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Association between Aspartate Aminotransferase to Platelet Ratio Index with Sepsis-Associated Liver Injury and Outcome in Children

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Abstract

BACKGROUND: Sepsis-associated liver injury (SALI) is among the major clinical characteristics of pediatric septicemia, and it is a distinct risk factor for multiorgan impairment and a high rate of death. The prompt identification and treatment of SALI in patients with septic conditions is critical.

AIM: We aimed to discover the relationship between aspartate aminotransferase to platelet ratio index (APRI) and Sepsis-associated liver injury (SALI) as an early predictor.

METHODS: Analytical observational study with a prospective cohort approach with primary data taken from 49 samples. Further, these results were analyzed to determine the relationship between the occurrence of SALI and laboratory results.

RESULTS: The results of the analysis conducted from 49 samples, 23 people (46.9%) had SALI, and 22 people (44.9%) died. The median length of stay in the pediatric intensive care unit (PICU) was 9 days (interquartile range = 6.5–12.5). Significant relationship between aspartate aminotransferase to platelet ratio index (APRI) and the incidence of SALI with odds ratio (95% confidence interval) 2.32 (1.21: 4.44) and p = 0.011. The higher the APRI value, the longer the stay in the PICU. The correlation value (r) is 0.348 or low correlation

CONCLUSION: There was a significant relationship between the APRI and sepsis-related liver injury as well as sepsis outcomes such as PICU length of stay and mortality. Increases in the APRI increase the risk of sepsis-related liver injury, mortality, and PICU length of stay.

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection and is a major cause of admission to the pediatric intensive care unit (PICU). Sepsis contributes to 19% of all deaths globally, with the highest age-specific incidence in children under 5 years of age. Epidemiological studies with clinical data found sepsis in children to be up to 8% of all PICU patients and contributes to one in four every PICU deaths [1], [2].

Sepsis-associated liver injury (SALI) is one of the main clinical features, which is an independent risk factor for multiple organ dysfunctions and a high mortality rate in pediatric patients with sepsis. Death from SALI is associated with failure of early detection, especially in children. Early diagnosis and appropriate treatment of SALI is very important in patient with septic condition. The estimated incidence of SALI ranges from 1.3% to 46.6%, and the mortality associated with SALI is 23.81%. This condition is also supported by the lack of diagnostic tools to detect the early phase (<24 h) of SALI. The early identification of SALI remains a challenge and has a significant impact on the outcome of pediatric sepsis. Moreover, SALI is correlated with poor sepsis outcome which is consistent with many previous studies [3], [4].

Platelets linked with the complications of multiorgan dysfunction in sepsis by regulating inflammation, tissue integrity, and defense against infection. The aspartate aminotransferase to platelet ratio index (APRI) is an effective non-invasive marker for assessing liver fibrosis in patients with non-alcoholic fatty liver or hepatitis C-associated fibrosis. Both liver cirrhosis and hepatic fibrosis are closely associated with hepatic dysfunction and early inflammatory processes, which share characteristics with SALI [5], [6].

A number of studies on APRI as a marker for liver fibrosis and cholestasis are published, but few on APRI as a predictor of SALI. As a result, authors are inclined to discover the relationship between APRI and SALI as an early predictor. Furthermore, SALI has been linked to poor sepsis outcomes in numerous previous studies. Researchers are interested in assessing the relationship between APRI and sepsis outcomes, which have never been studied.

Methods

This study was conducted using an observational analytic research method with a prospective cohort approach in all cases of sepsis in children. Research was conducted in the PICU ward of Prof. Hospital. Dr. R.D. Kandou Manado from June 2022 to September 2022. The study population was children or infants aged 1 month to age <18 years with a diagnosis of sepsis. Sample population was children or infants aged 1 month to age <18 years with diagnosed of sepsis who are hospitalized in the PICU of Prof. Dr. R. D. Kandou, Manado in the research time period. The sampling criteria were consecutive sampling.

Table 1: Characteristic of research sample

Variable	Total (N = 49)
Age (months), median (IQR)	16 (3.5–93.5)
Sex, n (%)	
Male	28 (57.1)
Female	21 (42.9)
AST (u/L), median (IQR)	63 (38–87.5)
ALT (u/L), median (IQR)	42 (28–95.5)
Platelets (10^3/mm^3), median (IQR)	253 (127–411)
APRI, median (IQR)	0.70 (0.26–1.39)
SALI, n (%)	
Yes	23 (46.9)
No	26 (53.1)
Outcome, n (%)	
Living	27 (55.1)
Death	22 (44.9)
Length of stay in PICU (days), median (IQR)	9 (6.5–12.5)

APRI: Aspartate aminotransferase to platelet ratio index, PICU: Pediatric intensive care unit, IQR: Interquartile range, AST: Aspartate aminotransferase, ALT: Alanine transaminase.

This research carried out under the approval of the Research Ethics Committee of Prof. RSUP. Dr. R. D. Kandou, Manado. Each action taken in this research was accompanied by the provision of information and the permission of the parents by signing an informed consent form.

This study was submitted to the Faculty of Medicine, Universitas Sam Ratulangi/R.D. Kandou Hospital Manado, Indonesia, and was conferred approval and ethical clearance under the number 134/EC/KEPK-KANDOU/VIII/2022. Management of research data mostly takes place in the Statistical Program for the Social Sciences software application for windows version 25.

Results

This research started from June 2022 to September 2022 in children aged 1 month–18 years with sepsis in the PICU Prof Dr. Hospital. R.D. Kandou Manado. There were 58 children aged 1 month to <18 years with a diagnosis of sepsis who met the study inclusion criteria. Nine children were excluded from the study, consisting of four children with post-operative surgery, one child with malaria, one child with liver and biliary system disease, and three blood samples failed to be collected because the patient died before alanine transaminase (ALT) blood samples were collected. Therefore, there were only 49 children who met the criteria to be used as the research sample.

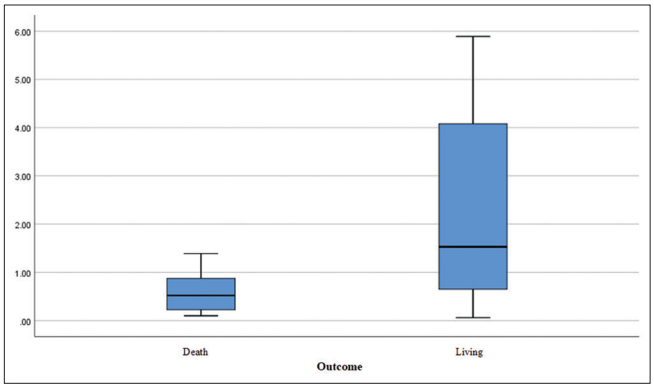

Figure 1: Aspartate aminotransferase to platelet ratio index boxplot on living and dead groups

Table 1 describes the basic characteristics of the research sample. Of the 49 people sampled, 23 people (46.9%) had SALI, and 22 people (44.9%) died. The median length of stay in the PICU was 9 days (IQR = 6.5–12.5).

Based on the boxplot in Figure 1, the APRI range in the dead group is much wider than that of the living group. Living patients have an APRI value between 0.1 and 1.39 while patients who die between 0.06 and 5.89. The median value shown by the center line of the boxplot also shows the difference between APRI in the living and dead groups.

Meanwhile, the range of length of stay in the PICU in the death group was much larger than in the living group, according to data from the boxplot in Figure 2. Patients who were still living had a stay of 6–20 days, whereas that group died between 3 and 23 days. The difference in length of stay in the PICU between the living and dead groups is also shown by the median value shown by the center line of the boxplot.

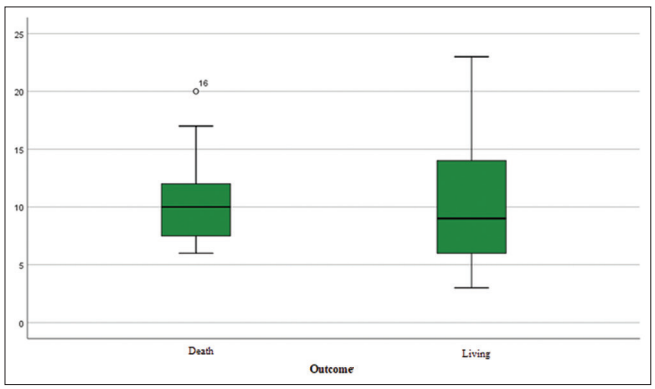

Figure 2: Boxplot of length of stay in the pediatric intensive care unit in the living and dead groups

Furthermore, Table 2 whereupon demonstrates the odd ratio (OR) value of the relationship between APRI and SALI. The analysis revealed a significant relationship between APRI and the incidence of SALI, with OR (95% confidence interval) 2.32 (1.21: 4.44) and

p = 0.011, suggesting that every unit increase in APRI increases the odds of SALI by 2.32 times.

Table 2. Relationship between APRI and length of stay in PICU

Variable	B	95%IK	p value
Total sample (n = 49)			
APRI	1.14	0.23:2.04	0.014
Living group (n = 27)			
APRI	1.12	−2.32:4.57	0.509

APRI: Aspartate aminotransferase to platelet ratio index, PICU: Pediatric intensive care unit.

Figure 3 below is a scatter diagram between APRI (X-axis) and length of stay in PICU (Y-axis). Based on the figure, it can be seen that the higher the APRI value, the longer the length of stay in the PICU. The correlation value (r) is 0.348 or low correlation.

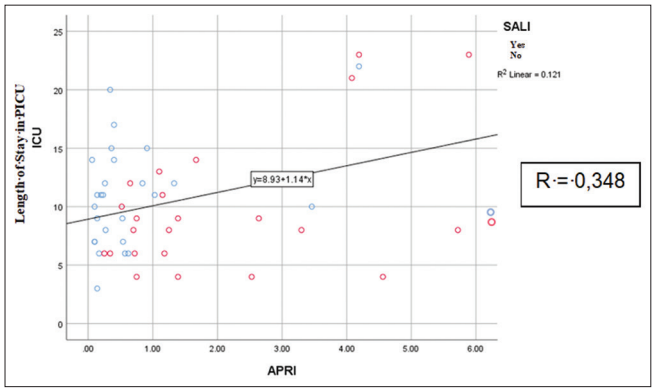

Figure 3: Aspartate aminotransferase to platelet ratio index scatter diagram with length of stay in the pediatric intensive care unit

A linear regression analysis of the relationship between APRI and length of stay in the PICU is shown in Figures 3 and 4. Each unit of APRI added rises the length of stay in the PICU by 1.14 days. This indicated that there was a significant relationship between APRI and PICU length of stay, with the higher the APRI value indicating a longer PICU stay (p = 0.014).

However, when the analysis of the relationship between APRI and length of stay in PICU was carried out only in the living group, it was found that there was no significant relationship between APRI and length of stay in PICU (R = 0.133; p= 0.509). Figure 4 is a scatter diagram of APRI on length of stay in the PICU in the living group. Based on the figure, it can be seen that APRI and duration of stay in the PICU are not correlated with each other as seen from the points that are spread and not linear.

Discussion

A significant relationship was found in this study between APRI and SALI, APRI and sepsis patient mortality, and APRI and length of stay in the PICU. It was discovered that as APRI increased, the likelihood of SALI increased. When the relationship with mortality was analyzed, a significant positive relationship was discovered, particularly regarding

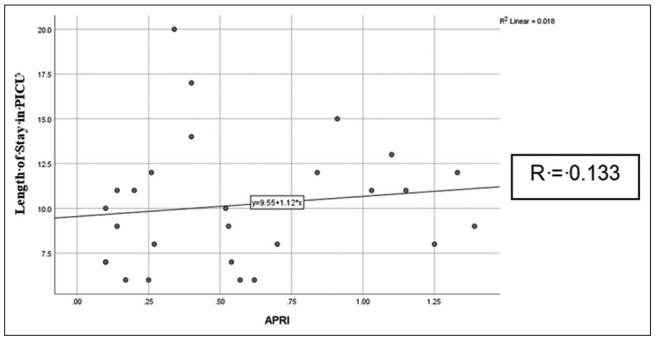

Figure 4*: Aspartate aminotransferase to platelet ratio index scatter diagram with length of stay in the pediatric intensive care unit in the living group*

that each increase in APRI increased the odds of greater mortality. The analysis of the relationship between APRI and length of stay in the PICU found a low and significant correlation with length of stay, with each increase in APRI increasing the length of stay. However, when the analysis was only performed on the group of living patients, there was no relationship between APRI and length of stay. APRI marker has the best value compared to other markers and can be a potential early warning biomarker to predict SALI. APRI is the best early warning biomarker for SALI, superior to LDH and the same as gamma-GT. The APRI cutoff value was 0.34 with a clinical sensitivity of 84.6% and a specificity of 84.3% for the prediction of SALI. The sensitivity of gamma-GT or LDH for predicting SALI was 76.9 and 47.5%, and the specificity of gamma-GT or LDH was 82.6 and 87.1%, respectively. Based on the ROC curve, APRI is superior to LDH and equal to gamma-GT.

An increase in the APRI value to >4.7 in the first 24 h after admission to the PICU is a significant predictor for assessing the onset of SALI in children with sepsis, this study also obtained a sensitivity of 81.5% and a specificity of 62.3%. Until this study was reported, no studies had assessed the relationship between APRI and sepsis outcomes in either adult or pediatric patients. The previous studies only assessed the relationship between APRI and SALI and presented descriptive data between SALI and sepsis which consistently showed worse outcomes in proportion to SALI patients.

The mean ratio of platelet volume (MPV) to platelets (MPV/platelet) is a promising predictor of early death in severe sepsis [7]. In another study, platelets and MPV/platelets were potential predictors of liver cirrhosis [8]. Early sepsis frequently results in impaired liver function. Sustained inflammation and hypoperfusion can result in liver damage and failure. The main predictors of mortality were disease severity, underlying septic shock, and the degree of liver damage. Furthermore, duration is an important factor; the longer the liver injury persists, the worse the outcome. Patients with a long duration of liver injury (elevated liver enzymes for more than 24 h) are at an increased risk of death.

The mortality rate in critically ill patients with early liver injury was twice as high (23%) [9].

In this study, the results showed that there was no relationship between APRI and length of stay in the living group, a low correlation was found and the relationship was not significant. This was because, in the death group, the range of APRI values and length of stay was wider. Research on the relationship between APRI and SALI has been studied, but this is the first time this research on APRI with sepsis which has been conducted. Further, research is needed to assess the involvement of APRI with sepsis outcomes in the form of mortality and length of stay.

From this study, it was also found that 23 patients had SALI (46.9%); these results are in accordance with studies conducted at Dr. Hasan Sadikin, Bandung, West Java, Indonesia in 2018, where 48.2% of septic pediatric patients were found to have SALI. The figure obtained from this study is indeed much higher when compared to research conducted in China, which is 9.15%. The incidence of SALI in pediatric patients ranges widely from 1.3 to 46.6% depending on the definition used; this may be due to the lack of early diagnostic tools to detect SALI [3].

APRI positively correlated with total bilirubin, ALT, and INR and negatively correlated with albumin. According to the Surviving Sepsis Campaign guidelines, the diagnosis of SALI is based on an increase in serum bilirubin concentration >2 mg/dL (34.2 mol/L) and the presence of coagulopathy (INR > 1.5). Several studies have used elevated ALT as the basis for the diagnosis of SALI. Consistently, APRI values correlated positively with total bilirubin and ALT values [4], [10].

Regarding this study, it was found that the proportion of the sample that died in the SALI group was significantly higher than without SALI. There was no significant difference in the length of stay in the PICU in patients with SALI and without SALI. The shorter length of stay in the PICU in the SALI group may be due to the non-separation of the analyses between the dead and the living patients. This is in accordance with the data that the length of stay in patients who died was shorter than the group who lived. The higher mortality rate in the SALI group suggested that SALI was correlated with a poorer sepsis prognosis, a result consistent with the previous studies.

This study also found that the APRI value was higher in the SALI group which correlated with worse outcomes. SALI often resolves concomitantly with sepsis remission. Conversely, persistent liver failure or liver failure within the 1st week of sepsis was associated with a lower 28-day survival rate. Persistence or development of liver failure within the 72 h period following the onset of severe sepsis is associated with poor outcome [11].

Until this study was reported, no studies had previously assessed the relationship between APRI and sepsis outcomes in either pediatric or adult patients. For diseases of the liver and biliary system, malignancies, blood diseases that interfere with the platelet count are only diagnosed on a clinical basis, not a definitive diagnosis. In this study, variables that might affect length of stay were not analyzed.

Conclusion

The existence of a significant relationship between the APRI with sepsis-associated liver injury and sepsis outcomes in the form of length of stay in the PICU and mortality was found to be significant in our study. An increase in the APRI increases the likelihood of sepsis-associated liver injury, mortality, and length of stay in the PICU. Consideration regarding the importance of using APRI obtained within the first 24 h of a sepsis diagnosis to predict, the occurrence of SALI and sepsis outcomes in children is quite necessary. In terms of scientific progress, we hope that future research can measure the cutoff value, sensitivity, specificity of APRI on SALI and mortality and conduct multivariate analysis to assess APRI with length of stay.

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