The association between supra-physiologic arterial oxygen levels and mortality in critically ill patients: a multi-centre observational cohort study

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Contributions

- EP: Design of study, statistical analysis, writing of manuscript
- BP: Writing of manuscript
- RK, GM: Statistical analysis, revision of manuscript
- NM, DB, AE, AJ, SA, PW, RB, SB, DY: Study database development, writing of manuscript
- CB, AR: Review of study statistical code, writing of manuscript
- DM, MS, SH: Design of study, writing and review of manuscript

Declarations

The views expressed are those of the authors and are not necessarily those of the NIHR, the NHS or the UK Department of Health and Social Care

Running Head

Hyperoxemia and outcome in critical care patients

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At a Glance Commentary

Scientific Knowledge on the Subject

Oxygen is a drug which 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 utilised 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.

Online Data Supplement

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

Abstract

Rationale

There is conflicting evidence on harm related to exposure to supra-physiologic arterial oxygen tensions (hyperoxemia) in critically ill patients.

Objectives

To examine the association between longitudinal exposure to hyperoxemia and mortality in patients admitted to intensive care units (ICUs) in 5 UK University Hospitals.

Methods

Retrospective cohort of ICU admissions between 31st January 2014 - 31st December 2018, from the National Institute of Health Research Critical Care Health Informatics Collaborative (CC-HIC). Multivariable logistic regression modelled death in ICU by exposure to hyperoxemia.

Measurements

Subsets with oxygen exposure windows of 0-1, 0-3, 0-5 and 0-7 days were evaluated, capturing 19,515, 10,525, 6,360 and 4,296 patients, respectively.

Hyperoxemia dose was defined as the area between the PaO_2 time curve and a boundary of 13.3 kPa (100 mmHg) divided by the hours of potential exposure (24, 72, 120, or 168 hours).

Main Results

An association was found between exposure to hyperoxemia and ICU mortality [odds ratios (95% compatibility intervals); 1.15 (0.95-1.38), p = 0.15; 1.35 (1.04-1.74), p = 0.02; 1.5 (1.07-2.13), p = 0.02; and 1.74 (1.11-2.72), p = 0.02 for exposure windows of 0-1, 0-3, 0-5 and 0-7 days' duration, respectively. 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.

Abstract word count: 250

Key Words: "Logistic Models", "Critical Care", "Hyperoxia"

Introduction

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), 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 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 arterial oxygen tension or inspired oxygen to define oxygen exposure for an entire ICU admission.

A recent systematic review and meta-analysis of over 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 supra-physiologic arterial oxygen tensions, 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, as concurrent lung inflammation may predispose to pulmonary oxygen toxicity and increased mortality (27).

Materials and Methods

Data were prospectively collected between 31st January 2014 and 31st December 2018 on all adult (≥ 18 years) patients attending an ICU from five UK University Hospitals contributing to the National Institute of Health Research (NIHR) Critical Care Health Informatics Collaborative (CC-HIC). The NIHR HIC themes are described elsewhere (34), as is a detailed description of the CC-HIC data specification (35). The legal basis for handling the data is provided in the Supplement. The present study was conducted as a retrospective cohort analysis, with findings reported in accordance with STROBE guidance (36).

Patients were included in the study if their ICU length of stay was greater than 24 hours. Those staying less than 24 hours were typically admitted after elective surgery with very

low mortality. These cases were removed as this would lead to prognostic de-enrichment, 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 resucitation in the 24 hours preceeding ICU admission, or failing pre-specified 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 measure. The cohort was narrowed to create nested subsets with progressively longer potential hyperoxemia exposure windows (between 0-3, 0-5 and 0-7 days, respectively). Each subset therefore had a period of potential exposure unaffected by informative censoring from either ICU discharge or death (Figure 1 and Supplement Figure S1).

ICU mortality was modelled as a function of hyperoxemia dose using multivariable logistic regression. Hyperoxemia dose was defined as the area under the PaO_2-time curve above a threshold PaO_2 value of 13.3 kPa (100 mmHg) divided by the number of hours of potential exposure. This was applied from the time of ICU admission (day 0) until either 1, 3, 5 or 7 days (Figure 1). Under this definition, 1 kPa (7.6 mmHg) of hyperoxemia dose describes that a patient's average PaO_2 was 1 kPa (7.6 mmHg) above 13.3 kPa (100 mmHg) for the duration of the exposure window. The 13.3 kPa (100 mmHg) threshold was chosen as values exceeding this can only be achieved with supplementary oxygen. This boundary therefore represents a range of PaO_2 that is unambiguously supraphysiological, and hence not confounded by treatment indication.

A substantial proportion of admissions had a hyperoxemia dose of zero. 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 APACHE 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 modelled non-linearly using restricted cubic splines (38). APACHE II score was also modelled with restricted cubic splines, as evidence from the data supported this decision.

To account for possible differential effects of exposure to hyperoxemia, interaction effects between exposure to hyperoxemia and 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 Supplement Figure S1 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 PaO_2, 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 Supplement Table S1. Where PaO_2 measures were still unavailable, the exposure was assumed to be zero. There were less than 1% missing variables, so a complete case analysis was conducted.

Model validation was performed using bootstrapped corrected calibration plots and Brier scores using 500 resamples. The c-index (area under the receiver operator characteristic curve), precision-recall, and AIC were calculated. The average treatment effect (ATE) of exposure to hyperoxemia was calculated by fitting models with each individual's own recorded exposure to hyperoxemia, and comparing with their counterfactual scenario had this exposure been zero.

All statistical analyses were performed using R Version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). The full analysis code was made publicly available prior to manuscript submission (39).

Results

Over the four year period of the study, 45,188 episodes were available. After exclusions, a primary cohort with a minimum one day ICU length of stay of 19,515 episodes remained (Supplement Figure S2). This cohort was further nested into those who remained in ICU for at least three (10,525), five (6,360) and seven (4,296) days. Baseline characteristics for the

primary cohort and nested exposure windows are shown in Table 1 and Supplement Table S2. 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, ranging from odds ratios (95% compatibility intervals) of 1.15 (0.95-1.38), p = 0.15 over days 0-1 to 1.74 (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 non-linearities in hyperoxemia dose; accordingly, this component was modelled linearly for parsimony. Point estimates for the odds ratios and their 95% compatibility intervals for covariables are presented in Figure 2. All results are presented in Supplement Table S3. These findings were robust to using probit or complimentary 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 Supplement Table S4. 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 (Supplement Table S5). 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 zero is shown in Figure 3, using the day 0-5 cohort as an illustrative example. All models are shown on the absolute risk scale in Supplement Figure S3. Point estimates for ATE were 0.4%, 0.9%, 1.6%, and 2.7% for

exposure windows of 0-1, 0-3, 0-5, and 0-7 respectively, favoring no exposure to hyperoxemia.

The overall model fit across the four exposure windows was good, with each model c-index, optimism-corrected (bootstrapped) Brier score and AIC detailed in Supplement Table 6. On calibration checks, there was a tendency for models to under-predict mortality in more severe cases (Supplement Figure S4).

Discussion

A consistent association was found across models between any exposure to hyperoxemia for up to seven 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. Eastwood *et al*, using a well controlled model, could not however 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 modelled 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 oxygenation 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, as 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; a procedure that impairs statistical inference, leading to both false positive findings and reduced statistical power (38). The most directly similar measure in their study to our own approach was a 96 hour area under the curve for PaO_2. This finding was associated with increased hospital (but not ICU) mortality, and at the upper quintile of exposure only. Under these constraints, there was no clear dose-response relationship. A small study by Reggiu *et al* (40) bears a resemblance to our approach in using any PaO_2 $\geq$13.3 kPa (100 mmHg) to indicate hyperoxemia. They modelled mortality with survival analysis and arrived at a similar conclusion that a dose-independent exposure to hyperoxemia was associated with harm. They did not however account for informative censoring of patient data.

The varied findings between studies may be due in part to a broad range of oxygenation criteria, statistical methods and heterogeneous study populations being used to assess the impact of excessive oxygen administration in the ICU (24). Studies have variously utilized values of oxygenation including PaO_2 (25, 42, 43), PaO_2 and SpO_2 (18, 44), PaO_2 and F_IO_2 (29, 41) and alveolar-arteriolar oxygen gradient (31). From a biological standpoint it remains unclear which of these (or combination thereof) provides the best measure to elucidate harm. SpO_2 has a ceiling effect at 100% and so is limited in its capacity to reveal

excess oxygenation. The relationship between SpO_2 and PaO_2 may be altered by pathophysiology and ageing (45). F_IO_2 is strongly confounded with a treatment effect as patients with high F_IO_2 requirements are more likely to have higher disease severity (46, 47). Our approach has the merit of utilizing longitudinal information regarding arterial oxygenation status of each patient throughout the study period. By calculating hyperoxemia dose, and accounting for the spike at zero effect (37), questions relating to dose response can be addressed in a principled manner. This approach may better explain systematic variance in outcomes above what could be achieved by previously reported strategies.

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 mmHg) was used to define hyperoxemia, rather than modelling the entire area under the PaO_2 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 PaO_2, is collapsed into a single measure to be included within a model. While 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 equally 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 prior to 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 time frame 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.) as the proximity of the outcome to our measure of oxygen exposure helps to elucidate a causal relationship, if one exists. We chose to censor re-admissions from the model for similar reasoning as this would induce a large unaccounted-for exposure to oxygen between admissions.

We chose to model a function of PaO_2 (hyperoxemia dose) as 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 PaO_2 above 13.3 kPa (100 mmHg) likely captures a surrogate of the mechanism that is causing harm (high inspired oxygen concentrations). Much of the preclinical data favors high F_IO_2 as being causative for lung parenchymal damage (9). However, there may be other unrecognized systemic effects that result from supra-physiological PaO_2.

We observed an association between surgical patients and harm in the day one model. This was in contrast to the other models and counter to expectations. As the patient type variable was not a primary inferential target of the study, we have avoided drawing conclusions on this isolated finding. It is possible that this is the result of conditioning the models over time, when medical and surgical patients tend to experience harm at different

points of their ICU stay. We cannot rule out the possibility that this is a false positive finding.

We did not model PaO_2 directly, as this holds a non-monotonic 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 non-random points in time). Second, in order 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 supra-physiologic 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 supra-physiologic 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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Tables

Table 1. Abridged patient characteristics, stratified by nested exposure window. Variables are presented as mean (sd), median [IQR], or count (%) as appropriate. For all characteristics, please see supplement table S1.

Characteristic	1 day exposure	3 days exposure	5 days exposure	7 days exposure
n	19593	10571	6391	4318
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)	15182 (77.5)	8865 (83.9)	5580 (87.3)	3912 (90.6)
Cumulative hyperoxemia exposure (kPa.hours)	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 (days)	1 [1, 2]	1 [1, 3]	1 [1, 3]	1 [1, 3]
Age (years)	65 [51, 74]	65 [51, 75]	64 [49, 74]	63 [48, 74]
Weight (kg)	77 (20)	77 (19)	77 (20)	77 (20)
Sex				
Female	7834 (40.0)	4149 (39.2)	2431 (38.0)	1621 (37.5)
Male	11758 (60.0)	6421 (60.7)	3959 (61.9)	2696 (62.4)
Not available	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
APACHE II score	15.4 (5.8)	16.5 (6.0)	17.2 (6.2)	17.7 (6.3)
Prior dependency (none)	16239 (82.9)	8575 (81.1)	5115 (80.0)	3433 (79.5)
Patient type				
Surgical	10721 (54.7)	4652 (44.0)	2319 (36.3)	1290 (29.9)

Medical	8861 (45.2)	5913 (55.9)	4067 (63.6)	3025 (70.1)
Not available	11 (0.1)	6 (0.1)	5 (0.1)	3 (0.1)
Surgical classification				
Elective	6758 (34.5)	2597 (24.6)	1144 (17.9)	539 (12.5)
Scheduled	1557 (7.9)	804 (7.6)	372 (5.8)	176 (4.1)
Urgent	1025 (5.2)	412 (3.9)	220 (3.4)	145 (3.4)
Emergency	1702 (8.7)	1029 (9.7)	699 (10.9)	517 (12.0)
Not applicable (Medical) or not available	8551 (43.6)	5729 (54.2)	3956 (61.9)	2941 (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 (2.8)	288 (2.7)	188 (2.9)	128 (3.0)
Black/black British Caribbean	430 (2.2)	211 (2.0)	123 (1.9)	82 (1.9)
Other or not stated	4746 (24.2)	2592 (24.5)	1574 (24.6)	1031 (23.9)
White British	11880 (60.6)	6337 (59.9)	3759 (58.8)	2541 (58.8)
White other	1312 (6.7)	757 (7.2)	483 (7.6)	332 (7.7)
ICU length of stay (days)	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)

Table 2. Odds ratios (95% compatibility intervals) for hyperoxemia dose (kPa) and any hyperoxemia exposure (as indicator variable) are shown. All other predictor variables are described in the Supplement. DoF = Degrees of freedom.

Model	Variable	Odds Ratio (95% CI)	Chi Square	DoF	p value
0-1 day	Hyperoxemia dose	1.01 (0.93-1.1)	0.071	1	0.790
	Any hyperoxemia exposure	1.15 (0.95-1.38)	2.110	1	0.146
0-3 days	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 days	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 days	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

Figure Legends

Figure 1. Illustration of the calculation of hyperoxemia dose.

The blue area defines hyperoxemia exposure for a real patient drawn from the CC-HIC database. Red points indicate actual observations. Black interrupted lines show the linear imputation strategy. Gaps exist in the imputation between observations greater than 12 hours apart. Hyperoxemia dose was calculated by summing the blue area and dividing by the hours of the potential exposure window for the given model (from top panel to bottom panel: 24, 72, 120 or 168 hours). This yields the natural units originally used to measure PaO_2 (shown in kPa). Vertical dashed lines indicate the point of censoring at the end of the exposure window.

Figure 2. Point estimates of odds ratios and 95% compatibility intervals are presented for all linear model terms. Hyperoxemia has been assessed in two ways: as an indicator (any hyperoxemia exposure) and hyperoxemia dose variables. There was a progressively stronger association between any hyperoxemia exposure and ICU mortality from the day 0-1 to 0-7 models. There was a lack of evidence to support a relationship between hyperoxemia dose and ICU mortality. Odds ratios are not presented for age, weight and APACHE II score, as these were modelled non-linearly.

Figure 3. Counterfactual risk plot illustrating the change in predicted mortality by setting all hyperoxemia exposure to zero. The model predicted risk of mortality with the observed hyperoxemia is shown on the y axis. The model predicted risk of mortality when setting hyperoxemia to zero is shown on the x axis. The day 0-5 cohort is used as an example (other cohorts demonstrate a similar pattern). The 45° identity line is marked as a dashed

diagonal line representing no change in risk. Several observations lie on the identify line, in keeping with the proportion of patients who had no exposure to hyperoxemia, and so cannot see an adjustment to their mortality risk via this mechanism.

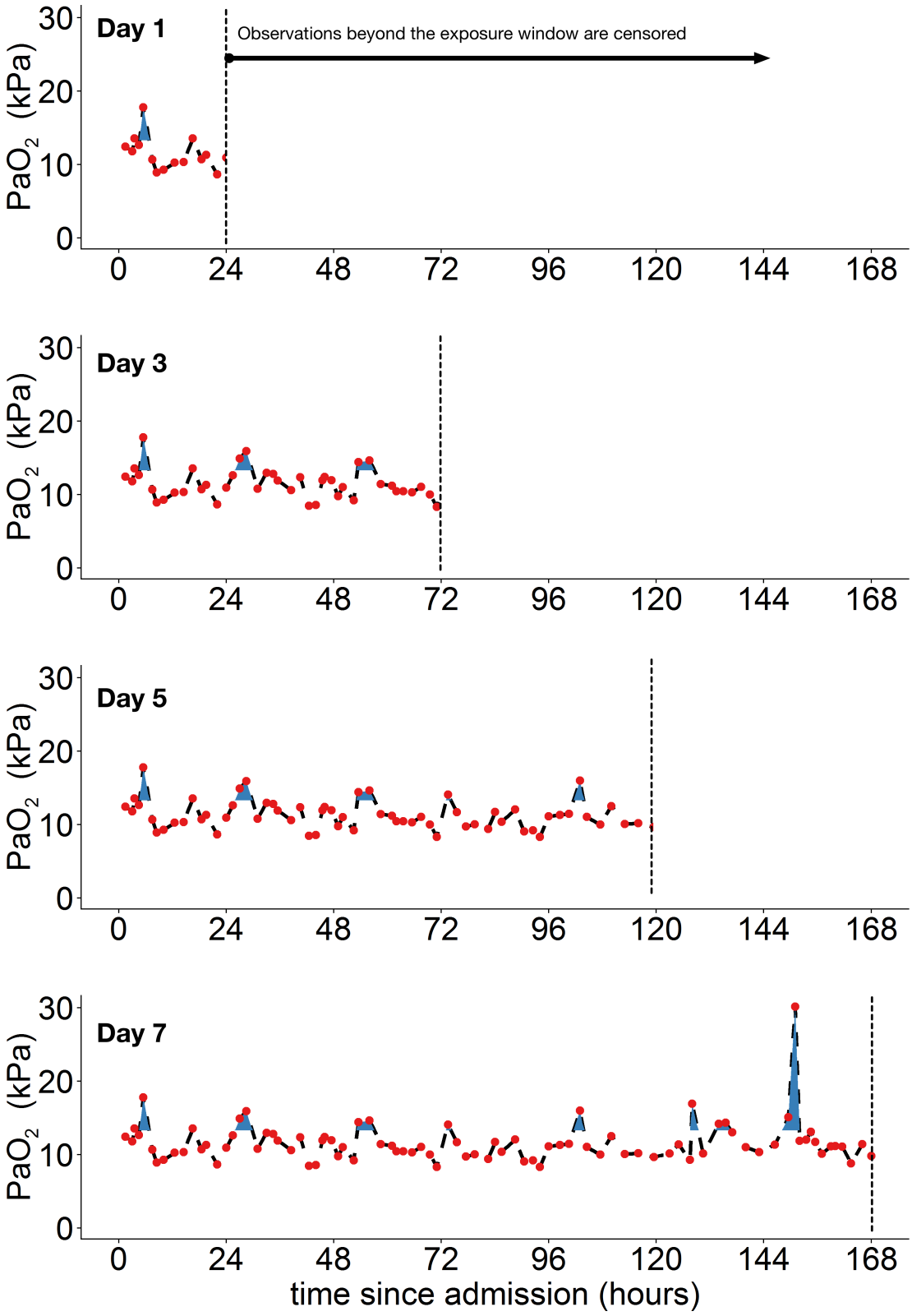
Day 1
Observations beyond the exposure window are censored
Day 3
Day 5
Day 7
PaO2 (kPa)
0
10
20
30
0
24
48
72
96
120
144
168
time since admission (hours)

Figure 1

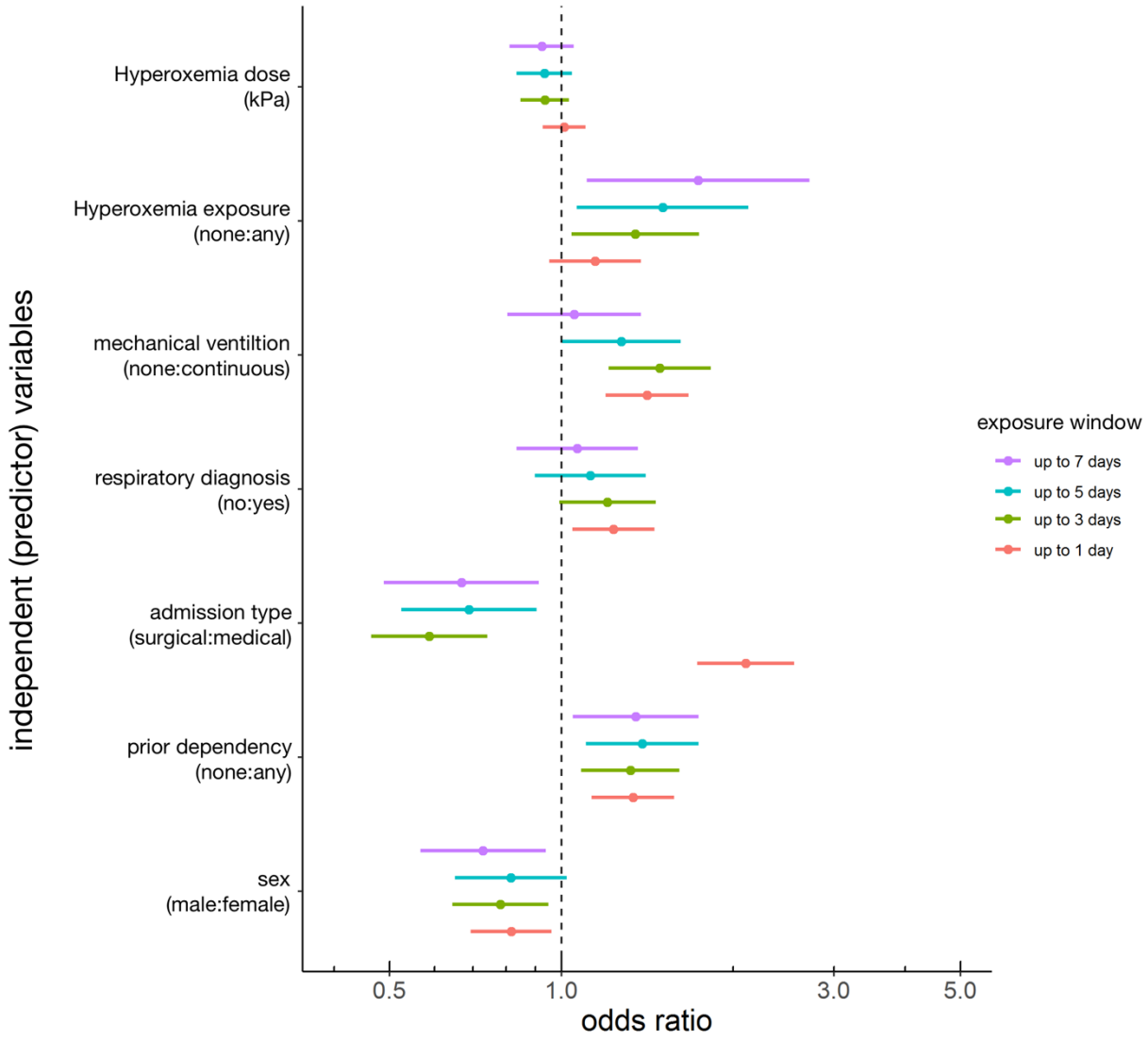
Hyperoxemia dose
(kPa)
Hyperoxemia exposure
(none:any)
mechanical ventiltion
(none:continuous)
respiratory diagnosis
(no:yes)
admission type
(surgical:medical)
prior dependency
(none:any)
sex
(male:female)
independent (predictor) variables
0.5
1.0
3.0
5.0
odds ratio
exposure window
up to 7 days
up to 5 days
up to 3 days
up to 1 day

Figure 2

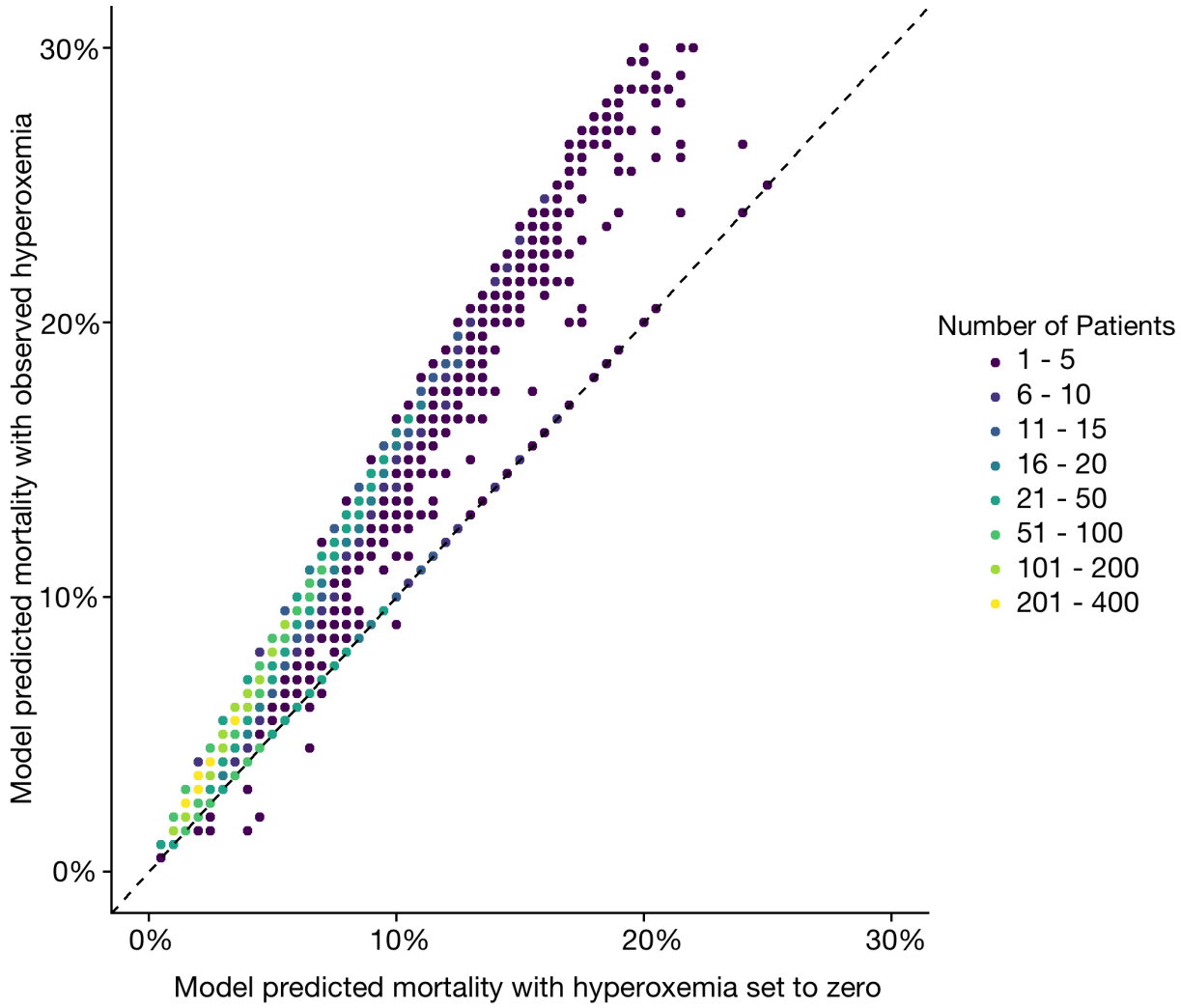
30%
20%
10%
0%
Model predicted mortality with observed hyperoxemia
0%
10%
20%
30%
Model predicted mortality with hyperoxemia set to zero
Number of Patients
1 - 5
6 - 10
11 - 15
16 - 20
21 - 50
51 - 100
101 - 200
201 - 400

Figure 3

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Supplement

Supplement Contents

Legal Basis for Data Transfer

A legal basis for transferring the data was provided under section 251 of the National Health Service Act 2006 (Confidentiality Advisory Group reference 14/CAG/1001); this process sets aside the common duty of confidentiality in the United Kingdom. Ethics approval was granted by a Health Research Authority Research Ethics Committee (14/LO/1031). Public task and substantial public interest provided the lawful basis for data processing under the General Data Protection Regulation Act.

Table S1. Information detailing the linear imputation scheme for PaO_2. A 30 minute sampling cadance was set for the study, so the imputation proportion does not correspond to a high rate of missing data. Figures are provided for when imputation occurred with 100% SpO_2 as this may result in a bias away from the null.

metric	value
Total study PaO_2 measures	865,240
Total imputed PaO_2 measures	4,433,712
Imputed PaO_2 at SpO_2 of 100%	241,047
Total 30 minute observations	7,419,420
Proportion of PaO_2 imputed	0.598
Proportion of PaO_2 imputed at SpO_2 100%	0.0325

Table S2. Full patient characteristics, stratified by nested exposure window. Variables are presented as mean (sd), median [IQR], or count (%) as appropriate. Primary organ systems are derived from the Intensive Care National Audit and Research Centre (ICNARC) diagnostic codes.

Characteristic	1 day exposure	3 days exposure	5 days exposure	7 days exposure
n	19593	10571	6391	4318
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)	15182 (77.5)	8865 (83.9)	5580 (87.3)	3912 (90.6)
Cumulative hyperoxemia exposure (kPa.hours)	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 (days)	1 [1, 2]	1 [1, 3]	1 [1, 3]	1 [1, 3]
Age (years)	65 [51, 74]	65 [51, 75]	64 [49, 74]	63 [48, 74]
Weight (kg)	77 (20)	77 (19)	77 (20)	77 (20)
Sex				
Female	7834 (40.0)	4149 (39.2)	2431 (38.0)	1621 (37.5)
Male	11758 (60.0)	6421 (60.7)	3959 (61.9)	2696 (62.4)
Not available	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
APACHE II score	15.4 (5.8)	16.5 (6.0)	17.2 (6.2)	17.7 (6.3)
Primary organ system				
Respiratory	4032 (20.6)	2670 (25.3)	1917 (30.0)	1486 (34.4)
Cardiovascular	6221 (31.8)	3181 (30.1)	1577 (24.7)	912 (21.1)
Gastrointestinal	3479 (17.8)	1766 (16.7)	1070 (16.7)	668 (15.5)

Neurological	1035 (5.3)	611 (5.8)	402 (6.3)	290 (6.7)
Poisoning	314 (1.6)	133 (1.3)	72 (1.1)	46 (1.1)
Genitourinary	2032 (10.4)	880 (8.3)	481 (7.5)	303 (7.0)
Endocrine, Metabolic, Thermoregulation and Poisoning	750 (3.8)	324 (3.1)	164 (2.6)	93 (2.2)
Haematologic/Immunological	301 (1.5)	199 (1.9)	141 (2.2)	101 (2.3)
Musculoskeletal	549 (2.8)	199 (1.9)	102 (1.6)	57 (1.3)
Dermatological	129 (0.7)	75 (0.7)	52 (0.8)	34 (0.8)
Psychiatric	7 (0.0)	5 (0.0)	3 (0.0)	3 (0.1)
Trauma	520 (2.7)	387 (3.7)	299 (4.7)	239 (5.5)
Not available	224 (1.1)	141 (1.3)	111 (1.7)	86 (2.0)
Prior location				
Emergency Department	3022 (15.4)	1780 (16.8)	1152 (18.0)	813 (18.8)
Critical Care	1488 (7.6)	1253 (11.9)	1057 (16.5)	906 (21.0)
Operating Room	11098 (56.6)	4847 (45.9)	2431 (38.0)	1367 (31.7)
Ward	3229 (16.5)	2219 (21.0)	1465 (22.9)	1034 (23.9)
Other	754 (3.8)	470 (4.4)	284 (4.4)	196 (4.5)
Not available	2 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)
Prior dependency (none)	16239 (82.9)	8575 (81.1)	5115 (80.0)	3433 (79.5)
Patient type				
Surgical	10721 (54.7)	4652 (44.0)	2319 (36.3)	1290 (29.9)
Medical	8861 (45.2)	5913 (55.9)	4067 (63.6)	3025 (70.1)
Not available	11 (0.1)	6 (0.1)	5 (0.1)	3 (0.1)

Surgical classification				
Elective	6758 (34.5)	2597 (24.6)	1144 (17.9)	539 (12.5)
Scheduled	1557 (7.9)	804 (7.6)	372 (5.8)	176 (4.1)
Urgent	1025 (5.2)	412 (3.9)	220 (3.4)	145 (3.4)
Emergency	1702 (8.7)	1029 (9.7)	699 (10.9)	517 (12.0)
Not applicable (medical) or not available	8551 (43.6)	5729 (54.2)	3956 (61.9)	2941 (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 (2.8)	288 (2.7)	188 (2.9)	128 (3.0)
Black/black British Caribbean	430 (2.2)	211 (2.0)	123 (1.9)	82 (1.9)
Other or not stated	4746 (24.2)	2592 (24.5)	1574 (24.6)	1031 (23.9)
White British	11880 (60.6)	6337 (59.9)	3759 (58.8)	2541 (58.8)
White other	1312 (6.7)	757 (7.2)	483 (7.6)	332 (7.7)
ICU length of stay (days)	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)

Table S3. Odds ratios (95% compatibility intervals) for all variables included in the analysis. The covariables for each multivariable logistic regression model are detailed. Models are listed by their potential exposure window of 0-1, 0-3, 0-5 and 0-7 days. Coefficients for non-linear covariables are determined over the quartile range observed for that covariable.

Model	Variable	Odds Ratio (95% CI)	p value
0-1 day	Hyperoxemia dose (kPa)	1.01 (0.93-1.1)	0.790
	Any hyperoxemia exposure (yes:no)	1.15 (0.95-1.38)	0.146
	APACHE II score	8.33 (5.72-12.13)	0.000
	Mechanical ventilation (yes:no)	1.41 (1.2-1.67)	0.000
	Weight (kg)	1.01 (0.83-1.22)	0.611
	Age (years)	0.87 (0.7-1.08)	0.646
	Respiratory diagnosis (yes:no)	1.23 (1.05-1.46)	0.013
	Admission type (medical:surgical)	2.11 (1.73-2.56)	0.000
	Prior dependency (any:none)	1.34 (1.13-1.58)	0.001
	Sex (female:male)	0.82 (0.69-0.96)	0.015
0-3 days	Hyperoxemia dose (kPa)	0.94 (0.85-1.03)	0.183
	Any hyperoxemia exposure (yes:no)	1.35 (1.04-1.74)	0.023
	APACHE II score	5.76 (3.97-8.34)	0.000
	Mechanical ventilation (yes:no)	1.49 (1.21-1.83)	0.000
	Weight (kg)	0.91 (0.72-1.15)	0.506
	Age (years)	0.97 (0.75-1.26)	0.533
	Respiratory diagnosis (yes:no)	1.2 (0.99-1.46)	0.061
	Admission type (medical:surgical)	0.59 (0.46-0.74)	0.000
	Prior dependency (any:none)	1.32 (1.08-1.61)	0.006
	Sex (female:male)	0.78 (0.64-0.95)	0.013

0-5 days	Hyperoxemia dose (kPa)	0.93 (0.83-1.04)	0.230
	Any hyperoxemia exposure (yes:no)	1.5 (1.07-2.13)	0.020
	APACHE II score	4.41 (3.03-6.42)	0.000
	Mechanical ventilation (yes:no)	1.27 (1-1.62)	0.047
	Weight (kg)	0.83 (0.64-1.08)	0.512
	Age (years)	1.12 (0.82-1.53)	0.548
	Respiratory diagnosis (yes:no)	1.12 (0.9-1.41)	0.307
	Admission type (medical:surgical)	0.69 (0.52-0.9)	0.007
	Prior dependency (any:none)	1.39 (1.1-1.74)	0.005
	Sex (female:male)	0.82 (0.65-1.02)	0.078
0-7 days	Hyperoxemia dose (kPa)	0.92 (0.81-1.05)	0.234
	Any hyperoxemia exposure (yes:no)	1.74 (1.11-2.72)	0.016
	APACHE II score	4.32 (2.89-6.46)	0.000
	Mechanical ventilation (yes:no)	1.05 (0.8-1.38)	0.707
	Weight (kg)	0.79 (0.59-1.06)	0.567
	Age (years)	1.36 (0.96-1.91)	0.385
	Respiratory diagnosis (yes:no)	1.07 (0.84-1.36)	0.603
	Admission type (medical:surgical)	0.67 (0.49-0.91)	0.011
	Prior dependency (any:none)	1.35 (1.05-1.74)	0.021
	Sex (female:male)	0.73 (0.57-0.94)	0.014

Table S4. Likelihood ratios comparing the base model for each exposure window (no interaction effects) with the models containing the interaction effects for hyperoxemia dose:respiratory diagnosis and hyperoxemia dose:mechanical ventilation

model	Likelihood ratio (Chi-Square)	Degrees of freedom	P value
0-1 day	0.81	2	0.67
0-3 days	5.00	2	0.08
0-5 days	3.43	2	0.18
0-7 days	3.37	2	0.18

Table S5. The double difference in log odds between those exposed and not exposed to hyperoxemia, and those with and without a primary respiratory diagnosis, or those who received or did not receive mechanical ventilation are shown. Note that asterisks show where rounding to zero has taken place for presentation purposes.

model	Interaction tested	Contrast	Standard error	Z score	P value
0-1 day	Respiratory diagnosis	0.00*	0.01	0.05	0.96
0-3 days	Respiratory diagnosis	-0.19	0.21	-0.89	0.37
0-5 days	Respiratory diagnosis	0.08	0.25	0.32	0.75
0-7 days	Respiratory diagnosis	0.28	0.30	0.95	0.34
0-1 day	Mechanical ventilation	0.00*	0.01	0.00*	0.99
0-3 days	Mechanical ventilation	0.42	0.25	1.66	0.09
0-5 days	Mechanical ventilation	0.36	0.29	1.23	0.22
0-7 days	Mechanical ventilation	0.24	0.36	0.69	0.49

Table S6. Model performance metrics. C-index: Otherwise referred to as the area under the receiver operator characteristic curve. Values above 0.7 are generally associated with acceptable model performance, however caution should be emphasised as imbalanced groups are present in this analysis. A Brier score closer to 0 is preferable. The Brier score quoted is optimism-corrected with 500 bootstrap samples. AIC = Akaike information criterion

model	c-index	Brier score	AIC
0-1 day	0.84	0.037	5570
0-3 days	0.78	0.048	3910
0-5 days	0.74	0.060	2870
0-7 days	0.72	0.073	2280

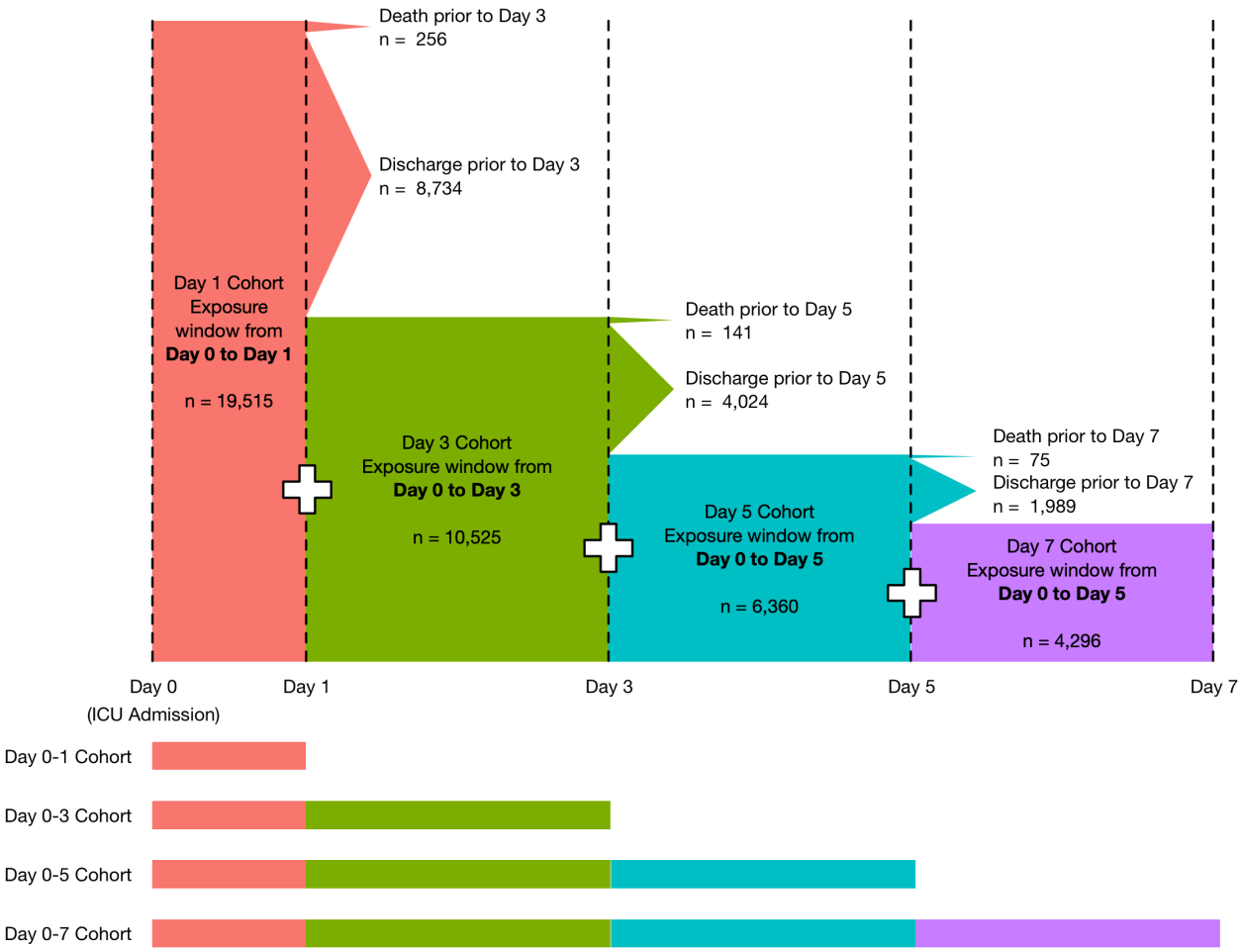

Figure S1. Illustration of the formation of the nested cohorts. Patients who pass all study entry criteria and who remain alive inside the ICU at day 1 (24 hours after admission) are eligible to be included in the day 1 cohort. This creates a cohort of patients with the same potential for exposure to hyperoxemia. Variable exposure from death or discharge (informative censoring) therefore does not present a risk of bias to the model. Nested cohorts are established for the exposure windows of 0-3, 0-5 and 0-7 days (referred to as days 3, 5 and 7 for brevity) with patients who leave the ICU from death or discharge between the boundary times removed from the cohort. All patients who reach the day 7 cohort will also feature in days 1, 3 and 5 cohorts.

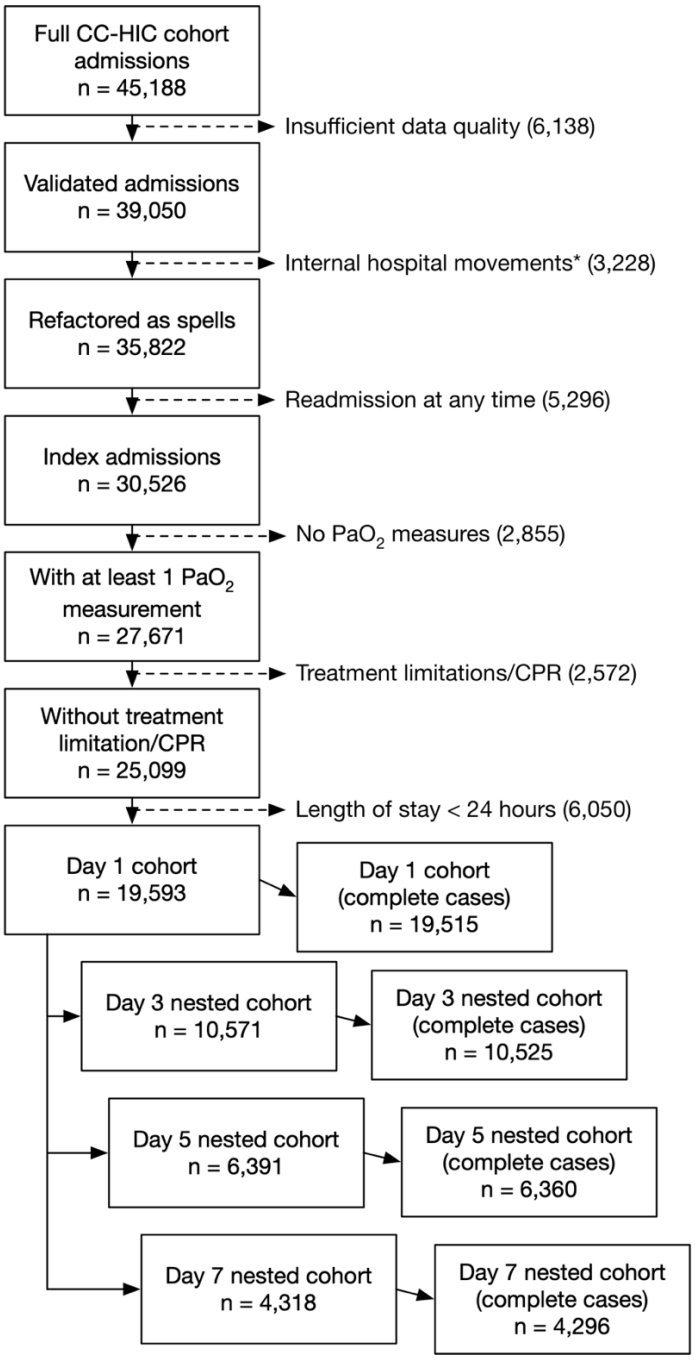

*Figure S2. Study flow diagram. *Internal hospital movements refers to the refactoring of critical admissions to represent a continuous period of critical care. This occurs for example when patients are moved from one unit to another within the same hospital. These moves are administrative in nature and hence reconciled as "spells".*

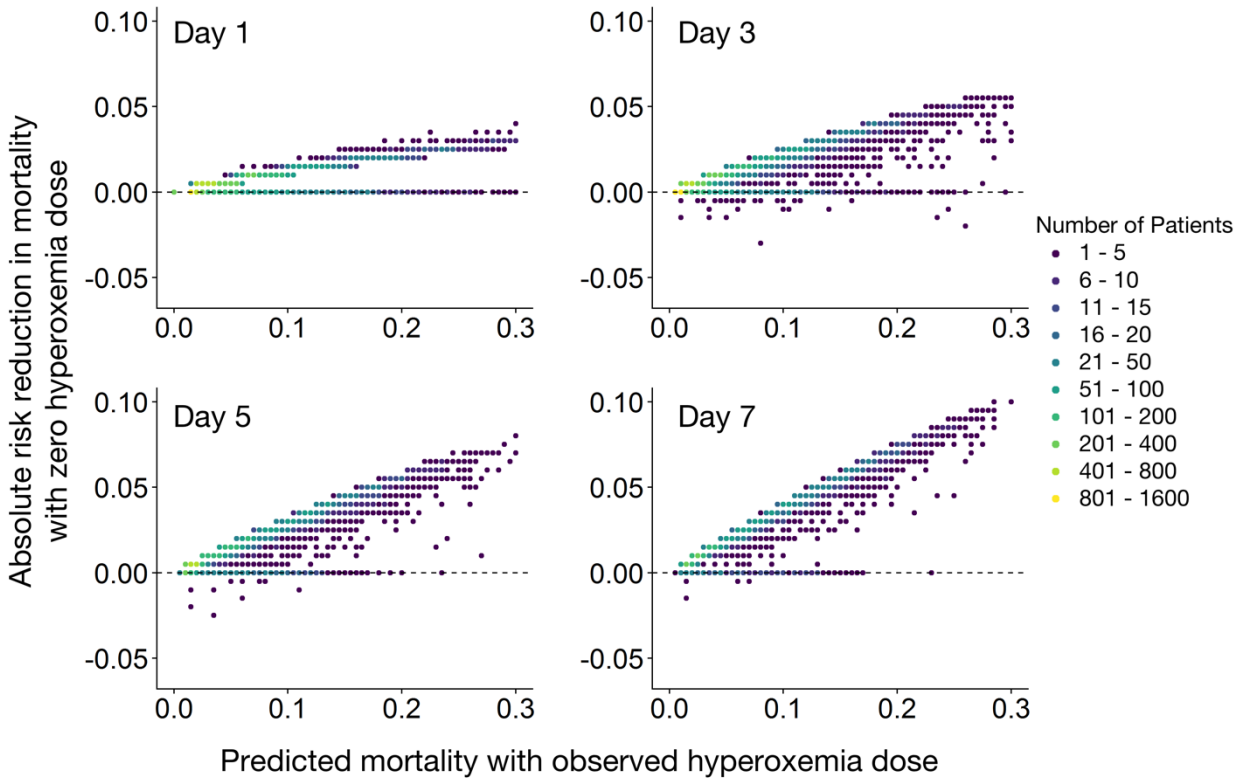

Figure S3. Counterfactual risk reduction plots on the absolute risk reduction scale. Models for exposure days 1, 3, 5 and 7 are presented in the four panels as labelled. Positive figures on the absolute risk reduction scale (y axis) imply a reduction in mortality. Note that cases with zero exposure (zero hyperoxemia dose) lie across the horizontal dashed identity line as these patients cannot see a modification to their mortality via this mechanism.

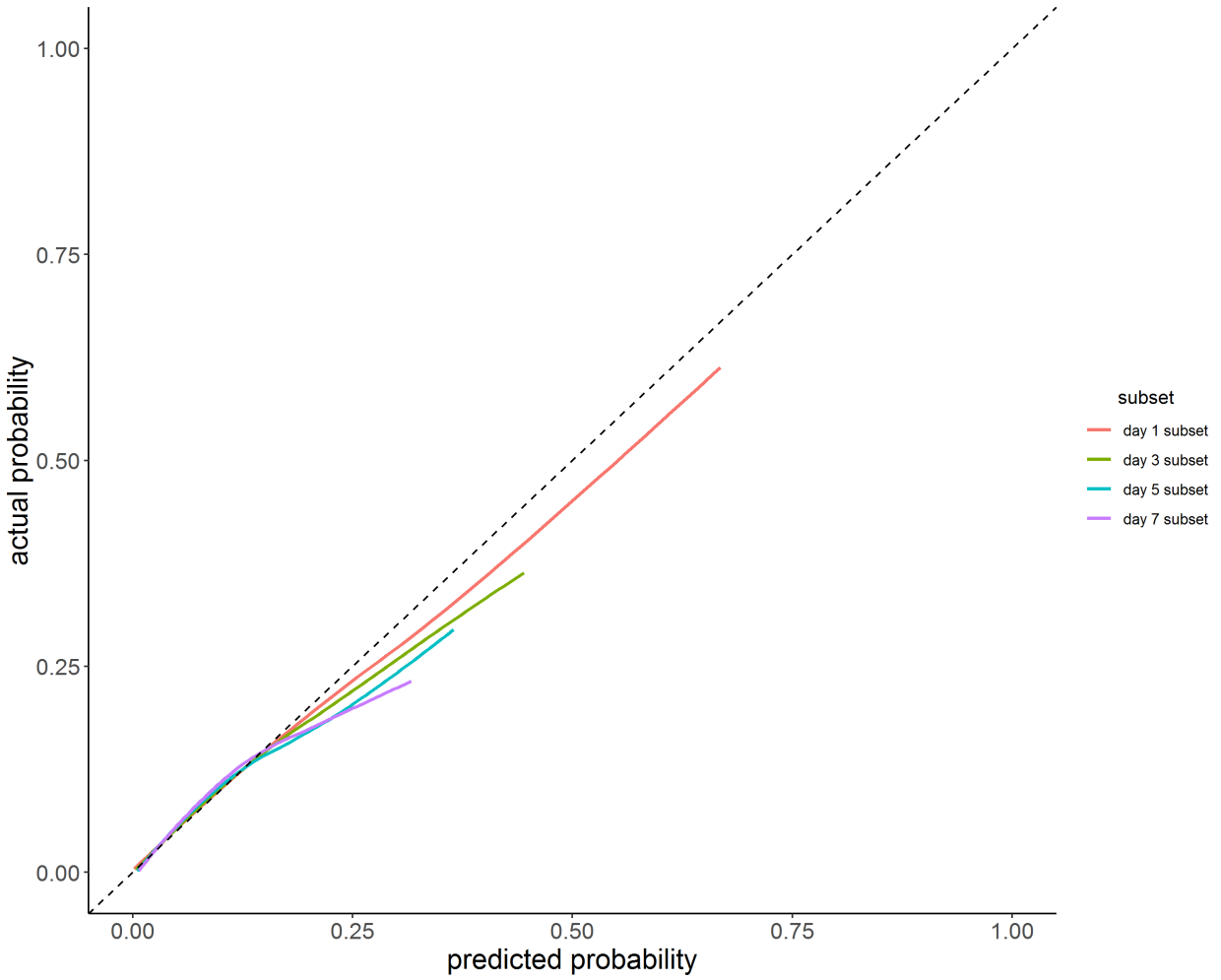

Figure S4. High resolution adjusted model calibration plots. Estimates of predicted versus actual values are based on subsetting predictions into many intervals. Five hundred bootstrap resamples are performed to obtain bias corrected (optimism corrected) estimates. A nonparametric smoothing calibration curve (locally estimated scatterplot smoothing) is applied.

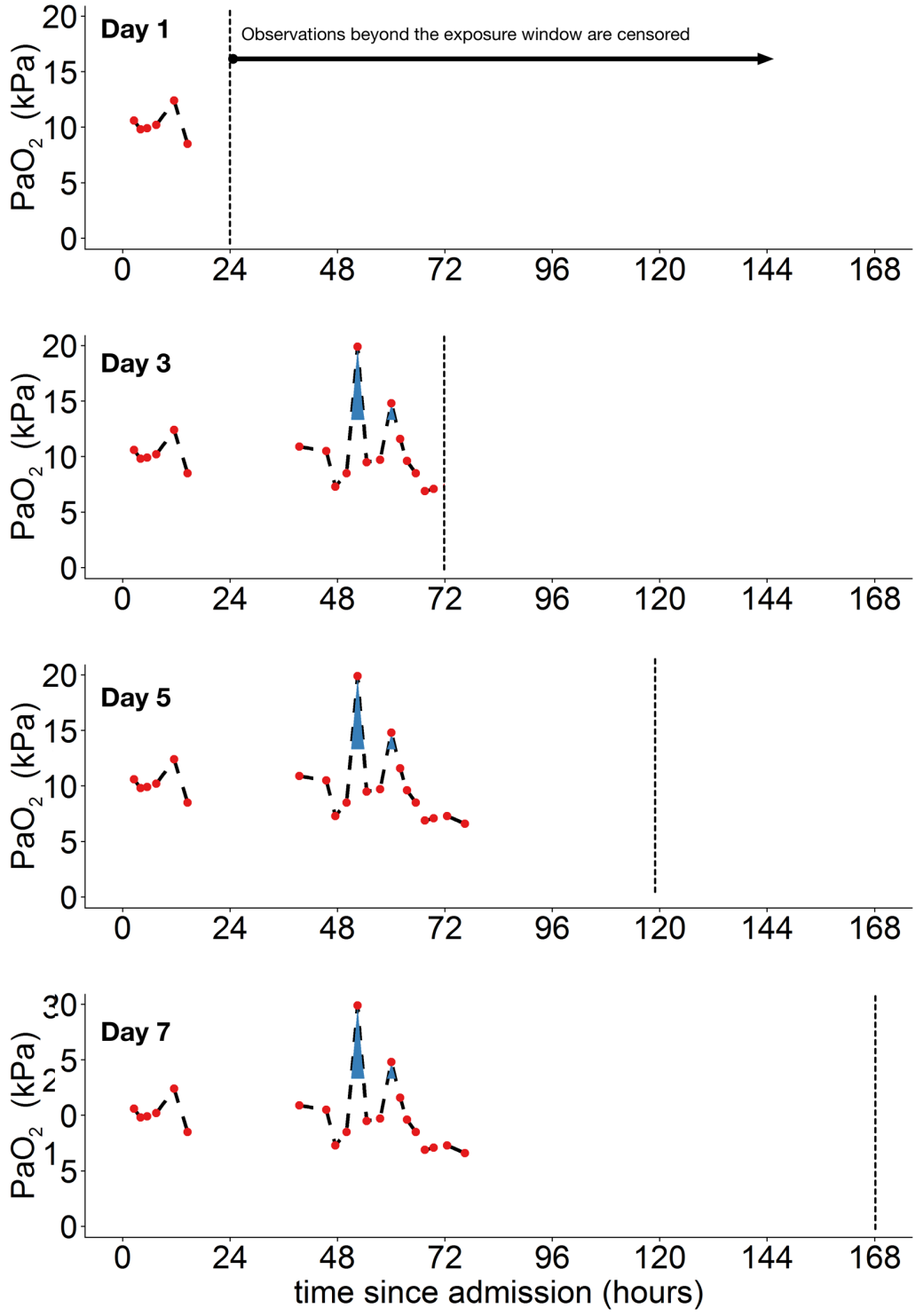

Figure S5. Further illustration of the calculation of hyperoxemia dose. This case was chosen as it reflects non zero exposure that is typical at the 25th quartile of hyperoxemia exposure. Note the early gap in observations, exceeding the 12 hour maximum for linear imputation. Zero hyperoxemia exposure is assumed during this period. For a full description, please refer to main figure 1.

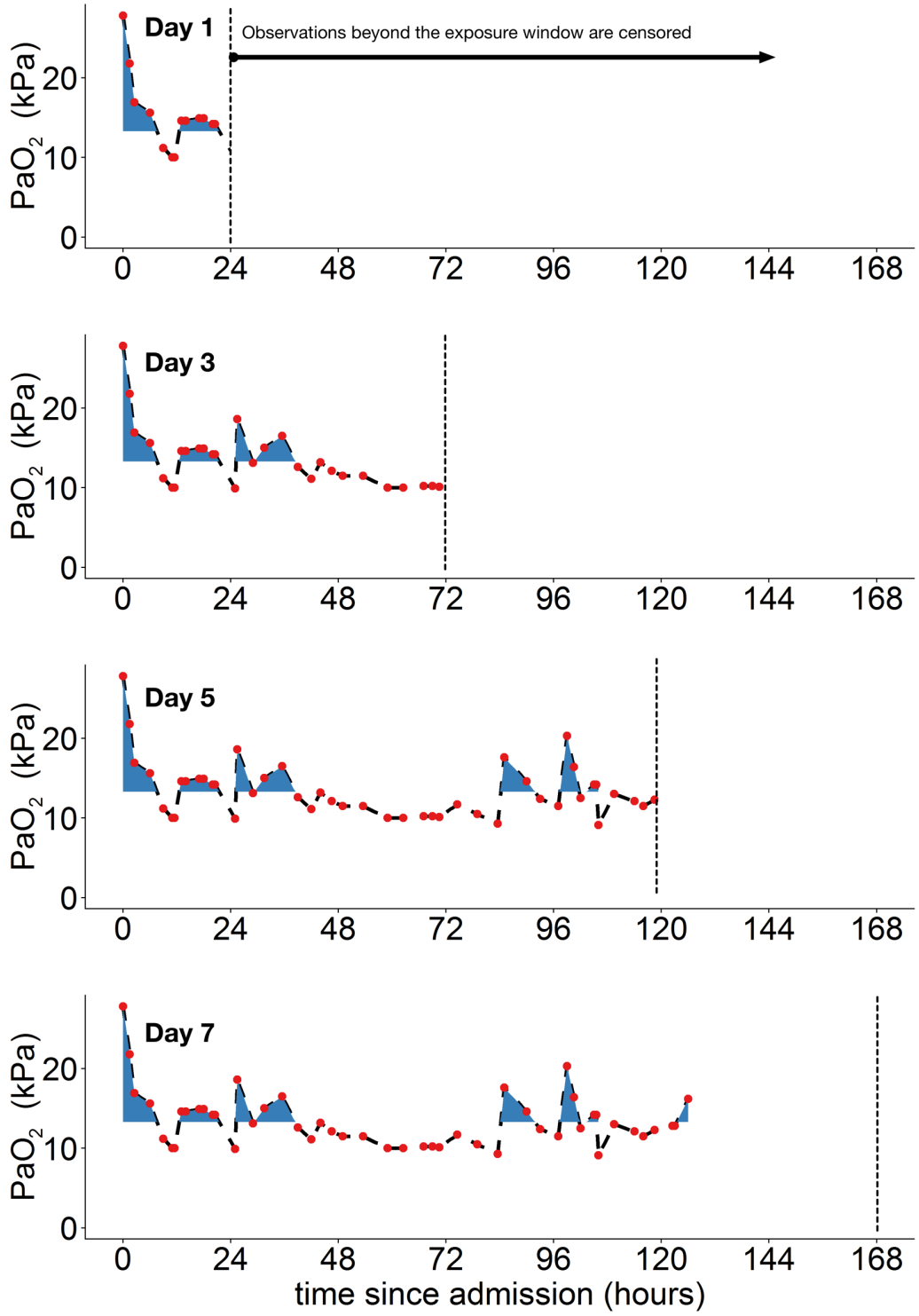

Figure S6. Further illustration of the calculation of hyperoxemia dose. This case was chosen as it reflects non zero exposure that is typical at the 75th quartile of hyperoxemia exposure. Note the gap in observations toward the end of the day 7 model. This likely corresponds to the removal of an arterial line, and no further PaO_2 samples being drawn. Zero hyperoxemia exposure is assumed during this period. For a full description, please refer to main figure 1.

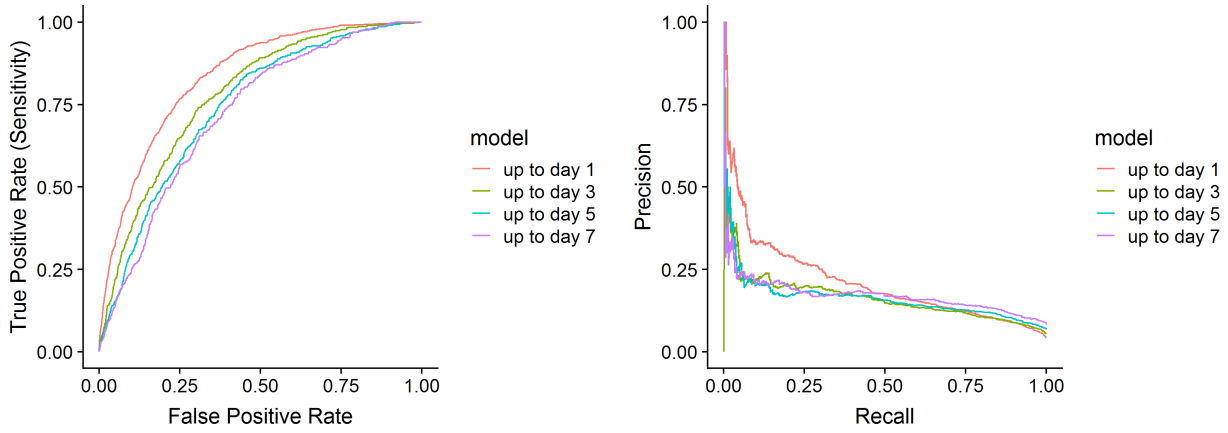

Figure S7. Receiver operator characteristic and precision-recall curves for each model.