

Identifying the Risk Factors for Sepsis in Pediatric Patients with Community-acquired Pneumonia

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Background: Community-acquired pneumonia (CAP), which is classified as pneumonia acquired outside healthcare settings, can progressively develop into sepsis—a leading cause of death in children if not properly managed. The risk factors for CAP-induced sepsis may vary with age due to differences in immune maturity, developmental factors, and the underlying causes of pneumonia. This study aims to identify the risk factors associated with CAP-induced sepsis, focusing on the demographic and clinical characteristics.

Objective: This study aimed to determine the risk factors associated with the occurrence of sepsis in pediatric patients with CAP, with an emphasis on both the demographic and clinical risk factors.

Methods: This cohort study included cases of CAP in children aged 1 month to 17 years, and their disease progression was followed up to determine whether or not they developed sepsis. The univariate analysis was performed using the chi-square and Fische's exact tests, while the multivariate analysis was performed using multiple logistic regression.

Results: Of the 107 pediatric patients with CAP, 90 children met the inclusion criteria. Of them, 20 developed sepsis, while 70 recovered. The data analysis from this study identified two factors that significantly increase the risk of a child with CAP developing sepsis. These factors were temperature (RR 3.5 [95% confidence interval (CI) 1.269~9.652]; $p = 0.007$) and absolute neutrophil count (ANC) (RR 3.5 [95% CI 1.708~7.171]; $p = 0.021$).

Conclusion: Temperature and ANC were found to be significant independent risk factors that may increase the likelihood of sepsis in children with CAP. Although these factors were significant in this study, future research is needed to determine how these risk factors vary by age, and CAP etiology can further refine early sepsis risk identification and improve targeted management strategies.

Key Words: Children, Community-acquired pneumonia, Pediatric, Pneumonia, Risk factors, Sepsis

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INTRODUCTION

Pneumonia is an inflammation affecting the pulmonary parenchyma, which is predominantly caused by microorganisms (viruses/bacteria) and, to a lesser extent, by other factors, such as aspiration and radiation. It is often believed to be commonly accompanied by a viral infection that subsequently complicates with the bacterial infection. The pattern of bacteria causing pneumonia typically varies by the age distribution of the patients. However, in general, the bacteria that have a significant influence in pneumonia include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, Group B *Streptococcus*, and atypical pathogens such as *Chlamydia* and *Mycoplasma*^{1,2}.

Pneumonia is considered a major health issue among children in developing countries and the leading cause of morbidity and mortality in children under five years of age. It is estimated that nearly one-fifth of all cases of child deaths worldwide (approximately two million children under five) die each year due to pneumonia, with the majority of these deaths occurring in Africa and Southeast Asia. Based on the 2001 National Health Survey, respiratory system diseases, predominantly pneumonia, accounted for 27.6% of all cases of infant deaths and 22.8% of all cases of deaths among children under five years old in Indonesia^{1,2}.

CAP is defined as pneumonia that is acquired in the community. If not properly managed, CAP may develop into sepsis, which is one of the leading causes of death in children, with approximately 7.5 million deaths annually^{1,2}. It encompasses four major causes of child mortality as reported by the World Health Organization (WHO): severe pneumonia, severe diarrhea, severe malaria, and severe measles³. The risk factors for CAP-induced sepsis, as well as the underlying cause of pneumonia (e.g., bacterial, viral, or atypical pathogens), may vary with age due to differences in immune maturity and developmental factors. Understanding these variations is crucial for an accurate risk assessment and early intervention. Thus, this study aimed to determine the risk factors associated with the occurrence of sepsis in pediatric patients with CAP, with an emphasis on both the demographic and clinical risk factors.

MATERIALS AND METHODS

This cohort study was initially designed to investigate the cases of CAP in children aged 1 month to 17 years who were admitted to the emergency and intensive care department of Dr. Wahidin Sudirohusodo Hospital in Makassar from April

to June 2024. The study approval was obtained from the ethics committee, specifically the medical records department, and the Biomedical Research Ethics Committee on Human Subjects at the Faculty of Medicine, Hasanuddin University, Makassar (approval number: UH24020121).

The sample collection was performed using the total sampling method. Moreover, the samples were collected through anamnesis, physical examination, and supporting investigations of CAP patients admitted through the emergency and intensive care department. However, patients with other sources of infection, those diagnosed with pneumonia more than 48 h after hospital admission, and those with congenital anomalies in the respiratory tract were excluded. The included patients were followed until discharge or death and were observed for sepsis and were then categorized into two groups: those with sepsis (case group) and those without sepsis (control group).

In this study, CAP was defined as a history of cough or difficulty breathing accompanied by lower chest wall indrawing or age-specific tachypnea (≥ 50 breaths per minute for children aged 2~11 months and ≥ 40 breaths per minute for those aged 12~59 months) without any general danger signs and occurring outside a hospital setting or within 48 h of hospital admission. However, sepsis in children with CAP is defined as the presence of pneumonia with an increase of ≥ 2 points in the Sequential Organ Failure Assessment score. Fever was defined as an axillary or tympanic temperature of $\geq 38.0^\circ\text{C}$. The ANC was classified as follows: normal count ($>1,500/\text{mm}^3$), mild neutropenia ($1,000\sim 1,500/\text{mm}^3$), moderate neutropenia ($500\sim 1,000/\text{mm}^3$), and severe neutropenia ($<500/\text{mm}^3$). The nutritional status was classified as normal (WHO weight/height between -2 SD and +1 SD or CDC chart weight/height between 90 and 110%) or malnourished (WHO weight/height below -2 SD or above +1 SD or CDC chart weight/height below 90% or above 110%). The immunization status was classified as complete (all age-appropriate immunizations given) or incomplete (missing one or more age-appropriate immunizations). The vitamin D levels were classified as normal (30~100 ng/mL) or deficient (below 30 ng/mL). The parental income was classified as below the minimum wage (below the regional minimum wage for Makassar) or at the minimum wage (equal to or above the regional minimum wage for Makassar).

The data collected for each subject comprised patient initials, registration number, age at diagnosis, sex, history of antibiotic use, duration of home care prior to hospital admission, and any comorbidities. Comprehensive clinical examinations and relevant diagnostic tests were performed to confirm the diagnosis of CAP and sepsis for all patients. The demographic

Table 1. Characteristics of CAP pediatric patients

Characteristics	n	%
Age		
≤2 years	52	57.8
>2 years	38	42.2
Gender		
Female	37	41.1
Male	53	58.9
Temperature		
Fever	48	53.3
Normothermia	42	46.7
LBW		
Yes	16	17.8
No	74	82.2
Comorbidities		
Yes	42	46.7
No	48	53.3
Duration of home care		
≥7 days	31	34.4
<7 days	59	65.5
Prehospital antibiotics		
Did not receive prehospital antibiotics	55	61.1
Received prehospital antibiotics	35	38.9
ANC		
Severe or moderate neutropenia	6	6.7
Mild neutropenia or normal	84	93.3
Nutritional status		
Malnourished	41	45.6
Normal	49	54.4
Vitamin D levels		
Deficient	76	84.4
Normal	14	15.6
EBF		
Did not receive the EBF	46	51.1
Received EBF	44	48.9

Table 1. Characteristics of CAP pediatric patients (Continued)

Characteristics	n	%
Immunization status		
Incomplete	51	56.7
Complete	39	43.3
Parental education		
Below high school	48	53.3
Above high school	42	46.7
Parental occupation		
Civil servant	49	54.4
Private sector	41	45.6
Place of residence		
Rural	40	44.4
Urban	50	55.6
Parental income		
Below minimum wage	37	41.1
At minimum wage	53	58.9
Household cooking fuel		
Wood	28	31.1
Gas	62	68.9
Smoking environment		
Lives in a smoking environment	50	55.6
Does not live in a smoking environment	40	44.4
Total Sample	90	100.0

risk factors that were assessed comprised age at diagnosis, sex, history of prehospital antibiotic use, duration of illness before hospital admission, parental educational background, parental occupation, place of residence, parental income, household cooking fuel, and the presence of a smoking environment within the family. In contrast, the clinical and laboratory risk factors included nutritional status, ANC, vitamin D levels, history of measles vaccination, history of low birth weight (LBW), and history of breastfeeding for less than six months.

All collected data were analyzed using the appropriate statistical methods. The categorical data were expressed as frequencies, while the numerical data were expressed as medians for the nonnormally distributed data and as means

Table 2. Univariate analysis of sepsis in CAP pediatric patients

Characteristics	Sepsis (n)	No sepsis (n)	Total (n)	<i>p</i> -value	RR	95% CI (Low)	95% CI (High)
Age							
≤2 years	11	41	52	0.775	0.893	0.411	1.939
>2 years	9	29	38				
Gender							
Female	8	29	37	0.909	0.955	0.433	2.104
Male	12	41	53				
Temperature							
Fever	16	32	48	0.007	3.500	1.269	9.652
Normothermia	4	38	42				
Low birth weight history							
Yes	4	12	16	0.748	1.156	0.446	2.999
No	16	58	74				
Comorbidities							
Yes	10	32	42	0.463	1.336	0.614	2.908
No	10	38	48				
Length of hospital stay							
≥7 days	9	22	31	0.260	1.557	0.724	3.350
<7 days	11	48	59				
Prehospital antibiotics							
No	13	42	55	0.686	1.182	0.523	2.671
Yes	7	28	35				
ANC							
Severe or moderate neutropenia	4	2	6	0.021	3.500	1.708	7.171
Mild neutropenia or normal	16	68	84				
Nutritional status							
Malnutrition	13	28	41	0.048	2.220	0.978	5.039
Normal	7	42	49				
Vitamin D levels							
Deficiency	20	56	76	0.034	0	0	0
Normal	0	14	14				
Breastfeeding							
No EBF	14	32	46	0.055	2.232	0.942	5.287
EBF	6	38	44				

Table 2. Univariate analysis of sepsis in CAP pediatric patients (Continued)

Characteristics	Sepsis (n)	No sepsis (n)	Total (n)	p-value	RR	95% CI (Low)	95% CI (High)
Immunization status							
Incomplete	14	37	51	0.172	1.784	0.755	4.220
Complete	6	33	39				
Education							
Below high school level	8	40	48	0.175	0.583	0.264	1.289
Above high school level	12	30	42				
Occupation							
Civil servant	7	42	49	0.058	0.451	0.198	1.023
Private sector	13	28	41				
Residence							
Rural	6	34	40	0.140	0.536	0.226	1.268
Urban	14	36	50				
Income							
Below minimum wage	8	29	37	0.909	0.955	0.433	2.104
Meets minimum wage	12	41	53				
Cooking fuel							
Wood	10	18	28	0.039	2.214	1.041	4.708
Gas	10	52	62				
Smoking environment							
Smoker	12	38	50	0.650	1.200	0.543	2.650
Nonsmoker	8	32	40				

with standard deviations for the normally distributed data. A univariate analysis was conducted using the chi-square test to compare the categorical independent variables between the groups with and without sepsis, provided that the chi-square test assumptions were met. Using Fisher's exact test, the categorical independent variables between the groups with and without sepsis were compared when the chi-square test assumptions were not met, and the relative risk with a 95% CI was calculated to determine the likelihood of sepsis occurrence in CAP patients with risk factors compared with those without risk factors. A multivariate analysis was performed using logistic regression (multiple logistic regression analysis) when the bivariate analysis identified more than one risk factor variable that was significantly associated with sepsis occurrence.

RESULTS

Of the 107 pediatric patients with CAP, 90 children met the inclusion criteria. Of them, 20 developed sepsis, while 70 recovered. The demographic characteristics showed that the majority of the patients with CAP were male (58.9%) aged ≤ 2 years (57.8%). A slightly higher number of patients with fever was observed compared with those with normothermia. Moreover, a slightly higher number of patients with no comorbidities was observed. Other characteristics have indicated more patients with a home care duration of < 7 days (65.5%) who did not receive prehospital antibiotics (61.1%). The clinical characteristics revealed more patients with normal nutritional status (54.4%), mild neutropenia or normal count (93.3%), and vitamin D deficiency (84.4%);

Table 3. Multivariate analysis of sepsis in CAP pediatric patients

Variables	B	S.E.	Wald	df	Sig.	Exp (B)
Temperature	4.316	1.540	7.857	1	0.005	74,870
ANC	4.844	1.899	6.506	1	0.011	126,948
Nutritional status	1.968	1.175	2.804	1	0.094	7,159
Vitamin D levels	21.456	8,109.376	0.000	1	0.998	2,081,664,340
Cooking fuel	0.553	0.978	0.320	1	0.572	1.739

those with no LBW (82.2%) and incomplete immunization status (56.7%); and those who did not receive exclusive breastfeeding (EBF) (51.1%). Table 1 shows the other characteristics, such as parental education, occupation, income, etc.

A bivariate analysis was conducted on each factor to analyze its relationship with the occurrence of sepsis in pediatric patients with CAP. The bivariate analysis revealed that a child with a fever is 3.5 times more at risk of developing sepsis compared with those with normothermia, with a CI of 1.269~9.652, indicating a significant association ($p = 0.007$). Furthermore, children with severe or moderate neutropenia are 3.5 times more at risk of developing sepsis compared with those with mild neutropenia or normal neutrophil counts, with a CI of 1.708~7.171, indicating a significant association ($p = 0.021$). The malnutrition status was predictive, with a 2.2 times increased risk of developing sepsis compared with children with good nutritional status (CI of 0.978~5.039), indicating a significant association ($p = 0.048$). Normal vitamin D levels reduce the risk of sepsis, indicating a significant association ($p = 0.034$). Furthermore, the use of wood as cooking fuel at home increases the risk of sepsis by 2.214 times compared with the use of gas, with a CI of 1.041~4.708, indicating a significant association ($p = 0.039$) (Table 2).

Based on the results of the logistic regression analysis (Table 3), two variables were considered to be the most dominant risk factors for sepsis: body temperature (p -value of 0.005) and ANC (p -value of 0.011).

DISCUSSION

Of the 90 patients with CAP, 20 (22%) developed sepsis. This result is not significantly different from that of a previous study conducted in Ethiopia, which reported that the prevalence of CAP progressing to sepsis was 26.8%. This is likely because the study was conducted in a tertiary care

center, where most patients commonly present with multiple complications that facilitate the development of sepsis⁴⁻⁶. The complex interactions between the immune-molecular pathways underlie sepsis and pneumonia, resulting in similar and overlapping disease characteristics. Sepsis can arise from poorly managed pneumonia⁷. Pneumonia in children has an incidence of 0.29 episodes per child per year in developing countries and 0.05 episodes per child per year in developed countries, making it the most common cause of sepsis in children. Furthermore, pneumonia is also a leading cause of death in children under five years of age⁸.

The present study revealed that the patients with low ANC had a significantly higher risk of developing sepsis ($p = 0.021$). Similarly, a study conducted by Liu et al. on a cohort of 116 patients with CAP reported that pediatric patients with severe neutropenia experienced more severe manifestations of pneumonia compared with those with mild neutropenia⁹. A retrospective cohort study conducted by Yin et al. on 141 severe sepsis/septic shock patients revealed that the patients with neutropenia were more susceptible to bacterial culture growth, with a higher prevalence of gram-negative bacteria¹⁰. In contrast, a study by Harmansyah et al.¹¹ suggested that the ANC values in pediatric sepsis patients tend to increase significantly. Previous studies reported that high white blood cell counts ($>20,000$ cells/ μ l) tend to be correlated with the occurrence of bacteremia¹²⁻¹⁵. Furthermore, children with fever and neutropenia have an increased risk of sepsis and other infectious processes¹⁶. Moreover, neutropenia has been identified as an independent risk factor for sepsis. Patients with severe neutropenia tend to have lower peripheral neutrophil levels¹⁰. The incidence and severity of the infections are correlated with the severity and duration of neutropenia¹⁷. In sepsis, neutrophils tend to exhibit an extended lifespan due to the augmented production of anti-apoptotic proteins resulting from the increased levels of inflammatory mediators that stimulate the signaling pathway of these anti-apoptotic proteins. Moreover, the release of neutrophils into

the bloodstream increases during sepsis because the inflammatory mediators boost the expression of neutrophil adhesion molecules, thereby increasing the number of neutrophils in the bloodstream¹⁸. Accumulating evidence suggests that neutrophils are a vital cellular component of the innate immune system's defense against infection. Since persistent infection likely contributes to immune suppression, neutropenia resulting from persistent immune suppression may provide a theoretical basis for predicting severe sepsis¹⁹.

The present study revealed that patients with elevated temperatures had a significantly higher risk of developing sepsis ($p = 0.007$). A retrospective cohort study conducted by Wang et al. reported that mild hyperthermia (OR 3.41, 95% CI 1.17~9.90) and severe hyperthermia (OR 5.15, 95% CI 1.84~14.43) were independent risk factors for in-hospital mortality²⁰. The results of this study are consistent with the study by Negah et al. conducted in Ethiopia, which reported that children with body temperatures exceeding 38.5°C had a higher risk of experiencing sepsis compared with children who had body temperatures between 37.5°C and 38.5°C²¹. Fever (pyrexia) can be considered as an adaptive response to infection. It is a common feature of sepsis and septic shock and appears to result in an enhanced innate immune response, with greater recruitment of innate immune cells, increased neutrophil survival, enhanced formation of neutrophil extracellular traps (NETosis), increased production of reactive oxygen species, and decreased secretion of pro-inflammatory cytokines by neutrophils. Moreover, higher temperatures tend to be accompanied by greater metabolism and higher oxygen consumption, a scarce resource for cells in sepsis scenarios²². As part of the body's normal immune response to infection, fever helps inhibit bacterial growth, increases antibody and cytokine synthesis, and activates T cells, neutrophils, and macrophages in the body, thereby facilitating the control of infection²⁰.

The present study also found that children with poor or inadequate nutritional status had a higher risk of developing sepsis ($p = 0.019$). This result is consistent with a previous study conducted in Kenya by Bejon et al.²³ which reported that children with poor or inadequate nutrition had a higher risk of developing bacteremia. This is because malnutrition has been associated with poor outcomes in various critical illnesses in both adults and children. The nutritional status of patients is determined by various anthropometric variables, which can influence the survival and morbidity associated with critical illnesses, including CAP. An individual's nutritional status, especially body composition, can also influence the degree and nature of the inflammatory response and stress to critical illness, thereby influencing the nutritional needs

and clinical outcomes. Therefore, monitoring the changes in nutritional status during illness can help prevent or immediately detect unwanted macronutrient imbalances and critical loss of muscle mass²⁴.

The type of cooking fuel used at home is also a significant factor in the emergence of pneumonia in children ($p = 0.039$), with children whose homes use wood as cooking fuel having a higher risk of developing sepsis. However, this study differs from the research conducted by Rahmawati et al.⁶ who did not find a significant relationship between fuel usage and the occurrence of pneumonia. In theory, the use of nonstandard cooking fuels, such as firewood, can cause indoor air pollution. The types of pollution commonly found indoors include CO₂, NH₃ (ammonia), and H₂S. High concentrations of cooking fuel combustion byproducts can damage the lung defense mechanisms, thereby increasing the risk of pneumonia, especially in children. Based on the multivariate analysis conducted in this study, several variables were identified (e.g., body temperature and ANC) as the most dominant risk factors for sepsis in pediatric CAP patients¹⁰.

Based on the multivariate analysis conducted in this study, several variables, including body temperature and ANC, were considered the most dominant factors in increasing the risk of sepsis in pediatric patients with CAP. The findings of this study also revealed both similarities and differences compared with previous research on sepsis risk factors in pediatric CAP patients. These variations may be attributed to the specific study population and differences in diagnostic criteria, geographic factors, and limited sample size and duration, all of which could influence the generalizability of our results.

However, this study has several limitations. First, patient recruitment was conducted at a tertiary care center, suggesting that the sample consisted solely of patients referred from secondary and primary healthcare facilities. Moreover, the short study duration compromised the number of patients that could be recruited. Future studies should implement a larger and more diverse sample size and a longer study duration. Furthermore, since the results of blood and sputum cultures were not analyzed in this study, it was not determined whether the type of pathogen significantly influences the severity of infection or whether infections caused by antibiotic-resistant organisms or atypical pathogens increase the susceptibility to sepsis.

CONCLUSION

Temperature and ANC were found to be significant independent risk factors that may increase the likelihood of

sepsis in children with CAP. Although these factors were significant in this study, future research addressing how these risk factors vary by age and CAP etiology could further improve early sepsis risk identification and facilitate the development of targeted management strategies.

CONFLICT OF INTEREST

The authors declare no conflicts of interest regarding this study.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ETHICAL APPROVAL STATEMENT

The study was approved by the Institutional Review Board of (IRB No. UH24020121). This study was conducted in accordance with the principles of the Declaration of Helsinki.

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