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Outcome Comparison Between Pulmonary and Extrapulmonary Acute Respiratory Distress Syndrome in Pediatric Intensive Care Unit

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Abstract: Acute respiratory distress syndrome (ARDS) is a lung disease characterized by severe diffuse inflammation and hypoxemia. The cause of ARDS can be pulmonary or extrapulmonary originated. The outcome of pulmonary and extrapulmonary pediatric ARDS are poorly described. The objective of this study was to determine the outcome differences between pulmonary and extrapulmonary pediatric ARDS. A retrospective study was carried out in 60 patients who admitted to the Pediatric Intensive Care Unit (PICU), Sanglah Hospital, between January 2018 until December 2019. All children aged 0-18 years old diagnosed with ARDS according to Pediatric Acute Lung Injury Consensus Conference (PALICC) criteria were included in this study. Length of ventilation, ventilator-free days, PICU length of stay, and PICU mortality as the outcome of this study were obtained from medical records. Statistical analysis was done using Chi-square and Mann-Whitney test. Most of the patients were supported by invasive ventilation with the severity of ARDS was mild to moderate. The underlying disease of pulmonary ARDS (ARDSp) was pneumonia (100%), whereas in extrapulmonary ARDS (ARDSexp) was sepsis (100%). Analysis of outcome showed significant difference in mortality (33.3% vs 73.3%, p=0.002). The mortality was higher among those in the moderate severity of oxygenation index (64.5%, p=0.001). No significant difference was found in length of ventilation and PICU length of stay. The ventilator-free days in ARDSp was higher (22 days vs 0 days, p=0.000) compared with the ARDSexp. This study concluded that patients with extrapulmonary ARDS had poorer outcomes (higher mortality and less ventilator-free day) compared with pulmonary ARDS. The severity of ARDS based on the oxygenation index measurement can be used to discriminate mortality.

Keywords: Pediatric, Pulmonary and Extrapulmonary ARDS, Outcome

1. Introduction

Acute respiratory distress syndrome (ARDS) is a lung disease characterized by severe diffuse inflammation and hypoxemia. ARDS is a heterogeneous syndrome with a complex pathology and mechanism of disease which results in important cause of Pediatric Intensive Care Unit (PICU) admission with significant contribution to morbidity and mortality in children [1-3]. The acute respiratory distress syndrome is characterized by acute onset of fast breathing, breathlessness, hypoxemia, and chest skiagram may show bilateral infiltrates [4]. The Pediatric Acute Lung Injury Consensus Conference (PALICC) was convened to propose specific definitions for pediatric ARDS. The main differences in the PALICC definition are the use of oxygenation index (OI) instead of PaO2/FiO2, the ability to diagnose pediatric ARDS in the absence of arterial blood gas analysis by using non-invasive measures of hypoxemia based on SpO2 (oxygen saturation index (OSI)), and less restrictive radiographic criteria [5]. Pediatric ARDS can affect all pediatric age groups, from the neonatal period through adolescence. Evidently, perinatal causes of acute hypoxemia

are excluded. Symptoms of hypoxemia and radiological changes must occur within 7 days of a known clinical insult. The presence of new infiltrates consistent with the lung parenchymal disease is required for the diagnosis, even if unilateral. The PALICC offered specific patient management recommendations for pediatric ARDS [6, 7].

Prevalence of ARDS in children in the United States, Europe, and Australia is 2-12.8 cases/100.000 people per year. It has been estimated that ARDS accounts for 1-4% of all PICU admissions, 8-10% patients requiring mechanical ventilation and estimated mortality of 20-75% despite advances in the management [8-10]. In North America, multicenter study reported that 1-4% of children undergoing mechanical ventilation had ARDS. In PICU Sanglah Hospital, Bali, acute lung injury and ARDS constituted 18% of all cases between 2013-2014 [11]. Many studies have revealed that the mortality rate in children suffering from ARDS ranges between 18-27%. Data from Australian study suggested that child mortality due to ARDS is high (35%). Due to high mortality rates, ARDS remains the ultimate challenge in PICU in terms of management and outcome [12-15].

The pathophysiology of ARDS in children is complex and multifactorial. The cause of ARDS can be pulmonary or extrapulmonary originated. In a comprehensive description of pediatric ARDS, the primary etiologies were pneumonia (35%), aspiration (15%), sepsis (13%), near-drowning (9%), and concomitant cardiac disease (7%) [7, 16]. The pulmonary and extrapulmonary ARDS have different pathophysiology, epidemiology, and radiologic profiles. Pulmonary ARDS results from a direct infective or inflammatory insult to the lung parenchyma leading to disruption of the alveolar epithelium, alterations of the type I and II cells and neutrophils, and filling of the intra-alveolar space with fibrinous exudate and collagen with minimal interstitial edema. Extrapulmonary ARDS results from a systemic insult leading to widespread circulation of inflammatory mediators, pulmonary vascular endothelial damage, increased vascular permeability, and interstitial edema [17-19].

Pulmonary and extrapulmonary pediatric ARDS are poorly described in the literature. A small single-center study reported no difference in mortality in the two subgroups of pediatric ARDS [20, 21]. Conversely, a multicenter analysis in ten multidisciplinary PICUs in Asia showed that patients with extrapulmonary pediatric ARDS were sicker and had poorer clinical outcomes [22]. In the current study, we sought to determine the outcome differences between pulmonary and extrapulmonary pediatric ARDS in PICU Sanglah Hospital.

2. Methods

A retrospective study was carried out in patients with diagnosed acute respiratory distress syndrome between January 2018 until December 2019 in the PICU, Sanglah Hospital. We compared the outcome between pulmonary and extrapulmonary ARDS. Cases and medical record number were obtained from a registry of patient in PICU. Medical

records were reviewed and the following data include the length of ventilation, ventilator-free days, PICU length of stay, and PICU mortality were collected. This study was approved by the Research Ethics Committee and Institutional.

Subjects were consecutively enrolled until complete the required sample size. After measured by the formula for estimating the sample size, the total minimum sample was 60 patients. The inclusion criteria were all children aged 0-18 years old and diagnosed with acute respiratory distress syndrome according to PALICC definition. The exclusion criteria were incompletely medical record, the patient had major congenital anomalies, and perinatal cause of hypoxemia.

The variables used in PALICC criteria were duration of onset of acute illness to ARDS of less than 7 days, origin of pulmonary edema, any new infiltrate on chest x-ray, and oxygenation defect based on $SpO_2:FiO_2$ (SF) ratio or $PaO_2:FiO_2$ (PF) ratio if on non-invasive mechanical ventilation and oxygenation index (OI) or oxygen saturation index (OSI) if on invasive mechanical ventilation. Length of ventilation defines as the total amount of time spent by the patient using mechanical ventilation. Ventilator-free days define number of days without mechanical ventilation in the first 28 days. Patients requiring ventilation for greater than or equal to 28 days and those who died within 28 days of PICU admission were assigned a ventilator-free day of zero. PICU length of stay defines as the total amount of time spent by the patient from initial diagnosis of acute respiratory distress syndrome until being transferred to a ward. PICU mortality defines as the number of deaths of patients with acute respiratory distress syndrome admitted to the Pediatric Intensive Care Unit.

Collected data were analyzed using SPSS for Windows. Analysis to compare the PICU mortality of pulmonary and extrapulmonary ARDS was using Chi-square test. Length of ventilation, ventilator-free days, and PICU length of stay were analyzed using the Mann-Whitney test. P-values of less than 0.05 was considered statistically significant for data analysis.

3. Result

There were 93 children with ARDS admitted in PICU, Sanglah Hospital, from January 2018 until December 2019. We excluded 33 cases which had major congenital anomalies, perinatal cause of hypoxemia, and incomplete medical record. Sixty cases were retained for analysis, which is 30 subjects in each group.

The characteristics of subjects are described in Table 1. The median age of subjects was 2 months for the ARDSp group and 6 months for the ARDSexp group. The median of the interval between onset of illness and symptoms of hypoxemia was 3 days in both groups. The median oxygenation index (OI) in the ARDSexp group was higher compared with the ARDSp group (6.2 vs 4.7). The ARDSexp group received more blood transfusions (73.3%) and inotropes (93.3%) compared with the ARDSp group. The underlying disease of ARDSp was

pneumonia (100%), whereas in ARDSexp was sepsis (100%). Most of the patients were supported by invasive ventilation with the severity of ARDS was mild to moderate as described in Table 2.

Table 1. Sample characteristics.

Variable	ARDSp (n=30)	ARDSexp (n=30)
Age, median (range), months	2 (1-180)	6 (1-144)
Sex		
Male, n (%)	20 (66.7)	15 (50)
Female, n (%)	10 (33.3)	15 (50)
Interval between onset of illness and symptoms of hypoxemia, median (range), days	3 (1-7)	3 (1-7)
Oxygenation		
SpO_2/FiO_2 ratio, median (range)	165 (161-242)	240 (161-242)
$PO2/FiO_2$ ratio, mean (SD)	234.2 (40.6)	229.3 (31)
Oxygen index, median (range)	4.7 (4-14.7)	6.2 (4-14.5)
Oxygen saturation index, median (range)	6.2 (5-11.9)	7.3 (5-12.3)
Ventilation		
Invasive, n (%)	25 (83.3)	27 (90)
Non-invasive, n (%)	5 (16.7)	3 (10)
PELOD-2 score, median (range)	3 (0-6)	9 (7-13)
Blood culture positivity, n (%)	0 (0)	1 (3.3)
Nutritional status		
Failure to thrive, n (%)	4 (13.3)	5 (16.7)
Well nourished, n (%)	12 (40)	10 (33.3)
Moderate malnutrition, n (%)	10 (33.3)	11 (36.7)
Severe malnutrition, n (%)	0 (0)	0 (0)
Overweight, n (%)	1 (3.3)	3 (10)
Obesity, n (%)	3 (10)	1 (3.3)
Blood transfussion, n (%)	14 (46.7)	22 (73.3)
Inotropes, n (%)	0 (0)	28 (93.3)
Underlying disease		
Pneumonia, n (%)	30 (100)	0 (0)
Sepsis, n (%)	0 (0)	30 (100)

Table 2. Severity stratification based on oxygenation.

Variable	ARDSp (n=25)	ARDSexp (n=27)
OI category		
Mild, n (%)	14 (56)	14 (51.9)
Moderate, n (%)	11 (44)	13 (48.1)
Severe, n (%)	0 (0)	0 (0)
OSI category		
Mild, n (%)	14 (56)	14 (51.9)
Moderate, n (%)	11 (44)	13 (48.1)
Severe, n (%)	0 (0)	0 (0)

Analysis of outcome showed significant difference in mortality between ARDSp group and ARDSexp group (33.3% vs 73.3%, p=0.002). The ventilator-free days in ARDSp group was higher (22 days vs 0 days, p=0.000) compared with the ARDSexp group. No significant difference was found in length of ventilation and PICU length of stay as shown in Table 3. The mortality was higher among those in moderate severity of oxygenation index (64.5%, p=0.001) as shown in Table 4. No severe case was found in this study.

Table 3. Comparison of outcome between ARDS groups.

Variable	ARDSp (n=30)	ARDSexp (n=30)	p
Mortality (%)	33.3	73.3	0.002
Length of ventilation, median (range), days	6 (1-19)	5 (1-19)	0.583
PICU length of stay, median (range), days	9 (1-20)	5 (1-19)	0.505
Ventilator-free days, median (range), days	22 (0-27)	0 (0-25)	0.000

Table 4. Comparison of mortality based on oxygenation index.

Variable	OI category		p
	Mild n=28	Moderate n=24	
Mortality (%)	35.5	64.5	0.001

4. Discussion

The median age of subjects in our study was 2 months for the ARDSp group and 6 months for the ARDSexp group with the majority of them were male. It is similar to another study showing the incidence of ARDS among patients admitted to the PICU was 2.6% and the majority of subjects were under 1 year old and male [23].

In this study, the underlying disease in ARDSexp group was sepsis (100%), whereas in ARDSp was pneumonia (100%). A study by Khemani in 2018 found pneumonia or lower respiratory tract infection and sepsis were the most common ARDS risk factors. The larger study reported a prevalence of ARDSexp was 40% with the majority due to sepsis (98.8%). This is consistent with a study by Gan in 2018 that the most common extrapulmonary risk factor of ARDS was sepsis (82.9%) [21, 22, 24].

We compared the outcome of ARDSp and ARDSexp. Mortality of patients with ARDSexp was higher as those with ARDSp (73.3% vs 33.3%, p=0.002). A study by Gan in 2018 found similar results in our study. The PICU mortality of children with ARDSexp was twice as high as those with ARDSp (48.8% vs 24.8%) [22]. Examine data from mixed cohorts of ARDS across the world, higher mortality in children with extrapulmonary etiologies was reported, compared with those with pulmonary etiologies (58-80% vs 28-60%) [2, 8, 25]. In a meta-analysis involving 3,283 pediatric ARDS patients, post hoc analysis demonstrated that extrapulmonary etiology had an odds ratio (OR) of mortality of 3.29 [26]. Patients with ARDSexp had higher Pediatric Logistic Organ Dysfunction (PELOD)-2 score (9 vs 3) as those with ARDSp. It describes the severity of organ dysfunction in patients with ARDSexp. A secondary study of a prospective pediatric sedation trial also demonstrated the association between ARDSexp and concurrent multiple organ dysfunction [27].

The pulmonary and extrapulmonary ARDS have different pathophysiology. In ARDSp, the prevalent damage in early stage is likely intra-alveolar, whereas in ARDSexp is interstitial edema with greater inflammatory agents in the bloodstream [17, 21]. In this inflammatory cascade, the release of chemokines by local antigen presenting cells and endothelial cells, leading to migration of activated neutrophils to the lungs and release of cytokines. These mechanisms lead to an increase in lung endothelial permeability and immune activation, which can propagate the cell damage. In a study by Zinter in 2017, there was a significant association between mortality and elevated plasma cytokines in children with ARDS. These cytokines were also associated with ARDS illness severity (including OI), intensive care unit morbidity (including PELOD score), and biochemical evidence of endothelial injury [28-30].

Patients with ARDSexp also had less ventilator free days compared with ARDSp (0 vs 22 days, p=0.000). Ventilator-free days in patients with ARDS who died within 28 days of PICU admission were assigned a ventilator-free day of zero. Mortality of patients with ARDSexp was higher as those with ARDSp. It implies in less ventilator free days of ARDSexp. A study by Gan in 2018 found similar results in our study. Ventilator free days in patient with ARDSexp was lower compared with ARDSp (2 days vs 19 days, p=0.001) [22]. In terms of respiratory mechanics, patients with ARDSexp have reduced chest wall compliance and increased chest wall elastance [31, 32]. The elastance of the chest wall was more than twofold higher in ARDSexp than in ARDSp, indicating a stiffer chest wall. The increase in elastance of the chest wall was related to an increase in the intra-abdominal pressure, which was threefold greater in ARDSexp. The resistance of the chest wall was also elevated in ARDSexp. It is significantly correlated to intra-abdominal pressure, suggesting that intra-abdominal pressure can affect the viscoelastic properties of the thoracoabdominal region [17].

The PALICC definition recommends the use of an oxygenation index to determine hypoxemia severity, rather than the PF ratio as in the Berlin definition. A study by Khemani in 2018 found that severity groups based on an oxygenation index or oxygen saturation index measurements generally outperformed those based on PF or SF ratios to discriminate mortality [24]. In our study, most of the patients were supported by invasive ventilation with the severity of ARDS was mild to moderate and no severe case was found. The median of oxygenation index (OI) in the ARDSexp group was higher compared with the ARDSp group (6.2 vs 4.7). The mortality was significantly higher among those in moderate severity of oxygenation index (64.5%, p=0.001).

There are some limitations of this study. The retrospective data of this study precludes us from making causal associations, introduces bias in case selection, and potential misclassification into ARDSp and ARDSexp groups. A number of these patients had to be excluded to avoid bias due to misclassification. A few patients in certain categories of ARDS could limit generalizability. The consequence of the small sample size was the lack of statistical significance in outcomes between ARDSp and ARDSexp groups.

5. Conclusion

Patients with extrapulmonary pediatric ARDS had poorer outcomes (higher mortality and less ventilator-free days) compared with pulmonary pediatric ARDS. The severity of ARDS based on the oxygenation index measurement can be used to discriminate mortality.

Conflict of Interest

All the authors do not have any possible conflicts of interest.

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