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Palmer, E

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The Association between Supraphysiologic Arterial Oxygen Levels and Mortality in Critically Ill Patients
A Multicenter Observational Cohort Study

Edward Palmer1,2, Benjamin Post2,3, Roman Klapaukh2,4, Giampiero Marra5, Niall S. MacCallum1,2,6, David Brealey1,2,6, Ari Ercole7, Andrew Jones8, Simon Ashworth9, Peter Watkinson10, Richard Beale8,11, Stephen J. Brett12, J. Duncan Young10, Claire Black2,13, Aasiyah Rashan2, Daniel Martin14,15, Mervyn Singer1,6, and Steve Harris1,2,6

1Bloomsbury Institute of Intensive Care Medicine, 2Research Software Development Group, Research IT Services, and 3Department of Statistical Science, University College London, London, United Kingdom; 4INFORM-lab, London, United Kingdom; 5Department of Critical Care, Barts Health National Health Service (NHS) Trust, London, United Kingdom; 6Department of Critical Care and 13Therapies and Rehabilitation, University College London Hospitals NHS Foundation Trust, London, United Kingdom; 7Division of Anaesthesia, University of Oxford, Oxford, United Kingdom; 8Department of Critical Care, Imperial College Healthcare NHS Trust, London, United Kingdom; 9Division of Critical Care, Imperial College Healthcare NHS Trust, London, United Kingdom; 10Critical Care Research Group (Kadoorie Centre), Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, Oxford, United Kingdom; 11Centre for Human Applied Physiological Science, King’s College London, London, United Kingdom; 12Department of Surgery and Cancer, Imperial College London, London, United Kingdom; and 13Division of Surgery and Interventional Science and 15Critical Care Unit, Royal Free Hospital, London, United Kingdom

Abstract

Rationale: There is conflicting evidence on harm related to exposure to supraphysiologic PaO2 (hyperoxemia) in critically ill patients.

Objectives: To examine the association between longitudinal exposure to hyperoxemia and mortality in patients admitted to ICUs in five United Kingdom university hospitals.

Methods: A retrospective cohort of ICU admissions between January 31, 2014, and December 31, 2018, from the National Institute of Health Research Critical Care Health Informatics Collaborative was studied. Multivariable logistic regression modeled death in ICU by exposure to hyperoxemia.

Measurements and Main Results: Subsets with oxygen exposure windows of 0 to 1, 0 to 3, 0 to 5, and 0 to 7 days were evaluated, capturing 19,515, 10,525, 6,360, and 4,296 patients, respectively. Hyperoxemia dose was defined as the area between the PaO2 time curve and a boundary of 13.3 kPa (100 mm Hg) divided by the hours of potential exposure (24, 72, 120, or 168 h). An association was found between exposure to hyperoxemia and ICU mortality for exposure windows of 0 to 1 days (odds ratio [OR], 1.15; 95% compatibility interval [CI], 0.95–1.38; \(P=0.02\)), 0 to 3 days (OR, 1.35; 95% CI, 1.04–1.74; \(P=0.02\)), 0 to 5 days (OR, 1.5; 95% CI, 1.07–2.13; \(P=0.02\)), and 0 to 7 days (OR, 1.74; 95% CI, 1.11–2.72; \(P=0.02\)). However, a dose–response relationship was not observed. There was no evidence to support a differential effect between hyperoxemia and either a respiratory diagnosis or mechanical ventilation.

Conclusions: An association between hyperoxemia and mortality was observed in our large, unselected multicenter cohort. The absence of a dose–response relationship weakens causal interpretation. Further experimental research is warranted to elucidate this important question.

Keywords: logistic models; critical care; hyperoxia

This article has an online supplement, which is accessible from this issue’s table of contents at www.atsjournals.org.
At a Glance Commentary

Scientific Knowledge on the Subject: Oxygen is a drug that carries potential toxicity, but this fact often passes unappreciated in clinical practice. In recent years, hyperoxemia has been increasingly linked with worse outcomes, though the literature is conflicting. Bias may be introduced into studies through confounding by treatment indication, failure to consider oxygen as a longitudinal exposure, and dropout of patients over time.

What this Study Adds to the Field:
We interrogated a large multicenter cohort of patients requiring at least 24 hours of critical care and used a modelling approach that addressed the above core concerns. We found an association between hyperoxemia and mortality; however, a lack of dose dependency challenges a causal relationship. Our findings support the need for prospective randomized trials with appropriate power.

Oxygen therapy is widely used to treat critically ill patients. British Thoracic Society guidelines regard oxygen as a drug and advise a prescription to accompany its use (1). These guidelines acknowledge potential harm and recommend targeting a specific oxygen saturation range in acutely unwell patients. In adult patients, hyperoxemia may induce hemodynamic changes (2, 3), including vasoconstriction (4, 5), reduced cardiac output, and increased peripheral vascular resistance (6–8); and inflammatory changes, including the generation of reactive oxygen species (9) and absorption atelectasis (10). In healthy subjects, exposure to high inspired oxygen concentrations causes alveolar leak and release of mediators responsible for lung fibrosis (11).

Despite these concerns, other than in patients with type II (hypercarbic) respiratory failure, oxygen use is still largely unregulated in clinical practice. Prospective randomized trials of oxygen therapy in patients suffering myocardial infarction have reported either harm (12, 13) or no effect (14). Increased mortality risk has been suggested in patients receiving higher concentrations of inspired oxygen (15–20) in conditions such as cardiac arrest (21–23) and septic shock (24–26), as well as in general critically ill populations (19, 27). However, most of these studies lack a delineation between harm from appropriately high levels of inspired oxygen used to maintain normoxemia and excessive concentrations that result in hyperoxemia (28). Similarly, analyses of ICU databases variably report an association (29, 30) or lack thereof (31) between hyperoxemia and poor outcomes in the critically ill. Many of these approaches are limited by using only a single measure of \( \text{PaO}_2 \) or inspired oxygen to define oxygen exposure for an entire ICU admission.

A recent systematic review and meta-analysis of more than 16,000 patients (32) indicated potential harm, concluding, “Patients treated liberally with oxygen had a dose-dependent increased risk of short-term and long-term mortality.” Yet, paradoxically, they could find “no significant difference in disability, hospital-acquired pneumonia, or length of hospital stay.”

The aim of the present study was to determine whether exposure to supraphysiologic \( \text{PaO}_2 \), measured as time-weighted mean exposure to hyperoxemia (referred to as “hyperoxemia dose” for brevity), was associated with excess ICU mortality. Particular attention was paid to dose-response as a proxy for a causal relationship (33). The specific impact of hyperoxemia was assessed in patients with a primary respiratory diagnosis for ICU admission or those who were mechanically ventilated because concurrent lung inflammation may predispose to pulmonary oxygen toxicity and increased mortality (27).

Methods

Data were prospectively collected between January 31, 2014, and December 31, 2018, on all adult (≥18 yr) patients attending an ICU from five United Kingdom university hospitals contributing to the National Institute of Health Research Critical Care Health Informatics Collaborative, for which the themes are described elsewhere (34), as is a detailed description of its data specification (35). The legal basis for handling the data is provided in the online supplement. The present study was conducted as a retrospective cohort analysis, with findings reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology guidance (36).

Patients were included in the study if their ICU length of stay was longer than 24 hours. Those staying less than 24 hours were typically admitted after elective surgery with very low mortality. These cases were removed because this would lead to prognostic deenrichment while not providing a large enough exposure window for the effects of hyperoxemia to become apparent. Patients with treatment limitation orders, in receipt of cardiopulmonary resuscitation in the 24 hours preceding ICU admission, or failing prespecified data quality checks were excluded. To limit confounding by an unknown exposure to oxygen, or other factors following ICU discharge, only the index admission was considered if a patient had more than one ICU admission. For similar reasons, ICU mortality for that index admission was chosen as the primary endpoint, in preference to hospital mortality or other distant outcome measures. The cohort was narrowed to create nested subsets with progressively longer potential hyperoxemia exposure windows (0–3, 0–5, and 0–7 days). Each subset, therefore, had a period of potential exposure unaffected by informative censoring from either ICU discharge or death (Figure 1; see Figure E1 in the online supplement).

ICU mortality was modeled as a function of hyperoxemia dose using multivariable logistic regression. Hyperoxemia dose was defined as the area under the \( \text{PaO}_2 \) time curve above a threshold.
The PaO₂ value of 13.3 kPa (100 mm Hg) divided by the number of hours of potential exposure. This was applied from the time of ICU admission (Day 0) until 1, 3, 5, or 7 days (Figure 1). Under this definition, 1 kPa (7.6 mm Hg) of hyperoxemia dose describes that a patient’s average PaO₂ was 1 kPa (7.6 mm Hg) above 13.3 kPa (100 mm Hg) for the duration of the exposure window. The 13.3 kPa (100 mm Hg) threshold was chosen because values exceeding this can only be achieved with supplementary oxygen. This boundary, therefore, represents a range of PaO₂ that is unambiguously supraphysiological and hence not confounded by treatment indication.

A substantial proportion of admissions had a hyperoxemia dose of 0. To address this “spike at zero,” an additional covariable indicating any hyperoxemia exposure was added to the model (37). Both covariables (“any hyperoxemia” and hyperoxemia dose) should be considered in concert when interpreting the model.

Other predictor covariables included a primary diagnosis of respiratory illness (yes/no), sex (male/female), age at admission (years), weight (kg), prior need for assisted daily living (independent or any level of dependence), mechanical ventilation for the entirety of the exposure window (yes/no), primary admission reason (medical/surgical), and the Acute Physiology and Chronic Health Evaluation II score. These variables were chosen on the basis of salience to the underlying research question, scientific plausibility, and after exclusion of significant collinearity. Continuous variables were entered without categorization. Age and weight were modeled nonlinearly using restricted cubic splines (38). The Acute Physiology and Chronic Health Evaluation II score was also modeled with restricted cubic splines because evidence from the data supported this decision.

To account for possible differential effects of exposure to hyperoxemia, interaction effects between exposure to hyperoxemia with an underlying respiratory diagnosis and continuous mechanical ventilation were evaluated. Penalized maximum likelihood was applied with a penalty factor determined by optimal model Akaike information criterion (AIC). Penalization was applied to interaction effects only.

Four models were fitted, one for each exposure subset. Figure 1 provides an exemplar case and Figure E1 provides an overview of this process. This procedure was undertaken to balance informative censoring of patient data with the investigation of hyperoxemia, thus maintaining a uniform exposure potential within each subset for this necessarily longitudinal measure.

To create the notion of a continuous time series for PaO₂, which is measured as a point process when arterial blood gas samples are drawn, linear imputation was performed with a 12-hour window. Details of the imputation procedure are presented in Table E1. Where PaO₂ measures were still unavailable, the exposure was assumed to be...
Results

Over the 4-year period of the study, 45,188 episodes were available. After exclusions, a primary cohort with a minimum 1-day ICU length of stay of 19,515 episodes remained (Figure E2). This cohort was further nested into those who remained in ICU for at least 3 (10,525), 5 (6,360), and 7 (4,296) days. Baseline characteristics for the primary cohort and nested exposure windows are shown in Table 1 and Table E2. A total of 77.5% of patients were exposed to hyperoxemia by Day 1, increasing to 90.6% by Day 7. We observed an association between any hyperoxemia exposure and increased ICU mortality, with an odds ratio (OR) ranging from 1.15 (95% compatibility interval [CI] 0.95–1.38; \( P = 0.15 \)) over Days 0–1 to 1.74 (95% CI, 1.11–2.72; \( P = 0.02 \)) over Days 0–7.

There was a lack of evidence to support a dose-dependent effect (Table 2) or the presence of nonlinearities in hyperoxemia dose; accordingly, this component was modeled linearly for parsimony. Point estimates for the ORs and their 95% CIs for covariates are presented in Figure 2. All results are presented in Table E3. These findings were robust to using probit or complementary log-log link functions.

There was no overall evidence to support an interaction effect between exposure to hyperoxemia and either an underlying respiratory diagnosis or mechanical ventilation. Likelihood ratios comparing the base model with the penalized maximum likelihood model are shown in Table E4. There was no evidence to support a change in the log odds for death from the interaction between hyperoxemia and either primary respiratory diagnosis or mechanical ventilation status (Table E5). The interaction terms were removed from the final model specification based upon likelihood criteria.

The modification to risk of mortality between observed exposure to hyperoxemia and the counterfactual scenario setting this exposure to 0 is shown in Figure 3, using the Day 0 to Day 5 cohort as an illustrative example. All models are shown on the absolute risk scale in Figure E3. Point

**Table 1. Abridged Patient Characteristics, Stratified by Nested Exposure Window**

| Characteristic                        | 1-d Exposure | 3-d Exposure | 5-d Exposure | 7-d Exposure |
|---------------------------------------|--------------|--------------|--------------|--------------|
| \( n \)                                | 19,593       | 10,571       | 6,391        | 4,318        |
| Hyperoxemia dose, kPa                  | 0.54 (0.01–1.75) | 0.30 (0.04–0.86) | 0.26 (0.04–0.68) | 0.27 (0.06–0.65) |
| Any hyperoxemia exposure (yes)        | 15,182 (77.5) | 8,865 (83.9) | 5,580 (87.3) | 3,912 (90.6) |
| Cumulative hyperoxemia exposure, kPa · h | 13.00 (0.4–42.1) | 21.84 (2.6–61.6) | 31.41 (5.3–81.9) | 45.03 (10.6–108.7) |
| Pre-ICU hospital length of stay, d     | 1 (1–2)       | 1 (1–3)      | 1 (1–3)      | 1 (1–3)      |
| Age, yr                               | 65 (51–74)   | 65 (51–75)   | 64 (49–74)   | 63 (48–74)   |
| Weight, kg                            | 77 ± 20       | 77 ± 19      | 77 ± 20      | 77 ± 20      |
| Sex                                   |              |              |              |              |
| M                                     | 7,834 (40.0) | 4,149 (39.2) | 2,431 (38.0) | 1,621 (37.5) |
| Not available                          | 11,758 (60.0) | 6,421 (60.7) | 3,959 (61.9) | 2,696 (62.4) |
| APACHE II score                       | 15.4 ± 5.8   | 16.5 ± 6.0   | 17.2 ± 6.2   | 17.7 ± 6.3   |
| Prior dependency (none)               | 16,239 (82.9) | 8,575 (81.1) | 5,115 (80.0) | 3,433 (79.5) |
| Patient type                          |              |              |              |              |
| Surgical                              | 10,721 (54.7) | 4,652 (44.0) | 2,319 (36.3) | 1,290 (29.9) |
| Medical                               | 8,861 (45.2) | 5,913 (55.9) | 4,067 (63.6) | 3,025 (70.1) |
| Not available                          | 11 (0.1)     | 6 (0.1)      | 5 (0.1)      | 3 (0.1)      |
| Surgical classification               |              |              |              |              |
| Elective                              | 6,758 (34.5) | 2,597 (24.6) | 1,144 (17.9) | 539 (12.5)   |
| Scheduled                             | 1,557 (7.9)  | 804 (7.6)    | 372 (5.8)    | 176 (4.1)    |
| Urgent                                | 1,025 (5.2)  | 412 (3.9)    | 220 (3.4)    | 145 (3.4)    |
| Emergency                             | 1,702 (8.7)  | 1,029 (9.7)  | 699 (10.9)   | 517 (12.0)   |
| Not applicable (medical or not available) | 8,551 (43.6) | 5,729 (54.2) | 3,956 (61.9) | 2,941 (68.1) |
| Ethnicity                             |              |              |              |              |
| Asian/Asian British Indian            | 335 (1.7)    | 180 (1.7)    | 112 (1.8)    | 85 (2.0)     |
| Asian/Asian British other             | 335 (1.7)    | 206 (1.9)    | 152 (2.4)    | 119 (2.8)    |
| Black/black British African           | 555 (2.6)    | 288 (2.7)    | 188 (2.9)    | 128 (3.0)    |
| Black/black British Caribbean         | 430 (2.2)    | 211 (2.0)    | 125 (1.9)    | 82 (1.9)     |
| Other or not stated                   | 4,746 (24.2) | 2,592 (24.5) | 1,574 (24.6) | 1,031 (23.9) |
| White British                         | 11,880 (60.6) | 6,337 (59.9) | 3,759 (58.8) | 2,541 (58.8) |
| White other                           | 1,312 (6.7)  | 757 (7.2)    | 483 (7.6)    | 332 (7.7)    |
| ICU length of stay, d                 | 3.5 (2.0–6.6) | 6.0 (4.1–11.0) | 9.2 (6.6–16.8) | 13.1 (9.1–21.7) |
| ICU mortality (deceased)              | 835 (4.3)    | 577 (5.5)    | 435 (6.8)    | 360 (8.3)    |

*Definition of abbreviation: APACHE = Acute Physiology and Chronic Health Evaluation. Variables are presented as mean (SD), median (interquartile range), or count (%) as appropriate. For all characteristics, please see Table E1.*
estimates for the average treatment effect were 0.4%, 0.9%, 1.6%, and 2.7% for exposure windows of 0 to 1, 0 to 3, 0 to 5, and 0 to 7, respectively, favoring no exposure to hyperoxemia.

The overall model fit across the four exposure windows was good; each model c-index, optimism-corrected (bootstrapped) Brier score, and AIC is detailed in Table E6. On calibration checks, there was a tendency for models to underpredict mortality in more severe cases (Figure E4).

Discussion

A consistent association was found across models between any exposure to hyperoxemia for up to 7 days following ICU admission and ICU mortality. This is in keeping with findings from most observational (29, 30, 40, 41) and interventional (17, 18, 27) studies. However, Eastwood and colleagues, using a well controlled model, could not find supporting evidence of an association between hyperoxemia and increased mortality (31).

Crucially, many prior retrospective studies examining the relationship between hyperoxemia and outcome are limited by the availability of longitudinal oxygenation data. A common approach has modeled outcomes as a function of a single arterial blood gas result, usually taken soon after ICU admission. The degree and duration of hyperoxemia before and after this result are undocumented. It is biologically implausible that a single measure of oxygen exposure could shift outcomes so dramatically. Any single measure of oxygen exposure is likely to be confounded by treatment effects. For example, sicker patients are more likely to be administered higher concentrations of oxygen. This confounding may exert a greater influence on the first arterial blood gas result because it will be this very sample that triggers a de-escalation of oxygen, should this be required.

To our knowledge, only one prior large database study has modeled a longitudinal notion of oxygen (30). The authors found “a dose-response relationship between supra-physiologic arterial oxygen levels and hospital mortality.” Such a hypothesis is difficult to discern, however, given that this effect was only seen in the uppermost category of exposure to oxygen, and a gradient of worsening outcomes across oxygen exposure levels was not demonstrated. Additionally, continuous measures of oxygenation were routinely categorized; this procedure impairs statistical inference, leading to both false-positive findings and reduced statistical power.

Table 2. Odds Ratios (95% Compatibility Intervals) for Hyperoxemia Dose (in Kilopascals) and Any Hyperoxemia Exposure (as Indicator Variable)

| Model       | Variable                  | Odds Ratio (95% CI) | Chi Square | DoF | P Value |
|-------------|---------------------------|---------------------|------------|-----|---------|
| 0–1 d       | Hyperoxemia dose          | 1.01 (0.93–1.10)    | 0.071      | 1   | 0.790   |
|             | Any hyperoxemia exposure  | 1.15 (0.95–1.38)    | 2.110      | 1   | 0.146   |
| 0–3 d       | Hyperoxemia dose          | 0.94 (0.85–1.03)    | 1.777      | 1   | 0.183   |
|             | Any hyperoxemia exposure  | 1.35 (1.04–1.74)    | 5.157      | 1   | 0.023   |
| 0–5 d       | Hyperoxemia dose          | 0.93 (0.83–1.04)    | 1.441      | 1   | 0.230   |
|             | Any hyperoxemia exposure  | 1.5 (1.07–2.13)     | 5.372      | 1   | 0.020   |
| 0–7 d       | Hyperoxemia dose          | 0.92 (0.81–1.05)    | 1.416      | 1   | 0.234   |
|             | Any hyperoxemia exposure  | 1.74 (1.11–2.72)    | 5.815      | 1   | 0.016   |

Definition of abbreviations: CI = compatibility interval; DoF = degrees of freedom. All other predictor variables are described in the online supplement.
We were unable to find supporting evidence for a dose–response relationship between hyperoxemia dose and ICU mortality. This does not necessarily mean that this effect is absent; however, this weakens causal interpretation of our findings. A cut point of 13.3 kPa (100 mm Hg) was used to define hyperoxemia, rather than modeling the entire area under the PaO₂ time curve. This latter approach would lead to inescapable unmeasured confounding by severity of illness that can prove challenging to adequately control for. In our experience, longitudinal measures of acute illness severity, particularly those that encompass a notion of respiratory dysfunction, are particularly volatile. Our definition makes minimal assumptions about what constitutes hyperoxemia but at the expense of reducing the number of cases from which to learn. Given the reducing number of cases without exposure to hyperoxemia, particularly toward 7 days, residual confounding remains a concern as a potential explanation of these findings.

There was no evidence to support the presence of a differential effect of exposure to hyperoxemia regardless of primary respiratory diagnosis or mechanical ventilation status. There may, however, have been inadequate power in our cohort to detect these effects.

In terms of limitations, we conducted a two-stage analysis of longitudinal data. In this approach, a longitudinal process, such as serial PaO₂, is collapsed into a single measure to be included within a model. Although this is a common approach, there is necessarily a loss of statistical information. We are thus unable to address questions related to, for example, the profile of oxygen exposure over an ICU admission. Under our approach, exposure to high levels of excess oxygen for a short period of time are thought of as equal to low levels of excess oxygen for a long period of time.

We sought to apply a methodologically rigorous approach to this problem, reducing the bias inherent in studies of this nature by accounting for informative censoring, exploring dose–response relationships and interaction effects. Nevertheless, the associations described could still represent particular patient subgroups known to experience higher mortality and regular exposure to hyperoxemia; for example, those who undergo multiple transfers and procedures. These patients are inherently less stable, experience higher mortality (48) and
morbidity (49), and may be placed on a high inspired oxygen concentration for transfer, regardless of clinical need. Such events are common and our model would highlight these associations.

There is likely a large and variable exposure to oxygen before ICU admission. Information with regard to oxygenation of patients outside the ICU was unavailable in our database. Given that patients from our cohort enter critical care after variable amounts of time in an operating room, emergency department, or ward, it is reasonable to assume that most have had a prior exposure to oxygen. Indeed, even if normoxemia is achieved after admission to ICU, a brief period of hyperoxemia in the emergency department has been suggested to be detrimental (50). Should exposure to hyperoxemia increase the risk of mortality, it is unclear over what timeframe following exposure this risk returns to baseline. We chose to model ICU mortality in place of other more distant measures of outcome (hospital mortality, 90-day mortality etc.) because the proximity of the outcome to our measure of oxygen exposure helps to elucidate a causal relationship, if one exists. We chose to censor readmissions from the model for similar reasoning because this would induce a large unaccounted-for exposure to oxygen between admissions.

We chose to model a function of PaO2 (hyperoxemia dose) because this approach implicitly addresses the problem of confounding by treatment effect, albeit at the expense of creating an imperfect definition of excess oxygen exposure. A PaO2 above 13.3 kPa (100 mm Hg) likely captures a surrogate of the mechanism that is causing harm (high inspired oxygen concentrations). Much of the preclinical data favors high FiO2 as being causative for lung parenchymal damage (9). However, there may be other unrecognized systemic effects that result from supraphysiologic PaO2.

We did not model PaO2 directly because this holds a nonmonotonic relationship with mortality; hypoxemia and hyperoxemia are both thought to be detrimental (51, 52). Thus, by constraining this variable as hyperoxemia dose, we could investigate the effect of hyperoxemia, without needing to account for hypoxemia, and thus create a more parsimonious model.

 Exposure to hyperoxemia is an inherently time-dependent variable. As such, it is difficult to model this phenomenon inside the ICU for two main reasons. First, informative censoring will bias results (patients get better or die, and stop contributing data at variable nonrandom points in time). Second, to measure hyperoxemia dose, a window of observation is required to demonstrate an effect. We tested over several time windows to balance the tension between patient numbers and the opportunity for hyperoxemia exposure.

Conclusions
This study suggests that exposure to supraphysiologic levels of oxygen is associated with harm in the critically ill patient. We were, however, unable to find evidence supporting a dose–response relationship between exposure to supraphysiologic oxygenation and mortality. The lack of a dose–response relationship weakens any causal interpretation of this finding or implies that the effect is relatively small and/or reaches a plateau. We cannot, however, exclude an undetected dose-dependent effect. Placing these findings within the context of the broader literature, our study suggests that a small but meaningful reduction in mortality could be achieved by avoiding exposure to hyperoxemia. However, the potential for unmeasured confounding to bias this result places strong caveats on a causal interpretation. Further experimental investigation into this controversial field is thus warranted.

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