The effects of oxygen in critical illness

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ASSOCIATION BETWEEN ARTERIAL HYPEROXIA AND OUTCOME IN SUBSETS OF CRITICAL ILLNESS: A SYSTEMATIC REVIEW, META-ANALYSIS AND META-REGRESSION OF COHORT STUDIES

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ABSTRACT

Objective

Oxygen is vital during critical illness but hyperoxia may harm patients. Our aim was to systematically evaluate the methodology and findings of cohort studies investigating the effects of hyperoxia in critically ill adults.

Data Source

A meta-analysis and meta-regression analysis of cohort studies published between 2008 and 2015 was conducted. Electronic databases of MEDLINE, EMBASE and Web of Science were systematically searched for the keywords hyperoxia and mortality or outcome.

Study Selection

Publications assessing the effect of arterial hyperoxia on outcome in critically ill adults (≥18 years) admitted to critical care units were eligible. We excluded studies in patients with chronic obstructive pulmonary disease (COPD), extracorporeal life support or hyperbaric oxygen therapy and animal studies. Due to a lack of data, no studies dedicated to patients with acute lung injury, sepsis, shock or multiple trauma could be included.

Data Extraction

Studies were included independent of admission diagnosis and definition of hyperoxia. The primary outcome measure was in-hospital mortality and results were stratified for relevant subgroups (cardiac arrest, traumatic brain injury, stroke, post cardiac surgery and any mechanical ventilation). The effects of arterial oxygenation on functional outcome, long-term mortality and discharge parameters were studied as secondary outcomes.

Data Synthesis

Twenty-four studies were included of which five studies were only for a subset of the analyses. Nineteen studies were pooled for meta-analyses and showed that arterial hyperoxia during admission increases hospital mortality: adjusted odds ratio 1.21 [95% CI 1.08–1.37] (P=0.001). Functional outcome measures were diverse and generally showed a more favorable outcome for normoxia.

Conclusions

In various subsets of critically ill patients, arterial hyperoxia was associated with poor hospital outcome. Considering the substantial heterogeneity of included studies and the lack of a clinical definition, more evidence is needed to provide optimal oxygen targets to critical care physicians.

INTRODUCTION

Oxygen supply is part of the routine treatment in critically ill patients and one of the most effective lifesaving strategies in emergency situations. During acute conditions such as cardiac arrest, myocardial ischemia, traumatic brain injury and stroke, oxygen is typically administered in a liberal manner in the pre-hospital setting. When patients survive the initial phase of such life-threatening diseases, the majority is admitted to the intensive care unit (ICU), mechanically ventilated and supported with oxygen. During ICU stay, applied fractions of oxygen (FiO_2) typically exceed accustomed concentrations of ambient air and critically ill patients often achieve supranormal arterial oxygen levels (PaO_2) in the first 24 hours of admission (1, 2). In this setting, hyperoxia may compensate and prevent tissue hypoxia by promoting oxygen delivery to the affected organs. However, arterial hyperoxia has also been shown to induce vasoconstriction and reduce cardiac output which may impair blood flow to the organs at risk (3-5). In addition, hyperoxia facilitates a complex pro-inflammatory response and has been associated with cell injury by reactive oxygen species (ROS) (6, 7). Accordingly, oxygen therapy yields a delicate balance between benefit and harm, depending on dose, duration and underlying diseases.

In critically ill patients, the harmful effects are accentuated and may eventually prevail, considering the extended duration of supplemental oxygen and the patient's susceptibility for inflammation and cardiovascular instability. In recent years, an increasing number of studies have investigated the association between arterial hyperoxia and (functional) outcome in these patients. The purpose of this review was to perform a meta-analysis and meta-regression of cohort studies comparing hyperoxia to normoxia in critically ill adults.

MATERIALS AND METHODS

This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses (8). Eligibility criteria included observational cohort studies assessing the effect of arterial hyperoxia on outcome in critically ill adults (≥18 years) admitted to critical care facilities (e.g. ICU, CCU).

Data Sources and Searches

After consultation of a librarian, the electronic databases of MEDLINE (1962-2015), EMBASE (1970-2014) and Web of Science (1970-2014) were systematically searched by combining the key words and MeSH headings *hyperoxia* and *mortality* or *outcome*. Related synonyms, alternatives and plural (e.g. hyperoxaemia, arterial oxygen tension, oxygen supply, outcome, survival, fatality) were also considered. The main search was performed in July 2014 and updated in January 2015. In addition, personal records and reference lists of relevant articles were screened. The full electronic search string is shown in the supplemental data (Supplemental Digital Content 1).

Study Selection

Studies were independently screened based on title and abstract by two authors (HH, MR) and differences were resolved by consensus. We excluded studies in chronic obstructive pulmonary disease (COPD) patients, patients on extracorporeal life support and patients undergoing surgery at the time of oxygen sampling. Data from studies with hyperbaric oxygen therapy were not considered.

We retrieved full text of potentially eligible articles. Data from full-text articles were preferred in case of duplicate reports with concurrent data in conference abstracts. Published conference abstracts were only included when requisite data for quality assessment of the database was available. No language restrictions were applied. As no formal definition for hyperoxia exists, we included studies independent of admission diagnosis and definition of arterial hyperoxia.

Data Extraction and Quality Assessment

Relevant data were extracted using a standardized data abstraction sheet. The primary outcome measure was in-hospital mortality. The effects of arterial oxygenation on functional outcomes, long-term mortality and discharge parameters were also noted as secondary outcomes. Predictive scores, including the Cerebral Performance Category (CPC), Glasgow Coma Scale (GCS) and the modified Rankin Scale (mRS), were used as a surrogate for functional outcome. Corresponding authors of included articles were contacted or data from prior analyses (9) were used in case of missing requisite data.

Quality scoring for observational studies is controversial and may lack validity and value (10). Therefore, risk of bias was estimated according to the Newcastle-Ottawa quality assessment scale (11), but no summary score for study quality was adopted. Furthermore, the studies substantially differed in methodology in terms of study population and definition of hyperoxia. Hence, results were stratified and if possible analyzed separately for subgroups, hyperoxia thresholds, selection of PaO_2 measurement and secondary outcomes.

Data Synthesis and Analysis

Effect estimates were primarily presented as adjusted odds ratios. Unadjusted odds ratios were used in absence of adjusted odds ratios, and for formal meta-analysis of the data. Odds ratios with 95% confidence intervals were pooled in a random effects model according to Mantel and Haenszel for crude effects and inverse variance for adjusted effects.

Heterogeneity was assessed, using the I^2 statistics, Chi^2 test, Tau^2 and by visualization in a funnel plot, respectively. Small study effect was visually estimated by symmetry in funnel plots. The subgroup of any mechanically ventilated patients was excluded when analyzing the crude effects in view of the heterogeneous illness severity of this population (12, 13). In case of overlapping study populations (14, 15), individuals were only counted when included in a non-overlapping time period. As a random effects model was used and in view of the model's reliability, pooled subgroup estimates were only reported in the results when five or more studies were included. In accordance, the I^2 statistics for subgroup analyses were omitted in case of few studies in order to avoid overestimation of this measure. For purposes of exploring heterogeneity, adjusted odds ratios were also graphically presented stratified by admission diagnosis, selection of PaO_2 measurement and secondary outcomes. The effects of hyperoxia by threshold were, independent of admission diagnosis, analyzed using a meta-regression framework (16). Mixed effects models were performed with subgroup, threshold, and timing and selection of the PaO_2 measurement as predictors for outcome. In these moderator analyses, threshold was categorized according to the primary PaO_2 cut-off used for defining hyperoxia. Subgroups were categorized as the subsets of critically ill patients. The selection of the PaO_2 measurement was categorized as first, worst, highest or mean and the timing was defined as measurement within or beyond 24 hours of admission.

Analyses were conducted with RevMan 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria) using RStudio version 0.98.1028 (RStudio Inc, Boston, MA).

RESULTS

Search Results and Study Characteristics

Our search strategy resulted in 1609 studies considered for inclusion. After screening of titles and abstracts 32 full-text articles were assessed for eligibility (Fig. 1).

In total, 24 cohort studies were included, of which five studies were included only for specific subset analyses or for secondary outcomes (Table 1). The included articles were published between 2008 and 2015 and data collection was conducted between 1987 and 2012. In total, twelve articles included cardiac arrest patients, five included patients with traumatic brain injury (TBI), three included stroke patients, one included post cardiac surgery patients, and the remaining two studies included mechanically ventilated ICU patients, independent of admission diagnosis. The estimated risk of bias of included studies was moderately low. Most studies used large and high quality national databases and adjusted the data for severity of illness. Two studies did not adjust the data for potential confounders (17, 18) and two studies included cardiac arrest patients only when treated with therapeutic hypothermia (19, 20).

Qualitative Data Synthesis

Adjusted odds ratios for the primary outcome ranged from 0.11 to 2.00 (Supplemental Table 1, Supplemental Digital Content 2).

Frequent confounders included in multivariate analysis were age, sex, illness severity, and subgroup specific confounders such as neurological or cardiac parameters. The most commonly used threshold to define hyperoxia was 300 mmHg (range 85–487 mmHg), although cohort specific thresholds based on data distribution across percentiles were also frequently chosen. The selected PaO_2 used for classification of patients were mainly based on measurements in the first 24 hours of admission in the hospital or ICU. Some studies used longer time frames (20, 29, 34) and/or estimated hyperoxia exposure from more than one blood gas sample (20, 21, 27, 30, 34). In most studies, the reference range for calculating odds ratios was chosen as self-defined normoxia range. In a few studies hyperoxia was compared to non-hyperoxia (17, 26).

Some studies were not pooled in the meta-analyzed models, due to missing requisite crude (12, 13, 18, 21, 25-27) and/or adjusted data (17, 34) for the primary outcome. One study (24) was excluded for meta-analysis in order to prevent duplicate data synthesis as this study used a secondary analysis of another included cohort (23).

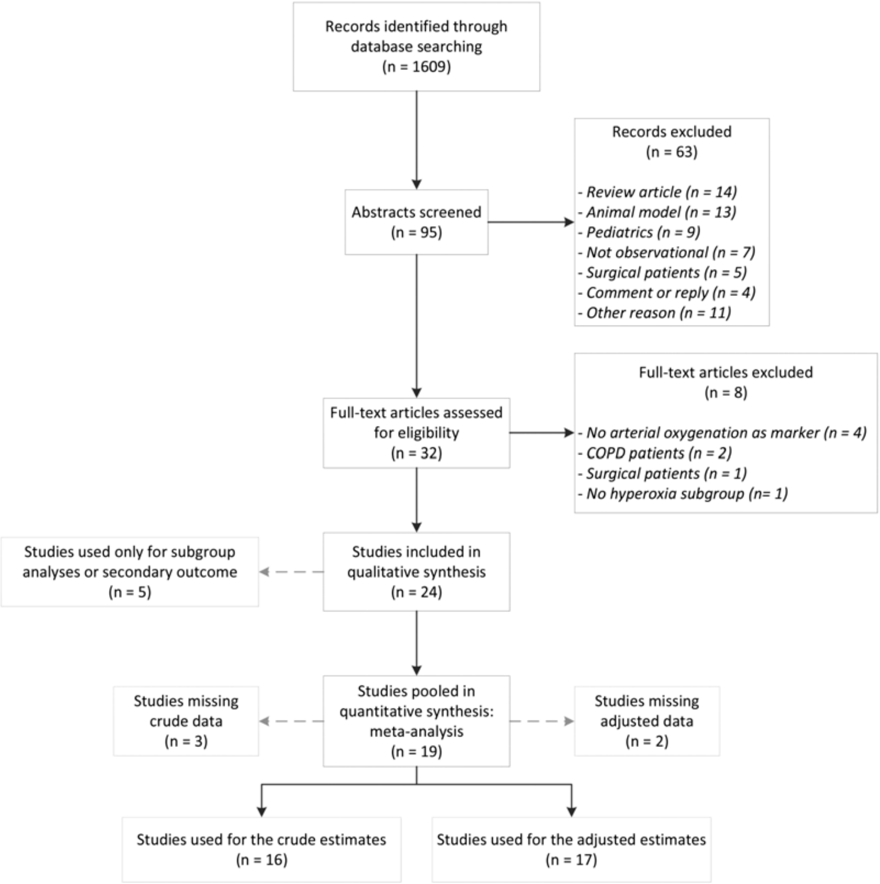


Figure 1. Flow diagram of study selection for the systematic review.
COPD, chronic obstructive pulmonary disease.

Quantitative Data Synthesis

Meta-analysis of sixteen studies covering 49,389 patients showed a crude odds ratio of 1.38 [95% CI 1.18–1.63] (P<0.0001) for in-hospital mortality, independent of admission diagnosis (Fig. 2). This corresponds with a risk ratio of 1.18 [95% CI 1.08–1.30] and a risk difference of 0.06 [95% CI -0.02–0.13]. The overall effects were statistically significant in subgroups of cardiac arrest (P=0.001) and ischemic stroke (P=0.03), but not for TBI (P=0.32), subarachnoid (P=0.47), intracerebral hemorrhage (P=0.09) and post cardiac surgery (P=0.19). Heterogeneity among all studies was substantial (I^2 76%), but unimportant among subgroups (I^2 0%).

Meta-analysis of adjusted estimates derived from seventeen studies showed an odds ratio of 1.21 [95% CI 1.08–1.37] (P=0.001) (Fig. 3). The tests for overall effect was only statistically significant for cardiac arrest patients (P=0.005). Again, heterogeneity among all studies was considerable (I^2 80%), and moderate among subgroups (I^2 41%).

Table 1. Characteristics of included studies sorted by subgroup

Author	Year	Country	Data collection	Subgroup	Setting	Inclusion period	Cohort size	Oxygen Supply	Remarks
de Jonge (12)	2008	The Netherlands	Retrospective	Any mechanical ventilation Subsample	ICU	1999-2006	36307	MV	High quality database
Eastwood (13)	2012	Australia/New Zealand	Retrospective	Any mechanical ventilation	ICU	2000-2009	152680	MV	High quality database
Bellomo (14)	2011	Australia/New Zealand	Retrospective	Cardiac arrest (non-traumatic)	ICU	2000-2009	12108	MV / SB	High quality database
Elmer (21)	2015	USA	Prospective	Cardiac arrest (all with ROSC)	-	2008-2010	184	MV	High quality database
Helmerhorst (22)	2014	The Netherlands	Retrospective	Cardiac arrest (non-traumatic)	ICU	2007-2012	5258	MV	High quality database Conference abstract
Ihle (15)	2013	Australia	Retrospective	Cardiac arrest (ventricular fibrillation)	ICU	2010-2011 2007-2011	207 584^{a}	MV / SB	High quality database
Janz (19)	2012	United States	Prospective	Cardiac arrest (mild therapeutic hypothermia)	CCU	2007-2012	170	MV	Specific subgroup
Kilgannon (23)	2010	United States	Retrospective	Cardiac arrest (non-traumatic)	ICU	2001-2005	6326	MV / SB	High quality database
Kilgannon (24)^{a}	2011	Unites States	Retrospective	Cardiac arrest (non-traumatic)	ICU	2001-2005	4459	MV / SB	High quality database
Lee (20)	2014	Republic of Korea	Retrospective	Cardiac arrest (therapeutic hypothermia)	-	2008-2012	213	-	Specific subgroup
Nelskyla (17)	2013	Australia	Prospective	Cardiac arrest (all with ROSC)	ICU	2008-2010	122	MV / SB	No adjustment for confounders
Roberts (25)^{a}	2013	United States	Prospective	Cardiac arrest (non-traumatic)	-	2009-2011	193	MV	High quality database

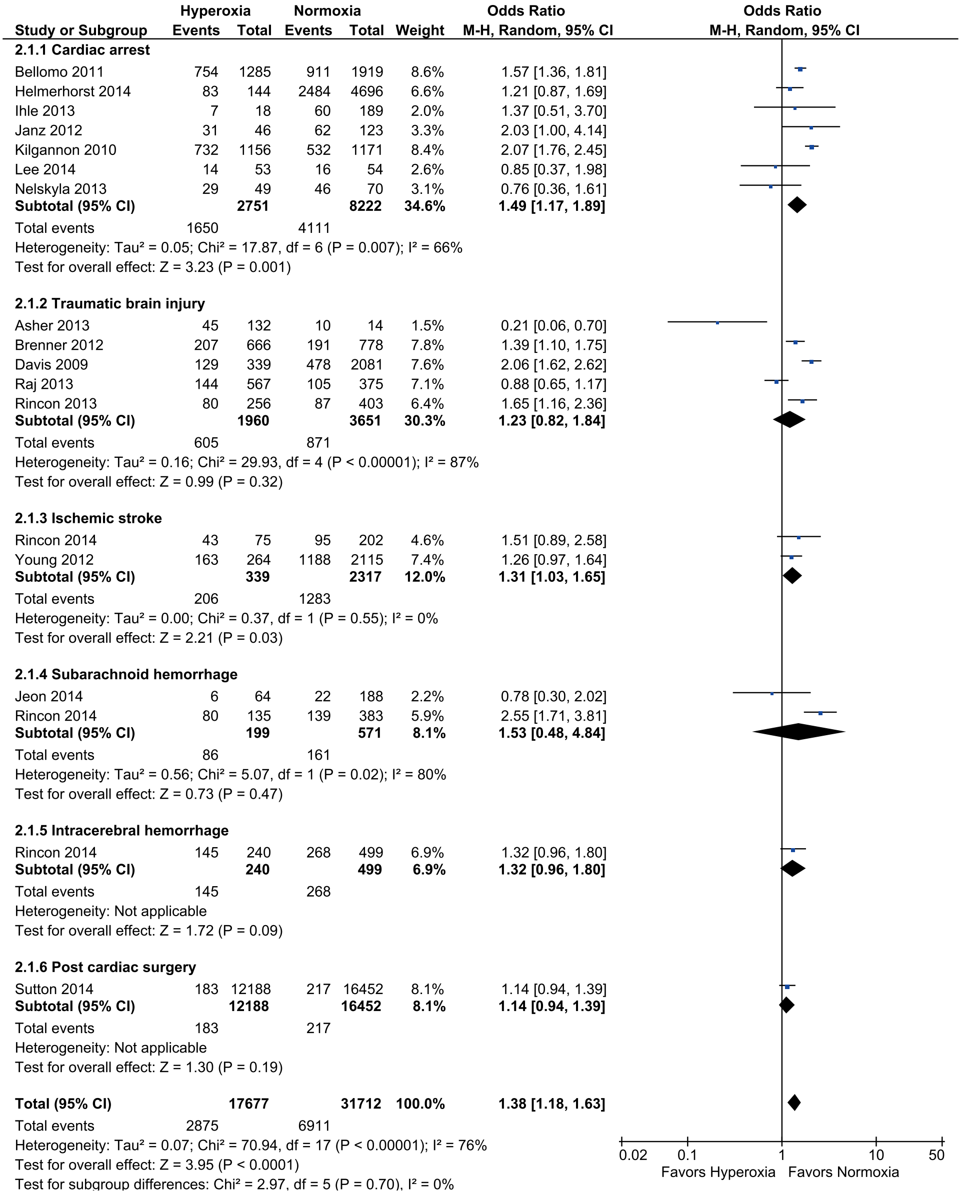
Table 1. (continued)

Author	Year	Country	Data collection	Subgroup	Setting	Inclusion period	Cohort size	Oxygen Supply	Remarks
Schneider (26)[a]	2013	Australia/New Zealand	Retrospective	Cardiac arrest (non-traumatic)	ICU	2000-2011	16542	MV	High quality database
Spindelboeck (18)[a]	2013	Austria	Retrospective	Cardiac arrest (non-traumatic)	CPR	2003-2010	145	MV	No adjustment for confounders
Vaahersalo (27)[a]	2014	Finland	Prospective	Cardiac arrest (out-of-hospital)	ICU	2010-2011	409	MV	High quality database
Sutton (28)	2014	Australia/New Zealand	Retrospective	Post cardiac surgery	ICU	2003-2012	83060	MV / SB	High quality database
Asher (29)	2013	United States	Retrospective	Traumatic brain injury	-	-	193	-	-
Brenner (30)	2012	United States	Retrospective	Traumatic brain injury	-	2002-2007	1547	-	-
Davis (31)	2009	United States	Retrospective	Traumatic brain injury	-	1987-2003	3420	-	-
Raj (32)	2013	Finland	Retrospective	Traumatic brain injury	ICU	2003-2012	1116	MV	High quality database
Rincon (33)	2013	United States	Retrospective	Traumatic brain injury	ICU	2003-2008	1212	MV	High quality database
Jeon (34)	2014	United States	Retrospective	Subarachnoid hemorrhage	-	1996-2011	252	MV	-
Rincon (35)	2014	United States	Retrospective	Stroke	ICU	2003-2008	2894	MV	High quality database
				Ischemic stroke			554[a]		
				Subarachnoid hemorrhage			936[a]		
				Intracerebral hemorrhage			1404[a]		
Young (36)	2012	Australia/New Zealand	Retrospective	Ischemic stroke	ICU	2000-2009	2643	MV	High quality database

MV, mechanical ventilation, SB, spontaneously breathing, ROSC, return of spontaneous circulation.

[a] Records are included for specific subgroup analyses or for secondary outcomes.

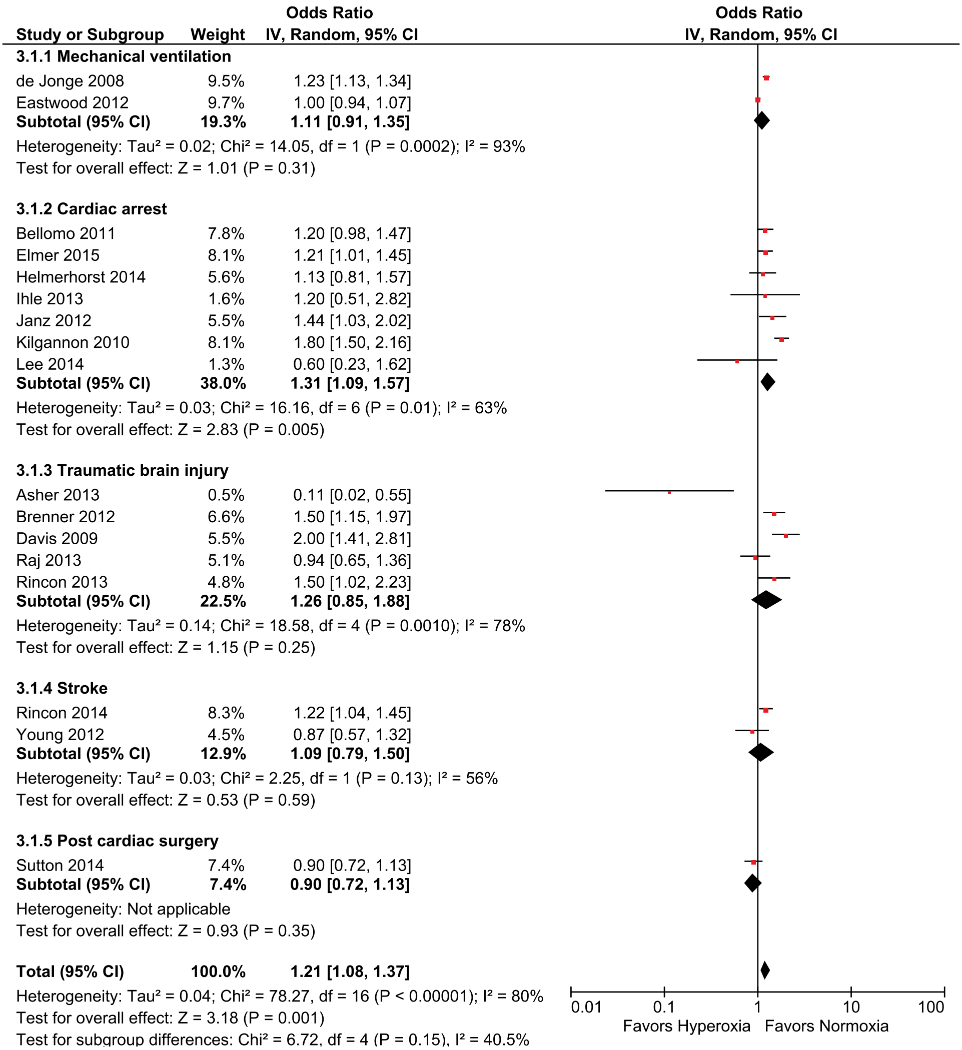
Dashes indicate not specifically stated.



	Hyperoxia		Normoxia			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
2.1.1 Cardiac arrest						
Bellomo 2011	754	1285	911	1919	8.6%	1.57 [1.36, 1.81]
Helmerhorst 2014	83	144	2484	4696	6.6%	1.21 [0.87, 1.69]
Ihle 2013	7	18	60	189	2.0%	1.37 [0.51, 3.70]
Janz 2012	31	46	62	123	3.3%	2.03 [1.00, 4.14]
Kilgannon 2010	732	1156	532	1171	8.4%	2.07 [1.76, 2.45]
Lee 2014	14	53	16	54	2.6%	0.85 [0.37, 1.98]
Nelskyla 2013	29	49	46	70	3.1%	0.76 [0.36, 1.61]
Subtotal (95% CI)		**2751**		**8222**	**34.6%**	**1.49 [1.17, 1.89]**
Total events	1650		4111			
Heterogeneity: Tau² = 0.05; Chi² = 17.87, df = 6 (P = 0.007); I² = 66%						
Test for overall effect: Z = 3.23 (P = 0.001)						
2.1.2 Traumatic brain injury						
Asher 2013	45	132	10	14	1.5%	0.21 [0.06, 0.70]
Brenner 2012	207	666	191	778	7.8%	1.39 [1.10, 1.75]
Davis 2009	129	339	478	2081	7.6%	2.06 [1.62, 2.62]
Raj 2013	144	567	105	375	7.1%	0.88 [0.65, 1.17]
Rincon 2013	80	256	87	403	6.4%	1.65 [1.16, 2.36]
Subtotal (95% CI)		**1960**		**3651**	**30.3%**	**1.23 [0.82, 1.84]**
Total events	605		871			
Heterogeneity: Tau² = 0.16; Chi² = 29.93, df = 4 (P < 0.00001); I² = 87%						
Test for overall effect: Z = 0.99 (P = 0.32)						
2.1.3 Ischemic stroke						
Rincon 2014	43	75	95	202	4.6%	1.51 [0.89, 2.58]
Young 2012	163	264	1188	2115	7.4%	1.26 [0.97, 1.64]
Subtotal (95% CI)		**339**		**2317**	**12.0%**	**1.31 [1.03, 1.65]**
Total events	206		1283			
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 2.21 (P = 0.03)						
2.1.4 Subarachnoid hemorrhage						
Jeon 2014	6	64	22	188	2.2%	0.78 [0.30, 2.02]
Rincon 2014	80	135	139	383	5.9%	2.55 [1.71, 3.81]
Subtotal (95% CI)		**199**		**571**	**8.1%**	**1.53 [0.48, 4.84]**
Total events	86		161			
Heterogeneity: Tau² = 0.56; Chi² = 5.07, df = 1 (P = 0.02); I² = 80%						
Test for overall effect: Z = 0.73 (P = 0.47)						
2.1.5 Intracerebral hemorrhage						
Rincon 2014	145	240	268	499	6.9%	1.32 [0.96, 1.80]
Subtotal (95% CI)		**240**		**499**	**6.9%**	**1.32 [0.96, 1.80]**
Total events	145		268			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.72 (P = 0.09)						
2.1.6 Post cardiac surgery						
Sutton 2014	183	12188	217	16452	8.1%	1.14 [0.94, 1.39]
Subtotal (95% CI)		**12188**		**16452**	**8.1%**	**1.14 [0.94, 1.39]**
Total events	183		217			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
Total (95% CI)		**17677**		**31712**	**100.0%**	**1.38 [1.18, 1.63]**
Total events	2875		6911			
Heterogeneity: Tau² = 0.07; Chi² = 70.94, df = 17 (P < 0.00001); I² = 76%						
Test for overall effect: Z = 3.95 (P < 0.0001)						
Test for subgroup differences: Chi² = 2.97, df = 5 (P = 0.70), I² = 0%						

Figure 2. Forest plot for the crude associations between arterial hyperoxia and hospital mortality by subsets of critical illness.
The pooled odds ratios were calculated using a random-effects model. Weight refers to the contribution of each study to the pooled estimates. CI, confidence interval, M-H, Mantel-Haenszel.

Adjusted odds ratios for mechanically ventilated patients (n=2 studies) were 1.00 [95% CI 0.94–1.07] and 1.23 [95% CI 1.13–1.34]. In cardiac arrest patients, the adjusted odds ratios (n=6 studies) ranged from 0.60 to 1.80, with a pooled estimate of 1.31 [95% CI 1.09–1.57] (I^2 63%). In patients with



Study or Subgroup	Weight	Odds Ratio IV, Random, 95% CI
3.1.1 Mechanical ventilation		
de Jonge 2008	9.5%	1.23 [1.13, 1.34]
Eastwood 2012	9.7%	1.00 [0.94, 1.07]
Subtotal (95% CI)	**19.3%**	**1.11 [0.91, 1.35]**
Heterogeneity: Tau² = 0.02; Chi² = 14.05, df = 1 (P = 0.0002); I² = 93%		
Test for overall effect: Z = 1.01 (P = 0.31)		
3.1.2 Cardiac arrest		
Bellomo 2011	7.8%	1.20 [0.98, 1.47]
Elmer 2015	8.1%	1.21 [1.01, 1.45]
Helmerhorst 2014	5.6%	1.13 [0.81, 1.57]
Ihle 2013	1.6%	1.20 [0.51, 2.82]
Janz 2012	5.5%	1.44 [1.03, 2.02]
Kilgannon 2010	8.1%	1.80 [1.50, 2.16]
Lee 2014	1.3%	0.60 [0.23, 1.62]
Subtotal (95% CI)	**38.0%**	**1.31 [1.09, 1.57]**
Heterogeneity: Tau² = 0.03; Chi² = 16.16, df = 6 (P = 0.01); I² = 63%		
Test for overall effect: Z = 2.83 (P = 0.005)		
3.1.3 Traumatic brain injury		
Asher 2013	0.5%	0.11 [0.02, 0.55]
Brenner 2012	6.6%	1.50 [1.15, 1.97]
Davis 2009	5.5%	2.00 [1.41, 2.81]
Raj 2013	5.1%	0.94 [0.65, 1.36]
Rincon 2013	4.8%	1.50 [1.02, 2.23]
Subtotal (95% CI)	**22.5%**	**1.26 [0.85, 1.88]**
Heterogeneity: Tau² = 0.14; Chi² = 18.58, df = 4 (P = 0.0010); I² = 78%		
Test for overall effect: Z = 1.15 (P = 0.25)		
3.1.4 Stroke		
Rincon 2014	8.3%	1.22 [1.04, 1.45]
Young 2012	4.5%	0.87 [0.57, 1.32]
Subtotal (95% CI)	**12.9%**	**1.09 [0.79, 1.50]**
Heterogeneity: Tau² = 0.03; Chi² = 2.25, df = 1 (P = 0.13); I² = 56%		
Test for overall effect: Z = 0.53 (P = 0.59)		
3.1.5 Post cardiac surgery		
Sutton 2014	7.4%	0.90 [0.72, 1.13]
Subtotal (95% CI)	**7.4%**	**0.90 [0.72, 1.13]**
Heterogeneity: Not applicable		
Test for overall effect: Z = 0.93 (P = 0.35)		
Total (95% CI)	**100.0%**	**1.21 [1.08, 1.37]**
Heterogeneity: Tau² = 0.04; Chi² = 78.27, df = 16 (P < 0.00001); I² = 80%		
Test for overall effect: Z = 3.18 (P = 0.001)		
Test for subgroup differences: Chi² = 6.72, df = 4 (P = 0.15), I² = 40.5%		

Figure 3. Forest plot for the adjusted associations between arterial hyperoxia and hospital mortality by subsets of critical illness.

The pooled odds ratios were calculated using a random-effects model. Weight refers to the contribution of each study to the pooled estimates. CI, confidence interval, IV, inverse variance.

TBI, adjusted odds ratios (n=5 studies) ranged from 0.11 to 2.00, with a pooled estimate of 1.26 [95% CI 0.85–1.88] (I^2 78%). Stroke patients were combined and adjusted odds ratios (n=2 studies) were 0.87 [95% CI 0.57–1.32] and 1.22 [95% CI 1.04–1.45]. In post cardiac surgery patients, the odds ratio (n=1) was 0.9 [95% CI 0.7–1.1].

The crude (Figure 4a) and adjusted (Figure 4b) effect estimates increased with increasing thresholds used for defining arterial hyperoxia (P=0.007 and P=0.22, respectively) and showed a significant difference between threshold categories (P<0.00001).

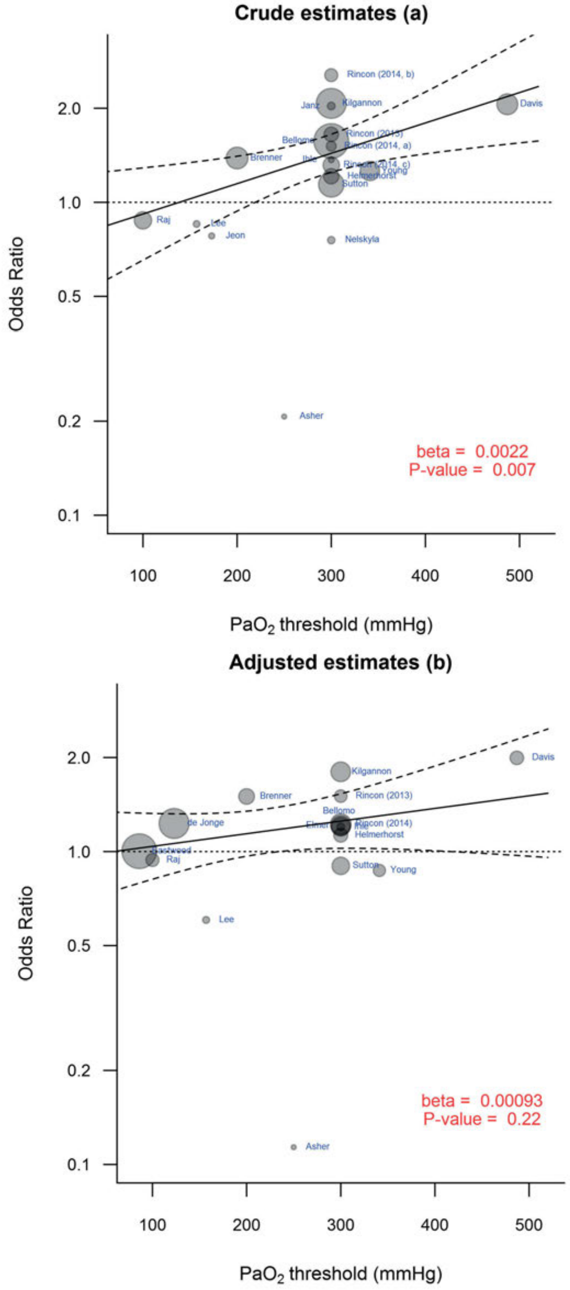


Figure 4. Meta-regression analysis for the crude (**a**) and adjusted (**b**) effects on hospital mortality by PaO$_2$ threshold.

Scatters indicate odds ratios for in-hospital mortality on a logarithmic scale, according to the hyperoxia threshold that was used as primary cutoff in the indicated studies. The point sizes are inversely proportional to the SEs of the individual studies (i.e., larger/more precise studies are shown as larger *circles*). The predicted effect sizes are modeled in a linear mixed-effects model with corresponding 95% CI boundaries and a β-coefficient with *p* value for the meta-regression line.

Figure 5 displays the effects stratified for selection of the PaO_2 measurement and also showed significant subgroup differences (P<0.001). When modeling the crude effects, subgroup (P=0.001), threshold (P=0.01) and timing and selection of the PaO_2 measurement (P=0.01 and P=0.003, respectively) were independent moderators of the outcome. The individual tests of moderators were not significant when modeling the adjusted estimates.

The symmetrical appearance of the funnel plots (Supplemental Fig. 1, Supplemental Digital Content 3 and Supplemental Fig. 2, Supplemental Digital Content 4) indicates that substantial publication bias is unlikely. Also, studies finding either statistically significant or non-significant

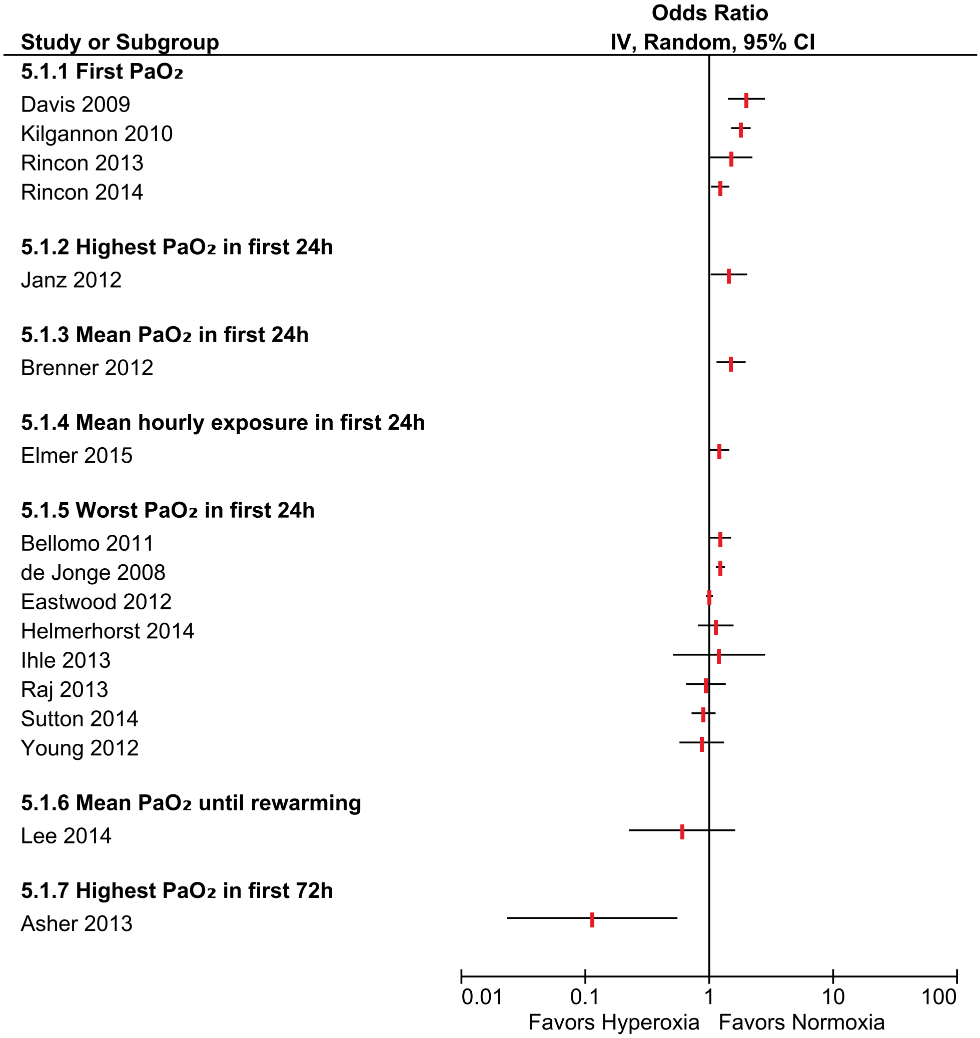


Figure 5. Forest plot for the adjusted effects of arterial hyperoxia by selection of PaO_2 measurements. Subgroups sorted in ascending order by timing and selection of PaO_2 measurements. Studies sorted alphabetically by name of first author.

effects were almost equally published and had a similar mean publication delay (129 vs. 121 days, respectively, P=0.68) (supplemental data, Supplemental Digital Content 1).

Secondary outcomes were diverse and results are listed in the Supplemental Table 2 (Supplemental Digital Content 5). Significant associations of adjusted analyses were found for CPC≥3 (cardiac arrest), GCS 3-8 (TBI), mRS 4-8 and delayed cerebral ischemia (stroke) (Fig. 6). Arterial hyperoxia was associated with hospital stay shorter than 7 days in TBI patients, although this association did not reach statistical significance for ICU stay in the same cohort (30), nor in

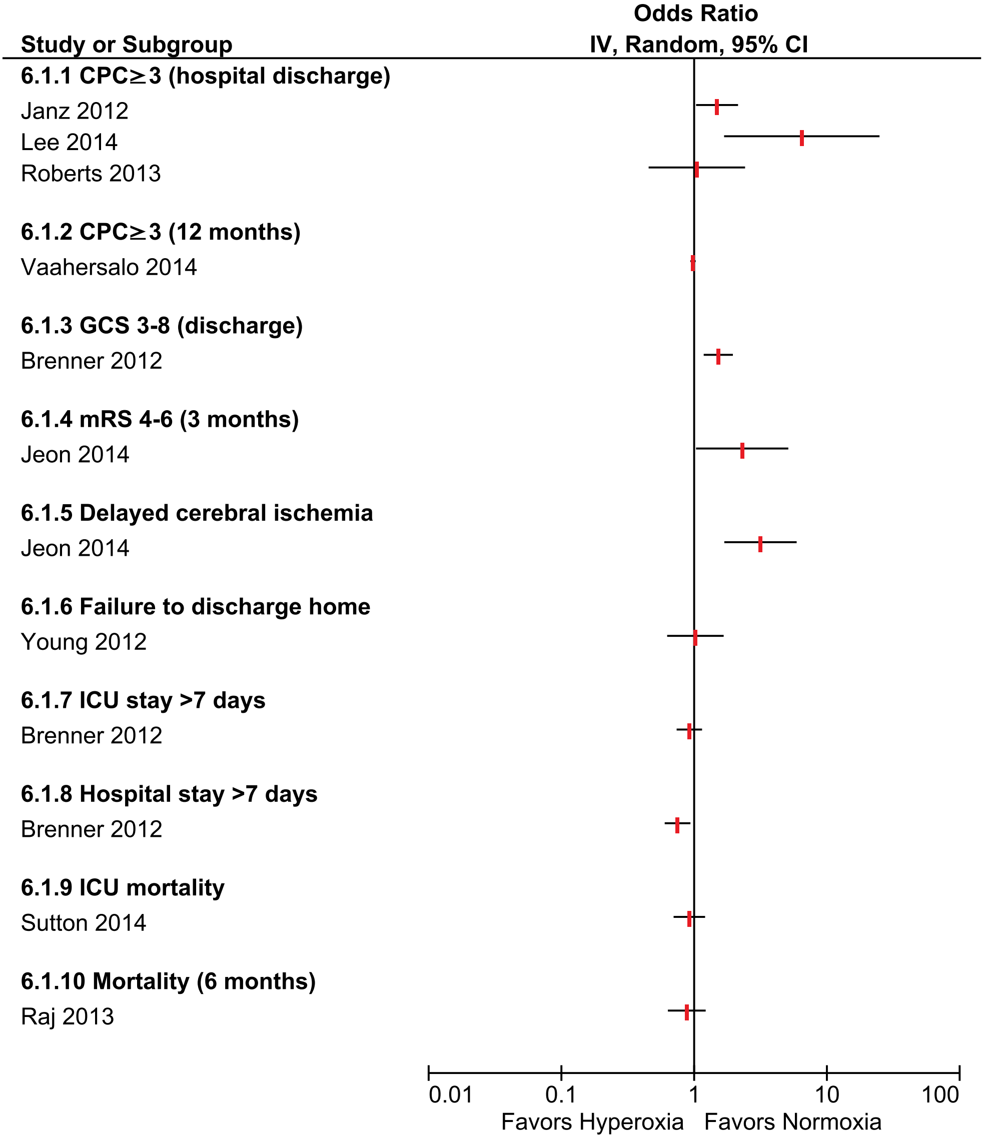


Figure 6. Forest plot for the adjusted effects of arterial hyperoxia by secondary outcomes. CPC, Cerebral Performance Category, GCS, Glasgow Coma Scale, mRS, modified Rankin Scale.

a prospective cohort of cardiac arrest patients (17). ICU mortality, 6 month-mortality and failure to discharge home were not significantly associated with arterial hyperoxia (17, 26, 28, 32, 36).

DISCUSSION

This systematic review identified nineteen observational cohort studies investigating the crude and/or adjusted effects of arterial hyperoxia on hospital mortality in major subgroups of critically ill patients. Meta-analysis of pooled data from all patients highlighted that arterial hyperoxia was associated with hospital mortality. After adjustment for confounders, this association was also established in patients admitted to critical care units following cardiac arrest, but this effect was not found in other subgroups. Functional outcome measures were diverse and showed a signal generally favoring normoxia. Other secondary outcomes were not associated with arterial hyperoxia. However, considerable heterogeneity and the observational character of included studies hamper profound conclusions and causal inferences.

The observed heterogeneity warrants cautious interpretation of pooled results. Our findings may be substantially influenced by the used methodology of the included studies and stress the importance of the used threshold, reference range, confounders, summary statistic, subgroup and outcome measure. The definition of hyperoxia and its reference range may be the most important factors determining the effect size. Indeed, increasing PaO_2 levels were more strongly associated with poor outcome, but this observation may have been attenuated by detrimental effects of hypoxia, in cases where this subgroup was not excluded from the reference group. Moreover, the prevalence of hyperoxia was highly dependent on the used threshold and also addresses the relevance of the risks of severe hyperoxia in different cohorts. The timing and selection of the PaO_2 measurement chosen to reflect arterial oxygenation emerged as another key determinant of the magnitude of the association. The choice of this summary statistic for defining hyperoxia can be essential in determining the relation between oxygenation and the outcome as oxygen toxicity may manifest during prolonged exposure, while direct effects may also be crucial in the acute and pre-hospital setting. Indeed, hyperoxia in the first arterial blood gas was more consistently associated with poor outcome than averaged oxygen levels, which may in fact not be a reliable marker of the total hyperoxic exposure during ICU stay. These findings suggest that oxygen may have both a time and dose dependent effect in which early (first samples) and severe hyperoxia are specifically hazardous. However, we cannot rule out that hyperoxia can also be harmful during prolonged exposure and when PaO_2 values are moderately higher than normal.

The study by Asher et al. (29) contradicts most other findings and is likely to be an outlier as a result of its small sample size which is also reflected in the funnel plots and by its weight in meta-analyses. Further, it is the only study to use the highest PaO_2 in the first 72 hours of admission, which may represent other oxygenation and ventilation strategies during this phase of admission than other summary statistics. Despite the addressed differences between all included studies, the direction of the pooled effects pertains, while the magnitude and significance level of individual results may be partially explained by methodological issues.

The following study strengths and limitations should be considered. First, well established confounders for outcome after ICU stay (e.g. illness severity scores), cardiac arrest (e.g. initial rhythm), TBI and stroke (e.g. Glasgow Coma Scale, Injury Severity Score), were assessed in some but not all included studies and may substantially determine the effect size. Moreover, authors should judiciously consider to recalculate illness severity scores when included as a confounder in multivariate analyses. These scores may contain the same PaO_2 derived from the first 24 hours of admission as the PaO_2 that is used for defining hyperoxia as outcome predictor. A recalculated score, omitting or standardizing oxygen components, may therefore avoid overadjustment in such analyses. In line, FiO_2 levels are closely related to PaO_2 levels, included in illness severity scores and may accordingly inflict multicollinearity.

Unmeasured bias may impose a further limitation inherent to analyses in observational studies. From the funnel plots, we cannot fully rule out that our findings are impacted by publication bias. On the other hand, the statistical significance level of the results did not appear to have an effect on publication delay and we also included data from a conference abstract study where database quality was previously assessed (37). Partially overlapping populations (14, 15, 26) (23, 24) in databases from included studies was accounted for by including only the main study in meta-analysis and by presenting the data as a subsample, where appropriate.

Experimental data from animal models have recently been summarized and showed an association between 100% oxygen therapy and worse neurological outcome following cardiac arrest (38). In accordance, aggregated data from observational studies focusing on cardiac arrest patients found a correlation between hyperoxia and hospital mortality (9). A recent meta-analysis found insufficient evidence regarding the safety of arterial hyperoxia, as the results may be impacted by methodological limitations (39). The current analyses extend these observations by including and aggregating all subgroups including post-operative cases, various secondary outcomes, novel data from recent cohort studies and by further exploring the impact of the definition of hyperoxia. Still, our findings may not depict a universal effect for all ICU patients and cannot be directly extrapolated to other subgroups.

Current guidelines aim at PaO_2 levels around 55 to 80 mmHg, but this target range was based on expert-consensus more than on evidence from clinical studies (40, 41). Conflicting findings from previous studies further impede the constitution of compelling clinical recommendations. Consequently, attitudes regarding the management of oxygen administration vary considerably and clinicians often consider hyperoxia acceptable as long as the FiO_2 is relatively low (1, 42). This may also be triggered by the double-edged nature of oxygen, which similarly urges strict prevention of hypoxia and its inherent hazards (12, 13). Furthermore, carbon dioxide may importantly mediate the effects of oxygen, although direct effects are assumed to be small (43). Hyperoxia may alternatively be a non-causal marker of disease severity as clinicians may intuitively treat the most severely ill patients with higher FiO_2 or PEEP levels in attempts to compensate for tissue hypoxia. Although this is less likely as the association between hyperoxia and mortality has also been shown to persist after adjustment for severity scores and FiO_2, future prospective intervention trials are needed to definitively study the effects of hyperoxia on outcome.

CONCLUSIONS

This systematic review has shown that, despite methodological limitations, arterial hyperoxia is associated with poor hospital outcome in various subsets of critically ill patients. The harmful effects depend on hyperoxic degree and may be more pertinent to certain subgroups at specific moments of admission. Taken together, the effect estimates favoring normoxia were quite consistent throughout our analyses, but were not universal for all subsets and secondary outcomes. In the absence of studies specifically addressing the effects in other important critical care subgroups, including acute lung injury, sepsis, shock and multiple trauma, the vast majority of the population in the current analysis consisted of patients with mechanical ventilation, cardiac arrest, traumatic brain injury and stroke. Furthermore, the impact of pursuing normoxia on the incidence of hypoxic episodes is unknown and the long-term effects of conservative oxygen therapy are still to be assessed in large cohorts. Given the lack of robust guidelines, more evidence is needed to provide tailored oxygen targets for critically ill patients.

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ONLINE SUPPLEMENT

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6a

TO THE EDITOR: ASSOCIATION BETWEEN HYPEROXIA AND MORTALITY AFTER CARDIAC ARREST

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We read the article by Helmerhorst et al. (1) with interest. Hyperoxia has been studied in emergency situations, such as cardiac arrest (CA), myocardial ischemia, traumatic brain injury, and stroke. The potential harm of hyperoxia due to the oxygen free radical formation has been discussed in several studies. Because of the diversity of diseases and the different definitions of hyperoxia, these conclusions remain contradictory.

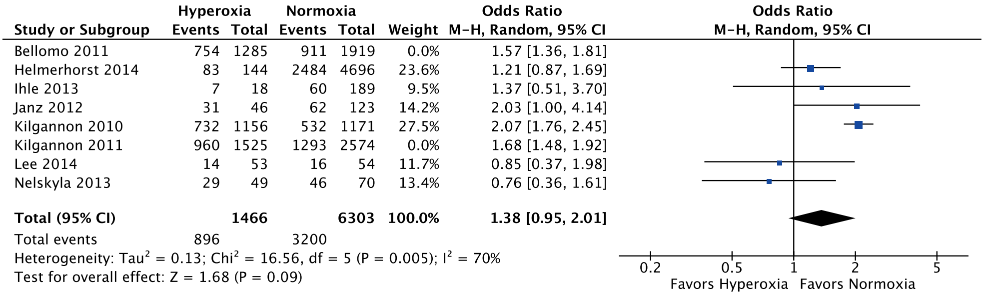
In this review, seven studies about CA have been pooled to investigate the association between hyperoxia and mortality. Because of the diversity of methodology, definitions of hyperoxia, reference range, and other confounders, the heterogeneity was significant (I^2 = 66%), which warrants cautious interpretation of the pooled results.

In a sensitivity analysis of this pooled outcome, we found that when the study by Bellomo et al. (2) was excluded, the conclusion became insignificant (odds ratio, 1.38; 95% CI, 0.95–2.01; I^2 = 70%) (**Fig. 1**).

This may be explained that Bellomo et al. (2) chose the lowest PaO_2 level or the PaO_2 associated with the arterial blood gas with the highest alveolar-arterial gradient, which may lead to the underestimation of the proportion of hyperoxia. According to the conclusion of Kilgannon et al. (3), there was a dose-dependent association between mortality and PaO_2 range, with a 24% increase in mortality risk for every 100 mmHg increase in PaO_2, which means that in the study by Bellomo et al. (2), the mortality associated with hyperoxia may be overestimated.

Besides, in the study by Kilgannon et al. (4) based on IMPACT database, a large critical-care database of ICU at 120 U.S. hospitals initially developed by the Society of Critical Care Medicine, the first blood gas measurement in the ICU was used and found that hyperoxia (PaO_2 of at least 300 mmHg) was associated with increased mortality. This excluded the temporal effect of hyperoxia, which has been debated whether the use of blood gas value at a single time point was appropriate.

In this sensitivity analysis, when the study by Kilgannon et al. (4) was excluded, the heterogeneity became insignificant, with I^2 decreasing from 66% to 33%, which raised the question: Is it appropriate to include this study in this analysis? In the reanalysis of IMPACT database by Kilgannon et al. (3), they defined the exposure by the highest partial pressure of arterial oxygen over the first 24 hours



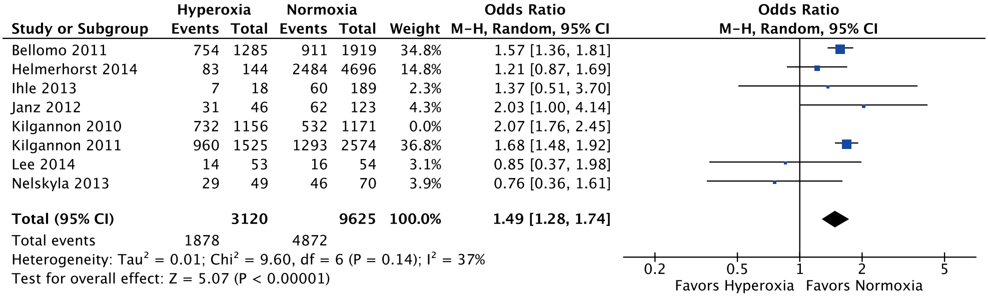
Study or Subgroup	Hyperoxia Events	Hyperoxia Total	Normoxia Events	Normoxia Total	Weight	Odds Ratio M-H, Random, 95% CI
Bellomo 2011	754	1285	911	1919	0.0%	1.57 [1.36, 1.81]
Helmerhorst 2014	83	144	2484	4696	23.6%	1.21 [0.87, 1.69]
Ihle 2013	7	18	60	189	9.5%	1.37 [0.51, 3.70]
Janz 2012	31	46	62	123	14.2%	2.03 [1.00, 4.14]
Kilgannon 2010	732	1156	532	1171	27.5%	2.07 [1.76, 2.45]
Kilgannon 2011	960	1525	1293	2574	0.0%	1.68 [1.48, 1.92]
Lee 2014	14	53	16	54	11.7%	0.85 [0.37, 1.98]
Nelskyla 2013	29	49	46	70	13.4%	0.76 [0.36, 1.61]
Total (95% CI)		**1466**		**6303**	**100.0%**	**1.38 [0.95, 2.01]**
Total events	896		3200			

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 16.56$, df = 5 (P = 0.005); $I^2 = 70\%$

Test for overall effect: Z = 1.68 (P = 0.09)

Figure 1. Sensitivity analysis of association between hyperoxia and mortality (Bellomo et al (2) was excluded). M-H, Mantel-Haenszel.

in the ICU, with the same inclusion and exclusion criteria of Kilgannon et al. (4). Because of different data acquisition time, the number of patients was slightly different. We extracted the mortality from Figure 1 in this article, with definition of hyperoxia as PaO_2 of at least 300 mmHg, and reanalyzed in Review Manager 5.1.6. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). The heterogeneity become insignificant (I^2 = 37%) (**Fig. 2**), and the sensitive analysis was stable.



	Hyperoxia		Normoxia			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Bellomo 2011	754	1285	911	1919	34.8%	1.57 [1.36, 1.81]
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Lee 2014	14	53	16	54	3.1%	0.85 [0.37, 1.98]
Nelskyla 2013	29	49	46	70	3.9%	0.76 [0.36, 1.61]
Total (95% CI)		**3120**		**9625**	**100.0%**	**1.49 [1.28, 1.74]**
Total events	1878		4872			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 9.60$, df = 6 (P = 0.14); $I^2 = 37\%$
Test for overall effect: Z = 5.07 (P < 0.00001)

Figure 2. Reanalysis of association between hyperoxia and mortality (Kilgannon et al (4) was replaced by Kilgannon et al (3)). M-H, Mantel-Haenszel.

Based on current studies, hyperoxia was associated with increased mortality in CA patients; because of the diversity definition of hyperoxia in these studies, the pooled results should be interpreted with caution.

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6b

THE AUTHORS REPLY

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We thank Shen and Zhang (1) for their interest and thoughtful analyses regarding our work. Their sensitivity analyses provide valuable insights in the relationship between arterial hyperoxia and hospital mortality after cardiac arrest and further emphasize the importance of the used definition for arterial hyperoxia. As discussed in our study (2), we strongly agree that the pooled results must be interpreted with caution in view of the observed heterogeneity.

The selection of a single PaO_2 yields considerable limitations and the time point at which the arterial blood gas was analysed may further lead to misinterpretation of the actual exposure to hyperoxia during ICU admission. Indeed, we showed that both timing and selection were independent moderators of the outcome when modeling the crude effects (2). Sensitivity analyses are useful alternatives to examine the impact of individual study results and methodology. The abstraction of arterial hyperoxia that was used in the studies by Bellomo et al. (3) and Kilgannon et al. (4) may indeed not be the most representative method, but the rationale for an eventual exclusion of these studies in analyses should also be carefully considered.

First, similar methods using the first, lowest or worst PaO_2 during admission were also frequently used in other cohorts and have not previously been shown to be inferior. Second, after exclusion of the study by Bellomo et al. (3), the recalculated pooled effect estimate reflects statistical insignificance by the strict use of statistical thresholds, but the absolute difference between the original estimate and the estimate in sensitivity analyses was actually marginal (odds ratio difference, 0.11) and showed a slight shift in magnitude yet not in direction. The shift in effect size should rather be interpreted as a loss of statistical power considering the size of the excluded cohort. This is also supported by the adjusted analyses, which may be used to overcome several other study limitations. When the study by Bellomo et al. (3) was excluded in sensitivity analyses using adjusted effect estimates, the pooled effects remained virtually unchanged (adjusted odds ratio, 1.32; 95% CI, 1.05–1.66 vs adjusted odds ratio, 1.31; 95% CI, 1.09–1.57). It can be debated whether this study essentially overestimated the mortality. The authors have comprehensively stratified the risks by deciles of PaO_2, whereas we selected only the reported risk estimate according to the primarily used threshold of hyperoxia (i.e., 300 mmHg). Their results have previously been compared with the Kilgannon studies, and other methodological differences may explain heterogeneity (5). It is yet interesting to note that the replacement of the original Kilgannon study data (4) by their secondary analysis reduces the heterogeneity, which may be attributed to the use of the highest PaO_2 in concordance with the study by Janz et al. (6). Nonetheless, the recalculated pooled effect estimates did not materially differ, which may in fact not be overly surprising because the data were generated from a subsample of the same cohort.

Finally, the temporal effect of hyperoxia has not been adequately accounted for in most studies and is typically only estimated within the first 24 hours of admission. The exact impact over the total ICU admission remains unknown although we have initiated comprehensive analyses comparing different strategies for defining hyperoxia. Preliminary results of such analyses in a Dutch multicenter cohort of ICU patients suggest that all strategies differ substantially, and results should therefore always be viewed in light of the used definition for arterial hyperoxia.

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7

METRICS OF ARTERIAL HYPEROXIA AND ASSOCIATED OUTCOMES IN CRITICAL CARE

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ABSTRACT

Objective

Emerging evidence has shown the potential risks of arterial hyperoxia, but the lack of a clinical definition and methodological limitations hamper the interpretation and clinical relevance of previous studies. Our purpose was to evaluate previously used and newly constructed metrics of arterial hyperoxia and systematically assess their association with clinical outcomes in different subgroups in the intensive care unit (ICU).

Design

Observational cohort study

Setting

Three large tertiary care ICUs in the Netherlands

Patients

A total of 14,441 eligible ICU patients

Interventions

None

Measurements and Main Results

In total, 295,079 arterial blood gas (ABG) analyses, including the partial pressure of arterial oxygen (PaO_2), between July 2011 and July 2014 were extracted from the patient data management system database. Data from all admissions with more than one PaO_2 measurement were supplemented with anonymous demographic and admission and discharge data from the Dutch National Intensive Care Evaluation registry. Mild hyperoxia was defined as PaO_2 between 120 and 200 mmHg; severe hyperoxia as PaO_2 >200 mmHg. Characteristics of existing and newly constructed metrics for arterial hyperoxia were examined and the associations with hospital mortality (primary outcome), ICU mortality and ventilator-free days and alive at day 28 (VFDs) were retrospectively analyzed using regression models in different subgroups of patients.

Severe hyperoxia was associated with higher mortality rates and fewer VFDs in comparison to both mild hyperoxia and normoxia for all metrics except for the worst PaO_2. Adjusted effect estimates for conditional mortality were larger for severe hyperoxia than for mild hyperoxia. This association was found both within and beyond the first 24 hours of admission and was consistent for large subgroups. The largest point estimates were found for the exposure identified by the average PaO_2, closely followed by the median PaO_2 and these estimates differed substantially between subsets. Time spent in hyperoxia showed a linear and positive relationship with hospital mortality.

Conclusions

Our results suggest that we should limit the PaO_2 levels of critically ill patients within a safe range, as we do with other physiological variables. Analytical metrics of arterial hyperoxia should be judiciously considered when interpreting and comparing study results and future studies are needed to validate our findings in a randomized fashion design.

INTRODUCTION

Oxygen therapy and arterial oxygenation play a vital role in the clinical course of patients in the intensive care unit (ICU). The effects of hypoxia are well established and are actively prevented in order to maintain physiological stability. In contrast, hyperoxia is frequently encountered in the ICU but generally accepted (1-3). In recent years, emerging evidence has shown the potential risks of arterial hyperoxia (4, 5), but observational studies failed to indisputably demonstrate its impact on clinical outcomes of critically ill patients (6-9). Most studies focus on hospital mortality of mechanically ventilated patients, but the lack of a clinical definition of hyperoxia and methodological limitations hamper the interpretation and clinical relevance of these studies (10). Importantly, it is unknown whether the partial pressure of arterial oxygen (PaO_2) from a single arterial blood gas (ABG) measurement in the first 24 hours of admission reliably estimates the actual exposure to hyperoxia and associated risks during the ICU stay. Also, we do not know whether high arterial peak-levels of oxygen or prolonged exposure to high PaO_2 are associated with adverse outcomes. Knowledge on oxygenation metrics and related summary statistics is important when interpreting studies on the effects of hyperoxia and for setting up future research. Oxygenation based metrics may be based on a certain time period (e.g. first 24 hours after ICU admission or complete ICU period) and on a single measurement, central tendency or cumulative exposure.

The aim of this study was to 1) comprehensively assess the metric-related association of arterial oxygenation with clinical outcomes in different subsets of critically ill patients and 2) systematically evaluate the influence of choosing a certain metric on the composition of subgroups of patients with arterial hyperoxia and mortality in those subgroups.

MATERIALS AND METHODS

Data collection

Data were collected between July 2011 and July 2014. Data collection procedures have been described in detail previously, and reviewed and approved by the Medical Ethical Committee of the Leiden University Medical Center (2, 11). In brief, arterial blood gas (ABG) analyses and concurrent ventilator settings were extracted from the patient data management system (PDMS) database (MetaVision, iMDsoft, Leiden, The Netherlands) of closed format, mixed medical and surgical, tertiary care ICUs of three participating hospitals in the Netherlands. Data were supplemented with anonymous demographic data, admission and discharge data, and variables to quantify severity of illness from the Dutch National Intensive Care Evaluation (NICE) registry, a high quality database, which has been described previously (12). According to the Dutch Medical Research Involving Human Subjects Act, there was no need for informed patient consent, as only registries without patient identifying information were used. Admissions were only eligible for inclusion when requisite data from more than one ABG measurement was available. Patients on extracorporeal membrane oxygenation were excluded from the study. Conservative oxygenation was promoted during the study in all three units, but actual strategies were left to the discretion of the attending physicians and nurses.

Hyperoxia metrics

We calculated several previously used and newly constructed metrics for arterial hyperoxia. Existing metrics were derived from a systematic literature review and included the first, highest, worst, and average PaO_2, typically assessed over the first 24 hours of admission (9). These metrics were compared to new metrics within specific time frames, namely the median, area under the curve and time spent in arterial hyperoxia.

As no formal definition for arterial hyperoxia exists, we stratified the analyses using previously used thresholds, while considering the incidence in the present cohort. Mild hyperoxia was defined as PaO_2 120 – 200 mmHg (13) and severe hyperoxia as $PaO_2 > 200$ mmHg (14).

Metrics of single sampling

The first PaO_2 (FIR) was the PaO_2 value that was measured in the first ABG registered in the PDMS after the patient was admitted to the ICU.

Highest PaO_2 (MAX) was the maximum value that was registered during the first 24 hours ($MAX_{0\text{-}24}$) or during the total ICU LOS ($MAX_{ICU\ LOS}$). Worst PaO_2 (WOR) was defined as the PaO_2 derived from the ABG associated with the lowest concurrent PaO_2 to fractions of inspired oxygen ratio (FiO_2) ratio (P/F ratio) and also calculated for the first 24 hours ($WOR_{0\text{-}24}$) and over the total ICU LOS ($WOR_{ICU\ LOS}$) (13, 15).

Metrics of central tendency

The average (AVG) and median (MED) PaO_2 were calculated over the first 24 hours and over the total ICU LOS per admission.

Metrics of cumulative exposure

Per patient, the area under the curve was computed over the first 24 hours ($AUC_{0\text{-}24}$), first 96 hours ($AUC_{0\text{-}96}$) and total duration of ICU admission ($AUC_{ICU\ LOS}$) using linear interpolation of the available PaO_2 measurements. We calculated the median PaO_2 over the respective time frames and inserted these values as PaO_2 measurements at the starting (T=0) and end point of the curve (T=24, T=96 or at discharge or death, depending on considered time frame).

Smoothing curves, using natural spline interpolation (16), were fitted to compute the individual time spent in the range of hyperoxia in a similar manner. Patients with an interval longer than 24 hours between two consecutive PaO_2 measurements were excluded from these analyses (n=392), as the amount of estimated data from the fitted curve would otherwise excessively exceed the amount of real data.

Statistical Analyses

In accordance with a study examining glucose metrics in critical care (17), we analyzed the associations between the metrics and hospital mortality (primary outcome) by logistic regression with each metric categorized by severity of the hyperoxic exposure based on specified thresholds (120 and 200 mmHg) or data distribution (quintiles) and compared these categories to normoxia (60-120 mmHg) or median quintiles. The associations between the metric and secondary outcomes, including ICU mortality, and ventilator-free days (VFDs) were also assessed. VFDs were calculated as the number of ventilator-free days and alive, 28 days after ICU admission according to a previously described definition (18).

Data were reanalyzed for specific subgroups categorized by use of mechanical ventilation, admission type and specific admission diagnoses that were studied in previous work (8, 9, 19). The multivariate models were adjusted for age and APACHE IV, which were found to be confounders in previous studies (17). The APACHE score was calculated from the data obtained within 24 hours of admission. ICU LOS was also included as potential confounder for the association with hospital mortality. In the multivariate logistic regression models, we quantify how the metrics are associated with the distribution between death and discharge at a specific time point, given that either of the two occurs (conditional hospital mortality). Adjusted associations with conditional hospital mortality were also depicted using loess smoothing curves.

The relationship between the individual metrics, that were not directly dependent on the ICU LOS, was examined using pairwise correlations and cluster analysis. The area under the receiver-operating characteristic curve (C-statistic), the Brier score and the Nagelkerke R^2 were determined as measures of discrimination and/or calibration for the univariate models of metrics using data from the first 24 hours of admission. In these models, spline based transformations of the metrics were used to predict hospital mortality. A recalibration of the APACHE IV score was explored by replacing the oxygen component by the first, mean, median, worst or highest PaO_2 within the first 24 hours of admission. The multivariate models were reanalyzed by additionally adjusting for applied FiO_2 levels and also if the oxygen component in the APACHE score covariate was removed.

All statistical analyses were conducted using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). To account for multiple testing, the indicated levels of statistical significance were lowered to 0.01.

RESULTS

In total, 14,441 patients were included and 295,079 ABG analyses were obtained from eligible admissions (Table 1). The median time to the first ABG measurement was 26 (IQR 13-69) minutes, the median interval between two consecutive ABG samples was 249 (IQR 147-358) minutes, and the median number of ABG measurements per patient was 7 (IQR 4-17).

Metric characteristics

All metrics calculated over the first 24 hours of admission were strongly related to the corresponding metrics calculated over the total ICU LOS (Pearson $r = 0.87–0.91$, Supplemental Fig. 1, Supplemental Digital Content 1). Also, $\text{AVG}_{\text{ICU LOS}}$ had high correlation with $\text{MED}_{\text{ICU LOS}}$ ($r = 0.92$). In contrast, very low correlation ($r < 0.25$) was shown for $\text{MAX}_{\text{ICU LOS}}$ with $\text{WOR}_{\text{ICU LOS}}$, and $\text{WOR}_{0\text{-}24}$. Cluster analysis in the Supplemental Digital Content showed that the metrics could be subdivided in multiple families, where the highest PaO_2 appeared to be least related to the other metrics (Supplemental Fig. 2, Supplemental Digital Content 1).

Table 1. Descriptive characteristics

	Total
Patients characteristics	
No. of patients	14,441
Demographics	
Age, y	65 (55-73)
Male, n (%)	9315 (64.5)
BMI, kg/m^2	25.8 (23.3-29.0)
Planned admission, n (%)	7328 (50.7)
Medical admission, n (%)	5130 (35.5)
Planned surgery, n (%)	5038 (34.9)
Emergency surgery, n (%)	1344 (9.3)
Clinical characteristics	
APACHE IV score	54 (41-75)
APACHE IV predicted mortality, %	5.2 (1.4-22.9)
SAPS II score	34 (26-45)
SAPS II predicted mortality, %	15 (7-34)
Clinical outcomes	
Mechanical ventilation time, hrs	11 (5-40)
ICU LOS, hrs	37 (21-85)
ICU mortality, n (%)	1427 (9.9)
Hospital mortality, n (%)	1989 (13.8)
Oxygenation and ventilation characteristics	
No. of arterial blood gas analyses	295,079
Arterial blood gas results	
PaO_2, mmHg	81 (70-98)
$PaCO_2$, mmHg	40 (34-46)
pH	7.42 (7.36-7.47)
Hb, mmol/L	6.2 (1.2)
Lactate, mmol/L	1.5 (1.0-2.2)
Glucose, mmol/L	7.6 (6.4-9.1)
Ventilator settings	
FiO_2, %	40 (31-50)
PEEP, cm H_2O	7 (5-10)
Mean airway pressure, cm H_2O	11 (9-14)
Oxygenation measures	
PaO_2/FiO_2 ratio	219 (165-290)
Oxygenation index	3.8 (2.5-6.1)

Data are means (±SD) or medians (IQR), unless stated otherwise, BMI, Body Mass Index; APACHE, Acute Physiology and Chronic Health Evaluation score; SAPS, Simplified Acute Physiology Score; ICU LOS, Intensive Care Unit Length of Stay; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; Hb, hemoglobin; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure. Oxygenation index was calculated as the FiO_2/PaO_2 ratio multiplied by the concurrent mean airway pressure

Within 24 hours of admission, a spline based transformation of the worst PaO_2 was the best discriminator for hospital mortality. When recalculating the APACHE score with different metrics using PaO_2 data from the first 24 hours of admission, equal discrimination (C-statistic) was found for APACHE IV with either worst, highest, first, average or median PaO_2 (Supplemental Table 1, Supplemental Digital Content 1).

Clinical outcomes

Unadjusted analyses showed higher mortality rates and fewer VFDs for severe hyperoxia in comparison to both mild hyperoxia and normoxia for all metrics except for the worst PaO_2, where lower or equal mortality rates and more VFDs for severe hyperoxia were assessed (Supplemental Table 2, Supplemental Digital Content 1).

Table 2 shows the event rates and adjusted estimates regarding patient-centered outcomes for each metric.

The estimates are pooled in forest plots (Supplemental Fig. 3–4, Supplemental Digital Content 1) and there were notable differences in effect size depending on the used metric for hyperoxia. The choice of a certain metric for oxygenation had major influence on the incidence of arterial hyperoxia. For example, severe hyperoxia was present in 20% of patients when using $MAX_{ICU\ LOS}$ compared to 1% of patients using $AVG_{ICU\ LOS}$.

Without exception, the point estimates for conditional mortality were larger for severe hyperoxia than for mild hyperoxia. The highest odds ratios were found for the exposure identified by the average PaO_2, closely followed by the median PaO_2. The AUC and time in arterial hyperoxia showed a consistent effect favoring the middle quintiles and no time in arterial hyperoxia. Mild hyperoxia was mainly associated with a slight increase in VFDS, whereas severe hyperoxia was associated with a decrease in VFDS. Mean PaO_2 ($AVG_{ICU\ LOS}$) showed a J-shaped relationship with hospital mortality (Figure 1).

Time spent in mild hyperoxia and time spent in severe hyperoxia both showed a linear and positive relationship with hospital mortality and were therefore also modeled linearly (Figure 2). U-shaped (FIR, $WOR_{ICU\ LOS}$, $MED_{ICU\ LOS}$) and linear ($MAX_{ICU\ LOS}$) relationships were found for the other metrics (Supplemental Fig. 5–8, Supplemental Digital Content 1).

Subpopulations

In mechanically ventilated patients, the adjusted odds ratios for conditional hospital mortality were highly comparable with the estimates for the total study population (Table 3). In large patient groups, such as planned and medical admissions, the odds ratios differed slightly from those in mechanically ventilated patients. In smaller subpopulations, including patients admitted with cardiac arrest, stroke, and sepsis, no statistically significant risks from arterial hyperoxia could be identified.

DISCUSSION

In this multicenter cohort study, we found a dose-response relationship between supraphysiological arterial oxygen levels and hospital mortality, ICU mortality and ventilator-free days. The effect size was importantly influenced by the definition of arterial hyperoxia and severe hyperoxia was more consistently associated with poor outcomes than mild hyperoxia. Furthermore, the oxygenation

Table 2. Event rates and adjusted estimates for patient-centered outcomes by metric of arterial hyperoxia

	No. of patients (%)	Deaths (%)	Hospital mortality[a] Odds Ratio [95% CI]	ICU Mortality[a] Odds Ratio [95% CI]	VFDs[b] Mean Difference [95% CI]
FIR	14441				
Mild hyperoxia[c]	4144 (29)	440 (11)	0.91 [0.79, 1.05]	0.92 [0.78, 1.09]	0.29 [-0.02, 0.59]
Severe hyperoxia[c]	1582 (11)	262 (17)	1.11 [0.92, 1.34]	1.06 [0.85, 1.31]	-0.10 [-0.54, 0.33]
$\text{AVG}_{\text{ICU LOS}}$	14441				
Mild hyperoxia[c]	2142 (15)	223 (10)	1.12 [0.93, 1.34]	1.35 [1.09, 1.67]*	0.32 [-0.06, 0.69]
Severe hyperoxia[c]	131 (1)	45 (34)	3.79 [2.32, 6.14]***	5.93 [3.56, 9.77]***	-3.38 [-4.81, -1.94]***
$\text{MED}_{\text{ICU LOS}}$	14441				
Mild hyperoxia[c]	1502 (10)	128 (9)	1.02 [0.80, 1.27]	1.12 [0.85, 1.47]	0.47 [0.04, 0.91]
Severe hyperoxia[c]	94 (1)	25 (27)	2.67 [1.42, 4.89]*	3.76 [1.93, 7.09]***	-1.50 [-3.26, 0.25]
$\text{WOR}_{\text{ICU LOS}}$	14062				
Mild hyperoxia[c]	1316 (9)	65 (5)	0.71 [0.52, 0.95]	0.65 [0.44, 0.93]	0.73 [0.29, 1.17]*
Severe hyperoxia[c]	86 (1)	8 (9)	1.29 [0.48, 3.05]	2.06 [0.74, 4.97]	-0.54 [-2.24, 1.16]
$\text{MAX}_{\text{ICU LOS}}$	14441				
Mild hyperoxia[c]	5986 (41)	745 (12)	1.07 [0.93, 1.23]	0.96 [0.81, 1.14]	-0.49 [-0.80, -0.19]*
Severe hyperoxia[c]	2854 (20)	679 (24)	1.74 [1.49, 2.03]***	1.92 [1.61, 2.30]***	-2.29 [-2.66, -1.91]***
$\text{AUC}_{\text{ICU LOS}}$	14049				
4th quintile[d]	2810 (20)	451 (16)	1.27 [1.04, 1.54]	1.24 [0.98, 1.57]	NA
Upper quintile[d]	2810 (20)	788 (28)	1.45 [1.18, 1.78]**	1.28 [1.01, 1.63]	NA
$\text{AVG}_{0\text{-}24}$	14425				
Mild hyperoxia[c]	2896 (20)	384 (13)	1.14 [0.98, 1.32]	1.12 [0.94, 1.33]	0.02 [-0.31, 0.35]
Severe hyperoxia[c]	168 (1)	49 (29)	2.55 [1.62, 3.94]***	3.14 [1.95, 4.99]***	-1.85 [-3.10, -0.61]*
$\text{MED}_{0\text{-}24}$	14425				
Mild hyperoxia[c]	2090 (14)	237 (11)	1.10 [0.92, 1.31]	1.09 [0.88, 1.34]	0.16 [-0.21, 0.54]
Severe hyperoxia[c]	122 (1)	31 (25)	2.49 [1.44, 4.20]**	2.60 [1.42, 4.61]*	-1.27 [-2.78, 0.23]
$\text{WOR}_{0\text{-}24}$	14046				
Mild hyperoxia[c]	1556 (11)	122 (8)	1.01 [0.80, 1.26]	0.98 [0.74, 1.28]	0.50 [0.09, 0.91]
Severe hyperoxia[c]	104 (1)	12 (12)	1.75 [0.79, 3.57]	2.37 [1.02, 5.02]	-0.85 [-2.39, 0.70]

Table 2. (continued)

	No. of patients (%)	Deaths (%)	Hospital mortality[a] Odds Ratio [95% CI]	ICU Mortality[a] Odds Ratio [95% CI]	VFDs[b] Mean Difference [95% CI]
MAX$_{0-24}$	14425				
Mild hyperoxia[c]	5617 (39)	674 (12)	0.89 [0.78, 1.02]	0.87 [0.74, 1.02]	0.33 [0.03, 0.62]
Severe hyperoxia[c]	2384 (17)	482 (20)	1.23 [1.05, 1.44]*	1.29 [1.08, 1.54]*	-0.39 [-0.78, -0.01]
AUC$_{0-24}$	8646				
4th quintile[d]	1729 (20)	316 (18)	0.99 [0.81, 1.21]	0.97 [0.77, 1.22]	-0.04 [-0.68, 0.60]
Upper quintile[d]	1729 (20)	359 (21)	1.29 [1.06, 1.57]	1.30 [1.04, 1.63]	-0.45 [-1.09, 0.18]
AUC$_{0-96}$	3083				
4th quintile[d]	616 (20)	170 (28)	1.20 [0.92, 1.57]	1.07 [0.79, 1.43]	NA
Upper quintile[d]	617 (20)	185 (30)	1.45 [1.11, 1.90]*	1.13 [0.84, 1.53]	NA
Time in mild hyperoxia					
Upper quintile[e]	2810 (20)	584 (21)	1.25 [1.06, 1.50]*	1.10 [0.89, 1.35]	NA
Time in severe hyperoxia					
Upper quintile[f]	2810 (20)	415 (16)	1.31 [1.12, 1.53]**	1.66 [1.39, 1.99]***	NA

FIR, first PaO_2; AVG, mean PaO_2; MED, median PaO_2; WOR, worst PaO_2; MAX, highest PaO_2; AUC, Area Under Curve of PaO_2 measurements in considered time frame. VFDs, ventilator-free days and alive at day 28;

Metrics are calculated over the total ICU length of stay (ICU LOS), over the first 24 hours of ICU admission (0-24) or over the first 96 hours of admission (0-96), as indicated.

Some patients were excluded for specific metric analyses if there was no requisite data within the first 24 hours of admission (0-24 subgroups), if there was no data on PaO_2/FiO_2 ratio (WOR) or if there was an interval longer than 24 hours between two consecutive PaO_2 measurements (AUC and time spent in hyperoxia).

* P<0.01; ** P<0.001; *** P<0.0001. NA, not applicable according to used model

Mild hyperoxia, PaO_2 120-200 mmHg; severe hyperoxia, PaO_2 >200 mmHg

[a] Model is adjusted for age, APACHE IV score, and ICU LOS.

Hospital and ICU mortality refer to mortality, given either death or discharge (conditional hospital mortality)

[b] Subgroup analyses on mechanically ventilated patients. Model is adjusted for age and APACHE IV score

[c] Arterial normoxia (PaO_2 60-120 mmHg) used as reference range

[d] Middle quintile (AUC) used as reference range

[e] Zero time in mild hyperoxia is used as reference range. Upper quintile is ≥ 470 minutes

[f] Zero time in severe hyperoxia is used as reference range. Upper quintile is ≥200 minutes

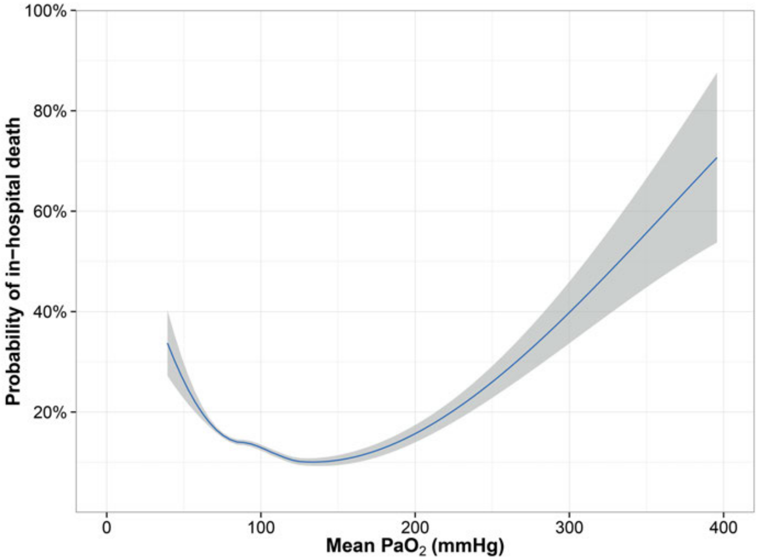

Figure 1. Adjusted probability of in-hospital death by mean PaO_2.
Loess smoothing curve predicted from logistic regression model adjusted for age, APACHE IV score and ICU LOS. Blue line represents oxygenation by mean PaO_2 over the total ICU LOS. Grey zones represent 95% confidence intervals.

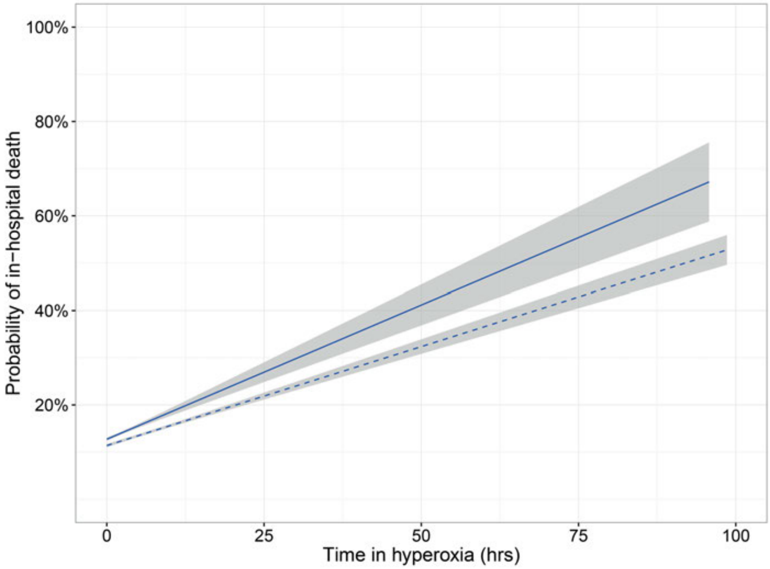

Figure 2. Adjusted probability of in-hospital death by time in hyperoxia.
Probability of death predicted from logistic regression model adjusted for age, APACHE IV score and ICU LOS. Lines represent estimated time in mild (dashed) and severe (solid) hyperoxia. Grey zones represent 95% confidence intervals. A linear model was presented, because the smoothing curve for both metrics showed a clear linear relationship between the predicted outcome and time in hyperoxia.

Table 3. Arterial hyperoxia and adjusted odds ratios (95%CI) for hospital mortality by subpopulation

	Mechanical ventilation	**Planned admission**	**Medical admission**	**Cardiac arrest**	**Stroke**	**Sepsis**
No. of patients (%)	11934 (82.6)	7328 (50.7)	5130 (35.5)	673 (4.7)	406 (2.8)	548 (3.9)
Deaths (%)	1746 (14.6)	241 (3.3)	1410 (27.5)	316 (47.0)	146 (36.0)	183 (33.4)
FIR						
Mild hyperoxia[a]	0.91 [0.78, 1.06]	0.95 [0.67, 1.32]	0.97 [0.80, 1.16]	1.27 [0.84, 1.91]	1.00 [0.57, 1.74]	1.18 [0.65, 2.11]
Severe hyperoxia[a]	1.14 [0.94, 1.39]	1.33 [0.81, 2.12]	1.06 [0.84, 1.35]	1.41 [0.88, 2.29]	0.61 [0.27, 1.32]	0.97 [0.40, 2.32]
AVG						
Mild hyperoxia[a]	1.11 [0.91, 1.35]	1.38 [0.89, 2.08]	1.17 [0.90, 1.50]	1.41 [0.80, 2.51]	0.98 [0.50, 1.90]	1.35 [0.57, 3.14]
Severe hyperoxia[a]	4.11 [2.42, 6.90]***	1.74 [0.10, 9.41]	4.00 [2.16, 7.48]***	3.24 [0.84, 16.57]	3.85 [0.91, 19.11]	NA
MED						
Mild hyperoxia[a]	0.99 [0.77, 1.26]	1.14 [0.63, 1.91]	1.15 [0.83, 1.57]	1.25 [0.59, 2.63]	0.89 [0.42, 1.83]	1.60 [0.51, 4.53]
Severe hyperoxia[a]	2.41 [1.19, 4.74]	3.11 [0.17, 16.99]	2.34 [1.07, 4.98]	2.33 [0.54, 12.58]	0.39 [0.01, 5.41]	NA
WOR						
Mild hyperoxia[a]	0.63 [0.46, 0.85]*	0.73 [0.33, 1.44]	0.71 [0.44, 1.10]	0.98 [0.40, 2.37]	0.77 [0.26, 2.12]	2.73 [0.37, 15.12]
Severe hyperoxia[a]	1.20 [0.44, 2.88]	2.68 [0.15, 13.12]	1.14 [0.29, 3.85]	0.86 [0.10, 6.29]	NA	NA
MAX						
Mild hyperoxia[a]	1.08 [0.93, 1.27]	0.93 [0.65, 1.33]	1.16 [0.98, 1.38]	1.10 [0.71, 1.71]	0.92 [0.49, 1.72]	1.00 [0.61, 1.61]
Severe hyperoxia[a]	1.82 [1.54, 2.16]***	2.10 [1.44, 3.06]**	1.78 [1.47, 2.17]***	2.14 [1.32, 3.49]*	0.96 [0.49, 1.91]	1.03 [0.55, 1.93]
Time in mild hyperoxia						
Upper quintile[c]	1.36 [1.14, 1.63]**	1.52 [0.99, 2.34]	1.35 [1.11, 1.64]*	1.45 [0.88, 2.39]	0.66 [0.32, 1.35]	1.18 [0.65, 2.14]
Time in severe hyperoxia						
Upper quintile[d]	1.36 [1.15, 1.61]**	1.75 [1.21, 2.52]*	1.57 [1.28, 1.94]***	1.59 [0.98, 2.58]	0.68 [0.36, 1.25]	0.71 [0.35, 1.40]

FIR, first PaO_2; AVG, mean PaO_2; MED, median PaO_2; WOR, worst PaO_2; MAX, highest PaO_2. All shown metrics are calculated over the total ICU length of stay. * $P<0.01$; ** $P<0.001$; *** $P<0.0001$. NA, not available (not enough patients in specific subset). Mild hyperoxia, PaO_2 120-200 mmHg; severe hyperoxia, PaO_2 >200 mmHg. Models are adjusted for age, APACHE IV score, and ICU LOS. Hospital mortality refers to mortality, given either death or discharge (conditional hospital mortality). [a] Normoxia (PaO_2 60-120 mmHg) used as reference range. [b] Middle quintile (AUC) used as reference range. [c] Zero time in mild hyperoxia is used as reference range. [d] Zero time in severe hyperoxia is used as reference range metric that defines the exposure was shown to be an essential factor in determining the risk for the studied population.

We selected a variety of metrics that were identified by a previous systematic review of the literature (9). These pre-existing metrics are usually calculated over the first 24 hours of admission, but our findings show that exposure to arterial hyperoxia in other time frames and using different definitions may substantially impact on the studied outcomes. For this study a new set of relevant oxygenation metrics was compiled for ICU patients. This allowed for comprehensive insights in the epidemiology and associated outcomes across multiple abstractions of arterial hyperoxia. However, we cannot rule out that the observed effects in this study can be subtly altered when alternative metrics are used.

By studying the continuous application-related adverse effects of hyperoxia this study addressed the timely clinical questions whether arterial hyperoxia is a biomarker for mortality and when the exposure is sufficient to cause harm (20-22). Metrics of central tendency (mean, median) were found to have the strongest relationship with outcome. The effects were smaller for the metrics of single measurements (i.e. highest, worst, first). In this context, the maximum PaO_2 value may be an incidental outlier but could also be indicative of a longer lasting, gradual process of increasing PaO_2 levels where a maximum is ultimately achieved, thereby mimicking metrics of central tendency. However, the latter explanation is less likely as this metric was shown to substantially differ from other metrics in cluster, correlation, and regression analyses.

Metrics of cumulative oxygen exposure, including hourly exposure and AUC in the first 24 hours, have recently been used by Elmer et al. to show associations with morbidity and mortality after cardiac arrest (23, 24). We additionally calculated AUC and time in arterial hyperoxia from admission to discharge, which may be a more accurate measure of total hyperoxia exposure even though exposure beyond the ICU admission, e.g. in the general wards, was not considered in this study. Assuming that these metrics closely reflect the actual exposure, the association between arterial hyperoxia and poor outcome is consistent in multivariate models which account for the total length of stay and illness severity. Notably, our results were essentially unchanged when the multivariate models were additionally adjusted for applied FiO_2 levels and also if the oxygen component in the APACHE score covariate was removed in order to avoid overadjustment. Still, we cannot exclude that residual confounding may be present from unmeasured variables.

In contrast with a previous study in mechanically ventilated patients (13) but in concordance with another (15), hyperoxia identified by the worst PaO_2 in the first 24 hours was not significantly associated with hospital mortality. Since the spline based transformation of this metric calculated over the total ICU LOS did emerge as the best discriminator for mortality, the association may be primarily driven by the discriminative capability of the arterial normoxia and/or hypoxia range. In other words, the worst PaO_2 is an important measure over the total ICU stay, but within the first 24 hours a hypoxic worst PaO_2 may predict mortality more precise than a hyperoxic measurement. When comparing previous studies, the selected metrics should be explicitly considered, as we showed that this may considerably impact on the observed effect sizes. Regional differences in oxygen management and cohort type may further be responsible for specific study differences. For careful interpretation of the outcome, the sample size and event rates in the studied oxygenation ranges by different metrics should also be taken into consideration. Indeed, the probability of type 2 errors increases with relatively low numbers of exposed patients in specific subsets. In smaller subsets of cardiac arrest, stroke, or sepsis patients, our risk estimates were in the same order of magnitude as previously found for arterial hyperoxia although subtle differences can be designated (7, 9, 25-27). The absence of significant effects in small subsets may be a signal of the used definition or may reflect indifferent outcome or a lack of statistical power. Analyses in different subpopulations should therefore mainly be considered exploratory and interpreted with caution. Also, we accounted for multiple testing by lowering the level for statistical significance.

Several limitations deserve further mention. First, methodological flaws following the retrospective nature of this study should be considered and causality cannot be inferred. Second, immortal time bias may play a role in models predicting hazard when no censored data is available. We therefore corrected for the total ICU LOS in multivariate analyses, modeled hospital mortality given either death or discharge, and only analyzed the predictive value for metrics that were not computed based on the total ICU LOS. The inherent limitation of non-continuous PaO_2 sampling with a lack of data between successive measurements was overcome by using linear and natural spline interpolation between separate PaO_2 measurements and calculate area under the curves and time spent in arterial hyperoxia, but it should be considered that real data of unmeasured arterial oxygenation and ventilatory management was not available. Further, our statistical models were fully calibrated on the data of the present cohort but may not universally fit other data and cannot be directly extrapolated to other cohorts. We used a cohort in which conservative oxygenation was promoted, and the exposure rates may therefore differ in comparison to other hospitals. However, we used a multicenter cohort and the concepts are likely to be comparable across different ICUs and regions. Indeed, our findings were quite consistent in the three participating centers and over time. The dose-response relationship was recently also illustrated in a meta-regression of cohort studies (9). When pooling these studies, heterogeneity of included studies was found to be substantial, which could be partially explained by the use of different metrics for arterial hyperoxia and different multivariate models.

Strengths of our study include the representation of arterial hyperoxia by several relevant and novel analytical metrics of PaO_2, the large multicenter cohort and an unprecedented set of ABG samples, including data within and beyond the first 24 hours of admission. We placed previously found associations of arterial hyperoxia with hospital mortality in a broader and clinically relevant context of varying definitions, durations and also included secondary outcomes, such as length of stay, mechanical ventilation time and ventilator-free days. Our strategies to investigate the effects of a continuously changing parameter on patient-centered outcomes can be further applied as a toolbox for other clinical challenges such as glucose and carbon dioxide management.

The present findings underline the importance of preventing excessive oxygenation during prolonged periods and urge careful oxygen titration in critically ill and mechanically ventilated patients. PaO_2 levels exceeding 200 mmHg were not only associated with ICU mortality and hospital mortality but may also lead to fewer ventilator-free days. Mild hyperoxia was not consistently shown to be harmful and may have beneficial properties when attempting to compensate and prevent impaired oxygen delivery. Interestingly, however, our analyses show that the probability of death increases linearly when the exposure time in mild hyperoxia increases strongly. Thus, on the short term mild hyperoxia may not directly impact on outcome, but clinicians should still be aware that cumulative exposure to even mild hyperoxia may be harmful. Taking this into account, exposure time may also be a marker of responsive care, even though the effect sizes were similar when adjusting for proxy markers of less responsive care (e.g. lowest glucose). It should be realized that hyperoxia is a label that admits to several definitions, where PaO_2 is not a single indicator of blood oxygen and may embrace both care given and the consequences of that care. The curvilinear relationship between the metrics and outcome, suggest that both arterial hypoxia and arterial hyperoxia should be actively avoided, and deviations from the normal may be a result of unfavorable oxygen management. Given the diversity of patients, clinical scenarios and characteristics of oxygen, universal recommendations remain cumbersome. However, in expectation of future randomized controlled trials, our findings may be auxiliary to guide targeted oxygen management by estimating the potential risk in different clinical situations.

CONCLUSIONS

We found that metrics of central tendency for severe arterial hyperoxia, as well as exposure time for mild and severe arterial hyperoxia, were associated with unfavorable outcomes of ICU patients and this association was found both within and beyond the first day of admission. Our results suggest that the relationship was consistent for large patient groups and that previously used approaches may not have completely captured the actual exposure effects.

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ONLINE SUPPLEMENT

For the online supplement, please use the following weblink, or scan the QR-code with your mobile device

Supplemental Table 1 – 2; Supplemental Fig. 1 – 8, Supplemental Digital Content 1: http://links.lww.com/CCM/C113

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