Hypertension

COVID-19

First-Phase Ejection Fraction, a Measure of Preclinical Heart Failure, Is Strongly Associated With Increased Mortality in Patients With COVID-19

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ABSTRACT: Presence of heart failure is associated with a poor prognosis in patients with coronavirus disease 2019 (COVID-19). The aim of the present study was to examine whether first-phase ejection fraction (EF1), the ejection fraction measured in early systole up to the time of peak aortic velocity, a sensitive measure of preclinical heart failure, is associated with survival in patients hospitalized with COVID-19. A retrospective outcome study was performed in patients hospitalized with COVID-19 who underwent echocardiography (n=380) at the West Branch of the Union Hospital, Wuhan, China and in patients admitted to King's Health Partners in South London, United Kingdom. Association of EF1 with survival was performed using Cox proportional hazards regression. EF1 was compared in patients with COVID-19 and in historical controls with similar comorbidities (n=266) who had undergone echocardiography before the COVID-19 pandemic. In patients with COVID-19, EF1 was a strong predictor of survival in each patient group (Wuhan and London). In the combined group, EF1 was a stronger predictor of survival than other clinical, laboratory, and echocardiographic characteristics including age, comorbidities, and biochemical markers. A cutoff value of 25% for EF1 gave a hazard ratio of 5.23 ([95% CI, 2.85–9.60]; $P<0.001$) unadjusted and 4.83 ([95% CI, 2.35–9.95], $P<0.001$) when adjusted for demographics, comorbidities, hs-cTnI (high-sensitive cardiac troponin), and CRP (C-reactive protein). EF1 was similar in patients with and without COVID-19 (23.2±7.3 versus 22.0±7.6%, $P=0.092$, adjusted for prevalence of risk factors and comorbidities). Impaired EF1 is strongly associated with mortality in COVID-19 and probably reflects preexisting, preclinical heart failure. **(*Hypertension*. 2021;77:2014–2022. DOI: 10.1161/HYPERTENSIONAHA.121.17099.)** • **Data Supplement**

Key Words: COVID-19 ■ ejection fraction ■ heart failure ■ prevalence ■ prognosis ■ risk factor ■ systole

Coronavirus disease 2019 (COVID-19), a highly infectious disease, first started in Wuhan, Hubei province, China and has since become a global pandemic. Risk factors for cardiovascular disease and the presence of cardiovascular disease are recognized to be factors that influence survival from COVID-19.[1–5] The presence of a preinfective clinical diagnosis of heart failure, while only affecting a small proportion of cases, is associated with more severe COVID-19.[6] First-phase ejection fraction (EF1), a measure of the ejection fraction up to the time of peak aortic flow velocity may be a sensitive measure of predisposition to heart failure, particularly in patients with

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Novelty and Significance

What Is New?

- First-phase ejection fraction (EF1), a measure of the ejection fraction up to the time of peak aortic flow velocity, is a sensitive measure of predisposition to heart failure, particularly in patients with the comorbidities of hypertension and diabetes that are highly prevalent in coronavirus disease 2019 (COVID-19).
- The finding of a strong association of EF1 with survival in COVID-19 in 2 independent cohorts from China and United Kingdom suggests that association is likely to be generalizable to most hospitalized patients.
- The association of EF1 with mortality probably reflects preexisting chronic injury to the left ventricle and may, in part, explain the association of severity of COVID-19 with conditions predisposing to left ventricle dysfunction.

What Is Relevant?

- An impairment of early systolic function as evidenced by reduced EF1 could be causally implicated in worse outcomes from COVID-19 through an elevation of left ventricle filling pressure.
- The much stronger association of EF1 than of individual risk factors or comorbidities with morbidity from COVID-19, if confirmed in larger series, may be useful in identifying patients who are at high risk of COVID-19, in patients who have undergone cardiac imaging.

Summary

EF1 is strongly predictive of survival from COVID-19 and implicates early left ventricular dysfunction, probably arising as a chronic condition before infection, as a determinant of survival. EF1 may be useful in stratifying preventive or therapeutic treatments and as a therapeutic target.

Nonstandard Abbreviations and Acronyms

BNP	brain natriuretic peptide
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
EF1	first-phase ejection fraction
HR	hazard ratio
hs-cTnI	high-sensitive cardiac troponin
RVFAC	right ventricular fractional area change

the comorbidities of hypertension and diabetes that are highly prevalent in COVID-19.[7–9] We hypothesized that predisposition to heart failure would be associated with the severity of COVID-19. We examined the association of EF1 in patients with COVID-19 to mortality in retrospective studies of patients hospitalized with COVID-19 in Wuhan, China, and in South London, United Kingdom who had undergone echocardiography. To determine whether an association of EF1 with mortality was likely to be related to preinfective, preclinical heart failure, or to acute cardiac injury arising as a result of COVID-19, we adjusted for markers of acute cardiac injury in the outcome analysis and compared values of EF1 in patients with COVID to a control group of patients without COVID-19 but with otherwise similar characteristics.

METHODS

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Patient Population

Consecutive patients diagnosed with COVID-19 according to the interim guidance of the World Health Organization[10] from the West Branch of Union Hospital (UH, n=129), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (a designated hospital for COVID-19) were studied retrospectively. Patients from King's Health Partners (n=251), which includes the NHS foundation trusts of Guy's and St Thomas' and King's College Hospitals, London, United Kingdom between February 2020 and May 2020 who underwent echocardiography to exclude cardiovascular complications were included in a second retrospective study. Operators were protected by appropriate personal protective equipment according to China and UK national guidelines, similar to those in recommendations from the American Society of Echocardiography.[11,12] The studies were approved by the Union Hospital Tongji Medical College Ethical committee (No. 20200022) and by the London SE Research Ethics Committee (reference 18/LO/248) for the use of de-identified data for research with specific work on COVID-19 approved by the King's Electronic Records Research Interface. All patients' clinical records were retrieved from electronic patient records, including patient demographics, medical history, treatment, and laboratory investigations. Outcome data were verified from hospital records. The primary outcome was in-hospital all-cause mortality.

In Wuhan, patients underwent echocardiography irrespective of the severity of COVID-19, and this cohort included patients who did not require intensive care. In London, echocardiography was performed mainly on patients requiring intensive care, and echocardiography requests were triaged by senior cardiologists according to local COVID-19 guidelines. In addition to hs-cTnI, (high-sensitive cardiac troponin) biochemical measures available in a subsample of the patients (Table 1) included BNP (brain natriuretic peptide), CRP (C-reactive

Table 1. Clinical, Laboratory, and Echocardiographic Characteristics in the Total Cohort and Cohorts From Wuhan and London

Characteristic*	Total n=380	Wuhan n=129	London n=251	*P* value†
Age, years	58.0±13.9	62.5±12.4	55.6±14.0	<0.001
Male sex, %	222 (58.4)	65 (50.4)	157 (62.5)	0.023
Body mass index, kg/m^2	26.7±5.5	23.6±2.8	28.3±5.9	<0.001
Heart rate, bpm	92.6±19.5	91.1±16.5	93.5±20.9	0.263
Systolic BP, mm Hg (n=259)	129±20	133±18	125±21	0.001
Diastolic BP, mm Hg (n=257)	77±14	81±12	73±14	<0.001
Ethnicity				<0.001
Asian, %	148 (38.9)	129 (100)	19 (7.6)	
Black, %	78 (20.5)	0	78 (31.1)	
Other, %	11 (2.9)	0	11 (4.4)	
White, %	99 (26.1)	0	99 (39.4)	
Unknown, %	44 (11.6)	0	44 (17.5)	
SOFA score (n=163)	8.78±4.70	-	8.78±4.70	…
Comorbidities				
Smoking, %	75 (19.7)	16 (12.4)	59 (23.5)	0.032
Hypertension, %	182 (47.9)	56 (43.4)	126 (50.2)	0.197
Diabetes, %	107 (28.2)	19 (14.7)	88 (35.1)	<0.001
Coronary artery disease, %	33 (8.9)	21 (16.3)	12 (4.8)	<0.001
COPD, %	31 (8.2)	9 (7.0)	22 (8.8)	0.532
Chronic kidney disease, %	31 (8.2)	3 (2.4)	28 (11.2)	0.003
Atrial fibrillation, %	19 (5)	6 (4.7)	13 (5.2)	0.823
Biochemistry‡				
BNP, ng/L (n=197)	148.1 (42.5–990.9)	53.3 (20.5–143.6)	1085.0 (71.0–4507.5)	<0.001
CRP, mg/L (n=364)	95.8 (32.0–212.7)	35.4 (7.3–74.0)	169.0 (60.0–282.9)	<0.001
D-dimer, mg/L (n=311)	3.2 (1.1–8.0)	2.0 (0.6–7.3)	3.8 (0.8–8.0)	<0.001
hs-cTnI, ng/L (n=294)	19.8 (7.0–63.3)	5.1 (2.3–41.0)	28.0 (13.8–75.3)	<0.001
Echocardiography				
LVEDV, mL	94.5±37.7	81.9±25.2	101.0±41.3	<0.001
LVM, g	152±45	144±32	157±51	0.007
RWT	0.48±0.13	0.41±0.05	0.52±0.14	<0.001
LVEF, %	59.5±9.8	62.9±5.3	57.7±11.0	<0.001
EF1, %	23.2±7.3	23.9±4.6	22.8±8.4	0.168
LVGLS, % (n=355)	−16.9±5.0	−19.0±3.0	−15.7±5.5	<0.001
E/A (n=123)	…	0.9±0.3	…	…
E/e' (n=129)	…	9.0±3.0	…	…
RVLS, % (n=199)	−22.1±5.6	−23.4±4.5	−20.0±6.4	<0.001
RVFAC, % (n=333)	39.9±10.4	45.3±5.7	36.8±11.2	<0.001
TAPSE, mm (n=334)	20.8±4.5	22.8±3.3	19.6±4.6	<0.001

BNP indicates brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; E/A, ratio of early mitral filling E wave and atrial contraction A wave; E/e', early mitral filling/tissue Doppler mitral annulus motion; EF1, first-phase ejection fraction; hs-cTnI, high-sensitive cardiac troponin; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; LVM, left ventricular mass; RVFAC, right ventricular fractional area change; RVLS, right ventricular longitudinal strain; RWT, relative wall thickness; SOFA, sequential organ failure assessment; and TAPSE, tricuspid annular plane systolic excursion.

*Where measures are available only in a subsample, this is shown in parenthesis.

†For difference between Wuhan and London.

‡Values are medians (interquartile range).

protein, and D-dimers. Biochemical measures were taken at the time of hospital admission and in most patients were repeated at intervals during admission.

EF1 was measured in a cohort of historical control patients (n=266) of similar age and with broadly similar comorbidities to the COVID-19 cohorts who underwent echocardiography

before the COVID-19 pandemic. Measurement of EF1 was performed using the same methods as in the COVID-19 cohorts. Characteristics of these patients (some of which have previously been published[8]) are shown in Table S1 in the Data Supplement.

Echocardiography and EF1

Transthoracic echocardiography was performed at bedside in all patients using Philips CX50/Epic7C (Philips Medical System, Andover, MA) or GE S6 ultrasound system (GE Healthcare, Guildford, United Kingdom). Echocardiographic images were analyzed off-line by ZS for data from Wuhan and HG for data from London, who were blinded to clinical data and outcomes. The median time from admission to echocardiography was 7.5 days (interquartile range, 2–15). All conventional echocardiographic parameters were measured according to American Society of Echocardiography guidelines.[13] Ejection fraction was measured using Simpson's method. Right ventricular fractional area change (RVFAC) was measured as percentage change between RV area at the end-diastole and area at the end-systole. Tricuspid annular plane systolic excursion was measured using M-mode from an apical 4-chamber view. Left ventricular global longitudinal strain (LVGLS) and right ventricular free wall strain (right ventricular free wall strain [RVLS]) were measured with speckle tracking from apical views using the Tomtec imaging system (Tomtec, Germany). LVGLS and RVLS were measured in 355 and 199 patients in the combined cohort, respectively. EF1 was taken as the percentage volume change between end-diastole to the time of peak aortic velocity (which approximates the time of peak myocardial contraction) using the following equation: EF1=(LVEDV−V1)/LVEDV×100% where LVEDV is end-diastolic left ventricle volume, and V1 is the LV volume at the time of peak aortic velocity (Figure S1). In cases where Doppler aortic flow velocity was not recorded, the time of peak aortic velocity was taken as the time of maximal rate of change of ventricular volume obtained using wall tracking using the Tomtec imaging system. The repeatability and reproducibility of this method for measuring EF1 has been previously reported.[7] In the presence of atrial fibrillation, RR intervals were measured and EF1 measurements were performed on cardiac cycles with the same R-R intervals to minimize beat-to-beat variations. LV diastolic function was measured in the Wuhan cohort. The E/A ratio was calculated as the ratio of transmitral Doppler E wave to A wave and the E/e' ratio as the ratio of transmitral Doppler E wave velocity to the mean of basal lateral and basal septal tissue Doppler e' wave velocity.

Statistical Analysis

Characteristics are presented as mean±SD, except those known to be non-normally distributed which are presented as median with interquartile range. Differences between groups were tested by Student *t* test for continuous variables and χ^2 test for categorical variables. Non-normally distributed variables were log-transformed to achieve an approximately normal distribution before statistical testing. Cox regression analysis was performed to identify potential predictors of death. Multivariate models were constructed to assess the prognostic utility of EF1, with adjustment for covariables, which were significant predictors in the univariate analysis and to calculate adjusted hazards ratios (HRs). Kaplan-Meier curves were used to examine cumulative death rate, and differences between groups were tested using a log-rank test. EF1 was dichotomized using a previously defined cut off value of 25%.[7] Receiver operating characteristic analyses were performed, and the area under the curves were calculated to determine the prediction of 28-day survival by EF1 and other variables. Analyses were performed independently for the Wuhan and London cohorts and repeated in the combined cohort. Comparison of EF1 in patients with and without COVID-19 was performed by ANCOVA. All statistical analyses were performed using SPSS version 25 (SPSS, Inc, Chicago, IL).

RESULTS

Characteristics of Patients With COVID-19

A total of 380 patients (129 from Wuhan and 251 from London) were included in the final analysis (Figure 1). Patients excluded because of poor image quality (n=95) were of similar age and sex and had similar comorbidities compared to those who were included. Clinical characteristics and echocardiographic measures of the total population stratified according to center (Wuhan or London) are shown in Table 1. Patients from the ITU population in London were younger than the unselected hospitalized population in Wuhan but had a higher prevalence of smoking, diabetes, coronary artery disease and chronic kidney disease compared with those from Wuhan. They had higher levels of D-dimers, hs-cTnI, BNP and CRP, and worse LV and RV function compared with patients from Wuhan.

Clinical, Laboratory, and Echocardiographic Data in COVID-19 Survivors and Nonsurvivors

After a median of 50 (interquartile range, 27–51) days of follow-up, 93/380 (24%) patients in the total population died (16% and 29% from the Wuhan and London

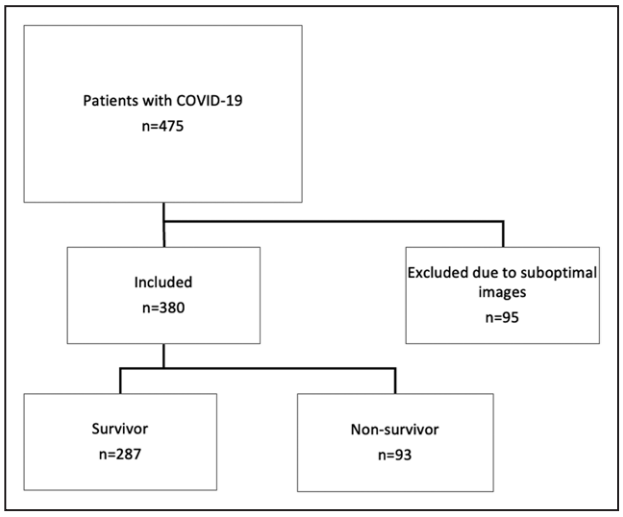

Figure 1. Study flow chart in the total population.
COVID-19 indicates coronavirus disease 2019.

cohorts respectively). Cause of death was recorded as multiorgan failure (47.3%), respiratory failure (24.7%), unknown (9.7%), cardiac (8.6%), septic shock (4.3%), stroke (3.2%), and other (2.2%). Clinical, laboratory, and echocardiographic measures in survivors and nonsurvivors are shown for the 2 centers in Table S2 and for the total population in Table 2. Nonsurvivors were older and had a higher prevalence of hypertension and chronic kidney disease (and a tendency to a higher prevalence of diabetes) compared with survivors. Nonsurvivors had significantly increased D-dimer, hs-cTnI, BNP, and CRP compared with survivors. Nonsurvivors had worse LV (as measured by EF, EF1, LVGLS) and worse RV systolic function (RVLS, RVFAC, and tricuspid annular plane systolic excursion) and increased relative wall thickness.

Prediction of Mortality by EF1 and Other Measures

Prediction of mortality by EF1 and other measures by univariate and multivariate Cox regression analysis at each center is shown in Table S3. EF1 was the measure most consistently and strongly predictive of mortality in each center. In the combined population, other measures significantly predicting mortality on univariate analysis included the following: age, sequential organ failure assessment score, presence of hypertension, BNP, CRP, D-dimer, hs-cTnI, relative wall thickness, EF1, LVGLS, RVLS, and RVFAC (Table 3). In a multivariate model, considering age, presence of hypertension, CRP, hs-cTnI, relative wall thickness, and EF1, EF1 was the measure most strongly associated with mortality (model 1, n=316, Table 3, HR per 1% change in EF1: 0.89 [95% CI, 0.86–0.92], $P<0.001$). Similar HRs for EF1 were observed when all biochemical markers were included in the subsample in which these were available or when the sequential organ failure assessment score was included and did not differ substantially if peak rather than admission values were used for biochemical markers. When adjusting for LVGLS and RVFAC in addition to variables considered in model 1 (model 2, n=236, Table 3), or when replacing RVFAC with RVLS (model 3, n=150, Table 3), the HR for EF1 was similar to model 1. Receiver operating characteristic analysis showed that EF1 had the largest area under the curve (0.75) compared with age, biochemistry, and EF (Figure 2). Kaplan-Meier analysis confirmed EF1 to be a strong predictor of death ($P<0.001$) in each center and in the total population (Figure 3), when a previously defined threshold of 25% (sensitivity: 86.4% and specificity: 47.2%) was used.[7] In the total population, when EF1 was <25%, 81/380 (35.7%) patients died compared with 12/380 (7.8%) in those with an EF1≥25%. When EF1 was considered as a categorical variable (EF1<25% versus EF1≥25%), the HR for an EF1<25% compared with ≥25% was 5.23 ([95% CI, 2.85–9.60], $P<0.001$) unadjusted and 4.83 ([95% CI, 2.35–9.95], $P<0.001$) adjusted for all variables in multivariate Cox regression model 2. Using the optimal threshold of 22.2%

Table 2. Clinical, Laboratory, and Echocardiographic Characteristics in Survivors and Nonsurvivors in the Combined Cohort

Characteristic*	Survivors n=287	Nonsurvivors n=93	*P* value
Age	56.9±13.8	61.4±13.7	0.006
Male sex, %	161 (56.1)	61 (65.6)	0.106
Body mass index, kg/m^2	26.6±5.3	27.2±6.2	0.396
Heart rate, bpm	92.6±19.6	92.7±19.2	0.964
SOFA score (n=163)	8.1±4.3	10.4±5.3	0.004
Comorbidities			
Smoking, %	57 (19.9)	18 (19.4)	0.362
Hypertension, %	126 (43.9)	56 (60.2)	0.007
Diabetes, %	74 (25.8)	33 (35.5)	0.074
Coronary artery disease, %	23 (8.0)	10 (10.8)	0.421
COPD, %	20 (7.0)	11 (11.8)	0.131
Chronic kidney disease, %	28 (9.8)	3 (3.2)	0.046
Atrial fibrillation, %	12 (4.2)	7 (7.5)	0.198
Biochemistry†			
BNP, ng/L (n=197)	112.4 (33.5–513.0)	891.1 (133.0–4527.3)	<0.001
CRP, mg/L (n=364)	65.2 (22.4–190.0)	169.0 (79.1–285.5)	<0.001
D-dimer, mg/L (n=311)	2.8 (0.9–7.6)	4.5 (1.8–8.0)	0.009
hs-cTnI, ng/L (n=294)	17.0 (4.5–50.5)	32.0 (16.4–125.2)	<0.001
Echocardiography			
LVEDV, mL	96.4±37.1	88.7±38.8	0.087
LVM, g	153±46	151±45	0.662
RWT	0.47±0.12	0.51±0.14	0.006
LVEF, %	60.3±8.4	57.0±12.9	0.005
EF1, %	25.0±6.4	17.7±7.3	<0.001
LVGLS, % (n=355)	−17.7±4.5	−14.8±5.7	<0.001
E/A (n=123)	0.92±0.32	0.98±0.39	0.477
E/e' (n=129)	8.8±2.9	9.8±3.1	0.681
RVLS, % (n=199)	−23.1±5.3	−18.4±5.0	<0.001
RVFAC, % (n=333)	41.1±9.9	36.0±11.1	<0.001
TAPSE, mm (n=334)	21.4±4.4	18.8±4.2	<0.001

BNP indicates brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; E/A, ratio of early mitral filling E wave and atrial contraction A wave; E/e', early mitral filling/tissue Doppler mitral annulus motion; EF1, first-phase ejection fraction; hs-cTnI, high-sensitive cardiac troponin; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVGLS, global longitudinal strain; LVM, left ventricular mass; RVFAC, right ventricular fractional area change; RVLS, right ventricular longitudinal strain; RWT, relative wall thickness; SOFA, sequential organ failure assessment; and TAPSE, tricuspid annular plane systolic excursion.

*Where measures are available only in a subsample this is shown in parenthesis.

†Values are medians (interquartile range).

Table 3. Univariate and Multivariate Cox Regression in the Combined Cohort

	HR	CI (95%)	*P* value	HR	CI (95%)	*P* value	HR	CI (95%)	*P* value	HR	CI (95%)	*P* value
	Univariate			Model 1			Model 2			Model 3		
				n=285			n=236			n=150		
Age	1.02	1.00–1.03	0.026	1.04	1.02–1.06	0.001	1.04	1.02–1.06	0.001	1.02	0.99–1.05	0.172
Male sex	1.40	0.92–2.15	0.120									
BMI	1.02	0.98–1.06	0.270									
SBP	1.01	0.99–1.03	0.099									
DBP	1.00	0.98–1.03	0.721									
SOFA score	1.08	1.02–1.15	0.006									
Hypertension	1.76	1.16–2.67	0.007	1.42	0.89–2.28	0.15	1.66	0.98–2.82	0.059	1.21	0.62–2.38	0.576
Diabetes	1.49	0.97–2.28	0.069									
CAD	1.21	0.63–2.33	0.571									
COPD	1.66	0.88–3.12	0.116									
CKD	2.87	0.91–9.07	0.073									
BNP	1.38	1.22–1.56	<0.001									
CRP	1.60	1.31–1.94	<0.001	1.43	1.15–1.77	0.001	1.31	1.02–1.67	0.033	1.27	0.92–1.75	0.153
D-dimer	1.29	1.07–1.56	0.007									
hs-cTnI	1.40	1.24–1.58	<0.001	1.20	1.04–1.38	0.014	1.25	1.07–1.46	0.005	1.31	1.08–1.59	0.007
LVEDV	1.00	0.99–1.00	0.112									
LVM	1.00	0.99–1.00	0.692									
RWT	8.85	2.24–34.9	0.002	1.45	0.27–7.63	0.66	0.80	0.13–4.91	0.811	3.22	0.24–43.5	0.379
LVEF	1.00	0.99–1.00	0.135									
EF1	0.87	0.85–0.90	<0.001	0.89	0.86–0.92	<0.001	0.89	0.86–0.93	<0.001	0.94	0.89–0.99	0.038
EF1<25%	5.23	2.85–9.60	<0.001									
LVGLS	1.11	1.07–1.17	<0.001				1.00	0.94–1.07	0.998	1.09	0.99–1.22	0.065
E/A	0.82	0.33–2.05	0.678									
E/e'	1.09	0.96–1.23	0.170									
RVLS	1.16	1.09–1.25	<0.001							1.04	0.98–1.10	0.247
RVFAC	0.96	0.94–0.98	<0.001				0.98	0.96–1.01	0.153			

BMI indicates body mass index; BNP, brain natriuretic peptide; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DBP, diastolic blood pressure; E/A, ratio of early mitral filling E wave and atrial contraction A wave; E/e', early mitral filling/tissue Doppler mitral annulus motion; EF1, first-phase ejection fraction; hs-cTnI, high-sensitive cardiac troponin; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVGLS, left ventricular longitudinal strain; LVM, left ventricular mass; RVFAC, right ventricular fractional area change; RVLS, right ventricular longitudinal strain; RWT, relative wall thickness; SBP, systolic blood pressure; and SOFA, sequential organ failure assessment.

for EF1 had a sensitivity of 75.3% and specificity of 67.6% with similar HR for impaired versus preserved EF1 (Figure S2).

Comparison of EF1 in Patients With and Without COVID-19

Patients without COVID-19 (studied before the pandemic) were of similar age but were of higher BMI and had a higher prevalence of comorbidities to those with COVID-19 (Table S1). However, EF1 was similar in the 2 groups whether adjusted or unadjusted for risk factors and comorbidities (EF1 23.2±7.3 versus 22.1±7.6% for COVID-19 versus non-COVID-19, unadjusted, *P*=0.073; EF1 23.2±7.3 versus 22.0±7.6% for COVID-19 versus non-COVID-19, adjusted for BMI and presence of hypertension, diabetes, and coronary artery disease, *P*=0.092, Table S1).

DISCUSSION

The main finding of the present study was a strong association between EF1, a measure of early systolic function and survival in patients with COVID-19. This was seen in Wuhan and London and in the combined cohort. The finding was robust being seen irrespective of adjustment for clinical and laboratory characteristics, comorbidities, and other echocardiographic measures of cardiac function and geometry, which made little difference to the ≈5-fold HR associated with EF1<25% compared with ≥25%. While the characteristics of the Wuhan and London cohorts differed, with the former being representative of unselected hospitalized patients and the latter of patients requiring ITU admission, the finding of a strong association of EF1 with survival in both cohorts suggests that association is likely to be generalizable to most hospitalized patients.

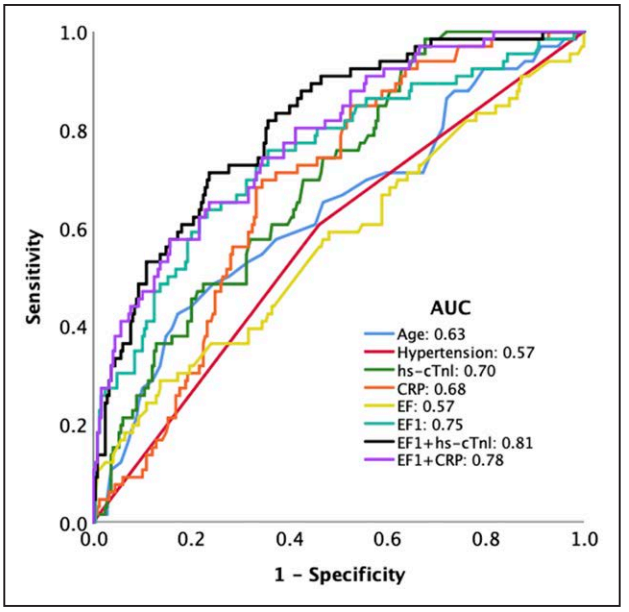

Figure 2. Receiver operating characteristic curve for prediction of mortality in the total population.
AUC indicates area under the curve; CRP, C-reactive protein; and EF1, first-phase ejection fraction.

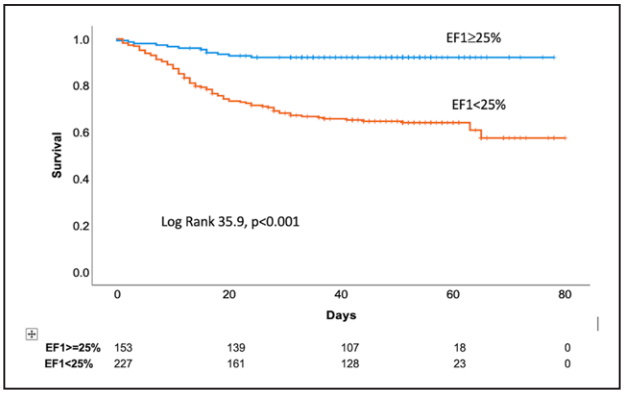

Figure 3. Kaplan-Meier curve of first-phase ejection fraction (EF1) stratified by a previously defined cut off value of 25% in the total population.

Previous studies of hospitalized patients who have undergone echocardiography to investigate suspected cardiovascular complications of COVID-19 have demonstrated little or no association between overall left ventricular EF and survival.[14,15] Results of the present study were consistent with these observations; overall EF was not independently associated with mortality. A differential association of early as opposed to overall systolic function with mortality is not unexpected since overall EF is preserved in the majority of patients with COVID-19 and will not detect patients predisposed to heart failure with preserved EF. EF1 is, by contrast, impaired in patients with hypertension who have preclinical evidence of heart failure.[7] This may be because early systolic function is more sensitive to compromise in cardiac contractility caused by acute or chronic injury with sarcomeric mechanotransduction maintaining overall contraction (and overall EF) at the expense of slower but sustained contraction during early systole.

An impairment of EF1 as a sensitive marker of early systolic dysfunction is thus likely to be a prelude to LV decompensation and to heart failure, particularly heart failure with preserved ejection fraction, and it is notable that diastolic dysfunction is common in patients with COVID-19.[14,16] The slow sustained contraction of the LV required to maintain overall EF leads to an increase in late systolic myocardial wall stress, which may delay diastolic filling[8,17] and result in increased LV filling pressures[8] to which patients with severe lung disease may be particularly vulnerable. The association of EF1 with poor outcomes is therefore consistent with previous observations of a high prevalence of clinical signs of heart failure and/or elevation of BNP in nonsurvivors compared with survivors of COVID-19.[1,18,19]

An impairment of early systolic function could arise through acute or preexisting chronic cardiac injury or a combination of the 2. Some degree of acute cardiac injury as evidenced by a rise in hs-cTnI is relatively common in hospitalized patients with COVID-19[2,19–22] and, as in the present study, has been associated with poorer outcomes.[1,2,19,23,24] However, in the present study, the association of EF1 with mortality was little influenced by adjustment for markers of acute cardiac injury such hs-cTnI and BNP. Furthermore, values of EF1 in patients with COVID-19 were similar to those in a control group of patients with broadly similar characteristics who were studied before the COVID-19 pandemic. Taken together, these observations suggest that the association of EF1 with mortality reflects preexisting preclinical injury to the LV and may, in part, explain the association of severity of COVID-19 with conditions such as hypertension, diabetes, and CKD[1–4] that are also risk factors for LV dysfunction. Impaired EF1 is associated with increased late systolic wall stress that may adversely impact on LV remodeling, and our finding of increased relative wall thickness in nonsurvivors is consistent with preexisting impairment of EF1 and increased late systolic wall stress.

EF1 is a new measure of early systolic function and its dependence on loading conditions has not been fully elucidated. Preliminary studies suggest that it has modest dependence on both preload and afterload. In the present study, we did not find an association of systolic blood pressure with mortality, but patients with impaired EF1 may be sensitive to cardiac loading conditions and to drugs that may influence cardiac contractility; this would need to be tested prospectively. The much stronger association of EF1 than of individual risk factors or comorbidities with morbidity from COVID-19, if confirmed in larger series, may be useful in identifying patients who are at high risk of COVID-19, particularly in patients who have undergone cardiac imaging.

This study is subject to several important limitations. The sample size was relatively small, patients were studied at different stages in the evolution of COVID-19, and were on a variety of different treatments. While the Wuhan cohorts were unselected, selection bias could have influenced findings in the London cohort. However, this would not be expected to affect the relative strengths of associations of EF1 and other cardiac biomarkers with outcomes, and it is notable that we observed similar findings in both cohorts. EF1 may be influenced by arterial stiffness, which associates with mortality in COVID-19.[5] Although we adjusted for systolic blood pressure, this may be a poor surrogate of arterial stiffness especially in acute COVID-19; direct measurement of EF1 and arterial stiffness will be required to assess their relative associations with COVID-19 mortality. Image quality was insufficient to allow measurement of EF1 in a relatively high proportion of cases. However, measurement of EF1 was not mandated at the time of study. If the clinical utility of EF1 is accepted, then it is likely that the addition of appropriate quality control would allow EF1 to be measured in most patients. The cross-sectional nature of the study limits conclusions with regard to causality.

PERSPECTIVES

EF1 is a sensitive measure of early left ventricular systolic function and can be measured from standard bedside echocardiography in most patients with COVID-19. EF1 is strongly predictive of survival from COVID-19 and implicates early left ventricular dysfunction, probably arising as a chronic condition before infection, as a determinant of survival. EF1 may be useful in stratifying preventive or therapeutic treatments and as a therapeutic target.

In conclusion, in hospitalized patients with COVID-19, EF1, a measure of early systolic function, is strongly predictive of survival.

ARTICLE INFORMATION

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Disclosures

H. Gu and P. Chowienczyk are named on a patent application for first-phase ejection fraction. The other authors report no conflicts.

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