascular complications

Two hundred five patients were investigated with CT pulmonary angiography and 60 (20%) were diagnosed with pulmonary embolism (PE). Four patients (1.3%) suffered a myocardial infarction (MI) (two ST-elevation MI and two non-ST-elevation MI) and stroke was observed in 7 patients (2.3%).

Differences between survivors and non-survivors

In a median follow-up of 38 days (IQR: 16–50 days), 91 (30.3%) patients died. Compared with non-survivors, the survivors were younger (52.4±12.8 vs 58.8±12.7 years; p<0.001), they had lower CRP levels on day of ICU admission (187.2±119.0 vs 242.9±150.9 mg/L; p=0.009), lower peak CRP levels (285.9±162.5 vs 345.7±142.4 mg/L; p=0.003), and lower creatinine (156.4±155.8 vs 193.6±210.6 µmol/L; p=0.011) levels on admission to the ICU.

They were also less likely to receive therapy with vasopressors and inotropes (65.1% vs 83.5%; p=0.040 and 4.3% vs 12.1%; p=0.040, respectively). The type of ventilation (invasive or non-invasive) and the use of ECMO were similar between groups. The survivors had higher LVEF (p=0.006), and LV GLS (−22.3±2.7 vs −19.7±3.3, p=0.013). There were no differences in RV echocardiographic parameters between the two groups. 6.7% of the survivors were found to have pleural effusion compared with 1.1% of non-survivors (p=0.043).

Random forests and Cox-regression analysis

In a univariable Cox-regression analysis, age, LVEF, RV dysfunction and CRP (on day of admission and peak) were found to have significant correlation with mortality (table 2). The correlation of D-Dimer with mortality was not possible to be explored in our cohort as different assays were used in the recruiting centres. In one centre, D-Dimer were correlated with mortality in a univariable analysis (HR: 1.014, 95% CI 1.002 to 1.027; p=0.026). LV GLS was available in 51 patients (17.0%) and was found to be associated with mortality (HR: 0.781, 95% CI 0.644 to 0.946; p=0.012) in a univariate analysis. Only 39 echocardiograms (13.0%) were analysable for RV GLS measurements, which was not found to correlate with mortality (HR: 1.066, 95% CI 0.932 to 1.219, p=0.349). Given the small number of available values, LV GLS was excluded from the multivariable model. Applying random forest analysis on 23 variables, peak CRP, creatinine level on ICU admission, age, and body mass index (BMI) had a high relative importance value>0.8 (figure 1).

The above variables along with history of coronary artery disease, which was found to have a p value<0.1

Table 1 Comparison of demographics, clinical characteristics and echocardiographic parameters between survivors and non-survivors in ICU patients with COVID-19

	All (N=300)			Survivors (N=209)			Non-survivors (N=91)			
	N (%)	Mean	SD	N	Mean	SD	N	Mean	SD	P value
Age	300 (100)	54.4	13.1	209	52.4	12.8	91	58.8	12.7	**<0.001**
BMI (kg/m^2)	281 (93.6)	29.0	6.4	195	29.3	6.5	86	28.2	5.9	0.250
CRP peak (mg/L)	297 (99.0)	303.8	158.8	208	285.9	162.5	89	345.7	142.4	**0.003**
CRP admission (mg/L)	174 (58.0)	205.8	132.7	116	187.2	119	58	242.9	150.9	**0.009**
Troponin admission (ng/L)	229 (76.3)	87.5	243.8	161	90.1	279.5	68	81.4	124.8	0.355
Creatinine admission (µmol/L)	298 (99.3)	167.6	174.7	208	156.4	155.8	90	193.6	210.6	**0.011**
SOFA score admission	232 (77.3)	8.5	4.6	156	8.2	4.6	76	9.2	4.5	0.102
RVD1 (mm)	217 (72.3)	39.9	6.4	155	39.8	6.2	62	40.2	7.0	0.684
RVD2 (mm)	203 (67.6)	34.2	6.9	146	34.3	6.8	57	33.9	7.2	0.713
RVD3 (mm)	125 (41.6)	72.5	8.5	94	72.6	8.5	31	72.1	8.4	0.772
TAPSE (mm)	230 (76.6)	19.4	4.7	164	19.6	4.8	66	18.8	4.3	0.229
RVSP (mm Hg)	116 (38.6)	33.8	13.2	75	33.1	13.3	41	35.2	12.9	0.424
		N	%		N	%		N	%	
Sex (male/female)		207/93	69.0%/31.0%		140/69	67.0%/33.0%		67/24	73.6%/26.4%	0.279
Ethnicity (white/others)		104/196	34.7%/65.3%		71/138	34.0%/66.0%		33/58	36.3%/63.7%	0.695
Diabetes mellitus		107	35.7%		71	34.0%		36	39.6%	0.432
Hypertension		153	51.0%		100	47.8%		53	58.2%	0.131
Coronary artery disease		19	6.3%		10	4.8%		9	9.9%	0.122
Heart failure		11	3.7%		5	2.4%		6	6.6%	0.096
Lung disease		49	16.3%		33	15.8%		16	17.6%	0.735
Smoke										0.594
Non-smokers		255	85.0%		175	83.7%		80	87.9%	
Active smokers		11	3.7%		9	4.3%		9	9.9%	
Ex-smokers		33	11.0%		24	11.5%		2	2.2%	
Invasive ventilation		277	92.3%		189	90.4%		88	96.7%	0.063
Non-invasive ventilation		30	10.05		23	11.0%		7	7.7%	0.404
VV ECMO		40	13.3%		30	14.4%		10	10.9%	0.447
Vasopressors		212	70.7%		136	65.1%		76	83.5%	**0.040**
Inotropes		20	6.7%		9	4.3%		11	12.1%	**0.046**
Pericardial effusion		43	14.3%		33	15.8%		10	11%	0.368
Pleural effusion		15	5.0%		14	6.7%		1	1.1%	**0.043**

Continued

Table 1 Continued

	All (N=300)			Survivors (N=209)			Non-survivors (N=91)			P value
	N (%)	Mean	SD	N	Mean	SD	N	Mean	SD	
RV function										0.074
Normal		219	73.0%		160	76.6%		59	64.8%	
Impaired		65	21.7%		40	19.1%		25	27.5%	
LVEF										**0.006**
LVEF≤35%		11	3.7%		3	1.4%		8	8.8%	
LVEF=36%–49%		22	7.3%		16	7.7%		6	6.6%	
LVEF≥50%		256	84.7%		183	87.6%		71	78.0%	

Bold values signify p values with statistical significance (p<0.05).
BMI, body mass index; CRP, C reactive protein; VV ECMO, veno-venous extracorporeal membrane oxygenation; hs-TnT, high-sensitivity troponin; ICU, intensive care unit; LVEF, Left ventricular ejection fraction; RV, right ventricle; RVD1, RV basal diameter; RVD2, RV mid diameter; RVD3, RV longitudinal dimension; RVSP, RV systolic pressure; SOFA score, sequential organ failure assessment score: ; TAPSE, tricuspid annular plane systolic excursion.

Table 2 Univariable and multivariable Cox-regression analysis: risk factors associated with in-hospital mortality

	Univariable analysis		
	HR	95% CI	P value
Age (years)	1.033	1.015 to 1.051	**<0.001**
Gender (male)	1.279	0.802 to 2.039	0.301
Ethnicity (white vs others)	0.945	0.616 to 1.449	0.796
BMI	0.978	0.942 to 1.014	0.231
Hypertension	1.385	0.913 to 2.101	0.126
Diabetes	1.226	0.805 to 1.867	0.342
Coronary artery disease	1.972	0.991 to 3.927	0.053
Smoking	0.566	0.139 to 2.300	0.427
Lung disease	1.080	0.629 to 1.852	0.781
LVEF			**<0.001**
Normal	Reference		
35%–49%	0.994	0.436 to 2.308	0.994
<35%	5.347	2.556 to 11.184	<0.001
RVD1	1.012	0.973 to 1.052	0.554
RVD2	0.996	0.958 to 1.035	0.827
TAPSE	0.962	0.912 to 1.015	0.155
RV dysfunction (visual)	1.641	1.028 to 2.620	**0.038**
RVSP	1.010	0.987 to 1.034	0.388
CRP peak	1.002	1.001 to 1.003	**0.003**
CRP on ICU admission	1.002	1.001 to 1.004	**0.008**
Troponin on ICU admission	1.000	0.999 to 1.001	0.864
Troponin peak	1.000	1.000 to 1.000	0.445
Creatinine on admission	1.001	1.000 to 1.002	0.165
SOFA score	1.028	0.982 to 1.077	0.237

Abbreviations as in table 1.
Bold values signify p values with statistical significance (p<0.05).

in the univariate Cox regression analysis, gender and history of lung disease, which were considered having a plausible correlation with outcome, were entered in a multivariable Cox-regression model. Peak CRP was available in more patients, and it was included in the model instead of CRP on admission. This is also prevented overfitting the model. Older age (HR: 1.027, 95% CI 1.007 to 1.047; p=0.008), LVEF<35% (HR: 5.908, 95% CI 2.609 to 13.376; p<0.001), and peak CRP (HR: 1.002, 95% CI 1.001 to 1.004, p=0.001) were independently correlated with mortality (table 3).

Following multiple imputation as described above, random forest analysis was applied again on the imputed data (figure 2). RV basal diameter (RVD1), RV mid-cavity diameter (RVD2), TAPSE, RV systolic pressure, hypertension, RV dysfunction, troponin level on admission, peak CRP, creatinine level on ICU admission, BMI and age were found to have a high relative importance>0.7. These variables were included in a multivariable Cox-regression

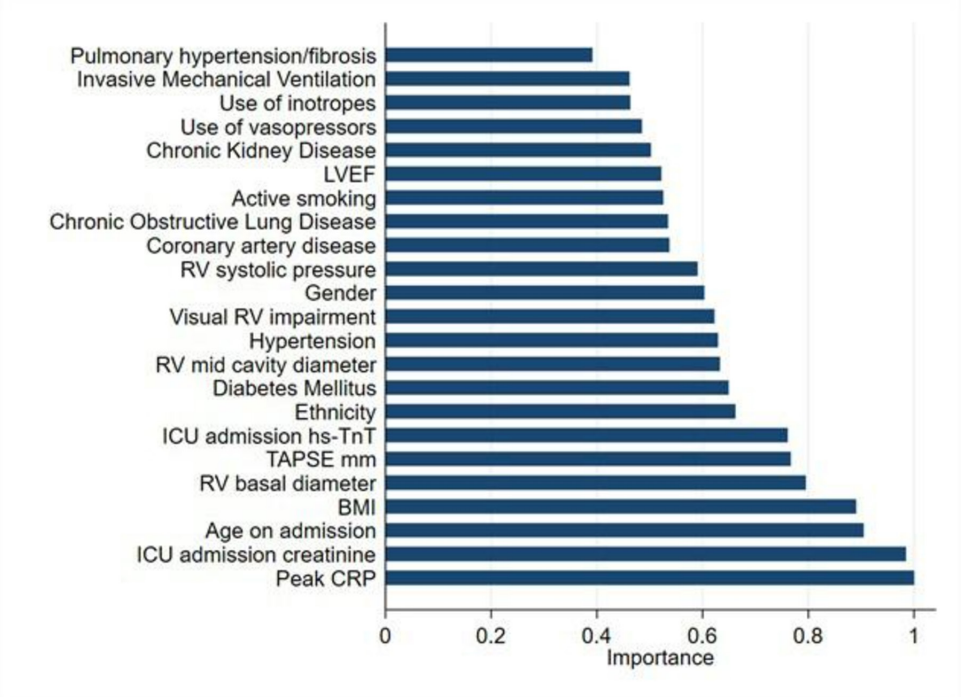

Figure 1 Random forests analysis. LVEF, left ventricular ejection fraction; RV, right ventricle; ICU, intensive care unit; hs-TnT, high-sensitivity troponin; TAPSE, tricuspid annular plane systolic excursion; BMI, body mass index; CRP, C reactive protein.

model (table 4) along with LVEF which was found to correlate with mortality in the multivariable Cox-regression analysis of raw data. From the RV dimensions only RVD1 was included and from RV dysfunction parameters only the visual assessment and not the TAPSE due to collinearity and to avoid overfitting the model. Similarly, to the raw data analysis, it was only the age (HR: 1.032, 95% CI 1.013 to 1.052; p=0.001), LVEF (HR: 1.972, 95% CI 1.309 to 2.971; p=0.001), and peak CRP (HR: 1.002, 95% CI 1.001 to 1.003; p=0.004) that were independently correlated with in-hospital mortality. When TAPSE and RVD2 were used interchangeably instead of RV dysfunction and RVD1, respectively, the same variables (age, LVEF and peak CRP) were found to correlate with mortality.

Table 3 Multivariable Cox-regression analysis: risk factors associated with in-hospital mortality

	Multivariable analysis		
	HR	**95% CI**	**P value**
Age	1.027	1.007 to 1.047	**0.008**
BMI	0.975	0.935 to 1.016	0.222
Gender	1.185	0.680 to 2.063	0.549
CAD	1.496	0.645 to 3.469	0.348
Lung disease	1.388	0.737 to 2.617	0.310
LVEF			**<0.001**
Normal	Reference		
35%–49%	0.799	0.320 to 1.997	0.631
<35%	5.908	2.609 to 13.376	<0.001
RV dysfunction	1.646	0.970 to 2.792	0.065
CRP peak	1.002	1.001 to 1.004	**0.001**
Creatinine on ICU admission	1.001	1.000 to 1.002	0.104

Abbreviations as in table 1.
Bold values signify p values with statistical significance (p<0.05).

DISCUSSION

To the best of our knowledge this is the largest study in critically ill patients with COVID-19 nursed in the ICU, investigating the relationship of echocardiographic parameters, laboratory findings and clinical characteristics in relation with in-hospital mortality. The main findings of our study on patients with COVID-19 nursed in the ICU, are: (1) older age, severely impaired LVEF and higher peak CRP levels are positively correlated with in-hospital mortality; (2) the RV echocardiographic parameters were ranked very high in the random forest analysis of imputed data, but were not found to predict in-hospital mortality in the multivariable Cox-regression model; (3) gender, ethnicity, BMI, diabetes, hypertension, history of coronary artery disease, cardiac troponin and creatinine levels on ICU admission do not seem to predict in-hospital mortality.

Older age, higher CRP and cardiac troponin were found to be associated with worse outcome in a prospective cohort study of 179 patients in Wuhan.[15] This is consistent with our study, though troponin did not reach statistical significance in our cohort. In this study, we investigated the troponin on admission to ICU, which

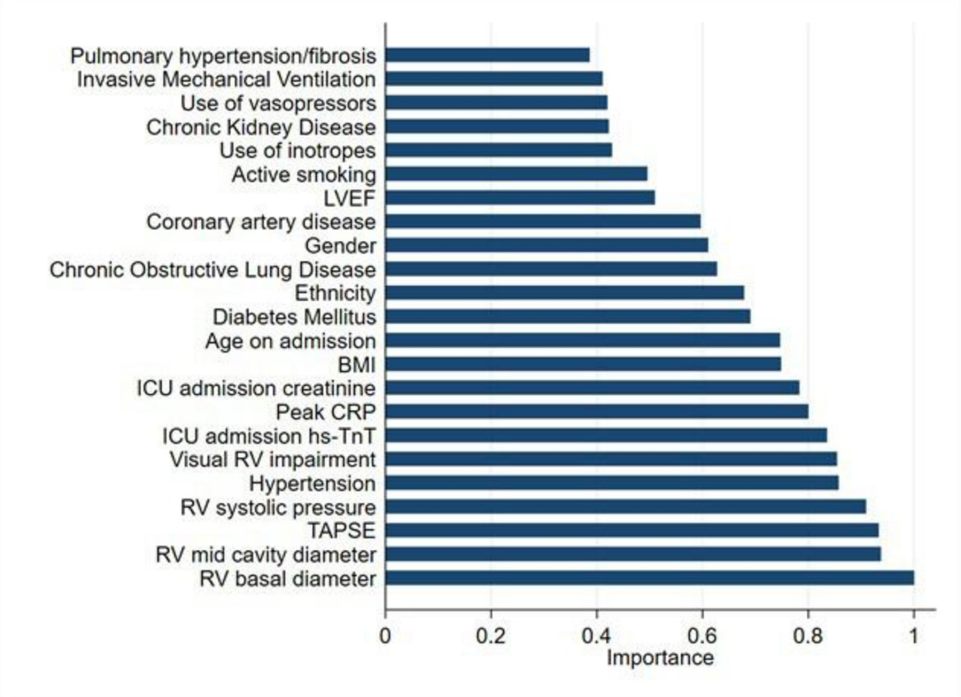

Figure 2 Random forest analysis of imputed data. LVEF, left ventricular ejection fraction; BMI, body mass index; ICU, intensive care unit; CRP, C reactive protein; hs-TnT, high-sensitivity troponin; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

was available in 224 patients, whereas Du *et al*.[15] have not specified whether they investigated admission or peak troponin. Shi *et al*.[8] reported that levels of cardiac troponin I on admission was a significant predictor for in-hospital mortality. However, a retrospective analysis of 242 patients with COVID-19 from two hospitals in Wuhan demonstrated that peak hs-troponin I instead of hs-troponin on admission was associated with in hospital mortality.[9] In our study, peak troponin in a univariate Cox regression analysis was not found to be related to mortality (table 2). Demir *et al*. explored the impact of hs-troponin T in one of the centres which were included in this study, and they concluded that it is an independent predictor of mortality in ICU patients.[16] However, they included lower risk patients (SOFA score 6.0 vs 8.5 in our study) and the admission CRP was also lower (150 vs 174 mg/L). Zhou *et al*. found a predictive value of older age, high SOFA score and d-dimer in a population of 191 patients in Wuhan.[17] SOFA score was not associated with mortality in our study (table 2), but the SOFA score was higher in our cohort, suggesting that we investigated a population in worse clinical condition.

Table 4 Multivariable Cox-regression analysis of imputed variables: risk factors associated with in-hospital mortality

	Multivariable analysis		
	HR	95% CI	P value
Age	1.032	1.013 to 1.052	**0.001**
BMI	0.978	0.942 to 1.017	0.264
Hypertension	0.917	0.567 to 1.484	0.725
LVEF	1.972	1.309 to 2.971	**0.001**
RV dysfunction	1.532	0.914 to 2.567	0.105
RVSP	0.993	0.970 to 1.016	0.534
RVD1	1.006	0.961 to 1.054	0.795
CRP peak	1.002	1.001 to 1.003	**0.004**
Creatinine on ICU admission	1.001	0.999 to 1.002	0.172
Troponin on ICU admission	1.000	0.998 to 1.001	0.643

Abbreviations as in table 1.
Bold values signify p values with statistical significance (p<0.05).

In addition to older age and CRP values, we found a strong association between severely impaired LVEF and mortality. This is in line with well-reported data that LVEF is one of the main determinants of all-cause mortality in cardiac and non-cardiac conditions.[18] A low LVEF in the setting of COVID-19 infection could reflect a pre-existing condition, a COVID-19 induced abnormality or a combination. In our cohort, 11 patients were found to have LVEF<35% on echocardiogram performed during their ICU stay. Five of them were known to have severe LVEF impairment, one had normal LVEF 6 years prior to admission and no previous echocardiogram was available in the remaining five patients. LV dysfunction has been reported in a smaller population of patients with COVID-19 infection,[4] but the authors did not investigate correlation with outcome. Similarly, Jain *et al*.[19] reported 34.7% of their population (n=72) having LVEF≤50%, but no correlation with outcome was sought.

In the ECHOVID-19 (Echocardiographic abnormalities and predictors of mortality in hospitalized COVID-19 patients) study, reduced LV systolic function determined by both LVEF and GLS was significantly correlated with high mortality risk at follow-up (median: 40 days).[5] In our cohort, LV GLS was available only in 51 patients (17%) and was found to be associated with mortality in a univariate analysis (p=0.012). However, the small number of available values prevented inclusion of LV GLS in the multivariable model.

In the WASE-COVID study, age, history of lung disease, lactic dehydrogenase, LV GLS and RV free wall strain were independently associated with mortality in patients with COVID-19 nursed in the ICU and the wards.[20] The researchers found no significant correlation between CRP and mortality, though they investigated CRP as a categorical variable. In our cohort, previous lung disease did not impact on outcome, but the LV and RV function along with age were found to play a role in both studies.

The COVID-19 infection is affecting primarily the lungs, by causing severe pneumonia, ARDS and PE.[21] Therefore, it is not surprising, to impact on the size and function of the RV as well. In our study, in the univariable Cox-regression analysis and random forest analysis of the imputed data the RV parameters, namely RV function, TAPSE and RV dimensions (RVD1 and RVD1) were found to have high predictive value. However, in the multivariable Cox-regression model of raw and imputed data, the RV dysfunction was not shown to have correlation with mortality, though a p value close to statistical significance was observed (p=0.065). This could be explained by the fact that some RV parameters were not available in the whole cohort (table 1). In addition, the reversibility of RV dysfunction with improvement of lung disease despite general deterioration of patients' condition due to excessive inflammatory response may account for the non-significant correlation between RV function parameters on admission and in-hospital mortality. Li *et al.* showed correlation between RV function and mortality, but the RV function was assessed with GLS.[7] In the ECHOVID-19 trial, reduced TAPSE and RV strain were significantly associated with mortality.[5] In our cohort, only 39 echocardiograms (13.0%) were analysable for RV GLS measurements which was not found to correlate with mortality. However, this may be related to the small number of cases. In addition, Li *et al.*[7] studied patients nursed both in general wards and ICU, whereas we studied only ICU patients.

Additionally, obesity, hypertension and diabetes have been considered as predictors of severe illness and hospitalisation in COVID-19.[22 23] In our cohort, we explored their correlation with mortality, and we found no significant predictive value. Notably, although there was no relationship between gender and mortality in our cohort, there is increasing evidence highlighting the dominance of male gender in COVID-19 related deaths.[24] Finally, the presence of pleural effusion was rare in our cohort but interestingly it was noted to be more common in survivors. This may possibly reflect the fact that inflammation of the pleura (serositis) may warrant better prognosis compared with inflammation of the lungs (pneumonitis), though no obvious difference in pneumonitis severity was noted visually on the CT scans of patients with and without pleural effusion. Another possible explanation could be the small number of cases; hence, this finding may represent noise rather than a true difference.

Overall, the observed discrepancies between the studied COVID-19 cohorts may reflect the wide spectrum of clinical presentation of the disease and combined data from multiple centres may shed more light to this new entity.

Limitations

This is an observational study with the inherent limitations and bias. The echocardiograms were of limited views to minimise the time of operator's exposure. This has limited the number of echocardiographic data set available for advanced analysis, such as tissue Doppler and 3D imaging. However, the image quality was within the expected limits in patients nursed in the ICU, reflecting a real life setting. In addition, the functional assessment of the LV and RV was done mainly visually, but all operators who performed the analyses were very experienced and TTE accredited for many years. We studied only patients with COVID-19 nursed on the ICU and our findings may not be applicable to patients with mild or moderate disease who do not require ICU admission. Finally, not all studied echocardiographic, laboratory and clinical parameters were available for all patients. We found that severely impaired LVEF is related to in-hospital mortality, but only a small number of patients (11; 3.7%) had severely impaired LVEF in our cohort, and this may have impacted on the results. In any event, LV function is well known to correlate with worse outcome and all-cause mortality in several clinical settings, and this would not be an unexpected finding in patients with COVID-19.

CONCLUSION

Our study showed that in patients with COVID-19 on the ICU, both severely impaired LV function and impaired RV function may have adverse prognostic implications, but older age and inflammatory markers appear to have a greater impact. A combination of echocardiographic and laboratory investigations as well as demographic and clinical characteristics appears appropriate for risk stratification in patients with COVID-19 who are admitted to the ICU.

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and revised the manuscript. MZ collected data and revised the manuscript. AMS, DP, and MM conceived the idea and revised the manuscript. GC-W coordinated and supervised the project, and revised the manuscript. AP coordinated and supervised the project, analysed the data, drafted and submitted the manuscript, and acted as the guarantor of the study.

Funding Prof. Divaka Perera received funding from the British Heart Foundation (PG/19/9/34228)

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by NHS Health Research Authority (REC20/EE/0131). This study was conducted in ICU mechanically ventilated patients.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data used in this study will be available upon reasonable request.

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