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Neutrophil to Lymphocyte Ratio, is it A Good Marker for Determining Degree of Fibrosis in Biliary Atresia?

Bagus Setyoboedi[1], Sunny Mariana Samosir[2], Rendi Aji Prihaningtyas[3], Sjamsul Arief [4], Alphania Rahniayu[5]

[1,2,3,4]Department of Child Health, Dr. Soetomo General Academic Hospital – Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia

[5]Department of Pathology Anatomy, Dr. Soetomo General Academic Hospital – Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia

ABSTRACT

Biliary atresia (BA) can progress to liver fibrosis and cirrhosis. The Neutrophil-to-lymphocyte ratio (NLR) integrates two immune pathways - neutrophils, which illustrate continuous inflammation, and lymphocytes, which illustrate the regulatory pathways. It has been used to evaluate the degree of fibrosis in other liver diseases, such as fatty liver disease and chronic hepatitis. This study aims to correlate NLR and the degree of fibrosis in infants with BA. A cross-sectional study was conducted at Dr. Soetomo General Academic Hospital, Surabaya between January 2014 and April 2019. Twenty-six paraffin blocks of wedge liver biopsy from Kasai procedure in BA children were examined. All paraffin blocks were re-stained with Masson's trichrome. The degree of liver fibrosis was evaluated. The fibrosis scores were calculated using the Metavir scoring system in 5 classes (F0 no fibrosis; F1 fibrous portal expansion; F2 few bridges or septa; F3 numerous bridges or septa; F4 cirrhosis). NLR was assessed from a complete blood count one week before surgery. Spearman correlation with p-value < 0.05 is considered significant. A total of 17 of 26 children were female. The median age at surgery was 159 (80-216) days. The mean NLR was 1.85 (0.39-5.97). After histopathologic examination, Metavir scores of F2, F3, and F4 were found in 2/26 patients, 12/26 patients, and 12/26 patients, respectively. There was no correlation between NLR and the degree of fibrosis (r=-0.31; p=0.882). The neutrophil-to-lymphocyte ratio could not represent fibrosis severity in BA children.

KEYWORDS: Biliary atresia, Degree of fibrosis**,** Neutrophil-to-lymphocyte ratio

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I. INTRODUCTION

Biliary atresia (BA) is an obliterative condition of the biliary tract presenting with jaundice and pale stools within the first few weeks of life. Liver fibrosis, cirrhosis, and end-stage liver failure and death will inevitably occur within the first year or so if left untreated[1,2]. Fibrosis develops rapidly and is more aggressive in children than other biliary cirrhosis in adults. Early surgical intervention by portoenterostomy reconstruction (Kasai procedure) gives a curative effect in some patients, while others progressed to end-stage liver disease in need of liver transplant[3,4]. Infants with advanced fibrosis had worse clinical outcomes and overall survival of the liver compared to mild and moderate fibrosis[5,6]. The current method to evaluate fibrosis is liver biopsy, which is considered invasive, time-consuming, costly, and not available in every center[7].

Several surrogate markers and scoring systems have been studied to evaluate fibrosis degrees, such as *Aspartate transaminase to Platelet Ratio Index (*APRi), *infant Biliary Atresia Fibrosis score*, FIB-4, FibroQ, King's *score*, Goteborg *University Cirrhosis index*, dan *Aspartate transaminase – Alanine transaminase score*, *infant BA liver fibrosis (iBALF)*[8,9]. Neutrophil to Lymphocyte Ratio (NLR) is a simple systemic inflammatory marker of the complete blood type count used as a less invasive method to determine the severity of liver fibrosis [10]. NLR is associated with the liver fibrosis stage, especially in patients with nonalcoholic fatty liver disease (NAFLD) and severe fibrosis[11]. In addition,

NLR may be a useful biomarker for assessing the prognosis of cirrhotic patients. Therefore, the aim of this study was to investigate the correlation between NLR and the degree of fibrosis in children with BA.

II. METHODS

The study was a cross sectional design. Patients with biliary atresia at the Dr. Soetomo General Academic Hospital in Surabaya were included in the study between January 2014 and April 2019. The diagnosis of BA was established by liver biopsy during Kasai surgery. Histological studies were performed from a core biopsy of the liver that was taken during the Kasai operation. Liver wedge biopsies were fixed with 10% formaldehyde. They were processed into paraffin blocks. The blocks were sectioned. They were stained with Masson's trichrome. The anatomy pathologist consultant assessed the degree of fibrosis based on Metafir criteria (F0: without fibrosis, F1 fibrosis porta without septa, F2 fibrosis porta with slight septa, F3 fibrosis porta with many septa without cirrhosis, F5 cirrhosis)[12]. Laboratory and clinical data were blinded by the anatomy pathologist.

The NLR was obtained from a complete blood count that was performed a maximum of one week prior to the Kasai procedure. Patients with a history of blood transfusion within 30 days before Kasai were excluded from the study. Clinical data, including sex, age at Kasai, and laboratory markers, were evaluated.

Descriptive analysis was carried out using statistical measures (frequency and mean). A normality test was performed using the Shapiro-Wilk test. Spearman's correlation strength test was then conducted with a significant value of 0.05.

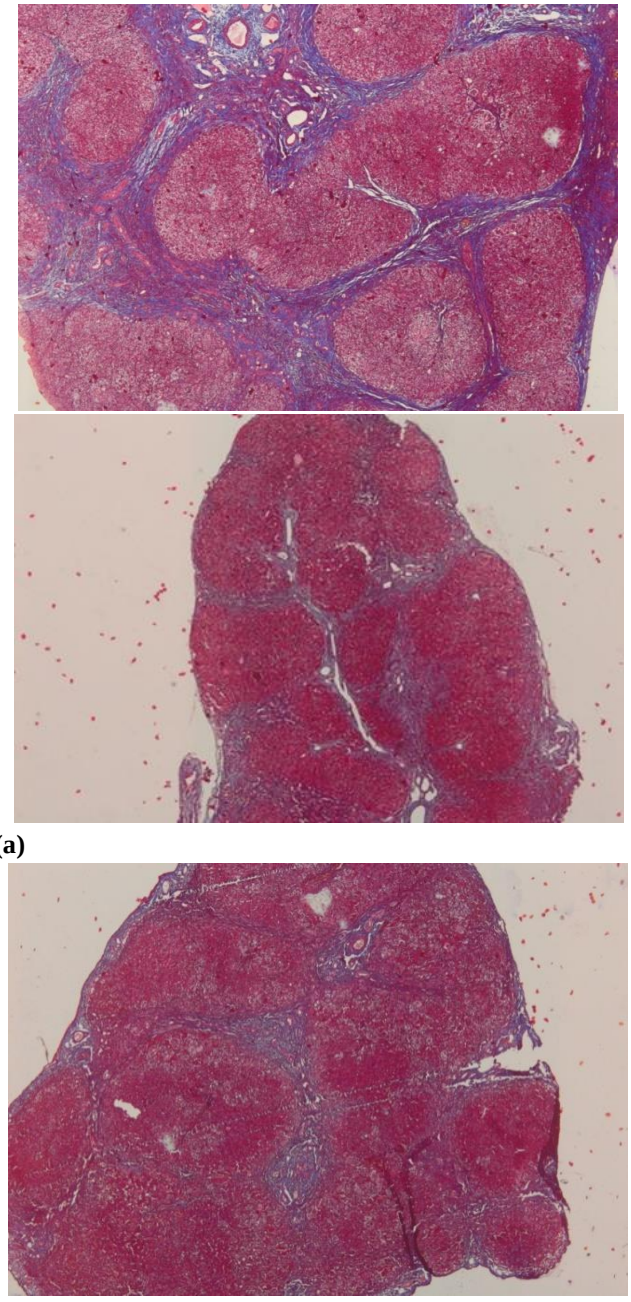
III.RESULTS

In 5 years, there were 30 children with BA, 26 of whom underwent Kasai procedure and a liver biopsy. Overall, 9/26 patients were male. The mean age at which the Kasai procedure was performed was 151 days (range 80 to 216 days). The average conjugated bilirubin before surgery was 9.17 mg/dL. The average NLR value of the patients was 1.85 (range 0.39 - 5.97). The degree of fibrosis varied in the specimens studied, with moderate to severe fibrosis predominant, leading to a poor prognosis (Table 1). Three months after surgery, the survival rate of the patients was 38%.

TABLE 1. PATIENT CHARACTERISTICS

Characteristics	Results	n = 26
Sex	Male	9
	Female	17
NLR	1.85	(0.39-5.97)
Age of Kasai (days)	151.65 (±39.61)	80-216
Degree of fibrosis	F0	0
	F1	0
	F2	2/26
	F3	12/26
	F4	12/26
Conjugated bilirubin level	9.17	3.044
Total bilirubin level	11.73	SD 4.342
ALT	Mean 306.73	SD 195.87
AST	Mean 283.96	SD (170.83)

**NLR: Neutrophil to Lymphocyte Ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase*



(a)

(b)

Figure 1. ***Examples of histologic fibrosis in BA, using glass slides stained with Masson Trichrome (40x magnification); (a) F2 few bridges/septa; and (b) F3 numerous bridges/septa without cirrhosis; F4 cirrhosis)***

IV. DISCUSSION

Previously, the evaluation of liver fibrosis in Biliary atresia has been conducted through the subjective inspection of bile ducts using trichrome staining of liver tissue taken from the Kasai surgery or liver transplantation.[13] Prior investigations utilizing histological methods have established a correlation between the presence of inflammation and fibrosis, and unwanted clinical outcomes.[6,14–16] The current method to evaluate fibrosis is liver biopsy, which is considered invasive and not available in every center.[7] Therefore, a reliable fibrogenesis marker is valuable in the management of biliary atresia.

Although after the atretic bile ducts are surgically removed and bile drainage is restored, the majority of patients still experience the progression of liver disease, which suggests the existence of non-cholestatic fibro genic pathways as well. These could involve both immunological and non-immune processes, like oxidative stress and recurrent cholangitis.[13] The mechanisms involved in the advancement of fibrosis in some particular patients remain unexplained.[3] There are various pathogenic processes of disease, but there is growing evidence that inflammation plays a role in causing damage to the bile ducts.[14] Progressive cirrhosis is known to be primarily caused by systemic inflammation.[10]

NLR and its correlation with liver fibrosis are evaluated in this study. Lymphocytes, which represent the regulatory system, and neutrophils, which maintain inflammation, contribute information regarding these markers.[17]

Kekilli et al. discovered that in adult chronic hepatitis B patients with significant fibrosis, lower levels of peripheral blood NLR had high sensitivity, specificity, and predictive values. Most of the patients were in the earlier stage of fibrosis[17] In contrast, a study in adult chronic hepatitis C patients shows that higher NLR is related to advanced fibrosis[11] Similar to the result from chronic hepatitis C patients, a study from non-alcoholic steatohepatitis revealed that with each one-unit increase in NLR, the likelihood of having fibrosis increased by 50%.[18] Unlike most previous studies that were performed in adult patients with several etiology of fibrosis and cirrhosis, all the subjects in this study were children.[10]

No correlation between NLR and degree of fibrosis was reported in this study. Neutrophil, lymphocyte, monocyte, basophil and absolute eosinophil numbers increase with age. In infants and children, there is a tendency to shed imaginal granulocytes into the circulation (causing very high WBC > 50,000/mm3). Newborn neutrophilia-acquired lymphocytes became a predominant WBC in the first two years of life. NLR becomes a neutrophil predomination as an adult when the child is five years old.[19]

However, this study has several weaknesses. First, the cross-sectional study design. Second, the sample is homogeneous. Most of the patients presented late with higher stage of fibrosis. Therefore, observation of other less invasive markers of liver fibrosis and referral algorithms to enroll younger patients are needed for further studies.

V. CONCLUSIONS

In summary, NLR is not a reliable indicator of the level of fibrosis in children with biliary atresia. However, the high rate of advanced fibrosis at the time of Kasai in our study encourages early referral in cases of prolonged cholestasis suspected to be biliary atresia for earlier treatment and a better outcome.

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