Noninvasive Ventilation for Pediatric Acute Respiratory Distress Syndrome: Experience From the 2016/2017 Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology Prospective Cohort Study*

OBJECTIVES: The worldwide practice and impact of noninvasive ventilation (NIV) in pediatric acute respiratory distress syndrome (PARDS) is unknown. We sought to describe NIV use and associated clinical outcomes in PARDS.

DESIGN: Planned ancillary study to the 2016/2017 prospective Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology study.

SETTING: One hundred five international PICUs.

PATIENTS: Patients with newly diagnosed PARDS admitted during 10 study weeks.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Children were categorized by their respiratory support at PARDS diagnosis into NIV or invasive mechanical ventilation (IMV) groups. Of 708 subjects with PARDS, 160 patients (23%) received NIV at PARDS diagnosis (NIV group). NIV failure rate (defined as tracheal intubation or death) was 84 of 160 patients (53%). Higher nonrespiratory pediatric logistic organ dysfunction (PELOD-2) score, Pao_2/Fio_2 was less than 100 at PARDS diagnosis, immunosuppression, and male sex were independently associated with NIV failure. NIV failure was 100% among patients with nonrespiratory PELOD-2 score greater than 2, Pao_2/Fio_2 less than 100, and immunosuppression all present. Among patients with Pao_2/Fio_2 greater than 100, children in the NIV group had shorter total duration of NIV and IMV, than the IMV at initial diagnosis group. We failed to identify associations between NIV use and PICU survival in a multivariable Cox regression analysis (hazard ratio 1.04 [95% CI, 0.61–1.80]) or mortality in a propensity score matched analysis ($p = 0.369$).

CONCLUSIONS: Use of NIV at PARDS diagnosis was associated with shorter exposure to IMV in children with mild to moderate hypoxemia. Even though risk of NIV failure was high in some children, we failed to identify greater hazard of mortality in these patients.

KEY WORDS: immunosuppression; mechanical ventilation; pediatric critical care; respiratory distress; tracheal intubation

Guillaume Emeriaud, MD, PhD[1]
Marti Pons-Òdena, MD, PhD[2,3]
Anoopindar K. Bhalla, MD, MSCI[4,5]
Steven L. Shein, MD, FCCM[6]
Elizabeth Y. Killien, MD, MPH[7]
Vicent Modesto i Alapont, MD, PhD[8]
Courtney Rowan, MD, MScr[9]
Florent Baudin, MD, PhD[10]
John C. Lin, MD[11]
Gabrielle Grégoire, MSc[12]
Natalie Napolitano, MPH, RRT-NPS[13]
Juan Mayordomo-Colunga, MD, PhD[14–16]
Franco Diaz, MD, MBA[17,18]
Pablo Cruces, MD[18,19]
Alberto Medina, MD, PhD[14,15]
Lincoln Smith, MD[20]
Robinder G. Khemani, MD, MSCI[4,5]
Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE) Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network

For over two decades, use of noninvasive ventilation (NIV) for patients with severe bronchiolitis in PICUs has been associated with an important reduction in the use of invasive mechanical ventilation (IMV) (1). For many other pediatric respiratory conditions, NIV has now become the primary modality of respiratory support in the PICU (2, 3) with the goal to prevent tracheal intubation and complications related to IMV and deeper

***See also p. 783.**

DOI: 10.1097/PCC.0000000000003281

RESEARCH IN CONTEXT

- The worldwide use of noninvasive ventilation (NIV) in pediatric acute respiratory distress syndrome (PARDS) is unknown.
- NIV may prevent tracheal intubation in some patients, but in others its use may contribute to lung injury (i.e., in the case of reduced unloading of high patient effort) or instability due to NIV failure.
- The characteristics of PARDS patients who may benefit from NIV, rather than be harmed, is also uncertain.

sedation (4). However, NIV is also associated with potential risks related to delay in securing the airway, intolerance of the interface, and reduced unloading of high patient effort possibly contributing to lung injury (5). Failure of NIV is associated with increased mortality and longer duration of IMV (6, 7). Over 20 years ago, patients with immunosuppression and acute respiratory distress syndrome (ARDS) were considered good candidates for NIV trials as mortality rates with IMV support was high (8). Although NIV is often used in children with immunosuppression and pediatric ARDS (PARDS), NIV failure is common and there is little new evidence supporting this practice (9).

The severity of hypoxemia is a major risk factor for NIV failure (10, 11). In the last 10 years, NIV failure in children with severe PARDS has been reported to exceed 50% (11–13). Therefore, it is crucial to identify additional characteristics of hypoxemic children where the likelihood of NIV failure is high, and the risk of NIV may outweigh potential benefits. Recently, the second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) highlighted the limited evidence on NIV use in PARDS, emphasizing the need for further research (14, 15). Therefore, as a planned ancillary study of the 2016/2017 Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE) study (16), we aimed to describe contemporary use of NIV in PARDS. Our three objectives were as follows: 1) to describe the characteristics associated with use of NIV, rather than use of IMV, at the initial diagnosis of PARDS; 2) to identify factors associated with NIV failure; and 3), to explore the association between NIV use and mortality and duration of ventilatory support.

MATERIAL AND METHODS

Study Design

PARDIE was a prospective, observational, cohort study carried out in 145 international PICUs (17). The study enrolled children with a new diagnosis of PARDS—according to the 2015 PALICC criteria—during 10 distinct weeks between May 2016 and June 2017. Detailed methods are published elsewhere (16). The Children's Hospital Los Angeles Institutional Review Board (CHLA 16-0043) approved the study, titled "Pediatric ARDS Incidence and Epidemiology (PARDIE)" on February 8, 2016, and procedures were followed in accordance with the ethical standards of the responsible committee and with the Helsinki Declaration of 1975. All PARDIE patients were included in the current study and categorized based on the respiratory support used at the time of PARDS diagnosis, NIV or IMV. In accordance with the 2015 PALICC guidelines, in patients on NIV, only those with a full-face mask interface and either continuous positive airway pressure (CPAP) greater than or equal to 5 cm H_2O, or bilevel ventilation were eligible to be diagnosed with PARDS (17).

Data Collection

Patient characteristics and respiratory parameters were collected for the first 3 days. Oxygenation severity was classified at the time of PARDS diagnosis according to the Berlin Pao_2 to Fio_2 strata: less than 100 mm Hg (severe), 101–200 mm Hg (moderate), and 201–300 mm Hg (mild), or their equivalent using the ratio of pulse oximetry oxygen saturation (Spo_2) to Fio_2 (Spo_2/Fio_2) strata (16, 17). NIV failure was defined as the occurrence of tracheal intubation or death in the PICU, whichever occurred first.

Statistical Analysis

The characteristics and outcomes of patients were reported using the median (interquartile range, IQR) or mean ± SD, then compared using Wilcoxon rank-sum or Student *t* tests. Categorical variables were reported using number (percentage) and compared using Chi-square or Fisher exact tests. Details of the analysis plan

are provided in **Supplemental methods** (http://links.lww.com/PCC/C386).

To assess risk factors for NIV failure in the NIV group, we conducted univariate generalized estimating equation (GEE) analyses with failure as the dependent variable. We then conducted a multivariable GEE analysis considering all independent variables that were statistically significant in univariate analyses. In patients who failed NIV, we explored the association between NIV duration and mortality using a GEE analysis.

We calculated duration of NIV, IMV, and total ventilatory support (sum of NIV and IMV), duration of PICU stay, and PICU mortality for both the NIV and IMV groups. We performed a Cox regression analysis to assess the effect of NIV exposure on time between PARDS diagnosis and PICU mortality adjusting for risk factors with imbalanced distributions across the two groups.

We used a propensity score matching approach to assess the association between NIV use and mortality, matching 1:1 on the logit propensity score that was developed for NIV use. We used McNemar's test to assess differences in mortality between matched NIV and IMV groups. We conducted a GEE analysis using mortality as a dependent variable in the entire group of patients, adjusting for the same covariates used in the propensity score model. Finally, we conducted a subgroup analysis to assess the association between NIV use and mortality in immunosuppressed patients, using a GEE analysis adjusted for the mortality risk factors identified in the entire population.

All analyses were clustered by site. In all multivariable analyses, we included the nonrespiratory pediatric logistic organ dysfunction (PELOD-2) score as a covariate rather than the PELOD-2 score given inclusion of oxygenation metric covariates (18). Statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC). Two-sided p values less than 0.05 were considered significant.

RESULTS

Patient Characteristics and NIV Use

Of 708 patients included in the original PARDIE study, 160 (23%) were supported with NIV at the time of PARDS diagnosis (**eFig. 1**, http://links.lww.com/PCC/C386). Compared with IMV patients (**Table 1**), NIV patients were older and more frequently had chronic pulmonary disease, neuromuscular disease, oncologic disease, and immunosuppression, while they were less frequently born prematurely (all $p < 0.01$). The causes of PARDS also differed, with pneumonia more common in the NIV patients. The use of NIV was associated with higher initial blood pH and lower pediatric risk of mortality (PRISM)-IV, PELOD-2, and nonrespiratory PELOD-2 scores (all $p < 0.01$). There were no differences in arterial $PaCO_2$ or PaO_2/FIO_2 ratio between the two groups.

The proportion of PARDS patients on NIV varied widely between sites (median 18%, IQR 0–36%, in sites with at least four patients enrolled) and across countries (**eFig. 2**, http://links.lww.com/PCC/C386), but did not differ between world bank income classification of the country (**eTable 1**, http://links.lww.com/PCC/C386). The use of NIV in PARDS patients was more frequent in sites that used NIV more frequently in the overall PICU population. NIV characteristics and settings used during the first 3 days are reported in **eTable 2** (http://links.lww.com/PCC/C386).

NIV Failure

NIV failure occurred in 84/160 (53%) patients on NIV at PARDS diagnosis, including 80 patients who required intubation and 4 patients who died without intubation. These four deaths had severe oncologic or neurological disorders, and documented limitations in support were clearly captured in two of the patients. **Table 2** shows that in univariate analyses NIV failure was associated with male sex, immunosuppression, lower initial PaO_2/FIO_2 ratio, PaO_2/FIO_2 less than 100 mm Hg, bilateral radiological infiltrates, higher PRISM-IV score, and higher nonrespiratory PELOD-2 score at PARDS diagnosis. On multivariable analysis (Table 2), immunosuppression, PaO_2/FIO_2 less than 100, nonrespiratory PELOD-2 score, and male sex were independently associated with NIV failure. Regarding the site characteristics, the frequency of NIV use in the site (in the entire PICU population, not just PARDS patients) was not associated with NIV failure rate in the PARDS cohort (odds ratio 0.80 [0.61–1.05]). Patients from sites in low-income or middle-income countries however had a higher risk of NIV failure: 13 of 16 (81%), versus 71 of 144 (49%), odds ratio 4.46 (1.44–13.9).

TABLE 1.

Characteristics of Patients With Pediatric Acute Respiratory Distress Syndrome Treated With Noninvasive Ventilation and Invasive Mechanical Ventilation at the Time of Pediatric Acute Respiratory Distress Syndrome Diagnosis

Variable	NIV, *n* = 160	IMV, *n* = 548	*p*
Age (yr)	7.1 (2.5–13.7)	2.2 (0.6–8.5)	< 0.0001
Sex/male	94 (59%)	340 (62%)	0.471
Primary cause of PARDS			0.004
Pneumonia	112 (70%)	298 (54%)	
Sepsis	22 (14%)	114 (21%)	
Aspiration	13 (8%)	39 (7%)	
Trauma	1 (1%)	26 (5%)	
Pancreatitis	1 (1%)	2 (0%)	
Near drowning	0 (0%)	5 (1%)	
Transfusion-related lung injury	0 (0%)	1 (0%)	
Other	11 (7%)	63 (11%)	
Comorbidities			
Prematurity	16 (10%)	115 (21%)	0.002
Chronic pulmonary disease	64 (40%)	133 (24%)	< 0.0001
Chronic respiratory support before PICU admission	34 (21%)	86 (16%)	0.099
Neuromuscular disease	47 (29%)	75 (14%)	< 0.0001
Congenital cardiac disease	18 (11%)	60 (11%)	0.915
Left ventricular dysfunction	9 (6%)	31 (6%)	0.988
Acquired heart disease	7 (4%)	49 (9%)	0.060
Oncologic disease	25 (16%)	34 (6%)	< 0.001
Immunosuppression	34 (21%)	61 (11%)	< 0.001
With oncologic disease	19 (12%)	30 (5%)	
Stem cell transplants	12 (7%)	14 (3%)	
Time of PARDS diagnosis since PICU admission (d)	0.2 (0.0–0.9)	0.25 (0.0–1.7)	0.032
Initial Pao_2/Fio_2 ratio	132 ± 70	142 ± 84	0.150
PARDS Berlin Pao_2/Fio_2 groups			0.854
Pao_2/Fio_2, 201–300 mm Hg	37 (23%)	129 (24%)	
Pao_2/Fio_2, 101–200 mm Hg	57 (36%)	206 (38%)	
Pao_2/Fio_2 < 100 mm Hg	66 (41%)	213 (39%)	
Bilateral infiltrates on chest imaging	110 (68.7)	413 (75.4)	0.094
Initial pH, mean ± SD; number of values[a]	7.34 ± 0.10; 100	7.30 ± 0.12; 453	0.001
Initial Pco_2 (mm Hg), mean ± SD; number of values	50.4 ± 18.0; 98	52.5 ± 19.5; 452	0.316
PRISM-IV score, median (IQR); number of values	5 (1–9); 142	8 (3–14); 492	< 0.0001
PELOD-2 score, median (IQR); number of values	2 (0–4); 138	6 (5–8); 483	< 0.0001
Nonrespiratory PELOD-2 score	2 (0–3)	2 (2–4)	< 0.0001

IMV = invasive mechanical ventilation, IQR = interquartile range, NIV = noninvasive ventilation, PARDS = pediatric acute respiratory distress syndrome, PELOD = pediatric logistic organ dysfunction.

[a]Number of values are reported when missing values were higher than 5%.

Data are presented as median (interquartile range), mean ± SD, or as number (percentage), as appropriate.

TABLE 2.

Characteristics Associated With Noninvasive Ventilation Failure in Univariate Analyses and Multivariable Generalized Estimating Equation

Variable	NIV Failure, *n* = 84	NIV Success, *n* = 76	OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Age (yr)	7.3 (2.0–13.9)	6.9 (3.4–13.7)	0.99 (0.95–1.05)	0.931		
Sex/male	55 (65%)	39 (51%)	1.80 (1.01–3.20)	0.045	2.39 (1.15–4.95)	0.019
PARDS risk factor				0.218		
Pneumonia	55 (65%)	57 (75%)	Ref			
Sepsis	16 (19%)	6 (8%)	2.76 (0.96–7.94)	0.059		
Aspiration	7 (8%)	6 (8%)	1.21 (0.43–3.41)	0.720		
Other	6 (7%)	7 (9%)	0.89 (0.29–2.70)	0.835		
Comorbidities						
Prematurity	7 (8%)	9 (12%)	0.68 (0.21–2.16)	0.510		
Chronic pulmonary disease	28 (33%)	36 (47%)	0.56 (0.27–1.13)	0.106		
Chronic respiratory support before PICU admission	17 (20%)	17 (22%)	0.88 (0.33–2.34)	0.799		
Neuromuscular disease	27 (32%)	20 (26%)	1.33 (0.72–2.44)	0.365		
Congenital cardiac disease	7 (8%)	11 (14%)	0.54 (0.18–1.59)	0.261		
Left ventricular dysfunction	7 (8%)	2 (3%)	3.36 (0.39–29.2)	0.271		
Acquired heart disease	4 (5%)	3 (4%)	1.22 (0.32–4.65)	0.774		
Oncologic disease	17 (20%)	8 (10%)	2.16 (0.79–5.89)	0.134		
Immunosuppression	27 (32%)	7 (9%)	4.67 (1.61–13.5)	0.005	3.75 (1.04–13.44)	0.043
Initial Pao_2/Fio_2 ratio	118 ± 66	147 ± 70	0.94 (0.90–0.99)	0.010		
PARDS Berlin PF groups				0.008		
Pao_2/Fio_2, 201–300 mm Hg	14 (17%)	23 (30%)	Ref.		Ref.	
Pao_2/Fio_2, 101–200 mm Hg	26 (31%)	31 (41%)	1.38 (0.60–3.14)	0.445	1.35 (0.53–3.41)	0.531
Pao_2/Fio_2, < 100 mm Hg	44 (52%)	22 (29%)	3.29 (1.46–7.37)	0.004	3.01 (1.08–8.37)	0.034
Bilateral infiltrates	65 (77%)	45 (59%)	2.36 (1.29–4.29)	0.005	1.59 (0.80–3.16)	0.187
Initial pH	7.33 (7.28–7.38)	7.37 (7.33–7.40)	0.58 (0.33–1.02)	0.058		
Initial Pco_2 (mm Hg)	51.9 ± 19.2	47.3 ± 15.0	1.02 (0.99–1.04)	0.243		
PRISM-IV score	6 (3–13)	2.5 (0–7)	1.12 (1.04–1.21)	0.003		
Nonrespiratory PELOD-2	2 (0–4)	2 (0–2)	1.22 (1.05–1.41)	0.008	1.19 (1.005–1.42)	0.044
PELOD-2 score	3 (0–5)	2 (0–2)	1.34 (1.18–1.51)	< 0.001		
Mode bilevel positive airway pressure vs continuous positive airway pressure	34 vs 5	40 vs 9	1.53 (0.43–5.50)	0.515		

NIV = noninvasive ventilation, OR = odds ratio, PARDS = pediatric acute respiratory distress syndrome, PELOD = pediatric logistic organ dysfunction.

Data are presented as median (first quartile–third quartile), mean ± SD, or as number (percentage), as appropriate. The effect estimates for continuous variables are per 1 unit increase.

Figure 1 illustrates the interaction between immunosuppression, severe hypoxemia, and nonrespiratory PELOD-2 score greater than 2. Inspection of the Venn diagram shows that the NIV success rate was 42 of 66 (64%) when none of these three factors were present. When only one of these three risk factors was present the cumulative success rate was 28 of 57 (49%). When a combination of any two risk factors was present the cumulative success rate was 6 of 31 (19%). When all three risk factors were present there were no successes (0/6, 0%). The proportion of NIV failure and the mortality rate depending on Spo_2/Fio_2 and Pao_2/Fio_2 ratio are illustrated in **Figure 2**.

In cases of NIV failure, tracheal intubation occurred after a median of 10 (IQR 2–26) hours of NIV. Higher nonrespiratory PELOD-2 score was the only factor independently associated with earlier intubation in multivariable modeling (**eTable 3**, http://links.lww.com/PCC/C386). NIV failure occurred before 6 hours in 39 of 84 (47%) cases, between 6 and 24 hours in 23 of 84 (27%) cases, and after 24 hours of NIV in 22 of 84 (26%) cases, and the mortality rates were 23%, 26%, and 42% in these subgroups, respectively (**eFig. 3**, http://links.lww.com/PCC/C386). In a multivariable GEE analysis restricted to this NIV failure group, immunosuppression was independently associated with mortality ($p = 0.001$) while the duration of NIV before intubation (for each hour) had an odds ratio of 1.32 (0.98–1.78, $p = 0.064$) for mortality (**eTable 4**, http://links.lww.com/PCC/C386).

PICU Outcome

PICU mortality rates were not different between NIV and IMV groups overall or within each oxygenation severity strata (**Table 3**). **eFigure 4** (http://links.lww.com/PCC/C386) illustrates the duration of total ventilatory support in surviving patients by Pao_2/Fio_2 strata. As detailed in Table 3, the total duration of ventilation support was shorter in the NIV group overall, with a significant difference for the mild and moderate severity strata only. Length of PICU stay was also shorter in the NIV group overall, with a significant difference in the mild severity strata. Compared with the NIV success group, the NIV failure group exhibited qualitatively worse PICU outcomes overall (Table 3). Duration of ventilation and length of PICU stay for the entire group (including nonsurvivors) are reported in **eTable 5** (http://links.lww.com/PCC/C386).

In a multivariable Cox analysis (**eTable 6**, http://links.lww.com/PCC/C386) adjusted for age, PARDS risk factor, comorbidities, PARDS severity class, initial pH, and nonrespiratory PELOD score, exposure to NIV was not associated with shorter survival time ($p = 0.877$). Chronic pulmonary disease, immunosuppression, severe Pao_2/Fio_2 class, initial pH, and nonrespiratory PELOD score were independently associated with earlier death. In a sensitivity analysis, censoring the Cox regression at 90 days instead of PICU discharge did not change the results (data not shown).

A propensity score analysis for NIV exposure was conducted, with a greedy matching 1:1 on the logit propensity score obtained by logistic

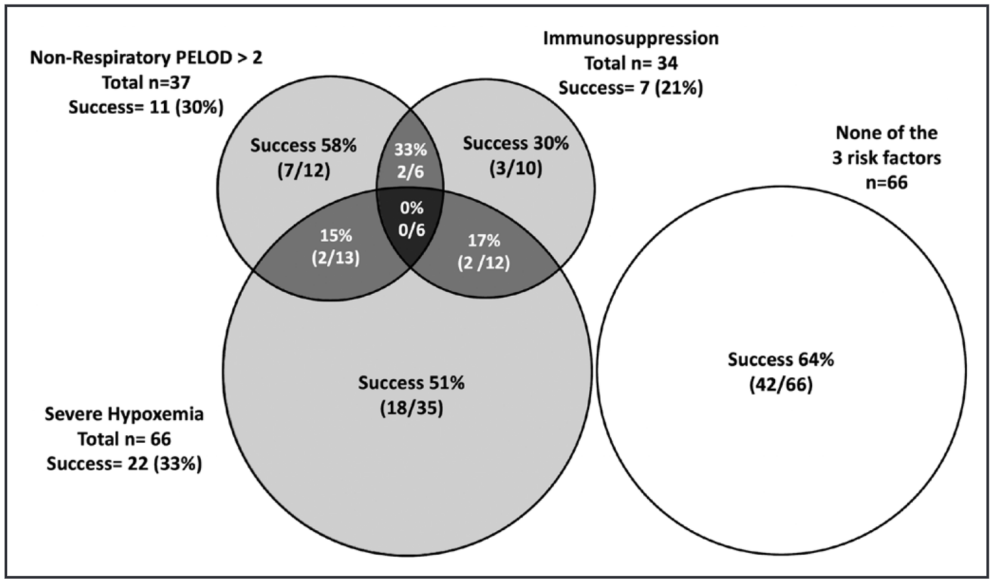

Figure 1. Number of patients treated with noninvasive ventilation (NIV) at PARDS diagnosis and success rate, depending on the presence of a high nonrespiratory pediatric logistic organ dysfunction-2 score, immunosuppression, severe hypoxemia ($Pao_2/Fio_2 < 100$), a combination of these factors.

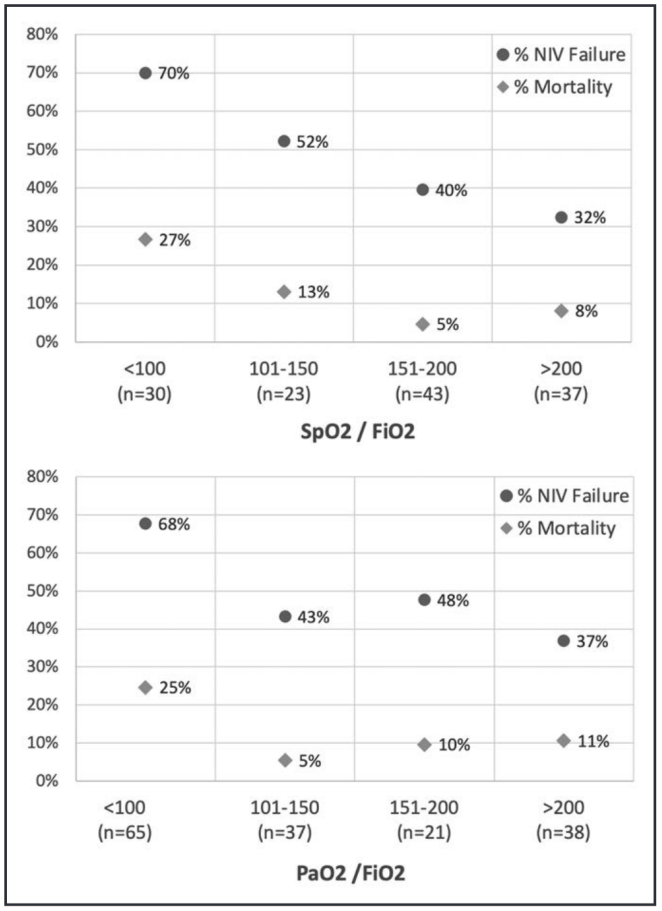

Figure 2. Proportion of NIV failure and mortality rate depending on initial SpO_2/FIO_2 ratio (upper panel) and PaO_2/FIO_2 ratio (lower panel). NIV = noninvasive ventilation, PARDS = pediatric acute respiratory distress syndrome.

regression, based on all variables presented in **eTable 7** (http://links.lww.com/PCC/C386). Propensity score matching was possible for 89 patients treated with NIV (56% of cohort) matched to 89 patients with PARDS not exposed to NIV (**eFig. 5**, http://links.lww.com/PCC/C386). The rate of NIV failure in the children who could be matched was 67%, illustrating the selection of a relatively severe subgroup (eTable 7, http://links.lww.com/PCC/C386). In these propensity score matched groups, the mortality rate was 19% in the NIV group versus 25% in the IMV group (p = 0.369). In the survivors of these groups, the length of PICU stay and ventilation duration did not differ. A GEE analysis conducted in the entire group of 708 patients, adjusting for the variables used in propensity score matching and clustering for site, also revealed no difference in mortality rates depending on NIV exposure (odds ratio 0.81, 95% CI, 0.41–1.58).

Subgroup Analysis

In immunosuppressed patients, the mortality rate was 38% (13/34) when initially treated with NIV (and 48% in the subgroup of children with NIV failure), and 51% (31/61) with primary IMV (p = 0.238). When adjusting for baseline nonrespiratory PELOD-2, PaO_2/FIO_2 severity group, and pH, NIV exposure was not associated with mortality (adjusted odds ratio: 1.26 [95% CI, 0.47–3.36], p = 0.650). A sensitivity analysis including all oncologic patients (in addition to the immunosuppressed patients) provided similar results (data not shown).

DISCUSSION

This study about using NIV as initial respiratory support for cases of PARDS is important and the largest reported to date, albeit reflecting contemporary practice in the 2016/2017 PARDIE dataset. Overall, 23% of children with PARDS were supported with NIV at the time of PARDS diagnosis. Previous data for comparison are limited, but this prevalence is significantly higher than the 14 of 165 (8.5%) observed in a 2007 international cross-sectional study of acute lung injury in children (19). It is also significantly higher than the 436 of 2,813 (15.5%) identified in the 2014 point prevalence study of NIV use in adults with ARDS (20). In pediatric practice, older age was associated with NIV use, which may be explained by the difficulty using

WHAT THIS STUDY MEANS?

- In this large international observational study from 2016/2017, 23% of children with PARDS were initially supported by NIV.
- Half of these NIV-supported patients were eventually placed on invasive mechanical ventilation, with hypoxemia severity, nonrespiratory PELOD-2 score, immunosuppression, and male sex being independently associated with NIV failure.
- Although children intubated after NIV failure have a high risk of adverse events, NIV exposure in children with PARDS was not independently associated with higher mortality.

TABLE 3.
Main PICU Outcomes in Patients With Pediatric Acute Respiratory Distress Syndrome Treated With Noninvasive Ventilation and Invasive Mechanical Ventilation

	IMV Group (n = 548)	Entire NIV Group (n = 160)	p	NIV Success Group (n = 76)	NIV Failure Group (n = 84)
PICU mortality rate					
All severity strata	97/548 (18%)	24/160 (15%)	0.425	0/76 (0)	24/84 (29%)
Pao_2/Fio_2, 201–300 mm Hg group	14/129 (11%)	4/37 (11%)	0.994	0/23 (0)	4/14 (29%)
Pao_2/Fio_2, 101–200 mmHg group	31/206 (15%)	4/57 (7%)	0.114	0/31 (0)	4/26 (15%)
Pao_2/Fio_2 < 100 mmHg group	52/213 (24%)	16/66 (24%)	0.977	0/22 (0)	16/44 (36%)
Total duration of ventilatory support in PICU survivors (d)					
All severity strata	7.0 (4.0–11.9)	5.6 (2.6–9.6)	< 0.001	3.2 (1.9–6.9)	8.0 (4.9–13.1)
Pao_2/Fio_2, 201–300 mm Hg group	6.1 (4.1–11.6)	5.2 (2.0–7.5)	0.015	2.5 (1.5–6.3)	7.0 (5.5–10.1)
Pao_2/Fio_2, 101–200 mm Hg group	6.6 (3.6–10.9)	5.2 (2.2–9.6)	0.019	2.8 (1.6–6.2)	9.7 (4.9–14.2)
Pao_2/Fio_2, < 100 mm Hg group	7.5 (4.2–13.0)	6.9 (3.3–10.2)	0.158	4.4 (2.6–8.0)	8.2 (4.7–13.8)
Duration of NIV in PICU survivors (d)					
All severity strata	0	1.6 (0.2–4.4)	–	3.2 (1.9–6.9)	0.2 (0.0–0.9)
Pao_2/Fio_2, 201–300 mm Hg group	0	1.8 (0.8–5.4)	–	2.5 (1.5–6.3)	0.8 (0.4–1.6)
Pao_2/Fio_2, 101–200 mm Hg group	0	1.8 (0.4–4.1)	–	2.8 (1.6–6.2)	0.4 (0.1–1.0)
Pao_2/Fio_2, < 100 mm Hg group	0	0.7 (0.1–4.4)	–	4.4 (2.6–8.0)	0.1 (0.0–0.4)
Duration of IMV in PICU survivors (d)					
All severity strata	7.0 (4.0–11.9)	0.0 (0.0–6.6)	–	0	7.5 (4.3–12.5)
Pao_2/Fio_2, 201–300 mm Hg group	6.1 (4.1–11.6)	0.0 (0.0–3.3)	–	0	5.5 (3.9–9.9)
Pao_2/Fio_2, 101–200 mm Hg group	6.6 (3.6–10.9)	0.0 (0.0–6.5)	–	0	7.5 (4.3–13.9)
Pao_2/Fio_2, < 100 mm Hg group	7.5 (4.2–13.0)	2.5 (0.0–9.0)	–	0	8.1 (4.7–13.8)
Length of PICU stay after PARDS diagnosis in PICU survivors (d)					
All severity strata	10.2 (6.4–19.2)	8.3 (5.4–15.1)	0.028	6.3 (3.8–9.6)	15.1 (8.0–23.9)
Pao_2/Fio_2, 201–300 mm Hg group	9.6 (6.3–19.5)	7.9 (4.2–11.0)	0.025	5.5 (2.8–8.5)	16.1 (9.1–23.8)
Pao_2/Fio_2, 101–200 mm Hg group	9.7 (5.9–17.6)	9.8 (5.3–18.1)	0.628	5.5 (3.8–10.1)	18.3 (10.7–39.1)
Pao_2/Fio_2, < 100 mm Hg group	11.1 (7.2–19.8)	8.5 (6.4–14.7)	0.129	7.0 (5.5–10.2)	12.2 (3.0–43.4)

IMV = invasive mechanical ventilation, NIV = noninvasive ventilation, PARDS = pediatric acute respiratory distress syndrome.
The mortality results are reported as number of deaths/number of patients (proportion). Durations of ventilation support are presented as median (interquartile range).

NIV in younger patients (21), more frequent use of nasal modes in younger patients (thereby excluding them from the PARDS diagnosis), as well as the different diagnoses observed in older children. In our PARDIE study, NIV was particularly used in patients with chronic pulmonary disease, neuromuscular disease, immune-oncologic disease, and lower illness severity scores.

The similar distribution of $Paco_2$ and Pao_2/Fio_2 strata in the NIV and IMV groups was more surprising. In 2015, the PALICC experts did not recommend the use of NIV in children with severe PARDS (22). This result may be partly explained by patients being placed on NIV before the occurrence of severe PARDS. It is also possible that a trial of NIV was attempted in these patients to assess their response to recruitment. Of note, while the rate of intubation in the patients with severe hypoxemia was high (66%), when no other risk factors were present about half the patients avoided intubation. The recent PALICC-2 conference updated the recommendations on NIV use and now suggests that NIV should be used for a time-limited trial. Transition

to IMV should occur when patients do not have improvement within the first 6 hours of NIV, particularly in those with severe PARDS when earlier transition to IMV should be considered (14, 15).

Independent risk factors associated with NIV failure included severe hypoxemia, immunosuppression, nonrespiratory PELOD-2 score greater than 2, and male sex. Severe hypoxemia has been consistently reported as a risk factor for NIV failure (10, 11, 13, 23). The risk of NIV failure associated with nonpulmonary organ dysfunction is also consistent with previous studies that reported higher NIV failure rates in the presence of sepsis (10, 12, 23, 24), vasoactive agents (25), or higher PRISM scores (10, 12, 23). Immunosuppression was associated with both NIV use and NIV failure in this study. NIV has long been advocated in this population (8, 12, 26) because of poor outcomes of these patients after intubation. Previous studies demonstrating high mortality rates (> 70%) of immunosuppressed patients who fail an NIV trial have raised concerns about the adverse impact of delaying intubation (9, 26), including significant risk of cardiac arrest (25). Moreover, a randomized controlled trial assessing the potential benefit of early PICU admission for CPAP in immunosuppressed children with respiratory failure provided no evidence in favor of this intervention (27). In the present study, the NIV failure rate in immunosuppressed patients was particularly high (79%). However, this high failure rate was not associated with an increased risk of mortality when adjusting for other risk factors. Additionally, the mortality rate in primarily intubated patients was also high (51%) and was similar to that observed in immunosuppressed patients who failed NIV and were subsequently intubated (48%). Our study does not allow us to make a conclusion about the benefit of NIV in this subpopulation. However, an important finding in our study is the cumulative burden of risk factors of immunosuppression, severe hypoxemia, and multiple organ failure, and clinicians should be particularly cautious when managing patients with two or more of these risk factors on NIV.

The duration of ventilatory support and PICU length of stay were shorter in the NIV group overall, and especially in patients with baseline Pao_2/Fio_2 greater than 100 mm Hg. This signal may support the use of NIV in this population, although it should be tempered by the fact that the NIV group appeared to be less severely ill at PARDS diagnosis. In patients with risk factors, the rate of NIV failure was relatively high, and the patients with NIV failure exhibited relatively poor outcomes, therefore the question of potential harm caused by the NIV exposure in this population is particularly important. In addition to the risk associated with intubation delay and instability, use of NIV could theoretically expose patients to the risk of NIV-induced lung injury, when the spontaneous ventilatory drive is high enough to induce excessive transpulmonary pressure or tidal volume (5, 28).

In adult patients with severe ARDS, NIV exposure is associated with an increased risk of death (20, 29). In a secondary analysis of a large pediatric prospective trial, preintubation exposure to NIV was also associated with increased mortality (30). However, only intubated patients were included and the outcome of patients with NIV success was therefore not considered. Somewhat reassuringly, we did not observe any increased risk in mortality associated with NIV use, while using several strategies to adjust for other risk factors. This does not confirm that NIV is without risk in patients with PARDS. The NIV duration was quite short in the NIV failure group, and we can speculate that the clinical teams avoided inappropriately prolonged NIV in most instances. Although the duration of NIV exposure prior to intubation was not an independent risk factor for mortality in the NIV failure group, the upper limit of the 95% CI for the odds ratio (1.32 [0.98–1.78], $p = 0.064$) shows what we cannot exclude as a potentially clinically meaningful effect which did not reach statistical significance because of limited power and sample size. These findings are consistent with PALICC-2 recommendations (14), in which tracheal intubation should be considered rapidly in patients with PARDS treated with NIV who do not show early clinical improvement.

We observed a particularly high failure rate in sites in low-income and middle-income countries. This subgroup was small, and further studies are needed to confirm the generalizability of this finding and to explore potential reasons for this failure rate, particularly with respect to specific diseases, available equipment, monitoring, and personnel (15, 31).

This study has several limitations. First, its observational design precludes conclusions on causality of observed associations. The use of NIV is intrinsically

linked with baseline condition and clinician preferences, and residual confounding in the multivariable analyses cannot be excluded. Second, although this is the largest cohort of PARDS patients treated with NIV, some analyses were limited by the sample size. Third, participation in the ancillary studies was voluntary and the burden of data collection was high. This may have led to a selection bias, and this limited some subanalyses; in particular, we could not assess the prognostic impact of the patient response (improvement or not) after NIV exposure, nor explore the potential impact of high patient effort on the lung injury. Fourth, consistent with PALICC definitions (17), only patients with a full-face or an oronasal mask were included. It is possible that some patients with similar clinical condition were only diagnosed as "at risk for PARDS" because they were supported with other nasal interface (32). It is uncertain how our findings translate to this population. Last, the data captured in PARDIE relates to practice and management in 2016/2017.

CONCLUSIONS

This ancillary study of a 2016/2017 international dataset shows that a one in five children with PARDS are first managed with NIV, with close to 50% success rate. While use of NIV is associated with some positive outcomes, other findings call for caution. These include the high failure rate when multiple risk factors are present, and the potentially poor outcomes of NIV failure patients. Interventional controlled trials appear particularly warranted to confirm the role of NIV in PARDS patients at high risk, including patients with severe PARDS, immunosuppression, and/or multiple organ dysfunction.

ACKNOWLEDGMENTS

The authors thank Margaret Klein for the supervision of the statistical analysis of the main study and the ancillary studies.

1 *Department of Pediatrics, Pediatric Intensive Care Unit, CHU Sainte-Justine, Université de Montréal, Montreal, QC, Canada.*

2 *Inmune and Respiratory Dysfunction in the Child Research Group, Institut de Recerca Sant Joan de Déu, Santa Rosa, Esplugues de Llobregat, Spain.*

3 *Pediatric Intensive Care and Intermediate Care Department, Sant Joan de Déu University Hospital, Universitat de Barcelona, Esplugues de Llobregat, Spain.*

4 *Department of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles, Los Angeles, CA.*

5 *Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA.*

6 *Division of Pediatric Critical Care Medicine, Rainbow Babies and Children's Hospital, Cleveland, OH.*

7 *Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Washington School of Medicine, Seattle, WA.*

8 *Pediatric Intensive Care Unit, Hospital Universitari I Politècnic La Fe, València, València, Spain.*

9 *Division of Pediatric Critical Care Medicine, Department of Pediatrics, Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, IN.*

10 *Réanimation Pédiatrique, Hospices Civils de Lyon, Hôpital Femme Mère Enfant, Lyon, France.*

11 *Division of Pediatric Critical Care Medicine, Department of Pediatrics, Washington University School of Medicine, St. Louis, MO.*

12 *Applied Clinical Research Unit, CHU Sainte-Justine, Montreal, QC, Canada.*

13 *Respiratory Therapy Department, Children's Hospital of Philadelphia, Philadelphia, PA.*

14 *Pediatric Intensive Care Unit, Hospital Universitario Central de Asturias, Asturias, Spain.*

15 *Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Asturias, Spain.*

16 *Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain.*

17 *Escuela de Medicina, Universidad Finis Terrae, Santiago, Chile.*

18 *Unidad de Paciente Crítico Pediátrico, Hospital El Carmen de Maipú, Santiago de Chile, Chile.*

19 *Escuela de Medicina Veterinaria, Facultad de Ciencias de la Vida, Universidad Andres Bello, Santiago, Chile.*

20 *Department of Pediatrics, University of Washington, Seattle Children's Hospital, Seattle, WA.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/pccmjournal).

Supported, in part, by grant from University of Southern California Clinical Translational Science Institute, Sainte Justine Children's Hospital, University of Montreal, Canada, Réseau en Santé Respiratoire du Fonds de Recherche Québec-Santé, and Children's Hospital Los Angeles, Department of Anesthesiology and Critical Care Medicine.

Dr. Emeriaud's institution received funding from Fonds de recherche du Quebec Santé (research public agency award) and Maquet. Dr. Pons-Òdena's institution received funding from Medtronic; he received funding from Philips Respironics. Drs. Bhalla and Killien received support for article research from the National Institutes of Health. Dr. Shein received

funding from Hill Ward Henderson. Dr. Killien's institution received funding from the National Institutes of Child Health and Human Development. Dr. Rowan's institution received funding from the National Heart, Lung, and Blood Institute (K23). Dr. Lin received funding from ROMTech. Dr. Napolitano's institution received funding from Drager, Actuated Medical, Philips/Respinronics, and VeroBiotech. Dr. Khemani received funding from Orange Med and Bayer. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: guillaume.emeriaud@umontreal.ca

PARDIE investigators are listed in ***Appendix*** *(http://links.lww.com/PCC/C386).*

REFERENCES

1. Essouri S, Laurent M, Chevret L, et al: Improved clinical and economic outcomes in severe bronchiolitis with pre-emptive nCPAP ventilatory strategy. *Intensive Care Med* 2014; 40:84–91
2. Wolfler A, Calderini E, Iannella E, et al; Network of Pediatric Intensive Care Unit Study Group: Evolution of noninvasive mechanical ventilation use: A cohort study among Italian PICUs. *Pediatr Crit Care Med* 2015; 16:418–427
3. Mayordomo-Colunga J, Pons-Odena M, Medina A, et al: Noninvasive ventilation practices in children across Europe. *Pediatr Pulmonol* 2018; 53:1107–1114
4. Boghi D, Kim KW, Kim JH, et al: Noninvasive ventilation for acute respiratory failure in pediatric patients: A systematic review and meta-analysis. *Pediatr Crit Care Med* 2023; 24:123–132
5. Brochard L, Slutsky A, Pesenti A: Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med* 2017; 195:438–442
6. Payen V, Jouvet P, Lacroix J, et al: Risk factors associated with increased length of mechanical ventilation in children. *Pediatr Crit Care Med* 2012; 13:152–157
7. Demoule A, Girou E, Richard JC, et al: Benefits and risks of success or failure of noninvasive ventilation. *Intensive Care Med* 2006; 32:1756–1765
8. Hilbert G, Gruson D, Vargas F, et al: Noninvasive continuous positive airway pressure in neutropenic patients with acute respiratory failure requiring intensive care unit admission. *Crit Care Med* 2000; 28:3185–3190
9. Rowan CM, Gertz SJ, McArthur J, et al; Investigators of the Pediatric Acute Lung Injury and Sepsis Network: Invasive mechanical ventilation and mortality in pediatric hematopoietic stem cell transplantation: A multicenter study. *Pediatr Crit Care Med* 2016; 17:294–302
10. Mayordomo-Colunga J, Pons M, Lopez Y, et al: Predicting noninvasive ventilation failure in children from the SpO(2)/FiO(2) (SF) ratio. *Intensive Care Med* 2013; 39:1095–1103
11. Munoz-Bonet JI, Flor-Macian EM, Brines J, et al: Predictive factors for the outcome of noninvasive ventilation in pediatric acute respiratory failure. *Pediatr Crit Care Med* 2010; 11:675–680
12. Piastra M, De Luca D, Pietrini D, et al: Noninvasive pressure-support ventilation in immunocompromised children with ARDS: A feasibility study. *Intensive Care Med* 2009; 35:1420–1427
13. Essouri S, Chevret L, Durand P, et al: Noninvasive positive pressure ventilation: Five years of experience in a pediatric intensive care unit. *Pediatr Crit Care Med* 2006; 7:329–334
14. Emeriaud G, Lopez-Fernandez YM, Iyer NP, et al; Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) Group on behalf of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Executive summary of the second international guidelines for the diagnosis and management of pediatric acute respiratory distress syndrome (PALICC-2). *Pediatr Crit Care Med* 2023; 24:143–168
15. Carroll CL, Napolitano N, Pons-Odena M, et al; Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Noninvasive respiratory support for pediatric acute respiratory distress syndrome: From the Second Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med* 2023; 24(Supplement 1 2S):S135–S147
16. Khemani RG, Smith L, Lopez-Fernandez YM, et al; Pediatric Acute Respiratory Distress syndrome Incidence and Epidemiology (PARDIE) Investigators: Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): An international, observational study. *Lancet Respir Med* 2019; 7:115–128
17. Khemani RG, Smith LS, Zimmerman JJ, et al; Pediatric Acute Lung Injury Consensus Conference Group: Pediatric acute respiratory distress syndrome: Definition, incidence, and epidemiology: Proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med* 2015; 16(5 Suppl 1):S23–S40
18. Leclerc F, Duhamel A, Deken V, et al; Groupe Francophone de Réanimation et d'Urgences Pédiatriques: Nonrespiratory pediatric logistic organ dysfunction-2 score is a good predictor of mortality in children with acute respiratory failure. *Pediatr Crit Care Med* 2014; 15:590–593
19. Santschi M, Jouvet P, Leclerc F, et al; PALIVE Investigators: Acute lung injury in children: Therapeutic practice and feasibility of international clinical trials. *Pediatr Crit Care Med* 2010; 11:681–689
20. Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators: 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
21. Pons-Odena M, Medina A, Modesto V, et al: What are the most reliable predictive factors of non-invasive ventilation failure in paediatric intensive care units?. *An Pediatr (Barc)* 2019; 91:307–316
22. Essouri S, Carroll C; Pediatric Acute Lung Injury Consensus Conference Group: Non-invasive support and ventilation for Pediatric Acute Respiratory Distress Syndrome: Proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med* 2015; 16(5 suppl 1):S102–S110
23. Lum LC, Abdel-Latif ME, de Bruyne JA, et al: Noninvasive ventilation in a tertiary pediatric intensive care unit in a middle-income country. *Pediatr Crit Care Med* 2011; 12:e7–13

24. Zeng JS, Qian SY, Wong JJ, et al: Non-invasive ventilation in children with paediatric acute respiratory distress syndrome. *Ann Acad Med Singap* 2019; 48:224–232
25. Rowan CM, Fitzgerald JC, Agulnik A, et al: Risk factors for noninvasive ventilation failure in children post-hematopoietic cell transplant. *Front Oncol* 2021; 11:653607
26. Pancera CF, Hayashi M, Fregnani JH, et al: Noninvasive ventilation in immunocompromised pediatric patients: Eight years of experience in a pediatric oncology intensive care unit. *J Pediatr Hematol Oncol* 2008; 30:533–538
27. Peters MJ, Agbeko R, Davis P, et al; SCARF Study Investigators and the Pediatric Intensive Care Society Study Group (PICS-SG): Randomized study of early continuous positive airways pressure in acute respiratory failure in children with impaired immunity (SCARF) ISRCTN82853500. *Pediatr Crit Care Med* 2018; 19:939–948
28. Gattinoni L: Ventilation-induced lung injury exists in spontaneously breathing patients with acute respiratory failure: We are not sure. *Intensive Care Med* 2017; 43:256–258
29. Dumas G, Lemiale V, Rathi N, et al: Survival in immunocompromised patients ultimately requiring invasive mechanical ventilation: A pooled individual patient data analysis. *Am J Respir Crit Care Med* 2021; 204:187–196
30. Kopp W, Gedeit RG, Asaro LA, et al; Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) Study Investigators: The impact of preintubation noninvasive ventilation on outcomes in pediatric acute respiratory distress syndrome. *Crit Care Med* 2021; 49:816–827
31. Morrow BM, Agulnik A, Brunow de Carvalho W, et al; Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) Group of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Diagnostic, management, and research considerations for pediatric acute respiratory distress syndrome in resource-limited settings: From the Second Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med* 2023; 24(12 Suppl 2):S148–S159
32. Shein SL, Maddux AB, Klein MJ, et al; V4 PARDIE Investigators and the PALISI Network: Epidemiology and outcomes of critically ill children at risk for pediatric acute respiratory distress syndrome: A pediatric acute respiratory distress syndrome incidence and epidemiology study. *Crit Care Med* 2022; 50:363–374