



Original Investigation | Pediatrics

Association of Arterial Hyperoxia With Outcomes in Critically Ill Children

A Systematic Review and Meta-analysis

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Abstract

IMPORTANCE Oxygen supplementation is a cornerstone treatment in pediatric critical care. Accumulating evidence suggests that overzealous use of oxygen, leading to hyperoxia, is associated with worse outcomes compared with patients with normoxia.

OBJECTIVES To evaluate the association of arterial hyperoxia with clinical outcome in critically ill children among studies using varied definitions of hyperoxia.

DATA SOURCES A systematic search of EMBASE, MEDLINE, Cochrane Library, and ClinicalTrials.gov from inception to February 1, 2021, was conducted.

STUDY SELECTION Clinical trials or observational studies of children admitted to the pediatric intensive care unit that examined hyperoxia, by any definition, and described at least 1 outcome of interest. No language restrictions were applied.

DATA EXTRACTION AND SYNTHESIS The Meta-analysis of Observational Studies in Epidemiology guideline and Newcastle-Ottawa Scale for study quality assessment were used. The review process was performed independently by 2 reviewers. Data were pooled with a random-effects model.

MAIN OUTCOMES AND MEASURES The primary outcome was 28-day mortality; this time was converted to mortality at the longest follow-up owing to insufficient studies reporting the initial primary outcome. Secondary outcomes included length of stay, ventilator-related outcomes, extracorporeal organ support, and functional performance.

RESULTS In this systematic review, 16 studies (27 555 patients) were included. All, except 1 randomized clinical pilot trial, were observational cohort studies. Study populations included were post-cardiac arrest ($n = 6$), traumatic brain injury ($n = 1$), extracorporeal membrane oxygenation ($n = 2$), and general critical care ($n = 7$). Definitions and assessment of hyperoxia differed among included studies. Partial pressure of arterial oxygen was most frequently used to define hyperoxia and mainly by categorical cutoff. In total, 11 studies (23 204 patients) were pooled for meta-analysis. Hyperoxia, by any definition, showed an odds ratio of 1.59 (95% CI, 1.00-2.51; after Hartung-Knapp adjustment, 95% CI, 1.05-2.38) for mortality with substantial between-study heterogeneity ($I^2 = 92\%$). This association was also found in less heterogeneous subsets. A signal of harm was observed at higher thresholds of arterial oxygen levels when grouped by definition of hyperoxia. Secondary outcomes were inadequate for meta-analysis.

CONCLUSIONS AND RELEVANCE These results suggest that, despite methodologic limitations of the studies, hyperoxia is associated with mortality in critically ill children. This finding identifies the

(continued)

Key Points

Question What is the association between arterial hyperoxia and outcomes in critically ill children admitted to the pediatric intensive care unit?

Findings This systematic review of 16 studies and meta-analysis of 11 studies comprising a total of 23 204 patients found an association between hyperoxia and mortality in children admitted to the pediatric intensive care unit.

Meaning These findings suggest that hyperoxia is associated with harm in critically ill children; the clinical implication of this association needs to be addressed in future studies.

+ Supplemental content

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Abstract (continued)

further need for prospective observational studies and importance to address the clinical implications of hyperoxia in critically ill children.

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Introduction

The administration of supplemental oxygen is a cornerstone treatment in critically ill patients to prevent and resolve cellular hypoxia. Although oxygen therapy can be lifesaving on many occasions, its overzealous use may lead to supraphysiological levels of the PaO_2 (ie, hyperoxia), which is associated with deleterious outcomes. For example, in critically ill adults, arterial hyperoxia has been associated with increased mortality, most pronounced at extreme levels of PaO_2 .^{1,2} Detrimental effects of hyperoxia may derive from increased formation of reactive oxygen species, which damage biomolecules, or from its pulmonary and vascular complications, such as atelectasis and hyperoxemic vasoconstriction.³⁻⁷

In the field of pediatrics, traditionally, most attention on oxygen toxicity has been focused on preterm neonates, a specific population with high vulnerability to develop hyperoxia-associated chronic disease, such as bronchopulmonary dysplasia and retinopathy of prematurity.^{8,9} A growing body of evidence suggests a similar hazard exists for increased mortality and morbidity associated with hyperoxia in critically ill children beyond the direct neonatal period.^{10,11} This increase may be equally important with respect to long-term disease trajectories, as many organs and tissues, including the lungs, continue to develop and mature for several years after birth.^{12,13} Yet, it remains unclear how generalizable these findings are, because these studies address various populations in the pediatric intensive care unit (PICU) and apply different definitions of hyperoxia. Consequently, the current practice of oxygen therapy and target oxygenation levels in the PICU are largely based on expert opinion.¹⁴⁻¹⁶ Rigorous synthesis of the literature on the association between hyperoxia and clinical outcomes in the PICU is necessary to aid in the development of novel study protocols and future strategies to prevent oxygen-associated injury.

In this study, our aims were to describe the definitions of hyperoxia and evaluate the association between hyperoxia and outcomes in critically ill children admitted to the PICU. We hypothesized that hyperoxia was associated with worse outcomes in critically ill children.

Methods

Data Sources and Searches

The literature search was performed in consultation with an experienced clinical librarian (F.v.E-J.). We searched the electronic databases Ovid MEDLINE (1946 to February 1, 2021), Ovid EMBASE (1947 to February 1, 2021), Cochrane Central Register of Controlled Trials (from inception to February 1, 2021), and ClinicalTrials.gov. References of full-text articles were screened for relevant studies. No language restrictions were applied. The complete search strategy is reported in eTable 1 in the [Supplement](#). This review is reported in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline¹⁷ and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.¹⁸ The protocol of this review was published before start of the study in the PROSPERO International Prospective Register of Systematic Reviews database.¹⁹

Study Selection

The citations were screened independently by 2 of us (T.A.L. and N.S.G.) on title and abstract, and discrepancies were resolved through discussion. Full-text articles on potentially eligible studies were

retrieved and checked independently for eligibility. Eligible studies were those including patients admitted to the PICU that examined hyperoxia and contained at least 1 outcome of interest. No predefined inclusion criteria were made for the definition of hyperoxia. Only clinical trials and cohort studies were selected. Studies that included only patients with cyanotic congenital heart disease were excluded, as were conference abstracts.

Outcome Measures

The primary outcome was all-cause 28-day mortality. Secondary outcomes were all-cause mortality at any follow-up, incidence and duration of invasive mechanical ventilation, duration of respiratory support, incidence of acute kidney injury, incidence and duration of organ support (continuous venovenous hemofiltration, extra corporeal membrane oxygenation [ECMO]), PICU and hospital length of stay, long-term lung function (spirometry or forced oscillation technique), and general functional status (Pediatric Overall Performance Category or Pediatric Cerebral Performance Category).²⁰

Data Extraction and Quality Assessment

Data were extracted independently by 2 of us (T.A.L. and N.S.G.) using a structured data extraction form. Differences were resolved through discussion. When necessary, 2 attempts were made to contact authors for missing data or to elucidate uncertainties.

Quality assessment of observational studies remains dubious in comparison with that of randomized clinical trials.¹⁷ Risk of bias was assessed with the Newcastle-Ottawa scale.²¹ Scoring was performed independently by 2 of us (T.A.L. and N.S.G.) and discrepancies were resolved through discussion with a third reviewer (R.A.B.). As previously suggested, a score below 7 was defined as moderate quality and below 4 as poor.²² Randomized clinical trials were scored using the Cochrane Handbook.²³ Authors were also contacted for individual patient data meta-analysis; however, owing to insufficient response, this analysis was not deemed feasible.

Statistical Analysis

Studies were grouped by patient population. If populations between studies overlapped, the study with the largest sample size was chosen for analysis. Studies including more than 10% to 15% noneligible patients (eg, adults) were omitted from quantitative analysis. Dichotomous outcomes are reported as odds ratio (OR) and corresponding 95% CI. The reported number of events and total number of events were used to calculate ORs; if only ORs were reported, these values were used. Unadjusted and adjusted ORs were analyzed separately. Inverse variance was used to pool all ORs in a random-effects model. Data were analyzed by the DerSimonian and Laird method, because we expected large differences in sample sizes. To account for the tendency of the DerSimonian and Laird method to result in smaller CIs,²⁴ additional Hartung-Knapp adjustment of the pooled effect size 95% CIs was performed.²⁵

Heterogeneity was assessed using I^2 statistics. The contribution of studies to the overall heterogeneity was explored by leave-1-out analyses and graphical display of study heterogeneity plots.²⁶ Predefined subgroup analyses were performed to analyze more homogenous groups (1) based on outlier analyses, (2) excluding ECMO-only studies, and (3) in studies correcting for confounders.

In addition, studies were grouped by their definition of hyperoxia to determine the association between the design and observed outcomes. Data were pooled for all definitions used or from which data were extractable. Publication bias was assessed with the use of funnel plots to explore small study effect size and P curve analysis to explore P hacking.²⁷

Statistical significance was defined as a 2-sided P value $< .05$. Analyses were performed using RevMan, version 5.3 (The Cochrane Collaboration) and R, version 3.6.1 (R Foundation for Statistical Computing) with RStudio, version 1.2.1335 (RStudio).

Results

The literature search resulted in 1817 potentially relevant studies. After the screening process, 16 studies, including 27 555 patients, remained (eFigure 1 in the [Supplement](#)).²⁸⁻⁴³ All included studies, except for 1 pilot randomized clinical trial, were observational (12 retrospective and 3 prospective). Study populations included were post-cardiac arrest (n = 6), traumatic brain injury (n = 1), ECMO (n = 2), and general critical care patients (n = 7). Other study characteristics are reported in **Table 1**. Newcastle-Ottawa scale scores for quality ranged from 7 to 9, with lack of correction for confounders the main contributor to a higher risk of bias (eTable 2 in the [Supplement](#)).

Table 1. Study Characteristics

Source	Design	Patients, No.	Age, median (IQR)	Population	Main measure of hyperoxia	Definition for hyperoxia	Main outcomes as by design
Bennett et al, ²⁸ 2013, US	RC	195	Only reported proportions for age groups	Cardiac arrest	Pao ₂	>200 mm Hg (27 kPa)	In-hospital mortality, neurological outcome
Cashen et al, ²⁹ 2018, US	PC	484	Only reported proportions for age groups	ECMO	Pao ₂	>200 torr (27 kPa)	In-hospital mortality, kidney failure, LOS PICU, LOS hospital, ECMO
Del Castillo et al, ³⁰ 2012, international (RIBEPCI Network)	PC	223	14 (5-60) mo	Cardiac arrest	Pao ₂ and P/F	>300 mm Hg (40 kPa) P/F>300	In-hospital mortality
Ferguson et al, ³¹ 2012, UK	RC	1875	11 (2-61) mo	Cardiac arrest	Pao ₂	>300 mm Hg (40 kPa)	In-hospital mortality
Guerra-Wallace et al, ³² 2013, US	RC	74	Median (range), 1.8 (0-18) y	Cardiac arrest	Pao ₂	>200 mm Hg (27 kPa) >300 mm Hg (40 kPa)	6-mo mortality
Ketharanathan et al, ³³ 2020, the Netherlands	RC	71	8.9 (4.6-12.9) y	Severe traumatic brain injury	Pao ₂	>200 mm Hg (27 kPa) >250 mm Hg (33 kPa) >300 mm Hg (40 kPa)	In-PICU mortality
Kraft et al, ³⁴ 2017, Austria	RC	419	Mean (SD), 57.8 (19.9) y	General PICU or ICU	Pao ₂	>120 mm Hg (>16 kPa)	In-hospital mortality, LOS ICU, LOS hospital
López-Herce et al, ³⁵ 2014, international (Latin America, Spain, Portugal, Italy)	PC	502	44.5 (5-60) mo	Cardiac arrest	Pao ₂ and Fio ₂	≥200 mm Hg (27 kPa) Fio ₂ 0.50-0.79 Fio ₂ ≥0.80	In-hospital mortality, neurological outcome
Numa et al, ³⁶ 2018, Australia	RC	1447	1.7 (0.3-7.1) y	General PICU (mostly postoperative)	Pao ₂	>250 mm Hg (33 kPa)	In-PICU mortality
Pelletier et al, ³⁷ 2020, US	RC	4469 or 4537	1.8 (0.4-8.4) y	General PICU	Pao ₂	No predefined cutoff; divided by bands of 100 mm Hg	In-hospital mortality
Peters et al, ³⁸ 2018, UK	RCT	159	Liberal median, 0.8 (0.1-2.0) y Conservative median, 1.9 (0.4-5.0) y	General PICU	Spo ₂ (target)	Liberal >94% Control 88%-92%	Feasibility of trial, LOS PICU, IMV duration, 30 VFD, in-PICU mortality
Raman et al, ³⁹ 2016, UK	RC	7410	Not reported	General PICU	Pao ₂	>300 mm Hg (>40 kPa)	Mortality (unspecified time point)
Ramgopal et al, ⁴⁰ 2019, US	RC	6250	Only reported proportions for age groups	General PICU	Pao ₂	≥300 mm Hg (40 kPa)	In-hospital mortality
Ramgopal et al, ⁴¹ 2020, US	RC	3616	Mean (SD), 8.7 (6.7) y	General PICU	Pao ₂	≥300 mm Hg (40 kPa)	In-hospital mortality
Szyncer-Taub et al, ⁴² 2016, US	RC	93	7 (5-20) d	ECMO	Pao ₂	>193 mm Hg (26 kPa)	30-d mortality, in-hospital mortality, kidney failure, LOS PICU, LOS hospital
van Zelle et al, ⁴³ 2015, the Netherlands	RC	200	Nonsurvivors, 20.4 (1.0-211.9) mo Survivors, 37.6 (1.0-262.6) mo	Cardiac arrest	Pao ₂	>200 mm Hg (27 kPa) >250 mm Hg (33 kPa) >300 mm Hg (40 kPa)	In-hospital mortality

Abbreviations: ECMO, extracorporeal membrane oxygenation; Fio₂, fraction of inspired oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; Pao₂, arterial partial pressure of oxygen; PC, prospective cohort study; P/F, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; PICU, pediatric intensive

care unit; RC, retrospective cohort study; RCT, randomized clinical trial; Spo₂, peripheral saturation of oxygen; VFD, ventilator-free days.

SI conversion factor: To convert millimeters of mercury to kilopascals, multiply by 0.133.

Hyperoxia Parameters and Definitions

Definitions, period of assessment, and measures of hyperoxia are reported in **Table 2**. The Pao_2 was most frequently used to assess hyperoxia (15 studies) and was usually defined as a categorical predictor with thresholds ranging from greater than 120 mm Hg (to convert to kilopascals, multiply by 0.133) up to greater than 300 mm Hg. In these studies, either absence of hyperoxia (ie, all patients below the threshold) or a custom range for normoxia was used as the comparator. With the custom range approach, the lower limit of normoxia was 60 mm Hg and the threshold for hyperoxia was the upper limit. Most studies evaluated hyperoxia within the first 24 hours of PICU admission. Several measures were used to select Pao_2 , but the highest value and the first value were the most common. Less common methods focused on cumulative exposure by grouping patients by the frequency of Pao_2 values in the hyperoxic range (1 study⁴⁰) or by analyzing the area under the Pao_2 to time relationship (3 studies^{33,40,43}).

Table 2. Overview of Definitions and Assessment Periods of Hyperoxia^a

	Assessment period			
Hyperoxia definition	Start	End	Selection criterion	Source
Pao ₂				
>120 mm Hg (16 kPa)	Start of IMV	IMV day 7	Time-weighted mean	Kraft et al, ³⁴ 2017
>193 mm Hg (26 kPa)	Start of ECMO	48 h after ECMO initiation	Mean value	Szzyrmer-Taub et al, ⁴² 2016
>200 mm Hg (27 kPa)	At ROSC	1 h after ROSC	None; 1 value	López-Herce et al, ³⁵ 2014
	24 h after cardiac arrest	24 h after cardiac arrest		
	At ROSC	6 h after ROSC	Highest and lowest value	Bennett et al, ²⁸ 2013
	PICU admission	24 h after PICU admission	Not specified	Guerra-Wallace et al, ³² 2013
	PICU admission	24 h after PICU admission	Highest and cumulative exposure	Ketharanathan et al, ³³ 2020
	PICU admission	24 h after PICU admission	Highest and cumulative exposure	van Zelle et al, ⁴³ 2015
	Start of ECMO	48 h after ECMO initiation	Highest	Cashen et al, ²⁹ 2018
	>250 mm Hg (33 kPa)	PICU admission	1 h after PICU admission	First value
PICU admission		24 h after PICU admission	Highest and cumulative exposure	Ketharanathan et al, ³³ 2020
PICU admission		24 h after PICU admission	Highest and cumulative exposure	van Zelle et al, ⁴³ 2015
>300 mm Hg (40 kPa)	At ROSC	1 h after ROSC	None; 1 value	Del Castillo et al, ³⁰ 2012
	24 h after cardiac arrest	24 h after cardiac arrest		
	PICU admission	1 h after PICU admission	First value	Ferguson et al, ³¹ 2012
	PICU admission	1 h after PICU admission	First value	Raman et al, ³⁹ 2016
	6 h preceding PICU admission	6 h after PICU admission	Highest	Ramgopal et al, ⁴¹ 2020
	PICU admission	24 h after PICU admission	Not specified	Guerra-Wallace et al, ³² 2013
	PICU admission	24 h after PICU admission	Highest and cumulative exposure	Ketharanathan et al, ³³ 2020
	PICU admission	24 h after PICU admission	Highest and cumulative exposure	van Zelle et al, ⁴³ 2015
	PICU admission	PICU discharge	Highest and cumulative exposure	Ramgopal et al, ⁴⁰ 2019
	No threshold defined	PICU admission	72 h after PICU admission	Highest
Fio ₂				
>50%	At ROSC	1 h after ROSC	None; 1 value	López-Herce et al, ³⁵ 2014
	24 h after cardiac arrest	24 h after cardiac arrest		
P/F				
>300	At ROSC	1 h after ROSC	None; 1 value	Del Castillo et al, ³⁰ 2012
	24 h after cardiac arrest	24 h after cardiac arrest		
Spo ₂				
>94%	PICU admission	PICU discharge	NA	Peters et al, ³⁸ 2018

Abbreviations: ECMO, extracorporeal membrane oxygenation; Fio_2 , fraction of inspired oxygen; IMV, invasive mechanical ventilation; NA, not applicable; P/F, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; PICU, pediatric intensive care unit; ROSC, return of spontaneous circulation; SpO_2 , peripheral saturation of oxygen.

^a Assessment period during which hyperoxia was assessed and the criterion used to select assessed measurements for all studies included.

Outcomes

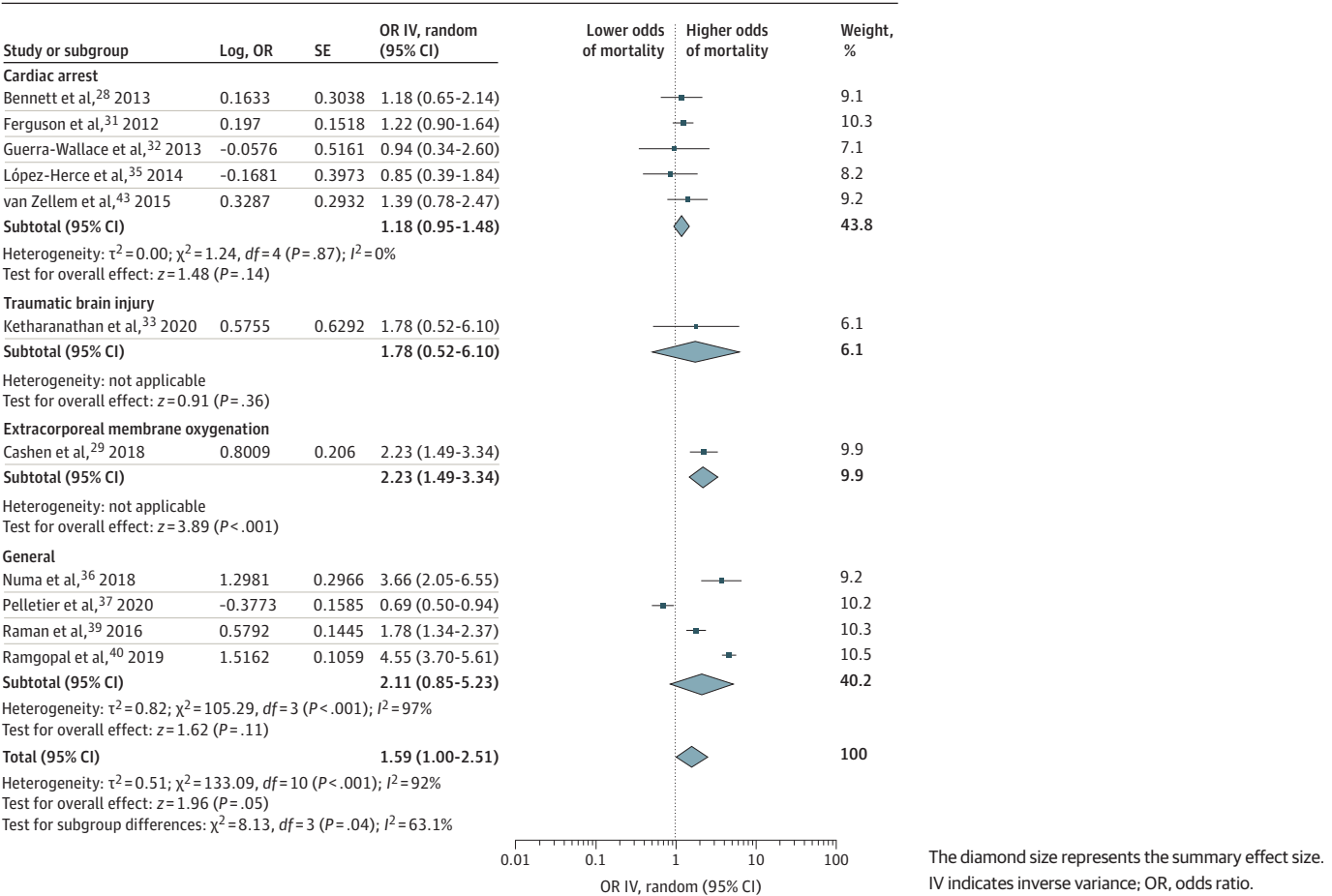
None of the studies reported the predefined primary outcome of 28-day mortality (eTable 3 in the Supplement) and we therefore converted the primary outcome to mortality at the longest follow-up. Other secondary outcomes could not be pooled owing to selective reporting. eFigure 1 in the Supplement shows studies that were omitted from the quantitative analysis.^{30,34,38,41,42}

Mortality

The association of hyperoxia with mortality for all 16 studies diverged substantially between studies (eFigure 2 in the Supplement). After omission of the aforementioned investigations,^{30,34,38,41,42} meta-analysis of 11 studies analyzed by subgroup of patients, including 23 204 patients, showed a crude OR of 1.59 (95% CI, 1.00-2.51; *P* = .05) (Figure 1) (95% CI, 1.05-2.38; *P* = .03 after Hartung-Knapp adjustment) (Table 3). Between-study heterogeneity was substantial (*I*² = 92%) and among-subgroup heterogeneity was significant (*I*² = 63%). Heterogeneity was also substantial within the subgroup of general PICU patients (*I*² = 97%). The subgroup of patients receiving ECMO (1 study²⁹) showed a significant association (OR, 2.23; 95% CI, 1.49-3.34; *P* < .001).

We performed several predefined sensitivity analyses to examine the pooled effect size in more homogeneous groups. Outlier analyses indicated 2 pronounced outliers^{37,40} and 1 potential outlier (eFigures 3-5 in the Supplement).³⁶ Secondary analyses excluding these outliers showed similar associations to the main analysis and reduced heterogeneity (Table 3; eFigure 6 and eFigure 7 in the

Figure 1. Random-Effects Meta-analysis of Hyperoxia (Categorical Exposure) on Mortality, at Longest Follow-up, Stratified by Case Mix



Supplement). Secondary analysis, excluding ECMO studies as predefined, resolved among-subgroup heterogeneity, but did not show an association with mortality (Table 3; eFigure 8 in the Supplement).

In addition, we pooled the effect estimate of confounder-adjusted ORs. Twelve studies were corrected for confounders either in multivariable logistic regression or in multivariable nonlinear prediction models.^{28,29,31,34-37,39-43} Of these, 7 studies corrected for severity of disease using (modified) severity of disease or risk of mortality scores, including Pediatric Logistic Organ Dysfunction, Pediatric Index of Mortality, and Pediatric Risk of Mortality scores.^{31,34,36,37,39-41} Adjusted ORs were obtainable from 6 studies and could be pooled for only 3 (Table 3; eFigure 9 in the Supplement).^{36,40,43}

Because we hypothesized that the definition of hyperoxia affects the association with mortality, we pooled study data for each primary threshold that was used or from which data were extractable (Figure 2). Within-group heterogeneity was significant for multiple thresholds (>200 mm Hg: $I^2 = 78\%$; >250 mm Hg: $I^2 = 49\%$; >300 mm Hg: $I^2 = 94\%$) and an association between hyperoxia and mortality was observed at the 250 mm Hg threshold (>200 mm Hg: OR, 1.21; 95% CI, 0.78-1.88; $P = .39$; >250 mm Hg: OR, 2.48; 95% CI, 1.36-4.51; $P = .003$; >300 mm Hg: OR, 1.72; 95% CI, 0.99-3.01; $P = .06$). Additional sensitivity analyses, based on previous outlier analysis, resolved within-group heterogeneity and showed an association between hyperoxia and mortality at higher thresholds of PaO_2 (>200 mm Hg: OR, 1.09; 95% CI 0.77-1.53; $P = .64$; $I^2 = 0\%$; >250 mm Hg: OR, 1.75; 95% CI, 1.04-2.95; $P = .04$; $I^2 = 0\%$; >300 mm Hg: OR, 1.47; 95% CI, 1.22-1.76; $P < .001$; $I^2 = 0\%$) (eFigure 10 and eFigure 11 in the Supplement)

Other Outcomes

Other secondary outcomes reported by studies and their outcomes are reported in eTable 3 and eTable 4 in the Supplement. Significant outcomes in terms of incidence and duration of organ support were found in 2 studies including only patients receiving ECMO.^{29,42} One study reported a positive association of hyperoxia with continuous venovenous hemofiltration incidence (hyperoxia vs normoxia: OR, 4.42; 95% CI, 1.19-16.42; $P = .03$), whereas the other study reported a negative association of hyperoxia with ECMO duration (hyperoxia: median, 4.7 [IQR, 2.5-8.0] days vs normoxia: 5.9 [IQR, 3.1-10.5] days; $P = .009$). Associations with hyperoxia were also observed for the length of stay in the pediatric critical care unit^{29,34} and hospital.³⁴ Both studies reported an association of hyperoxia with reduced length of stay (length of stay in PICU, hyperoxia: median, 25.0 [IQR, 12.8-48.2] days vs normoxia: median, 30.5 [IQR, 15.6-54.0] days; $P = .045$ ²⁹; hyperoxia: mean [SD], 24.5 [15.9] days vs normoxia: mean [SD], 30.7 [25.2]; $P = .04$ ³⁴; length of stay in hospital, hyperoxia: mean, 43.3 [30.2] days vs normoxia: mean, 58.9 [46.9] days; $P < .001$ ³⁴).

Publication bias was deemed as unlikely, based on the relative symmetrical shape of the funnel plot and exploratory P curve results (eFigure 12 and eTable 5 in the Supplement).

Table 3. Pooled Effect Estimates for Hyperoxia and Mortality^a

Analysis	Pooled effect estimate, OR (95% CI)	P value	95% CI adjusted ^b	P value adjusted ^b	I^2 , % (95% CI)
Main analysis, all studies in quantitative synthesis	1.59 (1.00-2.51)	.05	1.05-2.38	.03	92 (89-95)
Sensitivity 1, omitting clear outliers ^c	1.58 (1.21-2.07)	<.001	1.14-2.21	.01	58 (12-80)
Sensitivity 2, omitting possible outliers ^d	1.46 (1.17-1.83)	<.001	1.13-1.89	.01	34 (0-71)
Sensitivity 3, omitting ECMO-only studies	1.52 (0.92-2.54)	.11	0.97-2.39	.06	93 (90-96)
Sensitivity 4, confounder-corrected studies	1.51 (0.85-2.68)	.07	0.39-5.85	.32	63 (0-89)

Abbreviations: ECMO, extra corporeal membrane oxygenation; OR, odds ratio.

^a Pooled effect estimates from a random-effects model of hyperoxia and mortality using the DerSimonian and Laird method.

^b Hartung-Knapp adjustment.

^c Omitting Ramgopal et al⁴⁰ and Pelletier et al³⁷ based on outlier analyses.

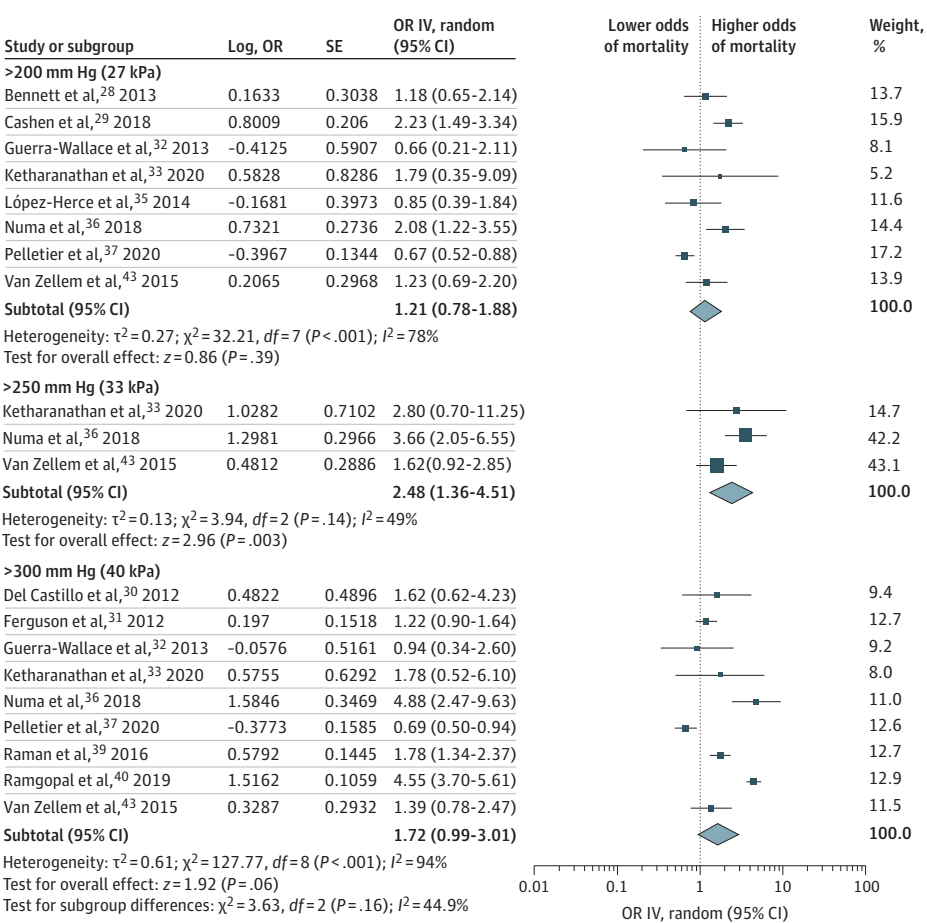
^d Omitting Ramgopal et al,⁴⁰ Pelletier et al,³⁷ and Numa et al³⁶ based on outlier analyses.

Discussion

In this systematic review, we identified 16 studies including 27 555 patients that described the association between hyperoxia and patient outcomes in critically ill children. Most evidence consisted of observational studies with heterogeneous study designs to define and assess hyperoxia. Five studies were excluded from quantitative synthesis. Meta-analysis of the remaining 11 studies showed, despite substantial heterogeneity, an association between hyperoxia and mortality in the main-analysis and in heterogeneity resolved sensitivity analyses, with a signal of harm at higher thresholds of Pao₂ when accounted for heterogeneity. Reports on outcomes other than mortality were scarce and inadequate for meta-analysis.

Our results may have been affected by differences in study design, such as the method used for measurement, the definition by cutoff, and the assessment period. First, the most common variable used to measure hyperoxia was Pao₂. In contrast to adults, a major downside to this method of measure in children is the less common use of arterial lines in the PICU, which could hamper generalizability of our results, because children with arterial lines might be in clinically worse condition compared with those without. Furthermore, although Pao₂ gives clear information on the systemic burden of oxygen, it does not necessarily inform us on alveolar hyperoxia (ie, the pulmonary burden of oxygen). For example, patients with severe hypoxemia may be exposed to a high fraction of inspired oxygen (Fio₂), thus a high pulmonary burden of oxygen, without leading to extremes of Pao₂ due to, for example, alveolar capillary diffusion disturbances or intrapulmonary shunting.⁴⁴ However, alveolar hyperoxia by itself may lead to lung injury.⁴⁵ Hyperoxia should therefore not only

Figure 2. Random-Effects Meta-analysis (Subtotals Only) of Hyperoxia (Categorical Exposure) on Mortality, at Longest Follow-up, Stratified by Threshold of Hyperoxia (Pao₂)



Studies were included for every primary threshold used by the study or from which data were extractable. The diamond size represents the summary effect size. IV indicates inverse variance; OR, odds ratio.

be estimated by PaO_2 , because FiO_2 might be of equal relevance to evaluate the harm of oxygen. Most of the included studies focused only on systemic hyperoxia, defined by PaO_2 , and thus did not sufficiently address the pulmonary burden of oxygen. Future studies on the potential harm of oxygen supplementation should evaluate both the pulmonary and systemic oxygen burden, for example, by assessment of pulmonary biomarkers of hyperoxia-induced injury.⁴⁵

Second, most studies used a categorical definition of hyperoxia by cutoff. Used thresholds are arbitrary and differences therein may affect the observed association as noted herein. Because detrimental effects from oxygen seem to be dose-dependent, observed in an U-shaped association,^{37,39} a sharp cutoff may not reflect this reality well. The degree of hyperoxia, its duration, and large fluctuations in oxygenation may be more important. In addition, the definition of the reference group is of equal importance to the observed outcome, especially if patients with hypoxemia are included.^{28,36,40,42,43} Furthermore, some patient groups may be more susceptible to hyperoxia. For instance, both studies including only patients receiving ECMO support showed an association between hyperoxia and mortality at lower thresholds of hyperoxia.^{29,42}

Third, because hyperoxia-induced oxidative stress seems to be time- and dose-dependent, the assessment period of hyperoxia is also of importance.^{33,40,46} Especially when periods exceeding initial admission day are taken into account, the cumulative exposure instead of a single maximum value may be a better representation of the degree of oxygen exposure. In this regard, one study showed that maximum PaO_2 correlated poorly to moderately with observed cumulative exposure, defined as the area under the PaO_2 to time relationship, over the first day of admission.³³

Another factor of importance is the primary outcome of the studies. Within this review, mortality (PICU and hospital) was the most frequently reported outcome among the studies. Although mortality is undoubtedly the most objective and most severe patient outcome, it is relatively uncommon in the PICU (2%-3%), especially compared with the rate in critically ill adults.^{47,48} In addition, next to potential effects on mortality, hyperoxia may have less-definitive, but equally important, long-term detrimental outcomes, because organ development proceeds during childhood and could be hampered by the toxic effects of oxygen on biomolecules.³⁻⁵ However, we found that outcomes related to such potential long-term effects of hyperoxia in critically ill children are lacking in the current evidence. Future studies addressing hyperoxia in the PICU should bring more focus on long-term outcomes, including lung function and general functional scores, as included by the Oxy-PICU trial.⁴⁹

Our findings partly mirror the literature in critically ill adults. The association between arterial hyperoxia and mortality was also observed in 2 meta-analyses of observational studies in adults.^{1,2} However, the association in critically ill adults appears to be more robust as the CI of the association was narrower and the association was maintained in confounder-adjusted analysis. One explanation may be the difference in power, as these adult reviews included more studies, with more than double the number of patients in their quantitative analysis. Another hypothesis could be that children's susceptibility to oxygen toxic effects differs from that of adults owing to age-related differences in vulnerability,⁵⁰⁻⁵² which, for example, appears to be true for ventilator-induced lung injury.^{53,54} Although there seems to be a sound pathophysiological explanation for the observed association in this review,⁵⁵ further insight of the complex association between oxygen supplementation and outcome from additional prospective pediatric studies is needed.^{10,56} In addition, the clinical implications need to be addressed in clinical trials. On this note, there have been several trials comparing liberal vs restrictive oxygen targets over the past years in critically ill adults.^{44,57-60} Although a meta-analysis of the earliest trials supported an increased risk for mortality on use of liberal oxygen targets,⁵⁷ these findings were disputed by a recent updated meta-analysis including more large-scale trials.⁵⁸ The most recent trials also did not find a clear harmful effect of liberal oxygenation on outcomes,^{44,59,60} which suggests that the true effect size of hyperoxia is probably much smaller than previously suggested from observational studies and more complex than thought.

Strengths and Limitations

A strength of this review is the rigorous search, independent screening, and detailed reporting of methods and findings. The observed association was consistent over multiple sensitivity analyses, including less heterogeneous groups and by grouping of hyperoxia definitions.

The study also has limitations. First, all studies included in the quantitative analysis were observational and most were retrospective. Second, many studies did not correct for severity of illness, most probably owing to small sample sizes or lack of significance in univariable analysis. This lack of correction complicated our sensitivity analysis adjusted for severity of illness. We could not resolve this limitation owing to insufficient response from authors for individual patient data meta-analysis. This lack of data is a noteworthy drawback of our study, because severity of illness is an important confounder. Sicker patients may receive more oxygen, which could lead to an overestimation of the effect of oxygen on mortality. Third, our predefined primary outcome was not reported by any included study. We therefore pooled data from mortality at the longest follow-up point, but this pooling may have contributed to the heterogeneity of our results. Fourth, there was substantial heterogeneity between studies, because of both the designs used and within the pooled effect estimates. Although the observed association was consistent in less heterogeneous groups, the wide variation in patient populations, definitions of hyperoxia, and assessment periods warrants caution with generalizability of these results.

Conclusions

This systematic review and meta-analysis of observational studies suggests an association between hyperoxia and mortality in the PICU, despite methodologic limitations of the included studies. Our findings support that oxygen may be harmful above a certain dose in critically ill children and that it perhaps should be supplied with caution. However, the substantial heterogeneity and the observational design of the included studies warrants judicious interpretation. Future research should further examine the implications of this association and its complex translation into clinical practice as observed in adults.

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SUPPLEMENT.

eTable 1. Search Strategy

eTable 2. Newcastle-Ottawa-Score for Quality of Cohort Studies

eTable 3. Overview of All Assessed Outcomes in This Review That Were Reported in Included Studies

eTable 4. Other Secondary Outcomes Found in Included Studies

eTable 5. P-Curve Summary of Statistics

eFigure 1. PRISMA Flowchart of Study Screening Process

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eFigure 3. Bajaj Plot of the Contribution to the Overall Heterogeneity and Pooled Effect Estimate of Each Study

eFigure 4. Leave-One-Out Plots Sorted by the Effect on Overall Heterogeneity and the Pooled Effect Estimate

eFigure 5. GOSH Plot of All Subsets of Studies With the Overall Heterogeneity and Estimated Pooled Effect Size and the Three Outlying Studies Based on the GOSH Plot

eFigure 6. Sensitivity Analysis 1: Excluding Pronounced Outliers

eFigure 7. Sensitivity Analysis 2: Excluding Pronounced and Potential Outliers

eFigure 8. Sensitivity Analysis 3: Excluding Studies With Only Patients on ECMO Support

eFigure 9. Sensitivity Analysis 4: Including Only Studies With Adjusted Odds Ratio for Mortality

eFigure 10. Random-Effects Meta-analysis of Hyperoxia (Categorical) and Mortality, Longest Follow-up, Stratified by the Threshold of Hyperoxia With Exclusion of Pronounced Outlying Studies and Those Including Only Patients on ECMO Support (Subtotals)

eFigure 11. Random-Effects Meta-analysis of Hyperoxia (Categorical) and Mortality, Longest Follow-up, Stratified by the Threshold of Hyperoxia With Exclusion of Pronounced and Potential Outlying Studies and Those Including Only Patients on ECMO Support (Subtotals)

eFigure 12. Funnel Plot of Included Studies in the Main Quantitative Synthesis

eReferences