Oxygenation Saturation Index Predicts Clinical Outcomes in ARDS

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BACKGROUND: Traditional measures of ARDS severity such as P_{aO_2}/F_{iO_2} may not reliably predict clinical outcomes. The oxygenation index (OI [$F_{iO_2} \times \text{mean airway pressure} \times 100/P_{aO_2}$]) may more accurately reflect ARDS severity but requires arterial blood gas measurement. We hypothesized that the oxygenation saturation index (OSI [$F_{iO_2} \times \text{mean airway pressure} \times 100/\text{oxygen saturation by pulse oximetry (SpO}_2\text{)}$]) is a reliable noninvasive surrogate for the OI that is associated with hospital mortality and ventilator-free days (VFDs) in patients with ARDS.

METHODS: Critically ill patients enrolled in a prospective cohort study were eligible if they developed ARDS (Berlin criteria) during the first 4 ICU days and had mean airway pressure, SpO_2/F_{iO_2} , and P_{aO_2}/F_{iO_2} values recorded on the first day of ARDS ($N = 329$). The highest mean airway pressure and lowest SpO_2/F_{iO_2} and P_{aO_2}/F_{iO_2} values were used to calculate OI and OSI. The association between OI or OSI and hospital mortality or VFD was analyzed by using logistic regression and linear regression, respectively. The area under the receiver-operating characteristic curve (AUC) for mortality was compared among OI, OSI, SpO_2/F_{iO_2} , P_{aO_2}/F_{iO_2} , and Acute Physiology and Chronic Health Evaluation II scores.

RESULTS: OI and OSI were strongly correlated ($\rho = 0.862$; $P < .001$). OSI was independently associated with hospital mortality (OR per 5-point increase in OSI, 1.228 [95% CI, 1.056-1.429]; $P = .008$). OI and OSI were each associated with a reduction in VFD (OI, $P = .023$; OSI, $P = .005$). The AUC for mortality prediction was greatest for Acute Physiology and Chronic Health Evaluation II scores (AUC, 0.695; $P < .005$) and OSI (AUC, 0.602; $P = .007$). The AUC for OSI was substantially better in patients aged < 40 years (AUC, 0.779; $P < .001$).

CONCLUSIONS: In patients with ARDS, the OSI was correlated with the OI. The OSI on the day of ARDS diagnosis was significantly associated with increased mortality and fewer VFDs. The findings suggest that OSI is a reliable surrogate for OI that can noninvasively provide prognostic information and assessment of ARDS severity.

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KEY WORDS: acute lung injury; APACHE; ARDS; critical care/shock; noninvasive technique

ABBREVIATIONS: AECC = American-European Consensus Conference; APACHE II = Acute Physiology and Chronic Health Evaluation II; AUC = area under the receiver-operating characteristic curve; IQR = interquartile range; LIS = Lung Injury Score; MAP = mean airway pressure; OI = oxygenation index; OSI = oxygenation saturation index; PEEP = positive end-expiratory pressure; SpO_2 = oxygen saturation measured by pulse oximetry; VFD = ventilator-free day

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Although it has been nearly 50 years since the first description of ARDS,¹ predicting the outcome of patients with ARDS continues to be a challenge. A recent international, multicenter observational cohort study found that morbidity and mortality from ARDS remain high.² Furthermore, interventions to improve outcomes are largely limited to supportive measures such as lung-protective ventilation strategies,³ differential positive end-expiratory pressure (PEEP) strategies,⁴ and prone positioning.⁵ One potential reason for the dearth of effective therapies is the lack of simple, reliable methods for risk stratification at the bedside that will help target therapies to the most severely ill patients. Although several measures, such as the ratio of PaO_2 to FiO_2 and the Lung Injury Score (LIS), have traditionally been used in both clinical practice and clinical trials, these offer limited prognostic information or require arterial blood gas analysis,^{6–11} highlighting the need for simple, noninvasive predictive measures.

Both current and previous ARDS definitions have attempted to incorporate severity assessments to reflect prognosis. The Berlin definition of ARDS¹² addresses some of the challenges and drawbacks of the American-European Consensus Conference (AECC) definition.¹³ For example, the Berlin definition includes a minimum PEEP value to account for the effect of mechanical ventilator settings on $\text{PaO}_2/\text{FiO}_2$. Despite these improvements, however, the Berlin definition is only slightly better than the AECC definition for prognostication in ARDS (area under the receiver-operating characteristic curve [AUC], 0.577 vs 0.536).¹² This scenario may be partially related to the dependence of

both the AECC and Berlin definitions on $\text{PaO}_2/\text{FiO}_2$ as the primary measure of ARDS severity. Multiple studies have shown that $\text{PaO}_2/\text{FiO}_2$ is not an independent predictor of mortality in patients with ARDS in multivariate analyses that control for other measures of severity of illness.^{7,10,14}

The $\text{PaO}_2/\text{FiO}_2$ does not reflect other aspects of the severity of acute lung injury such as mechanical ventilation settings, changes in lung compliance, and pulmonary shunt.^{6,11,15,16} A measure that better accounts for these factors is the oxygenation index (OI), measured as follows: $\text{FiO}_2/\text{PaO}_2 \times \text{mean airway pressure (MAP)} \times 100$. The OI was first investigated as a prognostic tool for acute hypoxemic respiratory failure in pediatric populations¹⁷ and has since been shown to be an independent risk factor for mortality in adults with ARDS.^{14,16,18,19} As with the $\text{PaO}_2/\text{FiO}_2$, however, this measure relies on invasive blood gas monitoring. Assessment of the severity of hypoxemia by using noninvasive pulse oximetry ($\text{SpO}_2/\text{FiO}_2$) has been used as a substitute for $\text{PaO}_2/\text{FiO}_2$ in Sequential Organ Failure Assessment scoring²⁰ and can be used for ARDS diagnosis.^{21,22} In pediatric patients, the oxygenation saturation index (OSI), measured as $(\text{FiO}_2 \times \text{MAP} \times 100)/\text{SpO}_2$, was as effective as the OI in predicting mortality, and saturation-based measurements identified more patients with ARDS than those identified on the basis of blood gas analysis.²³

Based on these findings, we hypothesized that the OSI is a noninvasive surrogate for OI in adults with ARDS that is associated with increased mortality and a reduction in ventilator-free days (VFDs).

Methods

Study Design

This trial was a nested retrospective cohort study of patients prospectively enrolled in the Validating Acute Lung Injury Markers for Diagnosis (VALID) study. Patients who were eligible for enrollment in VALID were ≥ 18 years old and admitted to the Vanderbilt University Medical Center medical, surgical, cardiovascular, or trauma ICU for at least 2 days. Full inclusion and exclusion criteria have been previously described elsewhere.²⁴ Written informed consent was obtained at the time of enrollment from the patients or a surrogate when possible. Because the study poses

minimal risk to patients, the Vanderbilt University institutional review board approved the study protocol with a waiver of informed consent if the patient was unable to consent and no surrogate was available (Vanderbilt institutional review board no. 051065).

Study Population

Patients meeting inclusion criteria for VALID were further eligible for the current study if they developed ARDS (Berlin criteria)¹² on any of the first 4 days of their ICU stay. MAP data were only captured in the electronic medical record after September 2009; therefore, patients eligible for the current study cohort include those enrolled in VALID between September 2009 and June 2016. Because we sought to directly compare the OI vs the OSI in the same cohort, patients missing any of the variables necessary to calculate each measure (MAP, $\text{PaO}_2/\text{FiO}_2$, or $\text{SpO}_2/\text{FiO}_2$) were excluded.

A total of 329 patients were included in the final analysis (Fig 1). In general, these patients were managed with a lower PEEP/ FiO_2 titration strategy and low tidal volume with plateau pressures of < 30 cm H_2O . Data were not collected on use of prone positioning but it was used only rarely.

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Figure 1 – Flow diagram for inclusion of VALID patients in final analysis. MAP = mean airway pressure; VALID = Validating Acute Lung Injury Markers for Diagnosis.

Data Collection

Demographic data, prehospital medications, medical history, and admission diagnoses were collected at VALID enrollment. Clinical data such as hemodynamic variables, ventilator settings, laboratory values, and in-hospital medications were collected daily for the first 4 days in the ICU. These values were used to calculate illness severity scores (Acute Physiology and Chronic Health Evaluation II [APACHE II] and Simplified Acute Physiology Score II). The lowest $\text{PaO}_2/\text{FiO}_2$ and $\text{SpO}_2/\text{FiO}_2$ were recorded from each ICU day. Pulse oximetry data was only used to calculate an $\text{SpO}_2/\text{FiO}_2$ ratio if the minimum saturation from that day was $< 97\%$.²¹ Diagnoses of ARDS, sepsis, and organ dysfunction were made during the first

4 days of ICU admission by consensus of two physician investigators according to consensus definitions.^{25,26} Outcomes, including length of hospital stay, length of ICU admission, VFDs (defined as the number of days alive and off mechanical ventilation in the 28 days following study enrollment),²⁷ and hospital mortality, were collected. All available MAP values in the electronic medical record were filtered to select for the highest available measurement on the day of ARDS diagnosis.

The OI and OSI were calculated for each patient by using the following formulas:

$$\text{OI} = \frac{\text{FiO}_2 \times \text{MAP} \times 100}{\text{PaO}_2}, \quad \text{OSI} = \frac{\text{FiO}_2 \times \text{MAP} \times 100}{\text{SpO}_2}$$

Statistical Analysis

Normally distributed continuous variables are presented as mean $\pm$ SD, and nonnormally distributed continuous variables are presented as medians with interquartile ranges (IQRs). Categorical variables are presented as counts and percentages. The relationship between OI and OSI was analyzed by using the Spearman correlation. A Mann-Whitney *U* test was used to compare OI and OSI between patients who lived and patients who died. Multivariable logistical regression modeling was used to analyze the association between OI or OSI and in-hospital mortality controlling for age, sex, and APACHE II score. For visual representation of the relationship between OSI and clinical outcomes, the relationship between quintile of OSI and mortality was analyzed according to a linear-by-linear association. Linear regression modeling was used to analyze the association between OI or OSI and VFD.

We also analyzed models including measures traditionally used to assess degree of lung injury ($\text{PaO}_2/\text{FiO}_2$, $\text{SpO}_2/\text{FiO}_2$, and LIS) in place of OI or OSI. Receiver-operating characteristic curves were used to analyze the prognostic value for mortality for each ARDS severity measure along with the APACHE II score. Statistical analysis was performed by using SPSS version 24.0 (IBM SPSS Statistics, IBM Corporation), and a two-sided significance level of 0.05 was used for statistical inference.

Results

Patient Characteristics

A total of 329 patients met inclusion criteria for this study. Demographic characteristics and clinical data are described in Table 1. Predicted body weights were not available in the VALID study. Average tidal volume/kilogram (based on actual weight on day of diagnosis as we did not have height available for all patients to calculate ideal body weight) was 5.7 ± 1.9 cc/kg. The highest PEEP value on the day of ARDS diagnosis was 10 ± 4 cm H_2O .

OI and OSI Are Strongly Correlated With Each Other

In this cohort of patients, OI and OSI were strongly correlated (Spearman $\rho = 0.862$; $P < .001$) (Fig 2), suggesting that the OSI, which is continuously available through noninvasive measures, is a reliable surrogate for the OI in adult patients with ARDS.

Clinical Outcomes Are Associated With OI and OSI

Table 2 compares the indices of ARDS severity between hospital survivors and nonsurvivors. Both the OI and the OSI were higher in patients who died in the hospital; however, only the difference in OSI was significant between survivors and nonsurvivors. The median OI was 13 (IQR, 8-26) in patients who died compared with 11 (IQR, 7-20; $P = .097$) in patients who survived. The median OSI was 11 (IQR, 8-21) in patients who died compared with 10 (IQR, 6-16; $P = .007$) in patients who survived. The $\text{PaO}_2/\text{FiO}_2$ was not significantly different between patients who lived and died. The $\text{SpO}_2/\text{FiO}_2$ was significantly lower in patients who died in the hospital ($P = .011$). There was no statistical difference between the LIS for patients who survived to hospital discharge and those who did not.

The primary outcome of interest was in-hospital mortality. As OSI increased, hospital mortality rose, as shown by the increase in hospital mortality according to

TABLE 1] Clinical Characteristics of 329 Patients With ARDS

Characteristic	Value
Age, y	51 ± 18
Male sex	208 (63)
Race	
White	288 (87)
Black	31 (9)
Other	10 (4)
Weight, kg	86 ± 27
ICU location	
Surgical	48 (15)
Medical	105 (32)
Trauma	172 (52)
Cardiovascular	4 (1)
ARDS risk factor	
Nonpulmonary sepsis	64 (20)
Pneumonia	45 (14)
Severe traumatic injuries	162 (49)
Aspiration	36 (11)
Multiple transfusions	8 (2)
Other	12 (4)
Severe sepsis present ^a	155 (47)
APACHE II score ^b	29 ± 7
Nonpulmonary organ failures, No. ^a	1 ± 1
Lowest Pao ₂ /Fio ₂ ratio ^a	148 (89-203)
Lowest Spo ₂ /Fio ₂ ratio ^a	162 (98-233)
Highest mean airway pressure, mm Hg	16 (13-22)
Oxygenation index ^a	12 (7-21)
Oxygen saturation index ^a	10 (6-17)
Lung Injury Score ^a	2.7 ± 0.7
Days in ICU	9 (6-15)
Death in hospital	78 (24)
Ventilator-free days	16 (1-22)

Continuous variables are presented as mean ± SD or median (interquartile range) if not normally distributed; categorical variables are presented as No. (%). APACHE II = Acute Physiology and Chronic Health Evaluation II; Spo₂ = oxygen saturation measured by pulse oximetry

^aOn day of ARDS diagnosis.

^bOn enrollment.

quintile of OSI in [Figure 3](#) ($P = .012$). In a multivariable logistic regression controlling for age, sex, and APACHE II score, OSI was independently associated with mortality ([Table 3](#)). Pao₂/Fio₂, Spo₂/Fio₂, OI, and LIS were not independently associated with mortality (data not shown). To determine if the relationship between OSI and hospital mortality differed according to etiology of ARDS, we repeated the analysis in patients with ARDS caused by sepsis and patients with nonseptic

Figure 2 – Oxygenation index vs oxygenation saturation index. Spearman rho = 0.862; $P < .001$.

ARDS. In logistic regression analysis controlling for the same variables, the odds of hospital mortality increased with increasing OSI for both patients with sepsis (OR for 5-point increase in OSI, 1.295) and for nonseptic patients (OR for 5-point increase in OSI, 1.154), although the association was no longer significant in the nonseptic patients, possibly due to reduced power.

Linear regression modeling was used to analyze the relationship between measures of ARDS severity and the number of VFDs. Controlling for the same covariates as noted earlier, increased OSI was independently associated with fewer VFDs ($\beta = -0.167$ [95% CI, -0.284 to -0.050]; $P = .005$). This association held true among both patients with sepsis ($\beta = -0.180$ [95% CI, -0.357 to -0.003]; $P = .047$) and nonseptic patients, although it did not remain statistically significant in nonseptic patients ($\beta = -0.154$ [95% CI, -0.313 to -0.005]; $P = .054$). Higher OI was also significantly associated with fewer VFDs ($\beta = -0.058$ [95% CI, -0.108 to -0.008]; $P = .023$), but higher LIS, lower Pao₂/Fio₂, and lower Spo₂/Fio₂ were not.

OI and OSI Improve Prognostic Discrimination

We tested the individual performance of OSI, OI, Pao₂/Fio₂, Spo₂/Fio₂, and LIS to predict hospital mortality by calculating the AUC ([Table 4](#)). The OSI (AUC, 0.602), OI (AUC, 0.562), and Spo₂/Fio₂ (AUC, 0.595) had moderate performance for mortality prediction, although the AUC for OI did not reach statistical significance. We also computed the AUC for APACHE II, which was shown in a single-center observational study to be a significant predictor of mortality in

TABLE 2] Comparison of Five Indices of ARDS Severity Between Patients Who Survived and Those Who Died in the Hospital

Index	Died in the Hospital	Survived	P value
Oxygen saturation index	11 (8-21)	10 (6-16)	.007
Oxygenation index	13 (8-26)	11 (7-20)	.097
SpO ₂ /FIO ₂	147 (93-228)	176 (115-233)	.011
PaO ₂ /FIO ₂	132 (86-195)	150 (92-209)	.206
Lung Injury Score	2.8 ± 0.7	2.7 ± 0.7	.295

Data are presented as median (interquartile range) for variables that are not normally distributed or as mean ± SD. See Table 1 legend for expansion of abbreviation.

patients with ARDS,²⁸ for comparison. As expected, the performance was greatest for APACHE II, a much more complex predictive variable that takes into account both acute and chronic multisystem organ function (AUC, 0.695 [95% CI, 0.629-0.761]; $P < .001$). Finally, because the association between OSI and mortality is reportedly much stronger in children (AUC, 0.793),²³ the analysis was restricted to younger patients (age < 40 years) to determine if discrimination was improved. The AUC was substantially better in the younger patient group (AUC, 0.779 [95% CI, 0.652-0.908]; $P < .001$) (Fig 4).

Discussion

In 329 adults with ARDS who were mechanically ventilated, the OSI was highly correlated with the OI. Both the OSI and the OI were independently associated with fewer VFDs, whereas the traditional metric for characterizing ARDS severity, PaO₂/FIO₂, was not. Among the ARDS severity measures analyzed, only OSI was significantly associated with mortality in this cohort. Furthermore, both OSI and OI were superior to the PaO₂/FIO₂ in prognostic performance. Based on analysis of receiver-operating curves, the OSI may have stronger performance than the OI, as the latter did not reach statistical significance for mortality prediction.

The results of our study reinforce the value of using a noninvasive saturation-based measurement when clinically appropriate. As previously described, relying on arterial blood gas measurements for the diagnosis of ARDS may contribute to its underrecognition by clinicians.^{2,21,23} Furthermore, repeated blood draws in the ICU setting contribute to iatrogenic anemia, need for blood transfusions, increased risk of infection, and higher cost of care.²⁹ Aside from decreasing harm, saturation-based measurements are continually available in almost all hospital settings, including relatively resource-poor ones such as developing countries. Rice et al²¹ and others have described the role that

saturation-based measurements play in the diagnosis of ARDS,²² and our study showed that saturation-based measurements are useful not only for diagnosis but also for prognostication.

In this cohort, PaO₂/FIO₂ on the day of ARDS diagnosis was not independently associated with clinical outcomes, whereas the saturation-based predictors (SpO₂/FIO₂ and OSI) and the OI were. Because we excluded patients for whom either PaO₂/FIO₂ or SpO₂/FIO₂ was not calculable, the difference cannot be explained simply by which patients had a blood gas sample drawn and which did not. One potential explanation is that saturation-based measurements are more sensitive for detecting changes in oxygenation that will affect a patient's clinical course because they are continuously available rather than intermittently available. A strength of using the OSI rather than the SpO₂/FIO₂ alone is its incorporation of MAP, which provides a more complete estimate of the extent of acute lung injury by reflecting not only oxygenation deficit but also aggressiveness of respiratory support and changes in lung compliance.

Figure 3 – Percent hospital mortality according to oxygenation saturation index quintile ($P = .012$).

TABLE 3] Logistic Regression Models for Hospital Mortality in 329 Patients With ARDS and Subgroups With or Without Severe Sepsis

Characteristic	OR ^a	95% CI	P Value
Entire cohort (N = 329, 24% mortality)			
Oxygen saturation index	1.228	1.056-1.429	.008
Age	1.019	1.002-1.035	.024
Male sex	1.458	0.839-2.535	.181
APACHE II	1.087	1.043-1.133	< .001
Patients with severe sepsis (n = 155, 32% mortality)			
Oxygen saturation index	1.295	1.046-1.589	.016
Age	1.020	0.997-1.043	.085
Male sex	1.213	0.583-2.524	.606
APACHE II	1.053	1.009-1.133	.012
Patients without severe sepsis (n = 174, 17% mortality)			
Oxygen saturation index	1.154	0.918-1.456	.222
Age	1.016	0.992-1.039	.188
Male sex	1.702	0.720-4.021	.226
APACHE II	1.089	1.015-1.168	.017

^aORs are per 5-point increases in OSI, 1-year increases in age, and 1-point increases in APACHE II scores. See Table 1 legend for expansion of abbreviation.

To the best of our knowledge, the present study is the first to investigate the OSI in adults. This research expands on the work of Khemani et al,²³ which showed that average saturation-based measurements on the first day of ARDS diagnosis were more predictive of mortality than arterial blood gas–based measurements when diagnosing ARDS in children for whom both arterial blood gas and pulse oximetry data were available. In children for whom pulse oximetry data were not available, saturation-based measurements had similarly strong prognostic value. In the present cohort, the OSI exhibited improved performance for mortality

prediction among patients aged < 40 years. The OSI may be particularly useful in these younger patients with ARDS, who are less likely to have complex comorbidities that affect clinical outcomes.

The present study has several strengths. The VALID cohort is a prospectively enrolled cohort with high-quality data, including very detailed phenotyping for ARDS. The large cohort size for the present study and the use of data that were collected for clinical indications rather than research purposes enhance the potential generalizability of the study. There are also some limitations, however. First, patients whose minimum

TABLE 4] Comparison of Areas Under the Receiver-Operating Characteristic Curve for Discrimination of Hospital Survival for Five Indices of ARDS Severity

Measure	Area Under the Receiver-Operating Characteristic Curve	95% CI	P Value
Oxygen saturation index	0.602	0.531-0.673	.007
Oxygenation index	0.562	0.490-0.635	.097
SpO ₂ /FIO ₂	0.595	0.520-0.670	.011
Pao ₂ /FIO ₂	0.547	0.476-0.619	.206
Lung Injury Score	0.540	0.465-0.616	.326
APACHE II	0.695	0.629-0.761	< .001
Oxygen saturation index (age < 40 y)	0.779	0.650-0.908	< .001
AECC definition ^a	0.536	0.520-0.553	< .001
Berlin definition ^a	0.577	0.561-0.593	< .001

AECC = American-European Consensus Conference. See Table 1 legend for expansion of other abbreviations.

^aValues from Force et al.¹²

Figure 4 – Receiver-operating characteristic (ROC) curve for mortality prediction. Red: ROC curve for the oxygenation saturation index ($P = .007$) for the entire cohort. Blue: ROC curve for Acute Physiology and Chronic Health Evaluation II scores ($P < .001$) for the entire cohort. Gray: ROC curve for the oxygenation saturation index ($P < .001$) for patients aged < 40 years. Orange: ROC for $\text{PaO}_2/\text{FiO}_2$ ($P = .206$).

SpO_2 value was $\geq 97\%$ were excluded because large changes in PaO_2 cause almost no change in the SpO_2 when the saturation is $\geq 97\%$, and the commonly used National Heart, Lung and Blood Institute ARDS Clinical Trials Network mechanical ventilation strategy recommends targeting an SpO_2 between 88% and 95%.³⁰ This criterion excluded from our study 86 patients in VALID who met the Berlin criteria of ARDS according to the $\text{PaO}_2/\text{FiO}_2$ ratio. Thirty-two additional patients were excluded who did not have a recorded $\text{SpO}_2/\text{FiO}_2$ ratio on the day of ARDS diagnosis. We also only investigated the prognostic value of OI and OSI on the

day of ARDS diagnosis and did not account for any information that could be gleaned from changes in these values over time. We focused on the day of ARDS diagnosis because the number of patients who had arterial blood gas analysis for calculation of OI on subsequent days was low, limiting power. Gajic et al¹⁴ reported that changes in variables (including the OI) over 3 days provides more prognostic information than the same data from the first day alone.

A potential limitation of our primary end point of hospital mortality is that it does not account for patients who were terminally ill and were discharged to another inpatient facility or hospice care and died shortly thereafter. However, OI and OSI were also associated with VFDs as a secondary end point, a respiratory-centered end point that may be more relevant to ARDS outcomes. Future studies could include a time-to-death analysis. In addition, the association between OSI and mortality was not statistically significant in patients without severe sepsis, which likely reflects a low event rate in nonseptic patients (17% mortality) rather than an inherent weakness of the OSI. Lastly, our study population was predominantly composed of white, male trauma patients. A larger, multicenter prospective study with a more heterogeneous population is necessary to validate our results.

Conclusions

Measurement of the OSI on the day of ARDS diagnosis performed as well as the OI in predicting clinical outcomes, was simple to calculate and continuously available, and offered more prognostic information than traditional measures of ARDS severity such as $\text{PaO}_2/\text{FiO}_2$, while avoiding invasive arterial blood gas monitoring.

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Author contributions: L. B. W. is the guarantor of this study and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. K. D. served as principal author; K. D. and L. B. W. contributed to the study concept design and writing of the manuscript; and J. B. M., C. M. S., J. A. B., and C. W. contributed to data analysis and interpretation, study design, statistical analysis, and revision of the manuscript.

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