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Hyperoxemia and excess oxygen use in early acute respiratory distress syndrome: insights from the LUNG SAFE study

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Abstract

Background: Concerns exist regarding the prevalence and impact of unnecessary oxygen use in patients with acute respiratory distress syndrome (ARDS). We examined this issue in patients with ARDS enrolled in the *L*arge observational study to *UN*derstand the *Gl*obal impact of *S*evere *A*cute respiratory *F*ailur*E* (LUNG SAFE) study.

Methods: In this secondary analysis of the LUNG SAFE study, we wished to determine the prevalence and the outcomes associated with hyperoxemia on day 1, sustained hyperoxemia, and excessive oxygen use in patients with early ARDS. Patients who fulfilled criteria of ARDS on day 1 and day 2 of acute hypoxemic respiratory failure were categorized based on the presence of hyperoxemia (PaO_2 > 100 mmHg) on day 1, sustained (i.e., present on day 1 and day 2) hyperoxemia, or excessive oxygen use (FIO_2 ≥ 0.60 during hyperoxemia).

Results: Of 2005 patients that met the inclusion criteria, 131 (6.5%) were hypoxemic (PaO_2 < 55 mmHg), 607 (30%) had hyperoxemia on day 1, and 250 (12%) had sustained hyperoxemia. Excess FIO_2 use occurred in 400 (66%) out of 607 patients with hyperoxemia. Excess FIO_2 use decreased from day 1 to day 2 of ARDS, with most hyperoxemic patients on day 2 receiving relatively low FIO_2. Multivariate analyses found no independent relationship between day 1 hyperoxemia, sustained hyperoxemia, or excess FIO_2 use and adverse clinical outcomes. Mortality was 42% in patients with excess FIO_2 use, compared to 39% in a propensity-matched sample of normoxemic (PaO_2 55–100 mmHg) patients ($P = 0.47$).

Conclusions: Hyperoxemia and excess oxygen use are both prevalent in early ARDS but are most often non-sustained. No relationship was found between hyperoxemia or excessive oxygen use and patient outcome in this cohort.

Trial registration: LUNG-SAFE is registered with ClinicalTrials.gov, NCT02010073

Keywords: Hyperoxia, Hypoxia, Hyperoxemia, Hypoxemia, Oxygen therapy, Acute respiratory distress syndrome, Mortality, Invasive mechanical ventilation

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Key messages

- Hyperoxemia and excess FIO_2 use was prevalent in patients with early ARDS. Hyperoxemia occurred in 30% of patients, while two thirds of these patients received excess oxygen therapy.
- While a similar proportion of patients were hyperoxemic on day 2 of ARDS, higher FIO_2 use did decrease. Consequently, most day 2 hyperoxemia was seen in patients at lower FIO_2, in whom gas exchange was improving.
- In the majority of patients, both hyperoxemia and excess oxygen use were transient, although sustained hyperoxemia occurred in 12% of patients.
- Higher FIO_2 use was independently associated with the risk of hyperoxemia, illustrating the need for close attention to oxygen use to reduce this risk.
- We found no relationship between the degree and duration of hyperoxemia or of excessive oxygen use, and outcome in early ARDS, in this patient cohort.

Background

Acute respiratory distress syndrome (ARDS) is a syndrome characterized by impaired gas exchange resulting in low oxygen tensions in the blood (i.e., hypoxemia) and tissues (i.e., hypoxia) [1]. Tissue hypoxia is harmful, leading to cell death, organ failure, and increased mortality in the critically ill [2]. While oxygen therapy can reverse tissue hypoxia, little evidence exists regarding the optimal use of oxygen in patients with ARDS. Critically ill patients frequently receive higher inspired oxygen concentrations than necessary [3], perhaps due to concerns regarding tissue hypoxia [4, 5].

Hyperoxemia and the resultant tissue hyperoxia may worsen systemic organ injury in the critically ill. Arterial hyperoxemia has been associated with increased mortality in some older [6–8] but not more recent [9, 10] studies of patients with acute brain injury. Hyperoxemia was associated with worse outcomes in cohort patients with acute ischemic stroke or subarachnoid/intracerebral hemorrhage that required invasive mechanical ventilation [11]. Supplemental oxygen therapy worsened myocardial injury and infarct size in patients post myocardial infarction [12]. In patients resuscitated post cardiac arrest, hyperoxia has been associated with harm in several [13–16] studies, although the most recent study [17] did not confirm this. Potential mechanisms of oxygen toxicity remain poorly understood and may include systemic arterial vasoconstriction [18, 19], and cytotoxic effects of reactive oxygen species [20–22]. In randomized trials, "induced" hyperoxia (using 100% oxygen) increased 28-day mortality in septic shock patients [23], while critically ill patients randomized to a target arterial oxygen tension (PaO_2) of 70–100 mmHg had lower mortality compared to patients with a "conventional" target of PaO_2 up to 150 mmHg [24] in a single-center study. While a recent large international multicenter trial demonstrated no effect of conservative oxygen therapy in a diverse cohort of critically ill patients [25], a subsequent sub-study raised the possibility of clinically important harm with conservative oxygen therapy in patients with sepsis [26].

In ARDS, the relationship between oxygen use and outcome is complex. The severely impaired gas exchange means that high fraction of inspired oxygen (FIO_2) use may simply reflect a more severe alveolar-arterial oxygen gradient and hence be a marker of ARDS severity. In mild ARDS, relatively modest levels of FIO_2 may result in (moderate) hyperoxemia and tissue hyperoxia. In addition, severe degrees of systemic hyperoxemia (i.e., $PaO_2 > 300$) associated with harm in other critically ill populations are not possible in ARDS. However, even moderate systemic hyperoxemia that may be more commonly seen in ARDS could be harmful [27]. Furthermore, the use of high FIO_2 can have direct toxic effects on the lung [28, 29], sensitize the lung to subsequent injury, adversely affect the lung innate immune response [30], and worsen ventilation-induced injury [31–33]. These complexities highlight the need to distinguish between hyperoxemia and high FIO_2 use. In patients receiving high FIO_2, it is important to determine whether this was necessary to achieve normoxemia or if it could have been avoided (i.e., excess oxygen use).

We wished to examine the impact of hyperoxemia and of excess oxygen use in this secondary analysis of patients with ARDS in the LUNG SAFE patient cohort [34]. Our primary objective was to determine the prevalence of early and sustained hyperoxemia and of excess oxygen use in patients with hyperoxemia. Secondary objectives included identifying factors associated with hyperoxemia and with excess oxygen use and examining the relationship between hyperoxemia and excess oxygen use and outcomes from ARDS.

Methods

Design, setting, and participants

This is a sub-study of the LUNG SAFE study, an international, multicenter, prospective cohort study of patients receiving invasive or noninvasive ventilation, and the detailed methods and protocol have been published elsewhere [34]. In brief, LUNG SAFE was an international, multicenter, prospective cohort study, with a 4-week enrolment window in the winter season in both hemispheres [34]. National coordinators and site investigators obtained ethics committee approval and ensured data integrity and validity.

Given the study focus on early hyperoxemia and excess oxygen use, we restricted the study population to patients that fulfilled ARDS criteria within 48 h of ICU admission, and who remained in the ICU for at least 2 days from ARDS onset. Patients transferred from other

ICUs after 2 days, patients that developed ARDS later in their ICU stay, and patients that received early ECMO were excluded (Fig. 1). Additional methodological details are available in Additional file 1.

Data collection and analysis

All data were recorded for each patient at the same time each day within participating ICUs, normally as close as possible to 10 a.m. each day. Data on ventilatory settings were recorded simultaneously with arterial blood gas analysis. The following definitions were applied on day 1 and on day 2 of ARDS: hypoxemia (PaO_2 < 55 mmHg), normoxemia (PaO_2 55–100 mmHg), and hyperoxemia (PaO_2 > 100 mmHg). Excess oxygen use was defined as the use of FIO_2 ≥ 0.6 in patients with hyperoxemia (PaO_2 > 100 mmHg). Patients with hyperoxemia on days 1 and 2 of ARDS were considered to have sustained hyperoxemia. Analogously, we also defined patients with sustained hypoxemia and sustained normoxemia.

The duration of invasive mechanical ventilation (MV) was calculated as the number of days between the date of intubation and the date of extubation in ICU (or death, if the patient died under invasive MV). Similarly, invasive ventilator-free days were calculated as the number of days from weaning from invasive MV to day 28, and for patients who died before weaning, we considered to have a ventilator-free-day value of 0. Patient survival was evaluated at hospital discharge, or at day 90, whichever occurred first. Our other data definitions have been previously reported [34–37].

Statistical analyses

Descriptive statistics included proportions for categorical and mean (standard deviation) or median (interquartile range) for continuous variables. No assumptions were made for missing data. To assess differences among three groups (systemic hypoxemia, normoxemia, and hyperoxemia), we performed chi-squared test (or Fisher exact test) for discrete variables and analysis of variance (ANOVA) (or Kruskal-Wallis test) for continuous variables. Bonferroni correction was applied to determine significance in the setting of multiple comparisons. Chi-square test (or Fisher exact test), Student's *t* test (or Wilcoxon Mann Whitney test) were used to assess

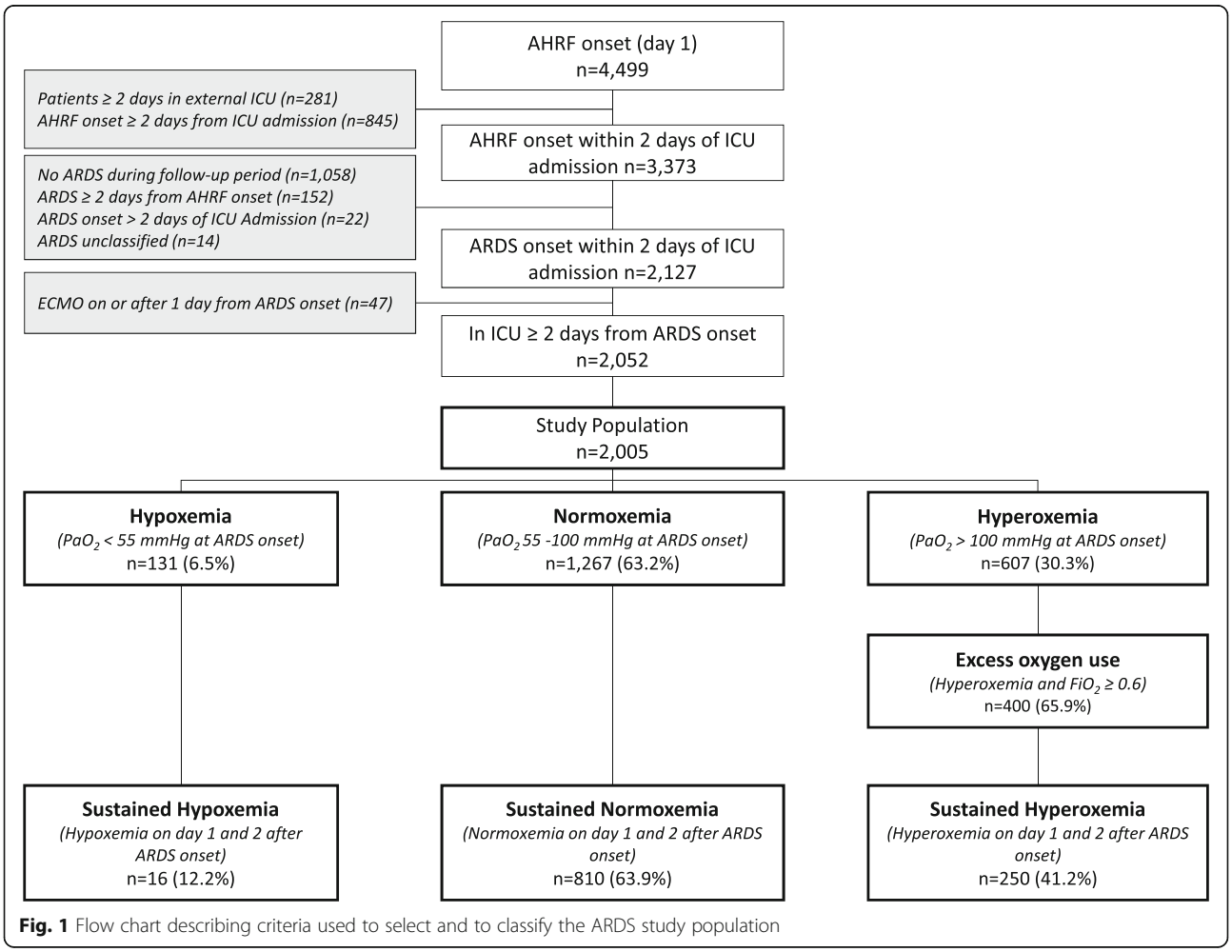

Fig. 1 Flow chart describing criteria used to select and to classify the ARDS study population

differences between groups (i.e., sustained hyperoxemia and sustained normoxemia) in discrete and continuous distributions of parameters, respectively.

Locally estimated scatterplot smoothing (LOESS) method was used to inspect the relationship between mortality and PaO_2 and FIO_2 measured on day 1 and on day 2 of ARDS.

Multivariable logistic regression models were used to evaluate factors associated with the presence of either hyperoxemia or excess of oxygen use, and with mortality. In each regression model, the independent predictors (demographic characteristics and clinical parameters measured at the first day of ARDS) were identified through a stepwise regression approach. This approach combines forward and backward selection methods in an iterative procedure (with a significance level of 0.05 both for entry and retention) to select predictors in the final multivariable model. Results were reported as odds ratio (OR) with 95% confidence interval (CI).

Propensity score matching method was applied to evaluate the possible impact of sustained hyperoxemia on main outcomes (mortality, ventilation-free days, and duration of MV) in patients with mild-moderate ARDS. Patients with severe ARDS were excluded as there were no such patients in the sustained hyperoxemia group. In detail, patients with sustained hyperoxemia and sustained normoxemia were matched (1:1 match without replacement), using a caliper of 0.2 standard deviation of the logit of the propensity score, and the balance between the matched groups was assessed by the standardized differences of each independent variable used in the propensity score estimation. Statistical significance of the difference in continuous variables, as ventilation-free days and duration of MV, was evaluated with Wilcoxon signed-rank test, while for difference in proportions of deaths, we applied McNemar's test. Survival probability in these matched groups was estimated using the Kaplan-Meier approach and assuming that patients discharged alive from hospital before 90 days were alive on day 90. Statistical difference between survival curves was assessed through Kein and Moeschberger test. The same approach was used to assess the possible impact of excess use of oxygen on main outcomes.

All p values were two-sided, with p values < 0.05 considered as statistically significant. Statistical analyses were performed with R, version 3.5.2. (R Project for

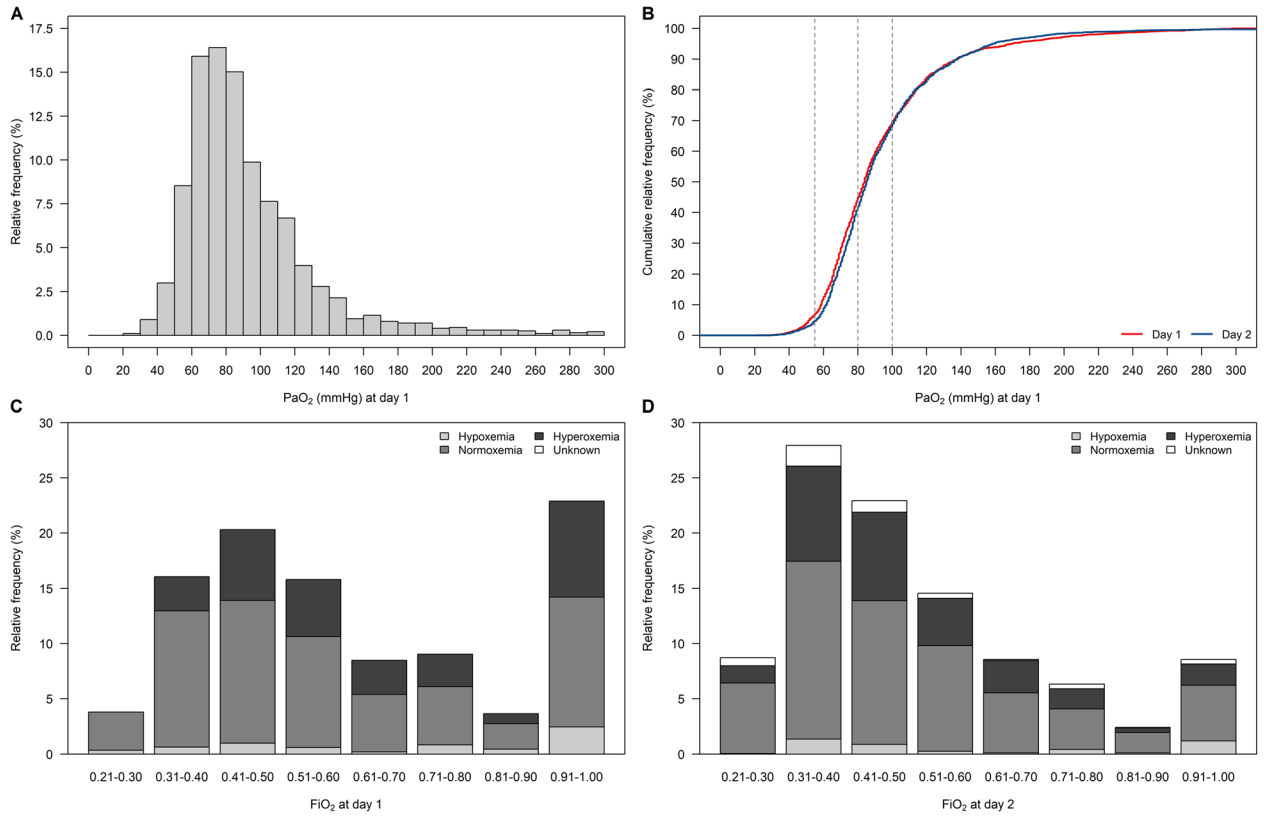

Fig. 2 Arterial oxygen tensions and use of oxygen in patients on days 1 and 2 of ARDS. **a** The distribution of PaO_2 on day 1 of ARDS, demonstrating a wide range of PaO_2. **b** Density distributions of PaO_2 on days 1 (red line) and day 2 (blue line) of ARDS. **c** Histogram of FIO_2 and PaO_2 on day 1 of ARDS. **d** Histogram of FIO_2 and PaO_2 on day 2 of ARDS. Note: in **c** and **d**, each bar is segmented into hyperoxemia (black), normoxemia (dark gray), hypoxemia (light gray), and unknown (white) component

Table 1 Characteristics of study population ($n = 2005$), stratified by arterial oxygenation on day 1

Parameter	Hypoxemia (PaO_2 < 55 mmHg)	Normoxemia (55 mmHg ≤ PaO_2 ≤ 100 mmHg)	Hyperoxemia (PaO_2 > 100 mmHg)	*p* value (among groups)
N (%)	131 (6.53)	1267 (63.19)	607 (30.27)	
Male, *n* (%)	73 (55.73)	796 (62.83)	359 (59.14)	0.1259
Age (years), mean ± SD	59.20 ± 16.86	62.21 ± 16.74	61.88 ± 16.82	0.1264
BMI (kg/m^2), mean ± SD	27.23 ± 6.82	27.66 ± 8.26	26.90 ± 6.84	0.5646
ARDS risk factors, *n* (%)				
None	9 (6.87)	103 (8.13)	52 (8.57)	0.8088
Only non-pulmonary	15 (11.45)	229 (18.07)	106 (17.46)	0.1641
Only pulmonary	92 (70.23)	769 (60.62)	357 (58.81)	0.0525
Both	15 (11.45)	167 (13.18)	92 (15.16)	0.3789
Illness severity at ARDS onset				
P_aO_2 (mmHg), mean ± SD	47.1 ± 6.2	76.8 ± 11.9*	137.8 ± 41.0*†	< 0.0001
P_aO_2/FIO_2 (mmHg), mean ± SD	75.12 ± 38.97	140.49 ± 56.70*	205.90 ± 54.88*†	< 0.0001
SpO_2 (%), median (q_1–q_3)	88 (82–94)	95 (92–97)*	98 (97–99)*†	< 0.0001
ARDS severity, *n* (%)				< 0.0001
Mild	4 (3.05)	205 (16.18)*	330 (54.37)*†	< 0.0001
Moderate	22 (16.79)	683 (53.91)*	273 (33.98)*†	< 0.0001
Severe	105 (80.15)	379 (29.91)*	4 (0.66)*†	< 0.0001
P_aCO_2 (mmHg), mean ± SD	54.3 ± 25.0	46.3 ± 15.3*	44.8 ± 14.6*	0.0031
pH, mean ± SD	7.31 ± 0.15	7.33 ± 0.12	7.32 ± 0.13	0.7446
Bicarbonate (mmol/L), mean ± SD	26.3 ± 10.9	23.3 ± 6.5	22.3 ± 6.3*†	< 0.0001
Base excess (mEq/L), mean ± SD	0.5 ± 10.8	−2.0 ± 6.8	−3.1 ± 6.8*†	0.0001
Non-respiratory SOFA score adjusted, mean ± SD	6.14 ± 4.15	6.08 ± 3.94	6.28 ± 4.00	0.6246
SOFA score adjusted, mean ± SD	10.25 ± 4.20	9.51 ± 3.98	8.87 ± 3.93*†	0.0005
Respiration	3.79 ± 0.46	3.15 ± 0.66	2.45 ± 0.50	< 0.0001
Central nervous system	1.68 ± 1.72	1.74 ± 1.66	1.92 ± 1.69	0.1161
Cardiovascular	1.77 ± 1.74	2.03 ± 1.76	1.93 ± 1.74	0.1760
Liver	0.65 ± 0.98	0.54 ± 0.96	0.51 ± 0.92	0.2855
Coagulation	1.20 ± 1.45	0.95 ± 1.31	0.98 ± 1.34	0.1751
Renal	0.69 ± 1.04	1.77 ± 1.10	0.88 ± 1.22	0.3333
Pressor support infusion rates				
Dopamine (μg/kg/min), mean ± SD	8.19 ± 6.94	8.58 ± 5.02	7.73 ± 5.98	0.4151
Dobutamine (μg/kg/min), mean ± SD	5.52 ± 3.74	5.72 ± 4.05	6.75 ± 3.53	0.3565
Noradrenaline (μg/kg/min), mean ± SD	0.50 ± 0.67	0.45 ± 0.75	0.54 ± 1.48	0.6701
Adrenaline (μg/kg/min), mean ± SD	1.10 ± 2.03	0.48 ± 0.69	0.43 ± 0.55	0.8434
Management factors at ARDS onset				
Invasive mechanical ventilation, *n* (%)	102 (77.86)	1000 (78.93)	506 (83.36)	0.0619
Control mode of ventilation, mean ± SD	70 (54.69)	693 (55.89)	386 (64.23)†	0.0021
FIO_2, median (q_1–q_3)	0.80 (0.50–1.00)	0.60 (0.41–0.80)*	0.65 (0.50–1.00)†	< 0.0001
FIO_2 ≥ 0.6, *n* (%)	90 (68.70)	670 (52.88)*	400 (65.90)†	< 0.0001
FIO_2 ≥ 0.6 at 2nd day, *n* (%)‡	64 (73.56)	372 (57.94)*	167 (43.60)*†	< 0.0001
Tidal volume (ml/kg), mean ± SD	7.9 ± 2.2	7.8 ± 2.0	7.9 ± 2.0	0.2256
PEEP (cmH_2O), mean ± SD	8.7 ± 3.33	8.1 ± 3.2	7.9 ± 3.1*	0.0174
PIP (cmH_2O), mean ± SD	25.7 ± 8.90	25.3 ± 8.5	25.6 ± 8.7	0.6295

Table 1 Characteristics of study population ($n = 2005$), stratified by arterial oxygenation on day 1 *(Continued)*

Parameter	Hypoxemia (PaO_2 < 55 mmHg)	Normoxemia (55 mmHg ≤ PaO_2 ≤ 100 mmHg)	Hyperoxemia (PaO_2 > 100 mmHg)	*p* value (among groups)
Dynamic compliance (ml/cmH_2O), mean ± SD	39.0 ± 38.4	36.9 ± 37.8	35.6 ± 38.9	0.7759
Total respiratory rate (breaths/min), mean ± SD	23.2 ± 7.1	21.9 ± 6.9	21.1 ± 7.0	0.0003
Standardized minute ventilation (L/min), mean ± SD	14.4 ± 7.8	11.4 ± 5.3*	10.8 ± 5.0*†	< 0.0001
Patients in whom plateau pressure measured, *n* (%)°	24 (18.32)	304 (23.99)	186 (30.64)	0.0012
Plateau pressure (cmH_2O), mean ± SD	24.3 ± 9.0	23.4 ± 6.1	23.0 ± 5.6	0.7512
Driving pressure (cmH_2O), mean ± SD	16.0 ± 8.2	14.6 ± 5.4	15.0 ± 5.2	0.4941
Clinical outcomes				
Hospital mortality (90 days), *n* (%)	47 (35.88)	486 (38.54)	227 (37.52)	0.7934
Ventilation free days (days), median (q_1–q_3)				
All	10.0 (0.0–22.0)	12.0 (0.0–23.0)	16.0 (0.0–24.0)†	0.0303
Survivors at ICU discharge	20.0 (14.0–24.0)	21.0 (15.0–25.0)	23.0 (18.0–26.0)*†	0.0002
Duration mechanical ventilation (days), median (q_1–q_3)				
All	7.0 (4.0–13.0)	8.0 (4.0–15.0)	7.0 (3.0–13.0)†	0.0074
Survivors at ICU discharge	9.0 (5.0–15.0)	8.0 (4.0–14.0)	6.0 (3.0–11.0)*†	0.0002

Abbreviations: *ARDS* acute respiratory distress syndrome, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *FIO_2* fraction of inspired oxygen, *P_aO_2* arterial oxygen partial pressure, *P_aCO_2* arterial carbon dioxide partial pressure, *PEEP* positive end-expiratory pressure, *PIP* peak inspiratory pressure, *q_1* first quartile, *q_3* third quartile, *SOFA* sepsis-related organ failure assessment, *SD* standard deviation, *SpO_2* peripheral oxygen saturation

°Plateau pressure and driving pressure values are limited to patients in whom this value was reported and in whom either an assist control mode was used or in whom a mode permitting spontaneous ventilation was used and where the set and total respiratory rates were equal. Patients receiving HFOV or ECMO were also excluded

‡Percentage was calculated on patients with FIO_2 available during the second day and with $FIO_2 \geq 0.60$ at day 1

*p value < 0.05 (Bonferroni's correction), comparison with "Hypoxemia" group

†p value < 0.05 (Bonferroni's correction), comparison with "Normoxemia" group

Statistical Computing, http://www.R-project.org) and SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Of 4499 patients that developed AHRF in the LUNG SAFE cohort, 2127 of these developed ARDS within 2 days of ICU admission, of whom 2052 remained in ICU for at least 2 days from ARDS onset. The study population consists of 2005 of these patients that did not receive ECMO (Fig. 1).

Systemic oxygen tensions

In the study population, 607 subjects (30%) were hyperoxemic, while 6.5% of patients remained hypoxemic, on day 1 of ARDS (Fig. 2a, Table 1, eTable 1). Density distributions of arterial oxygen tension on days 1 and 2 of ARDS (Fig. 2b) reveal similar PaO_2 profiles for days 1 and 2. In the hyperoxemic population at day 1, 59% had a transient hyperoxemia, while in 250 (41%) patients, the condition was sustained, with PaO_2 > 100 mmHg on both the first and second day of ARDS (Fig. 1; eTable 2). All eTables are included in Additional file 1.

A multivariable analysis of factors independently associated with day 1 hyperoxemia identified higher FIO_2 use, lower PEEP, lower respiratory rate, a lower sepsis-related organ failure assessment (SOFA) cardiovascular score, and comorbidities such as neoplasm and/or immunosuppression and heart failure (Table 2).

Use of oxygen

FIO_2 use varied widely across the spectrum of PaO_2 on day 1 of ARDS (Fig. 2c). In patients that received a FIO_2 greater than 0.9 (459 patients), 11% had systemic hypoxemia, while 38% had hyperoxemia (Fig. 2c). Median PaO_2 was similar across deciles of FIO_2 (Fig. 3a). On day 2 of ARDS, the proportions of patients receiving higher FIO_2 decreased, although around one third of patients were hyperoxemic at each decile of FIO_2 (Figs. 2d and 3b, c). In contrast, 40% (57/131) of patients with hypoxemia on day 1 received a FIO_2 of 0.5 or less. Median FIO_2 decreased between day 1 and day 2 in patients with hyperoxemia, normoxemia, and hypoxemia (Fig. 3b), although median PaO_2 remained similar across deciles of FIO_2 on day 2 (Fig. 3c).

Excess oxygen use was seen in 400 patients, comprising 66% of all patients with hyperoxemia, on day 1 of ARDS (Table 1). In 315 patients (79%), excess oxygen use was transient, while in 85 (21%) patients, excess oxygen use was also seen on day 2 of ARDS. In multivariable analysis, factors independently associated with excess oxygen use included lower PaO_2/FIO_2 ratio,

Table 2 Factors associated with day 1 hyperoxemia (PaO_2 > 100 mmHg) and with excess oxygen use ($FIO_2 \geq 0.6$ in patients with P_aO_2 > 100 mmHg) in the study population

Parameter	Odds ratio (95% confidence interval)	*p* value
Outcome—hyperoxemia at day 1 (model* on 1855 patients)		
FIO_2 (0.1 unit)	1.168 (1.115; 1.224)	< .0001
Bicarbonate (mmol/L)	0.967 (0.951; 0.984)	< .0001
Total respiratory rate (breath/min)	0.971 (0.956; 0.986)	0.0002
PEEP (cmH_2O)	0.944 (0.910; 0.979)	0.0017
Active/hematologic neoplasm or immunosuppression (ref. no.)	1.414 (1.111; 1.801)	0.0050
SOFA score – Cardiovascular	0.925 (0.870; 0.984)	0.0139
Heart failure (ref. no.)	1.482 (1.080; 2.033)	0.0148
Outcome—excess oxygen use at day 1 (model° on 1694 patients)		
P_aO_2/FIO_2 (mmHg)	0.978 (0.976; 0.980)	< .0001
PEEP (cmH_2O)	1.144 (1.091; 1.199)	< .0001
PIP (cmH_2O)	1.029 (1.014; 1.045)	0.0002
Bicarbonate (mmol/L)	0.971 (0.954; 0.989)	0.0013
Age (years)	0.988 (0.981; 0.996)	0.0023
BMI (kg/m^2)	0.980 (0.965; 0.995)	0.0111
Tidal volume (ml/kg IBW)	1.081 (1.017; 1.149)	0.0122

Abbreviations: *BMI* body mass index, *FIO_2* fraction of inspired oxygen, *PEEP* positive end-expiratory pressure, *PIP* peak inspiratory pressure, *SOFA* sepsis-related organ failure, *P_aO_2* arterial oxygen partial pressure, *IBW* ideal body weight

*Multivariable logistic model with presence of hyperoxemia (PaO_2 > 100 mmHg) as dependent dichotomous variable and the predictors were identified by stepwise approach. One hundred and fifty patients were excluded due to missing values for the response or explanatory variables. List of possible predictors in stepwise approach: age, sex, body mass index, comorbidities (presence of heart failure, diabetes mellitus chronic renal failure, chronic obstructive pulmonary disease or home ventilation, active neoplasm of hematologic neoplasm or immunosuppression), ARDS risk factors (none, only non-pulmonary, only pulmonary, both types), bicarbonates concentration, management factors (presence of invasive mechanical ventilation, tidal volume, PEEP, PIP, total respiratory rate, minute ventilation), and FIO_2 and SOFA components (CNS, cardiovascular, renal, liver, coagulation score)

°Multivariable logistic model with excess of oxygen use ($FIO_2 \geq 0.6$ and PaO_2 > 100 mmHg) as dependent dichotomous variable and predictors identified by stepwise approach. Three hundred and eleven observations were deleted due to missing values for the response or explanatory variables

List of possible predictors in stepwise approach: age, sex, body mass index, comorbidities (presence of heart failure, diabetes mellitus chronic renal failure, chronic obstructive pulmonary disease or home ventilation, active neoplasm of hematologic neoplasm or immunosuppression), ARDS risk factors (none, only non-pulmonary, only pulmonary, both types), bicarbonates concentration, management factors (presence of invasive mechanical ventilation, tidal volume, PEEP, PIP, total respiratory rate, minute ventilation), and PaO_2/FIO_2 ratio and non-respiratory SOFA components (CNS, cardiovascular, renal, liver, coagulation score)

higher PEEP, higher tidal volume, and chronic renal failure (Table 2).

Hyperoxemia, excess oxygen use, and outcome

On day 1, LOESS demonstrated the relationship between unadjusted mortality risk and PaO_2 was relatively flat over the range of PaO2 (Fig. 4a). On day 2, the unadjusted risk of hospital mortality increased in patients with systemic hypoxemia (Fig. 4b). LOESS in non-hypoxemic patients demonstrated that unadjusted mortality risk increased with increasing FIO_2 on both days 1 and 2 (Fig. 4c, d).

Multivariate analyses found no independent association between day 1 systemic oxygen tension or inspired oxygen concentration and outcome, in either the full study population or in the subset of patients with hyperoxemia (Table 3).

In a propensity-matched analysis ($n = 448$), no outcome differences were found in patients with sustained hyperoxemia compared to matched sustained normoxemia patients (Fig. 5a; eTable 3). Similarly, mortality in patients with hyperoxemia and excess oxygen use (42%) was not different to that in patients with normoxemia (39%, $P = 0.47$) in a propensity-matched sample ($n = 666$) (Fig. 5b; eTable 4).

Discussion

Our findings demonstrate that hyperoxemia and excess FIO_2 use was prevalent in patients with early ARDS in patients enrolled in the LUNG SAFE cohort. Hyperoxemia occurred in 30% of patients, while two thirds of these patients received excess oxygen therapy. While a similar proportion of patients was hyperoxemic on day 2 of ARDS, higher FIO_2 use did decrease. Consequently, most day 2 hyperoxemia was seen in patients at lower FIO_2, in whom gas exchange was improving. In the majority of patients, both hyperoxemia and excess oxygen use were transient, although sustained hyperoxemia occurred in 12% of patients. Higher FIO_2 use was independently associated with the risk of hyperoxemia, illustrating the need for close attention to oxygen use to reduce this risk. We found no relationship between the degree and duration of hyperoxemia or of excessive

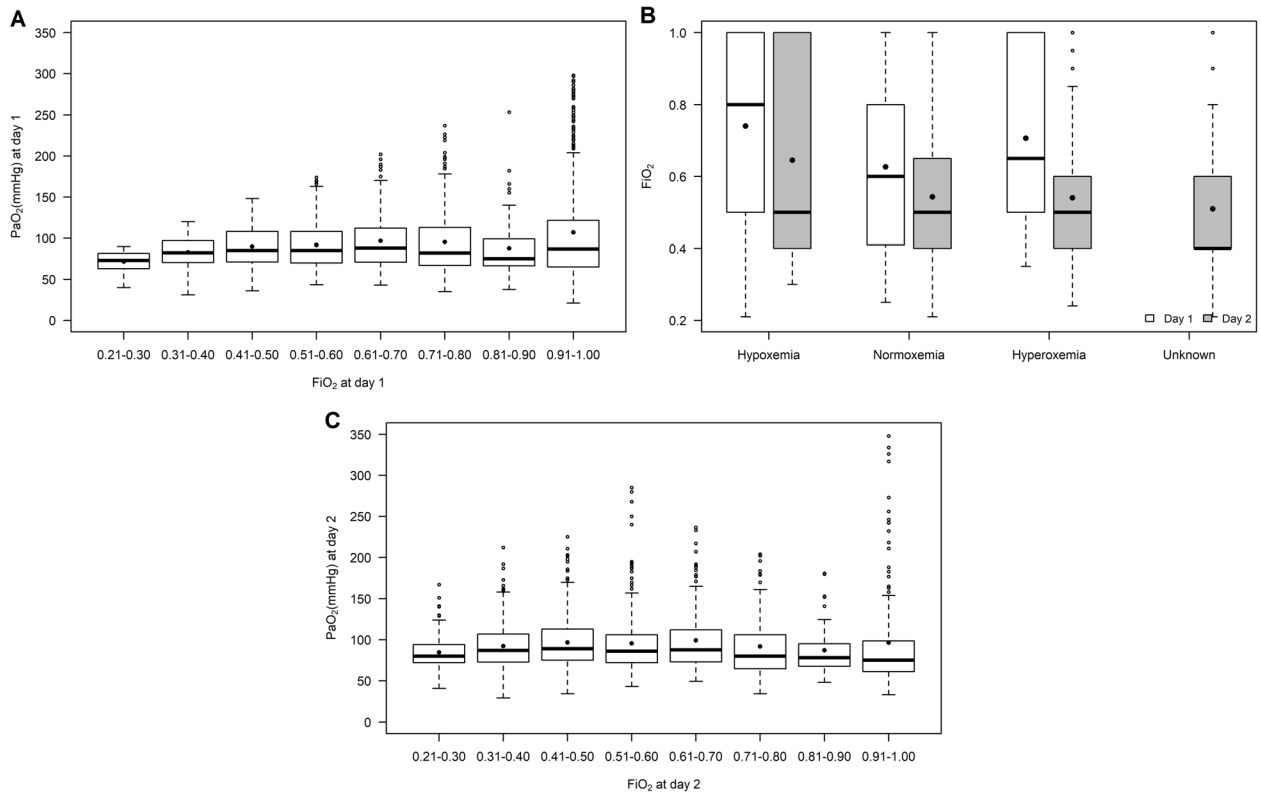

Fig. 3 Use of inspired oxygen in patients on days 1 and 2 of ARDS. **a** A box plot of PaO_2 at each decile of FIO_2 uses on day 1 of ARDS. **b** A box plot of FIO_2 used on day 1 and 2 of ARDS in the study population classified by PaO_2 on day 2 (hypoxemia, normoxemia, hyperoxemia, and unknown). **c** A box plot of PaO_2 at each decile of FIO_2 used on day 2 of ARDS

oxygen use, and outcome in early ARDS, in this patient cohort.

Oxygen use in ARDS

The optimal use of oxygen in patients with ARDS remains unclear. While guidelines recommend the use of supplemental oxygen during acute hypoxemia [38], specific therapeutic goals in terms of PaO_2 or SpO_2 are lacking. The ARDS Network targeted a PaO_2 of 55–80 mmHg in the ARMA trial of patients with ARDS [39]. The British Thoracic Society suggested a target SpO_2 of 94–98% in acutely ill patients who are not at risk of hypercapnic respiratory failure (only Grade D recommendation) [40, 41].

Tissue hypoxia directly causes cellular death, leading to organ failure and increased mortality in ICU patients. In contrast, high oxygen concentrations may be directly toxic to the lung via mechanisms that remain poorly characterized but may include alveolar-capillary "leak" and fibrogenesis [42, 43], arterial vasoconstriction [18, 19], and the production of reactive oxygen species with consequent proinflammatory and cytotoxic effects [20–22]. Consequently, clinicians are faced with the task of titrating the amount of oxygen delivered to avoid both hypoxemia and hyperoxemia. Prior studies show that clinicians appear to use higher FIO_2 than is necessary in the critically ill [3]. While the reasons are unclear, potential explanations include concerns over the need to avoid tissue hypoxia, [4, 5] a desire to provide a "buffer" should a clinical deterioration occur, or because the consequences of hyperoxia are considered less severe than hypoxia.

Hyperoxemia in ARDS

In this study, hyperoxemia was seen on day 1 in a third of ARDS patients enrolled in the LUNG SAFE study. The fact that hyperoxemia was more prevalent than hypoxemia in patients immediately following the onset of ARDS, might seem surprising given that ARDS is a syndrome defined by impaired gas exchange but presumably reflects the effectiveness of ventilatory support and oxygen therapy. Of interest, hyperoxemia was associated with lower SOFA cardiovascular scores, suggesting that clinicians were not permitting hyperoxemia as a "buffer" in patients with shock. In this patient cohort, hyperoxemia was relatively transient in the majority of patients in early ARDS.

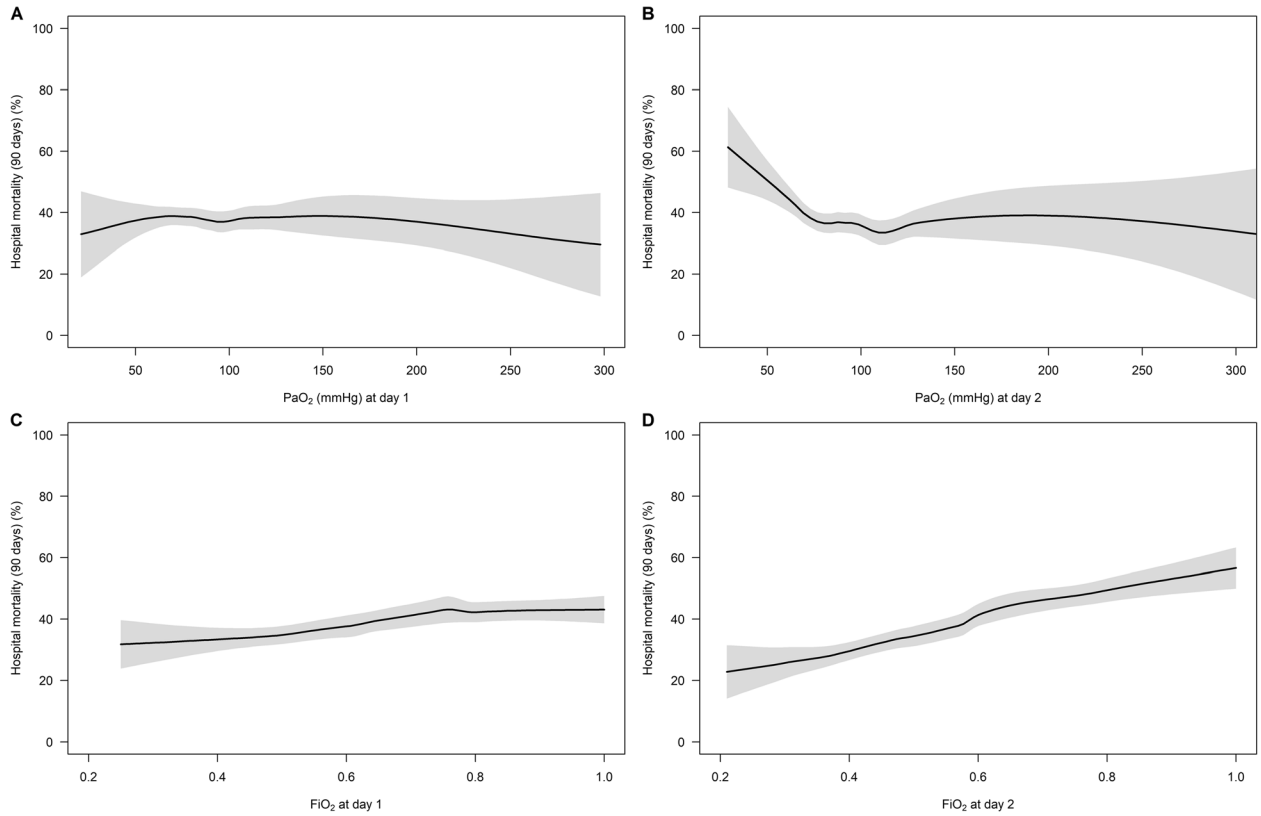

Fig. 4 Relationship between oxygen and outcome in patients with ARDS. **a** A locally estimated scatterplot smoothing (LOESS) of the relationship between PaO_2 on day 1 of ARDS and mortality risk. **b** A LOESS of the relationship between PaO_2 use on day 2 of ARDS and mortality risk. **c** A LOESS of the relationship between FIO_2 use on day 1 in non-hypoxemic patients with ARDS and mortality risk. **d** A LOESS of the relationship between FIO_2 use on day 2 in non-hypoxemic patients with ARDS and mortality risk. Note: LOESS uses a bandwidth 2/3 and 1 degree of polynomial regression

A minority of patients had sustained hyperoxemia in this cohort. Interestingly, day 2 median FIO_2 was the same in patients with sustained hyperoxemia and normoxemia, while P/F ratio was substantially higher in the hyperoxemic patients. These findings suggest that sustained hyperoxemia in these patients is a function of rapidly improving gas exchange rather than excess oxygen use. Sustained hyperoxemia did not have a demonstrable impact on patient mortality. In the matched propensity score analysis, outcomes in patients with sustained hyperoxemia were comparable to that seen in normoxemic patients.

These findings contrast with prior findings regarding hyperoxemia in other critically ill cohorts. However, an important difference between these studies and the current study relates to the severity of hyperoxemia. De Jonge and colleagues reported an association between early hyperoxemia and outcome in patients with acute respiratory failure in the Netherlands [44]. However, this association was only seen in patients with relatively severe hyperoxemia (PaO_2 > 123 mmHg; uncommon in our cohort) and only on day 1 of ICU admission, while there was no adverse association between hyperoxia over the entire ICU stay and patient outcome. The potential for harm from hyperoxia in the critically ill appears to be enhanced with greater severity and "dose" of hyperoxemia [45]. In fact, in critically ill patient groups where lung function was relatively preserved, such as patients post cardiac arrest, harm was mainly associated with systemic oxygen tensions over 300 mmHg [13]. Greater degrees of hyperoxemia were likely in both the study by Girardis et al. [24] and in the HYPERS2S trial [23] of "induced" systemic hyperoxemia in patients with sepsis. Our study was focused solely on patients with ARDS, where due to their impaired gas exchange, they cannot attain this severity of systemic hyperoxia.

Oxygen use in ARDS

High inspired oxygen use was frequent in patients on day 1 of ARDS, with two thirds of patients with systemic hyperoxia receiving at least 60% oxygen in day 1—which we termed "excess oxygen use" on the basis that these patients could safely have had their FIO_2 reduced while maintaining normoxemia. Of importance, high FIO_2 use

Table 3 Factors associated with hospital mortality in study population ($n = 2005$) and in patients with hyperoxemia at day 1 ($n = 607$)

Factor	Odds ratio (95% confidence interval)	*p* value
Study population ($n = 2005$)—model on 1360 patients		
Age (year)	1.022 (1.015; 1.030)	<.0001
BMI (kg/m^2)	0.978 (0.962; 0.995)	0.0098
SOFA score—cardiovascular	1.182 (1.096; 1.275)	<.0001
SOFA score—respiratory	1.405 (1.182; 1.669)	0.0001
SOFA score—renal	1.209 (1.087; 1.344)	0.0005
SOFA score—central nervous system	1.147 (1.061; 1.240)	0.0006
Active/hematologic neoplasm or immunosuppression (ref. no.)	2.248 (1.697; 2.978)	<.0001
Chronic liver failure (ref. no.)	4.315 (2.184; 8.523)	<.0001
PIP (cmH_2O)	1.030 (1.013; 1.046)	0.0003
Invasive mechanical ventilation (ref. no.)	0.497 (0.339; 0.729)	0.0004
Bicarbonate (mmol/L)	0.979 (0.960; 0.997)	0.0240
Patients with $P_aO_2 > 100$ mmHg ($n = 607$)—model on 530 patients		
Age (year)	1.031 (1.018; 1.044)	<.0001
SOFA score —renal	1.362 (1.152; 1.610)	0.0003
SOFA score—cardiovascular	1.205 (1.073; 1.352)	0.0016
Active/hematologic neoplasm or immunosuppression (ref. no)	1.828 (1.186; 2.819)	0.0063
Chronic liver failure (ref. no.)	4.091 (1.256; 13.328)	0.0194
Total respiratory rate (breath/min)	1.043 (1.015; 1.072)	0.0027
Bicarbonate (mmol/L)	0.958 (0.924; 0.994)	0.0210

Abbreviations: *BMI* body mass index, *PIP* peak inspiratory pressure, *SOFA* sepsis-related organ failure assessment

was frequently transient, with a marked decrease in higher inspired oxygen concentration use on day 2. Nevertheless, at each decile of FIO_2, approximately one third of patients were hyperoxemic, suggesting the potential existed to further reduce oxygen use. Of interest, there was an association between excess oxygen use and the use of higher tidal volumes.

Our unadjusted analyses suggested an association between higher FIO_2 and poorer outcome. However, in multivariate analyses, which accounted for lung injury severity, we found no independent association between high FIO_2 use and patient outcome. Propensity-matched analyses in patients excess FIO_2 confirmed no difference in mortality compared to normoxemic patients.

Our findings do not support prior concerns [24] raised regarding the use of higher FIO_2 in patients with ARDS that are not hypoxemic. This finding also contrasts with the analysis of patients in the ARDS Network trials that found that the cumulative duration of "above target" oxygen exposure (FIO_2 above 0.5 in ARDS patients while PaO_2 was > 80 mmHg) was associated with mortality [27]. While the reasons for the divergent findings are unclear, potential explanations include the fact that our analysis concentrated on early ARDS, the fact that high FIO_2 use was transient in most patients in our cohort, and the fact that this analysis may have been better adjusted for the impact of lung injury severity.

Limitations

This study has several limitations. The non-linearity of P/F ratio at different FIO_2 [46] makes it difficult to predict the effect of FIO_2 on PaO_2/FIO_2, especially when matching patients with mild ARDS. While we have adjusted our analyses to account for known measured confounders, the possibility remains that some of our findings may arise from unmeasured or residual confounding. Moreover, we cannot make causal inferences for any associations seen, given the observational nature of our study. Our dataset comprises daily arterial blood gas and FIO_2 data, taken at a standardized time each morning. It is possible that these data do not properly reflect the spectrum of FIO_2 use and PaO_2 data over the course of that day. Given this, in the hyperoxemia analyses, we focused on patients that were hyperoxemic on both days 1 and 2 of ARDS. There are no single accepted definitions for hyperoxemia, hypoxemia, or excess oxygen use, so our definitions are of necessity arbitrary, and other definitions have been used in other analyses. This could partly explain any divergence in findings across these studies. Lastly, our assumption that

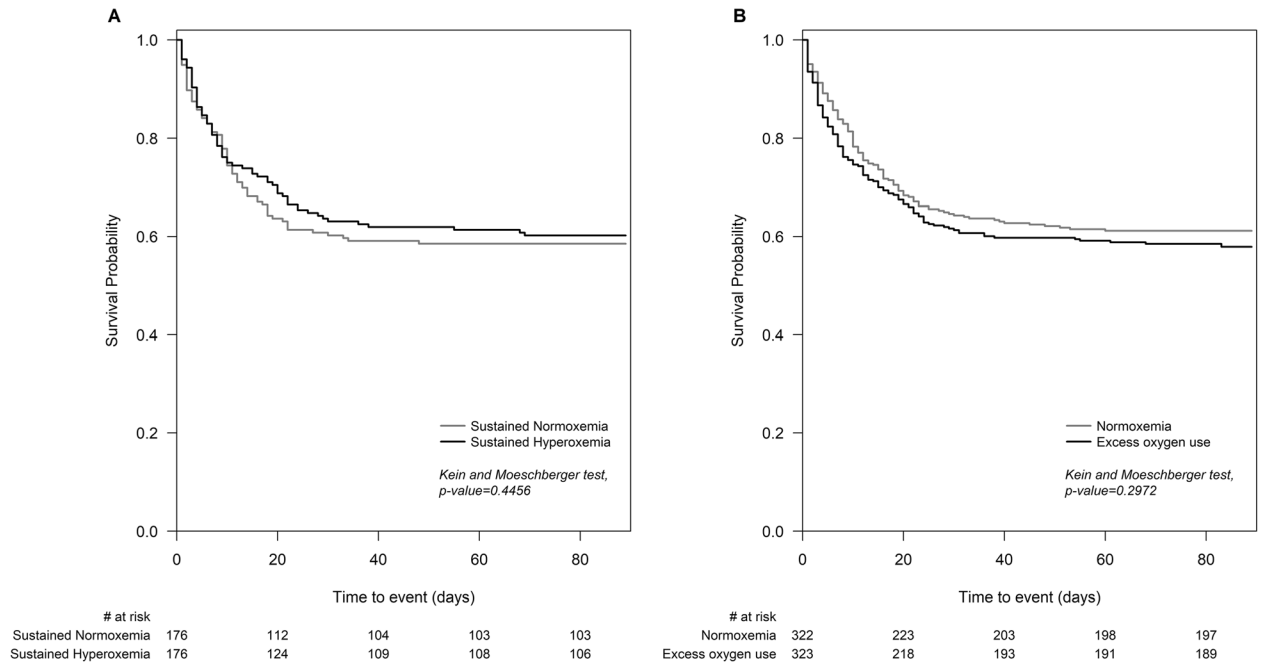

Fig. 5 Kaplan-Meier curves for hospital survival in matched samples. **a** Survival probability in matched sample ($n = 448$) of patients with sustained normoxemia and with sustained hyperoxemia. **b** Survival probability in matched sample ($n = 646$) of patients with normoxemia and with excess oxygen use at day 1. Notes: (1) Normoxemia is defined as 55 mmHg ≤ PaO_2 ≤ 100 mmHg on day 1 of ARDS, sustained normoxemia defined as normoxemia on day 1 and 2 of ARDS, sustained hyperoxemia defined as PaO_2 > 100 mmHg on day 1 and 2 of ARDS, and excess oxygen use defined as PaO_2 > 100 mmHg and FIO_2 ≥ 0.60 on day 1 of ARDS. (2) Mortality is defined as mortality at hospital discharge or at 90 days, whichever event occurred first. We assumed that patients discharged alive from the hospital before 90 days were alive on day 90. (3) The number of patients at risk reported at the bottom of the figure is referred to as the end of the corresponding day

inpatients at day 90 survived to hospital discharge is a further limitation.

Conclusions

Our findings demonstrate that hyperoxemia and high fractional inspired oxygen use is prevalent in patients with early ARDS in patients enrolled in the LUNG SAFE cohort. Higher FIO_2 use decreased from day 1 to day 2 of ARDS, with most day 2 hyperoxemia seen in patients at lower FIO_2, in whom gas exchange was improving. Reassuringly, we found no relationship between hyperoxemia or excessive oxygen use and patient outcome in this cohort.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13054-020-2826-6.

Additional file 1. Online Methodology and eTables. Expanded Methods and Materials. **eTable 1**: Comorbidities and risk factors in study population ($n = 2005$), stratified by arterial oxygenation on day 1. **eTable 2**. Characteristics of patients with sustained normoxemia and sustained hyperoxemia. **eTable 3**: Characteristics at ARDS onset and clinical outcomes in matched sample ($n = 354$) of patients with sustained normoxemia and with sustained hyperoxemia. **eTable 4**. Characteristics at ARDS onset and clinical outcomes in matched sample ($n = 646$) of patients with normoxemia and with excess oxygen use at day 1.

Abbreviations

ARDS: Acute respiratory distress syndrome; ICUs: Intensive care units; LUNG SAFE: Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure; ESICM: European Society of Intensive Care Medicine; PaO_2: Arterial oxygen tension; FIO_2: Fraction of inspired oxygen; MV: Invasive mechanical ventilation; ANOVA: Analysis of variance; LOESS: Locally estimated scatterplot smoothing; OR: Odds ratio; CI: Confidence interval; SOFA: Sepsis-related organ failure assessment

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JL, GB, and LB conceived of and designed this study, interpreted the data, drafted the manuscript, and revised the manuscript for important intellectual content. FM, TP, EF, and ER contributed to the acquisition of data, conducted data cleaning, analyzed the data, interpreted the data, and revised the manuscript for important intellectual content. BM, AP, RP, and FV interpreted the data and revised the manuscript for important intellectual content. All of the authors reviewed, discussed, and approved the final manuscript.

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All participating ICUs obtained ethics committee approval and obtained either patient consent or ethics committee waiver of consent in LUNG SAFE study. The study protocol was also reviewed and approved by the ethics committee of Mito Kyodo General Hospital, University of Tsukuba Hospital Mito Medical Center, Japan.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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