Clinical Characteristics of Liver Cirrhosis Patients in Internal Medicine Inpatient Ward of Fatmawati General Hospital and Factors Affecting Mortality during Hospitalization

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ABSTRACT

Background: *liver cirrhosis is a global health problem. The mortality rate due to cirrhosis was estimated to achieve 1 million per year worldwide. The aim of this study is to elaborate the characteristics of patients with liver cirrhosis and factors affecting mortality during hospitalization in Fatmawati General Hospital.*

Method: *The design of this study was retrospective cohort involving patients admitted to the hospital between January and March 2019.*

Results: *Among 41 liver cirrhosis patients, it was found that the average age was 52.9 ±13.8 years old and the percentage of male patients among participants was 75.6%. Patients who died during hospitalization was 12.2%. The average length of stay in hospital was 10.8 ± 6.4 days. Patients were admitted to the hospital with various complaints; the most common complaint was gastrointestinal bleeding in 46.3%, decreased consciousness in 22% and massive ascites in 17.1% patients. Physical examination findings of anaemic conjunctiva, icteric sclera, and shifting dullness were found in 73.2%; 29.3% and 61% patients, respectively. Icteric condition during hospital admission has higher mortality risk with RR = 9.6 (95% CI: 1.2-77.8). Approximately 53.7% cirrhosis patients were diagnosed with hepatitis B, while 22% of them were diagnosed with hepatitis C. Coinfection of hepatitis B and C were found in 4.8% patients, while 29% patients were neither infected with hepatitis B nor C. Based on the laboratory examination, creatinine level > 1.3 mg/dL had higher mortality risk with RR = 8.3 (95% CI: 1.04-66.7), while natrium level ≤ 125 mmol/L had higher mortality risk with RR 26.4 (95% CI: 3.6-191). Based on Child-Pugh classification, 24.4% patients had Child-Pugh A, while 14.6% had Child Pugh C, and 39% patients could not be classified. The mean Child-Pugh score in this study was 8 ± 2.2. Through the bivariate analysis, we found the association between Child-Pugh classification and mortality; higher classification has higher mortality risk (p = 0.028). Child-Pugh C had mortality risk with RR = 9.5 (95% CI: 1.2-75.1).*

Conclusion: *Liver cirrhosis patients were hospitalized due to the ongoing decompensation. The mortality rate during hospitalization in liver cirrhosis patients was high. Mortality in these patients was associated with icteric condition upon admission, high initial creatinine level, low sodium level, and high Child-Pugh classification.*

Keywords: *liver cirrhosis, mortality, affecting factors*

ABSTRAK

Latar belakang: *Sirosis hati saat ini telah menjadi masalah kesehatan nasional maupun global dengan angka kematian mencapai 1 juta/tahun di seluruh dunia. Tujuan penelitian ini untuk mengetahui karakteristik pasien sirosis hati, komplikasi dan hubungannya dengan mortalitas selama perawatan.*

Metode: *Desain penelitian ini adalah kohort retrospektif, pada pasien sirosis hati yang masuk dalam perawatan penyakit dalam di RSUP Fatmawati tahun 2019. Data demografi dan klinis dicatat dari rekam medis.*

Hasil: *Dari 41 pasien, rerata usia pasien 52.9 ±13.8 tahun dengan persentase laki-laki lebih dari ¾ pasien (75.6%). Pasien meninggal dalam perawatan sebesar 12,2%. Keluhan admisi perdarahan saluran cerna ditemukan pada 46.3%, penurunan kesadaran 22% dan asites masif 17.1%. Kondisi ikterik awal memiliki risiko kematian lebih tinggi (RR = 9.6(95% CI: 1.2-77.8)). 53.7% pasien terdiagnosis hepatitis B, sedangkan hepatitis C pada 22% pasien. Kadar creatinin > 1.3 mg/dL memiliki risiko kematian dengan RR = 8.3(95% CI: 1.04-66.7), sedangkan natirum ≤ 125 mmol/L memiliki risiko kematian dengan RR = 26.4(95% CI: 3.6-191). 24.4% pasien masuk dalam klasifikasi Child-Pugh A, 14.6% Child Pugh C. Rerata Skor Child Pugh pada penelitian ini adalah 8 ± 2.2. Pada anaisis bivariat ditemukan bahwa semakin tinggi klasifikasi Child-Pugh, semakin tinggi angka kematian (p 0.028). Child-Pugh C memiliki risiko relatif kematian sebesar RR = 9.5 (95% CI: 1.2-75.1).*

Simpulan*: Angka kematian dalam perawatan pada pasien sirosis masih cukup tinggi. Kematian terkait dengan kondisi ikterik saat admisi, kadar kreatinin awal yang tinggi, kadar natrium yang rendah dan tingginya klasifikasi Child-Pugh.*

Kata kunci: *sirosis hati, mortalitas, faktor yang berhubungan*

INTRODUCTION

Liver cirrhosis is a liver disorder that occurred as a result of necroinflammation and fibrogenesis process in the liver, which was marked histologically by the diffused nodular regeneration surrounded by dense fibrotic septa, with further parenchymal damage.[1] This process causes changes in the liver structure, which leads to the distortion of hepatic vascular architecture. The intrahepatic vascular architecture distortion stimulates the increased resistance in portal vein flow and results in portal hypertension as well as liver synthesis dysfunction. From clinical point of view, cirrhosis has been considered as an end-stage disease which may cause death, unless liver transplant is performed.[1]

Liver cirrhosis remains a community health problem, both at national and global level. The mortality rate due to cirrhosis is predicted to achieve 1 million per year worldwide.[2] Based on the WHO report, the mortality rate of liver cirrhosis in Indonesia in 2016 in male and female was 51.1 dan 27.1 per 100,000 population, respectively.[3] Cirrhosis usually develops over years after exposure to one or more risk factors, such as alcohol abuse, hepatitis B or C, and non-alcoholic fatty liver that causes inflammation and cell death in the liver. In Asia Pacific countries, hepatitis B virus infection is the main risk factor of cirrhosis.[4] Similar description was found in Indonesia as shown on the RISKESDAS 2013 which reported that 7.1% of population in Indonesia had positive HBsAg.[5]

The magnitude of the problem triggered by liver cirrhosis and its complication made this disease included as catastrophic disease which cause the burden of Jaminan Kesehatan Nasional (JKN) programme. Prompt treatment of liver cirrhosis is expected to decrease the ineffective health cost. Characteristic appearance including complication, length of stay, and its association within hospital mortality is required to manage and deliver prompt medical care to liver cirrhosis patients as it is important to determine the hospital policy to monitor cost and quality of care.

METHOD

The design of this study was retrospective cohort in liver cirrhosis patients admitted to the internal medicine inpatient ward in Fatmawati General Hospital in January- March 2019.

Inclusion and exclusion criteria in this study include: (1) Inclusion criteria: liver cirrhosis patients who were admitted to the inpatient ward of Fatmawati General Hospital in January-March 2019; (2) Exclusion criteria: incomplete medical record.

By definition, liver cirrhosis patients were patients who has been diagnosed with liver cirrhosis, either

using clinical examination (cirrhosis stigmata), laboratory, and/or imaging. Furthermore, Child-Pugh classification was determined in these patients based on the presence of hepatic encephalopathy, ascites, bilirubin level, coagulation, and albumin which were later classified into three criteria: A, B, or C.

Data was analysed using SPSS statistical software. Descriptive analysis was performed using table and graphics for categorical variable, mean or median for numerical data. Bivariate analysis was performed using Chi-square test, Fisher test with or without cell combination if prerequisites were not fulfilled and unpaired T-Test and Mann-Whitney test if pre-requisites were not fulfilled.

This study has been approved by the Ethical Committee of Fatmawati General Hospital with the number DM 01.01/VIII.2/7291/2019.

RESULTS

From 41 liver cirrhosis patients, it was found that the average age as 52.9 ±13.8 years with proportion of male patients reaching more than three quarter of all patients (75.6%). The mortality of liver cirrhosis patients during hospitalization was 12.2% patients. Patients were admitted to Fatmawati General Hospital with various complaints, with most common complaint was gastrointestinal bleeding due to oesophageal varices in 46.3%, decreased consciousness in 22%, and massive ascites in 17.1%.

Based on physical examination, anaemic conjunctiva, icteric sclera, and shifting dullness were found in 73.2%; 29.3% and 61% of hospitalized liver cirrhosis patients, respectively. More than fifty percent of cirrhosis patients being hospitalized were diagnosed with hepatitis B (53.7%), and hepatitis C were detected in 22% patients. Coinfection of hepatitis B and C was found in 4.8% patients, while 29 % patients were neither infected with hepatitis B nor C.

Based on the supporting examination, ultrasonography was performed in 73.2% patients, while EGD in 43.9% patients. Based on the Child-Pugh classification, 24.4% patients were included in Child-Pugh A classification, while 14.6% were included in Child-Pugh C classification, and 39% could not be classified due to the incomplete laboratory results. The average Child-Pugh score in this study was 8 ± 2.2. Patients who died had higher average of Child-Pugh score (9.5 vs. 7.7; $p > 0.05$).

Table 1. Baseline characteristics of categorical variables

Variables	n (%)
Sex	
Male	31 (75.6)
Female	10 (24.4)
Survival	
Survived	38 (87.8)
Died	5 (12.2)
Reason for admission	
Ascites	7 (17.1)
Gastrointestinal bleeding	19 (46.3)
Decreased consciousness	9 (22)
Others	6 (14.6)
Icteric sclera	
Present	12 (29.3)
Absent	29 (70.7)
Anaemic conjunctiva	
Present	30 (73.2
Absent	11 (28.8)
Shifting dullness	
Present	25 (61)
Absent	16 (39)
HbSAg	
Reactive	22 (53.7)
Non-reactive	19 (46.3)
Anti HCV	
Positive	9 (22)
Negative	32 (78)
Antibiotics	
Yes	33 (80.5)
No	8 (19.5)
Proton pump inhibitor	
Yes	29 (70.7)
No	12 (29.3)
Somatostatin	
Yes	10 (24.4)
No	31 (75.6)
Lactulose	
Yes	33 (80.5)
No	8 (19.5)
Child-Pugh classification	
Child-Pugh A	10 (24.4)
Child-Pugh B	9 (22)
Child-Pugh C	6 (14.6)
Unclassified	16 (39)

The timing of gastrointestinal bleeding varied and might happen in early hospitalization or occured during hospitalization. In patients who were hospitalized in Fatmawati General Hospital, bleeding might appear as the reason of hospital admission or might happen during hospitalization. The longest onset of bleeding was in day-16 of hospitalization. The length of bleeding varied between 1 and 7 days with the median length of bleeding to occur in 1 (min 1-max7) day. proton pump inhibitor (PPI) was often used in patients with upper gastrointestinal bleeding. In this study, PPI administration might decrease the length of hospitalization although it was not statistically significant (2.25 days vs. 5 days $p > 0.05$). PPI route of administration has important role as intravenous drip administration might decrease the length of bleeding (1.6 vs. 2.35 days; $p > 0.05$).

Decreased consciousness might be observed as the reason of admission or might occur during hospitalization. The duration of decreased of

consciousness varied between 1 and 5 days with an average of 2.25 ± 1.4 days. Although not significant statistically, patients who were admitted with the chief complaint of decreased consciousness had longer hospital stay compared to other chief complaints. In patients who were admitted due to decreased of consciousness, 11.1% of them died, while the mortality rate among patients with gastrointestinal bleeding was 10.5%. In patients who experienced decreased consciousness, the use of L-Ornitine L-Acetate (LOLA) might help to shorten the duration of unconsciousness compared to those who did not receive LOLA (1.71 vs. 3 days, $p > 0.05$).

In hospitalised liver cirrhosis patients, intravenous fluid maintenance was still utilized in 65.9% cases, while others did not need maintenance fluid. Maintenance fluid was mostly used in patients who had no shifting dullness. In regard to antibiotic use, 80.5% patients were known to have received antibiotics during hospitalization. Somatostatin was used in 24.4% hospitalized patients, particularly in patients who experienced gastrointestinal bleeding. Although statistically insignificant, the use of somatostatin is associated with shorter period of bleeding.

Table 2. Baseline characteristics of numerical variable

Variables	Average
Age	52.9 ±13.8 years
Length of hospitalization	10.8 ± 6.4 days
Child-Pugh Score	8 ± 2.2
Duration of decreased consciousness	2.25 ± 1.4 days
Length of bleeding	1 (min 1-max 7)

DISCUSSION

This study included 41 patients who fulfilled the inclusion criteria. In this study, it was found that the prevalence of mortality in hospitalized liver cirrhosis patients was 12.2%. This number resembled the study in Thailand performed by Charatcharoenwitthaya et al. In their study, it was stated that there was an increase of mortality rate during hospitalization from 9.6% in 2009 to 10.8% in 2013. Charatcharoenwitthaya et al showed that the mortality risk during hospitalization was significantly higher in patients with variceal bleeding, encephalopathy hepatic, and hepatorenal syndrome, even after adjustment of various potential confounding factors.[6] Iliass Charif et al in Morocco found that the prevalence of mortality during hospitalization was slightly lower, which was 8.7%, In their study, it was stated that variceal bleeding, jaundice, ascites, and hepatic encephalopathy was significantly associated with mortality.[7] Gastrointestinal bleeding, hepatic encephalopathy, and ascites were signs of decompensated liver cirrhosis. These complications are closely associated with portal hypertension and, if they are not managed properly, they will have significant role in increasing mortality.

Study in Morocco and Saudi Arabia shown that age was associated with mortality in liver cirrhosis patients. Older age was one of the mortality predictors during hospitalization in liver cirrhosis patients. Older age was also an independent risk factor for mortality

Table 3. Bivariate analysis

Variables	Died n (%)	Survived n (%)	P
Sex			
Male	4 (12.9	27(87.1)	0.647
Female	1 (10)	9(90)	
Reason for admission			
Ascites	0 (0)	7(100)	> 0.05
Gastrointestinal bleeding	2 (10.5)	17(89.5)	
Decreased consciousness	1 (11.1)	8(88.9)	
Others	2 (33.3)	4(66.7)	
Age (years)	56 ± 15.85	52.55 ± 13.7	> 0.05
Shifting dullness			
Yes	4 (16)	21 (84)	0.341
No	1 (6.2)	15 (93.8)	
Icteric sclera			
Present	4 (33,3)	8 (66.7)	RR = 9.6 (95%CI 1.2-77.8)
Absent	1 (3.4)	28 (96.6)	
Sodium level	134 ± 5 mmol/L	122 ± 7 mmol/L	0.000
Sodium (mmol/L)			
≤ 125	4 (60)	1 (20)	RR = 26.4 (95% CI: 3.6-191)
>125	1 (3)	32 (97)	
Creatinine serum (mg/dL)	1.0 ± 0.5	2.1±1	0.003
Creatinine level (mg/dL)			
>1.3	4 (33.3)	8 (66.7)	RR = 8.3 (95% CI: 1.04-66.7)
≤ 1.3	1 (4)	24 (96)	
Child-Pugh			
C	3 (50)	3 (50)	RR = 9.5 (95% CI: 1.2-75.1)
B*	0	9 (100)	P 0.031
A*	1 (10)	9 (90)	

*combined cell

which might occur due to degenerative factors, such as coronary artery disease, diabetes melitus, cerebrovascular bleeding, and infection.[7,8] This study demonstrated similar results as patients who died had older age compared to those who survived and discharged, although statistically not significant. Statistics that were not significant might be caused by the number of samples or endemicity characteristic of hepatitis B in Indonesia, thus liver cirrhosis might be found in younger age.

Advanced or decompensated cirrhosis is marked by the presence of complications due to portal hypertension, including gastrointestinal bleeding, hepatic encephalopathy, and massive ascites. In this study, mortality in liver cirrhosis patients during hospitalization was found in 10,5% patients with early symptoms of gastrointestinal bleeding, and 11.1% in patients admitted with decreased consciousness. The presence of portal hypertension increased the mortality risk in liver cirrhosis. Gastrointestinal bleeding and decreased consciousness were also signs of acute on chronic liver failure that has high mortality risk.[9,10]

Hepatic encephalopathy was one of the most severe liver cirrhosis complications and might be fatal. Epidemiological study showed that the survival rates in 1 and 3 years among cirrhotic patients with hepatic encephalopathy were 42% and 23%.[9] Even the latest study showed that the mortality rates in 28, 90 and 365 days in cirrhosis patients with hepatic encephalopathy was higher compared to those with decompensated non-encephalopathy cirrhosis.[11] In a study by Ventura-Cots et al it was revealed that not only the presence or absence of hepatic encephalopathy might increase mortality risk during hospitalization, but also the duration of encephalopathy might influence mortality risk. In this study, the length of HE did not determine the mortality rate during hospitalization, but the length of HE was associated with the length of hospitalization, although statistically not significant. In the study by Ventura-cots et al the survival rate was significantly different, with lower percentage found in the group of HE > 48 hours.[11]

Gastrointestinal bleeding is one of the most common cirrhosis complications but may need special care in the emergency unit because it might lead to mortality. Gastroesophageal variceal bleeding is the main complication of portal hypertension due to liver cirrhosis. The mortality rate ranges from 3% to 14% and there has been no significant changes in these numbers in the last 10 years.[12] Approximately 30-50% patients with liver cirrhosis died within 6 weeks after the first episode of variceal bleeding.[12] A study in India found that the prevalence of mortality in cirrhosis patient with bleeding reached 19.87%.[12] Predicting factors which were reported in various cohort study in patients with gastrointestinal bleeding varied including serum bilirubin, INR, recurrent bleeding during hospitalization, Child-Pugh score, albumin, serum creatinine, leukocyte count, thrombocyte count, encephalopathy, requirement of ventilator, moderate to severe ascites, and elevated liver function.[12]

In this study, we found association between Child-Pugh score and mortality rate, although it was not statistically significant. Statistical analysis performed after combining cells revealed a higher relative risk of mortality in patients with Child-Pugh C compared to those with A and B groups (RR = 9.5 (95% CI: 1.2-75.1). The average of Child-Pugh score was higher in patients who died compared to those who survived on discharge. In patients with Child-Pugh C, 50% of them died during hospitalization.

In this study, we also found that patients with low mean sodium level (122 vs. 134; p 0.019), high mean creatinine level (p = 0.003), and icteric sclera had higher mortality risks which were statistically significant.

In this study, we also found that patients with creatinine level of > 1.3 mg/dL upon admission had higher mortality risk with RR = 8.3 (95% CI: 1.04-66.7). The association between creatinine level and mortality during hospitalization in liver cirrhosis patients had been observed in the study by Alsutan et al, which showed that high creatinine level had significantly higher mortality risk.[8] This association was caused by the presence of hepatorenal syndrome or acute on chronic liver failure. Kidney failure was known as the most common organ failure in ACLF, followed by liver failure, cerebral or brain damage, and haematology/coagulation. In fact, kidney dysfunction is an important factor which most commonly occurs in ACLD and gives poor prognosis. Mortality was found to be higher in ACLF patients with single organ failure of the kidney compared with patients with other single organ failure.[10] Other study by Kumar Bal et al showed that based on multivariate regression, AKI (p = 0,001), septic shock (p = 0,029), MELD-Na (p < 0,001) was found as independent predictors of 50 days mortality in the hospital in SBP patients, with hazard ratio for AKI of 2.16 (95% CI: 1.36-3,42).[13]

Icterus and elevated bilirubin level further described the liver function, showing the severity degree of cirrhosis. In this study, it was found that icteric

condition upon admission had higher mortality risk during hospitalization with RR = 9.6 (95% CI: 1.2-77.8). Sodium level ≤ 125 mg/dL upon admission also had higher mortality risk RR = 26.4 (95% CI: 3.6-191). This is in accordance with other studies, in which MELD-Na included bilirubin level and serum sodium level showed that in surviving patients, the score was lower. Higher bilirubin level was associated with higher risk of mortality within 50 days.[13]

CONCLUSION

Liver cirrhosis is a chronic progressive condition with high mortality rate. Liver cirrhosis is mostly caused by chronic hepatitis virus infection, although it can also be affected by various metabolic diseases. Treatment of liver cirrhosis should be performed as soon as possible, particularly to prevent liver cirrhosis in patients with risk factors. Patient who has been diagnosed with liver cirrhosis needs to undergo treatment to prevent the complication of liver cirrhosis and the occurrence of decompensated liver cirrhosis. In decompensated liver cirrhosis patients, the most common complication includes massive ascites, hepatic encephalopathy, and gastrointestinal bleeding due to oesophageal varices. Adequate acute and chronic treatment is required to prevent mortality and readmission to the hospital. Several factors being analysed in this study included age, Child-Pugh score, kidney condition, sodium and electrolyte level became important to monitor to prevent and decrease mortality.

The limitations of this study included the limited sample size, causing a few variables proportionally resembled previous studies, but not significant statistically. Other limitation also included the study design which was cohort retrospective that may cause several biases and confounders which may affect the final result. Suggestions from the researcher is to perform further studies using prospective cohort design and larger sample size to further confirm other risk factors.

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