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The association between inhaled Nitric Oxide treatment and ICU Mortality and 28 day ventilator free days in Pediatric Acute Respiratory Distress Syndrome

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Abstract

Objective—To investigate the association between inhaled Nitric Oxide (iNO) treatment and ICU Mortality and 28-day ventilator free days (VFD) in Pediatric Acute Respiratory Distress Syndrome (PARDS).

Design—Retrospective cohort study. A propensity score for iNO treatment was developed and used in the analysis.

Setting—2 quaternary care pediatric intensive care units.

Patients—Children with PARDS.

Interventions—None.

Measurements and Main Results—There were 499 children enrolled in this study with 143 (28.7%) receiving iNO treatment. Children treated with iNO were more likely to have a primary diagnosis of pneumonia (72% versus 54.8%, p<0.001), had a higher initial oxygenation index (median 16.9 (IQR 10.1-27.3) versus 8.5 (IQR 5.8-12.2), p<0.001) and a higher 72-hour maximal vasoactive-inotrope score (median 15 (IQR 6-25) versus 8 (IQR 0-17.8), p<0.001) than those not receiving iNO. Mortality was higher in the iNO treatment group (25.2% versus 16.3%, p=0.02) and children in this group had fewer 28-day VFD (10 days (IQR 0-18) versus 17 days (IQR 5.5-22), p<0.0001).

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Conflict of Interest: None

We matched 176 children based on propensity score for iNO treatment. In the matched cohort, iNO treatment was not associated with mortality (OR 1.3 (95%CI 0.56-3.0)) or 28-day VFD (IRR 0.91 (95%CI 0.80-1.04)). These results remained consistent in the entire study cohort when the propensity score for iNO treatment was used for either inverse probability weighting or stratification in regression modeling with the exception that subjects treated with iNO were more likely to have zero VFDs ($p \leq 0.02$). In secondary analysis stratified by oxygenation response, iNO treatment was not associated with mortality or 28-day VFD in children with a positive oxygenation response (all $p > 0.2$)

Conclusions—Treatment with iNO in PARDS is not associated with improvement in either mortality or VFD and may be associated with harm. Further prospective trials are required to define the role of iNO treatment in PARDS.

Keywords

Acute Respiratory Distress Syndrome; Pediatrics; Nitric Oxide; Mortality; Mechanical Ventilation

Introduction

Pediatric Acute Respiratory Distress Syndrome (PARDS) affects 2-3,000 children in the United States per year.(1–4) Children with PARDS have poorly compliant lungs and severe refractory hypoxemia due to heterogeneous alveolar injury. Many critically ill children with PARDS are treated with inhaled Nitric Oxide (iNO) as a rescue therapy.(5) During early PARDS (the first 2-4 days) inflammation and increased permeability of the alveolar epithelium and capillary endothelium results in alveolar filling and collapse. iNO is a selective pulmonary vasodilator, decreasing pulmonary vascular resistance and improving ventilation-perfusion matching in areas of lung continuing to receive ventilation. As a signaling molecule, iNO also plays a key role in the inflammatory process.(6) iNO is theorized to impact outcomes in PARDS both through improvement of oxygenation and modulation of the inflammatory response.

While studies in children and adults with ARDS have demonstrated iNO treatment results in transient oxygenation improvement, there is little evidence to suggest iNO improves outcomes (mortality or length of mechanical ventilation) in either population. Recently the Pediatric Acute Lung Injury Consensus Conference (PALICC) recommended consideration of iNO treatment in severe PARDS.(5) However, this recommendation was based on minimal evidence. iNO continues to be used frequently but variably across institutions and providers.

We sought to use existing observational patient level data from two Pediatric Intensive Care Units (PICUs) to determine the association between iNO treatment and PICU mortality and 28-day ventilator free days (VFD) in PARDS. We hypothesized iNO treatment would be associated with decreased mortality and more VFD in children with PARDS.

Materials and Methods

This was a two center observational cohort study using existing datasets from Children's Hospital Los Angeles (CHLA) and Children's Hospital of Philadelphia (CHOP). At CHLA, invasively mechanically ventilated children meeting PALICC PARDS criteria and admitted to the PICU between March 2009 and April 2013 were retrospectively identified using oxygenation metrics and evaluation of the medical record as previously described.(7, 8) At CHOP, all children with two PaO_2/FiO_2 (PF) ratios <300 admitted to the PICU between July 2011 and June 2015 were screened prospectively, and those who met the 1994 American-European Consensus Conference (AECC) criteria for ARDS and PALICC PARDS criteria were included.(8–10) We excluded children <1 month or >18 years of age, those without an arterial line, and those on chronic mechanical ventilation. Children transferred to another ICU prior to extubation, were also excluded, as complete data on outcome was unavailable. This study was approved by the CHLA and CHOP Institutional Review Boards with a waiver of consent. Of note, iNO treatment in PARDS is not an FDA approved use and is considered off-label.

Variable Definition

The PALICC definition of PARDS for invasively ventilated children requires the acute onset of disease (within 7 days) of a known trigger, the presence of a new chest radiograph infiltrate, an oxygenation index ($OI=(\text{Mean Airway Pressure} \times FiO_2)/PaO_2$) ≥4, and respiratory failure not entirely explained by fluid overload or cardiac failure. Early PARDS was defined as the first 72 hours after meeting PARDS criteria. Children who received iNO during this time period were analyzed in the iNO treatment group. Children rarely receive iNO later in the course of PARDS. However children who did receive iNO after 72 hours were analyzed in the untreated group. The clinical insult triggering PARDS was categorized as one of the following; drowning, trauma, pneumonia, sepsis, or other. Comorbidities were defined as chronic pre-existing conditions and were categorized as chronic lung disease, chronic neurologic disease, hematologic/oncologic disease, stem cell transplant, solid organ transplant, or another comorbidity.(11) Children admitted with an acute change in their neurological status or after cardiac arrest were identified. Vasoactive-Inotrope score (VIS) was calculated as VIS=dopamine(mcg/kg/min) + dobutamine(mcg/kg/min) + 10x epinephrine(mcg/kg/min) + 100x norepinephrine(mcg/kg/min) + 100x phenylephrine(mcg/kg/min) + 10x milrinone(mcg/kg/min) + 10,000x vasopressin(U/kg/min).(12) The highest VIS within 72 hours of PARDS diagnosis was used for analysis. The initial OI at PARDS diagnosis was used in the analysis. Severity of illness was measured with 12-hour Pediatric Risk of Mortality (PRISM III).(13) Non-pulmonary organ failure was defined using pediatric definitions.(14) Non-conventional ventilation was defined as high frequency ventilation or airway pressure release ventilation. A positive oxygenation response to iNO treatment was defined as a 20% decrease in OI by 6 hours after the initiation of treatment. In children without an available arterial blood gas for OI calculation, Oxygen Saturation Index was used ($OSI=(\text{Mean Airway Pressure} \times FiO_2)/SpO_2$) as previously defined.(15)

Outcomes

PICU mortality was our primary outcome. A secondary outcome was VFD defined as the days alive and free of invasive mechanical ventilation in the first 28 days after intubation. Children who died were assigned VFD=0.

Statistical Analysis

Statistical analysis was performed with Stata v 15.0 (College Station, TX). The full details of the statistical analysis can be found in Supplemental Digital Content 1 Statistical Analysis. We developed a propensity score to estimate the probability of iNO treatment for use in adjusting for confounding variables associated with both the decision to start iNO treatment and mortality. We considered the following covariates for inclusion in the propensity score model; age, weight, PARDS trigger, comorbidities, initial OI, maximal VIS, PRISM III Score, acute neurologic injury, cardiac arrest, and admission hospital. Variables with $p<0.05$ were retained in the multivariable model. Two-way interaction terms were assessed between variables in the model and interaction terms with $p<0.1$ were included in the final propensity score model. Balance of covariates was assessed through graphics and standardized differences and additional variables were added to the propensity score model as required to achieve balance in an iterative approach. A common region of support was identified for the analysis (children in the treated group with a propensity score higher than any child in the untreated group and children in the untreated group with a propensity score lower than any child in the treated group were eliminated).

The developed propensity score was used in 3 ways for each outcome: 1) matching 2) inverse probability weighting 3) stratification. *Matching:* The psmatch2 command through STATA was used to match children who did and did not receive treatment with iNO based on propensity score. Children were matched 1:1 without replacement using a nearest neighbor approach. Once a matched sample was formed, the treatment effect was estimated by comparing mortality (mixed effects logistic regression model controlling for matched sample) and VFD (zero inflated negative binomial model (zinb) controlling for matched sample) between the two groups. A zero inflated model was used to model VFD due to the presence of excessive zeros; due to Poisson overdispersion of the data, a negative binomial model was used. Variables with a $p<0.2$ association with the outcome (died or VFD) and not included in the propensity score model were considered as possible confounders for the matched analysis models. Variables that changed the iNO effect estimate by >20% were included in the model. As matching decreased the analysis sample size significantly, inverse probability weighting and stratification by the propensity score were also used to analyze the association between iNO treatment and outcome using the entire sample. For consistency amongst models, the inverse probability weighted and stratification models were adjusted for the same confounding variables identified in the matched analysis.

Results

From the CHLA database of 254 patients, 142 children met inclusion and no exclusion criteria (Supplemental Digital Content 2 Figure 1). Of the children enrolled from CHLA, 14.1% received iNO treatment. From the CHOP database, all 357 children met inclusion and

no exclusion criteria. Of the subjects enrolled from CHOP, 34.4% received iNO treatment. The total combined cohort was 499 children. Of these 499 children, 143 (28.7%) received iNO within 72 hours of PARDS diagnosis with a median iNO duration of 4 days (IQR 2-8). There were 10 children who received iNO after 72 hours. Initial PARDS severity was as follows: 188 children (37.6%) with mild PARDS (4≤OI<8), 178 children (35.7%) with moderate PARDS (8≤OI<16), and 133 children (26.6%) with severe PARDS (OI≥16).

Children treated with iNO were more likely to have a primary diagnosis of pneumonia (72% versus 54.8%, p<0.001)(Table 1). They also had a higher initial OI (median 16.9 (IQR 10.1-27.3) versus 8.5 (IQR 5.8-12.2), p<0.001) and a higher maximal VIS (median 15 (IQR 6-25) versus 8 (IQR 0-17.8), p<0.001). PRISM III score was similar between the treated and untreated groups. Mortality was higher in the group treated with iNO (25.2% versus 16.3%, p=0.02) and they had fewer median VFD (10 days (IQR 0-18) versus 17 days (IQR 5.5-22), p<0.0001). Of the 143 children who received iNO, 61% (87 children) had a positive oxygenation response.

The final propensity score model included initial OI, maximal VIS, PARDS sepsis trigger, PARDS pneumonia trigger, a hematologic/oncologic comorbidity, having any other comorbidity, cardiac arrest, acute neurologic disease, extrapulmonary organ failures, and admission hospital. There were 464 children (93.2%) who had a propensity score for iNO treatment that fell within the zone of common support (as previously defined)(Supplemental Digital Content 3 Table 1).

We were able to match 176 children (88 per treatment group) by propensity score. Covariates were adequately balanced between the iNO-treated and untreated matched cohort, with the exception of treatment with non-conventional ventilation and extracorporeal membrane oxygenation (ECMO) (Table 2, Figure 1). There was 1 child in the matched cohort who received iNO after 72 hours and was analyzed as untreated.

After controlling for treatment with non-conventional ventilation and ECMO in the matched cohort, treatment with iNO was not associated with mortality (OR 1.3 (95% CI 0.56-3.0), p=0.54)(Table 3). In a zero inflated negative binomial model creating separate models for 0-28 day VFD and zero versus some VFD; treatment with iNO was not associated with number of VFD (IRR 0.91 (95% CI 0.8-1.04), p=0.17) or zero VFD (OR 1.7 (95% CI 0.77-3.9), p=0.19) after controlling for PRISM III Score, treatment with non-conventional ventilation, and treatment with ECMO (Table 4).

The effect estimates for the association of iNO with mortality were larger in the inverse probability weighted and the stratification analyses but continued not to be statistically significant (all p>0.1) (Table 3). Treatment with iNO also remained unassociated with number of VFD in the inverse probability weighted and the stratification analyses (all p>0.2) (Table 4). In these analyses, subjects treated with iNO were more likely to have zero VFD (i.e. die or remain on the ventilator for ≥28 days)(p≤0.02)(Table 4).

In a sensitivity analysis, when we limited the analysis to only children with moderate or severe PARDS, iNO treatment was not associated with either mortality or VFD (all p>0.1) (Supplemental Digital Content 4 Table 2 and Table 3). In additional secondary analysis

stratified by oxygenation response, iNO treatment was not associated with either mortality or VFD in children with a positive oxygenation response (all p>0.2)(Supplemental Digital Content 5 Table 4 and Table 5). In this analysis, in children without a positive oxygenation response, iNO treatment was associated with a higher odds of zero VFD (OR 6.1 (95% CI 1.4-26.3), p=0.02).

Discussion

Our results demonstrate consistently that iNO treatment is not associated with significant improvement in mortality or VFD in PARDS. This is the first retrospective study to use highly granular patient level data to evaluate the effect of iNO treatment on mortality and VFD in PARDS. We accounted for multiple confounding variables on the relationship between iNO and mortality including those that have a strong history of association with poor outcome in PARDS (OI, VIS, and hematologic/oncologic disease). Furthermore we used the developed propensity score in multiple ways to assess the relationship between iNO treatment and outcome.

A previous randomized, controlled trial of iNO treatment in children with PARDS highlights struggles with enrollment that have impacted the ability to prospectively evaluate the association between iNO treatment and outcomes in PARDS.(16) This study had a planned enrollment of 338 children but only enrolled 55 children from 9 centers over a 2 year period presumably due to a lack of clinical equipoise and was therefore stopped for slow enrollment. The authors found a difference in their primary outcome of VFD which just reached statistical significance (iNO treatment 14.2 ± 8.1 days versus control 9.1 ± 9.5 days, p=0.05).

Although our primary hypothesis was iNO treatment was associated with benefit in PARDS, in some of the models we found a suggestion of potential harm (more likely to have zero VFDs). While residual confounding may explain this result, there are reasons iNO treatment could be associated with true harm. Due to the concern for rebound pulmonary hypertension, it is common practice to slowly wean iNO. Therefore, children treated with iNO may require longer mechanical ventilation simply for weaning of the drug. In addition, there is emerging literature from adult studies of ARDS that iNO treatment is associated with renal failure and an increased need for renal replacement therapy.(17) We did not specifically study renal impairment as an outcome in our study.

Gupta et al. recently investigated the association between iNO treatment and outcomes in PARDS using a large database created by linking data from the Virtual Pediatric Systems (VPS) and Pediatric Health Information System (PHIS).(18) They created a propensity score to match children and control for confounding variables influencing the decision to initiate iNO treatment. Unfortunately, as both the VPS and the PHIS databases are primarily administrative databases, the authors were unable to verify children met PARDS criteria and they did not have data on PARDS severity or degree of hemodynamic instability. The inability to control for these important confounding variables led to this study being criticized by the pediatric critical care community.(19) When examining the subjects enrolled in their study many of them (58%) were treated with antiarrhythmics which is

unusual for PARDS and indicates a different study population than our study. The results for our primary outcome were similar; no significant difference in mortality. However in contrast to our primary analysis results, the Gupta et al. study found a significant association between iNO treatment and fewer VFD. This difference may be due to actual harm in their study population or the inability of their developed propensity score to adequately control for confounding variables in the matched sample.

Dowell et al. recently found that children with a positive oxygenation response to iNO may be most likely to benefit from treatment (fewer ventilator days).(19) We did not find similar results in our analysis with a positive oxygenation response not being associated with benefit. Rather the children who did not have a positive oxygenation response, had evidence of harm (more zero VFD). It is possible that the lack of an oxygenation response simply identifies children with more severe lung injury who may have worse outcomes regardless of iNO treatment. On the other hand, it is important to consider that while the heterogeneous general population of children with PARDS may derive no benefit from iNO, there may be discrete subgroups who respond either positively or negatively. Identifying markers that may identify these subgroups will be important for future trials.

We chose to use a zero inflated negative binomial model for VFD. This model combines separate models for 0-28 day VFD and zero VFD. The composite outcome of zero VFD comprises both children who die and those who receive mechanical ventilation for ≥28 days. We found in the matched primary analysis no association between zero VFD and iNO treatment however we did find a statistically significant association with more zero VFD in the stratification and inverse probability weighted analyses. The reason for this discrepancy may be that the stratification and inverse probability weighted analyses were more adequately powered to detect the association or that these methods do not adequately balance on propensity score. Overall, in their entirety, our results consistently demonstrate no significant benefit to iNO treatment and the possibility of harm.

iNO treatment is also associated with exorbitant costs, often not reimbursed by insurance companies as treatment in PARDS is not an FDA approved indication.(20) The results of this analysis and others call into question the relatively routine practice of prolonged iNO treatment in children with PARDS. Although the PALICC recommendations suggest considering iNO treatment in severe PARDS, this recommendation was based on minimal evidence and our analysis points towards no benefit in the moderate/severe PARDS group. A costly therapy with no definitive evidence for benefit and the possibility of harm, is not likely to survive in an era of cost cutting. Although a classic randomized controlled trial is probably unlikely to achieve adequate enrollment, newer more innovative clinical trial designs particulary with regards to protocolized rescue therapies, have the potential for increased acceptability to clinicians and should be considered by the pediatric critical care community.(21)

Although this study represents a robust analysis of available observational data, there were several limitations. While we controlled for all available clinical or management variables associated with either the decision to start iNO treatment or mortality, it is possible there are unmeasured influential clinical or management variables we were unable to control for in

our propensity score model. If these unknown clinical or management variables are associated with both the decision to initiate iNO treatment and either mortality or fewer VFD, this could have led to us not identifying a true benefit from iNO treatment. We combined prospectively collected data from one hospital with retrospectively collected data from another hospital to perform this analysis, therefore it is possible selection bias affected our results although we attempted to decrease this risk by including admission hospital as a variable in the propensity score model. Furthermore we were able to match only 61.5% of the children who received iNO with children who did not receive iNO in our primary analysis. This study was therefore powered to identify large changes in mortality or VFD and it is possible a smaller effect was not identified; nonetheless, the estimate of association was in the direction of higher mortality and fewer VFD in the iNO-treated children. It is also possible that the association between iNO treatment and outcome could be different in the children who were not matched, or the children who were not in the region of common support, and the generalizability of our findings may be limited.

Conclusions

This large observational study demonstrates iNO treatment in PARDS is not associated with a significant improvement in either mortality or VFD and may be associated with harm. As a costly treatment that remains frequently used for PARDS, this study in combination with other recent studies, calls attention to the need for clinical equipoise for future clinical trial enrollment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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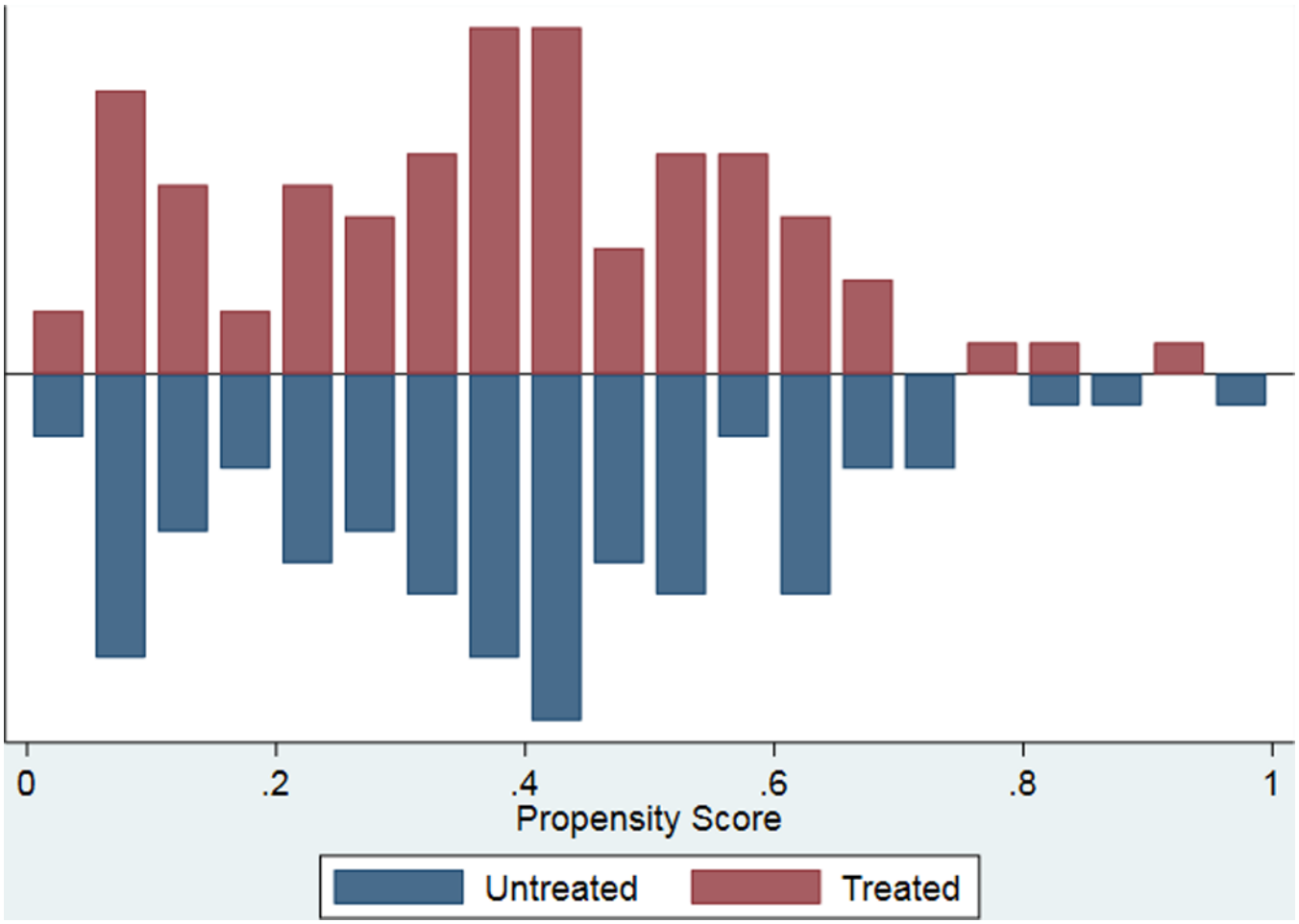

Figure 1.
Propensity Score histogram for matched children who were untreated and treated with inhaled Nitric Oxide.

Table 1

Unmatched Characteristics of Children with Acute Respiratory Distress Syndrome

Variables	Untreated (n=356)	Treated with iNO (n=143)	p value
Age (yrs)	4.1 (IQR 1.3-12.9)	3.8 (IQR 1.3-10.6)	0.95
Weight (kg)	15 (IQR 10-34)	15.5 (IQR 9.3-39.6)	0.95
Comorbidity			
Chronic Neurologic Disease	64 (18%)	30 (21%)	0.44
Chronic Lung Disease	22 (6.2%)	5 (3.5%)	0.23
Hematologic/Oncologic	75 (21.1%)	38 (26.6%)	0.18
Stem Cell Transplant	27 (7.6%)	17 (11.9%)	0.13
Solid Transplant	15 (4.2%)	1 (0.7%)	0.05
Another Comorbidity	71 (19.9%)	32 (22.4%)	0.54
ARDS Trigger			
Drowning	7 (2%)	3 (2.1%)	1
Pneumonia	195 (54.8%)	103 (72%)	<0.001
Sepsis	88 (24.7%)	25 (17.5%)	0.08
Trauma	26 (7.3%)	5 (3.5%)	0.11
Other	40 (11.2%)	7 (4.9%)	0.03
Acute Neurologic Disease	68 (19.1%)	19 (13.3%)	0.12
Initial Oxygenation Index	8.5 (IQR 5.8-12.2)	16.9 (IQR 10.1-27.3)	<0.001
72 hour Max Vasoactive Inotrope Score	8 (0, 17.8)	15 (6, 25)	<0.001
Non-Pulmonary Organ Failure>1	178 (50%)	83 (58%)	0.10
Non-Conventional Ventilation	56 (15.7%)	94 (65.7%)	<0.0001
Cardiac Arrest	28 (7.9%)	2 (1.4%)	0.006
Extracorporeal Membrane Oxygenation (ECMO)	1 (0.3%)	17 (11.9%)	0.0001
PRISM Score (Severity of Illness)	11 (IQR 6-17)	11 (IQR 5-20)	0.82

Continuous variables are presented as median and interquartile range and were compared with Mann Whitney U tests.

Categorical variables are presented as count and percentage and were compared with Chi Square tests (Fisher exact if n in any category <5)

Table 2

Matched Characteristics of Children with Acute Respiratory Distress Syndrome

Variables	Untreated (n=88)	Treated with iNO (n=88)	p value	Standardized Difference
Age (yrs)	4.9 (1.3-11.7)	3.6 (1.2-9.1)	0.30	−0.14
Comorbidity				
Chronic Neurologic Disease	14 (15.9%)	15 (17%)	0.84	0.03
Chronic Lung Disease	2 (2.3%)	5 (5.7%)	0.44	0.17
Hematologic/Oncologic	23 (26.1%)	24 (27.3%)	0.87	0.03
Stem Cell Transplant	7 (8%)	9 (10.2%)	0.60	0.08
Solid Transplant	2 (2.3%)	1 (1.1%)	1	−0.09
Another Comorbidity	24 (27.3%)	20 (22.7%)	0.49	−0.11
ARDS Trigger				
Drowning	0 (0%)	2 (2.3%)	0.50	0.21
Pneumonia	59 (67%)	57 (64.8%)	0.75	−0.05
Sepsis	21 (23.9%)	20 (22.7%)	0.86	−0.03
Trauma	5 (5.7%)	3 (3.4%)	0.72	−0.11
Other	3 (3.4%)	6 (6.8%)	0.31	0.15
Acute Neurologic Disease	10 (11.4%)	11 (12.5%)	0.82	0.04
Initial Oxygenation Index	11.6 (8.8-18.8)	11.1 (8.6-20.6)	0.97	0.01
Max 72 hour Vasoactive Inotrope Score	12 (6–21)	13 (5–20)	0.91	0.07
Non-Pulmonary Organ Failures	1 (1, 2.5)	2 (1, 3)	0.53	0.10
Non-Conventional Ventilation	25 (28.4%)	53 (60.2%)	<0.0001	0.67
Cardiac Arrest	3 (3.4%)	2 (2.3%)	0.65	−0.07
Extracorporeal Membrane Oxygenation (ECMO)	1 (1.1%)	8 (9.1%)	0.02	0.37
PRISM Score (severity of illness)	11 (7–17)	9.5 (4.5-16)	0.30	−0.13
Admission Hospital	69 (78.4%)	72 (81.8%)	0.57	0.09

Continuous variables are presented as median and interquartile range and were compared with Mann Whitney U tests.

Categorical variables are presented as count and percentage and were compared with Chi Square tests (Fisher exact if n in any category <5)

Table 3

The Association between Treatment with inhaled Nitric Oxide and Mortality

iNO Treatment	Unadjusted Analysis (n=499)[a]		Matched Analysis (n=176)[b,c]		Inverse Probability Weighting (n=464)[a,c]		Stratification Analysis (n=464)[a,c,d]	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
iNO Treatment	1.7 (1.1-2.8)	0.02	1.3 (0.56-3.0)	0.54	2.2 (0.59-8)	0.24	1) 1.6 (0.85-3.1) 2) 1.6 (0.74-3.3)	0.14 0.24

Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for multivariable models reported in Supplemental Digital Content 6

[a] logistic regression model

[b] mixed effects logistic regression model controlling for paired data

[c] Adjusted for confounding variables of treatment with non-conventional ventilation, treatment with ECMO

[d] Stratification Analysis was performed 1) using propensity score as a categorical variable in a logistic regression model 2) creating separate logistic regression models based on quartile of propensity score with a reported pooled OR (95%CI).

Table 4

The Association between Treatment with inhaled Nitric Oxide and 28 day Ventilator Free Days

iNO Treatment	Unadjusted Analysis (n=499)[a]		Matched Analysis (n=176)[b]		Inverse Probability Weighting (n=464)[a]		Stratification Analysis (n=464)[a,c]	
	Estimate (95% CI)	p value	Estimate (95% CI)	p value	Estimate (95% CI)	p value	Estimate (95% CI)	p value
Incidence Rate Ratio 0-28 day Ventilator Free Days	0.83 (0.77-0.91)	<0.001	0.91 (0.80-1.04)[d]	0.17	0.96 (0.87-1.06)[d]	0.39	1) 0.93 (0.84-1.04)[d] 2) 1 (0.89-1.1)[d]	0.22 0.94
Odds Ratio zero Ventilator Free Days	2.5 (1.63-3.8)	<0.001	1.7 (0.77-3.9)[e]	0.19	3.1 (1.2-8.9)[e]	0.02	1) 2.1 (1.2-3.8)[e] 2) 2.8 (1.4-5.4)[f]	0.02 0.003

Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for multivariable models reported in Supplemental Digital Content 6

[a] zero inflated negative binomial model

[b] zero inflated negative binomial model controlling for paired data

[c] Stratification Analysis was performed 1) using propensity score as a categorical variable in a zero inflated negative binomial model 2) creating separate zero inflated negative binomial models based on quartile of propensity score with a reported pooled IRR (95%CI) and OR (95% CI)

[d] Adjusted for confounding variables of PRISM III Score, treatment with non-conventional ventilation

[e] Adjusted for confounding variables of PRISM III Score, treatment with non-conventional ventilation, and treatment with ECMO

[f] Adjusted for the confounding variable of treatment with non-conventional ventilation (due to small number of zero observations within each strata unable to control for additional confounding variables in this analysis)