CHEST

Oxygen Targets for Patients Who Are Critically Ill

Emerging Data and State of Equipoise

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With roots dating back to the 18th century, supplemental oxygen is one of medicine's most common and fundamental therapies. However, despite generations of doctors using oxygen to treat hundreds of millions of patients, our understanding of how to use oxygen most effectively remains incomplete.

Humans and oxygen have a complicated relationship. During the early periods of life on earth, the atmosphere contained relatively little oxygen and organisms evolved in a hypoxic environment without significant pressure to develop mechanisms for coexisting with oxygen.[1] In this setting, oxygen was a toxin. Over time, the concentration of oxygen in the earth's atmosphere rose, applying evolutionary pressure for organisms to develop mechanisms to tolerate oxygen and ultimately use oxygen to enhance survival. As a result, aerobic respiration evolved, with oxygen serving an essential role in accepting electrons as part of the conversion of glucose to usable energy for cells. However, oxygen remains toxic to many components of eukaryotic organisms with so-called oxidative stress leading to cellular damage from unpaired electrons in oxygen-containing molecules (reactive oxygen species) reacting with nucleic acids, proteins, and lipids. Therefore, we are left with a paradox—oxygen is essential for life, but at the same time, it is toxic to the very life-forms that depend on it for survival.[2]

FOR RELATED ARTICLE, SEE PAGE 566

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With oxygen being both essential and toxic, it is rational to hypothesize that the dose of oxygen administration is key to its effective use as a therapeutic. The logical goal is to administer enough oxygen to maintain aerobic respiration but not so much that the body is overwhelmed with reactive oxygen species. How much oxygen is enough oxygen? How much oxygen is too much? Failure of aerobic respiration because of hypoxemia leads to obvious and immediate catastrophic consequences culminating with cardiac arrest. Therefore, historically, the predominant approach has been to ensure avoidance of hypoxemia with liberal use of supplemental oxygen and to tolerate hyperoxemia. However, we have begun to more fully appreciate the negative consequences of hyperoxemia, which may be delayed and insidious, such as reduced microvascular circulation, vasospasm, acute lung injury, and systemic inflammation.[3] With these advances in the biological understanding of oxygen toxicity, whether tolerating hyperoxemia to avoid hypoxemia is the safest course has become uncertain.

Now, clinical outcome data are needed to understand the effect of different oxygenation strategies on patient-centered outcomes. These data are beginning to emerge. In this issue of *CHEST*, van den Boom et al[4] report findings from a large retrospective observational study evaluating the association between peripheral oxygen saturation (Spo_2) and in-hospital mortality among adults managed with supplemental oxygen administered invasively or noninvasively in an ICU for at least 48 h. Similar to prior observational studies,[5,6] they found a U-shaped association between Spo_2 achieved and mortality, with Spo_2 on both the lower end (< 94%) and higher end (> 98%) of what is typically achieved in clinical practice associated with higher mortality than midrange Spo_2 values. Specifically, the authors found Spo_2 of 96% to be associated with the lowest mortality in this observational dataset. Subsequently, they chose to

analyze an Spo_2 range of 94% to 98% as a reasonable range surrounding 96% that physicians could potentially maintain over time. The authors found that patients with Spo_2 within the 94% to 98% range during 80% of the time in an ICU had approximately one-half the in-hospital mortality compared with patients who maintained Spo_2 within the 94% to 98% range only 40% of the time.

While these results are vulnerable to confounding and do not definitively identify an Spo_2 range for clinicians to target in practice, the findings are useful. Namely, this study reinforces the concept that the highest levels of oxygenation are associated with a measurable increase in mortality in observational data and avoidance of hyperoxemia may be an important component to maximizing survival in patients who are critically ill. Furthermore, this study implies that even using oxygen to maintain high-normal Spo_2 levels (eg, 99%) could be a detrimental practice. Specific oxygenation targets within the large range of Spo_2 values commonly achieved in clinical care may have the potential to improve outcomes. Considerably more work will be needed to understand the relative risks and benefits of, for example, maintaining a patient with pneumonia at an Spo_2 of 92% on room air vs 98% on supplemental oxygen, or maintaining a patient with ARDS at an Spo_2 of 88% with an Fio_2 of 0.5 vs 96% with an Fio_2 of 0.8. Data from this study help build the rationale for systematically testing Spo_2 targets in prospective trials to answer these questions.

Two of the completed trials in this field include the Oxygen-ICU trial[7] and the ICU-ROX trial.[8] In the Oxygen-ICU trial, Girardis et al[7] randomized 434 adults admitted to a single medical-surgical ICU to a conservative oxygen target (Spo_2 94%-98%) vs a conventional oxygen target (Spo_2 97%-100% while allowing Pao_2 values up to 150 mm Hg). They found a surprisingly large difference in ICU mortality—11.6% in the conservative group vs 20.2% in the conventional group ($P = .01$).[7] In the ICU-ROX trial, the Australian and New Zealand Intensive Care Society Clinical Trials Group conducted a multicenter trial in which they randomized 1,000 adults on mechanical ventilation to a conservative oxygen target (Spo_2 91%-96%) vs usual care (oxygenation strategy determined by the physician with no input from the study protocol other than avoidance of $Spo_2 < 91\%$).[8] They found no difference in ventilator-free days or survival between randomized groups in the full study population, but found significant heterogeneity of treatment effect with conservative oxygen therapy favored in patients with hypoxic-ischemic encephalopathy.[8]

The available data demonstrate a state of equipoise. Observational studies suggest that Spo_2 target may be an important determinant of outcomes for patients who are critically ill.[4,5,9] Liberal oxygen use to maintain Spo_2 near 100% remains common in clinical practice despite observational studies and small trials challenging its safety.[10] Alternative approaches targeting Spo_2 values in the low 90%s have been adopted in some settings despite limited data to inform their effectiveness.[11] Pilot trials suggest it is safe to test oxygenation strategies that explicitly avoid hyperoxemia.[8,12] Hence, after more than a century of patients receiving oxygen therapy, the conditions appear ripe for the critical care community to conduct the high-quality, large, randomized trials required to finally understand how to optimally deliver one of our oldest and most essential therapies.

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The Search for Optimal Oxygen Saturation Targets in Critically Ill Patients

Observational Data From Large ICU Databases

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BACKGROUND: Although low oxygen saturations are generally regarded as deleterious, recent studies in ICU patients have shown that a liberal oxygen strategy increases mortality. However, the optimal oxygen saturation target remains unclear. The goal of this study was to determine the optimal range by using real-world data.

METHODS: Replicate retrospective analyses were conducted of two electronic medical record databases: the eICU Collaborative Research Database (eICU-CRD) and the Medical Information Mart for Intensive Care III database (MIMIC). Only patients with at least 48 h of oxygen therapy were included. Nonlinear regression was used to analyze the association between median pulse oximetry-derived oxygen saturation (Spo_2) and hospital mortality. We derived an optimal range of Spo_2 and analyzed the association between the percentage of time within the optimal range of Spo_2 and hospital mortality. All models adjusted for age, BMI, sex, and Sequential Organ Failure Assessment score. Subgroup analyses included ICU types, main diagnosis, and comorbidities.

RESULTS: The analysis identified 26,723 patients from eICU-CRD and 8,564 patients from MIMIC. The optimal range of Spo_2 was 94% to 98% in both databases. The percentage of time patients were within the optimal range of Spo_2 was associated with decreased hospital mortality (OR of 80% vs 40% of the measurements within the optimal range, 0.42 [95% CI, 0.40-0.43] for eICU-CRD and 0.53 [95% CI, 0.50-0.55] for MIMIC). This association was consistent across subgroup analyses.

CONCLUSIONS: The optimal range of Spo_2 was 94% to 98% and should inform future trials of oxygen therapy.

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KEY WORDS: blood oxygen saturation; electronic medical records; hyperoxemia; ICU; oxygen therapy; pulse oximetry

FOR EDITORIAL COMMENT, SEE PAGE 487

ABBREVIATIONS: eICU-CRD = eICU Collaborative Research Database; MIMIC = Medical Information Mart for Intensive Care III; SOFA = Sequential Organ Failure Assessment; Spo_2 = pulse oximetry-derived oxygen saturation

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Drs Feng and See contributed equally to the manuscript and are joint senior authors.

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Human survival requires adequate tissue oxygenation, which depends on blood oxygenation. In critically ill patients with cardiorespiratory compromise, blood oxygen levels, commonly measured continuously by using peripheral pulse oximetry (Spo_2) or intermittently using Pao_2, are supported by methods such as supplemental oxygen, mechanical ventilation, and extracorporeal membrane oxygenation. However, an optimal target range of blood oxygenation in critically ill patients requiring oxygen therapy has not been defined.

The relation between blood oxygenation and clinical outcomes is unlikely to be linear. Low blood oxygenation predisposes to tissue hypoxia and eventual cellular death. High blood oxygenation may induce vasoconstriction of important vascular beds (eg, cerebral or coronary) and generates free radicals that cause cellular damage.[1] Because high inspired oxygen concentrations can drive high blood oxygenation, direct lung toxicity and atelectasis can also occur.[1,2] As such, blood oxygenation and outcomes likely have a U-shaped relation, although few empirical studies support this directly.

The available evidence, listed on the last page of the online supplemental material, has four broad issues. First, investigators are predisposed to show the harmful effects of hyperoxemia but not hypoxemia. For instance, a recent systematic review of 25 randomized trials reported that supplemental oxygen targeting $Spo_2 > 96\%$ increased mortality compared with $Spo_2 < 96\%$ but did not define a lower limit of safety.[3] Second, some studies assumed a linear relation between oxygenation and mortality,[4] which is biologically implausible. Third, some studies used Pao_2 rather than Spo_2 to define oxygenation.[4-6] Because Pao_2 cannot be continuously assayed, this method would have limited resolution in detecting hyperoxemia or hypoxemia, and would not allow correlation of outcomes with the proportion of time spent within a target oxygenation range. Interestingly, one study involving patients with sepsis showed optimal survival at a Pao_2 of 300 mm Hg,[7] which is considered hyperoxemia according to other studies. Finally, randomized trials[8,9] and some observational studies[6,10-13] defined oxygen in arbitrarily defined categories rather than as a continuous variable and were therefore unable to define an optimal target range. Furthermore, using categories that include both healthy and unhealthy oxygenation ranges simultaneously could lead to inconsistent results.[3,5] For instance, a cohort study reported higher mortality for normoxemia (defined as a Pao_2 between 60 and 120 mm Hg) than for hypoxemia (defined as < 60 mm Hg).[10]

There are also reports[14-17] that hyperoxemia is common in the ICU, with published hyperoxemia rates ranging from 15% to > 70% of ICU patients, and physicians intervening only limitedly. There are often no clear oxygen therapy guidelines that are being followed. The lack of evidence on the optimal oxygenation target contributes to this situation. With hyperoxemia's adverse effects, its prevalence provides an opportunity to improve outcomes.

A large-scale multicenter study was therefore required to elucidate oxygen saturation targets to guide clinical practice and future research. This study is now possible with the use of big data sources such as the eICU Collaborative Research Database (eICU-CRD)[18] and the Medical Information Mart for Intensive Care III database (MIMIC),[19] which are open-access, de-identified datasets of patients admitted to ICUs. Without making assumptions of linearity, the goal of the current study was to derive an optimal range of oxygen saturation by correlating Spo_2 with mortality. We then evaluated this oxygen saturation range by correlating the time within this range with mortality. Replicate analyses using eICU-CRD and MIMIC show the reliability of the findings.

Materials and Methods

Data Description

Data were collected from eICU-CRD v2.0 and MIMIC v1.4 in accordance with the ethical standards of the institutional review board of the Massachusetts Institute of Technology (no. 0403000206) and with the 1964 Declaration of Helsinki and its later amendments. eICU-CRD covered 200,859 ICU admissions in 2014 and 2015 of 139,367 patients at 208 US hospitals. MIMIC covered 61,532 ICU admissions between 2001 and 2012 of 46,476 patients at the Beth Israel Deaconess Medical Center in Boston, Massachusetts. Both databases are maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology. They include hourly physiological readings from bedside monitors, records of demographic characteristics, diagnoses via *International Classification of Diseases, Ninth Revision*, codes, and other clinical data collected during routine medical care. The databases have extensive documentation and public code from a community of users.[20] This study is reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology statement.[21]

The primary outcome was hospital mortality, with ICU mortality as a secondary outcome. The primary independent variable was Spo_2 while on oxygen therapy, in which oxygen therapy can be supplemental oxygen such as a nasal cannula, noninvasive, and invasive ventilation. We took the median of the Spo_2 measurements during oxygen therapy as a measure of the central tendency of oxygen exposure. We also considered the proportion of measurements within a range to evaluate oxygen therapy. Spo_2 is usually measured

hourly in eICU-CRD and MIMIC. The measurements were verified and entered into a chart by a nurse.

We excluded the following: repeat ICU stays; patients aged < 16 years; and ICU stays with < 48 h of oxygen therapy, with < 24 Spo_2 measurements, or with no signs of supplemental oxygen such as an Fio_2 > 21% or records of an oxygen flow rate. As with Spo_2, a nurse enters Fio_2 data and oxygen flow rate regularly such that the study determination of who is receiving supplemental oxygen is reliable. Only hospitals that contained at least 10 ICU stays in the data cohort were included to improve identifiability of the resulting statistical model.

Statistical Analysis

The fact that both hypoxemia and hyperoxemia are associated with adverse outcomes suggests a nonlinear relationship between Spo_2 and mortality. Generalized additive models,[22] a type of multivariable regression, allow for such nonlinearity. They were used to estimate the association between median Spo_2 and mortality while controlling for age, BMI, sex, Sequential Organ Failure Assessment (SOFA) score[23] on the first day of the ICU stay, and duration of oxygen therapy (any oxygen supplementation, noninvasive ventilation, or mechanical ventilation). In addition, for eICU-CRD, hospital was included as a random intercept to capture the correlation between cases from the same hospital while mitigating biases due to differences between hospitals. The results informed an optimal oxygen therapy range. We then estimated the association between mortality and the proportion of Spo_2 measurements within this range. All continuous predictors were treated as having potentially nonlinear associations.

Additional cohort characteristics are provided in e-Table 1, and sensitivity and subgroup analyses, results with ICU mortality (secondary outcome), results on the ICU stays excluded here because they did not have 48 h of oxygen therapy or too few Spo_2 measurements, and confirmatory results using G-computation (a method to estimate the causal effect of Spo_2 on hospital mortality) are given in e-Figures 1 to 30. To address concerns regarding time dependency of oxygen exposure, sensitivity analyses considered only the Spo_2 measurements during the first 24, 48, or 72 h of an oxygen therapy session. Because the Acute Physiology and Chronic Health Evaluation IV score[24] is readily available in eICU-CRD, one sensitivity analysis is to use that score instead of the SOFA score as a control variable. Subgroup analyses include oxygen therapy type, ICU type, ethnicity, and the presence of comorbidities such as atrial fibrillation and COPD.

Source code for all analyses can be found at https://github.com/nus-mornin-lab/oxygenation_kc.

Results

Figure 1 describes the selection of 26,723 and 8,564 ICU stays meeting study criteria from the 200,859 and 61,532 ICU stays in eICU-CRD and MIMIC, respectively, for analysis. Table 1 summarizes the demographic and clinical characteristics. Hospital mortality and SOFA scores were higher in those selected than in eICU-CRD and MIMIC overall. This scenario is probably a result of only selecting ICU stays that involved oxygen therapy for at least 48 h. The characteristics of the Spo_2 measurements are similar across eICU-CRD and MIMIC.

Figure 2 shows a U-shaped association between mortality and median Spo_2 ($P < .0001$ for both eICU-CRD and MIMIC). Although hypoxemia correlated more strongly with mortality, hyperoxemia was also associated with increased mortality. Table 2 confirms this, both when adjusting for confounders and when not adjusting for them. The median Spo_2 values 100%, 96%, and 92% in Table 2 were chosen based on the fact that the bottom of the U-shape in Figure 2 occurs around 96%, and we added 92% and 100% for symmetry.

The effect of hypoxemia and hyperoxemia on mortality motivates an Spo_2 range with both a lower and an upper limit. Informed by the flattest part of the U-shape in Figure 2, an Spo_2 range of 94% to 98% was chosen. We next evaluated how time in this range correlates with mortality.

Figure 3 shows the association of mortality with time in this range, as well as with the proportion of Spo_2 measurements below and above this range ($P < .0001$ for all associations in both eICU-CRD and MIMIC). Being within this range 80% of the time vs 40% of the time is associated with halving the odds of mortality in both eICU-CRD (adjusted OR, 0.42; 95% CI, 0.40-0.43) and MIMIC (adjusted OR, 0.53; 95% CI, 0.50-0.55) (Table 2). We chose to present the comparison of 80% vs 40% of Spo_2 measurements between 94% and 98% in Table 2 because 40% appears frequently in the data per Table 1 and achieving 80% seems feasible: 7% of the analyzed eICU-CRD data and 5% of the MIMIC data have > 80% of Spo_2 measurements between 94% and 98%. e-Figure 31 further shows the distribution of these proportions in the data. Table 2 and Figure 3 confirm that Spo_2 > 98% is indeed associated ($P < .0001$ for both eICU-CRD and MIMIC) with increased hospital mortality, supporting the need for an upper limit to a target range.

The sensitivity and subgroup analyses are consistent with these results except that the uncertainty is larger for some subgroups with small sample sizes.

Discussion

Our replicate analyses of two large databases consistently showed that, among patients requiring oxygen therapy, hospital mortality had a U-shaped association with Spo_2. The retrospective data exhibited

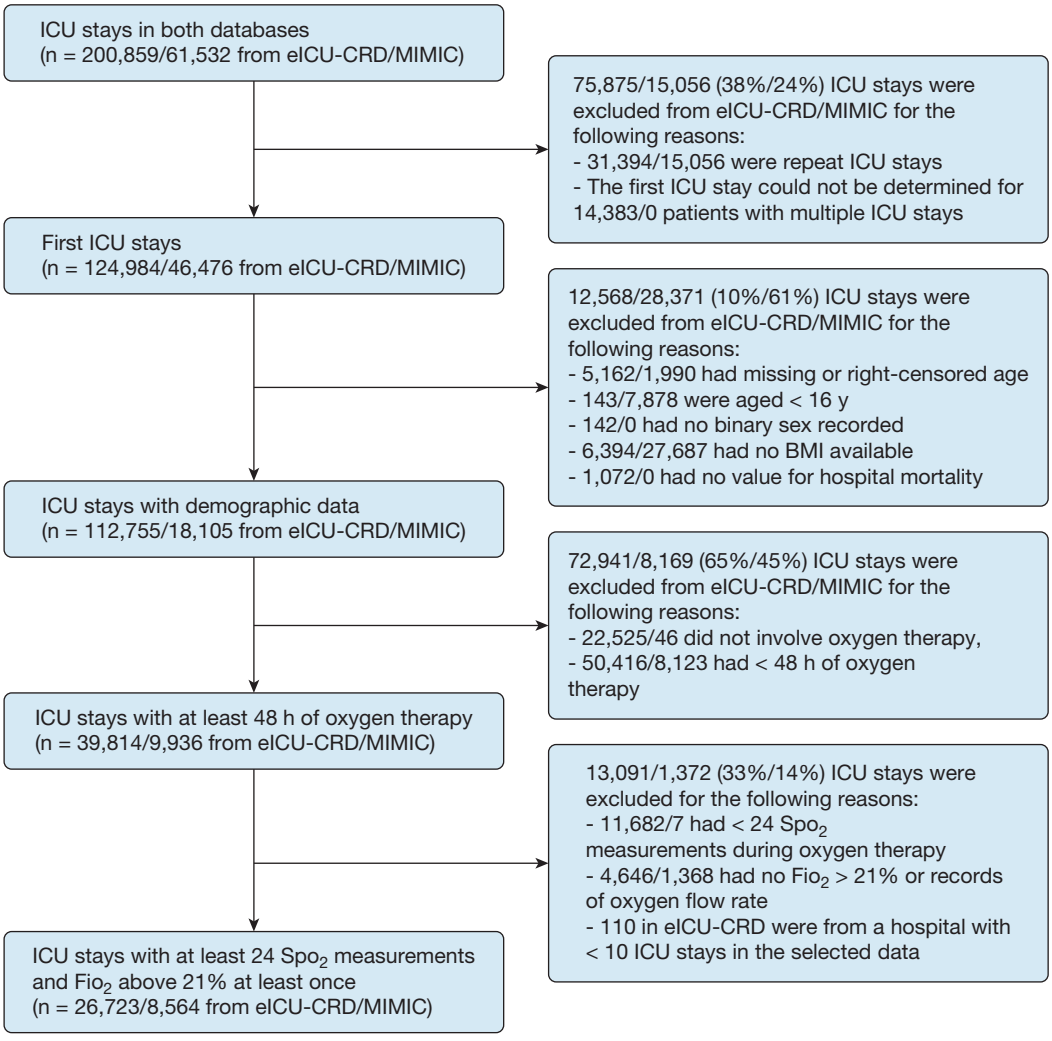

Figure 1 – *Case inclusion flowchart. Visual representation of how the 26,723/8,564 ICU stays that we analyzed were selected from the 200,859/61,532 ICU stays in eICU-CRD/MIMIC. eICU-CRD = eICU Collaborative Research Database; MIMIC = Medical Information Mart for Intensive Care III; Spo_2 = pulse oximetry-derived oxygen saturation.*

lowest mortality at a median Spo_2 within 94% to 98% and when patients spent a greater proportion of time within this range. These results were similar for different modes of oxygen therapy, across diagnostic and comorbidity subgroups, and when ICU mortality was used in place of hospital mortality.

The sensitivity analyses involving use of early Spo_2 readings (within 24, 48, and 72 h of ICU admission) revealed the same findings as our primary analysis using all Spo_2 readings. These findings suggest that disease recovery, as indicated by improved mortality, was not responsible for Spo_2 within the evaluated 94% to 98% range and that Spo_2 within that range was equally associated with reduced mortality throughout the ICU stay. Also, subgroup, sensitivity, and replicate analyses using both the eICU-CRD and MIMIC showed consistent results, while medical practice is continually evolving: MIMIC represents older practice patterns (from 2001 to 2012), and eICU-CRD represents more contemporary practice patterns (from 2014 to 2015).

An alternative means of measuring blood oxygenation is use of Pao_2. However, Spo_2 provides pragmatic advantages over Pao_2, including the ability to measure oxygenation cheaply, noninvasively, and repeatedly. Spo_2 is also clinically more relevant because adjustments of inspired oxygen and ventilator settings are based on Spo_2 changes rather than on intermittent arterial blood gas assays. For the Spo_2 range of 94% to 98%, the correlation between Spo_2 and Pao_2 would be fair, with

TABLE 1] Demographic and Clinical Characteristics

Characteristic	Mean ± SD or Count (%)	Quartile 1	Median	Quartile 3
Dataset	112,755 ICU stays from eICU-CRD with demographic data			
Age, y	62 ± 17	52	64	75
BMI, kg/m^2	29 ± 8.2	24	28	33
SOFA score	4.5 ± 3.2	2.0	4.0	6.0
Hospital mortality	10,417 (9%)			
Female sex	50,987 (45%)			
Dataset	26,723 ICU stays from eICU-CRD with at least 48 h of oxygen therapy and 24 Spo_2 measurements			
Age, y	64 ± 15	55	66	76
BMI, kg/m^2	30 ± 8.9	24	28	34
SOFA score	6.0 ± 3.4	4.0	6.0	8.0
Hospital mortality	3,841 (14%)			
Female	12,120 (45%)			
Oxygen therapy duration, h	157 ± 155	71	109	185
Median Spo_2, %	97 ± 2.0	96	97	99
Prop. of Spo_2 94%-98%	0.53 ± 0.21	0.39	0.56	0.68
Dataset	18,105 ICU stays from MIMIC with demographic data			
Age, y	64 ± 16	54	65	76
BMI, kg/m^2	29 ± 7.2	24	27	32
SOFA score	4.5 ± 3.1	2.0	4.0	6.0
Hospital mortality	1,783 (10%)			
Female sex	6,937 (38%)			
Dataset	8,564 ICU stays from MIMIC with at least 48 hours of oxygen therapy and 24 Spo_2 measurements			
Age, y	64 ± 16	55	67	77
BMI, kg/m^2	29 ± 7.7	24	28	32
SOFA score	5.5 ± 3.4	3.0	5.0	8.0
Hospital mortality	1,250 (15%)			
Female sex	3,449 (40%)			
Oxygen therapy duration, h	205 ± 228	74	122	240
Median Spo_2, %	97 ± 1.7	96	98	99
Prop. of Spo_2 94%-98%	0.54 ± 0.19	0.41	0.56	0.68

Summary statistics of demographic and clinical characteristics of the ICU stays. These are split out by the eICU-CRD and MIMIC. Statistics are presented for the analyzed cohort and for a cohort not constrained by having oxygen therapy and Spo_2 measurements. eICU-CRD = eICU Collaborative Research Database; MIMIC = Medical Information Mart for Intensive Care III database; Prop. = proportion; SOFA = Sequential Organ Failure Assessment; Spo_2 = pulse oximetry-derived oxygen saturation.

little risk of underestimation of either hypoxemia or hyperoxemia.[25] Furthermore, using Spo_2 to titrate supplemental oxygen is superior to fixed inspired oxygen fractions, which risk over-oxygenation in patients with narrow alveolar-arterial oxygen gradients and under-oxygenation in those with wide gradients.

Interestingly, one randomized trial showed that a target Spo_2 of 94% to 98% conferred a mortality benefit compared with using a target of 97% to 100% (ICU mortality, 11.6% vs 22.0% [$P = .01$]; hospital mortality, 24.2% vs 33.9% [$P = .03$]).[8] Although the trial was nonblinded, it supports our range of 94% to 98%. In contrast to relative normal blood oxygenation, trials in pediatric populations report mortality from permissive hypoxemia (Spo_2, 85%-89%).[26,27] Our study also found that $Spo_2 < 94\%$ was associated with increased mortality, reinforcing the need for caution if adult trials incorporate permissive hypoxemia.

Our results are potentially impactful and support the British Thoracic Society recommended target of 94% to

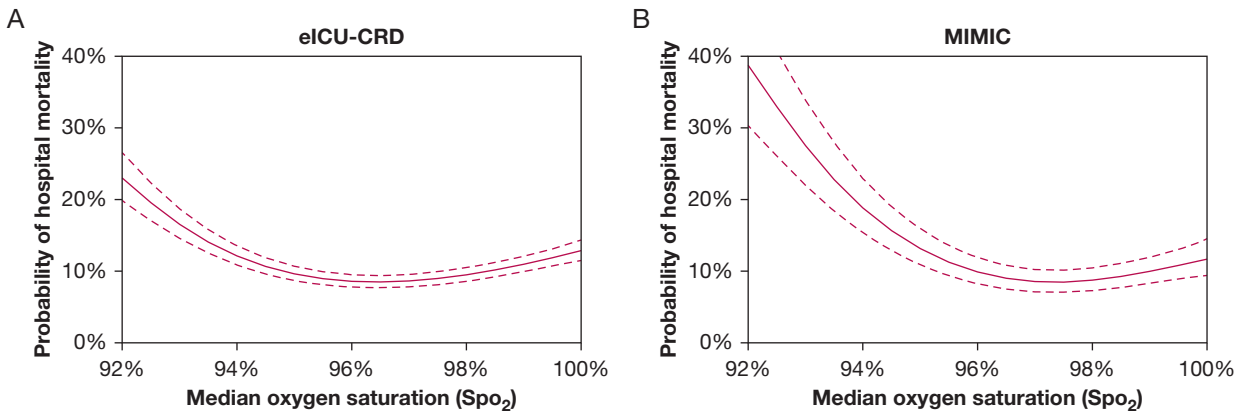

Figure 2 – *Probability of hospital mortality vs median Spo_2. Visual summary of the association between median blood oxygen saturation and probability of hospital mortality from the generalized additive model fit on (A) 26,723 ICU stays from eICU-CRD and (B) 8,564 ICU stays from MIMIC. The line is the mean prediction, and the dashed lines are the 95% CIs. See Figure 1 legend for expansion of abbreviations.*

98% for most acutely ill patients.[28] Some evidence suggests that overuse of oxygen therapy is prevalent and is associated with adverse outcomes, including more days undergoing mechanical ventilation and longer hospitalization.[14-17] Targeting Spo_2 between 94% and 98% might optimize survival for patients requiring oxygen therapy.[29] Because pulse oximetry is widespread and affordable, implementation of the 94% to 98% target would be feasible, even in resource-limited environments.

Although our study provides observational evidence for an Spo_2 target range of 94% to 98%, the target would not apply under some circumstances. For patients with severe ARDS, ventilator settings need to limit lung stress and strain.[30] A lower limit of $Spo_2 < 94\%$ could then be the target, as long as patients do not develop tissue hypoxia. Our results also do not extend to patients who are not hypoxemic, who are at high risk for hypercapnic respiratory failure, who are receiving extracorporeal membrane oxygenation, or who are not on oxygen therapy as these subjects were not included in the current analysis.

Despite the large sample size allowing multiple subgroup and sensitivity analyses, we acknowledge limitations to this study. First, the data were from the United States, and thus the results may not apply fully to ICUs elsewhere with different practices or resources. Second, even though we adjusted for covariates, residual confounding could exist. In particular, confounding by indication would mean overestimation of the association between hypoxemia and mortality, which we mitigated by adjusting for disease severity and by reporting consistency of our results using subgroup analysis according to disease type. Conversely, we would have underestimated the association between hyperoxemia and mortality, although this association remained statistically significant in the current analyses given the large sample size.

TABLE 2] ORs (95% CIs) of Hospital Mortality Based on the Median Spo_2 Measurements and Derived Spo_2 Range

	Median Spo_2		80% vs 40% of Spo_2 Measurements	
Comparison	92% vs 96%	100% vs 96%	Within 94%-98%	Above 98%
eICU-CRD				
Adjusted	3.2 (2.9-3.5)	1.6 (1.5-1.6)	0.42 (0.40-0.43)	1.19 (1.16-1.22)
Unadjusted	2.5 (2.3-2.8)	2.0 (2.0-2.1)	0.33 (0.32-0.38)	1.39 (1.36-1.42)
MIMIC				
Adjusted	5.8 (4.8-6.9)	1.2 (1.1-1.3)	0.53 (0.50-0.55)	1.28 (1.19-1.38)
Unadjusted	4.8 (3.9-6.0)	1.3 (1.2-1.3)	0.51 (0.48-0.55)	1.25 (1.15-1.35)

ORs of hospital mortality with 95% CIs in parentheses from the generalized additive models on the effect of median Spo_2, proportion of Spo_2 measurements between 94% and 98%, and proportion of Spo_2 measurements > 98%. The ORs are computed with (adjusted) and without (unadjusted) controlling for confounders. See Table 1 legend for expansion of abbreviations.

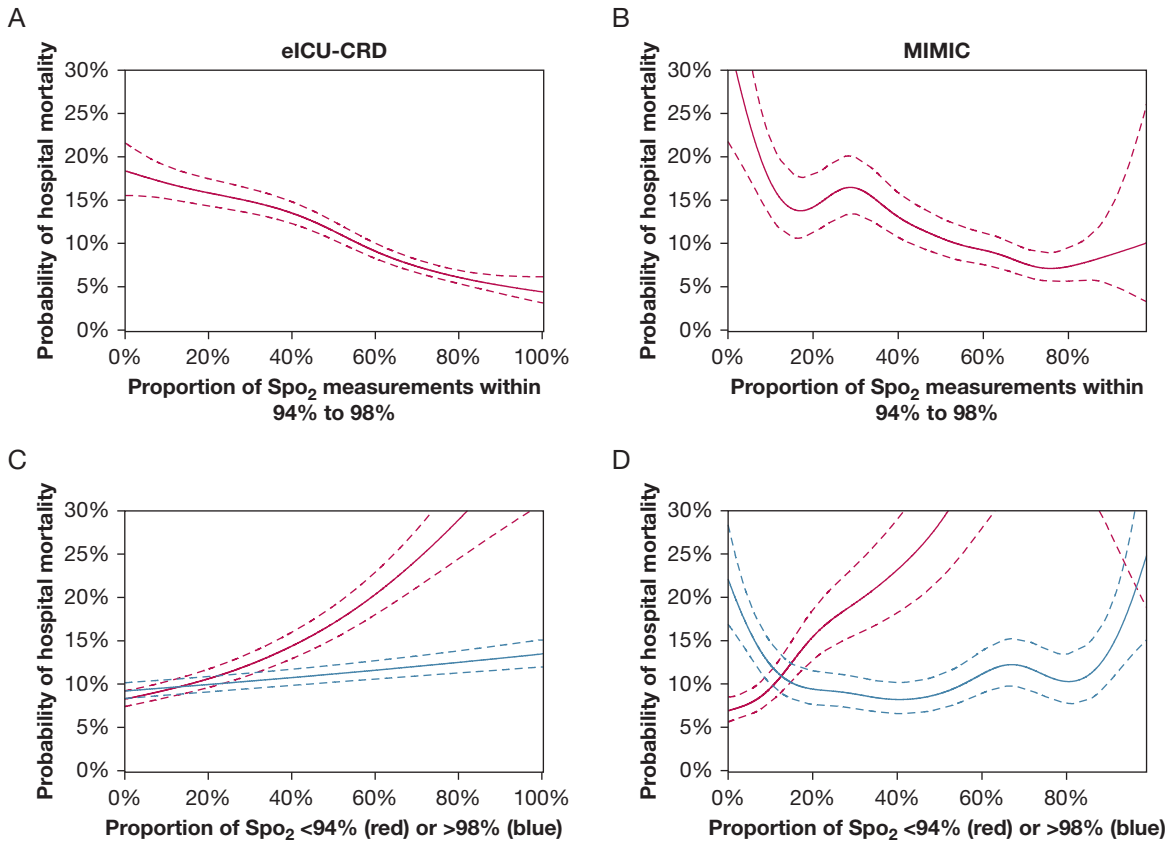

Figure 3 – *Probability of hospital mortality vs the proportion of time with Spo_2 within 94% to 98%. Visual summary of the association between the proportion of Spo_2 measurements between 94% and 98% and probability of hospital mortality from the generalized additive model fit on (A) 26,723 ICU stays from eICU-CRD and (B) 8,564 ICU stays from MIMIC, as well as the same for the proportion of measurements < 94% and > 98% (C and D, respectively). The lines are the mean prediction, and the dashed lines are the 95% CIs. See Figure 1 legend for expansion of abbreviations.*

Importantly, the range of 94% to 98% was determined retrospectively without knowledge of the oxygen saturation targeted by the oxygen therapy. To completely overcome confounding, randomized trials would be the ideal study design. Blinding of care providers to the blood oxygenation targets would be possible by electronically altering pulse oximeters.[26] In previous randomized trials of oxygen therapy, the treatment group cutoffs for Spo_2 or Pao_2 were essentially arbitrary. The current study provides a firmer basis for selection of Spo_2 targets within treatment groups. Given the U-shaped relation between Spo_2 and mortality, perhaps three, rather than two, treatment groups are required to compare therapeutic effects when blood oxygen exceeds, stays within, or goes below the target range.

Conclusions

Among patients requiring oxygen therapy, lowest mortality was observed at an Spo_2 between 94% and 98%. This range should apply broadly across different patient characteristics and settings. Future randomized trials could also adopt an Spo_2 range of 94% to 98% as the reference target.

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