The Relationships between Neutrophil/Lymphocyte Ratio and Child-Turcotte-Pugh Classification in Assessing Severity of Liver Cirrhosis

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Abstract

Background

Liver cirrhosis is a disease with high morbidity and mortality in Indonesia. The Child-Turcotte-Pugh classification is a noninvasive parameter to assess severity of liver cirrhosis. Meanwhile, the neutrophil/lymphocyte ratio can reflect person's immunity to liver cirrhosis.

Objective

This study was conducted to determine the conformity between neutrophil/lymphocyte ratio and Child-Turcotte-Pugh classification in assessing severity of liver cirrhosis.

Methods

Analytical observational study with Cohen's Kappa conformity test was conducted in 86 liver cirrhosis patients. Data was retrieved by observing the medical records. Neutrophil count, lymphocyte count, hepatic encephalopathy, ascites, albumin, bilirubin, and INR were all recorded. Documented variables were analyzed by the Cohen's Kappa conformity test.

Results

In Cohen's Kappa conformity test, there was moderate conformity between neutrophil/lymphocyte ratio and Child-Turcotte-Pugh classification in all samples (κ = 0.591 and p <0.001). Conformity between neutrophil/lymphocyte ratio and Child-Turcotte-Pugh classification based on age and gender was found to be κ = 0.777 at age ≤45 years, κ = 0.532 at age >45 years, κ = 0.682 in male, and κ = 0.445 in female (p <0.001). The highest conformity is the substantial conformity between neutrophil/lymphocyte ratio and Child-Turcotte-Pugh classification obtained at age ≤45 years (κ = 0.777 and p <0.001) and male (κ = 0.682 and p <0.001).

Conclusion

There is moderate conformity between neutrophil/lymphocyte ratio and Child-Turcotte-Pugh classification in assessing severity of liver cirrhosis. Substantial conformity obtained at age ≤45 years and male gender.

Keywords: Neutrophil/Lymphocyte Ratio, Child-Turcotte-Pugh, Liver Cirrhosis
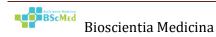
Background

Liver cirrhosis is the final stage of the diffuse process of progressive liver fibrosis characterized by distortion of liver architecture and regenerative nodule formation. Liver cirrhosis is the third highest cause of death in patients aged 45-46 years [1]. In 2017, there were 45,783,000 cases of liver cirrhosis in the world and 1,638,000 of them were new cases. [2]

Indonesia is one of ten developing countries with the highest cases of liver cirrhosis according to the World Health Organization (WHO). [3-4] The prevalence of liver cirrhosis in Indonesia in 2007 was 1.7% and increased to 3.5% in 2013. [5-6] Recent data recorded the mortality rate of liver cirrhosis in Indonesia according to gender by 52.7/100,000 population in men and 16.6/100,000 population in women. [4]

Neutrophil/lymphocyte ratio is a parameter that can reflect a person's immunity against liver cirrhosis because neutrophils and lymphocytes play an important role in the course of the disease of liver cirrhosis. [7-10] The neutrophil/lymphocyte ratio is a cheap, available and fast method to describe systemic inflammation, as well as complex pathophysiological processes that underlie the progression of liver cirrhosis. [11-15] However, an increase in the neutrophil/lymphocyte ratio is not only found in patients with liver cirrhosis, but it is also found in patients suffering from infections, autoimmune diseases, HIV-AIDS, malignancy, leukemia, or being pregnant so that the neutrophil/lymphocyte ratio cannot used if the patient with cirrhosis of the liver suffers from one of the accompaniers. [16] The neutrophil/lymphocyte ratio is obtained from laboratory results with a complete blood examination. The neutrophil/lymphocyte ratio can be calculated by dividing absolute neutrophil counts with absolute lymphocytes. [17]

The severity of liver cirrhosis can be measured using an objective, accurate and inexpensive scoring system such as the Child-Turcotte-Pugh classification and the Model of End-Stage Liver Disease (MELD). [11, 18-19] The Child-Turcotte-Pugh classification and MELD have similar prognosis significance in many cases. [20-21] However, in a recent study it was found that the Child-Turcotte-Pugh classification was intended to assess survival while MELD was intended to determine the optimal time for liver

transplantation. [22] Therefore, the Child-Turcotte-Pugh scoring system can be used to measure the severity associated with the survival of patients with liver cirrhosis.

In previous studies it was found that the neutrophil/lymphocyte ratio was significantly useful for predicting the prognosis of patients with liver cirrhosis. [23-25] The study was supported by research in Indonesia with a significant positive correlation between neutrophil/lymphocyte ratio and Child-Turcotte-Pugh scores in patients with liver cirrhosis ($r = 0.749$ and $p < 0.0001$). [11]

Liver cirrhosis is a disease that has a poor prognosis and Indonesia is one of the developing countries with high rates of morbidity and mortality of liver cirrhosis. [26] Therefore, a study was conducted on the conformity test between the neutrophil/lymphocyte ratio and the Child-Turcotte-Pugh classification in assessing severity of liver cirrhosis in RSUP Dr. Mohammad Hoesin Palembang.

The purpose of this study was to determine the conformity between the neutrophil/lymphocyte ratio and the Child-Turcotte-Pugh classification in assessing severity of liver cirrhosis. Identification of neutrophil/lymphocyte ratios and Child-Turcotte-Pugh classification in patients with liver cirrhosis in Indonesia can also illustrate the importance of improving early detection, early management and communication, information as well as education regarding the importance of treatment to prevent worsening of liver cirrhosis.

Methods

This study was an observational analytic study using the Cohen's Kappa conformity test conducted from January 2016 to October 2018. [27-28] The sample of this study was all liver cirrhosis patients who had undergone complete blood tests and liver function examinations during the period of January 2016 to October 2018 at RSUP Dr. Mohammad Hoesin Palembang who fulfilled the inclusion criteria. The inclusion criteria are all patients aged 18–65 years old who had been diagnosed with liver cirrhosis by a Gastroenterology and Hepatology specialist. Patients necessarily had undergone complete blood tests and liver function examination during the period of January 2016 to October 2018 in the Internal Medicine Installation of RSUP Dr. Mohammad Hoesin Palembang.

The research data was obtained from the patients' medical records. Factors studied included neutrophil count, lymphocyte count, hepatic encephalopathy, ascites, albumin, bilirubin, and INR. Diagnosis of liver cirrhosis is seen through diagnosis results in medical records.

Univariate analysis was used to determine the characteristics of patients with liver cirrhosis based on age and gender. In addition, the distribution of patients was based on cut-off point from neutrophil/lymphocyte ratio and Child-Turcotte-Pugh classification. The bivariate analysis used was the Cohen's Kappa test to determine the conformity of neutrophil/lymphocyte ratio and Child-Turcotte-Pugh classification.

Results

Research had been conducted at RSUP Dr. Mohammad Hoesin Palembang and it was found that there were 297 liver cirrhosis patients from January 1, 2016 - October 31, 2018. Eighty six out of 297 samples met the inclusion and exclusion criteria.

Table 1. Liver Cirrhosis Patients Data (n=86)

Characteristics	n	%
Age		
≤45 years old	22	25.6%
>45 years old	64	74.4%
Gender		
Male	54	62.8%
Female	32	37.2%
BMI		
<17.0	2	2.3%
17.0–18.4	13	15.1%
18.5–25.0	56	65.1%
25.1–27.0	4	4.7%
>27.0	11	12.8%
Etiology (Hepatitis)		
Hepatitis B	44	51.2%
Hepatitis C	5	5.8%
Hepatitis B dan C	2	2.3%
Not Hepatitis	35	40.7%

Table 1 shows the characteristics of liver cirrhosis patients. Patients with liver cirrhosis in this study were aged 25-65 years old. The mean±SD age of liver cirrhosis patients is 51 ± 8.54 years old. Based on gender, men dominate with a percentage of 62.8%. BMI of liver cirrhosis patients had a mean±SD of 22.04 ± 4.24 kg/m^2 and is dominated by patients with normal BMI (18.5–25.0). Meanwhile, the main etiology of patients with liver cirrhosis in Asia is hepatitis B and C infection so that hepatitis B infection is the highest in this study (51.2%). Liver cirrhosis patients with hepatitis B and C infections were obtained based on laboratory tests, namely HBsAg and anti-HCV.

Table 2. Distribution of Major Complaint in Patients (n=86)

Major Complaint	n	%
Enlarged stomach	31	36.0%
Black vomit and feces	15	17.4%
Limp body	14	16.3%
Black feces	10	11.6%
Stomach cramp	9	10.5%
Black vomit	3	3.5%
Loss of consciousness	3	3.5%
Icteric	1	1.2%

In table 2, distribution of the main complaints showed that the most major complaints in liver cirrhosis patients who came to RSUP Dr. Mohammad Hoesin Palembang was enlarged stomach (31 patients), black vomit and feces (15 patients), and limp body (14 patients). This main complaint is in accordance with the clinical findings presented in table 3.

Table 3. Distribution of Clinical Findings in Patients (n=86)

Clinical Findings	n	%
Esophageal Varices		
Esophageal Varices	36	41.9%
Not Esophageal Varices	50	58.1%
Hepatic Encephalopathy		
Hepatic Encephalopathy	10	11.6%
Not Hepatic Encephalopathy	76	88.4%
Ascites		
Ascites	50	58.1%
Not Ascites	36	41.9%

The distribution of clinical findings in patients with liver cirrhosis is presented in table 3. Clinical findings in the form of esophageal varices, hepatic encephalopathy, and ascites are a form of hepatocellular failure and portal hypertension in patients with liver cirrhosis.

Table 4. Distribution of Neutrophil/Lymphocyte Ratio and Child-Turcotte-Pugh Classification in Patients (n=86)

Variable	n	%
Neutrophil/Lymphocyte Ratio		
≤3,1482	21	24.4%
3,1483–6,5208	44	51.2%
≥6,5209	21	24.4%
Child-Turcotte-Pugh Classification		
Child-Turcotte-Pugh A	19	22.1%
Child-Turcotte-Pugh B	33	38.4%
Child-Turcotte-Pugh C	34	39.5%

Table 4 shows the distribution of neutrophil/lymphocyte ratio and the mean±SD in liver cirrhosis patients obtained is 4.77 ± 2.016. The minimum value of the neutrophil/lymphocyte ratio obtained was only 1.22 and the maximum value of the neutrophil/lymphocyte ratio obtained was 9.67. The cut-off point of neutrophil/lymphocyte ratio in liver cirrhosis patients was based on the 25th and 75th percentiles of IBM SPSS Statistic 23. Meanwhile, table 4 also presents the distribution of the Child-Turcotte-Pugh classification and it was found that liver cirrhosis patients in this study dominated by Child-Turcotte-

Pugh C classification (39.5%). The Child-Turcotte-Pugh classification is determined based on the parameters for hepatic encephalopathy, ascites, albumin, bilirubin, and INR.

Table 5. Conformity between Neutrophil/Lymphocyte Ratio and Child-Turcotte-Pugh Classification in Assessing Severity of Liver Cirrhosis

Agreement	κ	*p_value*
All Samples	0.591	0.000
Age		
≤45 years old	0.777	0.000
>45 years old	0.532	0.000
Sex		
Male	0.682	0.000
Female	0.445	0.000

Table 5 presents the value of conformity between the neutrophil/lymphocyte ratio and the Child-Turcotte-Pugh classification. In all samples, moderate conformity was found between the neutrophil/lymphocyte ratio and the Child-Turcotte-Pugh classification (κ=0.591, p<0.001). Meanwhile, based on age and gender, it was found that age ≤45 years and male gender had substantial conformity (0.61≤κ≤0.80).

Discussion

Liver cirrhosis patients, according to age and gender, were found to be higher at age >45 years (74.4%) and male gender (62.8%). Women aged ≤45 years have lower incidence of liver cirrhosis because the hormone estrogen, through ERβ (Estrogen Receptor β), is able to inhibit the activation and proliferation of liver cells which triggers the deposition of collagen, so that the fibrosis process in liver cirrhosis can be inhibited. [29-33]

Most liver cirrhosis patients have a normal BMI (65.1%). This is not in accordance with studies in the United States that found that there was a significant increase in BMI in patients with liver cirrhosis. [34] Nutritional factors and the necessities fulfilled in Asia, especially developing countries together with

dominant factors such as infections (hepatitis B and C) cause lower mean BMI and even normal in liver cirrhosis patients in Indonesia. [3-4, 35-36]
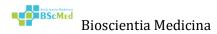
The distribution of hepatitis B in liver cirrhosis patients was found to be 51.2%. This was in accordance with previous studies which obtained a dominant percentage of hepatitis B which was 24.60% and 78.2%. [11, 13] However, liver cirrhosis patients who have hepatitis C have a mortality rate 25% higher than patients with hepatitis B. [15, 29, 37-38]

The results obtained in this study related to hepatocellular failure and portal hypertension manifestations included 41.9% incidence with esophageal varices, 11.6% with hepatic encephalopathy, and 58.1% with ascites. In the previous study, it was found that there were 6% of liver cirrhosis patients with esophageal varices, 10% with hepatic encephalopathy, and 50% with ascites. [30, 39] From the two studies it was found that there were a significant increase in the incidence of esophageal varices. This was because the study was dominated by liver cirrhosis patients with the Child-Turcotte-Pugh classification C. Eighty-five percent of liver cirrhosis patients with the Child-Turcotte-Pugh C classification had esophageal varices. [40]

The percentage of patients with neutrophil/lymphocyte ratios of 3.1483–6.5208 was obtained to be 51.2% of the total sample. An increase in the neutrophil/lymphocyte ratio in patients with liver cirrhosis reflects an increase in neutrophils due to the chronic inflammatory process and a decrease in lymphocyte activity due to the suppression made by neutrophils through arginase, nitric oxide synthase (NOS), and reactive oxygen species (ROS). [7-8, 11-16]

It was found that Child-Turcotte-Pugh C classification has results of 39.5%. In previous studies, it was found that the sample with the Child-Turcotte-Pugh B classification dominated with a percentage reaching 44.1% and 56.94%. [41-43] Liver cirrhosis patients with Child-Turcotte-Pugh C classification have a low survival rate. The 1-year and 2-year survival rate of liver cirrhosis patients with the Child-Turcotte-Pugh C classification were 45% and 35%, respectively. [40]

Conformity between neutrophil/lymphocyte ratio and Child-Turcotte-Pugh classification in assessing severity of liver cirrhosis in all samples was found to be at moderate agreement. Some theories

suggest that there is an increase in neutrophils and decrease in lymphocytes so that the ratio between the two increases in liver cirrhosis patients. [7-8, 16] In liver cirrhosis, the necroinflammatory process activates liver stellate cells. The liver stellate cells then produce cytokines that activate neutrophils so that an inflammatory response occurs. However, hepatocyte death in liver cirrhosis causes produced cytokines cannot be detoxified. As a result, cytokines activate neutrophils persistently so that the number of neutrophils in the body increases. [8, 11]

Meanwhile, neutrophils also have a mechanism to suppress lymphocyte formation through arginase, NOS, and ROS. Neutrophils have a high amount of arginase in azurophilic granules, whereas T cell activation depends on the availability of body arginine. The release of neutrophil arginase through degranulation or apoptosis causes a decrease in body arginine so T cell activation becomes inhibited. [12-14]

Based on age categories, conformity was found to be lower in the age group >45 years old (elderly). In elderly, there is a decrease in the function of the body's immune system (immunosenescence) so that the activation and migration of neutrophils to the site of infection is inhibited. [44-45] In addition, when there are severe and long-term infections, elderly patients can experience neutropenia due to the continuous stimulation of the Granulocyte-Colony Stimulating Factor (G-CSF) to the Common Myeloid Progenitor. The impact of immunonescence on lymphocytes can also be seen from a decrease in lymphocyte levels in both B and T lymphocytes. [46]

By gender, a lower level of conformity between neutrophil/lymphocyte ratio and Child-Turcotte-Pugh classification was obtained in women. The estrogen hormone in women is able to inhibit the activation and proliferation of liver cells that activate neutrophils through ERβ (Estrogen Receptor β). As a result, neutrophil levels in women with liver cirrhosis do not increase as much as in men, although worsening conditions in cirrhosis of the liver continue. [32]

The research conducted is limited on Cohen's Kappa conformity test because it only assess the compatibility between two methods which are not the gold standard. For this reason, it is recommended

that these two methods be tested and adjusted to the gold standard for examining the severity of liver cirrhosis in the future, which is liver biopsy.

Conclusion

Based on the results of this research on the conformity between neutrophil/lymphocyte ratio and Child-Turcotte-Pugh classification in assessing the severity of liver cirrhosis, it was concluded that there was a moderate conformity between neutrophil/lymphocyte ratio and Child-Turcotte-Pugh classification. Substantial conformity was found between neutrophil/lymphocyte ratio and Child-Turcotte-Pugh classification in the age group of ≤45 years old and in male.
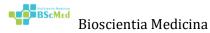
Acknowledgement

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