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Original Paper

Influenza Virus Associated Pediatric Acute Respiratory Distress Syndrome: Clinical Characteristics and Outcomes

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ABSTRACT

Background and Objective: The aim of this multicenter retrospective study was to determine the clinical characteristics, treatment approaches and the course of pediatric acute respiratory distress syndrome (PARDS) which developed associated with the influenza virus in the 2019–20 season.
Methods: Patients included 1 month to 18 years who were diagnosed with PARDS associated with the influenza virus in the 2019–20 season.

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Results: Sixty-seven patients were included in the study. The mean age of the patients was 64.16 ± 6.53 months, with 60% of the group <5 years. Influenza A was determined in 54 (80.5%) patients and Influenza B in 13 (19.5%). The majority of patients (73.1%) had a comorbidity. Fifty-eight (86.6%) patients were applied with invasive mechanical ventilation, Pediatric Acute Lung Injury Consensus Conference classification was mild in 5 (8.6%), moderate in 22 (37.9%) and severe in 31 (52.5%) patients. Ventilation was applied in the prone position to 40.3% of the patients, and in nonconventional modes to 24.1%. A total of 22 (33%) patients died, of which 4 had been previously healthy. Of the surviving 45 patients, 38 were discharged without support and 7 patients with a new morbidity.

Conclusion: Both Influenza A and Influenza B cause severe PARDS with similar characteristics and at high rates. Influenza-related PARDS cause 33% mortality and 15.5% morbidity among the study group. Healthy children, especially those aged younger than 5 years, are also at risk.

KEYWORDS: influenza, acute respiratory distress syndrome, pediatric, mechanical ventilation, mortality, morbidity

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a form of severe hypoxemic respiratory failure characterized by impaired pulmonary gas exchange due to inflammatory injury to the alveolar-capillary barrier. Pediatric ARDS (PARDS) continues to be important because of continuing high mortality and morbidity rates despite the developments in pediatric intensive care units (PICUs) and mechanical ventilation (MV) applications. The recent international Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE) study that investigated the frequency and epidemiology of PARDS according to the Pediatric Acute Lung Injury Consensus Conference (PALICC) definition, PARDS was determined in 3% of all PICU admissions and in 6% of all patients followed up with MV. Total mortality was reported as 17%, and 33% of these groups with severe PARDS group, and it was reported that the mortality rate may be 3-fold higher in under-developed and developing countries [1]. Studies conducted both during and after the 2009 H1N1 pandemic have shown that influenza virus pneumonia is a significant cause of PARDS [2, 3]. Although there are studies in the literature that have investigated the prognosis of PARDS associated with influenza virus in critical, to the best of our knowledge, there is no study that has researched the characteristics of influenza-related PARDS.

The aim of this study was to investigate the clinical characteristics, treatment approaches applied and the disease course of PARDS associated with the influenza virus (Influenza A and B).

MATERIALS AND METHODS

This retrospective study was conducted in 15 tertiary level PICUs (12 university hospitals, 3 training and research hospitals) in Turkey between 1 October 2019 and 31 March 2020. Each unit had at least one pediatric intensive care specialist and an on-call doctor. The mean number of intensive care beds in each unit was 12.4 (range, 6–20). The study included all pediatric patients admitted to the PICUs aged 1 month to 18 years who were diagnosed influenza-related PARDS according to the PALICC criteria in the 2019–20 season [4]. The patients who were receiving palliative care because of hematologic and oncologic disease were excluded from the study. The primary outcome was status at hospital discharge. This outcome was trichotomized to discharged without any support, discharged with respiratory support (tracheostomy, home ventilation or permanent oxygen) and death.

Standardized study form developed together by all participating pediatric critical care centers was completed for each patient by the pediatric intensive care specialist attending the patient for each center. On a form a record was made of demographic, laboratory, radiological and microbiological data, PARDS classification according to PALICC, the presence of comorbidities, the Pediatric Risk of Mortality III (PRISM III) and Pediatric Logistic Organ Dysfunction (PELOD-2) scores, the vaso-inotropic score (VIS) in vasopressor areas, treatments applied, MV methods, duration of MV, length of stay in PICU and hospital, MV-related complications, PARDS-related morbidity and mortality.

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PARDS-related morbidity was defined as discharge with respiratory support.

The influenza virus was identified on admission using the real-time polymerase chain reaction test (RT-PCR) or the rapid antigen detection test (RADT) from tracheobronchial samples taken from intubated patients and nasopharyngeal samples taken from those not intubated. When RT-PCR was performed, the sample was also tested for other respiratory tract virus pathogens. As arterial blood gas values were not available for all the patients, the PARDS diagnosis was made according to the SpO_2/FiO_2 ratio (S/F < 264) for those applied with noninvasive positive pressure ventilation (NIPPV) and the oxygenation saturation index (OSI) for those applied with invasive MV. Approval for the study was granted by the Clinical Research Ethics Committee of Ondokuz Mayis University.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS vn. 20.0 for Windows software. Descriptive statistics were stated as number (n) and percentage (%) for categorical variables, and as mean ± standard deviation (SD), or median, interquartile range (IQR) values for continuous variables. In the comparisons between groups, the Fisher exact test was used for categorical data and the Mann–Whitney U-test for continuous data. The data of all the centers were collected and analyzed in total. A value of $p < 0.05$ was accepted as the level of statistical alpha significance. Multivariate logistic regression models were performed to calculate the odds ratio (OR) with a 95% confidence interval (CI) to assess the association between risk factors and mortality. The two-sided significance level was set at 0.05.

RESULTS

A total of 220 patients with PARDS were admitted to the PICUs in the 2019–20 season, of which 152 (69%) were <5 years of age, and 67 (30.4%) were due to confirmed influenza viruses. Based on the initial radiological findings, diffuse ground-glass appearance was present in 45 patients, lobar-lobular involvement in 23 patients, paracardiac infiltration 19, air leak syndromes in 9 patients and pleural effusion in 4 patients. The patients comprised 59.7% males and 40.3% females with a mean age of 64.16 ± 6.53 months. Of the total cases, 38.8% were <3 years and 59.7% were <5 years of age (Fig. 1). The influenza virus was determined with RT-PCR in 58 patients and with RADT in 9. Of the 58 patients where the influenza subtype could be determined with RT-PCR, Influenza A (all H1N1) was determined in 48 cases and Influenza B in 10. Of those applied with RADT, Influenza A subtypes could not be determined, Influenza A was determined in six patients and Influenza B in three patients. In total, Influenza A was determined in 54 (80.5%) patients and Influenza B in 13 (19.5%) patients. Viral coinfections were determined in 11 (18.9%) of the 58 patients tested with RT-PCR, and these were respiratory syncytial virus in 3, adenovirus in 2, coronavirus in 2, bocavirus in 2, para-influenza virus in 1 and rhinovirus in 1. The frequency of viral coinfection was 14.8% in Influenza A and 23% in Influenza B. Comorbidities were present in 49 (73.1%) patients, and of these, chronic neurological disease was present in 65%. The comorbidity frequency was very high in the Influenza B group at 92.3% compared to 68.5% in the Influenza A group, but the difference between the groups was not statistically significant ($p = 0.160$). The median PELOD-2 and PRISM III scores were 9 (IQR: 3–13) and 15 (IQR: 8–23), respectively.

In 23 (34.3%) patients, NIPPV was applied first, and as this was not successful in 14 (61%), these patients were intubated and transferred to invasive MV. Of the 58 patients applied with invasive MV, PALICC classification was mild in 5 (8.6%), moderate in 22 (37.9%) and severe in 31 (52.5%) patients. The median OSI was 13.3 (IQR: 47–18.66). The median duration of MV was 9.5 days (IQR: 5–19 days), median length of stay in PICU was 15 days (IQR: 8–22 days) and median length of stay in hospital was 20 days (IQR: 12–33 days). All the patients applied with invasive MV were first applied with lung-protective MV with conventional MV modes. The median maximum positive end-expiratory pressure (PEEP) level was 10.5 cm H_2O (IQR: 8.75–13). The mean follow-up time of patients on conventional modes was 9 days (4.75–17.25 days). Due to worsening of hypoxemia in 14 (24.1%) patients, they

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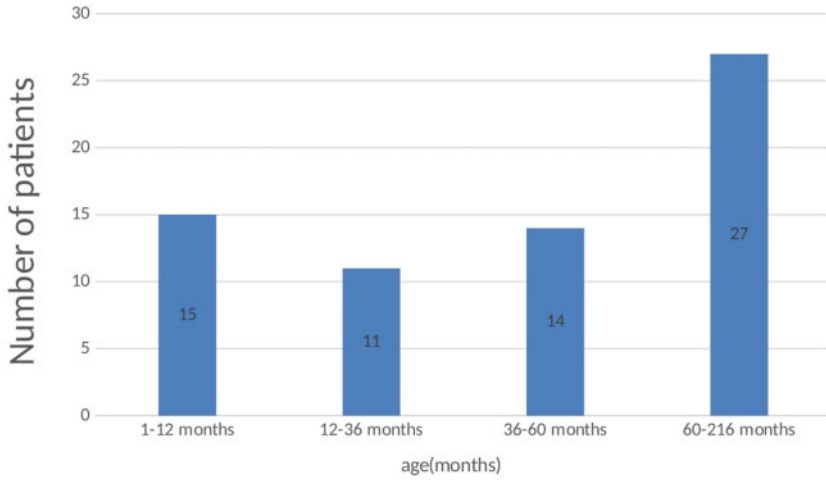

Fig. 1. Age distribution of the children with influenza virus associated acute respiratory distress syndrome.

were transferred to nonconventional modes of high-frequency oscillatory ventilation in 11 patients and airway pressure release ventilation in 3 patients. Ventilation was administered in the prone position in 27 (40.3%) patients. In 18 (31%) of the 58 patients with invasive MV, MV-related complications were observed of air leakage in 14 patients, ventilator-related pneumonia in 2, pulmonary hemorrhage in 1 and subglottic stenosis in 1. Bloodstream infection was detected in 17 patients. Ancillary treatments were administered of inhaled nitric oxide to 6% of cases, corticosteroids to 40.3% and surfactants to 13.4%. Sedation and analgesia were required for 63 (94%) patients and neuromuscular blockade for 33 (49.3%) patients. There was a need for vasopressors in 38 (56.7%) patients and the median VIS of these patients was 27.5 (IQR: 14.5–86.25). Renal replacement treatment was administered to 13 (19.4%) patients. Extracorporeal membrane oxygenation was not required by any patient.

In 24 of 36 patients who could be extubated following invasive MV, post-extubation NIPPV was performed (13 with high-flow nasal cannula, 11 with NIPPV), as prophylactic to 12 patients and as rescue to 12. Mortality developed in 22 (32.8%) patients, 18 (81.8%) of whom had an underlying chronic disease and 4 were previously healthy. Of the 9 patients applied with NIPPV, none died, the mortality rate of the PALICC severe group ($n = 31$) was higher than that of the PALICC mild and moderate ($n = 27$) but the difference was not statistically significant (42% vs. 33%, $p = 0.501$). The cause of death of 14 (64%) of the exitus cases was a worsening of hypoxemia associated with ARDS, and other reasons in 8. Of the 45 surviving patients, 38 were discharged without any support, while 4 patients required tracheostomy and 3 required permanent oxygen support. The demographic, clinical and laboratory data, and outcomes of all the patients are presented in Table 1.

The patients were separated into two groups as PARDS associated with Influenza A and Influenza B. Influenza B group has significantly higher serum aspartate aminotransferase (AST) level at the time of presentation (230.5 vs. 82.5, $p = 0.012$). No significant difference was determined between the groups with respect to other demographic, clinical and laboratory data, and outcomes (Table 1).

Broad-spectrum antibiotic treatment was initially started for all patients and oseltamivir was administered to 65 patients (36 empirical, 29 after testing). One patient died before the test results were obtained and one patient recovered after the test so oseltamivir was not started. No statistically significant difference was determined in MV duration (11.5 vs. 8.5 days), the need for nonconventional mode (25% vs. 25%) or mortality (30.6% vs. 43.5%) according to whether the oseltamivir treatment was started empirically or as a result of the test.

The patients were separated into two groups as survivors and nonsurvivors, and these groups were

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Table 1. Demographics, comorbidities and clinical data of 67 influenza virus-related PARDS patients and comparison of characteristics and outcomes between patients with influenza virus type A and B

	All patients ($n = 67$)	Influenza type A ($n = 54$)	Influenza type B ($n = 13$)	*p*-Value
Age (month), mean ± SD	64.16 ± 6.53	59.6 ± 7.28	83.2 ± 14.14	0.085
Gender (% M)	59.7	57.4	69.2	0.435
Weight (kg), mean ± SD	20 ± 1.92	20.02 ± 2.36	19.92 ± 1.78	0.155
Comorbidities, *n* (%)	49 (73.1)	37 (68.5)	12 (92.3)	0.160
Epilepsy, *n*	18	14	4	
Cerebral palsy, *n*	8	6	2	
Neuromuscular disease, *n*	6	5	1	
Cardiac disease, *n*	3	3	0	
Chronic lung disease, *n*	3	3	0	
Malnutrition, *n*	3	2	1	
Renal disease, *n*	2	2	0	
Others, *n*	6	2	4	
PELOD-2, median (IQR)	9 (3–13)	8.5 (3–13.25)	12 (4.5–13.5)	0.352
PRISM III, median (IQR)	15 (8–23)	14.5 (8–23)	16 (12–22)	0.313
Severity at PARDS diagnosis, *n*				
Mild	5	5	0	
Moderate	22	15	7	
Severe	31	26	5	
Laboratory findings, median (IQR)				
Platelet count	164 (96–276)	167.5 (99.75–282)	116 (79.5–235)	0.579
White blood cell count	8.43 (4.52–11.46)	8.83 (4.44–11.7)	8.42 (4.06–11)	0.692
CRP (mg/dl)	31 (12.2–71)	28 (12.8–70.25)	46 (11.5–95.5)	0.781
AST (U/l)	99.5 (51–191)	82.5 (48–163)	230.5 (99– 2078)	0.012
INR	1.2 (1.1–1.35)	1.19 (1.06–1.31)	1.28 (1.15–1.79)	0.053
NIPPV, *n*	23	21	2	
CMV, *n*	58	46	12	
NCMV, *n* (%)	14 (24.1)	11 (23.9)	3 (25)	0.603
Prone position, *n* (%)	27 (40.3)	22 (40.7)	5 (38.5)	1
Ancillary treatments, *n* (%)				
Inhaled nitric oxide	4 (6)	3 (5.6)	1 (7.7)	1
Surfactant	9 (13.4)	7 (13)	2 (15.4)	1
Corticosteroid therapy	27 (40.3)	23 (42.6)	4 (30.8)	0.642
Sedation and analgesia, *n* (%)	63 (94)	50 (92.6)	13 (100)	0.579
Neuromuscular blockade, *n* (%)	33 (49.3)	28 (51.9)	5 (38.5)	0.577
RRT, *n* (%)	13 (19.4)	10 (18.5)	3 (23.1)	0.706
Inotropes/vasopressors, *n* (%)	38 (56.7)	29 (53.7)	9 (69.2)	0.310
Duration of MV (days), median (IQR)	9.5 (5–19)	9 (5–19)	12.5 (7.25–19.5)	0.436
PICU length of stay (days), median (IQR)	15 (8–22)	13.5 (7–21.25)	15 (13–22.5)	0.337
Length of stay in hospital (days) median (IQR)	20 (12–33)	20 (11–32.5)	23 (13–39)	0.451
Mortality, *n* (%)	22 (32.8)	17 (%31.5)	5 (%38.5)	0.745
PARDS-related mortality, *n* (%)	14 (63.6)	12 (70.6)	2 (40)	0.309

IQR, interquartile range; PELOD-2, Pediatric Logistic Organ Dysfunction; PRISM III, Pediatric Risk of Mortality III; PARDS, pediatric acute respiratory distress syndrome; CRP, C-reactive protein; AST, aspartate aminotransferase; INR, international normalized ratio; NIPPV, noninvasive positive pressure ventilation; CMV, conventional mechanical ventilation; NCMV, nonconventional mechanical ventilation; RRT, renal replacement therapy.

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Table 2. Demographics, comorbidities and clinical data of survivors and nonsurvivors

	Survivors ($n=45$)	Nonsurvivors ($n=22$)	p-Value
Age (months)	62.11 ± 7.49	68.36 ± 12.92	1
Gender, *M* (%)	26 (57.8)	14 (63.6)	0.792
Comorbidities, *n* (%)	31 (68.9)	18 (81.8)	0.262
Viral coinfections, *n* (%)	9 (20)	2 (9.1)	0.316
PEEP (cmH_2O) median (IQR)	11 (8–13)	10.5 (10–14)	0.178
NCMV, *n* (%)	6 (16.7)	8 (36.4)	0.089
Complication of MV, *n* (%)	9 (20)	9 (40.9)	0.070
Prone positioning, *n* (%)	16 (35.6)	11 (50)	0.258
Ancillary therapies, *n* (%)			
Inhaled nitric oxide	2 (4.4)	2 (9.1)	0.593
Surfactant	5 (11.1)	4 (18.2)	0.461
Corticosteroid therapy	13 (28.9)	14 (63.6)	0.006
VIS, median (IQR)	15 (8–45)	80 (21.25–125)	0.002
PELOD-2, median (IQR)	11 (6–13.5)	13 (10.5–21)	0.000
PRISM III, median (IQR)	12 (7.5–20)	17.5 (8.75–28.25)	0.046

IQR, interquartile range; PEEP, positive end-expiratory pressure; NCMV, nonconventional mechanical ventilation; MV, mechanical ventilation; VIS, vasoactive-inotropic score; PELOD-2, pediatric logistic organ dysfunction; PRISM III, Pediatric Risk of Mortality III.

Table 3. Risk factors for mortality with binary logistic regression analysis

	OR (95% CI)	p
Age	0.985 (0.966–1.005)	0.137
Gender	0.585 (0.099–3.461)	0.554
OSI	0.87 (0.743–1.017)	0.080
PELOD-2	1.261 (1.093–1.456)	**0.002**
PEEP	1.449 (1.01–2.078)	**0.044**
Comorbidities	16.316 (1.203–221.32)	**0.036**
Viral coinfections	0.075 (0.006–0.921)	**0.043**
Corticosteroid therapy	28.289 (3.591–222.861)	**0.002**
Prone position	0.233 (0.024–2.275)	0.210

Wald method was used to include independent risk factors in the multivariate model. Statistically significant values ($p<0.05$) are indicated in bold.
OSI, oxygen saturation index; PEEP, positive end-expiratory pressure; PELOD-2, Pediatric Logistic Organ Dysfunction.

correlated with clinical data, PRISM III and PELOD 2 scores. The VIS, PELOD 2 and PRISM III scores were determined to be significantly higher in the nonsurvivors than the survivors ($p=0.02$, $p=0.00$, $p=0.046$, respectively). Steroid treatment was given to 13 (28.9%) of the survivors and 14 (63.6%) of the nonsurvivors, and the difference was statistically significant ($p=0.006$). Comorbidities, the need for nonconventional MV and the MV-related complication rates were higher in the nonsurvivor group but the difference was not statistically significant. The other parameters compared are shown in Table 2.

Multivariate logistic regression analysis was used to identify independent risk factors for mortality age, gender, OSI, PELOD-2, PEEP, comorbidities, viral coinfections, corticosteroid therapy and prone positioning. The results showed that PELOD 2 score (OR = 1.261; 95% CI, 1.093–1.456; $p=0.002$), PEEP (OR = 1.449; 95% CI, 1.01– 2.078; $p=0.044$), comorbidities (OR = 16.316; 95% CI, 1.203–221.32; $p=0.036$), corticosteroid therapy (OR = 28.289; 95% CI, 3.591–222.861; $p=0.002$) were independent risk factors for PARDS mortality (Table 3).

DISCUSSION

This retrospective study revealed the characteristics of 67 pediatric patients followed up for a diagnosis of ARDS related to Influenza virus in 15 PICUs in Turkey in the 2019–20 season. Approximately one-third of PARDS cases detected during this period were due to influenza virus. Although the influenza

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virus in children may be an ARDS agent at any age, the results of this study demonstrated that it was a cause of ARDS predominantly at an early age (<5 years). Chen, *et al.* [5] reported that age <5 years, chronic pulmonary disease, chronic cardiac disease and immunosuppression were risk factors for severe disease related to childhood influenza infection. In the current study, the majority of the children who developed ARDS (73.1%) had an underlying chronic disease but the most common comorbidity was neurological diseases. It was interesting that there was no significant difference in mortality between those with and without chronic comorbid disease. Roberts, *et al.* [6] investigated 222 patients with PARDS with viral causes and reported that influenza-related ARDS was seen more than other viral causes of ARDS in previously healthy children. In the current study, 4 of the 28 exitus cases were previously healthy, which supports the view that influenza-related ARDS can develop in healthy children and may be fatal.

In the current study, Influenza A caused ARDS 4-fold more than Influenza B. In a study by Shi, *et al.* [7], critical patients associated with influenza virus between 2013 and 2017 were investigated and the Influenza A/B ratio was determined as 4.9/1. This was similar to the current study ratio of Influenza A-related PARDS to Influenza B-related PARDS of 4.1/1. No study could be found in the literature that has compared the characteristics of PARDS related to Influenza A and B. Although clinical characteristics of both Influenza A and Influenza B are similar, Influenza B has more severe effects on children and adolescents [8]. In the current study, Influenza A and B-related PARDS showed similar characteristics. At the time of presentation, only the AST values were higher in the Influenza B patients. This can be thought to be due to the fact that Influenza B causes more myositis than Influenza A [9].

Of the 58 patients with influenza-related PARDS where the respiratory tract virus could be detected with RT-PCR, viral coinfection was determined in approximately one-fifth of the patients (18.9%). This rate was reported as 25% in a study by Roberts, *et al.*, and as 11.79% in another study of children with critical influenza-related disease followed up in PICU [6, 7]. The presence of viral coinfection was not determined to have significantly affected mortality in the current study. In the study by Roberts, *et al.* [6], mortality was higher in those with coinfection but it was reported that the majority of the exitus cases (85%) in this group were immunosuppressed.

NIPPV is recommended in selected patients in PALICC PARDS [10]. The NIPPV rate in influenza-related ARDS patients in the current study was 34% and the success rate in those applied was 39%. These rates were 22.6% and 50% in the PARDIE study and 16% and 14% in the study by Farias, *et al.* [1, 11]. Shi, *et al.* [7] reported the NIPPV rate as 6.5%. The NIPPV rate in the current study was higher than in these studies but the success rate was lower than reported in the PARDIE study.

In the majority of the current study patients who could be extubated (66.7%), post-extubation prophylactic or rescue NIPPV was applied. In patients who required invasive MV, the median MV duration was 9.5 days, which was shorter than the 17-day MV period reported by Margarita, *et al.* in a study of adults with influenza-related ARDS, and the 11.5 days in the Farias, *et al.* [11, 12] study. Although there were no data of NIPPV use after extubation in those studies, it was thought that the higher rate of NIPPV use after extubation could have contributed to the shorter MV duration in the current study. These results support the use of NIPPV in appropriate patients with influenza-related PARDS.

The use of oseltamivir is standard in severe cases of influenza. With the exception of 2 patients, oseltamivir treatment was started in all the other current study cases. Farias, *et al.* [11] reported that starting oseltamivir in the first 24 h reduced mortality. In a retrospective evaluation of 888 patients in PICU because of Influenza A (H1N1), Randolf, *et al.* [13] reported that oseltamivir was administered to 88% of cases, but no contribution to survival was seen. In the current study, no difference was seen in prognosis between those who started oseltamivir prophylactically and those who started after test results. All the patients who required invasive MV were ventilated with pulmonary-protective MV as recommended in PALICC. Despite the pulmonary-protective MV, because of a worsening of hypoxemia, it was applied in the prone position to 40.3%, and transfer to

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nonconventional MV mode was made in 24.1% of patients. In addition, corticosteroids, surfactants and inhaled NO were used as adjuvant therapies. However, the high mortality rate despite all these treatment methods indicates the need for more effective treatment methods in influenza-related PARDS.

The majority of studies in literature related to PARDS have focused on mortality and there are limited data on ARDS-related morbidity. Keim, *et al.* [14] investigated the frequency of new morbidities related to PARDS using the Functional Status Score and reported the frequency as 23%. In the current study, PARDS-related morbidity was determined in 7 (15.5%) patients who required tracheostomy or continuous oxygen support.

The mortality rate in the current study in both the severe ARDS group and in all the patients was higher than that of the international PARDIE study (42% vs. 33%; 32.8% vs. 17.2%) (1). Severe ARDS according to the PALICC criteria developed in 53.4% of the current study patients, and this rate was 32% in the PARDIE study. The results of the current study indicate that influenza-related PARDS was more severe and had a higher mortality rate than all-cause PARDS [1]. The mortality rate of the patients in this series (32.8%) was determined to be higher than that of children in the 2009 H1N1 pandemic (30.1%) and of influenza-related cases who became critical (16.9%) [7, 15]. In both studies, it was emphasized that the highest mortality rates within influenza-related critical patients were in children who developed ARDS. The mortality rate of influenza-related ARDS in adults has been reported to be 20–33.3%, which is lower than the general ARDS mortality [12, 16].

The PRISM, PELOD-2 and VIS scores of the nonsurvivors in the current study were significantly higher than those of the survivors in univariate analysis. This suggested that these scores could be used in the prognosis of patients with influenza-related PARDS.

We found that on logistic regression analysis higher PEEP, PELOD-2, comorbidities and corticosteroid exposure were independent predictors of death. In a study by Shi, *et al.* [7], the independent risk factors of mortality were oxygen saturation level of <90% at admission and influenza-related encephalopathy, and no relationship was found between death and comorbid conditions, in patients with severe influenza virus infection. Although use of systemic corticosteroids remains controversial, the administration is estimated at 20–60% of PARDS patients [10]. In a prospective single-center PARDS study demonstrated that corticosteroid exposure for >24 h was associated with increased mortality [17]. Similarly in the current study, 40.3% of patients received systemic corticosteroids and corticosteroid exposure was associated with increased mortality in both univariate and multivariate analysis. However, a cause and effect relationship between corticosteroid administration and mortality cannot be definitively established, given the retrospective study design and smaller sample size of the present study.

Limitations and strength of study

This is the first study to evaluate the characteristics of influenza-related PARDS from tertiary PICUs. However, there are some important limitations. Firstly, this was a retrospective study, and 67 patients with influenza-related PARDS were analyzed. Although more patients were needed to increase the power of this study. Secondly, it is a multicenter study with a variety of ventilation strategies, variable accessibility of adjunctive therapies. In addition, the lack of sufficient data on the dose, duration, timing and rationale of corticosteroid administration, and vaccination status of patients.

CONCLUSION

The results of this study showed that despite oseltamivir, pulmonary-protective MV, nonconventional MV and prone position application when necessary, and ancillary treatments, influenza-related PARDS has high mortality and significant morbidity. Healthy children, especially those aged <5 years, are also at risk of PARDS associated with influenza. The ratio of virus subtypes A/B is approximately 4/1, and PARDS associated with Influenza B shows similar characteristics to PARDS associated with Influenza A. The success rate of 39% in NIPPV recipients suggests that it can be used in selected patients. Additional studies are needed to further the understanding of PARDS in patients with influenza.

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