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Echocardiographic assessment of the right ventricle and its correlation with patient outcome in acute respiratory distress syndrome

Abstract

Introduction: Acute respiratory distress syndrome (ARDS) is a life-threatening chest disease associated with a poor outcome and increased mortality. It may lead to pulmonary hypertension and, eventually, right ventricular failure. These changes can be investigated by transthoracic echocardiography (TTE) which is considered a non-invasive and cost-effective modality. We studied the role of right ventricular function in the prediction of the severity and mortality in ARDS.

Material and methods: In this observational study, 94 patients suffering from ARDS were subjected to TTE to evaluate the parameters of right ventricular function by measuring tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area change (RV-FAC), myocardial performance index (Tei index), and systolic pulmonary artery pressure (SPAP) to assess their relation to the severity and mortality in ARDS.

Results: TAPSE, SPAP, Tei index, and RV-FAC showed significant differences between survivors and non-survivors after 30 days (all $p < 0.001$). An increased length of *intensive care unit* stay was significantly correlated with TAPSE, Tei index, and RV-FAC ($p = 0.002, 0.007$, and 0.013 , respectively). Meanwhile, the length of mechanical ventilation days was significantly correlated with the Tei index only ($p < 0.001$). Multivariate regression analysis found that TAPSE and the Tei index were independent factors affecting mortality ($p = 0.004$, and 0.006 , respectively). RV-FAC, with a cut-off point $\leq 57\%$, had the highest sensitivity, while TAPSE, with a cut-off point ≤ 17 mm, had the highest specificity to predict mortality.

Conclusions: Transthoracic echocardiographic parameters of the right ventricle could be used to predict severity and mortality in patients with ARDS with high sensitivity and specificity.

Key words: acute respiratory distress syndrome, transthoracic echocardiography, tricuspid annular plane systolic excursion, systolic pulmonary artery pressure, fractional area change

Adv Respir Med. 2020; 88: 412–419

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by hypoxemia, non-cardiac alveolar edema, and diminished lung compliance [1]. It varies in both incidence and outcome in the different healthcare facilities, but the incidence of ARDS was estimated to be between 1.5–79 cases per 100000 [2]. Death rates in ARDS are still significant despite management plans implemented by different health organizations; it was estimated to be between 35–45% according to an

international observational study carried out in 50 countries [3].

Although ARDS has circulatory complications such as hypotension, decreased cardiac output, myocardial infarction, and arrhythmias, it mainly affects the right heart [4]. The pathological effect of ARDS on pulmonary vasculature was described more than 30 years ago by the term pulmonary vascular disease (PVD). This term delineates the functional and structural sequences affecting the pulmonary vasculature and the right ventricle (RV) in ARDS [5]. Patients

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DOI: 10.5603/ARM.a2020.0153

Received: 04.03.2020

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ISSN 2451–4934

with PVD may progress to the severe form called acute cor pulmonale, which is classified as right ventricular dysfunction with a high mortality rate 60–70% [6].

Hypoxemia in ARDS is due to diffuse alveolar damage and pulmonary capillary endothelial damage leading to increased permeability of the alveolocapillary membrane and influx of exudate into the alveoli leading to diminished lung compliance [7]. Pulmonary hypertension in ARDS is developed by increased exudate in the alveoli, endothelial dysfunction with superimposed thrombosis in pulmonary capillaries, pulmonary vasoconstriction induced by hypoxemia to redistribute blood flow to ventilated alveoli and limit ventilation perfusion mismatch, and a high PEEP leading to alveolar distension and an increase in the resistance of pulmonary vasculature [8–10]. All these changes lead to right ventricular failure [11].

Pulmonary vascular diseases and right-sided heart failure could be assessed by invasive and noninvasive maneuvers. Most of the research about the function of the RV used invasive techniques such as pulmonary artery catheterization and transesophageal echocardiography (TEE) [12, 13]. However, due to the limited use and availability of these maneuvers in the management of ARDS across most intensive care units (ICUs), a more available screening modality to evaluate the function of the RV in ARDS is needed [14]. Transthoracic echocardiography (TTE) is a noninvasive and cost-effective method that can assess and monitor the right ventricular function [13].

Evaluation of the RV by TTE in ARDS could be done using indices such as systolic pulmonary artery pressure (SPAP), right ventricular fractional area change (RV-FAC), tricuspid annular plane systolic excursion (TAPSE), and myocardial performance index (MPI, Tei index) [15].

Our study aimed to identify the role of right ventricular function using TTE in predicting the mortality in ARDS.

Materials and methods

Patients

We studied 94 adult patients with ARDS criteria according to the Berlin definition. They were admitted between January 2018 and March 2019 to the Critical Care Medicine Department in Alexandria Main University Hospital. All patients were on invasive mechanical ventilation. We excluded patients who were less than 18 years old, had significant mitral or aortic stenosis and/or insufficiency, congestive heart failure, any lung

disease that may affect the right ventricular function and pressure such as interstitial lung diseases and COPD, a poor echocardiographic window, and patients with tricuspid regurgitation. All patients meeting the inclusion and exclusion criteria were enrolled in our study. Informed consent was taken from the next of kin before conducting the study. The study was approved by the ethics committee of our institution.

Data collection

Patients included in the study were classified as survivors and non-survivors according to 30 day mortality. Demographic data, arterial blood gases (ABG) just before the echocardiographic exam, $\text{PaO}_2/\text{FiO}_2$ ratio, Acute Physiology and Chronic Health Evaluation II score (APACHE II), ventilatory data just before the echocardiographic exam (PEEP, plateau pressure, driving pressure), days of mechanical ventilation (MV), and length of intensive care unit (ICU) stay were analyzed between both groups. Furthermore, TTE was done within 48 hours of ARDS diagnosis to assess the right ventricular function parameters which included TAPSE, SPAP, Tei index, and RV-FAC.

Transthoracic echocardiographic data

The following right ventricular function parameters were recorded and measured using the American society of echocardiography 2010 guidelines for right heart assessment in adults [15]:

1. Tricuspid annular plane systolic excursion (TAPSE) was obtained by placing the cursor of M-mode at the lateral border of the tricuspid annulus and calculating the annulus motion longitudinally at peak systole.
2. Right ventricular fractional area change (RV-FAC) was obtained by making a trace along the endocardium of the RV in both relaxation and contraction phases starting at the annulus, passing through apex, and ending back at the annulus in a four chamber view. FAC is calculated as $(\text{end diastolic area} - \text{end systolic area}) \times 100 / (\text{end diastolic area})$.
3. Systolic pulmonary artery pressure (SPAP) can be estimated only in the presence of tricuspid regurgitation. The doppler signal of tricuspid regurgitation was estimated by placing the continuous wave doppler line in line with the tricuspid regurgitation jet. SPAP is calculated using the Bernoulli equation $[4 (V)^2 + \text{right atrial pressure}]$ where V is the velocity of the tricuspid regurgitation jet (in meters per second), and the right atrial

pressure is obtained from central venous pressure (CVP).

4. Myocardial performance index (MPI; Tei index): Tei index is the sum of the isovolumic contraction and the isovolumic relaxation time divided by ejection time, or $[(IVRT + IVCT)/ET]$. For calculation of the Tei index, a pulsed tissue doppler cursor was placed along lateral margin of the tricuspid valve annulus.

Statistical analysis

Mean differences of age, pH, PaO_2/FiO_2 ratio, $PaCO_2$, serum bicarbonate (HCO_3), plateau pressures, PEEP, driving pressures, APACHE II score, TAPSE, RV-FAC, Tei index, and SPAP between survivors and non-survivors were analyzed using the Student t-test. Days of mechanical ventilation and length of ICU stay were analyzed using the Mann Whitney test. The Chi-square test was used to compare between sex, comorbidities, and ARDS classification (mild-moderate-severe) in both groups. The correlation between (TAPSE, RV-FAC, Tei index, SPAP) and (PaO_2/FiO_2 ratio, MV days, length of ICU stay) was evaluated using Pearson coefficients. The multivariate logistic regression model was used to assess the effect of covariates on mortality. Agreement (sensitivity, specificity) for PaO_2/FiO_2 ratio, APACHE II score, and echocardiographic right ventricular parameters were calculated to predict mortality. The results were analyzed using the IBM SPSS software package (version 20.0). Sample size calculation was done by the Community Medicine Department in our institution using Epi 7 software for sample size calculation. It was based on a 30% reported mortality rate among ICU-admitted ARDS patients [16] in the Alexandria Main University Hospital which has an average admission of 120 patients every 6 months (based on ICUs statistics). The minimum sample size required to achieve 80% study power and 95% confidence limits was 87 patients.

Results

Patients were classified into 2 groups, survivors (34 patients, 36.2%) and non-survivors (60 patients, 63.8%) according to 30 day mortality. With regards to demographic data, there was a significant difference between both groups regarding age; survivors were younger than non-survivors ($p = 0.045$). The same, however, was not true with regards to sex and the cause of ARDS ($p = 0.092$, 0.261 respectively). The arterial blood gases significantly differed between both groups with

survivors having a higher pH ($p < 0.001$), a lower $PaCO_2$ ($p < 0.001$), and a lower HCO_3 ($p = 0.013$) as compared to non-survivors. The PaO_2/FiO_2 ratio was significantly lower in the non-survivor group compared with the survivor group ($p = 0.006$). There was a significant difference between the two groups in terms of ARDS classification ($p = 0.025$) and APACHE II score as it was lower in survivors than non-survivors ($p < 0.001$) (Table 1).

Regarding the ventilatory parameters in both groups, there were a significant difference with regards to PEEP and plateau and driving pressures ($p < 0.001$). Survivors had lower days of mechanical ventilation compared to non-survivors (3.0 vs 7.5 days, respectively; $p = 0.001$). Also, survivors had a lower length of ICU stay in comparison to non-survivors (5.0 vs 8.0 days, respectively; $p = 0.001$) (Table 1).

Regarding the right ventricular function parameters survivors had a higher RV-FAC compared to non-survivors (57.91 ± 12.89 vs $41.88 \pm 11.70\%$, respectively; $p < 0.001$). TAPSE was significantly higher in survivors in comparison to non-survivors (20.91 ± 3.79 vs 14.12 ± 3.22 mm, respectively; $p < 0.001$). Survivors had a lower SPAP than non-survivors (46.76 ± 6.73 vs 54.65 ± 7.25 mm Hg, respectively; $p < 0.001$). Also, survivors had a lower Tei index compared to non-survivors (45.15 ± 4.48 vs 51.67 ± 5.02 , respectively; $p < 0.001$) (Table 1).

The right ventricular function parameters were analyzed according to their correlation with the severity of ARDS in terms of PaO_2/FiO_2 ratio, days of mechanical ventilation, and length of ICU stay. PaO_2/FiO_2 ratio and length of ICU stay were significantly correlated with RV-FAC, Tei index, and TAPSE, while the length of mechanical ventilation days was significantly correlated with the Tei index only (Table 2).

The association of the echocardiographic parameters of the right ventricle with mortality was further assessed with a logistic regression model using age, PaO_2/FiO_2 ratio, PEEP, RV-FAC, SPAP, Tei index, and TAPSE. Univariate analysis revealed that age, PaO_2/FiO_2 ratio, PEEP, RV-FAC, SPAP, Tei index, and TAPSE were associated with increased hospital mortality in ARDS. Multivariate regression was analyzed to determine which parameters were independently related to mortality and revealed that TAPSE ($p = 0.004$), Tei index ($p = 0.006$), and PEEP ($p = 0.036$) were independently associated with mortality (Table 3).

The ROC curve was used to test the right ventricular function parameters, PaO_2/FiO_2 ratio, and APACHE II score to predict mortality as shown

Table 1. Comparison between survivors and non-survivors of ARDS regarding baseline characteristics and right ventricular function parameters

Characteristics	Survivors (n = 34)	Non-survivors (n = 60)	P value
Age[years] (mean $\pm$ SD)	50.88 $\pm$ 14.99	57.2 $\pm$ 13.28	0.045
Sex [n%]			0.092
Male	22(64.7)	28(46.7)	
Female	12(35.3)	32(53.3)	
Cause of ARDS [n%]			0.261
Pulmonary causes			
Pneumonia	18 (52.9)	32 (53.3)	
Lung contusions	10 (29.4)	13 (21.7)	
Drowning	6 (17.6)	9 (15)	
Extra pulmonary causes			
Pancreatitis	0 (0)	3 (5)	
Intra-abdominal sepsis	0 (0)	2(3.3)	
Postoperative	0 (0)	1 (1.6)	
Diabetes mellitus [n%]	5 (14.7)	10 (16.6)	0.803
Hypertension [n%]	2 (5.8)	3 (5)	^{FE} p=1.00
Chronic kidney disease [n%]	3 (8.8)	6 (10)	^{FE} p=1.00
Liver failure [n%]	1(2.9)	2(3.3)	^{FE} p=1.00
Shock [n%]	4 (11.8)	9 (15)	^{FE} p=1.00
APACHE II (mean $\pm$ SD)	14.76 $\pm$ 4.60	42.57 $\pm$ 12.22	< 0.001
PaO ₂ /FiO ₂ ratio (mean $\pm$ SD)	150.0 $\pm$ 42.69	123.1 $\pm$ 46.19	0.006
ARDS classification [n%]			0.025
Mild	5 (14.7)	7 (11.7)	
Moderate	26 (76.5)	33 (55.0)	
Severe	3 (8.8)	20 (33.3)	
pH (mean $\pm$ SD)	7.43 $\pm$ 0.04	7.30 $\pm$ 0.05	< 0.001
PaCO ₂ [mm Hg] (mean $\pm$ SD)	32.62 $\pm$ 3.03	47.52 $\pm$ 6.29	< 0.001
HCO ₃ [mEq/L] (mean $\pm$ SD)	22.79 $\pm$ 2.28	23.83 $\pm$ 1.66	0.013
Plateau pressure [cmH ₂ O] (mean $\pm$ SD)	27.06 $\pm$ 5.67	34.03 $\pm$ 4.03	< 0.001
PEEP [cmH ₂ O] (mean $\pm$ SD)	12.18 $\pm$ 2.70	14.43 $\pm$ 2.34	< 0.001
Driving pressure [cmH ₂ O] (mean $\pm$ SD)	14.68 $\pm$ 4.92	19.52 $\pm$ 4.40	< 0.001
Days of MV min.–max. (median)	1.0 – 9.0 (3)	1.0 – 10.0 (7.5)	0.001
Length of ICU stay min.–max. (median)	3.0 – 11.0 (5)	3.0 – 10.0 (8)	0.001
RV-FAC [%] (mean $\pm$ SD)	57.91 $\pm$ 12.89	41.88 $\pm$ 11.70	< 0.001
SPAP [mm Hg] (mean $\pm$ SD)	46.76 $\pm$ 6.73	54.65 $\pm$ 7.25	< 0.001
Tei index (MPI) (mean $\pm$ SD)	45.15 $\pm$ 4.48	51.67 $\pm$ 5.02	< 0.001
TAPSE [mm] (mean $\pm$ SD)	20.91 $\pm$ 3.79	14.12 $\pm$ 3.22	< 0.001

P: p value for comparing between the two studied groups, statistically significant at $p \leq 0.05$ (Boldface type).

APACHE II — Acute Physiology Age Chronic Health Evaluation II; ARDS — acute respiratory distress syndrome; HCO₃ — serum bicarbonate; MV — mechanical ventilation; PaCO₂ — partial pressure of carbon dioxide; PEEP — positive end expiratory pressure; RV-FAC — right ventricle fractional area change; SPAP — systolic pulmonary artery pressure; TAPSE — tricuspid annular plane systolic excursion; Tei index (MPI) — myocardial performance index

in Figure 1. It became clear that the APACHE II score with a cutoff point < 24 had the highest sensitivity and specificity to predict mortality in ARDS (AUC 0.984; 95% CI 0.959–1.009) with $p < 0.001$. Regarding right ventricular function

parameters, we found that RV-FAC with a cutoff point $\leq 57\%$ had the highest sensitivity to predict mortality (AUC 0.825; 95% CI 0.732–0.918) with $p < 0.001$, followed by Tei index with a cutoff point > 47 (AUC 0.844; 95% CI 0.765–0.922) with

Table 2. Correlation between right ventricular function parameters with PaO₂/FiO₂ ratio, mechanical ventilation days, and length of ICU stay

Parameters of right ventricular function	PaO ₂ /FiO ₂ ratio		Mechanical ventilation days		Length of ICU stay	
	r	p	r	p	r	p
RV-FAC	0.292	0.004	-0.083	0.427	-0.255	0.013
SPAP	-0.146	0.160	0.048	0.643	0.117	0.260
Tei index (MPI)	-0.256	0.013	0.424	< 0.001	0.274	0.007
TAPSE	0.232	0.025	-0.182	0.079	-0.309	0.002

R: Pearson coefficient, statistically significant at $p \leq 0.05$ (Boldface type).

ICU — intensive care unit; RV-FAC — right ventricle fractional area change; SPAP — systolic pulmonary artery pressure; TAPSE — tricuspid annular plane systolic excursion; Tei index (MPI) — myocardial performance index

Table 3. Univariate and multivariate analysis of the parameters affecting mortality

	Univariate		Multivariate	
	P	OR (95%CI)	p	OR (95%CI)
PaO ₂ /FiO ₂ ratio	0.009	0.987 (0.978–0.997)	0.966	1.001 (0.974–1.028)
PEEP	< 0.001	1.436 (1.180–1.748)	0.036	2.030 (1.047–3.935)
RV-FAC	< 0.001	0.901 (0.862–0.942)	0.138	0.892 (0.767–1.037)
SPAP	< 0.001	1.180 (1.090–1.276)	0.054	1.424 (0.994–2.039)
Tei index (MPI)	< 0.001	1.31 (1.167–1.477)	0.006	1.796 (1.187–2.718)
TAPSE	< 0.001	0.631 (0.532–0.750)	0.004	0.396 (0.211–0.741)
Age	0.041	1.032 (1.001–1.065)	0.110	1.081 (0.983–1.189)

#: all variables with $p < 0.05$ was included in the multivariate, statistically significant at $p \leq 0.05$ (Boldface type).

CI — confidence interval; OR — odd's ratio; RV-FAC — right ventricle fractional area change; SPAP — systolic pulmonary artery pressure; TAPSE — tricuspid annular plane systolic excursion; Tei index (MPI) — myocardial performance index

Figure 1. ROC curve for right ventricular function parameters, APACHE II score, and PaO₂/FiO₂ ratio (HI) to predict mortality in ARDS

Table 4. Agreement (sensitivity, specificity) for right ventricular function parameters, APACHE II score, and PaO₂/FiO₂ ratio to predict mortality in ARDS

	AUC	P	95% CI	Cut off	Sensitivity	Specificity	PPV	NPV
APACHE II	0.984	< 0.001	0.959–1.009	> 24	95.00	97.06	98.3	91.7
TAPSE	0.904	< 0.001	0.844–0.964	≤ 17	83.33	82.35	89.3	73.7
Tei index	0.844	< 0.001	0.765–0.922	> 47	85.0	67.65	82.3	71.9
RV-FAC	0.825	< 0.001	0.732–0.918	≤ 57	91.67	64.71	82.1	81.5
SPAP	0.789	< 0.001	0.695–0.884	> 50	73.33	70.59	81.5	60.0
PaO ₂ /FiO ₂ ratio	0.708	0.001	0.605–0.812	≤ 124	68.33	76.47	83.7	57.8

Statistically significant at $p \leq 0.05$ (Boldface type).

APACHE II — Acute Physiology Age Chronic Health Evaluation II; ARDS — acute respiratory distress syndrome; AUC — area under a curve; CI — confidence intervals; MPI — myocardial performance index; p value — probability value; RV-FAC — right ventricle fractional area change; SPAP — systolic pulmonary artery pressure; TAPSE — tricuspid annular plane systolic excursion;

$p < 0.001$. TAPSE, with a cutoff point ≤ 17 mm, was the most specific right ventricular function parameter to predict mortality (AUC 0.904; 95% CI 0.844–0.964) with $p < 0.001$, followed by SPAP with a cutoff point > 50 mm Hg (AUC 0.789; 95% CI 0.695–0.884) with $p < 0.001$ (Table 4).

Discussion

Regarding demographic data of the patients, we found a significant difference between both groups with regards to age which was similar to the study by Balzer *et al.* who studied predictors of survival in ARDS [17].

In our study, ABG parameters differed significantly between both groups. In the study by Shah *et al.*, they found a significant difference only with regards to pH, which they explained as being a result of their small sample size which limited the ability of their study to reveal the differences among other parameters [18]. Similarly to our study, Osman *et al.*, who studied the prognosis of right ventricular failure in ARDS in a larger sample size than Shah *et al.*, found significant differences between both groups regarding pH and PaCO₂ [19].

We found significant differences between survivors and non-survivors with regards to PaO₂/FiO₂ ratio and APACHE II score. These results were also found in the studies completed by Shah *et al.* and Osman *et al.* [18–19]. Our results were similar to the LUNG SAFE study, which was performed in 459 ICUs in 50 countries, with regards to age, sex, etiology of ARDS, pH, and PaO₂/FiO₂ ratio [20].

In our study, we found significant differences between both studied groups regarding plateau, driving pressures, and PEEP. Claude Guerin *et al.*,

who studied the driving pressure effect on mortality in ARDS patients, also found that plateau and driving pressures were significantly different between survivors and non-survivors [21]. Also, Amato *et al.* found that driving pressure was most strongly associated with survival [22]. However, that was not found in the study conducted by Shah *et al.* as they did not find any significant difference with regards to ventilatory parameters between the studied groups. Again, they explained this result as a drawback of their small sample size [18].

Regarding the indices of right ventricular function, our study showed that survivors and non-survivors differed significantly with regards to TAPSE, Tei index, RV-FAC, and SPAP. In 2 studies by Shah *et al.* and Wadia *et al.*, they found a significant difference between survivors and non-survivors with regards to TAPSE only. This may be due to the sample size of their studies and due to the fact that they did not assess the parameters in all patients due to a poor echocardiographic window which was part of the exclusion criteria in our study [18, 23]. In another study by Adi Aran *et al.* who evaluated the prognostic value of echocardiography in pediatric ARDS, they found a higher mortality rate in patients with right ventricular dysfunction defined by RV-FAC less than 45% [24].

Our study showed that the PaO₂/FiO₂ ratio significantly correlated with RV-FAC, Tei index, and TAPSE. This was a similar finding in the Adi Aran *et al.* study which found a significant correlation between PaO₂/FiO₂ ratio and TAPSE and Tei index, respectively [24]. Also, the significant correlation between PaO₂/FiO₂ ratio and RV-FAC was found in a meta-analysis by Justin Lee *et al.* who concluded that acute hypoxemia mostly

affects systolic function of the right ventricle, which is accurately estimated with RV-FAC [25]. Meanwhile, there was no significant correlation between $\text{PaO}_2/\text{FiO}_2$ ratio and SPAP, and this could be explained by the pathophysiology of hypoxemia-associated pulmonary hypertension which is caused by vascular remodeling rather than hypoxemia-induced arterial narrowing. This results in SPAP being elevated only after a significant period of time [26].

We found a significant correlation between the length of ICU stay with TAPSE and RV-FAC. Gajanana *et al.* studied the association between TAPSE and mortality in the ICU and found a correlation between a prolonged ICU stay and low TAPSE [27]. Also, Vallabhajosyula *et al.* found that a RV-FAC less than 35% was associated with a prolonged ICU stay in comparison with normal right ventricular function in septic patients [28]. Also, we found a significant correlation between the Tei index and the duration of mechanical ventilation. Similarly, El Ashmawy *et al.*, who studied the role of the Tei index in the prediction of weaning failure in COPD patients, found higher Tei index values in patients with failed weaning [29].

Multivariate regression analysis found that TAPSE, Tei index, and PEEP were significant independent factors of mortality. Shah *et al.* found that TAPSE was the only independent factor associated with mortality and this could be explained by their small sample size [19]. We tested agreement for the right ventricular function parameters to predict mortality and found that TAPSE < 17 mm had the highest specificity (82.35%), and that RV-FAC had the highest sensitivity (91.67%). In a study by Tamborini *et al.* involving 750 patients with various heart diseases, a TAPSE value of < 17 mm was highly specific for right ventricular dysfunction but had very low sensitivity [30]. Also, Shah *et al.* found that non-survivors had a TAPSE value of < 17 mm (upper limit of 95% confidence interval: 16.77 mm) [19].

Limitation of the study

Larger sample size studies are needed to increase the power of the study and limit the margin of error. Multicenter studies are needed to improve the external validity and support wide changes in practice.

Conclusions

Transthoracic echocardiographic parameters of the right ventricle could be used to predict

mortality in patients with ARDS with high sensitivity and specificity.

Conflict of interest

The authors have declared no conflict of interest.

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