

# Correlation Between the Presences of Ascites with MELD-Na Scoring in Liver Cirrhosis Patients

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## ABSTRACT

**Background.** Global prevalence of liver cirrhosis (LC) ranges from 4.5% to 9.5% of the general population amounting to more than fifty million people in the world. The Model for End Stage Liver Disease (MELD-Na) is commonly used to determine the prognosis and survival of liver cirrhosis patient. MELD-Na scoring consists of creatinine, bilirubin, international normalized ratio (INR), and serum sodium. Ascites is one of the clinical signs of decompensated liver cirrhosis, as well as present in Child Turcotte Pugh (CTP). The purpose of this study was to investigate the association between the presence of ascites and MELD-Na scores of LC patients.

**Methods.** This cross-sectional study was performed in LC patients who met the inclusion without exclusion criteria. The study was conducted at RSUP Dr. Sardjito, Yogyakarta, Indonesia during 2017-2018 periods. The MELD-Na value was calculated using the following equation:

$$\text{MELD-Na} = 9.57 \ln(\text{creatinine mg/dL}) + 11.2 \ln(\text{INR}) + 3.78 \ln(\text{bilirubin mg/dL}) + 1.59 (135 - \text{Na [mEq/L]}) + 6.43.$$
Differences of mean MELD-Na scores based on presenting of ascites were tested by independent T-tests. The cut-off value of MELD-Na was determined through the Receiver Operating Characteristic (ROC) curve. The relationship between the presence of ascites and the MELD-Na value was determined by the Fisher exact test; the correlation strength was determined by Phi and Crammer's V test. Prevalence ratio (PR) was calculated for determining the predictor factors. The results were considered statistically significant when the probability value  $p < 0.05$  was obtained.

**Results.** There were 59 subjects (41 male and 18 female). The mean age of subjects was 52.05 years old. The 39 patients were found ascites and 20 patients were not. Based on independent T test results there was a significant difference in mean values of MELD-Na ( $p=0.006$ ). Based on the ROC curve result, a cut-off point of 20.7 (95% specificity, 35% sensitivity) with Area under the Curve (AUC) was 0.662 ( $p=0.042$ ). Based on the cut-off, Fisher test with 2x2 tables, Phi and Cramer's V test were done with  $p$  value 0.022; 0.015; 0.015 respectively. The PR value was 1.607 (95% CI: 1.203-2.145).

**Conclusion.** There was a significant correlation between the presences of ascites with MELD-Na scoring using cut-off point of 20.7 and value of Prevalence Ratio of 1.6.

**Keywords.** *Liver cirrhosis, Ascites, MELD-Na score*

## ABSTRAK

**Latar belakang.** Prevalensi sirosis hati (SH) secara global berkisar antara 4,5% hingga 9,5% dari populasi dunia, dengan total lebih dari lima puluh juta orang di dunia. Model for End Stage Liver Disease (MELD-Na) umumnya digunakan untuk menentukan prognosis dan kelangsungan hidup pasien SH. Penilaian MELD-Na terdiri dari kreatinin,

bilirubin, rasio normalisasi internasional (INR), dan natrium serum. Asites merupakan salah satu tanda klinis sirosis hati dekompensasi, dan juga terdapat pada Child Turcotte Pugh (CTP). Tujuan dari penelitian ini adalah untuk menyelidiki hubungan antara keberadaan asites dan skor MELD-Na pada pasien CTP.

**Metode.** Penelitian potong lintang ini dilakukan pada pasien SH yang memenuhi kriteria inklusi dan eksklusi. Penelitian dilakukan di RSUP Dr. Sardjito, Yogyakarta, Indonesia selama periode 2017-2018. Nilai MELD-Na dihitung dengan menggunakan persamaan berikut:  $MELD-Na = 9.57 \ln(\text{ kreatinin mg/dL}) + 11.2 \ln(\text{ INR}) + 3.78 \ln(\text{ bilirubin mg/dL}) + 1.59 (135-Na [mEq/L]) + 6.43$ . Perbedaan rata-rata skor MELD-Na berdasarkan presentasi asites diuji dengan uji-t independen. Nilai batas MELD-Na ditentukan melalui kurva Receiver Operating Characteristic (ROC). Hubungan antara keberadaan asites dan nilai MELD-Na ditentukan dengan uji eksak Fisher; kekuatan korelasi ditentukan dengan uji Phi dan Cramer's V. Rasio prevalensi (RP) dihitung untuk menentukan faktor prediktor. Hasilnya dianggap signifikan secara statistik jika diperoleh nilai probabilitas  $p < 0.05$ .

**Hasil.** Terdapat 59 subjek (41 laki-laki dan 18 perempuan). Usia rata-rata subjek adalah 52.05 tahun. Sebanyak 39 pasien ditemukan asites dan 20 pasien tidak ditemukan asites. Berdasarkan hasil uji T independen terdapat perbedaan yang signifikan pada nilai rata-rata MELD-Na ( $p=0.006$ ). Berdasarkan hasil kurva ROC, didapatkan titik potong 20.7 (spesifisitas 95%, sensitivitas 35%) dengan Area Under the Curve (AUC) sebesar 0.662 ( $p=0.042$ ). Berdasarkan cut-off tersebut, dilakukan uji Fisher dengan tabel 2x2, uji Phi dan Cramer's V dengan nilai  $p$  masing-masing 0.022; 0.015; 0.015. Nilai RP adalah 1.607 (95% CI: 1.203-2.145).

**Kesimpulan.** Terdapat korelasi yang signifikan antara keberadaan asites dengan penilaian MELD-Na dengan nilai cut-off 20,7 dan nilai Rasio Prevalensi 1,6.

**Kata kunci:** Sirosis hati, Asites, Skor MELD-Na

## INTRODUCTION

Chronic liver disease (CLD) and liver cirrhosis (LC) tend to develop with high risk of morbidity and mortality. Many patients die in their fourth or fifth decade of life due to liver disease. LC is the third largest cause of death in patients aged 45-46 years (after cardiovascular disease and cancer) and the seventh leading cause of death around the world. The incidence is 360 per 100,000 populations and the mortality rate is 9.7 in 100,000 populations. Based on a National public hospital report, the average of LC prevalence is 3.5% of all patients who were treated in the internal medicine ward, or an average of 47.4% of all liver disease patients who were treated in the hospital.<sup>1</sup>

An easy, objective, accurate and inexpensive score system is needed to determine the prognosis of LC. A number of factors of clinical and laboratory examinations have been used as prognostic criteria, including albumin,

hyponatremia, creatinine, prothrombin time, disease complications, etiology, and inflammatory markers.<sup>2</sup> Child-Turcotte-Pugh (CTP) and Model for End Stage Liver Disease (MELD) scores have been commonly used for assessing and predicting the prognosis and survival of LC.<sup>3</sup>

MELD scores were originally used to predict survival rates within 3 months in LC patients to be candidate for TIPS and liver transplantation.<sup>4</sup> Over the last few years, variables have been studied that can improve the MELD score to predict short-term mortality. Several studies have shown that adjustment of MELD scores to serum sodium (Na) and ascites may provide more information about the risk of poor outcomes. The addition of Na to MELD scores (MELD-Na scores) has proven to be a more effective model for risk prediction, especially in patients with low MELD scores.<sup>5</sup> The relationship between MELD-Na and ascites values has not been evaluated previously.

MELD-Na score is a scoring system based on laboratory values without incorporating clinical assessments such as Child-Turcotte-Pugh (CTP), therefore it is necessary to see the relationship between clinical signs in this case ascites to the scoring system of the prognosis as well as due to absence correlating the relationship between ascites and MELD-Na scores. The purpose of this study was to investigate the association between the presence of ascites and MELD-Na scores of LC patients.

## METHODS

An observational study with cross-sectional methods was conducted to LC cirrhosis outpatient clinic and inpatient at RSUP Dr. Sardjito based on inclusion and exclusion criteria during the years 2016-2018. The inclusion criteria were: cirrhosis patient with age 17-75 years old and agreed to be included in this research. The exclusion criteria were patient with malignancy, sepsis, shock, chronic kidney disease except hepatorenal syndrome. Subjects that meet the inclusion and exclusion criteria were asked for basic information and physically examined for finding signs of ascites. Also, blood samples were collected from the patients for MELD-Na scoring. After the data had been collected, we analyzed the correlation of the presence of ascites and MELD-Na score.

The data were analyzed by SPSS 24, and presented in mean and standard deviation. Because most of the subjects were more than 50, the Kolmogorov-Smirnov test was used for knowing normality of subject distribution ( $p > 0.05$ ). Differences in mean of MELD-Na scores on ascites and non-ascites patients were tested using unpaired student's t tests for

numerical variables of two groups with normal distribution data and Independent t-test. The cutoff value for MELD-Na was obtained based on the results of Receiver Operating Characteristic (ROC) curve. The relationship between the presence of ascites and the MELD-Na value was determined by the Fisher exact test, the correlation strength is determined by Phi and Cramer's V test. Prevalence ratio was calculated for determining the predictor factors. The results of the study were considered statistically significant when the probability  $p$  value  $< 0.05$  was obtained.

## RESULTS

There were 59 subjects who met the inclusion and exclusion criteria, with 41 males (69.5%) and 18 females (30.5%). The average of age was 52 years old with the youngest age at 17 years old and the oldest was 75 years old. As many as 39 (66.1%) patients were positive for ascites and 20 (33.9%) patients negative. Based on blood laboratory results, the median of total bilirubin concentration was 1.74 (0-2.9), creatinine 0.99 (0.5-9.89), INR 1.53 (1.08-3.96), sodium  $136.27 \pm 4.57$ . The mean of cirrhosis severity was based on MELD-Na score at  $17.97 \pm 6.88$ . Characteristics baseline data can be seen in Table 1.

Since both data were normally distributed using Kolmogorov-Smirnov test, so to know the mean difference of MELD-Na value in ascites groups towards non ascites group Independent T-tests were used. Based on independent T test results it was found that there was a significant difference in mean MELD-Na score with  $p$ -value 0.006 (95% CI: 1.31-7.49). Because the difference in the mean was significant, it can be continued to

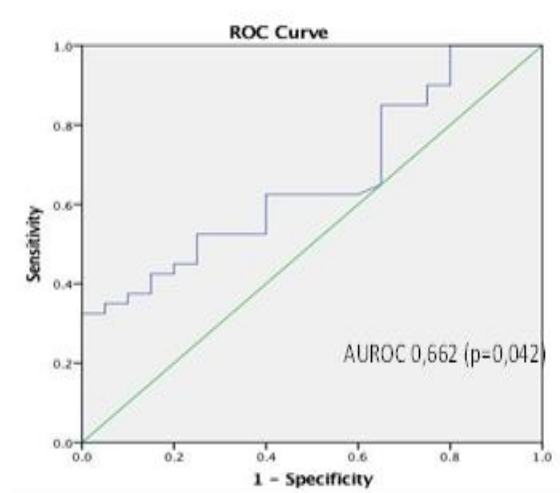
determine the relationship strength between the presence of ascites and the MELD-Na score, In order to be able to do correlation testing using 2x2 table test, it is necessary to determine the cut-off value for MELD-Na score so ROC curve was

used. Cut-off point of MELD-Na score was 20.7 (Sensitivity: 35% Specificity: 95%) based on Youden index with Area Under Curve (Figure 1) 0.662 ( $p = 0.042$ ).

**Table 1.** Research subjects basic characteristics

Parameter	Mean±SD	Median (minimum-maximum)	Frequency
Age (years)	52.05±11.657		
Gender			
- Male n(%)			41 (69.5%)
- Female n(%)			18 (30.5%)
Ascites			
- With ascites n(%)			39 (66.1%)
- Without ascites n(%)			20 (33.9%)
Bilirubin (mg/dL)		1.74 (0-2.9)	
Creatinine (mg/dL)		0.99 (0.5-9.89)	
International Normalized Ratio (INR)		1.53 (1.08-3.96)	
Sodium (mmol/L)	136.271±4.57		
MELD-Na	17.97±6.88		

SD Standard Deviation; n number of subjects



**Figure 1.** Receiver Operating Characteristic (ROC) curve. AUROC Area under the curve.

Based on the Fisher Exact test it was found that there was a significant relationship between the presence of ascites with MELD-Na scores shown from the value of  $p = 0.022$ , with Prevalence Ratio (PR) “with ascites” = 1.607 (95% CI: 1.203-2.145) (Table 2). The strength of the

relationship between the two variables was also measured using the Phi and Cramer's V tests with the second value of the test 0.315 ( $p = 0.015$ ).

**Table 2.** 2x2 table with Fisher exact test

Variable	Presence of ascites		<i>p</i> value	Prevalence Ratio (PR)	95% CI
	With Ascites	Without Ascites			
MELD-Na > 20.7	13	1	0.022*	1.607	1.203-2.145
MELD-Na ≤ 20.7	26	19			

\*) significant of  $p < 0.05$ 

## DISCUSSION

Previous studies found that the mean age of patients with cirrhosis was  $57.1 \pm 11.2$  years old<sup>6</sup> and patients with liver cirrhosis suffered the most at the average age between 35-69 years old with peak around the age of 40-49 years old<sup>1</sup>. Similarly, we also found the average age of patients with cirrhosis was approximately 52 years old. The ratio between males and females in this study was 2.278:1, which corresponded to epidemiological data of liver cirrhosis in Indonesia where the male: female ratio is 2.1: 1.<sup>1</sup>

Initially the MELD scoring system did not include the criteria of blood sodium levels but on the basis of every study showing the decrease in serum sodium 1 mmol/L in cirrhosis patients could lead to a 12% decrease in survival in 3 months as a result, the rating system was modified to MELD-Na.<sup>7</sup>

The four criteria on MELD-Na scoring system are associated with high mortality due to: One, plasma creatinine values increased due to the presence of hepatorenal syndrome which is a decrease in renal function caused by pathological conditions that are not derived from renal. It is characterized by a decreased creatinine clearance resulting in increased plasma creatinine value which is caused by a decrease in renal perfusion due to excessive vasoconstriction of blood vessels in the kidneys. Secondly, blood clotting

abnormalities, characterized by increases in INR resulting from disturbed synthesis of blood clotting factors and decreased anticoagulant clearance, followed by thrombocytopenia due to hypersplenism caused by portal hypertension. Factors II, VII, IX and X are blood clotting factors depending on vitamin K, and in cirrhosis there is a decrease in functional hepatic mass, so administration of vitamin K parentally will not improve blood coagulation disorders.<sup>8</sup>

Thirdly, increased bilirubin occurs due to decreasing liver function in conjugation and excretion of bilirubin. Hyponatremia is strongly related to the severity of cirrhosis, cirrhosis caused an increase in total body water but the effective volume of the artery is reduced, and this reduction is due to vasodilatation of the splanchnic arteries mediated by the production of nitric oxide (NO) and other excess vasodilator components under high intrahepatic resistance conditions. This process results in sodium avidity in the proximal portion of the nephron, by the activity of the renin-angiotensin-aldosterone system and the free-water reabsorption mediated by excess ADH in the collecting tubule. Baroreceptors on the side of the arteries found in some areas such as the left ventricle and carotid sinus proved to be a strong regulator of ADH secretion and capable of suppressing the effects of hypo-osmolality. Non-osmotic ADH secretions by the posterior pituitary

play a dominant role that cause free-water excretion disorder and cause dilution-induced hyponatremia.<sup>9</sup> Thus, the MELD-Na scoring system strongly reflects the severity of the patient's cirrhosis, the MELD-Na 20 values associated with 6% (95% CI: 3% -9%) mortality risk in 6 months, MELD-Na 30 values associated with 16% (95% CI: 9% -22%) and 40 with 37% risk (95% CI: 22% -49%).<sup>10</sup>

The pathogenesis of ascites itself results from vasoconstriction and sinusoidal fibrosis resulting in an increased portal resistance which causes portal hypertension. Increased portal venous resistance is offset by vasodilation of splanchnic beds by endogenous vasodilators. Increased portal system resistance followed by increased blood flow due to splanchnic bed vasodilation causes portal hypertension to persist. Portal hypertension will increase transudation pressure primarily in sinusoids and subsequent intestinal capillaries. Transudates will accumulate in the peritoneal cavity and cause ascites. Endogenous vasodilators will also affect systemic arterial circulation; there is an increase in peripheral vasodilation resulting in a relative under filling process. The body reacts by increasing the activity of the sympathetic nervous system, the renin-angiotensin-aldosterone system and arginine vasopressin. The subsequent consequence is increased reabsorption of water and salt by the kidneys and an increase in heart index.<sup>11</sup>

Based on the pathophysiology pathway, it was shown that the presence of ascites corresponds to MELD-Na values reflecting the severity of liver cirrhosis in which liver function impairment demonstrated by INR in MELD-Na

may also reflect a hypoalbuminemia state that increases the likelihood of ascites as well as liver architectural distortions that increase bilirubin levels which is one of the indicators used in MELD-Na value. This distortion also increases portal pressure causing transudation of fluid into the peritoneal cavity and causes ascites, because the effective blood volume is reduced by vasodilation process of the splanchnic arteriole causing decreased blood flow to the kidneys thus increasing blood creatinine. This lack of effective blood volume also causes hyperaldosteronism that contributes to the ascites formation, and the latter involves hyponatremia by non-osmotic ADH secretion caused by the lack of effective blood volume which increases the absorption of water in the kidneys and supports the formation of ascites.

In this study, there was a significant difference in mean MELD-Na values between ascites and non-ascites groups with  $p = 0.006$  (95% CI: 1.31-7.49) where patients with ascites had mean MELD-Na values higher. Based on Receiver Operating Characteristic curve (Figure 1), MELD-Na value of 20.7 (sensitivity: 35% specificity: 95%) has been applied as a cut-off point which by Younden index is the furthest point from the diagonal line. Based on the Fisher test score (Table 2) we found a significant relationship between the presence of ascites with MELD-NA score as shown from the value of  $p = 0.022$ . The strength of the relationship of the two variables was also measured using Phi and Cramer's V tests with the value of both test 0.315 ( $p = 0.015$ ) and it can be concluded that there is a moderate relationship that is statistically significant.

Based on relative risk analysis in Table 2, the Prevalence Ratio (PR) of MELD-Na with ascites = 1.607 (95% CI: 1.203-2.145). It can be concluded that patients with MELD-Na values >20.7 were 1.6 times as likely to have ascites compared to patients with MELD-Na  $\leq$ 20.7. This is consistent with the initial hypothesis that there is a relationship between the presence of ascites and MELD-Na values and it is clarified on the basis of the results of this study that high MELD-Na values correlate with the presence of ascites in the patient.

This study has several limitations. There are several factors that may affect the presence of ascites and MELD-Na scores that cannot be controlled such as doses of propranolol as well as other drugs given to patients and infusion of NaCl administered to inpatients. Some of the disadvantages of this study are the absence of the degree of ascites severity in the patient, no outpatient or inpatient classification, and the use of cross-sectional study methods which cannot describe the course of the disease because exposure and output are measured at the same time so that the data only illustrates state at the time of the study.

## CONCLUSION

There was a significant correlation between the presences of ascites with MELD-Na scoring using cut-off point of 20.7 and the value of Prevalence Ratio (PR) was 1.6.

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