Original Article

Non-Invasive Ventilation in Children with Paediatric Acute Respiratory Distress Syndrome

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Abstract

Introduction: Evidence supporting non-invasive ventilation (NIV) in paediatric acute respiratory distress syndrome (PARDS) remains sparse. We aimed to describe characteristics of patients with PARDS supported with NIV and risk factors for NIV failure. Materials and Methods: This is a multicentre retrospective study. Only patients supported on NIV with PARDS were included. Data on epidemiology and clinical outcomes were collected. Primary outcome was NIV failure which was defined as escalation to invasive mechanical ventilation within the first 7 days of PARDS. Patients in the NIV success and failure groups were compared. Results: There were 303 patients with PARDS; 53/303 (17.5%) patients were supported with NIV. The median age was 50.7 (interquartile range: 15.7-111.9) months. The Paediatric Logistic Organ Dysfunction score and oxygen saturation/fraction of inspired oxygen (SF) ratio were 2.0 (1.0-10.0) and 155.0 (119.4-187.3), respectively. Indications for NIV use were increased work of breathing (26/53 [49.1%]) and hypoxia (22/53 [41.5%]). Overall NIV failure rate was 77.4% (41/53). All patients with sepsis who developed PARDS experienced NIV failure. NIV failure was associated with an increased median paediatric intensive care unit stay (15.0 [9.5-26.5] vs 4.5 [3.0-6.8] days; *P* <0.001) and hospital length of stay (26.0 [17.0-39.0] days vs 10.5 [5.5-22.3] days; *P* = 0.004). Overall mortality rate was 32.1% (17/53). Conclusion: The use of NIV in children with PARDS was associated with high failure rate. As such, future studies should examine the optimal selection criteria for NIV use in these children.

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Key words: Bi-level positive airway pressure, Continuous positive airway pressure, Non-invasive ventilation

Introduction

The use of non-invasive ventilation (NIV) in children is widespread and has increased in the past decade.[1-3] The physiological benefits of NIV include increasing functional residual capacity, unloading respiratory muscles and promoting cardiopulmonary interactions that translate into improved gas exchange and symptom relief.[4,5] In certain paediatric patients such as those with bronchiolitis, pneumonia and asthma, NIV has been shown to reduce the need for endotracheal intubation and mechanical ventilation (MV).[6,7] However, whether early NIV support improves clinical outcomes in patients with paediatric acute respiratory distress syndrome (PARDS) remains contentious.[2,8] Indeed, some studies have reported high NIV failure rates such as 78% in PARDS.[9]

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At the Pediatric Acute Lung Injury Consensus Conference (PALICC), a paediatric-specific PARDS definition was developed for children supported on NIV but there were limited recommendations on the use of NIV in these patients.[10,11] The oxygenation criteria utilises a cut-off of partial pressure of arterial oxygen/fraction of inspired oxygen (F_iO_2) (PF) ratio ≤300 or oxygen saturation/F_iO_2 (SF) ratio ≤264. PALICC acknowledges that there is a lack of published data to support the routine use of NIV in PARDS.[11] Current limited data suggests that children with moderate-to-severe PARDS should not be supported with NIV and that early intubation is indicated.[10] A further limitation is that the PALICC definition does not allow stratification into mild/moderate/severe PARDS in patients supported on NIV and there is currently no proposed cut-off PF or SF ratio (below which NIV should not be considered).

To address the current lack of description of NIV use in children with PARDS, we utilised data collected from a multicentre retrospective study to examine the use of NIV in these children.[12] We aimed to answer the following questions: 1) How is NIV applied in children with PARDS in Asia?; and 2) What are the risk factors associated with NIV failure in this population? We hypothesised that the use of NIV in PARDS is associated with a high failure rate.

Materials and Methods

Dataset from a multicentre retrospective cohort study of PARDS patients across 4 Pediatric Acute and Critical Care Medicine Asian Network (PACCMAN) paediatric intensive care units (PICUs) in Asia from 2009 to 2015 was used for this study.[12] The centres were all tertiary referral teaching hospitals and the PICUs consisted of 8 to 31 multidisciplinary beds. The study was done in accordance with the Helsinki Declaration and was approved by all participating hospital institutional ethics review boards and waiver of consent was granted in all sites.

Patients

Patients aged from 1 day to 18 years and who had met the PALICC criteria for PARDS were included in the study. Only patients who were supported on NIV at diagnosis of PARDS were included in this study. We did not examine the utility of NIV postextubation. The PALICC's criteria for PARDS patients on NIV support included: 1) PF ratio ≤300 or SF ratio ≤264; 2) new radiological lung infiltrates; 3) within 7 days of a known clinical insult; and 4) was not explained by cardiac failure or fluid overload.[11] Children with congenital cyanotic heart disease, chronic lung disease and left ventricular dysfunction fulfilling the above criteria were included if acute deterioration in oxygenation and new pulmonary infiltrates could not be explained by their pre-existing diseases. We excluded neonates with a corrected age <35 weeks and/or with perinatal-related lung disease. The use of NIV was at the discretion of the managing physician at the respective sites.

Data Collection

The following demographic data were obtained: age, weight, gender, severity scores (Paediatric Index of Mortality 2 [PIM 2] score and Paediatric Logistic Organ Dysfunction [PELOD] score), risk factors for PARDS, presence of organ dysfunction, SF ratio, adjunct PARDS therapies and PICU supportive therapies. Organ dysfunction was defined according to the International Pediatric Sepsis Consensus Conference criteria.[13] PIM 2 and PELOD were scored on admission to the PICU.[14,15] We also collected data on the status of "limitations of care" or "do-not-resuscitate" on all patients with PARDS supported on NIV.

NIV Characteristics

NIV support referred to continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP), delivered through nasal prongs or face masks. Data on expiratory positive airway pressure (EPAP), inspiratory positive airway pressure (IPAP) and F_iO_2 were examined. We did not include patients on high-flow nasal cannula. For standardisation, data on NIV settings, pulse oximetry readings and blood gases were obtained between 6 am to 8 am daily.

Clinical Outcomes

The primary outcome was NIV failure. We defined NIV failure as the need to escalate to MV within the first 7 days of PARDS. The choice of 7 days was arbitrarily selected to exclude deterioration due to a completely different disease process (besides PARDS)—judged to occur in NIV failure beyond 7 days. Patients with NIV success did not require MV within the same time period. Our secondary outcomes were PICU mortality, PICU and hospital length of stay (LOS).

Statistical Analysis

Patients were analysed in 2 groups—NIV success and failure. Categorical data were expressed as frequencies (percentages) and continuous data were expressed as median (interquartile range [IQR]). Categorical and continuous variables were compared using the Fisher's exact test and Mann-Whitney U tests, respectively. Because "limitation of care" orders influence the decision for escalation of therapy, we performed a sensitivity analysis excluding patients with limitations of care. Statistical significance was taken as $P < 0.05$ for all tests. SAS software (version 9.4; SAS Institute, North Carolina, United States) was used for the analysis.

Results

Patients' Characteristics

A total of 303 patients from 4 centres were identified with PARDS; 53 (17.5%) patients were supported with NIV on day 1 of PARDS. A description of patients supported on MV has been previously published.[12] The median age of NIV patients was 50.7 (15.7-111.9) months. Overall PIM 2 score, PELOD score and SF ratio were 5.0 (2.3-7.4), 2.0 (1.0-10.0) and 155.0 (119.4-187.3), respectively (Table 1). The most frequent risk factors of PARDS were pneumonia (46/53 [86.8%]) and sepsis (13/53 [24.5%]).

Characteristics of NIV

NIV was used for the main indications of increased work of breathing (26/53 [49.1%]) and hypoxia (22/53 [41.5%]) (Table 2). Of the 53 patients supported with NIV, 30 (56.6%) patients were supported on BiPAP, whereas the remaining patients were supported with CPAP. Twenty-two out of

Table 1. Characteristics of Patients with Successful or Failed Non-Invasive Ventilation Support

Characteristic	Total (n = 53)	NIV Success (n = 12)	NIV Failure (n = 41)	*P* Value
Age (months)	50.7 (15.7 – 111.9)	52.2 (12.1 – 138.5)	50.7 (19.8 – 104.1)	0.782
Weight (kg)	17.0 (9.6 – 27.7)	15.0 (8.2 – 25.8)	17.0 (9.9 – 31.3)	0.425
Male gender	21 (39.6)	3 (25.0)	18 (43.9)	0.323
PIM 2 score	5.0 (2.3 – 7.4)	3.6 (1.6 – 6.4)	5.1 (2.7 – 7.8)	0.184
PELOD score	2.0 (1.0 – 10.0)	1.0 (1.0 – 10.8)	2.0 (1.0 – 10.0)	0.983
Comorbidities	28 (52.8)	9 (75.0)	19 (46.3)	0.107
Immunocompromised	8 (15.1)	1 (8.3)	7 (17.1)	0.665
Bacteraemia	9 (17.0)	0 (0.0)	9 (22.0)	0.100
Risk factors				
Pneumonia	46 (87.8)	12 (100.0)	34 (82.9)	0.329
Sepsis	13 (24.5)	0 (0.0)	13 (31.7)	0.026
Aspiration	2 (3.8)	0 (0.0)	2 (4.9)	1.000
Transfusion	5 (9.4)	2	3 (7.3)	0.315
Others	5 (9.4)	0 (0.0)	5 (12.2)	0.577
Organ dysfunction	19 (35.8)	4 (33.3)	15 (36.6)	1.000
Cardiovascular	7 (13.2)	0 (0.0)	7 (17.1)	0.329
Neurological	3 (5.7)	0 (0.0)	3 (7.3)	1.000
Haematological	15 (28.3)	3 (25.0)	12 (29.3)	1.000
Renal	10 (18.9)	3 (25.0)	7 (17.1)	0.677
Hepatic	14 (26.4)	4 (33.3)	10 (24.4)	0.711
SF ratio	155.0 (119.4 – 187.3)	165.8 (152.1 – 233.8)	150.0 (112.5 – 173.3)	0.148
SF ratio <150	22 (41.5)	2 (16.7)	20 (48.9)	0.093
Prone position	4 (7.5)	1 (8.3)	3 (7.3)	1.000
Systemic steroids	35 (66.0)	3 (25.0)	32 (78.0)	0.001
Beta agonist	30 (56.6)	9 (75.0)	21 (51.2)	0.193
Diuretics	38 (71.7)	4 (33.3)	34 (82.9)	0.002
Transfusion	29 (54.7)	4 (33.3)	25 (61.0)	0.111
Inotropes	27 (50.9)	1 (8.3)	26 (63.4)	0.001
CRRT	7 (13.2)	0 (0.0)	7 (17.1)	0.329
ECMO	1 (1.9)	0 (0.0)	1 (2.4)	1.000
Limitation of care	10 (18.9)	5 (41.7)	5 (12.2)	0.023
PICU LOS (days)	13.0 (7.0 – 24.5)	4.5 (3.0 – 6.8)	15.0 (9.5 – 26.5)	<0.001
Hospital LOS (days)	23.0 (13.5 – 34.0)	10.5 (5.5 – 22.3)	26.0 (17.0 – 39.0)	0.004
Mortality	17 (32.1)	6 (50.0)	11 (26.8)	0.167

CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation; LOS: Length of stay; NIV: Non-invasive ventilation; PELOD: Paediatric Logistic Organ Dysfunction; PICU: Paediatric intensive care unit; PIM 2: Paediatric Index of Mortality 2; SF ratio: Oxygen saturation/fraction of inspired oxygen ratio

Categorical and continuous data are expressed as number (percentages) and median (interquartile range), respectively.

Table 2. Non-Invasive Ventilation Characteristics in Patients with Successful or Failed Trials

Characteristic	Total (n = 53)	NIV Success (n = 12)	NIV Failure (n = 41)	*P* Value
NIV indications				0.203
Work of breathing	26 (49.1)	9 (75.0)	17 (41.5)	
Hypoxia	22 (41.5)	3 (25.0)	19 (46.3)	
Hypercarbia	2 (3.8)	0 (0.0)	2 (4.9)	
Others*	3 (5.7)	0 (0.0)	3 (7.3)	
NIV delivery device				0.665
NIV-specific ventilators	45 (84.9)	11 (91.7)	34 (82.9)	
Portable ventilators	8 (15.1)	1 (8.3)	7 (17.1)	
NIV mode				0.193
BiPAP	30 (56.6)	9 (75.0)	21 (51.2)	
CPAP	23 (43.4)	3 (25.0)	20 (48.8)	
NIV variables on day 1 (PARDS)				
IPAP, median (IQR)	14.0 (12.0 – 16.0)	14.0 (13.0 – 17.0)	14.0 (12.0 – 16.0)	0.533
EPAP, median (IQR)	6.0 (4.5 – 8.0)	8.0 (6.0 – 8.0)	5.0 (4.0 – 8.0)	0.014
F_iO_2, median (IQR)	60.0 (50.0 – 80.0)	50.0 (40.0 – 60.0)	60.0 (50.0 – 80.0)	0.026
SpO_2, median (IQR)	93.0 (89.5 – 96.0)	93.5 (90.5 – 96.8)	93.0 (89.0 – 96.0)	0.757
NIV variables prior to NIV failure				
IPAP, median (IQR)			14.0 (13.0 – 17.5)	
EPAP, median (IQR)			5.0 (4.0 – 8.0)	
F_iO_2, median (IQR)			60.0 (53.5 – 80.0)	
SpO_2, median (IQR)			93.0 (89.5 – 97.0)	

BiPAP: Bi-level positive airway pressure; CPAP: Continuous positive airway pressure; EPAP: Expiratory positive airway pressure; F_iO_2: Fraction of inspired oxygen; IPAP: Inspiratory positive airway pressure; IQR: Interquartile range; NIV: Non-invasive ventilation; PARDS: Paediatric acute respiratory distress syndrome; SpO_2: Oxygen saturation

Categorical and continuous data are expressed as number (percentages) and median (IQR), respectively.

*Two patients were on home NIV but required escalation of settings. One patient had >1 indication.

23 (95.7%) patients supported on initial CPAP required escalation to BiPAP.

Clinical Outcomes

Overall NIV failure rate was 77.4% (41/53). Median time from PARDS diagnosis to NIV failure was 1.0 (1.0-5.0) days. In this cohort, sepsis was associated with NIV failure (13/41 [31.7%] vs 0 [0.0%]; $P = 0.026$). The use of systemic steroids (32/41 [78.0%] vs 3/12 [25.0%]; $P = 0.001$), diuretics (34/41 [82.9%] vs 4/12 [33.3%]; $P = 0.002$) and inotropes (26/41 [63.4%] vs 1/12 [8.3%]; $P = 0.001$) were higher in the NIV failure group compared to the NIV success group. The SF ratio for patients that were successfully managed with NIV was similar to those that failed NIV (165.8 [152.1-233.8] vs 150.0 [112.5-173.3]; $P = 0.148$) (Table 1). Patients with SF ratio <150 had a trend towards higher failure rate (8.9% [20/41] vs 16.7% [2/12]; $P = 0.093$) compared to those with SF ratio ≥150. There was also no difference in organ dysfunction between the NIV success and failure groups (4/12 [33.3%] vs 15/41 [36.6%], $P = 1.000$). EPAP was lower (5.0 [4.0-8.0] vs 8.0 [6.0-8.0] cm H_2O; $P = 0.014$) and F_iO_2 higher (60.0 [50.0-80.0] vs 50.0 [40.0-60.0]%; $P = 0.026$) in the NIV failure group compared to the NIV success group. For patients who failed NIV, the oxygenation index (OI) and oxygen saturation index (OSI) after intubation on the subsequent day of PARDS was 14.3 (9.4-25.7) and 13.6 (8.0-18.3), respectively, which falls into the moderate-to-severe PARDS category. This was despite their NIV settings remaining unchanged from baseline prior to intubation (Table 2).

Compared to those patients who were supported successfully on NIV, those with NIV failure had an increased PICU (4.5 [3.0-6.8] vs 15.0 [9.5-26.5] days; $P < 0.001$) and hospital (10.5 [5.5-22.3] vs 26.0 [17.0-39.0] days; $P = 0.004$) LOS. Overall PICU mortality rate was 32.1% (17/53). There was no difference in mortality rates between patients who were supported successfully with NIV or not (50.0% [6/12] vs 26.8% [11/41]; $P = 0.167$).

Sensitivity Analysis

"Limitation of care" orders were present for 10/53 (18.9%) patients and of these, 7/10 (70.0%) died (Fig. 1). After

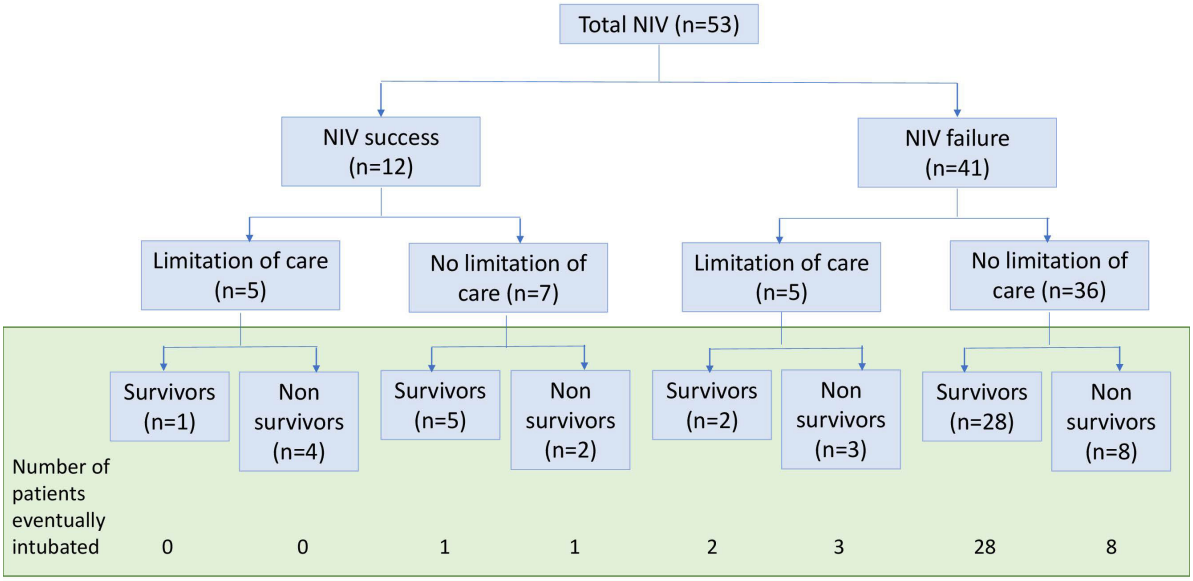

Fig. 1. Proportion of patients in the non-invasive ventilation success and failure groups. NIV: Non-invasive ventilation

excluding patients with "limitation of care", there was no difference in the SF ratio and organ dysfunction between the NIV success and failure groups (Table 3). Characteristics of NIV use were also similar (Table 4). After excluding patients with "limitation of care", there was no difference in mortality between the NIV success and failure groups (2/7 [28.6%] vs 8/36 [22.2%]; $P = 0.656$).

Discussion

Our report provides an overview on the use of early NIV in children with PARDS across multiple PICUs in Asia. A small but considerable proportion of children (53/303 [17.5%]) diagnosed with PARDS was supported on NIV on day 1 of PARDS. Of these, 10/53 (18.9%) had limitation of care. The rate of NIV failure and mortality was high (77.4% [41/53] and 32.1% [17/53], respectively) even after exclusion of patients with limitation of care (83.7% [36/43] and 23.3% [10/43], respectively). For patients who failed NIV, the OI and OSI after intubation were in the moderate-to-severe PARDS categories (14.3 [9.4-25.7] and 13.6 [8.0-18.3], respectively). In children with PARDS, NIV failure was associated with prolonged PICU and hospital LOS.

Few studies have reported data on the use of NIV in children with PARDS. A point-prevalence study conducted a decade ago described the ventilator strategies for acute lung injury in children from 52 PICUs in 12 countries and found that only 14/164 (8.5%) patients were supported on NIV.[16] The median OI (4 [4-5]) and PF ratio (183 ± 41) were lower and higher, respectively, compared to those on MV.[16] Comparatively, our current study reports a slightly higher rate of NIV use (17.5%). This may be due to the overall increasing trend of NIV use worldwide.[2,3] Indeed, 2 recent large studies—the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) in adults and the Paediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE) in children—reported comparable NIV use of 15.5% to 21.5%.[17,18]

In our current study, many patients who were initially supported with CPAP eventually required escalation to BiPAP (22/23 [95.7%]). The overall median IPAP (14.0 [12.0-16.0] cm H_2O) and EPAP (6.0 [4.5-8.0] cm H_2O) used in our cohort was comparable with other studies.[8,9] However, it is notable that physiologic studies in adult patients with acute lung injury demonstrated beneficial oxygenation effects of positive end-expiratory pressure (PEEP) only with EPAP levels above 10 cm H_2O (both CPAP and BiPAP), which suggests that a high level EPAP may be necessary to support patients with acute respiratory distress syndrome (ARDS) with NIV.[4] In our study, a significant proportion of patients required respiratory support for increased work of breathing. Hence, the pressure support component or IPAP may be necessary to relieve dyspnoea and respiratory muscle effort. We postulate that BiPAP may be advantageous in children with PARDS compared to CPAP. Future studies should examine the clinical efficacy of different types of NIV support on outcomes with children with PARDS.

In previous reports, depending on the aetiology of respiratory insufficiency, the rate of NIV failure or escalation from NIV to MV ranged from 16% to 78%.[1,9] A multicentre

Table 3. Characteristics of Patients with Successful or Failed Non-Invasive Ventilation Support Excluding Those with Limitation of Care

Characteristic	Total (n = 43)	NIV Success (n = 7)	NIV Failure (n = 36)	*P* Value
Age (months)	50.0 (12.8 – 101.0)	28.2 (11.8 – 75.5)	57.1 (19.2 – 105.6)	0.292
Weight (kg)	15.0 (9.5 – 28.0)	11.6 (6.8 – 17.0)	17.1 (9.8 – 32.9)	0.137
Male gender	25 (58.1)	5 (71.4)	20 (55.6)	0.680
PIM 2 score	5.0 (2.5 – 7.5)	3.6 (2.9 – 6.9)	5.4 (2.1 – 7.8)	0.448
PELOD score	2.0 (1.0 – 10.0)	1.0 (1.0 – 1.0)	2.0 (1.0 – 10.0)	0.146
Comorbidities	21 (48.8)	4 (57.1)	17 (47.2)	0.698
Immunocompromised	7 (16.3)	1 (14.3)	6 (16.7)	1.000
Bacteraemia	1 (2.3)	0 (0.0)	1 (2.8)	1.000
Risk factors				
Pneumonia	37 (86.0)	7 (100.0)	30 (83.3)	0.567
Sepsis	12 (27.9)	0 (0.0)	12 (33.3)	0.163
Aspiration	2 (4.7)	0 (0.0)	2 (5.6)	1.000
Transfusion	2 (4.7)	0 (0.0)	2 (5.6)	1.000
Others	5 (11.6)	0 (0.0)	5 (13.9)	0.572
Organ dysfunction	14 (32.6)	1 (14.3)	13 (36.1)	0.396
Cardiovascular	6 (14.0)	0 (0.0)	6 (16.7)	0.567
Neurological	1 (2.3)	0 (0.0)	1 (2.8)	1.000
Haematological	11 (24.6)	1 (14.3)	10 (27.8)	0.656
Renal	7 (16.3)	0 (0.0)	7 (19.4)	0.577
Hepatic	11 (25.6)	1 (14.3)	10	0.565
SF ratio	155.0 (120.0 – 192.0)	169.1 (150.0 – 235.0)	152.5 (114.1 – 182.0)	0.091
SF ratio <150	17 (39.5)	1 (14.3)	16 (44.4)	0.215
Prone position	4 (9.3)	1 (14.3)	3 (8.3)	0.523
Systemic steroids	30 (69.8)	3 (42.9)	27 (75.0)	0.172
Beta agonist	23 (53.5)	5 (71.4)	18 (50.0)	0.420
Diuretics	31 (72.1)	1 (14.3)	30 (83.3)	0.001
Transfusion	24 (55.8)	1 (14.3)	23 (63.9)	0.033
Inotropes	25 (58.1)	1 (14.3)	24 (66.7)	0.015
CRRT	7 (16.3)	0 (0.0)	7 (19.4)	0.577
ECMO	1 (2.3)	0 (0.0)	1 (2.8)	1.000
PICU LOS (days)	13.0 (8.0 – 26.0)	5.0 (4.0 – 8.0)	16.5 (11.0 – 27.0)	0.001
Hospital LOS (days)	25.0 (16.0 – 38.0)	11.0 (8.0 – 20.0)	27.0 (17.0 – 45.3)	0.003
Mortality	10 (23.3)	2 (28.6)	8 (22.2)	0.656

CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation; IFD: Intensive care unit free days; LOS: Length of stay; NIV: Non-invasive ventilation; PELOD: Paediatric Logistic Organ Dysfunction; PICU: Paediatric intensive care unit; PIM 2: Paediatric Index of Mortality 2; SF ratio: Oxygen saturation/fraction of inspired oxygen ratio
Categorical and continuous data are expressed as number (percentages) and median (IQR), respectively.

prospective observational study including 369 children with acute respiratory failure reported low NIV failure rates in children with pneumonia (17.2%), bronchiolitis (17.2%) and bronchospasm (18.9%).[7] In contrast, there were high NIV failure rates in children with ARDS (50.0%). NIV failure rate in our current study was high as well (77.4%). In particular, all patients with sepsis as a risk factor for PARDS—whether with or without limitation of care—ended up failing NIV. We were unable to evaluate other groups of interest, for example, immunocompromised or postbone marrow transplant patients which may also be associated with high NIV failure rates.[19,20] Our NIV failure rates were higher compared to other reports possibly due to a lower baseline SF ratio in our patients as compared to other studies, indicating a greater severity of lung disease.[7] Other factors that have been reported to be associated with increased NIV failure are younger age, greater oxygenation defect (higher mean airway pressure, higher F_iO_2 and lower SF ratio) and concomitant organ dysfunction.[2,6,8,21] In our study, we found that higher EPAP and F_iO_2 requirement

Table 4. Non-Invasive Ventilation Characteristics in Patients with Successful or Failed Trials

Characteristic	Total (n = 43)	NIV Success (n = 7)	NIV Failure (n = 36)	*P* Value
NIV indications				0.201
Work of breathing	21 (48.8)	6 (85.7)	15 (41.7)	
Hypoxia	18 (41.9)	1 (14.3)	17 (47.2)	
Hypercarbia	1 (2.3)	0 (0.0)	1 (2.8)	
Others*	3 (7.0)	0 (0.0)	3 (8.3)	
NIV delivery device				0.567
NIV-specific ventilators	37 (86.0)	7 (100.0)	30 (83.3)	
Portable ventilators	6 (14.0)	0 (0.0)	6 (16.7)	
NIV mode				1.000
BiPAP	24 (55.8)	4 (57.1)	20 (55.6)	
CPAP	19 (44.2)	3 (42.9)	16 (44.4)	
NIV variables on day 1 (PARDS)				
IPAP, median (IQR)	14 (12 – 16)	13 (12 – 15.5)	14 (12 – 16)	0.525
EPAP, median (IQR)	6 (5 – 8)	7 (6 – 8)	5 (4.3 – 8)	0.210
F_iO_2, median (IQR)	60 (50 – 80)	40 (40 – 60)	60 (50 – 80)	0.045
SpO_2, median (IQR)	92 (89 – 96)	92 (89 – 94)	92.5 (89.3 – 96)	0.640
NIV variables prior to NIV failure				
IPAP, median (IQR)			14.0 (13.0 – 18.0)	
EPAP, median (IQR)			5.0 (4.3 – 8.0)	
F_iO_2, median (IQR)			60.0 (50.5 – 80.0)	
SpO_2, median (IQR)			93.0 (90.0 – 97.0)	

BiPAP: Bi-level positive airway pressure; CPAP: Continuous positive airway pressure; EPAP: Expiratory positive airway pressure; F_iO_2: Fraction of inspired oxygen; IPAP: Inspiratory positive airway pressure; IQR: Interquartile range; NIV: Non-invasive ventilation; PARDS: Paediatric acute respiratory distress syndrome; SpO_2: Oxygen saturation
Categorical and continuous data are expressed as number (percentages) and median (IQR), respectively.
*Two patients were on home NIV but required escalation of settings. One patient had >1 indication.

were associated with NIV failure. A larger proportion of patients with NIV failure compared to NIV success also had a SF ratio <150 (20/41 [48.9%] vs 2/12 [16.7%]; *P* = 0.093), though this did not achieve statistical significance.

Another point of interest is the high observed mortality rate in our NIV cohort (32%). The high mortality can partly be accounted for by the number of patients with "limitation of care" in the NIV success group. However, after excluding these, mortality was still considered high (23%) as one would expect a patient supported with NIV to be less ill compared to a patient supported with MV. This high mortality rate is fairly similar to reported mortality in other PARDS cohorts that only included patients on MV (30%).[22,23] Indeed, if we examined the OI and OSI postintubation (14.3 [9.4-25.7] and 13.6 [8.0-18.3], respectively), most patients would satisfy the criteria for moderate-to-severe PARDS. Hence, one may postulate that these patients were not suitable candidates for a trial of NIV in the first place. Other reports concur with this finding, with mortality rates of 58% to 80% in PARDS patients who fail NIV.[7,21]

Indeed, one of the most challenging aspects of instituting NIV support is patient selection. Our data suggest that patient selection for NIV support in PARDS is suboptimal in our cohort. Further studies should explore optimal cut-offs for SF ratio (or PF ratio) in PARDS to identify patients who benefit most from NIV support.[24] One can consider the data from the LUNG SAFE study, where investigators demonstrated that patients supported on initial NIV had higher mortality compared to patients on MV when PF ratio was <150 (36.2% vs 24.7%; *P* = 0.033), but not when PF ratio was >150 (28.1% vs 26.2%; *P* = 0.608).[17] In addition to considering the degree of oxygenation deficiency in patient selection for NIV, the clinician must also be mindful of the need for monitoring for improvement during NIV support. Current literature suggests that, if an improvement in physiological parameters is not seen within 1 to 2 hours on NIV, the likelihood of failing NIV is higher.[6,25] Escalation to MV support should not be delayed further in patients who do not show improvement with NIV.

Although this study provided data on early NIV support in children with PARDS and their clinical outcomes across multiple countries, it does have limitations. First, this is a retrospective descriptive cohort study with a small sample size. As such, the clinical management of patients with

PARDS, including initiation and maintenance on NIV or MV was not standardised in each centre. We did not collect data on the type of interface used for NIV, which may be crucial for success of NIV.[26] We did not collect data on the adverse effects of NIV, such as skin breakdown, gastric distention, conjunctivitis and air leaks. Our data was also not granular enough to determine the timing of NIV failure in terms of hours. Since our study was limited to patients admitted to the PICU, we would have missed a proportion of patients treated with NIV in the high dependency/step down wards in some sites. This may have led to a selection bias of a sicker group of PARDS patients in this cohort. Additionally, due to the small numbers, we were unable to perform a robust multivariate model to adjust for possible confounders. Larger studies are required to investigate the association between NIV failure with clinical outcomes. Lastly, estimation of the F_iO_2 in NIV devices are often inaccurate due to variations in setup, leak and patients' peak inspiratory flow rates which could have affected the SF calculations.[27]

Conclusion

NIV was used in 17.5% of patients with PARDS. The mortality rate in this group of patients was high (32%), even after exclusion of patients with limitation of care (23%). Patients with PARDS had a high NIV failure rate (especially when sepsis was a risk factor), short time to intubation after diagnosis and a high OI/OSI postintubation, implying underestimation of the true oxygenation deficit. As such, these patients should be considered for early intubation. Future studies are needed to determine the optimal selection criteria for NIV support in children with PARDS.

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REFERENCES

1. Ganu SS, Gautam A, Wilkins B, Egan J. Increase in use of non-invasive ventilation for infants with severe bronchiolitis is associated with decline in intubation rates over a decade. Intensive Care Med 2012;38:1177-83.
2. Wolfler A, Calderini E, Iannella E, Conti G, Biban P, Dolcini A, et al. Evolution of noninvasive mechanical ventilation use: a cohort study among Italian PICUs. Pediatr Crit Care Med 2015;16:418-27.
3. Arnim A, Jamal SM, John-Stewart GC, Musa NL, Roberts J, Stanberry LI, et al. Pediatric respiratory support technology and practices: a global survey. Healthcare (Basel) 2017;5.pii: E34.
4. L'Her E, Deye N, Lellouche F, Taille S, Demoule A, Fraticelli A, et al. Physiologic effects of noninvasive ventilation during acute lung injury. Am J Respir Crit Care Med 2005;172:1112-8.
5. Morley SL. Non-invasive ventilation in paediatric critical care. Paediatr Respir Rev 2016;20:24-31.
6. Yanez LJ, Yunge M, Emilfork M, Lapadula M, Alcantara A, Fernandez C, et al. A prospective, randomized, controlled trial of noninvasive ventilation in pediatric acute respiratory failure. Pediatr Crit Care Med 2008;9:484-9.
7. Mayordomo-Colunga J, Pons M, Lopez Y, Jose Solana M, Rey C, Martinez-Camblor P, et al. Predicting non-invasive ventilation failure in children from the SpO(2)/FiO(2) (SF) ratio. Intensive Care Med 2013;39:1095-103.
8. Munoz-Bonet JI, Flor-Macian EM, Brines J, Rosello-Millet PM, Cruz Llopis M, Lopez-Prats JL, et al. Predictive factors for the outcome of noninvasive ventilation in pediatric acute respiratory failure. Pediatr Crit Care Med 2010;11:675-80.
9. Essouri S, Chevret L, Durand P, Haas V, Fauroux B, Devictor D. Noninvasive positive pressure ventilation: five years of experience in a pediatric intensive care unit. Pediatr Crit Care Med 2006;7:329-34.
10. Essouri S, Carroll C; Pediatric Acute Lung Injury Consensus Conference Group. Noninvasive support and ventilation for pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med 2015;16:S102-10 .
11. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med 2015;16:428-39.
12. Wong JJ, Phan HP, Phumeetham S, Ong JSM, Chor YK, Qian S, et al. Risk stratification in pediatric acute respiratory distress syndrome: a multicenter observational study. Crit Care Med 2017;45:1820-8.
13. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6:2-8.
14. Leteurtre S, Duhamel A, Grandbastien B, Lacroix J, Leclerc F. Paediatric logistic organ dysfunction (PELOD) score. Lancet 2006;367:897.
15. Slater A, Shann F, Pearson G; Paediatric Index of Mortality (PIM) Study Group. PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med 2003;29:278-85.
16. Santschi M, Jouvet P, Leclerc F, Gauvin F, Newth CJ, Carroll CL, et al. Acute lung injury in children: therapeutic practice and feasibility of international clinical trials. Pediatr Crit Care Med 2010;11:681-9.
17. Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, et al. Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE Study. Am J Respir Crit Care Med 2017;195:67-77.
18. Khemani RG, Smith L, Lopez-Fernandez YM, Kwok J, Morzov R, Klein MJ, et al. Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. Lancet Respir Med 2019;7:115-28.
19. Santhanam H, Ong JS, Shen L, Tan PL, Koh PL. Risk factors for mortality in Asian children admitted to the paediatric intensive care unit after

haematopoietic stem cell transplantation. Ann Acad Med Singapore 2017;46:44-9.

20. Lee AC. A child with rapid-onset respiratory distress after chemotherapy, lung irriadiation, general anaesthesia, and blood transfusion. Ann Acad Med Singapore 2015;44:548-9.
21. Piastra M, De Luca D, Marzano L, Stival E, Genovese O, Pietrini D, et al. The number of failing organs predicts non-invasive ventilation failure in children with ALI/ARDS. Intensive Care Med 2011;37:1510-6.
22. Schouten LR, Veltkamp F, Bos AP, van Woensel JB, Serpa Neto A, Schultz MJ, et al. Incidence and mortality of acute respiratory distress syndrome in children: a systematic review and meta-analysis. Crit Care Med 2016;44:819-29.
23. Wong JJ, Jit M, Sultana R, Mok YH, Yeo JG, Koh J, et al. Mortality in pediatric acute respiratory distress syndrome: a systematic review and meta-analysis. J Intensive Care Med 2019;34:563-71.
24. Khemani RG, Rubin S, Belani S, Leung D, Erickson S, Smith LS, et al. Pulse oximetry vs PaO2 metrics in mechanically ventilated children: Berlin definition of ARDS and mortality risk. Intensive Care Med 2015;41:94-102.
25. Piastra M, De Luca D, Pietrini D, Pulitano S, D'Arrigo S, Mancino A, et al. Noninvasive pressure-support ventilation in immunocompromised children with ARDS: a feasibility study. Intensive Care Med 2009;35:1420-7.
26. Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2016;315:2435-41.
27. Sedgwick P. Multiple hypothesis testing and Bonferroni's correction. BMJ 2014;20;349:g6284.