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THE PREVALENCE AND IMPACT OF INFECTIONS ON TREATMENT OUTCOMES OF ACUTE ON CHRONIC LIVER FAILURE - A PROSPECTIVE STUDY FROM A TERTIARY CARE CENTER IN CHENNAI

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Abstract

Background: Acute-on-chronic liver failure (ACLF) is a life-threatening condition in patients with chronic liver disease, characterised by acute decompensation and high mortality. Infections play a crucial role in the progression of ACLF, exacerbating liver dysfunction and increasing mortality. This study aimed to evaluate the prevalence of infections and their impact on treatment outcomes in patients with ACLF. **Materials and Methods:** This prospective observational study included 110 patients with ACLF at Rajiv Gandhi Government Hospital. Demographic, clinical, and laboratory data were collected, and infections were classified as community-acquired, healthcare-associated, or nosocomial infections. Disease severity was assessed using the MELD, APASL ACLF Research Consortium (AARC), and qSOFA scores. Survival analysis and logistic regression were performed to identify the predictors of mortality. **Results:** The mean age was 47.26±8.92 years, with a predominance of alcohol-related liver disease (64.5%). Infections were present in 28.2% of patients, with urinary tract infections (10%), sepsis (6.4%), and respiratory infections (4.5%) being the most common infections. Nosocomial and healthcare-associated infections were associated with significantly lower survival rates ($p<0.05$). Patients with infections had higher total bilirubin, serum creatinine, and INR levels than non-infected patients. MELD (AUC: 0.880) and AARC (AUC: 0.761) scores were strong predictors of mortality, whereas qSOFA had a lower predictive accuracy (AUC: 0.639). **Conclusions**: Infections significantly affect ACLF outcomes, with healthcare-associated and nosocomial infections associated with poor survival. The MELD score is the most reliable tool for predicting mortality in patients with cirrhosis.

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a life-threatening condition in patients with cirrhosis or chronic liver disease, marked by acute decompensation and high mortality rates. The CANONIC study defined ACLF as a distinct syndrome, showing higher mortality rates of 33% within 28 days and 51% within 90 days compared to those of typical acute decompensation. ACLF's pathogenesis is multifactorial, often triggered by infections leading to rapid liver deterioration and organ dysfunction, with bacterial infections affecting up to 81% of patients' outcomes.[1,2]

Cirrhosis, the underlying condition in ACLF, is characterised by progressive liver fibrosis due to

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chronic injury from aetiologies such as alcohol use, viral hepatitis, and non-alcoholic fatty liver disease (NAFLD).[3] The progression of cirrhosis leads to Cirrhosis-Associated Immune Dysfunction (CAID), marked by systemic inflammation and immune exhaustion. This dual mechanism increases susceptibility to infections, which frequently trigger ACLF. Studies have shown that bacterial translocation and damage-associated molecular patterns (DAMPs) activate the innate immune system, exacerbating inflammation and organ failure.4 Adaptive immune dysfunction hinders the body's ability to clear infections, leading to inflammation and immune suppression. Bacterial infections are the most common complication in patients with decompensated cirrhosis, triggering ACLF in about 33% of cases.[5]

Infections exacerbate liver dysfunction and complications, such as hepatic encephalopathy (HE), gastrointestinal bleeding, and acute kidney injury, increasing short-term mortality rates by two to four times.[6] The European Association for the Study of the Liver (EASL) reports that gram-negative bacteria, particularly Enterobacteriaceae, are the predominant pathogens. However, Gram-positive infections are also prevalent, especially in nosocomial settings.[7] These infections, categorised as community-acquired infections (CAI), healthcare-associated infections (HAI), or nosocomial infections (NI), influence treatment strategies and outcomes. Nosocomial infections are particularly concerning because of their association with multidrug-resistant organisms (MDROs). Delay in initiating appropriate antibiotic therapy can lead to rapid deterioration and increased mortality.[8]

Antibiotic regimens must be aligned with infection type, resistance patterns, and patient factors to optimise outcomes and reduce antibiotic resistance. Judicious antibiotic use results in shorter treatment duration, lower cost, and improved survival. Scoring systems are crucial for assessing the severity of ACLF and predicting outcomes. The Model for End-Stage Liver Disease (MELD) and MELD-sodium (MELD-Na) scores, which incorporate serum bilirubin, creatinine, and international normalised ratio (INR), are widely used to assess the severity of liver disease. The Child-Turcotte-Pugh (CTP) score offers an alternative by combining clinical and laboratory parameters to assess liver function. The Asia-Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium (AARC) score has also been developed to assess ACLF severity in Asian populations.[9]

The qSOFA score identifies high-risk patients for sepsis-related organ failure, which is key in stratifying risk and guiding ACLF clinical decisions.[10] Despite these advancements, gaps remain in understanding infection prevalence and its impact on treatment outcomes. The high rate of bacterial infections negatively affects the prognosis, highlighting the need for detailed studies. Analysing outcomes by liver disease stage and scoring systems provides valuable insights for clinical practice. This study aimed to assess the infection prevalence in patients with ACLF and its effects on treatment outcomes using AARC, qSOFA, and MELD scores to enhance strategies and improve patient care.

MATERIALS AND METHODS

This prospective observational study included 110 patients from the Institute of Hepatobiliary Sciences, Rajiv Gandhi Government Hospital, between April 2024 and October 2024. The Institutional Ethical Committee approved the study, and written informed consent was obtained from all participants before data collection.

Inclusion and exclusion criteria

Patients of both sexes, aged 18 years and older, were diagnosed with decompensated liver disease or acute-on-chronic liver disease (ACLD) according to the Study of the European Association for Liver guidelines. Patients were excluded if they had a Human Immunodeficiency Virus (HIV) infection, a history of organ transplantation, other immunodeficiencies, or malignancies, or if they had initiated antibiotic treatment before admission.

Methods

The sample size of 110 participants was determined based on an infection prevalence of 62% as reported by **Kumar et al.** Patient histories were recorded using semi-structured questionnaires, followed by clinical examinations and documentation of vital signs. Demographic data, including age, sex, and baseline characteristics, were collected.[11] The aetiology of liver disease was classified as alcoholic liver disease, viral hepatitis (HBV or HCV), drug-induced liver injury, or other causes, based on the Study of the European Association for Liver guidelines.[12] Complications related to liver disease, such as HE, were graded using the West Haven criteria, categorising HE from Grade I to Grade IV. Ascites severity was assessed through clinical examination and ultrasound findings and classified as mild (grade 1), moderate (grade 2), or severe (grade 3).

Blood samples were collected within two hours of admission for laboratory analyses, including complete blood count, liver function tests, prothrombin time/international normalised ratio (PT/INR), blood urea, and serum creatinine. Microbiological blood, urine, and ascitic fluid cultures were performed to identify the infections. Sputum cultures were performed for patients with suspected pneumonia. Pus cultures were collected from patients with cellulitis, and endotracheal cultures were collected from those on ventilator support. Weekly cultures were performed to monitor the infection status, and antimicrobial resistance patterns were evaluated based on the Clinical and Laboratory Standards Institute (CLSI) guidelines.

Infections were classified based on clinical criteria and time of onset. CAI was defined as an infection present at the time of hospital admission. HAI referred to infections that developed within 48–72 h

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of admission but did not meet the criteria for nosocomial infections. Nosocomial infections (NI) were observed 48 h or more after hospitalisation.

Organ failure was defined according to the European Association for the Study of the Liver (EASL) guidelines.[12] ACLF was diagnosed using criteria from the Asian Pacific Association for the Study of the Liver (APASL) and EASL guidelines.[12] Liver failure was identified by a total bilirubin level of ≥5 mg/dL according to EASL or ≥12 mg/dL based on APASL guidelines, with coagulopathy defined as an INR ≥1.5. Renal failure was defined as a serum creatinine level ≥1.5 mg/dL or an increase exceeding 0.3 mg/dL within 48 h. HE was graded according to the West Haven criteria.

The initiation of inotropes indicated circulatory dysfunction and respiratory insufficiency was characterised by a SpO_2 level of ≤93% on room air. The severity of ACLF was graded according to the EASL definitions. Grade 1 ACLF refers to single renal failure or a single non-renal organ failure with serum creatinine levels between 1.5 and 1.9 mg/dL. Grade 2 ACLF involved the failure of two organs, whereas grade 3 ACLF was characterised by the failure of three or more organs. The severity of liver disease was assessed using The MELD score, which was calculated using an online tool.[13] The MELD score was derived using the following formula:

- MELD = 3.78 × ln [serum bilirubin (mg/dL)] + 11.2 × ln [INR] + 9.57 × ln [serum creatinine (mg/dL)] + 6.43

The AARC (APASL ACLF Research Consortium) score was determined using total bilirubin, HE grades, INR, creatinine, and blood lactate levels. The qSOFA was evaluated as a categorical variable ranging from 0 to 3, based on the presence of the following criteria: systolic blood pressure of 100 mmHg or lower, respiratory rate of 22 breaths per minute or higher, and a Glasgow Coma Scale score below 15.[14]

Statistical analysis

The data were entered into Excel. Continuous variables were summarised as mean ± SD or median with IQR, depending on the distribution. Categorical variables were expressed as frequency and percentage. An independent t-test was used to compare continuous variables, such as serum bilirubin and creatinine levels, between the infected and non-infected groups. The chi-square test was used to analyse categorical variables, including infection type and survival outcomes. A nominal regression model identified mortality predictors, incorporating factors such as microbial culture positivity and clinical parameters. Survival analysis was performed using the Kaplan-Meier method, with differences in curves assessed using the log-rank test. The predictive performances of the MELD, AARC, and qSOFA scores were evaluated using AUROC, and pairwise comparisons of the AUC values were performed using the DeLong test. Statistical significance was defined as $p<0.05$ and analysed using SPSS version 20.

RESULTS

The mean age was 47.26±8.92 years, and the maximum number of participants was male, with 93 (84.5%) and 17 (15.5%) females. The leading aetiology of ACLF was alcohol-related liver disease (64.5%), followed by chronic hepatitis B virus infection (9.1%), mixed cases involving alcohol-related liver disease (8.2%), drug-induced liver injury (3.6%), and complementary and alternative medicine-induced liver injury (3.6%). Other aetiologies included autoimmune hepatitis (2.7%), chronic hepatitis C virus infection (3.6%), and rare mixed cases involving Wilson's disease and other factors (1.8%).

HE was observed in 76.4% of the participants, with 20% presenting with grade 1, 32.7% with grade 2, and 23.6% with grade 3 encephalopathy. Ascites were noted in 93.6% of the cases, predominantly moderate (79.1%), with 14.5% classified as severe. Infections were prevalent, with urinary tract infections identified in 10% of cases, sepsis in 6.4%, respiratory infections in 4.5%, and cellulitis in 5.5% of cases. Approximately three-fourths (75.5%) were alive at the end of treatment. [Table 1]

Table 1: Clinical and demographic characteristics of ACLF patients

		N (%)
Gender	Female	17 (15.5%)
	Male	93 (84.5%)
Aetiology of ACLF	Drug-induced liver injury	4 (3.6%)
	Autoimmune hepatitis	3 (2.7%)
	Chronic hepatitis B virus infection	10 (9.1%)
	Chronic hepatitis C virus infection	4 (3.6%)
	Alcohol-related liver disease	71 (64.5%)
	CAM-induced liver injury	4 (3.6%)
	Wilson's disease and CAM-induced liver injury	1 (0.9%)
	Wilson's disease and alcohol-related liver disease	1 (0.9%)
	Mixed cases involving alcohol-related liver disease	9 (8.2%)
	Mixed cases involving chronic hepatitis B virus	1 (0.9%)
	Mixed cases involving chronic hepatitis C virus	1 (0.9%)
HE	Grade 1	22 (20%)
	Grade 2	36 (32.7%)
	Grade 3	26 (23.6%)

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Ascites	Mild (Grade 1)	7 (6.4%)
	Moderate (Grade 2)	87 (79.1%)
	Severe (Grade 3)	16 (14.5%)
Infections	Sepsis (Blood Culture)	7 (6.4%)
	UTI (Urine Culture)	11 (10%)
	Respiratory infection (Sputum Culture)	5 (4.5%)
Clinical Outcome	Death	27 (24.5%)
	Alive	83 (75.5%)

The mean total bilirubin was 16.51±5.56 mg/dL, serum creatinine was 1.57±0.499 mg/dL, and INR was 2.72±0.86. The mean WBC count was 12,338.99±6,894.28/µL, serum albumin was 2.39±0.35 g/dL, and serum sodium was 132.05±5.08 mmol/L. The serum lactate level was 1.81±1.74 mmol/L. The mean duration of hospital stay was 17.10±9.28 days. [Table 2]

Table 2: Laboratory parameters and hospital stay duration

		Mean±SD
Laboratory parameters	Total bilirubin (mg/dL)	16.51±5.56
	S. Creatinine (mg/dL)	1.57±0.499
	INR	2.72±0.86
	WBC (µL)	12338.99±6894.28
	S. Albumin (g/dL)	2.39±0.35
	S. Sodium level (mmol/L)	132.05±5.08
	S. Lactate level (mmol/L)	1.81±1.74
	Duration of hospital stay (days)	17.10±9.28

Patients who died had significantly higher total bilirubin levels (8.37±5.14) than survivors (2.97±1.43, p<0.001). Similarly, serum creatinine levels were higher in the deceased group (1.99±0.68) than in survivors (0.91±0.43, p<0.001), reflecting poorer renal function. The INR was also significantly higher in patients who died (2.19±0.89) than in survivors (1.35±0.65, p=0.001). Serum sodium levels were lower in the deceased group (125.14±4.93) than in the survivor group (136.98±4.56, p<0.001).

MELD scores were significantly elevated among patients who died (26.74±6.58) versus survivors (14.98±4.23, p<0.001), as were AARC scores (9.33±3.41 vs. 5.24±2.02, p<0.001). The qSOFA score was also higher in the deceased group (1.22±0.65) than in the survivors (0.84±0.61, p=0.024). Notably, albumin levels did not differ significantly between the groups (2.85±0.46 in the deceased vs. 2.91±0.35 in survivors, p=0.464). [Table 3]

Table 3: Comparison of clinical parameters between deceased and survived patients

	Deceased (Mean ± SD)	**Survived (Mean ± SD)**	**P-value**
Total bilirubin (mg/dL)	8.37±5.14	2.97±1.43	<0.001
Serum creatinine (mg/dL)	1.99±0.68	0.91±0.43	<0.001
INR	2.19±0.89	1.35±0.65	0.001
Serum sodium (mEq/L)	125.14±4.93	136.98±4.56	<0.001
MELD Score	26.74±6.58	14.98±4.23	<0.001
AARC Score	9.33±3.41	5.24±2.02	<0.001
qSOFA Score	1.22±0.65	0.84±0.61	0.024
Albumin (g/dL)	2.85±0.46	2.91±0.35	0.464

The MELD score had the highest AUC (0.880, p=0.001) with a 95% CI of 0.81–0.951. The qSOFA score had the lowest AUC (0.639, p=0.03) with a 95% CI of 0.521–0.757. The AARC score showed moderate predictive ability, with an AUC of 0.761 (p=0.001, 95% CI: 0.66–0.861). [Table 4]

Table 4: Area under the curve values of MELD, QSOFA and AARC with clinical outcome

Variables	**Area**	**Std. Error**	**p-value**	**95% Confidence Interval**	
				Lower bound	**Upper bound**
MELD	0.88	0.036	0.001	0.81	0.951
QSOFA	0.639	0.06	0.03	0.521	0.757
AARC	0.761	0.051	0.001	0.66	0.861

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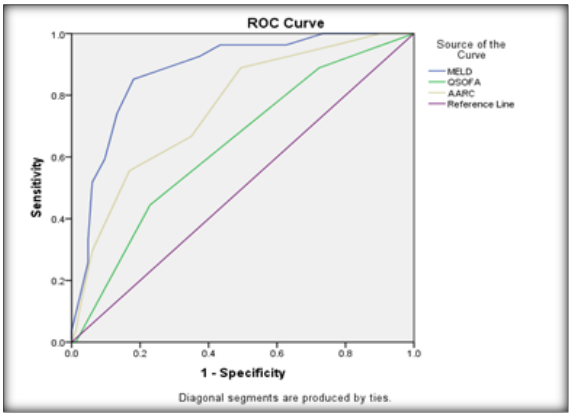

Figure 1: Receiver operating characteristic (ROC) curve for MELD, qSOFA, and AARC scores

The ROC curve shows the diagnostic performance of the MELD, qSOFA, and AARC scores for predicting clinical outcomes. Sensitivity is plotted on the Y-axis against (1 - Specificity) on the X-axis. The MELD (blue), qSOFA (green), and AARC (yellow) scores were compared against the reference line (purple), which represents no discrimination. A higher area under the curve (AUC) indicates a better predictive ability. The diagonal segments in the graph are produced by ties in the data.

Nominal regression analysis was used to assess the relationship between microbial culture results (blood, urine, and sputum cultures) and cellulitis with mortality outcomes. The model demonstrated a significant overall fit, with a chi-square value of 15.665 (df = 4, p = 0.004), indicating that the independent variables collectively contributed to the explanation of mortality. Patients with a positive urine culture had a significantly higher likelihood of mortality than those with a negative urine culture, with an 88% reduction in the odds of death observed in patients with a negative culture (OR = 0.120, 95% CI: 0.027–0.537, p = 0.006). Similarly, patients with a positive sputum culture had a significantly increased risk of death compared to those with a negative culture, with a 94.6% reduction in the odds of mortality for patients with a negative culture (OR = 0.054, 95% CI: 0.006–0.516, p = 0.011).

Blood culture results did not significantly affect mortality (OR = 0.537, 95% CI: 0.095–3.038, p = 0.482). Although cellulitis showed a trend toward higher odds of death (OR = 4.454, 95% CI: 0.348–57.042), this association was not statistically significant (p = 0.251). The prevalence of various infections was categorised into community-acquired, nosocomial, and healthcare-associated infections, which accounted for 14 (12.7%), 12 (10.9%), and 06 (5.5%) cases, respectively. The mean survival time in the community-acquired group was 25.371 ± 2.969 with a CI of (19.552–31.191), indicating moderate survival compared with other infection groups. The healthcare-associated infection group showed a poor survival rate with a mean survival time of 14.000 ± 6.646 and a wide CI of (0.974–27.026) and the nosocomial infection group also indicated poor survival, similar to the healthcare-associated infection group, with a mean survival time of 14.417 ± 3.809 and a CI of (6.952–21.882). Patients with no infections had the longest survival time among the groups and had more consistent outcomes, with a mean survival time of 32.283 ± 1.524 and a CI of (29.297–35.269).

DISCUSSION

Although bacterial infections are known to influence outcomes in patients with ACLF, the comprehensive characteristics of these infections and their impact on mortality remain unclear. In this study, which analysed 110 ACLF cases, the overall mortality rate was 24.5%. Previous studies by Amarapurkar et al. and Singh et al. reported higher mortality rates of 43.1% and 50%, respectively. This discrepancy could be attributed to differences in the type and severity of bacterial infections and variations in prognosis.[15,16]

Bacterial infections were identified as independent predictors of survival at the time of ACLF diagnosis or during follow-up. In the present study, the prevalence of CAI, nosocomial infections, and HAI was 12.7% (14 cases), 10.9% (12 cases), and 5.5% (6 cases), respectively. Comparatively, Li et al. reported that, among 194 episodes of bacterial infections in 159 patients with HBV-ACLF, 13.4% were CAI, 46.4% were HAI, and 40.2% were nosocomial.[17] Singh et al. found the prevalence of BI in patients with CLD and ACLF to be 47% and 36%, respectively.16 Wong et al. and Gupta et al. observed that 127 patients developed nosocomial infections, while 85 (83.3%) had CAI.[18,19]

In our study, patients without infection had better survival rates than those with infection. Among those with infections, CAI was associated with moderate survival, whereas HAI and nosocomial infections led to poorer outcomes. Li et al. reported a 28-day survival rate of 36.9% among patients with ACLF, emphasising the impact of infection type on prognosis. These differences in survival rates could be influenced by several factors, such as the likelihood of nosocomial bloodstream infections leading to secondary infections, prolonged hospital stay increasing the infection risk, and the severity of the disease itself. Additionally, the location of patient admission and the frequency of medical interventions significantly affect infection types and outcomes.[17]

Our study found that MELD scores were highly effective in predicting mortality, with an AUC value of 0.880 in the ROC analysis. The AARC score accuracy was reasonable at 0.761, whereas qSOFA showed poor diagnostic accuracy at 0.639. Moreover, Cai et al. determined the area under the ROC curve for 28-day mortality for MELD, CLIF-C-AD, MELD-Na, AARC-ACLF, and the newly introduced AD scores to be 0.663, 0.673, 0.657, 0.662, and 0.773, respectively.19 According to Lin et al., the AUROC for predicting 28-day mortality using the AARC ACLF score was 0.754.[20]

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The overall prevalence of multidrug resistance in our study was 43%, with Escherichia coli exhibiting the highest drug resistance among patients with UTI, spontaneous bacterial peritonitis (SBP), bacteraemia, and cellulitis. Kumar et al. found that bacteraemia was present in 14% of cases, with gram-negative bacilli, predominantly E. coli, identified in 92% of the cultures. Among the isolates, 26.8% showed multidrug resistance, while 29.2% displayed extensive drug resistance.[11] Fernandez et al. reported that 29.2% of organisms showed MDR among hospitalised patients with cirrhosis. Variations in resistance patterns may stem from antibiotic overuse or a lack of awareness regarding antibiotic stewardship practices in different healthcare settings.[21]

Markers of liver dysfunction, such as elevated total bilirubin (T. BILI), were significantly higher in deceased patients and those with positive blood, urine, and sputum cultures. These findings are consistent with those of Engelmann et al., who emphasised hepatic dysfunction as a critical determinant of infection-related mortality in ACLF. Furthermore, elevated serum creatinine levels were observed in deceased patients and those with positive urine and sputum cultures, underscoring the role of renal impairment in poor outcomes.[22] This observation aligns with Asrani et al., who identified renal dysfunction as a major contributor to ACLF mortality.[23]

The MELD, AARC, and qSOFA scores, which assess both liver and renal function, were significantly elevated in deceased patients and those with positive culture results.

CONCLUSION

Our study emphasises the significant burden of alcohol-related liver disease and its complications in patients with ACLF. Infections, particularly HAI and nosocomial infections, are critical in influencing treatment outcomes. Elevated markers of liver and renal dysfunction, along with coagulation abnormalities, underscore the complex interplay between organ failure and infection-related mortality. These findings emphasise the importance of early identification and targeted management of infections to improve outcomes in this high-risk population. Future research should focus on strategies to mitigate infection risks and address underlying immune dysfunction in ACLF.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Abbreviations

ACLF – Acute-on-Chronic Liver Failure
MELD – Model for End-Stage Liver Disease
AARC – APASL ACLF Research Consortium
qSOFA – Quick Sequential Organ Failure Assessment
CAID – Cirrhosis-Associated Immune Dysfunction
INR – International Normalized Ratio
HBV – Hepatitis B Virus
HCV – Hepatitis C Virus
EASL – European Association for the Study of the Liver
APASL – Asian Pacific Association for the Study of the Liver
NAFLD – Non-alcoholic Fatty Liver Disease
MDRO – Multidrug-Resistant Organism
UTI – Urinary Tract Infection
SBP – Spontaneous Bacterial Peritonitis
LRTI – Lower Respiratory Tract Infection.

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