Rapid prognostic stratification using Point of Care ultrasound in critically ill COVID patients: The role of epicardial fat thickness, myocardial injury and age

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ARTICLE INFO

ABSTRACT

Purpose: The burden of critical COVID-19 patients in intensive care units (ICU) demands new tools to stratify patient risk. We aimed to investigate the role of cardiac and lung ultrasound, together with clinical variables, to propose a simple score to help predict short-term mortality in these patients.
Material and methods: We collected clinical and laboratorial data, and a point-of-care cardiac and lung ultrasound was performed in the first 36 h of admission in the ICU.
Results: Out of 78 patients (61 ± 12y-o, 55% male), 33 (42%) died during the hospitalization. Deceased patients were generally older, had worse values for SOFA score, baseline troponin levels, left ventricular ejection fraction (LVEF), LV diastolic function, and increased epicardial fat thickness (EFT), despite a similar prevalence of severe lung ultrasound scores. Based on the multivariable model, we created the POCOVID score, including age (>60 years), myocardial injury (LVEF<50% and/or usTnI>99til), and increased EFT (>0.8 cm). The presence of two out of these three criteria identified patients with almost twice the risk of death.
Conclusions: A higher POCOVID score at ICU admission can be helpful to stratify critical COVID-19 patients with increased in-hospital mortality and to optimize medical resources allocation in more strict-resource settings.

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1. Introduction

The rapid spread and severity of SARS-CoV-2 disease (COVID-19) pandemic has been causing an unbearable burden on people and health systems [1]. The lung injury is the leading complication requiring intensive care for COVID-19 patients, with intensive care units (ICU) mortality reaching 41.6% [2,3]. Worse prognosis with aging could be attributed to a senescent immune system response [4], and the presence of clinical comorbidities. A wider set of risk factors, including cardiac injury [5,6], has been associated with more severe disease [7]. Obesity is particularly relevant for disease severity, as seen in the inverse association between BMI and age in ICU hospitalizations [8]. Beyond the presence of associated comorbidities, potential mechanisms attributed to the obesity effect on COVID-19 severity are the impairment of respiratory mechanics, and a worse immune response in the presence of a pro-inflammatory state [9]. Visceral fat has a high inflammatory activity, which might help triggering the cytokine storm seen in the inflammatory stage [10]. Epicardial adipose tissue is an ectopic fat depot related to total visceral fat [11] and previous studies suggested that EAT volume could be associated with severe forms of COVID and COVID myocarditis [12,13]. However, the integration of all these risk factors is not easily applicable to risk-stratify patients at bedside care.

Point of care ultrasound (POCUS) has demonstrated its usefulness in the intensive care environment. It supports hemodynamic monitoring, lung status evaluation, and procedural assistance [14,15]. The addition of point of care cardiac ultrasound permits cardiac evaluation of selected patients in the ICU, either performed by an echocardiography specialist or by a trained intensive care physician [16]. POCUS is potentially useful in COVID-19 patients admitted to ICU [17], once the bedside execution preclude patient from being transported to the imaging department. Performing a POCUS soon after the ICU admission work-up might provide clinically useful data and predict outcomes [18].

New applicable tools are much required to screen and stratify patients in the demanding and complex COVID-19 setting. In this study, we aimed to investigate the role of cardiac and lung ultrasound, bedside tools already used in ICU, together with clinical variables, to propose a simple score to help predict short-term mortality in critical COVID-19 patients.

2. Materials and methods

2.1. Study population

This study was conducted at the Hospital de Clínicas de Porto Alegre, a teaching hospital from Porto Alegre, Brazil, which was designated and prepared by the public health system as a reference center for critical COVID-19 cases requiring hospitalization or intensive care during the pandemic. It was also approved by institutional review board (IRB approval: 2020–0186), following national and international good clinical practice regulation. Due to the severity of the included cases, an electronic informed consent was obtained from close relatives or health care proxies of all included patients. The informed consent process was applied via digital communication systems and telephone support, following the hospital visiting restrictions to minimize exposure risk among relatives and health care professionals.

We included patients referred to the hospital, who required intensive care support and had a positive polymerase chain reaction test for COVID-19 and a clinical course compatible with COVID-19 diagnosis, as a convenience sample. Patients were prospectively included in the study from January to September 2020, period corresponding to the first coronavirus transmission outbreak in the community. Patients were followed up from admission time to hospital discharge or death.

The predefined endpoint of our study was in-hospital mortality. Also, we analyzed the days in need of mechanical ventilation, days in the ICU, and Sequential Organ Failure Assessment (SOFA) scores variation in the first ten days from admission.

2.2. Point of care ultrasound analysis

After being clinically stabilized, patients were submitted to the study interventions, which consisted of a limited point-of-care cardiac and lung ultrasound, performed in the first 36 h of admission by the intensive care resident researchers (M.M. and F.C.). Cine and static images were acquired and recorded following a predefined acquisition protocol and later transmitted for off-line analysis. Alarming ultrasound findings were immediately reported to the attending physician following institutional protocol, and clinical management and additional ancillary tests were ordered at the discretion of the attending physician.

Exams were performed using a Philips Envisor C Version C1.5 (Phillips, Amsterdam, Netherlands) and a GE Vivid 3 Pro GE (Healthcare, Chicago, IL, USA) ultrasound machines, equipped with adult sectorial and convex transducers. Lung ultrasound images were acquired with the convex transducer at the 12 pre-determined anatomical regions, and the lung ultrasound score (LUS) was later applied. A 0 to 3-point scale was attributed to each of the 12 segments (total score ranging from 0 to 36), using the following coding according to the ultrasound pattern: normal = 0, well-defined B-lines = 1, coalescent B-lines = 2, consolidation = 3 [15]. The point-of-care cardiac ultrasound consisted of: cine loops of bidimensional paraesternal longitudinal and short-axis views; four- and two-chambers apical views (all with and without color Doppler recordings); M-mode recordings for mitral and tricuspid annular excursion measurement; spectral pulsed Doppler of left ventricular outflow tract and mitral inflow; mitral and tricuspid annular tissue Doppler velocities; and spectral continuous Doppler of mitral and tricuspid regurgitant jets whenever identified. Incomplete acquisition due to technical limitation or suboptimal image quality was indicated on the exam sheet by the researcher.

A single trained echocardiographer (E.G.P.) evaluated qualitatively the cardiac ultrasound findings and performed all measurements from the recorded images, using a dedicated workstation (CPA 10.7.8; TomTec Imaging Systems, Unterschleißheim, Germany). The off-line reading included the assessment of left ventricular (LV) dimensions, and systolic function (global systolic function, regional contractility abnormalities, ejection fraction, mitral annular plane systolic excursion - MAPSE, and left ventricular outflow tract time velocity integral - LVOT-TVI), LV diastolic function (peak velocities of mitral E and A waves, mitral annular tissue Doppler e' wave peak velocity, E/A and E/e' ratios), right ventricular (RV) dimensions and global systolic function (tricuspid annular plane systolic excursion - TAPSE; and fractional area change - FAC), pulmonary artery systolic pressure estimated by peak systolic tricuspid regurgitant jet velocity, or indirect signs of pulmonary hypertension and RV strain, left atrial (LA) and right atrial (RA) enlargement, qualitative assessment of mild, moderate or severe regurgitant or stenotic valvular lesions, pericardial effusion, and epicardial fat thickness (EFT) at longitudinal paraesternal views [11].

2.3. Clinical correlates

Demographic and clinical data were collected from electronic medical records. Available laboratorial data such as hemogram, ultra-sensitive Troponin I (usTnI), D-dimer, C-reactive protein, electrolytes, and renal function were collected at baseline, and also the highest value of usTnI and C-reactive protein during the ICU stay. Baseline global multisystemic impairment at baseline was assessed by SOFA [19] and the Simplified Acute Physiology Score III (SAPS 3) scores [20].

2.4. Statistical analysis

Data were reported as mean ± standard deviation for normally distributed variables or median [interquartile range] for skewed distributed variables. Categorical variables were reported as N and prevalence. Associations among baseline characteristics, biomarkers, POCOVID score variables and predefined endpoints were compared using Student *t*-test, Wilcoxon or Qui-squared test when appropriate.

To identify the independent covariates for mortality, a reduced set of potential predictors variables was selected *a priori* including patient demographics, biomarkers and comorbidity conditions associated with COVID-19 prognosis, preferentially as categorized variables. The cut-off for categorical variables was chosen based on their clinical relevance for COVID-19 prognosis: age > 60 years (determined from the receiver operating characteristic (ROC) curve); BMI > 30 Kg/m^2 as the definition of obesity; cardiac injury defined as reduced left ventricular ejection fraction (LVEF <50%) and/or usTnI above the 99th percentile upper reference limit; and a EFT >0.8 cm, corresponding to increased epicardial adipose tissue (EAT) in the general population [11].

The variables were chosen to construct the POCOVID score focusing on parsimony and accuracy, estimated with ROC curves. The beta coefficients for each independent variable were rounded up to the closest integer and summed up. This model was tested using a bootstrap technique with 5000 bootstrap resamples.

The score performance was later tested in a time to event analysis using Cox proportional hazard models. Also, survival curves were plotted using the Kaplan-Meier method and compared between patients with lower *vs* higher POCOVID score using the log-rank test.

Analyses were performed in STATA 12.0, and *p*-values <0.05 were considered statistically significant.

3. Results

Along the period, we included in the research 78 (12%) out of 634 ICU hospitalizations of COVID patients, and the patient accrual was based on availability of staff and resources, which was affected by epidemic demands and institutional policies, thus representing a

nonconsecutive convenience sample. We were able to assume that the studied sample was representative of the pre-specified population of interest, supported by administrative anonymized data available from all the 634 hospitalizations, demonstrating that patients' demographics (59 ± 15 years old; 57% male) and mortality (259 out of 634; 41%) were similar to the studied patients.

The population included in the study was aged 61 ± 12 years, 43 (55%) were male, and the most common comorbidities were hypertension (60%), diabetes (46%), and obesity (49%). Thirty-three (42%) studied patients died during the hospitalization and 67 (86%) received mechanical ventilation. Deceased patients were generally older, had worse SOFA scores, higher baseline cardiac troponin levels, but did not differ from the alive group regarding baseline C-reactive protein or D-dimer levels (Table 1).

Some cardiac ultrasound abnormalities were more prevalent among the deceased, including reduced LVEF, LV diastolic dysfunction, and increased EFT. The deceased group had more B-lines in lung ultrasound, but the prevalence of severe lung ultrasound score (B lines >18) did not differ (Table 2).

The univariate and multivariate analyzes were summarized in Table 3. Based on these predictors, we created the POCOVID score. As the first step, we used the sum of B- coefficient of each independent predictor to construct the model AUC = 0.747 (0.64–0.86). Then, we created a simplified model summing one point for each predictor. This simplified POCOVID score (Fig. 1) presented an AUC of 0.741 (0.64–0.84), which did not statistically differ from the complete model (Fig. 2). In summary, critical COVID-19 patients that were older than 60, with elevated troponin and/or LV dysfunction, and increased EFT obtained, evaluated by POCUS soon after the ICU admission, represented the group with the highest in-hospital mortality.

The Kaplan-Meier survival curves for the primary outcome based on the POCOVID score showed that those with POCOVID score of 2 or 3 out of 3 points had a worse survival estimation (log rank $p = 0.0471$; Fig. 3),

their mortality was almost twice than those with POCOVID score of 0 or 1 (66% *vs* 34% $p = 0.001$).

The median length stay in ICU was 17 [8–28] days, requiring mechanical ventilation for 14 [5–25] days: 14 [7–27] days for those with low POCOVID score and 19 [12–29] days for high POCOVID score ($p = 0.3$). The median SOFA score at baseline among the 31 (51%) alive patients was 9 [8–11] showing a ten-day reduction in their SOFA scores of 3 [0–5] points. Low POCOVID score patients showed more 10-day improvement in their SOFA scores compared to high POCOVID score (-2 [-4–1] *vs* 0 [-2; 2]; $P = 0.046$).

4. Discussion

We were able to identify a minimal set of variables more likely to identify critical COVID-19 patients with an ominous clinical course. Patients presenting two or more of the following risk factors identified at ICU admission aided by a point-of-care ultrasound, defined as the POCOVID score (age > 60 years, cardiac injury, and increased epicardial fat thickness), had almost twice the mortality rate than those who had none or only one of these risk factors.

The COVID-19 patients' mortality requiring ICU assistance is very high, and simple and quick patient stratification may help to optimize patient care. This is particularly sensitive during COVID-19 pandemic, in which efficient allocation of resources can be crucial for patient care and hospital management. Notably, the mortality rates in our institution were similar to the previously reported in a meta-analysis that included 10,150 patients from centers across Asia, Europe, and North America [3], but lower than the numbers recently published from a Brazilian analysis (hospital mortality in the Southern Brazil was 55.5%) [21]. Despite originating from a reference hospital, these numbers suggest the characteristics of our sample are likely to be representative of a wide range of medical institutions involved in COVID-19 care during the pandemic.

Table 1
Baseline clinical characteristics and biomarkers of patients hospitalized in ICU due to critical COVID-19 ($n = 78$).

	All patients	Deceased ($n = 33$; 42%)	Alive ($n = 45$; 58%)	p-value
Age (years)	61 ± 12	64 ± 11	58 ± 13	0.03
Male	43 (55%)	21 (49%)	22 (51%)	0.20
Female	35 (45%)	12 (34%)	23 (66%)	
Weight (kg)	85.3 ± 19.6	84.2 ± 20.6	86.2 ± 19.1	0.67
Height (m)	1.65 ± 0.09	1.64 ± 0.09	1.66 ± 0.10	0.46
BMI (kg/m^2)	31.5 ± 7.5	31.3 ± 7.3	31.6 ± 7.7	0.85
BSA (m^2)	1.97 ± 0.24	1.95 ± 0.26	1.98 ± 0.24	0.56
SAPS 3	55.8 ± 12.1	58.3 ± 11.4	53.9 ± 12.5	0.11
SOFA	9.0 ± 3.4	9.9 ± 2.4	8.3 ± 3.9	0.02
Comorbidities				
Hypertension	47 (60%)	22 (67%)	25 (56%)	0.32
Diabetes mellitus	36 (46%)	19 (58%)	17 (38%)	0.08
Obesity (BMI >30 kg/m^2)	38 (49%)	18 (55%)	20 (44%)	0.38
Heart Failure	6 (8%)	2 (6%)	4 (9%)	0.64
Coronary Heart Disease	7 (9%)	5 (15%)	2 (4%)	0.10
Tobacco use	23 (29%)	10 (30%)	13 (29%)	0.89
Asthma	5 (6%)	1 (3%)	4 (9%)	0.30
Immunocompromised	5 (6%)	2 (6%)	3 (7%)	0.91
Chronic Kidney Disease	2 (3%)	1 (3%)	1 (2%)	0.82
Biomarkers				
us Troponin I (ng/mL)				
Baseline (n = 69)	33 [1;210]	88 [15;541]	15 [1;107]	0.02
Peak (n = 73)	34 [12;249]	124 [19;562]	16 [1;107]	0.007
C-reactive protein (mg/L)				
Baseline (n = 76)	165 [123;226]	166 [127;218]	165 [123;250]	0.97
Peak (n = 77)	262 [168;330]	295 [243;372]	223 [131;297]	0.001
D-dimer (ug/mL)				
Baseline (n = 76)	2.1 [0.9;5.3]	2.1 [1.1;4.7]	2.1 [0.8;5.6]	0.62

BMI: body mass index; BSA: body surface area; SAPS: Simplified Acute Physiology Score; SOFA Sequential Organ Failure Assessment.
Values noted as N (%), mean ± SD, or median [interquartile range].

Table 2

POint-of-care COVID-19 focused cardiac and lung ultrasound findings in patients hospitalized in ICU due to critical COVID-19 (N = 78).

	All patients	Deceased (n = 33; 42%)	Alive (n = 45; 58%)	p-value
LV diastolic diameter (cm) (n = 78)	4.7 ± 0.6	4.7 ± 0.6	4.7 ± 0.5	0.92
LV systolic diameter (cm) (n = 78)	3.2 ± 0.6	3.2 ± 0.6	3.2 ± 0.6	0.80
Septal thickness (cm) (n = 78)	1.0 ± 0.2	1.0 ± 0.1	1.0 ± 0.2	0.39
LV post. Wall thickness (cm) (n = 78)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.99
MAPSE (cm) (n = 52)	1.6 ± 0.3	1.5 ± 0.3	1.7 ± 0.3	0.08
LVOT TVI (cm) (n = 59)	20.5 ± 6.4	19.1 ± 5.7	21.8 ± 6.8	0.10
RV basal diameter (cm) (n = 78)	3.6 ± 0.4	3.5 ± 0.5	3.6 ± 0.3	0.44
RV FAC (%) (n = 76)	42.4 ± 6.5	42.4 ± 6.1	42.5 ± 6.9	0.95
TAPSE (cm) (n = 63)	2.2 ± 0.4	2.1 ± 0.4	2.2 ± 0.4	0.12
E/A (n = 66)	1.2 ± 0.4	1.1 ± 0.5	1.2 ± 0.4	0.60
e´ (cm/s) (n = 56)	7.9 ± 2.6	7.0 ± 2.1	8.4 ± 2.7	0.047
E/e´ (n = 56)	11.2 ± 5.5	12.9 ± 6.3	10.2 ± 4.8	0.09
LV dilation (n = 78)	7 (9%)	3 (9%)	4 (9%)	0.97
Reduced LV EF (<50%) (n = 78)	9 (12%)	7 (22%)	2 (4%)	0.022
LV Diastolic dysfunction (n = 54)	19 (35%)	11 (55%)	8 (24%)	0.035
RV dilation (n = 78)	12 (15%)	4 (12%)	8 (17%)	0.49
RV dysfunction (n = 77)	6 (8%)	2 (6%)	4 (9%)	0.62
LA dilation (n = 78)	25 (32%)	10 (31%)	15 (33%)	0.78
RA dilation (n = 78)	9 (12%)	3 (9%)	6 (13%)	0.56
EFT >0.8 cm (n = 76)	18 (24%)	12 (37%)	6 (14%)	0.016
CVP > 8 mmHg (n = 32)	13 (41%)	7 (39%)	6 (43%)	0.51
Pericardium effusion (n = 76)	19 (25%)	11 (34%)	8 (18%)	0.14
Lung ultrasound B-lines (n = 69)	16.2 ± 5.4	18.2 ± 4.7	14.7 ± 5.4	0.005
Lung ultrasound B-lines >18 (n = 69)	25 (36%)	12 (40%)	13 (33%)	0.57

LV: left ventricular; MAPSE: mitral annular plane systolic excursion; LVOT TVI: left ventricular outflow tract time velocity integral; RV:Right ventricular; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; EFT: epicardial fat thickness; CVP: central venous pressure.
Values noted as N (%), mean ± SD, or median [interquartile range].

There is already a large body of evidence reinforcing our findings, which state that old age is one of the main determinants of worse prognosis in COVID-19 patients [22]. Although more recent data suggest a higher number of younger patients with critical COVID-19, hospitalizations and disease lethality is highly dependent on age [23].

Despite the detection of myocardial injury based on troponin elevation has been an established risk factor in critical COVID-19 patient [24], this diagnosis based on LV dysfunction by cardiac ultrasound is not a consensus. In a prospective multicenter survey, including 1216 patients, 38% of COVID-19 patients presented LV impairment in the hospital setting [25] and a systematic review showed that most COVID-19 myocarditis has reduced LVEF [26]. However, LV dysfunction cannot be attributed to COVID-19, since preexistent cardiac disease is not adequately documented in a relevant proportion of patients. Jain et al. demonstrated that, despite 35% of the patients have presented LV dysfunction in the hospitalization, only about 10% could be related to COVID-19 [27]. Moreover, myocardial injury could be a consequence of multisystem organ dysfunction and not the primary cause of death.

Epicardial adipose tissue is a well-known ectopic deposit of visceral fat [11] and a marker of cardiovascular disease [28] and cardiac inflammation [29]. It has been proposed that visceral fat is a reservoir of SARS-Cov2, facilitating viral spread and increasing immune response activity [30]. Deng et al. suggested that visceral adiposity is a risk factor for COVID-19 complications in young adults [23]. Then, Iacobelis et al., studying 41 elderly hospitalized COVID-19 patients found differences in EAT density from computed tomography (CT) across the disease severity [31] and Abrishami et al. showed that EAT density was associated with higher mortality (n = 100) [32]. Recently, Grodecki et al. showed that EAT measures from CT were independently associated with extent of pneumonia, clinical deterioration, and death [12], suggesting that this tool may be used in clinical risk stratification. Although thoracic CT is routinely performed in COVID-19 patients, the EAT estimation with EFT measured at bedside cardiac ultrasound may help to estimate the risk profile in patients with critical illness.

An interesting finding that deserves attention is the limited role of lung ultrasound to discriminate patient prognosis. This finding could be attributed to the extension of lung compromise in our critical COVID-19 patients. The main reason for ICU admission was respiratory failure, which is strongly related to the extension of lung involvement

Table 3

Univariate and multivariate analysis of categorical variables in predicting mortality in patients hospitalized in ICU due to critical COVID-19.

	Univariate		Multivariate	
	Odds Ratio	p-value	Odds Ratio	p-value
Age > 60	3.27	0.019	3.93	0.028
Male	1.83	0.198	3.37	0.053
BMI >30 kg/m^2	1.5	0.379	3.25	0.069
Hypertension	1.6	0.323	1.39	0.589
Diabetes	2.24	0.085	1.27	0.682
EFT (>0.8 cm)	3.80	0.019	5.01	0.028
Myocardial Injury*	2.74	0.035	4.98	0.010

BMI: Body Mass Index; EFT: epicardial fat thickness.
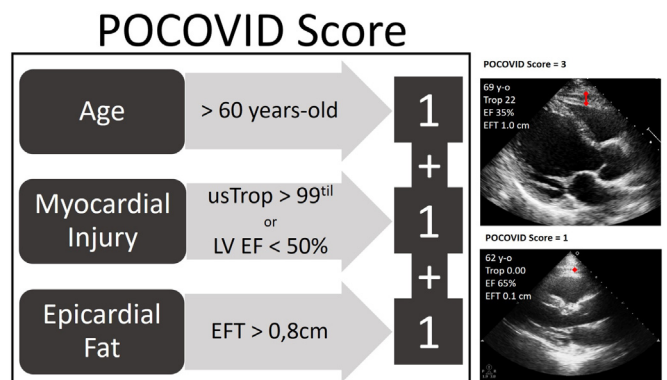* Left Ventricular Ejection Fraction <50% and/or us Troponin I > 99til.
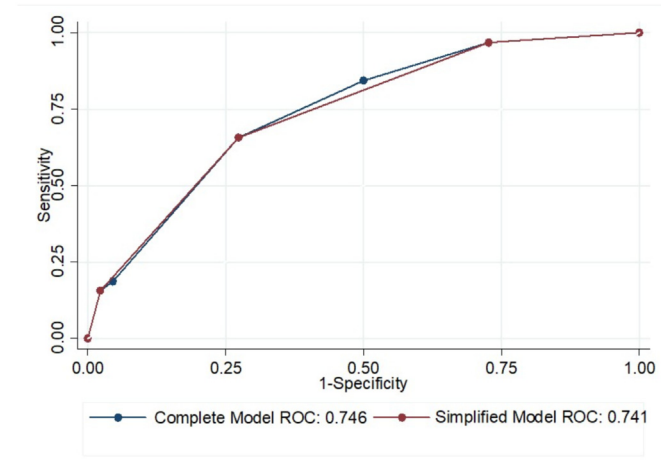

Fig. 1. POCOVID score.

Fig. 2. Receiver-Operating Characteristic curves of POCOVID score for mortality.
Legend: POCOVID Score: Age > 60, epicardial adipose tissue >0.8 cm, us Troponin I > 99til
and/or left ventricular ejection fraction <50%.

by COVID-19, and coincident with the very high LUS in all patients. These findings are consonant with existing literature, suggesting that LUS is more likely to have a role in pre-ICU admission as a tool to estimate lung compromise extension in patients without respiratory failure [33,34]. Similarly, the assessment of patients in the more severe spectrum of the disease may justify the prognostic insensitivity of right ventricular echocardiographic parameters, which have been associated with COVID-19 severity in other studies [25].

To this point, few studies proposed scores that predict clinical outcomes in COVID-19 patients. Some studies included clinical risk factors as predictors of disease progression [35], but do not integrate clinical, laboratorial and ultrasound bedside features into one score [36,37]. This is the first study that includes epicardial fat tissue as a marker of disease activity, giving it a pivotal role of echocardiographic analysis in critical COVID-19.

We acknowledge some study limitations. This was a single study center where the population studied may not reflect the whole spectrum of critical COVID. Moreover, our study completed the inclusion of patients in the early stage of the pandemic period which could
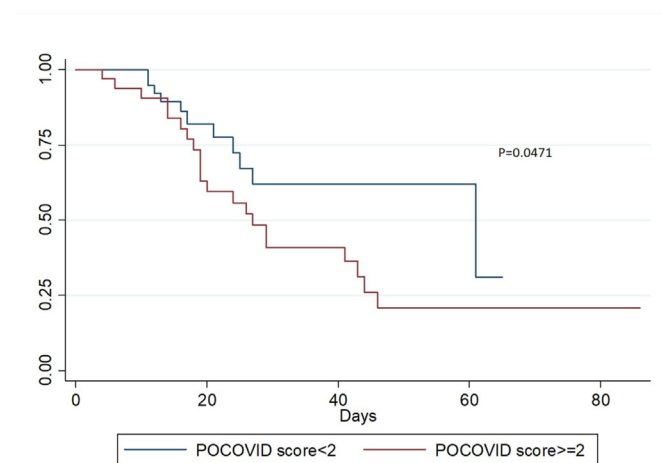

Fig. 3. Mortality during the hospitalization between patients with Low and High POCOVID score.
Legend: POCOVID Score: Age > 60, epicardial adipose tissue >0.8 cm, us Troponin I > 99til
and/or left ventricular ejection fraction <50%.

potentially limit the generalizability of our results in the vaccinated population and in the presence of emergent mutations in COVID-19. These results should be interpreted cautiously due to the relatively small sample size and pending external validation. A potential limitation is that bedside ultrasound image acquisition quality is dependent on examiners' skills, and it is expected technically difficult due to patient's body habitus, positioning, and ICU complex support equipment. This could lead to an increased proportion of non-diagnostic exams. However, that does not seem to be a serious limitation, as our data were acquired by two examiners, still in ICU training, who were not echocardiographers.

5. Conclusion

Performing a point-of-care COVID focused ultrasound at ICU admission adds prognostic information in critical COVID-19. A high POCOVID score, showing 2 out of 3 points, including older age, myocardial injury, and increased epicardial fat thickness, can be helpful to identify a subgroup of critical COVID-19 patients showing almost twice in-hospital mortality. Further replication of these results in other settings could represent a simple bedside tool, which may be useful to stratify patient risk and to optimize medical resources allocation in more strict-resource settings.

Author's contribution

MM, ABSS and MF were responsible for the conception, design, analysis, and interpretation of data. MM, FCC and EGP performed the data collection. MM, ABSS and MF were responsible for drafting the manuscript. EGP, JASP and FCC were responsible for critically revising the manuscript for important intellectual content. All authors have read and given final approval of the submitted manuscript.

Funding

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

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