

Prevalence and Risk Factors of Acute-on-Chronic Liver Failure at Sanglah General Hospital Denpasar Bali

Cokorda Agung Wahyu Purnamasidhi¹,
I Ketut Mariadi² and I Dewa Nyoman Wibawa^{2*}

¹Department of Internal Medicine, Udayana University/ Udayana University General Hospital,
²Division of Gastroenterology and Hepatology, Department of Internal Medicine, Udayana University/
Sanglah General Hospital, Bali.

*Corresponding author E-mail: dewa_wibawa@unud.ac.id

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Acute-on-chronic liver failure (ACLF) has been acknowledged as the sudden worsening of liver capacity in cirrhotic patients, which is typically linked to a triggering factor and results in the collapse of at least one organ. ACLF has been known to be a highly mortal case. The reason for this investigation was to decide the incidence, features, risk factors and death at 30 days of individuals with ACLF. The present study was conducted in Sanglah general hospital, included an amount of 110 cirrhotic patients whom admitted for hospitalization amid the period of June 2016 and July 2017. ACLF diagnostic criteria by the European Association for the Study of the Liver-Chronic Liver Failure-Consortium was utilized. Our population was separated into the ACLF and non-ACLF group. Clinical feature, triggering occasions, possible risk factors for promoting ACLF and explanation for death were figured out. Mortality and causes of death at 30 days was assessed regarding the matter. Thirty-days mortality of the subjects was assessed. Nine patients (8.2%) established ACLF. Bacterial infections were perceived as a triggering event of 100% of cases ACLF with Pneumonia (44.4%) and Peritonitis (33.3%) as a center contamination. Contrasting the ACLF and non-ACLF group, statistically important features were: existence of hepatic encephalopathy in 9 (100%) vs 30 (29.7%) ($P < 0.01$), leukocytosis of $19.34 \pm 1.97 \times 10^9$ vs $7.74 \pm 3.93 \times 10^9$ ($P < 0.01$) and nearness of ascites amid hospitalization 9 (100%) vs 43 (42.5%) ($P = 0.001$). Death rate was 100% (9 patients) vs 6.9% (7 patients), individually ($P < 0.01$). Our present study concluded that ACLF had a high mortality rate with noteworthy risk factors are liver encephalopathy, leukocytosis and ascites.

Keywords: Acute-on-chronic liver failure, Cirrhosis, Mortality, Risk factors.

Acute-on-chronic liver failure (ACLF) is an acute deterioration in the chronic liver disease, typically correlated with the existence of triggers, with at least one organ collapses and high death rate. The term ACLF was initially suggested in 1995¹. Beyond of thirteen unique definitions and diagnostic standards around the world, however barely two general consensus definitions are utilized and broadly acknowledged². The Asia Pacific

Association for Liver Studies set up a demarcation on ACLF as “a decrease in acute liver function that manifests as jaundice and coagulopathy, within four weeks, with clinical manifestations of ascites and/or encephalopathy in patients with previously diagnosed or not diagnosed with chronic liver disease”³. As indicated by the second definition, established at the joint symposium of the European Association for the Study of the Liver (EASL)

and the American Association for the Study of Liver Disease, ACLF has been defined as “acute deterioration in pre-existing chronic liver disease, usually associated with triggers, and associated with increased mortality at three months due to the failure of a multi organ system”⁴.

As of late, the European consortium was explicitly devoted to the analysis of liver failure in patients with chronic liver disease (EASL-CLIF-Consortium) directing CANONIC research with the point of identifying ACLF and determining high-risk cirrhotic patients. In view of an analysis of 1343 cirrhotic patients, the EASL-CLIF Consortium projected as acute decompensation criteria for liver disease (characterized by the nearness of ascites, encephalopathy, gastrointestinal draining or bacterial contamination) related with the occurrence of at least one organ disappointment. The Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score and mortality characterized by the organ failure at 28 days were acquired higher than 15%^{5,6}.

The primary cause for hospitalization in cirrhotic patients has been the sudden hepatic decompensation⁷. The CANONIC study demonstrates that ACLF is an exceptionally pertinent and vastly frequent condition, with an incidence of roughly 30% with a mortality rate multiple times higher⁸⁻¹⁰.

Because of the absence of an universally-acknowledged definition and diagnostic measure, numerous parts of this disorder, for example, incidence, natural history, precipitating events, clinical characteristics and pathophysiological means stay obscure^{11,12}.

The points of our investigation were to decide the incidence of ACLF among our study population by utilizing the analytic criteria built up by the CANONIC study, to depict the clinical features of ACLF, to weigh up the risk factors for developing ACLF, and to assess the mortality at 30 day, contrasting the cases of ACLF and non-ACLF group.

MATERIALS AND METHODS

We conducted a prospective review of 110 cirrhotic patients at Sanglah General Hospital in Denpasar, Bali, which was observed between June, 2016 and July, 2017. Patients’

data gathered according to medical records. The occurrence of past decompensation (spontaneous bacterial peritonitis, encephalopathy, ascites, varices esophagus, bleeding varices or hepatocellular carcinoma), result of physical assessment, laboratory testing, description about potential triggering factors (infection and gastrointestinal bleeding), and cause of cirrhosis.

The 30-days mortality rate was compared throughout the hospitalization and after discharge by monitoring the patients on outpatient polyclinic’s visit, through the medical record or reached by phone.

Statistical analyses were performed to all group’s clinical characteristics, probable risk factors for establishing ACLF, and causes of death. Studied clinical parameters included the emergence of hepatic encephalopathy and ascites on the admission or throughout the hospitalization. Complete blood analysis

Clinical features of both group, manifestation of causing events, hypothetical risk factors for progressing ACLF and causes of death were investigated. In the clinical issues analyzed, hepatic encephalopathy, emergence of ascites either at the beginning or during treatment. Complete blood test that allows the computation of Child-Pugh scores. The counts of leucocyte was utilized as inflammatory parameters^{13,14}.

Statistical analysis

Continuous variables of this study were matched using the Student t-test. Dichotomous variables were compared using χ^2 test or the Fisher exact test for categorical variables. Accuracy in predicting the correlation was evaluated by odd ratio (OR) with 95% CI.

RESULTS

A total of 110 inpatients with cirrhosis were qualified for this study. Eighty-three (75.4%) of the study population were male, with the mean of age was 50.4 ± 0.42 years (Table 1). Hepatitis B was found as the leading etiology of the cirrhosis, as many as 82 patients (74.5%), followed by hepatitis C infection affected 15 patients (13.6%), combination of the two topmost aforementioned in 8 patients (7.3%) and no known cause was found to initiate cirrhosis incidence in 5 patients (4.6%).

An amount of 9 patients (8.2%) were found to meet the ACLF criteria, which also showed male predominance (5; 55.5%). All of the patients met the criteria for ACLF upon hospital admission and none of them developed it throughout the hospitalization. Through the analysis of possible triggering cause for ACLF, infection was found to be the predominant factor, where pneumonia was found in 4 patients (44.4%) as the main source of infection, followed by peritonitis in 3 patients (33.3%), urinary tract infections in 1 patient (11.1%) and cholangitis in 1 patient (11.1%). All patients had hepatic encephalopathy, 3 of them (33.3%) were grade 2, 2 subject (22.2%) were grade 3 and 4 subject (44.5%) were grade 4. Contrasting to the group with no ACLF, following clinical events were found in roughly indifferent sum: Gastrointestinal bleeding in 27 (26.7%)patients, Hepatic Encephalopathy in 39 (37.6%) patients, bacterial infection in 24 (24.7%)patients. Other causes such as constipation in 5 (4.95%) patients and unknown in 6 (5.94%)patients.

Contrasting cirrhotic patients in the presence and absence of ACLF, we found a match in gender predominance of male (55.5% vs 77.2%, $P = 0.35$, $OR = 0.49$ [95%CI: 0.11-2.21]), consistent age of 50 ± 11.1 years vs 50 ± 0.07 years ($P = 1.00$), presence of preceding ascites episodes in 8 (88.8%) vs 29 (28.7%) ($P = 0.07$, $OR = 2.37$ [95%CI: 0.89-6.33]), prior

variceal hemorrhage 4 (44.4%) vs 10 (9.9%) [$P = 0.34$, $OR = 0.97$ (95%CI: 0.23-3.84)], occurrence of encephalopathy in the past 9 (100%) vs 30 (29.7%) [$P = 0.01$, $OR = 2.74$ (95%CI: 0.87-8.69)], manifestation of ascites throughout hospitalization in 9 (100%) vs 43 (42.5%) ($P = 0.001$, $OR = 8.79$ [95%CI: 1.80-8.10]), leucocyte count of $19.34 \pm$

Table 1. Demographic data characteristics of the patients

| Variable | Total Patient (n=110) |
|---------------------------------|-----------------------|
| Age (year) mean±SD | 50,4±0,42 |
| Gender | |
| Male (%) | 83(75,4%) |
| Female (%) | 27 (24,6%) |
| ACLF | |
| Yes (%) | 9 (8,2%) |
| No (%) | 101 (91,8%) |
| Cirrhosis | |
| Yes (%) | 97 (88,1%) |
| No (%) | 13 (11,9%) |
| Cause of Cirrhosis | |
| Hepatitis B | 82 (74,5%) |
| Hepatitis C | 15 (13,6%) |
| Combination (hepatitis B and C) | 8 (7,3%) |
| Unknown | 5 (4,6%) |
| Child pugh classification | |
| A (%) | 42 (38,5%) |
| B (%) | 37 (35,8%) |
| C (%) | 17 (15,6%) |

Table 2. Baseline characteristics and clinical manifestation of ACLF and non-ACLF cirrhotic patients

| Variable | ACLF (n=9) | Non-ACLF (n=101) | p Value | OR (95%CI) |
|---|-------------|------------------|---------|------------------|
| Age (year) (mean±SD) | 50 ± 11.1 | 50 ± 0.07 | 1,00 | |
| Male (%) | 5(55,5%) | 78 (77,2%) | 0.35 | 0,49 (0.11-2.21) |
| Previous episodes of ascites (%) | 8 (88,8%) | 29 (28,7%) | 0.07 | 2.37 (0.89-6.33) |
| Previous episodes of encephalopathy (%) | 9 (100%) | 30 (29,7%) | 0.01 | 2.74 (0.87-8.69) |
| Prior variceal hemorrhage (%) | 4 (44,4%) | 10 (9,9%) | 0.34 | 0.97 (0.23-3.84) |
| Presence of ascites during hospitalization (%) | 9 (100%) | 43 (42,5%) | 0.001 | 8.79 (1.80-8.10) |
| White blood cell count (per cubic millimeter) mean±SD | 19.34±1.97 | 7.74±3.93 | < 0.01 | |
| Sodium Level (mEq/L) mean±SD | 133.3 ± 6.9 | 135.1 ± 5.3 | 0.16 | |

1.97 per cubic millimeter vs 7.74 ± 3.93 per cubic millimeter ($P < 0.01$), sodium level of 133.3 ± 6.9 mEq/L vs 135.1 ± 5.3 mEq/L ($P = 0.16$) (Table 2).

Due to the limitation at our center, none of our patient had artificial liver support. All of the patients belong to the ACLF group were treated in the intensive care unit or semi-intensive room. In the ACLF group, 9 patients (100%) died, due to septic shock 6 patients (66.6%) and 3 patients (33.4%) due to Multiple Organ Failure. And in patient without ACLF 7 patients (6.9%) were died ($P < 0.01$).

DISCUSSION

The concept of ACLF is coined as a rapidly deteriorating liver capacity with high mortality, which is often triggered by definite causes such as bacterial infections and the development of a severe systemic inflammation^{15, 16}. With this life-threatening ailment, it is important to outline patients' organ failure status for ACLF and the CANONIC study provides an excellent clinical assessment^{4, 5, 15}. This criteria's superiority supports for its utility in our center and found a prevalence of 8.2%, whereas the CANONIC study themselves found a percentage of 30.9, which we concluded as reasonable due to smaller sample size and done at single center^{5, 10}.

Bacterial infection was found to be the leading precipitating events for the ACLF, and secondly the gastrointestinal bleeding, which is expected has no difference with prior studies^{5, 17-19}. We highlighted a percentage of 5.94 of total ACLF cases where the triggering causes have been indefinite, similar circumstance which is also observed by the previous authors⁵.

We observed that the presence of ascites, prior episodes of encephalopathy and greater value of leucocyte counts construct an important risk factor for the evidence of ACLF. Despite of no known value of the MELD score due to the lack of data, the statistical importance of hepatic ascites and encephalopathy in the CANONIC study permit us to conclude that our conclusions and the study are consistent. The involvement of leucocyte count as the parameter of inflammation also highlighted by former authors^{5, 9}.

Our study found that our ACLF cirrhotic patients had significantly higher mortality,

compared to the non-ACLF, which is indifferent from what prior studies observed. The mortality rate of our ACLF patients was alike when compared to what Gustot *et al.* explained (100% vs 92%). The advancing rate of mortality was also found parallel to the developing number of organ involvement, as less as three^{5, 10, 20}.

The chief weakness of our study is that this study was carried out in a one epicenter with a inadequate amount of patients. We considered a necessity for carrying out prolonged and multicenter study to achieve improved information in the future, related to the incidence and triggering factors of ACLF.

CONCLUSION

Acute-on-chronic liver failure (ACLF) is a clinical syndrome of sudden worsening observed in patients with pre-existing chronic liver disease that ensues with high occurrence in cirrhotic patients, achieving the incidence number of 8.2% in our hospital. As noticed in previous studies, ACLF is rightly a dynamic syndrome, where ACLF could occur earlier or throughout the hospitalization, whereas a number of risk factors capable to predict its development and mortality. As the consequence, it is essential to identify these risk factors and notice for its changes. Through the improvement of the triggering causes, a shrinking count for mortality is expected^{15, 21-23}.

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