Clinical Characteristics and Outcome of Acute on Chronic Liver Failure Patients at Fatmawati General Hospital

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ABSTRACT

Background: *Acute-on-chronic liver failure (ACLF) is a syndrome characterized by acute liver decompensation with extrahepatic organ failure in patients with pre-existing liver disease causing high short-term mortality. A good knowledge about characteristics and diagnostic of ACLF will help us to give proper treatment. The aim of this study is to know the profile and characteristics of ACLF patient*

Method: *Retrospective study was conducted to find patient with ACLF between January 2017-January 2018 at Fatmawati General Hospital.*

Results: *Ten patients were diagnosed with ACLF. Six patients admitted with a chief complaint: unconscious, 2 of them had hematemesis in the course-of-treatment. Three patients were admitted with abdominal pain, and 1 patient with hematemesis-melena. Seven patients had hepatitis-B infection. Aspartate-transaminase to platelet-ratio index (APRI) values varied (median 8.1;minimum 2.81-maximum 34.67). Hepatic encephalopathy, ascites, and acute renal failure were found in 90% of patients. Jaundice can be found in all patients, with mean values of bilirubin levels in patients undergoing test for bilirubin level were 18.56 mg/dL (9/10). Coagulation disorders were found in 60% of patients undergoing haemostasis test. Four patients were diagnosed with grade 3 ACLF. All ACLF patients eventually died during treatment, including third-degree patients who all died within 7 days. Only 2 patients survived more than 7 days, and 4 patients died within 3 days of treatment.*

Conclusion: *mortality rates of ACLF were very high, and are often found in patients with advanced liver disease characterized by high APRI values. The prognosis is related to the number of organ failures. Central nervous system, kidneys and liver are the organs that are often impaired. Because the current treatment method is still limited, further research is needed, especially on biomarkers for better prevention, diagnosis and treatment.*

Keywords: *acute on chronic liver failure, mortality, case-series*

ABSTRAK

Latar belakang: *Acute-on-chronic liver failure (ACLF) merupakan sindrom yang ditandai dengan dekompensasi hati akut dan kegagalan organ ekstrahepatik pada pasien dengan riwayat penyakit hati yang sering menyebabkan kematian jangka pendek. Pengetahuan yang baik tentang karakteristik dan diagnostik ACLF akan membantu kami memberikan perawatan yang tepat. Tujuan penelitian ini adalah untuk mengetahui profil dan karakteristik pasien ACLF.*

Metode: *Studi retrospektif dilakukan untuk menemukan pasien dengan ACLF antara Januari 2017-Januari 2018 di Rumah Sakit Umum Fatmawati.*

Hasil: *Didapatkan 10 pasien ACLF, enam pasien diantaranya datang dengan keluhan utama: tidak sadar. Tiga pasien masuk rumah sakit dengan keluhan utama sakit perut, dan 1 pasien datang dengan hematemesis-melena. Tujuh pasien memiliki riwayat infeksi hepatitis B. Nilai aspartate-transaminase to platelet-ratio index (APRI) bervariasi (median 8.1; minimum 2,81-maksimum 34,67). Ensefalopati hepatikum, asites, dan gagal ginjal akut ditemukan pada 90% pasien. Jaundice dapat ditemukan pada semua pasien, dengan rerata nilai kadar bilirubin pada pasien yang dilakukan pemeriksaan sebesar 18,56 mg/dL (9/10). Gangguan koagulasi ditemukan pada 60% pasien yang menjalani pemeriksaan hemostasis. Empat pasien terdiagnosis ACLF grade 3. Semua pasien ACLF pada akhirnya meninggal dalam perawatan termasuk pasien derajat 3 yang semua meninggal dalam waktu 7 hari. Hanya 2 pasien yang bertahan lebih dari 7 hari, dan 4 pasien meninggal dalam 3 hari perawatan.*

Simpulan: *Angka mortalitas ACLF sangat tinggi, dan sering dijumpai pada pasien dengan penyakit hati lanjut yang ditandai dengan tingginya nilai APRI. Prognosis terkait dengan jumlah kegagalan organ yang timbul. Sistem saraf pusat, ginjal dan hati adalah organ-organ yang sering mengalami gangguan. Oleh karena metode pengobatan saat ini masih terbatas maka diperlukan penelitian lebih lanjut, terutama pada biomarker untuk pencegahan, diagnosis dan perawatan yang lebih baik.*

Kata kunci: *acute-on-chronic liver failure (ACLF), angka kematian, serial kasus*

INTRODUCTION

Acute on chronic liver failure (ACLF) is a syndrome marked by liver decompensation accompanied by multi organ failure which has very high mortality rate.[1] Signs of acute liver decompensation observed in ACLF are jaundice and coagulation disorders. In addition to acute liver decompensation, ACLF can also be accompanied by one or more extrahepatic organ failure with very high 28 days to 3 months mortality. ACLF cases are usually started with a trigger in the form of bacterial infection, extrahepatic sepsis, alcoholism, and viral infection including relapse or acute exacerbation of viral hepatitis. But, in 40-50% cases, the trigger of ACLF is difficult to identify. Exaggerated systemic inflammation response is predicted to play an important role in the emergence of ACLF.[1]

For more than two decades the uniform definition of ACLF has not been agreed causing the reporting of prevalence, mortality rate, and prognosis to vary. High mortality rate in patients with ACLF is usually related to the number of organ dysfunction. ACLF has a mortality rate 15 times higher compared to acute decompensated condition without ACLF. CANONIC study showed that mortality in 28 days in overall ACLF degree was 33%. Meanwhile, the 28 days mortality rate in patients with grade 1, 2, and 3 ACLF was 22%, 32%, and 73%, respectively. In 3-7 days after ACLF diagnosis has been confirmed, patient might experience deterioration or even death. Therefore, it is very important to stratify patient according to the prognosis, evaluate treatment response, determine emergency condition for transplantation, treat patient in intensive care unit and decide whether the procedure to be performed will be beneficial or not.[1,2]

This preliminary study is performed to know the profile, characteristics, and clinical outcomes of ACLF patients in Fatmawati General Hospital in order to provide an illustration and advanced management in the future.

METHOD

This study used retrospective method through medical record review to find all patients with the diagnosis of ACLF in Fatmawati General Hospital between January 2017 and January 2018. ACLF diagnosis criteria being used was the European Association for the Study of the Liver (EASL) criteria. ACLF is defined as an acute decompensation from cirrhosis with multi organ failure and high short-term mortality (28 days mortality rate > 15%).[1] Condition and number of organ failure evaluated with chronic liver failure-sequential organ failure assessment (CLIF-SOFA) is associated with 28 days and 90 days mortality rate. Severity of ACLF is classified based on the number of failed organ which is grade 1, grade 2, grade 3 and the mortality rate is correlated with severity of ACLF. ACLF severity degree is as follows: (1) Not ACLF with 28 days mortality of < 5%: (a) no organ failure, (b) one organ failure in patient with creatinine serum of < 1.5 mg/dL and no hepatic encephalopathy, (c) cerebral failure in patient with creatinine serum of < 1.5 mg/dL; (2) grade I ACLF with 28 days mortality of 22%:

(a) kidney failure, (b) liver, coagulation, circulation or pulmonary failure which is associated with creatinine serum of 1.5-1.9 mg/dL and grade 1 or grade 2 hepatic encephalopathy, (c) brain failure with creatine serum of 1.5-1.9 mg/dL; (3) grade 2 ACLF with 28 days mortality of 32%: 2 organ failure; (4) grade 3 ACLF with 28 days mortality of 77%: 3 organs failure or more.

Data on patients' basic characteristics, chief complaint, physical examination, laboratory, and mortality were obtained from hospital medical records. Descriptive analysis was performed according to the collected data.

RESULTS

We obtained ten inpatient patients in Fatmawati General Hospital between January 2017 and January 2018 according to the EASL diagnosis criteria for ACLF. From those 10 patients, 6 patients were admitted to the hospital with the chief complaint of decrease consciousness, 3 patients were admitted with the chief complaint of abdominal pain, and 1 patient came with the chief complaint of hematemesis-melena. Two patients came without hematemesis complaint, but experienced hematemesis during hospitalization.

From the evaluation of aetiological factors and patients' background, it was found that from a total of 10 patients, 7 patients were infected with hepatitis-B, 2 patients were infected with hepatitis C, and one patient was not infected by either hepatitis B or C.

Degree of severity and fibrosis status in these patients was evaluated using APRI score. Aspartate-transaminase to platelet-ratio index (APRI) score in patients diagnosed with ACLF in Fatmawati General Hospital varied with a median score of 8.1; minimum 2.81-maksimum 34.67.

During the assessment of organ failure and liver decompensation in these patients, it was found that 90% patients who were admitted to the hospital experienced hepatic encephalopathy, ascites, and acute kidney failure during the hospitalization. Jaundice as a sign of acute liver decompensation can be found in all patients whose mean total bilirubin was 20.62 mg/dL. In addition to jaundice, coagulation disorder was found in 60% patients who underwent haemostasis examination.

ACLF classification according to the CLIF SOFA criteria in these 10 patients found that grade 3 ACLF was found in 4 patients, while the rest fell into grade 2 ACLF criteria. All patients who were diagnosed with ACLF passed away. From all patients who passed away, only two patients were able to survive for more than seven days, while four patients passed away within three days of hospitalization. All grade three ACLF patients passed away within seven days of hospitalization.

DISCUSSION

ACLF is a liver decompensated disease with high mortality rate, which the difficulty to diagnose often causes delay in its management. Epidemiology data on ACLF is still rare; several new studies stated that in the United States, more than 700,000 patients who were hospitalized in a year has a diagnosis of liver cirrhosis and apparently 5% of them can be categorized

Table 1. Basic and clinical characteristics of patients with acute on chronic liver failure (ACLF)

No	Sex	Age (years)	Chief complaint	Hepatic encephalopathy	Shock on vasopressor	Ascites	Jaundice	Viral hepatitis	Bacterial infection
1	F	36	Abdominal pain	No	Yes	Yes	Yes	B	Yes
2	M	67	Abdominal pain	Yes	No	Yes	Yes	Non B/C	No
3	M	39	Abdominal pain	Yes	No	Yes	Yes	B	Yes
4	M	47	Hematemesis melena	Yes	No	Yes	Yes	B	Yes
5	M	55	Unconscious	Yes	Yes	Yes	Yes	B	No
6	M	48	Unconscious	Yes	Yes	Yes	Yes	C	Yes
7	M	47	Unconscious	Yes	Yes	No	Yes	B	Yes
8	F	55	Unconscious	Yes	Yes	Yes	Yes	B	Yes
9	M	56	Unconscious	Yes	Yes	Yes	Yes	B	Yes
10	M	41	Unconscious	Yes	No	Yes	Yes	C	Yes

F= female, M=male

Table 2. Laboratory characteristics, severity of acute on chronic liver failure (ACLF) and time to death

No	Thrombocyte	AST	ALT	APRI	Urea	Creatinine	Total bilirubin	Prothrombin Time	ACLF	Length of hospitalization	Comments
1	84	289	104	10.12	214	5.4	39.6	-	3	2	Passed away
2	189	1172	382	18.24	96	1.8	18.4	18.8(13.6)	2	6	Passed away
3	149	1201	818	23.71	28	1.7	34.1	-	2	1	Passed away
4	165	1945	1192	34.67	297	13.2	11.2	21.8(13.6)	2	4	Passed away
5	73	132	85	5.32	47	1.7	5.5	20.5(13.6)	2	10	Passed away
6	147	272	114	5.44	137	2	-	-	3	1	Passed away
7	206	197	120	2.81	73	2	18	-	3	4	Passed away
8	399	396	129	2.92	214	2.1	18.8	21.1(13.6)	2	3	Passed away
9	70	233	155	9.79	60	1.1	11	-	2	8	Passed away
10	106	231	113	6.41	257	6	29	20.5(14.4)	3	4	Passed away

AST: asparte aminotransferase, ALT: alanine aminotransferase, APRI: AST to platelet ratio index

into ACLF. A study in China conducted by Qin et al, stated that ACLF is more often to be observed in male patient and the incidence in 10-year period was 2.53 from 100,000 population. Due to the difficulty in the diagnosis and delay in the management, patient with ACLF usually has a longer hospitalization period and is associated with high mortality rate in ACLF.[4,5]

A study by Qin et al in China in the year 2005-2014 on the aetiology and predisposing factors of ACLF found that the most frequent aetiology was chronic HBV infection with 91% (1760 cases). Autoimmune (58.3%), alcoholism (53 cases; 2.74%), and chronic hepatitis C (23 cases; 1.19%) were among other aetiologies observed in ACLF patients.[6] Bacterial infection and gastrointestinal bleeding are the most common triggers of ACLF.[7] Result of the aforementioned study was in accordance with the data of ACLF aetiologies in Fatmawati General Hospital where most cases were caused by hepatitis B.

Dysfunction up to multiple organ failure is the main manifestation in ACLF patient. Central nerves, kidney, and cardiovascular system are the most common organs involved in severe ACLF and are associated with high mortality rate.

Hepatic encephalopathy (HE) is one of the most common manifestations of ACLF. Research data has shown that hepatic encephalopathy may emerge in 40% patients.[8] Study has also shown that hepatic encephalopathy is associated with higher mortality rate, particularly grade 3 and 4 hepatic encephalopathy.[8] In this study which was performed in Fatmawati General Hospital, 90% patients suffered from HE. HE may occur either upon admission or emerge during hospitalization. HE may happen due to local or systemic disorder. Patients with HE showed increase of ammonia due to functional disturbance of the blood brain barrier. The increase of brain ammonia level and cerebral haemodynamic disturbance is known as the main aetiological factor. These changes include disorder in neurotransmission which is, disorder in the ergonom aminobutyric acid (GABA) system, energy disturbance (which is, decrease of cerebral blood flow, inhibition of cerebral energy metabolism by ammonia), brain oedema (which is elevated ammonia level, hyponatremia) and neuro-inflammation (nitrate oxide generation, prostanoid, astrocytic oedema).[9]

HE in ACLF setting has a different pathway from cirrhosis patient with acute decompensation without ACLF. Patient with HE related ACLF suffered due to the general inflammation reaction which may play role in brain and other organ dysfunction. This causes very bad survival rate. In addition to direct cause from liver dysfunction, HE in ACLF is often correlated with the presence of bacterial infection, alcoholism, or hyponatremia.[9] Isolated HE usually occur due to the long-term use of diuretic, exaggerated protein consumption, and is not correlated with decreased liver function. Absence of significant inflammation reaction and the low prevalence of organ failure causes HE in cirrhosis without ACLF has better prognosis.

Beside consciousness disorder in the form of hepatic encephalopathy, ACLF patients in Fatmawati General Hospital also suffered from acute kidney disorder in various degree in 90% patients. Kidney failure is defined by CLIF SOFA as creatinine > 2 gr/dL and the need of renal replacement therapy. From nine patients whose blood creatinine were elevated, six of them could be classified to kidney failure according to CLIF SOFA criteria. Renal dysfunction was observed in 22.8-34% ACLF patients and 51% if using acute kidney injury network (AKIN) criteria.[8]

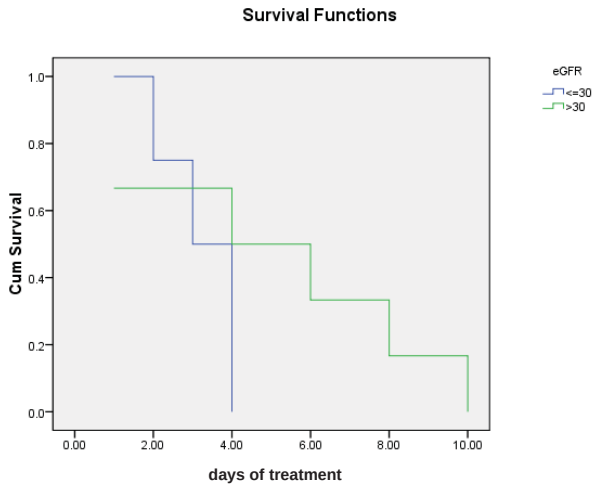

Figure 1. Correlation between kidney disorder and mortality in ACLF

In the study, it is known that kidney failure is the most common organ failure in ACLF (55.8%), followed by liver, cerebral/brain, and haematology/coagulation failure (43.6%, 27.7%, and 24.1%). In the reality, kidney disturbance is an important thing and often happens in ACLF and carries a bad prognosis. Higher mortality rate is found in ACLF patients with single organ failure of the kidney compared to patients with other single organ failure. In the above case series, in patients who fulfilled the criteria of renal failure according to CLIF SOFA, in average, they can survive up to 3 days after hospital admission compared to the group without renal failure who could survive longer up to 6.25 days.

In a study involving 562 hospitalized cirrhosis patients showed that the most common causes of renal failure in ACLF patients include bacterial infection (46%), hypovolemia (32%), hepato renal syndrome/ HRS (13%) and intrinsic renal failure (9%).[9]

Another organ system dysfunction frequently happen in ACLF patients is cardiovascular disturbance. Six from 10 patients who fell into the inclusion criteria need blood pressure support during the hospitalization. In ACLF patient, decreased systemic resistance, decreased mean arterial pressure, and increased hepatic vein pressure gradient may occur. This can happen as a result of circulating pro-inflammatory cytokines, such as tumor necrosis factor (TNF) alpha causing peripheral vasodilation and the worsening of intrahepatic resistance. This eventually may result in the decreased blood pressure which require blood pressure supporting agent. Decreasing blood pressure may also be caused by the relative insufficiency of adrenal until the serum cortisol level becomes low and finally causes the decreased peripheral response towards vasoconstrictor.[9]

Beside the difficult diagnosis and the frequency of delay, ACLF has a high mortality as a result of the absence of specific management. Currently, the treatment given is an effort to improve organ failure and decrease further complications. In the patient, infection needs to be considered because it could be the triggering factor; Thus, early identification and infection management with antibiotic administration becomes important. The most common predisposing and aetiology factor of ACLF is the presence of Hepatitis B infection. Management of hepatitis B patient with antiviral may show improvement if it is administered in the right time. Several studies have shown that the decrease of HBV-DNA > 2 logs in 2-week time may improve survival. This is associated with the suppression of hepatocellular necrosis and cytokine release. Nucleotide analogue needs to be given early in all HBV infected patients while waiting for HBV DNA level confirmation. Medicine which can be used include tenofovir, entecavir, or telbivudin.[8]

Currently, there are several alternatives beside liver transplant in ACLF management. Granulocyte colony-stimulating factor (GCSF) may help regeneration and mobilisation of CD34+ cell from bone marrow. Significantly, this therapy can increase survival rate and clinical improvement in ACLF related hepatitis B. GCSF administration may improve renal disturbance and hyponatremia.[10] However, more data is needed to recommend the routine use of this therapy. Additionally, there is an option of liver dialysis. Liver dialysis is known to improve bilirubin level, hepatic encephalopathy, and hepatorenal syndrome, but not affecting the 28 days survival or mortality.[11]

Patients with ACLF is better hospitalized in ICU or hospital which has a transplant centre. Organ function needs to be monitored closely and early management is given towards particular organ to prevent multiple organ failure. Liver transplantation is a definitive therapy in all ACLF patients. All patients needs to be evaluated for liver transplant consideration in the absence of contraindication. In grade II and III ACLF patients, survival rate without liver transplant is < 20%, but increases to 80% in patients who receive liver transplant.[3]

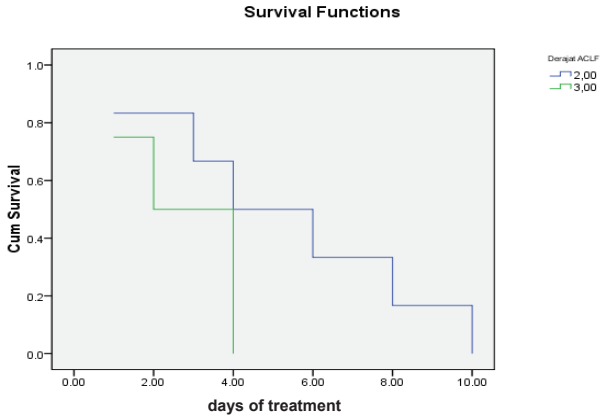

Figure 2. Survival comparison of grade 2 and 3 ACLF patients

ACLF is a dynamic proses which may improve or get worsened. It is known that the final clinical outcome can be assessed in the day-7 after diagnosis has been confirmed. ACLF can improve in 55% patients with grade 1 ACLF, and only 15% in patients with grade III ACLF.[1] In this study, all ACLF patients passed away and all patients with grade 3 ACLF passed away within 7 days of hospitalization.

CONCLUSION

ACLF is a new entity which still has no single definition that has been accepted universally. In addition, the main pathophysiology of ACLF is still controversial, although triggering factors such as infection and systemic inflammation has been estimated to be the main cause. ACLF prognosis is associated with the number of organ being involved and according to EASL criteria, the severity degree can be calculated using the chronic liver failure organ failure (CLIF-ACLF) score. This score determines the degree of severity and can be used to estimate short-term mortality rate quite well.

The management of ACLF is focused on the management and prevention of further extrahepatic organ failure. Liver transplantation is considered in several patients. Prevention of ACLF plays an important role because ACLF is still an entity which is considered new, and not all clinicians can identify this syndrome and its implications. Primary prevention can be done particularly in patients with chronic hepatitis infection. In ACLF case with one organ failure, secondary prevention can be done in the form of preventing the involvement of other organs with aggressive medical management.

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