# Predictors of the failure of non-invasive ventilation in children with acute respiratory distress: A prospective observational study

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## ABSTRACT

**Objective:** The objective of this study was to determine the predictors of non-invasive ventilation (NIV) failure in pediatric acute respiratory distress/failure. **Materials and Methods:** This prospective observational study was conducted in a tertiary care hospital pediatric intensive care unit (PICU) for a period of 18 months. Children 1 month–16 years presenting with acute respiratory distress/failure, who were started on NIV, were included in the study. Demographic data, pediatric risk of mortality (PRISM) III score, vitals, and blood gas variables were monitored at admission and regular intervals, and incidence of NIV failure, length of PICU stay, hospital stay, and mortality rate was observed. **Results:** A total of 108 from 264 children with respiratory distress (40%) received NIV and 20/108 (18.51%) required endotracheal intubation. NIV failure patients had higher PRISM III score (median [interquartile range] - 8 [6.5, 13.5] vs. 7 [4.5, 8], p=0.025), lower admission pH (7.30 [0.066] vs. 7.34 [0.69], p=0.021), and higher number of children had associated comorbid illness (11/20 [55%] vs. 16/88 [18.18%], p=0.001) compared to NIV success group. On multivariate regression analysis, comorbid illness remains the significant independent predictor of NIV failure ([odds ratio 4.24; 95% confidence interval 1.322–13.576] p=0.015). **Conclusion:** Higher PRISM III score and comorbid illness were found as predictors of NIV failure.

**Key words:** *Children, Non-invasive ventilation, Pediatric intensive care unit, Respiratory distress, Respiratory distress/failure*

Acute respiratory failure (ARF) is defined as hypoxemic or hypercarbic respiratory failure ($PaO_2$<60 mmHg or $SpO_2$ of ≤85%, with fraction of inspired oxygen [$FiO_2$] ≥0.6 and partial pressure of $CO_2$ [$PaCO_2$] >50 mmHg). Over the past two decades, non-invasive ventilation (NIV) has become the standard of care in treating ARF [1]. Several randomized controlled trials have shown that NIV improves dyspnea, gas exchange, and reduces the incidence of tracheal intubation [2]. Furthermore, compared to invasive mechanical ventilation, NIV reduces the length of intensive care unit (ICU) and hospital stay, morbidity, and mortality in patients with ARF [3].

NIV failure has been defined as the need for endotracheal intubation (ETI) or death. There has also been concern that NIV may delay intubation, leading to a worse outcome [4]. Several studies in adults have identified various factors which can predict NIV success [5-8]; however, studies in pediatric population are limited [1,9-11]. Thus, the objective of the study was to determine the predictors of NIV failure in pediatric acute respiratory distress/failure.

## MATERIALS AND METHODS

This was a prospective observational study conducted in a multidisciplinary, 12-bedded, pediatric ICU (PICU) in a tertiary care hospital during October 2016–May 2018. The study was approved by the Institutional Ethical Committee and informed consent was taken from the parents. Children from 1 month to 16 years of age presenting with acute respiratory distress (according to PALS guidelines) or failure (defined as $PaO_2$<60 mmHg or arterial oxygen saturation of ≤85%, with $FiO_2$≥0.6 and $PaCO_2$>50 mmHg) were included in the study. Patients were selected regardless of underlying disease process contributing to respiratory distress including post-extubation.

Children requiring immediate intubation (<1 h), low level of consciousness (Glasgow coma scale <10), absent cough/gag reflex, polytrauma, hemoptysis/copious respiratory secretions, facial injuries/burns, nasopharyngeal obstruction, hemodynamic instability, recent facial, upper airway or upper gastrointestinal tract surgery (<7 days), undrained pneumothorax, or basilar skull fracture/craniofacial malformations were excluded from the study. The reported success rate of NIV in a study by Bernet *et al.* [1] was 57%. Hence, to estimate the success rate of NIV with 9.5% absolute precision and 95% confidence interval (CI), the required minimum sample size was 104 children.

**Protocol for NIV Use in the PICU**

NIV was provided using either conventional ventilator with NIV pressure support/pressure control mode (Maquet servo-i ventilator with NIV-PS/PC mode) or a bilevel positive airway pressure (Weinmann ME17 0011). NIV-PS/PC mode on ventilator was used when precise titration of $FiO_2$ was mandatory as in hypoxic respiratory failure. Initial settings and titration of PS were done as shown in Fig. 1 and $FiO_2$ was adjusted to maintain the $SpO_2 > 94\%$. A backup ventilator frequency ("backup rate") was set at two breaths below the patient's spontaneous rate in case the patient becomes apneic. Patients were propped up at an angle of 30–45° to prevent reflux, aspiration, and ventilator-associated pneumonia. Nasogastric tube was inserted and decompression was done. Application of skin protectant barrier was considered to prevent skin breakdown. For NIV interface, a nasal mask/oronasal mask was used and adjusted for acceptable air leakage (20%). A baseline arterial blood gas (ABG) analysis was performed after patient's stabilization on NIV.

Demographic details such as age, gender, pediatric risk of mortality score (PRISM) III scores, primary diagnosis, and associated comorbid illness were tabulated. PRISM III was calculated using online-based PRISM III calculator. The following data were collected prospectively before initiating NIV and post-NIV at period intervals at 1 and 6 h: Respiratory rate (RR), heart rate (HR), transcutaneous oxygen saturation ($SpO_2$), $FiO_2$, and ABG (pH, $PaO_2$, $PCO_2$, and $HCO_3$). Each patient was evaluated periodically according to the institutional protocol by the attending physician to access the possibility to decrease or increase expiratory positive airway pressure or NIV discontinuation/continuation.

Identification of NIV failure and indications for ETI was on the basis of the judgment of the attending physician which included inability to protect the airways or to manage copious tracheal secretions, hemodynamic or electrocardiographic instability, inability to tolerate the face mask, inability to correct dyspnea, and progression of respiratory failure (Fig. 1).

The outcome was to determine the predictors of NIV failure in pediatric acute respiratory distress/failure. Patients were divided into NIV failure and success groups, depending on whether they failed NIV and had to be intubated. NIV was ceased every 4 h to look for any complications attributable to NIV. We followed standardized protocol for weaning patients from NIV. Once

improved, child was put on oxygen by face mask, nasal prongs, or onto room air. The outcome variables were analyzed and patients were followed up till day 28.

For comparisons between responders and non-responders, categorical variables were analyzed using Chi-square test. Approximately, normally distributed variables were compared with two-sample t-tests and skewed variables with Wilcoxon rank sums tests. The courses of vital and blood gas variables of responders and non-responders were compared by analysis of variance with repeated measures. Variables that were significantly different between responders and non-responders were entered a multiple logistic regression model to determine adjusted odds ratios (AORs) and 95% CIs and define which variables were independently associated with NIV failure. All continuous variables are presented as the mean (standard deviation) or median (interquartile range [IQR]). 28 days survival curves between responders and non-responders were compared using log-rank test. The median survival time was calculated using Kaplan–Meier method. For all analyses, $p < 0.05$ was considered statistically significant. All data analyses were performed using R-3.5.0 software.

**RESULTS**

During the study period, 264 children presented with acute respiratory distress/failure; out of which, 156 were excluded either for requirement of immediate intubation or due to the presence of other exclusion criteria and 108 patients (40%) received NIV. The overall success rate of NIV was 81.48%, failure occurred in 18.51% of cases.

The baseline characteristics of studied patients are presented in Table 1. Median age was 7.5 years (IQR 4, 10.5) and male:female ratio was 1.29:1. The main etiologies of acute respiratory distress/failure did not differ between the two groups, but the majority of patients received NIV for bronchopneumonia. No relationship was found between the outcome (success/failure) and age, sex, and underlying disease. Comorbid illnesses were present in 27 patients (25%). The median PRISM III score for the NIV failure group was significantly higher compared to success group ($p = .025$) and more patients in failure group had comorbid illness ($p=0.001$), suggesting these variables as predictive factors for NIV failure.

Eight patients (7.4%) developed minor complications such as skin erosions. NIV failure was observed between 1 and 50 h.

**Table 1: Baseline characteristics and outcome of study population**

| Variable | Study population (n=108) | NIV responders (n=88) | Non-responders (n=20) | p value |
|---|---|---|---|---|
| Age (years) median (IQR) | 7.5 (4,10.5) | 7.5 (4,11) | 7.5 (5,10) | 0.762 |
| Male: female | 1.29:1 | 1.3:1 | 1.2:1 | 0.882 |
| Comorbid illness | 27 | 16 (18.18%) | 11 (55%) | 0.001* |
| PRISM III score (median) IQR | 7 (5,8) | 7 (4.5,8) | 8 (6.5,13.5) | 0.025* |
| Duration of NIV (h) median (IQR) | 36 (24,48) | 40 (29,50) | 11 (6.5,15) | <0.001* |
| Duration of ICU stay (h) median (IQR) | 4 (3,6) | 4 (3,5) | 8 (5,11.5) | 0.001* |
| Duration of hospital stay (h) median (IQR) | 10 (7.5,15) | 9 (7,12) | 15.5 (12,24.5) | 0.001* |
| In hospital mortality | 15 | 4 (4.5%) | 11 (55%) | <0.001* |

*p<0.05 - significant. IQR: Interquartile range, ICU: Intensive care unit, NIV: Non-invasive ventilation, PRISM: Pediatric risk of mortality

Total 9 of 20 patients got intubated within 8 h, nine in the next 16 h, and only two failures were noted past the first 24 h. It was observed that the median duration of NIV (40 [29, 50] vs. 11 [6.5, 15]), PICU stay (4 [3, 5] vs. 8 [5, 11.5]), and hospital stay (9 [7, 12] vs. 15.5 [12, 24, 5] was significantly longer among the NIV failure compared with the NIV success group
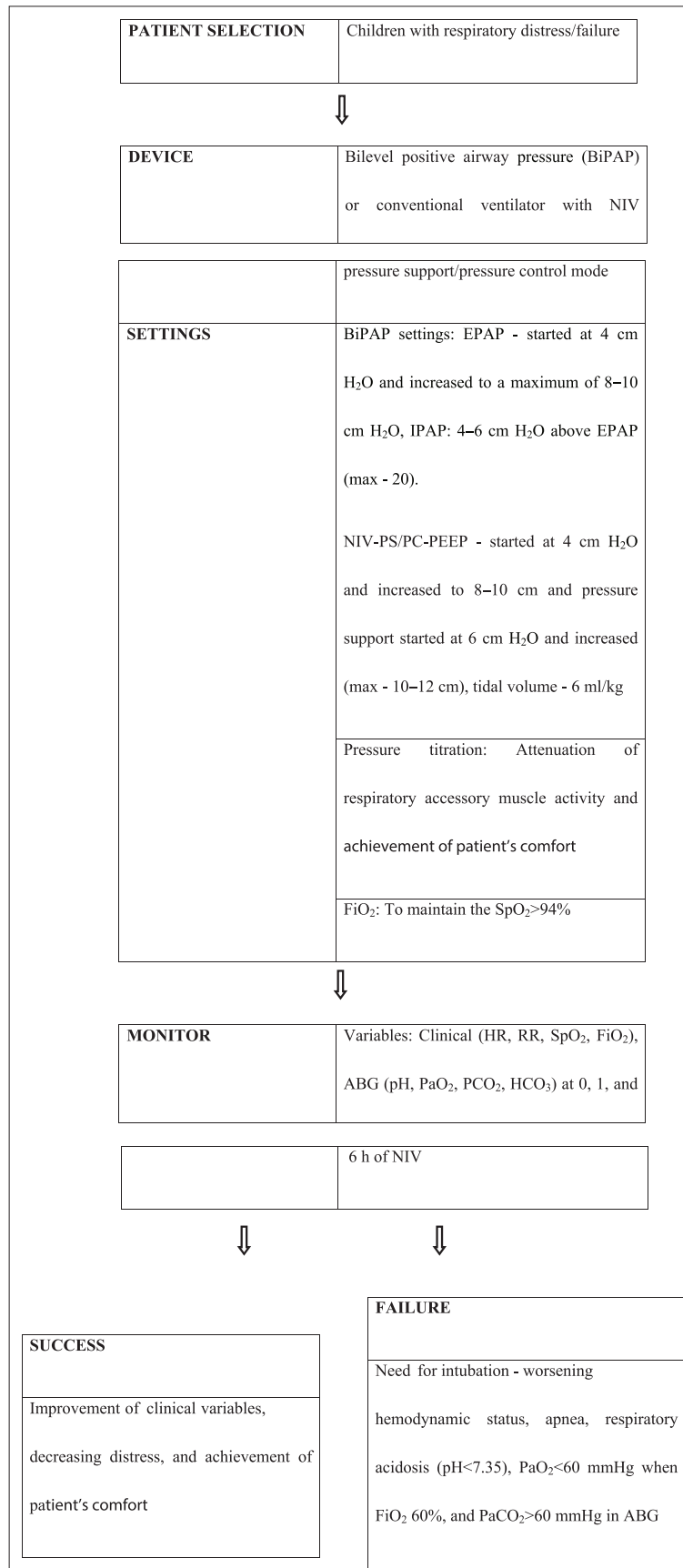
| PATIENT SELECTION | Children with respiratory distress/failure |
|---|---|

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| DEVICE | Bilevel positive airway pressure (BiPAP) or conventional ventilator with NIV |
|---|---|

| | pressure support/pressure control mode |
|---|---|
| SETTINGS | BiPAP settings: EPAP - started at 4 cm $H_2O$ and increased to a maximum of 8–10 cm $H_2O$, IPAP: 4–6 cm $H_2O$ above EPAP (max - 20). |
| | NIV-PS/PC-PEEP - started at 4 cm $H_2O$ and increased to 8–10 cm and pressure support started at 6 cm $H_2O$ and increased (max - 10–12 cm), tidal volume - 6 ml/kg |
| | Pressure titration: Attenuation of respiratory accessory muscle activity and achievement of patient's comfort |
| | $FiO_2$: To maintain the $SpO_2$>94% |

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| MONITOR | Variables: Clinical (HR, RR, $SpO_2$, $FiO_2$), ABG (pH, $PaO_2$, $PCO_2$, $HCO_3$) at 0, 1, and |
|---|---|
| | 6 h of NIV |

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| SUCCESS | FAILURE |
|---|---|
| Improvement of clinical variables, decreasing distress, and achievement of patient's comfort | Need for intubation - worsening hemodynamic status, apnea, respiratory acidosis (pH<7.35), $PaO_2$<60 mmHg when $FiO_2$ 60%, and $PaCO_2$>60 mmHg in ABG |

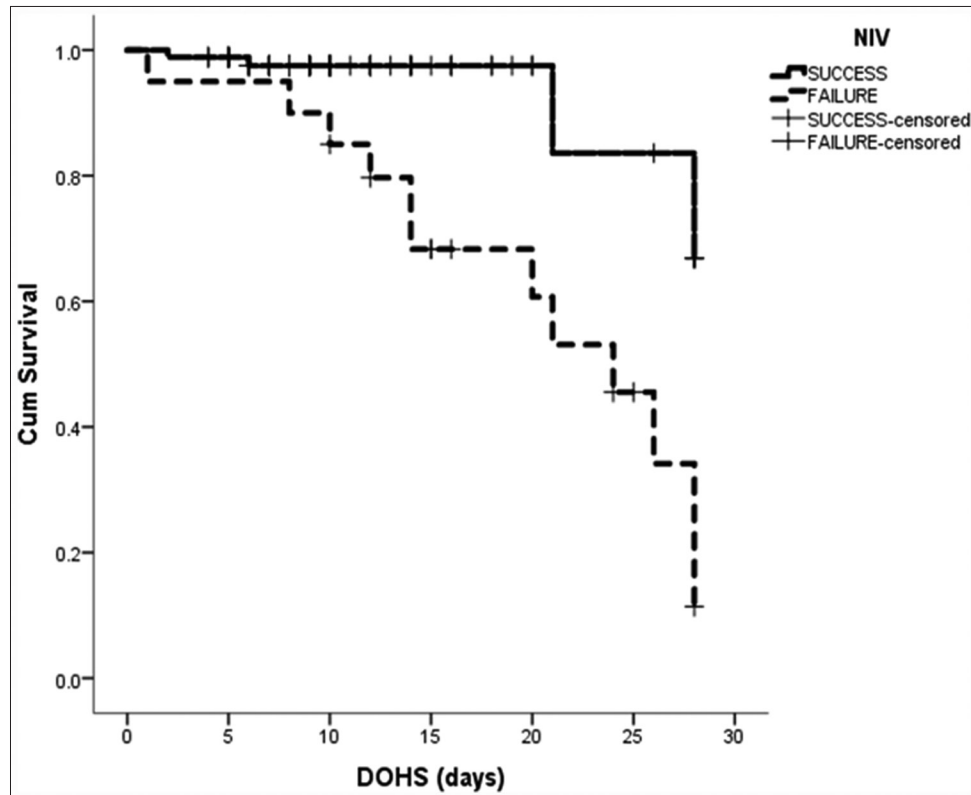**Figure 1: Protocol for initiation and monitoring of non-invasive ventilation**

**Figure 2: Kaplan–Meier curve for 28-day survival**

**Table 2: Clinical and blood gas variables pre-NIV and post-NIV (1, 6 h)**

| Variable | Before NIV | After 1 h | p value (0,1) | After 6 h | p value (0,6) |
|---|---|---|---|---|---|
| HR | 127.29±23.38 | 116.88±23 | <0.001* | 110.68±21.46 | <0.001* |
| RR | 44.58±12.26 | 41.04±10.93 | <0.001* | 36.51±8.79 | <0.001* |
| SpO$_2$ | 96.68±3.36 | 98.74±1.59 | <0.001* | 99.06±1.45 | <0.001* |
| pH | 7.08±0.07 | 7.37±0.07 | 0.24 | 7.40±0.07 | 0.89 |
| PCO$_2$ | 32.18±6.79 | 31.97±5.83 | 0.721 | 33.97±7.71 | 0.056 |
| PO$_2$ | 90.65±36 | 124.47±45 | <0.001* | 127.99±40.09 | <0.001* |

NIV: Non-invasive ventilation, Pre-NIV: Prospectively before initiating NIV, HR: Heart rate, RR: Respiratory rate

[Fig. 2]. Fig. 3 shows the Trends of heart rate, respiratory rate, SpO2, and pH among responders and non-responders at 0, 1, and 6 h.

Baseline values of the variables did not differ between groups except pH at admission which was significantly lower amongst failure group as compared to success group (p=0.021). Analysis of clinical and blood gas variables data showed an overall significant decrease in RR, HR, SpO$_2$, and improvement in blood gases (pH, PO$_2$, PCO$_2$, and HCO$_3$) from admission to 1 h and maintained through 6 h NIV (p<0.001) (Table 2). Although these variables decreased more in the success group, the difference was not statistically significant between the two groups.

Logistic regression analysis containing three independent variables (PRISM III score, presence of comorbid illness, and pH at admission) to predict NIV failure was also done. The presence of comorbid illness remains the statistically significant independent predictor of NIV failure, with OR of 4.24 (95% CI 1.322–13.576) p=0.015, whereby patients with the presence of comorbid illness were much more likely to fail NIV and require intubation (Table 3).

**Table 3: Logistic regression analysis for predictive factors for NIV failure**

| Risk factors (predictors) | Multivariate analysis | | |
|---|---|---|---|
| | OR | 95% CI | p value |
| Comorbid illness | 4.24 | 1.322–13.576 | 0.015* |
| PRISM III score | 1.074627 | 0.9332397–1.237435 | 0.317 |
| Admission pH | 0.0015 | 4.53–5.36 | 0.12 |

OR: Odds ratio, CI: Confidence interval, *p value - significant. NIV: Non-invasive ventilation, PRISM: Pediatric risk of mortality

| | | | | |
|---|---|---|---|---|
| Comorbid illness | 27 | 16 (18.18%) | 11 (55%) | 0.001 |
| Kidney disease | 17 | 11 (%) | 6 | |
| Chronic liver disease | 1 | 0 | 1 | |
| Congenital heart disease | 3 | 2 | 1 | |
| Hematoncologic diseases | 6 | 3 | 3 | |

## DISCUSSION

This study showed a success rate of NIV in children with respiratory distress/failure to be 81.5% which was similar to
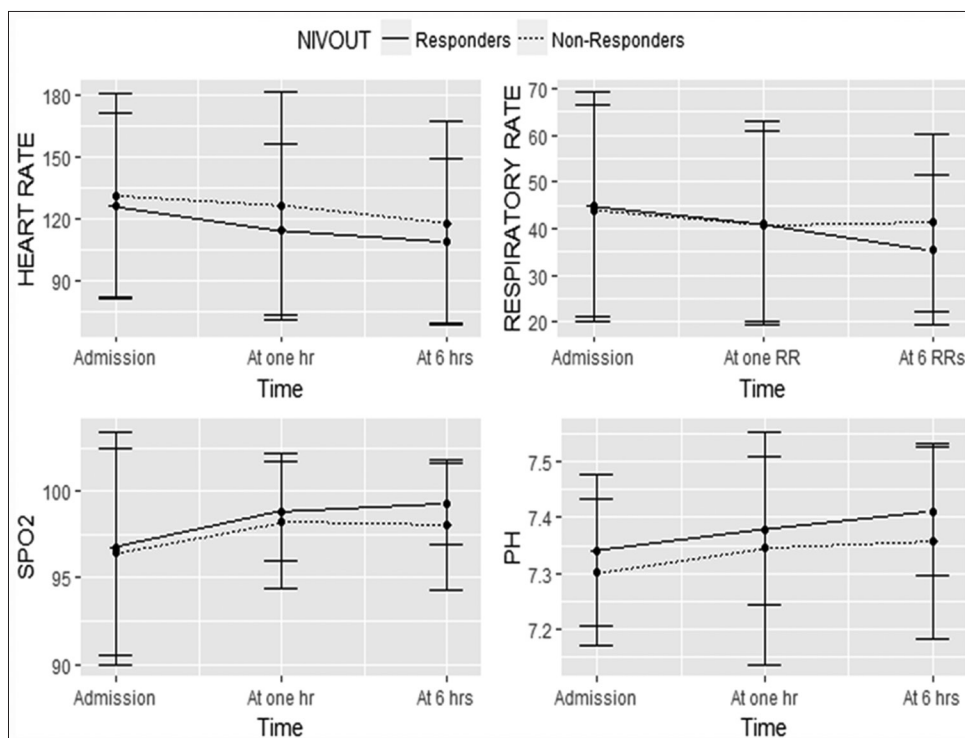
**Figure 3: Trends of heart rate, respiratory rate, SpO$_2$, and pH among responders and non-responders at 0, 1, and 6 h. Vertical lines represent 95% confidence interval**

other studies [12,13]. Therefore, we suggest that NIV can be successfully used in children with acute respiratory distress/failure of varied etiology in the PICU.

Our study population was a heterogeneous group with bronchopneumonia being the most common cause for the need of NIV support, comprising 44% and was similar to other pediatric ARF studies [1,14-16]. Further, analysis of our study for predictors of NIV failure showed results similar to Bonet *et al.* [13] where no relationship was found between the outcome (success/failure) and sex, underlying disease, and type of respiratory failure. However, PRISM III score at admission was higher in NIV failure group and was statistically significant. This observation is similar to Caples et al. and other studies [10,18-21] where success in the use of NIV in their population of patients was largely dependent on the illness severity. Another interesting finding of our study was the result of multivariable analysis which showed that the presence of comorbid illness was independently associated with increased risk of NIV failure, and therefore, we suggest careful selection of these patients at admission for NIV use.

In relation to the outcome of NIV, our results were similar to a study by Correa *et al.* [22] where NIV failure was associated with increased mortality rates and longer length of PICU and hospital stay. Furthermore, NIV application only caused minor complications which were interface related.

Clinical and blood gas variables showed improvement at 1 h and maintained at 6 h of post-NIV. Although these variables decreased more in the success group, the difference was not statistically significant. These results are comparable to a study by Bernet *et al.* [1] emphasizing the requirement of close monitoring in these patients.

Large sample size and application of NIV over varied etiology add to the strength of the study. However, there were certain limitations. This was a single-centric observational study; further, multicenter randomized controlled trials are required to comment on the efficacy of NIV therapy. Also, identification of NIV failure and indications for ETI was on basis of the judgment of the attending physician, which counted as another limitation.

## CONCLUSION

NIV can be successfully used in children with acute respiratory distress/failure of varied etiology in the PICU. Patients with higher PRISM III score, presence of comorbid illness, and lower pH at admission had higher failure rates, suggesting the need for a careful monitoring of these patients. Further studies are needed to select the right treatment at the initial point of contact in the patient with acute respiratory distress/failure.

## ACKNOWLEDGMENT

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