Severity of Impaired Oxygenation and Conservative Oxygenation Targets in Mechanically Ventilated Children: A Post Hoc Subgroup Analysis of the Oxy-PICU Trial of Conservative Oxygenation

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OBJECTIVES: A conservative oxygenation strategy is recommended in adult and pediatric guidelines for the management of acute respiratory distress syndrome to reduce iatrogenic lung damage. In the recently reported Oxy-PICU trial, targeting peripheral oxygen saturations (Spo_2) between 88% and 92% was associated with a shorter duration of organ support and greater survival, compared with Spo_2 greater than 94%, in mechanically ventilated children following unplanned admission to PICU. We investigated whether this benefit was greater in those who had severely impaired oxygenation at randomization.

DESIGN: Post hoc analysis of a pragmatic, open-label, multicenter randomized controlled trial.

SETTING: Fifteen PICUs across England and Scotland.

PATIENTS: Children between 38 weeks old corrected gestational age and 15 years accepted to a participating PICU as an unplanned admission and receiving invasive mechanical ventilation with supplemental oxygen for abnormal gas exchange.

INTERVENTIONS: A mixed-effects ordinal regression model was used to explore the effect of severity of lung injury, dichotomized to an oxygen saturation index (OSI) less than 12 or greater than or equal to 12 at randomization, the trial group allocation, age, and Pediatric Index of Mortality-3 on the composite ordinal outcome measure of duration of organ support at day 30 and mortality, with death being the worst outcome. An interaction term was included to specifically understand the effect of trial arm allocation on those with and OSI less than 12 and OSI greater than or equal to 12.

MEASUREMENTS AND MAIN RESULTS: Data were available for 1775 of 1986 eligible children. Two hundred twelve of 1775 children had an OSI greater than or equal to 12 at randomization. The trial primary outcome did not vary significantly according to OSI category. Both children with OSI less than 12 (odds ratio [OR], 0.85; 95% CI, 0.71–1.01) and OSI greater than or equal to 12 (OR, 0.95; 95% CI, 0.49–1.84) benefited from conservative arm allocation, with relative benefit greater for those with an OSI less than 12.

CONCLUSIONS: These data do not provide evidence that a conservative oxygenation strategy should be limited to mechanically ventilated children with severely impaired oxygenation.

KEYWORDS: artificial respiration; oxygen; oxygen saturation; respiratory distress syndrome

The second international guideline for the management of pediatric acute respiratory distress syndrome (PARDS) recommends maintaining peripheral oxygen saturations (Spo_2) between 88% and 97% in invasively

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ventilated children (1). These targets were based on strong expert consensus and adapted from the Acute Respiratory Distress Syndrome (ARDS) Network recommendation to maintain an Spo_2 between 88% and 95% in adults with ARDS (2). The rationale for so-called permissive hypoxemia is to protect lungs from further injury in targeting normoxemia in already diseased lungs.

In our recently published Oxy-PICU trial, we reported that an Spo_2 target of 88–92% offers a small but significant clinical benefit over an Spo_2 target of greater than 94% in all mechanically ventilated children needing supplemental oxygen after unplanned admission (3). It is unknown whether this clinical benefit of conservative oxygenation was consistent regardless of severity of oxygenation impairment, or it potentially benefitted those more with severely impaired oxygenation.

In this post hoc subgroup analysis of Oxy-PICU trial data, we investigated whether baseline severity of impaired oxygenation alters the treatment effect of conservative oxygenation on the primary outcome measure of a ranked composite of days of organ support and mortality. We performed a model-based analysis to investigate oxygen saturation index (OSI) as treatment modifier, analogously to the primary analysis of the original trial and subsequent ad hoc analyses.

MATERIALS AND METHODS

The protocol for the Oxy-PICU trial has been published previously (4). Briefly, children who were receiving invasive mechanical ventilation and supplemental oxygen following an unplanned admission to a PICU were randomized 1:1 to an Spo_2 target of 88–92% (conservative oxygenation) or greater than 94% (liberal oxygenation). The trial received U.K. Health Research Authority approval (integrated Research Application System number 272768) following a favorable ethical opinion from the East of England—Cambridge South Research Ethics Committee (reference 19/EE/0362). The trial was registered before recruitment (ISRCTN92103439). The trial was conducted according to the ethical principles of the Helsinki Declaration of 1975, as most recently amended. Recruitment occurred between September 2020 and May 2022, with data from 2040 admissions included in the primary analysis (3).

Data were collected at baseline for Spo_2, Fio_2, and mean airway pressure (MAP), with hourly data collection for all three variables in the first 7 days while on invasive mechanical ventilation and 12-hourly thereafter. The trial primary outcome was a ranked composite of the duration of organ support up to day 30, or death, as ordinal rank from 1 to 31 (death being ranked worse than 30 d of organ support).

Severity of oxygenation impairment at baseline was defined by the OSI calculated using the Spo_2, Fio_2, and MAP at randomization ($OSI = MAP \times Fio_2 \times 100/Spo_2$), dichotomized as severe ($OSI \geq 12$) or nonsevere ($OSI < 12$) consistent with the Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) guidelines (1). Baseline characteristics are described using summary statistics for demographics, comorbidities, and baseline physiological variables.

An ordinal regression model was constructed to explore the effect of severity of oxygenation impairment, the trial group allocation, age, and Pediatric Index of Mortality-3 on the composite outcome measure. We included a random effect at the level of recruitment site to account for heterogeneity at site level. The model included an interaction term between the severity of oxygenation impairment and the trial group allocation to explore the severity of impaired oxygenation as a treatment effect modifier.

As sensitivity analysis, we repeated these excluding all OSI measurements with Spo_2 values greater than 97%, as they remain outside the PALICC-2 guideline recommendations, and may represent children being exposed hyperoxia, or a higher OSI than necessary (5). Due to the over-representation of patients with comorbidities in patients with OSI greater than or equal to 12, we also repeated the primary analysis with the inclusion of a comorbidity indicator post hoc.

Analysis was performed in R, Version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/) using the lme4 and ordinal packages for the linear (lmer) and ordered logistic regression models (clmm2) (6, 7). The full implementation can be found on GitHub (https://github.com/Martin-Wiegand/Pulsoxy-projects.git).

RESULTS

A total of 2040 patients were recruited to Oxy-PICU; data from 1986 patients were available for analysis.

Data required for this subgroup analysis were missing for 211 patients; data from the remaining 1775 patients were taken forward for this subgroup analysis, as described in **Figure 1**.

There were 110 of 887 children (12.4%) with OSI greater than or equal to 12 in the conservative oxygenation group, and 102 of 888 (11.5%) in the liberal oxygenation group. The baseline characteristics are included in **Supplementary Table 1** (http://links.lww.com/PCC/C588).

For the analysis cohort, allocation to the conservative oxygenation group was associated with fewer days of organ support and increased survival. This was consistent with the primary trial result, although the 95% CI for the adjusted odds ratio included 1 (log odds ratio, –0.17; 95% CI, –0.34 to 0.01; odds ratio, 0.84; 95% CI, 0.71–1.01)—likely reflective of the smaller sample available for this subgroup analysis. A baseline OSI greater than or equal to 12 was associated with more days on organ support and death compared with an OSI less than 12 (log odds ratio, 0.93; 95% CI, 0.58–1.29; odds ratio, 2.53; 95% CI, 1.79–3.63) (**Fig. 2*A***).

Children with OSI greater than or equal to 12 and those with OSI less than 12 at baseline had improved outcomes in the conservative oxygenation group, compared with those in the liberal oxygenation group (**Fig. 2*B***). However, neither of these effects were statistically significant at the 5% level. The point estimate was lower in children with OSI less than 12—with the estimated odds ratio of a better outcome of 0.85 (95% CI, 0.71–1.01) compared with those with an OSI greater than or equal to 12—estimated odds ratio 0.95 (95% CI, 0.49–1.84). The overlapping CIs are in agreement with the nonsignificant interaction term, which imply there is no significant evidence for the treatment effect varying with OSI levels.

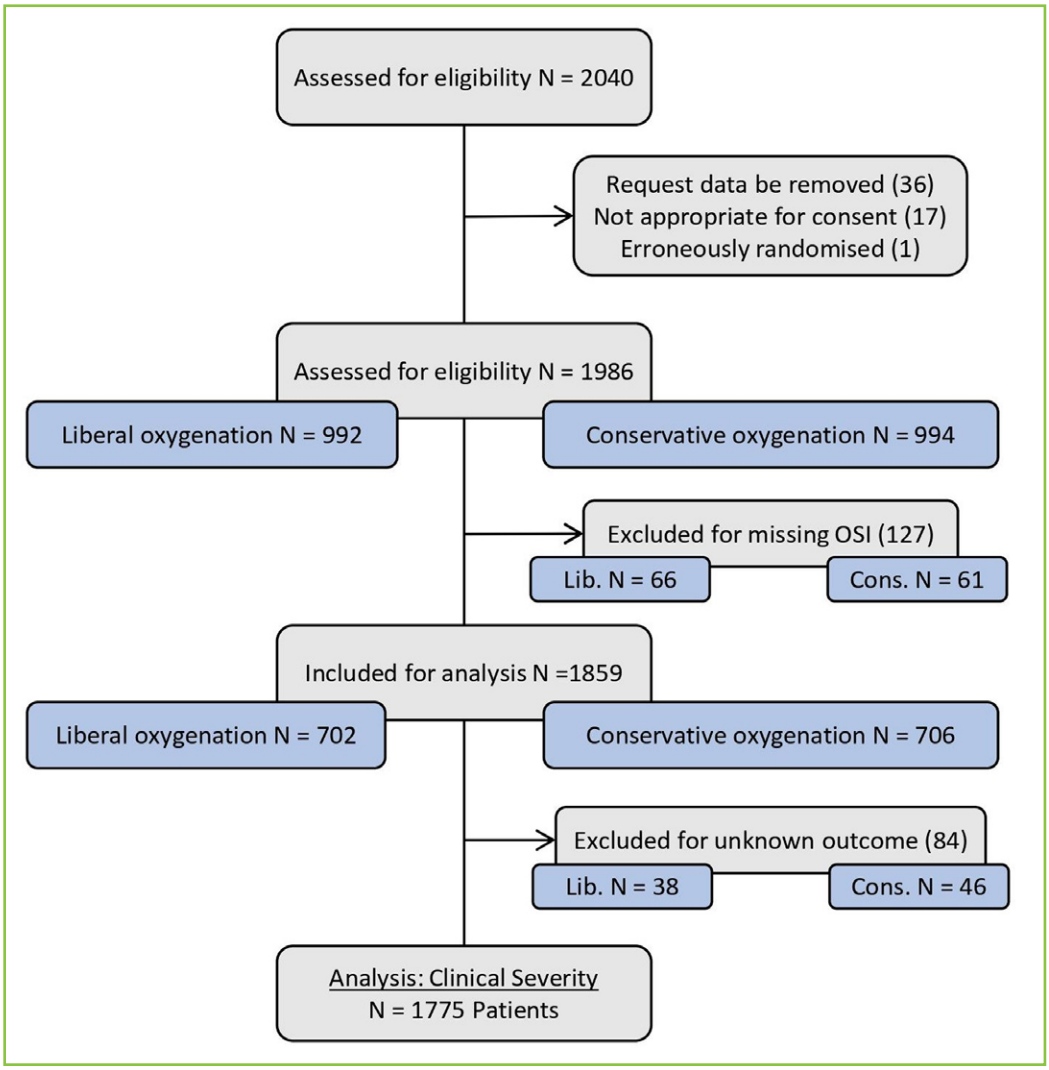

Figure 1. Flow chart of patients and observations included in the subgroup analysis of the relationship between baseline oxygen saturation index (OSI) on the composite primary outcome measure of days of organ support up to day 30 or death in the Oxy-PICU trial.

The sensitivity analysis excluding values of Spo_2 greater than 97% was consistent with the primary analysis and did not provide evidence for severity of impaired oxygenation as an effect modifier for conservative oxygenation (**Supplementary Fig. 1**, http://links.lww.com/PCC/C588). As in the primary analysis with all samples, the point estimate of the effect of conservative arm allocation favored better outcomes, although this was not statistically significant.

Including comorbidities in the primary model did not

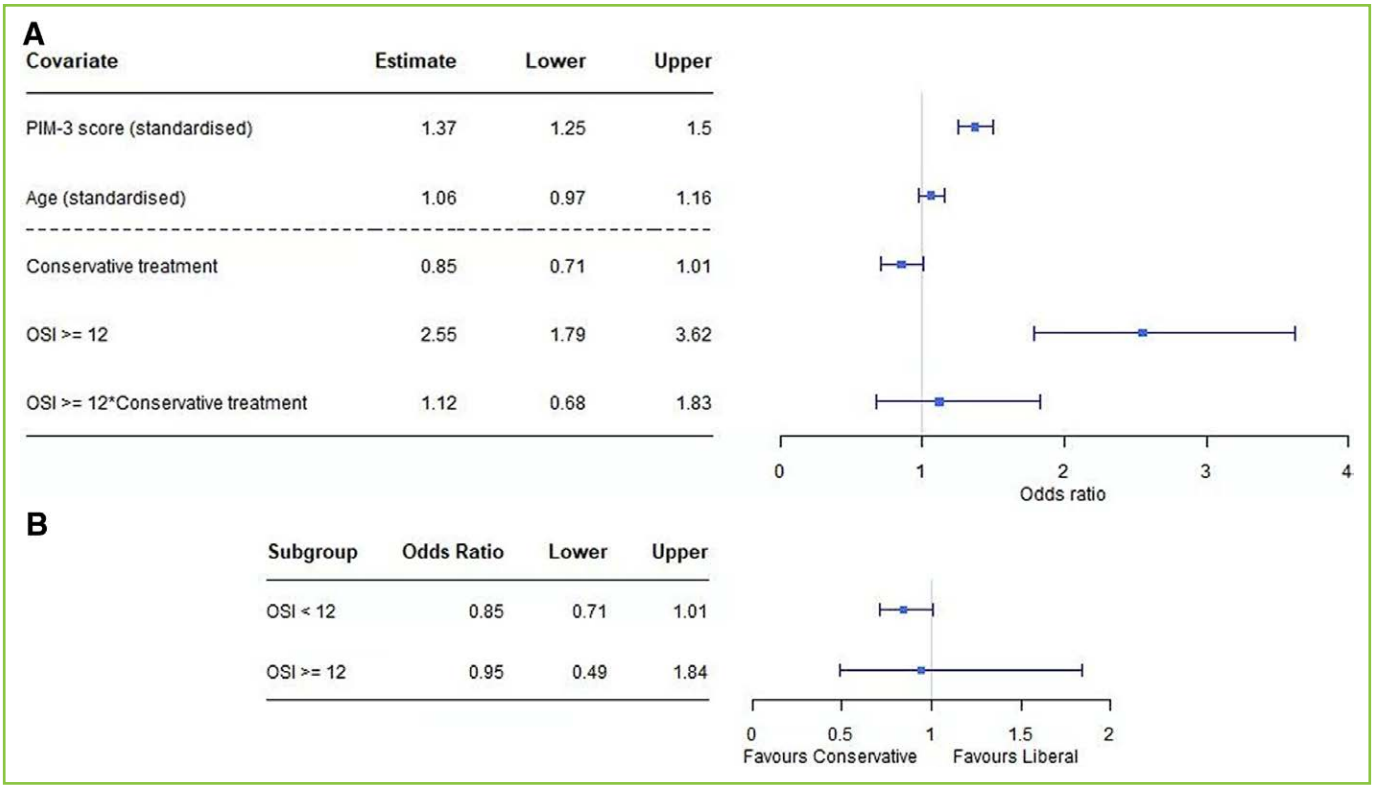

Figure 2. The effect of oxygen saturation index (OSI) and other covariates on the trial primary outcome. **A**, The regression model output is shown above, with a log odds ratio above 0 suggesting a worse outcome, and below 0 a better outcome. Children with higher Pediatric Index of Mortality-3 (PIM-3) scores and an OSI greater than or equal to 12 had significantly worse outcomes. The interaction term between conservative arm allocation and OSI greater than or equal to 12 has a lower log odds ratio than the OSI greater than or equal to 12 term alone, showing that conservative arm allocation had a beneficial (although not statistically significant) effect on those with OSI greater than or equal to 12. **B**, The beneficial effect, however, was similar in children with OSI less than 12 than those with OSI greater than or equal to 12, with the point estimate being better for the children with OSI less than 12 (although this is likely an effect of the imbalance in subgroup sizes).

significantly change the effects of the other covariates. While the presence of comorbidities significantly increases the length of organ support and mortality, it does not diminish the effect of OSI levels. It does not appear that the over-representation of comorbidities in patients with increased OSI levels impacted the primary analysis (**Supplementary Fig. 2**, http://links.lww.com/PCC/C588).

DISCUSSION

In this subgroup analysis of the Oxy-PICU trial, we did not find significant evidence that the severity of oxygenation impairment at baseline alters the treatment effect on the primary clinical outcome. While the point estimates from this subgroup analysis could be interpreted as that children with less severely impaired oxygenation at baseline demonstrated greater benefit from a conservative oxygenation strategy than those with more severely impaired oxygenation, this interaction was not significant at the 5% level.

Both the ARDSNet and pediatric PALICC-2 guidelines recommend the use of permissive hypoxemia in patients with severe lung disease. The rationale for these recommendations is to reduce the amount of iatrogenic injury through ventilator induced lung injury, and high Fio_2 that may be required to achieve higher Spo_2 values. The assumption is that any benefit with normoxemia may outweigh the risks of trying to achieve this. Children with severe lung disease require longer duration of mechanical ventilation and have higher mortality (8). Therefore, the treatment effect of a conservative oxygenation strategy may be expected to be greater in those with more severe lung disease. Counter to this, the only trial describing a point-estimate of harm with a conservative oxygenation strategy was in adults with ARDS, albeit not significantly so for the primary outcome of mortality at 28 days (9).

Our subgroup analysis suggests that there was no differential benefit in targeting a Spo_2 of 88–92% in mechanically ventilated children with or without severely impaired oxygenation. As a pragmatic trial, Oxy-PICU was highly inclusive in its eligibility, including most mechanically ventilated children following unplanned admission to PICU needing supplemental oxygen. We did not restrict inclusion to those who only fulfilled the PALICC-2 PARDS criteria. We did exclude children with known pulmonary hypertension and uncorrected congenital cardiac disease, but did not rule out cardiac failure or fluid overload as causes of impaired oxygenation. While it is possible that many of the children with a baseline OSI less than 12 may have required supplemental oxygenation because of atelectasis or fluid overload, it is likely, given the baseline characteristics and outcomes, that those with an OSI greater than or equal to 12 had more severe lung disease, consistent with PARDS. Less than 12% of children had an OSI greater than or equal to 12: given known worse clinical outcomes in this group, it was plausible that the trial outcome could have been dominated by this subgroup. As this is a subgroup analysis, it is not adequately powered to claim that conservative oxygenation is more effective in children with less severe oxygenation impairment compared those with severe oxygenation impairment, although the point-estimate may suggest so. The power is further reduced through missing data on baseline OSI, and loss of data following withdrawal of deferred consent. Our subgroups were defined only by OSI, not based on their inflammatory phenotypes, or other markers of lung injury measured clinically (such as using physiological dead-space) or radiologically, which theoretically may have uncovered differential effects.

CONCLUSIONS

In this subgroup analysis of the Oxy-PICU trial, we did not find evidence that the Oxy-PICU trial results were significantly altered by the severity of impaired oxygenation at baseline. This strengthens the argument to adopt conservative oxygenation targets for all mechanically ventilated children needing supplemental oxygen as described by the trial.

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Drs. Peters and Ray conceived, and designed this secondary analysis with Drs. Wiegand, Gould, Harrison, and Mouncey. Dr. Wiegand conducted the analyses. Drs. Peters, Ray, and Wiegand drafted the article. All authors critically revised and approved the article for submission.

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A complete list of the Oxy-PICU Investigators is provided in the ***Supplementary Appendix*** *(http://links.lww.com/PCC/C588).*

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