

Potential risk factors of pediatric acute respiratory distress syndrome in sepsis

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Abstract

Background Sepsis in children is characterized by a dysregulated host response to infection and life-threatening organ dysfunction. Pediatric acute respiratory distress syndrome (PARDS) is a severe complication of sepsis. Several known risk factors of PARDS are immunodeficiency, obesity, source of infection, and genetic factors.

Objective To describe the potential risk factors of PARDS in septic children at Haji Adam Malik General Hospital, Medan, North Sumatera.

Methods This descriptive study using eligible medical record data from sepsis patients aged 1 month - 18 years was conducted at Haji Adam Malik General Hospital, Medan, North Sumatera, in 2020-2022. A total sampling method was used for subject selection. Patients' demographic and clinical characteristics, mechanical ventilation modes and parameters, laboratory results, and outcomes were collected from medical records. Patients were classified as having sepsis with PARDS if *Pediatric Acute Lung Injury Consensus Conference* (PALICC) criteria of ARDS was met.

Results Of 112 pediatric sepsis patients, 33.9% developed PARDS. The mortality rate for PARDS was 73.7%. Of the patients with PARDS, 57.9% had immunodeficiency, 60.5% patients had an intrapulmonary infection, 39.5% had an extrapulmonary infection, and 23.7% of patients had a suspected genetic disorder. In addition, 39.5% had good nutritional status, followed by 21.1% with obese.

Conclusion The majority of patients with PARDS have intrapulmonary infection and immunodeficiency. Some of patients with PARDS have suspected genetic disorders and well nourished. [Paediatr Indones. 2024;64:193-201; DOI: 10.14238/pi64.3.2024.193-201].

Keywords: PARDS; pediatric sepsis; risk factors

Sepsis is characterized by a dysregulated host response to infection and life-threatening organ dysfunction. *The 2020 Surviving Sepsis Campaign* (SSC) defined sepsis as severe infection leading to cardiovascular and/or non-cardiovascular organ dysfunction, and septic shock as sepsis with cardiovascular dysfunction.¹ Sepsis is a leading cause of morbidity and mortality in children. In 2017, there were an estimated 20.3 million cases of sepsis, with 2.9 million sepsis-related deaths worldwide in children younger than 5 years, and 4.9 million cases of sepsis with 454,000 sepsis-related deaths worldwide in children and adolescents aged 5-19 years.² *The Southeast Asia Infectious Disease Clinical Research Network* (SEAICRN) study in 13 public hospitals from 3 Southeast Asian countries reported that the prevalence of sepsis was 36.5% and dominated by patients aged 1-5 years (50%).³ A study of 69 pediatric sepsis patients at the pediatric intensive care unit

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(PICU) Haji Adam Malik General Hospital, Medan, North Sumatera, in 2018 reported prevalences of 29% for pediatric sepsis, 4.3% for severe sepsis, and 66.7% for septic shock, with an overall mortality of 62.3%.⁴

Acute respiratory distress syndrome (ARDS) is a common acute inflammatory lung injury associated with sepsis. In ARDS, cytokine-mediated inflammation, endothelial activation, reactive oxygen species (ROS), and disruption of normal coagulation cascades in patients with sepsis can lead to the development of diffuse alveolar damage.⁵ Pediatric acute respiratory distress syndrome refers to ARDS that occurs in children.⁶ The prevalence of PARDS in sepsis is not well understood, as it depends on the definitions of PARDS and sepsis used. *The Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE)* study in 145 PICUs from 27 countries reported that 19% of PARDS patients had sepsis etiologies.⁷ *The Pediatric Acute and Critical Care Medicine Asian Network (PACCMAN)* study in 10 PICUs from 5 Asian countries found that sepsis was one of the risk factors associated with PARDS.⁸ The prevalence of PARDS in sepsis in Indonesia has not been widely studied. A retrospective study conducted in the PICU of Haji Adam Malik General Hospital, Medan, North Sumatera, from 2017-2020 found that sepsis was the most common cause of indirect lung injury-related PARDS.⁹

Several risk factors of ARDS in adults with sepsis have been clearly identified, but there have not been many clinical reviews and studies providing satisfactory details regarding the risk factors of PARDS in sepsis. Several known risk factors of PARDS are immunodeficiency, obesity, source of infection, and genetic factors.^{5,10} The lack of evidence-based data regarding risk factors leads to a lack of vigilance in preventing ARDS in pediatric sepsis. Therefore, we aimed to describe the potential risk factors of PARDS in sepsis at Haji Adam Malik General Hospital, Medan, North Sumatera, in 2020-2022.

Methods

This descriptive study was conducted at Haji Adam Malik General Hospital, Medan, North Sumatera, between August and September 2022. Data were collected from patients' medical records.

All sepsis patients aged 1 month - 18 years who were hospitalized at Haji Adam Malik General Hospital, Medan, North Sumatera in 2020-2022 were included in the study by a total sampling method. Patients with incomplete medical records were excluded. Patients' demographic and clinical characteristics, mechanical ventilation modes and parameters, laboratory results, and outcomes from medical records were collected and analyzed.

Patients were classified as having sepsis with PARDS if the PALICC definition of PARDS was met. The PALICC criteria was as follows: 1) pediatric patients of all age ranges without perinatal-related lung disease, 2) symptoms of hypoxemia with signs of acute respiratory distress and changes in radiographic examination occurring within 7 days of known clinical insult, 3) respiratory failure that could not be fully explained by cardiac failure or fluid overload, 4) discovery of an infiltrated chest imaging corresponding to an image of acute pulmonary parenchymal disease, and 5) the severity of PARDS was determined by the oxygenation index (OI) or oxygen saturation index (OSI) and then classified as mild, moderate, or severe in patients with mechanical ventilation. Oxygenation index was defined as the ratio of the inspired fraction of oxygen (FiO_2) multiplied by the mean airway pressure multiplied by 100, and divided by the partial pressure of oxygen in arterial blood (PaO_2) ($OI = FiO_2 \times \text{mean airway pressure} \times 100 / PaO_2$). Oxygen saturation index is calculated by dividing by the peripheral oxygen saturation (SpO_2) ($OSI = FiO_2 \times \text{mean airway pressure} \times 100 / SpO_2$). Severity assessment with OSI should be used when an OI was not available for patients receiving invasive mechanical ventilation. Mild PARDS was defined as $4 \leq OI < 8$ or $5 \leq OSI < 7.5$; moderate PARDS was defined as $8 \leq OI < 16$ or $7.5 \leq OSI < 12.3$; severe PARDS was defined as $OI \geq 16$ or $OSI \geq 12.3$. In patients receiving non-invasive ventilation, oxygenation criteria were P/F ratio < 300 or S/F ratio < 264 . Oxygen saturation S/F ratio can be used when P/F ratio is not available to diagnose PARDS in patients receiving non-invasive ventilation.⁶ Patients who do not meet this criteria were classified as having sepsis without PARDS.

Potential risk factors of PARDS were recorded, such as immunodeficiency, nutritional status, source of infection, and suspected genetic disorder.

Immunodeficiency was defined as various disease diagnoses such as cancer, autoimmune disorders, burn injury, other chronic diseases, as well as the use of immunosuppression therapy, which resulted in an impaired or weakened immune system. Nutritional status was determined based on anthropometric data of body mass index (BMI) for age using the WHO Growth Charts. Patients were categorized into severely wasted (BMI for age: z score < -3 SD), wasted (BMI for age: -3 SD $\leq z$ score < -2 SD), well-nourished (BMI for age: -2 SD $\leq z$ score $\leq +1$ SD), overweight (BMI for age: ≤ 5 years: $+2$ SD $< z$ score $\leq +3$ SD; $>5-18$ years: $+1$ SD $\leq z$ score $\leq +2$ SD), or obese (BMI for age: ≤ 5 years: z score $> +3$ SD; $>5-18$ years: z score $> +2$ SD).^{11,12} The source of infection was classified as intrapulmonary or extrapulmonary. Suspected genetic disorders were determined based on clinical characteristics, physical abnormalities and malformations, or diagnosis of congenital disease which may be caused by genetic factors and recorded in the medical records.

Categorical variables are presented as frequency and percentage. Continuous variables with normal distributions are presented as mean [standard deviation (SD)], while variables with non-normal distributions are presented as median (range). Data were entered into Microsoft Excel and analyzed using SPSS version 27.0 software. This study was approved by the Health Research Ethics Committee of Universitas Sumatera Utara and the Research and Development Installation of Haji Adam Malik General Hospital.

Results

Of 128 sepsis patients aged 1 month – 18 years who were hospitalized from 1 January 2020 to 30 August 2022, 112 patients fulfilled the inclusion and exclusion criteria. The majority of sepsis patients were boys (57.1%). Sepsis occurred more often in the age group of 12 - <18 years (29.5%) and followed by 5 - <12 years (28.6%). Most patients required mechanical ventilation support. The median length of PICU stay was 10 days. Sixty-four (57.1%) patients died and 48 (42.9%) patients survived. Of those who died, 78.1% used mechanical ventilation and their median length of stay was 7 days. Of those who survived, 37.5% used

mechanical ventilation and their median length of stay was 13 days (Table 1).

Based on PALICC criteria, 33.9% patients were diagnosed with PARDS. Of those with PARDS, the mortality rate 73.7% (Figure 1). Most sepsis patients with PARDS who received invasive mechanical ventilation had mild PARDS. Among 38 sepsis patients with PARDS, 57.9% had an immunodeficiency. Cancer was the most common type of immunodeficiency in sepsis patients with PARDS. The type of cancer includes acute lymphoblastic leukemia, acute myeloblastic leukemia, lymphoma, abdominal tumors, and brain tumors. Bonchopneumonia, pneumonia, and COVID-19 were the pulmonary infections in PARDS patients (60.5%), while 39.5% patients had an extrapulmonary infection. The most common extrapulmonary source of infection was the bloodstream (infection with positive blood culture and possibly due to insertion of an intravascular tube/central line associated blood stream infection/CLABSI). In patients with PARDS, 23.7% patients

Table 1. Characteristics of pediatric sepsis subjects

Characteristics	(N=112)
Gender, n (%)	
Male	64 (57.1)
Female	48 (42.9)
Age, n (%)	
1 months to <1 year	29 (25.9)
1 to <5 years	18 (16.1)
5 to <12 years	32 (28.5)
12 to <18 years	33 (29.5)
Median weight (range), kg	16.5 (1.9-60)
Median height (range), cm	115 (32-175)
Mean BMI (SD), kg/m ²	16.16 (4.03)
Mechanical ventilation, n (%)	
Yes	68 (60.7)
No	44 (39.3)
Median length of stay (range), days	10 (1-85)
Outcomes	
Died, n (%)	64 (57.1)
Mechanical ventilation, n (%)	
Yes	50 (78.1)
No	14 (21.9)
Median length of stay (range), days	7 (1-70)
Survived, n (%)	48 (42.9)
Mechanical ventilation, n (%)	
Yes	18 (37.5)
No	30 (62.5)
Median length of stay (range), days	13 (3-85)

had suspected genetic disorders, with Down syndrome was the most common (Table 2).

More sepsis patients who were severely wasted, overweight, or obese and who developed PARDS received mechanical ventilation than sepsis patients without PARDS with each of these nutritional status categories (Table 3).

Discussion

In this study, sepsis patients were predominantly male, similar to other studies.^{4,13} Cell-mediated immune responses have been shown to be suppressed by male sex hormones. Conversely, female sex hormones have a natural anti-inflammatory effect in sepsis.¹⁴ In our study sepsis occurred more often in the age group of 12 - <18 years, followed by 5 to <12 years. This result was in line with other study that revealed the incidence of sepsis was highest in the age of groups 13-18 years (40.1%) and 5-12 years (26.3%), respectively.¹⁵ However, other studies reported that sepsis occurred more often in infants or those aged 1 month to 1 year.^{16,17} The majority of sepsis patients in the adolescent age group who are hospitalized have chronic disease comorbidities such as respiratory disorders, heart disease, or immunodeficiency. The incidence of chronic disease increases with age, so adolescent sepsis patients with chronic diseases are susceptible to infection and have high mortality.^{15,18,19}

The majority of our patients required mechanical ventilation support. Similar studies showed that mechanical ventilation is a common treatment given to sepsis patients in the PICU for management of the respiratory disorders.^{4,13} The median length of PICU stay for our patients was 10 days. This finding was similar to other studies which reported median PICU length of stay for sepsis patients were 11 days and 8 days.^{20,21} Sixty-four (57.1%) of our patients died. Similar studies reported mortality of sepsis in 62.3% and 57.9% patients.^{4,13} Furthermore, a study reported that sepsis patients who died used mechanical ventilation more frequently and had a shorter length of stay than those who survived.¹³

Based on the PALICC criteria, 33.9% of our pediatric sepsis patients were diagnosed with PARDS. Previous studies reported PARDS incidence in sepsis based on PALICC criteria ranging from 19-26%.⁷⁻⁹ Yuan et al. reported that 45.4% of sepsis patients had PARDS based on PALICC criteria.²² In our study, the mortality rate of sepsis patients with PARDS was 73.7%. Similarly, a study also reported a high mortality rate of 79.2% in children with ARDS caused by sepsis.²³ However, this was very high compared to other studies that reported lower rates ranging from 28.9-30.1%.^{7,24} In sepsis-induced PARDS, widespread infection impacts more distal organs, leading to an increased number of extrapulmonary organ failures and an increased risk of death. Other predictors of death such as an immunocompromised condition,

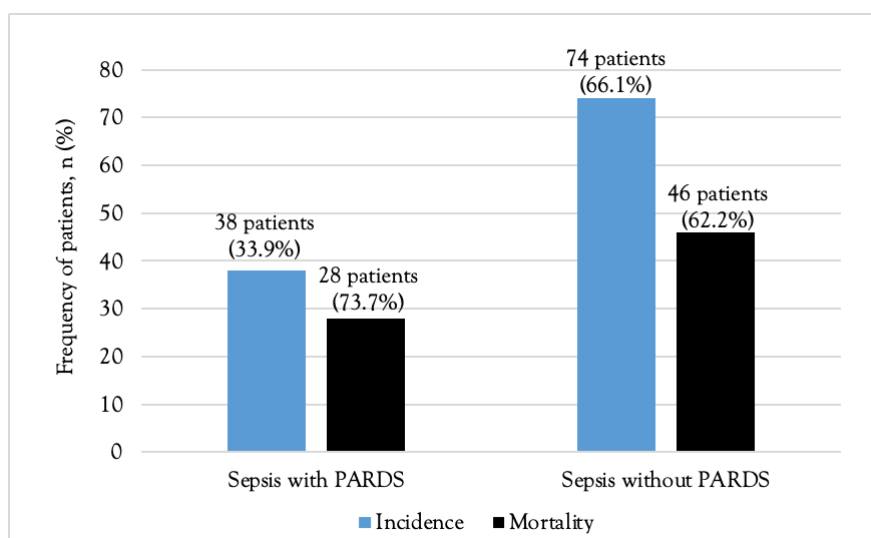


Figure 1. Incidence and mortality of PARDS in sepsis based on PALICC Criteria

Table 2. Mode of ventilation and frequency distribution of risk factors in sepsis with PARDS

Risk factors	Sepsis with PARDS (n=38)	Sepsis without PARDS (n=74)
Mode of ventilation		
Non-invasive mechanical ventilation	8	36
Invasive mechanical ventilation	30	38
Mild PARDS		
Moderate PARDS	4	
Severe PARDS	1	
Immunodeficiency		
Yes	22	36
Cancer	10	20
Autoimmune disease	4	5
Immunosuppressive therapy	3	2
Chronic kidney disease	3	7
Burn injury	2	2
No	16	38
Nutritional status (BMI for age)		
Severely wasted	7	14
Wasted	3	16
Well-nourished	15	36
Overweight	5	5
Obese	8	3
Site of infection		
Intrapulmonary (pulmonary infection)	23	23
Extrapulmonary	15	51
Bloodstream infection	8	27
Central nervous system infection	5	9
Gastrointestinal infection	1	6
Genitourinary infection	1	5
Skin and soft tissue infection	0	4
Suspected genetic disorder		
Yes	9	4
Down syndrome	4	1
Congenital heart disease	2	3
Sturge Weber syndrome	1	0
Spinal muscular atrophy	1	0
CTEV	1	0
No	29	70

Table 3. Frequency distribution of the use of mechanical ventilation based on nutritional status in sepsis with and without PARDS

Variables	Sepsis with PARDS (n=38)	Sepsis without PARDS (n=74)	Total (N=112)
Use of mechanical ventilation in severely wasted, n			
Yes	7	4	11
No	0	10	10
Use of mechanical ventilation in wasted, n			
Yes	3	6	9
No	0	10	10
Use of mechanical ventilation in well-nourished, n			
Yes	15	15	30
No	0	21	21
Use of mechanical ventilation in overweight, n			
Yes	5	4	9
No	0	1	1
Use of mechanical ventilation in obese, n			
Yes	8	1	9
No	0	2	2

degree of hypoxemia, and increased ventilator pressure have also been associated with increased risk of PARDS mortality.¹⁰

The majority of subjects with PARDS were given invasive mechanical ventilation (78.9%), and 65.8% had mild PARDS. A similar study showed that the majority of sepsis patients with PARDS were given invasive mechanical ventilation (90.1%), and 42.4% had mild PARDS.²⁵ Other study also showed that 53.3% had mild PARDS.²²

Of our PARDS patients, 57.9% had immunodeficiencies. Children with preexisting immunodeficiency are at increased risk of developing PARDS and having worse outcomes.²⁶ Children with immunodeficiency are at increased risk for infection, which can lead to both direct and indirect PARDS.^{27,28} We also noted that cancer was the most common type of immunodeficiency in sepsis patients with PARDS. Similarly, a previous study showed that 57.6% of children with cancer and sepsis had PARDS.²⁹ The majority of children with cancer, sepsis, and ARDS progressed with deterioration in ventilation indexes and catastrophic organ dysfunction, making this triad nearly fatal in children requiring mechanical ventilation.³⁰

The majority of our sepsis patients with PARDS had well-nourished status, followed by obese. A study showed that of 43 PARDS patients induced by sepsis, most patients had normal weight (69.7%), followed by obesity (27.9%), and overweight (2.3%).³¹ Obesity can trigger ARDS events through the decrease of functional residual capacity due to excess abdominal fat which can trigger the closure of peripheral dependent airways and decreased lung compliance. These changes can cause ventilation-perfusion mismatch and hypoxemia which can increase the risk of infection and trigger ARDS.³² In addition, obesity is associated with increased levels of circulating neutrophil levels and inflammatory cytokines (TNF- α , IL-1 β , IL-8, and IL-6) as well as dysregulation of adipokine release and response, which can increase acute lung injury and the risk of developing ARDS.^{33,34} The increased use of mechanical ventilation may be related to the possibility that overweight or obese children with sepsis are more likely to develop PARDS.³⁵ Increased BMI category is associated with higher tidal volumes, peak inspiratory pressures (PIP), and positive end-expiratory pressure (PEEP) during mechanical

ventilation and is associated with an increased risk of developing ARDS later in the ICU stay.³³

Our subjects with PARDS had more intrapulmonary infection than extrapulmonary infection. Bloodstream infection was the most common extrapulmonary site of infection. Other studies revealed that the most common site of infection in sepsis patients with PARDS was intrapulmonary infection.^{22,25,36} While the most common extrapulmonary site of infection coming from the bloodstream infection.^{25,36} In sepsis-induced ARDS from pulmonary infection, the underlying infection can cause direct epithelial injury, which disseminates and spreads to multiple lung regions in severe cases.¹⁰ Pulmonary pathogens activate a robust innate immune response in epithelial cells and alveolar macrophages, followed by neutrophil infiltration and monocyte recruitment. The release of pro-inflammatory mediators such as tumor necrosis factor (TNF), interleukin (IL)-1 β , and IL-6, lead to loss of alveolar-capillary barrier integrity, neutrophil recruitment, surfactant dysfunction, and alveolar edema. In sepsis-induced ARDS from extrapulmonary infection, the mechanism of lung injury occurs indirectly. Damage to the alveolar-capillary barrier can be fueled by microvascular endothelial cell alterations and microthrombi formation. Through alteration of the glycocalyx, formation of platelet-leukocyte aggregates, and triggered release of inflammatory mediators, endothelial cell surface injury can facilitate loss of alveolar-capillary barrier function.³⁷

Subjects with suspected genetic disorders had less PARDS than those without suspected genetic disorders. Down syndrome was the most common type of suspected genetic disorder in our PARDS subjects, similar to a study by Bruijn et al., which showed that as many as 12.5% of children with Down syndrome experienced sepsis as a cause of acute lung injury (ALI) or ARDS.³⁸ The mechanism of imbalance in free radical scavengers in the cytoplasm leads to increased oxidative stress, resulting in an increased level of apoptosis and inflammation in the respiratory epithelium, which may contribute to the increased risk of ARDS in children with Down syndrome.³⁹ We did not carry out genetic examinations in our study; our assumptions were based on clinical characteristics, physical abnormalities and malformations, or a diagnosis of congenital disease and recorded in the

medical records.

The limitation of this study was a retrospective study using medical records that was conducted only in one tertiary referral hospital, as such, the data were entirely dependent on the accuracy of existing medical records and the results cannot be generalized to other hospitals in Indonesia. Due to the nature of the study, no statistical analysis comparing the risk factors between sepsis with PARDS group and sepsis without PARDS group.

In conclusion, the majority of sepsis patients were boys, with the highest incidence in the age group of 12 - <18 years. Most sepsis patients received mechanical ventilation. The median length of PICU stay was 10 days. The most common outcome of sepsis was death. Thirty-eight (33.9%) patients developed PARDS based on PALICC criteria were and mortality was 73.7%. Most subjects with PARDS who received invasive mechanical ventilation had mild PARDS. The majority of our PARDS subjects had intrapulmonary infection, immunodeficiency, and were not malnourished. Some of our PARDS patients also had suspected genetic disorders.

Conflict of interest

None declared.

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