# Right ventricular failure is strongly associated with mortality in patients with moderate-to-severe Covid-19-related ARDS

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**Supplementary materials**

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## Supplementary Methods

The protocol was approved by the Ethics Committee of Limoges Teaching Hospital (#492-2021-14) which waived the need for written informed consent and only required a non-opposition of the patients to participate in the study.

***Patients' characteristics***

In each patient, the following parameters were recorded upon admission:

*Demographics and severity scores*: age, sex, body mass index, SOFA and SAPSII score.

*Comorbidities*: Hypertension, obesity, diabetes mellitus, cardiopathy, atrial fibrillation, peripheral arterial disease, stroke, chronic kidney disease, COPD, sleep apnea, immunosuppression.

*Biology*: arterial blood gas, lactate, creatinine, white blood cell count, lymphocytes, platelets, fibrinogen, ferritin, liver enzymes (AST, ALT), bilirubin, troponin.

*Hemodynamic parameters*: heart rate, systolic, diastolic and mean blood pressure, vasopressor support.

*Ventilation parameters*: type of respiratory support; if invasive mechanical ventilation: total positive end-expiratory pressure, tidal volume, plateau pressure, driving pressure and compliance.

In addition, the following organ supports were recorded throughout the ICU stay: invasive mechanical ventilation, timing of tracheal intubation, prone position under mechanical ventilation, muscle blocker agents, VV-ECMO, inhaled nitric oxide, vasopressor support and renal replacement therapy. Documented pulmonary embolism were collected throughout ICU stay.

At the time of hemodynamic assessments, respiratory parameters including $PaO_2/FiO_2$, $PaCO_2$, ventilatory ratio ($\frac{Measured\,minute\,ventilation\,(ml*min^{-1})*PaCO2\,measured\,(mmHg)}{Predicted\,minute\,ventilation\,(ml*min^{-1})*PaCO2\,ideal\,(mmHg)}$) - a

surrogate marker of pulmonary dead-space fraction - (E1), and driving pressure (E2) were recorded, as well as the SOFA score, lactate, bilirubin and creatinine level.

***Critical care echocardiography***

Transthoracic echocardiography was first performed and systematically completed by a transesophageal echocardiography in patients who were under invasive mechanical ventilation and had no contra-indication for esophageal intubation (E3). Particular attention was directed towards RV functional and anatomical assessment as part of a comprehe nsive hemodynamic evaluation. All examinations were conducted by experienced operator in advanced CCE (E4), and stored in a digital format for further analysis. Measurements were performed independently off-line by an experienced investigator who did not conduct CCE examinations. To determine inter-observer variability, parameters used to diagnose RVF were also measured independently by another expert who had no access to the medical chart in 20% of randomly selected patients.

Recent statement for conducting and reporting critical care echocardiography research study has been only partially followed since the present study was not evaluating a specific hemodynamic assessment or the effect of therapeutic interventions on hemodynamics (E5). The following measurements were performed in triplicate at end-expiration and averaged at each echocardiographic examination:

- Ratio of right ventricular (RV) and left ventricular (LV) end-diastolic area (RVEDA/LVEDA) in the long-axis view of the heart, grade of RV dilatation, and grade of acute cor pulmonale (ACP)
- RV end-systolic area (RVESA) in the long-axis view of the heart to compute the fractional area change (RVFAC) as: RVEDA - RVESA / RVEDA, expressed as a percentage

- Tricuspid Annulus Plane Systolic Excursion (TAPSE) measured at the lateral aspect using M-mode in the apical four-chamber view
- Maximal velocity of S' wave measured at the lateral tricuspid annulus using pulse wave tissue Doppler imaging in the apical four-chamber view
- -RV end-systolic eccentricity index (E6)
- Maximal velocity of tricuspid regurgitation measured using continuous wave Doppler to estimate systolic pulmonary artery pressure using the simplified Bernouilli's equation (E7)
- Pulmonary acceleration time measured in the upper transesophageal transverse view of the great vessels (E8)
- End-expiratory inferior vena cava diameter
- LV end-diastolic volume and LV end-systolic volume (to calculate ejection fraction) using the biplane modified Simpson's rule in the four- and two-chamber view
- E' wave maximal velocity using pulse wave tissue Doppler at the lateral and septal mitral annulus in the four-chamber view, while (i) narrowing the field width to obtain a frame rate of 100 to 150 Hz, (ii) limiting the Doppler beam angle with regard to the mitral annulus plane < 15°, (iii) decreasing the velocity scale to 20 cm/s (except for higher values), and (iv) using a 100 mm/s sweep speed for optimal measurement accuracy
- Maximal velocity of mitral E and A wave using pulse wave Doppler, and E wave deceleration time with the sample positioned at the tip of valvular leaflets in the four-chamber view; the E/A ratio was calculated in the presence of a sinus rhythm; lateral, septal and mean E/E' ratio were also calculated
- LV outflow tract velocity-time integral measured using pulse wave Doppler in the apical five-chamber view or in the 120° transgastric view or in the apical five-chamber view
- LV outflow tract diameter to calculate LV outflow tract area, hence LV stroke volume.

In ventilated patients, the collapsibility index of the superior vena cava using M-mode in the long axis view of the great vessels of the base in the upper transesophageal view was obtained.

***Statistical analysis***

Continuous variables were expressed as median [and quartiles], or as mean and standard deviation if normally distributed. Categorical variables were reported as numbers and percentages. No extrapolation of missing data was performed. Chi$^2$ test was used to compare proportion between two groups. The agreement of intra- and inter-observer measurements of CCE parameters of RVF (i.e., RV dilatation, paradoxical septal motion and ACP) was assessed with Fleiss kappa coefficient and their 95% confidence intervals.

Univariate Cox model analyses were used to determine the baseline variables to be included in the multivariate model. Variables with a p value < 0.10 or known to be associated with mortality were selected in the multivariate analysis. A multivariate Cox model analysis accounting for new-onset RVF as a time-dependent variable was used to identify parameters associated with mortality [E9]. The best model was selected using the likelihood ratio method. We forced the SAPSII score to be one of the co-variable in the final model as it is known to be associated with hospital mortality [E10]. Since the minority of patients who did not undergo initial hemodynamic assessment were considered as free of RVF at baseline, we conducted a sensitivity analysis excluding them.

In the subset of patients without RVF at baseline who subsequently developed RVF during the ICU stay, we compared the SOFA score and respiratory parameters between the day of the RVF diagnosis and the day of the preceding CCE assessment using a Wilcoxon signed-rank test. Finally, we used a Kaplan Meier curves to display the time lag between the

new-onset of RVF on the one hand, and ICU death and initiation of vasopressors on the other hand.

A p-value < 0.05 was considered statistically significant. Analyzes and plots were performed with R (version 4.2) using R-studio interface (Version 1.3.1073) and SPSS (IBM, version 28.0) for the time-dependent Cox regression.

**Supplementary references**

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## Supplementary Results

### *Study population*

During the study period, 255 of the 924 patients admitted to our ICU sustained ARDS, which was secondary to severe COVID-19 pneumonia in 172 of them (67%). Thirty-two of eligible patients were not studied mainly due to inadequate CCE image quality for RV assessment (n=20), all of them being spontaneously breathing and assessed using transthoracic echocardiography (Supplementary Figure 1).

Nine patients presented with a pulmonary embolism on admission, while 3 additional patients developed a pulmonary embolism during the ICU stay. Only 50% of patients with documented pulmonary embolism developed RVF. Only 2 patients underwent a CT pulmonary angiogram which ruled out a pulmonary embolism shortly after the diagnosis of RVF. Median CVP reached 11 mmHg [9-14] at the time of RVF diagnosis, whereas it remained at 7 mmHg [5-10] in patients without RVF. In patients with RVF at baseline, isolated RVF was predominantly diagnosed (58%), whereas ACP and severe ACP were identified in 17% and 25% of the cases, respectively. At the time of RVF diagnosis, 28 patients (37%) had a RV fractional area change < 35% and 7 patients (9%) had a TAPSE < 17mm. Forty-nine of RVF patients (64%) required a vasopressor support, 15 of them already receiving vasopressors at the time of RVF diagnosis and no one received inotropes. Forty-nine patients with RVF (65%) underwent prone positioning, 19 patients (25%) received inhaled Nitric Oxide, 19 patients (25%) had renal replacement therapy, and a single patient was placed under VV-ECMO.

Table E1: Patients' characteristics on ICU admission and organ support requirement during the ICU stay (n=140)

| **Demographics and severity scores** | |
|---|---|
| Age (years) | 68 (60-72) |
| Sex (male) | 93 (66%) |
| BMI (kg/m²) | 29.4 (26.2-33.6) |
| SOFA score | 4 (4-6) |
| SOFA score excluding the respiratory system | 2 [1-3.5] |
| SAPS II score | 37 (31-48) |
| **Comorbidity** | |
| Hypertension | 82 (59%) |
| Obesity | 67 (48%) |
| Diabetes mellitus | 54 (39%) |
| Ischemic cardiomyopathy | 23 (16%) |
| Atrial fibrillation | 7 (5%) |
| Peripheral arterial disease | 9 (6.4%) |
| Stroke | 8 (5.7%) |
| Chronic kidney disease | 17 (12%) |
| COPD | 9 (6.4%) |
| Sleep apnea | 16 (11%) |
| Immunosuppression | 15 (11%) |
| **Biology** | |
| $PaO_2$ (mmHg) | 77 (59-84) |
| $PaO_2/FiO_2$ (mmHg) | 95 (75-143) |
| $PaCO_2$ (mmHg) | 34 (29-40) |

| | |
|---|---|
| Bicarbonate (mmol/L) | 22.8 (20.7-25.1) |
| Lactate (mmol/L) | 1.36 (1.02-1.77) |
| Creatinine (µmol/L) | 76 (58-104) |
| Troponin (ng/L) | 16 (0-30) |
| Bilirubin (µmol/L) | 7.5 (5.4-10.1) |
| CRP (mg/L) | 126 (77-196) |
| WBC (G/L) | 8.6 (5.9-10.7) |
| Lymphocytes (G/L) | 0.71 (0.49-0.94) |
| Platelets (G/L) | 241 (188-303) |
| Fibrinogen (g/L) | 6.82 (5.78-7.69) |
| Ferritin (ng/mL) | 1427 (836- 2659) |
| **Respiratory and hemodynamic parameter on ICU admission** | |
| High-flow nasal cannula oxygen therapy | 102 (73%) |
| Invasive mechanical ventilation: | 19 (14%) |
| *Tidal volume (mL/kg)* | 6.9 (6.6-7.4) |
| *PEEP ($cmH_2O$)* | 10 (8-12) |
| *Plateau pressure ($cmH_2O$)* | 23 (21-26) |
| *Driving Pressure ($cmH_2O$)* | 15 (12-16) |
| *Compliance ($mL/cmH_2O$)* | 38 (28-43) |
| Vasopressor support | 3 (2.1%) |
| Heart rate (bpm) | 90 (78-101) |
| Systolic arterial pressure (mmHg) | 138 (122-152) |
| Diastolic arterial pressure (mmHg) | 76 (70-86) |
| Mean arterial pressure (mmHg) | 93 (82-104) |
| **Organ support during the ICU stay** | |

| | |
|---|---|
| Invasive mechanical ventilation | 110 (78%) |
| Timing of tracheal intubation (days from ICU admission) | 1 (0-2) |
| Prone position under mechanical ventilation | 64 (46%) |
| Muscle blocker agents | 108 (77%) |
| VV-ECMO | 2 (1.4%) |
| Inhaled Nitric Oxide | 19 (14%) |
| Vasopressor support | 57 (41%) |
| Renal replacement therapy | 19 (14%) |

Results are expressed in median and interquartile ranges, or in numbers and percentages.

Abbreviations: BMI, body mass index; SOFA, sepsis-related organ failure assessment; SAPS, simplified acute physiology score; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; WBC, white blood cells; VV-ECMO, veino-venous extracorporeal membrane oxygenation; ICU, intensive care unit.

Table E2: Echocardiography parameters measured at the time of 'baseline' hemodynamic assessment performed within 72h following ICU admission

| Parameters | n=105 |
|---|---|
| **RV assessment** | |
| RV/LV end-diastolic area | 0.72±0.22 |
| RV dilatation: | |
| Absent | 31 (30%) |
| Moderate | 64 (61%) |
| Severe | 10 (9%) |
| Acute cor pulmonale : | |
| Absent | 87 (83%) |
| Moderate | 10 (9%) |
| Severe | 8 (8%) |
| RV fractional area change (%) | 35±12 |
| Tricuspid annular plane systolic excursion (mm) | 22.8±4.9 |
| Tricuspid lateral S' wave (cm/s) | 15.6±3.9 |
| RV end-systolic eccentricity index | 1.12±0.19 |
| RA-RV systolic pressure gradient (mmHg) | 39±14 |
| Pulmonary acceleration time (ms) | 79±21 |
| IVC diameter (mm) | 20.5±5.6 |
| SVC collapsibility index (%) | 21±15 |
| **LV assessment** | |
| LV end-diastolic volume (mL) | 89±30 |

| | |
|---|---|
| LV end-systolic volume (mL) | 42±20 |
| LV ejection fraction (%) | 54±15 |
| LV global longitudinal strain (%) | -18.1±4.8 |
| LV outflow tract velocity-time integral (cm) | 20.7±4.9 |
| Mean E/E' | 9.68±3.08 |
| LV dynamic obstruction* | 3 (2.4%) |

Results are expressed as means and standard deviation, or as numbers and percentages in parentheses.

*: defined as a maximal systolic pressure gradient ≥ 50 mmHg.

Abbreviations: LV, Left ventricle; RV, right ventricle; FAC: fractional area change; RA, right atrium; IVC: inferior vena cava; SVC, superior vena cava.

Table E3: Sensitivity analysis to evaluate the risk of death at 90 days performed in patients who underwent a CEE assessment at baseline using a multivariate Cox model with new-onset right ventricular failure considered as a time-dependent variable

| | n | Event (n) | HR | 95% CI | p-value |
|---|---|---|---|---|---|
| Age (per 10 years) | 105 | 33 | 2.09 | 1.25-3.50 | 0.005 |
| SAPSII (per 10 points) | 105 | 33 | 0.90 | 0.69-1.18 | 0.45 |
| Ischemic cardiomyopathy | 105 | 33 | 2.80 | 1.34-5.87 | 0.006 |
| Right ventricular failure | 105 | 33 | 6.60 | 2.24-19.47 | <0.001 |

Figure E1: Flow chart of the study.

Figure E2: Timing of hemodynamic assessments using echocardiography and of diagnosis of right ventricular failure during the ICU stay (from ICU admission). **Panel A.** Bar plots depicting the number and type of echocardiography examinations performed at each time-point during the ICU stay. **Panel B.** Bar plots depicting the proportion of new-onset right ventricular failure at each time-point during the ICU stay. **Panel C.** Bar plots depicting the type of new-onset right ventricular failure at each time-point during the ICU stay.

Abbreviations: TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; RV, right ventricle.

Figure E3: Respective timing of initiation of vasopressor support and ICU death after the day of RVF diagnosis. **Panel A.** Kaplan Meier curve depicting the timing of initiation of vasopressors after the day of RVF diagnosis. **Panel B.** Kaplan Meier curve depicting the timing of ICU death with respect of RVF diagnosis.

Abbreviations: RVF, right ventricle failure; ICU, intensive care unit.