Time spent in oxygen saturation 95–99% is associated with reduced mortality in critically ill patients with mechanical ventilation

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To the Editor:

The administration of supplemental oxygen is one of the ubiquitous interventions in the intensive care unit (ICU) and can be life-saving for mechanically ventilated patients [1]. However, excessive oxygen could be detrimental. Recently, several studies comparing the effect of conservative and liberal oxygen therapy for critically ill patients did not achieve consistent results [2, 3]. Furthermore, in patients with acute respiratory distress syndrome (ARDS), conservative oxygen therapy even had a signal of increased mortality and mesenteric ischemia [4]. Of note, the target oxygen levels in these studies were not the same. It is of paramount importance to elucidate oxygen targets to guide future research. In the present study, with a big database, we aimed to evaluate the association of the proportion of time within arterial oxygen saturation (SpO2) with hospital mortality in an ICU population with mechanical ventilation (MV).

This study used data stored in the eICU (eicu-crd.mit.edu) database [5]. Adult patients admitted to ICU for the first time with MV during the first 24 h were included. The main exposure was SpO2, which was generally interfaced from bedside vital sign monitors as the 5-min median value. Thirteen categories of SpO2 were generated, which were ≤88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, and 100%. The proportion of time spent (PTS) in each of the predefined categories ranged from 0 to 100%. PTS was examined as both a continuous and categorical variable. The primary outcome was hospital mortality. Multivariable logistic regression models including PTS within each of these SpO2 categories along with the confounders were used to analyze the association of PTS-SpO2 with mortality outcome.

A total of 25,669 patients from 186 hospitals were included (Table 1), including 21,326 (83%) survivors and 4343 (17%) non-survivors. The median fraction of inspired oxygen was 45% (IQR, 43~60%) and the median duration of MV was 3 days (IQR, 2~5 days). After adjusted for confounders, PTS-SpO2 of ≤88%, 89%, 90%, 91%, 92%, 93%, and 100% were associated with a higher odds ratio for hospital mortality; PTS-SpO2 of 95%, 96%, 97%, 98%, and 99% were associated with a lower odds ratio; and PTS-SpO2 of 94% was not associated with hospital mortality (Fig. 1a). Based on the results, SpO2 was divided into three categories (≤94%, 95–99%, and 100%). PTS-SpO2 within categories of ≤94% (p < 0.001) and 100% (p < 0.001) were associated with a higher risk of hospital mortality, whereas an inverse trend was observed between PTS-SpO2 of 95–99% (p < 0.001) and hospital mortality (Fig. 1b).

The result of the present study was partially consistent with the British Thoracic Society guideline, which recommended the target of SpO2 94–98% [6]. In addition, the result could partly account for the discrepancy of the summarized time in each different SpO2 category divided by total time. Thus, during the first 24 h, patients had SpO2 values that fell in the 13 categories and for each patient PTS in each of the predefined categories ranged from 0 to 100%. PTS was examined as both a continuous and categorical variable. The primary outcome was hospital mortality. Multivariable logistic regression models including PTS within each of these SpO2 categories along with the confounders were used to analyze the association of PTS-SpO2 with mortality outcome.

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Table 1 Characteristics of study patients between survivors and non-survivors

| Variables                        | Total (n = 25,669) | Survivors (n = 21,326) | Non-survivors (n = 4343) | p value |
|----------------------------------|--------------------|------------------------|--------------------------|---------|
| Age, years (median, [IQR])       | 65 (54, 75)        | 65 (53, 74)            | 70 (58, 79)              | < 0.001 |
| Gender, male (n (%))             | 13,933 (54)        | 11,561 (54)            | 2372 (55)                | 0.636   |
| BMI (median, [IQR])              | 28.3 (23.9, 34.4)  | 28.5 (24.1, 34.6)      | 27.4 (23.2, 33.1)        | < 0.001 |
| Comorbidities (n (%))            |                    |                        |                          |         |
| Hypertension                     | 13,533 (53)        | 11,216 (53)            | 2317 (53)                | 0.371   |
| Diabetes mellitus                | 6149 (24)          | 5173 (24)              | 976 (22)                 | 0.013   |
| COPD                             | 5870 (23)          | 4919 (23)              | 951 (22)                 | 0.099   |
| Heart failure                    | 5011 (20)          | 4110 (19)              | 901 (21)                 | 0.027   |
| Cirrhosis                        | 443 (2)            | 335 (2)                | 108 (2)                  | < 0.001 |
| Cancer                           | 411 (2)            | 269 (1)                | 142 (3)                  | < 0.001 |
| Chronic renal failure            | 3585 (14)          | 2871 (13)              | 714 (16)                 | < 0.001 |
| ICU types (n (%))                |                    |                        |                          | < 0.001 |
| Med-Surg ICU                     | 13,737 (54)        | 11,477 (54)            | 2260 (52)                |         |
| Cardiac ICU                      | 1636 (6)           | 1216 (6)               | 420 (10)                 |         |
| CCU-CTICU                        | 2162 (8)           | 1843 (9)               | 319 (7)                  |         |
| CSICU                            | 889 (3)            | 768 (4)                | 121 (3)                  |         |
| CTICU                            | 1179 (5)           | 1083 (5)               | 96 (2)                   |         |
| MICU                             | 2587 (10)          | 2088 (10)              | 499 (11)                 |         |
| Neuro ICU                        | 1643 (6)           | 1295 (6)               | 348 (8)                  |         |
| SICU                             | 1836 (7)           | 1556 (7)               | 280 (6)                  |         |
| Admission diagnosis (n (%))      |                    |                        |                          | < 0.001 |
| Respiratory                      | 5910 (23)          | 5106 (24)              | 804 (19)                 |         |
| Sepsis                           | 3660 (14)          | 2856 (13)              | 804 (19)                 |         |
| Cardiac surgery                  | 3035 (12)          | 2847 (14)              | 88 (2)                   |         |
| Non-cardiac surgery              | 2495 (10)          | 2207 (10)              | 288 (7)                  |         |
| Neurological                     | 2560 (10)          | 1985 (9)               | 575 (13)                 |         |
| Cardiovascular                   | 2079 (8)           | 1783 (8)               | 296 (7)                  |         |
| Cardiac arrest                   | 2143 (8)           | 1149 (5)               | 994 (23)                 |         |
| Trauma                           | 1179 (5)           | 986 (5)                | 193 (4)                  |         |
| Gastrointestinal                 | 461 (2)            | 378 (2)                | 83 (2)                   |         |
| Others                           | 2147 (8)           | 1929 (9)               | 218 (5)                  |         |
| TWM-PaO2, mmHg (n (%))           |                    |                        |                          | < 0.001 |
| < 60                             | 622 (2)            | 480 (2)                | 142 (3)                  |         |
| 60–120                           | 10,593 (41)        | 8832 (41)              | 1761 (41)                |         |
| 120–300                          | 8226 (32)          | 6691 (31)              | 1535 (35)                |         |
| > 300                            | 579 (2)            | 453 (2)                | 126 (3)                  |         |
| Missing (n (%))                  | 5649 (22)          | 4870 (23)              | 779 (18)                 |         |
| TWM-PaCO2, mmHg (n (%))          |                    |                        |                          | < 0.001 |
| < 35                             | 4420 (17)          | 3336 (16)              | 1084 (25)                |         |
| 35–45                            | 9555 (37)          | 8041 (38)              | 1514 (33)                |         |
| > 45                             | 5849 (23)          | 4928 (23)              | 921 (21)                 |         |
| Missing (n (%))                  | 5845 (23)          | 5021 (24)              | 824 (19)                 |         |
| TWM-pH (n (%))                   |                    |                        |                          | < 0.001 |
| < 7.35                           | 6868 (27)          | 5311 (25)              | 1557 (36)                |         |
recent clinical trials of oxygen therapy, which adopted different target oxygen levels [2–4]. Despite several limitations to our study (e.g., retrospective design, potential residual confounders, unvalidated data from monitors, relatively short study period, lack of mode of MV, and missing data), our study provided observational evidence for a \( \text{SpO}_2 \) target range of 95–99% with real-world data. Further studies are warranted to validate the particular target.

In conclusion, the proportion of time spent in oxygen saturation 95–99% is associated with reduced mortality in critically ill patients with mechanical ventilation. These findings may have implications for the design of future trials of oxygen therapy.

Table 1 Characteristics of study patients between survivors and non-survivors (Continued)

| Variables          | Total (n = 25, 669) | Survivors (n = 21, 326) | Non-survivors (n = 4343) | \( p \) value |
|--------------------|---------------------|--------------------------|--------------------------|--------------|
| 7.35–7.45          | 10,085 (39)         | 8635 (40)                | 1450 (33)                |              |
| > 7.45             | 2626 (10)           | 2136 (10)                | 490 (11)                 |              |
| Missing (n (%))    | 6090 (24)           | 5244 (25)                | 846 (19)                 |              |
| TWM-Fio2, % (median, [IQR]) | 45 (43, 60)         | 45 (42, 59)              | 50 (45, 75)              | < 0.001      |
| APACHE IV (median, [IQR]) | 68 (50, 89)         | 63 (48, 83)              | 92 (72, 115)             | < 0.001      |
| SOFA (median, [IQR]) | 6 (4, 8)            | 6 (4, 8)                 | 8 (6, 11)                | < 0.001      |
| Vasopressors (n (%)) | 5734 (22)           | 4135 (19)                | 1599 (37)                | < 0.001      |
| Dialysis (n (%))   | 976 (4)             | 802 (4)                  | 174 (4)                  | 0.466        |
| Ventilation days (n (%)) | 3 (2, 5)           | 3 (2, 4)                 | 4 (2, 7)                 | < 0.001      |

IQR interquartile range, BMI body mass index, COPD chronic obstructive pulmonary disease, ICU intensive care unit, CCU coronary care unit, CTICU cardiothoracic ICU, CSCU cardiac surgery ICU, MICU medical ICU, SICU surgical ICU, TWM time-weighted mean, \( \text{SpO}_2 \) peripheral oxygen saturation, \( \text{PaO}_2 \) partial pressure of arterial oxygen, \( \text{PaCO}_2 \) partial pressure of arterial carbon dioxide, \( \text{FiO}_2 \) fraction of inspired oxygen, APACHE Acute Physiology and Chronic Health Evaluation, SOFA sequential organ failure assessment

Fig. 1 a Adjusted odds ratio for hospital mortality according to different \( \text{SpO}_2 \) categories. The proportion of time spent in thirteen different \( \text{SpO}_2 \) categories (≤ 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, and 100%) was considered as a continuous variable, ranging from 0 to 100%, and was included in separate multivariable regression models along with the confounders. In total, 13 models were created. The adjusted odds ratio for each \( \text{SpO}_2 \) category and 95% confidence intervals (error bars) were calculated after adjusting for age, body mass index (obesity or non-obesity), admission diagnosis, comorbidities (diabetes mellitus, cancer), time-weighted mean \( \text{FiO}_2 \), time-weighted mean pH, time-weighted mean \( \text{PaCO}_2 \), sequential organ failure assessment score (not including the respiratory part), and use of dialysis. An odds ratio is calculated per 5% increase in time in each given category. \( \text{SpO}_2 \), arterial oxygen saturation; \( \text{FiO}_2 \), fraction of inspired oxygen; \( \text{PaCO}_2 \), partial pressure of arterial carbon dioxide. b Observed hospital mortality of four predefined time ranges (0–25%, 25–50%, 50–75%, and 75–100%) spent in three different \( \text{SpO}_2 \) categories (≤ 94%, 95–99%, and 100%). Figures on each histogram column represented the crude hospital mortality.
Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: Acute respiratory distress syndrome; FiO₂: Fraction of inspired oxygen; ICU: Intensive care unit; IQR: Interquartile range; MV: Mechanical ventilation; OR: Odds ratio; PaO₂: Partial pressure of oxygen; PaCO₂: Partial pressure of arterial carbon dioxide; PTS-SpO₂: Proportion of time spent in SpO₂; SOFA: Sequential organ failure assessment; SpO₂: Arterial oxygen saturation; TWMP: Time-weighted mean.

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None.

Authors' contributions

DW and JX conceived this study. DW extracted the data. DW, ZM, and GZ designed and performed the statistical analyses. DW wrote the first draft of the manuscript. GZ and JX reviewed and modified the final manuscript. All authors read, critically reviewed, and approved the final manuscript.

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Availability of data and materials

Data analyzed during the present study are currently stored in the eICU database (eicu-crd.mit.edu). After completing the required training course (the Collaborative Institutional Training Initiative) and requesting access to the eICU Collaborative Research Database, researchers can seek to use the database.

Ethics approval and consent to participate

The schema of eICU was established in collaboration with Privacert (Cambridge, MA), who certified the re-identification risk as meeting safe harbor standards (HIPAA Certification no. 1031219-2). All tables in eICU were deidentified to meet the safe harbor provision of the US HIPAA. Due to the HIPAA compliant de-identification in this database, our IRB requirement was waived.

Consent for publication

Not applicable.

Competing interests

None of the authors has declared a conflict of interest.

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