

Correlation Between Neutrophil To Lymphocyte Ratio With *Child Turcotte Pugh* In Liver Cirrhosis Patients

Wiwiek Probowati¹, Putut Bayupurnama², Neneng Ratnasari³

¹The Specialty Training Program of Internal Medicine, Faculty of Medicine, Universitas Gadjah Mada, Dr. Sardjito General Hospita

^{2,3}The division of Gastroenterohepatolgy, Department of Internal Medicine, Faculty of Medicine, Universitas Gadjah Mada, Dr. Sardjito General Hospital

ABSTRACT

Background: Neutrophil to lymphocyte ratio (NLR) is an index that is widely used these days. NLR has been widely studied as a predictor of poor survival and outcome in patients with liver cirrhosis, hepatocellular carcinoma, coronary heart disease, rheumatoid arthritis, sepsis and malignancy.

Objective: To determine whether there is a correlation between NLR with a score of *Child turcotte pugh* (CTP) in patients with liver cirrhosis in Dr. Sardjito General Hospital.

Methods : The study design was cross-sectional study. The study began in December 2014 until the number of samples are met. The subjects of this study were patients with liver cirrhosis at affordable populations undergoing inpatient and outpatient care in the Dr. Sardjito Hospital that meet the inclusion and exclusion criteria. Venous blood test to measure neutrophils, lymphocytes, albumin, total bilirubin, INR (Internationale normalized ratio). Data presented in the form of descriptive analysis of the characteristics of the study subjects such as the mean and standard deviation values of lymphocyte and neutrophil ratio scores CTP. For analyze the correlation between NLR with CTP scores Spearman nonparametric analysis $p < 0.05$.

Results : There are 33 subjects in the study. Based on the results of this study found a positive significant correlation between the ratio of neutrophils to lymphocytes CTP with $r = 0.749$ and $p = < 0.0001$ and obtained the formula $Y = 7.797 + 0,067x$. Thus increasing of neutrophils to lymphocytes ratio positive correlated with the severity of liver cirrhosis.

Conclusion. There are positive correlation between the neutrophil to lymphocyte ratio with CTP scores in patients with liver cirrhosis.

Keywords: neutrophil to lymphocyte ratio, *child turcotte pugh*, liver cirrhosis

ABSTRAK

Latar Belakang: Rasio Neutrofil terhadap Lymphocyte (NLR) adalah indeks yang digunakan saat ini akhir-akhir ini. RNL telah banyak dipelajari sebagai prediktor tentang kelangsungan hidup dan hasil buruk pada pasien dengan sirosis hati, karsinoma hepatoseluler, penyakit jantung koroner, rheumatoid arthritis, sepsis dan keganasan.

Tujuan: Untuk mengetahui apakah ada hubungan antara NLR dengan skor Child turcotte pugh (CTP) pada pasien dengan sirosis hati di Rumah Sakit Dr. Sardjito.

Metode: Desain penelitian adalah penelitian cross-sectional. Penelitian dimulai pada bulan Desember 2014 sampai jumlah sampel terpenuhi. Subyek penelitian ini adalah pasien dengan sirosis hati pada populasi terjangkau yang menjalani rawat inap dan rawat jalan di Rumah Sakit Dr. Sardjito yang memenuhi kriteria inklusi dan eksklusi. Tes darah vena untuk mengukur neutrofil, limfosit, albumin, total bilirubin, INR (rasio normalisasi Internationale). Data yang disajikan berupa analisis deskriptif karakteristik subjek penelitian seperti mean dan nilai standar deviasi nilai rasio limfosit dan neutrofil CTP. Untuk analisis korelasi antara NLR dengan nilai CTP analisis Spearman nonparametrik $p < 0,05$.

Hasil: Ada 33 subjek dalam penelitian ini. Berdasarkan hasil penelitian ini ditemukan korelasi positif yang signifikan antara rasio neutrofil terhadap limfosit CTP dengan $r = 0,749$ dan $p = < 0,0001$ dan diperoleh rumus $Y = 7,797 + 0,067x$. Jadi peningkatan rasio neutrofil terhadap limfosit positif berkorelasi dengan tingkat keparahan sirosis hati.

Kesimpulan. Ada korelasi positif antara rasio neutrofil terhadap limfosit dengan skor CTP pada pasien dengan sirosis hati.

Kata kunci: rasio neutrofil terhadap lymphocyte, child turcotte pugh, sirosis hati

BACKGROUND

Chronic liver disease and liver cirrhosis is a disease with high morbidity and mortality. Many patients who died on the fourth or fifth decade of their lives as a result of this liver disease. Liver Cirrhosis is the third largest cause of death in people aged 45-46 years (after cardiovascular disease and cancer). Around the world, liver cirrhosis ranks seventh leading cause of death. In the United States the death rate of 9.7 per 100,000 population. About 25,000 die each year as a result of people with this disease.^{1,2}

Objective scoring system, accurate and inexpensive very important to determine the prognosis of liver cirrhosis. Child turcotte pugh (CTP) and the Model for

End Stage Liver Disease (MELD) scores have been commonly used and often the system for predicting prognosis and determined survival of liver cirrhosis.¹ The ratio of neutrophils lymphocytes (NLR) is a marker that is cheap, available, and a rapid test obtained and rapid inflammatory response system. Increased neutrophil lymphocyte ratio associated with poor outcomes cilinical heart disease, myocardial infarction, and some malignancies. This ratio gives an explanation on two different immune pathways, neutrophil responsible for the ongoing inflammatory, whereas lymphocytes describe regulatory pathways.^{1,3} In accordance with the background mentioned above, it can be formulated problem: is there a correlation

between the ratio of neutrophils to lymphocytes *Child turcotte pugh* score of patients with liver cirrhosis? The purpose of research is to determine the correlation between the ratio of neutrophils to lymphocytes *Child turcotte pugh* score of patients with liver cirrhosis.

METHODS

This study was a cross sectional study in patients with liver cirrhosis who do not suffer from malignancy, severe infections, sepsis, diabetes mellitus, hypertension, coronary heart disease, rheumatoid arthritis, kidney failure. The study was conducted during the period December 2014 to the number of samples are fullfilled. The target population of this research is all good liver cirrhosis patients with a score of CTP A, B and C. The population of patients with liver cirrhosis affordable is treated in ward and outpatient clinicin Dr. Sardjito general hospital. Subjects were patients with liver cirrhosis at affordable population who meet the inclusion and exclusion criteria. Subjects were patients with cirrhosis who meet the following criteria:inclusion criteria are patients with liver cirrhosis who are diagnosed by clinical, laboratory and ultrasound and CT-scan or patients with liver cirrhosis child A, B and C, the adult age (> 18 years), are willing to follow the study and signed a research agreement. Exclusion criteria included suffering from sepsis, suffering from a disease which has a tendency to have high neutrophil ratio (bacterial infection, hypertension, diabetes mellitus, coronary heart disease, rheumatoid arthritis), malignancy. From the calculation formula obtained a minimum sample size of

24 subjects.⁶Population of liver cirrhosis who are hospitalized at Dr Sardjito general hospitaland outpatient who meet the criteria for inclusion and exclusion doing research in laboratory tests. Laboratory tests performed routine blood CTP score calculation, which will then be compared with the ratio of neutrophils lymphocytes. In this study, the variables studied or dependent variable is the ratio of lymphocytes and neutrophils CTP scores (including albumin, bilirubin and INR) is the independent variable.

Statistical Analysis

Data characteristics of the study subjects are presented in figures mean and standard deviation. To determine the distribution of normal distribution of data or analytical method performed *Shapiro-Wilk* normality test for sample ≤ 50 , the data is said to be normally distributed if the level of significance when $p > 0.05$.⁶ The difference in the average value of the data group cirrhosis with neutrophil lymphocyte ratio were tested using *Student's t test* for unpaired numerical variables unpaired two groups with normal distribution of data and the *Mann-Whitney U test* for data distribution is not normal. Factors that affect neutrophil lymphocyte ratio analyzed using linear regression or logistic regression. This study used a cross-sectional design of the study does not provide treatment manipulation on the subject. This study uses the approval of biomedical research ethics committee of the Faculty of Medicine, University of Gadjah Mada and permission of the department Director Dr. Sardjito. All patients studied get willingness sheet (informed consent) to follow this study.

RESULT AND DISCUSSION

The study looked at the correlation between the ratio of neutrophils to lymphocytes *Child turcotte pugh* scores were treated in the clinic or ward hospitalized in Internal Medicine Dr Sardjito general hospital that meet the inclusion and exclusion criteria and willing to participate in research. During the study, obtained 33 subjects who meet the inclusion and exclusion criteria and consisted of 22 men (66.7%) and 11 women (33.3%). The average age of patients with cirrhosis of the study subjects was 53.87 ± 10.05 years with the youngest 39 and the oldest 85 years. The results of laboratory tests obtained average levels of neutrophil lymphocyte

ratio of 5.3 (1.7 to 90.14), neutrophils count was 69.57 (47-88), 12.9 lymphocyte count (4.2 to 44). Mean INR value of 1.51 (0.72 to 3.2), the mean value of albumin 2.8 (0.5 to 3.12) and bilirubin values mean 1.6 (0.5 to 31.2). The severity of cirrhosis based criteria CTP score, mostly Child B were 13 (39.3%), total Child A were 10 people (30.30%) and Child C by 10 Orang (30.30%). In this study, the number of men more than women 22:11 (66.7% vs. 33.3%). On the subject of research got hepatitis B patients were 26 (78.2%) patients, hepatitis C 5 (6.1%) patients, hepatitis B and C as much as 0%. According Nurdjanah (2014), causes of liver cirrhosis in Indonesia mainly due to infection with hepatitis B or C virus. Table 3 shows the characteristics of the study subjects in 33 subjects studied.

Table 3 Baseline clinicodemographic characteristics and laboratory parameters of the study (n=33)

Parameter	average \pm SB	Median (minimum- maksimum)	Frequency
Age (years)	53.87 \pm 10.05		
Gender			
Male n(%)			22 (66.7%)
Female n(%)			11 (33.3)
Leucocyte count (/mmk)	8.55 \pm 4.21		
Neutrophil count (%)		69.57(47-88)	
Internationale Normalized Ratio(INR)		1.51(0.72-3.2)	
Albumin (g/dL)		2.8(0.5-3.12)	
Bilirubin (mmol/L)		1.6(0.5-31.2)	
Neutrophil to lymphocyte ratio		5.3(1.7-90.14)	
Limphocyte count (%)		12.9 (4.2-44)	
<i>Child turcotte pugh</i>			
CTP A n (%)			10(30.30%)
CTP B n (%)			13 (39.3%)
CTPC n (%)			10 (30.30%)
Hepatitis B n(%)			26 (78.2%)
Hepatitis C n(%)			5 (6.1%)

Description: SB: Standard Deviation; * = distribution of data is abnormal

The process of transformation is done so that the normal distribution of data is not successful, the correlation is selected in the analysis of the relationship between the degree of CTP RNL patients with liver cirrhosis is a non-parametric Spearman

correlation test. There are scattered plot a graph that shows a positive correlation between the ratio of neutrophils to lymphocytes with CTP scores $R^2 = 0.185$ and obtained a formula $Y = 7.797 + 0,067x$.

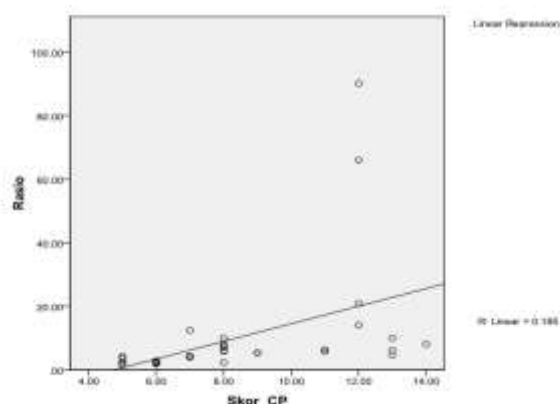


Figure 1 Positive Correlation between RNL and CTP Score

Table 4 Posthoc Analysis of the differences between NLR and CTPCategory

	CTP categories	n	Mean rank	p
Rasio N/L	A	10	6,2	<0,0001*
	B	13	16,46	
Rasio N/L	A	10	5,50	<0,0001*
	C	13	15,50	
Rasio N/L	B	10	9,31	0,030*
	C	10	15,5	

* Mann-Whitney test; significant $p < 0.05$

Table 5 The difference between RNL and CTP categories

	Skor CTP	N	Mean rank	p*
RNL	A	10	6,20	<0,0001
	B	13	18,77	
	C	10	25,50	

* Kruskal-Wallis test; p meaningful < 0.05

In this study the mean neutrophil to lymphocyte ratio in group A 6.2, while group B 16.46 and showed statistically significant differences $p < 0.0001$. In this study, the mean ratio of neutrophil to

lymphocytes in the CTP group A, mean of 5.5 compared to group C. NLR scores were 15.50 average and showed a statistically significant difference $p < 0.0001$. This study also showed the average NLR in category

CTP B CTP C 9.31 compared to the average of 15.50 gave the differences were statistically significant at $p < 0.030$. In this study the mean neutrophil to lymphocyte ratio in group CTP A 6.2 and B 18.77, while group C was 25.50 and showed statistically significant differences with $p < 0.001$. The results showed between NLR with the severity of liver cirrhosis by CTP scores significantly positive correlation with $p < 0.0001$, $r = 0.749$ and obtained the formula $Y = 7.797 + 0,067x$, while the value of $R^2 = 0.185$.

DISCUSSION

According to Nurdjanah (2014), patients with liver cirrhosis suffered the highest average age between the age group of 35-69 years with a peak around the age of 40-49 years.² It is almost similar to a study conducted in Mexico, where the number of patients with cirrhosis who underwent inpatient reach 25% of total patients treated in the ward of disease in the proportion of men than women 3: 1. Presumably it is because of the influence of estrogen in women has a protective effect against liver fibrosis.^{7,8}

Results of research in Indonesia mention of hepatitis B virus causes liver cirrhosis as much as 40-50%, hepatitis C virus as much as 30-40% and 10-20%, and the cause is unknown, including B and C virus is not (non-B non-C). The results of this study are patients with cirrhosis of the liver with hepatitis B etiology of 78.2%. There is a positive correlation between NLR with CTP score but RNL has little effect on the CTP score. This is according to research conducted by Biyik *et al.* in 2012 and Byong Sun *et al.* in 2013.^{1,2}

Byong Sun *et al.* states that there is a positive correlation between NLR with CTP group ($r = 0.306$, $p < 0.001$). In patients with liver cirrhosis, occurs permanent necroinflammation, immune system and activated inflammatory and inflammatory markers such as IL-6, TNF- α has been found to increase. In these patients, neutropenia and limfositopenia closely associated with hypersplenism but limfositopenia more as a result of malnutrition.^{4,7} Atakan Yesil *et al.*, show that NLR correlated with inflammation and fibrosis process occurs due to arterial hypertension which will activate pro-inflammatory pathway. Neutrophil lymphocyte ratio is a parameter that is quickly and easily obtained from peripheral blood tests that reflect systemic inflammation as well as the nutritional status of patients in general.^{8,9}

In general, no specific cut-off point for the ratio of neutrophils lymphocytes. Biyik found that lymphocytes neutrophil ratio above 2.75 have a higher mortality significantly in patients with liver cirrhosis.¹ Alkouri *et al.*, revealed that RNL is increased in patients with NASH and advanced fibrosis than patients not NASH. Our study is also in line with previous studies. That is because the relationship between limfomononuklear and part neutrophils through a complex interaction of inflammatory cytokines. Through pathophysiology, indicated that RNL reflect an increase in the severity of patients with liver cirrhosis.^{5,12} This study has several limitations. There are several factors that can affect the ratio of lymphocytes and neutrophils can not be controlled. In the cross sectional method can not describe the course of the disease because of exposure

and outcome are measured at the same time, the existing data only represents the state at the time of the research conducted. This study found a significant positive correlation between the ratio of neutrophils to lymphocytes *Child turcotte pugh* score.

CONCLUSION

There are positive correlation between the neutrophil to lymphocyte ratio with CTP scores in patients with liver.

SUGGESTION

Future research needs to be done to further investigate the correlation between the ratio of neutrophils to lymphocytes by considering the severity of liver cirrhosis counfounding factors that influence. Research with case control or cohort needs to be done to determine the morbidity and mortality that neutrophil lymphocyte ratio could be a predictor of the severity of liver cirrhosis at Dr. Sardjito general hospital.

REFERENCE

1. Biyik M, Ucar R, Solak Y, Yalcin Solak, Gokhan Gungor, Ilker Polar, Ozlem O.. Cakir,2012Blood neutrophil-to-lymphocyte ratio independently predicts survival in patients with liver cirrhosis of Internal Medicine, Division of Gastroenterology, Meram School of Medicine, *Eur J Gastroenterol Hepatol*.Apr;25(4):435-41.
2. Nurdjanah, S. 2014. Jilid II. Sirosis hati. In: A.W., Sudoyo, B., Setiyohadi, I., Alwi, M., Simadibrata, S., Setiati (eds).*Buku Ajar Ilmu Penyakit Dalam Edisi 6. Interna Publishing, Jakarta*.pp 668-673.
3. Starr S.P & Raines, D., 2011, Cirrhosis: Diagnosis, Management, and Prevention, *American Family Physician*, Volume 84, Number 12, hal 1353-9.
4. Fock RA, BlattSL, Beutler B, Pereira J, Tsucita M., De Barros FE, Study of Lymphocyte subpopulation in bone marrow in a model of protein energy malnutrition 2010: 26: 1021-1028.
5. Naim Alkhouri, Gareth Morris-Stiff, Carla Campbell, 2012, Neutrophil to Lymphocyte Ratio: A New Marker for Predicting Steatohepatitis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease, *Liver International* ;32(2):297-302.
6. Muhammad Sopiudin Dahlan, 2008, Statistik untuk Kedokteran dan Kesehatan, edisi 3, *Penerbit Salemba Medika*.
7. Jeffrey I. Zwicker, Reed E. Drews, 2007, Hematologic Disorders and the Liver, *Schiff's Diseases of the Liver, 10th Edition*, Chapter 12.
8. Cervoni JP, Thevenot T, Weil D, Muel E, Barbot O., 2012, C-reactive protein predicts short term mortality in patients with cirrhosis, *J Hepatology* Jun;56(6): 1299-304.
9. Atakan Yesil, Suleyman Cosgun, Emrulah Erdem, Koray Kochan, 2013, The Relationship between fibosis level and blood neutrophile to lymphocyte ratio in chronic HBV patients, *Akademik Gastroenteroloji Dergisi*: 12(2) 66-68.
10. Byong Sun Oh, Jeong Won Jang, Jung Hyun Kwon, 2013, Prognostic value of C-reactive protein and neutrophil-to-lymphocyte ratio in patients

- with hepatocellular carcinoma, *BMC Cancer*, 13:78.
11. Halazun, Ming Te Kuo, Tsung Hui Hu, Sheng Nan Lu, 2013, Neutrophil to Lymphocyte Ratio as a Predictor of Response to Peginterferon plus Ribavirin Therapy for Chronic Hepatitis C, *Disease Markers*, volume 2014:534-540.
 12. Alpasian, Tan og Lu and Ergon ekon Karagoz, 2014, Neutrophil to lymphocyte ratio acts: as a prognostic factor for patients with advanced hepatocellular carcinoma, *European Journal of Gastroenterology & Hepatology* vol 26 no 3, p 23-45.