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Relationship between Amiga Score and the Size of Esophageal Varycas Endoscopically On Patients of Cardiac Cirrhosis

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Background: Most patients with cardiac cirrhosis will have esophageal varices in the course of their illness. AIAG Score is a simple marker that can predict liver fibrosis with a good degree of accuracy and has been demonstrated in several studies. Based on the concept that liver fibrosis will ultimately lead to the occurrence of esophageal varices, non-invasive examination for liver fibrosis can be used as a predictor of esophageal varices.
Research Method: cross-sectional study was conducted on 80 patients with cardiac cirrhosis at Adam Malik Hospital from June 2014 to June 2015. The diagnosis of cardiac cirrhosis was based on clinical, biochemical and ultrasound, and esophageal varices with endoscopy. The AIAG Score was calculated on all patients, with statistical analysis of Mann Whitney test and $\alpha = 5\%$.
Results: Among 80 patients of cardiac cirrhosis with esophageal varices, 50% are caused by hepatitis B virus infection (HBV). Most research population has Child-Pugh C identification and F1 esophageal varices. AIAG Score on large varicose veins is significantly higher than on small varicose veins (0.99 ± 0.005 vs 0.9 ± 0.16; $p < 0.001$). The value of cut-off AIAG Score > 0.994 in predicting the existence of large esophageal varices have a sensitivity of 82.5%, specificity of 72.5 %, positive predictive value of 75%, negative predictive value of 80.6 %
Conclusion: AIAG Score is significantly associated with large esophageal varices. AIAG Score is a non-invasive marker, which is good for large esophageal varices in patients with cardiac cirrhosis.
Keywords: AIAG Score , non-invasive markers , esophageal varices .

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I. INTRODUCTION

Cardiac cirrhosis is a diffuse and chronic liver disease which, is characterized by the formation of connective tissue and nodule regeneration. Cardiac cirrhosis is an advanced stage of any chronic liver disease and this condition will lead to multiple complications resulting from the occurrence of portal hypertension. At the time of diagnosis, nearly 50% of people with cardiac cirrhosis have already had esophageal varices in various degrees.[1] Esophageal varices is a main complication that often occurs in 30-40% of patients with compensated stage of cardiac cirrhosis and 60% in patients with decompensated cardiac cirrhosis.[2] Esophageal variceal bleeding itself is a life-threatening condition with an estimated incidence of 5% in patients with small esophageal varices and more than 15% in those with large esophageal varices. The mortality rate of each bleeding incidence is between 10-20% and the 1-year survival rate is only about 63% . [3,4,5,6]

Liver fibrosis will lead to portal hypertension which will eventually lead to esophageal varices. Based on this concept then the non-invasive examination of liver fibrosis can be used as a predictor of esophageal varices . [7]

AIAG Score is a simple non-invasive marker of liver fibrosis, firstly introduced by Sheng-in Wu et al., to predict liver fibrosis in patients with chronic hepatitis B. [8] Until now there has been no study on the relationship between AIAG Score ($e^p/1+e^p$) and $p = -7 + (0.03x \text{ age (year)}) + (9x\text{INR}) - (0.08x\text{Albumin } (grL^{-1})) + (0.004x\text{GGT } (UL^{-1}))$ with the size of esophageal varices compared with endoscopy in patients with cardiac cirrhosis. Therefore the authors wanted to determine the relationship between the AIAG Score and the size of esophageal varices with a simple and non-invasive examination and also to predict the occurrence of esophageal varices in patients with cardiac cirrhosis and to compare it with endoscopy as a gold standard examination for the provision of diagnostic efficacy reference in terms of the introduction of non-invasive examination as predictors of esophageal varices (EV) at the patients of cardiac cirrhosis.

II. METHOD

The observational studies were done by analytic cross-sectional study. The study was conducted in the inpatient and Gastroentero-Hepatology clinic of RSUP H. Adam Malik Medan, from September 2014 to June 2015 with inclusion criteria including: men and women aged ≥18 years, patients with cardiac cirrhosis disease,

willing to follow the study and signing informed consent. Exclusion criteria: the previous varicose bleeding <1 week, patients who had previously received therapy of β-blocker or therapeutic endoscopy (ligation or sclerotherapy), patients who previously underwent surgical treatment for portal hypertension (TIPSS), patients with non-cirrhosis portal hypertension and hepatoma.

Subjects were subjected to anamnese, physical examination, laboratory examination in the form of routine blood, liver physiology, viral marker, albumin, INR, GGT and supportive ultrasound investigation.

Statistical analysis to see the relationship of endoscopic measurement results with AIAG Score was independent t-test if the data was normally distributed, and Mann Whitney test if the data was not normally distributed. To assess the relationship of sex, etiology of cardiac cirrhosis, Child Pugh and ascites with the size of varicose veins Chi Square test was used. To determine the value of AIAG Score cut off, the Receiver Operating Characteristic (ROC) Analysis was done. In this study, diagnostic tests by finding the value of sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) was also performed.

III. RESULTS

Overall, 80 patients with cardiac cirrhosis who met the inclusion criteria were included in the study. Characteristics of clinical, biochemical, the severity of cardiac cirrhosis, and the size of the patient's esophageal varices had been summarized and could be seen in Table 1 . The majority of male sex patients were 60 people (75%). The average of patients' age was 51. 55 years old. Ascites with moderate levels occurred in 40 patients (50%). The etiology of cardiac cirrhosis studied in this research was hepatitis B, with a number of 40 people (50%), 5 people suffering from hepatitis C (6.3 %), 1 person suffering from hepatitis B and C (1. 3%) and 34 people were not hepatitis B or C (42.5 %). Based on Child Pugh (CP) examination it was found 36 patients (45%) with a heavy level (CP C). Using endoscopy, 40 patients (50%) were F1 , 29 patients (36. 3%) were F2 and 11 patients (13.8%) were F3. Patients who had small esophageal varices were 40 people (50%) and large size were as many as 40 people (50%).

Table 1. Demographic Characteristics of Research Subjects

Demography characteristics	**n = 80**
Sex, n (%)	
Male	60 (75)
Female	20 (25)
Age, mean (SB), year	51,19 (11,11)
Asites, n (%)	
None	6 (7,5)
Minimal	25 (31,3)
Medium	40 (50)
Heavy	9 (11,3)
Etiology of Cardiac Cirrhosis, n (%)	
Non hepatitis B dan C	34 (42,5)
Hepatitis B	40 (50)
Hepatitis C	5 (6,3)
Hepatitis B dan C	1 (1,3)
Child Pugh (CP), n (%)	
A	16 (20)
B	28 (35)
C	36 (45)
Size of esophageal Varices (VE), n (%)	
F1	40 (50)
F2	29 (36,3)
F3	11 (13,8)
Size of esophageal Varices, n (%)	
Small	40 (50)
Large	40 (50)

SB, Standard Deviation; *CP, child pugh*; VE, esophageal Varices

From the results of endoscopic examination it was found 40 patients with large VE and 40 patients with small VE. The majority in both groups was male patients. There was no significant difference in the mean age and sex between groups of patients with large VE and patients with small VE (p> 0.5). Hepatitis B virus infection was the etiology of most cardiac cirrhosis in the group of patients with large VE (62.5%) whereas the etiology of cardiac cirrhosis in the group of patients with small VE was not hepatitis B or hepatitis C (55%). The

majority of patients had a Child Pugh (CP) C score in the group with large VE (70%) whereas in the group of patients with small VE had a CP A score (16%) and CP B (16%). From Chi Square test results it showed a significant difference in CP scores and ascites occurrence between groups of patients with large VE and small VE (p <0.05%) (table 2).

Table 2. Characteristics of Subjects by Size of Varicose Eesophage

Characteristic	Small VE (n=40)	Large VE (n=40)	p
sex, n (%)			
Male	30 (75)	30 (75)	1,000[a]
Female	10 (25)	10 (25)	
Age, mean (SB), year	52,08 (13,08)	50,34 (8,93)	0,442[b]
Asites, n (%)			
None	5 (12,5)	1 (2,5)	<0,001[a]
Minimal	20 (50)	5 (12,5)	
Medium	15 (37,5)	25 (62,5)	
Heavy	0	9 (22,5)	
Etiologi of cardiac cirrhosis, n (%)			
Not hepatitis B dan C	22 (55)	12 (30)	0,084[a]
Hepatitis B	15 (37,5)	25 (62,5)	
Hepatitis C	0	2 (5)	
Hepatitis B dan C			
Child Pugh, n (%)			
A	16 (40)	0	<0,001[a]
B	16 (40)	12 (30)	
C	8 (20)	28 (70)	

[a] Chi Square; [b] T Independent;* SB, Standard Deviation; VE, esophageal varices; *CP, child pugh

By using Kolmogorov-Smirnov test, it was obtained AIAG Score data and blood chemistry parameters that were not normally distributed so that the Mann Whitney test was selected with $\alpha = 5\%$. Furthermore, by using Mann Whitney test, there was a significant difference between mean AIAG Score in groups of patients with large VE and small VE . AIAG Score in the large varices was significantly higher than in the small one (0.99 ± 0.005 vs 0.9 ± 0.16; p <0.001) (Table 3). In addition, there were also significant differences between the values of mean platelet parameters, total bilirubin, AST, Albumin, INR, Gamma GT, ALT in the group of patients with large VE and small VE (p <0.001, p = 0.006; p = 0.004; p <0.001, p <0.001, p = 0.05, p = 0.042, p <0.001 respectively).

Table 3 . Differences of Blood Chemical Checkup Results between Small and Large VE Groups

Characteristic	Small VE (n=40)	Large VE (n=40)	P
Platelet, mean (SB), thousand/µl	242.45 (153.67)	111.7 (81.02)	<0.001[a]
Total Bilirubin, mean (SB),mg/dl	5.14 (8.24)	7.06 (8.29)	0.006[a]
AST, mean (SB), unit/L	94.68 (114.62)	178.8 (215.52)	0.004[a]
Albumin, mean (SB), g/L	2.76 (0.63)	2.22 (0.6)	<0.001[a]
INR, mean (SB)	1.42 (1.26)	1.62 (0.45)	<0.001[a]
Gamma GT, mean (SB), UI/L	111.05 (126.3)	207.13 (253.85)	0.05[a]
ALT , mean (SB), unit/L	52.88 (62.28)	58.25 (43.54)	0.042[a]
AIAG Score, mean (SB)	0.90 (0.16)	0.99 (0.01)	<0.001[a]

[a]Mann Whitney; SB, Standard Deviation; VE, Esophageal Varices, INR, internationale normalized ratio; AST, Aspartat aminotransferase; ALT, Alanin aminotransferase; Gamma GT, Gamma glutamyl transpeptidase; AIAG Score, Age-INR-Albumin-GGT Score

The cut-off AIAG Score was determined by means of Receiver Operating Characteristic (ROC) analysis. From the analysis result by using the ROC curve it was found that the area under the ROC curve (AUC) ROC was 85.3% (95% CI: 76.6%-93.9 %)). AIAG Score in this study had a good ability to predict the size of esophageal varices.

In this study , the cut-off AIAG Score was ≤ 0. 994 could identify the small VE of F1 according to the endoscopic examination, while the value of cut-off AIAG Score > 0. 994 could identify a large VE of F2- F3 according to the endoscopic image. Of 80 people with cardiac cirrhosis with endoscopic esophageal varices, 40 people (50 %) had large VE and 40 people (50%) had small VE. There were as many as 44 people (55 %) indicated the value of AIAG Score > 0.994 and 36 people (45%) indicated the value of AIAG Score ≤ 0.994.

Of the 40 patients with large VE, as many as 33 people (82.5%) indicated the value of AIAG Score >0.994 and only 7 people (17.5%) with AIAG Score ≤ 0.994 . Of the 40 patients of cardiac cirrhosis with small VE, as many as 29 people (72.5%) indicated value of AIAG Score ≤ 0.994 and 11 (27.5%) indicated the value AIAG Score >0.994 .

The predictive value of cut-off AIAG Score >0.994 in the diagnosis of large esophageal varices was with sensitivity of 82.5%, specificity of 72.5%, PPV 75%, NPV 80.6% (table 4) .

Table 4. Sensitivity, specificity, positive and negative predictive value of AIAG Score on VE Size

AIAG Score	**VE Size**		**Sensitivity**	**Specivicity**	***PPV***	***NPV***
	Large	**Small**				
> 0.994	33	11	82.5	72.5	75	80.6
≤ 0.994	7	29				

VE, esophageal varices*; PPV, Positive predictive value; NPV, negative predictive value; AUROC, area under receiver operating characteristic; AIAG Score, Age-INR-Albumin-GGT Score*

IV. DISCUSSION

Esophageal varices is a complication commonly found in patients with cardiac cirrhosis and bleeding from varicose veins is one of the causes of serious complications with mortality of up to 26.6% on patients with cardiac cirrhosis. Therefore screening of esophageal varices with endoscopic procedures at the start of diagnosis is important and recommended on all clinical guidelines. . [9,10,11]

AIAG Score is a simple non-invasive marker of liver fibrosis, firstly introduced by Sheng-in Wu et al., To predict liver fibrosis in patients with chronic hepatitis B. [8] The AIAG Score uses variables of Age, INR, albumin, and GGT (Gamma-Glutamyl Transferase).

Of the 80 subjects, it is found to be mostly male (75%), and the mean age is 51.55 years. This result is in line with other studies conducted by Stefanescu et al. (2011) which showed that the percentage of men who was also more than 58.4% with average age of 55.66 years.[12] As it is known that the progression of fibrosis will accelerate after the age of the patient reaches/above 45 years. This situation is actually not yet clearly explained, but experts suspect a change in the immune response associated with aging that causes the rapid process of liver fibrosis to occur. Similarly, type of sex influences in this study, in which men are found to be more than women. Some experts argue that this possibility is due to the dominant influence of the hormone estrogen in women has an anti-fibrosis effect, although such an investigator needs further verification .[13]

In this study we found that patients of cardiac cirrhosis with esophageal varices experienced escalation of INR, with a significantly higher INR value, especially in patients with large VE compared to patients with small VE ($p<0.05$). This is also in line with the research study by Garcia (2007) which mentioned the occurrence of esophageal varices and progression of size correlated with the severity of liver disease based on the Child-Pugh score in which one of the parameters was elongation of PT or INR .[10]

Progression of liver fibrosis resulted in the decrease of clearance of AST enzyme and an increase in GGT levels.[16] In a study by Neelesh Despande et al., it was said that GGT was a sensitive marker of hepatocellular damage. GGT levels were found to increase in high and low alcoholic liver disease in advanced stages of cardiac cirrhosis. Especially in cardiac cirrhosis, GGT levels increased in the compensated stage and decreased at decompensated stage. While in other studies different results were obtained.[17] In this study, higher levels of GGT in patients with large varicose veins compared with patients with small varieties (207.13 ± 253.85 vs 111 ± 126.3; $p = 0.05$) was obtained. These results are in line with the studies conducted by Hyder et al., that obtained level increases of GGT in patients with cardiac cirrhosis.[18]

A study by Stefanescu et al. (2011) had evaluated the four non-invasive methods, previously known as predictors of hepatic fibrosis degree to identify the presence of esophageal varices and its size with endoscopic examination as standard procedures. The methods evaluated were APRI, Fib-4, Forn's Index, and Lok score. They found that some of these methods were able to predict the presence of esophageal varices, especially the large one. In detecting the existence of oesophageal varices, APRI method (cut-off >1.434), Fib-4 (cut-off >3.98), Forn's Index (cut-off>0.297), Lok score (cut-off >0.62) had AUROC 0.545, 0.624, 0.648 and 0.690 respectively. While in detecting the presence of large esophageal varices, APRI method (cut-off>2.201), Fib-4 (cut-off>6.7498), Forn's Index (cut-off>8.538), Lok score (cut-of f> 0.796) had AUROC 0.538, 0.628, 0.645, and 0.731 respectively.[10]

In this study it was found a significant difference between the value of AIAG Score from the patients with Large VE and patients with small VE determined by endoscopy (0.99 ± 0.005 vs 0.9 ± 0.16; $p<0.001$). AIAG Score with a cut-off value >0.994 was able to identify the existence of large esophageal varices endoscopically while the cut-off value <0.994 was able to identify the presence of small esophageal varices

endoscopically. The predictive value of AIAG Score with cut- off > 0.994 in diagnosing large esophageal varices was 82.5% of sensitivity, 72.5% of specificity, 75% of NPP, 80% of NPN, and AUROC of 0.853. These results indicated that AIAG Score with the specified cut-off limit in this study was accurate in identifying large esophageal varices in patients with cardiac cirrhosis.

Thus, AIAG Score is a simple and inexpensive non-invasive method to ascertain the size of oesophageal varices in patients with cardiac cirrhosis and this assessment may also help to establish the indication of therapeutic to be given to the patient. AIAG score of which the formula is easy-to-calculate comprising age parameters and laboratory tests such as INR, Albumin and GGT are laboratory parameters that are generally examined in patients with cardiac cirrhosis. It is expected that the AIAG Score can become one of the non-invasive methods that can be done on screening the size of esophageal varices in patients with cardiac cirrhosis, especially at the inadequate facilities, especially in developing countries such as Indonesia.

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