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Risk prediction in patients with COVID-19 based on haemodynamic assessment of left and right ventricular function

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Aims Cardiovascular involvement is common in COVID-19. We sought to describe the haemodynamic profiles of hospitalized COVID-19 patients and determine their association with mortality.

Methods and results Consecutive hospitalized patients diagnosed with COVID-19 infection underwent clinical evaluation using the Modified Early Warning Score (MEWS) and a full non-invasive echocardiographic haemodynamic evaluation, irrespective of clinical indication, as part of a prospective predefined protocol. Patients were stratified based on filling pressure and output into four groups. Multivariable Cox-Hazard analyses determined the association between haemodynamic parameters with mortality. Among 531 consecutive patients, 44% of patients had normal left ventricular (LV) and right ventricular (RV) haemodynamic status. In contrast to LV haemodynamic parameters, RV parameters worsened with higher MEWS stage. While RV parameters did not have incremental risk prediction value above MEWS, LV stroke volume index, *E*/*e*′ ratio, and LV stroke work index were all independent predictors of outcome, particularly in severe disease. Patients with LV or RV with high filling pressure and low output had the worse outcome, and patients with normal haemodynamics had the best ($P < 0.0001$).

Conclusion In hospitalized patients with COVID-19, almost half have normal left and right haemodynamics at presentation. RV but not LV haemodynamics are related to easily obtainable clinical parameters. LV but not RV haemodynamics are independent predictors of mortality, mostly in patients with severe disease.

Keywords COVID-19 • echocardiography • haemodynamics • risk stratification

Introduction

The spectrum of COVID-19 infection ranges from asymptomatic carriers to severe progressive pneumonia.[1,2] Significant haemodynamic derangement can accompany the disease in its severe form, at least partially caused by cardiac involvement.[3] Haemodynamic parameters can influence mortality and aid in risk stratification in multiple conditions.[4–8] Non-invasive haemodynamic parameters measured by Doppler echocardiography correlate well with invasive haemodynamic measurements without the risk inherent to an invasive procedure.[9,10] We previously presented data regarding the cardiac manifestations of COVID-19 in 100 consecutive hospitalized patients,[11] but this limited number of patients prevented correlating haemodynamic profiles with mortality. We have now expanded our systematic echocardiographic evaluation of consecutive hospitalized COVID-19 patients to 531 patients, to describe the different non-

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invasive haemodynamic profiles and to evaluate their added value in prediction of in-hospital mortality.

Methods

Study population

We prospectively studied 531 consecutive adult patients (≥18 years old) admitted between 21 March 2020 and 16 September 2020 to the Tel Aviv Medical Center because of COVID-19 infection. All patients had a diagnosis of COVID-19 infection confirmed by a positive reverse-transcriptase–polymerase chain reaction assay for SARS-CoV-2 in a respiratory tract sample. Demographic data, comorbid conditions, medications, physical examination, and laboratory findings were recorded systematically. Coronary artery disease was defined based on history of either myocardial infarct, percutaneous coronary intervention, or coronary bypass surgery. Patients were risk stratified and staged according to their COVID-19 Modified Early Warning Score (MEWS), as previously described (Supplementary data online, *Table S1*).[12,13] MEWS is predictive of the need for invasive mechanical ventilation and mortality among patients with COVID-19,[11–13] and patients can be divided into four risk categories: low, medium, high, and very high risk.[13] All patients underwent non-invasive haemodynamic evaluation by transthoracic echocardiography within 48 h of admission, irrespective of disease severity or clinical need, as part of a predefined step-by-step-protocol. Clinical and imaging data were collected prospectively. The ethics committee of the Tel Aviv Medical Center approved the study (IRB number 0196-20-TLV).

Echocardiographic and non-invasive haemodynamic assessment

Oxygen saturation was measured by pulse oximetry. Blood pressure was measured using the Welch Allyn Vital Signs Monitor 300 Series ensuring the cuff is at heart level, using the correct cuff size. Echocardiography was performed in a standard manner using the same equipment (CX 50, Philips Medical Systems, Bothell, WA, USA) by cardiologists with expertise in echocardiographic recording and interpretation. In accordance with current guidelines,[14,15] the following measures were undertaken to minimize the risk of infection: (i) all echocardiographic studies were bedside studies performed at the designated COVID-19 intensive care or internal ward units; (ii) all echocardiographic examinations were performed with small dedicated scanners, because of their easier disinfection; (iii) personal protection at the time of echocardiographic recordings included airborne precautions comprising of N-95 respirator masks, fluid resistant gowns, two sets of gloves, head-covers, eye shields and shoe covers; and (iv) All measurements were performed offline to reduce exposure and contamination.

Left ventricular (LV) ejection fraction was calculated using the biplane volumes in all patients with segmental wall motion abnormalities or global systolic dysfunction. In patients with normal LV systolic function, ejection fraction was visually estimated. LV diameters were measured as recommended.[16] Right ventricular (RV) function was evaluated by tricuspid annular plane systolic excursion (TAPSE) and fractional area change (FAC).[16–18] Measurements of mitral inflow and tissue Doppler were measured as recommended.[19] Non-invasive haemodynamic variables, their measurement and calculation, as well as their normal range are detailed in *Table 1*.

Non-invasive LV haemodynamic variables included stroke volume, stroke volume index (SVI), heart rate (HR), cardiac index (CI), mean arterial pressure (MAP), systemic vascular resistance (SVR) index, average *E*/*e*′, and LV stroke work index (LVSWI). MAP was measured at the time of echocardiography. LV end-diastolic pressure (LVEDP) was calculated based on the formula 4.9 + (0.62 × *E*/*e*′ ratio).[6] SVR index was calculated based on the formula [MAP - right atrial pressure (RAP)]/CI.[7] LVSWI was calculated based on the formula 0.0136 × [SVI × (MAP-LVEDP)].[20] Non-

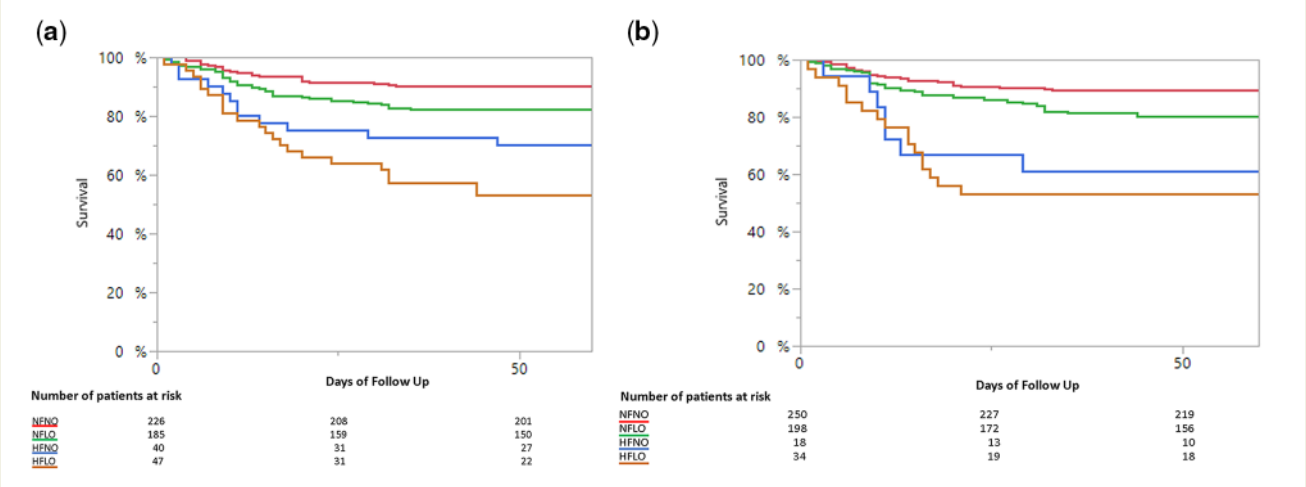

Figure 1 Kaplan–Meier curves for overall survival in patients with COVID-19 infection, stratified by haemodynamic status. (*A*) Overall survival in patients with COVID-19 infection, stratified by their position on the LV Frank–Starling curve (normal filling pressure and normal stroke volume red line, normal filling pressure and reduced stroke volume green line, high filling pressure and normal stroke volume blue line, and high filling pressure and low stroke volume brown line). Note that there is a decrease in survival with increasing filling pressure and decreasing forward flow ($P < 0.0001$). (*B*) Overall survival in patients with COVID-19 infection, stratified by their position on the RV Frank–Starling curve (normal filling pressure and normal stroke volume red line, normal filling pressure and reduced stroke volume green line, high filling pressure and normal stroke volume blue line, and high filling pressure and low stroke volume brown line). Note that there is decrease in survival with increasing filling pressure and decreasing forward flow ($P < 0.0001$). HFNO, high filling pressure and normal output; HFLO, high filling pressure and low output; LV, left ventricular; NFNO, normal filling pressure and normal output; NFLO, normal filling pressure and low output.

Table 1 Haemodynamic parameters

Parameter	Measurement/calculation	Normal range
Mean arterial pressure	(Systolic blood pressure + diastolic blood pressure × 2)/3	70–105 mmHg
Right atrial pressure[17]	Estimated based on inferior vena cava size and collapsibility	<10 mmHg
Stroke volume[11]	LVOT Doppler time velocity integral multiplied by LVOT cross-sectional area (LVOT diameter^2 × 0.785)	60–100 mL/beat
Stroke volume index	Stroke volume/body surface area	35–47 mL/m^2/beat
Cardiac output	Stroke volume × heart rate	4–8 L/min
Cardiac output index	Cardiac output/body surface area	2.5–4 L/min/m^2
Mitral *E*/*e*′ ratio[19]	Peak early filling velocity/average septal and lateral annular velocities	<14
Left ventricular end-diastolic pressure[6]	4.9 + (0.62 × *E*/*e*′ ratio)	<12 mmHg
Left ventricular stroke work index[6]	0.0136 × [stroke volume index × (mean arterial pressure-left ventricular end-diastolic pressure)]	50–62 gm m/m^2/beat
Systemic vascular resistance index	80 × (mean arterial pressure-right atrial pressure)/cardiac index	1970–2390 dynes×s/cm^5/m^2
Pulmonic flow acceleration time[17]	Measured by pulse-wave Doppler in the parasternal short-axis view at the level of the aortic valve	>90 ms
Mean pulmonary artery pressure[19]	48–0.28 × pulmonic flow acceleration time	<25 mmHg
Pulmonary vascular resistance index	80 × (mean pulmonary artery pressure-left ventricular end-diastolic pressure)/cardiac index	255–285 dynes×s/cm^5/m^2
Right ventricular stroke work index	0.0136 × [stroke volume index × (mean pulmonary arterial pressure-right atrial pressure)]	5–10 gm m/m^2/beat

LVOT, left ventricular outflow tract.

invasive RV haemodynamic variables included SVI, HR, CI, pulmonic acceleration time (PAT), estimated right atrial pressure (RAP), mean pulmonary artery pressure (MPAP), pulmonary vascular resistance index, and RV stroke work index (RVSWI). MPAP was calculated based on the formula 48 - (0.28 × PAT).[21] Pulmonary vascular resistance index was calculated based on the formula 80 × [(MPAP-LVEDP)/CI].[22] RVSWI was calculated based on the formula 0.0136 × [SVI × (MPAP-RAP)].[23]

Left and right ventricular haemodynamic profiles

We stratified patients based on LV filling pressure and output into four profiles, reflecting their point on the LV Frank–Starling curve: normal filling pressure and normal output (*E*/*e*′<14 and SVI ≥35 mL/m^2),[7] normal filling pressure and low output (*E*/*e*′<14 and SVI <35 mL/m^2), elevated filling pressure and normal output (*E*/*e*′≥14 and SVI ≥35 mL/m^2), and elevated filling pressure and low output (*E*/*e*′≥14 and SVI <35 mL/m^2). We also stratified patients based on RV filling pressure and output into four profiles: normal RV filling pressure and normal output (RAP < 10 mmHg and SVI ≥35 mL/m^2),[24] normal RV filling pressure and low output (RAP < 10 mmHg and SVI <35 mL/m^2), elevated RV filling pressure and normal output (RAP ≥ 10 mmHg and SVI ≥35 mL/m^2) and elevated RV filling pressure and low output (RAP ≥ 10 mmHg and SVI <35 mL/m^2).

Since using *E*/*e*′ to estimate LV filling pressures in patients with a normal LV systolic function may be limited,[25–27] we also defined elevated LV filling pressures based on a modification of the 2016 ASE-EACVI recommendations and algorithm for patients with EF ≥50%.[19] In this modified classification, we used three of the four recommended variables and their abnormal cut-off values: annular *e*′ velocity (septal *e*′ < 7 cm/s or lateral *e*′ < 10 cm/s), average *E*/*e*′ ratio >14, LA maximum volume index >34 mL/m^2. TR velocity, the fourth variable in this algorithm, was assessed in a minority of patients and was replaced with a surrogate marker of elevated pulmonary pressure, PAT < 90 ms.[28] LV filling pressure was considered to be elevated if more than half of the available parameters met these cut-off values. Inconclusive examinations with only half of the parameters meeting the cut-off values were counted as normal filling pressure. We then re-stratified patients based on LV filling pressure and output into four profiles, reflecting their point on the LV Frank–Starling curve: Normal filling pressure (based on the 2016 ASE-EACVI Recommendations and algorithm for patients with EF ≥ 50%) and normal output (SVI ≥35 mL/m^2), normal filling pressure and low output (SVI <35 mL/m^2), elevated filling pressure and normal output, and elevated filling pressure and low output.

Statistical analysis

Continuous normally distributed parameters were presented as mean ± SD and compared using the Student's *t*-test. Non-normally distributed data were presented by median, first and third quartiles and compared using the Wilcoxon rank-sum test. Categorical data were compared between groups using the χ^2 test, or Fisher's exact test and expressed as numbers and/or percentage. Repeated measurements multivariate analysis of variance was used to examine *P* of trend across

MEWS risk stages. The survival estimate was calculated using the Kaplan–Meier method and compared by log-rank test. Time of follow-up was calculated between baseline non-invasive haemodynamic echocardiographic evaluation and either death or last date of follow-up. Median follow-up time was assessed using the reversed Kaplan–Meier method. Analysis for survival was obtained for all patients. To assess the independent parameters associates of outcome, we used multivariable Cox proportional hazard models for the time to death, allowing calculation of adjusted hazard ratio (HR). The first step was to group the variables into LV and RV filling pressure, output or afterload parameters, since many parameters were correlated. The second step was to select for each group all the variables with $P < 0.05$ in a univariable analysis. The third step was to assess correlations between the selected variables within each group. If correlations between such variables were suggestive of co-linearity ($R^2 > 0.7$; $P < 0.0001$) then the variable with the most 'significant' P-value in univariable analysis was chosen. The final chosen parameters were SVI, E/e', RAP, and PAT. In the fourth step, dichotomous values for continuous parameters affecting survival were defined based on accepted cut-offs.[16,19] In the fifth step, we performed a multivariable Cox hazard analysis to assess which parameters were associated with mortality in adjusted analyses. Covariates were entered in a stepwise forward multivariable Cox model with the use of a probability value of ≤0.05. Compliance with the proportional hazard assumption was assessed by visually inspecting the Schoenfeld residuals plotted against time and by performing a goodness of fit test on these residuals. To determine whether non-invasive haemodynamic echocardiographic parameters provide incremental prognostic value on top of the MEWS score, we performed Cox hazard multivariable analyses for mortality adjusted for the score. These analyses included only the significant non-invasive haemodynamic dichotomous covariates. To assess whether the LV or RV haemodynamic parameters and/or MEWS score provide incremental prognostic value on top of the other, we used the stepwise forward and backwards Akaike Information Criterion (AIC) method which has the lowest AIC for the best model. Furthermore, the statistical significance for the additive value of LV and RV haemodynamic parameters, and/or MEWS score were examined by the χ^2 test of the LogLik reduction. All computations were performed using JMP statistical software for Windows (Version 14.0; SAS Institute) or the R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

Clinical data were collected for 664 consecutive patients hospitalized with COVID-19 infection. A total of 133 patients were excluded because they did not undergo non-invasive haemodynamic assessment. The reasons for not performing the echocardiographic assessment were: hospital discharge within 48 h of admission (35 patients), patient refusal (3 patients), and death shortly after hospitalization (95 patients, including 15 patients who died within 48 h from admission and 80 patients who had a 'do not intubate/resuscitate' status and received only palliative care). Thus, the study group included 531 patients (aged 63.1 ± 18.3 years, 62% male) who underwent clinical and non-invasive haemodynamic echocardiographic evaluation.

Clinical characteristics

At the time of the baseline haemodynamic evaluation, all patients had COVID-19 symptoms, stratified to mild/moderate disease (oxygen saturation ≥ 94% at room air) in 279 (52%), severe disease (need for non-invasive oxygen) in 233 (44%), and critical disease (need for mechanical ventilation, use of vasopressors and/or extracorporeal life support) in 19 (4%). Comorbidities were present in 73% of patients, with hypertension being the most common, followed by diabetes mellitus and coronary artery disease. Troponin-I and brain natriuretic peptide (BNP) were elevated in 16% and 37%, respectively. Bilateral infiltration was the most common chest radiograph manifestation (46%; *Table 2*).

Echocardiographic and non-invasive haemodynamic findings

The feasibility for most of the main parameters was reasonable, including the following: LV ejection fraction (531/531), RV FAC (408/531), TAPSE (488/531), e' (498/531), LV SV (496/531), and CO (496/531). The majority of patients ($N = 413$, 83%) had preserved LV ejection fraction. LV end-diastolic diameter was smaller than reference values in 106 (20%). Enlarged left atrial volume was seen in 191 (36%). RV was large in 186 (35%) of patients. Main indices of RV function (TAPSE and RV FAC) were lower than reference values in 132 (27%) for TAPSE and 118 (29%) for RV FAC. Low SVI was observed in 228 (46%) of patients. Evaluation of indices of LV filling pressure showed that only 89 (18%) of patients had clearly elevated LV filling pressure. Elevated SVR index was observed in 302 (61%) of patients. Compared with patients with normal or high SVR index, Patients with low SVR index had lower O_2 saturation (91.8 ± 8% vs. 93.5 ± 6%; $P = 0.04$), and higher prevalence of severe or critical COVID-19 infection (41% vs. 23%; $P = 0.01$). In 257 (52%) patients, LVSWI was below normal; in 222 (45%), it was normal; and in the remaining 16 (3%), it was above normal.

Evaluation of indices of RV filling pressure showed that only 53 (10%) of patients had clearly elevated RV filling pressure. The majority of patients ($N = 346$, 76%) had at least mildly elevated mean pulmonary artery pressure, and in 245 (54%) it was significantly elevated. The majority of patients ($N = 245$, 54%) had elevated pulmonary vascular resistance index. In 277 (61%) patients, RVSWI was above normal, in 178 (39%) it was normal, but it was not below normal in any one of the patients. Of the 495 patients who were evaluated both for RV and LV haemodynamics, in 216 (44%) LV and RV filling pressures and output were normal.

LV haemodynamic profiles

Stratifying patients according to LV haemodynamic profile revealed that 226 (45%) had normal filling pressure and output, 185 (37%) had normal filling pressure and low output, 40 (8%) had elevated filling pressure and normal output, and 47 (10%) had elevated filling pressure and low output. In 33 patients, E/e' was not measured thus they were not included in this analysis. There were significant differences in numerous variables of interest across the LV haemodynamic profiles (*Table 3*). The LV haemodynamic profile was significantly associated with mortality (*Figure 1A*). Patients with elevated filling pressure and low output had the worst outcome ($P < 0.0001$; $P = 0.05$, and $P = 0.003$ for comparisons to normal haemodynamics, elevated filling pressure and normal output, and normal filling pressure and low output, respectively), and patients with normal haemodynamics had the best ($P = 0.003$; $P = 0.004$, and $P < 0.0001$ for comparisons to elevated filling pressure and normal output, normal filling pressure and low

Table 2 Baseline clinical and echocardiographic characteristics

Parameter	All patients
Clinical characteristics	
Age (years), mean ± SD	63.1 ± 18
Male gender, *n* (%)	327 (61.6)
Disease severity, *n* (%)	
Mild/moderate	276 (52)
Severe	234 (44)
Critical	21 (4)
Modified Early Warning Score, mean ± SD	4.5 ± 3.5
Body mass index (kg/m^2), mean ± SD	27.3 ± 6
Ischaemic heart disease, *n* (%)	90 (17)
Stroke, *n* (%)	48 (9)
Chronic obstructive pulmonary disease, *n* (%)	32 (6)
Chronic kidney disease, *n* (%)	53 (10)
Diabetes mellitus, *n* (%)	159 (30)
Hypertension, *n* (%)	244 (46)
Physical examination	
Temperature (°C), mean ± SD	37.5 ± 0.9
Respiratory rate (breaths/min), mean ± SD	20 ± 6
O_2 saturation (%), mean ± SD	93.0 ± 8
Heart rate (bpm), mean ± SD	85 ± 16
Systolic blood pressure (mmHg), mean ± SD	135 ± 21
Diastolic blood pressure (mmHg), mean ± SD	76 ± 25
Leg oedema, *n* (%)	32 (6)
Laboratory evaluation	
Haemoglobin (g/dL), mean ± SD	13.2 ± 2.0
White blood cells (10^3/μL), mean ± SD	7.7 ± 4.6
Platelets (10^3/μL), mean ± SD	205 ± 84
Blood urea nitrogen (mg/dL), mean ± SD	21.6 ± 18
Creatinine (mg/dL), mean ± SD	1.1 ± 1.3
C-reactive protein (mg/L)	86.9 ± 78
D-dimer (mg/L), mean ± SD	2.0 ± 3.9
Troponin-I (ng/L), median (IQR)	10 (5–24)
Brain natriuretic peptide (pg/mL), mean ± SD	165 ± 401
Chest radiograph and ECG	
Bilateral infiltrate, *n* (%)	244 (46)
Normal sinus rhythm, *n* (%)	467 (88)
Atrial fibrillation, *n* (%)	32 (6)
ST/T wave changes, *n* (%)	85 (16)
Echocardiographic evaluation	
Left ventricular ejection fraction (%), mean ± SD	57.2 ± 6
Left ventricle *S′* (cm/s), mean ± SD	7.2 ± 2.2
Left ventricle end-diastolic diameter (mm), mean ± SD	47.7 ± 7
Left ventricle end-systolic diameter (mm), mean ± SD	28.8 ± 6
Left atrial volume index (mL/m^2), mean ± SD	31.4 ± 14
RV end-diastolic area (cm^2), mean ± SD	20.7 ± 5
RV end-systolic area (cm^2), mean ± SD	12.2 ± 4
RV fractional area change (%), mean ± SD	42.2 ± 12
TAPSE (cm), mean ± SD	2.3 ± 0.5
RV *S′* (cm/s), mean ± SD	11.1 ± 3
Non-invasive haemodynamic evaluation	
Stroke volume (mL), mean ± SD	67.2 ± 22
Stroke volume index (mL/m^2), mean ± SD	36.4 ± 11
Heart rate (bpm), mean ± SD	77 ± 15
Cardiac output (L/min), mean ± SD	5.1 ± 1.9
Cardiac index (L/min/m^2), mean ± SD	2.8 ± 0.9
E wave velocity (cm/s), mean ± SD	66.4 ± 21
A wave velocity (cm/s), mean ± SD	63.0 ± 19
E/*A* ratio, mean ± SD	1.09 ± 0.4
e′ septal (cm/s), mean ± SD	6.6 ± 2.0
e′ lateral (cm/s), mean ± SD	8.6 ± 3.0
E/*e′* average ratio, mean ± SD	9.9 ± 4.9
Calculated LVEDP (mmHg), mean ± SD	11.0 ± 3.0
SVRI (dynes×s/cm^5/m^2), mean ± SD	2973 ± 1263
LV stroke work (gm m/beat), mean ± SD	60.0 ± 25
LV stroke work index (gm m/m^2/beat), mean ± SD	32.2 ± 14
Right atrium pressure (mmHg), mean ± SD	7.6 ± 4
Pulmonic flow acceleration time (ms), mean ± SD	87.8 ± 27
Calculated mean pulmonary pressure (mmHg), mean ± SD	37.2 ± 14
PVRI (dynes×s/cm^5/m^2), mean ± SD	228 ± 152
RV stroke work (gm m/beat), mean ± SD	19.5 ± 13
RV stroke work index (gm m/m^2/beat), mean ± SD	10.3 ± 6

LV, left ventricular; LVEDP, left ventricle end-diastolic pressure; PVRI, pulmonary vascular resistance index; RV, right ventricular; SVRI, systemic vascular resistance index; TAPSE, tricuspid annular plane systolic excursion.

Table 3 Clinical and echocardiographic characteristics stratified based on left ventricular filling pressure and output

Parameter	Normal filling pressure and output *N* = 226	Normal filling pressure, low output *N* = 185	High filling pressure, normal output *N* = 40	High filling pressure, low output *N* = 47	*P*-value
Clinical characteristics					
Age (years), mean ± SD	58.4 ± 18	61.1 ± 18	77.7 ± 11	78.9 ± 16	<0.0001
Male gender, *n* (%)	153 (67.7)	113 (61.1)	22 (55.0)	14 (29.8)	<0.0001
Disease severity, *n* (%)					0.06
Mild/moderate	120 (53)	98 (53)	15 (37)	27 (57)	
Severe	104 (46)	78 (42)	24 (60)	16 (34)	
Critical	2 (1)	9 (5)	1 (3)	4 (9)	
Modified Early Warning Score, mean ± SD	3.9 ± 3.2	4.2 ± 3.6	6.3 ± 3.5	6.7 ± 3.2	<0.0001
Ischaemic heart disease, *n* (%)	34 (15)	30 (16)	7 (17)	16 (34)	0.06
Stroke, *n* (%)	16 (7)	17 (9)	3 (7.5)	14 (29)	0.003
Chronic kidney disease, *n* (%)	18 (8)	13 (7)	12 (30)	7.5 (16)	0.002
Diabetes mellitus, *n* (%)	70 (31)	43 (23)	17 (42)	20 (42)	0.05
Hypertension, *n* (%)	95 (42)	70 (38)	31 (78)	36 (76)	<0.0001
Physical examination					
O_2 saturation (%), mean ± SD	93.7 ± 6	93.2 ± 9	90.8 ± 9	93.4 ± 7	0.12
Heart rate (bpm), mean ± SD	85 ± 16	86 ± 15	82 ± 17	85 ± 15	0.55
Systolic blood pressure (mmHg) mean ± SD	135 ± 20	133 ± 21	139 ± 23	133 ± 26	0.1
Diastolic blood pressure (mmHg), mean ± SD	78 ± 35	76 ± 13	72 ± 13	75 ± 16	0.53
Laboratory evaluation					
Haemoglobin (g/dL), mean ± SD	13.4 ± 1.8	13.5 ± 1.9	12.2 ± 2.4	12.2 ± 2.3	<0.0001
Blood urea nitrogen (mg/dL), mean ± SD	19.6 ± 18	19.7 ± 15	30.5 ± 24	28.2 ± 15	<0.0001
Creatinine (mg/dL), mean ± SD	1.2 ± 1.7	1.0 ± 0.6	1.6 ± 1.3	1.4 ± 1.3	0.06
Troponin-I (ng/L), median (IQR)	8 (4–17)	9 (5–26)	17 (10–37)	22 (9–59)	0.05
Brain natriuretic peptide (pg/mL), mean ± SD	89 ± 133	84 ± 118	310. ± 349	657 ± 1015	<0.0001
Chest radiograph and ECG					
Bilateral infiltrate, *n* (%)	108 (48)	80 (43)	20 (50)	20 (43)	0.61
Atrial fibrillation, *n* (%)	9 (4)	7 (4)	4 (10)	8 (17)	0.09
Echocardiographic evaluation					
Left ventricular ejection fraction (%), mean ± SD	58.2 ± 5	57.5 ± 6	54.0 ± 7	53.6 ± 9	<0.0001
Left ventricle end-diastolic diameter (mm), mean ± SD	51.9 ± 5	42.5 ± 5	54.7 ± 7	41.2 ± 6	<0.0001
Left ventricle end-systolic diameter (mm), mean ± SD	30.9 ± 6	25.8 ± 5	34.0 ± 8	27.6 ± 7	<0.0001
Left atrial volume index (mL/m^2), mean ± SD	28.6 ± 13	27.7 ± 12	40.2 ± 14	42.3 ± 15	<0.0001
RV end-diastolic area (cm^2), mean ± SD	21.0 ± 4	20.3 ± 5	23.0 ± 7	20.0 ± 5	0.02
RV end-systolic area (cm^2), mean ± SD	11.7 ± 3	12.1 ± 4	14.5 ± 7	12.8 ± 5	0.07
RV fractional area change (%), mean ± SD	43.7 ± 11	42.7 ± 12	39.9 ± 11	36.8 ± 12	0.07
TAPSE (cm), mean ± SD	2.4 ± 0.5	2.2 ± 0.5	2.1 ± 0.5	1.9 ± 0.6	<0.0001
RV S′ (cm/s), mean ± SD	11.6 ± 2	10.9 ± 3	10.7 ± 4	9.7 ± 3	<0.0001
Non-invasive haemodynamic evaluation					
Stroke volume (mL), mean ± SD	82.4 ± 16	50.8 ± 12	85.1 ± 22	43.4 ± 11	<0.0001
Stroke volume index (mL/m^2), mean ± SD	43.4 ± 8	26.9 ± 5	47.0 ± 10	24.5 ± 6	<0.0001
Heart rate (bpm), mean ± SD	83 ± 17	83 ± 15	80 ± 18	82 ± 14	0.92
Cardiac output (L/min), mean ± SD	6.2 ± 1.7	3.9 ± 1.3	6.1 ± 1.8	3.3 ± 1.0	<0.0001
Cardiac index (L/min/m^2), mean ± SD	3.3 ± 0.8	2.1 ± 0.6	3.5 ± 0.7	1.9 ± 0.6	<0.0001
E wave velocity (cm/s), mean ± SD	63.8 ± 15	59.0 ± 15	89.0 ± 24	89.9 ± 30	<0.0001
A wave velocity (cm/s), mean ± SD	59.5 ± 15	60.8 ± 15	84.2 ± 32	78.1 ± 25	<0.0001
E/*A* ratio, mean ± SD	1.12 ± 0.4	1.01 ± 0.35	1.17 ± 0.5	1.21 ± 0.7	0.01
e′ septal (cm/s), mean ± SD	7.1 ± 1.9	6.9 ± 2.0	4.8 ± 1.0	4.5 ± 1.1	<0.0001
e′ lateral (cm/s), mean ± SD	9.4 ± 3.0	8.9 ± 2.8	5.5 ± 1.3	5.4 ± 1.3	<0.0001
E/e′ average ratio, mean ± SD	8.2 ± 1.9	8.0 ± 2.2	18.1 ± 5.1	18.5 ± 5.3	<0.0001

Continued

Table 3 *Continued*

Parameter	Normal filling pressure and output N = 226	Normal filling pressure, low output N = 185	High filling pressure, normal output N = 40	High filling pressure, low output N = 47	P-value
Calculated LVEDP (mmHg), mean ± SD	10.0 ± 1.2	9.9 ± 1.3	16.1 ± 3.2	16.3 ± 3.9	<0.0001
SVRI (dynes×s/cm^5/m^2), mean ± SD	2367 ± 835	3634 ± 1260	2130 ± 205	3964 ± 1430	<0.0001
LV stroke work (gm m/beat), mean ± SD	74.8 ± 24	45.7 ± 14	69.6 ± 23	37.1 ± 12	<0.0001
Right atrium pressure (mmHg), mean ± SD	6.7 ± 3	7.6 ± 4	9.6 ± 4	10.5 ± 5	<0.0001
Pulmonic flow acceleration time (ms), mean ± SD	93.4 ± 26	87.6 ± 27	74.6 ± 18	69.2 ± 24	<0.0001
Calculated mean pulmonary pressure (mmHg), mean ± SD	32.0 ± 16	35.6 ± 17	43.7 ± 11	46.8 ± 15	<0.0001
PVRI (dynes×s/cm^5/m^2), mean ± SD	196 ± 10	229 ± 11	302 ± 24	330 ± 22	<0.0001
RV stroke work (gm m/beat), mean ± SD	21.9 ± 15	15.2 ± 9	30.3 ± 12	16.6 ± 7	<0.0001

LV, left ventricular; LVEDP, left ventricle end-diastolic pressure; PVRI, pulmonary vascular resistance index; RV, right ventricular; SVRI, systemic vascular resistance index; TAPSE, tricuspid annular plane systolic excursion.

output, and elevated filling pressure and low output, respectively). Patients with elevated filling pressure and normal output had significantly higher mortality than patients with normal filling pressure and low output [HR 2.0 (1.01–3.7); $P = 0.04$].

Based on the 2016 ASE-EACVI Recommendations and algorithm for patients with EF ≥ 50%, we found 102 patients with elevated LV filling pressure. In 103 patients, at least one of the variables required in the algorithm or SVI were not measured, thus they were not included in this analysis. Stratification of patients according to LV haemodynamic profile revealed that 179 (42%) had normal filling pressure and output, 147 (34%) had normal filling pressure and low output, 47 (11%) had elevated filling pressure and normal output, and 55 (13%) had elevated filling pressure and low output. The LV haemodynamic profile was significantly associated with mortality (Supplementary data online, *Figure SI*).

RV haemodynamic profiles

Stratifying patients according to RV haemodynamic profile revealed that 50% had normal filling pressure and output, 39% had normal filling pressure and low output, 4% had elevated filling pressure and normal output, and 7% had elevated filling pressure and low output. In 31 patients, RAP could not be assessed thus they were not included in this analysis. There were significant differences in multiple parameters across the RV haemodynamic profiles (*Table 4*). In contrast to the LV haemodynamic profiles, O_2 saturation and chest radiograph findings worsened with poorer RV haemodynamic profiles. The RV haemodynamic profile was significantly associated with mortality (*Figure 1B*). Patients with elevated filling pressure and low output had the worst outcome ($P < 0.0001$; $P = 0.2$, and $P = 0.0003$ for comparisons to normal haemodynamics, elevated filling pressure and normal output, and normal filling pressure and low output, respectively), and patients with normal haemodynamics had the best ($P = 0.004$; $P < 0.0001$ and $P < 0.0001$ for comparisons to elevated filling pressure and normal output, normal filling pressure and low output, and elevated filling pressure and low output, respectively). The differences in mortality between patients with elevated RV filling pressure and normal output and patients with normal RV filling pressure and low output did not reach statistical significance [HR 1.5 (0.78–2.7); $P = 0.21$].

Outcome analyses

Results of univariable analysis for mortality by non-invasive haemodynamic parameters are presented in Supplementary data online, *Table SII*. There were 97 deaths observed for a median follow-up period of 117 days (IQR: 87–154 days). Mean time to death was 16.2 ± 13 days after admission. Non-invasive parameters significantly associated with mortality were low SVI ($P = 0.001$), all parameters denoting elevated LV filling pressure ($P < 0.0001$), low LVSWI ($P = 0.001$), high RAP ($P < 0.0001$), and all parameters reflecting increased RV afterload ($P < 0.0001$). In contrast, SVR was not associated with mortality. Furthermore, in distinction with LVSWI, increased but not decreased RVSWI was associated with increased mortality ($P = 0.01$).

The best associates of outcome between the non-invasive haemodynamic parameters stratified to LV and RV preload, afterload and output, were SVI < 35 mL/m^2, $E/e' \geq 14$, RAP ≥ 10 mmHg, and PAT < 90 ms.

Results of multivariate analysis for mortality are shown in *Table 5*. For the LV haemodynamic parameters, SVI < 35 mL/m^2 and $E/e' \geq 14$ were independently associated with mortality. For the RV haemodynamic parameters, SVI < 35 mL/m^2, RAP ≥ 10 mmHg and PAT < 90 ms were independently associated with mortality. The addition of RV haemodynamic parameters consecutively to the LV haemodynamic parameters improved prediction of mortality (AIC decreased from 1078 to 963; $P = 0.005$).

Interaction with disease severity

Non-invasive LV and RV haemodynamic parameters as a function of disease severity as reflected by MEWS risk stages in patients with COVID-19 infection are shown in *Figure 2*. Although all RV haemodynamic parameters worsened with disease severity, the only LV haemodynamic parameter that worsened with disease severity was LVEDP. Correlation analyses between RV haemodynamic parameters and MEWS revealed strong significant correlations with all parameters (RAP, $R^2 = 0.34$; RVSWI, $R^2 = 0.33$; pulmonary vascular resistance index, $R^2 = 0.44$, $P < 0.0001$ for all). However, the only significant correlation between MEWS and LV haemodynamic parameters was with LVEDP ($R^2 = 0.26$, $P < 0.0001$) while correlations with

Table 4 Clinical and echocardiographic characteristics stratified based on right ventricular filling pressure and output

Parameter	Normal filling pressure and output *N* = 250	Normal filling pressure, low output *N* = 198	High filling pressure, normal output *N* = 18	High filling pressure, low output *N* = 34	*P*-value
Clinical characteristics					
Age (years), mean ± SD	60.6 ± 18	63.1 ± 18	75.7 ± 12	74.0 ± 18	<0.0001
Male gender, *n* (%)	168 (67)	113 (57)	8 (44)	15 (44)	0.01
Disease severity, *n* (%)					<0.0001
Mild/moderate	128 (51)	113 (57)	5 (29)	14 (41)	
Severe	120 (48)	81 (41)	10 (55)	12 (35)	
Critical	2 (1)	4 (2)	3 (16)	8 (24)	
Modified Early Warning Score, mean ± SD	4.0 ± 3.2	4.3 ± 3.5	8.3 ± 3.8	7.4 ± 3.5	<0.0001
Ischaemic heart disease, *n* (%)	38 (15)	34 (17)	1 (6)	11 (33)	0.11
Chronic obstructive pulmonary disease, *n* (%)	10 (4)	10 (5)	3 (17)	4 (12)	0.05
Chronic kidney disease, *n* (%)	25 (10)	14 (7)	3 (17)	6 (18)	0.18
Diabetes mellitus, *n* (%)	78 (31)	50 (25)	10 (56)	13 (38)	0.05
Hypertension, *n* (%)	115 (46)	83 (42)	12 (66)	23 (67)	0.03
Physical examination					
O_2 saturation (%), mean ± SD	93.6 ± 5	93.1 ± 9	85.1 ± 15	94.2 ± 6	<0.0001
Heart rate (bpm), mean ± SD	85 ± 16	86 ± 15	86 ± 19	83 ± 13	0.69
Systolic blood pressure (mmHg), mean ± SD	135 ± 21	134 ± 21	138 ± 23	142 ± 29	0.21
Diastolic blood pressure (mmHg), mean ± SD	77 ± 34	76 ± 14	75 ± 13	75 ± 16	0.95
Laboratory evaluation					
Haemoglobin (g/dL), mean ± SD	13.3 ± 2	13.4 ± 2	12.1 ± 2	12.0 ± 2	0.002
Blood urea nitrogen (mg/dL), mean ± SD	19.9 ± 17	20.3 ± 15	36.3 ± 29	28.2 ± 15	<0.0001
Creatinine (mg/dL), mean ± SD	1.2 ± 0.8	1.06 ± 0.8	1.8 ± 1.6	1.2 ± 0.7	0.15
Troponin-I (ng/L), median (IQR)	9 (5–18)	9 (5–25)	26 (11–40)	25 (9–145)	0.004
Brain natriuretic peptide (pg/mL), mean ± SD	102 ± 161	119 ± 212	346 ± 375	729 ± 1178	<0.0001
Chest radiograph and ECG					
Bilateral infiltrate, *n* (%)	118 (47)	81 (41)	11 (62)	18 (52)	0.05
Atrial fibrillation, *n* (%)	8 (3)	8 (4)	4 (23)	8 (23)	0.002
Echocardiographic evaluation					
Left ventricular ejection fraction (%), mean ± SD	58.0 ± 5	57.3 ± 6	53.2 ± 10	52.6 ± 8	<0.0001
Left ventricle end-diastolic diameter (mm), mean ± SD	52.2 ± 5	42.4 ± 5	53.2 ± 8	42.0 ± 5	<0.0001
Left ventricle end-systolic diameter (mm), mean ± SD	31.0 ± 6	25.9 ± 5	34.2 ± 10	26.4 ± 5	<0.0001
Left atrial volume index (mL/m^2), mean ± SD	32.0 ± 13	29.0 ± 13	32.3 ± 12	41.6 ± 19	0.0004
RV end-diastolic area (cm^2), mean ± SD	21.2 ± 4	20.0 ± 5	23.7 ± 8	21.5 ± 5	0.01
RV end-systolic area (cm^2), mean ± SD	11.8 ± 3	11.8 ± 4	15.5 ± 7	14.2 ± 4	0.002
RV fractional area change (%), mean ± SD	43.9 ± 11	42.5 ± 12	36.4 ± 11	35.9 ± 12	0.01
TAPSE (cm), mean ± SD	2.4 ± 0.5	2.2 ± 0.5	1.8 ± 0.4	1.8 ± 0.4	<0.0001
RV S′ (cm/s), mean ± SD	11.6 ± 2	11.1 ± 3	10.4 ± 4	8.5 ± 2	<0.0001
Non-invasive haemodynamic evaluation					
Stroke volume (mL), mean ± SD	82.9 ± 17	50.1 ± 12	78.4 ± 17	45.4 ± 13	<0.0001
Stroke volume index (mL/m^2), mean ± SD	44.2 ± 8	26.7 ± 5	42.0 ± 6	25.5 ± 6	<0.0001
Heart rate (bpm), mean ± SD	82 ± 17	83 ± 14	89 ± 14	77 ± 18	0.49
Cardiac output (L/min), mean ± SD	6.2 ± 1.6	3.9 ± 1.3	6.0 ± 1.8	3.4 ± 1.1	<0.0001
Cardiac index (L/min/m^2), mean ± SD	3.3 ± 0.8	2.1 ± 0.6	3.3 ± 0.9	1.9 ± 0.5	<0.0001
E wave velocity (cm/s), mean ± SD	67.1 ± 18	62.0 ± 17	74.1 ± 23	82.8 ± 37	<0.0001
A wave velocity (cm/s), mean ± SD	62.3 ± 19	63.7 ± 18	67.3 ± 26	63.6 ± 18	0.7
E/*A* ratio, mean ± SD	1.12 ± 0.4	1.02 ± 0.4	1.19 ± 0.5	1.23 ± 0.8	0.02
e′ septal (cm/s), mean ± SD	6.9 ± 1.9	6.6 ± 2.1	5.5 ± 1.7	5.5 ± 1.5	0.0006
e′ lateral (cm/s), mean ± SD	8.9 ± 3.1	8.5 ± 2.9	7.1 ± 2.9	6.8 ± 2.5	0.0005
E/e′ average ratio, mean ± SD	9.5 ± 4.2	9.3 ± 4.1	13.6 ± 5.9	14.9 ± 8.7	<0.00001

Continued

Table 4 *Continued*

Parameter	Normal filling pressure and output N = 250	Normal filling pressure, low output N = 198	High filling pressure, normal output N = 18	High filling pressure, low output N = 34	P-value
Calculated LVEDP (mmHg), mean ± SD	10.7 ± 2.6	10.7 ± 2.6	13.3 ± 3.7	14.2 ± 5.4	<0.0001
Right atrium pressure (mmHg), mean ± SD	5.6 ± 2	6.8 ± 2.4	15.8 ± 1.9	16.0 ± 2.0	<0.0001
SVRI (dynes×s/cm^5/m^2), mean ± SD	2346 ± 799	3700 ± 1342	2133 ± 773	3652 ± 1176	<0.0001
LV stroke work, (gm m/beat), mean ± SD	74.4 ± 24	44.8 ± 14	68.2 ± 22	39.1 ± 13	<0.0001
Pulmonic flow acceleration time (ms), mean ± SD	92.0 ± 26	87.4 ± 25	75.2 ± 24	60.4 ± 24	<0.0001
Calculated mean pulmonary pressure (mmHg), mean ± SD	32.9 ± 16	35.7 ± 16	43.3 ± 15	52.5 ± 15	<0.0001
PVRI (dynes×s/cm^5/m^2), mean ± SD	204 ± 148	230 ± 144	198 ± 137	381 ± 135	<0.0001
RV stroke work (gm m/beat), mean ± SD	23.1 ± 15	15.2 ± 9	22.1 ± 12	17.1 ± 8	<0.0001

LV, left ventricular; LVEDP, left ventricle end-diastolic pressure; PVRI, pulmonary vascular resistance index; RV, right ventricular; SVRI, systemic vascular resistance index; TAPSE, tricuspid annular plane systolic excursion.

LVSWI (R^2 = -0.02, $P = 0.08$), SVI (R^2 = -0.005; $P = 0.3$), and SVR index (R^2 = 0.005; $P = 0.18$) were not significant. The prevalence of patients with extremely abnormal haemodynamic profile (elevated filling pressure and low output) was very small in the low MEWS risk categories but considerable in the higher ones (1%, 7%, 12%, and 18% for low, median, high, and very high risk, respectively). To assess whether the non-invasive haemodynamic assessment has added value on top of MEWS, we performed stepwise analyses evaluating the significant non-invasive LV and RV haemodynamic parameters and MEWS and presented them in *Table 5*. The non-invasive haemodynamic parameters were entered first (stratified to LV and RV separately), and the MEWS was entered last. Addition of the MEWS score to the mortality model resulted in removal of the RV (but not LV) haemodynamic parameters from the model, and improvement in prediction of mortality (AIC decreased to 742; $P < 0.0001$).

The prognostic value of the integrated LV and RV functional parameters, LVSWI and RVSWI, was assessed on top of the MEWS score using stepwise multivariate analyses. The MEWS score was entered first, and the LVSWI or RVSWI were entered last. We present the analyses in *Table 6*. Addition of LVSWI to the MEWS resulted in improvement in mortality prediction of the models. However, RVSWI did not have additive value on top of MEWS. To analyse whether LVSWI has added clinical value in all MEWS risk categories, we performed separate analyses for association of LVSWI and mortality for each MEWS risk category. Because of the small number of patients, we grouped the MEWS high and very high-risk categories together. There was no mortality in the low-risk MEWS category irrespective of LVSWI. In the medium-risk category, mortality was similar irrespective of LVSWI (6.7% vs. 6.0%; $P = 0.82$). However, in the high-risk MEWS groups mortality was 19% in patients with normal LVSWI, but 43% in the presence of abnormal LV performance ($P = 0.0002$).

Discussion

This is the first study to examine the prevalence and prognostic value of abnormal haemodynamic parameters assessed by Doppler echocardiography in a large, unselected cohort of consecutive hospitalized patients with COVID-19. Our main findings are (i) a large proportion (~50%) of patients hospitalized because of COVID-19 infection have normal left and right haemodynamics at presentation; (ii) RV (but not LV) haemodynamics are related to clinical parameters reflecting disease severity; and (iii) LV (but not RV) haemodynamics have additive prognostic value on top of clinical parameters, particularly in patients with severe disease.

Haemodynamic profiles in acute COVID-19 infection

Although the European Association of Cardiovascular Imaging and the American Society of Echocardiography recognize the importance of echocardiographic assessment of patients with COVID-19,[14,15] the amount of data collected prospectively is limited.[29–39] In majority of these reports, selection bias has been significant because echocardiographic examinations were performed only in patients who developed clinical deterioration. Furthermore, most of these reports has not emphasized Doppler based haemodynamic evaluation. This is the first large study to perform prospective comprehensive non-invasive haemodynamic assessment, using Doppler transthoracic echocardiography in consecutive hospitalized patients (irrespective of clinical indication) with acute COVID-19 infection. We found that almost half of patients have normal LV and RV haemodynamic performance. Low forward flow was also very common, related to either small LV or poor RV or LV contraction. However, elevated LV or RV filling pressures were rare, suggesting that in the majority of these patients, relative intravascular contraction is a major cause for low forward flow. SVR and pulmonary vascular resistance were elevated in the majority of patients. However, while elevated pulmonary vascular resistance was mostly seen in patients with severe pulmonary disease, suggesting that it is related to pulmonary involvement, elevated SVR was seen in all spectrum of disease severity, suggesting that heightened adrenergic tone may be an early manifestation of acute COVID-19 infection.

We demonstrated clear trends toward decreasing RV function, and increasing RV preload and afterload, in patients with increasing MEWS risk categories, suggesting that MEWS is a reasonable

Table 5 Multivariable analysis for prediction of mortality based on haemodynamics and Modified Early Warning Score

Variable	Univariable analysis HR (95% CI)	Multivariable analysis HR (95% CI)
Mortality—LV haemodynamic parameters		
SVI <35 mL/m^2	1.9 (1.2–2.9): $P = 0.002$	1.8 (1.17–2.7); $P = 0.006$
E/e' average ≥14	3.6 (2.3–5.4); $P < 0.0001$	3.4 (2.2–5.2); $P < 0.0001$
χ^2 for model		38.2
P-value for MEWS/model		<0.0001
AIC for MEWS/model		1078
Mortality—RV haemodynamic parameters		
SVI <35 mL/m^2	1.9 (1.2–2.9): $P = 0.002$	1.56 (1.01–2.45); $P = 0.04$
RA pressure ≥10 mmHg	3.9 (2.4–6.0); $P < 0.0001$	2.7 (1.6–4.4); $P = 0.003$
PAT <90 ms	3.8 (2.0–8.3); $P < 0.0001$	2.8 (1.7–5.0); $P < 0.0001$
χ^2 for model		44.7
P-value for MEWS/model		<0.0001
AIC for MEWS/model		970
P-value for LogLik		0.02
Mortality—LV and RV haemodynamic parameters		
SVI <35 mL/m^2	1.9 (1.2–2.9): $P = 0.002$	1.5 (0.97–2.4); $P = 0.06$
E/e' average ≥14	3.6 (2.3–5.4); $P < 0.0001$	2.1 (1.3–3.5); $P = 0.003$
RA pressure ≥10 mmHg	3.9 (2.4–6.0); $P < 0.0001$	2.05 (1.17–3.5); $P = 0.01$
PAT <90 ms	3.8 (2.0–8.3); $P < 0.0001$	2.4 (1.4–4.3); $P = 0.001$
χ^2 for MEWS/model		53.1
P-value for model		<0.0001
AIC for MEWS/model		963
P-value for LogLik		0.005
Mortality—LV and RV haemodynamic parameters with MEWS		
SVI <35 mL/m^2	1.9 (1.2–2.9): $P = 0.002$	1.7 (1.06–2.8); $P = 0.02$
E/e' average ≥14	3.6 (2.3–5.4); $P < 0.0001$	1.9 (1.15–3.3); $P = 0.01$
RA pressure ≥10 mmHg	3.9 (2.4–6.0); $P < 0.0001$	1.1 (0.6–2.0); $P = 0.73$
PAT <90 ms	3.8 (2.0–8.3); $P < 0.0001$	1.55 (0.86–3.0); $P = 0.15$
MEWS	1.4 (1.3–1.5); $P < 0.0001$	1.4 (1.3–1.5); $P < 0.0001$
χ^2 for MEWS/model	114	129.4
P-value for model		<0.0001
AIC for MEWS/model	920	742
P-value for LogLik		<0.001

AIC, Akaike Information Criterion; MEWS, Modified Early Warning Score; PAT, pulmonic flow acceleration time; RA, right atrial; SVI, stroke volume index.

surrogate marker for RV haemodynamics. However, LV output, afterload and integrated function did not change significantly within the MEWS risk categories. Thus, LV haemodynamic status cannot be inferred from routine clinical parameters. Once needed, LV haemodynamic assessment requires non-invasive Doppler echocardiographic evaluation or invasive measurements.

LV and RV stroke work are measures of integrated systolic and diastolic function. These parameters may be calculated non-invasively using Doppler echocardiography based on stroke volume, mitral E/e' ratio, and MAP for the LV and stroke volume, RAP, and mean pulmonary artery pressure for the RV.[8] We found that abnormal LVSWI and RVSWI are each common in more than half of patients with acute COVID-19 infection. However, there was a significant difference between them. While abnormal LVSWI was mostly below the normal range, suggestive of poor LV systolic or diastolic performance, in patients with abnormal RVSWI, it was always above normal values, suggesting normal RV performance combined with elevated RV afterload, probably secondary to the pulmonary disease.

Non-invasive haemodynamic evaluation and outcome

In this work, we were able to show that the non-invasive haemodynamic parameters associated with adverse outcome are related to low forward flow, high left and right filling pressure and high RV afterload. These results are not surprising, since the combination of forward flow and filling pressure reflects the point of each patient on the Frank–Starling curve—in which as the heart's function deteriorates, filling pressures rise to maintain output, and ultimately fail to produce

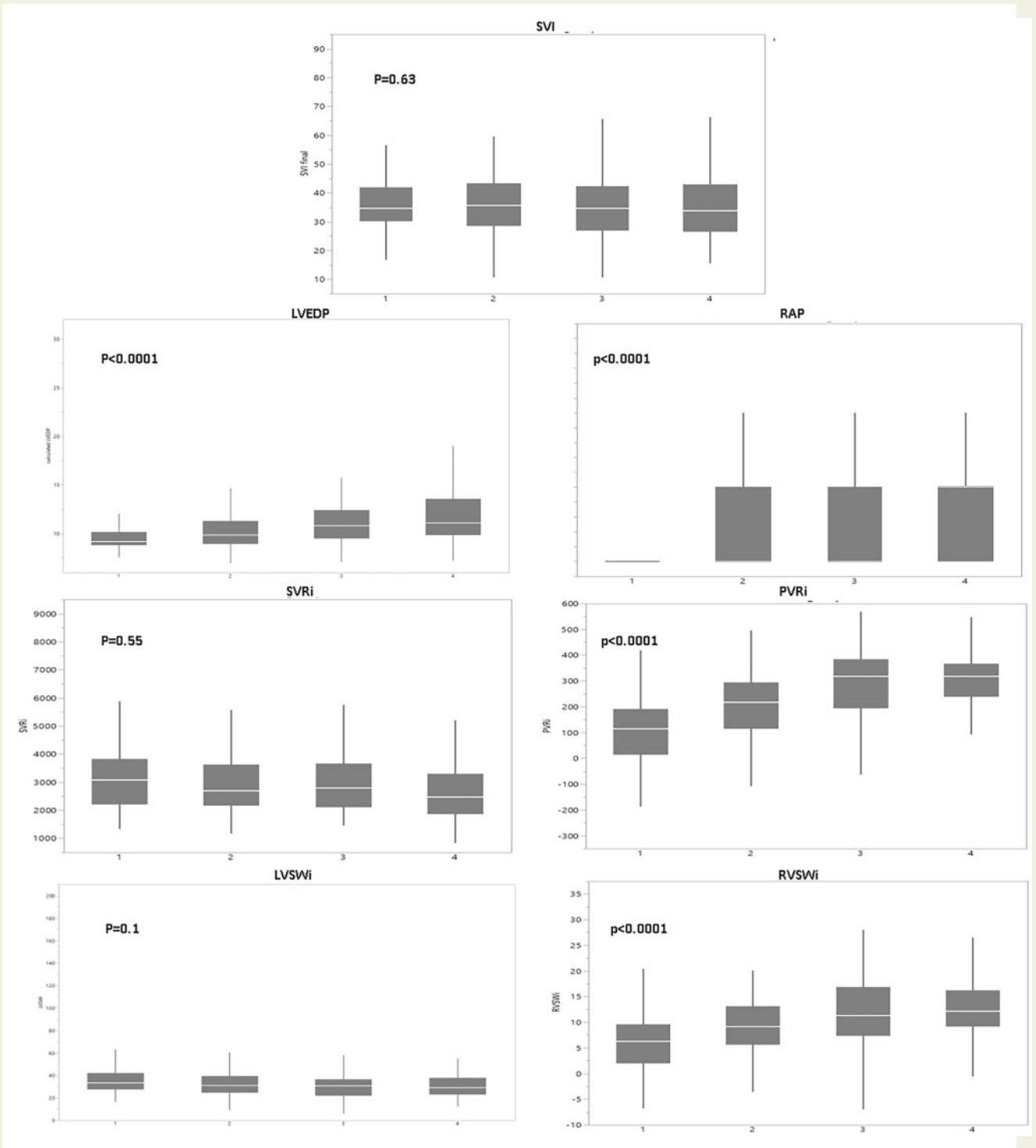

Figure 2 Non-invasive LV and RV haemodynamic parameters as a function of MEWS risk stages in patients with COVID-19 infection. Each parameter is presented separately stratified by MEWS risk category (1—low, 2—median, 3—high, and 4—very high). LV parameters are presented in the left column and RV parameters on the right. Each parameter is represented by a box plot (middle line of the box indicates the median; 25th to 75th percentiles is represented by the end caps of the box; whiskers extend to the last observed value within 1.5 the inter-quantile range above or below the 25th and 75th percentile). LVEDP, left ventricular end-diastolic pressure; LV, left ventricular; LVSWI, left ventricle stroke work index; MEWS, Modified Early Warning Score; PVRI; pulmonary vascular resistance index; RAP, right atrial pressure; RV, right ventricular; RVSWI, right ventricle stroke work index; SVRI, systemic vascular resistance index; SVI, stroke volume index.

Table 6 Prognostic value of the integrated left and right ventricular functional parameters

Variable	Univariable analysis	Multivariable analysis
Mortality—LVSWI with MEWS		
	Univariate HR	Multivariate HR
LVSWI	0.95 (0.93–0.97); $P = 0.0002$	0.95 (0.93–0.98); $P = 0.0006$
MEWS	1.4 (1.3–1.5); $P < 0.0001$	1.4 (1.3–1.5); $P < 0.0001$
P-value for LogLik		<0.0001
Mortality—RVSWI with MEWS		
RVSWI	1.04 (1.01–1.08); $P = 0.01$	0.99 (0.95–1.03); $P = 0.62$
MEWS	1.4 (1.3–1.5); $P < 0.0001$	1.5 (1.3–1.6); $P < 0.0001$
P-value for LogLik		NS

LVSWI, left ventricle stroke work index; MEWS, Modified Early Warning Score; RVSWI, right ventricle stroke work index.

sufficient output despite further elevation. Furthermore, these results are similar to those shown in different types of shock in critical care units.[4–6] Surprisingly, patients with low forward flow and/or high filling pressure, had higher hospital mortality only in the context of the higher MEWS risk categories. Patients with high and very high MEWS risk category combined with abnormal LV filling pressure and output had more than double the mortality, suggesting that at least part of the mortality in severe COVID-19 infection is related to left heart dysfunction. This finding is particularly important because diagnosis of left-sided heart failure is challenging in COVID-19, due to the limited ability to distinguish between cardiac-related pulmonary congestion and COVID-19 viral pneumonia, both on clinical examination and basic imaging. This emphasizes the importance of obtaining these Doppler-based parameters in patients with COVID-19 infection and high MEWS. On the other hand, in patients with low MEWS, the risk of mortality is low, irrespective of haemodynamic parameters. Because the MEWS is calculated based on easily obtainable clinical parameters (temperature, blood pressure, O_2 saturation, respiratory, and HR), we believe that to minimize the risk of infection spread, non-invasive echocardiographic haemodynamic evaluation should probably be reserved for patients with higher MEWS risk categories. In this work, we demonstrated intra-vascular contraction in a large proportion of patients with COVID-19 infection. Intensive care units in our centre used a conservative strategy of fluid management in patients with COVID-19 as part of their acute respiratory distress management. This may have been one of the causes contributing to the observed intra-vascular contraction. Interestingly, recent reports have suggested that COVID-19 infection is in fact an endothelial disease.[40,41] Elevated SVR was observed in a large proportion of our patients. This was unexpected, as COVID-19 is an infectious disease that can induce significant inflammatory process, which usually results in vasodilation. A minority of the patients ($N = 53$, 10%) were treated with vasopressors, explaining in part the increase in SVR. However, the majority of patients with elevated SVR was not treated with vasopressors, suggesting that they were probably sympathetically activated by dyspnoea, assisted ventilation, or psychological stress induced by their illness and hospitalization.

Small studies on non-invasive[42] and invasive[43] characterizations of haemodynamics in COVID-19 patients have been recently published. In both studies, COVID-19 patients had low SVR and high cardiac output suggesting a hyperdynamic circulation. Furthermore, both studies suggested that in COVID-19 infection low SVR and hyperdynamic circulation was associated with poorer gas exchange. However, the population of these trials was markedly different from our cohort and included only patients with hypoxia[42] or patients who were critically ill and mechanically ventilated.[43] This subset of patients is expected to present with profound inflammatory response that would result in vasodilation. Our cohort represents the entire spectrum of hospitalized COVID-19 patients, including patients without hypoxia, and only a minority of patients (4%) needing mechanical ventilation. Indeed, low SVR was more prevalent in severe and critical patients in our cohort.

Abnormal SVR, as opposed to pulmonary vascular resistance, was not associated with outcome even in univariate analysis. We believe that the lack of association between SVR and outcome reflects the fact that heightened adrenergic tone is an early manifestation of the disease, sometimes due to anxiety, but sometimes compensating for low forward flow. Thus, normal blood pressure should not infer normal LV performance in patients with COVID-19 infection, as it may conceal low forward flow combined with elevated SVR. As opposed to the LV-related haemodynamic parameters that had additive prognostic value on top of clinical assessment, most RV parameters were associated with outcome only in non-adjusted analyses. We believe that this is because easily obtainable clinical parameters (O_2 saturation, chest radiograph) or MEWS, afford accurate assessment of pulmonary disease, which in turn strongly correlates with right-sided haemodynamics. On the other side, LV haemodynamic parameters are independent of pulmonary disease, thus, cannot be accurately assessed by clinical parameters, and once needed require invasive or non-invasive haemodynamic assessment. Non-invasive haemodynamic parameters obtained by Doppler echocardiography can be used to characterize individual COVID-19 patients, and to provide mortality risk stratification. It allows identification of the mechanism of deterioration across the spectrum of disease, and may be used for tailored optimized therapy in severe and critical patients.

Study limitations

This was a medium-size single-centre study without a control group. It included only patients with COVID-19 infection who were hospitalized. The fact that only the minority of patients with COVID-19 infection are hospitalized may lead to over-estimation of the severity of

haemodynamic pathology in COVID-19 infection in this study. On the other hand, 80 patients were excluded because they had 'Do Not Resuscitate/Intubate' orders, thus received only palliative care and died shortly after their admission. This limitation might create selection bias resulting in under-estimation of haemodynamic abnormalities in patients with COVID-19 infection. The non-invasive haemodynamic data were not compared with invasive haemodynamic data. The fact that in some cases non-invasive haemodynamic parameters were measured by the cardiologist involved in caring for the patient may lead to bias. The inaccuracy of some of the non-invasive parameters limits their use in clinical practice, in particular the calculated estimates of LVEDP and MPAP. Furthermore, these parameters carry their inherent inaccuracy into composite measures, thus these measures should be used with caution. Inter-observer repeatability of non-invasive measurements may potentially be hampered by the obligatory use of COVID-19 protection equipment. However, to minimize the risk of infection, repeated examinations by different echo technicians were not performed in this study.

Conclusions

In this cohort of consecutive hospitalized patients with acute COVID-19 infection undergoing prospective non-invasive haemodynamic evaluation, different LV and RV haemodynamic profiles were associated with mortality. While RV haemodynamics are related to easily accessible clinical parameters and do not have added prediction value, LV haemodynamics can further aid in risk stratification of patients with severe COVID-19.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Data availability

The deidentified participant data generated in this research will be shared on reasonable request to the corresponding author.

Conflict of interest: none declared.

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