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CORRELATION OF SIMPLE LABORATORY RESULT PARAMETERS TO CTP AND MELD SCORES, AND THE DIAGNOSTIC ROLE OF SIMPLE LABORATORY INDEXES TO CIRRHOSIS DECOMPENSATION

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ABSTRACT

Background

Liver cirrhosis represents the ultimate stage of any chronic liver ailment. Systemic inflammation plays a crucial role in fostering continuous liver damage.

Aim of Study

Evaluate the correlation of NLR, ABR, ALBI, APRI, ACR, LMR, de ritis ratio to CTP and MELD score. Evaluated the diagnostic ability of NLR, ABR, ALBI, APRI, ACR, LMR, de ritis ratio, CTP and MELD scores in predicting decompensated liver cirrhosis.

Method

This cross-sectional study involving liver cirrhosis patients at RSUP Prof DR IGNG Ngoerah. Correlation tests employed either the Pearson or Spearman test, while diagnostic quality is assessed through the analysis of receiver operating characteristic (ROC) curves.

Result

Of the 96 patients, this study found a significant moderate to very strong relationship between MELD score to ACR, APRI, ALBI, ABR, LMR, WBC, sodium, and albumin. NLR, ACR, De ritis, APRI, LMR, ALBI, ABR, sodium levels, and albumin have a moderate to very strong significant relationship to CTP score. ACR, De ritis, APRI, LMR, ALBI, ABR, WBC, sodium, and albumin levels with respective cut-offs ≤ 3.6 ; ≥ 1.5 ; ≥ 0.3 ; ≤ 2.8 ; ≥ 0.7 ; ≤ 1.6 ; ≥ 6.7 , ≤ 136.50 , and ≤ 3.0 can be used to predict decompensated liver cirrhosis.

Conclusion

Using the CTP and MELD scores as predictive tools for assessing the severity of liver cirrhosis, information derived from laboratory test outcomes, specifically albumin and ABR levels, can aid in establishing the diagnosis of decompensated cirrhosis.

Key word : CTP score, decompensated liver cirrhosis, laboratory examination, MELD score

ABSTRAK

Latar Belakang

Sirosis hati merupakan kondisi akhir dari semua penyakit hati kronis. Inflamasi sistemik memainkan peran penting dalam menyebabkan kerusakan hati yang progresif.

Tujuan Penelitian

Menilai korelasi NLR, ABR, ALBI, APRI, ACR, LMR, rasio de ritis terhadap skor CTP dan MELD. Mengevaluasi kemampuan diagnostik NLR, ABR, ALBI, APRI, ACR, LMR, rasio de ritis, skor CTP, dan MELD dalam memprediksi sirosis hati dekompensasi.

Metode

Studi potong lintang ini melibatkan pasien sirosis hati di RSUP Prof DR IGNG Ngoerah. Uji korelasi menggunakan uji Pearson atau Spearman, sementara kualitas diagnostik dinilai melalui analisis kurva *receiver operating characteristic* (ROC).

Hasil

Dari 96 pasien, ³⁵ penelitian ini menemukan hubungan sedang hingga sangat kuat yang signifikan antara skor MELD dengan ACR, APRI, ALBI, ABR, LMR, leukosit, natrium, dan albumin. NLR, ACR, De ritis, APRI, LMR, ALBI, ABR, kadar natrium, dan albumin memiliki hubungan sedang hingga sangat kuat yang signifikan dengan skor CTP. ACR, De ritis, APRI, LMR, ALBI, ABR, leukosit, kadar natrium, dan albumin dengan cutoff masing-masing $\leq 3,6$; $\geq 1,5$; $\geq 0,3$; $\leq 2,8$; $\geq 0,7$; $\leq 1,6$; $\geq 6,7$, $\leq 136,50$, dan $\leq 3,0$ dapat digunakan untuk memprediksi sirosis hati dekompensasi.

Kesimpulan

Skor CTP dan MELD sebagai alat untuk memprediksi keparahan sirosis hati, data dari hasil pemeriksaan laboratorium berupa kadar albumin dan ABR dapat membantu menegaskan diagnosis sirosis dekompensasi.

Kata kunci: pemeriksaan laboratorium, sirosis hati dekompensasi, skor CTP dan MELD

INTRODUCTION

Liver cirrhosis contributes to elevated mortality and morbidity rates among individuals suffering from chronic liver disease. Liver cirrhosis is defined by the presence of fibrosis and nodules within the liver, which develop as a consequence of prolonged liver injury. Conditions that can injure the liver, namely viral infections, toxins, or autoimmune processes. In developed nations, prevalent factors leading to liver cirrhosis include hepatitis C (HCV), alcoholic liver disease, and non-alcoholic steatohepatitis (NASH). Meanwhile, in developing countries, hepatitis B (HBV) and C (HCV) virus infections are common culprits for liver cirrhosis. The progression of liver cirrhosis may give rise to complications such as hepatocellular carcinoma (HCC) and hepatic decompensation, marked by conditions like ascites, hepatic encephalopathy, and variceal bleeding. These complications significantly contribute to an increased mortality rate among individuals with liver cirrhosis.¹⁻²

Liver cirrhosis is the 11th and 15th cause of death for morbidity, causing 2.2% of deaths and 1.5% of morbidity in 2016. Based on world prevalence data for 2019, the mortality rate due to liver cirrhosis has reached 2.4%.³⁻⁴ However, the exact prevalence of cirrhosis worldwide is not known with certainty. The occurrence of liver cirrhosis is approximately 0.15% and 0.27% in the United States, respectively. Data regarding the prevalence of liver cirrhosis in Indonesia is still lacking. However, some studies state that the average prevalence of liver cirrhosis in Indonesia reaches 3.5% in internal medicine units in public hospitals.⁵

The systemic inflammatory process plays an essential role in liver damage. Systemic inflammation contributes to exacerbating liver damage and poor outcome. Therefore, inflammatory markers, such as neutrophils and lymphocytes, can predict outcomes in viral hepatitis, HCC, liver transplantation, and non-alcoholic fatty liver disease.⁶

Application of a scoring system to predict outcome and severity. Cirrhosis has been widely used.⁷ Health workers commonly use the child-Turcotte-Pugh score and model for end-stage liver disease (MELD) score scoring systems. However, simple laboratory tests, such as neutrophil-lymphocyte ratio (NLR), can be an option in developing countries with limited resources. Apart from NLR, albumin-bilirubin score (ALBI), aspartate aminotransferase to platelet ratio (APRI), de raitis ratio, albumin-bilirubin ratio (ABR), albumin-creatinine ratio (ACR), and lymphocyte-monocyte ratio (LMR) are also stated to be used to help predict liver cirrhosis outcomes.⁸⁻¹⁵ This study examines the relationship between NLR, APRI, ACR, LMR, de raitis ratio, and ABR on

CTP and MELD scores. In addition, this study also looked at each parameter's cut-off and the sensitivity and specificity level of each parameter in diagnosing decompensated cirrhosis.

MATERIAL AND METHODS

Ethical Clearance

This research is a component of the investigation⁴ approved by the Research Committee of the Faculty of Medicine at Udayana University/Sanglah General Hospital under the ethical clearance number 997/UN14.2.2.VII.14/LT/2021.

Population and study design

There were a total of 96³³ patients in this cross-sectional study. Twenty-three¹⁴ of them do not have data for calculating the MELD score. The MELD score was calculated³⁶ only in patients with complete sodium, creatinine, bilirubin, and INR data. The inclusion criteria used in this study were patients with a diagnosis of liver cirrhosis, at least 18 years old, both male and female, and willing to participate²³ by signing an informed consent. The exclusion criteria in this study were patients with cirrhosis of the liver with chronic kidney failure stages 1 to 5, as well as other malignancies other than primary malignancy in the liver. All patients in this study had complete blood count results in¹ white blood cell count and complete liver profile, including liver enzymes, serum albumin, total bilirubin, direct and indirect bilirubin, and blood clotting factors.

Demographic, clinical, and laboratory value of the study²

The demographic characteristics contained in this study are age, gender, and nutritional category. Age in this study was divided into <65 years and ≥ 65 years. The nutrition category is divided into two, malnutrition and non-malnutrition based on body mass index (BMI). The clinical manifestations found in the patients in this study were ascites, haematemesis/melena, or esophageal varices. This study's etiology of liver cirrhosis was divided into infection and non-infection. The causes of the disorder found were hepatitis B and C viruses. Positive HbsAg was located, liver cirrhosis was established due to hepatitis B infection, while anti-HCV reactive was diagnosed as hepatitis C. A complete blood count of all patients was obtained from the medical record. If laboratory results are expected, if WBC ($4.1-11.0 \times 10^3/\text{mL}$), platelet ($140-440 \times 10^3/\text{mL}$), hemoglobin ($12-16 \text{ g/dL}$), albumin ($3.40-4.80 \text{ g/dL}$), BUN ($8.00-23.00 \text{ mg/dL}$), dan sodium³¹ ($136-145 \text{ mmol/L}$).

Liver cirrhosis-related indicator and laboratory ratio

We identified seven ratios based on the results of laboratory tests that have a relationship with liver cirrhosis. We also calculate ALBI based on laboratory test results. The seven laboratory ratios are neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), aspartate aminotransferase-platelet ratio (APRI), albumin-bilirubin ratio (ABR), lymphocyte-monocyte ratio (LMR), serum glutamic oxaloacetic transaminase to serum glutamic pyruvic transaminase (de ritis) ratio, and serum albumin to creatinine ratio (ACR) were obtained for all patients which we calculated using the assistance of Ms. Excel. The albumin to bilirubin index score (ALBI) was calculated using an online calculator.

The liver function indicator in this study uses the CTP and MELD scores. There are three classifications based on the results of calculating the CTP score, namely CTP A (total score 5-6), CTP B (total score 7-9), and CTP C (total score 10-15). The MELD score in this study was calculated using an application calculator and divided into two categories, namely ≥ 20 (high) and < 20 (low).[16] Patients are categorized into decompensated and compensated cirrhosis. Decompensated cirrhosis for patients with CTP scores B and C with clinical symptoms such as upper gastrointestinal bleeding, hepatic encephalopathy, or ascites.

Statistical Analysis of the Data

Data were collected into a computer and analyzed using IBM SPSS software package version 24.0 (Armonk, NY: IBM). Qualitative data are described using numbers and percentages. Quantitative data were tested for normality with the Kolmogorov-Smirnov test. The data is said to be normally distributed if the $p\text{-value} > 0.05$. Data with a normal distribution are presented as mean $\pm$ standard deviation, while data with a normal distribution are shown as the median (minimum-maximum value). Categorical data were analyzed by the Chi-square or Fisher's exact test, which was said to be statistically significant when the $p\text{-value} < 0.05$. A mean followed the data compare analysis using the Independent t-test for normally distributed data. In contrast, data not normally distributed were analyzed using the Mann-Whitney U-test. Correlation tests were performed on NLR, PLR, LMR, ABR, serum ACR, de ritis, APRI, ALBI, WBC, sodium, serum creatinine, and albumin levels against MELD and CTP scores using the Pearson test for normally distributed data and Spearman for non-distributed data—normal distribution. The results were declared significant if the value of $p < 0.005$ had a moderate, strong, and solid relationship if $r > 0.4$ - < 0.6 , 0.6 - < 0.8 , and 0.8 - 1.00 , respectively. The quality of each variable in diagnosing decompensated liver

cirrhosis is assessed by analysis of receiver operating characteristic (ROC) curves so that the value of the area under the curve, cut-off, sensitivity, and specificity of each variable will be obtained.

RESULT

Assessment of the Severity Level of Liver Cirrhosis Using Different Indices

The total number of patients included in this cross-sectional study was 96. The mean age of patients in the decompensated cirrhosis group was 54.52 ± 10.431 , with 69.7% being male. Based on the results of the compare mean analysis, it was found that there were significant differences in the twelve variables between the decompensated and compensated cirrhosis groups. The ten variables, namely NLR, serum ACR, de ritis, APRI, LMR, ALBI, ABR, albumin, CTP score, and MELD score, had a p-value <0.001 . The other variables, WBC and sodium levels, had a p-value <0.005 .

Table 1. Demographic Characteristics of Study Population

Characteristic	Decompensated	Compensated	P value
Demogragraphic			
Age, years	54.52 ± 10.431	52.20 ± 9.734	0.307*
Gender			
Male	46 (69.7%)	20 (30.3%)	0.537 [#]
Female	19 (63.3%)	11 (36.7%)	
Nutritional category		0:31	
Malnourished	32 (100%)	0 (0.0%)	<0.001[#]
Non malnourished	33 (51.6%)	31 (48.4%)	
Blood Examination Result			
WBC	8.35 (1.59-34.37)	6.29 (2.01-21.05)	0.014**
Serum Creatinin	0.89 (0.57-1.25)	0.94 $\pm$ 0.215	0.962**
Na	131.22 ± 8.024	138.00 (103.00-145.00)	0.018**
Albumin	2.465 ± 0.58	3.54 ± 0.558	<0.001*
Laboratory Ratio			
NLR	4.725 (0.55 – 43.91)	3.816 ± 2.163	<0.001**
ACR	2.741 ± 0.852	3.923 ± 0.881	<0.001*
De Ritis	1.88 (0.47-11.71)	1.44 (0.66-5.13)	<0.001**
APRI	0.52 (0.03-68.10)	0.27 (0.14-2.96)	<0.001**
PLR	97.48 (0.69-712.31)	103.639 ± 67.185	0.395**
LMR	1.81 (0.32-6.10)	2.673 ± 1.394	<0.001**
ALBI	0.94 ± 0.32	0.55 ± 0.21	<0.001*
ABR	0.75 (0.07-5.07)	2.78 (0.68-10.48)	<0.001**
Liver Function Indicator			

MELD Score	20.345 ± 7.964	10.00 (7.00-24.00)	<0.001**
CTP Score	9.5 (7.00-14.00)	6.00 (5.00-7.00)	<0.001**

WBC: white blood cell; NLR: neutrophile-lymphocyte ratio; ACR: albumin creatinine ratio; APRI: albumin platelet ratio index; PLR: platelet lymphocyte ratio; LMR: lymphocyte monocyte ratio; ALBI: albumin bilirubin; ABR: albumin bilirubine ratio. Data analyzed by independent samples t-test, data analyzed by Mann-Whitney, #data analyzed by chi-square

The correlation test results using the Pearson and Spearman tests found a negative correlation in four variables to the MELD score. The CTP score also found that five variables had a negative correlation. NLR, serum ACR, de Ritis, APRI, LMR, ALBI, ABR, levels of WBC, sodium, and albumin significantly correlated with the MELD score with a p-value <0.005, and only PLR and serum creatinine which were not significantly associated with the CTP score.

Table 2. Correlation between laboratory ratio to MELD and CTP Score.

Parameter	MELD Score		CTP Score	
	r	p	r	p
NLR	0.379	0.001*	0.457	<0.001*
ACR	-0.518	<0.001*	-0.684	<0.001*
De Ritis	0.283	0.015*	0.459	<0.001*
APRI	0.575	<0.001*	0.585	<0.001*
PLR	0.074	0.534	0.038	0.712
LMR	-0.483	<0.001*	-0.496	<0.001*
ALBI	0.864	<0.001*	0.806	<0.001*
ABR	-0.839	<0.001*	-0.850	<0.001*
WBC	0.405	<0.001*	0.295	0.003*
Serum Creatinin	0.046	0.697	-0.002	0.985
Na	-0.824	<0.001*	-0.485	<0.001*
Albumin	1.652	<0.001*	-0.809	<0.001*

r = spearman or pearson coefficient, *statistically significant at p < 0.05

Diagnostic Performance of Laboratory Ratio

Serum albumin to creatinine ratio ≥ 3.6 can help in establishing the condition of decompensated liver cirrhosis with a sensitivity level of 80.6% and a specificity of 83%. There are several other variables with cut-off and sensitivity, as well as specificity of each, namely de Ritis (cut off ≥ 1.5 , sensitivity 69%, specificity 80%), APRI (cut off ≥ 0.35 , sensitivity 79.3%, specificity 66.7%), LMR (cut off ≥ 2.8 , sensitivity 67.7%, specificity 78.5%), ALBI (cut off ≥ 0.68 , sensitivity 79.3%, specificity 80%), ABR (cut off 1.65, sensitivity 96.8%, specificity 75.4%), WBC level (cut off ≥ 6.76 , sensitivity 63.1%, specificity 65%), sodium level (cut off ≥ 136.50 , sensitivity 66.7%, specificity 72%), and albumin level (cut off ≥ 3 , sensitivity 93.5%, specificity (81.5) to

enforcement diagnosis of DLC. This study found that the CTP score is superior to the MELD score in differentiating decompensated and compensated liver cirrhosis. The MELD score had a cut-off ≥ 10.5 , a sensitivity of 86.2%, and a specificity of 73%, while the CTP score had a cut-off of ≥ 6.5 , a sensitivity of 100%, and a specificity of 93%.

Table 3. Validity (AUC, Sensitivity, and Specificity)

Parameter	AUC	p	95%CI	Cut-off	Sensitivity	Specificity
NLR	0.633	0.115	0.474-0.792			
ACR	0.884	<0.001*	0.814-0.955	≤ 3.6	80.6%	83%
De ritis	0.717	0.010*	0.578-0.856	≥ 1.5	69%	80%
APRI	0.685	0.028*	0.522-0.848	≥ 0.3	79.3%	66.7%
PLR	0.551	0.548	0.389-0.712			
LMR	0.779	<0.001*	0.682-0.877	≤ 2.8	67.7%	78.5%
ALBI	0.843	<0.001*	0.741-0.944	≥ 0.7	79.3%	80%
ABR	0.909	<0.001*	0.851-0.967	≤ 1.6	96.8%	75.4%
WBC	0.656	0.014*	0.546-0.766	≥ 6.7	63.1%	65%
Serum Creatinin	0.497	0.963				
Na	0.699	0.018*	0.546-0.852	≤ 136.50	66.7%	72%
Albumin	0.956	<0.001*	0.921-0.991	≤ 3.0	93.5%	81.5%
MELD	0.833	<0.001*	0.717-0.948	≥ 10.5	86.2%	73%
CTP	0.995	<0.001*	0.982-100	≥ 6.5	100%	93%

*significant statistically at $p < 0.05$

DISCUSSION

Liver cirrhosis is a condition that is generally known as an end-stage process. Liver cirrhosis is characterized by the formation of fibrosis and nodules in the liver due to chronic liver injury. The most common causes of liver cirrhosis are alcohol use disorders, nonalcoholic fatty liver disease, and hepatitis B and C infections.¹⁻³ Liver cirrhosis can cause hepatocellular

carcinoma.¹⁷ Therefore, cirrhosis of the liver can lead to increased mortality and morbidity. Establishing a good diagnosis will help in reducing mortality due to liver cirrhosis.

In areas with limited resources, supporting examinations in the form of a biopsy will be difficult, so it is difficult to predict the severity of liver cirrhosis and determine which patients should be referred for liver transplantation. Using simple laboratory results, apart from clinical ones, will greatly help predict the severity of liver cirrhosis. It is hoped that the laboratory examination results will assist in developing a scoring system that can be used by medical personnel in predicting the severity of liver cirrhosis.

In the pathophysiology of the cirrhotic liver, it is stated that there is a role of excessive inflammatory response. The liver comprises hepatocytes, which are parenchyma cells, and other cells collectively referred to as nonparenchymal cells. Three types of nonparenchymal cells—endothelial cells, liver sinusoidal endothelial cells (LSECs), Kupffer cells (KCs), and hepatic stellate cells (HSCs)—line the walls of the liver sinusoids. Both parenchymal and nonparenchymal cells play crucial roles in the onset and progression of liver fibrosis and cirrhosis. The primary mechanism for initiating fibrosis involves the activation of hepatic stellate cells, occurring in two phases. The initial phase, known as the initiation or pre-inflammatory phase, is triggered by factors such as cellular apoptosis, oxidative stress, stimuli from Kupffer cells, hepatocytes, platelets, and the endothelium. The subsequent perpetuation phase involves cell proliferation, fibrogenesis, and a significant inflammatory response.¹⁸⁻¹⁹

Neutrophil to lymphocyte ratio and PLR are inflammatory markers that are simple and affordable to examine. NLR and PLR can categorize liver cirrhosis based on its severity. Apart from NLR and PLR, other markers such as ABR, ALBI, and ACR are also stated to help assess the severity of liver cirrhosis by relating it to the MELD score or CTP score. De ritis and APRI obtained from calculating SGOT, SGPT, and platelets were also stated to have a relationship with liver cirrhosis. This study found that those with a moderate to strong positive relationship with CTP score were NLR, de ritis, APRI, ALBI, sodium levels, and albumin.

In contrast, ACR, LMR, ABR, Na levels, and albumin had a moderate to strong negative correlation direction. The MELD score found a moderate to strong positive significant relationship were NLR, APRI, ALBI, and WBC levels. In contrast, ACR, LMR, ABR, sodium, and albumin levels had a moderate to strong negative correlation.

This study found that significant prognostic markers of decompensated cirrhosis were ACR (cut off ≤ 3.6 , sensitivity 80.6%, specificity 83%), de ritis (cut off ≥ 1.5 , sensitivity 69%, specificity 80%), APRI (cut off ≥ 0.3 , sensitivity 79.3%, specificity 66.7%), LMR (cut off ≤ 2.8 , sensitivity 67.7%, specificity 78.5%), ALBI (cut off ≥ 0.7 , sensitivity 79.3%, specificity 80%), ABR (cut off ≤ 1.6 , sensitivity 96.8%, specificity 75.4%), WBC level (cut off ≥ 6.7 , sensitivity 63.1, specificity 65%) and sodium level (cut off ≤ 136.50 , sensitivity 66.7%, specificity 72%), and albumin (cut off ≤ 3.0 , sensitivity 93.5, specificity 81%).¹² The results of this study are in line with several other studies which state that ACR, de ritis, APRI, LMR, ALBI, ABR, WBC, Sodium, and Albumin have a relationship with liver disease conditions, one of which is liver cirrhosis. [8-15,20-23] The MELD score has a cut-off of ≥ 10.5 , a sensitivity of 86.2%, and a specificity of 73, while the CTP score cut-off of ≥ 6.5 , with a sensitivity of 100% and a specificity of 93%. The results of this study indicate⁸ that the CTP score is superior to the MELD score.

This study succeeded²² in assessing the correlation of several markers based on laboratory results on MELD and CTP scores and the diagnostic performance of laboratory ratios, MELD, and CTP scores in establishing decompensated cirrhosis conditions. There have been previous studies addressing topics like this. However, that study only assessed NLR, PLR, ALBI, and ABR. This study has the advantage of assessing the correlation and diagnostic performance of other markers, namely WBC, sodium level, albumin level, serum creatinine, ACR, de ritis, APRI, and LMR. The results of this study will be useful for future studies in determining a scoring system for diagnostic or prognostic enforcement related to liver cirrhosis.

There are several areas for improvement in this study. First, this study was a small sample based on only one center data. Second, this study has not attempted to assess the diagnostic ability of these markers for²⁷ spontaneous bacterial peritonitis (SBP), acute-on-chronic liver failure (ACLF), and hepatocellular carcinoma (HCC).

⁶ Conclusion

Based on the study results, it can be concluded that ALBI, ABR, and sodium levels strongly correlate with the MELD score. ALBI, ABR, and albumin levels strongly correlate with the CTP score. The quality of the diagnostic performance for decompensated cirrhosis from ALBI and ABR has good results. The sensitivity and specificity of ABR were 96.8% and 75.4% with a cut-off of

1.6, while albumin levels were 93.5% and 81.5% with a cut of 3.0. Based on these results, the results of laboratory tests can be used as a marker to help diagnose decompensated cirrhosis.

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