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Nonlinear Imputation of Pa_{O_2}/F_{IO_2} From Sp_{O_2}/F_{IO_2} Among Patients With Acute Respiratory Distress Syndrome

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BACKGROUND: ARDS is an important clinical problem. The definition of ARDS requires testing of arterial blood gas to define the ratio of Pa_{O_2} to F_{IO_2} (Pa_{O_2}/F_{IO_2} ratio). However, many patients with ARDS do not undergo blood gas measurement, which may result in underdiagnosis of the condition. As a consequence, a method for estimating Pa_{O_2} on the basis of noninvasive measurements is desirable.

METHODS: Using data from three ARDS Network studies, we analyzed the enrollment arterial blood gas measurements to compare nonlinear with linear and log-linear imputation methods of estimating Pa_{O_2} from percent saturation of hemoglobin with oxygen as measured by pulse oximetry (Sp_{O_2}). We compared mortality on the basis of various measured and imputed Pa_{O_2}/F_{IO_2} ratio cutoffs to ensure clinical equivalence.

RESULTS: We studied 1,184 patients, in 707 of whom the $Sp_{O_2} \leq 96\%$. Nonlinear imputation from the Sp_{O_2}/F_{IO_2} ratio resulted in lower error than linear or log-linear imputation ($P < .001$) for patients with $Sp_{O_2} \leq 96\%$ but was equivalent to log-linear imputation in all patients. Ninety-day hospital mortality was 26% to 30%, depending on the Pa_{O_2}/F_{IO_2} ratio, whether nonlinearly imputed or measured. On multivariate regression, the association between imputed and measured Pa_{O_2} varied by use of vasopressors and Sp_{O_2}.

CONCLUSIONS: A nonlinear equation more accurately imputes Pa_{O_2}/F_{IO_2} from Sp_{O_2}/F_{IO_2} than linear or log-linear equations, with similar observed hospital mortality depending on Sp_{O_2}/F_{IO_2} ratio vs measured Pa_{O_2}/F_{IO_2} ratios. While further refinement through prospective validation is indicated, a nonlinear imputation appears superior to prior approaches to imputation.

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KEY WORDS: acute respiratory distress syndrome; pulse oximetry; respiratory failure; severity scores

FOR EDITORIAL COMMENT SEE PAGE 266

ABBREVIATIONS: ABG = arterial blood gas; ALTA = Albuterol for the Treatment of ALI; CRF = case report form; EDEN = Early vs Delayed Enteral Nutrition; OMEGA = Omega-3 Fatty Acid Supplementation; PETAL = Prevention and Early Treatment of Acute Lung Injury; RMSE = root mean square error; SAILS = Statins for Acutely Injured Lungs From Sepsis; Sa_{O_2} = arterial oxygen saturation; Sp_{O_2} = oxygen saturation as measured by pulse oximetry

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ARDS is an important clinical, research, and public health problem, affecting approximately 200,000 Americans annually.[1] ARDS is a syndrome with a range of severities. The ratio of Pa_{O_2} to F_{IO_2} (Pa_{O_2}/F_{IO_2} ratio) measures the severity of hypoxemia in patients with ARDS. The Pa_{O_2}/F_{IO_2} ratio has been incorporated into the consensus definition of ARDS: Pa_{O_2}/F_{IO_2} ratios of 201 to 300, 101 to 200, and $\leq$ 100 define mild, moderate, and severe ARDS, respectively.[2] The Pa_{O_2}/F_{IO_2} ratio has also been incorporated into general critical illness severity indices such as the Sequential Organ Failure Assessment score.[3]

Arterial blood gas (ABG) measurement is required to determine Pa_{O_2} and calculate the Pa_{O_2}/F_{IO_2} ratio. However, patients with ARDS may not be able to undergo ABG testing in a relevant time frame: arterial catheters (which increase the convenience of ABG testing) are falling out of favor,[4,5] pulse oximeters have become more accurate and consistent, and some physicians use venous blood gases to monitor P_{CO_2} and pH.[6] The lack of ABG results could potentially lead to underdiagnosis or late recognition of patients with ARDS, potentially delaying application of appropriate treatments such as lung-protective ventilation strategies. A noninvasive surrogate for the Pa_{O_2}/F_{IO_2} ratio, based on measuring the oxyhemoglobin percent saturation with a pulse oximeter (Sp_{O_2}), would allow patients without ABG data to be evaluated for ARDS, including in assessment of disease severity. To ensure equivalence, a noninvasive surrogate would require imputation of Pa_{O_2} from Sp_{O_2}. The Sp_{O_2}/F_{IO_2} ratio has been proposed as a noninvasive surrogate for the Pa_{O_2}/F_{IO_2} ratio.[7-12]

The oxyhemoglobin percent saturation can be measured with a pulse oximeter (Sp_{O_2}), or directly in the arterial blood (Sa_{O_2}). The relationship between Pa_{O_2} and Sa_{O_2} (and therefore Sp_{O_2}) is sigmoidal. However, prior work investigating the association between Sp_{O_2}/F_{IO_2} and Pa_{O_2}/F_{IO_2} ratios employed linear (or log-linear) regression modeling in adults[7,8] and children.[9-12]

The Ellis inversion[13] of the Severinghaus equation[14] (the Ellis equation is included in e-Table 1) provides a useful nonlinear method for imputing Pa_{O_2} from Sa_{O_2}. This technique has been used in cohorts of mostly nonintubated patients with pneumonia[15-18] but not in patients with ARDS. We hypothesized that (1) nonlinear imputation of Pa_{O_2} based on measured Sp_{O_2} would outperform linear and log-linear imputations among patients with ARDS; (2) imputed and measured Pa_{O_2}/F_{IO_2} ratios would identify patients with similar 90-day hospital mortality; (3) certain patient characteristics, such as positive end-expiratory pressure or shock requiring vasopressors, would affect the accuracy of imputation; and (4) imputation would be inaccurate for $Sp_{O_2} > 96\%$ (based on the plateau in the hemoglobin-oxygen dissociation curve).[14]

Materials and Methods

We studied patients enrolled in studies within the second round of funding for the NIH/NHLBI ARDS Network: Early vs Delayed Enteral Nutrition (EDEN),[19] Omega-3 Fatty Acid Supplementation (OMEGA),[20] and Statins for Acutely Injured Lungs From Sepsis (SAILS).[21] Because Albuterol for the Treatment of Acute Lung Injury (ALTA)[22] did not collect baseline ABG data with an associated Sp_{O_2}, we excluded those patients. Patients were enrolled in included trials using largely consistent inclusion and exclusion criteria (while SAILS enrolled only patients with sepsis-associated ARDS, sepsis was a common cause of ARDS in all studies) that matched general consensus criteria for the diagnosis of ARDS.[23] To be eligible, patients had to have a Pa_{O_2}/F_{IO_2} ratio $<$ 300 at some point before randomization.

We obtained data for all subjects from the prospectively completed case report forms (CRFs). We used ABG data from the "baseline ventilator parameters" CRF, which is completed with the data closest to 8 AM on the day of enrollment. We also obtained age, sex, body mass index, mean arterial pressure, use of vasopressors (including any dose of norepinephrine, epinephrine, dopamine, phenylephrine, or vasopressin) at enrollment, ventilator parameters, study hospital, volume of fluid administered in the 24 hours before enrollment, serum bilirubin, F_{IO_2} and Sp_{O_2} at the time of ABG measurement, and 90-day hospital mortality. Research coordinators were instructed to record the Sp_{O_2} value reported with the ABG test results.

We used the formulas presented in e-Table 1 to impute Pa_{O_2} values from available Sp_{O_2}, using the Ellis nonlinear,[13] Rice linear,[7] and Pandharipande log-linear[8] equations. The Pa_{O_2} values imputed from the respective equations were compared with the measured Pa_{O_2} from the given ABG results. While expanded equations that

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incorporate other parameters (eg, pH and P_{CO_2}) exist, we chose equations that depended only on oxygen saturation to avoid dependence on ABG results, the unavailability of which is the primary motivation for the use of noninvasive surrogates for Pa_{O_2}.

We excluded patients for whom F_{IO_2}, Pa_{O_2}, and Sp_{O_2} were not recorded for ABG analyses on their baseline ventilator parameters CRF. Because Pa_{O_2} varies by both F_{IO_2} and barometric pressure, we adjusted Pa_{O_2}/F_{IO_2} ratios at the Denver and Utah sites (altitude, approximately 1,500 m) by the ratio of local to sea-level barometric pressure (0.836 in Denver, 0.845 in Utah).

This secondary analysis of deidentified, previously collected prospective clinical trial data was classified as exempt by the Intermountain Healthcare Institutional Review Board (protocol no. 1040561).

Statistical Analysis

For the purposes of description, we calculated Spearman correlation for imputed Pa_{O_2}/F_{IO_2} vs measured Pa_{O_2}/F_{IO_2}, both for all patients and among patients in whom $Sp_{O_2} \leq 96\%$. For ease of exposition, we defined correlation as high (0.7-1.0), moderate (0.5-0.7), low (0.3-0.5), and negligible (0-0.3). For purposes of comparison, we calculated the root mean square error (RMSE) of the estimates (with Pa_{O_2}/F_{IO_2} as the true value) and compared the RMSE among the methods of imputation with a paired *t* test on the squared differences between the imputed and measured values.[24] Secondarily, we evaluated the imputation of Pa_{O_2}. Since the Rice equation converts Sp_{O_2}/F_{IO_2} to Pa_{O_2}/F_{IO_2}, we inverted the Rice equation and multiplied it by F_{IO_2} in order to generate a linearly imputed Pa_{O_2}. We followed a similar method with the Pandharipande log-linear equation. To understand the possible effect of other variables on the association between measured and imputed Pa_{O_2}/F_{IO_2} ratios, we incorporated relevant clinical covariates into a linear regression of imputed vs measured Pa_{O_2}/F_{IO_2} ratio. We used backward stepwise selection to select variables for inclusion in the linear regression model. For the Pa_{O_2}/F_{IO_2} thresholds that were used to define mortality strata in the Berlin ARDS definition,[2] we calculated the imputed Pa_{O_2}/F_{IO_2} that was associated with the same mortality as the measured Pa_{O_2}/F_{IO_2} threshold; we also calculated the 90-day hospital mortality associated with an imputed Pa_{O_2}/F_{IO_2} identical to the measured Pa_{O_2}/F_{IO_2}. All analyses were performed with the R Statistical Package version 3.2.1.[25]

Results

Among 1,628 patients enrolled in the ARDS Network studies, we identified 1,184 patients who met our inclusion criteria, as outlined in Figure 1. Of those 1,184 patients, 707 had $Sp_{O_2} \leq 96\%$. Table 1 displays the baseline characteristics of these patients, stratified by the study in which they were enrolled (all OMEGA patients were co-enrolled in EDEN, and therefore the two studies were merged for the purposes of Table 1).

The overall correlation between measured and imputed Pa_{O_2}/F_{IO_2} was high for nonlinear ($\rho = 0.84$), linear ($\rho = 0.73$), and log-linear ($\rho = 0.73$) imputation. The RMSE of the estimates was lower for nonlinear than linear ($P < .001$) imputation but not different from log-linear ($P = .92$) imputation. The overall correlation between measured and imputed Pa_{O_2} (n = 1,184) was high ($\rho = 0.72$) for nonlinear imputation, and negligible for linear imputation ($\rho = 0.13$) and log-linear imputation ($\rho = 0.30$). The RMSE of the estimates was lower for nonlinear than log-linear ($P < .001$) or linear ($P < .001$) imputation.

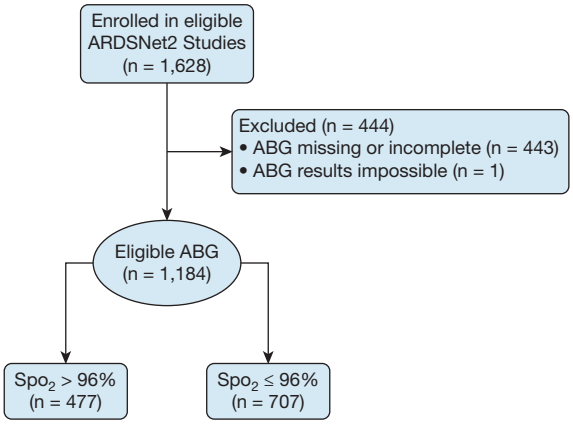

Figure 1 – *Identification of subjects for this study. ABG = arterial blood gas; ARDSNet = Acute Respiratory Distress Syndrome Network; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.*

When restricted to patients with $Sp_{O_2} \leq 96\%$ (n = 707), correlation between imputed and measured Pa_{O_2}/F_{IO_2} ratios was high for all imputations: nonlinear ($\rho = 0.90$), linear (0.88), and log-linear (0.88). For both Pa_{O_2} and Pa_{O_2}/F_{IO_2} estimates in this subgroup, nonlinear imputation had lower (mean, SD) RMSE (28.6, 51.7) than log-linear (32.2, 52.0) or linear (46.4, 66.4) imputation (all $P < .0001$). At $Pa_{O_2}/F_{IO_2} < 150$, the linear equation underestimated Pa_{O_2}/F_{IO_2} ratios and the log-linear equation overestimated Pa_{O_2}/F_{IO_2} ratios, while at $Pa_{O_2}/F_{IO_2} > 300$, the nonlinear equation tended to overestimate Pa_{O_2}/F_{IO_2} ratios. These findings are visually depicted in Figure 2, in which the error in each imputation strategy is plotted against the measured Pa_{O_2}/F_{IO_2} ratio, in a Bland-Altman plot adapted for use when one measurement is taken to be the "gold standard."

Mortality rates for threshold values of the Pa_{O_2}/F_{IO_2} ratio are displayed in Table 2. While the differences were slight, the nonlinear imputed Pa_{O_2}/F_{IO_2} thresholds were associated with mortality that was closer to the mortality associated with measured Pa_{O_2}/F_{IO_2} thresholds than linearly imputed Pa_{O_2}/F_{IO_2} thresholds. Specifically, percent mortality for measured and nonlinearly imputed Pa_{O_2}/F_{IO_2} were almost identical at Pa_{O_2}/F_{IO_2} thresholds of 100 (32% vs 32%), 150 (28% vs 29%), 200 (27% vs 28%), and 300 (26% vs 26%).

TABLE 1] Patient Characteristics by Study

Characteristic	EDEN/OMEGA (n = 534)	SAILS (n = 650)	*P* Value (for comparison)
Age, y	50.5 (15.5)	54.4 (16.3)	< .001
Female sex, %	49.8	49.2	.861
Race/ethnicity, %			
Latino/Hispanic	13.9	11.2	.184
White	75.7	78.3	.297
Black	15.5	14.3	.566
Sepsis as cause of ARDS, %	59.7	75.4	< .001
APACHE III score, points	90.2 (27)	93.6 (27.9)	.039
Vasopressors at baseline, %	35.8	44.5	.002
Baseline PEEP, cm H_2O	10 (4.4)	9.3 (3.8)	.003
Baseline tidal volume, mL	419.5 (96.7)	413.8 (83.8)	.352
Baseline Pao_2/Fio_2 ratio	163.3 (71.6)	170.2 (68.8)	.094
Death in health-care facility to 90 d, %	23.8	27.5	.143

APACHE = Acute Physiology and Chronic Health Evaluation; EDEN = Early vs Delayed Enteral Nutrition; OMEGA = Omega-3 Fatty Acid Supplementation; PEEP = positive end-expiratory pressure.

Discordant classification was relatively uncommon. Of the 1,184 patients, 764 (65%) were classified as having moderate or severe (as opposed to mild) ARDS ($Pao_2/Fio_2 \leq 200$) by both measured and imputed Pao_2/Fio_2; 70 (6%) met criteria only by measured Pao_2/Fio_2 (ie, false negative classification by imputed Pao_2/Fio_2), and 101 (9%) met criteria only by imputed Pao_2/Fio_2 (ie, false positive classification by imputed Pao_2/Fio_2). (The remaining 249 patients had mild ARDS by both measured and imputed Pao_2/Fio_2.) Patients with false negative results had higher mortality (27%) than patients with false positive results (21% mortality); the mortality of concordant patients with moderate ARDS was 28%, while that of concordant patients with mild ARDS was 22%. Concordance was not associated with mortality after controlling for age, positive end-expiratory pressure, and Acute Physiology and Chronic Health Evaluation (APACHE) III score.

On linear regression of imputed or measured Pao_2/Fio_2 restricted to patients with $Spo_2 \leq 96\%$, univariate regression had an R^2 of 0.75. Details of bivariate and multivariate regression are presented in Table 3. In the multivariate model only the imputed Pao_2/Fio_2 ratio, Spo_2, and vasopressor administration at the time of enrollment were significantly associated with the measured Pao_2/Fio_2 ratio (the final model had an adjusted R^2 of 0.76). The mean absolute difference between measured and imputed Pao_2/Fio_2 ratio for patients not receiving vasopressors was 11.0, while the mean absolute difference between measured and imputed Pao_2/Fio_2 ratio for patients receiving vasopressors was 15.8 ($P = .005$).

Discussion

In this secondary analysis of data from three clinical trials, we demonstrate that a nonlinear imputation based on the Severinghaus equation outperforms linear and log-linear imputations for Pao_2/Fio_2 in patients with ARDS. The superior performance was visible both in terms of error of the estimate and association with hospital mortality, particularly at low Pao_2/Fio_2 ratios. For defining severe ARDS as judged by low Pao_2/Fio_2, linear imputation performs relatively poorly, despite an overall reasonable correlation, because of its systematic bias. Our findings also confirm concerns about imputing Pao_2 for patients with $Spo_2 > 96\%$, as substantial variation of Pao_2 is present in higher Spo_2 ranges. We also found that the association of measured Pao_2/Fio_2 ratio and imputed Pao_2/Fio_2 ratio was affected by the use of vasopressors at the time of ABG testing, with patients receiving vasopressors having on average a lower imputed than measured Pao_2/Fio_2 ratio.

Our work on nonlinear imputation of Pao_2/Fio_2 extends prior studies in pneumonia,[15-18] which focused on emergency department patients, many of whom were not mechanically ventilated and whose data may not be applicable to ICU patients with ARDS. For convenience of use and reference, we include e-Tables 2 and 3 in the online article to demonstrate how one could incorporate physiologically based nonlinear

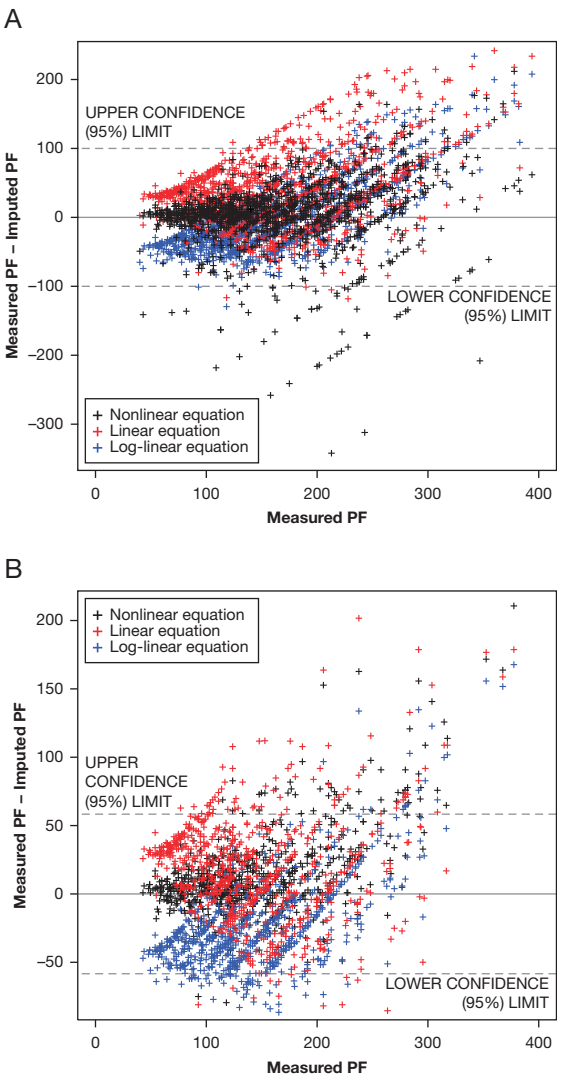

Figure 2 – *Measured vs imputed Pao_2/Fio_2 ratios. Imputation results: black = nonlinear; red = linear; blue = log-linear. A, Results from all patients (N = 1,184); B, Results from patients with $Spo_2 \leq 96\%$ (n = 707). PF = Pao_2/Fio_2 ratio. See Figure 1 legend for expansion of other abbreviations.*

imputation into screening and scoring activities, without the requirement for separate computer programs.

We note that 8% of patients had an Spo_2 of 100% at the time of enrollment. These patients on average were receiving a median Fio_2 of 60%. Forty percent of patients had saturations (> 96%) that placed them on the flat part of the hemoglobin dissociation curve; they too were receiving a median Fio_2 of 60%. These high oxygen levels were observed in hospitals that, as part of participation in ARDSNet studies, had access to oxygen titration protocols that target an Spo_2 of 88% to 95%. While debates about safe ranges for Fio_2 persist in the literature, the evidence for pulmonary oxygen toxicity[26,27] and the risk of oxidation related to hyperoxia suggest that needless hyperoxia should be avoided.[28] Decreases in Fio_2 for patients with high oxygen saturations would make imputation of Pao_2 more accurate, thereby potentially improving the accuracy of severity scores and clinical trial enrollments that depend on hypoxemia, and may also decrease the risk of pulmonary oxygen toxicity.

We note that the mortality observed in this cohort was lower for patients with moderate and severe ARDS (as judged by Pao_2/Fio_2 criteria) than was observed in the Berlin definition review of multiple studies.[2] The reasons for this difference in mortality are not immediately clear but may relate to the Berlin review's inclusion of patients not enrolled in clinical trials or to our studying only patients who underwent ABG testing on the day of enrollment and our use of the Pao_2/Fio_2 ratio on the day of enrollment rather than the Pao_2/Fio_2 ratio by which a patient qualified for study inclusion. Study exclusion criteria (eg, excluding moribund patients), and improvements in mortality between the studies evaluated for the Berlin definition and the more recent studies in our analysis, may also explain this difference. It is also possible that differences in ventilator management strategies account for the difference in mortality.[29]

Our study has limitations, most importantly the fact that the included ABG data were the result of routine clinical ABG testing, with the associated risk of

TABLE 2] Mortality Thresholds

Pao_2/Fio_2 Threshold	Total Patients	Mortality	Equivalent Nonlinear Imputed Pao_2/Fio_2 Threshold	Mortality for Nonlinear Imputed Pao_2/Fio_2 at Threshold	Equivalent Linear Imputed Pao_2/Fio_2 Threshold	Mortality for Linear Imputed Pao_2/Fio_2 at Threshold
100	199	0.322	98	0.316	81	0.290
150	547	0.283	162	0.286	118	0.274
200	834	0.276	164	0.268	138	0.259
300	1,144	0.261	218	0.260	244	0.259

TABLE 3] Linear Regression of Measured Pao_2/Fio_2 Ratio, With Potential Covariates

	Bivariate		Multivariate	
Predictor	Coefficient	*P* Value	Coefficient	*P* Value
Imputed Pao_2/Fio_2[a]	1.05 (1.005-1.093)	< .001	1.08 (1.03-1.13)	< .001
Vasopressors	5.27 (0.75-9.78)	.02	4.59 (0.16-9.03)	.04
Spo_2	−0.83 (−0.143 to −0.23)	.007	−0.79 (−1.39 to −0.19)	.01
Fio_2	−6.99 (−28.1 to 14.1)	.51	NA	NA
White race	−0.05 (−5.37 to 5.27)	.99	NA	NA
Black race	−1.27 (−7.73 to 5.20)	.7	NA	NA
Latino ethnicity	−2.12 (−8.54 to 4.31)	.52	NA	NA
Age, y	−0.11 (−0.25 to 0.04)	.14	NA	NA
Peak bilirubin, mg/dL	0.46 (−0.70 to 1.61)	.44	NA	NA
24-hour fluid input, mL	0.0009 (−4.5 to 0.002)	.06	NA	NA
MAP, mm Hg	−0.07 (−0.25 to 0.1)	.42	NA	NA
Tidal volume, mL	0.005 (−0.02 to 0.03)	.7	NA	NA
PEEP, cm H_2O	0.02 (−0.58 to 0.62)	.95	NA	NA
BMI, kg/m^2	−0.04 (−0.28 to 0.20)	.75	NA	NA
APACHE III, points	0.04 (−0.04 to 0.12)	.35	NA	NA
Peak hematocrit, %	0.26 (−0.08 to 0.61)	.14	NA	NA

MAP = mean arterial pressure; NA = not applicable. See Table 1 legend for expansion of other abbreviations.
[a]This model was univariate.

nonstandardization. We also acknowledge that we studied patients with diagnosed ARDS rather than a larger group of patients in whom ARDS was suspected but not necessarily confirmed. Such patients may be even more likely to have Spo_2 values on the flat portion of the hemoglobin dissociation curve, making Spo_2-based screening methods less useful in that population. In addition, we used the ABG measurement done on the day of enrollment rather than the initial qualifying ABG data (which lacked simultaneous Spo_2 measurement), which may have been performed on blood drawn up to 24 hours before randomization. The outcomes reported may therefore not match reports from patients in whom the nadir Pao_2/Fio_2 ratio on the first hospital day was considered to be the Pao_2/Fio_2 ratio that best represents disease severity. We also did not have information on oximeter type,[30] skin pigmentation,[30,31] body temperature, or other factors that may affect the accuracy of Spo_2 measurements. Whether our results would apply in patients without ARDS is unknown; similar results have been obtained in patients with pneumonia, but not in other cohorts.

In summary, a nonlinear equation more accurately imputes Pao_2/Fio_2 from Spo_2/Fio_2 than linear or log-linear equations, especially at low Pao_2 values. Mortality rates among patients with ARDS are similar whether their Pao_2/Fio_2 ratios are imputed or measured. Prospective validation of these findings, incorporating measurement of other factors relevant to the accuracy of Spo_2, is indicated.

Conclusions

Because the association between Spo_2 and Pao_2 is sigmoidal, the use of a nonlinear imputation strategy appears preferable to linear imputation strategies.

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Author contributions: S. M. B. had full access to all of the data and takes responsibility for the content of the manuscript, including data and analysis. S. M. B., D. S., and R. B. conceived the study in consultation with all other authors; S. M. B. and D. S. analyzed the data; S. M. B. wrote the first draft; all authors reviewed and revised the manuscript for important intellectual content; all authors approved the submitted version.

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

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