Research Article

ORGAN FAILURES AND OUTCOMES IN PATIENTS WITH ACUTE ON CHRONIC LIVER FAILURE

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A R T I C L E   I N F O

A B S T R A C T

Background and Aims: The patients with acute on chronic organ failure (ACLF) have both hepatic and extrahepatic insults. The number of organ failures and grades of ACLF determine outcome of the patient. We aimed to study the outcome in ACLF patient with different organ failures in this single center study.

Methods: A total of 52 ACLF patients with different numbers of organ failures at time of admission (9patients with one, 17 with two, 11 with three, 8 with four and 7 with five organ failures) were taken. The outcome during hospital stay and survival at 90 days were analyzed.

Results: Majority of patients (82.6 %) were male. Alcohol consumption was most common cause of cirrhosis; present in 32 (61.5%) patients. 28 (53.8%)patients had continued alcohol consumption as an acute precipitating event. None of the 15 patients with 4 and 5 organ failures survived during hospital stay whereas hospital survival was highest in patients with one (6/9; 66.6%) followed by patients with three (4/11; 36.3%) and two (6/17; 35.2%) organ failures. 90 days survival analysis showed only 7 (13.5%) patients surviving. The mortality rates were higher in ACLF grade 3 (92.3%) as compared to ACLF grade 2 (76.4%) and ACLF grade 1 (55.5%).

Conclusion: In ACLF, the outcome is determined by the number of organ failures and different grades of ACLF subsequently. Mere analysis of liver function test in ACLF patients can lead to erroneous decisions in management and poor outcome.

INTRODUCTION

Acute on chronic liver failure (ACLF) is an entity with controversies in defining criteria and presentation. This syndrome describes astage when patients deteriorate rapidly with liver failure, multiple extrahepatic organ failures with high short-term mortality usually following some precipitating event, instead of usual steady decline inliver function with decompensate cirrhosis. The two most commonly used definitions proposed by the Asia-Pacific Association for the Study of Liver (APASL) (Sarin *et al*, 2014)and the European Association for the Study of Liver - Chronic Liver Failure (EASL-CLIF)(Moreau *et al*, 2013) consortium are different and appear to identify different sets of patients. As per APASL group, ACLF is defined as acute hepatic insult manifesting as jaundice (S.bil $\geq$ 5mg/dl) and coagulopathy (INR $\geq$ 1.5 or prothrombin activity <40%), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease. On the other hand, EASL group defined ACLF as an acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure. Systemic inflammation is a hallmark of ACLF (Moreau *et al*, 2013; Bernsmeier*et al*, 2015) leading to derangements in organ functions with inflammatory response developing when inducers of inflammation (exogenous and endogenous)are recognized by sensors that engage effectors of the response (Arroyo *et al*, 2016; Medzhitov, 2008; Moreau, 2016).

We often encounter that mere derangements in hepatic functions as defined by APASL criterion are overwhelmed by the presence of other organ failures viz renal, circulatory, cerebral, coagulation and respiratory failures. The number of organ failures and ACLF grades are likely to influence outcome of these patients. We aimed to study the presence of various organ failures and grades of ACLF and to assess the outcome of these patients during hospitalization and at 90 day.

MATERIAL AND METHODS

In this prospective Cohort study, we included 52 patients admitted in the Department of Medicine at our tertiary care centre with ACLF as per the CANONIC study criteria (Moreau 2013). Exclusion criteria were: transfusion of blood

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products within 48h prior to admission, therapy with anti-platelet drugs/ anticoagulants and history of a primary disease with coagulation disturbance (paroxysmal nocturnal hemoglobinuria, polycythemia, idiopathic thrombocytopenia or hemophilia), pregnancy or post-partum period, and concomitant chronic kidney disease. Informed consent was obtained from patients or from their nearest relatives in cases with altered sensorium.CLD was diagnosed based on liver biopsy or a combination of conventional endoscopic and imaging criteria (Achraya *et al*, 2007; Brown *et al*,1997; Garg *et al*, 2011).Sepsis and GI bleed were taken as acute events in defining acute on chronic liver failure as per definition of CLIF SOFA (Moreau *et al*, 2013). Baseline parameters including complete blood counts, liver function tests, kidney function tests and cultures (blood, urine, ascitic fluid, endotracheal aspirate culture wherever applicable) were sent to look for possible source of sepsis. Acute gastrointestinal bleed was defined by upper or lower gastrointestinal hemorrhage of any etiology. Infections were diagnosed as patients having ≥ 2 SIRS criteria with positive blood/urine/endotracheal tube aspirate culture or radiological evidence of pneumonia or clinical examination consistent with cellulitis (Acharya *et al*, 1996).SBP was diagnosed as ascitic fluid polymorph nuclear count > 250 cells/µL with or without positive culture report. Organ failures were defined by CLIF OF score as per criterion laid down by EASL AASLD. The OFs were assessed as per the CLIF-OF scoring system (Moreau *et al* , 2013). ACLF was defined and graded as per the CANONIC study.

No ACLF - This group consists of 3 subgroups

- ✓ Patients with no organ failure
- ✓ Patients with a single "non-kidney" organ failure (*i.e.*, single failure of the liver, coagulation, circulation, or respiration) who had a serum creatinine level < 1.5 mg/dL and no hepatic encephalopathy
- ✓ Patients with single cerebral failure who had a serum creatinine level < 1.5 mg/dL

ACLF grade 1 - This group consists of 3 subgroups

- ✓ Patients with single kidney failure
- ✓ Patients with single failure of the liver, coagulation, circulation or respiration who had a serum creatinine level ranging from 1.5 to 1.9 mg/dL and/or mild to moderate hepatic encephalopathy
- ✓ Patients with single cerebral failure who had a serum creatinine level ranging from 1.5 and 1.9 mg/dL

ACLF grade 2 - This group consists of patients with 2 organ failures

ACLF grade 3 - This group consists of patients with 3 organ failures or more

Sample Collection and analysis

Within 24 hours of admission, blood sample and ABG analysis was done for assessment of organ failure and grades of ACLF and disposables were disposed off asper guidelines laid down by infection control committee of institute.

Statistical Analysis

The normally distributed variables were expressed as mean ± standard deviation (SD) and continuous variables with skewed distribution as median (inter-quartile range). Categorical data was presented as frequency and proportions. The comparison of continuous variables between two groups was done using paired ttest. Comparison of continuous and normally distributed variables between more than two groups was analyzed using One way Analysis of Variance (ANOVA) with Bonferroni correction for multiple comparison tests. Variables with skewed distribution were compared using the Kruskal-Wallis ANOVA test followed by the Mann-Whitney U test with adjusted P values. P value ≤ 0.05 was considered as statistically significant. Data analysis was done using STATA version 14 (Stata Corp, Texas, USA) and Medcalc software (version15.11.4, MedCalc Software, Ostend, Belgium).

RESULTS

Demographic Profile of patient, Etiology of cirrhosis and underlying precipitating events in ACLF patients (Table 1)

Mean age of patients was 42.6 ± 13.8years with male to female ratio being 4.77. Alcohol consumption was the most common cause of underlying cirrhosis among 32 (61.5%) patients followed by Non alcoholic hepatitis related cirrhosis in 6(11.6 %) patients. Chronic hepatitis B and hepatitis C infections were found in 3(5.7%) and 5 (9.6%) patients respectively. 3 (5.7%) patients had cryptogenic cirrhosis whereas in 3 (5.7%) patients no etiology of cirrhosis was present till the final outcome was reached. The etiology of acute event leading to de compensation of cirrhosis included active alcohol consumption in 15 (28.8 %) patients, reactivation of hepatitis B in 2 (3.8%), sepsis in 4(7.6%), GI bleed in 9 (17.4%), drug induced in 2(3.8%), hepatitis E infection in 3 (5.9%) and no cause was identified in 4 (7.6%) patients. 13 (25%) patients with active alcoholic consumption (with in previous 3 months) had GI bleed at presentation.

Organ failures in ACLF patients

All patients had one or more organ failure as defined by the CLIF OF scoring. Renal Failure (S.creatinine≥2) and coagulation failure (INR >2.5) was the most common organ failure in 29 (55.7%) patients followed by liver failure (S.Bilirubin >12 mg%) in 28 (53.8%).24 (46.1%) patients had cerebral failure (West Heaven HE grade 3-4). Circulatory failure as defined by the use of vasopressors and respiratory failures as defined by PaO$_2$/FiO$_2$ <200 were among the least common organ failures encountered in these patients; 17 (32.7%) and 16 (30.8%) respectively. 17 (32.7%) patients had two organ failures as compared to 9 (17.3%) patients with one and 11 (21.2%) patients with three organ failures.7 (13.5%) patients had four organ failures with rest of 8 (15.4%) patients had five organ failures. None of the patients had all the six organ failures.(Table2)

ACLF grades according to organ failures

Incorporating the cut off value for defining the organ failure in ACLF patients, we had 9 patients with ACLF grade 1, 17 patients with ACLF grade 2 and 26 patients with grade 3 ACLF.

Baseline characteristics of patients with different grades of ACLF

Demographic profile and baseline characteristic of the patients with different grades of ACLF were extracted from the patient database and compared for any significant changes with respect to different grades (Table 3). Patient with ACLF grade 3 had high blood urea and serum creatinine value as compared to grade 1 and 2 ACLF patients. Total Bilirubin values were significantly higher in grade 2 and 3 patients as compared to grade 1 patients. PTI, INR and a PTT values were higher with increasing grade of ACLF.

Organ Failures and Outcome during Hospital stay

The patient with 4 and 5 failures had markedly less hospital stay than patients with 1-3 organ failures. In addition none of the 15 patients with 4 and 5 organ failures survived and had dismal outcome during hospital stay. A total of 36 (69.2%) patients died during hospital stay (Table 4)

Organ failure, ACLF grades and Outcome at 90 days

90 days survival outcome showed only 7 patients surviving at 90 days. The status of 3 patients could not be known despite best efforts. A total of 42 patients died in study cohort within 90 days (Table 5, Fig.1). Patients with ACLF grade 3 had marked mortality at 90 days with only 1 patient surviving at 90 days as compared to 3 in each 1 and 2 ACLF grades (Table 5, Fig 2)

Table 1 Demographic Profile, Etiology of cirrhosis and underlying precipitating events in ACLF patients

Parameters	Acute on chronic liver failure (n = 52)
Age (years)	42.9 ± 13.2
Sex (M:F)	43:9
Hemoglobin (gm/dl)	9.1 ± 2.1
WBC Count (x 10^3percumm)	14.5 ± 7.8
Platelets (x 10^3per cumm)	89.1 ± 50.3
Urea (mg/dl)	80.8 ± 54.3
Creatinine (mg/dl)	1.9 ± 1.5
S.Bilirubin (mg/dl)	14.3 ± 11.6
Aspartate aminotransferase(SGOT; IU/L)	178.5 ± 146.5
Alanine aminotransferase (SGPT; IU/L)	130.1 ± 116.0
SAP (U/L)	287.3 ± 175.1
Serum Albumin (g/dl)	2.6 ± 0.5
Prothrombin time (seconds)	33.2 ± 17.3
Activated partial thromboplastin time (seconds)	56.8 ± 23.2
International normalized ratio	3.0 ± 1.4
Etiology of chronic liver disease	
Alcohol	32 (61.5%)
Hepatitis B	3 (5.7%)
Hepatitis C	5 (9.6%)
Non alcoholicsteatohepatitis	6 (11.6%)
Cryptogenic	3(5.7 %)
Not Known	3 (5.7%)
Etiology of acute event	
Alcohol	15 (28.8%)
Not Known	4 (7.6%)
Bleed	9 (17.4 %)
Drug induced	2 (3.8%)
Sepsis	4 (7.6%)
Hepatitis E infection	3 (5.9%)
Hepatitis B reactivation	2 (3.8%)
Alcohol + Bleed	13 (25%)

Table 2 Number of patients with organ failures

Organ Failure	Number of Patients (%)
Kidney	29 (55.7)
Coagulation	29 (55.7)
Liver	28 (53.8)
Cerebral	24 (46.1)
Respiratory	17 (32.7)
Cardiovascular	16 (30.8)
Number of organ failure	
1	9 (17.3)
2	17 (32.7)
3	11 (21.2)
4	7 (13.5)
5	8 (15.4)
6	0 (0.0)

Table 3 Demograhic Profile, Baseline Parameters in patients with different grades of ACLF

Variables	ACLF grade 1 (n=9)	ACLF grade 2(n= 17)	ACLF grade 3(n=26)	P value
Age	48.1 ± 6.8	36.7± 12.7	44.4± 14.8	< 0.05*$
Sex (M:F)	7:2	14:3	23:3	
Hb(in g%)	8.8 ± 2.2	9.1 ± 2.8	9.1 ± 1.6	< 0.05*^
TLC (x 10^3/cumm)	10.1+5.1	15.0 ± 8.9	16.1 ± 7.6	< 0.05*^
Platelets (x 10^3/cumm)	82± 48.2	92.3± 63.6	90.1± 46.1	< 0.05*^
Blood Urea (mg%)	51.7± 33.7	57.5± 36.4	107.1± 58.9	< 0.05*$^
S. Creatinine (mg%)	1.4 ± 1.1	1.15 ±0.5	2.7 ± 1.7	< 0.05*$^
Total Bilirubin (mg%)	10.5+11.3	16.2+10.5	14.8+12.4	< 0.05*$^
Aspartate aminotransferase, IU/L	82.9+48.6	151.5+104.5	240.1+224.2	< 0.05*$^
Alanine aminotransferase, IU/L	47.3± 25.5	146.4 ±125.7	127.2 ±164.1	< 0.05*$^
Serum alkaline phosphatase, U/L	326.8 ± 202.3	236 ± 79.6	257.7 ± 138.3	< 0.05*^
Serum albumin, g/dL	2.5 ± 0.4	2.7±0.4	2.7 ± 0.6	<0.05*^
Prothrombin time (PT) , seconds	28.2 ± 10.4	34.2± 23.1	39.5 ± 20.2	<0.05*$^
Activated partial thromboplastin time (aPTT), seconds	52.6 ± 16.3	54.5 ±26.1	59.6 ± 24.6	< 0.05*$^
International normalized ratio(INR)	2.7 ± 0.9	3.1 ± 2.1	3.5 ± 1.6	< 0.05*$^

* - Between ACLF grade 1 and grade 2, \$- Between ACLF grade 2 and 3, ^ - Between ACLF grade 1 and 3

Table 4 Outcome during Hospital Stay

Organ Failure	Hospital stay (in Days)Mean ± S.D.	Outcome Dead	Outcome Alive
1	15.7 ± 10.1	3	6
2	10.7 ± 8.1	11	6
3	8.7 ± 3.9	7	4
4	3.6 ± 1.8	7	0
5	4.2 ± 2.1	8	0

Table 5 Organ failure, ACLF Grades and Outcome at 90 Days

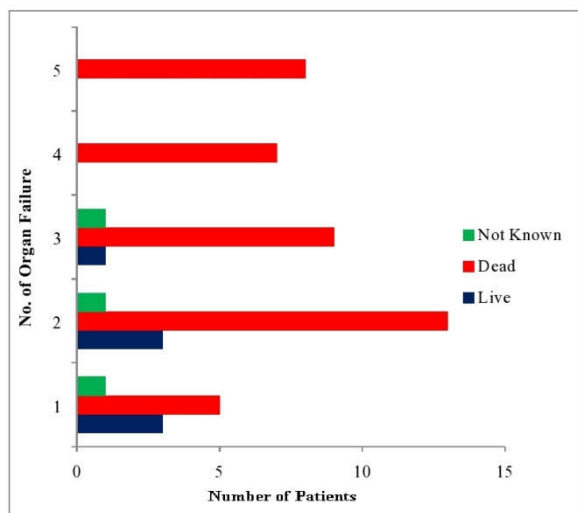| Organ Failure	Dead	Alive	Not known
		Status 90 days	
1	5	3	1
2	13	3	1
3	9	1	1
4	7	0	0
5	8	0	0
ACLF Grades			
1	5	3	1
2	13	3	1
3	24	1	1

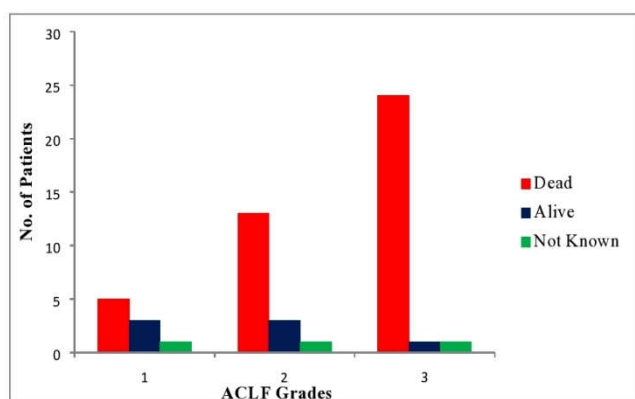Fig 1: Organ failure and status at 90 days

Fig 2: ACLF grades and status at 90 days

DISCUSSION

ACLF is a relatively new entity with involvement of various organs in addition to acute hepatic insult. The concept of ACLF was established to describe the frequent episodes of deteriorations in liver function associated with organ failures and high short-term mortality that occur in decompensate cirrhosis. The decline in other organ functions in addition to liver failure has been largely attributed to development of systemic inflammation, as indicated by increased white cell count, C-reactive protein, the presence of various inflammatory cytokines, and oxidative stress in cirrhosis patients following acute insult (Claria *et al*, 2016; Sole *et al*, 2016).The involvement of PAMPS(pathogen-associated molecular patterns) and DAMPS (Damage -associated molecular patterns) as inflammation inducers in response to endogenous and exogenous noxious stimuli have been studied and found to account for the systemic inflammation and subsequent organ failures in ACLF patients (Moreau, 2016; Gustot *et al*, 2009; Takeuchi O *et al*, 2010; Kono *et al*, 2008).

Majority of the patients were male (84.6%) and continued alcohol consumption was the most common cause of both acute hepatic insult and underlying cirrhosis in patients with acute on chronic liver failure with 28 (53.8%) and 32 patients

(61.5%) respectively. These results are similar to those published previously from other studies and to those reported from a large multicenter ACLF study which included data from 10 centers in India and enrolled 1049 patients of ACLF with predominantly male patients (82% with etiology of CLD being alcohol consumption in 56.7 % cases (Shalimar *et al*, 2016) .GI Bleed was among the other major causes of acute precipitation of organ failures in 22 (42.4%) cases.

Renal and coagulation failure were among the most common organ failure each occurring in 29 (55.7%) of cases. The circulation and respiratory failures were among the least common causes of organ failure occurring in 30.8% and 32.7% cases respectively. These findings were largely similar those observed in CANONIC study (Moreau *et al*, 2013).17 (32.6%) patients were with two organ failure followed by three organ failures in 11 (21.1%) patients. 9 patients had one organ failure and none of the patient had all 6 organ failures. Four and five organ failures were present in 7 and 8 patients respectively. We analyzed our data with respect to both organ failures and ACLF grade. As per CANONIC study, patients were divided in various ACLF grades according to organ failures and we had 9 (17.3%) patients with ACLF grade 1, 17 (32.7%) patients with grade 2 and 26 (50%) patients with grade 3. Patients with ACLF grade 3 had more significant derangements in renal, liver and coagulation parameters than patients with grade 1 ACLF.

The mean hospital stay declined gradually with the addition of organ failures with 15.7 ± 10.1 days in patients with one organ failures as compared to 4.2 ± 2.1 days in patients with 5 organ failures. 16 (43.2%) out of 37 patients with organ failure 1-3 were discharged from the hospital under stable condition. On the contrary none of the 15 patients with 4 and 5 organ failures survived and had 100 % mortality during hospital stay. These findings further highlight the potential role of extrahepatic organ failures in ACLF patients. Our finding got further strength by the similar outcome with increasing organ failures as evaluated by other study (Aggarwal *et al*, 2015).In addition we had the survival outcome at 90 days w.r.t. organ failures and ACLF grades. Only 7 (13.5%) patients had survival at 90 days. 3 (5.7%) patients could not be traced despite best efforts. On further analysis as per ACLF grades, the 90 days survival was least for ACLF grade 3 (1/26; 3.8%) as compared to (3/17; 17.6%) and (3/9; 33.3%) for ACLF grade 2 and1 respectively.

We had certain limitations with this study. First, the sample size was small with unequal number of patients with different organ failure and ACLF grades. Secondly, we did not calculate the validated scores for outcome like SOFA, APACHE and MELD score which might have put more highlight on the association of organ failures and outcome. Thirdly, the values of variables defining the various organ failures were taken at time of admission only and no serial data was analyzed which might have contributed in a more accurate outcome.

To conclude we hereby stress that mere derangement of liver functions in patients with chronic liver disease with acute decompensation may represent as tip of an iceburg like situation. The patients should be evaluated for the precipitating events and presence of other organ failures. The involvement of other organ failures decides the final outcome and in current

scenario, its role can't be underestimated in patients with ACLF.

Main Points

1. ACLF is an entity with multiple organ failures
2. Numbers of organ failures determine the outcome.
3. More the number of organ failures, higher is the mortality.
4. Renal and Coagulation failure predominates over other organ failure.
5. ACLF carries a high 3 month mortality rate.

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