CLINICAL FEATURES AND PREDICTORS OF MORTALITY IN ACUTE ON CHRONIC LIVER FAILURE: A PROSPECTIVE STUDY

G.C.A. Carpio, M.D.[1]
J.D. Sollano, M.D.[1]

[1]Section of Gastroenterology.
Department of Medicine,
University of Santo Tomas Hospital

Table of Contents

INTRODUCTION

Acute-on-chronic liver failure (ACLF) has been an emerging disease definition. Because it is a relatively new and increasingly recognized separate entity from previous liver disease terms, it has been a hot topic for several years now and has been discussed repeatedly in many international conventions. Several consensus statements have been made with regards to this disease entity such as the APASL and EASL consensus statements. ACLF is defined as an acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in patients with previously diagnosed or undiagnosed chronic liver disease.1 ACLF is a clinical syndrome manifesting as acute and severe hepatic derangements resulting from varied insults.

ACLF has been an emerging term in Gastroenterology for several years now. The growing interest in ACLF after the first consensus definition of ACLF from APASL in 2009 is seen by the fact that more than 200 research papers have been published and yet there is still a paucity of data in the Philippines. This study aims to determine the clinical profile, etiology and prognostic factors of patients with acute-on-chronic liver failure in the Philippines.

REVIEW OF RELATED LITERATURE AND SIGNIFICANCE OF THE STUDY

Liver failure or severe hepatic dysfunction can present in patients with a previously normal liver (acute liver failure), in patients with previously known or unknown liver disease (acute on chronic liver failure) and as decompensation of chronic liver disease.2 ACLF has been a relatively new disease entity that is being

given great attention due to its many possible severe consequences and its high mortality rate.3 The liver failure of ACLF has a wide spectrum with increasing levels of severity leading to multi-organ failure and subsequently, demise.3

In some studies, it was shown that alcohol and drugs were the major cause of acute insult in the west while infectious etiologies including HBV reactivation were the predominant causes of the acute event in the East.4,5,6 In some other studies, sepsis and upper GI bleeding were common causes of the acute event.7, 8 For the chronic liver disease, Hepatitis B cirrhosis and alcoholic liver disease were the common causes of liver cirrhosis.

Because of the severity of ACLF, several prognostic models have been used and studied to guide outcomes of patients. The MELD, APACHE II, and SOFA have been found to be good prognostic indices for predicting mortality in ACLF although with some limitations.3,9,10,11 These scoring systems were found to be better than the Child Pugh in several studies.3

In terms of prognostic factors, one study showed that past history of decompensation, leukocytosis, increased serum bilirubin and creatinine, and INR, presence of spontaneous bacterial peritonitis, Child-Pugh score and hepatorenal syndrome were significant predictors of mortality. A MELD score of >27 and presence of encephalopathy were also found to be independent predictors.12 In another study, presence of high INR (>2), low sodium (<133) and hepatic encephalopathy were predictors of mortality.3

ACLF is a grave disease with a very high mortality. There is a need for continuous research to better familiarize physicians on how to treat this condition.

GENERAL OBJECTIVE OF THE STUDY

This study aimed to determine the clinical profile and factors related to mortality in patients with acute-on-chronic liver failure in the University of Santo Tomas Hospital from June 1, 2015 up to November 30, 2016

SPECIFIC OBJECTIVES OF THE STUDY

1. To determine the demographic profile of patients with ACLF
2. To determine the usual etiology of the acute hepatic failure on top of the chronic liver disease
3. To determine the usual clinical features of ACLF
4. To determine the clinical profile of admitted patients including vital signs, laboratory test findings, imaging findings
5. To determine the different liver severity scores of ACLF including Child Pugh, MELD, MELD Na, SOFA, APACHE II, Glasgow AHS and CLIF SOFA
6. To discuss different treatment options for ACLF
7. To determine the mortality rate of ACLF
8. To determine the factors related to mortality

METHODOLOGY

Study Design

This is a prospective analytical study which included all admitted adult patients who were diagnosed with acute on chronic liver failure in the University of Santo Tomas Hospital from June 1, 2015 up to November 30, 2016. The inclusion criteria will included all patients who fit the APASL definition of ACLF; patients with acute hepatic insult manifesting as jaundice with serum bilirubin $\geq$ 5 mg/dl (85 umol/L), coagulopathy with international normalized ratio (INR) $\geq$ 1.5 and complicated by ascites and/or clinical encephalopathy within 4 weeks of jaundice. These patients either had previously diagnosed or newly diagnosed compensated chronic liver disease. The exclusion criteria included underlying decompensated cirrhosis prior to acute insult, hepatocellular carcinoma, portal vein thrombosis and those who refused to participate and give consent in the study.

Data on patient demographics, evaluation of etiology of acute insult and underlying chronic liver disease, clinical features, laboratory variables, liver severity scores, complications during hospital course and possible causes of mortality were analyzed.

Privacy and Confidentiality

All the data from the patients were kept private and confidential. Only the authors had access to the names of the patients and the data being presented.

Benefits

Data from this paper can be used to improve current practices on acute on chronic liver failure

Risk

There were no risks involved in the study.

Conflict of Interest

All the investigators do not have financial and commercial affiliations.

Data Analysis

Categorical data were summarized as frequencies and percentages. Continuous data will be reported as means and standard deviation. Statistical analysis was done using Excel and SPSS for MS Windows. Comparison of continuous variables was done using Independent T test and categorical variables by Fischer exact test or Pearson's chi square test.

RESULTS

16 patients were diagnosed with ACLF during the duration of the study based on the APASL criteria. The mean age of patients was 57.2 $\pm$ 11.7 years. There was equal gender distribution. For the acute insults, the most common was infection (62.5%) from pneumonia (31.2%), UTI/urosepsis (18.8%) and cellulitis (12.5%). 18.8% had drug induced events from anti-tuberculosis medications (Rifampicin, Isoniazid, Pyrazinamide, 12.5%) and from immunosuppresants (steroids, Azathioprine, 6.3%). 12.5% had acute variceal bleed and 6.3% had surgery as the acute event.

For the cause of chronic liver disease, majority (56.3%) were from Hepatitis B cirrhosis. 3 patients (18.8%) had alcoholic liver disease. 2 patients (12.5%) had NASH cirrhosis. 1 patient each (6.3%) had autoimmune hepatitis and cardiac cirrhosis.

The duration of jaundice to admission is 12.1 ± 9.8 days. Duration of ascites is 20 ± 21.7 days. Majority (50%) had moderate ascites. 37.5% had mild ascites while 12.5% had severe ascites. Duration of encephalopathy to event is 3.9 ± 5 days. 43.8% had grade 1 encephalopathy while 31.3% had grade 2. 2 patients (12.5%) each had Grade 3 and 4 encephalopathy.

For clinical parameters, the mean heart rate was 100.3 ± 18.9 beats per minute. Systolic BP mean was 121.3 ± 23.3 with a MAP of 92.5 ± 16.8. Respiratory rate was 24.6 ± 4.9 breaths per minute. The mean temperature was 37.2 ± 0.9 and the mean Glasgow Coma Scale score was 11.9 ± 4.0. The number of SIRS component was 2.19 ± 1.

Laboratory parameters were also assessed. The mean hemoglobin was 117.3 ± 20.1. WBC was at 13.2 ± 5.9 x 10^3 cells/mm3 with neutrophils of 73.4 ± 12.2. The mean platelet was 191.1 ± 64. BUN was seen at 27.2 ± 18.2 and Creatinine was at 1.7 ± 1.2 mg/dl. The mean sodium and potassium were 136.7 ± 5 and 4.1 ± 0.6, respectively. The total bilirubin was 8.4 ± 4.9 with direct bilirubin of 7.4 ± 4.4. AST level was 403.5 ± 541.7 and ALT level was 560.9 ± 807.9. The mean total protein, albumin and globulin were 6.2 ± 0.9, 2.3 ± 0.5, and 4.0 ± 1.1, respectively. The mean INR was 2.4 ± 1.6.

The common liver severity scoring systems for severity of disease and prognosis were also assessed. The mean Child Pugh Score was 11.9 ± 1.0. The MELD and MELD-Na scores were 25.4 ± 7.7 and 26.6 ± 7.2, respectively. The mean

SOFA score was 7.8 ± 3.7 and the APACHE II of 11.4 ± 5.1. The mean CLIF-SOFA score was 11.1 ± 4.6.

Mortality rate during hospitalization was 56.3% (9 patients). All patients died due to multi-organ failure.

The different factors were analyzed in relation to mortality. The grading of hepatic encephalopathy was found to be statistically different (p=0.017) with 22.4% at grade 4 and 55.6% at grade 2 for the group with expired patients. For the group of live patients, majority (71.4%) had only grade 1 encephalopathy. An increased heart rate was also found to be associated with mortality (108.4 ± 17.9 vs 89.9 ± 15.6, p=0.047). The Glasgow Coma Scale score (10.1 ± 4.9 vs. 14.3 ± 1.5, p=0.034) and number of SIRS component (2.6 ± 0.7 vs. 1.5 ± 1.0, p=0.038) were also found to be significant. For the laboratory parameters, there is an association found with ALT levels (p=0.028). For the liver severity scores, the SOFA scoring system was found to be statistically significant in relation to mortality (10.1 ± 3.3 vs. 4.7± 1.0, p =0.001).

Table 1 Clinical Characteristics

	Total n=16	Alive n=7	Expired n=9	P value
Age Mean	57.2 ± 11.7	55.4 ± 12.9	58.6± 11.2	0.62
Gender Male (n/%) Female (n/%)	 8 (50%) 8 (50%)	 3 (42.9%) 4 (57.1%)	 5 (55.6%) 4 (44.4%)	0.614
Acute Insult Infection Pneumonia UTI	 10 (62.5%) 5 (31.2%) 3 (18.8%)	 5 (71.4%) 2 (28.6%) 1 (14.3%	 5 (55.6%) 3 (33.3% 2 (22.3%)	

Cellulitis	2 (12.5%)	2 (28.6%)	0	
Drug induced	3 (18.8%)	0	3 (33.3%)	
Anti-TB Meds	2 (12.5%)	0	2 (22.2%)	
Steroids/ Azathioprine	1 (6.3%)	0	1 (11.1%)	
Acute variceal bleed	2 (12.5%)	1 (14.3%)	1 (11.1%)	
Surgery	1 (6.3%)	1 (14.3%)	0	
Chronic Insult				
HBV Cirrhosis	9 (56.3%)	3 (42.8%)	6 (66.7%)	
NASH cirrhosis	2 (12.5%)	1 (14.3%)	1 (11.1%)	
Autoimmune	1 (6.3%)	0	1(11.1%)	
Alcoholic Liver Disease	3 (18.8%)	2 (28.6%)	1(11.1%)	
Cardiac cirrhosis	1 (6.3%)	1 (14.3%)	0	
Clinical features				
Jaundice				
Duration of jaundice	12.1 ± 9.8	8.3 ± 9.8	15 ± 9.2	0.181
Ascites				0.227
Mild	6 (37.5%)	4 (57.1%)	2 (22.2%)	
Moderate	8 (50%)	3 (42.9%)	5 (55.6%)	
Gross/tense	2 (12.5%)	0	2 (22.2%)	
Duration of Ascites	20 ± 21.7	11.7 ± 10.5	26.4 ± 26.3	0.187
Hepatic encephalopathy				**0.017**
Grade 1	7 (43.8%)	5 (71.4%)	2 (22.2%)	
Grade 2	5 (31.3%)	0	5 (55.6%)	
Grade 3	2 (12.5%)	2 (28.6%)	0	
Grade 4	2 (12.5%)	0	2 (22.2%)	
Duration of encephalopathy	3.9 ± 5	2.3 ± 4.9	5.2 ± 6.5	0.253
Vital Signs during Onset				
Heart rate	100.3 ± 18.9	89.9 ± 15.6	108.4± 17.9	**0.047**
Systolic BP	121.3 ± 23.3	125.7 ± 26.4	117.8± 21.7	0.519
Diastolic BP	77.5 ± 14.8	77.1 ± 16	77.8 ± 14.8	0.937
MAP	92.5 ± 16.8	94.2 ± 17.6	91.1 ± 16.7	0.72
RR	24.6 ± 4.9	23.1 ± 3.2	25.8± 5.8	0.301
Temperature	37.2 ± 0.9	37.0 ± 0.6	37.3 ±1.1	0.431
GCS	11.9 ± 4.0	14.3 ± 1.5	10.1 ± 4.9	**0.034**
Number of SIRS component	2.19 ± 1	1.5 ± 1.0	2.6 ± 0.7	0.038
Laboratory Findings				
Hgb	117.3 ± 20.1	115.6 ± 14.5	118.6± 24.4	0.779
WBC	13.2 ± 5.9	12.6 ± 6.3	13.7 ± 5.9	0.722
Neutrophils	73.4 ± 12.2	67.4 ± 14.8	78 ± 7.7	0.084
Platelet	191.1 ± 64	175.6 ± 53.5	203.1± 71.9	0.412
Urea	27.2 ± 18.2	29.6 ± 9.1	23.9 ± 27.6	0.620
Crea	1.7 ± 1.2	1.8 ± 1.0	1.6 ± 1.4	0.825
Na	136.7 ± 5	137.9 ± 5.7	135.8 ± 4.5	0.428
K	4.1 ± 0.6	4.4 ± 0.5	3.8 ± 0.5	0.054
Total bilirubin	8.4 ± 4.9	7.0 ± 4.3	9.8 ± 5.4	0.349
Direct bilirubin	7.4 ± 4.4	5.2 ± 3.6	9.1 ± 4.4	0.08

AST	403.5 ± 541.7	95.5 ± 47.4	667.5± 639	0.053
ALT	560.9 ± 807.9	51.8 ± 19.6	997.1± 908	**0.028**
T. Protein	6.2 ± 0.9	6.1 ± 0.9	6.2 ± 1.1	0.79
Albumin	2.3 ± 0.5	2.22 ± 0.7	2.4± 0.3	0.578
Globulin	4.0 ± 1.1	4.1 ± 1.3	3.9 ± 1.0	0.744
INR	2.4 ± 1.6	1.9 ± 0.6	2.9 ± 2.0	0.199
Liver Severity Scores				
Child Pugh	11.9 ± 1.0	11.7 ± 1.5	12 ± 0.5	0.598
MELD	25.4 ± 7.7	24.4 ± 7.4	26.1 ± 8.3	0.681
MELD Na	26.6 ± 7.2	25.6 ± 6.8	27.4 ± 7.8	0.621
SOFA	7.8 ± 3.7	4.7± 1.0	10.1 ± 3.3	**0.001**
APACHE II	11.4 ± 5.1	8.7 ± 2.0	13.4 ± 6.0	0.066
CLIF SOFA	11.1 ± 4.6	9.5 ± 2.1	11.6 ± 5.2	0.612
Eventual Outcome				
Mortality	9 (56.3%)			

DISCUSSION

Acute on chronic liver failure is a relatively new disease entity that is being given great attention globally due to its many possible severe consequences and its high mortality rate.3 The liver failure of ACLF has a variable spectrum with high possibility for multi-organ failure and subsequently, demise.3

Mean age in our study was similar to one study 13 but in 3 other studies mean age was younger and usually less than 50 years old.13,14,15 Gender distribution was also different as most studies had male predominance of patients to even as high as 7.78:1 male: female ratio.4 Infection or sepsis was the most common cause of decompensation in our study and this is consistent with other studies that showed infectious etiologies as the predominant cause in the East. 6, 7, 8, 14 Liver injury from various drugs was also manifest in the study and this is a common cause of ACLF in both Eastern and Western countries.4,5 For the chronic liver disease, majority had Hepatitis B Cirrhosis followed by alcoholic liver disease. Other studies also have these 2 disease conditions as their top causes of cirrhosis in ACLF.

All patients who were included in the study had jaundice and coagulopathy as shown by elevated INR and ascites and encephalopathy present within 30 days of hospitalization.

Clinical and laboratory parameters were assessed to see usual characteristics of patients with ACLF and to determine factors that have an association with mortality. In patients with ACLF, there is a need to look for such markers of severity as to be able to detect early warning signs that may lead to a worse condition so that it can guide us in correctly treating the patient.

Patients with ACLF as shown in the study usually have abnormal clinical values when hospitalized with increased heart and respiratory rate, and they usually have several components of SIRS positive. Laboratory parameters are also deranged especially liver parameters such as increased bilirubin, AST and ALT and abnormal prothrombin time.

The clinical factors that were found to be associated with mortality were the grading of hepatic encephalopathy, increased heart rate, Glasgow Coma Scale score and the number of SIRS component present. For the laboratory parameters, ALT levels were associated with mortality. Prognostic factors that were present in other studies were different from the ones in our study except for presence of encephalopathy that was consistently present in other studies.3

Several prognostic models have been used to guide outcomes of patients with ACLF. The MELD, APACHE II, and SOFA have been found to be good prognostic

indices for predicting mortality in ACLF.3,9,10,11 and they were found to be better than the Child Pugh in some studies.3 In our study, we found the SOFA score to be the one significantly associated with mortality.

Mortality rate during hospitalization was high at 56.3%. Patients would have multiple organ failure due to the ACLF. The study by Jha, et al. and the CANONIC study had similar mortality rates of 53.8% and 51.2%, respectively.13,15

There are several limitations to the study. First is the small population size of participants. It would be better to analyze the different factors if there were more patients included in the study. Also, at least a 90 day follow up to determine changes in factors and mortality would give us more information on the disease trend. The authors would like to recommend a prospective study with longer duration to include more patients and with at least a 90 day follow up for better analysis of variables.

CONCLUSION

ACLF is a life threatening condition with a rapid course and high in-hospital mortality. The factors found to be associated with increased mortality are grading of hepatic encephalopathy, heart rate, GCS score, Number of SIRS component, ALT level, and the SOFA scoring system. Emphasis must therefore be placed in early detection, close monitoring and increased vigilance in these patients.

REFERENCES

1. Sarin SK, Kumar A, Almeida JA, et al., Acute-on-Chronic-Liver Failure: Consensus Recommendations of the Asian Pacific Association for the Study of the Liver (APASL). Hepatol Int 2009; 3:269-82.

2. Vizzutti, F, et al., Acute on Chronic Liver Failure: From Pathophysiology to Clinical Management. Trends in Anaesthesia and Critical Care 3 (2013) 122e129124.
3. Garg, H, Kumar A, Garg V, Sharma P, Sharma B, Sarin S.Clinical Profile and Predictors of Mortality in Patients of Acute-on-Chronic Liver Failure. Digestive and Liver Disease 44 (2012) 166-171.
4. Pati G, et al. Acute-on-Chronic Liver Failure (ACLF) in Coastal Eastern India: A Singe Center Experience. Journal of Clin and Exp Hepatology 6 (2016) 1: 26-32.
5. Kohrt HE, Ouyang DL, Keeffe EB. Antiviral Prophylaxis for Chemotherapy-induced Reactivation of Chronic Hepatitis B virus Infection. Clin Liver Dis. (2007) 11:965-991.
6. Sera T, Hiasa Y, Michitaka K, et al. Anti-HBs Positive Liver Failure due to Hepatitis B Virus Reactivation Induced by Rituximab. Intern Med. (2006) 45:721-724.
7. Wehler M, Kokoska J, et al. Short Term Prognosis in Critically Ill Patients with Cirrhosis Assessed by Prognostic Scoring Systems. Hepatology (2001) 34:255-261.
8. Sen S, et al. Pathophysiological effect of Albumin Dialysis in Acute-on-Chronic Liver Failure: A Randomized Controlled Study. Liver Transpl (2004) 10:1109-19.
9. Tsai M, Peng Y, et al. Multiple Organ System Failure in Critically Ill Cirrhotic Patients. A Comparison of Two Multiple Organ Dysfunction/ Failure Scoring Systems. Digestion (2004) 12: 517-22.
10. Liu X, Hu J, Wang H. Analysis of Prognostic Factors for Patients with Acute on Chronic Liver Failure. Zhonghua Gan Zang Bing Za Zhi (2009) 17: 607-18
11. STauber R, et al. Evaluation of Four Prognostic Scores in Patients with Acute on Chronic Liver Failure. J Hepatol (2006) 44(Supp. 2): 569-70.
12. Khot AA, Somani P, Rathi P, Amarapurkar A.Prognostic factors in acute-on-chronic liver failure: A prospective study from western India. Indian J Gastroenterol. (2013)
13. Moreau R, Jalan R, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology (2013) 144:1426-37.
14. Duseja A, et al. Non-hepatic insults are common acute precipitants in patients with acute on chronic liver failure. Dig Dis Sci (2010) 55:3188-92.
15. Jha A, et al. Etiology, clinical profile and in-hospital mortality of acute-on-chronic liver failure: a prospective study. Indian J gastroenterol (2013) 32(2):108-14.