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Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact

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Abstract *Rationale:* Increased right ventricle (RV) afterload during acute respiratory distress syndrome (ARDS) may induce acute cor pulmonale (ACP). *Objectives:* To determine the prevalence and prognosis of ACP and build a clinical risk score for the early detection of ACP. *Methods:* This was a prospective study in which 752 patients with moderate-to-severe

ARDS receiving protective ventilation were assessed using transesophageal echocardiography in 11 intensive care units. The study cohort was randomly split in a derivation ($n = 502$) and a validation ($n = 250$) cohort.

Measurements and main results: ACP was defined as septal dyskinesia with a dilated RV [end-diastolic RV/left ventricle (LV) area ratio >0.6 (≥ 1 for severe dilatation)]. ACP was found in 164 of the 752 patients (prevalence of 22 %; 95 % confidence interval 19–25 %). In the derivation cohort, the ACP risk score included four variables [pneumonia as a cause of ARDS, driving pressure ≥ 18 cm H₂O, arterial oxygen partial pressure to fractional inspired oxygen (PaO₂/FiO₂) ratio <150 mmHg, and arterial carbon dioxide partial pressure ≥ 48 mmHg]. The ACP risk score had a reasonable discrimination and a good calibration. Hospital mortality did not differ between patients with or without ACP, but it was significantly higher in patients with severe ACP than in the other patients [31/54 (57 %) vs. 291/698 (42 %); $p = 0.03$]. Independent risk factors for hospital mortality included severe ACP along with male gender, age, SAPS II, shock, PaO₂/FiO₂ ratio, respiratory rate, and driving pressure, while prone position was protective.

Conclusions: We report a 22 % prevalence of ACP and a poor outcome of severe ACP. We propose a simple clinical risk score for early identification of ACP that could trigger specific therapeutic strategies to reduce RV afterload.

Keywords ARDS · Right ventricle · Mechanical ventilation · Echocardiography

Introduction

Acute cor pulmonale (ACP) is the most severe presentation of right ventricular (RV) dysfunction due to an acute increase in RV afterload. The diagnosis of ACP relies on echocardiographic findings [1]. Since the landmark study by Zapol et al. [2] describing pulmonary hypertension in patients presenting with acute respiratory distress syndrome (ARDS), it has been shown that the prevalence of ACP during the first 3 days of protective mechanical ventilation ranges between 20 and 25 % [3–5]. ACP may be associated with the level of plateau pressure, driving pressure, or hypercapnia [3–7]. The deleterious impact of ACP on hemodynamics, as uniformly reported in echocardiographic studies [1, 5, 8], has not been consistently associated with a poor clinical outcome [3–5], as opposed to pulmonary vascular dysfunction [9]. Accordingly, identifying ACP at the initial phase of ARDS is of uncertain clinical relevance. If ACP does influence the outcome of ARDS patients, early assessment of RV function would be important to best adapt their management in addition to current therapeutic guidelines mainly based on the arterial oxygen partial pressure to fractional inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio and ventilator settings [10]. For this purpose, a clinical score reflecting the risk of ACP would facilitate the attending physician in selecting patients who require echocardiographic assessment and close monitoring.

In generating the largest collaborative prospective echocardiographic cohort of ARDS patients reported to date, our objective was twofold: first, to determine risk factors associated with ACP and derive a clinical risk score specifically aimed at predicting the probability of early ACP; second, to assess the prognostic value of ACP in a large sample of patients receiving protective ventilation for moderate-to-severe ARDS [11]. This study has been presented in abstract format [12], and approximately two-thirds of the patients have been included in previously reported studies [3–5].

Patients and methods

Patients

We prospectively included patients in the study who had been admitted to 11 French intensive care units (ICU) between 1994 and 2012. The study cohort comprised two-

thirds of patients who have been reported in previously published studies [3–5] and more than 250 additional patients unique to the present study. The protocols were approved by Institutional Review Boards of the participating centers as a component of standard of care. Accordingly, the requirement for patient's consent was waived, and both written and oral information about the protocols were provided to the next-of-kin. Although many patients were included before 2011, all actually met the Berlin definition criteria for moderate-to-severe ARDS [11], with acute respiratory failure within 1 week of a known clinical insult or new or worsening respiratory symptoms; bilateral chest opacities not fully explained by effusions, lobar/lung collapse, nodules, or cardiac failure or fluid overload; a $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 200 mmHg with positive end-expiratory pressure (PEEP) of ≥ 5 cmH₂O [11]. All patients were routinely assessed using trans-esophageal echocardiography (TEE) within the first 3 days following the diagnosis of ARDS. All patients underwent TEE while fulfilling the criteria for moderate-to-severe ARDS, and the TEE data reported here pertain to the first or second TEE. Non-inclusion criteria were contra-indications to TEE examination (esophageal disease or major uncontrolled bleeding) or the presence of a chronic pulmonary disease requiring long-term oxygen therapy or home mechanical ventilation. Severity of illness upon ICU admission was evaluated by the Simplified Acute Physiologic Score (SAPS II) [13]. Shock was defined as the need for catecholamine infusion to maintain adequate arterial pressure [14]. Pneumonia, aspiration, and sepsis were diagnosed as previously described [14–16]. Hospital mortality was recorded.

Respiratory settings and echocardiography

Mechanical ventilation was applied in the volume-assist control mode, with a target tidal volume of 6–8 ml/kg (predicted body weight) and a target plateau pressure (P_{plat}) of <30 cmH₂O. Respiratory rate could be increased in case of high arterial carbon dioxide partial pressure (PaCO_2) level, while avoiding intrinsic PEEP. The use of prone position was left to the discretion of the attending physician, but was typically performed in patients with a $\text{PaO}_2/\text{FiO}_2$ ratio of <100 mmHg and/or an ACP depending on the clinical practice of each participating center. TEE was performed using a multiplane esophageal probe by trained operators who were qualified

in advanced critical care echocardiography, using a standardized procedure [17]. Echocardiographic images were recorded in digital format, and a computer-assisted consensual interpretation was performed off-line by at least two trained senior investigators. ACP was defined as a dilated RV in the mid-esophagus longitudinal view [end-diastolic RV/left ventricle (LV) area ratio >0.6] associated with the presence of a septal dyskinesia in the transgastric short-axis view of the heart [18]. Severe ACP was defined as a severely dilated RV (end-diastolic RV/LV area ratio ≥ 1) with septal dyskinesia. Septal dyskinesia was particularly sought at end-systole, while analyzing loops in slow motion. At the time of TEE, tidal volume, total PEEP, and Pplat (after applying an end-inspiratory pause of 0.5 s) were systematically recorded; driving pressure was calculated as the difference between Pplat and total PEEP, and total respiratory system compliance as tidal volume/driving pressure. Ventilator settings were recorded just before TEE. Blood gas analyses obtained before TEE (last available value on day of TEE) were also recorded.

Statistical analysis

The data were analyzed using the SPSS Base 19.0 statistical software package (IBM Corp., Armonk, NY) and R 2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous data were expressed as the mean \pm standard deviation unless otherwise specified and were compared using the Student *t* test or Mann–Whitney test for independent samples, as appropriate. Categorical variables, expressed as number and percentages, were evaluated using the chi-square test or Fisher exact test. To evaluate independent factors associated with ACP or hospital mortality, significant or marginally significant ($p < 0.20$) bivariate risk factors (using the above-mentioned tests) were examined using univariate and multivariable backward stepwise logistic regression analysis. Coefficients were computed by the method of maximum likelihood. The calibrations of models were assessed by the Hosmer–Lemeshow goodness-of-fit statistic (good fit was defined as a *p* value of >0.05) [19], and discrimination was assessed by the area under the receiver operating characteristics curve (ROC-AUC, with a value of 1 indicating perfect discrimination and a value of 0.5 indicating the effects of chance alone) [20]. The ACP risk score was constructed after splitting the sample into a derivation cohort ($n = 502$) and a validation cohort ($n = 250$) by random sampling, using independent factors recorded before TEE and associated with ACP as candidate variables. For multivariable analyses and ACP risk score, continuous data were converted into categorical variables, with the selection of threshold values based on Youden's method (highest sum sensitivity + specificity). Variables with *p* values of <0.05 by multivariable logistic

regression were retained for inclusion in the ACP risk score. Because the relative contribution of all β parameters was close to each other, equivalent weights were generated for all items of the ACP risk score in keeping with parsimony [21]. Individual patient ACP risk scores were generated and tested in the validation cohort by assessing model calibration and discrimination using the Hosmer–Lemeshow goodness-of-fit statistic and the ROC-AUC, respectively. All tests were two-tailed, and *p* values of <0.05 were considered to be statistically significant.

Results

Risk factors for ACP and ACP risk score

We included 752 patients (507 men and 245 women), with a mean age of 58 ± 16 years and a mean SAPS II at 24 h of ICU admission of 53 ± 21 . Patients received mechanical ventilation with a mean Pplat of 24 ± 5 cmH₂O, a tidal volume of 6.3 ± 1.3 ml/kg, total PEEP of 8 ± 4 cmH₂O, and respiratory rate of 23 ± 6 cycles/min. ACP was detected in 164 patients [prevalence of 22 %; 95 % confidence interval (CI) 19–25 %]. Of the 83 (11 %) patients with a severe RV dilatation, 54 exhibited severe ACP. ARDS was secondary to pneumonia more frequently in patients with ACP than in others (Table 1). Respiratory settings and blood gas values on the day of TEE also differed between groups, with lower values of tidal volume and respiratory system compliance, higher values of Pplat and driving pressure, and a higher degree of hypoxemia and hypercapnia in the ACP group (Table 1). Multivariable logistic regression analysis identified pneumonia as a cause of ARDS, a driving pressure ≥ 18 cm H₂O, PaO₂/FiO₂ ratio <150 mmHg, and PaCO₂ ≥ 48 mmHg as the four independent factors associated with ACP (Table 2). The ACP risk score was developed in the derivation cohort using these “candidate variables” (Table 3). Clinical characteristics and outcome of patients were similar in the derivation and validation cohorts (Electronic Supplementary Material Table S1). The prediction of ACP according to the ACP risk score in the derivation and validation cohorts is described in Fig. 1a, b. The prevalence of ACP for ACP risk scores of 0, 1, 2, 3, and 4 was 7, 10, 19, 35, and 75 % in the derivation cohort and 7, 10, 20, 32, and 73 % in the validation cohort, respectively. A proposal for performing TEE according to ACP risk score is given in Fig. 1c, with the suggestion that TEE could be routinely performed when the ACP risk score is ≥ 2 . In the derivation and validation cohorts, the ACP risk score demonstrated reasonable discrimination (ROC-AUC 0.73; 95 % CI 0.67–0.78; $p < 0.001$ and ROC-AUC 0.70; 95 % CI 0.62–0.78; $p < 0.001$, respectively) and good calibration [χ^2 (3 *df*) = 4.43; $p = 0.22$ and χ^2 (2 *df*) = 0.24; $p = 0.89$, for the Hosmer–Lemeshow goodness of fit test, respectively].

Table 1 Clinical characteristics and outcome of patients having acute respiratory distress syndrome with or without cor pulmonale

	N ^a	All patients (n = 752)	No cor pulmonale (n = 588)	Cor pulmonale (n = 164)	P value
Age (years)	752	58 ± 16	58 ± 17	57 ± 16	0.59
Male gender	752	507 (67 %)	403 (69 %)	104 (63 %)	0.21
SAPS II at 24 h of ICU admission	750	53 ± 21	54 ± 21	50 ± 19	0.06
Cause of ARDS	736				<0.01
Pneumonia		293 (40 %)	200 (35 %)	93 (58 %)	
Aspiration		91 (12 %)	75 (13 %)	16 (10 %)	
Non-pulmonary sepsis		262 (36 %)	228 (40 %)	34 (21 %)	
Other causes		90 (12 %)	73 (13 %)	17 (11 %)	
Respiratory settings at the time of TEE					
Tidal volume (ml/kg)	722	6.8 ± 1.3	6.9 ± 1.3	6.5 ± 1.3	<0.01
Respiratory rate (cycle/min)	717	23 ± 6	22 ± 6	23 ± 6	0.17
PEEP (cmH ₂ O)	730	8 ± 4	8 ± 4	8 ± 4	0.60
Plateau pressure (cmH ₂ O)	719	24 ± 5	24 ± 4	26 ± 5	<0.01
Compliance (ml/cmH ₂ O)	715	32 ± 12	32 ± 12	28 ± 11	<0.01
Driving pressure (cmH ₂ O)	718	16 ± 5	16 ± 5	18 ± 5	<0.01
Arterial blood gases on TEE day ^b					
PaO ₂ /FiO ₂ ratio (mmHg)	748	115 ± 42	118 ± 42	106 ± 40	<0.01
PaCO ₂ (mmHg)	743	47 ± 12	45 ± 11	52 ± 15	<0.01
Shock on TEE day	746	502 (67 %)	389 (67 %)	113 (69 %)	0.53
Prone positioning during ARDS course	752	218 (29 %)	144 (25 %)	74 (45 %)	<0.01
Hospital mortality	752	322 (43 %)	244 (42 %)	78 (48 %)	0.17
MV duration in survivors	464				0.07
Mean days ± SD		18 ± 19	18 ± 20	17 ± 12	
Median days (25th–75th centiles)		12 [8–21]	12 [7–21]	13 [9–23]	

Data are presented as the mean ± standard deviation or as the number with the percentage in parenthesis, as appropriate, unless indicated otherwise

ICU Intensive care unit, MV mechanical ventilation

^a Number of patients with available data

^b Latest available measurement before echocardiography

Table 2 Factors associated with acute cor pulmonale in patients with acute respiratory distress syndrome

Variable	Odds ratio (95 % CI) by logistic regression	
	Univariate	Multivariable ^a
Pneumonia as cause of ARDS	2.54 (1.79–3.62), <i>p</i> < 0.01	2.73 (1.84–4.05), <i>p</i> < 0.01
Respiratory settings on TEE day		
Tidal volume <7 mL/kg	1.70 (1.17–2.47), <i>p</i> < 0.01	I/NR
Respiratory rate ≥30 breaths/min	1.70 (1.11–2.60), <i>p</i> = 0.02	I/NR
Plateau pressure ≥27 cmH ₂ O	1.91 (1.33–2.73), <i>p</i> < 0.01	I/NR
Compliance <30 ml/cmH ₂ O	1.91 (1.33–2.73), <i>p</i> < 0.01	I/NR
Driving pressure ≥18 cmH ₂ O ^b	2.16 (1.51–3.10), <i>p</i> < 0.01	2.28 (1.53–3.38), <i>p</i> < 0.01
Arterial blood gases on TEE day		
PaO ₂ /FiO ₂ ratio <150 mmHg	2.41 (1.49–3.92), <i>p</i> < 0.01	2.60 (1.50–4.52), <i>p</i> < 0.01
PaCO ₂ ≥48 mmHg	2.95 (2.06–4.21), <i>p</i> < 0.01	2.39 (1.62–3.52), <i>p</i> < 0.01

CI confidence interval, ARDS acute respiratory distress syndrome, TEE transesophageal echocardiography, PaO₂/FiO₂ arterial oxygen partial pressure to fractional inspired oxygen ratio, PaCO₂ arterial carbon dioxide partial pressure, I/NR included, but not retained by the final model

^a The multivariable model showed a good calibration as assessed by the Hosmer and Lemeshow goodness of fit test [χ^2 (6 df) = 7.17,

p = 0.31] and a fair discrimination as assessed by the receiver operating characteristics curve [area under the curve (AUC) 0.72; 95 % CI 0.68–0.77; *p* < 0.01]

^b Driving pressure is defined as the difference between plateau pressure and end-expiratory positive pressure

Outcome

Prone positioning was more often used for patients with ACP than for their counterparts [74 (45 %) vs. 144 (25 %); *p* < 0.01]. Hospital mortality was marginally higher in patients with ACP than in those without [78

(48 %) vs. 244 (42 %); *p* = 0.17] and significantly higher in patients with severe ACP than in all other patients [31/54 (57 %) vs. 291/698 (42 %); *p* = 0.03]. Factors associated with hospital mortality by bivariate and multivariable logistic regression are listed in Table 4. Independent risk factors for hospital mortality included

Table 3 The acute cor pulmonale risk score

Parameter	Score
Pneumonia as cause of ARDS	1
Driving pressure ≥ 18 cmH ₂ O ^a	1
PaO ₂ /FiO ₂ ratio <150 mmHg	1
PaCO ₂ ≥ 48 mmHg	1
Total score	0–4

ARDS Acute respiratory distress syndrome

^a Driving pressure is defined as the difference between plateau pressure and total end-expiratory positive pressure. Because the relative contribution of all β parameters was close to each other, equivalent weights were generated for all items of the Score in keeping with parsimony [21]

male gender, age ≥ 58 years, SAPS II at 24 h of ICU admission ≥ 56 points, respiratory rate ≥ 30 cycles/min, driving pressure ≥ 15 cmH₂O, PaO₂/FiO₂ ratio <100 mmHg, severe cor pulmonale and shock on TEE day, while prone positioning during ARDS had a protective effect (Table 4).

Discussion

The results of our prospective study, which is to date the largest series of patients with moderate-to-severe ARDS in whom early echocardiography was routinely performed, confirm that ACP occurs in about one of five patients during the first 3 days of protective mechanical ventilation. A clinical risk score based on four variables (pneumonia as cause of ARDS, driving pressure, PaO₂/FiO₂ ratio, and PaCO₂) had a reasonable discrimination ability and good calibration for detecting early ACP in the derivation and validation cohorts. Severe ACP was associated with increased hospital mortality. The main contribution of our study to research in this area includes the study size, the proposal of a simple and reliable clinical risk score, and examination of the prognostic impact of ACP depending on its severity. In light of recent studies in this field, our finding in this large cohort of an association between driving pressure and the occurrence of ACP is also of major interest.

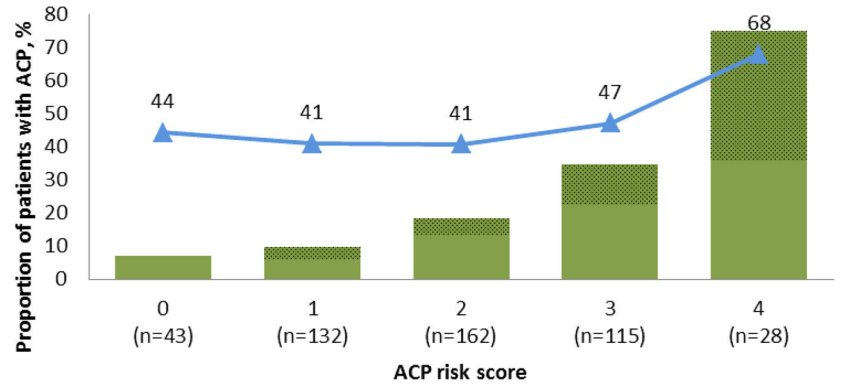
Prior to the widespread use of protective ventilation, ACP was observed in almost 60 % of patients [22]. Our study shows that ACP remains common in the era of protective ventilation, reaching a 22 % prevalence despite a target Pplat of <30 cmH₂O. Chiumello et al. reported a large variability of transpulmonary pressure induced by tidal volume in patients ventilated with Pplat of <30 cmH₂O [23], and Terragni et al. showed that despite the limitation of Pplat, tidal hyperinflation of the normally aerated compartment may still occur in ARDS patients with a larger non-aerated compartment [24]. These results are consistent with our finding that driving pressure was

associated with ACP. In our study, patients were ventilated with a mean PEEP of 8 cmH₂O, a level that could be considered as “low” in patients with moderate-to-severe ARDS and potentially responsible for lung derecruitment. Indeed, Duggan et al. suggested that induction of lung atelectasis impaired RV function in experimental animals, whereas lung recruitment reversed RV dysfunction [25]. A similar mechanism was suggested in a small population of severe ARDS patients who exhibited an inverse relationship between lung recruitment induced by increasing PEEP from 7 to 14 cmH₂O and the related change in RV stroke volume [7]. However, in our large cohort of patients, mean PEEP level was similar in patients with or without ACP. Higher PEEP levels have also been reported to induce hyperinflation in the nondependent areas of the lung [26], a key factor promoting pulmonary hypertension [27].

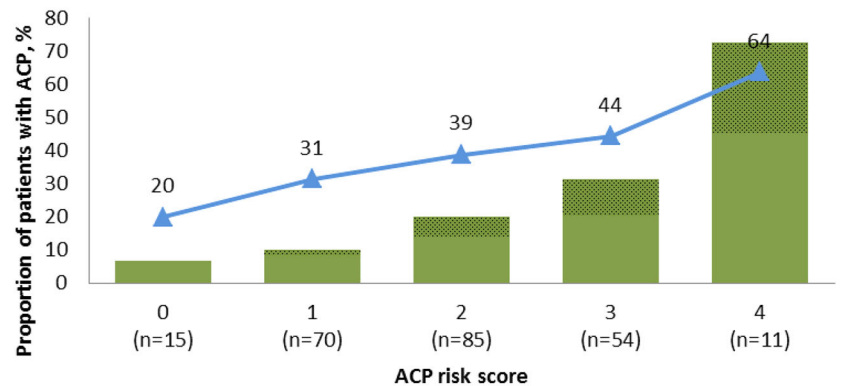
We propose a clinical risk score to select patients at higher risk of ACP that includes four variables: pneumonia as cause of ARDS, driving pressure, PaO₂/FiO₂ ratio, and PaCO₂ level. The effect of pneumonia on ACP may be driven by one of the following hypotheses: (1) pneumonia may induce lung vascular dysfunction via local inflammation and in situ thrombosis; (2) pneumonia and mechanical ventilation may potentiate each other in a double-hit model [28]. The other three risk factors for ACP reflect the ventilatory strategy and lung injury severity. The role of lung injury severity on ACP may explain the consistency of its prevalence over the long time-frame of our study. Driving pressure is used as a surrogate of lung stress related to tidal ventilation. An increase in driving pressure worsens the deleterious effect of lung distension on pulmonary capillaries and, consequently, on RV afterload and function [28, 29]. In our study, a higher driving pressure was a risk factor for both ACP and mortality. Driving pressure was recently reported as the ventilation variable that best stratified the risk of death in a large cohort of ARDS patients [30]. Taken together, these results suggest a potential link between driving pressure, ACP, and mortality. We found that hypercapnia (PaCO₂ ≥ 48 mmHg) was also associated with ACP, which is in line with its known vasoconstrictive effects on pulmonary circulation [31] and with previous reports in ARDS patients [3–5, 7, 8]. Hypercapnia is a consequence of low tidal volume but also reflects alveolar dead space, which has been reported to be associated with mortality in ARDS patients [32, 33]. Finally, a PaO₂/FiO₂ of <150 mmHg was also associated with ACP in our series. This finding may reflect the severity of lung injury and/or the potential role of hypoxic pulmonary hypertension, as suggested in previous animal [34] and human [35] studies of ARDS. A clinical approach to prevent ACP and limit its consequences was recently proposed (“RV protective strategy”) [36]. This strategy, which uses simple tools to set the ventilator in order to limit plateau and driving pressures and avoid

Fig. 1 Prevalence of acute cor pulmonale (ACP) in patients with acute respiratory distress syndrome according to the ACP risk score in the derivation cohort (*upper panel*), validation cohort (*middle panel*), and entire series with a proposal for echocardiography monitoring (*lower panel*). *Stippled parts of bars* denote severe ACP, *solid line with triangles* denote percentage hospital mortality. The ACP risk score could not be computed because of missing data in 22 and 15 patients of the derivation and validation cohorts, respectively

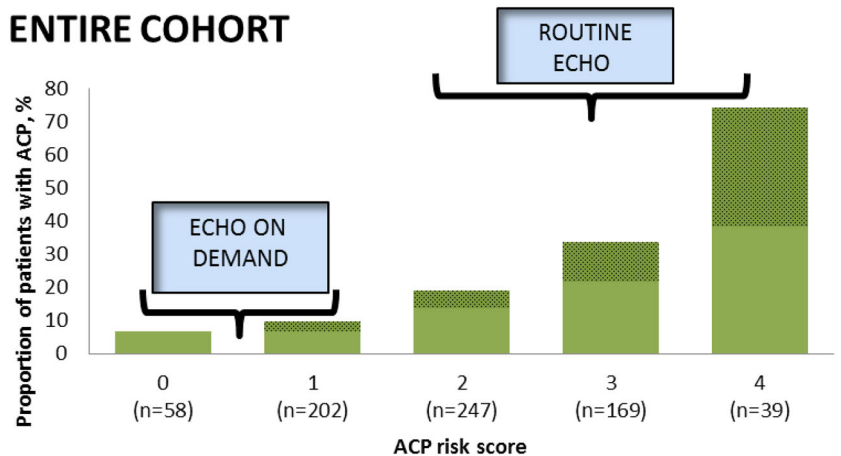
DERIVATION COHORT



VALIDATION COHORT



ENTIRE COHORT



overt hypercapnia, remains to be validated in terms of prognosis. The ACP risk score we propose provides a framework for testing this strategy.

In addition to severe ACP and respiratory parameters (driving pressure, respiratory rate, and severe hypoxemia), age, male gender, SAPS II, and shock were independent risk factors for mortality in our series. The

high prevalence (two-thirds of patients at the time of TEE) and prognostic effect of shock in our series are in line with previous reports in ARDS patients [38, 39]. We also found a protective effect of prone positioning, consistent with the results of the PROSEVA study [40] and with those of previous echocardiography [41] and pulmonary artery catheterization [42] studies showing a

Table 4 Factors associated with hospital mortality in patients with acute respiratory distress syndrome

Variable	Odds ratio (95 % CI)	
	Univariate logistic regression	Multivariable logistic regression ^a
Male gender	1.35 (0.99–1.84), <i>p</i> = 0.06	1.46 (1.01–2.11), <i>p</i> = 0.045
Age ≥58 years	2.33 (1.73–3.14), <i>p</i> < 0.01	2.42 (1.71–3.45), <i>p</i> < 0.01
SAPS II ≥56 points	2.79 (2.06–3.76), <i>p</i> < 0.01	1.88 (1.32–2.69), <i>p</i> < 0.01
Respiratory settings on TEE day		
Respiratory rate ≥30 cycles/min	2.06 (1.41–3.02), <i>p</i> < 0.01	3.29 (2.07–5.22), <i>p</i> < 0.01
PEEP ≥12 cmH ₂ O	0.64 (0.45–0.91), <i>p</i> = 0.01	I/NR
Plateau pressure ≥25 cmH ₂ O	1.40 (1.04–1.89), <i>p</i> = 0.03	I/NR
Compliance <35 ml/cmH ₂ O	1.46 (1.07–2.00), <i>p</i> = 0.02	I/NR
Driving pressure ≥15 cmH ₂ O	1.90 (1.40–2.58), <i>p</i> < 0.01	2.26 (1.58–3.23), <i>p</i> < 0.01
PaO ₂ /FiO ₂ ratio <100 mmHg on TEE day	1.45 (1.09–1.95), <i>p</i> = 0.01	1.45 (1.02–2.08), <i>p</i> = 0.04
Severe cor pulmonale	1.89 (1.08–3.30), <i>p</i> = 0.03	2.00 (1.03–3.88), <i>p</i> = 0.04
Shock on TEE day	3.25 (2.32–4.56), <i>p</i> < 0.01	2.57 (1.73–3.80), <i>p</i> < 0.01
Prone position during ARDS	0.72 (0.52–0.99), <i>p</i> = 0.045	0.56 (0.37–0.84), <i>p</i> < 0.01

SAPS II Simplified Acute Physiologic Score II

^a The multivariable model showed a good calibration as assessed by the Hosmer–Lemeshow goodness of fit test [χ^2 (8 *df*) = 3.72; *p* = 0.88] and a fair discrimination as assessed by the receiver operating characteristics curve (AUC 0.76; 95 % CI 0.72–0.79; *p* < 0.01)

reduction of ACP by prone positioning together with an improvement in blood gases and respiratory mechanics.

The ACP risk score could be very useful in clinical practice to select those ARDS patients who should be assessed by echocardiography. Indeed, TEE has a greater diagnostic accuracy than surface echocardiography for the identification of ACP in mechanically ventilated patients [4]. Although critical care echocardiography is increasingly used worldwide, some issues persist regarding the training of intensivists for routine TEE, as well as the 24/7 availability of echocardiography machines and esophageal probes in ICUs. Our data indicate that for a patient with an ACP risk score of <2, ACP is uncommon and echocardiography could be performed on demand only. In contrast, an ACP risk score of 2, 3, or 4 suggests a higher likelihood of ACP (in 19, 34, and 74 % of patients, respectively). We thus suggest that TEE should be routinely performed when the risk score is ≥2 (Fig. 1c).

Alternative approaches to detect or confirm ACP have been suggested, but to date these have been insufficiently evaluated. For example, elevated cardiac troponin levels (which have been proposed to identify RV failure in the setting of pulmonary embolism) are common in patients with ARDS and are associated with worsened clinical outcomes. However, high troponin levels may be associated with various echocardiographic abnormalities during ARDS, involving both the RV (tricuspid regurgitation grade) and the LV (wall motion abnormalities) [37]. The potential of the ACP risk score to select ARDS patients to be monitored with a pulmonary artery catheter is unknown. Many pulmonary artery catheter parameters assessing pulmonary vascular dysfunction (e.g., transpulmonary gradient [9] and central venous pressure exceeding pulmonary artery occlusion pressure [43]) have been associated with increased mortality during ARDS.

However, criteria to characterize ACP using the pulmonary artery catheter have not been validated.

Severe ACP presumably reflects a less reversible status which may be poorly responsive to interventions aimed at decreasing RV afterload. Accordingly, performing TEE in the case of a moderate-to-high ACP risk score could help tailoring the ventilator management to decrease RV afterload when ACP is detected, thus potentially avoiding further deterioration towards severe ACP [36]. Various interventions could be tested in the future using such an approach, including prone positioning, nitric oxide or extracorporeal CO₂ removal. Prone positioning has the potential to correct hypoxemia and hypercapnia without worsening ventilatory pressures, thus unloading the RV during ARDS [41, 42]. Whether the prone position should be proposed to patients with ACP in addition to those with a PaO₂/FiO₂ ratio of <150 mmHg [40] warrants further research. Despite its demonstrated effects on pulmonary hemodynamics, inhaled nitric oxide did not reduce mortality in ARDS patients in randomized controlled trials; future trials should test its usefulness in selected patients with ACP. Extracorporeal CO₂ removal may represent a novel therapeutic option to prevent or correct ACP in hypercapnic patients.

Our study has a number of limitations. First, the ventilator management may have varied across patients and centers during the extended time-frame of the study, but the use of low tidal volumes and limitation of Pplat were constant targets throughout the study period. Second, the respiratory management was probably influenced by TEE results in some cases, introducing a potential bias when assessing the impact of ACP on patient outcome. Third, we did not report on fluid balance or dead space, which may interact with ACP and alter mortality during ARDS [32, 44]. In addition, we report on a single TEE

examination during the first 3 days of ARDS, and future studies should explore the exact time-frame of ACP during ARDS. Fourth, experts in critical care echocardiography were present at many of the participating centers, possibly influencing the accuracy of diagnosis. Finally, although we used a split-sample validation method, future studies are needed to further confirm our results on an independent cohort.

In conclusion, in this large prospective cohort of 752 moderate-to-severe ARDS patients receiving protective mechanical ventilation and monitored with TEE at the early phase of ARDS, we report a 22 % prevalence of ACP and an association of severe ACP with a poor outcome. We also propose a clinical risk score to select patients at high risk of ACP who should be assessed by TEE. The early identification of ACP through the ACP

risk score provides a framework for testing specific therapeutic interventions aimed at reducing RV afterload and their impact on the outcome of ARDS patients.

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Compliance with ethical standards

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Conflicts of interest The authors declare that they have no conflicts of interest.

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