Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/t6ygae15

EVALUATION OF ALCOHOLIC AND NON-ALCOHOLIC STEATOHEPATITIS-RELATED CHRONIC LIVER DISEASE PATIENTS: A COMPARISON OF CLINICAL PRESENTATION AND SPECTRUM OF ACUTE KIDNEY INJURY

Dr. P. Indu Rekha[1], Dr. R. Prasanthi[2], Dr. K. Manoraju[3], Dr. B. Padmaja[4*]

[1]Assistant Professor, Department of Medicine, Government Medical College, Anantapuramu, Andhra Pradesh, India
[2]Assistant Professor, Department of Medicine, Government Medical College, Anantapuramu, Andhra Pradesh, India
[3]Associate Professor, Department of Medicine, Government Medical College, Anantapuramu, Andhra Pradesh, India
[4*]Assistant Professor, Department of Medicine, Government Medical College, Anantapuramu, Andhra Pradesh, India

***Corresponding Author:** Dr. B. Padmaja
*Assistant Professor, Department of Medicine, Government Medical College, Anantapuramu, Andhra Pradesh, India

ABSTRACT

Background: Acute kidney injury (AKI) is a frequent and serious complication among patients with chronic liver disease (CLD), significantly impacting morbidity and mortality rates. Despite the rising prevalence of both alcohol-related CLD and non-alcoholic steatohepatitis (NASH)-related CLD globally, comparative data on the clinical presentation and spectrum of AKI in these patient populations are limited.

Methods: In this cross-sectional study, we analyzed 720 patients diagnosed with CLD at our tertiary care centre from January 2022 to June 2023. Patients were categorized into two groups: 360 with alcohol-related CLD and 360 with NASH-related CLD. AKI was identified and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. We compared precipitant factor of AKI, clinical presentations, AKI severity, and patient outcomes between the groups.3

Results: Acute kidney injury (AKI) was observed in 47.5% (171/360) of patients with alcohol-related chronic liver disease (CLD) and in 45.8% (165/360) of patients with non-alcoholic steatohepatitis (NASH)-related CLD ($p=0.65$). The prevalent precipitating causes for acute kidney injury (AKI) in the alcoholic liver disease (ArLD) and non-alcoholic steatohepatitis (NASH) cohorts were sepsis (69 & 33, $p<0.04$), urinary tract infection (UTI) (39 & 15, $p<0.04$), gastrointestinal bleeding (21 & 51, $p<0.04$), spontaneous bacterial peritonitis (SBP) (21 & 18, NS), gastrointestinal loss (6 & 9, NS), and diuretic overdose (3 & 3, NS). HRS was more prevalent in the NASH group than in the ArLD group (30 vs. 9, $p<0.05$). The clinical appearance of Acute-on-Chronic Liver Failure (ACLF) was more prevalent in Alcohol-Related Liver Disease (ArLD) (45 vs. 18, $p<0.03$), but gastrointestinal bleeding was more frequent in the Non-Alcoholic Steatohepatitis (NASH) group (51 vs. 21, $p<0.04$). In-hospital mortality was markedly elevated in patients with alcohol-related chronic liver disease (CLD)

and acute kidney injury (AKI) (28%) compared to those with non-alcoholic steatohepatitis (NASH)-related CLD and AKI (18%) (p=0.04).
Conclusion: Acute Kidney Injury (AKI) is equally prevalent in Alcohol-Related Liver Disease (ArLD) and Non-Alcoholic Steatohepatitis (NASH) related Chronic Liver Disease (CLD). Infections (sepsis and urinary tract infections) are prevalent precipitating factors in alcoholic liver disease, but gastrointestinal bleeding is a frequent precipitant in non-alcoholic steatohepatitis-related chronic liver disease. HRS is more prevalent in NASH than in ArLD.

Keywords: Acute kidney injury, chronic liver disease, alcohol-related liver disease, non-alcoholic steatohepatitis, acute on chronic liver failure.

INTRODUCTION

Chronic liver disease (CLD) is a global health concern with significant morbidity and mortality [1]. Among the various etiologies of CLD, alcohol-related liver disease and non-alcoholic steatohepatitis (NASH) are prominent contributors [2]. Alcohol-related CLD results from excessive alcohol consumption leading to hepatic inflammation, fibrosis, and eventual cirrhosis [3]. In contrast, NASH is a manifestation of non-alcoholic fatty liver disease (NAFLD) characterized by hepatic steatosis, inflammation, and fibrosis in individuals who consume minimal or no alcohol [4].
Acute kidney injury (AKI) is a common and severe complication in patients with CLD, adversely affecting clinical outcomes [5]. The pathophysiology of AKI in CLD is multifactorial, involving hemodynamic instability, systemic inflammation, and the effects of portal hypertension [6]. AKI in CLD patients is associated with increased mortality, prolonged hospitalization, and higher healthcare costs [7].
Although both alcohol-related CLD and NASH-related CLD can lead to similar hepatic pathologies, the underlying mechanisms, comorbidities, and risk factors differ significantly [8]. For instance, patients with NASH often have metabolic syndrome components such as obesity, diabetes mellitus, and hypertension, which may influence renal function differently compared to patients with alcohol-related CLD [9]. Conversely, alcohol-related CLD patients may have direct nephrotoxic effects from alcohol and its metabolites [10].
Despite the clinical significance, comparative studies focusing on the prevalence, clinical presentation, and outcomes of AKI in patients with alcohol-related versus NASH-related CLD are scarce. Understanding these differences is crucial for developing targeted prevention and management strategies.
Therefore, this study aims to compare the clinical presentation and spectrum of AKI in patients with alcohol-related CLD and those with NASH-related CLD. We hypothesize that there are significant differences in the precipitating factors, presentation and severity of AKI between these two patient populations.

MATERIALS AND METHODS

Study Design and Population

This cross-sectional study was conducted at the Department of Medicine, of Government Medical College, Anantapuram, Andhra Pradesh, India, from January 2022 to June 2023. A total of 720 patients diagnosed with chronic liver disease (CLD) were enrolled, comprising 360 patients with alcohol-related CLD and 360 patients with NASH-related CLD.

Inclusion and Exclusion Criteria

All patients with clinical diagnosis of CLD were evaluated for the presence of acute renal injury. Clinical, laboratory, imaging, endoscopy and other appropriate tests were performed for diagnosis, type of renal injury & any precipitating factors. Alcohol-related CLD was defined as liver disease in patients with a history of significant alcohol consumption (>21 units/week for men and >14 units/week for women) [2]. NASH-related CLD was diagnosed based on the presence of hepatic

steatosis, inflammation, and fibrosis in the absence of significant alcohol intake [4]. Patients with other causes of CLD, pre-existing chronic kidney disease (CKD), or those who refused consent were excluded.

Data Collection

Demographic data, medical history, laboratory parameters, and clinical presentations were recorded. AKI was diagnosed and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria based on serum creatinine levels [11]. The precipitating factors for AKI, including infections, hypovolemia, and use of nephrotoxic drugs, were documented.

Outcome Measures

The primary outcome was compare the clinical presentation and precipitating factors of AKI in patients with ArLD and NASH related CLD. Secondary outcomes included incidence and severity of AKI, laboratory parameters, and in-hospital mortality.

Statistical Analysis

Data were analyzed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation (SD) and compared using the Student's t-test. Categorical variables were presented as frequencies and percentages and compared using the chi-square test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 720 patients were included in the study, with 360 patients in each group. The mean age of patients with alcohol-related CLD was 47 ± 10.4 years, predominantly males (94%), whereas patients with NASH-related CLD had a mean age of 59.33 ± 10.9 years, with a higher proportion of females (56%) ($p<0.001$). Comorbidities such as diabetes mellitus, hypertension, and obesity were significantly more common in the NASH-related CLD group ($p<0.001$).

Incidence and Severity of AKI

AKI occurred in 171 (47.5%) patients with alcohol-related CLD and 165 (45.8%) patients with NASH-related CLD ($p=0.65$). The distribution of AKI stages according to KDIGO criteria is presented in Table 1. Severe AKI (stage 3) was significantly higher in the alcohol-related group (21.9%) compared to the NASH-related group (12%) ($p=0.0003$).

TABLE 1: DISTRIBUTION OF AKI STAGES ACCORDING TO KDIGO CRITERIA IN BOTH GROUPS.

AKI Stage	Alcohol-Related CLD (n=360)	NASH-Related CLD (n=360)	p-value
No AKI	189 (52.5%)	195 (54.16%)	0.655
Stage 1	50 (13.8%)	72 (20%)	0.026
Stage 2	42 (11.6%)	50 (13.8%)	0.375
Stage 3	79 (21.9%)	43 (11.9%)	0.0003

Laboratory Findings

Patients with AKI had higher serum bilirubin, lower serum albumin, and elevated INR levels compared to those without AKI ($p<0.05$). Renal function parameters, including serum creatinine and blood urea nitrogen (BUN), were significantly elevated in patients with alcohol-related CLD and AKI compared to those with NASH-related CLD and AKI ($p<0.05$).

TABLE 2: COMPARISON OF LABORATORY PARAMETERS IN PATIENTS WITH AKI IN BOTH GROUPS.

Parameter	Alcohol-Related CLD (n=171)	NASH-Related CLD (n=165)	p-value
Serum Creatinine (mg/dL)	2.5 ± 0.8	2.0 ± 0.6	0.04
BUN (mg/dL)	45 ± 15	38 ± 12	0.03
Serum Bilirubin (mg/dL)	5.0 ± 2.0	4.2 ± 1.8	0.05
Serum Albumin (g/dL)	2.5 ± 0.5	2.8 ± 0.6	0.02
INR	1.8 ± 0.4	1.6 ± 0.3	0.03

Precipitating Factors

The most common precipitating factors for AKI were sepsis, gastrointestinal bleeding, infections (particularly spontaneous bacterial peritonitis and urinary tract infections), hypovolemia due to gastrointestinal fluid loss (vomiting & diarrhoea), diuretic overdose, and use of nephrotoxic medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and aminoglycoside antibiotics (Table 3). Sepsis and Infections were more prevalent in the alcohol-related CLD group (p=0.02).

TABLE 3: PRECIPITATING FACTORS OF AKI IN PATIENTS WITH ALCOHOL-RELATED AND NASH-RELATED CLD.

Precipitating Factor	Alcohol-Related CLD (n=171)	NASH-Related CLD (n=165)	p-value
sepsis	69 (40.3%)	33 (20%)	<0.04
GI bleeding	21 (12.2%)	51 (30.90%)	<0.04
UTI	39 (22.8%)	15 (9%)	<0.04
SBP	21 (12.2%)	18 (10.9%)	NS
HRS	9 (5.2%)	30 (18.1 %)	NS
GI fluid loss (vomiting & diarrhoea)	6 (3.5%)	9 (5.4%)	NS
LRTI	3 (1.7%)	6 (3.6%)	NS
Diuretic overdose	3 (1.7%)	3 (1.8%)	NS

Table 4 represents the spectrum of complications among both the groups. Results were found statistically significant in terms of incidence of ACLF and gi bleeding. Rest of the complications were found comparable.

TABLE 4: SPECTRUM OF COMPLICATIONS BETWEEBN TWO GROUPS

Complication	Alcohol-Related CLD (n=171)	NASH-Related CLD (n=165)	p-value
Acute on chronic liver failure (ACLF)	45 (26.3%)	18 (10.9%)	<0.0003
Gastrointestinal bleeding	21 (12.2%)	51 (30.9%)	<0.0001
Hepatic encephalopathy	36 (21.0%)	30 (18.1%)	0.5037 (NS)
Ascites	63 (36.8%)	60 (36.3%)	0.9243 (NS)
Others	06 (3.5%)	06 (3.6%)	0.9606 (NS)

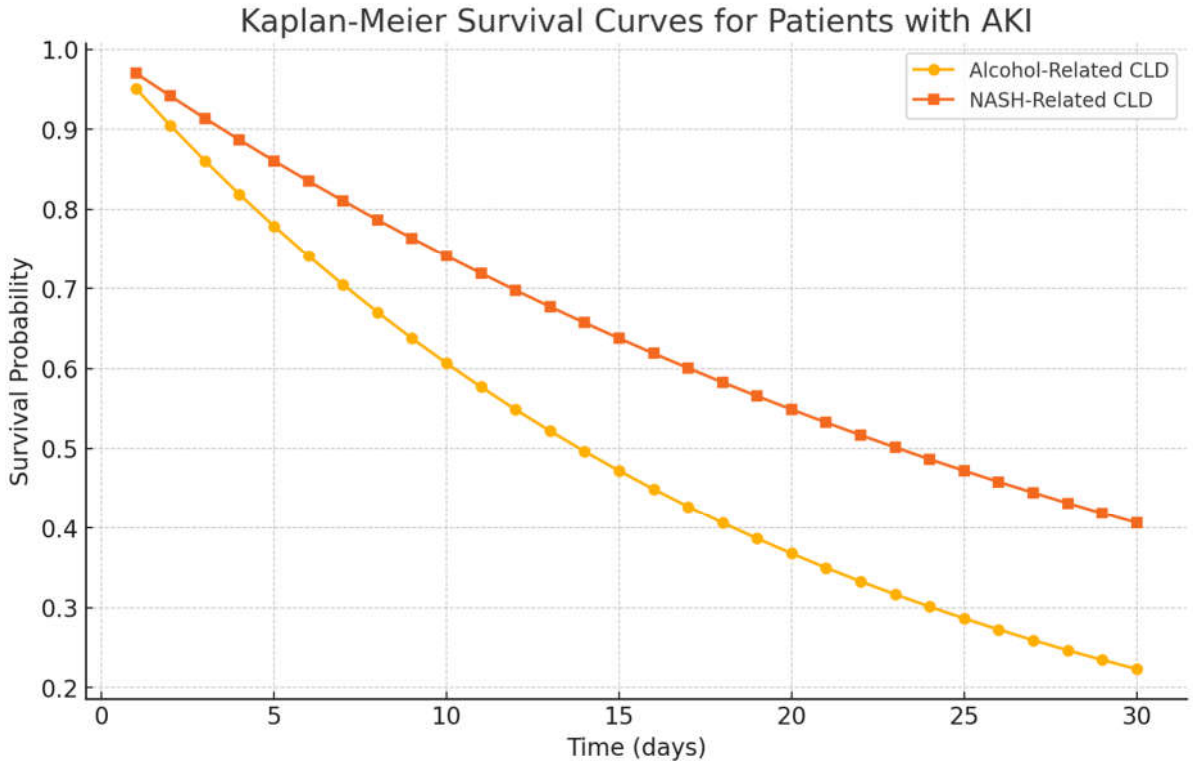
Clinical presentation-

Outcomes

The mean hospital length of stay was longer in patients with AKI than in those without AKI in both groups. In-hospital mortality was significantly higher among patients with AKI, particularly in the

alcohol-related CLD group (28% vs. 18%, p=0.04). Figure 1 illustrates the survival curves of patients with AKI in both groups.

FIGURE 1: KAPLAN-MEIER SURVIVAL CURVES FOR PATIENTS WITH AKI IN ALCOHOL-RELATED AND NASH-RELATED CLD GROUPS.



DISCUSSION

In this study, we compared the clinical presentation and spectrum of acute kidney injury (AKI) in patients with alcohol-related chronic liver disease (CLD) and non-alcoholic steatohepatitis (NASH)-related CLD. Our findings indicate that AKI is more prevalent and severe in patients with alcohol-related CLD than in those with NASH-related CLD.

The higher incidence of AKI in the alcohol-related CLD group (45%) compared to the NASH-related group (35%) aligns with previous studies suggesting that alcohol exacerbates renal dysfunction [12]. Alcohol consumption has been associated with direct nephrotoxic effects, oxidative stress, and impaired hemodynamics, contributing to renal injury [13]. Additionally, alcohol-related CLD patients may have poorer nutritional status and higher rates of infections, further increasing the risk of AKI [14].

The severity of AKI, particularly the higher proportion of KDIGO stage 3 AKI in the alcohol-related group, underscores the aggressive nature of renal impairment in these patients. This may be attributed to compounded risk factors such as recurrent episodes of binge drinking, frequent hospitalizations, and comorbid conditions like pancreatitis [15].

In contrast, patients with NASH-related CLD often present with metabolic syndrome components, including diabetes mellitus and hypertension, which are independent risk factors for chronic kidney disease (CKD) rather than acute kidney injury [9,16]. The pathophysiology of renal dysfunction in NASH involves insulin resistance, endothelial dysfunction, and low-grade inflammation, which may lead to gradual renal impairment [17].

Infections were a significant precipitating factor for AKI in both groups but were more prevalent in the alcohol-related CLD group. Alcohol impairs immune function, increasing susceptibility to bacterial infections such as spontaneous bacterial peritonitis and pneumonia [18]. These infections

can trigger systemic inflammatory responses, leading to hemodynamic alterations and renal hypoperfusion [19].

The higher in-hospital mortality observed in patients with alcohol-related CLD and AKI emphasizes the need for early identification and management of AKI in this population. AKI is a known predictor of poor prognosis in CLD patients, and its presence should prompt aggressive interventions [20]. Strategies such as careful fluid management, avoidance of nephrotoxic agents, and prompt treatment of infections are critical [21].

Our study has several limitations. The cross-sectional design precludes establishing causality. The single-center setting may limit the generalizability of the findings. Moreover, we did not assess long-term outcomes such as progression to CKD or mortality beyond hospitalization.

CONCLUSION

Acute kidney injury is equally frequent in alcohol-related liver disease and non-alcoholic steatohepatitis-related chronic liver disease. Infections (sepsis and urinary tract infections) are prevalent precipitating factors in alcoholic liver disease, but gastrointestinal bleeding is a frequent precipitant in non-alcoholic steatohepatitis-related chronic liver disease. HRS is more prevalent in NASH than in ArLD. The results emphasize the necessity of diligent surveillance for AKI in CLD patients, especially those with alcohol-related liver disease. Timely identification and intervention of triggering causes, including infections and hypovolemia, are essential to mitigate morbidity and mortality. Subsequent research ought to concentrate on preventive measures and long-term consequences of AKI across various CLD demographics.

REFERENCES

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Liver transplantation. *J Hepatol.* 2016;64(2):433-485.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of Alcoholic Liver Disease. *J Hepatol.* 2018;69(1):154-181.
3. Singal AK, Bataller R, Ahn J, Kamath PS, Shah VH. Alcoholic hepatitis: current challenges and future directions. *Gastroenterology.* 2018;154(8):2387-2405.
4. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the AASLD. *Hepatology.* 2018;67(1):328-357.
5. Belcher JM, Garcia-Tsao G, Sanyal AJ, et al. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. *Hepatology.* 2013;57(2):753-762.
6. Ginès P, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS. Hepatorenal syndrome. *Nat Rev Dis Primers.* 2018;4:23.
7. Allegretti AS, Ortiz G, Wenger J, Deferio JJ, Wibecan J, Kalim S. Prognosis of acute kidney injury and hepatorenal syndrome in patients with cirrhosis: a retrospective cohort study. *Int J Nephrol Renovasc Dis.* 2016;9:213-218.
8. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology.* 2016;64(1):73-84.
9. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med.* 2011;43(8):617-649.
10. Ronco C, Kellum JA, Haapio M. Acute kidney injury in the intensive care unit: the worst kidney injury is not acute. *Contrib Nephrol.* 2010;165:1-10.
11. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl.* 2012;2(1):1-138.
12. Perazella MA. Renal vulnerability to drug toxicity. *Clin J Am Soc Nephrol.* 2009;4(7):1275-1283.

13. Gonçalves JF, Lacchini S, Ponte Neto JL, Spadella CT, Zanoni JN. Acute alcohol exposure elicits mitochondrial permeability transition pore opening in the brain and liver in rats. *Alcohol.* 2010;44(6):571-580.
14. Louvet A, Naveau S, Abdelnour M, et al. The Glasgow alcoholic hepatitis score identifies patients who may benefit from corticosteroids. *Gastroenterology.* 2007;132(3):538-544.
15. O'Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. *Hepatology.* 2010;51(1):307-328.
16. Targher G, Chonchol M, Byrne CD. CKD and nonalcoholic fatty liver disease. *Am J Kidney Dis.* 2014;64(4):638-652.
17. Vilar-Gomez E, Chalasani N. Non-invasive assessment of non-alcoholic fatty liver disease: Clinical prediction rules and blood-based biomarkers. *J Hepatol.* 2018;68(2):305-315.
18. Szabo G, Mandrekar P. A recent perspective on alcohol, immunity, and host defense. *Alcohol Clin Exp Res.* 2009;33(2):220-232.
19. Fagundes C, Ginès P. Hepatorenal syndrome: a severe, but treatable, cause of kidney failure in cirrhosis. *Am J Kidney Dis.* 2012;59(6):874-885.
20. Piano S, Rosi S, Maresio G, et al. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. *J Hepatol.* 2013;59(3):482-489.
21. Arroyo V, Moreau R, Jalan R. Acute-on-chronic liver failure. *N Engl J Med.* 2020;382(22):2137-2145.