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ASSOCIATION BETWEEN IMMUNE-INFLAMMATION INDEX (SII) AND FERRITIN WITH HEPATIC FUNCTION IN PATIENTS WITH THALASSEMIA MAJOR

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ABSTRACT

Background: Thalassemia major is associated with ferritin levels and SII values with impaired liver function. Furthermore, the measurement of impaired liver function is carried out using Serum Glutamate Oxaloacetate Transaminase (SGOT) and Serum Glutamate Pyruvate Transaminase (SGPT) levels. Increased SGPT and SGOT levels are indicators of liver necrosis. **Objective**: This study aimed to prove the association between SII and ferritin with SGPT and SGOT levels in thalassemia major patients. **Methods**: An observational analysis with a cross-sectional approach was adopted to analyze the medical records of pediatric patients at the Kasuari Clinic of Dr. Kariadi Hospital Semarang from September to October 2023. SII value and ferritin level were the independent variables, while SGOT and SGPT were dependent. Data were collected and analyzed univariately for characteristic description and bivariately using the Spearman test. **Results:** The median SII value, ferritin level, SGPT level, and SGOT level in thalassemia major patients were 451.73/L, 2097.30 ng/mL, 20.00 U/L, and 40.00 U/L. The results showed there was a moderately significant association between SII values and SGOT levels (p=0.010, r=-0.457) as well as ferritin and SGPT (p=007, r=0.475). There was no significant association between SII values and SGPT levels, as shown by a p-value of 0.122. Similarly, there was no association between ferritin and SGOT levels (p=0.088). **Conclusion**: A moderately significant association was found between SII values and SGOT levels, as well as ferritin levels and SGPT levels in thalassemia major patients.

Keywords: *Thalassemia Major; SII; Ferritin Level; SGPT Level; SGOT Level*

INTRODUCTION

Thalassemia is a genetic disease characterized by hemolysis due to impaired hemoglobin formation in red blood cells. This disease is divided into three clinical types, namely major, intermedia, and minor. A precious study has shown that thalassemia major - is the most severe type of the disease[1].

The World Health Organization (WHO) stated that 7% of the world's population are carriers of thalassemia β. A report from the Thalassemia International Federation states that the prevalence in Asia ranged from 1-15%[2]. In the Southeast Asian population, the number of carriers of hemoglobinopathies and thalassemia is 45.5%. Data in Indonesia states that the prevalence ranges between 3% and 10%[1]. According to Basic Health Research of Central Java Province (2007), 0.3% of patients who suffered from this disease in Semarang City were 0.3%[3]. Based on these reports, thalassemia can be regarded as a genetic hemolytic disease with the highest incidence[1].

Thalassemia patients are managed using routine transfusions, which can cause iron accumulation, thereby increasing the level of ferritin[4]. Iron overload can also cause several significant complications in thalassemia major patients. Consequently, factors, such as the immune system, may contribute to the development of complications in these patients[5].

The systemic immune-inflammation index (SII) is a new marker of inflammation. It is calculated by the formula SII = P x N/L where P, N, and L are the number of cells per liter of peripheral blood for platelets (P), neutrophils (N), and lymphocytes (L)[6,7]. This new marker is a prognosis factor for decreased overall survival (OS)[8]. SII values reflect systemic inflammation and also serve as a between innate and adaptive immunity[9]. Compared to the other markers, such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR), SII more accurately reflects the balance between immune conditions and the inflammatory status of patients[10]. Thalassemia major patients are known to have high numbers of neutrophils and lymphocytes[5]. A previous study by Origa (2017) found changes in platelet-derived growth factor in thalassemia major patients[11].

Ferritin is the main protein that stores iron in the human body. The level of ferritin is a good marker for

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iron overload as it is easy to test, available in various laboratories, and has a good association with the results of liver histology examinations. High ferritin levels show an increased level of plasma iron[5]. A study by Mishra et al. (2013) concluded that patients with thalassemia major have high ferritin levels[12].

Routine life-saving blood transfusions for thalassemia β major patients and iron accumulation in the liver can cause liver function impairment. It is measured by serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels[13]. Furthermore, routine management of blood transfusions causes an increase in SGPT and SGOT after ten times[14,15]. SGPT is an enzyme found in liver, heart, muscle, and kidney tissues. An increase in the enzyme is a sign of liver cell damage because it is the earliest and exhibits a slower return to normalcy compared to other examinations[16]. A study by Salama et al. (2015) showed that iron overload was the leading cause of increased SGPT[17]. Meanwhile, SGOT is an enzyme found in the heart and liver[18]. The levels of SGOT are used to determine inflammation that occurs in the body and is often an indication of liver problems[19]. A previous study by Joniarti et al. (2022) suggested that the average SGOT level in thalassemia major patients was 54.96 U/l[20].

SII value has a positive association with increased liver steatosis, which can progress to hepatocyte damage[21]. Furthermore, the accumulation of iron (Fe) in the liver can cause the appearance of reactive oxygen substances, or free radicals[4].

A previous study showed that inflammation in thalassemia patients can occur due to iron accumulation[22]. The onset of inflammation can also lead to liver dysfunction[23]. Ferritin levels exceeding 1,000 ng/mL in thalassemia patients due to iron overload cause organ dysfunction, appearing first in the liver[24]. Nuari et al. (2016) showed an association between increased ferritin levels and impaired liver function in patients with thalassemia β major[25]. None of these studies focused on SII with liver function in thalassemia major patients and its association with ferritin. Therefore, further studies need to be carried out on SII and ferritin with SGPT and SGOT in thalassemia major patients.

METHODS

This was an analytic observational study with a cross-sectional approach. The study used the medical records of patients with thalassemia major at the Dr. Kariadi Hospital Semarang from 2020 to October 2023. The inclusion criteria were patients diagnosed with thalassemia major, aged 0-18 years, male and female, and who had performed blood transfusions a minimum of ten times. The exclusion criteria were patients having liver cirrhosis before being diagnosed with thalassemia major, currently suffering from infection (hepatitis), those with other hematological disorders (hemolysis anemia), and cancer. The number of subjects based on the calculation was 30 samples.

The independent variables included SII value and ferritin, while the dependent variables were SGOT and SGPT levels. The variables used in this study were defined on a numerical scale. Furthermore, the collected data were processed using computer software. A univariate analysis was carried out on ferritin, SGOT, and SGPT levels of thalassemia major patients at Dr. Kariadi Hospital to determine the description of the data characteristics. This was followed by bivariate analysis using the Spearman test because the variables were numerical. The test was carried out four times according to the number of independent and dependent variables. The details included (1) association of SII values with SGPT levels, (2) association of SII values with SGOT levels, (3) association of ferritin with SGPT levels, and (4) association of ferritin levels with SGOT levels.

RESULTS AND DISCUSSION

Results

The population data were obtained from the medical records of Dr. Kariadi Hospital, Semarang. The required sample was 31 determined through calculation, satisfying the inclusion and exclusion criteria. All subjects were thalassemia major patients diagnosed based on anamnesis, physical examination, supporting examination, and had performed ≥10× blood transfusions. The subjects did not suffer from hepatitis, hemolysis, anemia, and cancer, and there was also no history of liver cirrhosis.

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Table 1. Characteristics of research subjects

Variable	n (%)	Median (Min – Max)	p*
Sex		-	-
Male	16 (51.6%)		
Female	15 (48.4%)		
Age		-	-
Toddler (1 – 5 years)	1 (3.2%)		
Children (6 – 10 years)	11 (35.5%)		
Teenager (10 – 18 years)	19 (61.3%)		
Number of Blood Transfusions (×)		49 (15 – 106)	-
Ferritin Level (ng/mL)		2097.30 (291.40 – 7833.30)	0.002
SII Value (/L)		45.73 (129.48 – 1307.21)	0.113**
SGPT Level (U/L)		20.00 (9.00 – 134.00)	0.000
SGOT Value (U/L)		40.00 (17.00 – 138.00)	0.000

* = *Saphiro-Wilk test*
** = Significant (p < 0.05)

Table 2. Association between SII values and SGPT and SGOT levels

Dependent Variable	Independent Variable SII Value(/L)*	
	r	p
SGPT Level (U/L)	-0.283	0.122
SGOT Level (U/L)	-0.457	0.010**

* = *Spearman test*
** = Significant (p < 0.05)

A Spearman test was used to analyze the association between SII values and SGPT levels because the data were not normally distributed (p < 0.05). The results showed that there was no significant association between SII and SGPT levels, as indicated by p> 0.05. Similarly, the Spearman test was used to analyze the association between SII values and SGOT levels and the result showed a significant association (p < 0.05). The coefficient was -0.457 indicating moderate and negative associations.

Table 3. Association between ferritin levels and SGPT and SGOT levels

Dependent Variable	Independent Variable Ferritin Level (ng/mL)*	
	r	p
SGPT Level (U/L)	0.475	0.007**
SGOT Level (U/L)	0.311	0.088

* = Spearman test
** = Significant (p < 0.05)

The results of the Spearman test in Table 2 showed a significant association (p < 0.05) between ferritin and SGPT levels with a coefficient of 0.475, which was moderate. Furthermore, there was no significant association (p> 0.05) between ferritin and SGOT levels.

Discussion

This study was conducted by recording and processing data from 31 medical records of pediatric patients at Dr. Kariadi Hospital Semarang from July to September 2023. It is aimed at discussing the association between SII values and ferritin levels with hepatic function in patients with thalassemia major.

Association between SII Value and SGPT Level

The association between SII value and SGPT levels was found to be insignificant. The results contradict the previous report by Song et al. (2022), which stated that there is an association between SII values and hepatocyte damage[21]. A previous study reported that injury to liver cells resulted in increased SGPT production[13]. There was no significant association between SII values and SGPT levels due to the routine use of iron chelation therapy in thalassemia patients[24].

Association between SII Value and SGOT Level

The association between SII values and SGOT levels was significant, with a moderate coefficient and a negative direction. This result was consistent with the report of Song et al. (2022), where the SII value was shown to be associated with liver function failure. Despite the association with inflammation, some hepatic diseases do not have a clear mechanism for the association that exists. This may affect the association coefficient of SII values and SGOT levels, which is moderate. Liver steatosis can cause cell damage, thereby accelerating the occurrence of liver function failure[21]. Patients with thalassemia major require continuous blood transfusions to survive, which can cause iron accumulation in various organs, such as the liver, resulting in severe damage. SGOT levels increase in the blood when liver cell injury occurs. It can be concluded that the SII value has a significant association with SGOT levels[13].

Thalassemia major patients experience immune mechanisms in the form of neutropenia, thrombocytosis, and lymphocytosis[5,26,27]. While chronic hypercoagulability is widely observed in thalassemia patients, it is mainly reported in adult subjects. Furthermore, 29.6% of pediatric patients

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were reported to experience epistaxis and gum bleeding[28]. The events of neutropenia, thrombocytopenia, and lymphocytosis may have caused the negative direction of the association between SII values and SGOT levels.

Association between ferritin and SGPT levels

The association between ferritin and SGPT levels in this study was significant at a moderate level. This result is consistent with the study conducted by Joniarti et al. (2022), which showed a statistically significant positive association between ferritin and SGPT levels, as indicated by r = 0.380 and p = 0.003[20].

Ferritin levels above 1000 ng/ml constitute a risk factor for increased SGPT in transfusion-dependent thalassemia major patients. Increased SGPT production is a response to liver cell injury, initiated by iron accumulation from ineffective erythropoiesis. This results in a physiological decline in the body's ability to excrete iron, and most importantly, thalassemia major patients (severe cases) require repeated blood transfusions[20].

Association between ferritin and SGOT levels

The association between ferritin and SGOT levels in this study was insignificant. This result is consistent with the report of Yutarti et al. (2023) that the significance value for serum ferritin with SGOT levels was 0.766, showing no association[24].

The result of this study showed that there is no association between ferritin and SGOT levels because SGOT was produced in the liver and various organs, such as muscles, heart, pancreas, and kidneys. Several factors are also responsible, such as people who sleep less than 7 or 8 hours, fatigue due to too much activity or exercise, and consumption of drugs[13].

This study had limitations as it lacks total chelation therapy, potentially influencing the value of variables and factors that affect the SII, namely insulin resistance and ferritin levels, such as kidney disorders, hypothyroidism, and obesity.

CONCLUSION

In conclusion, there is no association between SII value and SGPT level in thalassemia major patients. However, the result of this study indicates a significant association in the moderate category between the SII value and SGOT level, as well as between ferritin and SGPT level. There is also no association between ferritin and SGOT levels in thalassemia major patients.

SUGGESTION

Future studies can analyze the effect of the number of chelation therapy and factors on SII values and ferritin levels.

ETHICAL APPROVAL

Ethical clearance was obtained from the Health Research Ethics Commission (KEPK) of the Faculty of Medicine, Diponegoro University Semarang Number 415/EC/KEPK/FK-UNDIP/VIII/2023. A study permit was also obtained from Dr. Kariadi Hospital Semarang.

CONFLICTS OF INTEREST

The authors report no conflicts of interest in this study.

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AUTHOR CONTRIBUTIONS

Conceptualization, Titis Yoga Safitri, Nyoman Suci Widyastiti; methodology, Nyoman Suci Widyastiti, and I Edward Kurnia Setiawan L; software, Titis Yoga Safitri; validation, Titis Yoga Safitri, Nyoman Suci Widyastiti, I Edward Kurnia Setiawan L, and Nahwa Arkhaesi; formal analysis, Titis Yoga Safitri, Nyoman Suci Widyastiti, and I Edward Kurnia Setiawan L; investigation, Titis Yoga Safitri and Nyoman Suci Widyastiti; resources, Titis Yoga Safitri; data curation, Titis Yoga Safitri; writing—original draft preparation, Titis Yoga Safitri; writing—review and editing, Titis Yoga Safitri, Nyoman Suci Widyastiti, I Edward Kurnia Setiawan L, and Nahwa Arkhaesi; visualization, Titis Yoga Safitri, Nyoman Suci Widyastiti, and I Edward Kurnia Setiawan L; supervision, Nyoman Suci Widyastiti and I Edward Kurnia Setiawan L; project administration, Titis Yoga Safitri, Nyoman Suci Widyastiti, and I Edward Kurnia Setiawan L; funding acquisition, Titis Yoga Safitri and Nyoman Suci Widyastiti.

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