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ORIGINAL ARTICLE

Prognostic value of the novel P/FPE index to classify ARDS severity: A cohort study

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Mechanical ventilation;
Positive end-expiratory pressure;
Protective ventilation

Abstract
Objective: To evaluate the impact of the novel P/FP_E index to classify ARDS severity on mortality of patients with ARDS.
Design: A retrospective cohort study.
Setting: Twelve-bed medical and surgical intensive care unit from January 2018 to December 2020.
Patients: A total of 217 ARDS patients managed with invasive mechanical ventilation >48 h.
Interventions: None.
Variables: ARDS severity on day 1 and day 3 was measured based on PaO_2/FiO_2 ratio and P/FP_E index [$PaO_2/(FiO_2 \times PEEP)$]. Primary outcome was the hospital mortality.
Results: Hospital mortality rate was 59.9%. Relative to PaO_2/FiO_2 ratio, 31.8% of patients on day 1 and 77.0% on day 3 were reclassified into a different category of ARDS severity by P/FP_E index. The level of PEEP was lower by P/FP_E index-based ARDS severity classification than by using PaO_2/FiO_2 ratio. The performance for predicting mortality of P/FP_E index was superior to PaO_2/FiO_2 ratio in term of AROC (*day 1:* 0.72 vs. 0.62; *day 3:* 0.87 vs. 0.68) and CORR (*day 1:* 0.370 vs. 0.213; *day 3:* 0.634 vs. 0.301). P/FP_E index improved prediction of risk of death compared to PaO_2/FiO_2 ratio as showed by the qNRI (*day 1:* 72.0%, $p < 0.0001$; *day 3:* 132.4%, $p < 0.0001$) and IDI (*day 1:* 0.09, $p < 0.0001$; *day 3:* 0.31, $p < 0.0001$).
Conclusions: Assessment of ARDS severity based on P/FP_E index seems better than PaO_2/FiO_2 ratio for predicting mortality. The value of P/FP_E index for clinical decision-making requires confirmation by randomized controlled trials.

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PALABRAS CLAVE
Síndrome de distrés respiratorio agudo/clasificación;
Síndrome de distrés respiratorio agudo/diagnóstico;
Síndrome de distrés respiratorio agudo/mortalidad;
Ventilación mecánica;
Presión positiva tele-espiratoria;
Ventilación protectiva

Valor pronóstico del nuevo índice P/FPE para clasificar la severidad del SDRA: Estudio de cohorte

Resumen
Objetivo: Evaluar el impacto del índice P/FP_E para clasificar la severidad del SDRA y su relación con la mortalidad.
Diseño: Estudio de cohorte retrospectivo.
Contexto: Unidad de cuidados intensivos polivalentes de 12 camas desde enero de 2018 hasta diciembre de 2020.
Pacientes: Se estudió a 217 pacientes con SDRA con ventilación invasiva > 48 horas.
Intervenciones: Ninguna.
Variables: La severidad del SDRA se evaluó el primer y el tercer día, según el índice PaO_2/FiO_2 y el índice P/FP_E ($PaO_2/[FiO_2 \times PEEP]$). El desenlace primario evaluado fue la mortalidad hospitalaria.
Resultados: La mortalidad hospitalaria fue 59,9%. Con relación al índice PaO_2/FiO_2, el 31,8% de los pacientes el día 1 y el 77,0% el día 3 fue reclasificado en categorías diferentes de severidad del SDRA mediante el índice P/FP_E. El nivel de PEEP fue más bajo con el uso del índice P/FP_E que con el PaO_2/FiO_2. La predicción de la mortalidad fue superior con el índice P/FP_E que con PaO_2/FiO_2, en términos de AROC (día 1: 0,72 vs. 0,62; día 3: 0,87 vs. 0,68) y CORR (día 1: 0,370 vs. 0,213; día 3: 0,634 vs. 0,301). El índice P/FP_E mejoró la predicción del riesgo de muerte comparado con el PaO_2/FiO_2, como demuestra el qNRI (día 1: 72,0%, $p < 0,0001$; día 3: 132,4%, $p < 0,0001$) y el IDI (día 1: 0,09, $p < 0,0001$; día 3: 0,31, $p < 0,0001$).
Conclusiones: La evaluación de severidad del SDRA mediante el índice P/FP_E parece ser mejor que la del índice PaO_2/FiO_2 para predecir la mortalidad. El valor del P/FP_E para la toma de decisiones clínicas requiere confirmación mediante ensayos clínicos.

Introduction

Acute respiratory distress syndrome (ARDS) is a heterogeneous syndrome characterized by an acute inflammation, increased permeability, and edema of the lung tissue, with a typical histological hallmark of diffuse alveolar damage, leading to alveolar collapse and a severe impairment in oxygen diffusion.[1] ARDS accounts for 10% of intensive care unit (ICU) admissions and 23% of patients receiving mechanical ventilation, with a mortality rate that ranges from 35% in mild cases to 46% in severe cases.[2] According to the Berlin definition, severity of ARDS is classified into 3 categories (mild, moderate, and severe) based on the arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio, with a minimum positive end-expiratory pressure (PEEP) level of 5 cm H_2O.[3] These criteria have been useful for designing clinical trials and observational studies, as well as for improving clinical decision-makings and therapeutic interventions.[4]

However, the PaO_2/FiO_2 ratio has some limitations for assessing ARDS severity. First, PaO_2/FiO_2 ratio is affected by ventilatory setting such as PEEP and inspiratory/expiratory time ratio. Villar et al. improved ARDS risk stratification using standard ventilatory settings ($PEEP \geq 10\,cmH_2O$ and $FiO_2 \geq 0.5$).[5,6] Second, PaO_2/FiO_2 ratio may change over time. A number of authors found a better mortality prediction by patients' reclassification ≥24 h after ARDS onset.[5–7] And third, PaO_2/FiO_2 ratio is not always linked to mortality in patients with ARDS.[8,9]

Recently, Sayed and coworkers proposed a novel criterion to address Berlin definition gap by including PEEP in the new index named P/FP_E, defined as $PaO_2/(FiO_2 \times PEEP)$. The increase the PEEP level with the same FiO_2 yields different degree of blood oxygenation. By using machine learning approaches, the authors demonstrated that the P/FP_E index after onset and at third day is markedly better than the current PaO_2/FiO_2 ratio to assess ARDS severity.[10] The present study was aimed to evaluate the impact of the P/FP_E index on mortality of patients with ARDS.

Patients and methods

Design and setting

The current study is presented as stated by The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (Supplementary material 1).[11] This is a retrospective cohort study of patients collected between January 2018 and December 2020 in the medical and surgical ICU-8 of the Hermanos Ameijeiras Hospital. This is a 640-bed, university-affiliated, tertiary referral hospital in Havana, Cuba. The ICU-8 has 12 beds and provides care for approximately 300–350 critically ill patients per year. Information regarding origin, demography, epidemiology, chronic comorbidities, clinical status, laboratory tests, image results, and outcomes of all patients were recorded in the ICU-8 database by the attending physician day by day from patients' admission until discharge or death. Quality of

data was daily verified by a supervisor physician. A complete list of data used for this study is provided in Supplementary material 2.

The current study was conducted in accordance with the 1964 Helsinki Declaration, and was approved by the Scientific Council and the Ethics Committee for Scientific Research of the Hermanos Ameijeiras Hospital (Approval number 01-10-06-2021). Written informed consent was waived in view of retrospective nature of the study.

Subjects

All consecutive subjects with ARDS admitted to ICU were included. The following subjects were excluded: 1. Subjects without invasive mechanical ventilation (IMV), because failure in noninvasive respiratory support therapies may have a negative impact on outcomes[12,13]; 2. Subjects with duration of IMV $\leq$48 h to improve ARDS classification,[7,9,10,14] and avoid confounders related to systemic pathophysiological disturbances of the acutely ill patients; and 3. Subjects on IMV before ARDS onset, since several clinical, therapeutic, and ventilatory setting confounders may contribute for developing ARDS in subjects previously intubated for other reasons and may have effects on outcomes.[15,16] Finally, 217 subjects were analyzed (Fig. 1).

Data collection

The following data were recorded on ICU admission: age, sex, body mass index, predictive body weight (PBW), history of chronic diseases, length of hospitalization before ICU admission, reason for ICU admission, type of patient, Simplified Acute Physiology Score (SAPS) 3, Sequential Organ Failure Assessment (SOFA) score, and use and dose of vasoactive drugs. Within 2 h after starting IMV the following variables were collected: ventilatory setting (ventilatory mode, peak inspiratory pressure, plateau pressure, mean pressure, PEEP, driving pressure, tidal volume, tidal volume/PBW, respiratory rate, minute ventilation, standardized minute ventilation, static compliance, and FiO_2), recruitment maneuvers, prone positioning, infusion of neuromuscular blocking agents, pH and blood gases parameters (hemoglobin oxygen saturation, arterial partial pressure of oxygen, arterial partial pressure of carbon dioxide). Risk factors for ARDS were collected on ARDS diagnosis. ICU-acquired ARDS was defined as ARDS onset >48 h after ICU admission.[17]

ARDS severity evaluation

Severity of ARDS was assessed on day 1 (within 2 h after starting IMV) and day 3 (within 48–72 h after starting IMV) with the patient in supine position. All subjects were stratified into mild (200 mm Hg < PaO_2/FiO_2 ratio $\leq$ 300 mm Hg), moderate (100 mm Hg < PaO_2/FiO_2 ratio $\leq$ 200 mm Hg) or severe ARDS (PaO_2/FiO_2 ratio $\leq$100 mm Hg) in line with the Berlin definition.[3] According to P/FP_E index, patients were classified as mild (40 < P/FP_E index $\leq$ 60), moderate (20 < P/FP_E index $\leq$ 40) or severe ARDS (P/FP_E index $\leq$ 20).[10] All cases had PEEP $\geq$ 5 cm H_2O; minimal PaO_2/FiO_2 ratio and P/FP_E index values were used because minimal values during the day might better predict mortality. Diagnosis and severity of ARDS along with decision-making for therapeutic interventions were collectively taken by the physician team of the ICU (all of them blinded to the study objective).

Ventilatory management

Ventilatory adjustments of patients were left to the attending physician, but by using a protective approach. For patients with PaO_2/FiO_2 ratio $\leq$ 150 mm Hg, prone positioning, lung recruitment maneuvers, higher PEEP, and neuromuscular blocking agents were considered.[18] Sedative and analgesic drugs were used as needed. Ventilatory settings and arterial blood gases on day 1 and day 3 are depicted in Supplementary Table 1 (Supplementary material 3).

Outcomes

Primary outcome of interest was the hospital mortality. Secondary outcomes were ICU mortality, duration of IMV, length of ICU stay, and length of hospitalization.

Statistical analysis

Study objective was unknown for attending physicians, nurses and patients, which allowed to minimize the following sources of biases: 1. Over or underreport of ARDS; 2. Selective ICU admission of patients with ARDS; 3. Selective detection of ICU-acquired ARDS; and 4. Selective use of any therapeutic intervention with impact on clinical outcomes.

Assuming hospital mortality rates of 20% in mild ARDS patients and 40% in severe ARDS patients on 3 day after starting IMV, as previously reported by Sayed and coworkers using large datasets,[10] with a statistical power of 80% and two-side confidence level of 95%, we calculated a sample size of 166 patients. Finally, we enrolled 217 patients.

Multiple imputation method was used for treating missing values. Categorical variables are shown as absolute numbers with percentage, whereas numerical variables are represented as median with 25–75 interquartile rank (IQR). Differences between groups were assessed using chi-square test for categorical variables and Mann–Whitney *U* test for continuous variables.

Multivariate logistic regression analysis was used to explore the impact of ventilatory settings and respiratory indexes on primary outcome. Model assumptions were verified. To avoid collinearity, after checking the correlation matrix, only weakly correlated and clinically significant covariates were included. SOFA score was included as a covariate in order to interpret results in a valid clinical scenario. Two models were explored, the first used the PaO_2/FiO_2 ratio as a covariate, and the second used the P/FP_E index.

The area under receiver operating characteristic curve (AROC) and the correlation between the predicted and actual value (CORR) were used to assess the performance of the PaO_2/FiO_2 ratio and P/FP_E index in predicting hospital mortality. For assessment the incremental value of the P/FP_E index compared to the PaO_2/FiO_2 ratio, the quantitative

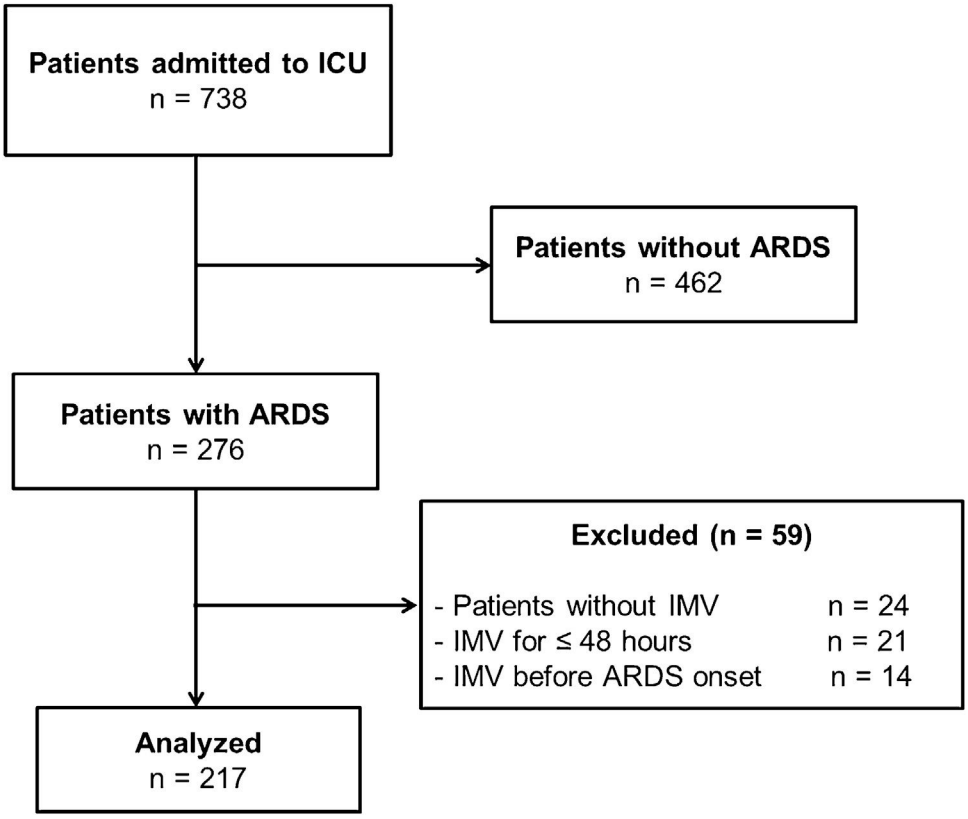

Figure 1 Flow diagram of participants (dates of inclusion: between January 2018 and December 2020). ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IMV = invasive mechanical ventilation.

net reclassification improvement (qNRI, for quantifying the amount of correct change in predicting hospital mortality by using the P/FP_E index relative to the PaO_2/FiO_2 ratio) and the integrated discrimination improvement (IDI, for quantifying the increase in separation of events and nonevents of death by using the P/FP_E index relative to the PaO_2/FiO_2 ratio) with its 95% confidence interval (CI) were estimated.

Statistical tests with a two-tailed *p*-value <0.05 were considered as significant. Data were analyzed using IBM® SPSS® Statistics 23.0 (IBM, Chicago, IL, USA).

Results

Characteristics of patients

In the 217 studied patients, the most common chronic comorbidities were hypertension, cancer, and immunoincompetence. The main reasons for ICU admission were acute respiratory failure, shock, and disturbed consciousness. Nonsurgical and surgical patients accounted for 61.8% and 38.2% of participants, respectively. The median SOFA score was 8.0 points, and the median SAPS 3 score was 55.0 points. During the ICU stay, vasoactive drugs were used in 36.4% of patients. ICU and hospital mortality rates were 41.0% and 59.9%, respectively. History of cardiovascular diseases, type of patient, and SOFA score were associated with hospital mortality in univariate analysis (Table 1).

Pneumonia, noncardiogenic shock, and extrapulmonary sepsis were the most common risk factors for ARDS. ICU-acquired ARDS accounted for 22.9% of subjects and was related to increased mortality (13.8% vs. 28.5%; $p = 0.011$). General characteristics of patients are depicted in Table 1. Relationship of ventilatory settings and arterial blood gases with hospital mortality is illustrated in Supplementary Tables 2 and 3 (see Supplementary material 3).

ARDS severity classification

The median PaO_2/FiO_2 ratio and P/FP_E index on first day after starting IMV was 187.0 mm Hg (IQR 117.3–221.8 mm Hg) and 21.6 (IQR 10.2–33.2), respectively. On third day, the median value of PaO_2/FiO_2 ratio was 222.5 mm Hg (IQR 176.7–297.8 mm Hg) and the median value of P/FP_E index was 23.3 (IQR 15.8–37.5).

According to the PaO_2/FiO_2 ratio on day 1, 30.9%, 46.5%, and 22.6% of patients had a mild, moderate, and severe ARDS, respectively; on day 3, 23.0% of patients were free of ARDS while patients with mild, moderate, and severe ARDS accounted for 42.4%, 31.3%, and 3.2%, respectively. Using the P/FP_E index on day 1, patients with mild, moderate, and severe ARDS accounted for 18.0%, 39.6%, and 42.4%, respectively; on day 3, 6.5% of patients were free of ARDS, whereas 14.3%, 40.6%, and 38.7% had a mild, moderate, and severe ARDS, respectively.

A number of patients were reclassified into a different category of ARDS severity by using the P/FP_E index (31.8% on day 1 and 77.0% on day 3) (Fig. 2). Of note, 72% of patients without ARDS by the PaO_2/FiO_2 ratio on day 3 remained with

Table 1 General characteristics of subjects.

Characteristics	Total ($n = 217$)	Survivors ($n = 87$)	Nonsurvivors ($n = 130$)	p
Age, years	63.0 (53.0–73.0)	62.0 (51.5–72.0)	64.5 (54.0–73.0)	0.261
Sex, male	103 (47.5)	45 (51.7)	58 (44.6)	0.304
Body mass index, kg/m²	25.0 (24.1–27.5)	25.4 (24.3–27.4)	24.8 (23.5–27.5)	0.444
Chronic diseases[a]				
Chronic respiratory disease	35 (16.1)	10 (11.5)	25 (19.2)	0.129
Diabetes mellitus	48 (22.1)	16 (18.4)	32 (24.6)	0.279
Immunoincompetence	64 (29.5)	21 (24.1)	43 (3.1)	0.157
High blood pressure	128 (59.0)	42 (48.3)	86 (66.2)	0.009
Coronary artery disease	38 (17.5)	9 (10.3)	29 (22.3)	0.023
Other cardiovascular disease	33 (15.2)	8 (9.2)	25 (19.2)	0.044
Cancer	82 (37.8)	30 (34.5)	52 (40.0)	0.411
Chronic kidney disease	25 (11.5)	8 (9.2)	17 (13.1)	0.380
Chronic liver disease	12 (5.5)	5 (5.7)	7 (5.4)	1.000
Length of stay before ICU admission, days	6.0 (3.0–16.0)	7.0 (2.0–14.0)	6.0 (3.0–16.0)	0.461
Reason for ICU admission[b]				
Acute respiratory failure	180 (82.9)	77 (88.5)	103 (79.2)	0.075
Shock	64 (29.5)	23 (26.4)	41 (31.5)	0.419
Rhythm disturbances	9 (4.1)	2 (2.3)	7 (5.4)	0.264
Acute abdomen	20 (9.2)	7 (8.0)	13 (10.0)	0.626
Severe acute pancreatitis	5 (2.3)	2 (2.3)	3 (2.3)	0.997
Disturbed consciousness	49 (22.6)	20 (23.0)	29 (22.3)	0.906
Intracranial mass effect	24 (11.1)	14 (16.1)	10 (7.7)	0.053
Liver failure	7 (3.2)	1 (1.1)	6 (4.6)	0.247
Type of patient				0.007
Nonsurgery	134 (61.8)	44 (50.6)	90 (69.2)	
Elective surgery	40 (18.4)	24 (27.6)	16 (12.3)	
Emergency surgery	43 (19.8)	19 (21.8)	24 (18.5)	
SAPS 3 score, points	55.0 (44.0–66.0)	55.0 (42.5–65.5)	55.0 (44.0–66.0)	0.957
SOFA score, points	8.0 (6.0–11.0)	4.0 (3.0–7.0)	8.0 (8.0–12.0)	<0.0001
Risk factor for ARDS[c]				
Pneumonia	88 (40.6)	40 (46.0)	48 (36.9)	0.183
Extrapulmonary sepsis	67 (30.9)	24 (27.6)	43 (33.1)	0.391
Aspiration	15 (6.9)	8 (9.2)	7 (5.4)	0.278
Noncardiogenic shock	75 (34.6)	31 (35.6)	44 (33.8)	0.786
Blood transfusion	9 (4.1)	2 (2.3)	7 (5.4)	0.320
Drug overdose	6 (2.8)	0 (0.0)	6 (4.6)	0.083
Other risk factor	10 (4.6)	4 (4.6)	6 (4.6)	1.000
No risk factor	15 (6.9)	4 (4.6)	11 (8.5)	0.271
ICU-acquired ARDS	49 (22.6)	12 (13.8)	37 (28.5)	0.011
Time from ICU admission to ARDS onset, days	4.0 (3.5–5.0)	4.0 (3.3–4.)	4.0 (3.5–5.0)	0.556
Duration of MV, days	7.0 (4.0–10.0)	6.0 (4.0–10.0)	7.0 (4.0–10.0)	0.820
Length of ICU stay, days	9.0 (6.0–13.0)	10.0 (8.0–14.0)	8.0 (5.0–12.0)	<0.0001
Length of hospitalization, days	12.0 (7.0–16.5)	16.0 (12.0–19.0)	8.5 (5.0–13.3)	<0.0001

Data are presented as the number (%) or the median (interquartile range). The p-values are calculated using the Mann–Whitney U test for continuous variables and chi-square test for categorical variables.
ARDS = acute respiratory distress syndrome; ICU = intensive care unit; MV = invasive mechanical ventilation; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.
[a] Some patients had >1 chronic comorbidity.
[b] Some patients had >1 reason for ICU admission.
[c] Some patients had >1 risk factor for ARDS.

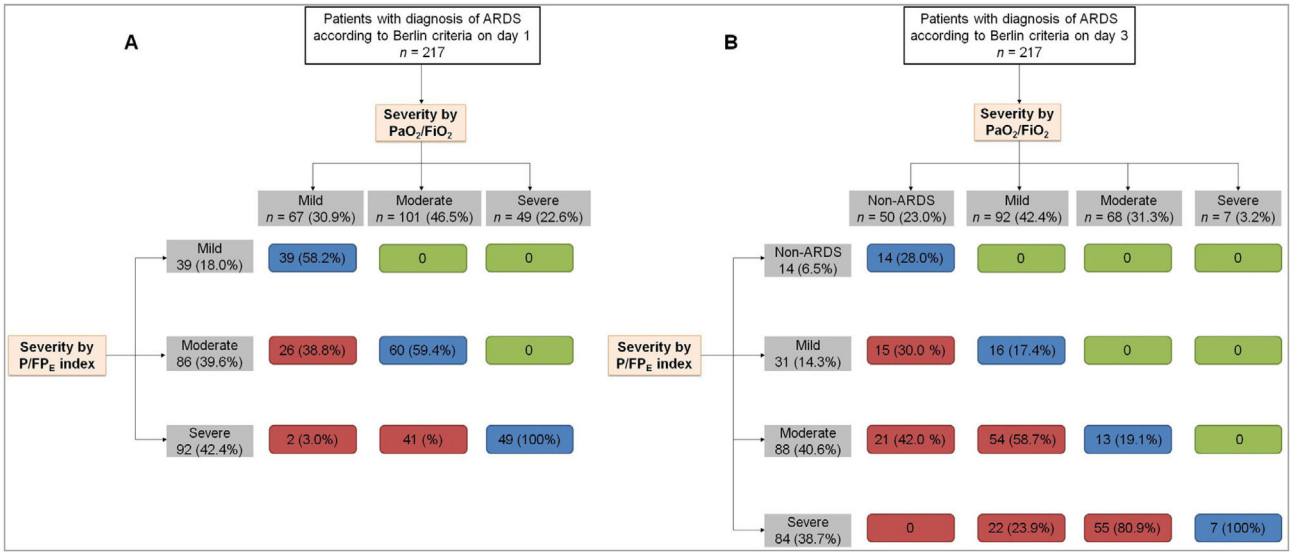

Figure 2 Agreement in classification of ARDS severity using PaO_2/FiO_2 ratio and P/FP_E index on day 1 (A) and day 3 (B). Blue boxes represent patients whose categories remained unchanged. Red boxes represent patients who were reclassified to a more severe category. Green boxes represent patients who were reclassified to a milder category. $P/F = PaO_2/FiO_2$ ratio; P/FP_E index $= PaO_2/(FiO_2 \times PEEP)$.

ARDS by using the P/FP_E index (Fig. 2). Severity of ARDS was linked to a higher PEEP level; however, the level of PEEP was lower by the P/FP_E index-based ARDS severity than using the PaO_2/FiO_2 ratio-based ARDS severity (Fig. 3).

ARDS severity and outcomes

PaO_2/FiO_2 ratio and P/FP_E index was related to mortality both on day 1 and day 3 (Supplementary figure* 1, Supplementary material 3). However, on multivariate analyses only the P/FP_E index was consistently associated with hospital mortality (Table 2). Driving pressure, tidal volume/PBW and SOFA score were also independent risk factors related to increased mortality (Table 2).

The capability of the PaO_2/FiO_2 ratio and P/FP_E index for predicting hospital mortality improved from day 1 to day 3. Nonetheless, the performance of the P/FP_E index was superior to the PaO_2/FiO_2 ratio in term of AROC (*day 1* 0.72 vs. 0.62; *day 3* 0.87 vs. 0.68) and CORR (*day 1* 0.370 vs. 0.213; *day 3* 0.634 vs. 0.301) (Table 3 and Supplementary figure* 2, Supplementary material 3). P/FP_E index improved the prediction of risk of death compared to PaO_2/FiO_2 ratio as showed by the qNRI (*day 1* 72.0%, $p < 0.0001$; *day 3* 132.4%, $p < 0.0001$) and IDI (*day 1* 0.09, 95% CI 0.06–0.12, $p < 0.0001$; *day 3* 0.31, 95% CI 0.26–0.35, $p < 0.0001$) (Supplementary figures 3 and 4, Supplementary material 3).

Discussion

The present study found that 31.8% of patients with ARDS on day 1 and 77.0% on day 3 were reclassified into a different category of ARDS severity using the P/FP_E index. The performance for predicting hospital mortality increased with the P/FP_E index, compared to the PaO_2/FiO_2 ratio. The P/FP_E index and ventilatory settings, such as tidal volume and driving pressure, were independently related to increased mortality in multivariate analysis. ARDS severity stratification improved on third day after ARDS diagnosis. Mean PEEP level was lower when ARDS severity was categorized according to the P/FP_E index rather than the PaO_2/FiO_2 ratio.

In order to overcome the gap of the Berlin criteria, Sayed et al. recently proposed the PaO_2 to $(FiO_2 \times PEEP)$ ratio, named P/FP_E index, as a novel criterion to reclassify ARDS patients in terms of severity.[10] Improvement of ARDS severity classification is essential for current critical care medicine since misclassification may lead to errors in clinical judgment and decision-making. For instance, we found that a number of patients were reclassified in a higher category of ARDS severity using the P/FP_E index, whereas 72.0% of patients without ARDS on day 3 according to the PaO_2/FiO_2 ratio truly had ARDS by the P/FP_E index. Recently, Palanidurai et al. observed that more than half of the patients were reclassified into a different severity category of ARDS by the P/FP_E index, compared to the PaO_2/FiO_2 ratio. These similar results indicate that changes in severity classification with the P/FP_E index reflect the true severity of ARDS and the applied PEEP strategy.[19]

Under-recognition of ARDS is a common and serious problem with important clinical consequences, particularly in terms of therapeutic options not considered.[20] The LUNG SAFE study demonstrated that the diagnosis of ARDS is delayed or missed in 40% of patients.[2] P/FP_E index is able to identify patients with ARDS who would not be classified with ARDS according to the PaO_2/FiO_2 ratio, and is also a better predictor of mortality.[19] Therefore, by using the P/FP_E index clinicians may implement strategies to improve mortality such as optimal PEEP, lower FiO_2, prone positioning and the use of neuromuscular blocking agents.

PEEP is a confounder in clinical practice since optimal PEEP is difficult to obtain through several methods,[21] and clinicians commonly prescribes high PEEP in patients with

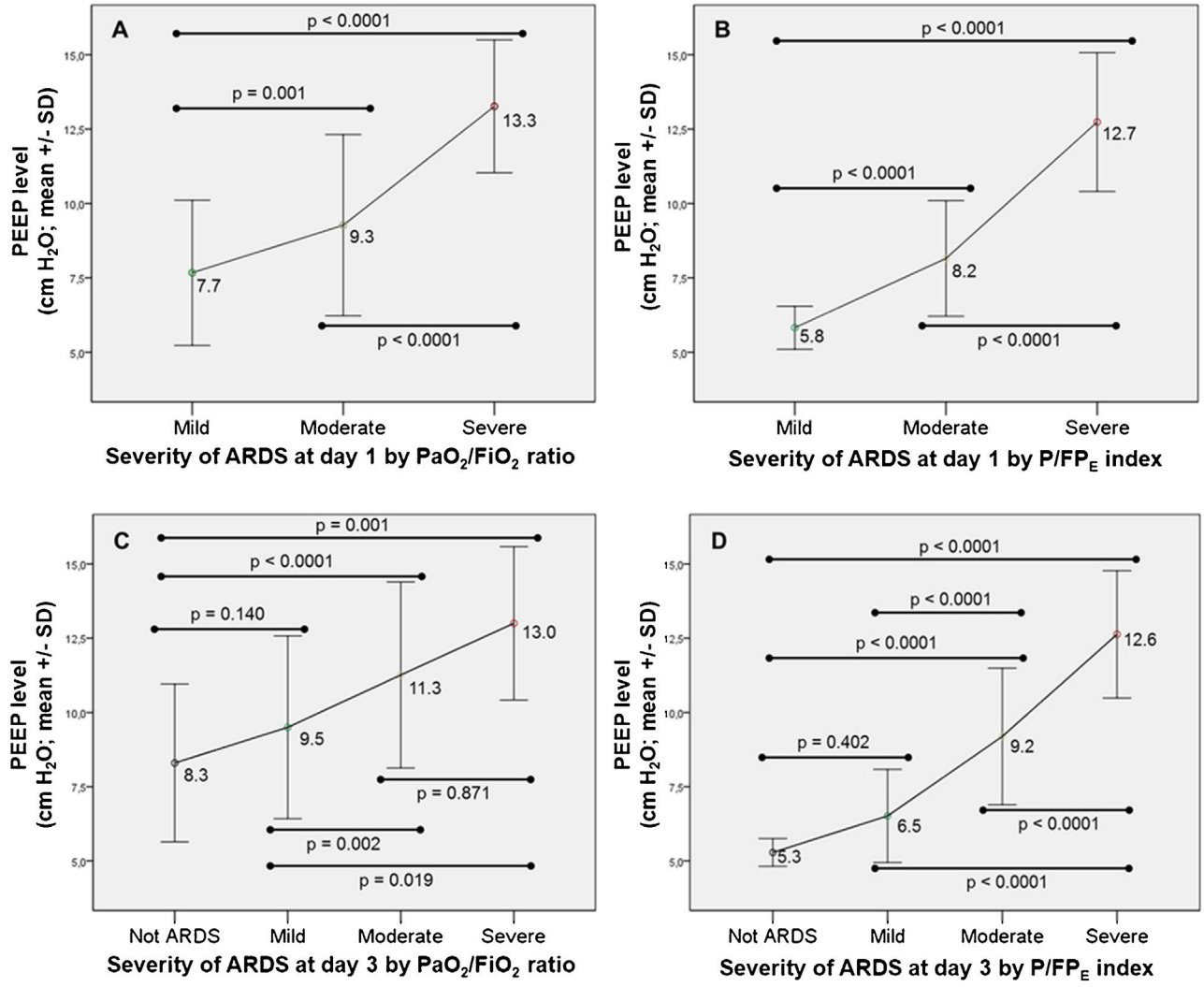

Figure 3 Relationship between PEEP level and ARDS severity according to the PaO_2/FiO_2 ratio at day 1 (pictures A) and day 3 (picture C), and the P/FP_E index at day 1 (pictures B) and day 3 (picture D). ARDS = acute respiratory distress syndrome; PaO_2/FiO_2 = arterial partial pressure of oxygen to fraction of inspired oxygen ratio; PEEP = positive end-expiratory pressure; P/FP_E index = $PaO_2/(FiO_2 \times PEEP)$.

adequate oxygenation goals.[6,22] Clinical interpretation of the PaO_2/FiO_2 ratio may be biased by nonpulmonary factors such as hemoglobin concentration and arterial-venous oxygen content difference.[23] Consequently, oxygen toxicity with adverse impact on outcomes may be developed due to excess FiO_2.[24] P/FP_E index is attractive because physicians can achieve the best combination of FiO_2 and PEEP to reach adequate oxygenation. In our cohort, the frequency of prone positioning was similar to that reported in epidemiologic studies while infusion of neuromuscular blocking agents was lower.[2] However, the use of these drugs is controversial because of its side effects and unclear benefits[25]; currently they are indicated only for the treatment of ventilatory asynchrony, supporting pronation, or assuring protective ventilation goals.[21]

Our findings demonstrated the clinical validity of P/FP_E index. The better performance, compared to PaO_2/FiO_2 ratio, shows the usefulness of P/FP_E index in predicting mortality. Palanidurai et al. also found that P/FP_E index has a greater predictive validity for predicting hospital mortality in ARDS patients than the PaO_2/FiO_2 ratio.[19] In fact, the AROC for P/FP_E index (0.71 vs. 0.72) and PaO_2/FiO_2 ratio (0.66 vs. 0.62) was similar to the present study, which supports external validity of our results.

ARDS is one of the major reasons of ICU admission, and continues to have high mortality rates despite advances in supportive care.[2,26] Ventilatory support is the keystone in the management of patients with ARDS, but ventilatory setting may have an impact on outcomes.[27] Since tidal volume and driving pressure, along with the P/FP_E index, were related to increased mortality in multivariate analysis, our findings suggest that the negative effect of ventilatory variables remains unchanged through the course of the disease, which is in line with recent evidences.[28,29] Additionally, the relationship between the P/FP_E index with mortality explains ARDS severity, but also the potentially harmful effects of PEEP.

Table 2 Ventilatory settings and respiratory indexes related to hospital mortality by multivariate logistic regression analysis.

Risk factors	OR	95% CI	*p*
Model including PaO_2/FiO_2 ratio (day 1)			
Driving pressure	1.52	1.26–1.84	<0.0001
V_T/PBW	3.51	1.55–7.98	0.003
Respiratory rate	1.11	1.00–1.23	0.047
PaO_2/FiO_2 ratio	0.996	0.989–1.002	0.213
SOFA score	2.19	1.69–2.83	<0.0001
Model including P/FP_E index (day 1)			
Driving pressure	1.58	1.29–1.95	<0.0001
V_T/PBW	3.17	1.30–7.74	0.011
Respiratory rate	1.11	1.00–1.24	0.051
P/FP_E index	0.93	0.89–0.97	0.001
SOFA score	2.27	1.70–3.02	<0.0001
Model including PaO_2/FiO_2 ratio (day 3)			
Driving pressure	1.33	1.06–1.66	0.015
V_T/PBW	3.87	1.17–12.84	0.027
Respiratory rate	1.10	1.00–1.22	0.054
PaO_2/FiO_2 ratio	0.994	0.989–1.000	0.048
SOFA score	2.59	1.92–3.50	<0.0001
Model including P/FP_E index (day 3)			
Driving pressure	1.50	1.13–1.98	0.005
V_T/PBW	5.34	1.21–23.51	0.027
Respiratory rate	1.11	0.99–1.25	0.071
P/FP_E index	0.87	0.83–0.92	<0.0001
SOFA score	2.50	1.78–3.52	<0.0001

Data are presented as the odds ratio (OR) with 95% confidence interval (CI). The *p*-values were calculated using the multivariate logistic regression analysis.
PaO_2/FiO_2 = arterial partial pressure of oxygen to fraction of inspired oxygen ratio; P/FP_E index = $PaO_2/(FiO_2 \times PEEP)$; SOFA = Sequential Organ Failure Assessment; V_T/PBW = tidal volume/predictive body weight.

Table 3 Performance of PaO_2/FiO_2 Ratio and P/FP_E Index in Predicting Hospital Mortality.

Index	AROC			CORR	
	Estimate	95% CI	*p*	Estimate	*p*
Assessment on day 1					
PaO_2/FiO_2 ratio	0.62	0.54–0.69	0.004	0.213	0.002
P/FP_E index	0.72	0.65–0.78	<0.0001	0.370	<0.0001
Assessment on day 3					
PaO_2/FiO_2 ratio	0.68	0.60–0.75	<0.0001	0.301	<0.0001
P/FP_E index	0.87	0.82–0.92	<0.0001	0.634	<0.0001

Data are presented as the area under receiver operating characteristic curve (AROC) with 95% confidence interval (CI), and the correlation between the predicted and actual value (CORR). The *p*-values were calculated using the Pearson's correlation test for CORR.
ICU = intensive care unit; PaO_2/FiO_2 = arterial partial pressure of oxygen to fraction of inspired oxygen ratio; P/FP_E index = $PaO_2/(FiO_2 \times PEEP)$.

The present study confirmed that ARDS severity stratification is improved on third day after ARDS diagnosis.[7,10] Lai et al. demonstrated that the PaO_2/FiO_2 ratio after a period of stabilization may be a more appropriate predictor of mortality than the initial PaO_2/FiO_2 ratio at the onset of ARDS.[30] Chiu et al. found that patients with resolved or improving ARDS severity on day 3 had lower mortality, whereas patients with the same or worsening ARDS severity on day 3 had higher mortality.[7] Apparently, patients need to be exposed to a sufficient period of time for response to medical therapies and adjusted IMV settings before being classified.

We found that a lower mean PEEP was used in all class of ARDS severity when patients were stratified by P/FP_E index, which might reduce the risk of excess PEEP. Palanidurai et al. observed that the predictive validity of P/FP_E index improved with progressively higher levels of PEEP, indicative of the negative effects of higher PEEP.[19] PEEP is

not considered for ARDS severity evaluation by the Berlin definition. Adding PEEP to the PaO_2/FiO_2 ratio takes into consideration the respiratory system compliance and lung recruitment. Furthermore, by using PEEP as a quantitative variable, P/FP_E index conserves information and improves accuracy of estimations.[31] However, although PEEP increases functional residual capacity and improves blood oxygenation, tissue oxygen delivery decreases because of reduced cardiac output.[32] PEEP also increases the risk of volutrauma and ventilator-induced lung injury,[33] causing increased mortality when a high-PEEP strategy is used.[34]

This study has a number of strengths. First, the study was conducted in a center with high standard of health care and in an ICU with qualified intensivists 24 h a day, seven days a week. Second, potential sources of bias were reduced, which lend additional strength to our analysis. Third, this is a well-powered study with a representative sample size so estimation errors were minimized. Fourth, by multivariate analysis we were able to control for potential confounders including ventilatory setting, and severity of illness. Fifth, the LUNG SAFE study showed that most ARDS patients are not ventilated using a protective ventilation approach.[2] We reached ventilatory goals on day 3, which indicates an improvement in quality of ventilatory management according to current recommendations.[18,29]

There are several limitations of our study. First, this is an observational study from a single center, thus results may not be representative of other institutions or regions. Second, a mixed cohort of surgical and nonsurgical patients with several clinical and pathophysiological disorders were analyzed, which could have effects on outcomes. Indeed, hospital mortality rate was higher than reported in recent epidemiologic studies.[2] Since our hospital is a national referral center, case-mix of patients with more severe diseases were more likely included compared with community-based hospitals. Compared with patients enrolled in the LUNG SAFE study,[2] our analyzed patients had more chronic diseases including immunoincompetence, cardiovascular disease, and cancer, and had a higher rate of extrapulmonary sepsis and noncardiogenic shock, all which may explain the higher mortality rate observed in the study. Third, trauma patients were not included in the study so results cannot be applied to this type of patients. Fourth, several phenotypes and subphenotypes have been recognized in ARDS patients with impact on outcomes.[35,36] In the present study, analyses were not stratified according to ARDS phenotypes; consequently, further studies are required to define the effects of the interaction or association of P/FP_E index-based ARDS severity and ARDS phenotypes, as well as its clinical implications, which opens a new agenda of work for future researches. Finally, we explored ARDS severity within the first 72 h after starting IMV, and the clinical course of patients beyond this period of time may affect outcomes.

In conclusion, assessment of ARDS severity based on P/FP_E index is better than current PaO_2/FiO_2 criteria for predicting mortality, especially on third day after starting IMV. P/FP_E index is easy to use at the bedside by involving information of the two therapeutic strategies used for managing hypoxemia such as FiO_2 and PEEP. We recommend further clinical trials to clarify the advantages of ARDS severity classification based on P/FP_E index for clinical decision-making.

Author's contributions

FDMB contributed in the concepts, design, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review.

REM and VOR contributed in the design, definition of intellectual content, clinical studies, data acquisition, manuscript editing, and manuscript review.

TTS contributed in the literature search, manuscript preparation, manuscript editing, and manuscript review.

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Conflict of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.medin.2022.06.006.

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