ORIGINAL ARTICLE

Correlation and Prognostic Significance of Oxygenation Indices in Invasively Ventilated Adults (OXIVA-CARDS) with COVID-19-associated ARDS: A Retrospective Study

Sonali Vadi[1], Durga Suthar[2], Neha Sanwalka[3]

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Abstract

Background: Oxygenation index [OI = (MAP × FiO_2 × 100)/PaO_2] assesses the severity of hypoxic respiratory failure. Oxygen saturation index [OSI = (MAP × FiO_2 × 100)/SpO_2] is a noninvasive method to assesses the severity of hypoxic respiratory failure. Conventionally used PaO_2/FiO_2 (P/F) ratio to measure the severity of ARDS requires arterial blood gas (ABG) sampling. It tenders limited prognostic information mandating the need for better markers. Oxygenation index (needs arterial sampling) and OSI (a noninvasive method) are substitutes to provide mortality information in ARDS patients. We evaluated the correlation between P/F, OI, and OSI in invasively ventilated COVID-19 ARDS patients (C-ARDS) and looked at its relationship with mortality.

Patients and methods: A retrospective study of invasively ventilated C-ARDS >18 years of age managed in COVID ICU. Ventilator settings (FiO_2, mean airway pressure), pulse oximetry (SpO_2), and ABG values (PaO_2) were simultaneously noted at the time of sample collection. Patient outcomes (alive and deceased) were documented. Differences in parameters between survivors and nonsurvivors were assessed using independent sample *t*-test. Receiver operating characteristic (ROC) analysis with Youden's index was used to identify cutoff values to determine survival.

Results: A total of 1557 measurements for 203 patients were collected over the maximum duration of 21 days after ventilation. About 147 (72.4%) were males and 56 (27.6%) were females. On day one of ventilation, 161 (79.3%) had P/F ratio <200, 28 (13.8%) had P/F ratio between 200 and 300, and 14 (6.9%) had P/F ratio >300. There was a linear relationship between P/F ratio and OSI ($r = -0.671$), P/F and OI ($r = -0.753$), and OSI and OI ($r = 0.893$) ($p < 0.001$). After natural log transform, the correlation between these factors became stronger [P/F ratio and OSI ($r = -0.797$), PF and OI ($r = -0.949$), and OSI and OI ($r = 0.902$) ($p < 0.001$)]. About 74 (36.5%) patients survived. Survivors had significantly higher P/F ratio as compared with nonsurvivors ($p < 0.05$). Oxygen saturation index and OI were significantly lower in survivors as compared with nonsurvivors. Based on day-1 reading, a higher OSI (AUC = 0.719, 95% CI = 0.648–0.790) and OI (AUC = 0.752. 95% CI = 0.684–0.819) significantly can predict mortality. On the other hand, a higher P/F ratio can predict survival (AUC = 0.734, 95% CI = 0.664–0.805). P/F ratio of 160 on day 1 can predict survival. Oxygen saturation index values above 10.4% and OI above 13.5% were the cutoff derived for day 1 values to predict mortality.

Conclusion: Noninvasive OSI can be used to assess the severity of hypoxic respiratory failure in C-ARDS without arterial access in resource-limited settings. Oxygen saturation index can noninvasively provide prognostic information in invasively ventilated C-ARDS patients.

Keywords: COVID-19 acute respiratory distress syndrome, Oxygenation index, Oxygen saturation index, PaO_2/FiO_2, Prognostication.

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Introduction

Partial pressure of oxygen in arterial blood (PaO_2) to inspired fraction of oxygen (FiO_2) (P/F) ratio is used to denote the severity of lung injury in mechanically ventilated patients. However, P/F ratio does not reflect mechanical ventilation settings, changes in lung compliance, and pulmonary shunt factors that influence the severity of lung injury. P/F ratio does not account for mean airway pressure (MAP). Mean airway pressure is determined by peak inspiratory pressure, positive end-expiratory pressure, and inspiratory-to-expiratory time ratio.[1] Mean airway pressure is sensitive to increased airway resistance, reduced lung/chest wall compliance, or increased dead space and work of breathing.[2] Mean airway pressure reflects mean alveolar pressure throughout inspiration and expiration. It is a component of OI and OSI. Mean airway pressure correlates with arterial oxygenation, alveolar ventilation, hemodynamic performance, and barotrauma.[3] It is measured by the ventilator with each breath. These are better accounted for by the oxygenation index (OI = MAP × FiO_2 × 100/PaO_2)[4] and oxygen saturation index (OSI = MAP × FiO_2/SpO_2).[5] Oxygenation index [OI = (MAP × FiO_2 × 100)/PaO_2] assesses the severity of hypoxic respiratory failure. PaO_2 requires arterial puncture. Pulse oximetry is a noninvasive method to monitor arterial hemoglobin oxygen saturation. Pulse oximetry oxygen saturation (SpO_2) is the standard of care for continuous recording of oxygenation status, a noninvasive and cost-effective substitute to snapshot arterial blood gas (ABG) employed to quantify the ratio of PaO_2 to the fraction of inspired oxygen

[1,2]Department of Intensive Care Medicine, Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute, Mumbai, India

[3]Department of Nutrition and Biostatistics, NutriCanvas, Mumbai, Maharashtra, India

Corresponding Author: Sonali Vadi, Department of Intensive Care Medicine, Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute, Mumbai, India, Phone: +91 2242696969, e-mail: sonalivadi@hotmail.com

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(PaO_2/FiO_2 ratio).[6] Oxygen saturation index is a noninvasive method to assess the severity of hypoxic respiratory failure. Oxygen titration is done commonly using pulse oximetry readings.

In a previously reported study on non-COVID ARDS patients,[7] a correlation was noted between P/F, OI, and OSI. COVID-19-associated acute respiratory distress syndrome (C-ARDS) has impacted the lung majorly. Patients have required lung-protective ventilation. Oxygenation was titrated using PaO_2. This requires arterial puncture. Given the dynamic nature of C-ARDS, frequent arterial blood sampling was required. Frequent ABG sampling may not be feasible in resource-limited settings. Oxygen saturation index is a noninvasive alternative for P/F ratio.

Herein, we looked at the correlation between PaO_2/FiO_2 (P/F), OI, and OSI in invasively ventilated COVID-19 ARDS patients (C-ARDS) where ABG monitoring is not readily accessible. We studied their relationship with mortality.

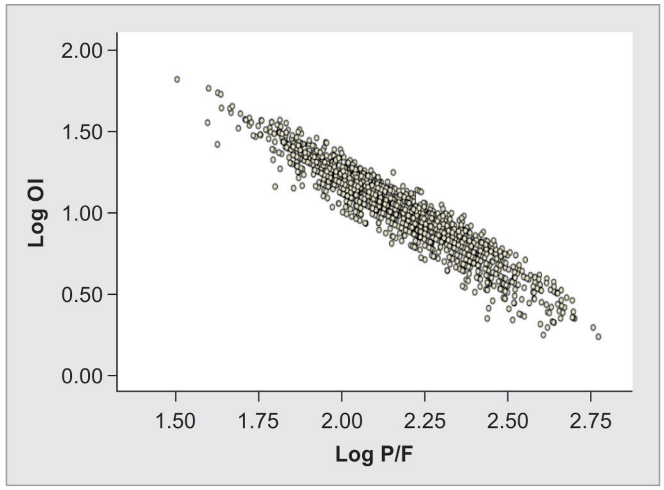

Fig. 1: Scatter plot showing ln (P/F ratio) and ln (OI) for 1557 measurements. The axes for P/F ratio and OI are on natural logarithmic scale

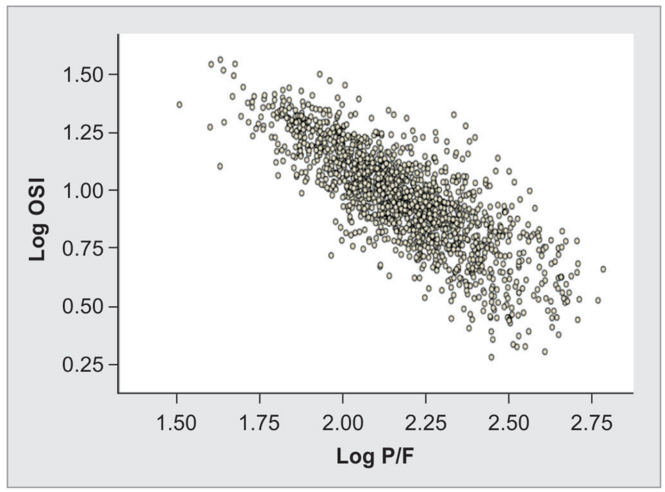

Fig. 2: Scatter plot showing ln (P/F ratio) and ln (OSI) for 1557 measurements. The axes for P/F ratio and OSI are on natural logarithmic scale

Patients and Methods

Study Design, Patient Selection, and Data Collection

OXIVA-CARDS study was a retrospective study of mechanically ventilated COVID-19 ARDS patients in Mumbai, India. Eligibility criteria included adult patients more than 18 years of age who were invasively ventilated for C-ARDS for more than 24 hours. All patients had an arterial catheter *in situ*. Data collected included ventilator settings [FiO_2, mean airway pressure, and positive end-expiratory pressure], pulse oximetry (SpO_2), and ABG values [PaO_2]. Mechanical ventilation data and SpO_2 were recorded simultaneously at the time of the first ABG sampling of the day between 5:00 and 6:00 AM during their stay in the COVID ICU. SpO_2 reading ensuring a clean and fitting sensor was noted after a consistent, pulsatile tracing was obtained for at least a minute. Patients were prone ventilated as per their oxygenation status. Patients were followed until hospital discharge or death. Data were collected in 203 patients. Data were noted daily till the patient got discharged or died. A total of 1557 measurements for 203 consecutive invasively mechanically ventilated patients were collected over a maximum duration of 21 days after ventilation from August 2020 to September 2022.

The study was approved by the Institutional Ethics Committee (047/2021). Written informed consent was waived owing to the observational nature of the study.

Definition

- Acute respiratory distress syndrome = ARDS was identified at baseline if patients met the Berlin criteria.[8]
- Shock = systolic blood pressure $\leq$ 90 mm Hg, or mean arterial pressure $\leq$ 65 mm Hg for at least 1 hour despite adequate fluid resuscitation or the need of vasoactive medications to maintain systolic blood pressure $\geq$90 mm Hg, or mean arterial pressure $\geq$65 mm Hg.
- P/F ratio = PaO_2/FiO_2
- Oxygenation index [$OI = (MAP \times FiO_2 \times 100)/PaO_2$]
- Oxygen saturation index [$OSI = (MAP \times FiO_2 \times 100)/SpO_2$].

Statistical Analysis

Analyses were performed using SPSS software for Windows (version 25, 2007, IBM Corporation, Armonk, New York, United States). Data are presented as frequency (%) or mean $\pm$ SD. Differences in parameters between survivors and nonsurvivors were assessed using independent sample *t*-test. Receiver operating characteristic (ROC) analysis with Youden's index was used to identify cutoff values to determine survival. Area under the curve was calculated. Odds ratio with 95% confidence interval was calculated to predict the risk of mortality using cutoffs developed in the current study. Data were analyzed for day 1 as well as a cumulative data of 1557 readings. $p < 0.05$ was considered to be statistically significant (Figs 1 and 2).

Results

A total of 1557 measurements for 203 consecutive invasively mechanically ventilated patients were collected over a maximum duration of 21 days after ventilation from August 2020 to September 2022. From the 203 patients, 147 (72.4%) were males and 56 (27.6%) were females. The age group of patients was 61.5 $\pm$ 13.9 years.

On day 1 of ventilation, 161 (79.3%) had P/F ratio <200, 28 (13.8%) had P/F ratio between 200 and 300, and 14 (6.9%) had P/F ratio >300.

There was a linear relationship between P/F ratio and OSI ($r = -0.671$), PF and OI ($r = -0.753$), and OSI and OI ($r = 0.893$) ($p < 0.001$). After natural log transform, the correlation between these factors became stronger [P/F ratio and OSI ($r = -0.797$), PF and OI ($r = -0.949$), and OSI and OI ($r = 0.902$) ($p < 0.001$)] (Fig. 3).

About 74 (36.5%) patients survived, whereas 129 (63.5%) patients did not survive.

Survivors had significantly higher SpO_2 and PaO_2 as compared with nonsurvivors ($p < 0.05$) (Table 1). Mean airway pressure was significantly higher in nonsurvivors as compared with survivors ($p < 0.05$). No significant difference in hemoglobin was observed.

P/F ratio, OI, and OSI levels on day 1 as well as cumulative 1557 readings were compared between survivors and nonsurvivors (Table 2). Survivors had significantly higher P/F ratio as compared with nonsurvivors (both day 1 and over 1557 readings) ($p < 0.05$). On the other hand, OSI and OI were significantly lower in survivors as compared with nonsurvivors (both day 1 and over 1557 readings) ($p < 0.05$).

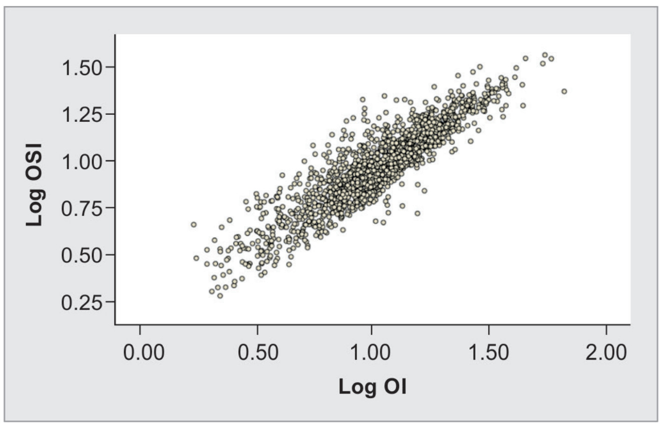

Fig. 3: Scatter plot showing ln (OI) and ln (OSI) for 1557 measurements. The axes for P/F ratio and OSI are on natural logarithmic scale

Table 1: Baseline findings

	Survivors	*Nonsurvivors*	*Total*	*p-value*
Day 1 SpO_2	95.8 ± 4.7	93.9 ± 5.9	94.6 ± 5.5	0.020
Day 1 PaO_2	112.4 ± 39.4	93.5 ± 28.4	100.4 ± 34	0.001
Day 1 MAP	15.5 ± 3.0	17.0 ± 2.8	16.5 ± 2.9	0.001
Day 1 hemoglobin	11.8 ± 2.3	11.8 ± 2.3	11.8 ± 2.3	0.993

MAP, mean airway pressure; PaO_2, partial pressure of oxygen in arterial blood; SpO_2, pulse oximetry oxygen saturation

We evaluated the ability of P/F ratio, OI, and OSI discreetly to predict in-hospital mortality of C-ARDS patients (Figs 4 and 5).

Day 1 Reading ROC

A higher OSI (AUC = 0.719, 95% CI = 0.648–0.790) and OI (AUC = 0.752, 95% CI = 0.684–0.819) significantly can predict mortality. A higher P/F ratio can predict survival (AUC = 0.734, 95% CI = 0.664–0.805). Oxygen saturation index values above 10.4% and

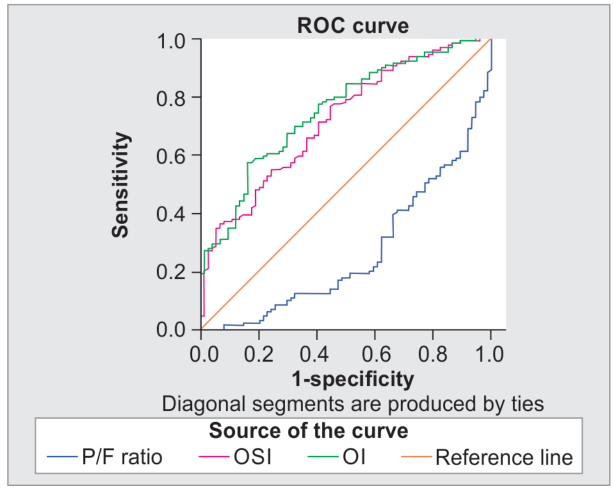

Fig. 4: Receiver operating characteristics (ROC) curves of P/F ratio, OI, and OSI on day 1 for mortality prediction

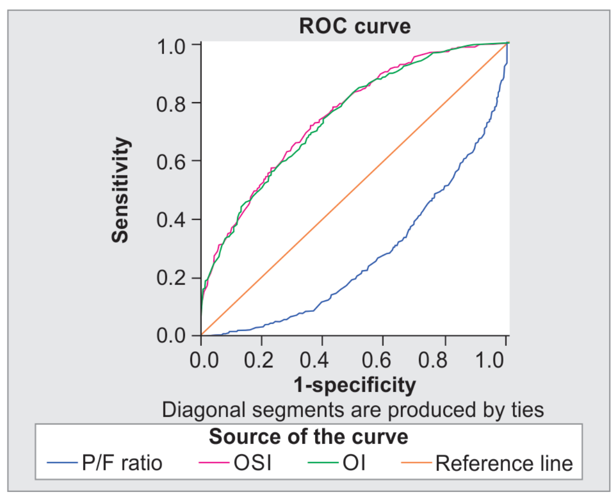

Fig. 5: Receiver operating characteristics (ROC) curves of P/F ratio, OI, and OSI over 1557 readings for mortality prediction

Table 2: Oxygenation indices compared between survivors and nonsurvivors

		Survivors	*Nonsurvivors*	*Total*	*p-value*
P/F ratio	Day 1	194 ± 94.6	128.8 ± 59.4	152.6 ± 80.4	0.001
	1557 reading	205.5 ± 94	138.9 ± 60	166.3 ± 82.8	0.001
OSI	Day 1	10.6 ± 4.4	14.7 ± 4.6	13.2 ± 5.4	0.001
	1557 reading	7.9 ± 3.6	12.1 ± 5.3	10.4 ± 5.1	0.001
OI	Day 1	9.8 ± 4.7	16.1 ± 8.2	13.8 ± 7.7	0.001
	1557 reading	8.8 ± 4.5	14.5 ± 7.8	12.1 ± 7.2	0.001

Table 3: Risk factor of mortality based on cutoffs developed in the study

	Day 1 cutoff				*Cutoff derived from 1557 readings*			
	Cutoff	*OR*	*95% CI*	*p-value*	*Cutoff*	*OR*	*95% CI*	*p-value*
P/F ratio	≤160	1			≤162			
	>160	0.172	0.091–0.324	0.001	>162	0.172	0.091–0.324	0.001
OSI	≤10.4	1			≤8.5			
	>10.4	4.057	2.190–7.514	0.001	≤8.5	5.00	2.41–10.344	0.001
OI	≤13.5	1			≤9.1	1		
	>13.5	6.952	3.418–14.137	0.001	9.1	4.633	2.393–8.968	0.001

CI, confidence interval; OI, oxygenation index; OR, odds ratio; OSI, oxygen saturation index; P/F, PaO_2/FiO_2

OI above 13.5% were the cutoff derived for day 1 values to predict mortality. On the other hand, P/F ratio of 160 on day 1 can predict survival.

ROC of 1557 Readings

A higher OSI (AUC = 0.750, 95% CI = 0.726–0.774), OI (AUC = 0.744, 95% CI = 0.720–0.768) significantly can predict mortality. A higher P/F ratio can predict survival (AUC = 0.731, 95% CI = 0.706–0.756). Oxygen saturation index values above 8.5% and OI above 9.1% were the cutoff derived for 1557 values to predict mortality. On the other hand, P/F ratio of 162 overall could predict survival.

Based on the cutoffs derived from the ROC, patients with OSI >10.4 (77.5% vs 45.9%) and OI >13.5 (57.4% vs 16.2%) had higher risk of mortality, whereas patients with P/F ratio <160 had higher risk of mortality (59.5% vs 20.2%) based on day 1 cutoffs.

Based on 1557 readings, patients with OSI >8.5 (89.1% vs 62.2%) and OI >9.1 (84.5% vs 54.1%) had higher risk of mortality, whereas patients with P/F ratio <162 had higher risk of mortality (59.5% vs 20.2%). Table 3 gives the odds ratio for mortality based on cutoffs derived from the study.

Discussion

Arterial blood gas sampling requires arterial access and is coupled with complications of arterial access, its pre-analytic errors, variation in its method of sampling and transportation, and issues that are magnified in resource-limited settings. Our main aim was to search for a correlation between P/F ratio, OI, and OSI to facilitate use of OSI as a monitoring parameter that reflects oxygenation status in the invasively ventilated.

We noted a strong correlation between the P/F ratio and OI and OI and OSI in our study cohort. By incorporating MAP into the new oxygenation index, changes in PEEP, inspiratory-to-expiratory time ratio, and tidal volume, which can all affect the MAP, are reflected in the new oxygenation index.[9] Mean airway pressure reflects changes in lung compliance and oxygenation deficit, presenting a better estimate of the degree of acute lung injury.[10] The gold-standard for oxygenation status, a clinician needs to take a call on the use of alternatives of ABG in clinical practice. Noninvasively monitored SpO_2 can be considered to be a reasonable alternative to PaO_2 to monitor invasively ventilated C-ARDS.

P/F ratio was higher, while OI and OSI were lower in survivors. Analyzed on day 1 and as a cumulative, all these oxygenation indices were associated with mortality in the C-ARDS cohort.

Oxygen saturation index discriminates mortality irrespective of an ABG. This was seen on day 1 as well as over cumulative readings. It seems reasonable to use SpO_2 metrics for severity of illness scoring when employed in resource-limited settings. We identified a cutoff value for these oxygenation indices to predict mortality. Oxygenation index cutoff value of 13.5 and OSI cutoff value of 10.4 had the best predictive performance, with OI >13.5 having seven times the risk of death than patients with OI ≤ 13.5 and OSI >10.4 having four times the risk of death than patients with OSI ≤ 10.4. Overall, OI and OSI were good prognostic indicators than P/F ratio in C-ARDS. On the whole, noninvasive SpO_2 can be counted on as an effective and useful surrogate of mortality in C-ARDS in contrast to PaO_2, which requires ABG sampling. Oxygenation index and OSI are not yet incorporated in the hypoxemia criteria for invasively ventilated ARDS patients. Both have a better prognostic validity than P/F ratio.

More frequent use of prone positioning and higher use of neuromuscular blockade in C-ARDS patients reflect the severity of lung involvement.

A major strength of our study is the correlation of variables over a period of several days rather than a snapshot in time. To our knowledge, this study is the first to examine OSI in C-ARDS from India. The strength of using OSI is that which incorporates MAP. Mean airway pressure provides estimation of the severity of pulmonary disease, compliance of the respiratory system, and the need for respiratory support. Oxygen saturation index is indicative of mortality, irrespective of ABG as shown in our findings.

This study has some limitations. This was a retrospective, single-center study. Patients received a controlled mode of ventilation. Hence, the relationship of MAP and OI and OSI to mortality in those receiving spontaneous mode of ventilation cannot be extrapolated. Our cohort is from a single center that influences the generalizability of results.

Our study reiterates the use of OSI to understand the severity of and prognosticate C-ARDS. With data available on the diagnostic and prognostic ability of OI and OSI in invasively ventilated non-COVID-19 as well as COVID-19 ARDS, further prospective studies are required on severity classification and outcomes in this group of patients.

Conclusion

We observed a strong correlation between the P/F ratio and OI and OI and OSI in C-ARDS adults receiving invasive mechanical ventilation. Future prospective studies will help evaluate whether monitoring OSI and/or OI over the P/F ratio will impact treatment outcomes.

Oxygen saturation index noninvasively prognosticates the severity of C-ARDS irrespective of an ABG. Inclusion of SpO_2 metrics for severity of illness scoring should be considered.

Orcid

Sonali Vadi https://orcid.org/0000-0002-7341-2407
Durga Suthar https://orcid.org/0000-0002-9533-1069
Neha Sanwalka https://orcid.org/0000-0003-3428-3144

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