


ORIGINAL



Echocardiography findings in COVID-19 patients admitted to intensive care units: a multi-national observational study (the ECHO-COVID study)

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Abstract

Purpose: Severely ill patients affected by coronavirus disease 2019 (COVID-19) develop circulatory failure. We aimed to report patterns of left and right ventricular dysfunction in the first echocardiography following admission to intensive care unit (ICU).

Methods: Retrospective, descriptive study that collected echocardiographic and clinical information from severely ill COVID-19 patients admitted to 14 ICUs in 8 countries. Patients admitted to ICU who received at least one echocardiography between 1st February 2020 and 30th June 2021 were included. Clinical and echocardiographic data were uploaded using a secured web-based electronic database (REDCap).

Results: Six hundred and seventy-seven patients were included and the first echo was performed 2 [1, 4] days after ICU admission. The median age was 65 [56, 73] years, and 71% were male. Left ventricle (LV) and/or right ventricle (RV) systolic dysfunction were found in 234 (34.5%) patients. 149 (22%) patients had LV systolic dysfunction (with or without RV dysfunction) without LV dilatation and no elevation in filling pressure. 152 (22.5%) had RV systolic dysfunction. In 517 patients with information on both paradoxical septal motion and quantitative RV size, 90 (17.4%) had acute cor pulmonale (ACP). ACP was associated with mechanical ventilation (OR > 4), pulmonary embolism (OR > 5) and increased PaCO₂. Exploratory analyses showed that patients with ACP and older age were more likely to die in hospital (including ICU).

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Conclusion: Almost one-third of this cohort of critically ill COVID-19 patients exhibited abnormal LV and/or RV systolic function in their first echocardiography assessment. While LV systolic dysfunction appears similar to septic cardiomyopathy, RV systolic dysfunction was related to pressure overload due to positive pressure ventilation, hypercapnia and pulmonary embolism. ACP and age seemed to be associated with mortality in this cohort.

Keywords: COVID-19, Intensive care unit, Cardiac function, Echocardiography

Introduction

A large proportion of severely ill coronavirus disease 2019 (COVID-19) patients develop circulatory failure and require catecholamine infusions [1]. Myocardial injury and heart failure are associated with increased mortality [2, 3] with a large spectrum of mechanisms [4]. COVID-19 frequently induces pulmonary artery thrombosis [5]. The cytokine storm may also induce vasoplegia and distributive shock and COVID-19-related pneumonia may lead to acute respiratory distress syndrome (ARDS) [6], a condition well known to alter right ventricular (RV) function [7].

COVID-19 may then affect cardiac function by different mechanisms [8] but to the best of our knowledge, there is currently no clear information about cardiac function and echocardiographic patterns in critically ill COVID-19 patients. Echocardiographic findings was mostly reported in non-critically ill patients, frequently without any quantitative evaluation [9]. Given the mortality rate in these patients, data are urgently required to better understand this new disease and to improve hemodynamic support.

The primary aim of our study was to investigate the incidences and patterns of left and right ventricular dysfunction in the first echocardiographic examination performed after admission to the intensive care unit (ICU) in a large series of patients hospitalized for severe COVID-19. We took advantage of previous international collaborations with experts in the field of critical care echocardiography (CCE) that use echocardiography in their usual practice to manage critically ill patients [10].

Methods

This is a retrospective longitudinal observational study involving 14 intensive care units of tertiary teaching hospitals in 8 countries, registered in ClinicalTrials (April 28, 2021, number NCT 04414410). Unfortunately, we were unable to report the incidences of vasoplegia and hypovolemia due to insufficient superior vena cava (SVC) respiratory variability data available. The planned period of inclusion was extended to include the different waves of COVID-19. Consecutive patients with confirmed SARS-CoV-2 infection between 1 February 2020 and 30 June 2021, admitted

Take-home message

In a cohort of 677 patients affected by coronavirus disease 2019 (COVID-19) admitted in the intensive care unit (ICU), echocardiography is abnormal in one-third of cases with left and right ventricular systolic dysfunction observed in 23% and 22.5% of cases, respectively. Acute cor pulmonale is observed in 17% of cases and associated with hypercapnia, pulmonary embolism and mechanical ventilation. Acute cor pulmonale and age are associated with in-ICU mortality.

to an ICU and who received at least one echocardiography, either a transthoracic (TTE) or transesophageal echocardiography (TEE), during their ICU stay were included. Patients were imaged as part of routine care, and non-identifiable patient data were captured. The study protocol was approved by ethics committee (CE SRLF 20–40). Main investigators were part of the echo working group of the European Society of Intensive Care Medicine (ESICM).

Data collection

Study data were collected and managed using REDCap, a secure web-based platform (hosted at The University of Sydney, <https://redcap.sydney.edu.au>). Data were collected according to recent guidelines [10] in three major domains: (1) patient characteristics, including co-morbidities, (2) clinical data, including ventilation and hemodynamic data, at the time of echocardiography, and (3) echocardiography data. Clinical and echocardiography data were collected at least once during their stay in ICU, however we only report results from the first echocardiographic examination in the present study. Length of ICU stay and outcome were also collected.

The web-based platform was opened to investigators until 30 June 2021 for uploading data. Data integrity and quality were then examined thoroughly by a methodologist (SH), and the investigators were contacted to provide details if any errors, inconsistencies or discrepancies were found. Specific data (values) were excluded if the errors were unrectifiable.

Clinical information

If available, clinical data that were relevant for the interpretation of echocardiography data were also collected, including ventilation mode and settings, arterial blood

gases and hemodynamic data (vasopressor and inotrope infusions and blood pressures).

Echocardiography

Both TTE and TEE studies were included in the study. All studies were recorded and interpreted off-line by international experts in the field, all of whom have European Diploma in Advanced Critical Care Echocardiography or equivalent qualifications and experience. Common echocardiography parameters for left ventricular (LV) function, right ventricular (RV) function, and hemodynamic status were collected. These include, among others, LV ejection fraction (LVEF), RV tricuspid annular plane systolic excursion (TAPSE) and ventricular sizes. Both objective measurements and visual evaluation data were also collected for LV and RV function and sizes. Acute cor pulmonale (ACP) was defined as the presence of paradoxical septal motion (PSM) and RV end-diastolic area to LV end-diastolic area ratio (RVEDA/LVEDA) > 0.6.

Data analysis

Main results were of descriptive in nature. Categorical data were reported as count data, and mean \pm standard deviation (SD) and/or median [Q1, Q3] were reported for continuous data. Values that were not available (not measured) were treated as missing values, and were not included in the analyses. Percentages were reported as percent of total number of patients (N) wherever possible, or as percent of available data (n) (excluding missing values) when stated. Little's test for data missing completely at random pattern was performed. Data imputation was not carried out due to the presence of data missing not at random.

In addition to the planned investigation of the association between mechanical ventilation parameters and RV function, we also performed exploratory association analyses between outcome and global left and right heart function taking age into account. Categorical contingency tables were analyzed using Fisher's exact test and reported as odds ratio (OR) [95% confidence interval (CI)]. Logistic regression was used in analyzing in-hospital and in-ICU mortalities. We included visual LV function, ACP and age as predictors based on the context of the study, and these are known or suspected prognosticator for ICU mortality [2, 3]. Visual assessment of RV function was not included as it showed strong association with ACP (collinearity). Nested models were compared using deviance goodness-of-fit test. All statistical tests were two-sided and were performed using the R software (version 4.1.0, R Foundation for Statistical Computing, Vienna) using *tidyverse* (version 1.3.1) package.

Results

Patients

A total number of 689 patients were included. Twelve patients were excluded due to missing patient information, resulting in a total of 677 patients in the analysis. This comprised of an average of 33.4% of COVID-19 patients admissions per center during this period (mean total COVID-19 admission per center = 244 ± 137 patients). Most ($n=641$, 94.7%) were from European centers. Number of included patients per week, distribution according to age, gender and symptoms duration before ICU admission are reported in Supplementary Figure S1. Using 1 August 2020 as arbitrary demarcation date, the number of patients in the first and second/third waves included were 336 and 341, respectively. Patients over 60 years old constituted the majority of the admissions. Half of patients had symptoms of SARS-CoV-2 infection for 8 [6, 11] days (median [IQR]) prior to ICU admission.

Table 1 summarizes the patients' characteristics and pre-existing medical history. The median age was 65 [56, 73]), and 71% of the patients were male. Mean body mass index (BMI) was 29.8 ± 6.4 kg m⁻². Of the 675 patients with data on co-morbidities, 487 patients (72%) had at least one co-morbidity. Most frequent co-morbidities were hypertension (58%) and diabetes (30%). Only four patients had all pre-existing medical conditions and 102 (17%) had a history of cardiomyopathy. 241 patients were either taking angiotensin-converting enzyme inhibitor, angiotensin receptor blocker or both, and 146 were on beta-blockers.

Clinical information at the time of first echocardiography

About two-thirds of the patients (69%, $n=467$) were receiving mechanical ventilation, with a mean tidal volume of 435 ± 80 ml ($n=391$ available data, 84% of ventilated patients) and a mean plateau pressure of 24.7 ± 4.5 cmH₂O ($n=394$, 84% of ventilated patients). PaO₂/FiO₂ ($n=634$) was 134 ± 68 mmHg and the mean PaO₂/FiO₂ in spontaneously breathing patients and in mechanical ventilated patients were 138 ± 77 mmHg (median = 119 [88, 166]) and 133 ± 64 mmHg (median = 118 [86, 167]), respectively. The mean difference was -4.6 mmHg [95% CI = -16.3 to 7.1].

Two hundred and seventy-seven (41%) patients were on norepinephrine alone or in combination with another inotrope or vasopressor. Nineteen patients received extra-corporeal membrane oxygenation (ECMO) due to severe or refractory ARDS: 1 patient were on venous-arterious (VA) ECMO and 18 on venous-venous (VV) ECMO. Out of 447 patients for whom it was searched, pulmonary embolism was reported in 55 (11.5%) patients (Table 2).

Table 1 Patient characteristics

Characteristic	n (available/total) ^{a#}	Summary statistics ^b
Sex	677/677 (100%)	
M		481 (71%)
F		196 (29%)
Age	581/677 (86%)	65 (56, 73)
Weight	664/677 (98%)	85 (74, 98)
Height	648/677 (96%)	172 (165, 178)
BMI	646/677 (95%)	28.4 (25.4, 33.2)
Smoker	449/677 (66%)	
Non-smoker		268 (60%)
Ex-smoker		141 (31%)
Current smoker		40 (8.9%)
Pre-ICU admission symptoms duration (days)	571/677 (84%)	8 (6, 11)
Cardiac failure	600/677 (89%)	
Yes		102 (17%)
No		498 (83%)
Hypertension	670/677 (99%)	
Yes		388 (58%)
No		282 (42%)
COPD	670/677 (99%)	
Yes		126 (19%)
No		544 (81%)
Diabetes	673/677 (99%)	
Yes		204 (30%)
No		469 (70%)
Chronic renal disease	670/677 (99%)	
Yes		58 (8.7%)
No		612 (91%)
ACE inhibitors	588/677 (87%)	
Yes		114 (19%)
No		474 (81%)
ARBs	587/677 (87%)	
Yes		127 (22%)
No		460 (78%)
Beta-blockers	587/677 (87%)	
Yes		146 (25%)
No		441 (75%)

ACE inhibitors angiotensin-converting enzymes inhibitors, ARBs angiotensin receptor blockers, CRD chronic renal disease, COPD chronic obstructive pulmonary disease

[#] Most data were missing at random or missing not at random. (Little's test for missing completely at random, $p < 0.0001$)

^a Number of available data (%) / total number of patients (%)

^b Median (IQR) for continuous data; n (%) for categorical data

Echocardiography

In half of the patients, the first echocardiography was performed on the first two days of ICU admission (median = 2 [1, 4]) and 80% were performed on or before day 5 (Table 3). Most patients (81.4%, $n = 551$) received

TTE of which 342 were mechanically ventilated, and 126 (18.6%) patients received TEE where all except one were mechanically ventilated. Most of the patients were in sinus rhythm (91.8%).

Four hundred and sixty-five patients had one or more echocardiographic identifiable pathologies and the presentations were shown in Supplementary Figure S2. A total of 234 (34.5%) patients were reported to have LV and/or RV systolic dysfunction visually: 67 (9.9%) patients had biventricular dysfunction, 85 (12.5%) had isolated RV dysfunction, 82 (12.1%) had isolated LV dysfunction, and 441 (65.1%) patients displayed normal LV and RV function (Fig. 1A).

Characteristics of LV systolic dysfunction

LV systolic dysfunction (moderate or severe) was observed in 149 (22%) patients, among them 45 (30.2%) had previous history of cardiomyopathy, 50 previously received beta-blockers and only 15 were under dobutamine. The visual assessment of LV systolic function was consistent with measured LVEF (Supplementary Figure S3A). There were no discernible differences in the means of LVEF between the age groups, although a larger proportion of patients (27.5%, $n = 91$) in the >60 age group had LVEF < 50% (Fig. 2A). Only a relatively small proportion of patients (10.5%) displayed visually dilated LV. LV end-diastolic volume (LVEDV) indexed to body surface area was available in 409 patients (Table 3), and its relationship with visual assessment of LV size is shown in Supplementary Figure S3B. Out of 563 patients with available information on segmental wall motion abnormality (SWMA), 77 (13.7%) were found to have SWMA, and 46 of these patients were reported to have visually impaired LV function (Supplementary Figure S2). The mean LV E/A ratio was 1 ± 0.37 ($n = 567$).

Characteristics of RV systolic dysfunction

RV systolic dysfunction (moderate or severe dysfunction) was observed in 152 (22.5%) patients. The visual assessment of RV function was consistent with measured TAPSE (Supplementary Figure S3C). There were no discernible differences in the means of TAPSE between the age groups, although a slightly larger proportion of patients (22.1%, $n = 62$) in the >60 age group had TAPSE ≤ 16 mm (Fig. 2B). About 41% ($n = 277$, $N_{\text{available}} = 675$) of the patients were reported to have either moderately or severely dilated RV visually, and higher RVEDA/LVEDA (Supplementary Figure S3D). The mean RVEDA/LVEDA, when available ($N_{\text{available}} = 521$), was 0.67 ± 0.25 and 262 (50%) patients had a dilated RV (RVEDA/LVEDA > 0.6). The proportion of RV systolic dysfunction increases with the severity of LV dysfunction ($p < 0.001$) (Fig. 1B). TAPSE was also positively correlated

Table 2 Clinical data during the first echocardiography

Clinical parameters	n (available/total) ^{a#}	Summary statistics ^b
Ventilation mode	677/677 (100%)	
Spontaneously breathing		210 (31%)
Mechanically ventilated		467 (69%)
FiO ₂ (%)	661/677 (98%)	65 (50, 90)
High flow O ₂	199/677 (29%)	
Yes		149 (75%)
No		50 (25%)
Respiratory rate (per min)	597/677 (88%)	24 (20, 28)
Tidal volume (ml) ^c	391/467 (84%)	440 (400, 480)
PEEP (cmH ₂ O) ^c	294/467 (63%)	10 (8, 12)
Total PEEP (cmH ₂ O) ^c	359/467 (77%)	11 (10, 14)
Plateau pressure (cmH ₂ O) ^c	394/467 (84%)	25 (22, 28)
PaO ₂ (mmHg)	649/677 (96%)	75 (64, 90)
PaO ₂ /FiO ₂	634/677 (94%)	118 (86, 167)
SaO ₂	503/677 (74%)	94 (91, 96.2)
PaCO ₂ (mmHg)	597/677 (88%)	42 (35, 50)
pH	597/677 (88%)	7.40 (7.32, 7.46)
Base deficit (mmol/L)	403/677 (60%)	0.7 (− 2, 2.8)
Lactate (mmol/L)	510/677 (75%)	1.50 (1.10, 2)
Heart rate (bpm)	639/677 (94%)	87 (74, 103)
Systolic arterial pressure (mmHg)	634/677 (94%)	125 (110, 140)
Diastolic arterial pressure (mmHg)	634/677 (94%)	65 (55, 77)
Mean arterial pressure (mmHg)	627/677 (93%)	83 (72, 95)
Central venous pressure (cmH ₂ O)	183/677 (27%)	9 (7, 11)
Pulmonary embolism	447/677 (66%)	
Yes		55 (12%)
No		392 (88%)
ECMO	509/677 (75%)	
VA ECMO		1 (0.2%)
VV ECMO		18 (3.5%)
No		490 (96%)
Vasopressors/inotropes	677/677 (100%)	
Dobutamine		31 (4.6%)
Dopamine		1 (0.1%)
Epinephrine		4 (0.6%)
Norepinephrine		277 (40.9%)
Not administered		364 (53.8%)

PEEP positive end-expiratory pressure, VA and VV ECMO veno-arterial and veno-venous extra-corporeal membrane oxygenation

^a Number of available data/Total number of patients (%)

^b Median (IQR) for continuous data; n (%) for categorical data

^c Total number of patients receiving mechanical ventilation = 467

[#] Most data were missing at random or missing not at random. (Little's test for missing completely at random pattern, $p < 0.0001$)

with LVEF [$r = 0.28$ (95% CI 0.19, 0.36)] (Fig. 1C). The mean LVEF was similar in different RV size groups (Fig. 1D).

PSM was found in 130 out of 670 patients (19.4%) with an RVEDA/LVEDA ratio higher than in patients without PSM [difference = 0.28 (95% CI 0.23 to 0.33)] (Fig. 3A).

90 (17.4%, $N_{\text{available}} = 517$) patients displayed PSM and RVEDA/LVEDA > 0.6 indicating ACP (Fig. 3B). The PaO₂/FiO₂ between those with and without PSM were similar, 140 ± 72 vs 133 ± 67 mmHg, respectively [difference = 7.5 mmHg (95% CI − 5.8 to 20.7)] (Fig. 3C) and also similar in patients with and without ACP (138 ± 68 mmHg

Table 3 Echocardiography findings

Echo parameters	n (available/total) ^{a#}	Summary statistics ^b
Echo types	677/677 (100%)	
TTE		551 (81%)
TEE		126 (19%)
Day in ICU had echo	677/677 (100%)	2 (1, 4)
Cardiac rhythm	660/677 (97%)	
Sinus		606 (92%)
Atrial fibrillation / flutter		54 (8.2%)
LV function (visual)	676/677 (99.1%)	
Hyperkinetic		113 (17%)
Normal		414 (61%)
Moderately depressed		105 (16%)
Severely depressed		44 (6.5%)
LVEF (%)	598/677 (88%)	60 (50, 65)
SWMA	563/677 (83%)	
Yes		77 (14%)
No		486 (86%)
LV size (visual)	675/677 (99.7%)	
Reduced		49 (7.3%)
Not dilated		555 (82%)
Moderately dilated		54 (8%)
Severely dilated		17 (2.5%)
LV end-diastolic diameter (mm)	345/677 (51%)	46 (42, 50)
LV end-diastolic volume (ml)	433/677 (64%)	90 (70, 118)
LVEDV indexed (per BSA) (ml/m ²)	409/677 (60%)	46 (37, 57)
RV function (visual)	675/677 (99.7%)	
Hyperkinetic		58 (8.6%)
Normal		465 (69%)
Moderately depressed		108 (16%)
Severely depressed		44 (6.5%)
TAPSE (mm)	537/677 (79%)	20.9 (17, 24)
FAC (%)	333/677 (49%)	36 (28, 45)
RV size (visual)	668/677 (99%)	
Reduced		28 (4.2%)
Not dilated		363 (54%)
Moderately dilated		217 (32%)
Severely dilated		60 (9%)
RV hypertrophy	489 / 677 (72%)	
Yes		82 (17%)
No		407 (83%)
RVEDA/LVEDA ratio	521/677 (77%)	0.61 (0.5, 0.8)
PSM	670/677 (99%)	
Yes		130 (19%)
No		540 (81%)
Acute cor pulmonale	519/677 (77%)	
Yes		90 (17%)
No		429 (83%)
TRmax velocity (cm/s)	278/677 (41%)	2.7 (2.15, 3.1)

Table 3 (continued)

Echo parameters	n (available/total) ^{a#}	Summary statistics ^b
PAAT	133/677 (20%)	87 (66, 105)
IVC diameter (TTE, n = 551)	433/677 (64%)	
Small		52 (12%)
Normal		198 (46%)
Dilated		183 (42%)
Mitral E/A ratio	567/677 (84%)	0.9 (0.75, 1.17)
Aorta VTI (cm)	570/677 (84%)	19.2 (16.7, 22.6)
Aortic regurgitation	582/677 (86%)	
None		482 (83%)
Mild		90 (15%)
Moderate		10 (1.7%)
Severe		0 (0%)
Mitral regurgitation	592/677 (87%)	
None		381 (64%)
Mild		175 (30%)
Moderate		35 (5.9%)
Severe		1 (0.2%)
Pericardial effusion	605/677 (89%)	
Yes		74 (12%)
No		531 (88%)
PFO	256/677 (38%)	
Yes		14 (5.5%)
No		242 (95%)

TTE transthoracic echocardiography, TEE transesophageal echocardiography, SWMA segmental wall motion abnormality, LVEDV left ventricular end-diastolic volume, BSA body surface area, TAPSE tricuspid annular plane systolic excursion, FAC fractional area change, EDA end-diastolic area, PSM paradoxical septal motion, ACP acute cor pulmonale, TR tricuspid regurgitation, PAAT pulmonary artery acceleration time, IVC inferior vena cava, VTI velocity time integral

^a Number of available data/total number of patients (%)

^b Median (IQR) for continuous data; n (%) for categorical data

[#] Most data were missing at random or missing not at random. (Little's test for missing completely at random pattern, $p < 0.0001$)

vs 131 ± 67 mmHg) [difference = 6.5 mmHg (95% CI - 9 to 21.9)]. There was also no difference in PaO₂/FiO₂ in different RV size (Fig. 3D). However, patients with PSM or ACP was associated with higher incidences of pulmonary embolism (OR > 5) or mechanical ventilation (OR > 4) (Supplementary Table S1 and Supplementary Figure S4). They also displayed higher PaCO₂, while plateau pressure did not differ. Tidal volume was slightly lower in PSM (Supplementary Table S1). On the other hand, a significant proportion of patients with RV dysfunction (57%) did not experienced ACP, and there was no association between visual RV function and pulmonary embolism [OR = 0.614 (95% CI 0.319 to 1.223)].

Other echo findings

Valvular (aortic and mitral) regurgitations were absent in most patients, and only a few had severe valvular

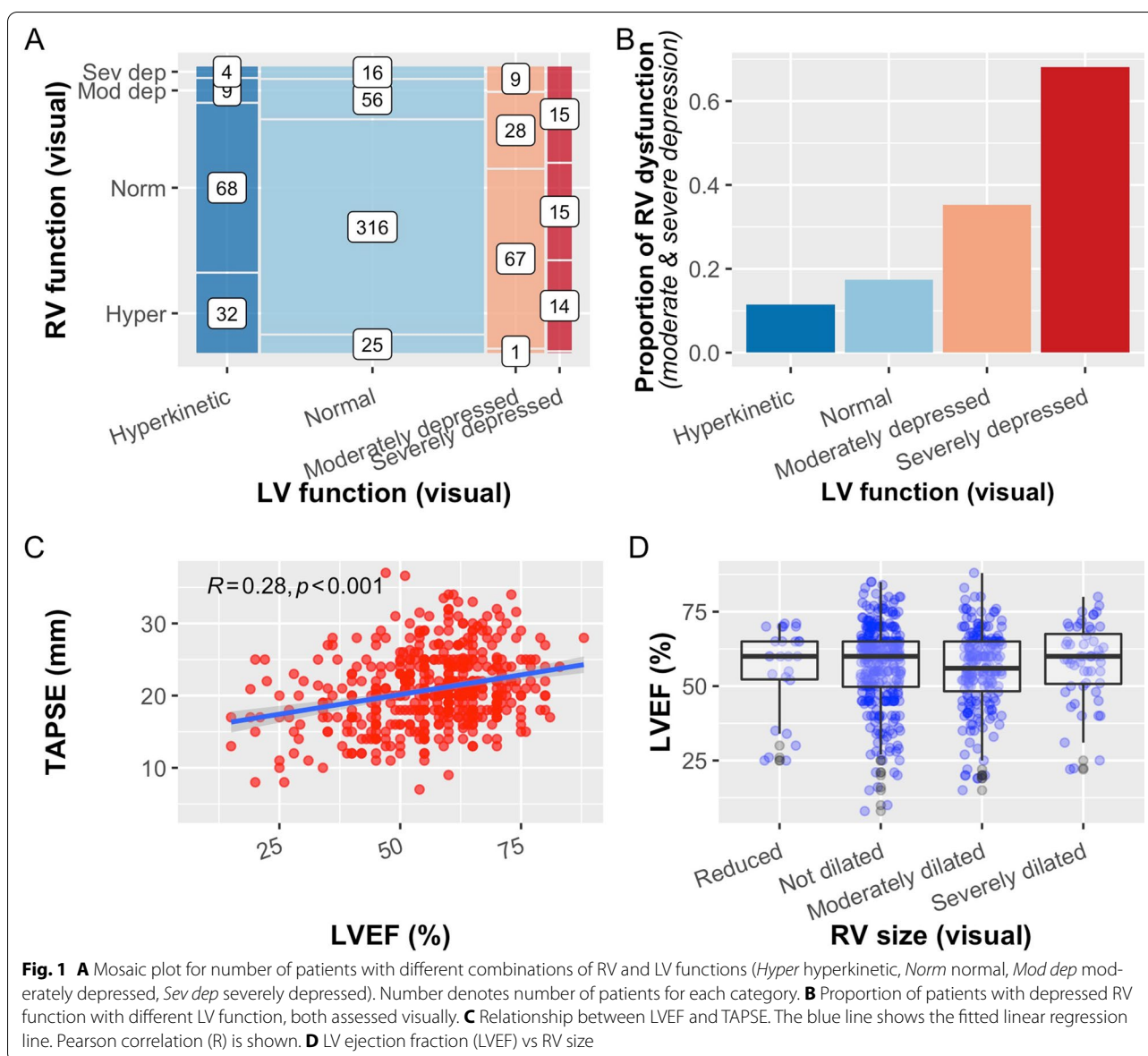


Fig. 1 **A** Mosaic plot for number of patients with different combinations of RV and LV functions (*Hyper* hyperkinetic, *Norm* normal, *Mod dep* moderately depressed, *Sev dep* severely depressed). Number denotes number of patients for each category. **B** Proportion of patients with depressed RV function with different LV function, both assessed visually. **C** Relationship between LVEF and TAPSE. The blue line shows the fitted linear regression line. Pearson correlation (R) is shown. **D** LV ejection fraction (LVEF) vs RV size

regurgitations (Table 3). Among the 256 patients in whom it was actively sought, patent foramen ovale (PFO) was detected in 14 patients. 74/605 (12.2%) patients had a pericardial effusion, with no case of tamponade.

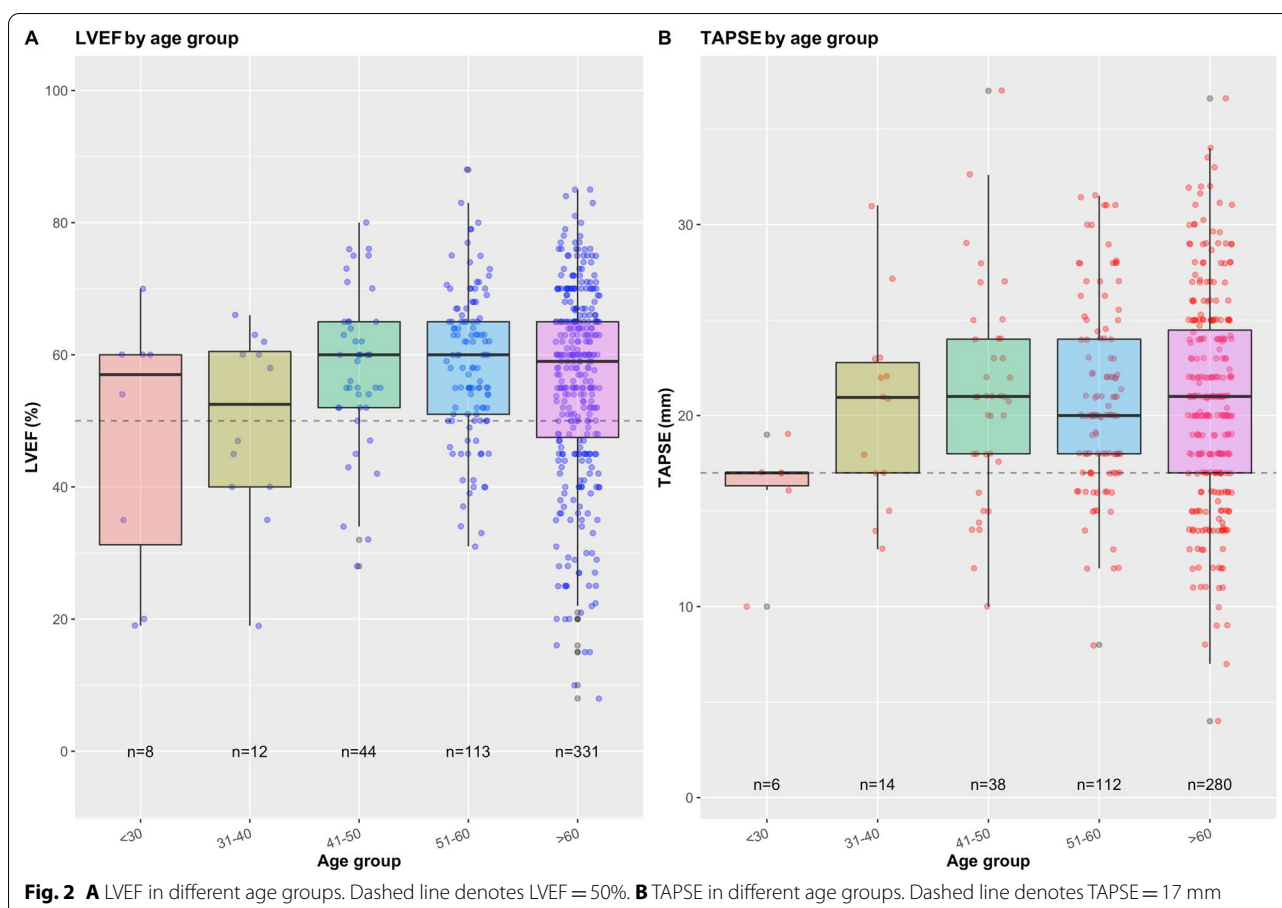
Patient outcomes

The median ICU length of stay was 14 [8, 26] days. The in-ICU mortality rate was 32.1% and in-hospital mortality rate 34.3%. Exploratory analyses in this cohort showed that both ACP and age were significantly associated with in-hospital and in-ICU mortalities. Patients with ACP were twice as likely to die when compared to those without (OR=2.02 [1.11, 3.66] for in-hospital mortality, and OR=2.01 [1.09, 3.69] for in-ICU

mortality). The odds for dying increases by 6% for every year increase in age (OR=1.06 [1.04, 1.08]) for both in-hospital and in-ICU mortalities (Supplementary Figure S5). Visual LV systolic dysfunction was associated with in-hospital mortality (OR=1.52 [1.04, 2.23]), but this association disappeared after adjusting for age. There is no significant association between visual RV dysfunction and mortality (results not shown). Sensitivity analyses excluding patients ($n=19$) receiving ECMO yielded similar results and conclusions.

Discussion

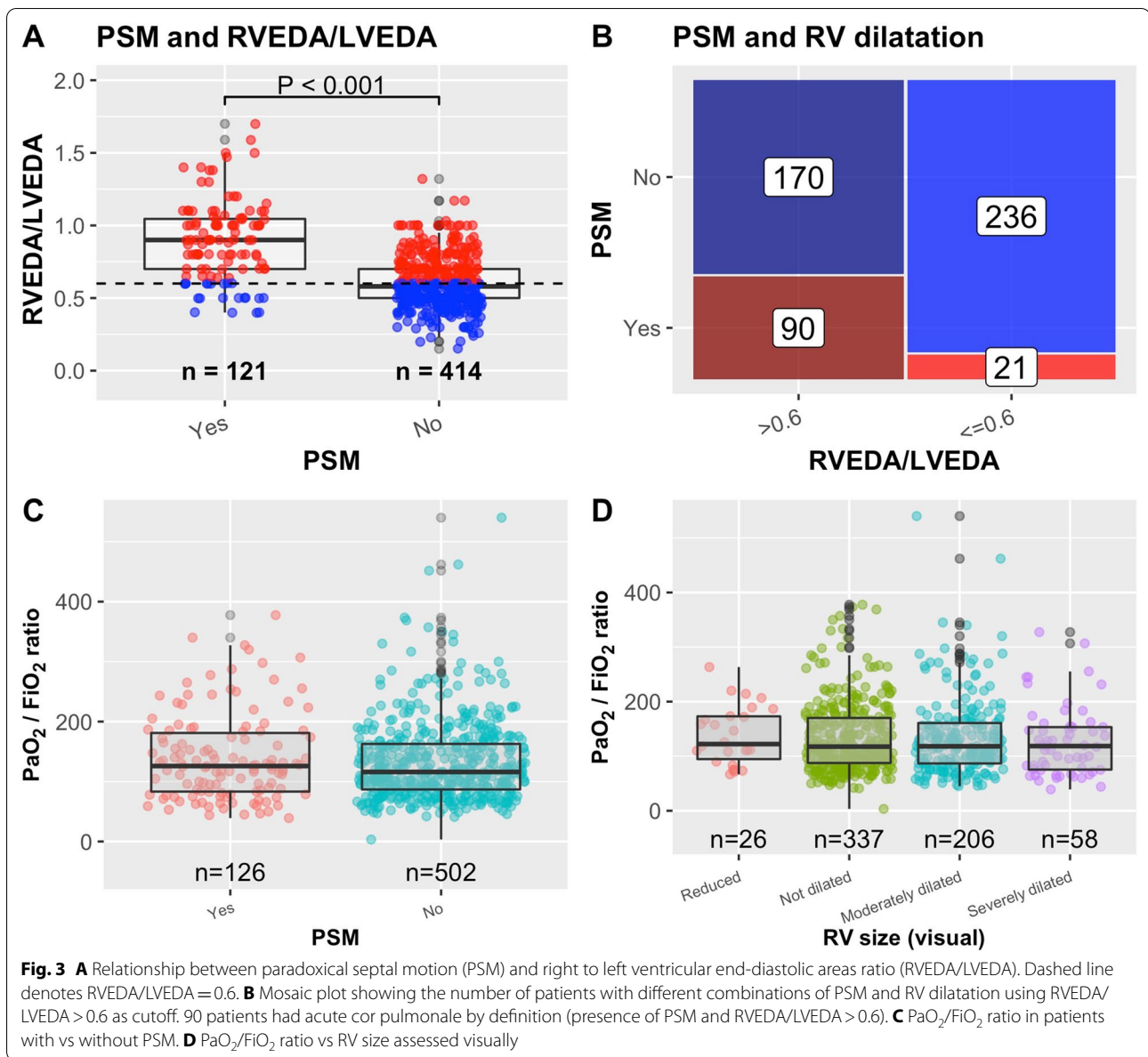
We report here cardiac function evaluated by CCE in 677 severe COVID-19 patients admitted in 14 different



ICUs, mostly in Europe. Cardiac function at the time of the first echocardiography after ICU admission was abnormal in 34% of the patients, 149 (22%) exhibiting LV systolic dysfunction and 152 (22.5%) RV systolic dysfunction. It is known that COVID-19 may affect the heart by different mechanisms [8]. Clear data regarding cardiac function is very limited in critically ill patients. In a large international survey, Dweck et al. reported LV and RV abnormalities in 39% and 33% respectively [9]. However, this survey only included 54% of critically ill patients and no quantitative evaluation of cardiac function was done. In another study of 43 consecutive patients admitted in 2 ICUs for COVID-19, Doyen et al. found that 30% of patients with myocardial injury had concurrent LV wall motion abnormalities, 47% had RV systolic dysfunction and 30% had ACP [11]. Patients' characteristics in our cohort were very similar to previous publications in terms of age, gender, BMI, delay between symptoms onset and ICU admission and comorbidities, as well as outcome [12, 13]. We included a similar number of patients between the first wave and the second/third wave. Many patients required catecholamine infusions at the time of CCE.

As expected, CCE was mainly performed by a transthoracic route, even when patients were mechanically ventilated. While LV and RV systolic function were only evaluated visually in most patients, our results show that CCE was reliably interpreted by experts in the field as visual and quantitative data, when available, did not show significant discrepancies. CCE was also performed early after ICU admission (half were within 2 days) and so reports the initial cardiac function before potential complications. As recommended by the PRICES consensus statement [10], we were also able to report important clinical data at the time of CCE, helping us to adequately interpret our findings.

A larger proportion of patients with age > 60 years had LV and RV dysfunction (LVEF < 50% or TAPSE ≤ 16 mm), while the means of LVEF and TAPSE did not differ across the age. Depressed LV systolic function, which was observed in 22%, was usually global and in most patients, the LV was non-dilated, suggesting an acute injury. In the majority of patients who did not have previous history of cardiomyopathy, the pattern of LV systolic dysfunction is similar to that previously described in septic cardiomyopathy [14], and is likely mediated by systemic



inflammation [15, 16]. This was reinforced by a non-elevated E/A ratio, suggesting the absence of LV filling pressure elevation [17]. However, the presence of potential LV ischemia cannot be formally ruled out as a minority of patients had segmental wall motion abnormalities, and we did not collect data on myocardial injury as well as types I and II myocardial infarction. Interestingly, only 12 patients had the association of LV systolic dysfunction with segmental wall motion abnormalities and LV dilatation which frequently occur in case of chronic cardiomyopathy. In 156 patients with COVID-19 in shock, Hollenberg et al. reported a 15% incidence of LV systolic dysfunction [18].

RV systolic dysfunction was found in 22.5%. The RV was frequently dilated with an incidence of 41% from visual assessment alone, and 50% when quantitative measurements were available. Paradoxical septal motion, a marker of RV pressure overload, was reported in 19% of cases. In the 517 patients who had required data [19], ACP was observed in 17% of cases. This remains slightly lower than what was reported in moderate to severe non-COVID-19 ARDS [7], but similar than what was reported in a previous small series of 18 COVID-19 patients [20]. In a recent retrospective study including 510 selected patients, of which 68% were admitted to ICU, RV dilatation was observed in 35% of cases but RV dysfunction,

based on decreased TAPSE and tissue Doppler imaging velocity, was much less frequent (15%) [21]. Interestingly, Bleakley et al. reported in 90 critically ill patients, 42% of them under VV ECMO, that RV systolic dysfunction was frequent but that COVID-19 led to a specific phenotype of radial impairment with sparing of longitudinal function [22]. As a matter of fact, TAPSE and tissue Doppler imaging velocity were less sensitive than fractional area change to detect RV abnormalities [22]. They also suggested that strain approach was less sensitive which has to be confirmed in the future. Three mechanisms partly responsible for ACP may be supported by our results: (1) the effect of positive pressure ventilation (at least 4 times the risk of spontaneously breathing patients), despite the application of a lung protective ventilation, (2) the effect of hypercapnia as PaCO_2 was slightly but significantly higher in case of ACP, and (3) the consequence of pulmonary embolism (more than 5 times the risk of patients without pulmonary embolism), all being intricate with strong pathophysiological rationale. Although history of lung disease, as COPD, is also a potential cause of RV failure, we were unable to draw any conclusion due to the very small number of patients ($n=9$) who had concomitant ACP and history of COPD, of which 3 of them had pulmonary embolism. Hypercapnia and mechanical ventilation, by increasing RV afterload, are already known risk factors for ACP in non-COVID ARDS [7]. Pulmonary embolism, when severe, is associated with RV failure in general, and has been reported as a risk for ACP in COVID-19 related ARDS in particular [23]. On the other hand, it is noteworthy that alterations in the pulmonary circulation in patients with COVID-19 through angiogenesis development [24] and limited adaptive hypoxic vasoconstriction [25, 26] compared to more usual ARDS could also protect the right ventricle by limiting the increase in pulmonary pressure. As a matter of fact, we did not find any association between $\text{PaO}_2/\text{FiO}_2$ and ACP or RV size while it was previously reported in non-COVID-19 ARDS [7].

We found that ACP and age, but not LV dysfunction, are associated with mortality. In 2 studies performed in non-critically ill COVID-19 patients, RV dilatation was independently associated with death or subsequent ICU transfer [27] in one and echo parameters of LV and RV dysfunction were independently associated with poor prognosis in the other [28].

Our study suffered from the usual limitations seen in retrospective studies. The impact of pandemic on the burden of healthcare workers, and the ICU surge with its unforeseeable and unpredictable COVID-19 infection rate (and trajectory) at the time precluded us from conducting a prospective study. The main limitations of this retrospective observational study were:

first, echocardiography studies were only performed as per clinical necessity and not on every patients (only 33.4% of all COVID-19 patients per center), and these resulted in selection bias and limits its generalization to other COVID-19 patients. However, the large number of recruitment centers in different geographical locations provided a meaningful representative of COVID-19 patients with characteristics similar to our cohort. Second, the echocardiography procedures were not designed for a proper echocardiography research study, hence the procedure were not standardized and missing data were common. Most missing data were not missing completely at random, but were missing at random (e.g., some centers may not perform certain measurements in their practice) or not at random (e.g., LVEF was missing due to poor image quality, or PFO or thrombus was not entered because it was not observed). While we were unable to impute missing data due to large number of the latter, our main results were based on visual assessments which were available in most patients. Third, we were unable to report any definitive causality between ACP and mortality but only a statistical association. We also could not evaluate the potential impact of VV ECMO on this association as the number of patients with such a technique was too small, while we found similar results after excluding the 19 patients who received ECMO. Finally, another (minor) limitation was the lack of severity index (Acute Physiology and Chronic Health Disease Classification System (APACHE), Simplified Acute Physiology Score (SAPS) and Sequential Organ Failure Assessment (SOFA) scores), although all patients were admitted to ICU due to severe COVID-19. On the other hand, there were several strengths in our study. First, the visual assessments were performed by experts in CCE, and we find the relationship between visual and quantitative assessment was consistent and reliable. Second, previous studies in hospitalized COVID-19 patients have shown that myocardial injury (as reflected by increased troponin level) is common and is associated with death [2, 3]. However, in these studies, cardiac biomarkers were used as the sole marker of cardiac injury [2, 3]. Although we did not report cardiac biomarkers in our study, we used echocardiography to assess cardiac function which has better specificity in identifying clinically important cardiac dysfunction, the types of dysfunction and other salient features not detected using cardiac biomarkers. While this retrospective study showed some limitations, the strength of the study is that it is one of the largest critical care echocardiography study in ICU COVID-19 patients and has provided important clinical and echocardiography information in this special population. This study was not designed to provide explanation of pathophysiology nor treatment options in COVID-19 patients.

In conclusion, cardiac function evaluated during the first echocardiography performed after ICU admission was abnormal in 34% in this cohort of critically ill COVID-19 patients. While LV systolic dysfunction seemed similar to septic cardiomyopathy, RV dysfunction was related to pressure overload due to positive pressure ventilation, hypercapnia and pulmonary embolism, while not to severity of hypoxemia which appears different from non-COVID-19 ARDS. No other significant cardiac abnormalities were observed. Our data should help intensivists to better understand hemodynamic impairment in these patients to guide therapy.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s00134-022-06685-2>.

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Acknowledgements

Collaborators of the ECHO-COVID study are listed as follows: Anne-Marie Welsh (Nepean Hospital, Sydney, Australia), H Didriksson (Linköping University hospital, Sweden), Yoann Zerbib (University hospital of Amiens, Amiens, France), Clément Brault (University hospital of Amiens, Amiens, France), Laetitia Bodénes (CHU La Cavale Blanche, Brest, France), Nicolas Ferrière (CHU La Cavale Blanche, Brest, France), S Clavier (Hôpital Européen Georges Pompidou, AP-HP and Université de Paris, Paris, France), I Ma (Hôpital Européen Georges Pompidou, AP-HP and Université de Paris, Paris, France), Luigi La Via (Department of Anesthesia and Intensive Care, Policlinico-Vittorio Emanuele University Hospital, Catania, Italy), Veronica Dezio (Department of Anesthesia and Intensive Care, Policlinico-Vittorio Emanuele University Hospital, Catania, Italy), JB Rius (Vall d'Hebron University hospital, Barcelona, Spain), JR Palomares (Vall d'Hebron University hospital, Barcelona, Spain), Fernando Piscionei (Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, University of Rome, "La Sapienza", Policlinico Umberto Primo), S Giglioli (CHIREC Hospitals, Université Libre de Bruxelles, Brussels, Belgium), S Banauch-Mayer (The University hospital for University of Massachusetts, Worcester, MA, USA), Bruno François (Medical-surgical ICU, Dupuytren Teaching Hospital, Limoges,

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Author contributions

All the authors contribute to read, interpret and enter patients in the secure web-based platform. SH did the statistical analysis. AV-B interpreted the results. SH and AV-B wrote the manuscript. All the authors confirm they have full access to all of data in the study and accept responsibility to submit for publication. They all agree with the manuscript.

Funding

None.

Declarations

Conflicts of interest

AVB declares research grant from GSK and Air Liquid companies. DDB declares honoraria from Philips company for lecture and honoraria for consulting from Edwards Lifesciences, Pfizer and Baxter companies. The other authors declare that they have no conflict of interest.

Ethical approval

The study protocol was approved by ethics committee (CE SRLF 20–40).

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 19 January 2022 Accepted: 16 March 2022

Published online: 21 April 2022

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