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Original Article

Relationship between aspartate aminotransferase to platelet ratio index and liver injury in pediatric sepsis

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Abstract

Background Sepsis-associated liver injury (SALI) is one of the main clinical manifestations of sepsis, as well as an independent risk factor for multiple organ dysfunction syndrome and mortality in pediatric sepsis. The early warning biomarkers for identifying SALI remain poorly defined.

Objective To analyze the relationship between aspartate aminotransferase to platelet ratio index (APRi) and liver injury occurrence in pediatric sepsis, as well as determine the APRi cut-off value for early identification of SALI.

Methods This retrospective study used secondary data derived from January 2019 to August 2020. The study population comprised admitted children aged 1 month to <18 years who met the criteria for sepsis, and had aspartate aminotransferase (AST) and platelet laboratory parameters checked in the first 24 hours of sepsis and before administration of antibiotics. Pearson's Chi-square test was used to analyze for correlations. Estimation of the APRi cut-off value in the early occurence of SALI was performed with logistic regression analysis and receiver operating characteristic (ROC) curve.

Results Of the 112 subjects, 94.6% were categorized as having septic shock and 48.2% had SALI. Logistic regression revealed that APRi was a significant predictor of SALI, as indicated by cut-off 4.726 [OR 1.098; 95%CI 1.002 to1.203; P=0.045]. The area under the curve (AUC) was 0.831 or 83.1%.

Conclusion The APRi is a reliable early predictor of SALI in pediatric sepsis, as indicated by an increase in APRi (> 4.726) within the first 24 hours of sepsis. **[Paediatr Indones. 2021;61:149-54 ; DOI: 10.14238/pi61.2.2021.149-54**].

Keywords: *aspartate aminotransferase to platelet ratio index; pediatric; sepsis; sepsis-associated liver injury*

Sepsis is a leading cause of morbidity and mortality in pediatric populations worldwide. Globally, an estimated 1.2 million children experience sepsis each year. The mortality of children with sepsis ranges from 4-50%, depending on the severity of disease, risk factors, and geographic location.[1] Indonesia has very high sepsis death rates. The mortality rate due to sepsis and septic shock in children at Dr. Hasan Sadikin General Hospital, Bandung, a referral hospital for the West Java Province, was quite high at 40% in 2018.[2]

The pathogenesis of inflammation and organ injury leading to death from sepsis is not fully understood, including injury to the liver, a lymphoid organ with "central roles" in inflammatory processes and organ damage during sepsis. Sepsis is like a double-edged sword, the liver-mediated immune response eradicates bacteria and toxins but also causes inflammatory processes, suppression of the immune system, and organ damage. Sepsis causes liver injury, thus increasing the severity of sepsis. Liver injury

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in children with sepsis can increase morbidity and mortality.[3] Sepsis-associated liver injury (SALI) is one of the main clinical manifestations of sepsis, an independent risk factor for multiple organ dysfunction syndrome (MODS) and mortality in pediatric sepsis.[4] The incidence of SALI was estimated to range from 1.3% to 46.6%, and mortality associated with SALI was 23.81%. This condition is also promoted by the lack of diagnostic tools to detect early phase (less than 24 hours) liver disorders. Early identification of SALI remains a challenge and has a significant impact on the outcomes of pediatric sepsis.[3] In addition, SALI is correlated with poor sepsis outcomes which was consistent with many previous studies.[4-6]

The gold standard criteria to diagnose SALI are an increase in total bilirubin (TBIL) or alanine aminotransferase (ALT). However, neither TBIL nor ALT can identify liver injury in the first 24 hours of sepsis.[5] These findings are related to the half-life of TBIL and ALT in blood which are 48 and 47 hours, respectively. Thus, another marker is needed as an accurate and simple predictor of early SALI.[5,6] A previous study compared several markers to predict the early incidence of SALI in pediatric sepsis. The APRi marker had the best value compared to other markers and could be a 'potential early-warning biomarker' to predict SALI in pediatric sepsis. An increase in APRi value to >0.34 in the first 24 hours after pediatric intensive care unit (PICU) admission was a significant predictor to assess the early incidence of SALI in pediatric sepsis.[5]

Several previous studies on APRi in both children and adults showed it to be a useful marker of liver fibrosis, esophageal varices, and cholestasis.[7-9] However, studies on the relationship between APRi and liver injury, as well as APRi cut-off value to predict early incidence of SALI in pediatric sepsis are still lacking. Therefore, we aimed to understand the relationship between APRi and occurrence of liver injury in pediatric sepsis, and determine an APRi cut-off value in order to identify SALI in an early manner to reduce the risk of mortality.

Methods

This retrospective study used secondary data from the sepsis registry of the Emergency and Pediatric Intensive Care Division/Pediatric Medical Staff Group, Universitas Padjadjaran Medical School/Dr. Hasan Sadikin General Hospital, Bandung, West Java, between January 2019 and August 2020. The sepsis registry was done according to recommendations of *International Pediatric Sepsis Consensus*.[4] Sepsis was defined as a life-threatening condition of organ dysfunction resulting from dysregulation of the host's response to the infection. Septic shock was sepsis accompanied by circulatory, cellular, and metabolic disturbances, characterized by dependence on vasopressors to maintain mean arterial pressure (MAP) and hyperlactatemia that was not caused by hypovolemia. Sepsis-associated liver injury (SALI) was defined as total birlirubin level (TBIL) ≥4 mg/dL or alanine aminotransferase (ALT) >2 times the upper limit of normal range for age.[7]

The inclusion criteria for this study were: children aged 1 month to <18 years, admitted in high care unit (HCU), or PICU at Dr. Hasan Sadikin General Hospital, Bandung, met the criteria for sepsis according to the operational definition, and had aspartate aminotransferase (AST) and platelet laboratory parameters checked in the first 24 hours of sepsis and before administration of antibiotics. The exclusion criteria for this study were: liver and biliary system disorders, including perinatal conditions, (e.g. cholestatic jaundice, choledochal cysts, biliary atresia, or liver cirrhosis), blood disorders that interfere with platelet count, (e.g. immune thrombocytopenic purpura or aplastic anemia), malignancy, steroid or immunosuppressive drug use, congenital metabolic disorders, burns, as well as post-trauma or post-operative patients, and incomplete sepsis registry data. The definitions of respiratory failure, acute kidney injury, hematologic, and neurologic disorder were defined by the *International Pediatric Sepsis Consensus Conference*.[4] The basic subject data recorded were name, gender, age, diagnosis, length of treatment, complications, outcomes, laboratory results that supported the diagnosis of SALI, ALT, AST, and platelets. The APRi was calculated by the formula shown below:[8]

$$\frac{\text{AST : normal upper limit of AST}}{\text{platelet}} \times 100$$

Laboratory measurements were typically taken once within first 24 hours of sepsis. The results of the data analysis were grouped with the distribution of frequencies and proportions for categorical variables. Descriptive processing of numerical data included the mean statistical size, standard deviation, median, and range. Categorical data were analyzed by Chi-square test, while numerical data (both characteristic data and APRi data for inferential tests) were analyzed using T-test for two independent groups, if data were normally distributed, or Mann-Whitney U test if data were not normally distributed. Data analyses were performed using the *Statistical Package for Social Sciences (SPSS)* program for *Windows version 26.0*. Results with P values <0.05 and 95% confidence intervals were considered to be statistically significant. Estimation of the APRi cut-off value for early prediction of SALI was done with logistic regression analysis and receiver operating characteristic (ROC) curve.

This study was approved by the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung.

Results

From January 2019 until August 2020, 237 pediatric patients were registered in the sepsis register. A total of 112 patients met the inclusion criteria, with almost all categorized as having septic shock (94.6%). In addition, 48.2% had SALI (**Table 1**). All subjects who had SALI also suffered from septic shock.

As shown in **Table 2**, there were no significant differences in gender, length of stay, or acute renal impairment in the sepsis and septic shock groups (P>0.05 for all). Other variables had significant differences in the two groups, as follows: mean age of the septic shock group (50.60 months) was significantly greater than the sepsis group (18.83 months) (P=0.020), the septic shock group had significantly more complications

Table 1. Subjects classification based on sepsis and SALI categories

Categories	(N= 112)
Sepsis, n(%)	
Sepsis	6 (5.4)
Septic shock	106 (94.6)
SALI, n(%)	
Yes	54 (48.2)
No	58 (51.8)

Table 2. Characteristics of sepsis, septic shock, and SALI patients

Characteristics	Sepsis (n=6)	Septic shock (n=106)	P value	SALI (N=54)	Non-SALI (N=58)	P value
Gender, n(%)						
Male	5	56 (52.8)	0.299[a]	31 (57.4)	30 (51.7)	0.679[a]
Female	1	50 (47.2)		23 (42.6)	28 (48.3)	
Age, n(%)						
1-23 months	5	60 (56.6)	0.526[a]	32 (59.3)	33 (56.9)	0.191[a]
24-72 months	1	19 (17.9)		6 (11.1)	14 (24.1)	
72-155 months	0	12 (11.3)		6 (11.1)	6 (10.3)	
156-216 months	0	15 (14.2)		10 (18.5)	5 (8.6)	
Mean age (SD), months	18.83 (23.67)	50.60 (66.46)	0.020[b]	1.89 (1.21)	1.71 (0.97)	0.384[b]
Median age (range), months	9.5 (2-66)	17 (1-216)		16 (1-216)	17.5 (1-204)	
Mean length of stay (SD), days	10.50 (4.37)	10.82 (16.19)	0.962[b]	10.15 (16.94)	11.41 (14.73)	0.673[b]
Complication, n(%)						
Respiratory failure	0	87 (82.1)	0.000[a]	43 (79.6)	44 (75.8)	0.802[a]
Acute kidney injury	1	30 (28.3)	0.880[a]	13 (24.1)	18 (31)	0.541[a]
Hematologic disorder	0	53 (50)	0.049[a]	27 (50)	26 (44.8)	0.720[a]
Neurologic disorder	1	85 (80.2)	0.002[a]	44 (81.5)	44 (75.8)	0.362[a]
Outcomes, n(%)						
Improved*	6	23 (21.7)	0.000[a]	12 (22.2)	17 (29.3)	0.522[a]
Died	0	83 (78.3)		42 (77.8)	41 (70.7)	

Note: *improved=got better and were discharged from hospital; a) Chi-square; b) independent T-test of two groups

of respiratory failure (82.1%) than the sepsis group which had none (P=0.000), 50% of the septic shock group had hematological disorders, while none of the sepsis group did (P=0.049), neurological disorders were significantly higher in the septic shock group (80.2%) than in the sepsis group (1/6) (P=0.002), and there was a significant difference in outcome in the sepsis and septic shock groups, as all subjects in the sepsis group experienced improvement (100%) while 78.3% of the sepsis shock group died. In the SALI group, there were no significant differences in any of the variables (gender, age, length of stay, complications, and outcomes).

There were no significant differences in the four variables compared (ALT, AST, platelet, and APRi) in the sepsis and septic shock groups (**Table 3**). However, the ALT and AST levels were significantly higher in SALI compared to non-SALI group. Logistic regression analysis revealed that APRi was a significant predictor of SALI (P=0.045). The OR value of 1.098 (95%CI 1.002 to 1.203) indicates that APRi elevation increases the risk of SALI. Using an APRi cut-off of 4.726, we noted that 75% of subjects had an APRi value that exceeded the cut-off. The ROC curve is shown in **Figure 1**, with AUC 0.831 (or 83.1%), a value classified as strong (80-90%), and with 81.5% sensitivity and 62.4% specificity.

Discussion

In our study, the septic shock group had a significantly higher mean age than the sepsis group (50.60 *vs.* 18.83 months, respectively. A previous study reported that sepsis contributes to 19% of deaths globally, with the highest incidence in children less than 5 years of age.[10] The different functions of innate and adaptive immune responses in children and adults greatly influence the response of the host to infection and response to therapy.[11]

Table 3. Results of SALI laboratory analysis and APRi calculations

Variables	Sepsis (n=6)	Septic shock (n=106)	P value	SALI (n=54)	Non-SALI (n=58)	P value
Mean ALT (SD), mg/dL	681.17 (1,597.5)	148.09 (224.42)	0.451	331.11 (569.01)	32.84 (15.69)	0.000
Mean AST (SD), mg/dL	404.67 (814.41)	231.37 (346.48)	0.626	430.54 (479.13)	63.86 (53.9)	0.000
Mean platelet count (SD), /mm^3	186,166.67 (141,502.53)	265,288.68 (175,643.99)	0.776	269,296.3 (164,069.66)	263,717.24 (183,262.61)	0.866
Mean APRi (SD)	10.19 (23.47)	9.18 (47.92)	0.959	16.65 (66.58)	2.33 (7.5)	0.122

Note: unpaired two groups T-test

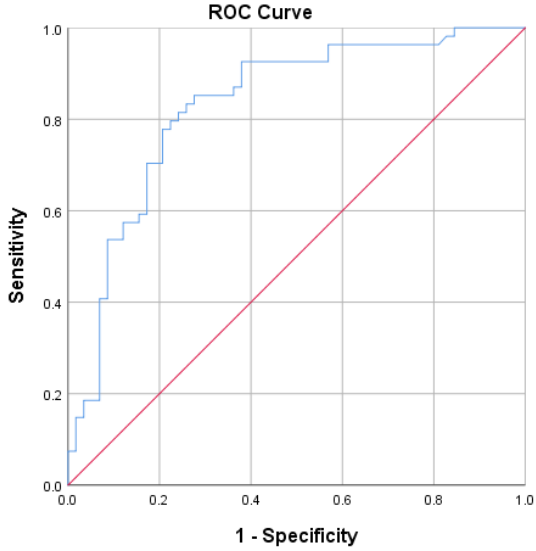

Figure 1. APRi ROC curve as a predictor of SALI

In our study, significantly more septic shock patients had complications such as respiratory failure, neurological and hematological disorders than sepsis patients without shock. However, SALI accompanied by other complications was not significantly different compared to non-SALI group (($P>0.05$). Sepsis-associated liver injury is an independent risk factor for multiple organ dysfunction syndrome (MODS) and mortality in pediatric sepsis.[4] A study reported a mean occurence of SALI of 39.9%, lower than the occurence of respiratory, renal and neurological dysfunction, but similar to the occurence of cardiovascular dysfunction.[6] Another study also reported that the incidence of SALI accompanied by complications of respiratory failure and neurological disorders was not significant ($P>0.05$).[5]

Outcomes in the sepsis and septic shock groups were significantly different, as all sepsis patients (6/6) had improvements while the septic shock group mostly died (78.3%). In 2017, the *American College of Critical Care Medicine* (ACCM) recommended the use of the trigger tool algorithm as a standard for clinical assessment of septic shock in a short period of time and to establish criteria to diagnose septic shock in children. Every hour of delay in identification and management of septic shock was associated with increased risk of patient mortality. In the pediatric emergency room, the triage device and sepsis management protocol are continuously modified to accelerate the recognition of sepsis signs, initiation of fluid resuscitation, and administration of antibiotics. Early identification and management of sepsis and septic shock lead to better outcomes.[12]

The ALT and AST variables in the SALI group were significantly higher from the septic shock group, respectively. Increased aminotransferase enzymes indicate acute cellular and mitochondrial injury. During the first 24 hours of acute hepatocellular injuries, such as hypotension or shock episodes, AST levels in the blood elevate higher than ALT, followed by a minimal elevation of gamma-glutamyl transferase (GGT). This occurrence is because AST activity in hepatocytes is higher than other enzymes. If the hepatocellular damage continues for 24-48 hours, the ALT level will rise higher than the AST level due to the shorter half-life of AST.[6,13] Hepatocellular injury can trigger the release of AST and ALT into the blood circulation.[14]

A study reported that APRi to predict SALI in children had a sensitivity and specificity of 84.6% and 84.3%, respectively.[5] Compared to the GGT and lactate dehydrogenase (LDH) markers, APRi had the best value for predicting SALI, thus, it can be used as a 'potential early-warning biomarker' to predict SALI in pediatric sepsis. An APRi increase to >0.34 in the first 24 hours was a significant predictor for assessing the early incidence of SALI in pediatric sepsis.[5] We also found that APRi was a significant predictor of SALI, as indicated by the logistic regression results. The OR value of 1.098 ((95% CI 1.002 to 1.203) indicated that increased APRi increased the risk of SALI, with an APRi cut-off value of 4.726. The APRi AUC was 0.831 or 83.1%, which was classified as strong (80-90%). Thus, the logistic regression estimation model obtained was considered to have met the requirements of being a reliable predictor model.

A limitation of our study was the retrospective design, thus, a longitudinal prospective study would be required to further elucidate the role of APRi in SALI. In conclusion, APRi is a reliable predictor of early detection of SALI in pediatric sepsis. The increase in APRi (> 4.726) within the first 24 hours of sepsis can predict the early occurrence of SALI in pediatric septic shock.

Conflict of Interest

None declared.

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