RESEARCH

Time-varying intensity of oxygen exposure is associated with mortality in critically ill patients with mechanical ventilation

Zhu Zhu[1†], Mingqin Zhou[2†], Yao Wei[3] and Hui Chen[3*]

Abstract

Background: There is no consensus exists regarding the association between oxygen exposure (arterial oxygen tension or fraction of inspired oxygen) and outcomes for patients with mechanical ventilation. Additionally, whether the association remains persistent over time is unknown. We aimed to explore the association between exposure to different intensities of oxygen exposure over time and 28-day mortality in patients with mechanical ventilation.

Methods: We obtained data from the Medical Information Mart for Intensive Care IV (MIMIC-IV), which included adult ($\geq$ 18 years) patients who received invasive mechanical ventilation for at least 48 h. We excluded patients who received extracorporeal membrane oxygenation (ECMO) or who initiated ventilation more than 24 h after ICU admission. The primary outcome was 28-day mortality. Piece-wise exponential additive mixed models were employed to estimate the strength of associations over time.

Results: A total of 7784 patients were included in the final analysis. Patients had a median duration of invasive mechanical ventilation of 8.1 days (IQR: 3.8–28 days), and the overall 28-day mortality rate was 26.3%. After adjustment for baseline and time-dependent confounders, both daily time-weighted average (TWA) arterial oxygen tension (PaO_2) and fraction of inspired oxygen (FiO_2) were associated with increased 28-day mortality, and the strength of the association manifested predominantly in the early-middle course of illness. A significant increase in the hazard of death was found to be associated with daily exposure to TWA-$PaO_2 \geq 120$ mmHg (Hazard ratio 1.166, 95% CI 1.059–1.284) or TWA-$FiO_2 \geq 0.5$ (Hazard ratio 1.496, 95% CI 1.363–1.641) during the entire course. A cumulative effect of harmful exposure (TWA-$PaO_2 \geq 120$ mmHg or TWA-$FiO_2 \geq 0.5$) was also observed.

Conclusion: PaO_2 and FiO_2 should be carefully monitored in patients with mechanical ventilation, especially during the early-middle course after ICU admission. Cumulative exposure to higher intensities of oxygen exposure was associated with an increased risk of death.

Keywords: Oxygen exposure, Intensive care unit, Mechanical ventilation, 28-day mortality

[†]Zhu Zhu and Mingqin Zhou have contributed equal to this work.

*Correspondence: 15905162429@163.com

[3] Department of Critical Care Medicine, The First Affiliated Hospital of Soochow University, Soochow University, No. 899 Pinghai Road, Suzhou 215000, People's Republic of China
Full list of author information is available at the end of the article

Introduction

The administration of supplemental oxygen is a standard treatment in mechanically ventilated patients in Intensive Care Units (ICU). Oxygen therapy can reverse tissue hypoxia and can be lifesaving on many occasions, while its overzealous use might result in hyperoxemia with supraphysiological levels of the arterial oxygen tension (PaO_2) [1]. Additionally, most patients with mechanical

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ventilation frequently required a higher fraction of inspired oxygen (FiO$_2$) to maintain an adequate PaO$_2$.

PaO$_2$ and FiO$_2$ outside the normal physiological range can be detrimental and exacerbate systemic organ injury in critically ill patients [2–5], while numerous studies provided conflicting evidence concerning the impact of PaO$_2$ and FiO$_2$ on clinical outcomes of critically ill patients [6–10]. The cut-off values of PaO$_2$ and FiO$_2$ associated with increased risk of death were various, and still uncertain. Meanwhile, previous studies focused on only the association between PaO$_2$ or FiO$_2$ during the early onset of illness and mortality, usually within 24 h after ICU admission, and many of these studies are limited by using only a single measure of PaO$_2$ or FiO$_2$ to define oxygen exposure for entire ICU admission. Whether the association between time-varying oxygen exposure and mortality is significant and remains persistent over time is unknown. Besides, high FiO$_2$ can increase PaO$_2$ and impair lung tissues simultaneously [11, 12], while the direct and indirect effects (mediated by hyperoxemia) of high FiO$_2$ on mortality in the real world have never been explored.

Therefore, our primary objective was to estimate the effect of time-varying exposure to different intensities of oxygen exposure (as measured either by PaO$_2$ or FiO$_2$) on 28-day mortality in patients with mechanical ventilation. We also examined whether the strength of the effect changed over time, and whether there was a cumulative effect of exposure over time. Finally, we aimed to identify the direct and indirect effects of high FiO$_2$ on mortality.

Methods

Study design and participants

We conducted a retrospective cohort study using electronic health records data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) [13]. The MIMIC-IV database contains comprehensive and high-quality data of well-defined and characterized ICU patients admitted to ICUs at the Beth Israel Deaconess Medical Center between 2008 and 2019. One author (HC) obtained access to the database and was responsible for data extraction (certification number 27252652). Our study complied with the Reporting of Studies Conducted using Observational Routinely Collected Health Data (RECORD) statement.

All patients in the MIMIC-IV who received invasive mechanical ventilation were eligible for inclusion in the present study. The exclusion criteria included (1) Patients who were younger than 18 years; (2) Patients ventilated for less than 48 h; (3) Patients who received extracorporeal membrane oxygenation (ECMO); (4) Patients who initiated ventilation more than 24 h after ICU admission.

Additionally, we analyzed only the first ICU stay for patients who were admitted to the ICU more than once.

Variable extraction

We collected age, sex, weight, height, ethnicity, admission type, and severity at admission, as measured by the Sequential Organ Failure Assessment (SOFA) score, the Simplified Acute Physiology Score II (SAPS II), and Oxford Acute Severity of Illness Score (OASIS). Comorbidities were also collected to calculate the Elixhauser comorbidity score. Initial diagnoses were extracted according to the recorded ICD-9 and ICU-10 codes in the database. Longitudinal data including SOFA score, blood gas, ventilation parameters, and laboratory measurements were collected for each 24 h. If a variable was recorded more than once in the 24 h, we used the value related to the greatest severity of illness. Specifically, PaO$_2$ and FiO$_2$ were extracted per each time frame of 4 h after ICU admission. For each 24 h, the time-weighted average (TWA) PaO$_2$ or FiO$_2$ was calculated as the area under the PaO$_2$ or FiO$_2$ versus the time plot. All included patients were followed up from inclusion until death, ICU discharge, or 28 days in the ICU, whichever occurred first.

Exposures and outcomes

The primary exposures in the present study were time-varying TWA-PaO$_2$ and TWA-FiO$_2$. Since our research indicated that there is a consistent increase in the risk of death with TWA-PaO$_2$ higher than or equal to 120 mmHg and TWA-FiO$_2$ higher than or equal to 0.5, we defined hyperoxemia and high FiO$_2$ as TWA-PaO$_2 \geq 120$ mmHg, and TWA-FiO$_2 \geq 0.5$, respectively, and employed three approaches to quantifying the effect of harmful exposure: (1) Any exposure to hyperoxemia or high FiO$_2$ during the entire course of ICU admission; (2) The proportion of time spent in hyperoxemia or high FiO$_2$; (3) The area under the longitudinal profiles for either TWA-PaO$_2$ of 120 mmHg or more, or TWA-FiO$_2$ of 0.5 or more.

The primary outcome was 28-day mortality. Secondary outcomes included in-hospital mortality, ventilation-free days (VFDs) in 28 days, length of ICU, and hospital stay. Patients who died before day 28 were considered to have zero VFDs.

Statistical analysis

Values are presented as the mean (standard deviation) or median [interquartile range (IQR)] for continuous variables as appropriate and as the total number (percentage) for categorical variables. Comparisons between groups were made using the X^2 test or Fisher's exact test for

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categorical variables and Student's t test or Mann–Whitney U test for continuous variables as appropriate.

We first used piece-wise exponential additive mixed models (PAMMs) [14–16] to estimate the association of subject-specific longitudinal profiles of either TWA-PaO_2 or TWA-FiO_2 with 28-day mortality. PAMMs allow one to examine the time-varying effect of a time-varying exposure (time-varying TWA-PaO_2 or TWA-FiO_2 in the present study) on a time-to-event outcome (Additional file 1). Based on prior knowledge, baseline variables were purposefully selected to be used in the PAMMs as time-fixed confounders and included age, gender, admission type, weight, and Elixhauser comorbidity score. Considering that the confounders may change over time during the follow-up period, and that the effect of such confounders on outcomes is time-varying, we treated longitudinal data including the use of mechanical ventilation and vasopressor, SOFA score, and $PaCO_2$ during follow-up as time-varying confounders in the PAMMs. To investigate whether the association between TWA-PaO_2 or TWA-FiO_2 and 28-day mortality changed over time, we included an interaction term with time and exposures in the model. To avoid bias induced by missing data, we used multiple imputations by chained equation (MICE) to account for the missing data.

We identified the approximate PaO_2 and FiO_2 threshold above which the risk of 28-day mortality began to increase based on PAMMs. And then, three secondary analyses were performed. We included any hyperoxemia or high FiO_2 as time-varying exposure variables and explored the impact of any exposure to hyperoxemia or high FiO_2 on mortality; we also estimated the association between the proportion of time spent in harmful exposure (TWA-$PaO_2 \geq 120$ mmHg or TWA-$FiO_2 \geq 0.5$) and mortality. Furthermore, we investigated the relationship between cumulative dose and 28-day mortality using the area under the longitudinal profiles for either TWA-PaO_2 of 120 mmHg or more, or TWA-FiO_2 of 0.5 or more.

Based on the additive hazards model, we conduct a causal mediation analysis (CMA) to explore whether the effect of time-varying high FiO_2 (TWA-$FiO_2 \geq 0.5$) on the primary outcome is mediated by the time-varying hyperoxemia. The additive hazards model allows for a time-varying mediator in survival analysis [17]. CMA separates the total effect of exposure into direct and indirect effects. The indirect impact on the outcome is mediated via a mediator. Our study used time-varying high FiO_2 as a harmful exposure and time-varying hyperoxemia as a mediator variable.

Several subgroup analyses were performed according to exposure window (up to 3 days, 5 days, 7 days, 14 days, and 21 days), admission type, gender, and initial diagnosis. Since patients could liberate from mechanical ventilation during the follow-up period, we duplicated the analysis after changing the follow-up period. Specifically, patients were followed up from inclusion until death, liberated from mechanical ventilation, ICU discharge, or 28 days in the ICU, whichever occurred first. We also conducted sensitivity analyses after excluding missing values of daily TWA-PaO_2 or TWA-FiO_2 during follow-up.

All statistical analyses were performed using R (version 4.0.3), and $p < 0.05$ was considered statistically significant.

Results

Patients in study

After reviewing the data of 29,119 patients with mechanical ventilation, a total of 7784 patients were included in the final analysis. The flow diagram of patient selections is presented in Additional file 2: Figure S1. Baseline characteristics are shown in Table 1. The patients had a median age of 65.0 years (IQR: 54.0–76.0), and 57.2% of them were men. Of the study cohort, 89.5% of patients had sepsis and 50.6% had acute respiratory failure. Patients had a median duration of invasive mechanical ventilation of 8.1 days (IQR: 3.8–28) and the overall 28-day mortality rate was 26.3%.

A total of 6544 (84.1%) patients had complete data of TWA-PaO_2 on Day 1, and 58.1% of patients were exposed to hyperoxemia (TWA-$PaO_2 \geq 120$ mmHg), while 7778 (99.9%) patients had complete data of TWA-FiO_2 on Day 1, and 52.7% of patients were exposed to TWA-$FiO_2 \geq 0.5$. There were lots of differences in patient characteristics and outcomes based on their level of TWA-PaO_2 (Additional file 2: Table S1) and TWA-FiO_2 (Additional file 2: Table S2) on Day 1.

Primary analysis

Based on the PAMMs, we identified a U-shaped relationship between time-varying TWA-PaO_2 or TWA-FiO_2 (Figs. 1 and 2) and the risk of 28-day mortality. There was a consistent increase in the risk of death with TWA-PaO_2 higher than or equal to 120 mmHg and TWA-FiO_2 higher than or equal to 0.5 (Figs. 1A and 2A). After adjusting for age, gender, admission type, weight, Elixhauser comorbidity score, use of mechanical ventilation, use of vasopressor, SOFA score, and $PaCO_2$, both the time-varying TWA-PaO_2 (Hazard ratio (HR) per 5 mmHg 1.801, 95% CI 1.585–2.046) and TWA-FiO_2 (HR per 0.05 2.688, 95% CI 2.407–3.002) were associated with an increased risk of 28-day mortality (Additional file 2: Table S3).

The strength of the association between the intensity of oxygen exposure (as measured by either TWA-PaO_2 or TWA-FiO_2) and 28-day mortality was not persistent across the entire course of ICU admission (Additional file 2: Figure S2). TWA-PaO_2 significantly impacts

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Table 1 Baseline characteristics and outcomes in included patients

	All patients(*n* = 7784)	Missing, *n* (%)
Age (years)	65.0 (54.0–76.0)	0 (%)
Male (gender)	4452 (57.2)	0 (%)
Weight (kg)	80.0 (66.7–97.0)	202 (2.6%)
Height (cm)	170.0 (163.0–178.0)	1384 (17.8%)
Admission type, n (%)		0 (%)
Medical	4714 (60.6)	
Surgical elective	153 (2.0)	
Surgical urgent	1830 (23.5)	
Other	1087 (14.0)	
Ethnicity, n (%)		0 (%)
White	4695 (60.3)	
Black	823 (10.6)	
Hispanic	266 (3.4)	
Other	1787 (23.0)	
Elixhauser comorbidity score	6.0 (4.0–8.0)	0 (%)
Severity of illness		
GCS	14.6 (1.1)	4 (0.1%)
SAPS II	43.0 (33.0–54.0)	0 (%)
OASIS	42.0 (36.0–47.2)	0 (%)
SOFA	3.0 (2.0–5.0)	820 (10.5%)
Use of vasopressor (1 st 24 h)	4462 (57.3)	0 (%)
Initial diagnosis, n (%)		0 (%)
Sepsis	6964 (89.5)	
Acute respiratory failure	3938 (50.6)	
Cardiac arrest	493 (6.3)	
Vital signs (1 st 24 h)		
Heart rate (bpm)	86.5 (75.2–99.1)	1 (0.0%)
MAP (mmHg)	75.8 (70.4–82.6)	1 (0.0%)
Temperature (℃)	37.0 (36.7–37.4)	463 (5.9%)
Parameters of mechanical ventilation (1 st 24 h)		
TWA-FiO$_2$	0.50 (0.42–0.59)	6 (0.1%)
Total respiratory rate (bpm)	20.1 (17.5–23.0)	12 (0.2%)
Tidal volume (ml/kg PBW)	7.0 (6.4–7.8)	1385 (17.8%)
PEEP (cmH$_2$O)	6.1 (5.1–8.1)	2 (0.0%)
Plateau pressure (cmH$_2$O)	18.8 (16.1–22.0)	297 (3.8%)
Use of NMBA, *n* (%)	413 (5.3)	0 (%)
Laboratory data (1 st 24 h)		
pH	7.4 (7.3–7.4)	1221 (15.7%)
PaCO$_2$ (mmHg)	39.8 (35.0–45.0)	1221 (15.7%)
TWA-PaO$_2$ (mmHg)	130.5 (100.5–171.0)	1240 (15.9%)
Lactate (mmol/L)	2.0 (1.3–3.3)	1829 (23.5%)
Bicarbonate (mmol/L)	22.2 (19.5–25.3)	46 (0.6%)
Fluid balance in the first 24 h (L)	1.54 (− 0.24–4.59)	90 (1.2%)
Clinical outcomes		
28-day mortality, n (%)	2044 (26.3)	0 (%)
In-hospital mortality, n (%)	2154 (27.7)	0 (%)
Alive and VFDs (days)	19.9 (0.0–24.2)	0 (%)

Table 1 (continued)

	All patients(*n* = 7784)	Missing, *n* (%)
Length of ICU stay (days)	7.8 (4.9–13.1)	0 (%)
Length of hospital stay (days)	14.0 (8.0–22.0)	0 (%)

GCS Glasgow Coma Scale; SAPS II: Simplified acute physiology score II; *OASIS* Oxford Acute Severity of Illness Score; *SOFA* sequential organ failure assessment; *MAP* mean arterial pressure; *TWA* Time-weighted average; *FiO$_2$* Fraction of inspired oxygen; *PBW* Predicted body weight; *PEEP* Positive end-expiratory pressure; *NMBA* neuromuscular blocking agent; *PCO$_2$* partial pressure of carbon dioxide; *PO$_2$* partial pressure of oxygen; *VFDs* Ventilation-free days; *ICU* Intensive Care Unit
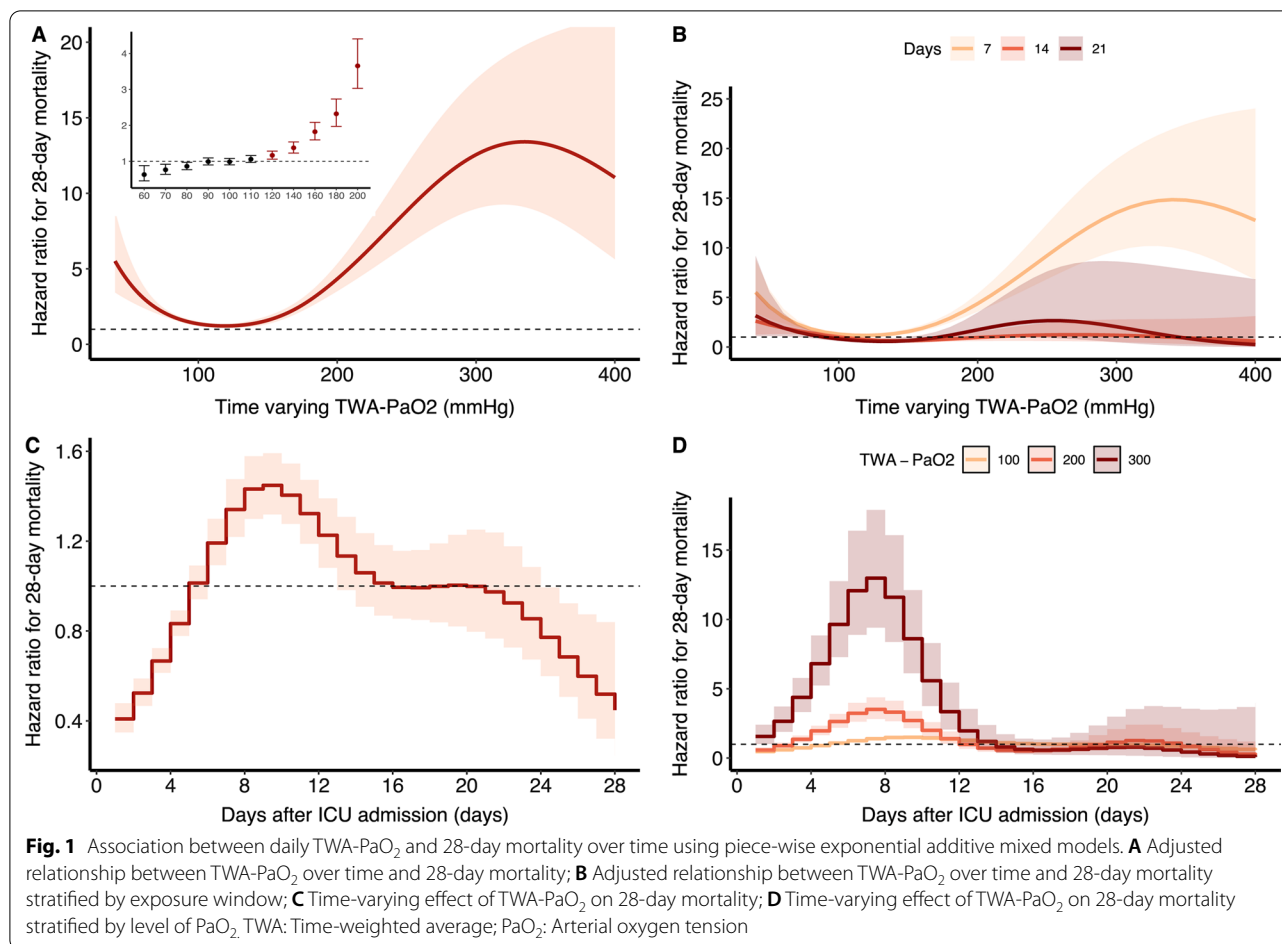
mortality in the early-middle course of illness (approximately 4–12 days after ICU admission) (Fig. 1C), regardless of the level of TWA-PaO$_2$ (Fig. 1D). While the impacts of TWA-FiO$_2$ predominantly in the early-middle course of illness (approximately 4–16 days after ICU admission) (Fig. 2C), and for the high level of TWA-FiO$_2$, the impact on mortality remained persistent across the entire course of ICU admission (Fig. 2D).

Secondary analysis

Three secondary analyses were performed after we identified the approximate PaO$_2$ and FiO$_2$ threshold above which the risk of 28-day mortality began to increase. First, PAMMs demonstrated that both time-varying hyperoxemia (HR 1.166, 95% CI 1.059–1.284) and high FiO$_2$ (HR 1.496, 95% CI 1.363–1.641) were associated with an increased risk of 28-day mortality (Table 2). Likewise, both the proportion of time spent in hyperoxemia (HR per 5% 1.412 95% CI 1.302–1.531) and high FiO$_2$ (HR per 5% 1.284, 95% CI 1.204–1.369) significantly impact mortality (Additional file 2: Table S4 and Fig. 3). Third, a higher cumulative dose of the potentially injurious intensity of oxygen exposure was associated with an increased hazard of death for hyperoxemia (HR 1.0014, 95% CI 1.001–1.0017) and high FiO$_2$ (HR 1.003, 95% CI 1·0023–1.0036) (Additional file 2: Table S5).

Causal mediation analysis

Any exposure to hyperoxemia (TWA-PaO$_2 \geq$ 120 mmHg) was significantly associated with the 28-day mortality in patients with TWA-FiO$_2 \geq$ 0.5 (HR 1.203, 95% CI 1.088–1.331), but not in patients with TWA-FiO$_2 <$ 0.5 (HR 1.056, 95% CI 0.760–1.469). Meanwhile, the association between any exposure to TWA-FiO$_2 \geq$ 0.5 and 28-day mortality was significant both in patients with hyperoxemia (HR 1.60, 95% CI 1.40–1.874) and non-hyperoxemia (HR 1.556, 95% CI 1.389–1.742). To explore whether the effect of time-varying high FiO$_2$ (TWA-FiO$_2 \geq$ 0.5) on the primary outcome was mediated by the time-varying hyperoxemia. We treated time-varying high FiO$_2$ as a

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Fig. 1 Association between daily TWA-PaO$_2$ and 28-day mortality over time using piece-wise exponential additive mixed models. **A** Adjusted relationship between TWA-PaO$_2$ over time and 28-day mortality; **B** Adjusted relationship between TWA-PaO$_2$ over time and 28-day mortality stratified by exposure window; **C** Time-varying effect of TWA-PaO$_2$ on 28-day mortality; **D** Time-varying effect of TWA-PaO$_2$ on 28-day mortality stratified by level of PaO$_2$. TWA: Time-weighted average; PaO$_2$: Arterial oxygen tension

harmful exposure and time-varying hyperoxemia as a mediator variable, and visual inspection showed that both the direct effect of high FiO$_2$ ($p < 0.001$) and an indirect effect via hyperoxemia ($p < 0.001$) on mortality were significant (Fig. 4).

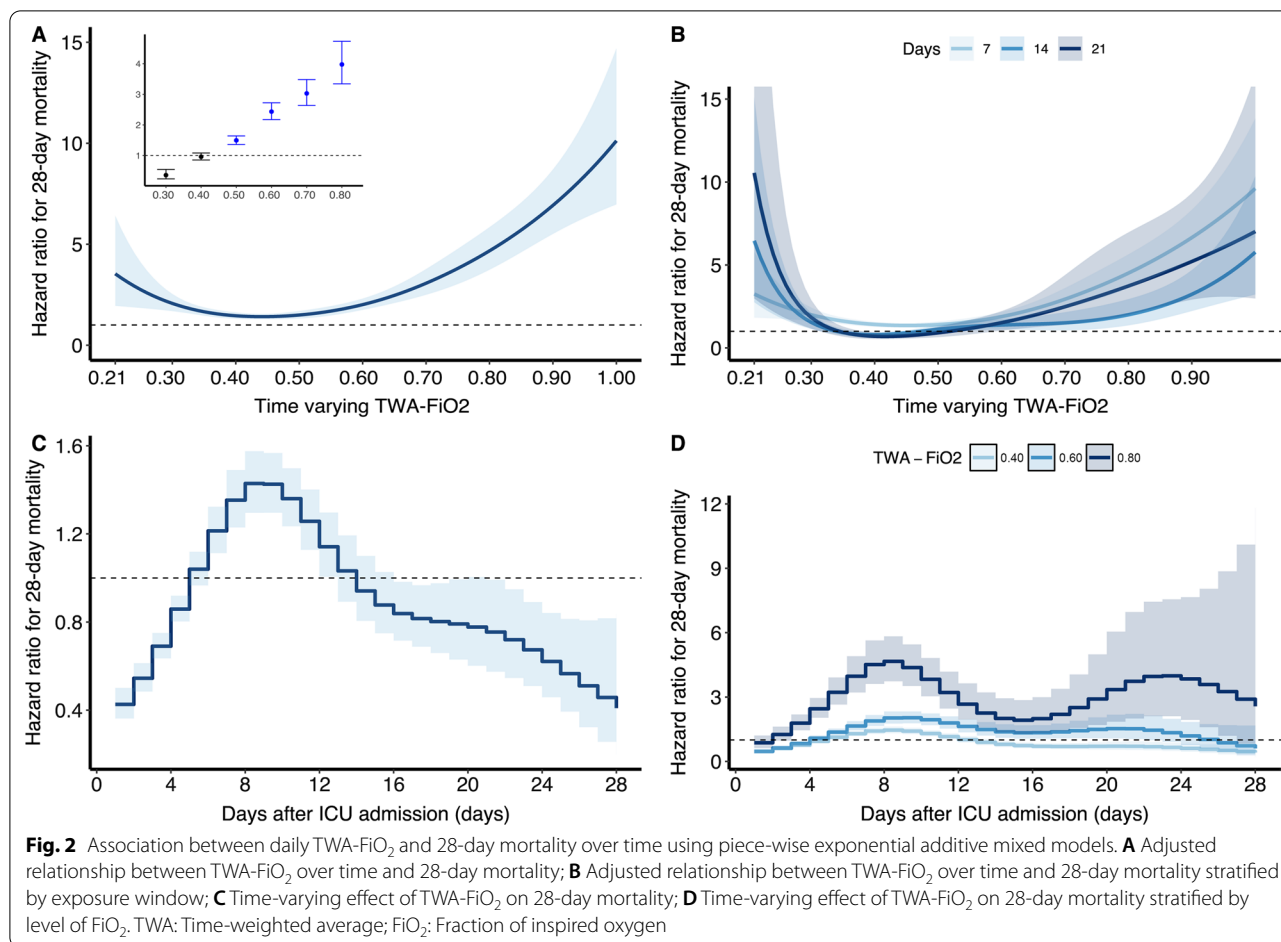**Subgroup analyses and sensitivity analyses**

Subgroup analyses of the association between time-varying hyperoxemia and high FiO$_2$ with 28-day mortality are shown in Fig. 5. Accomplished by the increase in exposure window, the hazard of death for hyperoxemia was decreased, while the hazard of death for high FiO$_2$ was persistent. Two sensitivity analyses were performed. First, after excluding missing values of daily TWA-PaO$_2$ or TWA-FiO$_2$, any exposure to hyperoxemia (HR 1.232, 95% CI 1.059–1.435) or high FiO$_2$ (HR 1.744, 95% CI 1.355–2.245) was associated with an increased risk of 28-day mortality (Additional file 2: Table S6). Second, we changed the follow-up period to ensure all patients were ventilated during follow-up and found that hyperoxemia was associated with a 1.207-fold increase risk of death (HR 1.207, 95% CI 1.098–1.327), while high FiO$_2$

was associated with 1.242-fold increase risk of death (HR 1.242, 95% CI 1.133–1.363) (Additional file 2: Table S7).

Discussion

Time-varying intensity of oxygen exposure, as measured by daily TWA-PaO$_2$ or TWA-FiO$_2$, was associated with the increased 28-day mortality for patients with mechanical ventilation, and the strength of the association manifested predominantly in the early-middle course of illness. Importantly, we observed a cumulative effect of harmful exposure (TWA-PaO$_2 \geq 120$ mmHg or TWA-FiO$_2 \geq 0.5$) over time. The impact of high FiO$_2$ on mortality was partly mediated by hyperoxemia, meanwhile, high FiO$_2$ can also impact mortality directly.

Our findings that oxygen exposure is associated with mortality is generally in accordance with the results of previous studies [6, 18, 19], although some differences exist. First, the assessment period of oxygen exposure was different. Prior retrospective studies exploring the association between oxygen exposure and outcome are limited by using a single measure of PaO$_2$ or FiO$_2$, usually taken within 24 h after ICU admission. It is biologically

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Fig. 2 Association between daily TWA-FiO$_2$ and 28-day mortality over time using piece-wise exponential additive mixed models. **A** Adjusted relationship between TWA-FiO$_2$ over time and 28-day mortality; **B** Adjusted relationship between TWA-FiO$_2$ over time and 28-day mortality stratified by exposure window; **C** Time-varying effect of TWA-FiO$_2$ on 28-day mortality; **D** Time-varying effect of TWA-FiO$_2$ on 28-day mortality stratified by level of FiO$_2$. TWA: Time-weighted average; FiO$_2$: Fraction of inspired oxygen

implausible that a single measure of oxygen exposure could shift outcomes so dramatically. To address this limitation, we evaluated the oxygen exposure throughout the entire course of ICU admission (up to 28 days) and treated daily oxygen exposure as a time-varying exposure in PAMMs to explore the time-varying effects over time. Second, the threshold to define hyperoxemia and high FiO$_2$ varied in previous studies, the threshold ranges from 100 to 200 mmHg for hyperoxemia and 0.5–1.0 for high FiO$_2$ [20, 21], which simply from an empirical or biological standpoint, and remains unclear whether these values could provide the best measure to elucidate harm. From another aspect, we identified the PaO$_2$ and FiO$_2$ threshold above which the risk of 28-day mortality began to increase. Third, in previous observational studies, the multivariable regression model only adjusted for baseline confounders, which could lead to residual confounders, such as the postbaseline time-dependent patient differences. The difference in present study is that we employed PAMMs to account for both baseline and time-dependent confounders.
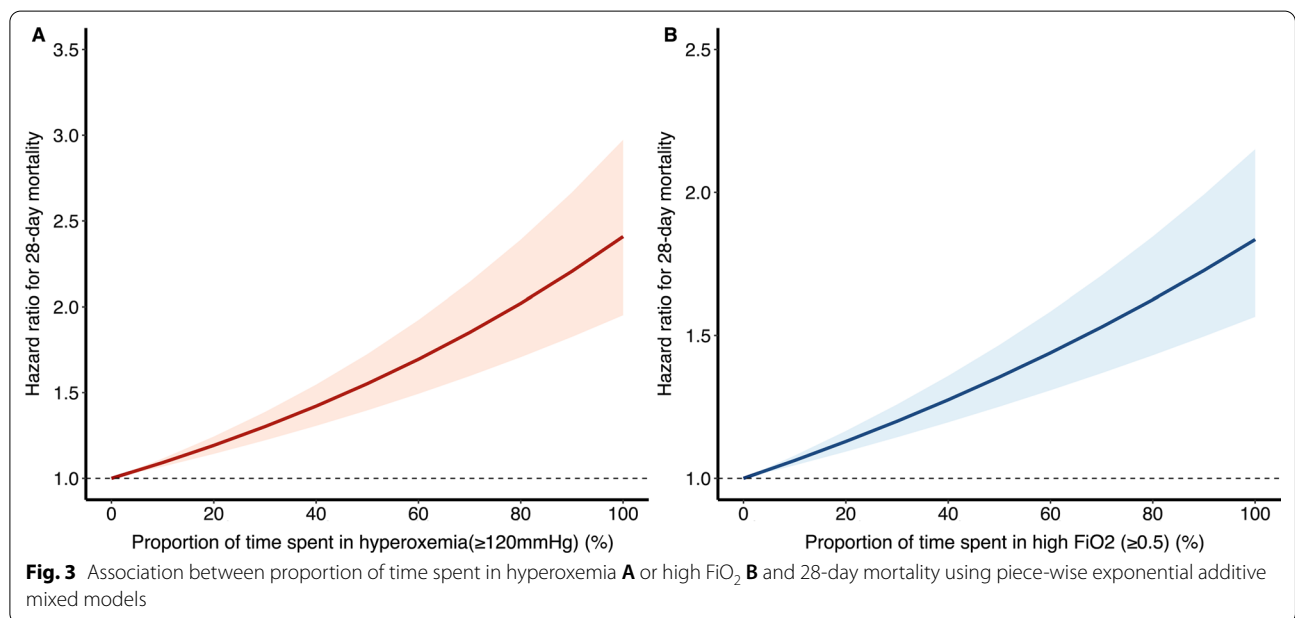
We visualized the longitudinal association between TWA-PaO$_2$ or TWA-FiO$_2$ and 28-day mortality throughout the entire course of ICU admission and suggested that clinicians should pay more attention to PaO$_2$ and FiO$_2$ during the early-middle course of illness (approximately 4–16 days after ICU admission). While for the high level of FiO$_2$, the impact on mortality was persistent over time. Visual inspection showed that the optimum range for PaO$_2$ was approximately 80–120 mmHg, and FiO$_2$ should be kept as low as possible to sustain the target PaO$_2$.

The current study has implications for interpreting recent randomized control trials (RCTs) evaluating the association between conservative oxygen targets and clinical outcomes. The Oxygen-ICU trial [22] found that oxygen supplementation titrated to more conservative oxygen targets (targeting a PaO$_2$ of 70–100 mmHg during the ICU stay) was associated with improved outcomes compared with conventional oxygen targets (allowing a PaO$_2$ up to 150 mmHg during the ICU stay), with no mention about the proportion of patients exposed to hyperoxemia. The LOCO$_2$ trial [23] assigned patients

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Table 2 Effect of time-varying hyperoxemia and high FiO$_2$ on 28-day mortality of 7784 patients with mechanical ventilation using PAMMs
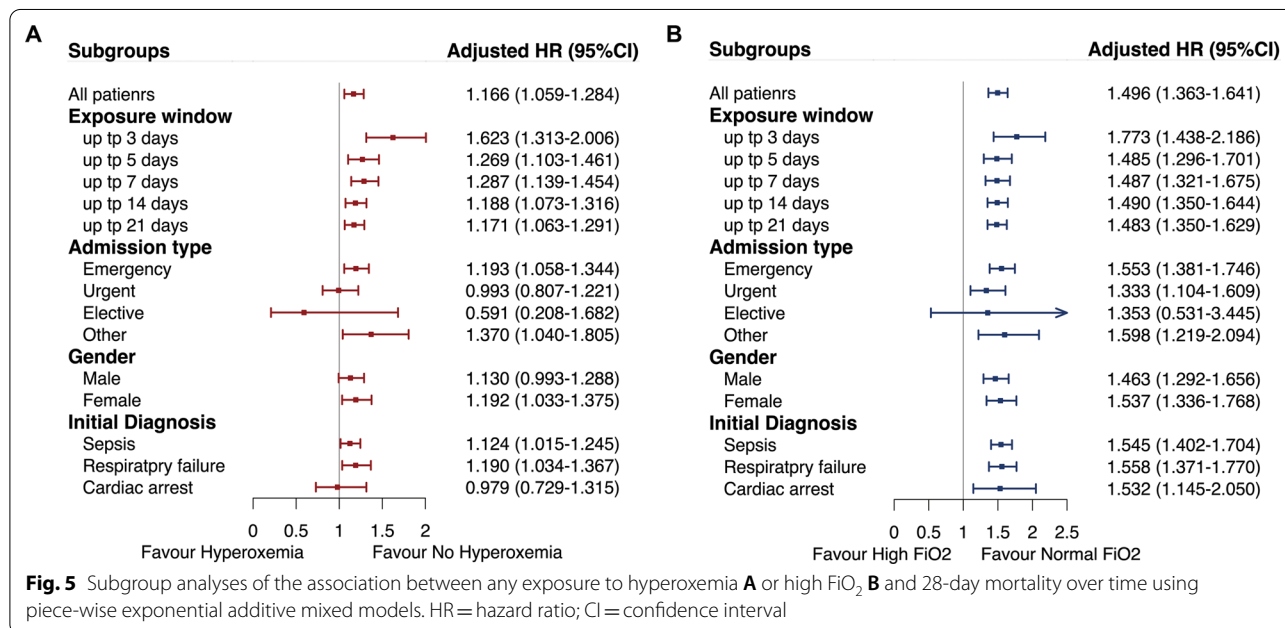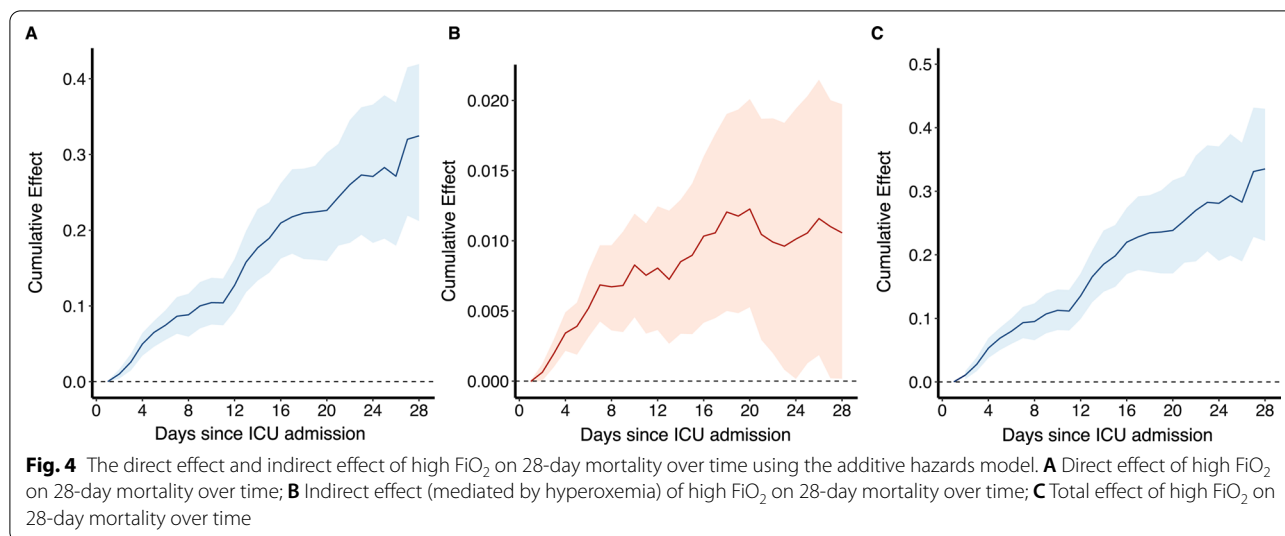
	Exposure to hyperoxemia		Exposure to high FiO$_2$	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Baseline variables				
Age, years	1.018(1.014–1.022)	< 0.001	1.018(1.014–1.022)	< 0.001
Male	0.981 (0.892–1.078)	0.69	0.972 (0.885–1.069)	0.57
Admission type				
Medical	Reference		Reference	
Surgical elective	0.248 (0.158–0.389	< 0.001	0.246 (0.157–0.386)	< 0.001
Surgical urgent	0.846 (0.759–0.943)	0.024	0.834 (0.748–0.929)	< 0.001
Other	0.643 (0.558–0.742)	< 0.001	0.642 (0.557–0.741)	< 0.001
Weight, kg	0.993 (0.990–0.994)	< 0.001	0.992 (0.990–0.994)	< 0.001
Elixhauser comorbidity score	1.033 (1.014–1.052)	< 0.001	1.038 (1.019–1.057)	< 0.001
Time-varying variables				
Receiving IMV	0.417 (0.375–0.463)	< 0.001	0.437 (0.393–0.486)	< 0.001
Use of vasopressor	1.370 (1.223–1.534)	< 0.001	1.380 (1.232–1.546)	< 0.001
SOFA score	1.145 (1.129–1.160)	< 0.001	1.131 (1.116–1.147)	< 0.001
PaCO$_2$, mmHg	1.016 (1.013–1.020)	< 0.001	1.014 (1.010–1.017)	< 0.001
Any hyperoxemia (TWA-PaO$_2 \geq$ 120 mmHg)	1.166 (1.059–1.284)	0.0017	–	–
Any exposure to high FiO$_2$ (TWA-FiO$_2 \geq$ 0.5)	–	–	1.496 (1.363–1.641	< 0.001

PAMMs Piece-wise exponential additive mixed models; *HR* Hazard ratio; *CI* Confidence interval; *IMV* Invasive mechanical ventilation; *SOFA* sequential organ failure assessment; *TWA* Time-weighted average; *PCO$_2$* partial pressure of carbon dioxide; *FiO$_2$* Fraction of inspired oxygen

Fig. 3 Association between proportion of time spent in hyperoxemia **A** or high FiO$_2$ **B** and 28-day mortality using piece-wise exponential additive mixed models

with acute respiratory distress syndrome to receive either conservative oxygen therapy (target PaO$_2$, 50–70 mmHg) or liberal oxygen therapy (target PaO$_2$, 90–105 mmHg) for 7 days and found that conservative oxygen therapy did not increase survival at 28 days, while was associated with mesenteric ischemic events. Recently, a Dutch RCT conducted in ICU patients fulfilling the systemic inflammatory response syndrome criteria found no

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Fig. 4 The direct effect and indirect effect of high FiO$_2$ on 28-day mortality over time using the additive hazards model. **A** Direct effect of high FiO$_2$ on 28-day mortality over time; **B** Indirect effect (mediated by hyperoxemia) of high FiO$_2$ on 28-day mortality over time; **C** Total effect of high FiO$_2$ on 28-day mortality over time

Fig. 5 Subgroup analyses of the association between any exposure to hyperoxemia **A** or high FiO$_2$ **B** and 28-day mortality over time using piece-wise exponential additive mixed models. HR = hazard ratio; CI = confidence interval

significant difference between high-normal (14–18 kPa) and low-normal (targeting a PaO$_2$ of 8–12 kPa) oxygenation targets for non-respiratory organ dysfunction over the first 14 days [24]. The HOT-ICU trial [25] randomly assigned patients with acute hypoxemic respiratory failure to receive oxygen therapy targeting a PaO$_2$ of either 60 mmHg (lower-oxygenation group) or 90 mmHg (higher-oxygenation group) for a maximum of 90 days and declared that a lower-oxygenation target did not result in lower mortality than a higher target at 90 days. These RCTs are unlikely to represent the frequency and persistence of hyperoxemia in clinical practice. In our

research, the median TWA-PaO$_2$ was 130.5 mmHg, and it seems that a more conservative strategy in the early phase of disease would demonstrate a clinical benefit. However, a PaO$_2$ target that is too conservative may expose patients to harmful hypoxemia, as was likely the case in the LOCO$_2$ trial.

Oxygen exposure-induced oxidative stress was time- and dose-dependent [26, 27], and the assessment of cumulative exposure was equally important. We concluded that a time- and dose-dependent exposure to hyperoxemia were both associated with harm, which was consistent with two studies [19, 28] and at odds with one

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prior study. Palmer et al. [29] defined hyperoxemia dose as the area between the PaO_2 time curve and a boundary of 100 mmHg divided by the hours of potential exposure (24, 72, 120, or 168 h) and did not observe a dose–response relationship. The inconsistencies are probably attributable, at least partly, to the different threshold values of hyperoxemia and exposure window used.

Limited data was available regarding the cumulative effect of exposure to high FiO_2 on mortality, which was also restricted by a single measurement or a shorter exposure window [30–32]. According to 73,992 patients undergoing non-cardiothoracic surgery, Staehr-Rye et al. [33] found that high intraoperative FiO_2 (0.79, range 0.64–1.0) was associated in a dose-dependent manner with major respiratory complications and 30-day mortality. In the present study, the cumulative effect of exposure to high FiO_2 (TWA-$FiO_2 \geq 0.5$) on mortality during the entire course of ICU admission was significant. Besides, we also found that the higher FiO_2 could directly impact the mortality, independently from PaO_2, which supports the causal relationship between higher FiO_2 and mortality.

Several limitations to the present study should be considered. First, the design of our study is a retrospective observational study, we considered only segmental measured confounders, and the residual measured confounders and unmeasured confounders cannot be fully included. Second, we included all patients who received mechanical ventilation, which makes the results more generalizable. Consequently, significant heterogeneity might exist between groups [34]. We performed several subgroup analyses based on initial admission diagnosis to account for this limitation. Further research is required to explore the impact of time-varying oxygen exposure on mortality in specific patients. Finally, the MIMIV-IV, like all databases with routinely collected data, comprises records with missing values. However, the results from our primary analysis were robust in sensitivity analyses after excluding the missing data.

Conclusion

In conclusion, PaO_2 and FiO_2 should be carefully monitored in patients with mechanical ventilation, especially during the early-middle course after ICU admission. Cumulative exposure to higher intensities of oxygen exposure was associated with an increased risk of death. Additionally, high FiO_2 can impact mortality directly, independently from hyperoxemia.

Abbreviations

ICU: Intensive care units; PaO_2: Arterial oxygen tension; FiO_2: Fraction of inspired oxygen; MIMIC-IV: Medical information mart for intensive care IV; ECMO: Extracorporeal membrane oxygenation; SOFA: Sequential organ failure assessment; SAPS II: Simplified acute physiology score II; OASIS: Oxford acute severity of illness score; TWA: Time-weighted average; VFDs: Ventilation-free days; PAMMs: Piece-wise exponential additive mixed models; MICE: Multiple imputations by chained equation; CMA: Causal mediation analysis; RCTs: Randomized control trials.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-022-04114-w.

Additional file 1. : Codes for piece-wise exponential additive mixed models

Additional file 2. Table S1: Baseline characteristics and outcomes of patients stratified by TWA-PaO2 on Day 1; **Table S2**: Baseline characteristics and outcomes of patients stratified by TWA-FiO_2 on Day 1; **Table S3**: Effect of time-varying TWA-PaO_2 and TWA-FiO_2 on 28-day mortality of 7784 patients with mechanical ventilation; **Table S4**: Effect of time spent with hyperoxemia and high FiO_2 on 28-day mortality of 7784 patients with mechanical ventilation; **Table S5**: Effect of cumulative exposure of hyperoxemia and high FiO_2 on 28-day mortality of 7784 patients with mechanical ventilation; **Table S6**: Effect of time-varying hyperoxemia and high FiO_2 on 28-day mortality after excluding missing data of daily TWA-PaO_2 or TWA-FiO_2; **Table S7**: Effect of time-varying hyperoxemia and high FiO_2 on 28-day mortality in patients with mechanical ventilation, patients were followed up from inclusion until death, liberated from mechanical ventilation, ICU discharge, or 28 days in the ICU, whichever occurred first; **Figure S1**: Study flow diagram in present study. **Figure S2**: Time-varying effect of TWA-PaO_2 (A) or TWA-FiO_2 (B) on 28-day mortality

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Availability of data and materials
The datasets presented in the current study are available in the MIMIC-IV database (https://physionet.org/content/mimiciv/2.0/).

Declarations

Ethic approval and consent to participate
The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA), and consent was obtained for the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived for this manuscript.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of General Surgery, Suzhou Science & Technology Town Hospital, Suzhou 215153, Jiangsu, People's Republic of China. [2]Department of Critical Care Medicine, Cancer Hospital of Shantou University Medical College, No.7 Raoping Road, Shantou 515100, Guangdong, People's Republic of China.

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[3]Department of Critical Care Medicine, The First Affiliated Hospital of Soochow University, Soochow University, No. 899 Pinghai Road, Suzhou 215000, People's Republic of China.

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