ORIGINAL ARTICLE

Oxygenation Index, Oxygen Saturation Index vs PaO_2/FiO_2 *PEEP: A Secondary Analysis of OXIVA-CARDS Study

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Abstract

Background: The classification of Berlin definition is based on the PaO_2/FiO_2 ratio, which has been found to have a poor association with mortality. Airway pressures reflect lung compliance and the settings of mechanical ventilators. In this study, we aimed to investigate the change in the severity of COVID-19-associated acute respiratory distress syndrome (ARDS) classification using [$PaO_2/FiO_2 \times$ PEEP] (P/FP) ratio compared to the traditional P/F ratio, and whether the P/FP ratio improves the predictive validity of in-hospital mortality.

Methods: Our study sample included patients from the OXIVA-CARDS study. In this secondary analysis, we examined the oxygenation index and oxygen saturation index in relation to the P/FP ratio, as well as the risk of P/FP in mortality. We used Pearson's correlation to assess the relationships between various parameters. Receiver operating characteristic analysis with Youden's index was used to compare the prognostic value of the oxygenation index (OI), oxygen saturation index (OSI), P/F ratio, P/FP ratio, and SaO_2/FiO_2 ratio for predicting overall mortality. Multiple logistic regression was also performed to determine the impact of mean airway pressure (Pmean), S/F ratio, OI, and P/FP ratio on mortality.

Results: A total of 201 patients (with 1543 measurements) were included in the analysis. Overall, 522 (34%) were reclassified into either more or less severe categories. Patients who were classified as having severe ARDS based on the P/FP ratio had significantly lower P/FP ratio, oxygenation index, and A-a O2 gradient as compared to those classified as having severe ARDS based on the P/F ratio ($p < 0.05$) at all levels of ARDS severity. On multivariate regression analysis, only the OI significantly impacted mortality ($p < 0.05$).

Conclusion: We observed that the oxygen index and oxygen saturation index were more sensitive than the PaO_2/FiO_2 ratio and P/FP ratio. Additionally, only the oxygenation index had a significant impact on mortality. By including airway pressures in the calculation of the OI, its predictive ability is enhanced compared to using the S/F ratio, P/F ratio, or P/FP ratio.

Highlights: The sensitivity of mortality by including Pmean is higher as compared to when only PEEP is taken into consideration. P/FP is a weak predictor of mortality as compared to OI and OSI.

Keywords: Oxygenation indices, Oxygenation index, Oxygen saturation index, P/F ratio, P/FP ratio.

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Introduction

The Berlin definition[1] of acute respiratory distress syndrome (ARDS) classifies its severity based on the PaO_2/FiO_2 (P/F) ratio. However, it has been observed that patients requiring higher positive end-expiratory pressure (PEEP) have more severe lung injury compared to those requiring lower PEEP. This means that the inclusion of PEEP in the P/F ratio[2] can reclassify patients with higher PEEP and FiO_2 into a more severe category. In our previously published study,[3] we examined the oxygenation index (OI) and oxygenation saturation index (OSI) as indicators of mean airway pressure in COVID-19 ARDS (C-ARDS). In this secondary analysis, we will be looking at the $PaO_2/FiO_2 \times$ PEEP (P/FP) ratio, which takes into account the set PEEP value. Our goal is to determine if using the P/FP ratio instead of P/F ratio changes the severity classification of ARDS and if it improves the predictive validity of in-hospital mortality.

Methods

Source of Data

The study sample consisted of patients from the OXIVA-CARDS study,[3] a study conducted from August 2020 to September 2022. This study included 203 patients with C-ARDS who were mechanically ventilated.

Definition

Berlin definition:[1] partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) (P/F ratio) of <100 = severe, 101–200 = moderate, and 201–300 = severe

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Oxygenation index [OI = (Pmean × FiO_2 × 100)/PaO_2] where Pmean is mean airway pressure
Oxygen saturation index [OSI = (Pmean × FiO_2 × 100)/SpO_2]
P/F ratio = PaO_2/FiO_2 (patients were prone positioned if P/F ratio was less than 150)
P/FP ratio[2] = PaO_2 × 10/FiO_2 × PEEP
S/F ratio= SpO_2/FiO_2

Outcomes

The primary outcome of interest is oxygenation index and oxygen saturation index vs P/FP ratio. The secondary outcome of interest is the risk of P/FP in mortality.

Statistical Analysis

Analyses were conducted using SPSS software for Windows (version 25, 2007, IBM Corporation, Armonk, New York, United States). The data is presented as frequency (%) or Mean ± SD. Cohen's Kappa was used to determine the agreement between the P/F ratio and P/FP ratio in identifying ARDS. Pearson's correlation was used to assess the relationships between various parameters. The difference in blood gases between the ARDS groups, as identified by the P/F ratio or P/FP ratio, was determined using an Independent Sample *t-test*. Cross tabulations were computed to compare mortality rates among different ARDS categories, and the results were analyzed using a Chi-square test. Receiver operating characteristic (ROC) analysis with Youden's index was used to compare the prognostic value of OI, OSI, P/F, P/FP, and S/F in predicting overall mortality. The area under the curve was calculated, and sensitivity and specificity values were identified from the ROC curves. Multiple logistic regression was performed to determine the impact of P mean, S/F ratio, OI, and P/FP ratio on mortality. Before running the regression equation, variables were assessed for collinearity. A p-value of <0.05 was considered statistically significant.

Results

Patient Characteristics

From the original cohort of 203 patients (1557 measurements), a total of 201 patients (1543 measurements) were included in the analysis. PEEP data was not available for 2 patients (14 measurements) from the original study group. Table 1 gives the basic patient demographics and blood gas analysis.

Table 1: Patient information

Variable	*Frequency*
Patient demographics (n = 201)	
Age (years)	61.5 ± 13.9
Gender	
Males	145 (72.1%)
Females	56 (27.9%)
Outcome	
Survivors	72 (35.8%)
Non-survivors	129 (64.2%)
Investigations (n = 1,543)	
pH	7.4 ± 0.3
$PaCO_2$	48.4 ± 16.2
PaO_2	87.9 ± 26.9
SpO_2	94.1 ± 4.5
FiO_2	0.6 ± 0.2
Lactate	2.2±1.8
PEEP	8.5 ± 0.3
S/F ratio	177 ± 64
P/F ratio	166 ± 83
P/FP ratio	221 ± 154
Oxygenation factor	11.6 ± 7.9

FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; PEEP, positive end-expiratory pressure; P/F, PaO_2/FiO_2; P/FP, PaO_2/FiO_2 × PEEP; SpO_2, oxygen saturation; S/F, SpO_2/FiO_2

Severity of ARDS by P/FP Ratio vs P/F Ratio

Figure 1 gives the change in severity of ARDS when P/FP ratio is used rather than using P/F ratio. From 1543, 42 (2.7%) were moved to a more severe category (green oval) whereas 480 (31.3%) were moved to a further milder category (blue oval). Thus, overall 522 (34%) were reclassified into either more or less severe categories. The number of people in the non-ARDS group increased by 181 wherein 2 were moved from severe to non-ARDS, 45 were moved from moderate to non-ARDS, 134 were moved from mild to non-ARDS (blue oval), and 24 patients were moved from severe to moderate ARDS (green oval).

Based on the P/F ratio, 304 (19.7%) had severe ARDS, 850 (55.1%) had moderate ARDS, 274 (7.8%) had mild ARDS whereas 115 (7.5%) were normal. Using the P/FP ratio, 232 (15%) had severe ARDS, 683 (44.3%) had moderate ARDS, 334 (21.6%) had mild ARDS and 294 (19.1%) were normal. There was a moderate agreement between the two scales in identifying ARDS (Cohen's Kappa = 0.498, 95% CI = 0.465–0.531, $p < 0.001$) (Table 2).

Correlation amongst PEEP, P/F Ratio, and P/FP Ratio

A significant negative correlation of PEEP was observed with the P/F ratio ($r = -0.260$, $p < 0.001$) (Fig. 2) and the P/FP ratio ($r = -0.604$, $p < 0.001$) (Fig. 3). A significant positive correlation of the P/F ratio and P/FP ratio ($r = 0.873$, $p < 0.001$) was observed (Fig. 4).

Blood Gas when Classified into Different Categories of ARDS by P/F Ratio or P/FP Ratio

Table 3 gives blood gas when classified into different categories of ARDS by P/F ratio or P/FP ratio. Patients who had severe ARDS when classified by P/FP ratio had significantly lower P/FP ratio, oxygenation factor, and A-a O_2 gradient as compared to those who had severe ARDS when classified by P/F ratio ($p < 0.05$) at all levels of ARDS severity. Similarly, similar significant differences were found in FiO_2, S/F ratio, and P/F ratio between patients classified using P/F ratio or P/FP ratio at moderate ARDS, mild ARDS, and normal levels ($p < 0.05$). PaO_2 and SpO_2 showed similar results at mild and moderate ARDS levels ($p < 0.05$). On the other hand, $PaCO_2$ was significantly lower in patients who were identified to have moderate ARDS by P/FP ratio as compared to P/F ratio ($p < 0.05$). A-a O_2 gradient was also higher in patients who were identified to have moderate ARDS, mild ARDS, or normal levels by P/FP ratio as compared to P/F ratio ($p < 0.05$).

Prognostic Utility

Mortality decreased (Table 4) as the severity of ARDS decreased when classified by both P/F ratio and P/FP ratio ($p < 0.05$).

The ROC curve (Fig. 5) was plotted to analyze the diagnostic accuracy of OSI, OI, P/F ratio, P/FP ratio, and S/F ratio in identifying

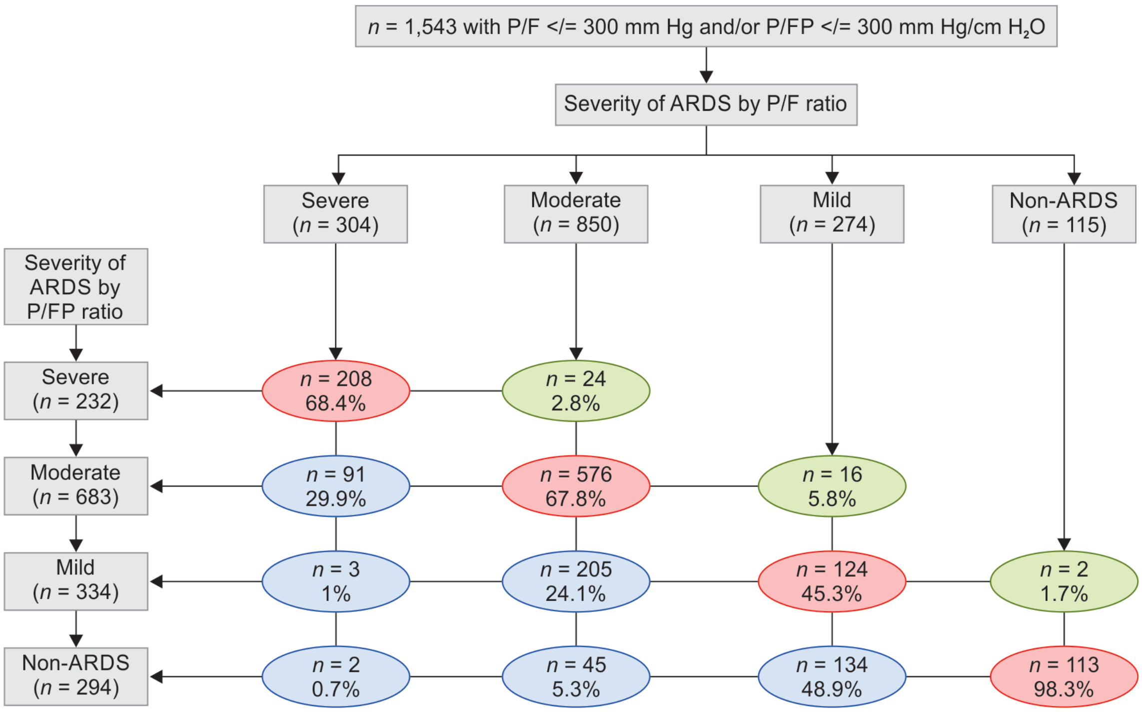

Fig. 1: Change of severity when P/FP ratio is used instead of P/F ratio

Table 2: Prevalence of ARDS as identified using P/F ratio and P/FP ratio

P/F ratio	*P/FP ratio*				*Cohen Kappa (p-value)*
	Severe (<100)	Moderate (100–200)	Mild (200–300)	Normal (>300)	0.498 (0.001)
Severe (<100)	208 (89.7%)	91 (13.3%)	3 (0.9%)	2 (0.7%)	
Moderate (100–200)	24 (10.3%)	576 (84.3%)	205 (61.4%)	45 (15.3%)	
Mild (200–300)	0 (0%)	16 (2.3%)	124 (37.1%)	134 (45.6%)	
Normal (>300)	0 (0%)	0 (0%)	2 (0.6%)	113 (38.4%)	

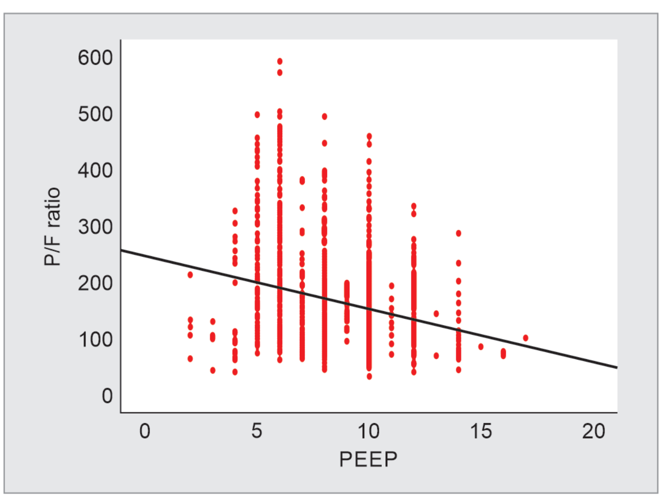

Fig. 2: Correlation between P/F ratio and PEEP

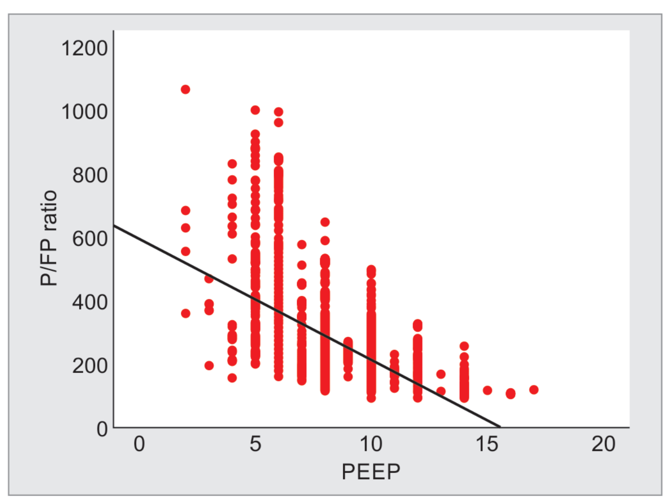

Fig. 3: Correlation between P/FP ratio and PEEP

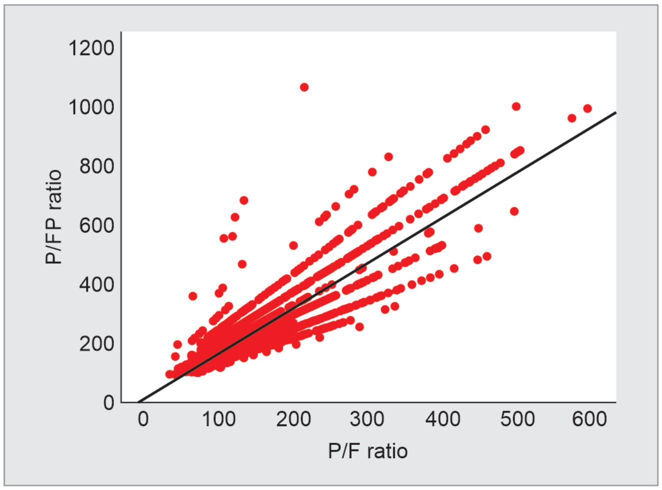

Fig. 4: Correlation between P/F ratio and P/FP ratio

mortality or survival. A higher OSI and OI predicted mortality, whereas a lower P/F ratio, P/FP ratio, and S/F ratio predicted mortality.

Higher OSI (AUC = 0.750, 95% CI = 0.726–0.774), OI (AUC = 0.744. 95% CI = 0.720–0.768)[3] predicted mortality whereas higher P/F ratio (AUC = 0.732, 95% CI = 0.707–0.757), P/FP ratio (AUC = 0.727, 95% CI = 0.702–0.753), and S/F ratio (AUC = 0.744, 95% CI = 0.719–0.768) predicted survival ($p < 0.001$).

The cut-offs for OSI and OI to predict mortality were previously published in our prior publication.[3] According to the P/F ratio, a cut-off of <162 was identified as increasing the risk of mortality, with a sensitivity of 62.7%, specificity of 71%, and Youden's index of 0.34. Similarly using the P/FP ratio, a cut-off of <213 was identified as increasing the risk of mortality, with a sensitivity of 56.2%, specificity of 77%, and Youden's index of 0.34. For the S/F ratio, a cut-off of <190 was identified as increasing the risk of mortality, with a sensitivity of 56.6%, specificity of 78%, and Youden's index of 0.35 (Table 5).

Multivariate Logistic Regression

A multivariate logistic regression (Table 6) was conducted to determine the impact of Pmean, S/F ratio, OI, and P/FP ratio on mortality. P/F ratio and OSI were not included in the analysis as they were collinear with other variables. The regression equation was found to be statistically significant ($p < 0.05$), and the model explained 18.9 to 25.9% of the variation in mortality (Cox & Snell R square and Nagelkerke R square). Based on the regression analysis, only the OI ratio had a significant impact on mortality ($p < 0.05$), while Pmean, S/F ratio, and P/FP ratio did not have a significant impact ($p < 0.05$). The odds of mortality increased by 0.853 times as the OI value decreased ($p = 0.002$).

Discussion

In this secondary analysis, we aimed to study the correlation between P/F ratio and P/FP ratio in C-ARDS. We analyzed individual measurements and re-categorized them based on P/FP values, as the clinical progression of C-ARDS can vary greatly.[4] The spectrum of pulmonary compliance in C-ARDS ranges from a benign L-type with higher compliance to a severe H-type with lower compliance. Patients who were reclassified into the severe and moderate ARDS categories had higher PEEP and FiO_2 levels, indicating a greater

Table 3: Blood gas when classified into different categories of ARDS by P/F ratio or P/FP ratio [*p*-value for comparison between patients identified for various levels of ARDS by P/F ratio vs P/FP ratio]

Blood gas and oxygenation parameters	*Severe ARDS (≤100)*			*Moderate ARDS (101–200)*			*Mild ARDS (201–300)*			*Normal (≥301)*		
	P/F ratio	*P/FP ratio*	*p-value*	*P/F ratio*	*P/FP ratio*	*p-value*	*P/F ratio*	*P/FP ratio*	*p-value*	*P/F ratio*	*P/FP ratio*	*p-value*
N	304	232		850	683		274	334		115	294	
pH	7.3 ± 0.6	7.2 ± 0.6	0.836	7.4 ± 0.1	7.4 ± 0.1	0.648	7.4 ± 0.1	7.4 ± 0.1	0.641	7.4 ± 0.1	7.4 ± 0.1	0.523
$PaCO_2$	60.1 ± 19	60 ± 19.2	0.970	47.6 ± 15	49.6 ± 14	0.007	41.9 ± 10.5	44.6 ± 16.8	0.023	38.7 ± 8.4	40.6 ± 10.9	0.086
PaO_2	69.7 ± 12.7	68.5 ± 12.1	0.257	82.9 ± 18	83.2 ± 19.5	0.700	103.4 ± 27.6	92.9 ± 27.4	0.001	135.6 ± 34.5	108.1 ± 34.4	0.001
SpO_2	90.3 ± 6.3	90.2 ± 6.7	0.823	94.4 ± 3.3	94.1 ± 3.5	0.101	96.3 ± 2.5	95.1 ± 3.4	0.001	97.4 ± 3.1	96.3 ± 3.4	0.006
FiO_2	0.9 ± 0.1	0.9 ± 0.1	0.502	0.6 ± 0.1	0.6 ± 0.2	0.001	0.4 ± 0.1	0.5 ± 0.1	0.001	0.4 ± 0.1	0.4 ± 0.1	0.008
Lactate	2.8 ± 2.6	2.8 ± 2.3	0.830	2.1 ± 1.6	2.2 ± 1.9	0.263	2 ± 1.4	2 ± 1.2	0.982	1.8 ± 0.8	2 ± 1.5	0.232
PEEP	9.2 ± 2.6	10.7 ± 1.9	0.001	8.6 ± 2.1	9.1 ± 1.8	0.001	8 ± 2.3	7.8 ± 1.9	0.214	6.8 ± 1.8	6.1 ± 1.5	0.001
S/F ratio	104.8 ± 22.6	105.9 ± 22.3	0.583	170.3 ± 38.7	155.6 ± 37.2	0.001	234.9 ± 53.1	198.1 ± 44	0.001	281.4 ± 59.7	259.9 ± 59.6	0.001
P/F ratio	79.6 ± 14.4	79.6 ± 17.3	0.997	145.4 ± 27.9	134.6 ± 32.6	0.001	239.7 ± 27.3	187.1 ± 45.4	0.001	376.2 ± 63.9	285.1 ± 90.3	0.001
P/FP ratio	96.4 ± 41.5	76.1 ± 16.4	0.001	181.6 ± 65.7	150.2 ± 28.7	0.001	328.3 ± 117.5	241.1 ± 27.5	0.001	591 ± 175.7	479 ± 160.4	0.001
Oxygenation factor	4.8 ± 1.3	4.4 ± 1.1	0.001	9.5 ± 2.6	8.3 ± 2	0.001	17.5 ± 5.2	12.8 ± 2.9	0.001	31.7 ± 9.1	23.8 ± 9.7	0.001
A-a O_2 gradient	487.5 ± 86.4	483.3 ± 93	0.589	274 ± 86	311.5 ± 102.3	0.001	154.3 ± 59	213.5 ± 82.6	0.001	75.2 ± 41	121.9 ± 70.6	0.001

Table 4: Mortality across ARDS severity categories

Outcomes	*Severe (<100)*	*Moderate (100–200)*	*Mild (200–300)*	*Normal (>300)*	*p-value*
Mortality when classified by P/F ratio					
N	61	98	28	14	
Non-survivor	53 (86.9%)	60 (61.2%)	13 (46.4%)	3 (21.4%)	0.001
Survivor	8 (13.1%)	38 (38.8%)	15 (53.6%)	11 (78.6%)	
Mortality when classified by P/FP ratio					
N	47	100	31	23	
Non-survivor	37 (78.7%)	70 (70%)	14 (45.2%)	8 (34.8%)	0.001
Survivor	10 (21.3%)	30 (30%)	17 (54.8%)	15 (65.2%)	

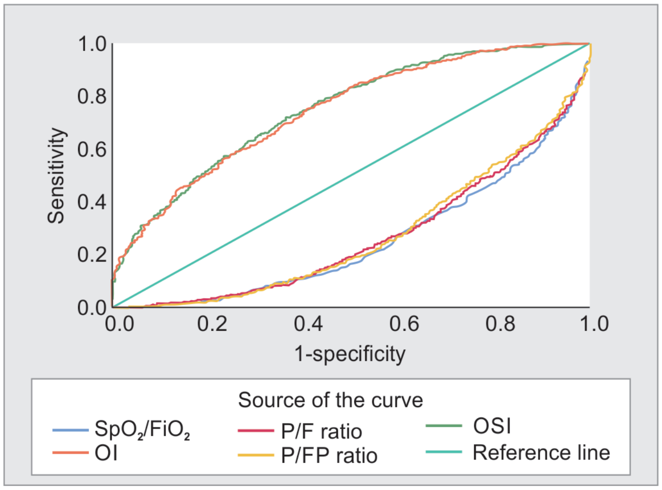

Fig. 5: ROC curves (overall) for identifying mortality or survival risk based on OSI, OI, P/F ratio, P/FP ratio, and S/F ratio

Table 5: Overall ROC sensitivity and specificity

ROC analysis	*OI*	*OSI*	*P/F*	*P/FP*	*S/F*
Sensitivity	74.1%	72%	62.7%	56.2%	56.6%
Specificity	60%	64%	71%	77%	78%

Table 6: Multivariable logistic regression analysis

Variable	*B*	*p-value*	*Expo B (odd's ratio)*	*95% CI*
Pmean	−0.014	0.843	0.986	0.862–1.129
S/F ratio	0.004	0.413	1.004	0.995–1.013
OI	−0.159	0.002	0.853	0.772–0.944
P/FP ratio	−0.001	0.692	0.999	0.995–1.033

degree of diffuse alveolar damage. The P/F ratio, which is used to define ARDS, can vary depending on the levels of FiO_2 and PEEP. Therefore, measuring the P/F ratio at standardized levels of FiO_2 and PEEP would better reflect the severity of lung injury and allow for better monitoring of patient progress. Pmean is influenced by PEEP, peak inspiratory pressure, and inspiratory to expiratory ratio, and it correlates with mean alveolar pressure,[5] venous return, arterial oxygenation, and the risk of barotrauma.[6] *P* mean also reflects the stresses applied to the lungs during invasive ventilation.[7]

In the original study, it was noted that higher oxygenation indices (OI and OSI) significantly predict mortality.[3] In this cohort, the area under the curve (AUC) for OI and OSI is better compared to P/FP ratio. The sensitivity of mortality is also higher when *P* mean is included in the analysis, rather than just considering PEEP. P/FP ratio is a weak predictor of mortality compared to OI and OSI. *P* mean is a better variable for prognostication, as it is captured on all modes of ventilation and is affected by factors such as increased airway resistance, decreased chest wall compliance, decreased pulmonary compliance, increased dead space, or increased work of breathing. Pmean, an important variable in OI and OSI, is better able to reflect the severity of lung disease. Multiple studies have shown OI and OSI to have significant correlation in predicting mortality in ARDS.[8,9]

As noted, not all C-ARDS patients have the same phenotype, and an individual's phenotype may change over time.[10] The lung in C-ARDS demonstrates dynamic and heterogeneous alveolar damage, both from the primary pathology and ventilator-induced lung injury. Given the dynamic nature of C-ARDS, we analyzed independent measurements for this study.

The strengths of our study include analyzing changes in severity by looking at trends at varying FiO_2 and PEEP levels, corresponding to the dynamic nature of C-ARDS with variable lung injury. This was an exploratory analysis.

Limitations of this study include its retrospective and single-center design. Additionally, patients were only given controlled mode of ventilation, so the findings may not be applicable to those who received spontaneous ventilation. It is important to note that the impact of regional pulmonary heterogeneity, chest wall stiffness, and patient positioning on the studied parameters was not considered.

Oxygenation indices that incorporate mechanical ventilator parameters are superior in assessing oxygenation status and classifying the severity of ARDS, with a greater predictive validity of in-hospital mortality compared to the P/F ratio. These indices provide a more realistic picture of the severity of ARDS by integrating values from mechanical ventilation.

Conclusion

We observed that the OI and OSI were more sensitive than the PaO_2/FiO_2 ratio and P/FP ratio. Additionally, only the oxygenation index had a significant impact on mortality. By including airway pressures in the calculation of the OI, its predictive ability is enhanced compared to using the S/F ratio, P/F ratio, or P/FP ratio. Our data support the need for studies that include Pmean to evaluate oxygenation status in ARDS patients.

Ethics Approval

The study was approved by the Institutional Ethics Committee (IEC – A Code: 018/2020, IEC – A Code: 047/2021).

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