BMJ Open Respiratory Research

Hyperoxia for sepsis and development of acute lung injury with increased mortality

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To cite: Yamamoto R, Fujishima S, Yamakawa K, *et al*. Hyperoxia for sepsis and development of acute lung injury with increased mortality. *BMJ Open Respir Res* 2023;**10**:e001968. doi:10.1136/bmjresp-2023-001968

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjresp-2023-001968).

Received 18 July 2023
Accepted 30 November 2023

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ABSTRACT

Background Supraphysiological oxygen administration causes unfavourable clinical outcomes in various diseases. This study aimed to determine whether hyperoxia would be associated with increased mortality in patients with severe infection.

Methods A post-hoc analysis of a nationwide multicentre prospective observational study on sepsis (SPICE Study) was conducted, including adult patients admitted to the intensive care unit with available arterial partial pressure of oxygen (PaO_2) at the treatment initiation for severe infection. Hyperoxia was defined as a PaO_2 level of ≥300 mm Hg and in-hospital mortality was compared between patients with and without hyperoxia.

Results Of the 563 patients eligible for the study, 49 had hyperoxia at treatment initiation for severe infection. The in-hospital all-cause mortality rates of patients with and without hyperoxia were 14 (29.2%) and 90 (17.6%), respectively. Inverse probability weighting analyses with propensity scores revealed the association between hyperoxia and increased in-hospital mortality rate (28.8% vs 18.8%; adjusted OR 1.75 (1.03 to 2.97); p=0.038), adjusting for patient demographics, comorbidities, site of infection, severity of infection, haemodynamic and respiratory status, laboratory data and location of patient at infection development. Acute lung injury developed more frequently in patients with hyperoxia on the following days after infection treatment, whereas sepsis-related mortality was comparable regardless of hyperoxia exposure.

Conclusion Hyperoxia with PaO_2 ≥300 mm Hg at treatment initiation of severe infection was associated with an increased in-hospital mortality rate in patients requiring intensive care. The amount of oxygen to administer to patients with severe infection should be carefully determined.

Trial registration number University Hospital Medical Information Network Clinical Trial Registry (UMIN000027452).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hyperoxia exposure is associated with adverse clinical events in various diseases.

WHAT THIS STUDY ADDS

⇒ A nationwide retrospective observational study on 563 patients with severe infection requiring intensive care showed the association between hyperoxia (arterial partial pressure of oxygen (PaO_2) ≥300 mm Hg) at treatment initiation and higher in-hospital mortality, as well as higher incidence of acute lung injury, compared with no hyperoxia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Restriction of oxygen administration to avoid hyperoxia during resuscitation should be carefully considered in daily practice, and the appropriate PaO_2 for patients with sepsis should be validated in future studies.

INTRODUCTION

Oxygen administration is a fundamental treatment for patients with critical illnesses.[1 2] However, a supraphysiological amount of oxygen in the blood and/or tissue has been related to unfavourable clinical outcomes in various diseases, including postcardiac arrest syndrome, accidental hypothermia, traumatic brain injury and postcardiac surgery.[3–6] A recent randomised controlled trial (RCT) on patients receiving mechanical ventilation showed that oxygen titration targeting at 70–100 mm Hg of arterial partial pressure of oxygen (PaO_2) reduced the mortality rate in the intensive care unit (ICU).[7]

The pathophysiology behind the harmful effects of hyperoxia has been investigated, and oxygen toxicity in the brain and pulmonary tissues affects critically ill patients.[8–11] Cerebral vasoconstriction and mitochondrial dysfunction were reportedly due to hyperoxia in the injured brain, which paradoxically decreases oxygen delivery to the cerebral tissues.[8 10] Additionally, pulmonary vasoconstriction with alveolar damages by unnecessary reactive oxygen species was observed, particularly in patients experiencing hyperoxia under mechanical ventilation.[9 11] Furthermore, hyperoxia-induced acute lung injury (ALI) was another adverse effect caused by

excessive oxygen, which leads to unfavourable clinical outcomes.[9 11]

Under critical illness such as sepsis, impaired oxygen utilisation at the intracellular mitochondria and reactive oxygen species production were observed.[12–14] Although such toxic oxygen derivatives were considered to lead to several organ dysfunctions, appropriate tissue oxygen tension during such cytopathic hypoxia remains unclear. Subgroup analyses of RCTs on conservative oxygen usage during mechanical ventilation reported conflicting results on the harmful effects of hyperoxia among patients with sepsis.[15 16] Moreover, several post-hoc analyses targeting on the association between PaO_2 and mortality due to sepsis also showed various effects of hyperoxia from benefits to harms.[17 18]

Accordingly, to eventually elucidate an optimal PaO_2 target for patients with sepsis, this study conducted a post-hoc analysis on a multicentre prospective observational study on ICU patients with severe infections. We aimed to determine whether hyperoxia would be associated with unfavourable clinical outcomes in these patients. We hypothesise that hyperoxia at treatment initiation for severe infection in the ICU was associated with increased in-hospital mortality rate post-ICU admission.

METHODS

Study design

This is a post-hoc analysis of a nationwide multicentre prospective observational study that was conducted by the Japanese Association for Acute Medicine Sepsis Prognostication in Intensive Care Unit and Emergency Room (SPICE-ICU) from December 2017 to May 2018.[19] The SPICE-ICU Study included patients with newly developed infectious diseases requiring ICU admission at 22 participating tertiary care centres and was registered at the University Hospital Medical Information Network Clinical Trial Registry on 22 May 2017 (UMIN-CTR ID: UMIN000027452) prior to study initiation. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

The SPICE-ICU Study enrolled consecutive patients aged ≥16 years, with newly developed severe infectious diseases requiring intensive care with the aim to describe the characteristics of patients fulfilling the existing sepsis definitions (eg, sepsis-3 and sepsis-2).[20 21] Although the SPICE-ICU Study screened all patients admitted to or stayed in the ICU with newly developed suspected infections rather than only those who met any existing criteria for sepsis, 619 of 652 (94.9%) met either sepsis-3 or severe sepsis at sepsis-2 criteria. Suspected infection at screening was defined as receiving newly initiated antibiotics with obtainment of culture specimen or imaging tests for infection identification, and data retrieval was initiated immediately after the screening. At screening, patients could be located at the emergency department (ED), regular ward or ICU, but those transferred from other hospitals were not included. Patient inclusion was confirmed when any infectious diseases were finally diagnosed regardless of presence of bacteraemia or organs infected.

Study subjects

Data from the SPICE-ICU Study (2017–2018) were reviewed retrospectively. Patients with severe infections were included if they (1) were ≥16 years old, (2) had any infectious diseases, (3) were admitted to the ICU and (4) had available PaO_2 data obtained at the time of study inclusion (treatment initiation for severe infection). Patients diagnosed with acute respiratory distress syndrome (ARDS) during ICU admission were excluded because previous studies have already suggested that hyperoxia can be harmful and should be avoided in patients with ARDS.[22]

Methods

Patient data for the SPICE-ICU Study were prospectively collected and entered into an online data collection portal at each hospital. Age, sex, body mass index, Charlson Comorbidity Index, Clinical Frailty Scale (CFS), infection site, place of patient before ICU admission, vital signs on ICU admission, laboratory investigations and arterial blood gas assay with fraction of inspired oxygen (FiO_2) obtained at the diagnosis of severe infection (treatment initiation) and on following days until day 4, presence of bacteraemia, Sequential Organ Failure Assessment (SOFA) score during study inclusion and mechanical ventilation use were all recorded. The timing of diagnosis of severe infection was clinically determined by a treating physician. Additionally, data on length of ICU and hospital stay, duration of ventilator use, survival status at discharge, sepsis-related death and new diagnosis of ALI after ICU admission were obtained.

Severe sepsis at sepsis-2 was defined as having a suspected infection site, ≥2 systemic inflammatory response syndrome criteria and ≥1 organ dysfunction. Sepsis-3 was defined as having a suspected infection site and organ dysfunction (an acute change in the total SOFA score of ≥2 points consequent to the infection). Septic shock was defined according to the sepsis-3 or sepsis-2 definitions. High frailty was defined as CFS ≥5.[23] Suspected infection source was recorded during treatment initiation for severe infection and the diagnosis of the infection site was recorded at discharge. Based on previous literature on hyperoxia in other diseases, hyperoxia was defined as PaO_2 of ≥300 mm Hg.[2 4 24] Hyperoxia during treatment initiation for severe infection was defined as hyperoxia at ICU admission. The database lacked detailed indications for high amount of oxygen administration and haemodynamic status before, during and after oxygen administration.

The primary outcome was in-hospital all-cause mortality after inclusion. Secondary outcomes included sepsis-related mortality (failure to resuscitation from sepsis), ICU-free, hospital-free and ventilator-free days to 28 days

after inclusion, and incidence of newly developed ALI after inclusion.

Analysis

Inverse probability weighting (IPW) using propensity scores was conducted to adjust for background characteristics between patients with and without hyperoxia.[25 26] The propensity score for weighting was developed using a logistic regression model to estimate the probability of hyperoxia exposure. Based on previous studies, relevant covariates were carefully selected from known or potential predictors for receiving supraphysiological amounts of oxygen and predicting clinical outcomes in patients with sepsis or severe infections.[19 21 27–29] These covariates included age, sex, Charlson Comorbidity Index, high frailty, patient location during infection development (ED, ward or ICU), and vital signs (Glasgow Coma Scale (GCS), systolic blood pressure (SBP) and respiratory rate), lactate and invasive mechanical ventilation use during treatment initiation for severe infection. SOFA score and PaO_2/FiO_2 ratio (PF ratio) were also included as covariates because they are considered survival predictors in sepsis and would be related to the amount of oxygen administered.[25 29] Patients with missing covariates were excluded from the propensity score calculation. The discrimination ability of the propensity score was evaluated using the c-statistic.[26] The weight was calculated as the inverse of the propensity score of hyperoxia exposure. To avoid extreme weight, patients with a propensity score of ≤0.05 or ≥0.95 were excluded from the IPW analyses. The primary outcome was compared using the X^2 test, and secondary outcomes were compared using ORs or Hodges-Lehmann estimator.[26]

Four sensitivity analyses were performed to validate the primary results. First, to confirm that results were not dependent on the propensity score calculation, generalised estimating equation analysis with the logit link function was used to adjust for patient backgrounds and differences in pre-sepsis conditions among locations at infection development.[30] Second, multivariate logistic regression was conducted with covariates selected from those for propensity score calculation. Third, IPW was conducted with further restriction on the propensity score to minimise the effects of overweighting.[25 26] Finally, the primary analysis was repeated only on patients meeting either the sepsis-3 or severe sepsis at sepsis-2 criteria to validate that the results were consistent across pre-existing criteria.

Additionally, restricted cubic spline curves for estimating in-hospital mortality by PaO_2 at treatment initiation for severe infection in the ICU were drawn, in which a generalised additive model was adopted using the same covariates for propensity score calculation. Then, any PaO_2 thresholds affecting the clinical outcomes of patients with sepsis were explored.

Subgroup analyses were performed to analyse the relationships between hyperoxia, clinical characteristics and in-hospital mortality. Targeted subgroups were selected based on previous research on the clinical outcomes of patients with sepsis. The IPW analyses on the primary outcome were repeated in patient subgroups stratified by age (<65 vs ≥65 years); presence of chronic cardiopulmonary diseases including congestive heart failure, coronary artery disease and chronic lung disease; confirmed infection site (pulmonary vs extrapulmonary) and presence of septic shock. Subgroup analyses were also conducted on patients without hypoxia, defined as having PaO_2 of <60 mm Hg.

Descriptive statistics are presented as a median (IQR) or a number (percentage). The results were presented with standardised difference and 95% CI. The balance of covariates before and after weighting was evaluated with a standardised difference, with <0.1 considered insignificant.[25] The hypothesis was tested only on the primary outcome, with a two-sided alpha threshold of 0.05 considered significant. All statistical analyses were conducted using the IBM SPSS for Windows V.29.0 (IBM Corp) and R V.4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

Of the 652 patients with severe infection in the SPICE-ICU Study, 563 had available PaO_2 data at treatment initiation for severe infection and were not diagnosed with ARDS at infection development; therefore, they were eligible for this study (online supplemental figure 1).

Altogether, 49 patients (8.7%) had hyperoxia with PaO_2 of ≥300 mm Hg at treatment initiation for severe infection in the ICU. The patient characteristics are shown in table 1. The median PaO_2 levels were 356 and 95 mm Hg in patients with and without hyperoxia, respectively. Patients with hyperoxia were older and had higher FiO_2, PF ratio and SOFA score at treatment initiation for severe infection, as well as lower GCS and SBP at infection development than those without hyperoxia. Furthermore, a higher proportion of patients with hyperoxia had gastrointestinal/hepatobiliary/pancreatic infection, developed septic shock and received invasive mechanical ventilation.

A propensity model for hyperoxia exposure was developed, and a discrimination power was calculated, yielding a c-statistic of 0.813 (0.743–0.883). No patient with hyperoxia and 12 patients without hyperoxia were excluded from the IPW analyses due to missing covariates for propensity score calculation. Table 1 shows the patient characteristics after IPW with standardised differences, where differences in covariates such as patient demographics, comorbidities, severity of sepsis, respiratory status, vital signs and laboratory data at treatment initiation for severe infection were successfully attenuated using the propensity score (standardised difference <0.1).

Table 1 Characteristics of patients with sepsis

	Before IPW			After IPW		
	Hyperoxia	**No hyperoxia**	**Standardised difference**	**Hyperoxia**	**No hyperoxia**	**Standardised difference**
Case	49	514				
Confirmed sepsis*	49 (100%)	491 (95.9%)				
Oxygenation, median (IQR)						
PaO_2, mm Hg	356 (322–441)	95 (74–140)	3.789	349 (319–399)	156 (111–190)	3.293
FiO_2	1.0 (0.9–1.0)	0.4 (0.3–0.6)	0.254	1.0 (0.9–1.0)	0.4 (0.2–0.5)	3.929
PF ratio, mm Hg	397 (343–521)	256 (161–374)	1.023	368 (334–430)	349 (350–461)	0.071
Demographics						
Age, years, median (IQR)	76 (65–83)	72 (60–82)	0.207	77 (64–81)	75 (64–83)	0.069
Sex, male, n (%)	26 (53.1)	296 (57.6)	0.096	76 (51.0)	85 (51.2)	0.004
Body mass index, median (IQR)	21 (18–24)	22 (19–25)	0.137	21 (17–24)	21 (19–23)	0.040
Charlson Comorbidity Index, median (IQR)	1 (0–3)	1 (0–3)	0.056	1 (1–3)	1 (0–3)	0.004
High frailty, CFS ≥5, n (%)	23 (46.9)	151 (29.5)	0.368	69 (46.3)	73 (44.0)	0.047
Source of infection—suspected, n (%)						
CNS/head/neck	1 (2.0)	17 (3.3)	0.079	4 (2.7)	6 (3.6)	0.053
GI/hepatobiliary/pancreas	11 (22.4)	69 (13.4)	0.237	25 (16.8)	29 (17.5)	0.018
Urinary tract	11 (22.4)	101 (19.6)	0.069	51 (34.2)	57 (34.3)	0.002
Soft tissue	3 (6.1)	68 (13.2)	0.242	9 (6.0)	13 (7.8)	0.071
Respiratory†	15 (30.6)	180 (35.0)	0.094	32 (21.5)	33 (19.9)	0.039
Unknown	8 (16.3)	75 (14.6)	0.048	28 (18.8)	26 (15.7)	0.083
Vital signs on ICU admission, median (IQR)						
Glasgow Coma Scale	7 (3–12)	13 (8–15)	0.690	11 (6–14)	10 (6–14)	0.001
Blood pressure—systolic, mm Hg	95 (78–115)	109 (87–132)	0.411	106 (85–116)	103 (82–121)	0.004
Respiratory rate, /min	24 (19–30)	23 (18–29)	0.090	22 (19–28)	23 (19–29)	0.053
Body temperature, °C	36.8 (36.2–38.1)	37.3 (36.5–38.5)	0.177	37.1 (36.3–38.8)	37.5 (36.5–38.3)	0.092
Laboratory, median (IQR)						
Lactate, mmol/L	3.3 (1.7–6.0)	2.6 (1.4–4.3)	0.012	2.6 (1.7–4.9)	2.7 (1.3–4.8)	0.010
White cell count, 10^9/L	11.3 (4.1–18.1)	11.6 (6.8–16.5)	0.118	12.3 (5.3–16.2)	11.0 (7.3–15.9)	0.066
Haematocrit, L/L	0.33 (0.29–0.40)	0.35 (0.29–0.40)	0.106	0.33 (0.29–0.38)	0.34 (0.29–0.41)	0.092
Creatinine, mg/dL	1.6 (0.9–3.1)	1.4 (0.8–2.5)	0.033	2.0 (1.1–3.6)	1.6 (0.9–2.9)	0.064
Severity of sepsis						
Place of diagnosis, at ER, n (%)	25 (53.1)	284 (55.3)	0.048	81 (54.4)	92 (55.4)	0.021
SOFA score, median (IQR)	8 (5–13)	7 (4–10)	0.500	8 (5–11)	7 (5–10)	0.000
No bacteraemia, n (%)	20 (55.6)	273 (62.9)	0.150	68 (45.6)	72 (43.4)	0.079
Septic shock, n (%)	13 (26.5)	80 (15.6)	0.271	40 (26.7)	43 (25.9)	0.021
Invasive mechanical ventilation, n (%)	34 (69.4)	161 (31.3)	0.823	86 (57.7)	88 (53.0)	0.095

*Sepsis was confirmed using the sepsis-3 or septic shock at sepsis-2 criteria.
†Included other non-specific sources of infection.
CFS, Clinical Frailty Scale; CNS, central nervous system; ER, emergency room; FiO_2, fraction of inspired oxygen; GI, gastrointestinal; ICU, intensive care unit; IPW, inverse probability weighting; PaO_2, arterial partial pressure of oxygen; PF ratio, PaO_2/FiO_2 ratio; SOFA, Sequential Organ Failure Assessment.

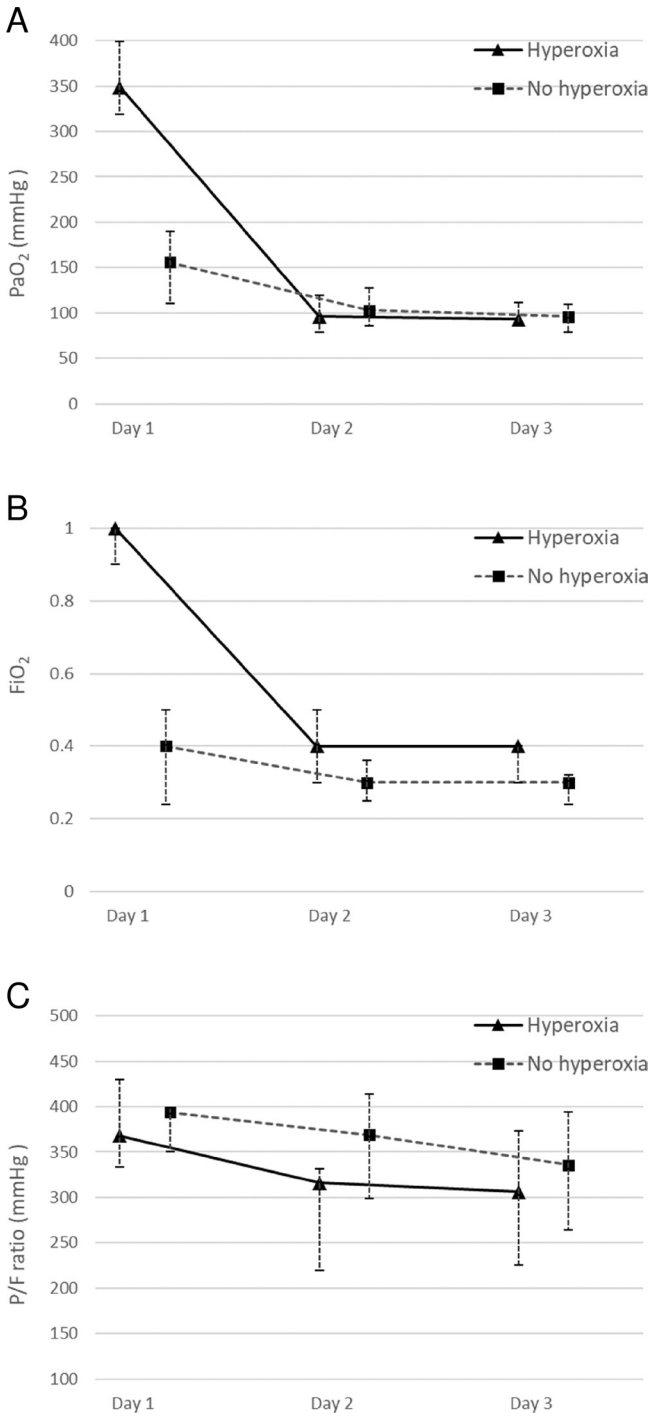

Figure 1 Daily arterial partial pressure of oxygen (PaO_2) and fraction of inspired oxygen (FiO_2). Daily PaO_2 (A), FiO_2 (B) and PF ratio (C) are shown with median and IQR. PaO_2 and FiO_2 were higher in patients with hyperoxia than in those without on day 1 (356 (322–441) vs 95 (74–140) mm Hg and 1.0 (0.9–1.0) vs 0.4 (0.3–0.6), respectively), but they had comparable data on the following days. PF ratio was also similar between patients with and without hyperoxia. PF ratio, PaO_2/FiO_2 ratio.

PaO_2 and FiO_2 were higher in patients with hyperoxia than in those without on day 1 (356 (322–441) vs 95 (74–140) mm Hg and 1.0 (0.9–1.0) vs 0.4 (0.3–0.6), respectively), but they had comparable data on the following days. PF ratio was also similar between patients with and without hyperoxia (figure 1).

In-hospital mortality and secondary outcomes

The in-hospital all-cause mortality rates of patients with and without hyperoxia were 14 (29.2%) and 90 (17.6%), respectively, and the IPW analyses revealed the association between hyperoxia and increased in-hospital mortality (28.8% vs 18.8%; adjusted OR 1.75 (1.03 to 2.97); p=0.038; table 2). The four sensitivity analyses also showed a relationship between hyperoxia and increased in-hospital mortality (online supplemental table 1).

Furthermore, the restricted cubic spline curve of mortality prediction by PaO_2 was shown as a convex downward curve of mortality odds, with the PaO_2 levels of approximately 60–240 mm Hg indicating a lower in-hospital mortality risk in patients with severe infections (figure 2).

The secondary outcomes are summarised in table 2. Hyperoxia was associated with more frequent ALI developments on days 2 and 3 after treatment initiation for severe infection (figure 3), whereas the incidence of sepsis-related mortality was comparable between patients with and without hyperoxia. Additionally, ICU-free and ventilator-free days were relatively shorter in patients with hyperoxia, with the median differences between them being not significant. Hospital-free days were similar between patients with and without hyperoxia.

Subgroup analysis

In the subgroup analyses (table 3), a relationship between higher in-hospital mortality and hyperoxia was observed in several subgroups, including the elderly aged >65 years and patients without chronic cardiopulmonary diseases, pulmonary infection and septic shock (OR 2.25 (1.25 to 4.04), 2.49 (1.35 to 4.60), 2.24 (1.26 to 3.99) and 1.96 (1.05 to 3.68), respectively).

Contrarily, younger patients (<65 years) and those with chronic cardiopulmonary diseases, pulmonary infection or septic shock had comparable mortality regardless of hyperoxia exposure.

Furthermore, in the subgroup excluding patients with hypoxia (PaO_2<60 mm Hg), hyperoxia was also associated with a higher in-hospital mortality rate (OR 1.75 (1.03 to 2.97)).

DISCUSSION

This study showed that the exposure to hyperoxia at PaO_2≥300 mm Hg at treatment initiation for severe infection was associated with an increased in-hospital mortality risk among patients requiring intensive care. The results remained after adjustment for background characteristics, sepsis severity, respiratory function and mechanical ventilation use, and were also validated through several sensitivity analyses.

Table 2 Hyperoxia and clinical outcomes

	Hyperoxia	No hyperoxia	P value	OR (95% CI)	Median difference (95% CI)
In-hospital mortality					
Unadjusted, n/total (%)	14/48 (29.2)	90/510 (17.6)			
IPW, %	28.8	18.8	0.038	1.75 (1.03 to 2.97)	
Sepsis-related mortality, %	40.5	44.6		0.85 (0.42 to 1.71)	
Length of treatment, days, mean, median (IQR)					
Hospital-free days–day 28	5, 0 (0–8)	3, 0 (0–0)			0 (0 to 0)
ICU-free days–day 28	12, 15 (0–21)	14, 17 (0–22)			0 (–3 to 0)
Ventilator-free days–day 28	14, 18 (0–24)	18, 22 (7–28)			–3 (–5 to 0)
Development of acute lung injury, % (95% CI)					
At day 1	3.4 (0.5 to 6.2)	1.8 (0.0 to 3.8)		1.89 (0.44 to 8.03)	
At day 2	16.7 (10.3 to 23.0)	7.2 (3.3 to 11.2)		2.57 (1.22 to 5.41)	
At day 3	19.4 (12.6 to 26.2)	10.5 (5.8 to 15.2)		2.05 (1.05 to 3.99)	
At day 4	15.5 (9.3 to 21.7)	8.2 (3.9 to 12.5)		2.05 (0.98 to 4.29)	

Secondary outcomes were compared using IPW analyses.
ICU, intensive care unit; IPW, inverse probability weighting.

One of the pathophysiological mechanisms underlying the harmful effects of hyperoxia on severe infection is lung injury developed due to supraphysiological FiO_2. Hyperoxia-induced ALI should be considered when the FiO_2 exceeds 0.6–0.7 and becomes clinically manifested when it is >0.8.[31 32] In our study, the median FiO_2 at treatment initiation for severe infection was 1.0 and 0.4 in patients with and without hyperoxia, respectively. Although FiO_2 was decreased to 0.3–0.4 on the next day and the duration of inhaling higher PaO_2 was unclear, incidences of ALI in patients with hyperoxia were higher on following days after hyperoxia exposure. Notably, patients with hyperoxia had relatively longer ventilator use and ICU stay, although the median differences were not significant.

Another possible rationale for the unfavourable outcomes due to hyperoxia is synergistic tissue toxicity caused by systemic inflammation and hyperoxia.[9] Several studies on traumatic brain injury reported that supranormal oxygen suppressed cell metabolism, resulting in neuronal death.[33] Additionally, hyperoxia in the early resuscitation phase was related to increased 28-day mortality risk and/or length of ICU stay among patients with severe injury or accidental hypothermia,[6 34] suggesting that redundant oxygen by hyperoxia may affect tissue or cell metabolism particularly in patients with systemic inflammation, which becomes problematic as organ dysfunction can occur days later

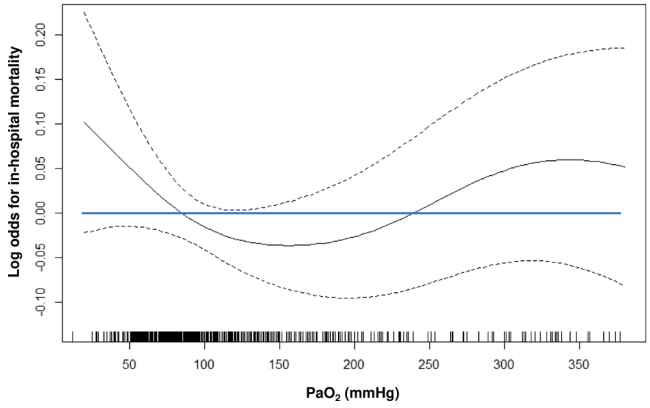

Figure 2 Restricted cubic spline curve of mortality prediction by arterial PaO_2. The restricted cubic spline curve of mortality prediction by PaO_2 revealed a convex downward curve of mortality odds as PaO_2 increased, with PaO_2 levels of approximately 60–240 mm Hg indicating a lower in-hospital mortality risk among patients with severe infection. PaO_2, arterial partial pressure of oxygen.

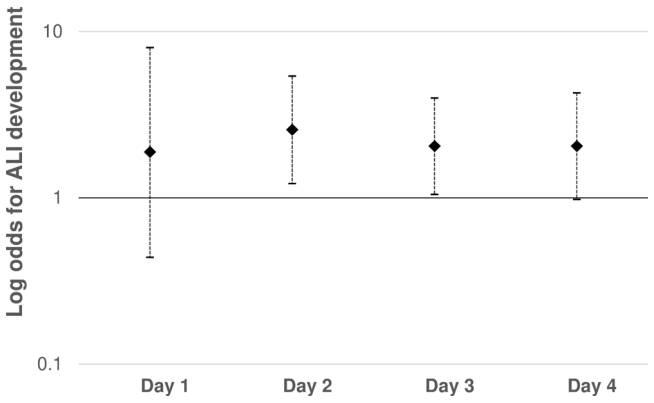

Figure 3 Daily risks for development of ALI. Daily risks of ALI development are shown with ORs and 95% CI. Hyperoxia was associated with more frequent ALI developments on days 2 and 3 after treatment initiation for severe infection. ALI, acute lung injury.

Table 3 28-day mortality in the subgroup analyses

	Hyperoxia	No hyperoxia	OR	95% CI
Age				
<65 years	4.9% (0.0–11.5%)	11.4% (2.0–20.7%)	0.40	0.73 to 2.19
≥65 years	38.1% (28.8–47.4%)	21.5% (14.2–28.8%)	2.25	1.25 to 4.04
Chronic cardiopulmonary disease*				
(–)	28.8% (21.1–36.5%)	14.0% (8.1–19.8%)	2.49	1.35 to 4.60
(+)	26.7% (4.3–49.0%)	39.3% (21.2–57.4%)	0.56	0.14 to 2.22
Source of infection confirmed				
Pulmonary	12.8% (2.3–23.3%)	18.2% (2.1–34.3%)	0.66	0.16 to 2.78
Extrapulmonary	34.3% (25.3–43.2%)	18.9% (12.5–25.3%)	2.24	1.26 to 3.99
Septic shock				
(–)	29.0% (20.4–37.6%)	17.2% (10.5–23.9%)	1.96	1.05 to 3.68
(+)	27.5% (13.7–41.3%)	23.3% (10.6–35.9%)	1.25	0.47 to 3.37
Without hypoxia†	28.8% (21.4–36.1%)	18.8% (12.8–24.7%)	1.75	1.03 to 2.97

IPW analyses were performed in each subgroup.
*Chronic cardiopulmonary diseases included congestive heart failure, coronary artery disease and chronic lung diseases.
†Hypoxia was defined as PaO_2 <60 mm Hg.
IPW, inverse probability weighting; PaO_2, arterial partial pressure of oxygen.

rather than during resuscitation. Of note, the incidence of sepsis-related mortality (failure to resuscitation from sepsis) was comparable regardless of hyperoxia exposure in this study.

Subgroup analyses suggested that hyperoxia should be avoided particularly in the elderly and patients without chronic cardiopulmonary diseases, pulmonary infections and septic shock. Considering that the elderly are vulnerable to suboptimal tissue/organ oxygenation,[35] the adverse effects of hyperoxia would have emerged in such populations. Contrarily, as patients with cardiopulmonary diseases, pulmonary infections or septic shock would have high baseline risks for the development of pulmonary dysfunction, additional harms due to hyperoxia would not become clinically obvious. Safe oxygen ranges in sepsis should be further examined in these populations because the results need to be carefully interpreted because the sample size of each subgroup was limited.

This study does not recommend invariably administering restricted oxygen for patients with severe infection. Although higher risks of in-hospital mortality with approximately PaO_2 >240 mm Hg were observed in the restricted spline curve for mortality prediction, hypoxia at approximately <60 mm Hg was also inappropriate. Therefore, it would be recommended adjusting the target PaO_2 between 60 and 240 mm Hg or at least to avoid PaO_2 ≥300 mm Hg once severe infection is suspected. However, as other potential diagnoses usually exist even when sepsis is sufficiently suspected, a higher oxygen amount will be needed depending on other possible aetiologies for critical illness.

The duration of hyperoxia exposure during resuscitation was unknown in this study, which is a major limitation to validate the association between hyperoxia (PaO_2 ≥300 mm Hg) and increased in-hospital mortality. In addition, as PaO_2 would have been adjusted to <300 mm Hg following a standard practice in ICU in most patients, the generalisability of the current results for oxygen treatment with longer exposure of hyperoxia would be limited. Moreover, other thresholds for inappropriate PaO_2 may exist depending on the timing of hyperoxia exposure, infection severity and patient characteristics.

The results must be interpreted in the context of the study's design. We retrospectively retrieved data from the SPICE-ICU Study that did not record the indications for administering high oxygen amounts instead of low to moderate one. Therefore, the findings may differ if the reasons for oxygen therapy with high FiO_2 are dependent on unrecorded, strong prognostic factors, such as the intensive care quality, intubation indication/requirement and peripheral oxygen saturation measurement reliability. Another limitation was the lack of detailed clinical information on pulmonary and other organ functions before, during and after hyperoxia exposure. Although supraphysiological oxygen tension would cause tissue toxicity, they could not be objectively evaluated. Finally, various subsets of population with severe infection exist, depending on infection site, types of bacteria, critical care practices and degree of disturbed organ function, which were not analysed in this study because of limited sample size. Therefore, the association between hyperoxia and higher

mortality would be different in these subgroups and should be further revealed in other studies.

In conclusion, hyperoxia defined as PaO_2 ≥300 mm Hg at treatment initiation for severe infection was associated with increased in-hospital mortality risk in patients requiring intensive care. Restriction of oxygen administration to avoid hyperoxia during resuscitation should be carefully considered in daily practice, and the appropriate arterial oxygen tension for patients with sepsis should be validated in future studies.

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Funding This research was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, and Technology (KAKENHI, 22K16631).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants. The SPICE-ICU Study was supported by the Japanese Association for Acute Medicine (approval no. 2014-01) andwas approved by the institutional review board for conducting research with human participants in accordance with the Helsinki Declaration at the head institute of the SPICE-ICU Study group (approval no. 016-0386 from Hokkaido University on 8 February 2017; study title, 'Japanese Association for Acute Medicine Sepsis Prognostication in Intensive Care Unit and Emergency Room'). The institutional review board at the head institute of the study group waived informed consent because of the anonymous nature of the data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The study data are available from the SPICE-ICU Study group; however, restrictions apply to the availability of these data, which were used under licence for the current study and are not publicly available. However, data are available from the authors upon reasonable request and with the permission of the SPICE-ICU Study group.

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