

Hypochloremia, blood transfusion, and neuromuscular drug use can be associated with prolonged mechanical ventilation in pediatric intensive care

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Abstract

Background: Mechanical ventilation (MV) is one of the most important components of modern intensive care practice. Longer MV time is associated with increased morbidity and mortality. Therefore, it is important to identify the risk factors associated with longer duration of MV. The objective of this study was to determine the clinical and the laboratory risk factors for prolonged invasive MV in the pediatric intensive care unit (PICU).

Methods: We performed a retrospective analysis of the records of all patients admitted to our PICU between October 2016 and March 2018. Patients with invasive MV were included in the study.

Results: A total of 121 children with a mean age of 3.58 ± 4.84 years were enrolled in this study. The most frequent diagnosis at the time of admission to the PICU was primary respiratory disease (31.4%), followed by neurological diseases (22.3%), and sepsis (17.4%). Pressure control was the most commonly used MV method in 97 (80.2%) patients. Pressure regulated volume control was used in the other (19.8%) patients. The mean duration of mechanical ventilation was 9.17 ± 8.12 days. Risk factors for prolonged MV in the PICU included red blood cell (RBC) transfusion, hypochloremia, high gamma-glutamyl transferase (GGT), and low body mass index (BMI). The logistic regression analysis showed that hypochloremia prolonged MV by 3.234 fold, neuromuscular blocker drug uses prolonged MV by 3.689 fold, and RBC transfusion prolonged MV by 8.031 fold.

Conclusion: Hypochloremia, need for RBC transfusion, and neuromuscular blocker drug use may be early predictors of prolonged MV in critically ill children.

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Abbreviations:

MV: Mechanical Ventilation; PICU: Pediatric Intensive Care Unit; RBC: Red Blood Cell; GGT: Gamma-glutamyl Transferase; BMI: Body Mass Index; PRISM: Pediatric Risk of Mortality; ETT: Endotracheal Tube; ANOVA: Analysis of Variance; ROC: Receiver Operating Characteristic; ORs: Odds Ratios; CIs: Confidence Interval; AKI: Acute Kidney Injury; BPD: Bronchopulmonary Dysplasia; NIV: Noninvasive Ventilation; TRALI: Transfusion

Related Acute Lung Injury; SF: SpO₂/FiO₂ Ratio; PF: PaO₂/FiO₂ Ratio.

Introduction

Mechanical ventilation (MV) is one of the most important components of modern intensive care practice, and the need for MV support is one of the most common causes of intensive care admissions [1]. Respiratory disease is the main indication for ventilator support in children; however, MV may be applied in numerous circumstances [2]. In the

pediatric intensive care unit (PICU) about 30% (20% to 64%) of patients are mechanically ventilated. Average invasive MV time has been found to be five to six days, in literature [3,4]. Though it has lifesaving benefits, mechanical ventilation can result in important complications and adverse physiological effects which may increase mortality, especially prolonged MV. Longer MV time is associated with infections, longer hospital stays, barotrauma and volutrauma, increased cost of treatment, and increased mortality [5,6]. Therefore, it is important to identify the risk factors associated with a longer duration of MV. There are only a few published studies on early predictors of prolonged MV in children. The objective of this study was to determine the clinical and laboratory risk factors for prolonged invasive MV in PICU.

Methods

Study design

We performed a retrospective analysis of the records of all patients admitted to our PICU between October 2016 and March 2018. We have a tertiary, multidisciplinary PICU located in a training and research hospital. Our PICU provides healthcare for children aged between one month and eighteen years. It has twelve beds, eleven ventilators, and two isolation rooms. Our unit employs a pediatric intensive care specialist, two assistants, and 27 nurses.

Patient population and data collection

Patients admitted in the PICU with critical illness due to various causes were included in this study. Patients with invasive MV were included. Patients with tracheostomy, brain death, patients who died on the first day after admission to the PICU, and postoperative patients were excluded from the study.

The demographic, prognostic, and laboratory findings of patients were collected. The patients' sex, age, diagnosis at admission, duration of MV, pediatric risk of mortality (PRISM-III) score, duration of intensive care unit stay, body mass index (BMI), body weight, SpO₂/FiO₂ (SF) ratio, neuromuscular drugs, and mortality were investigated.

MV devices and equipment

Maquet Servo-i® and Servo-u® (Maquet, Solna, Sweden) were the devices used as ventilators. The Evaqua™ Breathing Circuit (Fisher Paykel Healthcare, Auckland, New Zealand) was used for ventilation circuit. The MR850 (Fisher Paykel Healthcare, Auckland, New Zealand) was used as the humidifier for the patients on MV in a ventilator. All patients were continuously monitored by B40 Patient Monitors (GE Healthcare) during MV treatment.

Ventilation strategy and protocol

Mechanically ventilated patients were sedated. The goal was to achieve patient comfort and patient-ventilator synchrony. Midazolam, dexmedetomidine, fentanyl, and ketamine were used for sedation-analgesia. Curare was not routinely applied.

Pressure control and pressure regulated volume control were the modes used in patients requiring a mechanical ventilator. Pressure support was used during the weaning from MV. The initial parameter was set according to need of the patients. Chest radiographs were obtained of all patients and blood gas control was taken.

The standard suctioning practices of the endotracheal tube (ETT) and normal saline were used as needed. ETTs were not routinely changed. The threshold for red blood cell (RBC) transfusion was hemoglobin level ≤ 7 g/dl.

Laboratory analysis

The initial hemogram, biochemical markers, C-reactive protein, and procalcitonin test results were recorded. For assessment of hemogram and biochemistry, peripheral blood was collected into vacutainer tubes and analyzed by the same machines (Cell-Dyn 3700 for hemogram and Beckman Coulter for biochemistry).

Statistical analysis

The statistical analysis was performed using the IBM SPSS 21.0 (SPSS Inc., Chicago, IL, USA) program. Continuous variables are expressed as mean \pm standard deviation, and categorical variables are expressed as frequency. Pearson's chi-square and analysis of variance (ANOVA) tests were used for the comparison of categorical data

between groups. Multivariate binary logistic regression models were used to calculate the odds ratios (ORs) and 95% confidence interval (CIs) for prognoses. For all tests, $p < 0.05$ was considered to be statistically significant.

Results

Demographics and prognostic factors

Between October 2016 and March 2018, 469 children were admitted to the PICU. Of those, 445 patients were eligible for the present study. Only 121 (27.2%) patients used the MV. Patients were divided into two groups as those using MV and those not using MV. The prognostic differences between the groups were examined (Table 1 and Figure 1).

Table 1. Comparison of prognostic factors of patients hospitalized between October 2016 and March 2018 according to ventilator usage

	Mechanical ventilation use		p
	Yes (n=121)	No (n=324)	
Sex			
• Male	53 (43.8%)	151 (46.6%)	0.597
• Female	68 (56.2%)	173 (53.4%)	
Age (years)	3.58 ± 4.84	3.79 ± 4.66	0.677
PRISM-III score	19.38 ± 14.41	12.15 ± 9.09	<0.001
Duration of stay in PICU (days)	15.01 ± 13.19	4.43 ± 4.18	<0.001
Inotropic Drug Use	72 (59.5%)	27 (8.3%)	<0.001
Acute Kidney Injury	53 (43.8%)	58 (17.9%)	<0.001
CRRT	16 (13.2%)	34 (10.5%)	0.417
Red blood cell transfusion	90 (74.4%)	69 (21.3%)	<0.001
BMI (Z score)	0.17 ± 1.22	0.58 ± 1.01	<0.001

Mortality	14 (11.6%)	0	<0.001
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There were 68 (56.2%) male and 53 (43.8%) female participants in the MV groups. The age distribution was one month to seventeen years, with a mean of 3.58 ± 4.84 years. The mean duration of intensive care unit stay was 15.01 ± 13.19 days. The most frequent diagnosis at admission to the PICU was primary respiratory disease (31.4%), followed by neurological diseases (22.3%), and sepsis (17.4%). Pressure control was the most commonly used MV method in 97 (80.2%) patients.

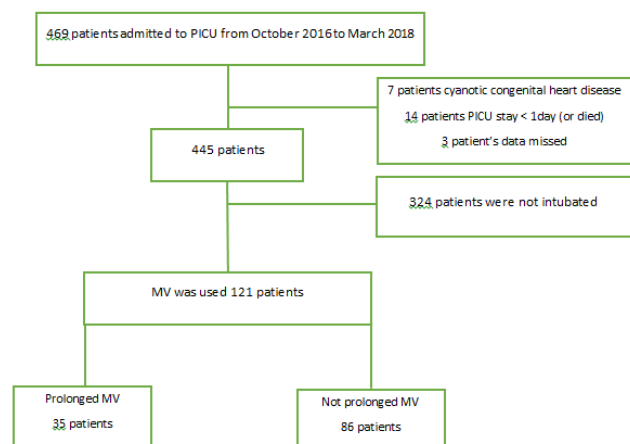


Figure 1. Cohort flow

Pressure regulated volume control was used in other (19.8%) patients. Fourteen (11.6%) patients died within the time of follow-up (Table 1).

There was a statistically significant relationship between MV and prognostic factors including inotropic drug usage ($p < 0.001$), acute kidney injury (AKI) ($p < 0.001$), RBC transfusion ($p < 0.001$), PRISM-III score ($p < 0.001$), BMI ($p < 0.001$), mortality ($p < 0.001$), and duration of intensive care unit stay ($p < 0.001$) (Table 1).

Prolonged mechanical ventilator use and prognostic factors

The mean duration of MV was 9.17 ± 8.12 days. The patients were divided into two groups according to the duration of MV: > 9 days and ≤ 9 days. The groups were compared. Both groups did not show association with sex, diagnosis at the admission or age difference. PRISM scores were similar. RBC transfusion was more frequent in patients who required prolonged MV ($p < 0.001$). When the laboratory findings were reviewed,

application sodium and chlorine levels were significantly lower and gamma glutamyl transferase (GGT) levels were significantly higher in patients with prolonged MV. Neuromuscular blocker drugs

use was higher in the prolonged MV group. In addition, the SF ratio was lower in the prolonged MV group (Table 2).

Table 2. Comparison of prognostic and laboratory findings of patients according to the requirement of prolonged mechanical ventilator

	Length of Mechanical Ventilation Duration		p value	
	>9 days (n = 35)	≤ 9 days (n = 86)		
Sex (Female)	21 (60.0%)	47 (54.7%)	0.591	
Age (years)	3.69 ± 5.25	3.53 ± 4.70	0.872	
PRISM-III score	21.75 ± 14.47	18.40 ± 12.39	0.341	
Inotropic drug use	20 (57.1%)	52 (60.5%)	0.736	
Acute kidney injury	17 (48.6%)	36 (41.9%)	0.5	
CRRT	6 (17.1%)	10 (11.6%)	0.417	
NIV failure (failure/success)	12-May	15/40	<0.001	
Duration of NIV (before the intubation) (days)	3.78 ± 4.34	4.67 ± 5.52	0.451	
Neuromuscular blocker drugs use	6 (17.1%)	5 (5.8%)	0.033	
S/F Ratio before the intubation	145.03 ± 26.96	156.36 ± 22.25	0.019	
Respiratory failure type (Type-1)	13 (37.1%)	49 (56.9%)	0.204	
Red blood cell transfusion	33 (94.3%)	57 (66.3%)	<0.001	
Laboratory	Leucocyte count (103/uL)	13336 ± 10640	12157 ± 8300	0.482
	Platelet count (103/uL)	301844 ± 188295	309702 ± 187222	0.837
	C-reactive protein (mg/L)	60.6 ± 53.76	67.3 ± 70.72	0.701
	Procalcitonin (ng/ml)	23.0 ± 27.87	18.5 ± 22.5	0.534
	Sodium (mmol/L)	135.6 ± 8.8	138.7 ± 6.0	0.028
	Chlorine (mmol/L)	97.80 ± 8.20	102.99 ± 6.39	<0.001
	Calcium (mg/dl)	9.1 ± 1.1	8.9 ± 1.2	0.453
	Magnesium (mg/dl)	2.2 ± 0.5	2.2 ± 0.5	0.877
	ALT (IU/L)	70.6 ± 147.9	48.2 ± 81.3	0.314
	AST (IU/L)	84.4 ± 84.6	123.2 ± 274.5	0.442
	GGT (IU/L)	94.4 ± 124.6	52.1 ± 66.2	0.023
	LDH (IU/L)	602.7 ± 359.16	510.5 ± 401.9	0.289

Mortality		3 (8.6%)	11(12.8%)	0.511
Bronchopulmonary Dysplasia		8 (22.9%)	6 (6.9%)	0.013
Congenital heart disease		6 (17.1%)	11 (12.8%)	0.532
Diagnosis admission at	Respiratory	12 (34.3%)	26 (30.2%)	0.839
	Neurology	6 (17.1%)	21 (24.4%)	
	Sepsis	8 (22.9%)	13 (15.1%)	
	Cardiac Disease	5 (14.3%)	10 (11.6%)	
	Others	4 (11.4%)	16 (18.6%)	

PRISM: Pediatric risk of mortality score, CRRT: Continuous renal replacement therapy, NIV: Non-invasive mechanical ventilation ALT: alanine aminotransferase AST: aspartate aminotransferase GGT: gamma glutamyl transferase, LDH: lactate dehydrogenase

Logistic regression analysis of the risk factors of prolonged MV use

The ORs and relationship between the prognostic factors and prolonged MV (> 9 days) were calculated using logistic regression models. The OR was 8.031 (95% CI, 1.756-39.578) for RBC transfusion, 2.862 (95% CI, 1.053-14.404) for bronchopulmonary dysplasia (BPD), 3.234 (95% CI, 1.011-9.431) for hypochloremia (< 96 mmol/L), 2.128 (95% CI, 0.759-5.966) for noninvasive ventilation (NIV) failure, 2.083 (95% CI, 0.689-6.355) for inotropic drug usage, 1.449 (95% CI, 0.497-4.219) for AKI, 1.333 (95% CI, 0.390-4.560) for continuous renal replacement therapy, 3.689 (95% CI, 1.042-13.054) for neuromuscular blocker drug use, and 2.379 (95% CI, 0.973-4.884) for SpO₂/FiO₂ ratio>150, 0.708 (95% CI, 0.072-6.981) for blood sodium < 130 mmol/L (Table 3).

Table 3. Logistic regression analysis of the risk factors of prolonged mechanical ventilator use

Risk	p value	Odds Ratio	95% Confidence interval
Red blood cell transfusion	0.011	8.031	1.756-39.578

Non-invasive mechanical ventilation failure	0.151	2.128	0.759-5.966
Inotropic drug usage	0.199	2.083	0.689-6.355
Acute kidney Injury	0.497	1.449	0.497-4.219
Continuous renal replacement therapy	0.646	1.333	0.390-4.560
Bronchopulmonary dysplasia	0.042	2.862	1.053-14.404
Hypochloremia (<96 mmol/L)	0.035	3.234	1.011-9.431
Neuromuscular Blocker Drug Use	0.033	3.689	1.042-13.054
SpO ₂ /FiO ₂ ratio>150	0.058	2.379	0.973-4.884
Blood sodium < 130 mmol/L	0.087	0.708	0.072-6.981

Discussion

In this study, a prolonged duration of MV has been found in 35 patients. The findings show that, as the proportion of ventilated children decreases, the duration of invasive MV increases. Risk factors for prolonged MV in the PICU include RBC transfusion, serum chloride, serum GGT, NIV failure, hyponatremia and BMI (Z score). However, in logistic regression analysis, there were only relationship between prolonged MV and RBC transfusion, BPD, hypochloremia, neuromuscular blocker drug use.

The RBC suspension is commonly administered to improve oxygenation in pulmonary deficiencies

during hypoxemia. However, the immune mediators released after RBC transfusion can cause pulmonary damage, clinical deterioration in critically ill patients, and increased mortality [6,7]. Thus, the duration of MV increases. In this study, RBC transfusion ratio in patients with MV was 74.4%. Long-term hospitalization and perhaps frequent blood sampling may have caused this situation. The RBC transfusion frequency increased to 94.3% in prolonged MV group (> 9 days) and this ratio is very high.

Recently, in a prospective study, it was reported that RBC transfusion is independently associated with a longer duration of MV [6]. Blood transfusion imparts injury to the lung known as transfusion related acute lung injury (TRALI). It is a blood transfusion complication in which respiratory distress develops within six hours of transfusion of blood products [8]. Patients with prolonged MV require more frequent blood sampling. In addition, increased risk of bleeding and inadequate lung function may also hasten the need for transfusion. As a result, it is expected that the need for blood products will be higher in the prolonged MV group. In this study, blood transfusion has been associated with MV use and longer duration of MV. The logistic regression analysis showed that RBC transfusion prolonged MV by 8.031-fold.

BMI Z-score is a possible assessment of nutritional status in children. BMI can easily be measured and is a better indicator than body weight after infant ages. Nutritional status on admission to the PICU has been associated with poor outcomes [9]. In a prospective study on children, malnutrition was significantly associated with the duration of mechanical ventilation [10]. In another study on PICU patients, it was reported that malnutrition was associated with increased risk of acquired infections and length of intensive care unit stay [11]. In this study, BMI was not associated with prolonged duration of MV. F. de Souza Menezes et al. have found longer duration of MV use in patients with malnutrition; and patients with cardiac diseases had the highest incidence of BMI status of underweight, followed by those suffering from renal and respiratory illness [10].

In this study, no correlation was found between the diagnosis leading to hospitalization and duration of MV. Differing from other studies, congenital heart disease and AKI were not associated with length of

MV in this study. However, there was a statistically significant relationship between BPD and prolonged MV. The logistic regression analysis showed that BPD prolonged MV by 2.862-fold.

In the last two decades, the use of NIV has achieved a significant breakthrough improvement in the treatment of acute respiratory failure [12]. NIV can reduce the requirement of invasive MV, decrease respiratory workload, and improve oxygenation and gas exchange [13]. NIV failure drastically increases the risk of prolonged MV. This may be influenced by the severity of respiratory failure or delay in the need for MV. Payen et al. have shown that NIV was associated with an increased risk of prolonged MV. In this study, the duration of MV was prolonged in the NIV failure group. However, the logistic regression analysis showed that NIV failure did not statistically increase the duration of MV.

Specific acid–base abnormalities may also be associated with hypochloremia. When negatively charged bicarbonate ion level is higher, negatively charged chloride ion is displaced to the intracellular space. Metabolic alkalosis may lead to alveolar hypoventilation and an increase in arterial pCO₂. In literature, chronic obstructive pulmonary disease has been found to be associated with a decrease in plasma chloride level [14]. Another study showed that metabolic alkalosis has been associated with a longer duration of MV in critically ill children [15]. In this study, serum chloride level and duration of MV were found to have a statistically significant correlation. The ROC curves showed that the chlorine level covered an AUC of 0.716 for cutoff value 99.85 mmol/L and was associated with prolonged duration of MV. In addition, the logistic regression analysis showed that hypochloremia prolonged MV by 3.234-fold.

GGT is a plasma membrane enzyme that is commonly used in clinical practice as a marker for liver function. GGT catalyzes the hydrolysis of extracellular glutathione and is essential for antioxidant defense. Thus, it is suggested that GGT may be a predictor for diseases involving oxidative stress and inflammatory reactions [16–18]. Therefore, GGT may indicate the severity of the disease. This study showed that GGT levels were associated with the duration of MV use.

While the PaO₂/FiO₂ (PF) ratio in arterial blood gas is an invasive measurement used for oxygenation,

the SF ratio has been safely used in recent years as a noninvasive method instead of the PF ratio [19]. The SF ratio has been demonstrated to be well correlated with the PF ratio among patients with mechanical ventilation and hypoxemia [20]. In this study, arterial blood gas was not taken routinely from NIV patients and instead the SF ratio was utilized to determine oxygenation levels. The SF ratio at admission was associated prolonged MV in this study. However, the logistic regression analysis showed that SF ratio at admission did not statistically increase the duration of MV.

This study has some limitations. It is a retrospective and single-center study. The blood gas parameters at admission were not investigated. Fever, nosocomial infections, and other complications were not evaluated. The long-term outcomes were not followed-up. The positive side of this study is that there are only a few published studies on early predictors of prolonged MV in children.

Conclusion

Increased mortality in critically ill children has been associated with numerous factors, including prolonged MV. In this study, RBC transfusion was significantly higher in patients of the MV group, and it has been associated with prolonged of MV in critically ill children. In addition, serum chloride level, neuromuscular blocker drug use, and duration of MV were found to have statistically significant correlation.

Hypochloremia, need for RBC transfusion, and neuromuscular blocker drug use may be early predictors of prolonged MV in critically ill children. Further studies on factors that affect the duration of mechanical ventilation in children are warranted.

Ethics committee approval

Ethics committee approval was obtained from the Local Ethics Committee (Health Sciences University, Okmeydani Training and Research Hospital, Ethics Committee, No: 2018-907, March 06, 2018).

References

1. Meduri GU. Noninvasive ventilation. In: Marini J, Slutsky A (eds.). *Physiological basis of ventilatory support: A series on lung biology in health and disease*. Marcel Dekker Inc. New York. 1998;921-999.

2. Fontela PS, Piva JP, Garcia PC, Bered PL, Zilles K. Risk factors for extubation failure in mechanically ventilated pediatric patients. *Pediatr Crit Care Med*. 2005;6:166-170.
3. Farias JA, Monteverde E. We need to predict extubation failure. *J Pediatr (Rio J)*. 2006;2:322-324.
4. Newth CJ, Venkataraman S, Willson DF, Meert KL, Harrison R, Dean JM, et al. Weaning and extubation readiness in pediatric patients. *Pediatr Crit Care Med*. 2009;10:1-11.
5. Baisch SD, Wheeler WB, Kurachek SC, Cornfield DN. Extubation failure in pediatric intensive care incidence and outcomes. *Pediatr Crit Care Med*. 2005;6:312-318.
6. Zubrow ME, Thomas NJ, Friedman DF, Yehya N. RBC transfusions are associated with prolonged mechanical ventilation in pediatric acute respiratory distress syndrome. *Pediatr Crit Care Med*. 2018;19(2):88-96.
7. Zilberberg MD, Carter C, Lefebvre P. Red blood cell transfusions and the risk of acute respiratory distress syndrome among the critically ill: A cohort study. *Crit Care*. 2007;11(3):R63:1-9.
8. Silliman CC, Boshkov LK, Mehdizadehkashi Z. Transfusion related acute lung injury: Epidemiology and a prospective analysis of etiologic factors. *Blood*. 2003;101:454-462.
9. Numa A, McAweeney J, Williams G, Awad J, Ravindranathan H. Extremes of weight centile are associated with increased risk of mortality in pediatric intensive care. *Crit Care*. 2011;15(2):R106:1-6.
10. de Souza Menezes F, Leite HP, Koch Nogueira PC. Malnutrition as an independent predictor of clinical outcome in critically ill children. *Nutrition*. 2012;28(3):267-270.
11. Bagri NK, Jose B, Shah SK, Bhutia TD, Kabra SK, Lodha R. Impact of malnutrition on the outcome of critically ill children. *Indian J Pediatr*. 2015;82(7):601-5.
12. Rocker GM, Mackenzie MG, Williams B, Logan PM. Noninvasive positive pressure ventilation: successful outcome in patients with acute lung injury/ARDS. *Chest*. 1999;115(1):173-177.
13. Demaret P, Mulder A, Loeckx I, Trippaerts M, Lebrun F. Non-invasive ventilation is useful in paediatric intensive care units if children are appropriately selected and carefully monitored. *Acta Paediatr*. 2015;104(9):861-871.
14. Alfaro V, Torras R, Ibanez J, Palacios L. A physical-chemical analysis of the acid-base response to chronic obstructive pulmonary disease. *Can J Physiol Pharmacol*. 1996;74(11):1229-35.
15. Bar A, Cies J, Stapleton K. Acetazolamide therapy for metabolic alkalosis in critically ill pediatric patients. *Pediatr Crit Care Med*. 2015;16 2: e34-40.
16. Ikeda Y, Fujii J, Taniguchi N, Meister A. Expression of an active glycosylated human gamma-glutamyl transpeptidase mutant that lacks a membrane anchor domain. *Proc Natl Acad Sci*. 1995;92:126-130.
17. Rahman I, MacNee W. Oxidative stress and regulation of glutathione in lung inflammation. *Eur Respir J*. 2000;16:534-554.
18. Moreno-Villares JM, Gomis Munoz P, Galiano Segovia MJ, Valero Zanuy MA, Serrano Garrote O, Leon Sanz M. Liver complications associated with short-term parenteral nutrition in children. *An Esp Pediatr*. 1999;51:22-26.

19. Lobete C, Medina A, Rey C, Mayordomo-Colunga J, Concha A, Menéndez S. Correlation of oxygen saturation as measured by pulse oximetry/fraction of inspired oxygen ratio with Pao₂/fraction of inspired oxygen ratio in a heterogeneous sample of critically ill children. *J Crit Care*. 2013;28(4):538.e1-7.
20. Brown SM, Duggal A, Hou PC. Nonlinear imputation of PaO₂/FIO₂ from SpO₂/FIO₂ among mechanically ventilated patients in the ICU: A prospective, observational study. *Crit Care Med*. 2017;45(8):1317-1324.