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Predictors of Acute-on-Chronic Liver Failure (ACLF) and Mortality in Ambulatory Cirrhotic Patients

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1. Abstract

1.1. Background

Acute-On-Chronic Liver Failure (ACLF) is life-threatening complication of cirrhosis. ACLF's prevalence and outcomes have been described in hospitalized patients with cirrhosis. However, no data is available on the prevalence and predictors of ACLF in ambulatory cirrhotic patients.

1.2. Aims

Assessment of the incidence and predictors of ACLF in cirrhotic ambulatory patients.

1.3. Methods

A retrospective study of 202 ambulatory patients with cirrhosis was evaluated in a tertiary hospital at the Galilee Medical Center from Feb. 2015 to Dec. 2022 and followed for eight years. Data on developing hepatic and extra hepatic organ failures were collected. ACLF was defined and graded according to the European Association for the Study of Liver-Chronic Liver Failure (EASL-CLIF) Consortium definition.

1.4. Results

Ambulatory with cirrhosis developed ACLF in 37% of cases (74 patients). The mortality rate was significantly high in the ACLF group as compared to the non-ACLF group (38% VS 8.5%, respectively P<0.001). Patients with ACLF were older, had increased CRP, NLR and WBC, increased LFTS and kidney function, MELD, Child-Pugh, CLIF-C and PADUA scores. Univariate regression showed that MELD score was the most powerful predictor of organ failure. Multivariate analysis showed that MELD and CLIF-C scores were associated with organ failure and developing ACLF (OR 4.5, P<0.001, OR 3.2, P<0.001, respectively). Discriminant analysis showed that BUN, MELD, CLIF-C and PADUA scores predicted mortality with 87% accuracy.

1.5. Conclusion

Outpatients with cirrhosis developed ACLF in 40% of cases. MELD and CLIF-C scores are the best ACLF development predictors. PADUA, CLIF-C and MELD scores are the best predictors of mortality. Therefore, we should use MELD, PADUA and CLIF-C scores to evaluate and follow up cirrhotic outpatients in liver units.

2. Keywords

Predictors;Cirrhosis;Acute on chronic liver failure; ACLF;Mortality; MELD; CLIF; CHILD-PUGH; PADUA

3. Introduction

The diagnosis of Organ Failures (OFs) is based on a modified Sequential Organ Failure Assessment (SOFA) score, called CLIF-C organ failure (CLIF-C OF), which considers the function of six organ systems (liver, kidney, brain, coagulation, circulation and respiration) [3-8]. ACLF severity has three grading stages: Stage 1 (ACLF 1): patients with single failure of the liver, coagulation, circulation, or respiration, hepatic encephalopathy; Stage 2 (ACLF2): patients with two organ failures; Stage 3 (ACLF3): patients with three or more organ failures. Bacterial infections, gastrointestinal bleeding, active alcoholism, surgery, and paracentesis are considered potential precipitating events of ACLF [3-6]. The causes of death in these patients are sepsis, bacterial/fungal infection, ACLF without a precipitating event, Hepatocellular Carcinoma (HCC) and refractory gastrointestinal bleeding [3-6].

Management of ACLF is etiology dependent. Patients with acute kidney injury are managed with fluid administration in case

of dehydration and those with hepatorenal syndrome are treated with vasoconstrictors and with albumin. Mechanical ventilation is used in patients with respiratory failure when indicated. Circulatory failure is managed with vasoactive drugs (noradrenaline, dopamine or terlipressin) and fluid administration. Hepatic encephalopathy is treated with lactulose and rifaximin. Precipitating events of ACLF, such as bacterial infections and gastrointestinal bleeding are managed according to the available recommendations [7]. Patients with spontaneous bacterial peritonitis receive antibiotics with albumin [3-8]. There is not enough data about ACLF development in outpatient cirrhotic patients. Studies assessing the occurrence of ACLF in the natural history of cirrhosis are lacking and neither incidence nor predictors of ACLF are known in outpatients. Such information may be helpful in identifying a target population such as outpatients with cirrhosis for planning preventive strategies.

The Aim of the study is to assess the incidence of ACLF in outpatient cirrhotic patients during a follow up of eight years (2015-2022) in the Galil Medical Center's (GMC) Liver Clinic and finding predictors of ACLF development in outpatients with cirrhosis.

4. Materials and Methods

4.1. Study Population

This is a retrospective study that included 204 patients with cirrhosis. The patients were referred to our liver clinic for evaluation, follow up and treatment as part of their routine clinical care. Electronic Medical Records (EMRs) were collected and analysis of all charts of eligible outpatients with cirrhosis who were retrospectively and consecutively followed in the liver clinic at GMC from February 2015 to December 2022 were done.

4.2. Eligibility Criteria

Inclusion criteria

a) Diagnosis of liver cirrhosis based on histological findings or on clinical, biochemical, ultra-sonographic, and/or endoscopic findings or FibroScan

b) Age between 18 and 80 years

c) The patient was referred to our liver clinic

Exclusion criteria

a) Hepatocellular carcinoma (HCC)

b) Ongoing bacterial infection

c) Chronic kidney disease (CKD) needing dialysis

d) Overt hepatic encephalopathy

e) Severe extrahepatic disease (i.e., congestive heart failure (New York Heart Association NYHA 2), chronic obstructive pulmonary disease)

f) Extrahepatic malignancy

g) Previous liver transplant

h) HIV infection

4.3. Study design

Demographic, clinical, and routine laboratory data were collected from the first contact visit in the liver clinic. Data on previous decompensation of cirrhosis were assessed from the patients' medical history like age, gender, and etiology of liver cirrhosis (HBV, HCV, alcohol and others). Decompensated events as previously described, were also recorded [9]. Acute decompensation was defined as the presence of varices, ascites, and hepatic encephalopathy, GI bleeding, Spontaneous Bacterial Peritonitis (SBP) and Acute Kidney Injury (AKI). Mean arterial pressure (mmHg), heart rate (bpm), BMI (kg/m2), history of diabetes mellitus type 2 was also collected. Scores of hepatic disease severity were calculated using MELD, CLIFC-c acute decompensation, Child Pugh and Padua scores [10-16]. Laboratory parameters were also recorded. These include INR, bilirubin (mg/dL), albumin (g/dl), serum creatinine, serum sodium (mmol/L), hemoglobin (g/dl), PT, PTT, white blood cell count, platelets, CRP, D-dimers, PAI-1, fibrinogen, ammonia, ALT, AST, gamma GGT, alkaline phosphate, PH, LDH, Neutrophil to Lymphocyte Ratio (NLR) [17], organ failure (kidney, liver coagulation, brain, respiratory and circulation). Precipitating events like bacterial infection, Gastrointestinal Bleeding (GIB), active alcoholism and others were recorded as well.

Briefly, all patients with compensated liver cirrhosis were examined at least every six months while those with decompensated cirrhosis were examined at least every three months with clinical and laboratory examinations. Alcohol consumption was assessed by a questionnaire [18]. All the charts of emergent admissions to the hospital were carefully reviewed and clinical and laboratory data were recorded.

The definition of ACLF, proposed by the European Association for the Study of the Liver Chronic Liver Failure (EASL-CLIF) Consortium, is based on the results of the CANONIC Study, a multi-center prospective investigation as described above [3-8].

4.4. Study endpoints

The primary endpoint of the study was to assess the incidence of ACLF in outpatients with cirrhosis. Predictors of ACLF during the 8-year follow-up were also evaluated. The secondary endpoints included: a) survival in patients with/without ACLF; b) predictors of survival in outpatients with cirrhosis.

4.5. Ethics

This study was approved by our medical center's local ethics committee (0194-22-NHR). Retrospective analysis of the data from our electronic medical record database was performed under the oversight of the ICH guidelines for good clinical practice.

4.6. Statistical analysis

Normally distributed continuous variables are reported as means with standard deviation and were compared with Student's T tests. Non-normally distributed continuous variables are reported as median, interquartile range and compared using a Mann-Whitney U test. The Wilcoxon rank sum test was used to compare changes in hemoglobin levels during follow-up. Categorical variables are reported as proportions and compared using the chi square test with continuity correction and/or Fisher's exact test when appropriate. The incidence of ACLF was estimated by the Kaplan-Meier method and comparisons between groups were made with the log-rank test. Patients who died or who received a transplant before developing ACLF were censored at time of death or transplantation. Survival curves were estimated using the Kaplan-Meier method. Patients transplanted during follow-up were censored at the time of transplantation. Variables found to have a p value of less than 0.05 in the univariate analysis were included in a multivariate Cox proportional hazards model, with backward elimination. The Hazard Ratios (HR) and their 95% Confidence Intervals (CI) were calculated. Non-normally distributed continuous variables were log-transformed to be included in the multivariate models. The sample size was estimated on the number of ACLF episodes at 12 months.

5. Results

5.1.Clinical and labarotory characteristics of the patients with and without acute-on chronic liver faliure

The data of 202 patients who fit the inclusion criteria were analyzed. Of these patients, 74 patients (37%) suffered from acute on chronic liver failure, and 128 patients (60%) were not. About 38% of the ACLF group died, while just 8.5% of the non-ACLF group died (Table 1).

Patients with ACLF were older than the non-ACLF group (68.5±5 *vs* 62.7±11.1, p<0.05) (Table 1). Both groups had the same BMI and same number of type 2 diabetes mellitus patients. The main artery pressure was lower in the ACLF group (81.5±12.6 *vs.* 88±13.2, p<0.05) (Table 1). Cirrhosis was more severe in the ACLF group as seen by the MELD score (18.5±7.9 *vs.* 11.3±5.1, p<0.001), the Child-Pugh score (8.6±1.9 *vs.* 7.6±1.8, p<0.001), CLIF-C score (44.8±8.9 *vs.*

Table 1: Clinical Characteristics of the ACLF and non-ACLF groups in ambulatory patients with no cirrhotic livers. NS: non-significant (P value<0.05).

VARIABLE	ACLF	NON-ACLF	P-VALUE
Total	N=74	N=128 Compensated (4%)	
Age	68.5±5	62.7±11.1	0.0001
Male (% of total)	52%	60%	0.45
Etiology of Cirrhosis	Alcohol:15% NASH: 55% HBV: 10% HCV:8% WILSON: 0.5% Autoimmune: 1.5% Cryptogenic 4.5% Cardiac 4% Biliary 1.5%	Alcohol:16% NASH: 56% HBV: 8% HCV:7% WILSON: 0.7% Autoimmune: 2% Cryptogenic: 1% Cardiac: 5% Biliary: 4%	>0.05
MAP (mmHg)	81.5±12.6	88 ±13.2	0.0008
BMI	29.6±6.9	28±4.7	0.1
Diabetes	67%	62%	0.5
Precipitating events: Alcohol Infection GI bleeding Idiopathic	 8% 47% 35% 10%	 22% 40% 36.50% 2%	>0.05
Decompensation: Ascites: GI bleeding: Encephalopathy: Sepsis:	 30% 25% 42% 2%	 8% 35% 56% 1%	<0.05
MELD score	18.5±7.9	11.3±5.1	0
Child-Pugh score	8.6±1.9	7.6±1.8	0
CLIF-C score	44.8±8.9	38±7.5	0
PADUA score	3.0±2.3	1.7±1.5	0.0003
Laboratory parameters			
INR	1.6±0.7	1.4±0.4	0.001
Bilirubin (mg/dl)	2.6±4.2	1.7±1.5	0.002
Albumin (g/dl)	2.9±0.6	3.1±0.7	0.002
Creatinine (mg/dl)	2.0±1.3	0.8±0.7	0.0001
Sodium (mmol/l)	136±5.5	137±12.0	0.82
Hemoglobin (g/dl)	9.8±2	9.7±2.6	0.04
WBC (x103/µl)	6.9±4.1	6.1±2.9	0.03
Platelet (x103/µl)	141±87	136±86	0.9
C-reactive protein (CRP) (mg/dl)	60±62	44±34	0.0001
Fibrinogen (g/dl)	402±192	399±1.39	0.58
Ammonia (micromol/L)	77±49	84±47	0.7
ALT (U/L)	147±55	34±30	0.1
AST (U/L)	340±111	96±92	0.08
GGT (U/L)	266±205	296±196	0.4
LDH (U/L)	831±490	222±110	0.04
NLR	5.7±4.3	5.1±3.8	0.004
Mortality (% of total)	38	8.5	0.00001

38±7.5, p<0.001), and the VTE predicating score, the PADUA score (3.0±2.3 *vs.* 1.7±1.5, p<0.001) (Table 1). Liver function was reduced in the ACLF group: INR was higher in the ACLF group (1.6±0.7 *vs* 1.4±0.4, p<0.05), total bilirubin also was higher in the ACLF group (2.6±4.2 *vs.* 1.7±1.5, p<0.05), and albumin was lower (2.9±0.6 *vs* 3.1±0.7, p<0.05) (Table 1). Although the liver enzymes were high in the ACLF group, there was no significant differences between liver enzymes (AST, ALT, GGT and fibrinogen) in the ACLF and non-ACLF groups (Table 1). LDH was higher in the ACLF group (831±490 *vs* 222±110, p<0.05). Kidney function was disturbed more in the ACLF group with the creatinine being higher in the ACLF group (2.0±1.3 *vs.* 0.8±0.7, p<0.05) (Table 1). Inflammatory markers like CRP, NLR and WBC were also significantly high in the ACLF group (60±62 *vs* 44±34 (p<0.01), 5.7±4.3 *vs.* 5.1±3.8 (p<0.05) and 6.9±4.1 *vs* 6.1±2.9 (p<0.05), respectively). No significant changes in the platelet count and ammonia levels were seen (Table 1).

5.2. Association between liver failure scores, demographic parameters and inflammatory markers, and ACLF development

In addition to gender and age, liver failure scores and inflammatory markers were studied for their correlation to organ failure and ACLF

development in the cirrhotic patient groups. The results show that the MELD (MELD>18) score was the best predictor of organ failure in a univariate regression (Table 2A). Multivariate analysis showed that both MELD score and CLIF-C ACLF were associated with organ failure (Table 2B).

Table 2: Association between liver failure scores, inflammatory markers and organ failure. A: Univariate analysis of the risk factor strength with organ failure. B: Multivariate analysis of the risk factor strength. SE are the standard errors of the regression coefficients. T is the quotient of the coefficient. P value is the two-sided p values or observed significance levels.

(A)					
Coefficient	**95% Conf. (±)**	**Std. Error**	**T**	**P-value**	
Constant					
0.85	0.179	0.0042	0.008	0.0007	Age
0.66	0.43	0.071	0.14	0.03	Gender
MELD score	0.0007	3.45	0.006	0.012	0.02
CHILD PUGH score	0.4	0.83	0.022	0.044	0.01
CLIF-C ACLF	0.14	1.48	0.0062	0.012	0.009
PADUA	0.32	0.99	0.02	0.0397	0.02
CRP	0.47	0.7	0.0008	0.0016	0.0005
Fibrinogen	0.327	0.94	0.00027	0.0005	0.0002
NLR	0.259	1.15	0.01	0.02	-0.011

(B)					
P-value	**T**	**Std. Error**	**95% Conf. (±)**	**Coefficient**	
Constant					
0.001	4.58	0.005	0.01	0.024	MELD score
0.001	3.21	0.0042	0.009	0.013	CLIF-C ACLF

5.3. The correlation between the MELD score, and CLIF-C score or Child-Pugh scores with the development of ACLF

Severity of liver failure scores were used to predict mortality. We wanted to assess the ability of these scores to predict development of acute or chronic liver failure. The MELD score, especially above 18, significantly correlated with development of ACLF (Figure 1A&B) more than both CLIF-C and Child-Pugh scores (Figure 1A&B).

5.4. Association between liver failure scores, inflammatory markers and mortality in patients with liver disease

In addition to gender and age, liver failure scores and inflammatory markers were studied for their correlation to mortality. The results show that the MELD and PADUA scores significantly predict mortality in the liver patients suffering from cirrhosis (Table 3A). Furthermore, multivariate analysis showed that both MELD and PADUA scores were significantly and independently associated with mortality (Table 3B).

5.5. Patient severity in the ACLF group

Patients in the ACLF group had different liver failure severity. The CLIF-C score had a high accuracy in predicting 28-day mortality, particularly when it was calculated at 48 hours after ACLF diagnosis. CLIF-C scores were higher in the non-ACLF group as seen in figure 1. The ACLF-C score up to 45 was more frequent in the non-ACLF group, but above 45, the ACLF group was more frequent (Figure 2A). The majority of the patients who suffered from ACLF were with low CLIF-C scores (<45), and few of them had higher scores (>60) (Figure 2B). This group showed a high prevlance of mortality. In the surviving patients, the majority had sepsis followed by acute Gastrointestinal Bleeding (GIB) then idopathic and finally acute kidney injuries.

5.6. Inflammation marker levels in ACLF and in non-ACLF patients

The liver failures severity mediated changes in inflammatory marker levels. CRP and NLR were highly elevated in ACLF, but only moderately elevated in decompsation liver failure without ACLF

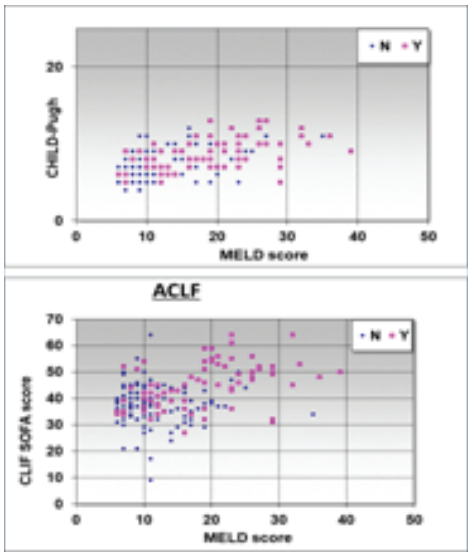

Figure 1: Correlations between the MELD score and CLIF-C or Child Pugh scores with ACLF development.

Table 3: Association between liver failure scores, inflammatory markers and mortality. A: Univariate analysis of the risk factors' strength with mortality. B: Multivariate analysis of the risk factors' strength with mortality. SE are the standard errors of the regression coefficients. T is the quotient of the coefficient. P-values are two-sided p values or observed significance levels.

(A)					
P-value	**T**	**Std. Error**	**95% Conf. (±)**	**Coefficient**	
Constant					
Age	0.003	0.006	0.003	0.97	0.3
Gender	0.005	0.108	0.054	0.08	0.9
MELD score	0.028	0.009	0.0049	4.78	0.001
CHILD PUGH score	0.026	0.03	0.017	1.5	0.12
CLIF-C ACLF	0.004	0.009	0.004	0.895	0.3
PADUA	0.036	0.03	0.0167	2.3	0.01
CRP	0.0009	0.001	0.00064	1.5	0.11
NLR	0.006	0.015	0.0078	0.77	0.44

(B)					
P-value	**T**	**Std. Error**	**95% Conf (±)**	**Coefficient**	
Constant					
0.0001	6.39	0.003	0.007	0.025	MELD score
0.0001	3.82	0.014	0.027	0.053	PADUA

(Figure 3 A,B). The CRP level is correlated with the patient severity. Patients with high CLIF-C scores had high CRP levels, and low CLIF-C scores has low CRP levels (Figure 3C).

5.7. Discriminant analysis with diagnostic accuracy of the correlations between clinical parameters and survival

The PADUA score, creatinine levels and MAP were able to discriminate between dead and alive patients with an 82% diagnostic accuracy. There is a good correlation between the PADUA score, creatinine and MAP, and disease severity and mortality in the cirrhotic patients. The sensitivity, specificity, positive predictive value and negative predictive value are 97%, 55%, 97% and 63%, respectively (Table 4). In addition, PADUA, MELD, CLIF-C scores and BUN, highly predict mortality (87%) in all cirrhotic patients. The sensitivity, specificity, positive predictive value and negative predictive value are 95%, 63%, 88% and 83%, respectively (Table 5).

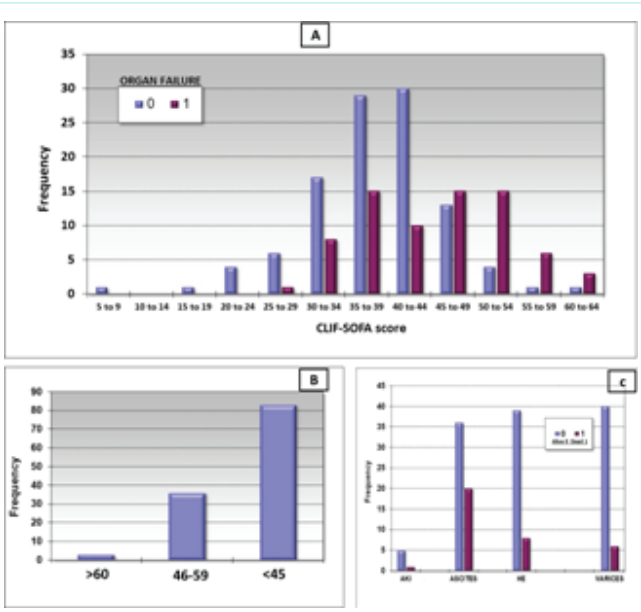

Figure 2: CLIF-C score degrees in ACLF and non-ACLF scores (A), with score frequencies in the ACLF group (B). C: The frequency of decompensation type in surviving and non-surviving cirrhotic patients.

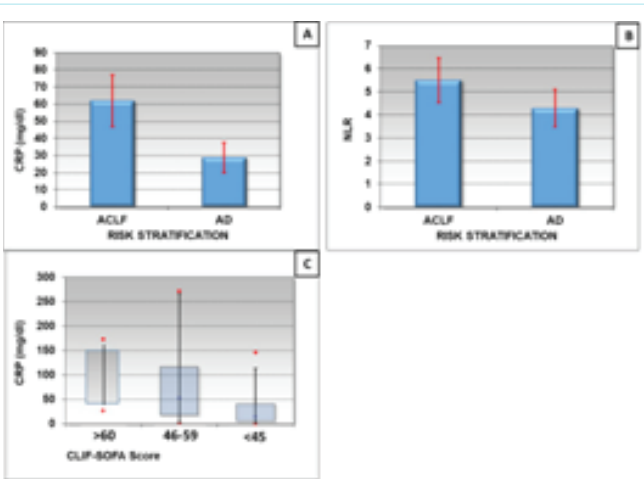

Figure 3: Inflammation marker levels in ACLF and in decompensation liver failure patients without ACLF. A: CRP level in ACLF and non-ACLF patients. B: NLR levels in ACLF and non ACLF patients. C: CRP levels in different CLIF-C score degrees.

6. Discussion

The results of this study indicate that the prevalence of ACLF in ambulatory cirrhotic patients is around 40% in our eight-year follow up. Moreover, the results of this study indicate that MELD and CLIF-C scores are the most powerful predictors of ACLF development. Finally, this study shows the PADUA score, creatinine and MAP predicts mortality with 85% accuracy.

There is a need to identify predictors of acute-on-chronic liver failure in outpatients with cirrhosis to identify patients at high risk of developing ACLF and to plan prevention strategies for these ambulatory patients. Although some studies have developed prediction scores for ACLF mortality, including the recent Chronic Liver Failure Consortium (CLIF-C) ACLF score, no scores were developed using large cohorts, reflective of diverse liver disease etiologies and none were developed to predict ACLF in ambulatory patients [19]. Piano et al. evaluated possible predictors and used an outpatient cohort of 406 patients, of whom 61 developed ACLF (15%) within 12 months. Significant predictors included age, mean arterial blood pressure, MELD and anemia. Despite an excellent C-statistic, this model has limited generalizability as two-thirds of the cohort had decompensated cirrhosis and the ACLF incidence rate was an order of magnitude higher than that of a general population-based cohort [20]. Nadim et al. obtained models for developing ACLF, as well as for ACLF short-term mortality in a diverse United States cohort. They performed a retrospective cohort study of 74,790 patients with incident cirrhosis. ACLF events were identified per the European ACLF criteria. Mortality models were compared to MELD, MELD-sodium, and the CLIF-C ACLF score [21]. these may be used to identify outpatients at significant risk of ACLF, which may prompt closer follow-up or early transplant referral, and facilitate decision making for patients with diagnosed ACLF, including escalation of care, expedited transplant evaluation or palliation.

In this study, we identified variables which may help in identifying outpatients with cirrhosis who are at a high risk of developing ACLF and might be candidates for new surveillance and prevention strategies. Our study shows that the MELD score was significantly the most single powerful predictor of organ failure and ACLF development in stable ambulatory cirrhotic patients (Table 2A). Multivariate analysis showed that both MELD score and CLIF-C ACLF were associated with organ failure and ACLF development (Table 2B). Furthermore, MELD score, especially >18, significantly correlated with development of ACLF (as seen in Figure 2A&B) more than the ACLF-C and Child-Pugh scores.

ACLF and non-ACLF patient severity were different. The ACLF group has more severe disease as seen by the MELD, CHILD-Pugh, CLIF-C and PADUA scores. The ACLF group suffered from low blood pressure and they were older than the non-ACLF group. The mortality rate was significantly higher in the ACLF group. About 38% of the ACLF group died compared to 8.5% in the non-ACLF group (Table 1).

Table 4: The validity (predictive power) of age, CRP, CRE and PADUA scores on patient mortality. The accuracy of the calculations is 82%. (A): The number of samples: Predicted condition — 129 survivals; 35 deaths; and true condition, 0 for disease and 1 for no disease. (B): The sensitivity, specificity, positive predictive value and negative predictive value are shown.

(A)		
Actual count		
	0	1
132	114	18
35	12	23

(B)	
Specificity	55%
Sensitivity	97%
Positive predictive value	93%
Negative predictive value	63%

Table 5: The validity (predictive power) of BUN, MELD score, CLIF-C and PADUA score on mortality in cirrhotic patients. The accuracy of the calculations is 87%. (A): The number of samples: Predicted condition — 96 survivals; 24 deaths; and true condition, 0 for disease and 1 for no disease. (B): The sensitivity, specificity, positive predictive value and negative predictive value are shown.

(A)		
Actual count		
	0	1
96	84	12
24	4	20

(B)	
Specificity	63%
Sensitivity	95%
Positive predictive value	88%
Negative predictive value	83%

Our study confirms that the MELD score (particularly above 18) is the most powerful predictor of ACLF development in acute decompensation (the non-ACLF outpatient group). The Model for End-Stage Liver Disease (MELD) consists of serum bilirubin and creatinine levels, International Normalized Ratio (INR) for prothrombin time, and etiology of liver disease. The model's validity was tested in four independent datasets, including patients hospitalized for hepatic decompensation, ambulatory patients with non-cholestatic cirrhosis, patients with primary biliary cirrhosis and unselected patients from the 1980s with cirrhosis [10-12]. In these patients, the MELD scale performed well in predicting death within three months.The MELD score is a reliable measure of mortality risk in patients with end-stage liver disease and is suitable for use as a disease severity index to determine organ allocation priorities [10-12].

The MELD score and ACLF interact in predicting the cumulative risk of the 90-day waiting list mortality with a higher impact of ACLF grade at lower MELD scores [22].The CLIF-C ACLF is a clinically relevant validated scoring system that is used sequentially to stratify the risk of mortality in ACLF patients [23]. However, some studies show that CLIF scores are not good predictors of mortality in cirrhotic patients [24-26]. The predictive ability of CLIF-C ACLFs is relatively low in predicting short- and long-term mortality in ACLF patients with a concomitant need for ICU treatment [24-26]. However, the MELD score is the most predictive score [27]. Our results confirm the ability of both scores in predicting ACLF development in these patients.

Our results also show that the MELD and PADUA scores significantly predict mortality in outpatients who suffered from cirrhosis (Table 3). High PADUA scores correlate with a high prevalence of mortality. The purpose of the Padua score is to risk-stratify patients admitted to an internal medicine ward to either high or low risk of Venous Thromboembolism (VTE), and the to assess whether prophylaxis in high-risk patients reduced the number of VTE events [28]. The parameters in this score are known active cancer, previous VTEs, reduced mobility, known thrombophilia conditions, recent trauma or surgery, age above 70 years, heart or respiratory failure, acute MI, infection and obesity [28]. VTE is a leading cause of preventable death in hospitalized patients. Many studies show that the PADUA score has shown significant ability to predict early intra-hospital mortality in a population of septic patients admitted to an internal medicine department [29-31]. An Italian study has shown in a population of internal medicine patients that the PADUA score is associated with early mortality [29]. VTE in cirrhosis is a growing clinical problem, demonstrating once again that patients with liver cirrhosis are not naturally protected from thrombotic events. The low platelet count and elevated INR levels in patients with liver failure do not reduce the risk of developing deep vein thrombosis or pulmonary embolism [32-34]. However, there are significant concerns about using anticoagulants prophylactically in patients with cirrhosis for fear of facilitating bleeding events [33]. The availability of a tool able to predict in-hospital mortality of internal medicine and cirrhotic patients would allow physicians to allocate resources more accurately and appropriately.

Liver enzymes and kidney function were significantly more elevated in the ACLF group. Acute clinical deterioration of a patient with cirrhosis is the important turning point in the management of these patients, since it is frequently associated with rapidly evolving multiorgan dysfunction, significant morbidity, and high short-term mortality. As seen in our results, liver enzymes and kidney function were elevated in the ACLF group. Most of them deteriorated to severe conditions and some of them died. These parameters correlated to the liver function deterioration which affected the kidney function by the hepato-renal mechanisms. Survival is correlated with low age, normal serum sodium levels, low serum creatinine levels, normal white blood cell count and normal international normalized ratio [37]. In the ACLF group, high levels of liver enzymes and creatinine were recorded, and this could explain the high mortality rate in this group.

Inflammatory markers in the ACLF group are important patient severity markers, as seen in our results. Inflammatory markers like CRP, NLR and WBC were significantly higher in the ACLF group and predict mortality in 75% of patients. These markers indicated that patients are prone to develop ACLF. The CANONIC study exposed several premises with regard to the pathophysiology of ACLF and in particular, a pivotal role for dysregulated inflammation [35]. More specifically, the degree of inflammatory response, as estimated by the leukocyte count and C-reactive protein levels was found to be an independent predictor of post-enrolment development of ACLF and paralleled the severity and outcome of ACLF [35]. Inflammation imbalance is central to ACLF's pathogenesis and outcome with an associated initial excessive systemic inflammatory response that drives organ failure and mortality. This mediated exhaustion of the immune system predisposes the patient to secondary infectious events and to a reescalation in end-organ dysfunction and mortality [36].

In summary, in the outpatient setting, primary care physicians, gastroenterologists, and hepatologists may shorten follow-up intervals for patients at high risk of developing ACLF. Clinicians could focus on mitigating modifiable risk factors for ACLF development, such as alcohol cessation and improved management of diabetes and obesity. These modifiable risk factors may be used to identify outpatients at a significant risk of ACLF, which may prompt closer follow-up or early transplant referral, and facilitate decision-making for patients with diagnosed ACLF, including escalation of care, expedited transplant evaluation, or palliation.

6.1. Limitation of the study

The study is a small study with a limited number of participants of about 200 patients. Therefore, it is necessary to conduct a wider multi-center study with a larger number of patients. The study is a retrospective one, and the data analysis may have some weakness because some potential contributory factors that might influence the outcome may not have been assessed at the time of enrollment.

7. Conclusions

Outpatients with cirrhosis have a high risk of developing ACLF. The degree of liver failure and circulatory dysfunction are associated with the development of ACLF. The MELD score is a powerful predictor of ACLF development in these patients. The PADUA score together with the MELD score are better predictors of mortality. These simple variables may help in identifying patients at a high risk of developing ACLF and to plan a program of close surveillance and prevention in these patients. The MELD, CLIF-C and PADUA scores could be used to evaluate and follow up on cirrhotic outpatients.

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