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TRANSAMINASE AND BILIRUBIN LEVELS AS PREDICTORS OF CHOLESTASIS MORTALITY RELATED TO NEONATUS SEPSIS

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ABSTRACT

Sepsis-associated cholestasis itself has a mortality rate of 52.8% in neonates. This high mortality rate is accompanied by the absence of methods in predicting death due to sepsis-related cholestasis. This study aims to determine the role of transaminase and bilirubin levels in predicting the death of patients with sepsis-associated cholestasis in neonates. Analytic observational research study with a cross sectional approach at Dr. Moewardi Hospital. Samples were obtained from the medical records of patients with cholestasis related to neonatal sepsis from 2020-2022. Bilirubin and transaminase statistically analyzed using ROC curves and logistic regression multivariate analysis. Of the 85 samples, 48 (56.5%) male patients and 37 (43.5%) female patients were obtained. In the analysis with the ROC curve, it was obtained for total bilirubin cut-off 10.13 mg/dl, direct bilirubin obtained cut-off 6.7 mg/dl, and indirect bilirubin obtained cut-off 3.62. AST had a cut-off of 49.5 IU/L and ALT had a cut-off of 30.5. In multivariate analysis, the direct bilirubin level had a p value of 0.001 with an adjusted OR of 10.93 and the AST level had a p value of 0.000 with an adjusted OR of 19.73. Direct bilirubin and AST levels can predict mortality in patients with neonate sepsis-associated cholestasis.

Keywords: Transaminase, Bilirubin, Mortality, Sepsis-related Cholestasis

ABSTRAK

Kolestasis terkait sepsis memiliki persentase kematian 52,8% pada neonatus. Tingginya angka kematian ini disertai dengan belum adanya metode dalam memprediksi kematian akibat kolestasis terkait sepsis. Penelitian ini bertujuan untuk mengetahui peran kadar transaminase dan bilirubin dalam memprediksi kematian pasien kolestasis terkait sepsis neonatus. Studi penelitian observasional analitik dengan pendekatan cross sectional. Penelitian ini dilaksanakan di RSUD Dr. Moewardi. Sampel didapatkan dari rekam medis pasien kolestasis terkait sepsis neonatus dari tahun 2020-2022. Data bilirubin dan transaminase dianalisis secara statistik menggunakan kurva ROC dan analisis multivariat regresi logistik menggunakan aplikasi SPSS. 85 pasien kolestasis terkait sepsis pada neonatus di RSUD Dr. Moewardi Surakarta. Dari 85 sampel didapatkan 48 (56,5%) pasien laki-laki dan 37 (43,5%) pasien perempuan. Pada analisis dengan kurva ROC didapatkan untuk bilirubin total cut-off 10,13 mg/dl, bilirubin direk didapatkan cut-off 6,7 mg/dl, serta bilirubin indirek mendapatkan cut-off 3,62. AST mendapatkan cut-off 49,5 IU/L dan ALT mendapatkan cut-off 30,5. Pada analisis multivariat, kadar bilirubin direk mendapatkan nilai p 0,001 dengan adjusted OR 10,93 dan kadar AST mendapatkan nilai p 0,000 dengan adjusted OR 19,73. Kadar bilirubin direk dan AST dapat memprediksi mortalitas pada pasien kolestasis terkait sepsis neonatus.

Kata Kunci**:** Transaminase, Bilirubin, Mortalitas, Kolestasis terkait Sepsis

INTRODUCTION

Sepsis in neonates is a substantial cause of mortality and morbidity for neonates (Chhavi *et al.*, 2022). Data from 2019 states that sepsis is one of the leading causes of neonate mortality in Indonesia. This high mortality rate is accompanied by the absence of methods in predicting death due to sepsis-related cholestasis. Although there have been studies that examined several methods and indications for predicting death from neonatal cholestasis (Choi *et al.*, 2022; Mahmud *et al.*, 2022; Singh et *al.*, 2022).

Elevated levels of direct bilirubin may occur in the presence of hepatocellular damage or in cholestasis (Tripathi and Jialal, 2022). (Tripathi dand Jialal, 2022). Cholestasis is diagnosed if the level of directed bilirubin is >20% of total bilirubin. There are two types of transaminase enzymes used in liver function tests, namely *Serum Glutamic Oxaloacetic Transaminase (*AST) and *Serum Glutamic Pyruvic Transaminase (*ALT). Both of these enzymes are specific indicators of hepatocellular damage with the ALT enzyme being a more specific indicator than AST (Lala *et al.*, 2021).

High transaminase enzyme levels indicate a worse prognosis in cases of cholestasis (Hall dand Cash, 2012; Choi *et al.*, 2022). High bilirubin levels in the blood can also cause damage to the neonate's still developing central nervous system. Higher levels of total bilirubin and AST are also related with an increased risk of mortality (Choi *et al.*, 2022).

With a high incidence of mortality in cholestasis associated with neonatal sepsis. This study aims to determine the role of transaminase and bilirubin levels in predicting the mortality of patients with cholestasis associated with neonatal sepsis by utilizing liver function tests, namely bilirubin and transaminase, which are commonly performed supporting examinations with minimal costs.

METHODS

This study used an analytic observational research study with a *cross sectional* approach. The population used was neonate patients with sepsis-related cholestasis. This study was conducted at Dr. Moewardi Regional General Hospital, Surakarta, Central Java. Samples were obtained from medical records of patients with cholestasis related to sepsis neonates from 2020-2022. Bilirubin and transaminase data will be statistically analyzed using ROC curve and logistic regression multivariate analysis using SPSS application.

RESULTS

A sample of 85 patients with sepsis-related cholestasis in neonates at Dr. Moewardi Surakarta Hospital was obtained. Of the 85 samples, 48 (56.5%) male patients and 37 (43.5%) female patients were obtained with an average initial age of 5.41 days and an average length of treatment of 21.81 days. Based on birth weight, there were 58 (68.2%) patients with low birth weight (BBLR) and 27 (31.8%) patients with adequate birth weight (BBLC). Then the gestational age of preterm patients was 49 (57.6%) patients and 36 (42.4%) aterm patients. In the sample characteristics, the significant variables ($p < 0.05$) were gender and birth weight with p values of 0.039 and 0.043. The characteristics of this study sample can be seen more fully in Table 1.

Table 1.
Characteristics of the Research Sample

Characteristics	Mortality		Total	p-value
	Died	Live		
Gender[a]				0,039*
Female	14	23	37 (43,5%)	
Male	29	19	48 (56,5%)	
Age[b]				0.412
Mean +SD	6,23	4,57	5.41 ± 8.46	
Median (min-max)	1	0	0 (0-30)	
Length of treatment[b]				0.836
Mean +SD	22,72	20,88	21,81 ±15,4	
Median (min-max)	18	20	19 (3-95)	
Birth Weight[a]				0,043*
BBLR	25	33	58 (68,2%)	
BBLC	28	9	27 (31,8%)	
Pregnancy Age[a]				0,221
Preterm	22	27	49 (57,6%)	
Aterm	21	15	36 (42,4%)	

Notes: a. *Pearson's Chi Square* Test; b. *Mann Whitney* Test*; *)* significant $p<0.05$

The results of the examination of serum bilirubin levels consisting of total, directed and indirected bilirubin as well as transaminase enzymes, namely AST and ALT, can be seen in Table 2. The p value <0.05 was obtained in the variables of total, directed and indirected bilirubin as well as AST and ALT which showed a significant relationship between these variables and the mortality of patients with cholestasis related to neonatal sepsis.

Table 2.
Bilirubin and Transaminase Levels on Mortality

Variables	Mortality		p-value
	Died	Live	
Total Bilirubin			0.000*
Mean +SD	15,53 ±12,78	6,72 ±5,03	
Median (min-max)	12,58 (1,33-57,75)	5,1 (2,24-30,49)	
Direct Bilirubin			0.000*
Mean +SD	11,09 ±9,51	3,8 ±3,68	
Median (min-max)	8,86 (1,2 - 41,23)	2,28 (1,08 - 21,4)	
Indirect Bilirubin			0.034*
Mean +SD	4,67 ±4,04	2,92 ±2,92	
Median (min-max)	3,69 (0,13 - 16,52)	2 (0,31 - 16,4)	
AST			0.000*
Mean +SD	279,74 ±393,22	49,36 ±60,06	
Median (min-max)	104 (29 - 2281)	35 (13 - 386)	
ALT			0.000*
Mean +SD	132,19 +190,02	24,67 ±29,55	
Median (min-max)	60 (11 - 915)	16,5 (6 - 190)	
Notes: *Mann Whitney* test, **)* significant *(p < 0.05)*			

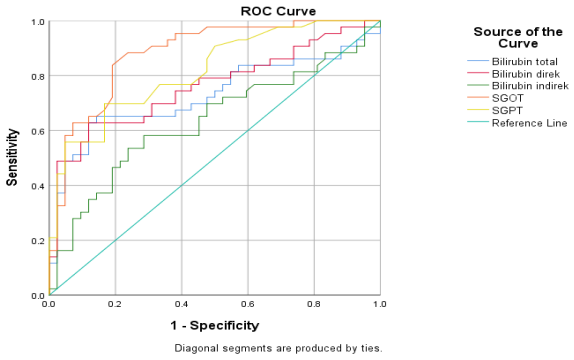

Figure 1. ROC Curve of Transaminase and Bilirubin on Patient Mortality

In the diagnostic test analysis using the *Receiver Operating Characteristic* (ROC) curve. The *Area Under Curve* (AUC), Cut-off, Sensitivity, Specificity, NDP, and NDN values can be seen in table 3.

Table 3.
Diagnostic Test of Bilirubin and Transaminase in Prediction of Mortality of Sepsis-Associated Cholestasis of Neonates

Variables	AUC	Cut-off	Sensitivity	Specificity	NDP	NDN
Total Bilirubin	0,729	10,13	62,80%	88,10%	84,40%	69,80%

Direct Bilirubin	0,761	6,7	62,80%	88,10%	84,40%	69,80%
Indirect Bilirubin	0,633	3,62	53,50%	76,20%	69,70%	61,50%
AST	0,882	49,5	83,70%	81,00%	81,80%	82,90%
ALT	0,818	30,5	69,80%	83,30%	81,80%	72,90%

In the analysis with the ROC curve, it was obtained for total bilirubin cut-off 10.13 mg/dl with AUC 0.729, direct bilirubin obtained cut-off 6.7 mg/dl with AUC 0.761, and indirect bilirubin obtained cut-off 3.62 with AUC 0.633. As for transaminase enzymes, AST had a cut-off of 49.5 IU/L with an AUC of 0.882 and ALT had a cut-off of 30.5 with an AUC of 0.818.

Table 4.
Multivariate Analysis Using Logistic Regression

	Crude		Adjusted	
	OR (95%IK)	p	OR (95%IK)	p
Total Bilirubin				
≥10,13	12,48 (4,07-38,27)	0,000	0,43 (0,26-7,45)	0,568
<10,13	Ref.		Ref.	
Direct Bilirubin				
≥6,7	12,48 (4,07-38,27)	0,000	10,93 (2,72-43,85)	0,001*
<6,7	Ref.		Ref.	
Indirect Bilirubin				
≥3,62	3,68 (1,45-9,31)	0,006	2,44 (0,58-10,19)	0,221
<3,62	Ref.		Ref.	
AST				
≥49,5	21,85 (7,15-66,81)	0.002	19,73 (5,50-70,74)	0,000*
<49,5	Ref.		Ref.	
ALT				
≥30,5	11,53 (4,07-32,65)	0,000	2,10 (0,46-9,48)	0,333
<30,5	Ref.		Ref.	
Gender				
Male	0,39 (0,16-0,96)	0.041	0,608 (0,16-2,25)	0,457
Female	Ref.		Ref.	
Birth Weight				
BBLR	0,379 (0,146-0,98)	0,046	0,79 (019-3,2)	0,742
BBLC	Ref.		Ref.	

Notes: **)* significant *(p < 0*.05)

Variables with a p value <0.05 will be included in the logistic regression multivariate analysis model so that the Odds Ratio (OR) can be seen in Table 4. In the multivariate analysis, direct bilirubin levels had a p value of 0.001 with an *adjusted* OR of 10.93 and AST levels had a p value of 0.000 with an *adjusted* OR of 19.73.

DISCUSSION

Cholestasis is defined as an anatomical or functional obstruction to bile flow resulting in the accumulation of bile products (bilirubin, bile acids, and cholesterol) in the liver, blood and extrahepatic tissues. (Fischler and Lamireau, 2014; Kaur and Wadhwa, 2019; Chhavi *et al.*, 2022). Neonatal cholestasis is characterized by yellow skin for more than 14 days or recurrent after the second week of life (or by hepatomegaly, failure to thrive, gray stools, and dark urine before or after 2 weeks of age) 2.16 44 Cholestasis is classified according to its etiology into extrahepatic and intrahepatic (Fischler and Lamireau, 2014; Kaur and Wadhwa, 2019; Chhavi *et al.*, 2022)

Sepsis-associated cholestasis has a 2.25 times risk of death compared to neonates without cholestasis and has a mortality percentage of 52.8% in neonates (Ghenu *et al.*, 2022).

Cholestasis is characterized by an increase in bilirubin, namely where the direct bilirubin is more than 20% of the total bilirubin if the total bilirubin is more than 5 mg/dl or the directed bilirubin is more than 1 mg/dl if the total bilirubin is less than 5 mg/dl.(Ghenu *et al.*, 2022). In addition to bilirubin, liver enzymes such as AST and ALT that increase in serum levels indicate hepatocellular damage (Dani *et al.*, 2015). This is in accordance with research (Ghenu *et al.*, 2022) which explains the occurrence of hyperbilirubinemia and an increase in liver serum indicates the occurrence of liver disorders. Liver function tests in this study were taken data on total bilirubin levels, directed bilirubin, indirected bilirubin, AST and ALT and then analyzed.

In the sample characteristics, it was found that patients died more in the male gender, namely 29 samples while living patients were more in women, namely 23 samples. (Basha, Woya and Tekil, 2020) in his research stated that there was an connection between perinatal mortality and male gender (OR = 1.2; 95%CI, 1.07 - 1.34). 29 Female neonates compared to male neonates were 0.60 times less likely to die (AOR=0.60; 95%CI: 0.47-0.75).

The total number of BBLR patients in this study was 58 (68.2%) patients which was more than BBLC patients. Patients with a history of preterm gestational age also had more than aterm patients where preterm patients amounted to 49 (57.6%) patients. This is in accordance with research (Menalu *et al.*, 2022) which states that preterm newborns have a 4 times higher risk of death than full-term newborns [AHR 4.2 (95% CI: 1.32-8.83)]. Low birth weight is at higher risk for complications of birth asphyxia, hypothermia, feeding problems, infection, and prematurity, having surfactant deficiency, intraventricular hemorrhage, respiratory distress syndrome, and/or necrotizing enterocolitis which increases the risk of death compared to normal birth weight infants. (Mengesha and Sahle, 2017; Menalu *et al.*, 2022).

Prematurity and low birth weight are associated with an increased risk of neonatal sepsis. (Liang *et al.*, 2018) explained that the main causes of death were prematurity 23 (34%), and asphyxia 21 (31%) which accounted for 2 out of 3 deaths. The rest were caused by infection 8 (12%), congenital abnormalities 5 (7%), and other causes 11 (16%). (Ezeh *et al.*, 2014; Mengesha and Sahle, 2017) in his research explained that the chance of perinatal death in low birth weight infants is about 9.6 times higher than infants with normal birth weight (OR = 9.6; 95%CI, 6.12-15.02).

In bivariate analysis using *mann whitney*, the *p-value of* total bilirubin (p=0.000), directed bilirubin (p=0.000), indirected bilirubin (p=0.034), AST (p=0.000) and ALT (p=0.000) were found to be $p<0.05$ which means that the examination was statistically proven to show significant differences between patients with cholestasis related to sepsis neonates who died and those who lived.

In the diagnostic test analysis using the ROC curve, the AUC values for total bilirubin (AUC=0.729), direct bilirubin (AUC=0.761), indirect bilirubin (AUC=0.633), AST (AUC=0.882) and ALT (AUC=0.818) were obtained. The AUC of indirect bilirubin was between 0.7-0.8 which is acceptable and the AUC of total bilirubin, direct, AST, and ALT were between 0.8-0.9 which is very good.(Mandrekar, 2010). Cut-offs were obtained for total bilirubin (cut-off = 10.13mg/dl), directed bilirubin (cut-off = 6.7 mg/dl), indirected bilirubin (cut-off = 3.62 mg/dl), AST (cut-off = 409.5 IU/L), and ALT (cut-off = 30.5 IU/L). After obtaining these cut-offs, the variables will be categorized according to the cut-offs obtained respectively**.**

Neonatal sepsis is classified according to the time of onset as early or late. Early neonatal sepsis is the onset of clinical conditions within the first 72 hours of life. Late neonatal sepsis is the onset of clinical conditions after 72 hours of life.(Chhavi *et al.*, 2022). (Procianoy and Silveira, 2020)

mentioned that the initial signs and symptoms of neonatal sepsis are often mild and non-specific. However, the course of the disease continues until septic shock, respiratory distress, neurological dysfunction, and even death occur. Thus, rapid, appropriate and adequate examination is essential for the diagnosis of neonatal sepsis (Dong *et al.*, 2020)

(Liang *et al.*, 2018; Vizcarra-Jiménez *et al.*, 2022) mentioned that neonatal sepsis is a significant contributor to morbidity and mortality. In their study, they explained that the three main causes of neonatal mortality in developing countries are prematurity (21.8%), infection (18.5%), asphyxia (31.6%) which causes almost 70% of deaths. 26 36 The initial diagnosis is usually based on laboratory results, showing hyperglycemia, hypoglycemia, acidosis, and hyperbilirubinemia. (Singh, Alsaleem and Gray, 2022).

In multivariate analysis, the *adjusted Odds Ratio* and *p-value* were obtained where only bilirubin direct and AST had a *p-value* <0.05 so that these two variables were the dominant factors in predicting mortality of patients with cholestasis associated with neonatal sepsis. Directed bilirubin got OR 10.93 which means if the patient's direct bilirubin level ≥ 6.7 mg/dl has a risk of death 10.93 times greater than in patients with direct bilirubin < 6.7 mg/dl. AST had an OR of 19.73 which means that patients with AST levels ≥ 49.5 IU/L had a risk of death 19.73 times greater than patients with AST levels < 49.5 IU/L. Explaining that sepsis can be associated with increased liver and bile enzymes due to abnormal liver excretory function (Ghenu *et al.*, 2022)

AST enzyme is one of the liver enzymes located in the mitochondria and cytosol of hepatocytes. AST enzyme can also be found in the heart, skeletal muscle, kidney, brain and red blood cells. Severe liver damage will lead to increased AST enzyme secretion and increased AST is also associated with multi-organ damage caused by sepsis. (Ghenu *et al.*, 2022). According to a study by Choi *et al.*, 2022 peak direct bilirubin levels are positively correlated with mortality within 1 year (Choi *et al.*, 2022). High direct bilirubin is also associated with worse prognosis in neonatal cholestasis(Carneiro *et al.*, 2017).

LIMITATION OF THE STUDY

The limitations of this study include the fact that laboratory data were collected at only one point in time, with no follow-up, making it impossible to observe the progression of patients over time. Another limitation is that the treatment and management practices were not included in the study, which could potentially act as confounding factors.

CONCLUSIONS

Direct bilirubin and AST levels can predict mortality in patients with cholestasis associated with neonatal sepsis. Patients with cholestasis related to neonatal sepsis who had direct bilirubin levels ≥ 6.7 mg/ml and AST levels ≥ 49.5 IU/L had a higher chance of death. Patients with direct bilirubin level (≥ 6.7 mg/ml) had an OR of 10.93 for death and patients with AST level (≥ 49.5 IU/L) had an OR of 19.73 for death.

SUGGESTIONS FOR FUTURE RESEARCH

This study could be advanced by employing alternative analytical methods or by using a cohort study design to gain more comprehensive insights throughout the entire treatment process. Furthermore, future research could include more frequent assessments across multiple centers, focusing on their ability to predict mortality in neonates with sepsis-related cholestasis.

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