Serum Cystatin C Level in Liver Cirrhosis Patients with MELD-Na > 22

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ABSTRACT

Background: *Hepatorenal syndrome is a part of the prerenal acute kidney injury (AKI) characterized by kidney dysfunction which is secondary to the decreased renal blood flow that occurs in liver cirrhosis with portal hypertension and is a fatal complication. Hepatorenal syndrome (HRS) occurs in about 20% of liver cirrhosis patients with refractory ascites.*

Method: *This study was conducted on 24 liver cirrhosis patients with ascites who visited Gastroenterohepatology Outpatient Ward and Internal Medicine Inpatient Unit, Dr. M. Djamil Padang. Samples were collected and data analyses were conducted in December 2019 to March 2020.*

Results: *In this study, the model for end-stage liver disease (MELD)-Na score was used to determine the risk of HRS in liver cirrhosis patients with ascites, in which patients with a MELD-Na score ≥22 belonged to the group at risk of developing HRS. From 24 patients, the mean MELD-Na score was 24.58 ± 3.5. The lowest MELD-Na score was 22 in 8 patients (33.3%), while 1 patient (4.2%) had the highest MELD-Na score of 35. In this study, serum CysC levels were measured in patients with normal creatinine, and the mean serum CysC level was 2.69 ± 0.46 mg/L. The minimum value of CysC was 2.03 mg/L, while the maximum value was 3.9 mg/L. Serum CysC levels in all 24 patients were increased compared to the normal values.*

Conclusion: *Liver cirrhosis patients who were at risk to develop HRS based on the MELD-Na score have increased serum Cystatin C levels, although serum creatinine levels were still normal.*

Keywords: *MELD-Na score, serum cystatin C, hepatorenal syndrome, hepatic cirrhosis*

ABSTRAK

Latar belakang: *Sindrom hepatorenal merupakan bagian dari gangguan ginjal akut (GnGA) prerenal yang ditandai dengan disfungsi ginjal sekunder akibat penurunan aliran darah ginjal yang muncul pada sirosis hati dengan hipertensi portal dan merupakan komplikasi yang fatal. Sindrom hepatorenal (SHR) terjadi sekitar 20% pasien sirosis hati dengan asites refrakter.*

Metode: *Penelitian dilakukan terhadap 24 orang pasien sirosis hati dengan asites di Poliklinik Khusus Gastroentero Hepatologi dan instalasi rawat inap penyakit dalam RSUP Dr. M. Djamil Padang. Sampel dilakukan pengambilan dan pengolahan data dari bulan Desember 2019 sampai Maret 2020.*

Hasil: *Dalam penelitian ini, skor model for end-stage liver disease (MELD)-Na digunakan untuk menentukan risiko terjadinya SHR pada pasien sirosis hati dengan asites, di mana pasien dengan skor MELD-Na ≥22 termasuk kelompok yang berisiko mengalami SHR. Dari 24 pasien, didapatkan rerata skor MELD-Na adalah 24,58 ± 3,5. Skor MELD-Na terendah adalah 22 sebanyak 8 pasien (33,3%), sedangkan 1 orang pasien (4,2%)*

memiliki skor MELD-Na tertinggi yaitu 35. Dalam penelitian ini, kadar CysC serum diukur pada pasien dengan kreatinin yang normal, dan didapatkan rata-rata kadar CysC serum adalah 2,69 ± 0,46 mg/L. Nilai minimum CysC adalah 2,03 mg/L sedangkan nilai maksimum 3,9 mg/L. Kadar CysC serum pada 24 pasien mengalami peningkatan dari nilai normal.

Simpulan: *Pasien sirosis hepatis yang berisiko mengalami SHR berdasarkan skor MELD-Na didapatkan peningkatan kadar Cystatin C serum, walaupun kadar kreatinin serum masih normal.*

Keywords: *skor MELD-Na, cystatin C serum, sindrom hepatorenal, sirosis hepatis*

INTRODUCTION

Hepatorenal syndrome is a part of the prerenal acute kidney injury (AKI) characterized by renal dysfunction which is secondary to the decreased renal blood flow that occurs in liver cirrhosis with portal hypertension and is a fatal complication. Hepatorenal syndrome (HRS) occurs in about 20% of liver cirrhosis patients with refractory ascites.[1] Martin Llahi et al (2011) found that the prevalence of HRS was 13% out of 562 cirrhotic patients.[2] Machado (2018) reported that the incidence of HRS was 10% in cirrhotic patients with ascites.[3] Patients with decompensated cirrhosis have an 8–20% chance of developing HRS per year and 40% within 5 years.[4] Acute kidney injury (AKI) especially HRS is associated with an increased risk of mortality, in which the mortality rate reaches 2-31% in liver cirrhosis patients who were hospitalized with AKI. The reported mortality rate in month 1 and 12 in these patients were 58% and 63%, respectively. The presence of HRS carries a poor prognosis, with 40% requiring renal replacement therapy and 60% passing away within 90 days.[5] Even patients who survived become more susceptible to complications of liver cirrhosis including ascites and hepatic encephalopathy.[6]

Currently, the International Club of Ascites (ICA) uses creatinine as a marker in diagnosing HRS in cirrhotic patients, in which HRS is diagnosed if there is an increase in serum creatinine of ≥ 0.3 mg/dL within 48 hours or an increase of more than 50% of initial serum creatinine within 7 days.[7] However, in liver cirrhosis patients the use of creatinine as a marker of decreased renal function has several limitations. Serum creatinine in patients with liver cirrhosis has a lower value due to decreased hepatic synthesis and muscle mass, thereby reducing endogenous creatinine production and may result in false negative results.[8]

The high mortality and morbidity of patients suffering from HRS and the inaccuracy of creatinine levels in assessing kidney function in cirrhotic patients cause the need for an early risk assessment of hepatorenal syndrome, one of which is using the MELD score. MELD score is a score that is used to determine the priority of patients who will undergo liver transplantation, which is also used in the prediction of hepatorenal syndrome. Variables in this score include serum total bilirubin, INR, and serum creatinine.[9] MELD score > 20 is closely related to the occurrence of impaired kidney function in cirrhotic patients.[10] In its development, it was found that in addition to the MELD score, serum sodium concentration was also associated with HRS, ascites, and mortality due to liver cirrhosis, resulting in a modified MELD-Na score that includes serum sodium as the variable.[11]

Developments in the study of biomarkers of kidney damage have found cystatin C (CysC) as an endogenous biomarker that is more sensitive than serum creatinine.[12] Cystatin C is a protein with a low molecular weight (13 kDa) found in various human body fluids. Cystatin C has few characteristics which make it to be considered an ideal biomarker of renal function because it is produced at constant levels, freely filtered, and ultimately catabolized; hence, its concentration in serum is almost completely dependent on kidney function. Unlike creatinine whose concentration is influenced by various non-renal factors in cirrhotic patients, CysC concentration is considered sensitive to glomerular damage; thus, it increases earlier than serum creatinine and can assess HRS in the early phase.[13] Considering the high mortality rate in liver cirrhosis patients who developed hepatorenal syndrome, it is very important to know HRS during its early phase. This study aims to determine the levels of Cystatin C in liver cirrhosis patients who are at risk of developing hepatorenal syndrome.

METHOD

This study was conducted in the Gastroentero-hepatology Outpatient Ward and the Internal Medicine Inpatient Unit, Dr. M. Djamil Padang to liver cirrhosis patients with ascites and had no impaired renal

function with a MELD Na score of 22. Patients were excluded if the patient had a creatinine level of >1.5 mg/dL, had renal structural abnormalities, had shock, received nephrotoxic drugs, had malignancy, diabetes mellitus, hypertension, or suffered from hematemesis melena. Patients who met the requirements were asked to volunteer by filling out an informed consent form.

RESULTS

In this study, the average serum sodium level was 127.25 ± 3.05 mmol/L with a minimum value of 118 mmol/L and a maximum value of 131 mmol/L. The mean serum total bilirubin level was 7.85 ± 6.75 mg/dL, with maximum and maximum values of 1.6 mg/dL and 25 mg/dL, respectively. The mean INR value was 1.45 ± 0.52 with the minimum and maximum values of 0.97 and 3.58, respectively; while the mean serum creatinine level was 0.917 ± 0.3 mg/dL. The minimum level of serum creatinine was 0.4 mg/dL and the maximum level was 1.4 mg/dL. The mean MELD Na score in this study was 24.58 ± 3.5. These can be seen in Table 1.

In this study, serum cystatin C levels were examined in cirrhotic patients who were at risk for hepatorenal syndrome, and the results are shown in Table 2.

From the table above, the average serum cystatin C level in cirrhotic patients at risk for hepatorenal syndrome was 2.69 (0.46) mg/L. The mean serum cystatin C level in this study was much higher than the normal values.

Table 1. Baseline characteristics

Characteristics	n = 24 n (%)	Mean (SD)
Sex		
Male	13 (54.2)	
Female	11 (45.8)	
Age (years)		55,88 (5,48)
Serum sodium (mmol/L)		127,25 (3,054)
Serum total bilirubin (mg/dL)		7,85 (6,75)
INR		1,45 (0,52)
Serum creatinine (mg/dL)		0,917 (0,3)
MELD Na		24,58 (3,5)

INR: International normalized ratio, MELD Na: model for end-stage liver disease

Table 2. Mean of serum cystatin C level in cirrhosis patients who were at risk to develop hepatorenal syndrome

Variable	n	Mean (SD)	Normal value
Cystatin C (mg/L)	24	2,69 (0,46)	0,63 – 1,04

DISCUSSION

The study was conducted on 24 liver cirrhosis patients with ascites in the Gastroenterohepatology Outpatient Ward and Department of Internal Medicine Inpatient Unit, Dr. M. Djamil Padang. Sample collection and data analysis were carried out from December 2019 to March 2020. In this study, the MELD-Na score was used to determine the risk of developing HRS in liver cirrhosis patients with ascites; in which patients with a MELD-Na score $\geq$22 were included in the group at risk of developing HRS. From a total of 24 patients, the mean MELD-Na score was 24.58 ± 3.5. The lowest MELD-Na score was 22 found in 8 patients (33.3%), while 1 patient (4.2%) had the highest MELD-Na score of 35.

Mauro et al (2019) studied liver cirrhosis patients without impaired kidney function. In the study, they reported that the average MELD-Na score was 21.[14] A study by Lu et al (2019) in liver cirrhosis patients with ascites without impaired kidney function reported that the average MELD-Na score was 21.65 ± 11.24.[15]

Grodin et al (2017) stated that the MELD-Na score was closely related to the patient's clinical deterioration. MELD-Na scores were positively correlated with CysC ($r = 0.48$; $p < 0.0001$) and plasma renin ($r = 0.33$; $p < 0.001$).[16] MELD-Na scores indicate the severity of cirrhosis and can predict 3 months mortality in liver cirrhosis patients. The total MELD-Na score of 20 – 29 has a mortality prediction of 19.6%.[17]

Cystatin C is a marker of decreased kidney function that appears earlier than serum creatinine. Assessment of renal function with CysC is particularly useful in patients with liver cirrhosis where creatinine levels are affected by various non-renal factors such as protein-calorie malnutrition, loss of muscle mass, and increased tubular secretion, as well as impaired liver function leading to decreased creatinine. Omar et al (2015) found that serum CysC levels with a cut-off of 1.2 mg/L could detect impaired kidney function in the early phase with a sensitivity of 89.6% and a specificity of 63.6%.[19]

In this study, serum CysC levels were measured in patients with normal creatinine, and the mean serum CysC levels were 2.69 ± 0.46 mg/L. The minimum value of CysC is 2.03 mg/L while the maximum value is 3.9 mg/L. Serum CysC levels in 24 patients increased compared to normal values.

These results are in line with the study conducted by Thomas et al (2019) who found the mean cystatin C level in 41 cirrhotic patients was 2.2 mg/L. In this study, the comparison of CysC levels in cirrhotic patients with a MELD score < 20 and a MELD score $\geq$ 20 was calculated. A total of 17 patients with a MELD score < 20 had an average CysC level of 1.9 mg/L, and in 24 cirrhotic patients with a MELD score $\geq$20, the mean CysC level was 2.3 mg/L. The difference in mean CysC levels was statistically significant with $p < 0.05$.[19]

The role of CysC in predicting hepatorenal syndrome was investigated by Sharawey et al (2011) who included 80 patients with liver cirrhosis with ascites. It was reported that serum CysC levels were the most independent factor in predicting HRS and mortality, whereas serum creatinine and eGFR could not be used to predict HRS.

CONCLUSION

Patients with liver cirrhosis who were at risk for HRS based on the MELD-Na score had higher serum Cystatin C levels, although their serum creatinine levels were still within normal limits.

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