

Research Article

Alkaline Phosphatase, Bilirubin, and Gamma-Glutamyl Transferase Profiles as Supporting Diagnosis in Liver Cirrhosis Based on Aspartate Aminotransferase to Platelet Ratio Index Score

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Abstract

Liver cirrhosis is defined as the end-stage of chronic liver disease, marked by fibrosis and alteration of the liver's architecture from regular to nodular, and causing alteration of liver function markers. The aspartate aminotransferase (AST) to platelet ratio index (APRI) score has been used as the non-invasive methods to diagnose and classify liver cirrhosis progression. The aim of this study was to assess several profiles of liver function tests namely alkaline phosphatase (ALP), bilirubin, and gamma-glutamyl transferase (GGT) to determine their conditional uses in the classification of liver cirrhosis based on APRI scores. This study used a cross-sectional design with 60 subjects, classified into three stages of APRI scores: <0.5, 0.5 to 2.0, and >2.0. Data were obtained from medical records of dr. Cipto Mangunkusumo National Hospital in 2017. ALP, bilirubin, and GGT profiles were analysed using Kruskal-Wallis. The bilirubin profile showed a significantly higher APRI score of <0.5 and 0.5-2.0 with >2.0 ($p<0.05$). The GGT profile showed significantly higher in the APRI stage, with scores <0.5 with 0.5-2.0 ($p<0.05$). There were significant differences in bilirubin and GGT profiles at the stage of liver cirrhosis based on APRI scores; however, this finding did not occur in the ALP profile.

Keywords: liver cirrhosis, alkaline phosphatase, APRI score, bilirubin, gamma-glutamyl transferase.

Profil Fosfatase Alkali, Bilirubin, dan Gamma-Glutamyl Transferase sebagai Pendukung Diagnosis Sirosis Hati Berdasarkan Skor Aspartate Aminotransferase Platelet Ratio Index

Abstrak

Sirosis hati adalah penyakit hati kronik tahap akhir yang ditandai dengan fibrosis dan kerusakan struktur hati dari regular menjadi noduler dan menyebabkan tes fungsi hati terganggu. Skor aspartat aminotransferase (AST) terhadap platelet ratio index (APRI) telah digunakan sebagai salah satu metode non-invasif untuk menentukan diagnosis dan klasifikasi proses sirosis hati. Tujuan penelitian ini adalah untuk menilai profil tes fungsi hati yaitu alkaline phosphatase (ALP), bilirubin, dan gama-glutamil transferase (GGT) untuk menentukan kegunaan komparatifnya dalam klasifikasi sirosis hati berdasarkan skor APRI. Penelitian ini menggunakan desain potong lintang dengan 60 subjek yang dibagi menjadi 3 kelompok berdasarkan skor APRI, yaitu <0,5; 0,5-2,0 dan >2,0. Data diperoleh dari rekam medis RSUPN dr. Cipto Mangunkusumo tahun 2017. Profil ALP, bilirubin, dan GGT dianalisis dengan uji Kruskal Wallis. Profil bilirubin menunjukkan skor APRI lebih tinggi secara signifikan pada skor <0,5 dan 0,5-2,0 dibandingkan skor >2,0 ($p<0,05$). Profil GGT menunjukkan stadium APRI yang lebih tinggi secara bermakna dengan skor <0,5 dibandingkan skor 0,5-2,0 ($p<0,05$). Terdapat perbedaan bermakna pada profil bilirubin dan GGT pada stadium sirosis hati berdasarkan skor APRI namun tidak terjadi pada profil ALP.

Kata kunci: sirosis hati, alkali fosfatase, skor APRI, bilirubin, gamma-glutamil transferase.

Introduction

In Indonesia, liver cirrhosis is one of the most significant causes of death with a mortality rate of 48,900 people or approximately 3.2% of total deaths each year.¹ The gold standard used to diagnose liver cirrhosis is a liver biopsy.² However, liver biopsy has several weaknesses, it is expensive and invasive, it poses a risk of mortality and morbidity, limited facilities exist, and there is potential for bias due to sampling errors or inter- and intra-observer variations.³

Aspartate aminotransferase (AST) to platelet ratio index (APRI) is one of the scoring systems that have been used to diagnose and classify progression of liver cirrhosis. However, APRI scores still have some weaknesses, the APRI score cannot be used under some conditions and there are possible variations in scores due to necroinflammatory activity.⁴ Markers of liver function including alkaline phosphatase (ALP), bilirubin, and gamma-glutamyl transferase (GGT), will change along with alteration in liver function in liver cirrhosis.⁵

The aim of this study is to assess selected liver function test's profiles (ALP, bilirubin, and GGT) to determine their comparative effectiveness in liver cirrhosis classification based on the APRI score.

Methods

A cross-sectional design was used by taking laboratory examination data from the laboratory information system of the Department of Clinical Pathology, dr. Cipto Mangunkusumo National Hospital (CMNH) from March to November 2017.

The samples were all taken from patients who had AST, platelet counts, ALP, bilirubin, and GGT data, and were divided into three groups based on their APRI score. The APRI score was calculated from AST levels divided by the standard upper limit of AST (44 UL), divided by the number of platelets ($10^9/L$), then multiplied by 100. The group with an APRI score of <0.5 were patients with various diseases. The group with an APRI score of 0.5 to 2.0 were patients with various liver diseases and an APRI score of >2.0 were patients with a final diagnosis of liver cirrhosis. Patients with uncompleted data and under 17 years were excluded.

The sample size was calculated based on an unpaired analytical formula for numerical data. The minimum number of subjects was 18 per group. Sampling was done by a consecutive non-probability sampling method. The ANOVA test was

used if the normality test of the data was normal and the Kruskal-Wallis test if the normality test was not normal. If the p-value was significant, it was followed by a post hoc test, in this case, the Bonferroni test (ANOVA) or the Mann-Whitney test (Kruskal-Wallis). This study was approved by the Ethics Committee of the Faculty of Medicine Universitas Indonesia (no. 460/UN2.F1.D1/KBK/PDP.01/2017)

Results

The total subjects were 60, with 20 in each group based on their APRI score. Sixty percent were male, with an average age of 50 years. The most dominant etiology in the APRI <0.5 group was carcinoma of hepato/gastrointestinal regions (25%), and in the APRI 0.5-2.0 and >2.0 groups, it was hepatitis B (35% and 40% respectively). The etiology of subjects is shown in Table 1.

Table 1. Etiology of Subjects Based on APRI Score

Etiology	n
APRI score <0.5 (normal, n=20)	
Hepato-gastrointestinal carcinoma	5
Betathalassemia	3
Hepatitis B and C	3
Mammary carcinoma	1
Diabetes mellitus	1
Cholangitis	1
Esophageal varices	1
Liver donation	1
Not known	4
APRI score 0.5–2.0 (fibrosis, n=20)	
Hepatitis B	7
Hepatitis C	2
Cholangitis	2
Biliary atresia	2
Hepatocellular carcinoma	1
Cholecystitis	1
Metastasis of carcinoma	1
Others	4
APRI score >2.0 (cirrhosis), n=20	
Hepatitis B	8
Hepatitis C	5
Hepatitis B and hepatitis C	1
Primary biliary cirrhosis	2
Others	4

Table 2. ALP, Bilirubin, and GGT Profiles in the Stages of Liver Cirrhosis Based on APRI Scores

Marker	APRI Score (median, min-max)			p
	<0.5	0.5-2	>2	
ALP (U/L)	95.5 (64-410)	125.5 (73-342)	132.5 (59-285)	0.123
Bilirubin (mg/dL)	0.68 (0.18-18.02)	1.36 (0.32-30.7)	6.58 (1.12-29.59)	<0.001
GGT (U/L)	54 (10-935)	138 (28-636)	153 (9-819)	0.045

The ALP profile was not significantly different across the groups. Comparison of bilirubin and GGT profiles in each group based on APRI scores showed a significant difference ($p < 0.05$), thus only bilirubin and GGT were continued to post hoc testing (Table 2).

After post hoc testing, bilirubin in the APRI >2.0 group was significantly higher than in the APRI <0.5 and 0.5-2.0 groups, but not significantly different between the APRI score <0.5 and 0.5-2.0 groups. GGT in the APRI 0.5-2.0 group was significantly higher than in the APRI <0.5 group, but not significantly different in the APRI score <0.5 and 0.5-2.0 groups compared with the >2.0 group (Table 3).

Table 3. Post Hoc Test of Bilirubin and GGT Profiles

Per Group Comparison	p	
	Bilirubin	GGT
APRI <0.5 and APRI 0.5-2.0	0.267	0.015
APRI 0.5-2.0 and APRI >2.0	0.0004	0.892
APRI <0.5 and APRI >2.0	0.0001	0.066

Of the three parameters, bilirubin was the best examination to distinguish three stages of liver cirrhosis. GGT only distinguished normal APRI score to fibrosis while ALP could not be used to the differentiated staging of liver cirrhosis.

Discussion

APRI scores were grouped into three classifications (<0.5 , 0.5–2.0, and >2.0) based on the APRI score of <0.5 found in patients with normal liver conditions or with a low likelihood of having significant fibrosis. An APRI score of 0.5–2.0 occurs in patients with a high likelihood of developing liver fibrosis and an APRI score of >2.0 shows a high specificity of liver cirrhosis (94%).⁶

The most common etiology in the groups with APRI scores of 0.5–2.0 (fibrosis) and >2.0 (cirrhosis) of the liver was hepatitis B. This result was consistent with a report from the Ministry of Health in 2013 which showed an increase

in hepatitis B patients in Indonesia.⁷ Based on Schuppan et al⁸ an age of 50 is a risk factor for liver cirrhosis. As Guy et al⁹ report, men's mortality due to chronic liver disease and cirrhosis was twice that of women, so men could be said to be more vulnerable.

In contrast to Hyder et al¹⁰ and Gowda et al¹¹ the comparison of ALP profiles in the stages of liver cirrhosis based on APRI scores in this study showed non-significant differences. Increased ALP synthesis is mediated by conditions of hyperbilirubinemia, especially in hepatobiliary disease such as primary biliary cirrhosis due to ALP's junction with the canalicular membrane where it is dissolved by bilirubin.¹² Meanwhile, viral hepatitis can interfere with the immune system that is associated with primary biliary cirrhosis (having autoimmune dysfunction as its etiology) or can increase the progression of damage in primary biliary cirrhosis.¹² Wang et al¹³ made a new predictive model using ALP to predict liver fibrosis but only for chronic hepatitis B patients, while in this study the causes of liver fibrosis and cirrhosis were not only hepatitis B.

Comparison of bilirubin profiles in the stages of liver cirrhosis based on APRI scores shows a significant difference. Ohkubo et al¹⁴ reported an increase in bilirubin profiles is caused by impaired portal blood flow, causing inhibition of bilirubin and portosystemic shunting excretion, resulting in increased hemolysis. In the case of hepatitis, toxins from the virus can damage hepatocytes, causing a blockade of the bilirubin conjugation process and disruption of conjugated bilirubin excretion which results in hyperbilirubinemia. The non-significant difference in the comparison of bilirubin profiles between normal and fibrosis stages is related to the low median bilirubin profile in the stages of liver fibrosis. This can occur due to liver fibrosis that has been reversed or due to insignificant fibrosis severity.

Consistent with the results of Eminler et al¹⁵ and Elhamid et al¹⁶ a comparison of GGT profiles in the stages of liver cirrhosis based on APRI scores

in our study showed significant differences. The mechanism by which GGT levels can increase remains unclear, but several hypotheses suggest that in cases of chronic hepatitis C, an increase in GGT occurs due to oxidative stress resulting from liver inflammation and bile interlobular duct damage.¹⁶ The non-significant differences found when comparing GGT levels with the estimated stages of cirrhosis are due to the fact that GGT is affected by other factors outside the liver cells, such as obesity, alcohol consumption, and production in other tissues, potentially causing a high median GGT profile in normal stages and fibrosis.¹⁷

Some biases influence this study because the background of the subject disease varies widely (e.g. viral infection, cholangitis, carcinoma, etc.). Nevertheless, the data can be used for creating new non-invasive models to predict liver cirrhosis in future studies alongside the APRI score.

Conclusions

Bilirubin significantly different in various stages of liver cirrhosis based on APRI scores, GGT only distinguished between APRI score <0.5 with APRI 0.5-2.0, and ALP could not use to differ the stages of liver cirrhosis. Bilirubin and GGT can be used as parameters to predict liver cirrhosis in addition to APRI scores.

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