

# Admission Oxygen Saturation and Mortality in Acute Pulmonary Embolism Patients: Observational Data From Large ICU Databases

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## Research

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# Abstract

## Background

The relationship between blood oxygenation and clinical outcomes of acute pulmonary embolism (APE) patients in intensive care unit (ICU) is unclear, which could be nonlinear. The study aimed to determine the association between admission pulse oximetry-derived oxygen saturation (SpO<sub>2</sub>) levels and mortality, and to determine the optimal range with real-world data.

## Methods

Patients diagnosed with APE on admission and staying in ICU for at least 24 hours in the Medical Information Mart for Intensive Care III (MIMIC-III) database and the eICU Collaborative Research Database (eICU-CRD) were included. Logistic regression and restricted cubic spline (RCS) models were applied to determine the nonlinear relationship between mean SpO<sub>2</sub> levels within the first 24 hours after ICU admission and in-hospital mortality, from which we derived an optimal range of SpO<sub>2</sub>. Subgroup analyses were based on demographics, treatment information, scoring system and comorbidities.

## Results

We included 1109 patients who fulfilled inclusion criteria, among whom 129 (12%) died during hospitalization and 80 (7.2%) died in ICU. The RCS showed that the relationship between admission SpO<sub>2</sub> levels and in-hospital mortality of APE patients was nonlinear and U-shaped. The optimal range of SpO<sub>2</sub> with the lowest mortality was 95–98%. Multivariate stepwise logistic regression analysis with backward elimination confirmed that the admission SpO<sub>2</sub> levels of 95%-98% was associated with decreased hospital mortality compared to the group with SpO<sub>2</sub> < 95% (Odds ratio [OR] = 2.321; 95% confidence interval [CI]: 1.405–3.786; P < 0.001) and 100% (OR = 2.853; 95% CI: 1.294–5.936; P = 0.007), but there was no significant difference compared with 99% SpO<sub>2</sub> (OR = 0.670, 95% CI: 0.326–1.287; P > 0.05). This association was consistent across subgroup analyses.

## Conclusions

The relationship between admission SpO<sub>2</sub> levels and in-hospital mortality followed a U-shaped curve among patients with APE. The optimal range of SpO<sub>2</sub> for APE patients was 95–98%.

## Background

Acute pulmonary embolism (APE) is a life-threatening disease with high morbidity and mortality worldwide, which causes an annual incidence rates range from 39 to 115 per 100,000 population and an in-hospital mortality of 13.9%[1, 2]. APE interferes with both circulation and gas change, and results in the

mismatch between ventilation and perfusion, which contributes to hypoxaemia and threaten the life of patients. Therefore, supplemental oxygen including conventional oxygen supplementation, high-flow oxygen or mechanical ventilation is needed in treatment of APE patients with arterial oxygen saturation ( $\text{SaO}_2$ ) < 90%[3]. However, animal and human studies have shown that excessive oxygen can promote vasoconstriction, inflammation, and oxidative stress on pulmonary and cardiovascular systems, and may increase mortality risk in critically ill adults[4–6]. There are also reports that hyperoxaemia is common in intensive care unit (ICU), which was associated with increased in-hospital and in-ICU mortality[7–10]. In addition, a retrospective study has shown that the in-hospital mortality of APE patients in ICU requiring mechanical ventilation reached 41.0% compared with 8.0% in the non-ventilated group ( $P < 0.0001$ )[11]. Thus, blood oxygenation and mortality of APE patients in ICU may be nonlinear and have a U-shaped relation, which means that too low or too high blood oxygenation may correlate with higher mortality. However, few studies support this hypothesis. Considering the poor prognosis of APE patients and the prevalent use of blood oxygenation in many risk factor studies, it is necessary to determine the association between blood oxygenation and mortality, which may help predict the mortality risk accurately and optimize oxygen therapy support of APE patients.

In critically ill patients with cardiorespiratory compromise, the blood oxygen level is commonly measured continuously by using peripheral pulse oximetry ( $\text{SpO}_2$ ), which helps detecting hypoxaemia and guiding oxygen therapy[12, 13]. Interestingly, one study involving APE patients showed oxygen saturation in air < 88% at admission was an independent predictor of PE-related death with incremental prognostic value to the 2014 European Society of Cardiology (ESC) risk model[14]. However, the study defined oxygen in arbitrarily defined categories rather than as a continuous variable and were unable to define an optimal target range. A meta-analysis study indicated oxygen supplementation with higher versus lower fractions or oxygenation targets may increase mortality of patients admitted to ICU[15]. Furthermore, there is still a lack of available recommendations on the optimal range of  $\text{SpO}_2$  in the current APE guidelines[3, 16].

Since hypoxaemia and hyperoxaemia are both related to adverse outcomes, it is necessary to determine the optimal range of  $\text{SpO}_2$ , which helps minimize the competing risks of hypoxaemia and hyperoxaemia of APE patients in ICU, especially those who need oxygen therapy. A large-scale multicenter study was therefore required to elucidate oxygen saturation targets of APE patients to optimize clinical treatment and guide future research. This study is now feasible with the application of large data sources such as the Medical Information Mart for Intensive Care III database (MIMIC-III) and the eICU Collaborative Research Database (eICU-CRD) which are open-access databases of ICU patients[17, 18]. In this study, we aimed to determine the nonlinear relationship between admission  $\text{SpO}_2$  levels and in-hospital mortality of patients with APE in ICU, and to determine the optimal range of oxygen saturation for clinical practice and future researches.

## Methods

## Data Description

Data were collected from the MIMIC-III (Version: 1.4) and the eICU-CRD (Version: 2.0) in accordance with the ethical standards of the institutional review board of the Massachusetts Institute of Technology (authorization code: 35655780) and with the 1964 Declaration of Helsinki and its later amendments[19]. Requirement for individual patient consent was waived because the project did not impact clinical care and all protected health information was deidentified, which was approved by the institutional review boards of Beth Israel Deaconess Medical Center. MIMIC-III covered 61,532 ICU admissions between 2001 and 2012 of 46,746 patients at the Beth Israel Deaconess Medical Center in Boston, Massachusetts. eICU-CRD covered 200,859 ICU admissions in 2014 and 2015 of 139,367 patients at 208 US hospitals. Both databases are maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology. They include hourly physiological readings from bedside monitors, records of demographic characteristics, diagnoses via International Classification of Diseases, Ninth Revision (ICD-9) codes, and other clinical data collected during routine medical care. This study is reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology statement (STROBE) [20].

We included all ICU patients diagnosed with APE using ICD-9 diagnosis codes of MIMIC-III (41512, 41513, 41519), and diagnosis codes of eICU-CRD (415.19, I26.99; 785.51, R57.0; 786.3, 415.19, R04.9, I26). Eligible patients had to have typical symptoms suggestive of APE (defined as dyspnoea, chest pain, pre-syncope or syncope, haemoptysis, atrial arrhythmias, electrocardiographic changes indicative of right ventricular strain-such as inversion of T waves in leads V1-V4, a QR pattern in V1, a S1Q3T3 pattern, and incomplete or complete right bundle branch block)[3, 21]. Patients were excluded meeting the following criteria: repeat ICU stays; patients aged < 18 years; stayed in the ICU less than 24 hours; had no value for hospital mortality; had no value for SpO2 and other important medical data records. Patients 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 de-enrichment while not providing a large enough exposure window for the effects of hyperoxaemia or hypoxaemia to become apparent.

The primary outcome was hospital mortality, with ICU mortality as a secondary outcome. The primary independent variable was SpO2, which were measured multiple times within the first 24 hours after ICU admission. The mean values of SpO2 were used in our analysis as a measure of the central tendency of patients' conditions. SpO2 is usually measured hourly in MIMIC-III and eICU-CRD, which were verified and entered into a chart by a nurse.

The data were extracted from the databases with PostgreSQL (Version:10.14). The codes that support the MIMIC-III and eICU-CRD documentation and website are publicly available, and contributions from the community of users are encouraged (<https://github.com/MIT-LCP/mimic-code>, <https://github.com/MIT-LCP/eicu-code>). The variables in the study contained demographics, vital signs, comorbidities, scoring system, treatment information. Only the records of the first 24 hours after ICU admission were included. For treatment information, the oxygen therapy subgroup using mechanical ventilation was included. The vasopressor subgroup (defined as using any of dopamine, epinephrine, milrinone, norepinephrine, phenylephrine, vasopressin) were included. As extensive missing data could lead to bias, variables with

over 20% missing values were excluded in the subsequent analyses. Correspondingly, single imputation was conducted for variables with less than 20% missing values based on the complete conditional specification and predictive mean matching method[22, 23]. Each incomplete variable was imputed with by an independent model, which ensured the validity of the results.

## Statistical analysis

Baseline characteristics of enrolled patients were presented and compared among groups of SpO<sub>2</sub> < 95%, SpO<sub>2</sub> within 95–98%, 98%<SpO<sub>2</sub> by using either Kruskal-Wallis rank test or Pearson's chi-square test as appropriate. Continuous variables were characterized as median (interquartile range [IQR]), while categorical data were presented as count and proportion.

Both hypoxaemia and hyperoxaemia are associated with adverse outcomes suggest a nonlinear relationship between SpO<sub>2</sub> and mortality. Therefore, restricted cubic splines (RCS) based on logistic regression models[24], were used to identify the nonlinear relationship between ICU admission SpO<sub>2</sub> and mortality. According to the plot results, an optimal oxygen saturation was determined, and the total cohort was then divided into several subgroups with different SpO<sub>2</sub> levels for the subsequent analyses.

Univariate logistic regression analysis was used to confirm the associations between SpO<sub>2</sub> levels and mortality among the total cohort and different subgroups. For the calculation of estimated odds ratio (OR) in each group, 95–98% SpO<sub>2</sub> was defined as non-exposed group, while SpO<sub>2</sub><95%, 98%<SpO<sub>2</sub> were defined as exposed group. Results were presented as a forest plot with group sizes, estimated OR (95% confidence interval [CI]), P values for the independent variable. Furthermore, multivariate logistic regression analyses including the full logistic regression analysis and stepwise logistic regression analysis with backward elimination of the total cohort were conducted to identify the relationship between SpO<sub>2</sub> levels and mortality. The grouping strategy was consistent with univariate logistic regression analysis. Results were presented as a table with OR (95% CI) and P values.

A two-tailed P value of less than 0.05 was set up to be statistically significant. All statistical analyses were conducted using R software (Version: 4.0.4).

## Results

After application of the inclusion and exclusion criteria, the final study cohort consisted of 1109 APE patients, of whom 129 (12%) patients died during hospitalization and 80 (7.2%) died in ICU. The detailed information on the inclusion and selection process was summarized in Fig. 1. In total, 32 variables were extracted from the MIMIC-III and eICU-CRD databases, among which 11 variables had missing values (**Additional file 1: Table S1**). The baseline characteristics of APE patients grouped by different SpO<sub>2</sub> levels (SpO<sub>2</sub> < 95%, SpO<sub>2</sub> within 95–98%, 98%<SpO<sub>2</sub>) were summarized in Table 1. The total cohort with a median age of 64 (IQR: 51–75) comprised 542 (49%) male patients. Notably, patients with SpO<sub>2</sub> < 95% and 98%<SpO<sub>2</sub> both had higher hospital mortality than those of patients with SpO<sub>2</sub> within 95–98% (SpO<sub>2</sub> < 95% versus 95–98% SpO<sub>2</sub> versus 98%<SpO<sub>2</sub>: 16% versus 10% versus 14%; P = 0.056).

**Table 1 Baseline characteristics of patients with APE admitted to ICU.**

Variable	Overall (n=1109)	SpO2<95% (n=197)	95%≤SpO2≤98% (n=720)	98% <SpO2≤100% (n=192)	P value
Demographics					
Age, years	64 (51, 75)	65 (53, 74)	64 (52, 75)	64 (50, 77)	0.9
Gender					0.01
Male	542 (49%)	107 (54%)	359 (50%)	76 (40%)	
Female	567 (51%)	90 (46%)	361 (50%)	116 (60%)	
Ethnicity					<0.001
White	779 (70%)	157 (80%)	508 (71%)	114 (59%)	
Black	132 (12%)	12 (6.1%)	81 (11%)	39 (20%)	
Others/Unknown	198 (18%)	28 (14%)	131 (18%)	39 (20%)	
ICU type					0.032
Medical ICU	481 (43%)	92 (47%)	302 (42%)	87 (45%)	
Medical-Surgical ICU	305 (28%)	65 (33%)	194 (27%)	46 (24%)	
Other ICU	323 (29%)	40 (20%)	224 (31%)	59 (31%)	
Other ICU	7 (4, 12)	6 (4, 10)	7 (5, 12)	8 (5, 13)	<0.001
LOS in hospital, days	129 (12%)	31 (16%)	72 (10%)	26 (14%)	0.056
Death in hospital	2.2 (1.6, 3.8)	2.0 (1.6, 3.3)	2.2 (1.6, 3.7)	2.4 (1.6, 5.2)	0.091
LOS in ICU, days	80 (7.2%)	20 (10%)	42 (5.8%)	18 (9.4%)	0.052
Death in ICU		89 (80, 100)	90 (79, 101)	91 (80, 101)	>0.9
Vital signs	90 (79, 101)	121 (108, 131)	118 (107, 130)	114 (107, 128)	0.15
HR, beats/min	118 (107, 130)	67 (60, 75)	65 (56, 72)		0.002
SBP, mmHg	67 (59, 75)	20.4 (17.9, 23.4)	20.0 (17.6, 22.5)		<0.001
DBP, mmHg	20.5 (18.0, 23.5)	21.1 (18.9, 24.9)	36.74 (36.49, 37.02)	36.76 (36.55, 37.12)	0.3
RR, beats/min	36.75 (36.47, 37.02)	36.75 (36.47, 36.98)	97.00 (96.00, 97.00)	99.00 (99.00, 100.00)	<0.001
T, °C	36.75 (36.49, 37.02)	94.00 (93.00, 94.00)	294 (41%)	83 (43%)	0.015
SpO <sub>2</sub> , %	97.00 (95.00, 98.00)		66 (9.2%)	32 (17%)	0.005
Comorbidities					0.061
Infectious disease					

Sepsis		60 (30%)	142 (20%)	42 (22%)	0.5
Cancer	437 (39%)	16 (8.1%)	105 (15%)	33 (17%)	0.15
Congestive heart failure	114 (10%)	26 (13%)	57 (7.9%)	20 (10%)	0.2
Chronic kidney disease	210 (19%)	25 (13%)	230 (32%)	54 (28%)	0.088
Hypertension	163 (15%)	10 (5.1%)	77 (11%)	31 (16%)	0.13
Ischemic heart disease	87 (7.8%)	52 (26%)	142 (20%)	49 (26%)	0.14
Atrial fibrillation	336 (30%)	20 (10%)	98 (14%)	36 (19%)	
COPD	128 (12%)	35 (18%)			0.149
Scoring system	226 (20%)	34 (17%)	0 (0, 1)	1 (0, 1)	0.2
sPESI	168 (15%)		83 (68, 106)	88 (71, 112)	0.051
PESI		0 (0, 1)	15 (14, 15)	15 (14, 15)	<0.001
GCS	0 (0, 1)	80 (69, 97)	31 (26, 38)	36 (30, 42)	<0.001
OASIS	84 (68, 106)	15 (15, 15)	34 (25, 44)	39 (31, 51)	
SAPS II	15 (14, 15)	32 (28, 38)			
	32 (27, 39)	31 (23, 43)			
	35 (25, 46)				
SOFA	3 (1, 5)	3 (2, 5)	3 (1, 5)	4 (2, 8)	0.005
APACHE IV	42 (31, 54)	41 (33, 52)	41 (30, 54)	46 (36, 60)	0.037
Treatment information					
Mechanical ventilation	163 (15%)	19 (9.6%)	81 (11%)	63 (33%)	<0.001
Vasopressor	153 (14%)	16 (8.1%)	89 (12%)	48 (25%)	<0.001

Values are n (%), or median (interquartile range). Kruskal-Wallis and Chi-square tests were used to compare continuous and categorical variables of groups. ICU, intensive care unit; LOS, length of stay; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory rate; T, temperature; SpO<sub>2</sub>, oxygen saturation; COPD, chronic obstructive pulmonary disease; sPESI, simplified Pulmonary Embolism Severity Index; PESI, Pulmonary Embolism Severity Index; GCS, Glasgow Coma Scale; OASIS, Oxford Acute Severity of Illness Score; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; APACHE IV, Acute Physiology and Chronic Health Evaluation IV.

The relationship between admission SpO<sub>2</sub> level and all-cause in-hospital mortality of APE patients was nonlinear, and the smooth curve fitted between them was a U-shaped curve ( $P_{\text{overall}}=0.0002$ ,

$P_{\text{nonlinear}}=0.0001$ ), as shown in Fig. 2. Although low SpO<sub>2</sub> levels correlated more strongly with mortality, high SpO<sub>2</sub> levels were also associated with increased mortality. Based on the flattest part of the U-shape in Fig. 2, we determined the range of SpO<sub>2</sub> within 95–98% as the optimal oxygen saturation range. Furthermore, the total cohort was divided into three groups with different SpO<sub>2</sub> levels: the groups with SpO<sub>2</sub> < 95%, or SpO<sub>2</sub> within 95–98%, or 98%<SpO<sub>2</sub>. For subgroup analyses of demographics, treatment information and scoring system in Fig. 3, there were 8 out of 15 subgroups that had a non-linear U-shaped relationship between admission SpO<sub>2</sub> level and in-hospital mortality: age (including < 70 years, ≥ 70 years), female, medical ICU, other ICU, high risk of simplified Pulmonary Embolism Severity Index (sPESI), high risk of Pulmonary Embolism Severity Index (PESI), mild and moderate of Glasgow Coma Scale (GCS) (All  $P_{\text{overall}}$  and  $P_{\text{nonlinear}}<0.05$ ). For subgroup analyses of comorbidities in Fig. 4, there were 4 of 9 comorbidity subgroups that had a non-linear U-shaped association between SpO<sub>2</sub> level and in-hospital mortality: infectious disease, cancer, congestive heart failure, hypertension (All  $P_{\text{overall}}$  and  $P_{\text{nonlinear}}<0.05$ ). Except sepsis subgroup, the bottom of the curves for all subgroups appeared within the range of 95–98% SpO<sub>2</sub>.

Univariate logistic regression was performed to determine the association between different SpO<sub>2</sub> groups and hospital mortality among the total cohort and subgroups (Fig. 5). Since there was no statistical significance about mortality between the reference group (95–98% SpO<sub>2</sub>) and the group with 98%<SpO<sub>2</sub> from the results of univariate logistic analysis for the total cohort (**Additional file 1: Table S2**), the group with 98%<SpO<sub>2</sub> was further divided into 99% SpO<sub>2</sub> and 100% SpO<sub>2</sub> for more detailed analyses. In the total cohort, 95–98% SpO<sub>2</sub> was associated with decreased risk of all-cause in-hospital mortality compared to SpO<sub>2</sub> < 95% (OR = 1.681; 95% CI: 1.055–2.625; P = 0.025) and 100% SpO<sub>2</sub> (OR = 2.455; 95% CI: 1.192–4.728; P = 0.01), but it was not significantly different from the group with 99% SpO<sub>2</sub> about in-hospital mortality (OR = 1.033; 95% CI: 0.544–1.837; P > 0.05), which meant that under high blood oxygenation 100% SpO<sub>2</sub> was a risk factor of mortality for APE patients rather than 99% SpO<sub>2</sub>. Multivariate logistic regression analyses were further performed to validate their association (Table 2). For stepwise logistic regression analysis with backward elimination, 95–98% SpO<sub>2</sub> was also associated with reduced risk of in-hospital mortality compared to the group with SpO<sub>2</sub> < 95% (OR = 2.321; 95% CI: 1.405–3.786; P < 0.001) and 100% (OR = 2.853; 95% CI: 1.294–5.936; P = 0.007), but it was not significantly different from the group with 99% SpO<sub>2</sub> about hospital mortality (OR = 0.670, 95% CI: 0.326–1.287; P > 0.05). The multivariate logistic regression analyses suggested that age, ICU type (Medical-Surgical ICU), SpO<sub>2</sub> levels, sepsis, cancer, atrial fibrillation were all independent prognostic factors for predicting hospital mortality in patients with APE (All P < 0.05).

**Table 2 Multivariate regression analysis of the association of characteristics with having in-hospital death events in people with APE in ICU.**

Variable	Model 1		Model 2	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
<b>Demographics</b>				
Age, years	1.024 (1.009 - 1.039)	0.002	1.027 (1.013 - 1.042)	<0.001
<b>Gender</b>				
Male	1 (Ref)			
Female	1.313 (0.873 - 1.983)	0.192		
<b>ICU type</b>				
Medical ICU	1 (Ref)		1 (Ref)	
Medical-Surgical ICU	0.464 (0.225 - 0.910)	0.030	0.469 (0.236 - 0.876)	0.023
Other ICU	1.296 (0.822 - 2.035)	0.262	1.291 (0.827 - 2.010)	0.259
<b>Vital signs</b>				
<b>SpO<sub>2</sub>, %</b>				
95%≤SpO <sub>2</sub> ≤98%	1 (Ref)		1 (Ref)	
SpO <sub>2</sub> <95%	2.296 (1.384 - 3.760)	0.001	2.321 (1.405 - 3.786)	<0.001
99% SpO <sub>2</sub>	0.611 (0.292 - 1.191)	0.167	0.670 (0.326 - 1.287)	0.250
100% SpO <sub>2</sub>	2.820 (1.272 - 5.899)	0.008	2.853 (1.294 - 5.936)	0.007
<b>Comorbidities</b>				
Infectious disease	0.838 (0.495 - 1.413)	0.509		
Sepsis	4.347 (2.445 - 7.773)	<0.001	3.923 (2.347 - 6.508)	<0.001
Cancer	3.777 (2.421 - 5.896)	<0.001	3.665 (2.376 - 5.653)	<0.001
Congestive heart failure	0.926 (0.527 - 1.577)	0.781		
Chronic kidney disease	1.209 (0.598 - 2.324)	0.581		
Hypertension	1.023 (0.651 - 1.596)	0.921		
Ischemic heart disease	1.257 (0.698 - 2.205)	0.435		
Atrial fibrillation	1.656 (1.045 - 2.605)	0.030	1.621 (1.042 - 2.498)	0.030
COPD	1.307 (0.781 - 2.146)	0.298		

Note: Model 1: full logistic regression analysis. Model 2: stepwise logistic regression analysis with backward elimination.

CI, confidence interval; Ref, reference; ICU, intensive care unit; SpO<sub>2</sub>, oxygen saturation; COPD, chronic obstructive pulmonary disease.

## Discussion

In this study, our analyses demonstrated a U-shaped relationship between ICU admission SpO<sub>2</sub> levels and all-cause in-hospital mortality of patients with APE. Furthermore, our study also presented the lowest mortality for the mean of SpO<sub>2</sub> within 95–98%, which could be the optimal oxygen saturation targets and benefit oxygen therapy for patients with APE. These results were consistent for demographics, treatment information, scoring system, comorbidity subgroups, and when ICU mortality was used in place of hospital mortality.

Pulse oximetry is universally used for monitoring respiratory status of patients in ICU, which assess SaO<sub>2</sub> based on Beer-Lambert law, and the correlation between SaO<sub>2</sub> and SpO<sub>2</sub> is generally high which makes SpO<sub>2</sub> significant in the continuous monitoring and titration of oxygen supplement in ICU[25, 26]. In addition, arterial oxygen tension (PaO<sub>2</sub>) is commonly used to guide oxygen therapy in ICU as well. Compared to PaO<sub>2</sub>, SpO<sub>2</sub> has the advantages of low cost, noninvasive, and repetitive measurement of oxygenation. Furthermore, SpO<sub>2</sub> is also clinically more relevant, for which the ventilator and inspired oxygen fraction settings are based on SpO<sub>2</sub> changes rather than on intermittent arterial blood gas assays[27]. Additionally, using SpO<sub>2</sub> to titrate supplemental oxygen is better than fixed inspired oxygen fractions, which risk over-oxygenation in patients with narrow alveolar-arterial oxygen gradients and under-oxygenation in those with wide gradients. Because of the sigmoid shape of the oxyhemoglobin dissociation curve, oximetry may not detect hypoxaemia in patients with high PaO<sub>2</sub> levels[28]. However, for the SpO<sub>2</sub> range of 95–98%, the correlation between SpO<sub>2</sub> and PaO<sub>2</sub> would be fair, with little risk of underestimation of either hypoxaemia or hyperoxaemia[29].

Risk stratification of patients with APE is mandatory for determining the appropriate therapeutic management approach. Blood oxygen saturation has been used as one of the important prognostic indicators of several APE risk scores such as PESI and sPESI[30, 31]. However, few studies have explored the prognostic value of SpO<sub>2</sub> level as a continuous variable of APE patients. In our study, the assessment of SpO<sub>2</sub> level within the first day after ICU admission could serve as a preliminary prognostic marker for short-term mortality among all APE patients, which could help stratify the risk of APE patients and personalize their treatment. Similar to our results, Kline et al. found that a room-air pulse oximetry reading < 95% at diagnosis was associated with a significantly higher probability of in-hospital complications (death, cardiogenic shock, or respiratory failure) from pulmonary embolism[32]. However, this study was composed of emergency department patients, the proportion of patients with SpO<sub>2</sub> within 98–100% was less, which may not fully reflect the harm of hyperoxaemia in APE patients. Considering the U-shaped relationship between SpO<sub>2</sub> and mortality, perhaps at least three groups of SpO<sub>2</sub> level groups are required to explore its impact on the prognosis of APE patients.

Although oxygen therapy is recommended in patients with APE and  $\text{SaO}_2 < 90\%$ , there is still lack of strong evidence on the optimal oxygenation target for guiding the oxygen therapy in the current APE guidelines[3, 16]. Our study presented the lowest mortality at a  $\text{SpO}_2$  within 95–98%. However, for the group with  $98\% < \text{SpO}_2$ , the univariate logistic regression showed 100%  $\text{SpO}_2$  was associated with higher increased risk of all-cause in-hospital mortality compared to 95%-98%  $\text{SpO}_2$  (OR: 2.455;  $P = 0.01$ ), but there was no significant difference between 99%  $\text{SpO}_2$  and 95%-98%  $\text{SpO}_2$  (OR: 1.033;  $P > 0.05$ ), and then multivariate logistic regression analyses further presented that there was no significant difference between 99%  $\text{SpO}_2$  and the reference group (OR: 0.611;  $P > 0.05$ ). This indicates that 99%  $\text{SpO}_2$  is not a risk indicator for APE patients which could serve as a buffer range for oxygen targets. Additionally, the  $\text{SpO}_2$  range with the lowest mortality in the mechanical ventilation subgroup was 97–99%, which also indicated 99%  $\text{SpO}_2$  was less risk and was consistent with the findings by Zhou et al. that time spent oxygen saturation 95–99% is associated with reduced mortality in critically ill patients with mechanical ventilation[33]. However, considering that patients with 99%  $\text{SpO}_2$  still have a relatively high risk of hyperoxaemia, we cautiously set the upper limit of the optimal  $\text{SpO}_2$  target at 98%[29, 34]. Besides, an upper level of 98% may reduce excessive use of high concentration oxygen therapy and avoid the potential risks of hyperoxia.

Notably, the British Thoracic Society (BTS) guideline recommends oxygen should be prescribed to achieve a target saturation of 94%-98% in patients with pulmonary embolism except for in those at risk of hypercapnic respiratory failure[5]. However, the recommendations about the use of oxygen in pulmonary embolism are based on expert opinion in BTS guideline and the evidence level is relatively low, lacking strong evidence support. Our findings are consistent with the recommendations of BTS guideline and could provide it with a higher level of evidence support. Additionally, the Oxygen-ICU trial showed that patients who received conservative oxygen therapy with  $\text{SpO}_2$  levels between 94% and 98% had lower in-hospital mortality and in-ICU mortality than those received conventional therapy with  $\text{SpO}_2$  levels between 97% and 100% (hospital mortality, 24.2% vs. 33.9%,  $P = 0.03$ ; ICU mortality, 11.6% vs. 20.2%,  $P = 0.01$ ), which also supports our optimal range of 95–98% for APE patients although this trial may overestimate the true treatment effect of conservative group[35, 36]. Furthermore, a retrospective study involving ICU patients with at least 48 hours of oxygen therapy showed that the optimal range of  $\text{SpO}_2$  was 94–98%, which is also consistent with our findings[37]. Our results are potentially impactful and targeting  $\text{SpO}_2$  between 95% and 98% might optimize survival for all APE patients in ICU. Since pulse oximetry is widespread and affordable, implementation of the 95–98% target would be feasible, even in resource-limited environments.

Several studies showed that overuse of oxygen therapy in ICU is common and is associated with adverse outcomes, including higher mortality, longer duration of mechanical ventilation and longer hospitalization[10, 38, 39]. Furthermore, from a dose-response relationship between arterial oxygen levels and outcomes, severe hyperoxia was more consistently associated with poor outcomes (hospital and ICU mortality) than mild hyperoxia[9]. On the other side, the hypoxaemia could be induced by APE, which contributes to the increase in pulmonary artery pressure and in severe cases it aggravates the hemodynamic impairment[40]. Thus, optimal oxygen targets are required to minimize and balance the

competing risks of hypoxaemia and hyperoxaemia in APE patients. From a physiological standpoint, it is necessary to avoid hypoxaemia to maintain sufficient oxygen delivery to important tissues, while avoiding hyperoxaemia is also necessary to avoid the formation and toxic effects of reactive oxygen species (ROS)[5, 41]. Since our study included all APE patients, the results were applicable to APE patients with or without oxygen therapy. Our findings could provide a more solid foundation for the selection of SpO<sub>2</sub> targets in the treatment groups for future treatment and research on APE patients.

Several limitations of our study should be acknowledged. Firstly, the data were from the United States, and the results may not be fully applicable to other ICUs with different practices or resources. Second, even though we performed multiple subgroup and multivariate regression analyses, residual confounding could exist. Particularly, confounding by comorbidities would mean overestimation of the association between hyperoxaemia or hypoxaemia and mortality. Finally, the study is a retrospective study based on large ICU databases and shared the same flaws as other observational studies. Thus, prospective cohorts were needed for further validation.

## Conclusion

Among patients with APE, the relationship between admission SpO<sub>2</sub> levels and in-hospital mortality followed a U-shaped curve. The lowest mortality was observed for an SpO<sub>2</sub> range of 95–98%. Future randomized trial could adopt an SpO<sub>2</sub> range of 95–98% as the reference target.

## Abbreviations

APE: Acute pulmonary embolism; BTS: British Thoracic Society; CI: Confidence interval; eICU-CRD: eICU Collaborative Research Database; ESC: European Society of Cardiology; GCS: Glasgow Coma Scale; ICD-9: International Classification of Diseases, Ninth Revision; ICU: Intensive care unit; IQR: Interquartile range; MIMIC-III: Medical Information Mart for Intensive Care III; OR: Odds ratio; PaO<sub>2</sub>: Arterial oxygen tension; PE: Pulmonary embolism; PESI: Pulmonary Embolism Severity Index; RCS: Restricted cubic spline; ROS: Reactive oxygen species; SaO<sub>2</sub>: arterial oxygen saturation; sPESI: Simplified Pulmonary Embolism Severity Index; SpO<sub>2</sub>: Pulse oximetry-derived oxygen saturation; STROBE: Strengthening the Reporting of Observational studies in Epidemiology

## Declarations

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## Availability of data and materials

The datasets used and/or analysed during the current study are available from the Medical Information Mart for Intensive Care III database and eICU Collaborative Research Database. Researchers are required to formally request access via a process documented on their website: <https://mimic.mit.edu/>, <https://eicu-crd.mit.edu/>.

## Authors' Contributions

KH, XLX, APP, MG and JT designed the research study. RNS collected the data and performed analysis. RNS, GCY and SMK helped to perform programming. KH, XLX, APP, JT, RNS, GCY, XC, LL, DXZ helped to write the manuscript.

## Ethics approval and consent to participate

The access of the database was approved by the institutional review boards of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates after completing the CITI (Collaborative Institutional Training Initiative) "Data or Specimens Only Research" course. No informed consent was required since the data are anonymized.

## Consent for publication

Not applicable

## Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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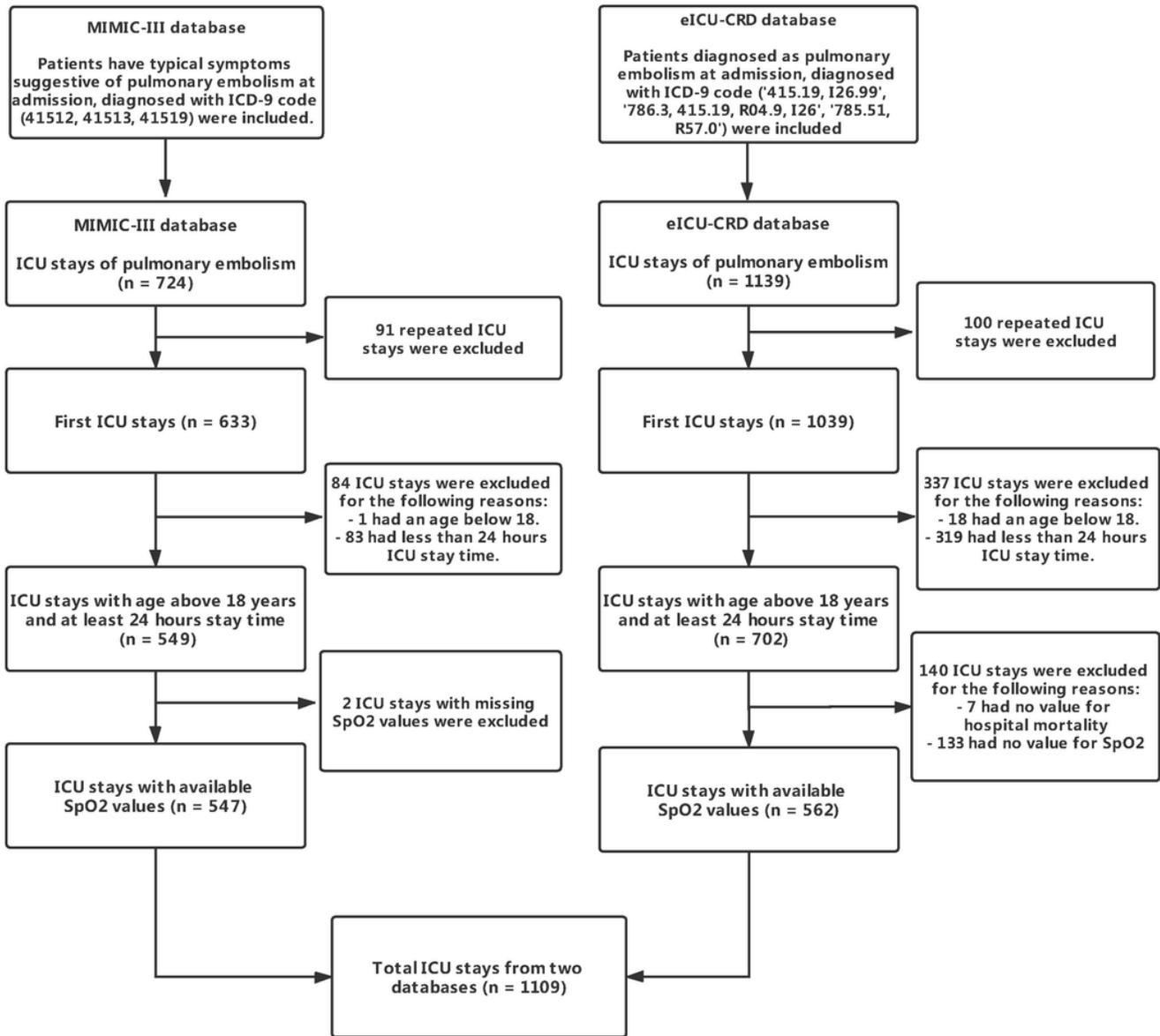
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## Figures



**Figure 1**

Flowchart of inclusion and selection of APE patients. APE = Acute pulmonary embolism; eICU-CRD = eICU Collaborative Research Database; ICD-9 = International Classification of Diseases, Ninth Revision; ICU = Intensive care unit; MIMIC-III = Medical Information Mart for Intensive Care III; SpO2 = Pulse oximetry-derived oxygen saturation.

## All-cause mortality

P(overall) = 0.0002  
P(nonlinear) = 0.0001

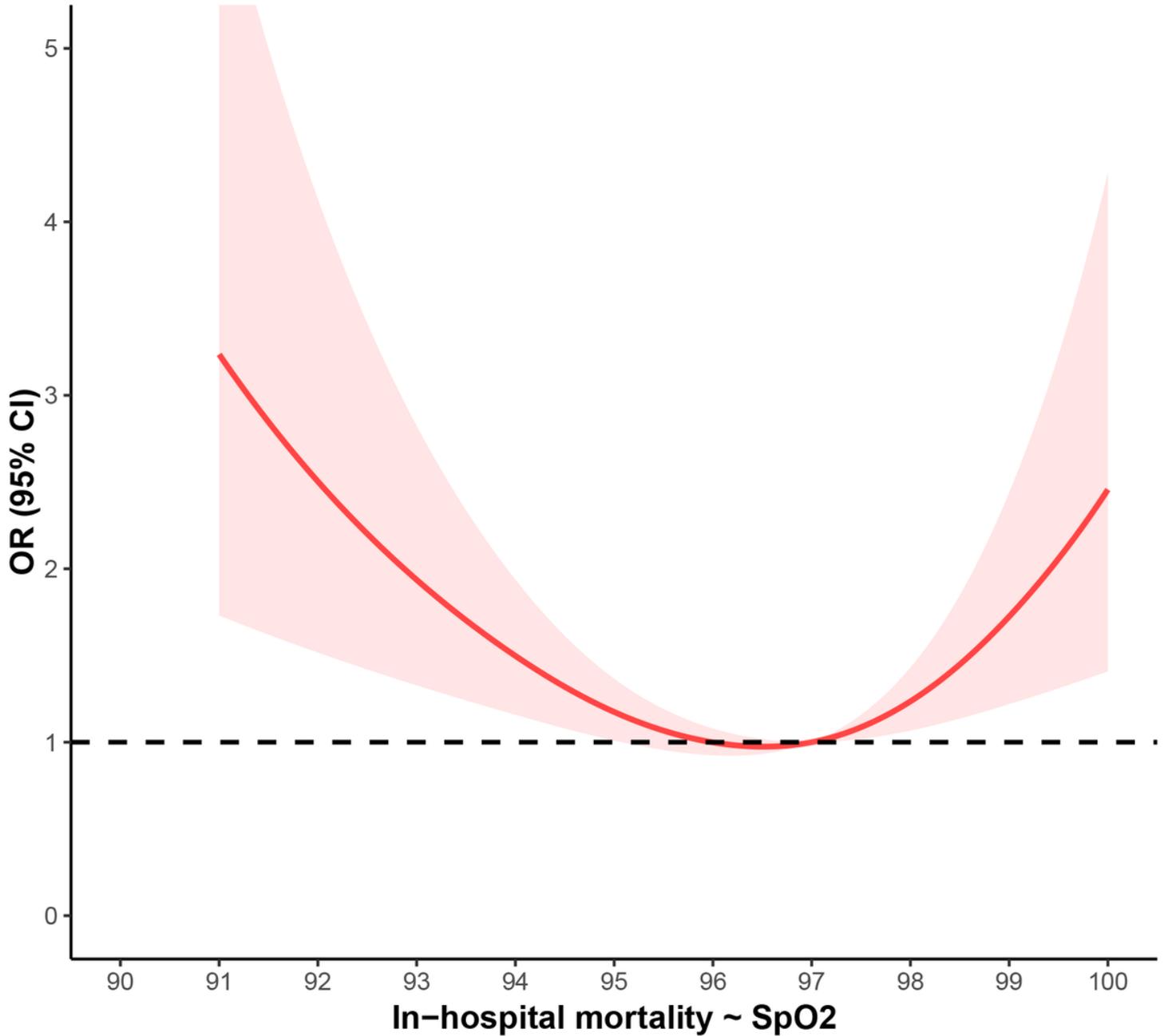
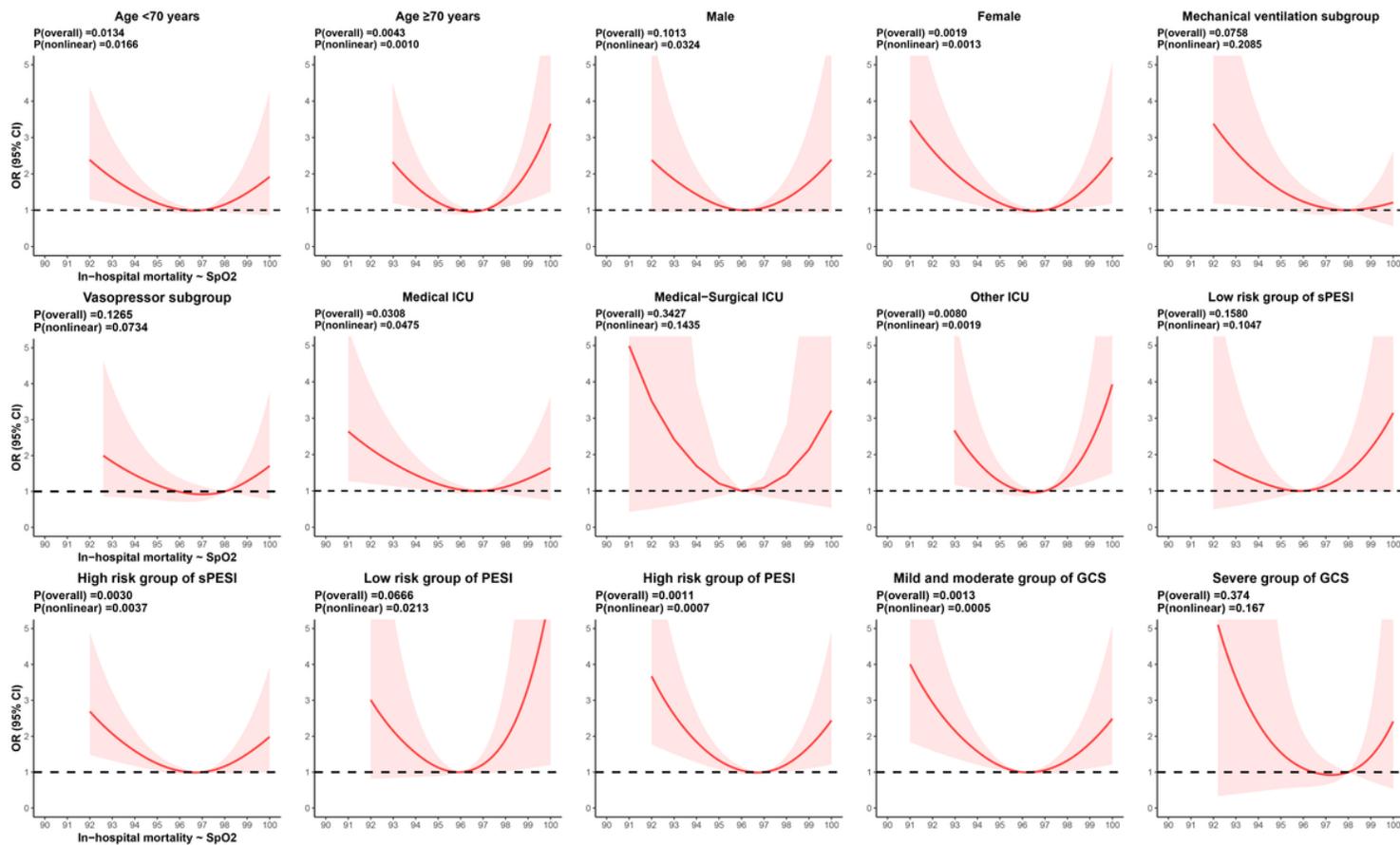


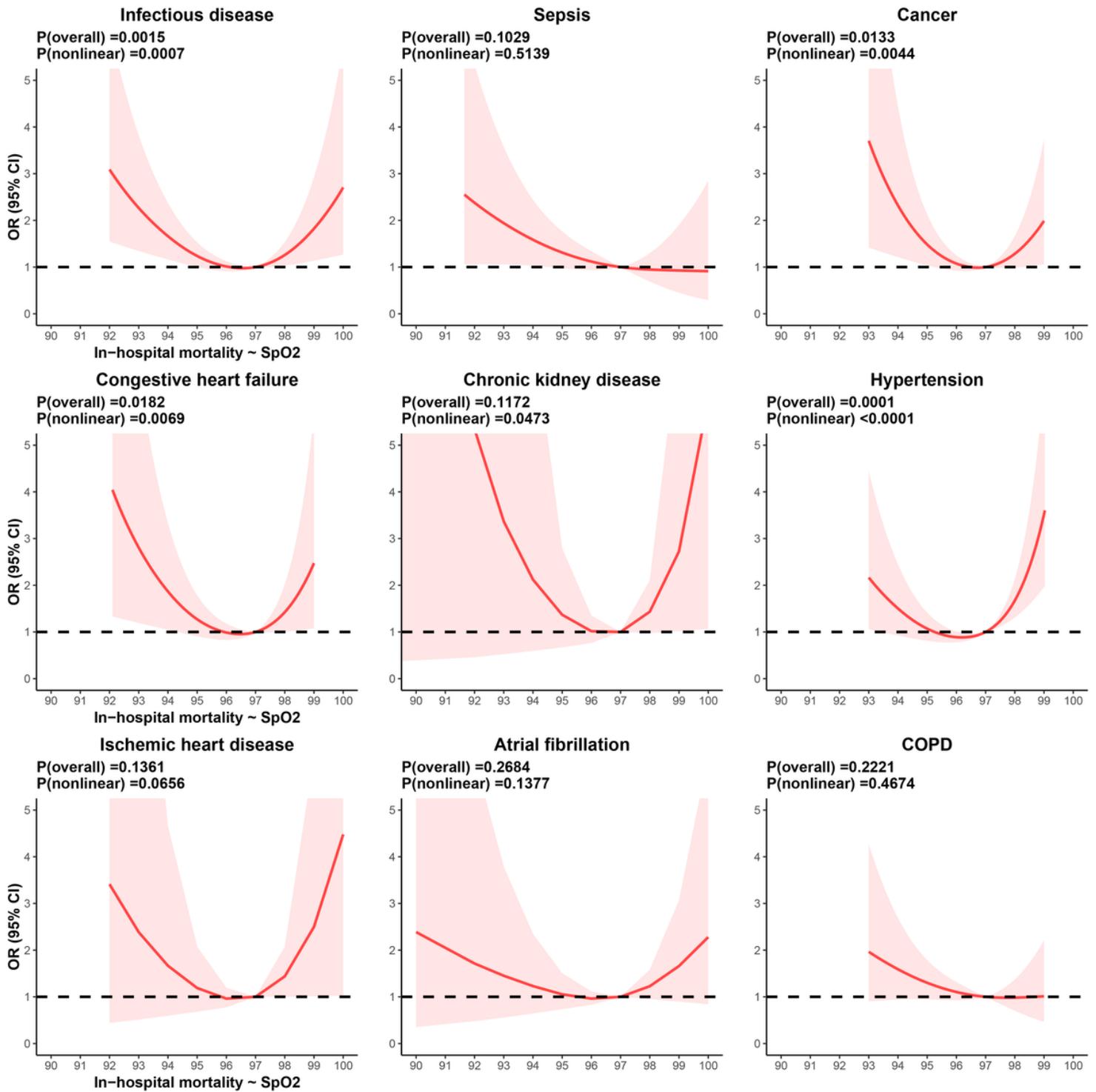
Figure 2

Restricted cubic spline plot of the relationship between mean SpO2 levels and the odds ratio for all-cause in-hospital mortality in APE patients. Solid red line represents the smooth curve fit between variables. The shaded area around the spline curve represents the 95% confidence interval. The reference for the odd ratio was set at 1. The P value for overall association and P value for non-linearity are shown in the subtitle position. APE = Acute pulmonary embolism; CI = Confidence interval; OR = Odds ratio; SpO2 = Pulse oximetry-derived oxygen saturation.



**Figure 3**

Restricted cubic spline plots of the relationship between mean SpO2 levels and the odds ratio for in-hospital mortality in APE patients from different subgroups. The subgroup analyses were based on demographics, treatment information, scoring system. Solid red line represents the smooth curve fit between variables. The shaded area around the splines curve represent the 95% confidence interval. The reference for the odd ratio was set at 1. The P value for overall association and P value for non-linearity are shown in the subtitle position. APE = Acute pulmonary embolism; CI = Confidence interval; GCS = Glasgow Coma Scale; ICU = Intensive care unit; OR = Odds ratio; PESI = Pulmonary Embolism Severity Index; sPESI = Simplified Pulmonary Embolism Severity Index; SpO2 = Pulse oximetry-derived oxygen saturation.



**Figure 4**

Restricted cubic spline plots of the relationship between mean SpO<sub>2</sub> levels and the odds ratio for in-hospital mortality in APE patients with different comorbidities subgroups. Solid red line represents the smooth curve fit between variables. The shaded area around the splines curve represent the 95% confidence interval. The reference for the odd ratio was set at 1. The P value for overall association and P value for non-linearity are shown in the subtitle position. APE = Acute pulmonary embolism; CI =

Confidence interval; COPD = Chronic obstructive pulmonary disease; OR = Odds ratio; SpO2 = Pulse oximetry-derived oxygen saturation.

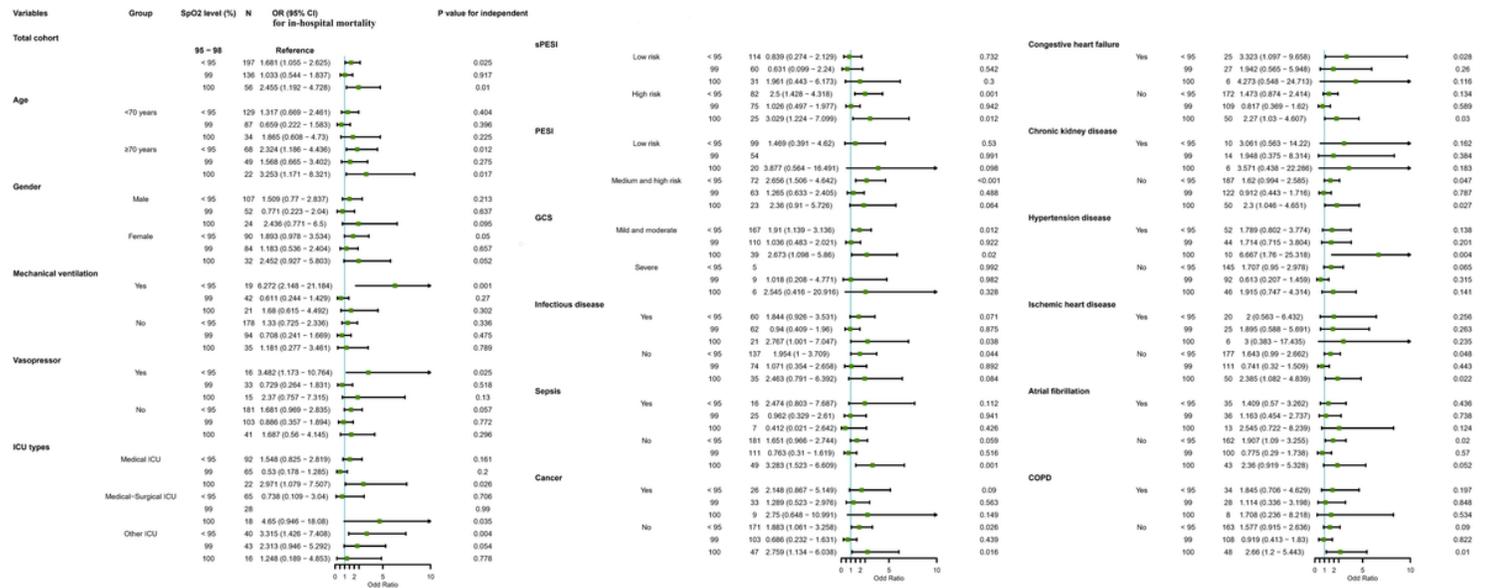


Figure 5

Forest plot with odds ratio for in-hospital mortality and 95% confidence interval of the total cohort and different subgroups. The subgroup analyses were based on demographics, treatment information, scoring system, comorbidities. The solid vertical line indicates no risk (odds ratio = 1.000). See Table 1 legend for expansion of abbreviations.

## Supplementary Files

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