Right ventricular dysfunction and right ventricular–arterial uncoupling at admission increase the in-hospital mortality in patients with COVID-19 disease

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Abstract

Background: Coronavirus disease 2019 (COVID-19) frequently involves cardiovascular manifestations such as right ventricular (RV) dysfunction and alterations in pulmonary hemodynamics. We evaluated the application of the critical care ultrasonography ORACLE protocol to identify the most frequent alterations and their influence on adverse outcomes, especially those involving the RV (dilatation and dysfunction).

Methods: This cross-sectional study included 204 adult patients with confirmed COVID-19 admitted at three centers. Echocardiography and lung ultrasound images were acquired on admission using the ORACLE ultrasonography algorithm.

Results: Two-hundred and four consecutive patients were evaluated: 22 (11.9%) demonstrated a fractional shortening of < 35%; 33 (17.1%) a tricuspid annular plane systolic excursion (TAPSE) of < 17 mm; 26 (13.5%) a tricuspid peak systolic S wave tissue Doppler velocity of < 9.5 cm/sec; 69 (37.5%) a RV basal diameter of > 41 mm; 119 (58.3%) a pulmonary artery systolic pressure (PASP) of > 35 mm Hg; and 14 (11%) a TAPSE/PASP ratio of < .31. The in-hospital mortality rate was 37.6% (n = 71). Multiple logistic regression modeling showed that PASP > 35 mm Hg, RV FS of < 35%, TAPSE < 17 mm, RV S wave < 9.5, and TAPSE/PASP ratio < .31 mm/mm Hg were associated with this outcome. PASP and the TAPSE/PASP ratio had the lowest feasibility of being obtained among the investigators (62.2%).

Conclusion: The presence of RV dysfunction, pulmonary hypertension, and alteration of the RV–arterial coupling conveys an increased risk of in-hospital mortality in patients presenting with COVID-19 upon admission; therefore, searching for these alterations should be routine. These parameters can be obtained quickly and safely with the ORACLE protocol.
INTRODUCTION

1.1 Background

Coronavirus disease 2019 (COVID-19) has a wide clinical spectrum, ranging from mild asymptomatic disease to acute respiratory distress syndrome (ARDS). Traditional cardiovascular (CV) risk factors, which are reported in up to 46% of patients with COVID-19, increase the severity of the disease, leading to hemodynamic deterioration and the appearance of adverse complications.1,2 CV manifestations include myocardial injury, acute myocarditis, heart failure, acute myocardial infarction, arrhythmias, and thromboembolic disease. The development of these complications conveys a worse prognosis for the patient.3

1.2 Importance

The development of heart failure in patients with COVID-19 is not only a consequence of left ventricular (LV) dysfunction, but also right ventricular (RV) dysfunction, with an estimated frequency of 28%–39%.4,5 The mechanism of RV dysfunction is multifactorial, including microvascular thrombi in the pulmonary vessels and pulmonary vasoconstriction produced by hypoxemia and hypercapnia, all producing an increase in RV afterload.6,7 Severe COVID-19 disease usually requires invasive mechanical ventilation with high ventilatory parameters. This high transpulmonary pressure can lead to alveolar overdistension that causes compression of the alveolar capillaries, resulting in an increased pulmonary vascular resistance, which contributes to the RV dysfunction.3,9 García-Cruz et al. reported an increased pulmonary artery systolic pressure (PASP) in up to 69.5% of patients.4 Ventricular–arterial coupling involves the relationship between contractility and afterload, which can be evaluated with echocardiography by the tricuspid annular plane systolic excursion (TAPSE)/PASP ratio. Patients with a TAPSE/PASP ratio of < .31 mm/mm Hg had a significantly worse prognosis in cases of severe pulmonary hypertension.10

1.3 Investigation goals

The critical care ultrasonography algorithm—the ORACLE protocol—allows the evaluation of LV and RV function, valves, pericardial effusion, diastolic function and filling pressures, pulmonary hemodynamics, regional wall motion, and stratification of the severity of pulmonary affection, to obtain greater prognostic certainty and thereby determine the most appropriate treatment.5 The objective of our research was to evaluate the application of a critical care ultrasound protocol in patients admitted to three intensive care units with SARS-CoV-2 infection leading to COVID-19 to identify the most frequent alterations and their influence with adverse outcomes, especially those involving the RV (dilatation and dysfunction) and RV–arterial coupling.

METHODS

This cross-sectional study included 204 adult patients with confirmed COVID-19 disease admitted to the critical care unit at three centers (Instituto Nacional de Cardiología Ignacio Chávez and Hospital Naval de Especialidades Veracruz in Mexico and Hospital de Clínicas in Bolivia) from April 1, 2020 to October 31, 2020. The local institutional research and ethics committees of the three centers waived approval for this study. Written informed consent for patient information and images to be published were provided by the patient or a legally authorized representative. The echocardiography and lung ultrasound (LUS) images were acquired upon admission using the critical care ultrasonography algorithm “the ORACLE protocol” as described (Appendix 1).4 The feasibility of echocardiographic measurements was calculated by dividing the total number of echocardiographic parameters with the total number of patients and are reported as percentages.2.1 Statistical analysis

We performed the Shapiro–Wilk test of normality for continuous variables. After determining their distribution, we reported them as the mean and standard deviation if they were parametric and as the median and interquartile range (IQR) if they were nonparametric. We used Student’s t or Kruskal–Wallis tests for comparisons among continuous variables. We describe categorical variables as frequencies and percentages, and we used chi-squared or Fisher’s exact tests as appropriate for comparisons according to the expected values. We applied a multivariate logistic regression model adjusted by age and gender to evaluate the variables that helped in predicting mortality. All statistical analyses were considered significant at \( p < 0.05 \). Statistical analysis was performed using STATA v.14 (https://www.stata.com). Some results (e.g., in Table 1) are presented as the odds ratio (OR) and 95% confidence interval (CI).

RESULTS

Clinical data were collected from 204 consecutive patients with confirmed SARS-CoV-2 infection and COVID-19 disease.

3.1 Demographic characteristics, clinical presentation, and in-hospital outcomes

Most of the patients were men (59.3%), with a median age of 59 (range 48–67) years, and the most frequent comorbidities were hypertension...
### Table 1

Demographic and clinical characteristics of patients

| Variable                  | Total n = 204 | PaO₂/FiO₂ > 300 Median (IQR) | PaO₂/FiO₂ 300–200 Median (IQR) | PaO₂/FiO₂ 200–100 Median (IQR) | PaO₂/FiO₂ < 100 Median (IQR) |
|---------------------------|---------------|------------------------------|---------------------------------|--------------------------------|-------------------------------|
|                           | n (%)         | n (%)                        | n (%)                           | n (%)                          | n (%)                        | p     |
| Age (years)               | 59 (48–67)    | 61.5 (55–67)                 | 62 (51–67)                      | 57 (48–65)                     | 59 (51–71)                   | 0.33  |
| Heart rate (bpm)          | 88 (78–100)   | 86 (75–100)                  | 81 (70–93)                      | 88 (79–95)                     | 89 (79–113)                  | 0.04  |
| Systolic blood pressure (mm Hg) | 120 (109–130) | 127 (113–133)               | 120 (109–128)                   | 124 (110–132)                  | 110 (100–121)                | 0.01  |
| Diastolic blood pressure (mm Hg) | 68 (60–76)   | 75 (67–80)                   | 80 (65–85)                      | 68 (60–74)                     | 65 (57–69)                   | <0.001|
| Troponin I (pg/ml) (14–42.9 pg/ml) | 15 (5–56)    | 23 (6–35)                    | 13 (6–89)                       | 15 (5–45)                      | 14 (2–56)                    | 0.11  |
| D-dimer (ng/ml) (<500 ng/ml) | 589 (250–935) | 569 (246–7835)               | 675 (310–2226)                  | 457 (200–767)                  | 750 (428–921)                | 0.02  |
| NT-proBNP (pg/ml) (15–125 pg/ml) | 390 (154–789) | 938 (316–3011)              | 1659 (210–4353)                | 345 (120–672)                  | 389 (163–629)                | 0.01  |
| Creatinine (mg/dl)        | 1.1 (0.8–1.7) | 1.7 (1.4–2.0)                | 1.6 (1.3–2.1)                   | 1.1 (0.9–1.3)                  | 2.1 (1.2–2.6)                | <0.001|
| C reactive protein (mg/L) (1–3 mg/L) | 68 (20–155)  | 171 (109–307)                | 121 (32–193)                    | 56 (16–133)                    | 51 (11–111)                  | <0.001|
| Ferritin (ng/ml) (23.9–336 ng/ml) | 496 (122–911) | 1058 (366–1470)             | 721 (268–1488)                  | 380 (102–775)                  | 234 (18–901)                 | <0.001|

Abbreviations: IQR, interquartile range; NT-proBNP, N-terminal B-type natriuretic peptide.

and diabetes (50% and 32.8%, respectively) (Table 2). Eighty-two percent of the patients required invasive mechanical ventilation at admission. According to the Berlin definition, 14.7% (n = 30) had mild, 48% (n = 98) had moderate, and 30.4% (n = 62) had severe ARDS. Patients were hemodynamically stable at admission, with a median heart rate (HR) of 88 (78–100) beats per minute (bpm), systolic blood pressure (SBP) of 120 (109–130) mm Hg, and diastolic blood pressure (DBP) of 68 (60–76) mm Hg. Patients with a PaO₂/FiO₂ ratio of < 100 had lower SBP and DBP (medians of 110 mm Hg and 65 mm Hg, respectively, p = 0.00). Laboratory determinations revealed elevated troponin I, D-dimer, NT-proBNP, C-reactive protein, and ferritin levels upon admission. The in-hospital mortality rate among these patients was 37.6% (Table 2).

### 3.2 Ultrasonography results

From all the echocardiographic measurements, PASP and TAPSE/PASP had the lowest feasibility (62.2%), whereas the other parameters had more than 80% feasibility among operators. RV S wave and TAPSE were the most commonly feasible measurements among operators at 94.6% and 94.1%, respectively (Appendix Table 1).

### 3.3 RV function

The median fractional shortening (FS), TAPSE, S wave, RV basal diameter, PASP and TAPSE/PASP ratio were within normal ranges, independent of PaO₂/FiO₂ values (Table 3). Twenty-two patients (11.9%) demonstrated a FS of < 35%; 33 (17.1%) had a TAPSE of < 17 mm, 26 (13.5%) demonstrated an S wave of < 9.5 cm/seg, 69 (37.5%) had a RV basal diameter of > 41 mm, and 14 (11%) a TAPSE/PASP ratio < 0.31 mm/mm Hg (Table 4).

### 3.4 Pulmonary hemodynamics

The median PASP was 30 mm Hg, and 119 patients (58.3%) demonstrated values of > 35 mm Hg, most frequently in the group with PaO₂/FiO₂ < 100 mm Hg (median 37, p = 0.00). The median pulmonary
TABLE 2 Description of echocardiographic parameters

| Variable         | Total Median (IQR) | PaO$_2$/FiO$_2$ > 300 Median (IQR) | PaO$_2$/FiO$_2$ 300–200 Median (IQR) | PaO$_2$/FiO$_2$ 200–100 Median (IQR) | PaO$_2$/FiO$_2$ < 100 Median (IQR) | p    |
|------------------|--------------------|-------------------------------------|--------------------------------------|--------------------------------------|-----------------------------------|------|
| LVDD             | 43 (40–45)         | 41 (40–46)                          | 43 (40–46)                           | 44 (41–46)                           | 42 (40–45)                       | 0.26 |
| LVEF             | 56 (50–62)         | 55 (45–60)                          | 55 (45–56)                           | 58 (50–62)                           | 59 (54–64)                       | <0.001 |
| MAPSE            | 14 (12–18)         | 15 (12–17)                          | 14 (12–16)                           | 14 (12–18)                           | 18 (13–19)                       | <0.001 |
| LVOT VTI         | 17 (15–19)         | 18 (16–18)                          | 17 (15–19)                           | 17 (15–19)                           | 17 (15–19)                       | 0.68 |
| SV               | 53.8 (45.8–65.6)   | 55.9 (51–59.7)                      | 51.9 (43–64.6)                       | 53 (46.7–62.8)                       | 56.5 (47.1–65.8)                 | 0.84 |
| CO               | 4.6 (3.9–5.5)      | 4.2 (3.9–6.2)                       | 4.4 (3.5–4.8)                        | 4.6 (3.8–5.2)                        | 5.1 (4.3–5.8)                    | 0.02 |
| RV basal diameter| 39 (35–43)         | 39 (34–45)                          | 39 (33–42)                           | 40 (34–43)                           | 38 (35–44)                       | 0.80 |
| RV FS            | 42 (39–46)         | 40 (35–45)                          | 40 (37–41)                           | 44 (40–46)                           | 45 (36–48)                       | <0.001 |
| TAPSE            | 19 (17–21)         | 19 (17–21)                          | 18 (17–20)                           | 20 (18–22)                           | 19 (16–20)                       | 0.02 |
| RV S wave        | 12 (11–13)         | 11 (12–16)                          | 12 (10–13)                           | 12 (11–13)                           | 12 (10–12)                       | 0.14 |
| TAPSE/PASP ratio | .6 (.45–.77)       | .59 (.5–.65)                        | .56 (.44–.63)                        | .70 (.56–.92)                       | .46 (.23–.64)                    | <0.001 |
| E/e′ ratio       | 8.7 (5.7–12)       | 5 (4.1–8.2)                         | 8.5 (5.5–9.6)                        | 8.1 (6–13)                           | 12 (6.5–13.8)                    | <0.001 |
| E/A ratio        | 1 (0.8–1.4)        | .73 (.6–1.1)                        | .9 (.7–1.1)                          | 1.1 (0.8–1.4)                       | 1.2 (0.8–1.4)                    | 0.01 |
| LUS score        | 17 (13–22)         | 20 (17–22)                          | 19 (16–22)                           | 17 (16–21)                           | 14 (12–21)                       | 0.23 |
| PASP             | 30 (25–37)         | 32 (30–50)                          | 30 (30–37)                           | 28 (24–33)                           | 37 (29–43)                       | 0.02 |
| PAAT             | 90 (78–98)         | 78 (68–90)                          | 84 (77–97)                           | 92 (85–98)                           | 89 (78–98)                       | 0.06 |
| IVC diameter (max)| 18 (16–20)        | 17 (16–20)                          | 19 (17–21)                           | 18 (15–21)                           | 17 (16–20)                       | 0.42 |
| IVC diameter (min)| 13 (10–16)        | 11 (10–14)                          | 11 (9–14)                            | 12 (10–15)                           | 14 (11–17)                       | 0.03 |
| IVC distensibility| 37.5 (16.6–63.6)  | 40.8 (33.3–60)                      | 50 (32.1–72.7)                       | 40 (20–75)                           | 45 (9.4–43.5)                    | <0.001 |

Abbreviations: LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MAPSE, mitral annular plane systolic excursion; LVOT VTI, left ventricular outflow tract velocity-time integral; SV, stroke volume; CO, cardiac output; RV, right ventricular; FS, fractional shortening; TAPSE, tricuspid annular plane systolic excursion; S wave, peak systolic tissue velocity at the tricuspid annulus; LUS, lung ultrasound; PASP, pulmonary artery systolic pressure; PAat, pulmonary acceleration time; IVC, inferior vena cava.

Normal values: LVDD: < 55 mm; LVEF: ≥ 50%; MAPSE: ≥ 13 mm; LVOT VTI: 18–22 cm; SV: 60–100 ml/beat; CO: 4–8 L/min; RV basal diameter: ≤ 41 mm; FS: ≥ 35%; TAPSE: ≥ 17 mm; S wave: ≥ 9.5 cm/seg; TAPSE/PASP ratio: < .31 mm Hg; E/e′ ratio: < 14; E/A ratio: > 2; PASP: < 35 mm Hg; PAAT: > 106 mseg; IVC diameter (max): < 21 mm; IVC distensibility: > 18%.

artery acceleration time (PAAT) was 90 msec, and 162 patients (91%) demonstrated values < 106 msec (Tables 3 and 4).

3.5 | LV function

The median LV diastolic diameter (LVDD), LV outflow tract, velocity-time index, cardiac output, LV ejection fraction (LVEF), and mitral annular plane systolic excursion (MAPSE) were within normal ranges, independent of the PaO$_2$/FiO$_2$ value (Table 3). Twenty-seven patients (13.2%) demonstrated an LVDD of > 55 mm, 33 (17.5%) had a LVEF of < 50%, and 46 (27.5%) had a MAPSE of < 13 mm (Table 4). Regional wall motion abnormalities were observed in 18 patients (8.8%), with hypokinesia being more frequent in the inferior, anterior, and inferolateral segments (Table 3).

3.6 | Valve disease

Twenty-three patients (12.6%) had valvular heart disease: eight with mild mitral regurgitation; 12 with mild tricuspid regurgitation; three with moderate aortic regurgitation; one with moderate tricuspid regurgitation; one with prosthetic mitral valve dysfunction; and one with moderate aortic stenosis.

3.7 | Pericardium

Sixteen patients (8.4%) had pericardial effusion (Table 3). Two patients had a final diagnosis of cardiac tamponade.

3.8 | Lung ultrasonography

An average LUS score of 17 points was documented (Table 3), without any statistically significant difference between different PaO$_2$/FiO$_2$ groups (p = 0.22). PASP ≥ 35 mm Hg and a TAPSE/PASP ratio of < 0.31 were associated with a trend in augmentation according to LUS score (OR 1.11, p = 0.70; OR 4.11, p = 0.07, respectively).

3.9 | Other hemodynamic parameters

Considering diastolic function, the median of the E/e′ ratio was 8.7, with 31 patients (18.9%) demonstrating values of > 14. The median
TABLE 3  Description of echocardiographic parameters

| Variable                  | Total n(%) | PaO₂/FiO₂ > 300 n(%) | PaO₂/FiO₂ 300–200 n(%) | PaO₂/FiO₂ 200–100 n(%) | PaO₂/FiO₂ < 100 n(%) | p  |
|---------------------------|------------|-----------------------|-------------------------|------------------------|---------------------|----|
|                    |            |                       |                         |                        |                     |    |
| LVDD                  | 27 (13.2)  | 0                     | 3 (10)                  | 12 (12.2)              | 12 (19.3)           | 0.21|
| LVEF                   | 33 (17.5)  | 4 (12.1)              | 8 (24.2)                | 14 (42.4)              | 7 (21.2)            | 0.24|
| MAPSE                  | 46 (27.5)  | 4 (8.7)               | 10 (21.7)               | 24 (52.2)              | 8 (17.4)            | 0.39|
| RV basal diameter      | 69 (37.5)  | 6 (8.7)               | 9 (13)                  | 34 (49.3)              | 20 (29)             | 0.87|
| RV FS                  | 22 (11.9)  | 2 (9.1)               | 4 (18.2)                | 7 (31.8)               | 9 (40.9)            | 0.32|
| TAPSE                  | 33 (17.1)  | 3 (9.1)               | 4 (12.1)                | 8 (24.2)               | 18 (54.5)           | <0.001|
| RV S wave              | 26 (13.5)  | 2 (7.7)               | 6 (23.1)                | 12 (46.1)              | 0.03                |    |
| TAPSE/PASP ratio       | 14 (11.0)  | 2 (14.3)              | 0                      | 2 (14.3)               | 10 (71.4)           | <0.001|
| E/e ratio              | 31 (18.9)  | 0                     | 2 (6.4)                 | 17 (54.8)              | 12 (38.7)           | 0.10|
| E/A ratio              | 43 (21.1)  | 9 (64.3)              | 15 (56.7)               | 46 (46.9)              | 47 (75.8)           | <0.001|
| PASP                   | 119 (58.3) | 2 (14.3)              | 5 (16.7)                | 19 (19.4)              | 17 (27.4)           | 0.54|
| PAAT                   | 162 (91)   | 12 (7.4)              | 21 (48.1)               | 78 (48.1)              | 51 (31.5)           | 0.25|
| IVC diameter (max)     | 45 (23.9)  | 2 (4.4)               | 8 (17.8)                | 25 (55.6)              | 10 (22.2)           | 0.47|
| IVC distensibility     | 130 (72.6) | 12 (9.2)              | 23 (17.7)               | 65 (50)                | 30 (23.1)           | 0.04|
| Anterior hypokinesia   | 15 (7.9)   | 4 (28.6)              | 5 (16.7)                | 5 (5.6)                | 1 (1.8)             | <0.001|
| Anterior dyskinesia    | 1 (.5)     | 0                     | 1 (3.3)                 | 0                      | 0                   | 0.001|
| Inferior hypokinesia   | 17 (9)     | 4 (28.6)              | 7 (23.3)                | 5 (5.6)                | 1 (1.8)             | <0.001|
| Anteroseptal hypokinesia | 14 (7.4)  | 3 (21.4)              | 6 (20)                  | 4 (4.4)                | 1 (1.8)             | <0.001|
| Inferolateral hypokinesia | 13 (6.9)  | 3 (21.4)              | 5 (16.7)                | 4 (4.4)                | 1 (1.8)             | 0.01|
| Anterolateral hypokinesia | 14 (7.4)  | 3 (21.4)              | 6 (20)                  | 4 (4.4)                | 1 (1.8)             | <0.001|
| Inferoseptal hypokinesia | 13 (6.9)  | 3 (21.4)              | 5 (16.7)                | 4 (4.4)                | 1 (1.8)             | 0.01|
| PE                     | 16 (8.4)   | 1 (7.7)               | 1 (3.4)                 | 10 (10.7)              | 4 (7.3)             | 0.69|
| Valvular diseases      | 23 (12.6)  | 3 (21.4)              | 6 (20)                  | 12 (13.5)              | 2 (4)               | 0.06|

Values out of range.

Abbreviations: LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MAPSE, mitral annular plane systolic excursion; LVOT VTI, left ventricular outflow tract velocity-time integral; SV, stroke volume; CO, cardiac output; RV, right ventricular; FS, fractional shortening; TAPSE, tricuspid annular plane systolic excursion; S wave, peak systolic tissue velocity at the tricuspid annulus; LUS, lung ultrasound; PASP, pulmonary artery systolic pressure; PAAT, pulmonary acceleration time; IVC, inferior vena cava; PE, pericardial effusion.

Normal values: LVDD: < 55 mm; LVEF: ≥ 50%; MAPSE: ≥ 13 mm; LVOT VTI: 18–22 cm; SV: 60–100 ml/beat; CO: 4–8 L/min; RV basal diameter: ≤ 41 mm; FS: ≥ 35%; TAPSE: ≥ 17 mm; S wave: ≥ 9.5 cm/seg; TAPSE/PASP ratio: < 0.31; E/e ratio: < 14; E/A ratio: > 2; PASP: < 35 mm Hg; Paat: > 106 mseg; IVC diameter (max): < 21 mm; IVC distensibility: > 18%.

E/A ratio was one, with 43 patients (21.1%) demonstrating values of > 2 (Tables 3 and 4). Considering fluid responsiveness, 130 patients (82.9%) had an inferior vena cava (IVC) distensibility index of > 18% (Table 4).

3.10 Other findings

Pulmonary embolism was diagnosed in 17 patients, cardiac tamponade in two, and Takotsubo syndrome, pneumothorax, right atrium thrombus, ventricular septal defect, pleural effusion, apical aneurysm, and a left atrium thrombus each were found in one patient.

Our multiple logistic regression model for predicting mortality showed that the echocardiographic findings associated with in-hospital death were PASP > 35 mm Hg (OR 3.4, p = 0.01), TAPSE < 17 mm (OR 3.06, p = 0.01), RV S wave < 9.5 (OR 2.4, p = 0.05), and TAPSE/PASP < 0.31 mm/mm Hg (OR 17.8, p = 0.00). Furthermore, the presence of a IVC distensibility > 18% protected against fatal outcomes (OR .3, p = 0.00) (Table 1). Among the clinical variables, a PaO₂ /FiO₂ < 100 (OR 11.1, p = 0.00) and a D-dimer > 500 mg/dl (OR 3.75, p = 0.00) also were associated with in-hospital death.

4 DISCUSSION

Our study highlights not only the elevated rate of dysfunction and dilation of the RV (although less than previously reported) and the alterations in pulmonary hemodynamics, but also the impact on mortality when detected at hospital admission. Routine critical care
ultrasonographic evaluation is essential given the high frequency of CV manifestations in patients presenting with COVID-19 disease. Given the high frequency of refractory hypoxemia using prone position ventilation, these evaluations have been also described during this maneuver. Critical care ultrasonography should be focused to maximize the time at the patient’s bedside to limit exposure to airborne SARS-CoV-2 shedding to protect the staff caring for the patient. One of the main conditions that determine the high mortality and mortality in patients with severe COVID-19 is myocardial involvement and the risk of developing RV dysfunction along with pulmonary hypertension.

The frequency of RV dysfunction and dilation was greater than 10% at hospital admission among these patients, and the elevation of PAP was close to 60%. RV alterations were not closely linked to PaO₂/FiO₂ levels when compared with PAP; which suggests that there could be other pathophysiological phenomena other than just hypoxemia, hypercapnia, and elevated intra-thoracic pressure leading to pulmonary hypertension and an increased RV afterload (all which are related to the severity of pulmonary infection and the high mechanical ventilation parameters required in this group of patients). In our logistic regression model, all the altered RV functional parameters were associated with increased mortality at hospital admission. Thus, the RV FS < 35% (OR 3.4, p = 0.01) showed the greatest trend. In patients with COVID-19, the ability of the RV to maintain ventricular–arterial coupling was limited (established by the TAPSE/PASP ratio of < 0.31). In our study, this was clearly one of the parameters with the highest prediction of mortality. Thus, practically all the patients who presented with this altered parameter died, which suggests that the combination of RV dysfunction associated with pulmonary hypertension could be two independent and simultaneous pathophysiological phenomena. This finding challenges the notion that only pulmonary hypertension generates RV dysfunction in response to increased afterload. Likewise, the high percentage of patients with PaO₂/FiO₂ < 106 msec suggests that there is elevated RV pressure in the context of pressure overload in a non-adapted RV, which reflects its acute clinical presentation. Only a few of our patients (n = 14) had RV–arterial uncoupling but it was more common in the group with PaO₂/FiO₂ < 100 (10 patients), suggesting that this phenomenon could also be linked with the severity of COVID-19 disease; furthermore, lower PaO₂/FiO₂ is related to an increased mortality, which could be related to these hemodynamic phenomena. Another relevant finding was the high rate of fluid responsiveness protecting against death, which suggests that these patients were less overloaded. This has been demonstrated previously with the well-known positive impact on mortality of negative fluid balances in the survival of critically ill patients. The ORACLE protocol, originally designed for rapid and safe hemodynamic and pulmonary evaluation in patients with severe COVID-19 disease, suggested these findings, especially those related to the elevation of PASP, but given the small cohort of patients in the original protocol (n = 84), it failed to fully demonstrate the impact of RV dysfunction, pulmonary hypertension, and the presence of RV–arterial uncoupling elucidated in this research. There is a marked difference in the rate of pulmonary hypertension in our study compared with other investigations, which could be related to the fact that our patients were critically ill, with a higher degree of hypoxemia and clinical severity. In addition, this study was conducted at three centers, where the protocol was applied by intensive care physicians with training in critical care ultrasonography and relevant measurements were obtained in more than 90% of the patients, except in the case of PASP and the TAPSE/PASP ratio. This situation could reflect the difficulty in achieving adequate aligning to obtain tricuspid regurgitation flow in all cases. Regarding the other relevant echocardiographic findings, the presence of low LVEF (< 50%) was present in close to 20% of the patients with a pericardial effusion close to 10%. This was probably related to the myocardial and pericardial inflammatory involvement already described in patients with COVID-19. Elevation of the LV filling pressures (E/e′ > 14) was found in approximately 20% of patients. This could be linked with LV dysfunction or with the fluid overload following the initial aggressive fluid resuscitation usually required in these patients associated with severe sepsis or septic shock status at the hospital admission in this population. Finally, the ORACLE protocol orientated not only the hemodynamic profile and guided resuscitation in the patients, but also established the final diagnosis of a specific CV entity in 24 patients with the most common diagnosis being a pulmonary embolism.

## Study Limitations

The cross-sectional nature of our study precluded the possibility of ascertaining causal relationships but provided some rationale to establish questions about the pathophysiology of COVID-19. Furthermore, our research was conducted at three medical centers. Thus, this protocol should be replicated at other centers to assess its reproducibility. In addition, the parameters that showed higher mortality were

### Table 4: Multiple logistic regression model for prediction of mortality

| Variable               | OR     | p      | 95% CI       |
|------------------------|--------|--------|--------------|
| RV FS < 35%            | 3.40   | 0.01   | 1.25–9.18    |
| TAPSE < 17 mm          | 3.06   | 0.01   | 1.30–7.18    |
| RV S wave < 9.5 cm/s   | 2.40   | 0.05   | 0.99–5.83    |
| TAPSE/PASP ratio < 0.31 mm/mm Hg | 17.87 < 0.001 | 3.70–86.31 |
| PASP > 35 mm Hg        | 5.82   | < 0.001 | 2.84–11.9    |
| IVC distensibility > 18% | .30   | < 0.001 | 0.14–6.4    |
| PaO₂/FiO₂              | 11.1   | < 0.001 | 5.1–24.25    |
| D dimer > 500 ng/ml    | 3.75   | < 0.001 | 1.81–7.76    |
| Troponin I > 40 pg/ml  | 1.55   | 0.30   | 0.67–3.59    |
| Ferritin > 500 ng/ml   | 1.34   | 0.49   | 0.56–3.20    |
| C reactive protein > 70 mg/ml | 1.30   | 0.52   | 0.57–2.92    |
| NT-proBNP > 1000 pg/ml | .66   | 0.31   | .26–1.65     |

Abbreviations: RV, right ventricular; FS, fractional shortening; TAPSE, tricuspid annular plane systolic excursion; S wave, peak systolic tissue velocity at the tricuspid annulus; PASP, pulmonary artery systolic pressure; IVC, inferior vena cava; NT-proBNP, N-terminal B-type natriuretic peptide.
more difficult to quantify than the rest of the echocardiographic variables.

6 CONCLUSIONS

The presence of RV dysfunction, elevated PASP, and a poor RV–arterial coupling at hospital admission in patients with COVID-19 disease conferred a higher risk for in-hospital mortality. Therefore, these conditions should be searched for in a targeted manner to identify those at higher risk, especially in patients with a higher degree of hypoxemia. The ORACLE protocol can help to obtain these parameters quickly and safely at the bedside and is also a tool that—given its ease and versatility—allows most of the echocardiographic parameters to be acquired.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest to disclose.

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