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The Search for Optimal Oxygen Saturation Targets in Critically Ill Patients: Observational Data from Large ICU Databases

Running head: Oxygen Saturation Target in ICU Patients

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Declaration of interests

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Abbreviations list

APACHE IV = Acute Physiology, Age, Chronic Health Evaluation IV

BMI = body mass index

eICU-CRD = eICU Collaborative Research Database

ICU = intensive care unit

MIMIC = Medical Information Mart for Intensive Care III

PaO_2 = arterial blood gas

SOFA = Sequential Organ Failure Assessment

SpO_2 = pulse oximetry-derived oxygen saturation

Abstract

Background

While low oxygen saturations are generally regarded as deleterious, recent studies in intensive care unit (ICU) patients have shown that a liberal oxygen strategy increases mortality. However, the optimal oxygen saturation target remains unclear. We therefore aimed to elucidate this optimal range with real world data.

Methods

Replicate retrospective analyses of two electronic medical record databases were done: eICU Collaborative Research Database (eICU-CRD) and the Medical Information Mart for Intensive Care III (MIMIC). Only patients with at least 48 hours 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, body mass index, gender, and SOFA score. Subgroup analyses included ICU types, main diagnosis, and comorbidities.

Results

We identified 26,723 patients from eICU-CRD and 8,564 patients from MIMIC. The optimal range of SpO_2 was 94–98% in both eICU-CRD and MIMIC. The percentage of time patients were within the optimal range of SpO_2 was associated with decreased hospital mortality (odds ratio of 80% versus 40% of the measurements within the optimal range: 0.42, 95% CI 0.40 to 0.43, for eICU-CRD and 0.53, 95% CI 0.50 to 0.55 for MIMIC). This association was consistent across subgroup analyses.

Conclusions

The optimal range of SpO_2 was 94–98% and should inform future trials of oxygen therapy.

Keywords

Blood oxygen saturation; electronic medical records; hyperoxemia; intensive care unit; oxygen therapy; pulse oximetry

Introduction

Human survival requires adequate tissue oxygenation, which depends on blood oxygenation. In critically ill patients with cardiorespiratory compromise, blood oxygen levels – commonly measured continuously using peripheral pulse oximetry (SpO_2) or intermittently using arterial blood gas analysis (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 relationship 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, e.g. cerebral or coronary, and generates free radicals that cause cellular damage.[1] Since 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, though few empirical studies support this directly.

The available evidence, listed in the supplement, has four broad issues. Firstly, investigators are predisposed to demonstrate the harmful effects of hyperoxemia but not hypoxemia. For instance, a recent systematic review of 25 randomized trials demonstrated that supplemental oxygen targeting SpO_2 >96% increased mortality compared to SpO_2 <96%, but did not define a lower limit of safety.[3] Secondly, some studies assumed a linear relationship between oxygenation and mortality,[4] which is biologically implausible. Thirdly, some studies used PaO_2 rather than SpO_2 to define oxygenation.[4-6] As 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 septic patients showed optimal survival at a PaO_2 of 300 mmHg,[7] which is considered hyperoxemia by 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 showed *higher* mortality for normoxemia, defined as a PaO_2 between 60-120 mmHg, than for hypoxemia, defined as <60 mmHg.[10]

Additionally, there are reports[14-17] that hyperoxemia is common in the ICU, with hyperoxemia rates published ranging from 15% to over 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. With hyperoxemia's adverse effects, its prevalence provides an opportunity to improve outcomes.

A large-scale multicentre study is therefore required to elucidate oxygen saturation targets to guide clinical practice and future research. This is now possible using big data sources such as the eICU Collaborative Research Database[18] (eICU-CRD) and the Medical Information Mart for Intensive Care III[19] (MIMIC) which are open-access, de-identified data sets of patients admitted to ICUs. Without making assumptions of linearity, our study aims to derive an optimal range of oxygen saturation by correlating SpO_2 with mortality. We then evaluate this oxygen saturation range by correlating the time within this range with mortality. Replicate analyses using eICU-CRD and MIMIC demonstrate the reliability of our findings.

Materials and Methods

Data Description

We collected data from eICU-CRD v2.0 and MIMIC-III 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 Helsinki declaration and its later amendments. eICU-CRD covers 200,859 ICU admissions in 2014 and 2015 of 139,367 patients at 208 U.S. hospitals. MIMIC covers 61,532 ICU admissions between 2001 and 2012 of 46,476 patients at the Beth Israel Deaconess Medical Center in Boston, MA, USA. Both databases are maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology. They include hourly physiologic readings from bedside monitors, records of demographics, diagnoses via International Classification of Diseases, Ninth Revision (ICD-9) 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 (STROBE) 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, where oxygen therapy can be supplemental oxygen such as a nasal cannula, non-invasive, 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. Additionally, we 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 repeat ICU stays, patients under 16, and ICU stays with less than 48 hours of oxygen therapy, with fewer than 24 SpO_2 measurements or with no signs of supplemental oxygen such as a fraction of inspired oxygen (FiO_2) above 21% or records of an oxygen flow rate. Like SpO_2, a nurse enters FiO_2 and oxygen flow rate regularly such that our

determination of who is on supplemental oxygen is reliable. We included only hospitals that contained at least ten ICU stays in the data cohort to improve identifiability of the resulting statistical model.

Statistical Analysis

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. We used them to estimate the association between median SpO_2 and mortality while controlling for age, body mass index (BMI), gender, Sequential Organ Failure Assessment (SOFA) score[23] on the first day of the ICU stay, and duration of oxygen therapy (i.e. any oxygen supplementation, non-invasive ventilation or mechanical ventilation). Additionally, for eICU-CRD, we included hospital 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.

The supplement contains additional cohort characteristics, sensitivity and subgroup analyses, results with ICU mortality (secondary outcome), results on the ICU stays excluded here because they did not have 48 hours 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). To address concerns about time dependency of oxygen exposure, sensitivity analyses consider only using the SpO_2 measurements during the first 24, 48, or 72 hours of an oxygen therapy session. Since APACHE IV score[24] is readily available in eICU-CRD, one sensitivity analysis is to use that score instead of SOFA score as control variable. Subgroup analyses include oxygen therapy type, ICU type, ethnicity, and the presence of comorbidities such as atrial fibrillation and chronic obstructive pulmonary disease.

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

Results

Figure 1 describes the selection of 26,723/8,564 ICU stays meeting our criteria from the 200,859/61,532 ICU stays in eICU-CRD/MIMIC for analysis. Table 1 summarizes the demographic and clinical characteristics. Hospital mortality and SOFA scores are higher in those selected than in eICU-CRD and MIMIC overall. This is probably a result of only selecting ICU stays that involved oxygen therapy for at least 48 hours. 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<0.0001 for both eICU-CRD and MIMIC). While hypoxemia correlates more strongly with mortality, hyperoxemia is also associated with increased mortality. Table 2 confirms this, both when adjusting for confounders and when not adjusting for them. We chose the median SpO_2 values 100%, 96%, and 92% in Table 2 based on that the bottom of the U-shape in Figure 2 occurs around 96%, and 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, we chose an SpO_2 range of 94–98%. Next, we evaluate 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<0.0001 for all associations in both eICU-CRD and MIMIC). Being within this range 80% of the time versus 40% of the time is associated with reducing the odds of mortality by half in both eICU-CRD (adjusted odds ratio 0.42, 95% CI 0.40 to 0.43) and MIMIC (adjusted odds ratio 0.53, 95% CI 0.50 to 0.55) per Table 2: We chose to present the comparison 80% versus 40% of SpO_2 measurements between 94–98% in Table 2 because 40% appears frequently in the data per Table 1 and achieving 80% seems feasible: 7%/5% of the analysed eICU-CRD/MIMIC data have more than 80% of SpO_2 measurements between 94–98%. e-Figure 30 further shows the distribution of these proportions in the data. Table 2 and Figures 3C and 3D confirm that SpO_2 above 98% is indeed associated (P<0.0001 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 in the supplement 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 demonstrated that, among patients requiring oxygen therapy, hospital mortality had a U-shaped association with SpO_2. The retrospective data exhibited lowest mortality at a median SpO_2 within 94–98%, 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.

Our sensitivity analyses involving using early SpO_2 readings, within 24, 48 and 72 hours of ICU admission, showed the same as our primary analysis using all SpO_2 readings. These suggest that disease recovery, as shown by improved mortality, was not responsible for SpO_2 within the evaluated 94–98% 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 2001-2012. eICU-CRD represents more contemporary practice patterns from 2014-2015.

An alternative means of measuring blood oxygenation is 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 as 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 94–98%, the correlation between SpO_2 and PaO_2 would be fair, with 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 94–98% conferred a mortality benefit compared to using a target of 97-100% (ICU mortality 11.6% versus 22.0%, P=0.01; hospital mortality 24.2% versus 33.9%, P=0.03).[8] Although the trial was non-blinded, it supports our range of 94–98%. In contrast to relative normal blood oxygenation, trials in paediatric populations demonstrate mortality from permissive hypoxemia (SpO_2 85–89%).[27,28] 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 94–98% for most acutely ill patients.[29] Recent evidence suggests that overuse of oxygen therapy is prevalent and is associated with adverse outcomes including more days on mechanical ventilation and longer hospitalization.[14-17] Targeting SpO_2 between 94 to 98% might optimize survival for patients requiring oxygen therapy.[30] As pulse oximetry is widespread and affordable, implementation of the 94–98% target would be feasible, even in resource-limited environments.

Although our study provides observational evidence for an SpO_2 target range of 94–98%, the target would not apply under some circumstances. For patients with severe acute respiratory distress syndrome, ventilator settings need to limit lung stress and strain.[31] A lower limit of SpO_2 below 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 on extracorporeal membrane oxygenation, or who are not on oxygen therapy since we did not include them in our analysis.

Despite the large sample size, allowing multiple subgroup and sensitivity analyses, we acknowledge limitations. Firstly, the data were from the U.S., so the results may not apply fully to ICUs elsewhere with different practices or resources. Secondly, 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 demonstrating consistency of our results using subgroup analysis by disease type. Conversely, we would have underestimated the association between hyperoxemia and mortality, though this association remained statistically significant in our analyses given the large sample size.

Importantly, the range of 94–98% 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.[27] In prior randomized trials of oxygen therapy, the treatment-group cut-offs for SpO_2 or PaO_2 were essentially arbitrary. Our study provides a firmer basis for selection of SpO_2 targets within treatment groups. Given the U-shaped relationship 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 94–98%. This range should apply broadly across different patient characteristics and settings. Future randomized trials could also adopt SpO_2 94–98% as the reference target.

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Author contributions

MF and KCS conceived the study. WvdB, MH, and HC curated the data. WvdB performed the data analysis. WvdB and KCS produced an initial draft of the manuscript. All authors provided feedback on the manuscript. WvdB had full access to all the data. KCS had final responsibility for the decision to submit for publication.

Declaration of interests

The authors report no conflicts of interest.

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Table 1. Demographic and clinical characteristics

Characteristic	Mean or count (%)	Standard deviation	Quartiles		
			Q1	Median	Q3
Data set	112,755 ICU stays from eICU-CRD with demographic data				
Age	62	17	52	64	75
BMI	29	8.2	24	28	33
SOFA score	4.5	3.2	2.0	4.0	6.0
Hospital mortality	10,417 (9%)				
Female	50,987 (45%)				
Data set	26,723 ICU stays from eICU-CRD with at least 48 hours of oxygen therapy and 24 SpO_2 measurements				
Age	64	15	55	66	76
BMI	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 (hours)	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
Data set	18,105 ICU stays from MIMIC with demographic data				
Age	64	16	54	65	76
BMI	29	7.2	24	27	32
SOFA score	4.5	3.1	2.0	4.0	6.0
Hospital mortality	1,783 (10%)				
Female	6,937 (38%)				
Data set	8,564 ICU stays from MIMIC with at least 48 hours of oxygen therapy and 24 SpO_2 measurements				
Age	64	16	55	67	77
BMI	29	7.7	24	28	32
SOFA score	5.5	3.4	3.0	5.0	8.0
Hospital mortality	1,250 (15%)				
Female	3,449 (40%)				
Oxygen therapy duration (hours)	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 for the eICU-CRD and MIMIC ICU stays not constrained by and constrained by having 48 hours of oxygen therapy and 24 SpO_2 measurements.

Table 2. Odds ratios (95% confidence interval) of hospital mortality based on the median of SpO_2 measurements and derived SpO_2 range

Comparison	Median SpO_2		80% versus 40% of SpO_2 measurements	
	92% versus 96%	100% versus 96%	within 94% to 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)

Odds ratios of hospital mortality with 95% confidence intervals in parentheses from the generalized additive models on the effect of median SpO_2, proportion of SpO_2 measurements between 94% to 98%, and proportion of SpO_2 measurements above 98%. The odds ratios are computed with (adjusted) and without (unadjusted) controlling for confounders.

Figure legends

Fig. 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.

Fig. 2 Probability of hospital mortality versus 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 26,723/8,564 ICU stays from eICU-CRD/MIMIC (A/B). The line is the mean prediction and the dashed lines are the 95% confidence interval.

Fig. 3 Probability of hospital mortality versus the proportion of time with SpO_2 within 94% to 98%
Visual summary of the association between the proportion of SpO_2 measurements from 94% to 98% and probability of hospital mortality from the generalized additive model fit on 26,723/8,564 ICU stays from eICU-CRD/MIMIC (A/B) as well as the same for the proportion of measurements below 94% and above 98% (C/D). The lines are the mean prediction and the dashed lines are the 95% confidence interval.

Supplemental Material to:
The Search for Optimal Oxygen Saturation Targets in Critically Ill Patients: Observational Data from Large ICU Databases

By Willem van den Boom, Michael Hoy, Jagadish Sankaran, Mengru Liu, Haroun Chahed, Mengling Feng, and Kay Choong See

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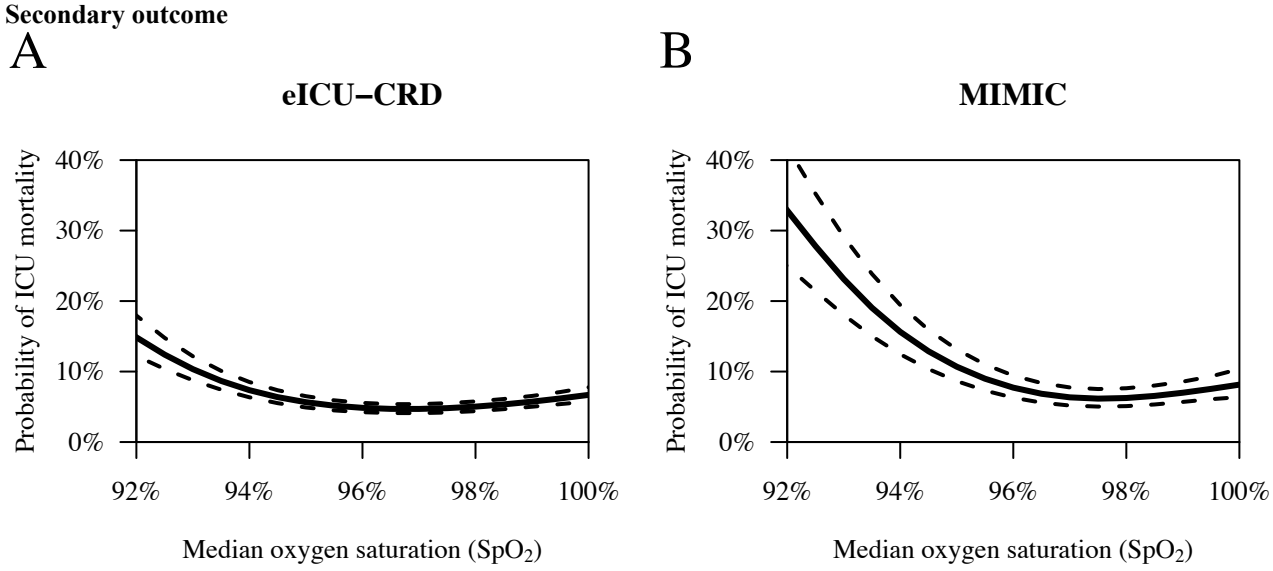
e-Table 1. Cohort diagnoses and comorbidities

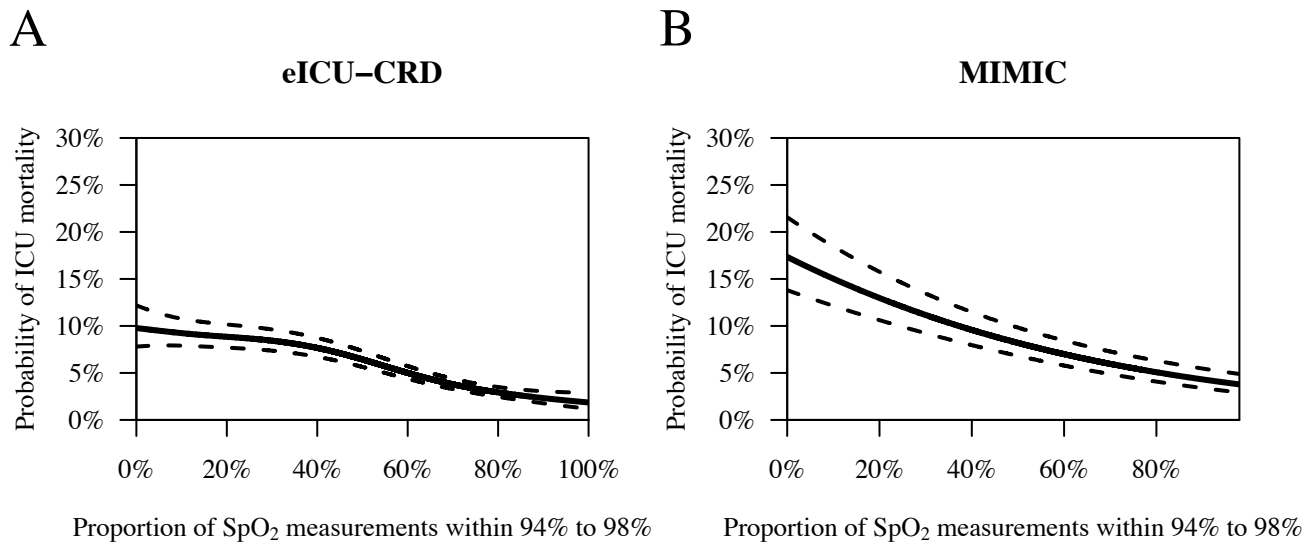
Diagnosis	Count	Percentage
Data set	112,755 ICU stays from eICU-CRD with demographic data	
Atrial fibrillation	14,458	13%
Cancer	5,258	5%
Congestive heart failure	8,109	7%
Chronic kidney disease	7,485	7%
Chronic liver disease	1,074	1%
Chronic obstructive pulmonary disease	8,489	8%
Diabetes mellitus	3,606	3%
Hypertension	15,187	13%
Ischemic heart disease	9,371	8%
Sepsis	8,448	7%
Stroke	2,742	2%
Data set	26,723 ICU stays from eICU-CRD with at least 48 hours of oxygen therapy and 24 SpO_2 measurements	
Atrial fibrillation	4,550	17%
Cancer	1,413	5%
Congestive heart failure	2,795	10%
Chronic kidney disease	2,115	8%
Chronic liver disease	284	1%
Chronic obstructive pulmonary disease	2,878	11%
Diabetes mellitus	493	2%
Hypertension	3,637	14%
Ischemic heart disease	2,075	8%
Sepsis	2,750	10%
Stroke	597	2%
Data set	18,105 ICU stays from MIMIC with demographic data	
Atrial fibrillation	6,884	38%
Cancer	2,040	11%
Congestive heart failure	4,503	25%
Chronic kidney disease	1,721	10%
Chronic liver disease	942	5%
Chronic obstructive pulmonary disease	3,145	17%
Diabetes mellitus	4,943	27%
Hypertension	10,351	57%
Ischemic heart disease	8,109	45%
Sepsis	1,911	11%
Stroke	525	3%
Data set	8,564 ICU stays from MIMIC with at least 48 hours of oxygen therapy and 24 SpO_2 measurements	
Atrial fibrillation	3,838	45%
Cancer	984	11%
Congestive heart failure	2,633	31%
Chronic kidney disease	881	10%
Chronic liver disease	532	6%
Chronic obstructive pulmonary disease	1,656	19%
Diabetes mellitus	2,389	28%
Hypertension	4,806	56%
Ischemic heart disease	3,701	43%
Sepsis	1,327	15%
Stroke	372	4%

Prevalence of the diagnoses and comorbidities considered in the subgroup analysis for the ICU-CRD and MIMIC ICU stays not constrained by and constrained by having 48 hours of oxygen therapy and 24 SpO_2 measurements.

Secondary outcome



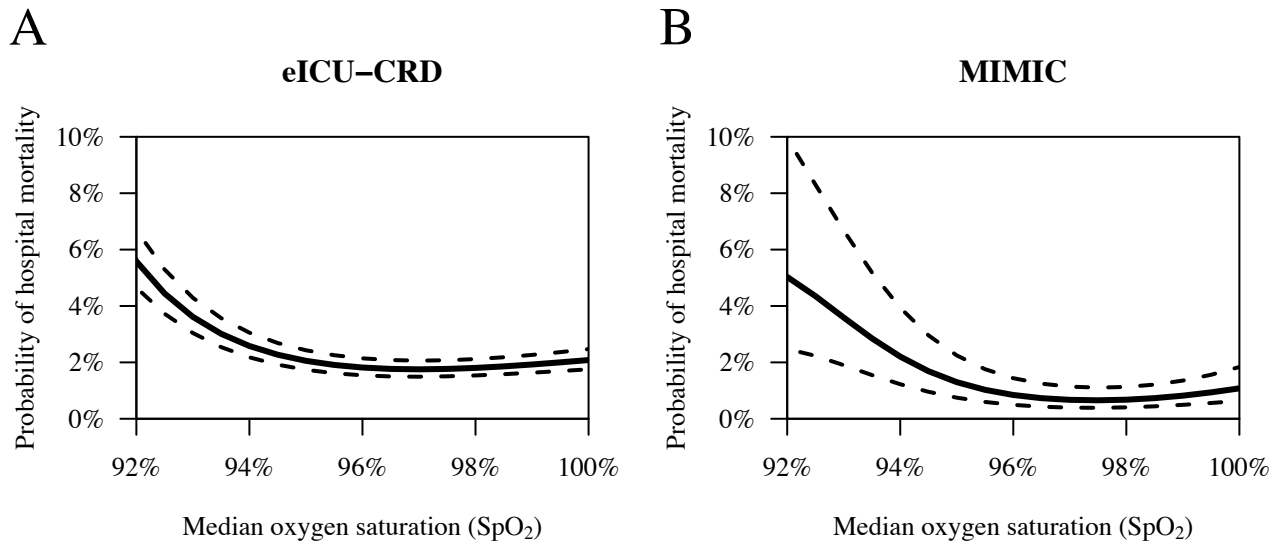
e-Figure 1. Probability of ICU mortality versus median SpO_2 with ICU mortality as outcome
These plots are analogous to Figure 2 of the main text but use ICU mortality instead of hospital mortality as outcome.



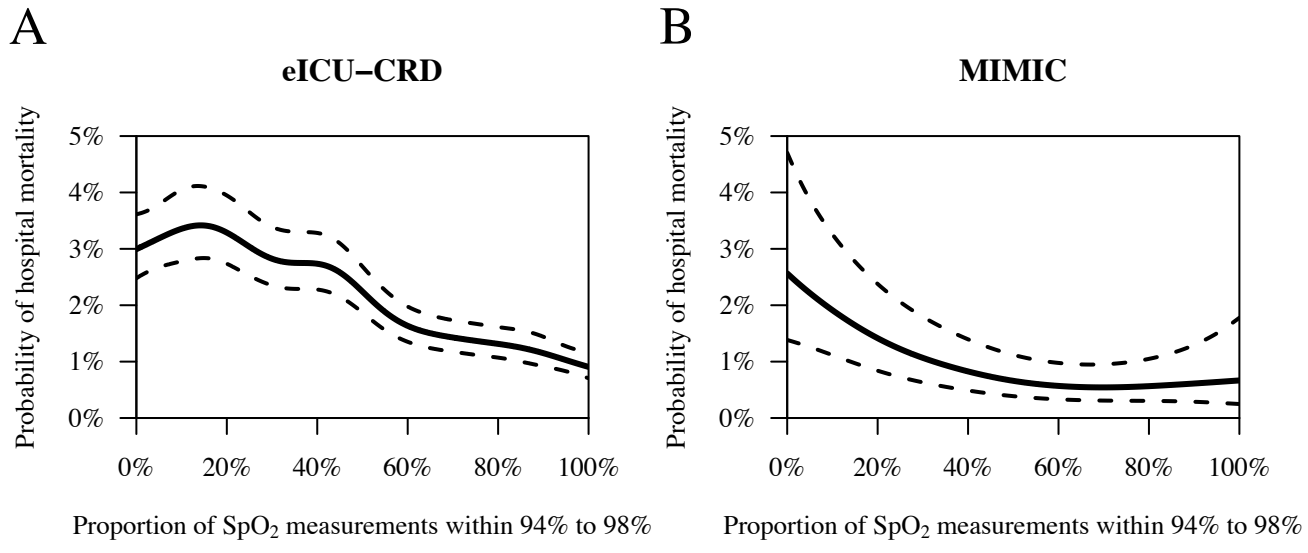
e-Figure 2. Probability of ICU mortality versus the proportion of time with SpO_2 within 94% to 98% with ICU mortality as outcome
These plots are analogous to Figures 3A and 3B of the main text but use ICU mortality instead of hospital mortality as outcome.

Sensitivity analyses
The first sensitivity analysis considers the ICU stays that were excluded because their first oxygen therapy session lasted less than 48 hours. Specifically, we consider the 36,021/4,827 ICU stays from eICU-CRD/MIMIC that were not repeat stays, had demographic data, underwent oxygen therapy for less than 48 hours, had FiO_2 above 21% or a record of oxygen flow rate at least once, and had at least one SpO_2 measurement. We present the results as in Figures 2, 3A, and 3B but with a different range on the vertical axis.

Mortality is lower in this subset compared to the main text. Also, the median SpO_2 is less stable due to the lower number of SpO_2 measurements. Nonetheless, the U-shaped relation from Figure 2 and downward trend from Figure 3 of the main text are also present here.

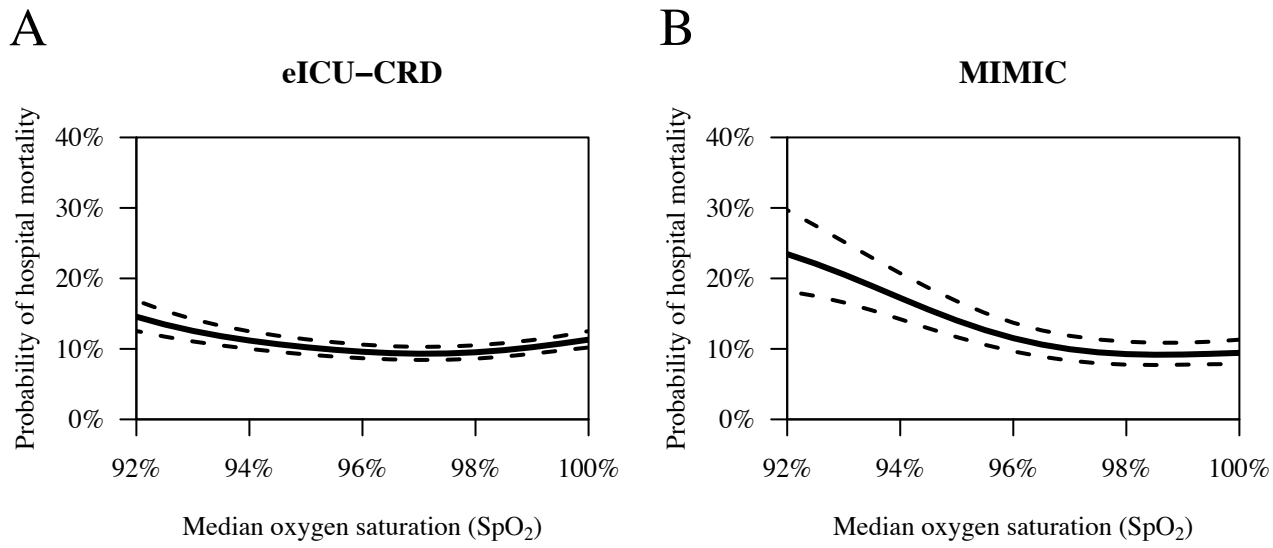


e-Figure 3. Probability of hospital mortality versus median SpO_2 for cases with less than 48 hours of oxygen therapy
These plots are analogous to Figure 2 of the main text and consider the set of ICU stays described at the top of this page which does not overlap with the sample analyzed in the main text.



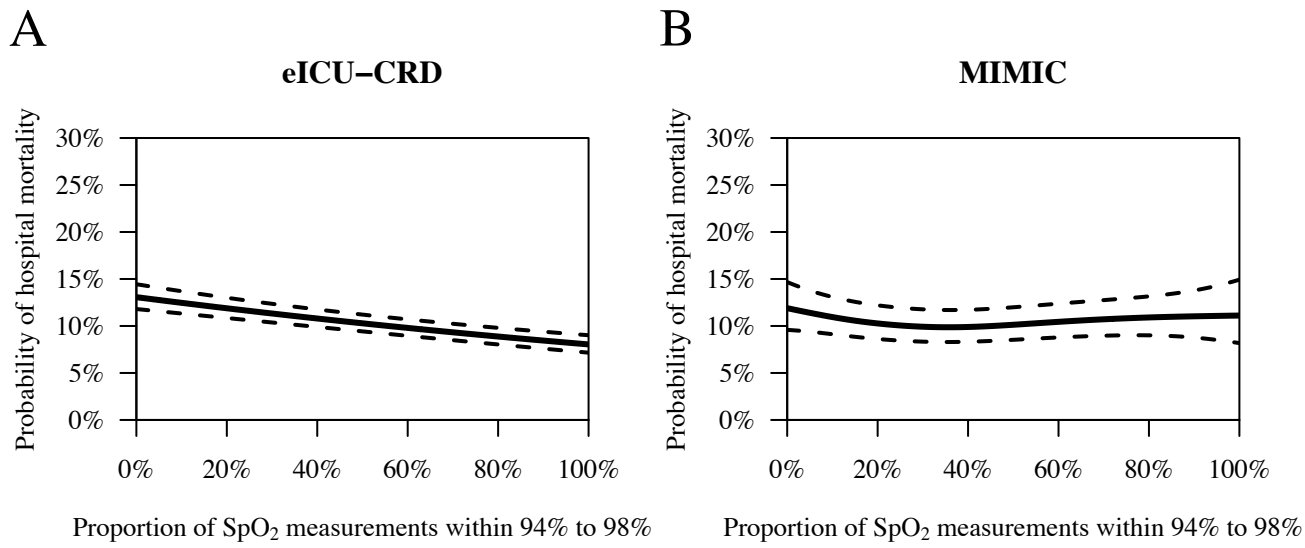
e-Figure 4. Probability of hospital mortality versus the proportion of time with SpO_2 within 94% to 98% for cases with less than 48 hours of oxygen therapy
These plots are analogous to Figures 3A and 3B of the main text and consider the set of ICU stays described at the top of this page which does not overlap with the sample analyzed in the main text.

The second sensitivity analysis is that we only consider the first 24, 48, or 72 hours of each oxygen therapy session while computing summaries of SpO_2 measurements.



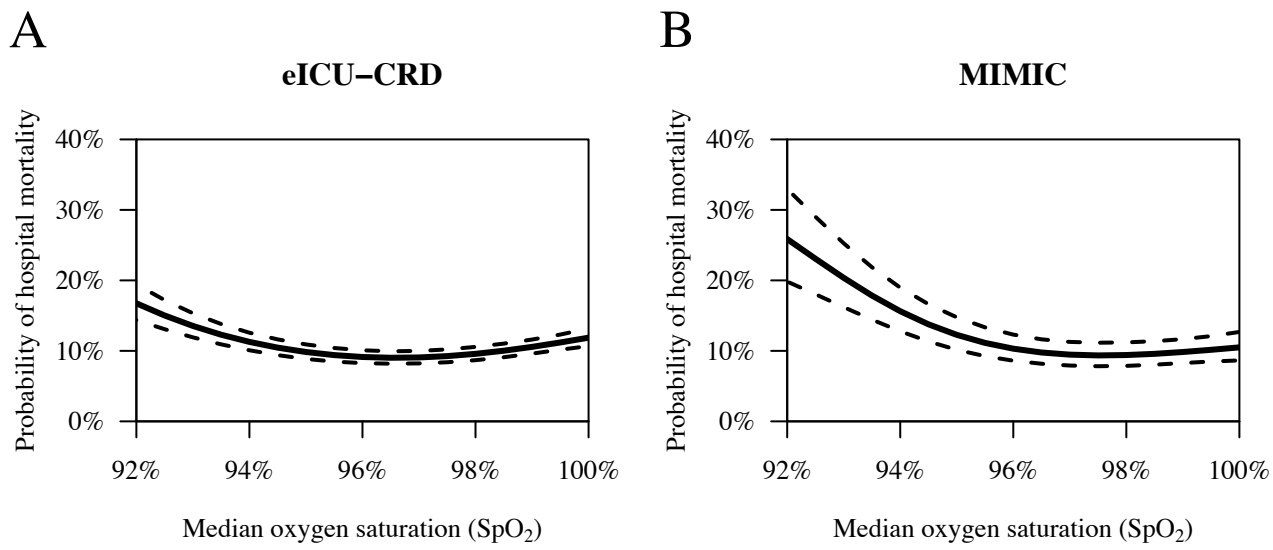
e-Figure 5. Probability of hospital mortality versus median SpO_2 including only SpO_2 measurements within the first 24 hours

These plots are analogous to Figure 2 of the main text but only use SpO_2 measurements during the first 24 hours of the first oxygen therapy session of 25,505/8,533 ICU stays from eICU-CRD/MIMIC that had at least 12 SpO_2 measurements in this period.



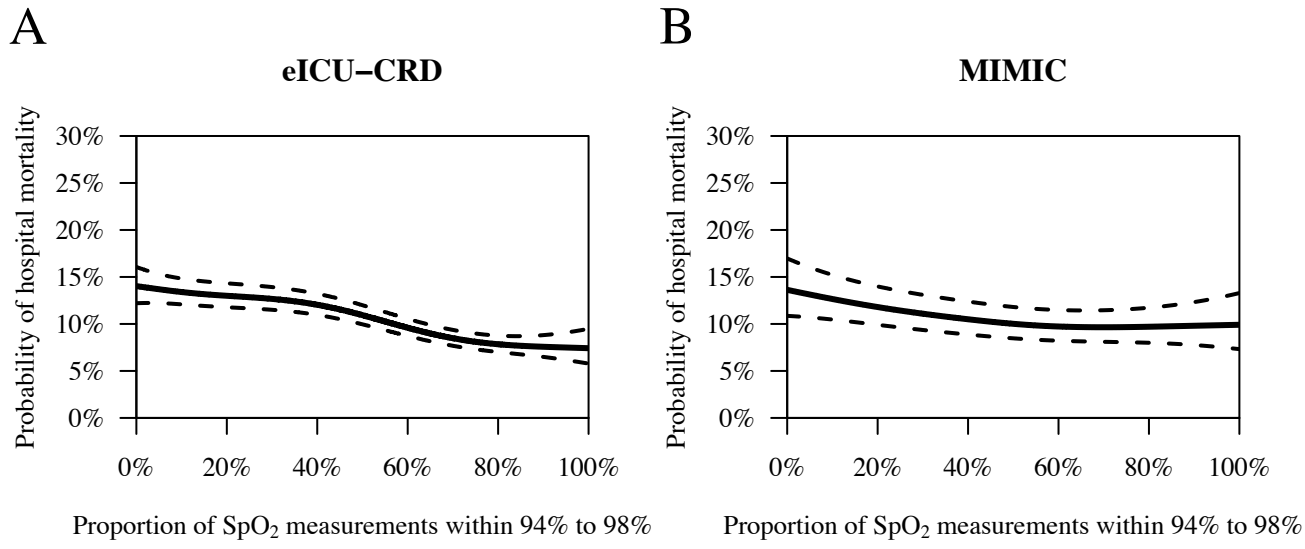
e-Figure 6. Probability of hospital mortality versus the proportion of time with SpO_2 within 94% to 98% during the first 24 hours

These plots are analogous to Figures 3A and 3B of the main text but only use SpO_2 measurements during the first 24 hours of the first oxygen therapy session of 25,505/8,533 ICU stays from eICU-CRD/MIMIC that had at least 12 SpO_2 measurements in this period.



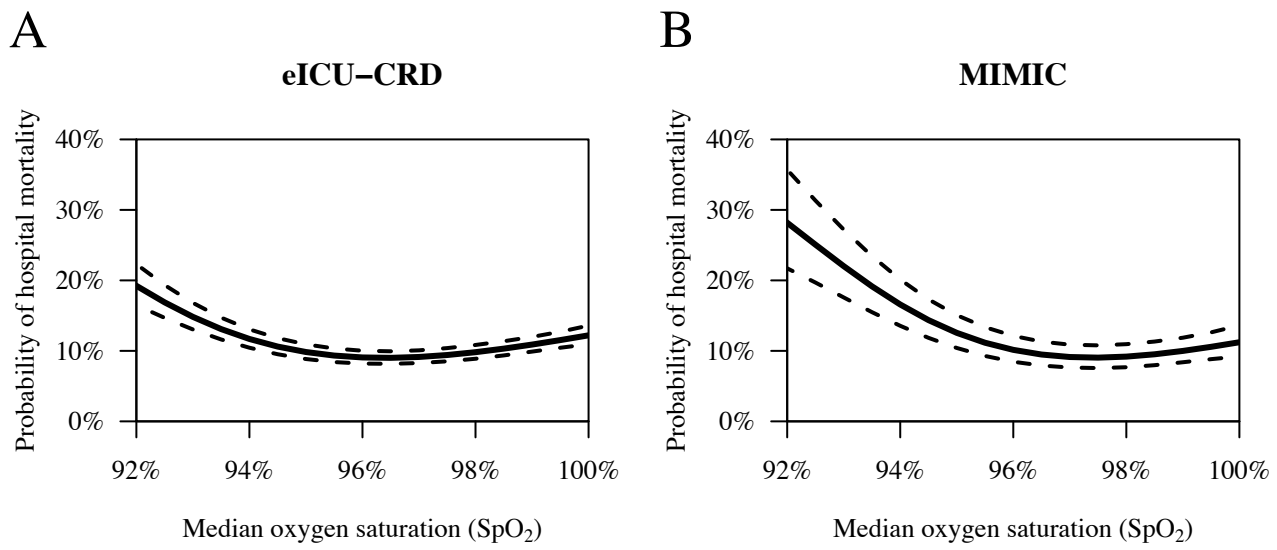
e-Figure 7. Probability of hospital mortality versus median SpO_2 including only SpO_2 measurements within the first 48 hours

These plots are analogous to Figure 2 of the main text but only use SpO_2 measurements during the first 48 hours of the first oxygen therapy session of 25,385/8,547 ICU stays from eICU-CRD/MIMIC that had at least 24 SpO_2 measurements in this period.



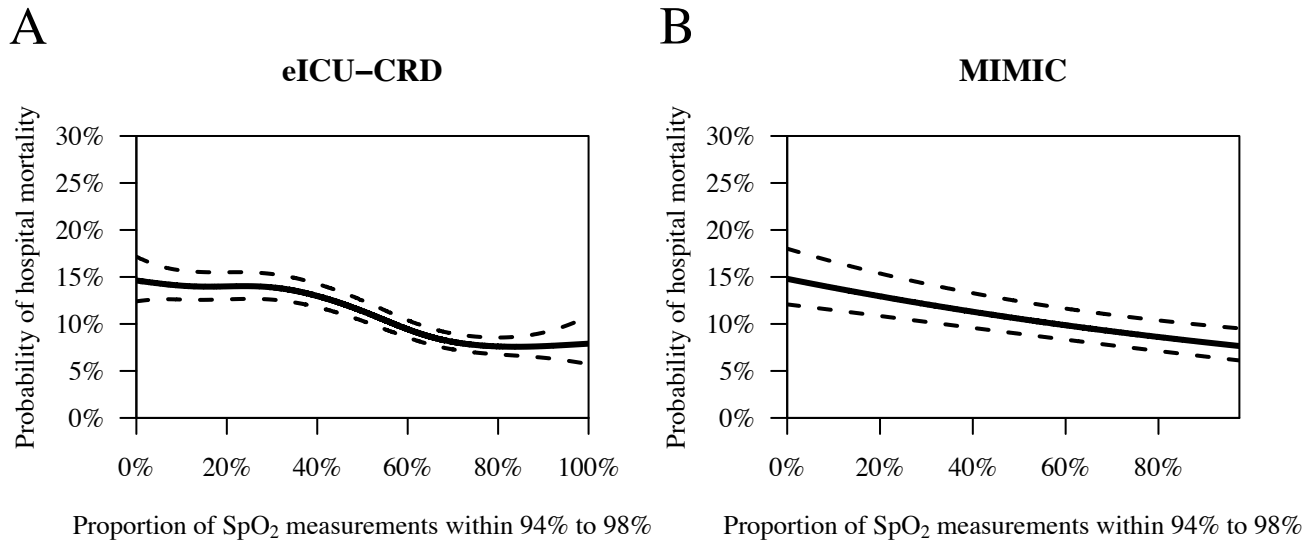
e-Figure 8. Probability of hospital mortality versus the proportion of time with SpO_2 within 94% to 98% during the first 48 hours

These plots are analogous to Figures 3A and 3B of the main text but only use SpO_2 measurements during the first 48 hours of the first oxygen therapy session of 25,385/8,547 ICU stays from eICU-CRD/MIMIC that had at least 24 SpO_2 measurements in this period.



e-Figure 9. Probability of hospital mortality versus median SpO_2 including only SpO_2 measurements within the first 72 hours

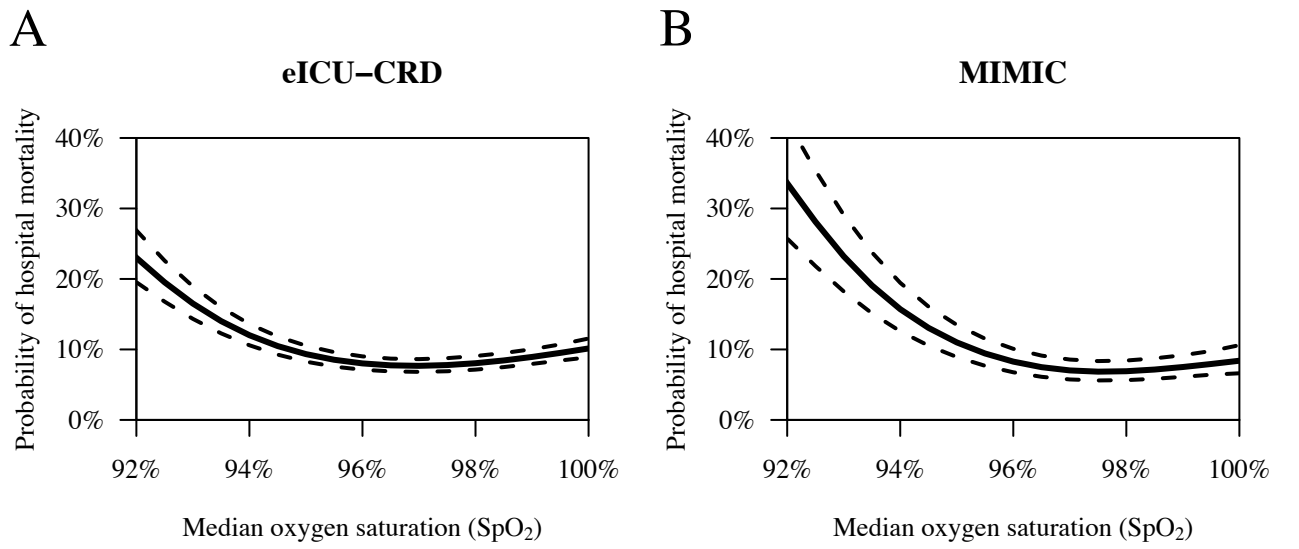
These plots are analogous to Figure 2 of the main text but only use SpO_2 measurements during the first 72 hours of the first oxygen therapy session of 24,885/8,552 ICU stays from eICU-CRD/MIMIC that had at least 36 SpO_2 measurements in this period.



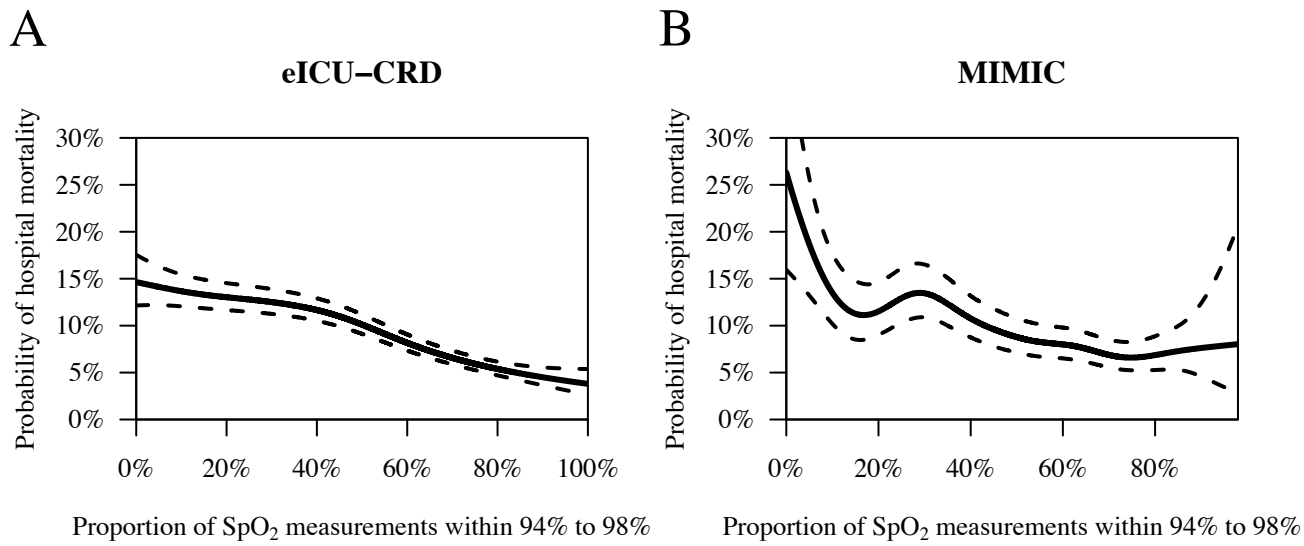
e-Figure 10. Probability of hospital mortality versus the proportion of time with SpO_2 within 94% to 98% during the first 72 hours

These plots are analogous to Figures 3A and 3B of the main text but only use SpO_2 measurements during the first 72 hours of the first oxygen therapy session of 24,885/8,552 ICU stays from eICU-CRD/MIMIC that had at least 36 SpO_2 measurements in this period.

The third sensitivity analysis considers controlling for APACHE IV score instead of SOFA score.

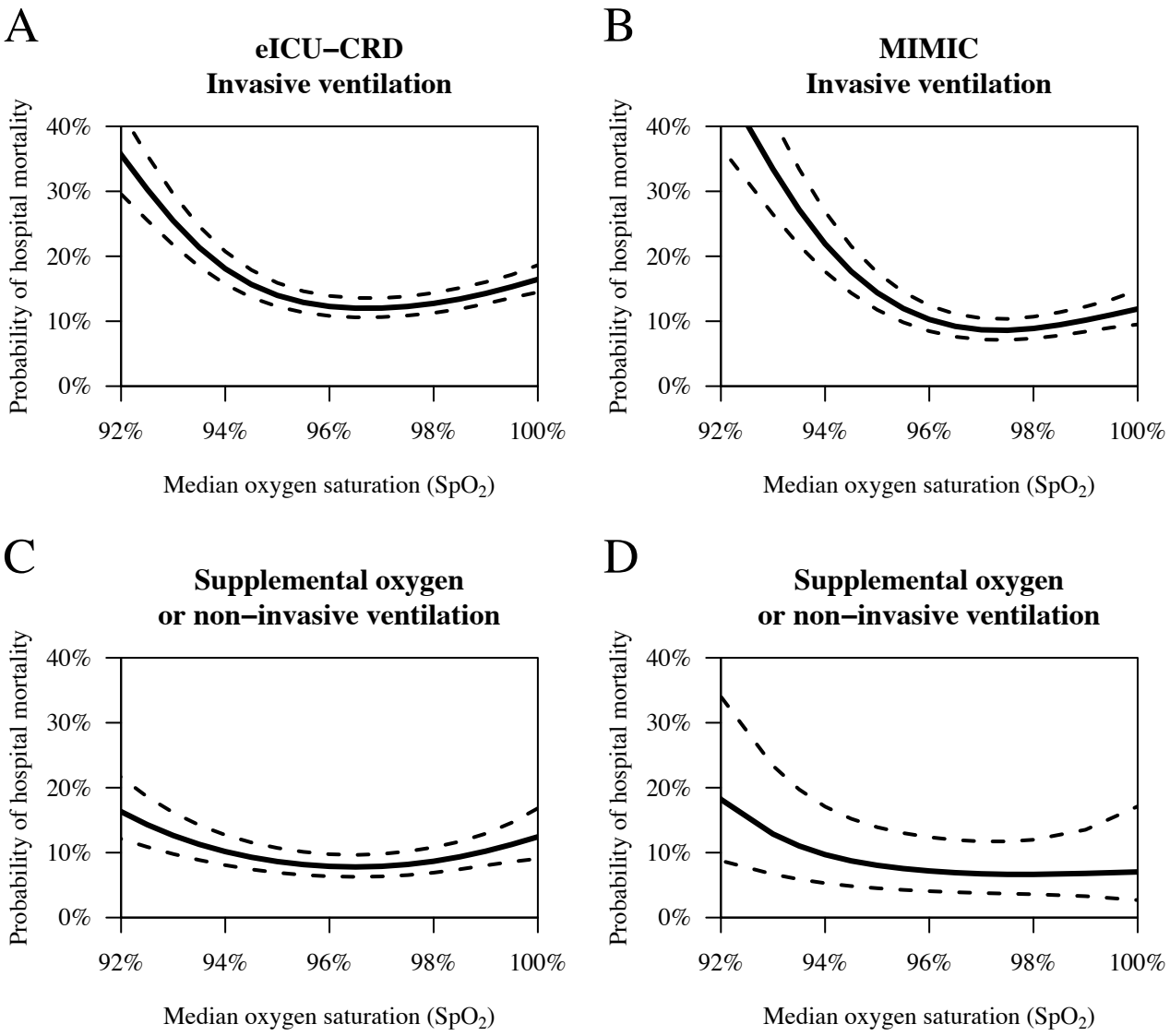


e-Figure 11. Probability of hospital mortality versus median SpO_2 while controlling for APACHE score
These plots are analogous to Figure 2 of the main text but control for APACHE instead of SOFA score while fitting the model on 24,885/8,564 ICU stays from eICU-CRD/MIMIC that have an APACHE score.

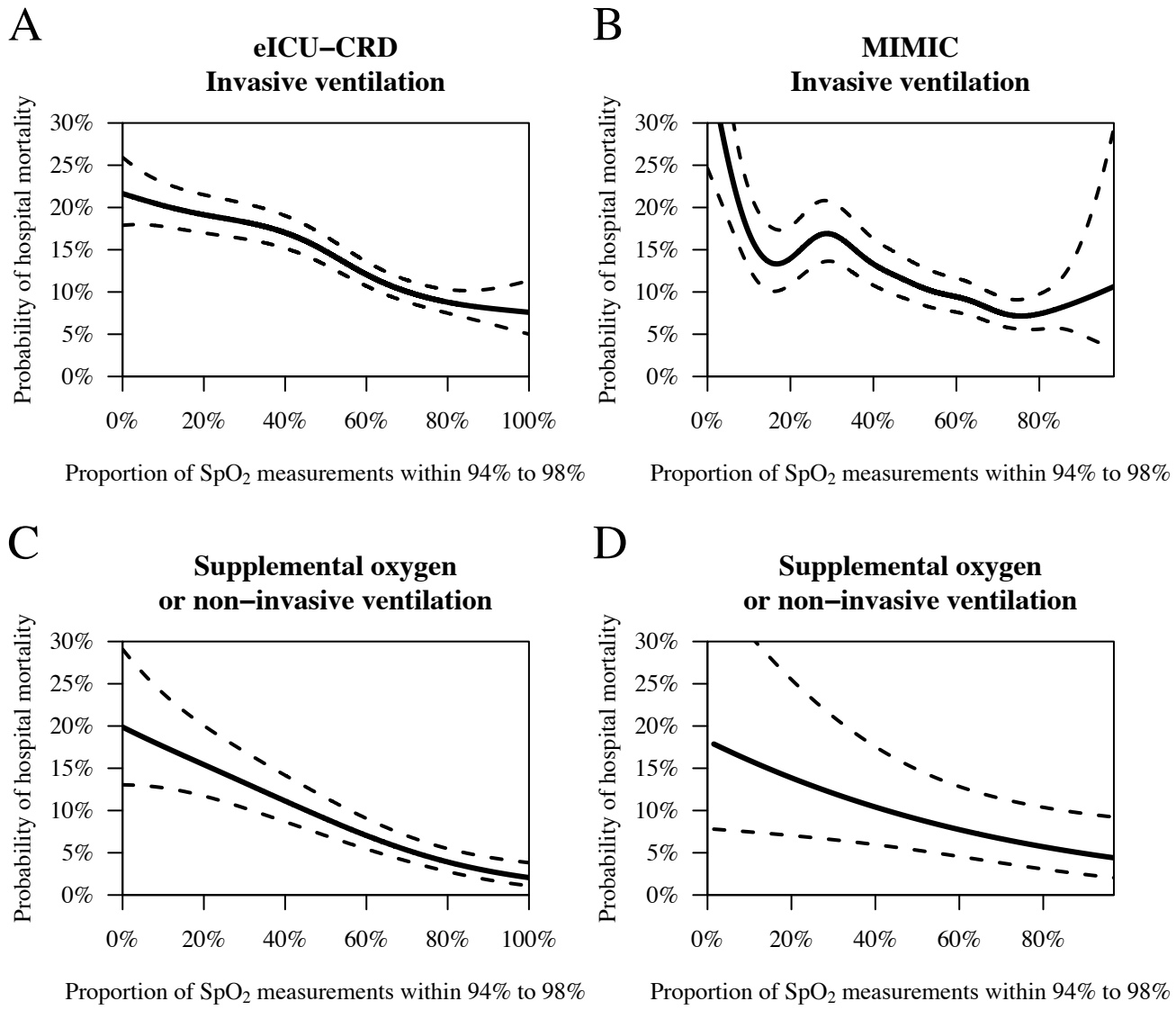


e-Figure 12. Probability of hospital mortality versus the proportion of time with SpO_2 within 94% to 98% while controlling for APACHE score
These plots are analogous to Figures 3A and 3B of the main text but control for APACHE instead of SOFA score while fitting the model on 24,855/8,564 ICU stays from eICU-CRD/MIMIC that have an APACHE score.

Subgroup analyses
The first subgroup analysis is by ventilation type. The ventilation type could not be determined for all ICU stays. These results are based on 14,148/7,860 ICU stays with invasive ventilation and 3,641/697 ICU stays with supplemental oxygen or non-invasive ventilation from eICU-CRD/MIMIC, respectively.

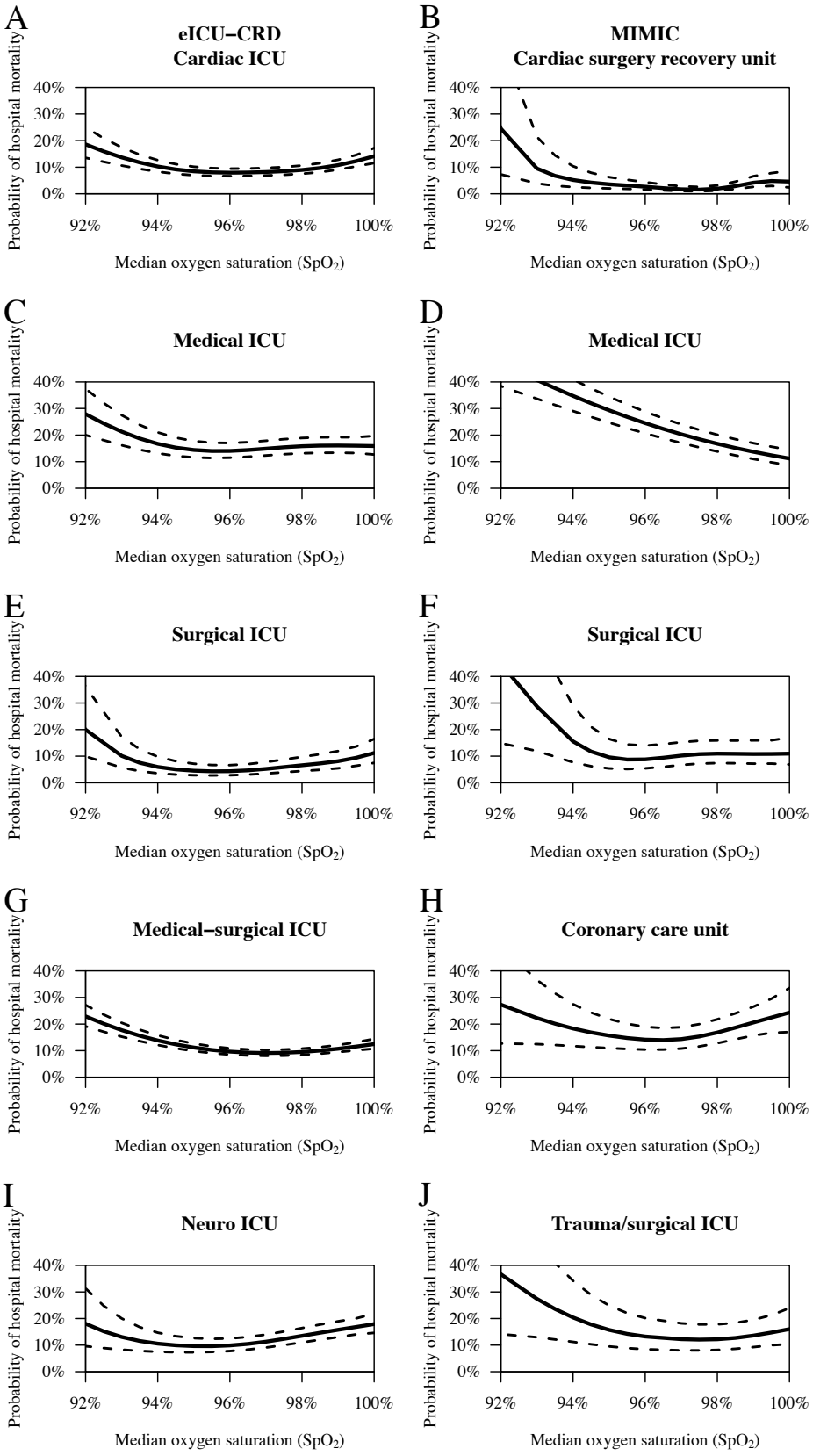


e-Figure 13. Probability of hospital mortality versus median SpO_2 grouped by ventilation type
These plots are analogous to Figure 2 of the main text but group the ICU stays by their ventilation types.

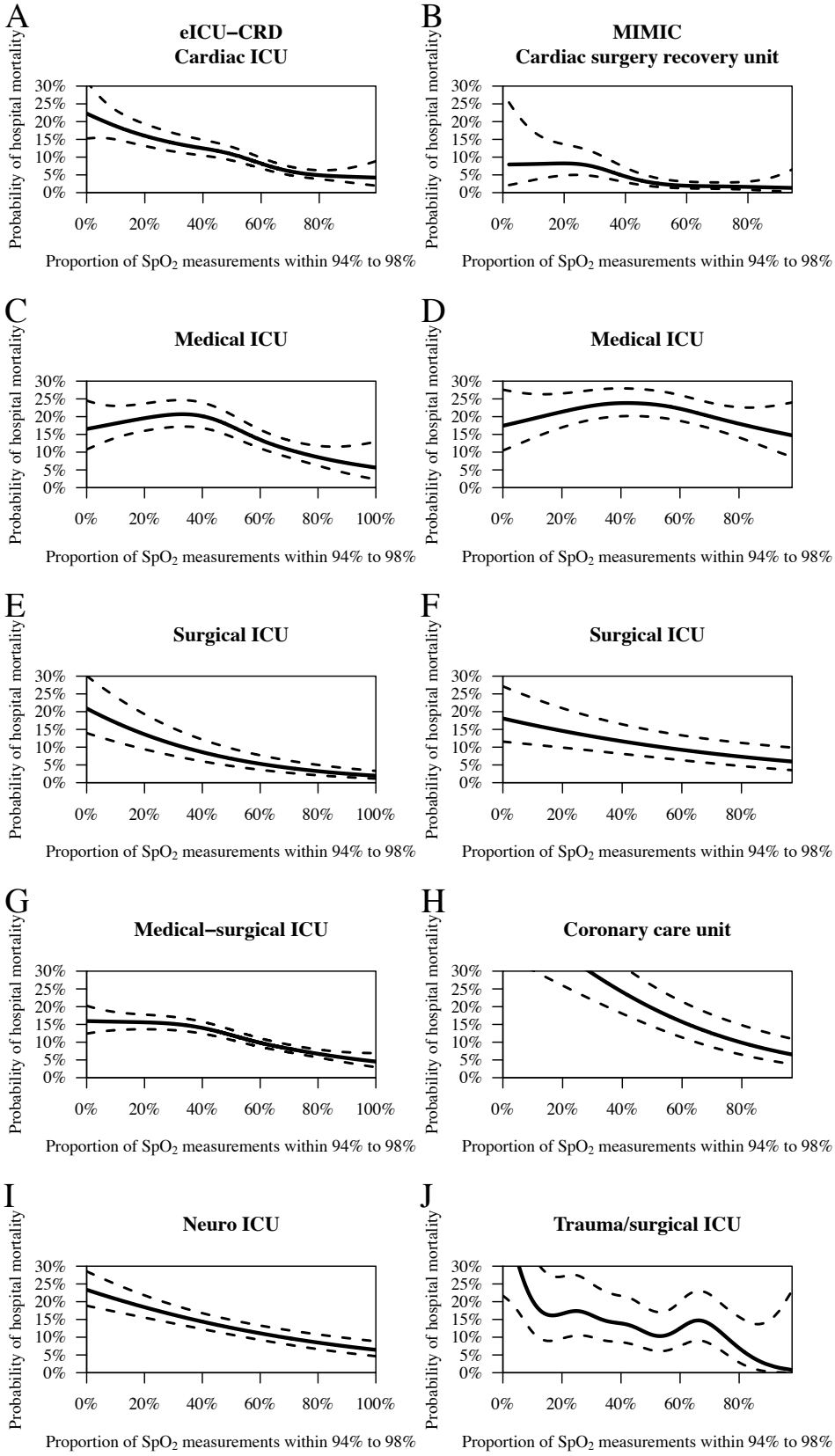


e-Figure 14. Probability of hospital mortality versus the proportion of time with SpO_2 within 94% to 98% grouped by ventilation type
These plots are analogous to Figures 3A and 3B of the main text but group the ICU stays by their ventilation types.

The second subgroup analysis is by ICU type. The results for eICU-CRD are based on 6,963 stays in the cardiac ICU, 2,613 stays in the medical ICU, 2,202 stays in the Surgical ICU, 12,400 stays in the medical-surgical ICU, and 2,545 stays in the neuro ICU. The results for MIMIC are based on 3,073 stays in the cardiac surgery recovery unit, 1,932 stays in the medical ICU, 1,349 stays in the surgical ICU, 1,199 stays in coronary care unit, and 1,010 stays in the trauma/surgical ICU. Henceforth, we do not control for hospital in eICU-CRD for numerical stability.



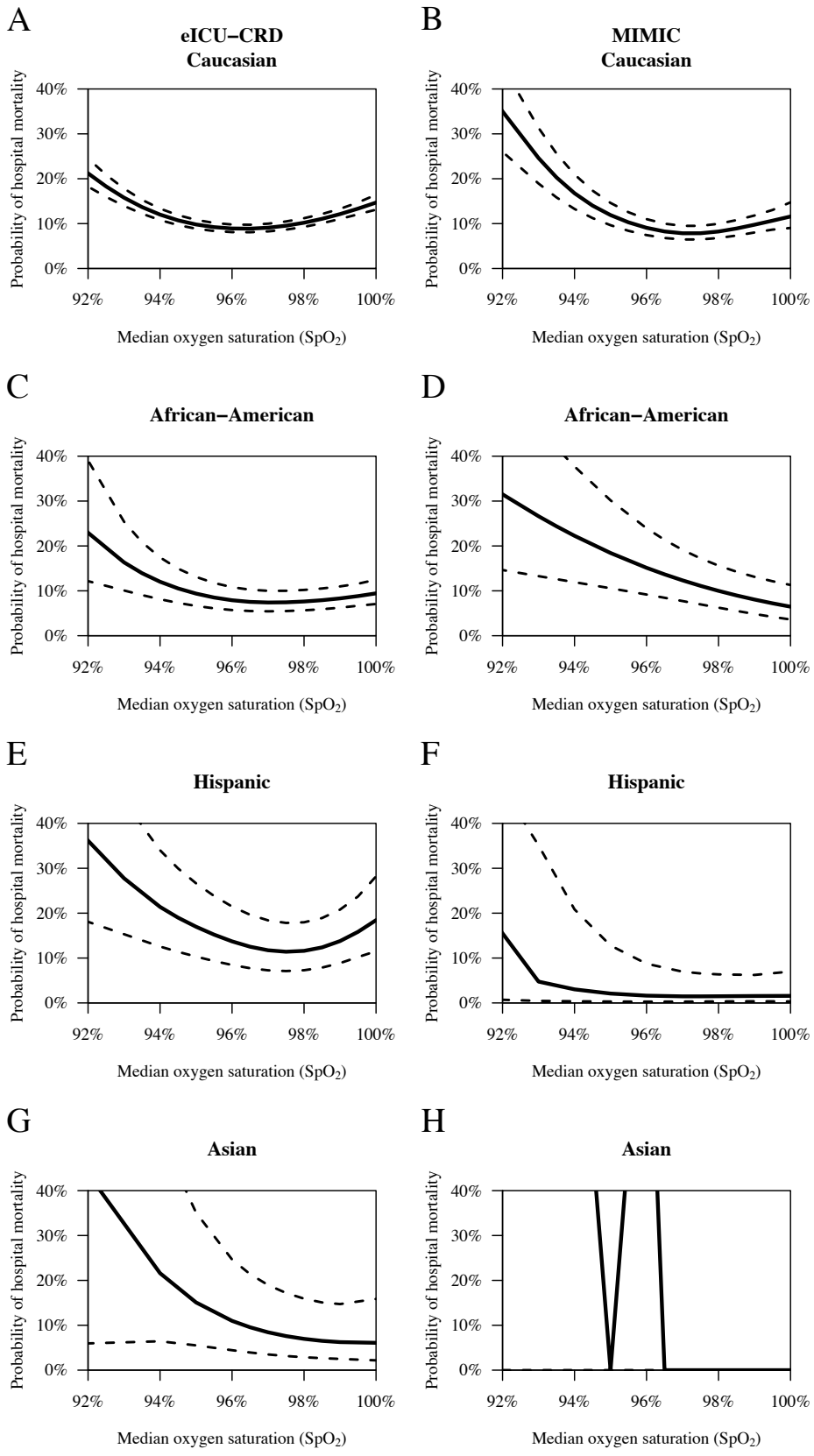
e-Figure 15. Probability of hospital mortality versus median SpO_2 grouped by ICU type
These plots are analogous to Figure 2 of the main text but group the ICU stays by their unit's type.



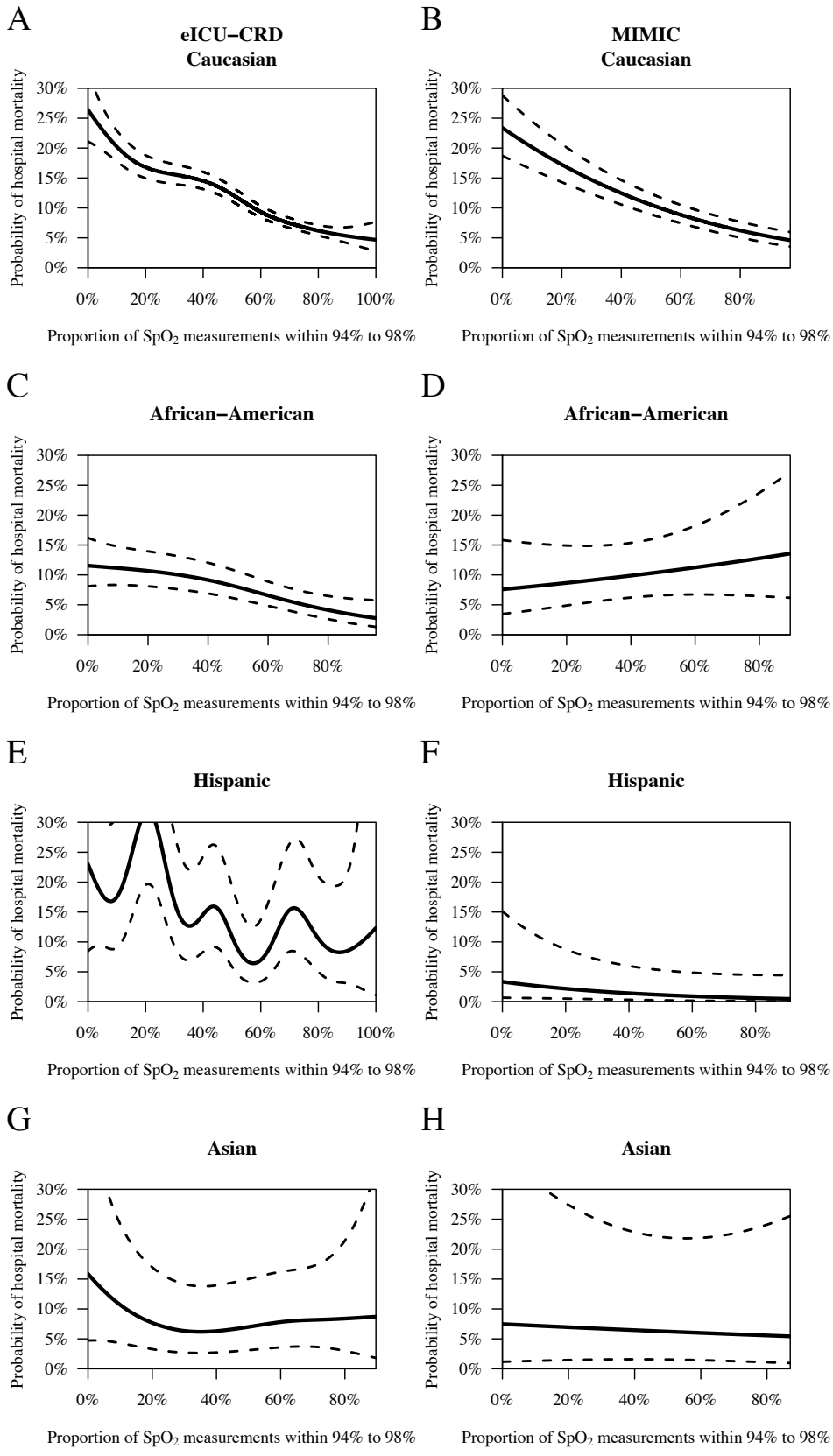
e-Figure 16. Probability of hospital mortality versus the proportion of time with SpO_2 within 94% to 98% grouped by ICU type

These plots are analogous to Figures 3A and 3B of the main text but group the ICU stays by their unit's type.

The third subgroup analysis is by ethnicity. The results are based on 21,123/6,038 Caucasian, 3,090/469 African-American, 819/248 Hispanic, and 253/157 Asian patients from eICU-CRD/MIMIC, respectively.



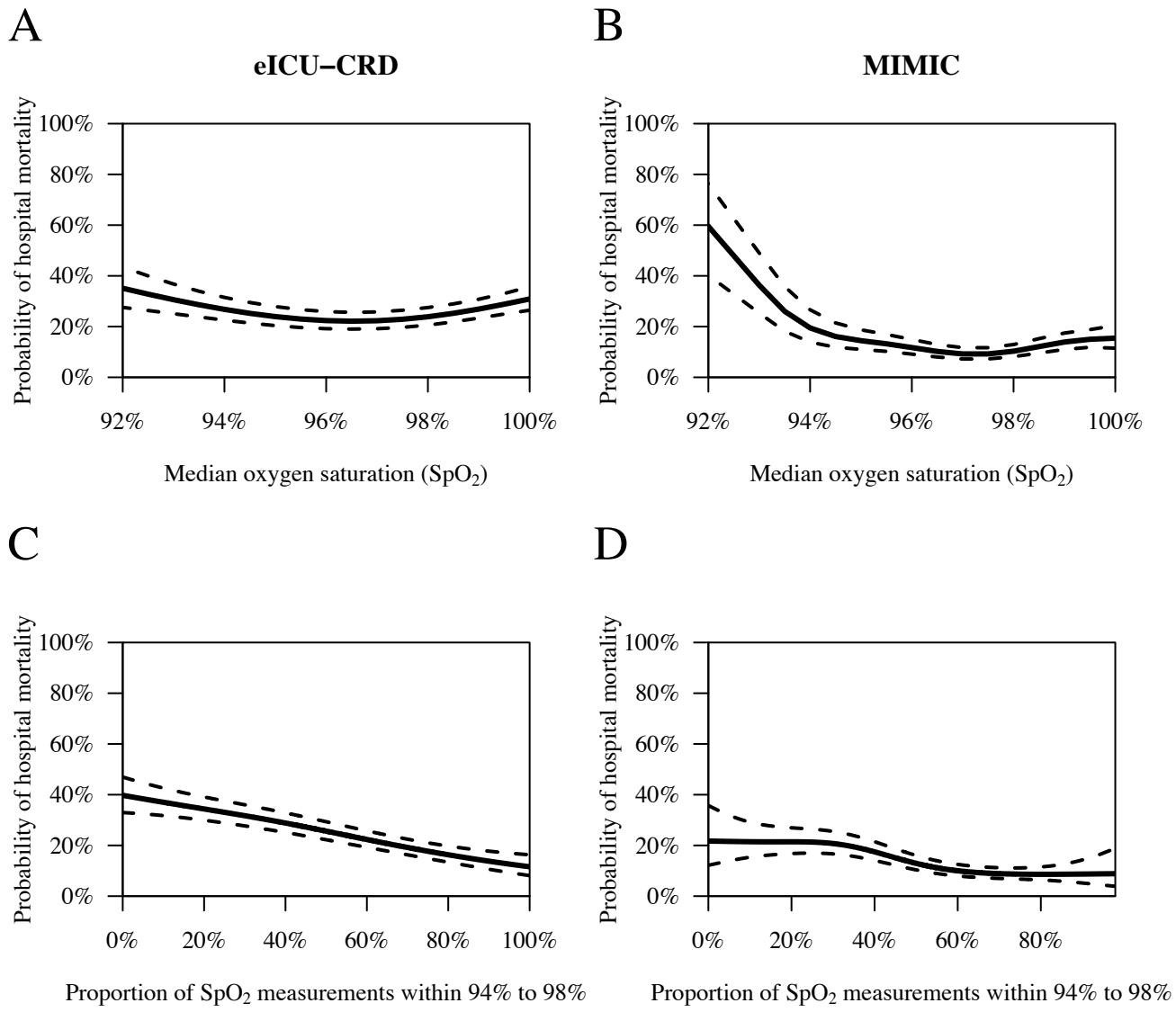
e-Figure 17. Probability of hospital mortality versus median SpO_2 grouped by ethnicity
These plots are analogous to Figure 2 of the main text but group the ICU stays by their patient's ethnicity.



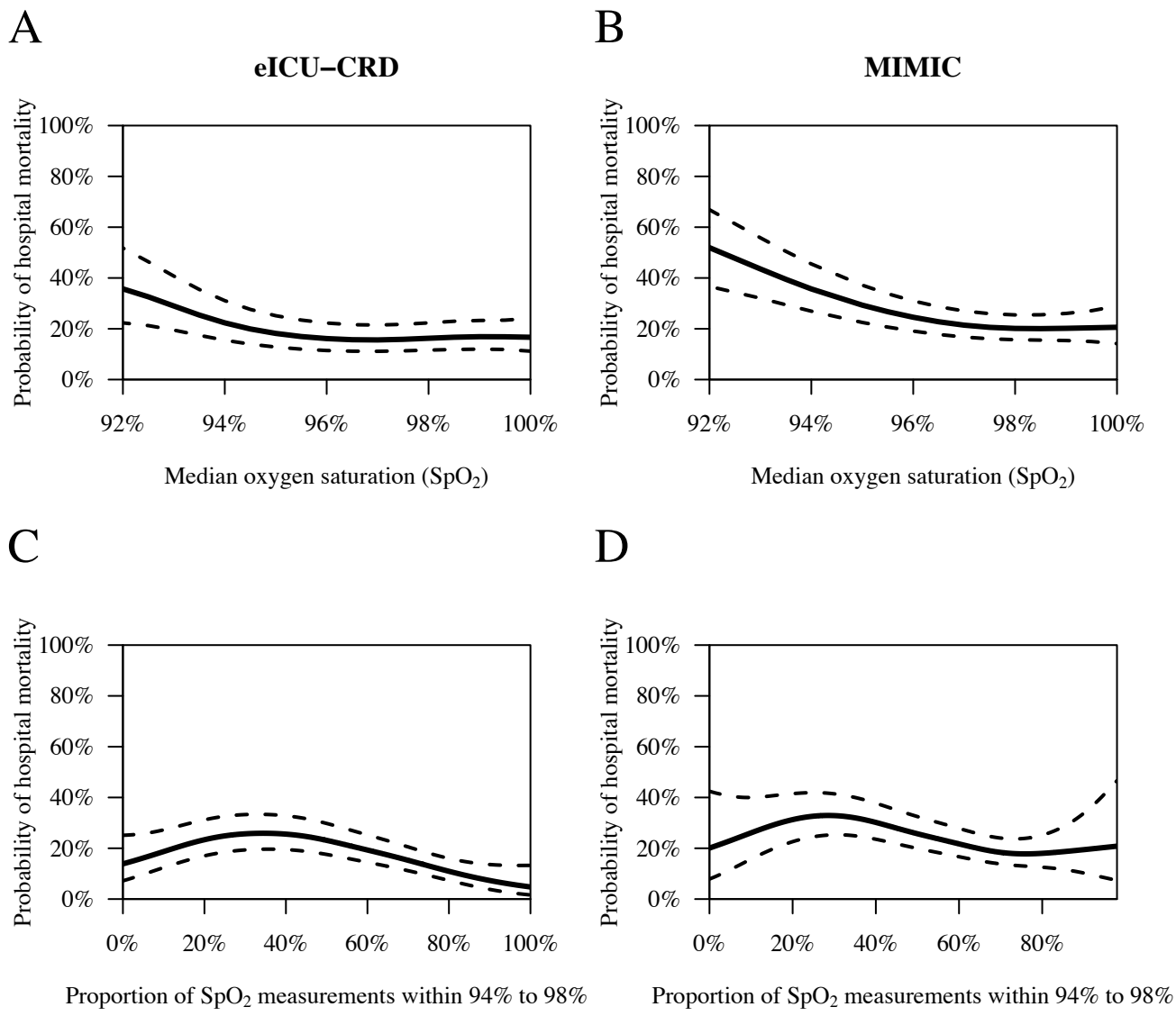
e-Figure 18. Probability of hospital mortality versus the proportion of time with SpO_2 within 94% to 98% grouped by ethnicity

These plots are analogous to Figures 3A and 3B of the main text but group the ICU stays by their patient's ethnicity.

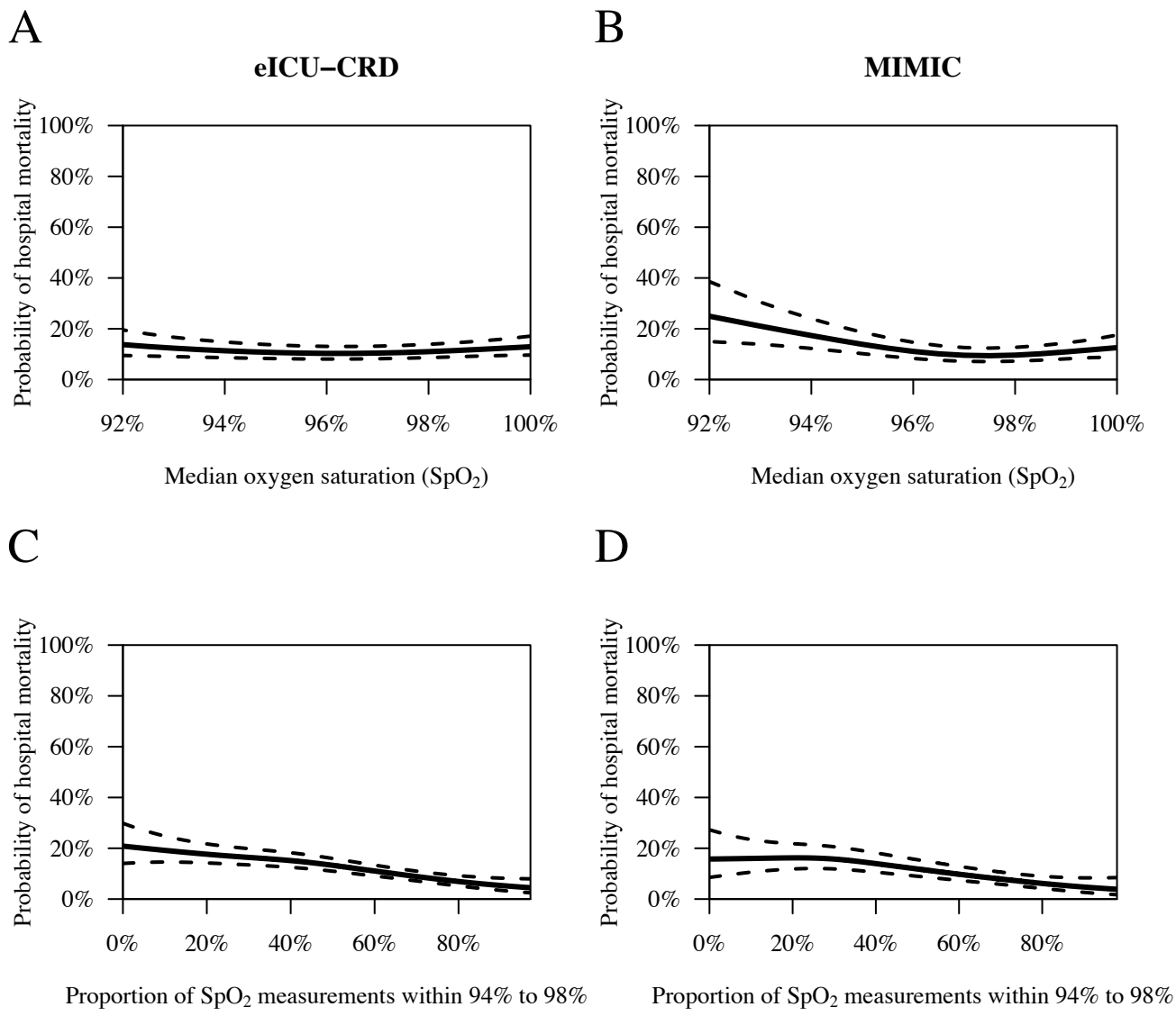
The fourth subgroup analysis is based on the presence of diagnoses and comorbidities. The diagnoses considered are atrial fibrillation, cancer, congestive heart failure, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypertension, ischemic heart disease, sepsis, and stroke. The diagnoses were determined by ICD-9 diagnosis codes. We present the results as in Figures 2, 3A, and 3B but with a different range on the vertical axis.



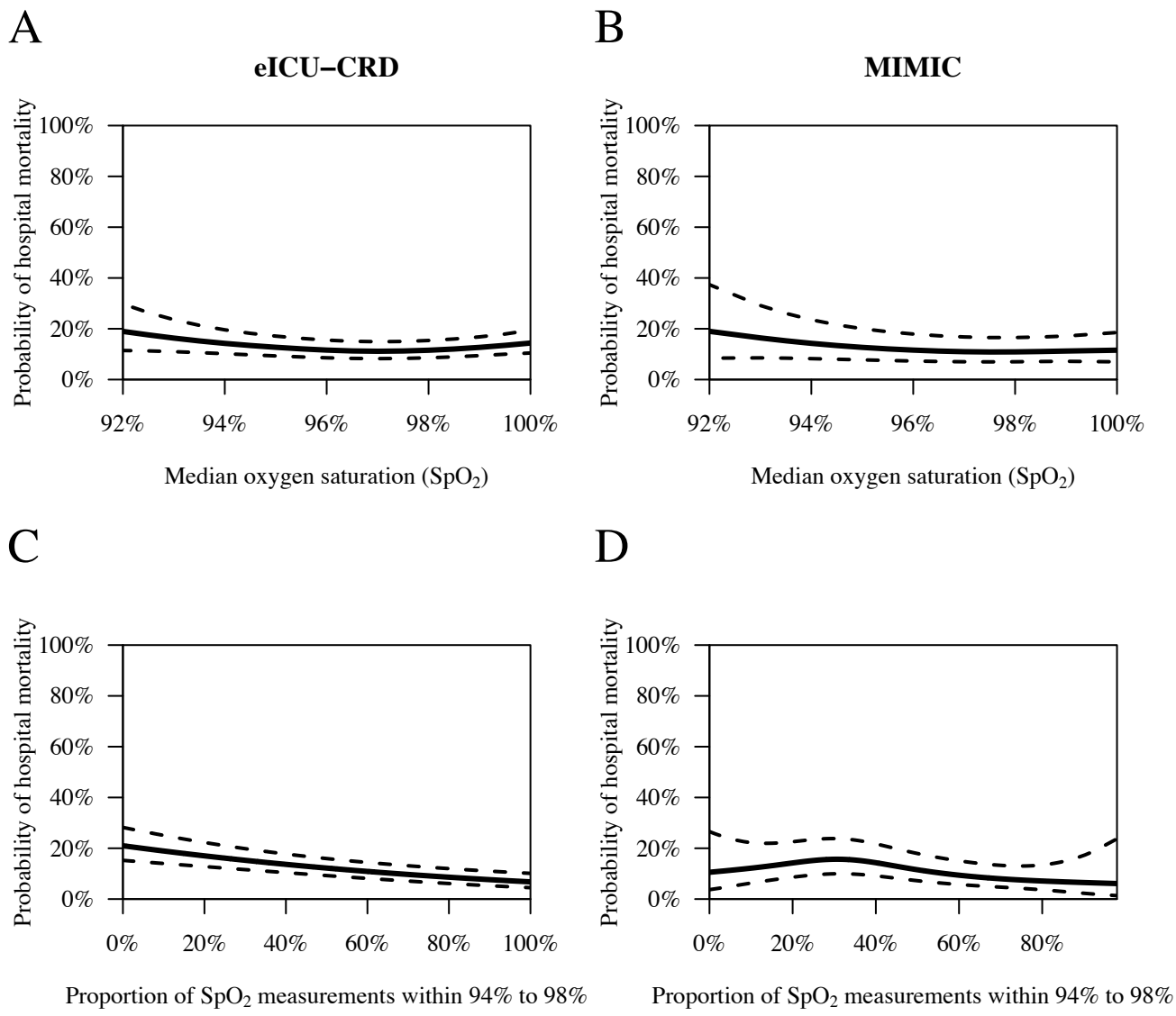
e-Figure 19. Results for ICU stays with an atrial fibrillation diagnosis
4,550/3,838 patients in eICU-CRD/MIMIC had an atrial fibrillation diagnosis.



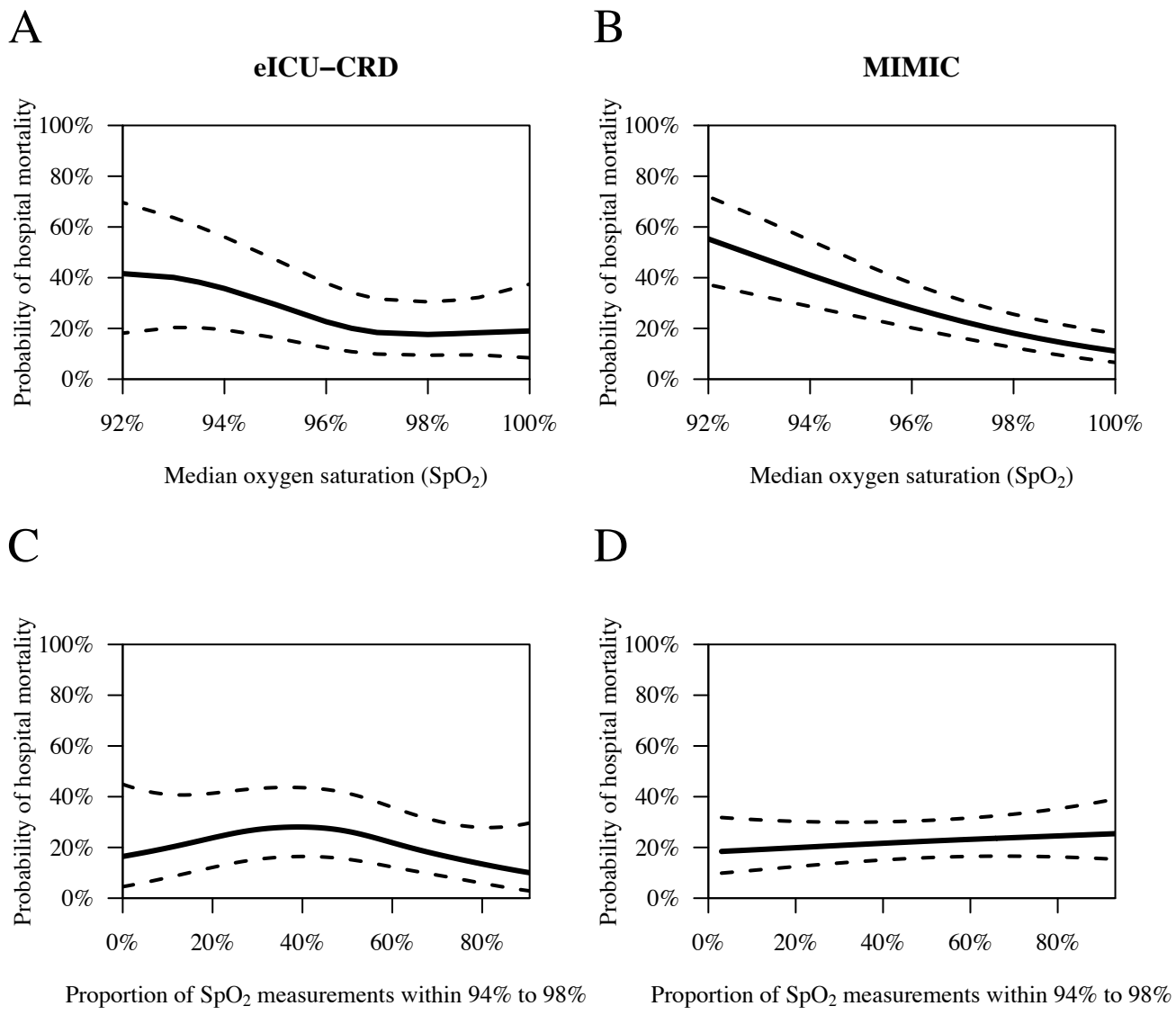
e-Figure 20. Results for ICU stays with a cancer diagnosis
1,413/984 patients in eICU-CRD/MIMIC had a cancer diagnosis.



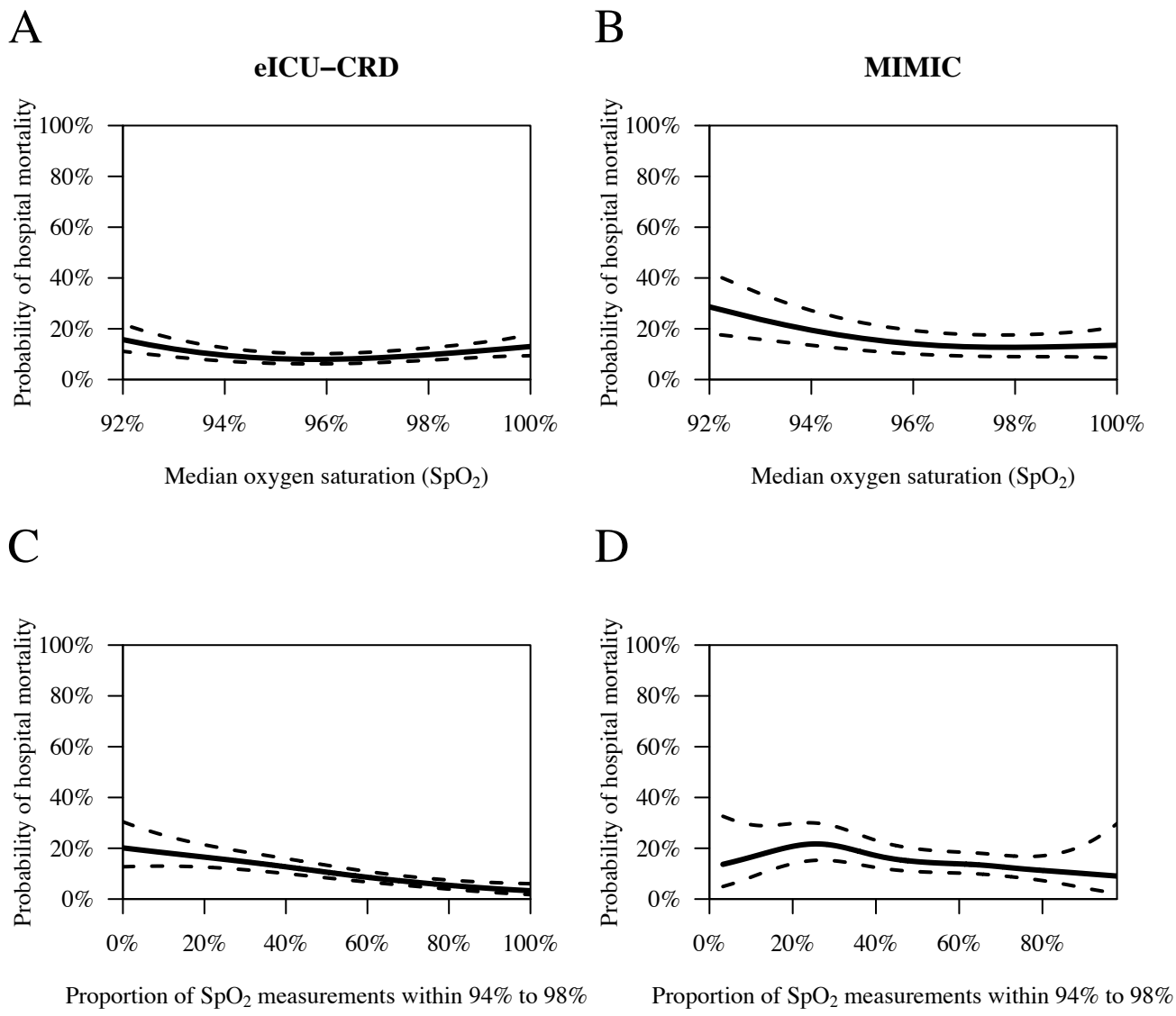
e-Figure 21. Results for ICU stays with a congestive heart failure diagnosis
2,795/2,633 patients in eICU-CRD/MIMIC had a congestive heart failure diagnosis.



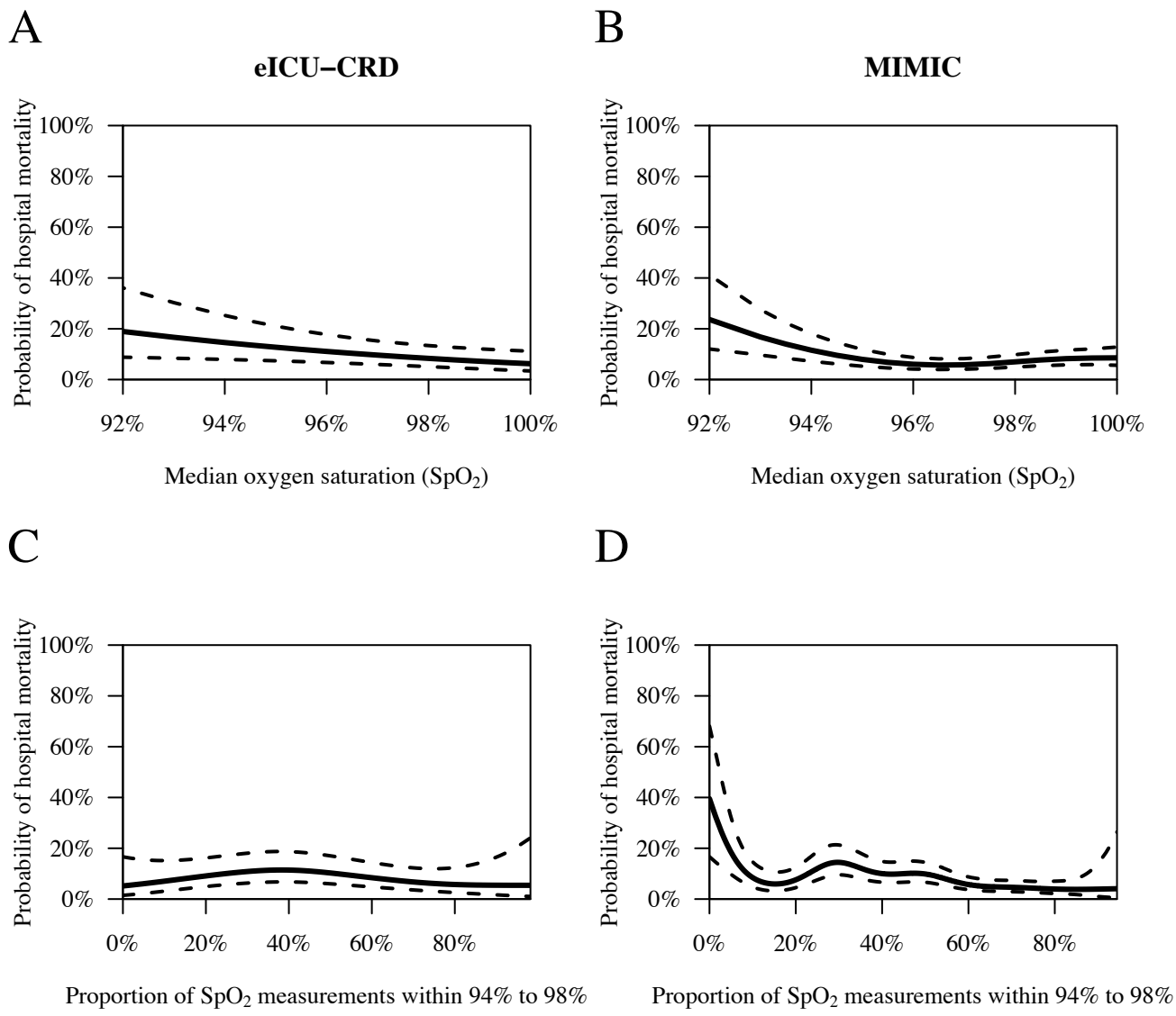
e-Figure 22. Results for ICU stays with a chronic kidney disease diagnosis
2,155/881 patients in eICU-CRD/MIMIC had a chronic kidney disease diagnosis.



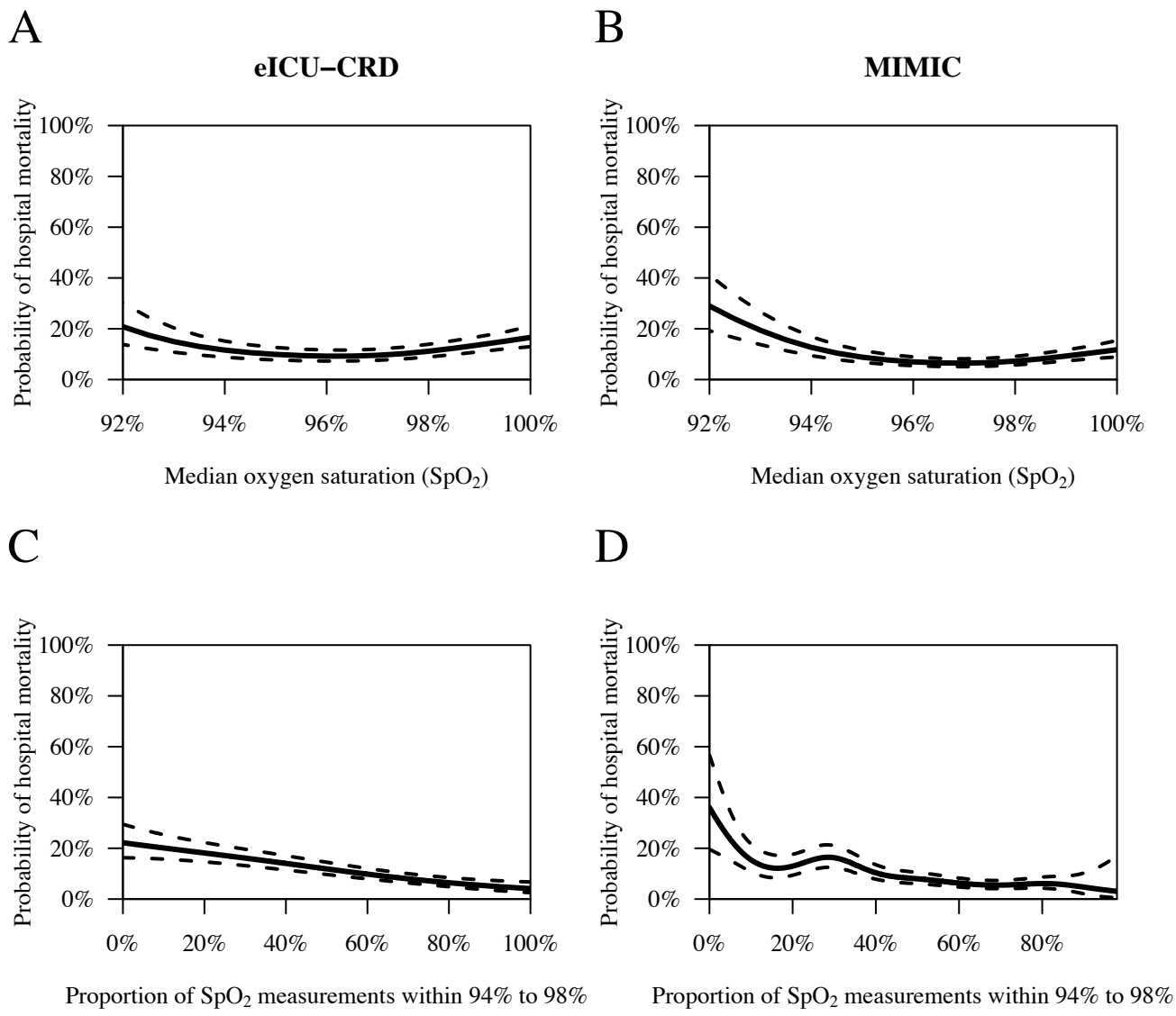
e-Figure 23. Results for ICU stays with a chronic liver disease diagnosis
284/532 patients in eICU-CRD/MIMIC had a chronic liver disease diagnosis.



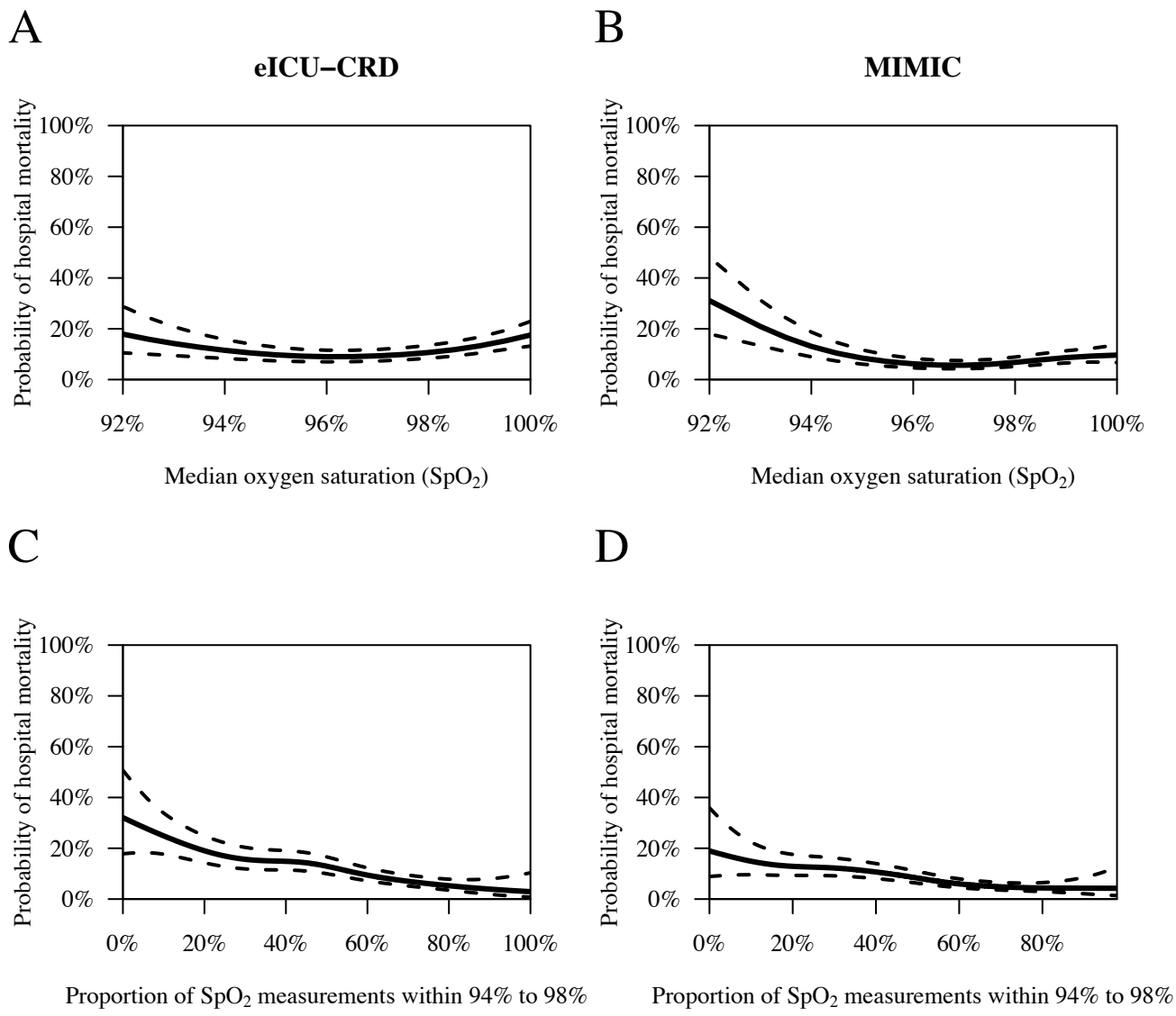
e-Figure 24. Results for ICU stays with a COPD diagnosis
2,878/1,656 patients in eICU-CRD/MIMIC had a COPD diagnosis.



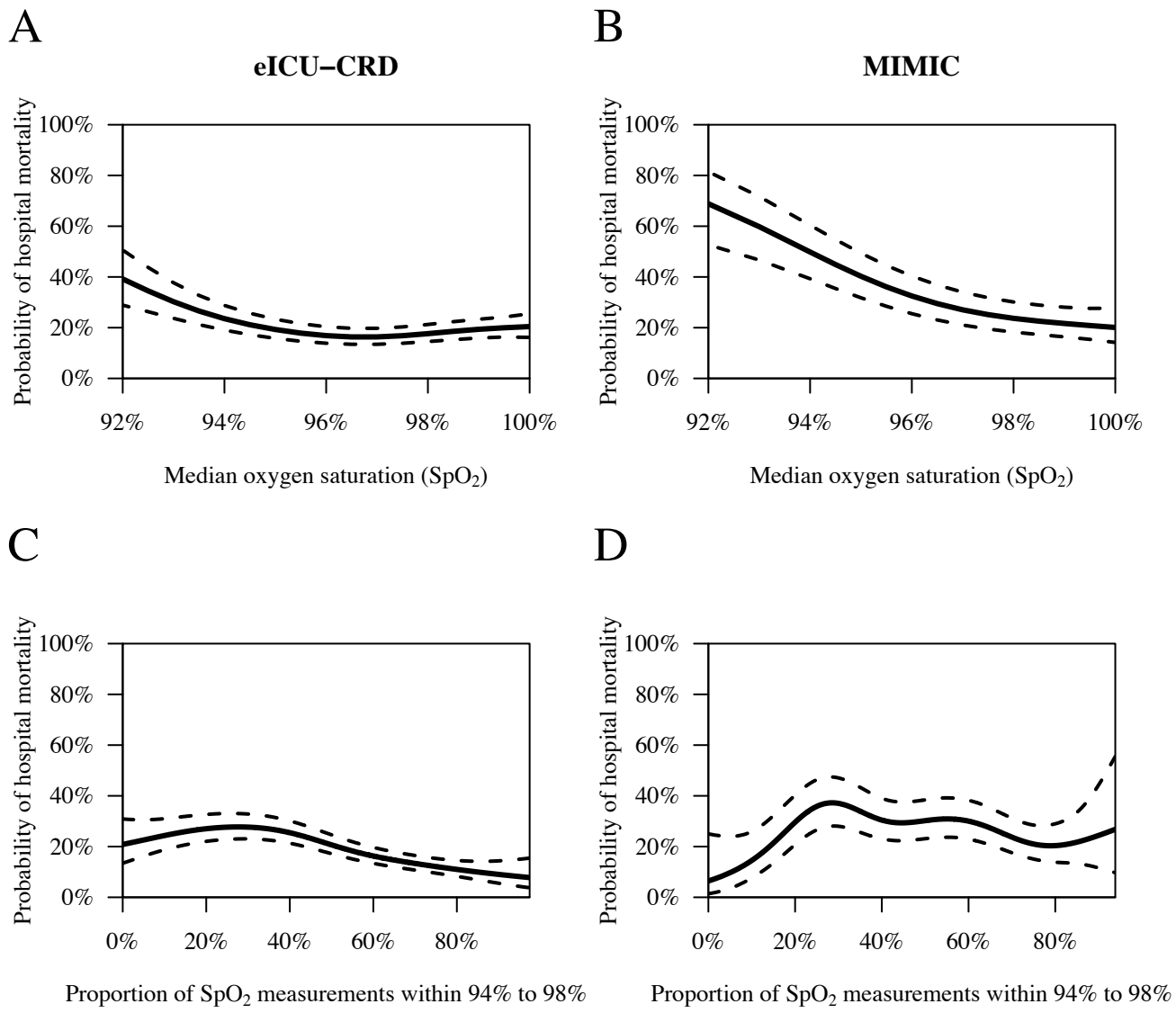
e-Figure 25. Results for ICU stays with a diabetes mellitus diagnosis
493/2,389 patients in eICU-CRD/MIMIC had a diabetes mellitus diagnosis.



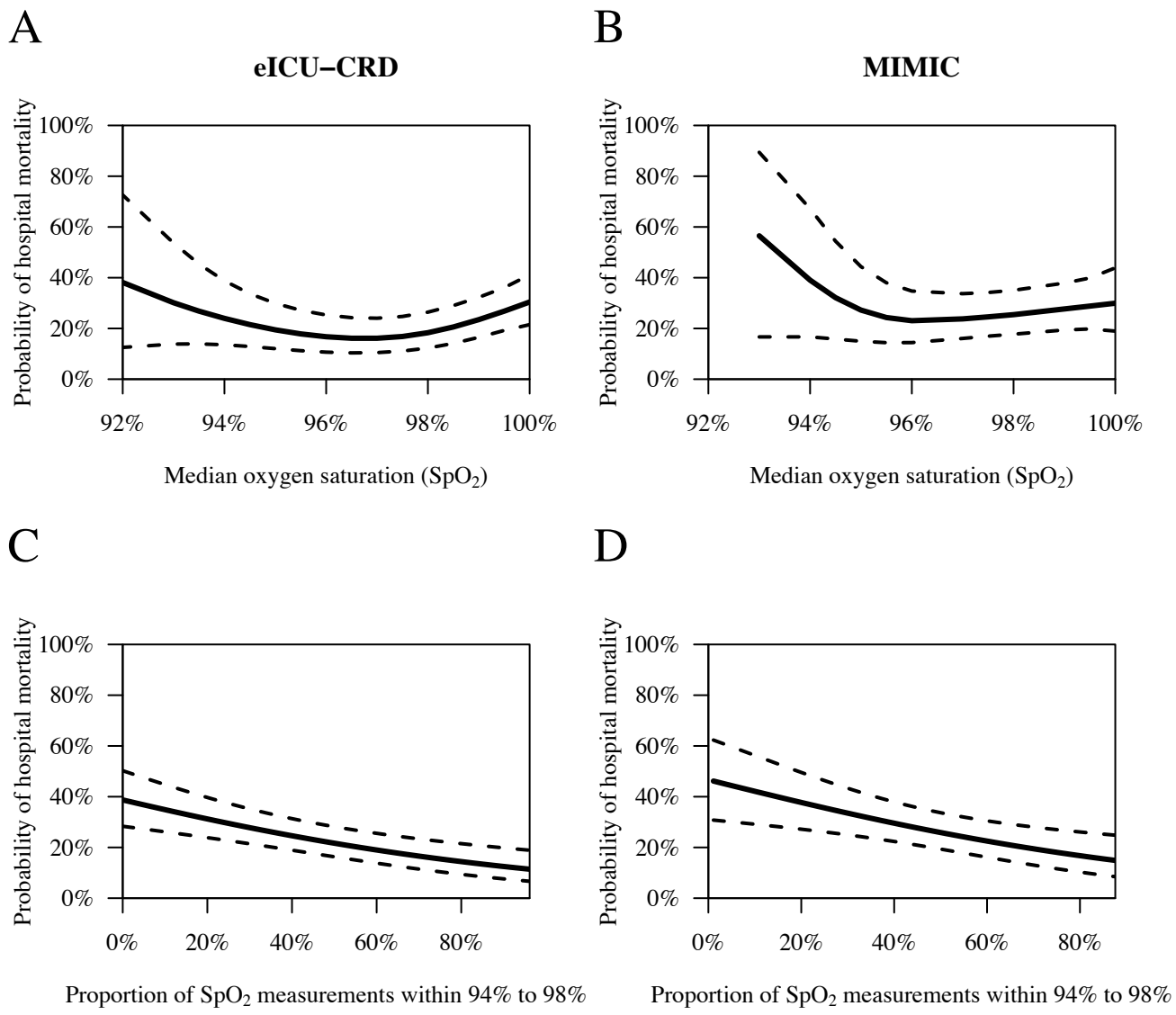
e-Figure 26. Results for ICU stays with a hypertension diagnosis
3,637/4,806 patients in eICU-CRD/MIMIC had a hypertension diagnosis.



e-Figure 27. Results for ICU stays with an ischemic heart disease diagnosis
2,075/3,701 patients in eICU-CRD/MIMIC had an ischemic heart disease diagnosis.

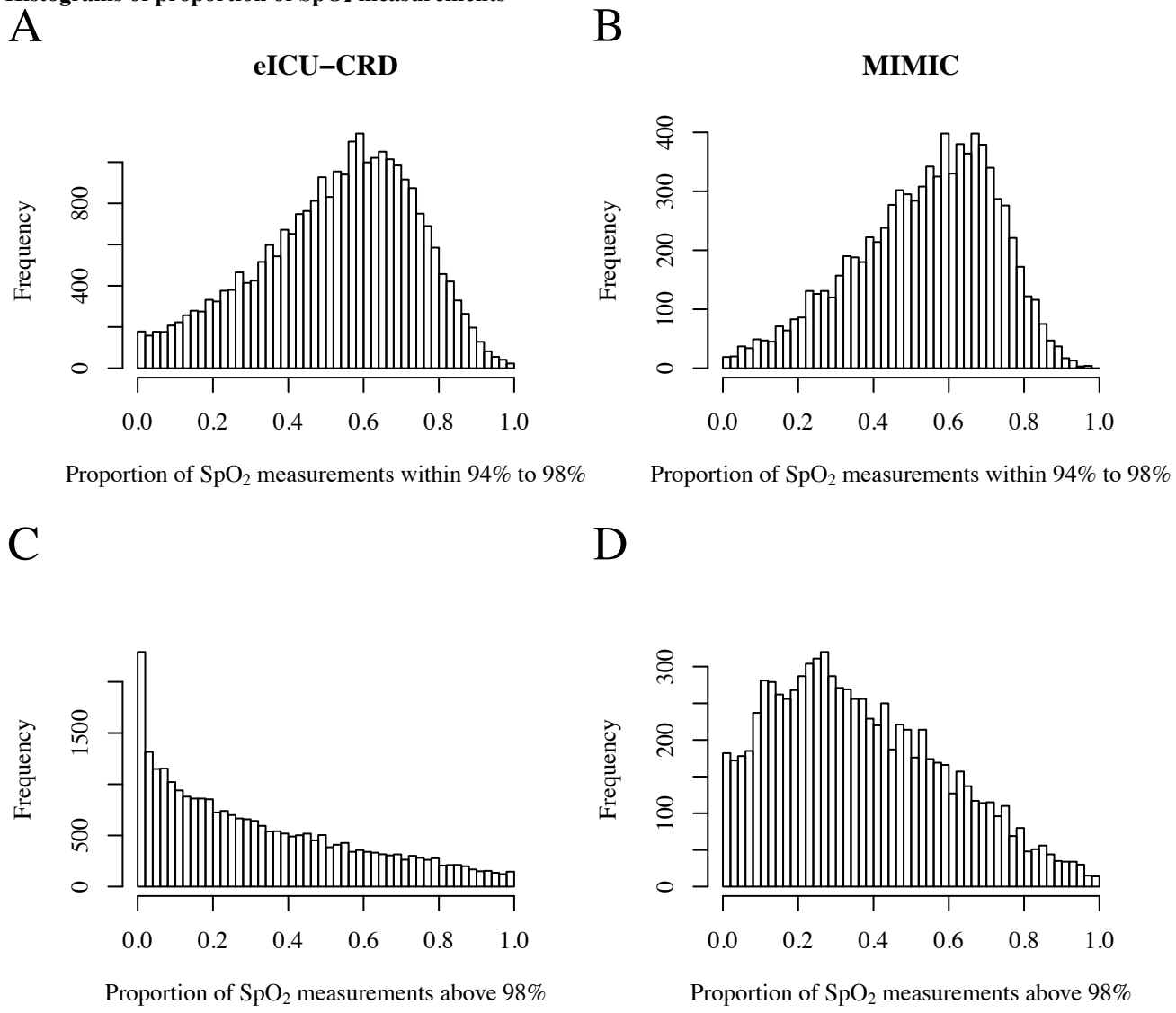


e-Figure 28. Results for ICU stays with a sepsis diagnosis
2,750/1,327 patients in eICU-CRD/MIMIC had a sepsis diagnosis.



e-Figure 29. Results for ICU stays with a stroke diagnosis
597/372 patients in eICU-CRD/MIMIC had a stroke diagnosis.

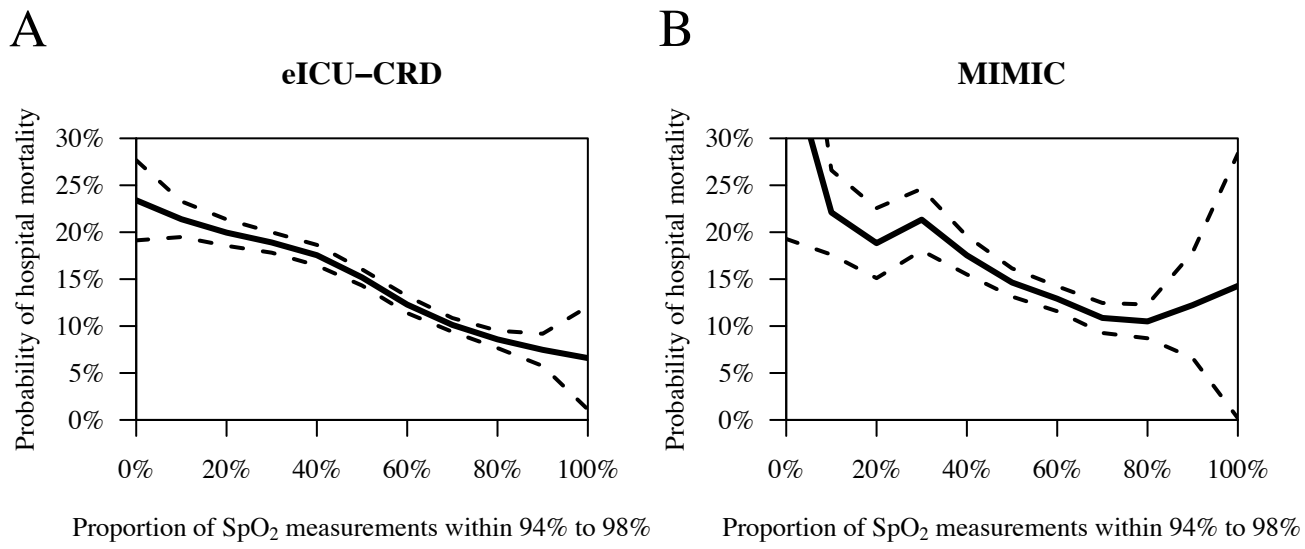
Histograms of proportion of SpO_2 measurements



e-Figure 30. Histograms of proportion of SpO_2 measurements within 94% to 98% and above 98%
The histograms cover 26,723/8,564 ICU stays from eICU-CRD/MIMIC.

Causal inference
So far, the analysis has focused on the effect of the exposure, SpO_2, conditional on the control variables. Alternatively, one can consider the marginal effect of the exposure, that is the effect averaged over the control variables, also known as the average treatment effect. Causal inference methods provide computation of average treatment effects. We use G-computation as it is well-suited to a continuous exposure:[1]

To obtain the counterfactual mortality risk at unobserved exposures, we use the generalized additive models described in the main text. They provide mortality risk for any proportion of SpO_2 within the 94–98% range for each patient in the data. We do this for the proportions 0%, 10%, 20%, …, 90%, 100%. For each proportion, we can average the counterfactual risk of all patients to obtain an average treatment effect. The results are in e-Figure 31. The confidence intervals follow from standard errors that were estimate from 100 bootstrap samples. While the effect sizes vary from the results in Figure 3 due to being the average treatment effect, the overall trend is the same.



e-Figure 31. Probability of hospital mortality versus the proportion of time with SpO_2 within 94% to 98% based on G-computation.
These plots are analogous to Figures 3A and 3B of the main text but show the average treatment effects based on G-computation instead of the treatment effect conditional on the control variables.

Literature review

We searched PubMed up to Feb 7, 2019, using the search terms ("hyperoxia"[MeSH Terms] OR "oxygen"[MeSH Terms]) AND "humans"[MeSH Terms] AND "adult"[MeSH Terms] AND "mortality"[MeSH Terms], and found 1 systematic review of randomized trials,[2] 2 systematic reviews of observational studies involving cardiac arrest patients,[3,4] 4 systematic reviews of observational studies and randomized trials involving multiple types of critically ill patients,[5-8] and 8 observational studies not included in the systematic reviews.[9-16]

References

1. Snowden JM, Rose S, Mortimer KM. Implementation of G-Computation on a Simulated Data Set: Demonstration of a Causal Inference Technique. American Journal of Epidemiology. 2011;173(7):731-738.
2. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018;391(10131):1693-1705.
3. Wang CH, Chang WT, Huang CH, et al. The effect of hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of observational studies. Resuscitation. 2014;85(9):1142-1148.
4. Patel JK, Kataya A, Parikh PB. Association between intra- and post-arrest hyperoxia on mortality in adults with cardiac arrest: A systematic review and meta-analysis. Resuscitation. 2018;127:83-88.
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