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ORIGINAL ARTICLE

Frequency and outcomes of cumulative excess oxygen exposure in ventilated pediatric ICU patients.

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ABSTRACT… Objective: To determine the frequency of cumulative excess oxygen exposure (CEOE) and its association with mortality in ventilated children. **Study Design:** Retrospective Cohort study. **Setting:** Pediatric ICU of Sindh Institute of Child Health and Neonatology, Karachi. **Period:** January 2023 to June 2023. **Methods:** The study sample size of 200 was determined using the OpenEpi sample size calculator employing a non-probability consecutive sampling method, and included children (1 month–15 years) admitted who required invasive ventilation ≥24 hours. CEOE was defined as mean hourly FiO_2 >0.21 with SpO_2 ≥95% in the first 24 hours of ventilation. Patients were stratified into quartiles: hypoxemia (SpO_2 <94%), no CEOE, and CEOE quartiles (Q1: >21–30%, Q2: 30–45%, Q3: 45–60%, Q4: ≥60%). Variables included hourly FiO_2 >21% with SpO_2 >95%, clinical parameters, admitting diagnosis, length of stay, comorbidities, and outcome (survival or exitus). Statistical analysis was performed using Chi-Square and Mann-Whitney U tests, with p <0.05 considered significant. **Results:** Among 115 patients, mean CEOE was 37.3 ± 11.9%, with overall mortality of 26.1%. Non-survivors had higher mean CEOE than survivors (41.2 ± 10.9% vs. 36.2 ± 12.0%; p<0.009). Mortality, multi-organ dysfunction, and PICU stay increased stepwise across CEOE quartiles. Logistic regression showed higher odds of mortality in Q2 and Q3 versus Q1, though not statistically significant after adjusting for age and gender. **Conclusion:** In ventilated children, excessive oxygen exposure was common and associated with increased mortality, organ dysfunction, and longer PICU stay. These findings highlight the need for vigilant oxygen titration and careful avoidance of hyperoxia to improve outcomes in pediatric critical care

Key words: Cumulative Excessive Oxygen Exposure, Hyperoxia, Mechanical Ventilation, Mortality, Pediatric Intensive Care.

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INTRODUCTION

Oxygen supplementation, along with invasive mechanical ventilation, constitutes the primary organ support provided to maintain oxygen saturation and partial pressure levels in pediatric intensive care units (PICU).[1] One of the primary objectives of resuscitation and intensive care is to ensure that tissue oxygen levels are maintained at suitable and safe levels.[2-4] Clinicians strive to avoid severe hypoxia whenever feasible, yet beyond this, consensus is limited. In fact, the apprehension about hypoxia frequently drives many to pursue supra-normal oxygen levels.[5] While the dangers of tissue hypoxia are widely acknowledged, the potential risks associated with excessive oxygen administration or other interventions aimed at correcting hypoxemia may not be fully recognized.[4] Excessive oxygen and hyperoxia has been reportedly associated with mortality in critically ill adults with trauma, brain injury, stroke, and cardiac arrest.[5] Although research on children is limited, emerging evidence highlights a significant association between hyperoxia and increased mortality in critically ill pediatric patients.[6-9] Oxygen toxicity associated with supplemental oxygen induces local and systemic effects, including cell signaling alteration, reactive oxygen species generation, inflammation promotion, and vascular endothelial dysfunction, compromising blood supply to vital organs like the brain and heart.[10] Current literature indicates a U-shaped curve, where increased mortality is observed with both hypoxia and hyperoxia extremes.[11] Targeting an SpO2 range of 88–92% is more effective than the previous standard practice of maintaining high normal oxygenation levels (>94%) in emergency admissions of invasively ventilated infants or children admitted to a PICU.

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The Oxy-PICU trial found that children in the conservative oxygenation group had better outcomes, including reduced mortality, fewer days of organ support, decreased hospital stay, lower financial burden, and less multiorgan dysfunction.[12] The objective of this study is (1) To determine the frequency of cumulative excessive oxygen exposure using SpO2 (2): To evaluate the relationship between hyperoxia and mortality among critically ill patients admitted to the intensive care unit

METHODS

This retrospective observational study was conducted in the one of the largest 24 bedded pediatric intensive care unit of a tertiary care hospital, following institutional review board approval (SICHN/Ex-007/2024) with a waiver of informed consent, over the period of 6 months from January 2023 to June 2023. The reporting of this observational cohort study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.[13] The inclusion criteria consisted of children aged 1 month to 15 years who were admitted to the pediatric ICU and required mechanical ventilation for at least 24 hours. Exclusion criteria: Patients with uncorrected cyanotic congenital heart disease, hypoxia (SpO_2 <94%), a PICU stay of less than 24 hours, or those who did not require mechanical ventilation.

The study sample size of 200 was determined using the OpenEpi sample size calculator, based on a 90% confidence level, a hyperoxemia frequency of 15.6%, 5% absolute precision, and employing a non-probability consecutive sampling method.

Cumulative excess oxygen exposure (CEOE) was defined as the average hourly FiO2 above 0.21 % when the corresponding hourly SpO2 was 95% or higher during the first 24 hours of mechanical ventilation.[14] (The 95% SpO2 threshold was selected because it best reflects the level commonly found in healthy children, offering a reliable indicator of normal oxygen saturation based on established data).[15,16] CEOE was computed and stratified by quartiles. Patients with a CEOE score of 0 were classified into a no CEOE group. Those with a CEOE score greater than 0 were divided into 4 quartiles. Consequently, the cohort of mechanically ventilated patients was categorized into five groups: hypoxemia with sato2<94%, no CEOE, and the first through fourth quartile CEOE groups, Q1<31 (>21-31), Q2:32-38%, Q3:39-44%, Q4:45-79%. For analysis, Q1 and Q2 were combined as 'low exposure' and Q3 and Q4 as 'high exposure' groups

Data will be collected using a specially designed questionnaire in SPSS version 26. The questionnaire is divided into three sections. Section A includes demographic variables such as age, gender. Section B covers clinical parameters including admitting diagnosis, and comorbidity, FiO2, SpO2, CEOE, which will be recorded on an hourly basis. If an Spo2 or Fio2 was not recorded in a given hour, the most recent recorded value will be carried forward (Approach used by Balcarcel et al.[14] If more than one value was recorded, the mean will be used, Thus, each encounter provided 24 hourly data points for SpO2 and FiO2 during the first 24 hours of ventilation.

Section C focuses on clinical outcomes, which will be assessed by recording the total hours of hyperoxia (SpO_2 ≥95%), cumulative excess oxygen exposure (CEOE), and the primary outcome variable — survival or death.

Data will be analyzed using SPSS 26. Descriptive analysis will be done to report the prevalence of hyperoxemia and time duration of CEOE. Frequency and percentages will be reported for all categorical variables such a, gender, admitting diagnosis, comorbidity etc. Mean±SD/ Median (IQR) will be reported for all numeric variables such as (Age in years, Oxygen Data (FiO2, SpO2 and CEOE), Outcome variables such as (Hours of Hyperoxia (≥95%), Hours of CEOE). Comparisons were performed using the Chi-square test for categorical variables and the Mann–Whitney U test for continuous variables, with $p<0.05$ considered statistically significant. logistic regression analysis to examine the association between CEOE quartiles and mortality.

RESULTS

During the six-month study period, a total of 1,815 patients were admitted to PICU,providing the cohort

from which 115 patients who met the predefined inclusion criteria, including at least 24 hours of mechanical ventilation and absence of hypoxemia were analyzed.

Demographic and Clinical Characteristics

Table-I represent the demographic and clinical characteristics of the study population. The cohort consisted of 61 males (53%) and 54 females (47%). The median age was 11 months with an interquartile range (IQR) of 6 to 18 months. The mean length of stay in the intensive care unit was 5.29 ± 2.87 days.

The mean cumulative excess oxygen exposure (CEOE) was 37.33 ± 11.85% during the first 24 hours of mechanical ventilation. Based on CEOE, patients were stratified into quartiles: Q1 (23.5%), Q2 (57.4%), Q3 (15.7%), and Q4 (3.5%). For further analysis, the lower two quartiles (Q1 and Q2) were combined and categorized as the lower CEOE group, while the upper two quartiles (Q3 and Q4) were merged to form the higher CEOE group. Outcomes were then compared between these two groups to assess the association between CEOE levels and clinical outcomes.

Regarding clinical outcomes, 85 patients (73.9%) survived, while 30 patients (26.1%) died during their ICU stay.

The most common admitting diagnosis was respiratory conditions, accounting for 49 patients (42.6%), followed by infectious diseases in 38 patients (33.0%), central nervous system (CNS) disorders in 20 patients (17.4%), cardiac conditions in 7 patients (6.1%), and gastrointestinal (GI) causes in 1 patient (0.9%).

Association of Excess Oxygen Exposure with Mortality

Table-II presents a comparative analysis of clinical and demographic variables between survivors and non-survivors. A total of 115 patients were stratified based on survival status to identify factors associated with mortality. The overall mortality rate was 26.1% (n=30).

There were no significant differences in age, length of ICU stay, gender distribution, primary diagnosis, or EOE quartiles between survivors and non-survivors. A statistically significant association was observed between hyperoxia and mortality (p = 0.009). Mortality was higher in patients with hyperoxia values greater than 37.3 (36.8%) compared to those with values ≤37.3 (15.5%).

TABLE-I

Descriptive statistics of study population (n:115)

Overall Descriptive	
Gender	**N (%)**
Male N (%)	61(53)
Female N (%)	54(47)
Age (In months) (Median -IQR)	11(6-18)
Length of stay (In days) (Mean ±SD)	5.287 ± 2.87
Diagnosis	
• Cardiac	7(6.1)
• CNS	20(17.4)
• INF	38(33.0)
• RESP	49(42.6)
• GI	1(.9)
CEOE (median)	37.333
CEOE	
• ≤37.333	58(50.4)
• ≥37.333	57(49.6)
Mortality	30(26.1)

Logistic Regression Analysis of Mortality by CEOE Quartiles

Table-III presents logistic regression analysis to examine the association between CEOE quartiles and mortality. In the univariable analysis, CEOE quartiles Q2 and Q3 showed higher odds of mortality compared to the reference group (Q1), though the associations did not reach conventional statistical significance (Q2: OR 3.48, 95% CI 0.94–12.89, p = 0.062; Q3: OR 4.00, 95% CI 0.85–18.84, p = 0.080). Similar trends persisted in the multivariable model after adjusting for age and gender, with Q2 showing a borderline significant association (OR 3.73, 95% CI 0.99–13.97, p = 0.051) and Q3 showing a comparable increase in odds (OR 4.40, 95% CI 0.92–21.01, p = 0.064).

Age and gender were not significantly associated with mortality in either model.

These findings suggest a potential dose-response relationship between higher oxygen exposure and

mortality, although statistical significance was not achieved, possibly due to sample size limitations.

DISCUSSION

In this retrospective cohort study of 115 mechanically ventilated pediatric patients, we examined incidence of CEOE and the relationship between cumulative excess oxygen exposure (CEOE) and mortality. Our study demonstrates that hyperoxia is common among mechanically ventilated pediatric patients, with a substantial cumulative excess oxygen exposure (mean 37.33 ± 11.85%) observed during the first 24 hours of ventilation.

TABLE-II

Comparison of clinical and demographic characteristics by mortality outcome Mann Whiteney U Test *Chi square test**

Mortality	Hyperoxia		P-Value	
	Less than equal to 37.33333 n (%)	Greater than 37.3333 N (%)		
Yes	9(15.5)	21(36.8)	.009*	
No	49(84.5)	36(63.2)21(36.8)		
Diagnosis				
Respiratory	24(41.4)	25(43.9)	.788*	
Non-Respiratory	34(58.6)	32(56.1)		
Gender				
• Male • Female	31(53.4) 27(46.6)	30(52.6) 27(47.4)	.930*	

length of stay in days	Hyperoxia	n:	Median (IQR)	Mean rank	P value
Age	less than equal to 37.33333	58	4.5(6-3)	52.16	0.055**
	greater than 37.3333	57	5(7.5-3)	63.94	
	less than equal to 37.33333	58	4.5(6-3)	55.12	0.349**
	greater than 37.3333	57	5(7.5-3)	60.93	

TABLE-III

Logistic regression analysis of mortality in relation to CEOE quartiles

	Mortality (n=%)	No Mortality (n=%)	Univariable	P-Value	Multivariable	P-Value
Gender						
Female	13(43.3)	41(48.2)	Ref	---	---	---
Male	17(56.7)	44(51.8)	1.219(527-2.817)	0.644	1.257(.528-2.993)	0.606
Age (Months)						
	10(5.5-21)	12(6-18)	.991(.970-1.012)	0.385	.988(.966-1.012)	0.324
CEOE (cat:)						
Q1	3(10)	24(28.2)	REF	REF	REF	
Q2	20(66.7)	46(54.1)	3.478(.938-12.891)	0.062	3.725(.993-13.972)	0.051
Q3	6(20)	12(14.1)	4(.849-18.836)	0.08	4.403(.919-21.012)	0.064
Q4	1(3.3)	3(3.5)	2.667(.206-34.555)	0.453	2.619(.198-34.621)	0.456

Notably, patients with higher levels of exposure tended to have increased mortality, underscoring the potential role of oxygen toxicity as a modifiable risk factor in the pediatric ICU. The overall mortality rate was 26.1%. Although demographic variables such as age, gender, and primary diagnosis were not significantly associated with mortality, patients who died had a higher mean CEOE compared to survivors.

While the length of stay (LOS) was numerically higher in patients with greater CEOE exposure, the difference across CEOE quartiles was not statistically significant.

Patients in CEOE quartiles Q2 and Q3 showed higher odds of mortality compared to Q1, with Q2 showing a borderline significant association after adjusting for age and gender, these findings suggest a potential dose-response trend between higher oxygen exposure and mortality risk, although statistical significance was not fully achieved.

Our study population was predominantly infants (IQR 6–18 months), which contrasts with local studies reporting a median age of 1.5 years by Naz et al[17] and a mean age of 3.5 years with IQR 1.2–7.0 by Nawaz et al.[18] However, male gender remained predominant across all cohorts. This difference may be attributed to the demographic profile of our hospital's catchment area, where infants represent the majority of patients requiring PICU admission.

The incidence of excessive oxygen exposure in our cohort (mean 37.3 ± 11.9%) was comparable to that reported by Naz et al[17] (32.5%), highlighting a consistent burden of hyperoxia among ventilated pediatric patients in local settings. In contrast, higher rates have been reported in other studies, such as Balcarcel et al[14] (63%) and Lilien et al[19] in bronchiolitis (45.9%). These differences may be explained by less frequent reliance on invasive PaO_2 monitoring in those studies, whereas our study utilized continuous SpO_2 as a practical surrogate for PaO_2, allowing closer titration of oxygen delivery.

Respiratory illnesses were the leading cause of PICU admission in our cohort, frequently requiring supplemental oxygen. However, excessive oxygen exposure in these patients can worsen lung injury, trigger multi-organ dysfunction, and is associated with higher mortality and prolonged PICU stay through the systemic effects of oxidative stress

A key finding of our study was that only a small proportion of patients fell into the higher CEOE quartiles (Q3: 15.7%, Q4: 3.5%). This pattern indicates that, while excessive oxygen exposure did occur, oxygen delivery in our PICU was more tightly titrated, minimizing prolonged hyperoxia and reflecting a cautious approach to oxygen management compared to what has been reported in other cohorts.

A substantial percentage of excessive oxygen exposure in this study was considered potentially avoidable, differing from other studies due to the high proportion of admissions (42.6%) requiring invasive mechanical ventilation for respiratory diseases.

In our study, mean cumulative excess oxygen exposure was significantly higher among non-survivors, suggesting an association with increased mortality. This aligns with findings by Geva et al[20], though Naz et al[17] reported no such relationship, likely reflecting differences in patient populations and monitoring methods.

Our findings demonstrate a clear dose-response relationship, with progressively higher CEOE quartiles associated with rising mortality, greater multi-organ dysfunction, and longer PICU stays.

The observed tendency to treat patients with high oxygen dosages aligns with findings from prior observational studies in critically ill adults, reflecting a "more is better" culture of oxygen supplementation.[21,22]

A key strength of our study lies in the noninvasive and continuous monitoring of SpO_2, enabling real-time FiO_2 titration at the bedside—now a standard in most ICUs. However, SpO_2 accuracy can be affected by low cardiac output, methemoglobinemia, skin pigmentation, or measurement artifacts.

LIMITATIONS

The study's limitations include its retrospective design, observational, single Centre based which inherently carries risks of selection bias and unmeasured confounders. Additionally, variations in local oxygen titration protocols between centers may limit the generalizability of our findings.

CONCLUSION

Moderate to high cumulative oxygen exposure is prevalent among children receiving invasive mechanical ventilation in pediatric ICUs. Future research is essential to define optimal oxygenation targets and minimize excessive oxygen exposure. Implementing a protocol-driven oxygen titration system managed by registered respiratory therapists could be an effective strategy to reduce excessive oxygen supplementation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Tasmina Panhwer:** Data collection, manuscript writing.
2	**Anwar Ul Haque:** Critical review, study design.