Evaluation of the PaO_2/FiO_2 Ratio as a Risk Factor for Hypoxemia against Septicemia Mortality in Children who Treated at Dr. Soetomo General Hospital

Yuli Astika[1], Arina Setyaningtyas[2], Dominicus Husada[2], Retno Asih Setyoningrum[2]

[1]Pediatric Resident, [2]Pediatrician and Researcher, Department of Peditrics, Faculty of Medicine Universitas Airlangga - Dr. Soetomo General Hospital Surabaya, Indonesia

Abstract

Background: Severe septicemia can result in impaired oxygen perfusion to the tissues. The PaO_2/FiO_2 ratio (P/F ratio) is one of the measurement parameters for hypoxemia. This study aims to evaluate the P/F ratio as a risk factor for hypoxemia against septicemia mortality in children.

Method: An observational with a prospective cohort design was conducted. Thirty-six patients with septicemia, consisting of 18 patients who living (survivor) and 18 patients who died (non-survivor). The P/F ratio is obtained based on blood gas analysis carried out in the first 24 hours of treatment recorded on medical records and calculated manually. The P/F ratio has an area under the curve (AUC) of 0.83 (95% CI 0.71–0.95) with a cut-off of 226. Septicemia children with P/F ratio < 226 who have a mortality risk of up to 6.9 times (RR 6.9; 95% CI 1.719-27.957; *p*= 0.005) with sensitivity 72.70%; specificity 72.20%; PPV 76.19%; NPV 68.42%. The mean P/F ratio in the non-survivor group was significantly lower than the survivor group 161.60 (95% CI 1.05) compared to 391.09 (95% CI 2.13); *p*= 0.005).

Conclusion: The P/F ratio can be a risk factor for hypoxemia on septicemia mortality.

Keywords: *Septicemia; P/F ratio; children; hypoxemia*

Introduction

Septicemia is a complex and multifactorial syndrome that occurs due to the body's response to infections that tend to be harmful, dangerous, or destructive. Untreated septicemia will progress to severe septicemia.[1] Currently, septicemia is associated with high morbidity, mortality, and care costs, and is the leading cause of infant and child mortality worldwide.[2] The high mortality in septicemia, often caused by delay in diagnosis and treatment.[3] In severe septicemia or septic shock, there is impaired oxygen perfusion to the tissues. The result of hypoxemia will affect outcomes such as length of stay, mortality, and morbidity. Based on the medical records at the Dr. Soetomo General Hospital (2015), septicemia in children was recorded as 124 cases, while in 2016 and 2017 there were 52 and 109 cases.[4] The number of deaths in PICU Dr. Soetomo General Hospital in 2018 with 23 cases of severe septicemia (35%) and 16 cases of septic shock (25%).[5] Therefore, it is necessary to recognize signs of hypoxemia both clinically and in laboratories examination. The diagnostic criteria for acute respiratory failure in children are varied and inconsistent. The PaO_2/FiO_2 ratio (P/F ratio) is one of the measurement parameters for hypoxemia.[6] This study has validated the cut-off value for the P/F ratio which can be

Corresponding author:
Arina Setyaningtyas,
a Pediatrician And Researcher. Department of Peditrics, Faculty of Medicine Universitas Airlangga - Dr. Soetomo General Hospital Surabaya, Indonesia. Jl. Mayjend. Prof. Dr. Moestopo No. 6-8, Surabaya.
Email: dr.arina.spa@gmail.com.
Phone: +62 812-3452-326

used as a predictor of septicemia mortality.[7] Until now, research on the P/F ratio as a risk factor for hypoxemia on septicemia mortality has not been widely used. The examination of the P/F ratio is considered to be more accurate and easily available, allowing the application of appropriate therapy. This study was conducted to evaluate the P/F ratio as a risk factor for hypoxemia against septicemia mortality in children.

Materials and Methods

This study was an analytical observational study with a prospective cohort study design to analyze the role of the PaO_2/FiO_2 ratio (P/F ratio), as a risk factor for hypoxemia on septicemia mortality in children treated at Dr. Soetomo General Hospital, Surabaya. The sample of the study were pediatric patients with septicemia who were treated in the pediatric intensive care unit (PICU), emergency department, and pediatric ward at Dr. Soetomo General Hospital Surabaya in the period time from March 1st – September 30th 2020. Thirty-six patients met the inclusion and exclusion criteria with living (survivor) septicemia and 18 patients have died (non-survivor). We used a primary data based on the supporting examinations carried out during the treatment at Dr. Soetomo General Hospital Surabaya. The data collection instrument used in this study was the data collection sheet (DCS). The data from each examination result is confirmed to be complete and relevant first before further processing. The examination was carried out on incomplete and less relevant data. The demographic characteristics of participants were analyzed using T independent test. The correlation test between variables presented in cross-tabulation was analyzed using the Chi-Square test. The cut-off value is obtained using the receiver operating characteristic (ROC) curve. Statistical analysis using Chi-Square test, the significance value $p < 0.05$. The collected data were analyzed using the IBM SPSS Statistic program.

Results and Discussion

The basic characteristics of the participants were presented based on the basic characteristics of gender, age, Pelod II score. Meanwhile, for laboratory characteristics, various parameters were assessed from the results of blood gas analysis and complete blood counts such as PCO_2, PaO_2, SO_2, FiO_2, $AaDO_2$, Hb, and leukocytes. The basic characteristics of the groups are listed in Table 1. and Table 2.

Table 1. The basic characteristics of the participants in the septicemia group, survivor and non-survivor

Characteristics	Survivor (N = 18)	Non-survivor (N = 18)	p
Gender Male (%) Female (%)	10 (47.6) 8 (53.3)	11 (52.4) 7 (46.7)	0.726
Age of months (mean± SD)	58.5 ± 55.1	87.4 ± 80.51	0.258
Pelod II Score (mean ± SD)	10.83 ± 2.149	12.55 ± 1.969	0.021*

*a p-value < 0.05 was statistically signifcant.

Table 2. Laboratory characteristics of participants in the septicemia group survivor and non-survivor

Characteristics	Survivor (N = 18)		Non-survivor (N = 18)		p
	Mean	SD	Mean	SD	
PaO2	121.67	75.179	89.14	53.311	0.219
FiO2	26.00	10.765	41.91	22.320	0.020*
PaCO2	48.83	26.206	50.95	31.029	1.000
SO2	91.83	11.242	87.18	11.603	0.099
AaDO2	90.72	53.685	139.55	75.503	0.027*
Hb	10.37	3.182	10.20	2.835	0.857
Leukocyte	15993.89	8410.961	16971.82	9777.629	0.740

*a *p*-value < 0.05 was statistically signifcant.

The highest gender in the survivor and non-survivor septicemia group was male. The mean age in the survival septicemia group was 58.5 months while in the non-survivor group was 87.4 months. The mean Pelod II score was higher in the non-survivor group with *p*-value < 0.05. The number of $AaDO_2$ and FiO_2 in septicemia patients who non-survivor was significantly higher than in survivors with *p*-value < 0.05. The number of FiO_2 (41.91 vs 26.00) had a relevant and significantly higher increase found in the septicemia patients who non-survivor with a *p*-value of 0.020. Meanwhile, for the values of PaO_2, $PaCO_2$, SO_2, Hb, and leukocytes, there were no significant differences were found in non-survivor and survivor. A total of 36 patients with septicemia divided into 18 survivors and 18 non-survivors with the P/F ratio was calculated as shown in Table 3.

Table 3. P/F Ratio value of survivor and non-survivor septicemia group

P/F *Ratio*	Outcome		*p*	RR (CI 95%)
	Survivor N (%)	Non-survivor N (%)		
Low (< 226)	5 (30)	16(70)	0.005*	6.933
High (> 226)	13 (60)	6 (40)		(1.719 -27.957)
Mean ± SD	391.09 ± 2.13	161.60 ± 1.05		

*a *p*-value < 0.05 was statistically signifcant.

The results of this study showed a significant difference in the value of the P/F ratio (161.60 ± 1.05 vs. 391.09 ± 2.13; $p = 0.001$) between survivor and non-survivor septicemia patients as shown in Table 3. In patients with septicemia, a low P/F ratio value is significant for the occurrence of death, meaning that the lower the P/F ratio value, the risk of death is 6.9 times higher than those with a high P/F ratio value as shown in Table 3.

P/F ratio in septicemia has an area under the curve (area under curve / AUC) of 0.83 (95% CI 0.71-0.95). The cut-off reference value P/F ratio of 226 has a sensitivity of 72.70%, specificity of 72.20%, a positive predictive value of 76.19%, and a negative predictive value of 68.42% (Figure 1 and Figure 2).

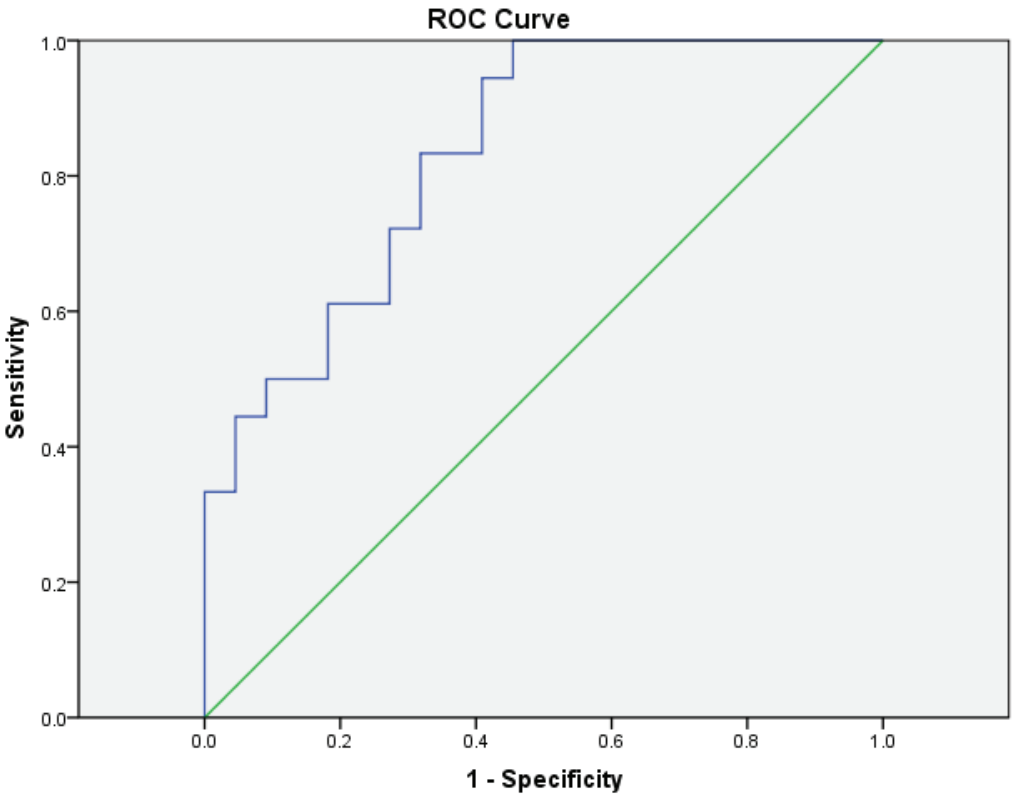

Figure 1. Area under curve P/F ratio to mortality in septicemia patients

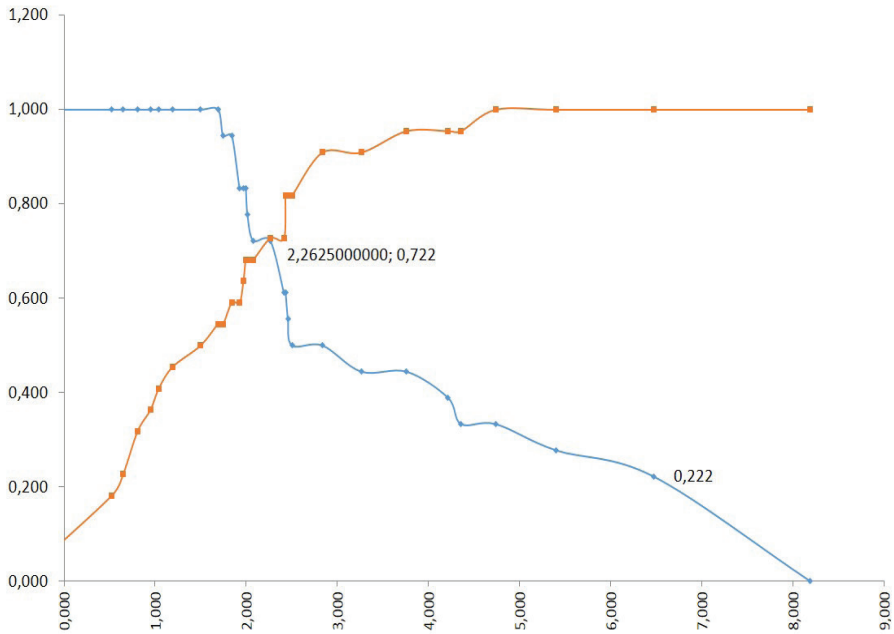

Figure 2. The cut off P/F ratio in septicemia

It was found that the number of males (52.5%) was greater than that of females (47.5%) in both the survivor and non-survivor septicemia group. Following the study of Zhou J et al. (2014) in China regarding the features and prognosis of severe septicemia and septic shock in the ICU saying that 60.4% of the study subjects were male. This is influenced by the female hormone estrogen which has a protective effect against infection, septicemia, and trauma. A study in Bandung found that in the case group, 50 (51%) subjects were male and 48 (49%) female subjects. Meanwhile, in the control group, 66 (66.7%) were male and 34 (33.3%) were female. There was no significant difference between the two sex groups.[8]

Many studies show that gender has a role in infectious diseases and septicemia. The female sex has shown to be protective against septicemia, whereas the male sex, on the other hand, interferes with cell-mediated immune responses and cardiovascular function. Male sex hormones, namely androgens, have been shown to suppress cell-mediated immunity. In contrast, female sex hormones exhibit a protective effect that may contribute to naturally benefiting women in septic conditions. The hormone estrogen affects increasing the immune system by increasing the production of IL-4 and IL-10 so that antibodies increase.[9]

A study in China on 461 children reported that the age of less than 1 year had the greatest percentage of 50.5% who were admitted to the PICU.[10] This occurs because the responses of macrophages and other innate immune systems such as mucosal cells, skin cells, cilia, and acute-phase protein formation have decreased and the number of T lymphocytes is decreased due to thymus reabsorption. The median ages of cases and controls were 12 and 24 months.[11]

The number of $AaDO_2$ and FiO_2 in septic patients who died was significantly higher than in living septicemia patients with *p*-value <0.05. The number of FiO_2 (41.91 vs 26.00) had a relevant and significantly higher increase found in the septic patients who died with a *p*-value of 0.020. Meanwhile, for the values of PaO_2, $PaCO_2$, SO_2, Hb, and leukocytes, there were no significant differences were found in non-survivor and survivor septicemia patients.

The results of this study indicate a decrease in the P/F ratio value in patients with non-survivor septicemia compared to living septicemia. The mean PaO_2/FiO_2 ratio in this study was 161.60 in non-survivor septicemia and 391.09 in survivor septicemia. The decrease in the P/F ratio occurs due to a mechanism of impaired oxygen perfusion to the tissue. Hypoxia tissue condition will cause metabolism to be ineffective due to anaerobic metabolism and accumulation of lactate resulting in cell dysfunction and destruction which leads to multi-organ failure and death.[12,13]

The above studies show that the excessive release of proinflammatory cytokines triggers the release of vasoactive amines and chemokines as well as activation of the complement system, coagulation, and release of reactive oxygen species (ROS). These mediators are responsible for increased vascular permeability, hypotension, and septic shock. In an advanced stage, the release of a mediator such as high protein group box 1 (HMGB1), which allows the inflammatory reaction to being continued. Since O_2 is the final receptor for electrons in the electron transport chain, measuring oxygen consumption is a good choice for assessing mitochondrial function. The peripheral blood of septic patients shows normal PO2 levels although the oxygen consumption by the cells may be reduced, which can lead to tissue hypoxemia followed by tissue damage and ultimately organ system failure. Multi-organ damage is the cause of death.[14,15]

P/F ratio is the partial pressure of arterial oxygen (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2 is expressed as a fraction, not %) so that PaO_2/FiO_2 is commonly known by the abbreviation P/F Ratio. P/F Ratio is used to determine hypoxemia, although there are still several things that need to be reviewed regarding its function as a basis for diagnosis.[16] The PaO_2/FiO_2 ratio (P/F ratio) is a commonly used oxygenation measurement tool. The normal P/F ratio is 300-500

mmHg, with values less than 300 mmHg indicating abnormal gas exchange and values less than 200 mmHg indicating severe hypoxemia.[17]

The severity of hypoxemia classified according to the Berlin criteria was associated with an increase in mortality in adult patients, namely 27% (95% CI 24-30%) in mild hypoxemia, 32% (95% CI 29-34%) in moderate hypoxemia and 45% (95% CI 42-48%) for severe hypoxemia with *p*-value <0.001. The severity of hypoxemia was also associated with an increase in the mean duration of mechanical ventilation in the survivor group, namely 5 days (interquartile range/ IQR 2-11) in mild hypoxemia, 7 days (IQR 4-14) in moderate hypoxemia, and 9 days (IQR 5-17) in severe hypoxemia with *p*-value <0.001. The value of the PaO_2/FiO_2 ratio has an area under the curve (area under curve/ AUC) of 0.577 (95% CI 0.561-0.593) as a predictor of mortality.[18,19]

A study by Rice et al in patients with acute respiratory distress syndrome (ARDS) has the most common causes of being septicemia, pneumonia, and trauma, found a mortality rate of 53.0% at a PaO_2/FiO_2 ratio <100, a mortality rate of 39.8%, at $100<PaO_2<200$, the mortality rate was 39.8% at $200<PaO_2/FiO_2<300$, and the mortality rate was 16.75% at PaO_2/FiO_2 >300 ($p = 0.064$). The results of the insignificant relationship between the PaO_2/FiO_2 ratio and the incidence of death can be due to the PaO_2/FiO_2 ratio data obtained from this study all above 100 mmHg /%, while according to Viviani et al, the PaO_2/FiO_2 ratio can only be used as a predictor of mortality if it is below that 100 mmHg/%.[7,20]

Hypoxemia is defined as a decrease in the partial pressure of oxygen in the blood. Hypoxemia does not necessarily indicate tissue hypoxia. This can be caused by hypoventilation, ventilation-perfusion mismatch, right-to-left shunt, diffusion disturbance, or reduced inspired oxygen pressure.[21] Arterial (PaCO) and alveolar (PACO) carbon dioxide pressure increase during hypoventilation, which causes alveolar oxygen pressure (PAO) to decrease. As a result, the diffusion of oxygen from the alveoli to the pulmonary capillaries is decreased, resulting in hypoxemia and hypercapnia. The results of the P/F ratio prognostic test in this study also showed that the cut-off P/F Ratio reference value of 226 had a sensitivity of 72.70%, a specificity of 72.20%, a positive predictive value of 76.19%, and a negative predictive value of 68.42%. In this study, the increase in mortality rate was inversely proportional to the degree of hypoxemia based on the PaO_2/FiO_2 ratio in this study, namely the lower the PaO_2/FiO_2 ratio, the higher the mortality rate.[22]

Rice et al reported the cut-off ratio of PaO_2/FiO_2 300 AUC 0.878 with a specificity of 56% with positive predictive value and negative predictive value were 2.06 (95% CI 1.64-2.76) and 0.16 (95% CI 0.12-0.21). PaO_2/FiO_2 ratio of 200 specificity 85% with positive predictive value and negative predictive value of 5.64 (95% CI 4.69-7.08) and 0.17 (95% CI 0.15-0.20).[7]

This study has validated the cut-off point for the SaO_2/FiO_2 ratio which can be used as a substitute for a prognostic predictor of severe septicemia when the PaO_2/FiO_2 ratio is not available.[7] Perez et al investigated that the S/F ratio can be used in the assessment of respiratory distress and as a predictor of mortality in patients with septicemia in the ICU and has a correlation with the P/F ratio.[6] Laila et al found that a low S/F ratio is associated with mortality and has a good correlation with the P/F ratio. The cut-off of S/F ratio <300 indicates high specificity of mortality prognosis.[23]

Data on the first-day in septicemia patients who are non-survivor showed a low P/F ratio. Meanwhile, survivor septicemia patients showed a higher P/F ratio, but we still need further study, because the patient's condition is certainly supported by many factors. In this study, the relationship between comorbid patients and the changes in the value of P/F ratio was not examined. However, the data showed that comorbid patients compared to a lower P/F ratio than non-comorbid patients, so indirectly there is a possibility that the patient's comorbidities can influence the decrease in P/F ratio.

This study is the first study to investigate the P/F ratio as a risk factor for hypoxemia to septicemia

mortality in children at Dr. Soetomo General Hospital. While the weakness of this study is the blood test. The blood gas analysis was done once when the patient was first diagnosed with septicemia (blood retrieval ws only one observation). In this study, first-day data in septicemia patients who died showed a low P/F ratio. While in septicemia life shows a higher P /F ratio value, but still needs further evaluation, because of the patient's condition is certainly supported by many factors. Many things can affect the level of P/F ratio in a person, be it heart, lung, and other abnormalities. We are aware that this study did not assess some aspects regarding the relationship between the comorbidity of the patient and the changes in the value of the P/F ratio. But, we believe that this study provides valuable information which help the health personnel treating the septicemia in children.

Conclusion

The cut-off value of the PaO_2/FiO_2 (P/F ratio) as a risk factor for hypoxemia on mortality in children with septicemia was 226.The lower the P/F ratio, the relative risk of death in children with sepsis is 6.9 times higher than children with sepsis who have higher P/F ratio.

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Ethical Clearance: We obtained an approval of whole project from Ethical Committee Review Board of Dr. Soetomo General Hospital Surabaya. The Ethical Clearance has issued by the Clinical Research Unit of Dr. Soetomo General Hospital Surabaya, Indonesia number 1852/KEPK/III/2020.

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Conflict of Interest: We declare that the authors have no conflict of interest.

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