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A study of clinical profile in patients with acute on chronic liver failure in a teritary hospital

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ABSTRACT

Aim: To study the clinical profile, aetiology, precipitating insults of patients presenting with acute on chronic liver failure. To study the various predictors of mortality and outcome of acute chronic liver failure. **Materials and Methods:** This prospective observational study was conducted on 50 consecutive patients of acute on chronic liver failure for a period of 2 years. **Results:** ACLF has a predominant male preponderance with a male: female ratio of 5.25:1. The mean age of patients presenting with ACLF was 40.88 ± 1.1 yrs. Most common cause of underlying liver disease is alcoholic liver disease (76 %) followed by hepatitis B (6 %). Among the alcoholic liver disease super added alcoholic hepatitis is the most common (36.8%) cause followed by acute hepatitis E (18.4%). Among patients with chronic hepatitis B, reactivation of hepatitis B is the most common cause. The cause for acute deterioration could not be found in about 13.2% of patients. Higher mean Blood urea, Creatinine, prothrombin time, INR and CRP was significantly higher in the patients who died compared to patients who survived (P<0.05.). SOFA score is a better predictor of mortality than MELD and CTP score. SOFA score of 7.5 has a sensitivity of 81.5% and specificity of 91.3 % in predicting mortality. MELD score of 36 has a sensitivity of 25.9% and specificity of 100 % in predicting mortality. CTP score of 11.5 has a sensitivity of 81.5% and specificity of 87 % in detecting mortality. Most common cause of death is the multi organ failure. Increasing number of organ failures is associated with increasing risk of death. **Conclusion:** ACLF is characterized by rapidly deteriorating course in a previously diagnosed or undiagnosed chronic liver disease with a potential for reversibility. It has generally been shown that MELD and SOFA scores are better predictors of mortality than Child score and APACHE score

Key words: Chronic liver failure, Sequential organ failure, Maddrey's Discriminant function.

Introduction

Acute on chronic liver failure (ACLF) is an acute deterioration of a chronic liver disease distinct from acute liver failure and decompensated chronic liver disease[1].Asia Pacific Association for the Study of the Liver (APASL) defined it as "acute hepatic insult manifesting as jaundice (defined as serum bilirubin level ≥5 mg/dL) and coagulopathy (defined as international normalized ratio ≥1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease [2].ACLF occurs in about 30% of patients with an acute decompensation of cirrhosis[3]. and it has a significantly higher short-term mortality of 30-50% than expected with decompensated liver cirrhosis[3-5].Multiple organ failure and an increased mortality risk are key to the diagnosis of ACLF. The occurrence of organ failure(s) in patients with cirrhosis indicates a dismal prognosis. It is usually associated with a precipitating event which can be reversed if diagnosed early, although the underlying cirrhosis is irreversible. ACLF constitutes about 30-35% of all admissions and about 50% of all liver failures admitted in dedicated liver units in tertiary care setup[3-5]The causes of acute insult in ACLF are variable and depend mainly on the geographical area and the population under study, and they can be both infectious and non

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infectious. In some patients with ACLF, there may be simultaneous presence of more than one acute insult. Data on ACLF is scarce, heterogeneous, and mostly retrospective. The present study was chosen to look into the various etiologies of acute precipitating events, the underlying chronic liver disease, the clinical and biochemical spectrum and also the factors predicting mortality in ACLF patients of this region. Lack of a unifying definition causes difficulty in comparison studies. This study was taken up in a government run tertiary care centre with adequate facilities for necessary investigations and treatment of ACLF patients. Management consists of general supportive measures, treatment of underlying infection if present and treatment of underlying etiology of chronic and acute liver disease if possible. Currently ACLF patients do not have a priority in liver transplant listing and often these patients are considered too sick for the surgery.

Materials and Methods

This prospective observational study was conducted in Department of Medical Gastroenterology, Osmania Medical College and General Hospital, Hyderabad. Consecutive patients of acute on chronic liver failure were enrolled in this study. The study period was from November 2013 to December 2015.

Inclusion criteria: Consecutive patients with ACLF as defined by APASL were included. These patients may have either previously diagnosed or undiagnosed compensated cirrhosis. The diagnosis of cirrhosis of liver was based on previous liver biopsy findings if available or based on clinical, imaging (heterogenous echotexture of liver with irregular outline, altered liver size, or portosystemic collaterals), laboratory (low serum albumin, aspartate aminotransferase/alanine aminotransferase ratio > 1) and endoscopic findings (oesophageal varices > 5mm).

Exclusion criteria: Age less than 18 years or more than 80 years, Hepatocellular carcinoma, Portal vein thrombosis, Patients with any disseminated malignancy, HIV/ AIDS, Pregnant women, Previously decompensated cirrhosis and Acute liver failure.

Assessment of severity and organ dysfunction: Severity assessment scores -Child –Turcotte-Pugh (Table 2), MELD and modified SOFA score were calculated for all patients (Table 3). MELD score is calculated as follows -logarithmic equation (0.957 × log [creatinine mg/dl]+0.378 × log [bilirubin mg/dl] + 1.120 × log [international normalized ratio] +0.643). Presence or absence of Systemic Inflammatory response syndrome (SIRS) was noted. Maddrey's Discriminant function (MDF) was calculated in patients who had alcoholic liver disease as follows: [4.6×(patient's prothrombin time - control prothrombin time, in seconds)] + serum bilirubin level, in milligrams per deciliter. These scores were calculated at baseline and also repeated at weekly intervals. Organ failure was defined by the presence of SOFA score of 3 or more for the respective organ system. Presence of two or more extra hepatic organ failure is defined as multiorgan failure. Systemic Inflammatory response syndrome (SIRS): Evidence of a systemic response to infection defined by the presence of two or more of the following signs namely Fever (temperature >38.3^0 C) or hypothermia (rectal temperature <35.6^0 C). Tachycardia (heart rate >90 beats/min). Tachypnea (respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg) or need for invasive mechanical ventilation. Alteration of the white cell count > 12,000 cells/mm^3,<4,000 cells/mm^3 or >10% immature neutrophils (bands)

Table 1: Severity assessment scores -Child –Turcotte-Pugh

Criteria	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate	Large or refractory to diuretics
Bilirubin (mg/dl)	<2	2-3	>3
Albumin	>3.5	2.8-3.5	<2.8
Prothrombin time (Seconds prolonged)	<4	4-6	>6
Class A 5-6 points, Class B 7-9 points, Class C 10-15 points			

Table 2: Shows SOFA Score (Sequential organ failure)

SOFA	0	1	2	3	4
RESPIRATION					
PaO_2/FIO_2(mm Hg)	>400	≤400	≤300	≤200	≤100
pulse oximeter oxygen saturation (SpO2) *	SpO2 >90% at room air	SpO2 ≤90% at room air, increased above 90% with FiO2 0.24 (1 L/min nasal O2)	SpO2 ≤90% at room air, increased above 90% with FiO2 0.30 (mask	SpO2 ≤90% at room air, increased above 90% with FiO2 0.50 (mask)	SpO2 ≤90% at room air and despite FiO2 0.50 (mask)
COAGULATION					
Platelets $\times 10^3/mm^3$	>150	≤150	≤100	≤50	≤20
LIVER					
Bilirubin(mg /dl)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
CARDIOVASCULAR					
Hypotension	No hypotension	MAP <70 mm Hg	Dopamine ≤ 5 or dobutamine (any dose)	Dopamine >5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
CENTRAL NERVOUS SYSTEM					
Glasgow Coma Score	15	13–14	10–12	6–9	<6
RENAL					
Creatinine mg/dL (μmol/ L) or	<1.2 (<110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) or <500 mL/day	>5.0 (>440) or <200

Respiratory failure is defined by a SOFA score ≥3 or requirement for mechanical ventilation; hematologic failure by a score of 4 and/or INR >2.5; liver failure by a score of 4; cardiovascular failure by a score ≥2;neurologic failure by a West Haven score ≥3 or requirement for endotracheal intubation to prevent aspiration
pneumonia; renal failure by a score ≥2 or requirement for renal-replacement therapy.

Results:
A total of 50 cases are enrolled in study of acute on chronic liver failure

Table 3: Shows the distribution based on age and sex

Age group in yrs	Cases	
	No.	%
≤ 20 yrs	2	4
21 – 30 yrs	6	12
31- 40 yrs	17	34
41 – 50 yrs	18	36
51 – 60 yrs	6	12
≥ 61	1	2
Total	50	100
Mean ± SD	40.88 ± 1.1	
Sex		
Female	8	16
Male	42	84
Total	50	100

Table 3 shows that in the present study it was observed that the mean age in cases was 40.88 yrs. In the present study it was observed that 84 % of patients were male and 16% patients were females. The ratio between male: female was 5.25: 1.

Table 4: Shows clinical features in all patients

Clinical Features	Number	Percentage
Jaundice	50	100
Ascites	50	100
Mean duration of symptoms	23.2	10 – 30
Encephalopathy	30	60
Grade ≥ 2 encephalopathy	20	40
Upper GI bleeding	5	10
Large esophageal varices	16	32
Portal hypertensive gastropathy	17	34

Hepatomegaly	23	46
Spleenomegaly	32	64
Asterixis	12	24
Parotid enlargement	14	28
SIRS	28	56

Table 4 shows that acute onset of jaundice with ascites was seen in all the 50 patients. Most patients had severe jaundice with a median of 12.5 mg/dl (range between 5.9 – 36.9).

Table 5: Shows laboratory findings in all patients and features of sepsis

Laboratory findings	Median	Percentage
WBC	11400	5100 – 26400
HB (gm/dl)	10	5 – 13.2
Platelet count	110000	12500 – 200000
RBS (mg/dl)	101	40 – 176
Blood urea (mg/dl)	34	18 – 302
Creatinine (mg/dl)	1	0.6 – 4.8
Na+	134	114 – 148
K+	3.9	2.0 – 6.2
t. bilirubin (mg/dl)	12.5	5.9 – 36.9
AST (IU/L)	86.5	22 – 1501
ALT (IU/L)	124.5	26 – 1085
ALP	115	32 – 588
Total Protein (gm/dl)	5.8	4.5 – 7.8
Albumin (gm/dl)	2.5	1.8 – 3.5
PT (sec)	20	16 – 60
INR	1.8	1.6 – 6
CRP (mg/dl)	48	2 – 102
MDF	99.6	54.28 – 201.5
MELD	26.5	19 – 41
SOFA	7	3 – 14
CTP	11.5	9 – 15
Features of sepsis		
Elevated WBC	25	50
Fever	24	48
Elevated CRP	30	60
SIRS	28	56
Documented Sepsis	16	32

Sepsis was seen in 16 patients. Among the patients with documented sepsis 4 patients survived and 12 died. All

patients had elevated CRP except 2 (4%).Median values was 48 mg/dl (range 2 – 102).

Aetiology of chronic liver disease and reasons for acute exacerbation was evaluated. Most common cause of underlying liver disease is alcoholic liver disease (76 %) followed by hepatitis B (6 %) there were 5 patients (13.2%) in whom cause for acute deterioration could not be found. Among the alcoholic liver disease super added alcoholic hepatitis is the most common (36.8%) cause followed by acute hepatitis E (18.4%). Most patients were actively drinking alcohol almost till few days before admission. Among patients with chronic hepatitis B, reactivation of hepatitis B is the most common cause. There were two patients with autoimmune liver disease whose cause of deterioration was AIH flare. In one patient with Wilsons disease cause for acute deterioration was acute Hepatitis E.In one case of crytogenic the cause of deterioration was was drug induced, in two patients of Budd chiari syndrome cause of deterioration was hepatitis A infection in one patient and urinary tract infection in other, in two patients of HCV cause of deterioration was alcoholic hepatitis in one patient and Hepatitis E infection in other.

Table 6: Shows comparison of various laboratory parameters

Laboratory Parameters	Survivors		Dead		t value	p value
	Mean	SD	Mean	SD		
WBC	10247.8	3967.8	12322.2	5164.2	1.5	0.123
HB (gm/dl)	10.1	1.9	9.5	2	1.11	0.27
Platelet count	117934.8	36809.2	103666.7	28952.2	1.53	0.13
RBS (mg/dl)	104.6	17.6	109.6	30.1	0.69	0.49
Blood urea (mg/dl)	38.04	21.6	73.6	66.5	2.4	0.018
Creatinine (mg/dl)	1.05	0.85	1.75	1.2	2.3	0.02
Na+	133.3	7.6	132.5	8.9	0.35	0.73
K+	3.95	0.72	3.5	1.08	1.4	0.15
T. bilirubin (mg/dl)	12.7	6.3	15.8	7.9	1.5	0.13
AST (IU/L)	121.5	118.2	194.2	299.2	1.09	0.27
ALT (IU/L)	144.1	69.9	223.7	232	1.58	0.12
ALP	156.3	92	189.4	159.7	0.87	0.38
Total Protein (gm/dl)	6.01	0.7	5.8	0.7	0.7	0.4
Albumin (gm/dl)	2.5	0.48	2.5	0.37	0.4	0.68
PT (sec)	19.65	2	25.7	8.6	3.26	0.002
INR	1.7	0.11	2.5	0.95	4.02	<0.001
CRP (mg/dl)	32	16.2	76	21.9	7.9	<0.001
MDF	84.9	41.5	126.9	37	2.12	0.05
MELD	22.9	4.1	30.5	6.1	5.06	<0.001
SOFA	5.6	1.7	9.6	2	7.4	<0.001

Table 6 shows that in the present study it was observed that mean Blood urea, Creatinine, prothrombin time, INR and CRP was significantly higher in the patients who died compared to patients who survived. P<0.05.

In the present study it was observed that 3.7 % of patients who died had 3 organ failure 18.5 % of patients

who died had 2 organ failure compared to 4.3 % patients who survived. 77.8 % of patients who died had 1 organ failure compared to 95.7 % patients who survived. There was no statistical significant association between death and no. of organ failures.19 patients died within two weeks. So 14 day mortality was 28% another 8 patient died in the next two weeks So the expected 90 day mortality was 54 % (27/50). Of all the patients who died 26 patients had organ failure. The mean time from hospital admission to death was 12.5 days (4-37 days). The ability of various scoring systems like SOFA score, MELD and CTP score was assessed to predict mortality between survivors and non survivors using area under receiver operating curve. AUROC was significantly higher for SOFA and (.932) score compared to MELD (.857) CTP score (.858).MELD score of 36 has a sensitivity of 25.9% and specificity of 100 % in predicting mortality. SOFA score of 7.5 has a sensitivity of 81.5% and specificity of 91.3 % in predicting mortality. CTP score of 11.5 has a sensitivity of 81.5% and specificity of 87 % in detecting mortality. CRP levels of 76 has a sensitivity of 63% and specificity of 100 % in predicting mortality. PT value of 24.5 has a sensitivity of 55.6 % and specificity of 95.7 % in predicting mortality. INR value of 24.5 has a sensitivity of 63 % and specificity of 100 % in predicting mortality.

Discussion

This prospective observational study was done to look into the clinical profile, precipitating factors, prognostic factors and outcome in acute on chronic liver failure patients presenting to a tertiary care centre. ACLF is a unique entity with a rapidly deteriorating course but with a potential for reversibility if diagnosed and treated early. ACLF constitutes about 30-35% of all admissions and about 50% of all liver failures admitted to dedicate liver units in tertiary care centers. Multiple organ failure and an increased mortality risk are key to the diagnosis of ACLF. As defined by APASL guidelines all patients in this study had jaundice and coagulopathy. Investigations for etiology of underlying chronic liver disease and cause of acute deterioration were performed as required on an individual case based approach.

Age Distribution: In this study it was observed that the mean age with standard deviation in cases was 40.88 ± 1.1 yrs. Majority of patients in the study group were in the age group of 41 – 50 yrs (36%) followed by 31 – 40 yrs (34%), 21 – 30 yrs (12%), 51 – 60 yrs (12%). The median age of the patients was 36 (range 15 to 80) years in a large prospective study done by H.Garg et al in Delhi[6]. In a study done by Khatun UF et al[7] majority of the patients were between 45-54 years. Dhiman RK *et al* reported in their study that the mean age with standard deviation was 46 ± 13 years in ACLF patients[8].The median age was 53 years in a study reported by Deepak amarapurkar *et al.*

Sex Distribution:In the present study it was observed that 84 % of patients were male and 16% were female. The ratio between male: female was 5.25 : 1. Male patients consisted of 74%, 86%, 86%, 81.8% in studies by H Garg et al [6] Khatun UF et al [7],Dhiman RK et al [8],Deepak amarapurkar et al [9].respectively. The sex distribution of ACLF patients is similar to that of in cirrhotic patients presenting to our hospital.

Clinical Presentation: Jaundice was present in all 50(100%) cases and was severe in most patients with a median of 12.5 mg/dl (range 5.9 – 36.9) . H Garg et al[6] study showed a median bilirubin of 23.1mg/dl, Dhiman RK et al study showed a median bilirubin of 13.2 mg/dl and Deepak amarapurkar et al study showed a mean serum bilirubin of 11.3+/- 8.7 mg/dl. Ascites was seen in all 50 patients but grade 3 ascites according to the International Ascites Club Classification was seen in 10(20%) patients. Encephalopathy was seen in 30 (60%) patients in this study. Khatun UF et al showed that encephalopathy was present in all cases (100%) whereas encephalopathy was present in only 34% in a studies by H Garg et al and Dhiman RK et al. Out of 30 patients with hepatic encephalopathy in this study, 20 patients had grade 2 or grade 3 encephalopathy. Non survivors had higher grades of hepatic encephalopathy when compared to survivors. Acute hepatic encephalopathy was defined as acute change in metal status in the absence of other acute neurological disease, either as first episode or recurrence in a previously treated patient. Worsening of chronic hepatic encephalopathy was not considered as acute decompensation. The mean duration of symptoms in this study was 23.2 (10-30) days.Hepatomegaly was seen in 46% in the present study. In a study by H Garg *et al* hepatomegaly was seen in 53% patients . Splenomegaly was present in 64% patients in this study whereas in the study by H Garg et al splenomegaly was seen in only 12% . In this study astrexis was seen in 24% and parotid enlargement in 28% of the cases. Spider naevi were seen in only 3

patients and only 2 male patients had gynaecomastia. Large varices were seen in 16(32%), PHG in 17(34%) patients but only 5(10%) patients in this study developed upper gastrointestinal bleed after the symptom onset and it was mild to moderate which responded to medical and endoscopic management. Upper gastrointestinal tract bleeding was seen in 4.4% in a study by H Garg et al and 13.33% in a study by Khatun UF et al. There is a controversy regarding including gastrointestinal bleeding as an acute precipitant. No consensus has been reached about including gastrointestinal bleeding as an acute event by the APASL consensus committee[2].. Based on this study an observation, bleeding was probably due to coagulopathy and stress and may not be a trigger for acute deterioration.

Chronic Liver Disease: Two thirds of the patients had a previous history of chronic liver disease whereas about a third of patients had no previous history of chronic liver disease. The most common cause of chronic liver disease in this study was alcoholic liver disease (76%). Most western studies have shown alcohol as the most common etiology followed by viral hepatitis. In a large prospective study by H Garg et al chronic hepatitis B (37%) followed by alcohol (34%) and cryptogenic cirrhosis were the common causes of underlying chronic liver disease. Duseja et al from Chandigarh found alcohol as the most common insult followed by viral hepatitis and autoimmune hepatitis[5]. Dhiman RK et al from chandigarh reported that alcoholic liver disease (68%) was the most common etiology of cirrhosis in ACLF. Khatun UF et al from bangladesh reported in their study that common causes of chronic liver diseases were hepatitis B (50%), hepatitis C (26.67%) and alcohol (16.67%). Deepak Amarapurkar et al showed in their study that alcohol as a primary etiology for cirrhosis was present in 25 (56.8 %) patients, followed by cryptogenic/NASH in 12 (27.2 %) patients. Most of the patients presenting with compensated and decompensated cirrhosis in our department are alcohol related and similar trend was seen in ACLF patients too.

Acute Precipitating Insult: Alcohol was the most common acute precipitant (36.8%) in underlying alcoholic liver disease in our study. Dhiman RK et al in their study showed active alcohol intake as the acute precipitating event in 40% of their cases . In a study by Deepak Amarapurkar et al 25% of the acute insults was due to alcohol. Alcohol as an acute insult was considered if the patient had his last drink within 28 days preceding the symptoms. After the direct hepatic injury, the immunologic injury starts to decline[10], so a period of 28 days was considered adequate for inclusion as the last drink. Active alcoholism was defined as alcohol consumption within the previous 3 months in a study by Dhiman RK et al.In alcoholic hepatitis, elevated interleukin (IL)-18 levels result in neutrophil accumulation in the liver with subsequent release of reactive oxygen species resulting in hepatocyte injury. Acute ethanol ingestion may also result in a suppressed T-cell response, decreased monocyte function, and increased levels of IL-1 and IL-6. Severity of alcoholic hepatitis was calculated by Maddrey discriminant function (MDF) as 4.6 x [patient's prothrombin time- control prothrombin time] + total bilirubin(mg/dl). They were managed by pentoxyfylline 400mg thrice daily in addition to other routine treatment.Hepatitis E virus accounted to 18.4% of acute insults in patients with underlying chronic alcoholic liver disease, whereas infection with pneumonia, SBP, UTI and cholangitis together accounted to 21.1%. Patients with alcoholic liver disease are more prone for infection and its complications. Mookerjee et al observed that these patients have defective neutrophil function and phagocytosis[11]. These neutrophils show increased oxidative burst depicting a functional failure. In all 3 patients with chronic hepatitis B, reactivation of hepatitis B was the cause of acute deterioration (100%). The diagnosis of hepatitis B virus (HBV) flare was based on the American Association for the Study of Liver Diseases (AASLD) practice guidelines. In a study by H Garg et al reactivation of hepatitis B was seen in 85% patients whereas in a study by Dhiman RK et al reactivation of hepatitis B was seen in only 4% . Our findings were similar to findings published in other studies they were started on antiviral Tenofovir 300mg once daily modified according to the renal function of the patient. Acute hepatitis E as a cause of deterioration was seen in 10(20%) patients. In a study from Acharya et al from Delhi published in 2007 HEV was positive in 50% of patients with acute deterioration[12].Most studies from Indian subcontinent have found acute hepatitis E in 40-60% of patients. However these studies cannot be directly compared as the diagnosis of ACLF has not been clearly defined. HAV was the acute precipitating event in 3(6%) patients in this study. Most studies from India did not show HAV as a precipitating event, this disperancy may be due to geographical and socioeconomic factors. Acute viral hepatitis was diagnosed based on compatible clinical presentation, liver function tests and a positive

serology for hepatitis E virus (IgM anti-HEV) or hepatitis A virus (IgM anti-HAV) by ELISA). In two patients with underlying chronic hepatitis C the reason for acute decompensation was alcohol in one and HEV in the other. Transaminases were elevated in both patients and HCV RNA levels were low. Both patients with HCV were genotype 3.

Sepsis: History of fever was present in 24(48%) and elevated WBC count was present in 25(50%) patients. The median white blood cell (WBC count) in the present study was 11400. In a study by H.Garg et al the median WBC count was 12.3 (range 3.1 to 40.8)×10^3 cells/mm^3. Even though these two features are suggestive of sepsis, it could be documented in only 32% of our patients. Due to the hyperdynamic circulation and complications of portal hypertension, the currently accepted clinical definition of SIRS and hence sepsis may not be entirely applicable to patients with cirrhosis or ACLF. Hence, a high index of suspicion is required for making a clinical diagnosis of sepsis in these patients. Two patients had drug induced liver injury and two patients had a flare of autoimmune hepatitis as their precipitating event. The diagnosis of autoimmune hepatitis (AIH) was based on the simplified criteria for AIN[13]..No definitive cause of acute deterioration could be found in 5(10%) patients. In a study by H Garg et al definitive cause of an acute insult was not found in15(16.48%) patients .In a study by KhatunUF et al from Bangladesh unknown acute events were 30%.

Laboratory Findings: The median hemoglobin was 10 gm/dl (range 5 – 13.2).The median platelets were 110000/cu mm (12500 – 900000). Median AST and ALT values were 86.5 and 124.5 IU/L .Median Total Protein was 5.8 gm/dl (4.5 – 7.8), albumin values were low 2.5 gm/dl (1.8- 3.5). INR was prolonged (median 1.8, range1.6- 6). INR was more than 2.5 in 9 patients (18%). Median MDF was 99.6 (54.28 – 201.5), MELD score was 26.5 (19 – 41), SOFA 7 (3 – 14) and CTP was 11.5 (9 – 15).

Organ Failure: Single organ failure was seen in 22 patients who survived and in 21 patients who died. Only one patient with 2 failed organ responded to treatment and survived, while 5 patients with two organ failures died. There was only one patient with 3 or more organ failures and he did not survive. Though there was a clinical significance between no of organs failed and mortality, a statistical significance couldn't be reached . In a large prospective study done by H Garget al from delhi.one-third patients had multi organ failure. The course of ACLF was found to be quite rapid and within one week of presentation, more than 10% patients died ofmulti organ failure. In a study by Deepak amarapurkar *et al* 50 patients (80.6 %) had at least 1 organ failure whereas 15 had ≥3 organ failures (mortality rate >75 %). One of the important features of ACLF is the development of organ failure. Presence of two or more extra hepatic organ failures is considered multi organ failure.

Mortality: Out of 50 patients in our study, 27(54%) died. Few patients were referred for transplantation but because of financial constraints, transplant was not feasible. This mortality rate is similar to mortality in other published studies. However it is lesser than the mortality seen in the study by H Garg et al. The mean time from hospital admission to death was 12.5 days (4-37). Nine (33.33%) patients died within first week and another 10 patients died (37.03%) in the second week. 19 of the 27 patients who died (70.37%) died within the initial two weeks. These findings show that initial two weeks is very critical in the management of these patients. ''Golden window'' is a short period of about 1 week before the onset of sepsis and development of extra-hepatic organ failure in a patient with ACLF. Early diagnosis and therapeutic interventions during this period are likely to prevent organ failure and provide a potential opportunity for reversing the hepatic injury. This importance of initial two weeks has been highlighted in other studies. In a large proportion of ACLF patients liver transplant is not feasible, due to the lack of an organ or a donor, severity of the illness, or other socio economic challenges. Garg et al[14] have shown that granulocyte colony- stimulating factor (G-CSF) can mobilize bone marrow-derived CD34 + cells which help in hepatic regeneration. In addition, it was shown to significantly reduce the development of sepsis and subsequent multi organ failure. A study from the East in patients with HBV-related ACLF has substantiated the role of G-CSF. However, despite the encouraging results presently routine use of these agents is not yet recommended.

Predictors of mortality: In the present study it was observed that mean blood urea, serum creatinine, prothrombin time, INR and CRP was significantly higher in the patients who died compared to patients who survived $p<0.05$. CRP levels of 76 has a sensitivity of 63% and specificity of 100 % in predicting mortality in this study.In the present study, PT value of 24.5 has a sensitivity of 55.6 % and specificity of 95.7 % in predicting mortality. INR value of 24.5 has a sensitivity of 63 % and specificity of 100 % in predicting mortality. The ability of various scoring systems like SOFA score, MELD and CTP score was assessed to predict

mortality between survivors and non survivors using area under receiver operating curve. AUROC was significantly higher for SOFA (.932) score compared to MELD (.857) and CTP score (.858). H.Garg et al showed that amongst all severity scores studied, MELD, SOFA and APACHE-II scores had AUROCs of >0.8 which was significantly higher than that of Child-Turcotte–Pugh score. In this study MELD score of 36 has a sensitivity of 25.9% and specificity of 100 % in predicting mortality. SOFA score of 7.5 has a sensitivity of 81.5% and specificity of 91.3 % in predicting mortality and CTP score of 11.5 has a sensitivity of 81.5% and specificity of 87 % in detecting mortality. There are no prospectively validated scoring systems for ACLF. For critically ill cirrhotic patients admitted to ICU with multi-organ failure, SOFA appears to be the best prognostic model (AUC 0.84).In ACLF-B patients, liver-specific models are described and perform reasonably well, namely MELD, modifications of MELD (AUC 0.7–0.84), and logistic regression models (AUC 0.844–0.891). In cirrhotics with acute decompensation, CLIF– SOFA score has been validated in Europe but it remains to be prospectively evaluated in patients with ACLF, where liver failure is the predominant presentation. It has generally been shown that MELD and SOFA scores are better predictors of mortality than Child score and APACHE score .

Conclusion

ACLF is characterized by rapidly deteriorating course in a previously diagnosed or undiagnosed chronic liver disease with a potential for reversibility It has generally been shown that MELD and SOFA scores are better predictors of mortality than Child score and APACHE score .

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