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Aspartate Aminotransferase to Platelet Ratio Index Score in Correlation with Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio to Predict Hepatic Cirrhosis in Hepatitis C Patients

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Abstract

Background: Tissue biopsy examination which is an invasive procedure has become the mainstay for hepatic cirrhosis identification in patients with hepatitis. Alternatively, noninvasive method using the aspartate aminotransferase (AST) to platelet ratio index (APRI) score has been developed to predict hepatic cirrhosis. Furthermore, the neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) have been used to predict the severity of hepatitis C. This study aimed to analyze the relationship between APRI scores and NLR and PLR in chronic hepatitis C patients.

Methods: This correlative cross-sectional observational study used secondary data of complete blood counts such as neutrophil, lymphocyte, and platelet values, as well as AST values of patients with hepatitis C in the outpatient and inpatient installation of Dr. Hasan Sadikin General Hospital during 2019. The inclusion criteria were patients aged ≥18 years, male and female, who were diagnosed as hepatitis C patients, patients who had AST examination data, leukocytes, count type, and platelets. Data were analyzed using the Spearman rank correlation test.

Results: The 123 subjects were dominantly male with an age range of 46–55 years. There was no correlation between the APRI and NLR scores (p=0.229). However, there was a moderate and significant negative correlation between APRI and PLR scores with a correlation coefficient of -0.468 (p=0.000).

Conclusion: There is a significant negative correlation between APRI and PLR scores to predict the occurrence of hepatic cirrhosis in patients with Hepatitis C.

Keywords: APRI Score, hepatitis C, hepatic cirrhosis, NLR, PLR

Introduction

Hepatitis C is one of the causes of hepatic cirrhosis. Patients with hepatitis C have a 50–85% chance of developing hepatic cirrhosis. Hepatic cirrhosis causes 1.4 millions death each year; the causes of cirrhosis of the hepatic are due to alcohol, 348,000 cirrhosis patients; hepatitis C, 326,000 patients; and hepatitis B, 371,000 patients.[1,2] Liver tissue biopsy still uses as the gold standard for diagnosis of hepatic cirrhosis despite its very invasive nature and various risks that accompany procedures such as bleeding. Furthermore, the results of biopsy are highly dependent on the accuracy of the tissue drawing and the expertise of the anatomical pathologist in carrying out the biopsy procedure.[3] As the biopsy procedure has many limitations, alternative non-invasive procedures are explored to determine the accurate and acceptable diagnosis of liver fibrosis. Some simple serum markers have been widely reported as the substitutes for assessing liver fibrosis, such as aspartate aminotransferase to platelet ratio index (APRI), and many other markers. Among all markers, APRI has been extensively used since it is simple and inexpensive.[4–8]

Other research have stated that the aspartate aminotransferase (AST) score to platelet ratio index (APRI) can distinguish mild and severe fibrosis in people with chronic hepatitis C, so that, it can predict the possibility of hepatic cirrhosis in patients with hepatitis

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C.[4–7,9] Indicators of systemic inflammation such as Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) are expected to be activated in chronic inflammatory processes that occur in people with hepatitis C.[10] The progressivity of hepatitis C disease will cause fibrosis of the liver. Thus, the NLR and PLR can assess the severity of liver fibrosis.[11–12] Based on the literature study, the authors wanted to identify the relationship between the APRI score and the NLR and the PLR as predictors for determining the severity of mild fibrosis and severe hepatic cirrhosis in patients with hepatitis C.[10–18]

This study aimed to determine the correlation between APRI scores with NLR and PLR in patients with hepatitis C. The study's results are expected to predict the state of hepatitis C patients who experienced hepatic cirrhosis without having invasive examination.

Methods

This study was conducted at the Laboratory of Clinical Pathology, Dr. Hasan Sadikin General Hospital, Bandung (RSHS). The research method was a cross-sectional study using a correlative analytic observational design. The subjects were Hepatitis C patients treated in the Inpatient and Outpatient Installation of Internal Medicine Department RSHS. Clinical data were collected from the patient's medical records from January to December 2019.

The inclusion criteria were patients aged ≥18 years, male and female, diagnosed as hepatitis C patients, with AST examination data measured by an enzymatic method (Pyridoxal-5-Phosphate UV method), leukocytes, count type, and platelets measured by flow cytometry method. Exclusion criteria were hepatitis C patients younger than 18 years old with a history of thrombocytopenia due to other diseases.

The sample size in this study was all patients diagnosed with hepatitis C and treated in the Internal Medicine ward, as well as outpatients at the Gastroenterohepatology Clinic of the Dr. Hasan Sadikin General Hospital from January-December 2019. The research data were statistically processed with Microsoft Excel and SPSS 17.0. The collected data were checked for distribution using the Kolmogorov-Smirnov test and then analyzed by Pearson or Spearman rank Correlation Test to determine the correlation between APRI score with NLR and PLR in chronic hepatitis C patients. The ethical clearance was obtained from the Ethical Committee in Dr. Hasan Sadikin General Hospital with No. LB.02.01/X.6.5/271/2020.

Table 1 Characteristics of Patient Data

Characteristics	Total (n=123)	
	n	%
Age (year)		
18–35	9	7.3
36–45	50	40.7
46–55	34	27.6
56–65	15	12.2
> 65	15	12.2
Gender		
Male	83	67.5
Female	40	32.5
Patient status		
Inpatient	65	52.8
Outpatient	58	47.2

Results

During the January to December 2019 period, the number of subjects who met the inclusion criteria was 65 inpatients and 58 outpatients. Twenty-six subjects were excluded from this study due to a lack of laboratory results. The normality test showed that all patient subjects' age data and APRI scores were abnormally distributed ($p>0.05$). The data characteristics of the study subject are shown in Table 1.

Subjects with severe malignancy were found in males by 67.5 % compared to females (32.5%), and most occurred in the 36–45 year age group, namely 40.7% (Table 1).

The results of APRI Scores, Neutrophils Lymphocytes Ratio (NLR), Platelet Lymphocyte Ratio (PLR) in Hepatitis C patients can be seen in Table 2.

Findings of the analysis using Spearman Rank found that the correlation coefficient between the NLR APRI scores was 0.109, $p=0.229$ ($p>0.05$), meaning that there was a weak and insignificant relationship between the APRI scores and NLR.

From the results of the analysis using Spearman Rank, the correlation coefficient between APRI and PLR scores was -0.468, $p=0.000$ ($p<0.05$), meaning that there was a significant negative correlation between APRI and PLR scores.

Discussion

Table 2 Results of APRI Scores, Neutrophils Lymphocytes Ratio (NLR), Platelet Lymphocyte Ratio (PLR) in Hepatitis C Patients

Parameter	Median	Min-max
APRI	0.94	0.12-123.92
Neutrophil lymphocyte ratio (NLR)	2.96	0.68-98.00
Platelet lymphocyte ratio (PLR)	110.51	4,97-2,038.83

This study was dominated by patients aged 36–55 years, or 60–70% of the subjects. It is similar to findings of Klevens et al.[14] reporting that hepatitis C patients mostly were 40–59 years old. The study subject's average age is 49 years, compared to other studies that reported the age of hepatitis C patients, was 49.51±10.45 in patients with cirrhosis and 45.31±14.28 in patients with chronic hepatitis C.[17] Two different studies also reported similar results that the subject's average age is 52 years.[17,19] However, there are studies in which the mean or median age of the subjects is more than or equal to 60 years.[19,20]

The predominance of male subjects found in this study is also reported in most literatures. In this study, male hepatitis C patients reached 67.5%. Likewise, in other studies, male subjects are reported more than female subjects (59–81%).[21–23]

The APRI score correlated significantly to the fibrosis stage in patients with CHC. It was known that platelet counts decreased, and AST levels increased with the progression of liver fibrosis. Platelet generation diminished secondary to a decreased production of thrombopoietin by hepatocytes. Also, platelets were sequestered and destructed in the spleen as liver fibrosis advanced and portal hypertension developed. As to AST, ongoing liver injury increased its release from mitochondria, and fibrosis decreased its clearance.[24,25] Several studies have shown that the NLR and PLR values can predict the severity of patients with hepatitis C.[10,26] In cirrhotic patients, immune and inflammatory systems are activated and inflammatory markers, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and neutrophil counts are elevated.[27] Thus, NLR can be used as a marker of systemic inflammatory response. It has found that increased NLR reflects the progression of systemic inflammation which is associated with poor clinical outcomes in liver disease.[27]

The primary mechanisms for thrombocytopenia in cirrhosis are decreased production of thrombopoietin (TPO) in the liver and splenic platelet sequestration. Thrombopoietin acts at all stages of thrombopoiesis and synergizes with other cytokines to stimulate both megakaryocytopoiesis and thrombopoiesis as well as platelet release into the circulation. Liver fibrosis (grade 3/4) and liver function correlate with low TPO serum levels. As TPO is synthesized in the liver, impaired hepatic function may reduce TPO production.[28] Thus, a low PLR can predict an undesirable progression of HCV infection-related liver disease.[10,28]

Statistical tests showed no correlation between APRI scores and NLRs in hepatitis C patients. This was following another study which stated that the value of leukocytes such as neutrophils fluctuated in response to infection.[29] These variations are not correlated with the possible NLR APRI scores in patients with hepatitis C. Serial NLR screening will increase the validity in predicting the severity of patients with hepatitis C.[24,29] This is in line with study conducted by Wróblewska A et al.[16] who have got the NLR correlation to assess the degree of damage in hepatitis C patients with serial NLR examinations at week 24th.

Statistical tests on the correlation between APRI and PLR scores in hepatitis C patients showed a significant negative correlation. If the APRI score was minor, the PLR value would be even more significant, and vice versa. These results are following research which have stated that PLR is negatively correlated with hepatic fibrosis, which in this study is assessed by the APRI score.[15] The regulation of platelet formation is influenced by thrombopoietin (TPO) which is formed in the liver.[24] So liver infection will disrupt TPO production, affecting platelet production.[17,24] This is in line with the research which stated that the greater the liver damage, the more it will affect platelet productivity.[19] Another study showed that PLR and NLR are known biomarkers of systemic inflammation, indicating the immune response.[10]

Platelets are thought to act as carriers of effect or immune cells in chronic systemic inflammation, although the mechanism is still widely studied.[20] NLR is a parameter that reflects systemic inflammation and the general nutrition status of patients.[27] Besides, PLR is a parameter that reflects systemic inflammation as well as the liver function. The primary mechanism for thrombocytopenia in cirrhosis is decreased production of TPO in the liver.[28] Thus, a decrease in the PLR value can predict the progression of hepatitis C disease, characterized by liver fibrosis.[10]

The limitations of this study were that the study subjects were not normally distributed, periodic hematologic examinations were not included, as well as data regarding the history of previous drug consumption and duration of illness that could affect the NLR and PLR values in predicting fibrosis severity in patients with hepatitis C.

To conclude, there is a moderate and significant negative correlation between APRI and PLR scores to determine the severity of fibrosis in hepatitis C patients. PLR can be considered as biomarker to predict the occurrence of hepatic cirrhosis in patients with Hepatitis C

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