

## Correlation Between Esophageal Varices and Lok Score as a Non-invasive Parameter in Liver Cirrhosis Patients

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### ABSTRACT

**Background:** Bleeding from gastro-esophageal varices is the most serious and life-threatening complication of cirrhosis. Endoscopic surveillance of esophageal varices in cirrhotic patients is expensive and uncomfortable for the patients. Therefore, there is a particular need for non-invasive predictors for esophageal varices. The aim of the present study was to evaluate association of esophageal varices and Lok Score as non-invasive parameter in liver cirrhosis patients.

**Method:** This is a cross-sectional study of patients admitted at the Adam Malik hospital Medan between September to December 2014 with a diagnosis of cirrhosis based on clinical, biochemical examination, ultrasound, and gastroscopy. Lok Score was calculated for all patients, tabulated and analyzed.

**Results:** Among 76 patients with esophageal varices, 55.3% was due to hepatitis B virus (HBV). The majority of patients were Child C with only 13,2% being Child Pugh class A. Majority of the population had F2 esophageal varices (42.1%), F1 (32.9%), and F3 (25%). There is significance difference between Lok Score and grading of esophageal varices, in which Lok Score is higher in large esophageal varices compared with small esophageal varices ( $0.92 \pm 0.14$  vs.  $0.70 \pm 0.29$ ;  $p = 0.001$ ). Lok Score with cut-off point of  $> 0.9141$  was highly predictive in the diagnosis large esophageal varices with a sensitivity of 74.5%, specificity of 72%, positive predictive value of 84%, negative predictive value 58%, and accuracy was 73.7%.

**Conclusion:** Lok Score was significantly associated with esophageal varices. Lok Score is a good non-invasive predictor of large esophageal varices in cirrhotic patients.

**Keywords:** Lok Score, non-invasive parameter, esophageal varices

### ABSTRAK

**Latar belakang:** Perdarahan dari varises gastro-esophageal adalah komplikasi yang paling serius dan menyebabkan kematian pada penderita sirosis hati. Surveilans Endoskopi varises esofagus pada pasien sirosis mahal dan tidak nyaman untuk pasien. Oleh karena itu, dibutuhkan adanya parameter non-invasif sebagai prediktor varises esofagus. Tujuan dari penelitian ini adalah untuk mengevaluasi hubungan varises esofagus dan Lok Score sebagai parameter non-invasif pada pasien sirosis hati.

**Metode:** Penelitian potong lintang dari pasien yang dirawat di Rumah Sakit Adam Malik Medan antara bulan September hingga Desember 2014 dengan diagnosis sirosis berdasarkan klinis, biokimia, ultrasonografi, dan gastroskopi. Lok Score dihitung untuk semua pasien, ditabulasi, dan dianalisis.

**Hasil:** Di antara 76 pasien sirosis hati dengan varises esofagus, 55.3% disebabkan oleh infeksi hepatitis B virus. Sebagian besar populasi penelitian memiliki klasifikasi Child-Pugh C dan hanya 13,2% memiliki Child-Pugh kelas A. Mayoritas populasi penelitian memiliki varises esofagus F2 (42,1%), F1 (32,9), dan F3 (25%).

*Ada perbedaan yang signifikan antara Lok Score dan ukuran besar varises esofagus, dimana Lok Score lebih tinggi pada varises esofagus besar dibandingkan dengan varises esofagus kecil ( $0,92 \pm 0,14$  vs.  $0,70 \pm 0,29$ ;  $p = 0,001$ ). Nilai titik potong Lok Score  $> 0,9141$  dalam memprediksi adanya varises esofagus ukuran besar memiliki sensitivitas 74,5%, spesifisitas 72%, nilai prediksi positif 84%, nilai prediksi negatif 58%, dan akurasi sebesar 73,7%.*

**Simpulan:** Terdapat hubungan yang bermakna antara Lok Score dengan besar varises esofagus. Lok Score merupakan parameter non-invasif yang baik dalam memprediksi adanya varises esofagus berukuran besar pada pasien sirosis hati.

**Kata kunci:** Lok Score, parameter non-invasif, varises esofagus

## INTRODUCTION

Liver cirrhosis is a chronic liver disease characterized by inflammation, necrosis and regeneration process in the form of fibrosis and the formation of nodules in the surrounding of liver parenchyma.<sup>1,2</sup> Cirrhosis of the liver is an advanced stage of any chronic liver disease and this condition can lead to multiple complications due to portal hypertension. At the time of diagnosis of liver cirrhosis approximately 60% of patients with liver cirrhosis have undergone varying degrees of esophageal varices.<sup>3</sup> Esophageal varices is a major complication that often appear in more than 90% of patients with liver cirrhosis.<sup>4</sup> In 1998 at Cipto Mangunkusumo Hospital, Djojongrat reported that the prevalence of upper gastrointestinal bleeding caused by rupture of esophageal varices is 70.2% with a mortality rate of 26.6%.<sup>5</sup> Therefore, screening of esophageal varices in patients with cirrhosis of the liver is highly recommended in every consensus.<sup>6,7,8</sup> However, endoscopic examination periodically or regularly is very expensive and is often associated with complications that can arise from endoscopic examination, such as bleeding or perforation. Furthermore, not all the health care provider centers, especially in remote areas, have endoscopy facilities as well as the limited competence of a doctor to perform endoscopic examination that required non-invasive examination (marker) associated with portal hypertension, which can identify the presence of esophageal varices in liver cirrhosis patients.<sup>1,9,10</sup>

Nowadays there are several methods such as: clinical, biochemical examination, ultrasound, and elastography (transient elastography - TE) that have been proposed and some of the methods have been validated as non-invasive alternatives to endoscopy.<sup>11,12</sup> Non-invasive markers of liver fibrosis by blood serum examination were tested as predictors of esophageal varices in liver cirrhosis patients with promising results.<sup>13</sup>

Lok Score is a serum biomarker used to predict liver fibrosis and predicted to be able to replace the role of liver biopsy, in which serum variables which included in the formula Lok Score are the number of platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and international normalized ratio (INR). Several studies suggest an association between liver fibrosis, portal hypertension and esophageal varices, therefore several studies try to examine Lok Score in predicting esophageal varices. Stefanescu et al examined various non-invasive serum markers in predicting the presence of esophageal varices in patients with cirrhosis of the liver, where it was found that the Lok Score is the best non-invasive examination in predicting the presence of esophageal varices, especially large esophageal varices with cut-off points of  $> 0.62$  and  $> 0.796$  which have 76.16% and 76.92% sensitivity respectively.<sup>14</sup> In Indonesia, the research on the accuracy of Lok Score in predicting the presence of esophageal varices has not been investigated, therefore we intends to assess the accuracy of Lok Score as non-invasive examination in predicting the size of esophageal varices in patients with cirrhosis of the liver.

## METHOD

This study is an observational study which was done with analytical cross-sectional design. This study was conducted in Gastroentero-hepatologist Ward and Polyclinic of Adam Malik General Hospital, from July to August 2014 with inclusion criterias: men and women aged  $\geq 18$  years; liver cirrhosis patients; willing to participate in the study and signed the informed consent. The exclusion criterias are previous history variseal bleeding  $< 3$  months, patients who have previously received blocker drugs or endoscopic therapy (ligation or sclerotherapy)  $> 2$  years, patients who had previously undergone surgical treatment for portal hypertension (TIPS), patients with non-cirrhotic portal hypertension and hepatoma. Anamnesis, physical examination,

laboratory tests such as complete blood count (CBC), liver function, a marker of virus, albumin, INR, ultrasonography, and gastroscopy examinations were conducted to the study subjects.

Statistical analysis to study the relationship between the endoscopy measurement results with the Lok Score was done using independent t-test if the data are normally distributed and using Mann Whitney test if the data are not normally distributed. To assess the relationship between sex, etiology of liver cirrhosis, Child Pugh and ascites with the size of the varicose veins, Chi-square test was used. To determine cut off points, analysis of receiver operating characteristic (ROC) was done. In this study, we also done diagnostic tests to search for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-).

## RESULTS

It was obtained a total of 76 liver cirrhosis patients who enrolled in this study, consisting of 57 men and 19 women. Age average (mean) of patients is  $49.76 \pm 11.63$  years. The median of platelets is  $111.50 \times 10^9/L$  ( $23-647 \times 10^9/L$ ), the mean of albumin levels is  $2.49 \pm 0.72$  g/dL, the mean of INR is  $1.41 \pm 0.43$ . The median of AST is 72 U/L (12-1075 U/L), the median of ALT is 37.5 U/L (8-536 U/L), the median of total bilirubin is 2.5 mg/dL (0.25 to 32.18 mg/dL), the elongation of prothrombin time is  $5.26 \pm 5.37$  seconds. For the clinical characteristics of all patients, it was obtained 14 patients (18.4%) without ascites, 12 patients (15.8%) with minimal ascites, 40 patients (52.6%) with moderate ascites, and 10 patients (13.2%) with severe ascites. For the etiology of liver cirrhosis, it was found 42 patients (55.3%) with hepatitis B, 4 patients (5.3%) with hepatitis C, 1 patient (1.3%) with concomitant hepatitis B and hepatitis C, and 29 patients (38.2%) without hepatitis B and C. For the severity of liver cirrhosis, 10 patients (13.2%) found with Child-Pugh A, 26 patients (34.2%) with Child-Pugh B, and 40 patients (52.6%) with Child-Pugh C.

From the size grading of esophageal varices, it was found that esophageal varices with size F1 in 25 patients (32.9%), F2 in 32 patients (42.1%), and F3 in 19 patients (25%) (Table 2).

There are significant difference in Lok Score means between groups of large esophageal varices and group of small esophageal varices, where the value of Lok Score in group of large esophageal varices was significantly higher compared with the

group of small esophageal varices ( $0.92 \pm 0.14$  vs.  $0.70 \pm 0.29$ ) with  $p = 0.001$ . Furthermore, it was also found significant differences in parameters's means of platelet, total bilirubin, AST, Albumin, PT, INR, ALT in small esophageal varices compared to means in large esophageal varices ( $p = 0.005$ ;  $p = 0.015$ ;  $p = 0.027$ ;  $p = 0.006$ ;  $p = 0.025$ ;  $p = 0.005$ ;  $p = 0.001$ ;  $p = 0.023$  respectively) (Table 3).

Predictive values of Lok Score cut-off  $> 0.9141$  in diagnosis large esophageal varices have 74.5% sensitivity, 72% specificity, 84% PPV, 58% NPV, 2.66 LR (+), 0.33 LR (-) and 73.7% diagnostic accuracy (Table 4).

**Table 1. Demographic characteristics of study subjects (n = 76)**

Parameters	n (%)
Sex	
Male	57 (75)
Female	19 (25)
Age (years old)	$49.76 \pm 11.63^*$
Platelets ( $\times 10^9/L$ )	$111.50$ (23-647)**
Aspartate aminotransferase (U/L)	72 (12-1075)**
Alanin aminotransferase (U/L)	37.5 (8-536)**
Gamma GT (U/L)	68 (10-901)**
Total bilirubin (mg/dL)	2.5 (0.25-32.18)**
Albumin (gr/dL)	$2.49 \pm 0.72^*$
$\Delta$ Prothrombine time (PT) (second)	$5.26 \pm 5.37^*$
International normalized ratio (INR)	$1.41 \pm 0.43^*$
Ascites	
No	14 (18.4)
Minimal	12 (15.8)
Mild	40 (52.6)
Severe	10 (13.2)
Child – Pugh	
A	10 (13.2)
B	26 (34.2)
C	40 (52.6)
Etiology of liver cirrhosis	
Hepatitis B	42 (55.3)
Hepatitis C	4 (5.3)
Hepatitis B + C	1 (1.3)
Non-B & C	29 (38.2)
Lok Score	$0.85 \pm 0.23^*$

\*mean; \*\*median, min-max

**Table 2. Prevalence of esophageal varices degree in liver cirrhosis patients (n = 76)**

Esophageal Varices Degree	Data of Patients n (%)
Small esophageal varices	25 (32.9)
F1	25 (32.9)
Large esophageal varices	51 (67.1)
F2	32 (42.1)
F3	19 (25)

**Table 3. Bivariate analysis of corellation between independent variables with the size of esophageal varices**

	Size of Esophageal Varices		p
	Small (n = 25) mean $\pm$ SD	Large (n = 51) mean $\pm$ SD	
Age	$50.40 \pm 11.871$	$49.45 \pm 11.618$	0.741
Platelet	$199.04 \pm 145.58$	$121.75 \pm 88.655$	0.005*
Total bilirubin	$3.9732 \pm 6.377$	$6.278 \pm 7.84$	0.015*
AST	$79.92 \pm 81.361$	$168.65 \pm 120.120$	0.027*
Albumin	$2.808 \pm 0.707$	$2.333 \pm 0.678$	0.006*
PT	$3.30 \pm 4.683$	$6.216 \pm 5.472$	0.025*
INR	$1.21 \pm 0.378$	$1.507 \pm 0.426$	0.005*
ALT	$41.24 \pm 36.449$	$67.45 \pm 81.979$	0.023*
Lok Score	$0.70 \pm 0.29$	$0.92 \pm 0.14$	0.001*

\* Uji T-independent; \*: uji mann whitney; \*: signifikan; AST: aspartate amino transferase; PT: prothombine time; INR: international normalized ratio; ALT: alanine aminotransferase

**Table 4. Predictive values of Lok Score in identifying the size of esophageal varices in liver cirrhosis patients**

Model	Cut-off	Varices size (endoscopy)		Se (%)	Sp (%)	PPV (%)	NPV (%)	LR (+)	LR (-)	Acc
		F2-F3 (n = 51)	F1 (n = 25)							
Lok score	> 0.9141	38	7	74.5	72	84	58	2.66	0.35	73.7
	≤ 0.9141	13	18							

Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; Acc: accuracy

## DISCUSSION

The growing need for upper gastrointestinal tract endoscopy and the limitations to meet these needs as well as the difficulties to perform endoscopy periodically every 1 or 2 years in patients with high-risk esophageal varices prompted some researchers to examine non-invasive methods in predicting the presence of esophagus varices so that the needs of endoscopy and health costs could be reduced.<sup>15</sup>

From 76 subjects of this study, we found that the most common cause of liver cirrhosis is chronic hepatitis B infection (55.3%). This is similar to a study conducted by Limquiaco et al, where the most common cause of cirrhosis is chronic hepatitis B infection (40%).<sup>16</sup>

In this study we found that Child Pugh score in the patients are 13.2% with Child A, 34.2% with Child B, and 52.6% with Child C. High prevalence of Child C in this study because this study was conducted at a referral hospital, where most patients referred to our institution are in the late phase of the disease.

Mild to moderate thrombocytopenia occurred in 49-64% of patients with liver cirrhosis. The etiology of thrombocytopenia is multifactorial including increased sequestration of platelets in the spleen during congestive splenomegaly due to portal hypertension, decreased production of thrombopoietin (TPO), and the process of platelet destruction due to autoantibodies or immune processes.<sup>17,18</sup> This study reported that thrombocytopenia happened in 52 liver cirrhosis patients (68.4%) which have esophageal varices.

In this study, we found the size of esophageal varices are 32.9% in F1, 42.1% in F2 and 25% in F3. In this study, we also found a significant difference between the means of Lok Score between patients with large esophageal varices and small esophageal varices which determined by endoscopy ( $0.92 \pm 0.14$  vs.  $0.70 \pm 0.29$ ;  $p = 0.001$ ).

Lok Score cut-off > 0.9141 in diagnosing large esophageal varices are found have 74.4% sensitivity, 72% specificity, 84% PPV, 58% NPV, and has an accuracy of 73.7%. Beside it could be used as one of the non-invasive method to detect esophageal varices, Lok Score is expected to could be used as a basis for giving the  $\beta$ -blockers treatment as primary prevention against

esophageal varices bleeding especially in areas with no endoscopy facilities as well as limitation of physician's competence of endoscopy.<sup>1</sup> Therefore, it needed an non-invasive examination (marker) which correlated with portal hypertension, which can identify the presence of esophageal varices in liver cirrhosis patients.<sup>9</sup>

## CONCLUSION

There are significant differences between the means of Lok Score between patients with large esophageal varices and patients with small esophageal varices which determined by endoscopy. Lok Score is a non-invasive parameters which good at predicting the size of esophageal varices in patients with liver cirrhosis. Further studies on Lok Score need to be done, which should be combined with another methods of non-invasive predictor of esophageal varices, so that a non-invasive algorithm to predicting the presence or absence of esophageal varices and their size in liver cirrhosis patients can be formulated.

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