ASSOCIATION BETWEEN ALCOHOL-RELATED LIVER CIRRHOSIS AND LATE STAGES AT DIAGNOSIS OF HEPATOCELLULAR CARCINOMA

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ASSOCIATION BETWEEN ALCOHOL-RELATED LIVER CIRRHOSIS AND LATE STAGES AT DIAGNOSIS OF HEPATOCELLULAR CARCINOMA (Abstract): Hepatocellular carcinoma (HCC) is a major complication of liver cirrhosis (LC), and its prognosis is highly dependent on the stage at diagnosis. Alcohol-related liver disease (ALD) is an increasing cause of cirrhosis worldwide, but its impact on the stage of HCC diagnosis remains unclear. **Aim** of the study: to evaluate the stage at which HCC is diagnosed and assess whether alcohol-related cirrhosis predisposes patients to a more advanced-stage presentation. **Materials and methods:** We conducted a retrospective observational study of 152 patients diagnosed with HCC at a tertiary center between January 2022 and December 2023. Patients were classified by cirrhosis etiology (alcohol-related vs. viral hepatitis-related) and categorized by HCC stage at diagnosis according to the 2022 Barcelona Clinic Liver Cancer (BCLC) classification. For analysis, patients were grouped based on curative treatment eligibility: curative stages (BCLC 0-A and selected B1 cases) and non-curative stages (BCLC B2-B3, C, and D). **Results:** Among the 152 patients analyzed, 54 (35.5%) had alcohol-related cirrhosis, and 96 (63.2%) had viral hepatitis-related cirrhosis. At diagnosis, no patients were identified at the very early stage (BCLC 0), while 18.4% were diagnosed at a curative stage and 81.6% at a non-curative stage. Notably, nearly half of all patients (46%) presented at the terminal stage (BCLC D). The proportion of patients diagnosed at a curative stage was significantly lower in those with alcohol-related cirrhosis (7.4%) compared to those with viral hepatitis-related cirrhosis (24%) ($p = 0.01$). Multivariate analysis confirmed that alcohol-related cirrhosis was independently associated with a higher likelihood of non-curative stage diagnosis. **Conclusions**: Patients with alcohol-related cirrhosis are significantly more likely to be diagnosed with HCC at a non-curative stage compared to those with viral hepatitis-related cirrhosis. This disparity underscores the need for improved HCC surveillance strategies in this high-risk population, including better patient engagement, integration of hepatology with addiction services, and enhanced screening adherence programs. Addressing these challenges could facilitate earlier diagnosis and improve treatment opportunities for patients with alcohol-related cirrhosis. **Keywords:** ALCOHOL-RELATED LIVER DISEASE, CIRRHOSIS, HEPATOCELLULAR CARCINOMA, STAGING, CURATIVE TREATMENT.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and represents a major global health burden. It is one of the most serious long-term complications of liver cirrhosis (LC), with most cases developing in patients with underlying cirrhotic disease (1). The prognosis of HCC is highly dependent on the stage at the time of diagnosis, as early-stage detection allows for potentially curative treatments such as liver transplantation, surgical resection, or locoregional therapies (2). In contrast, advanced-stage HCC is associated with limited therapeutic options and poor survival outcomes.

The development of HCC is strongly linked to various etiological factors that contribute to chronic liver disease and cirrhosis, including viral hepatitis - hepatitis B virus (HBV) with or without hepatitis D virus (HDV), and hepatitis C virus (HCV), metabolic dysfunction-associated steatotic liver disease (MASLD, formerly non-alcoholic fatty liver disease - NAFLD), and alcohol-related liver disease (ALD) (3,4). Among these, ALD remains a significant and growing cause of cirrhosis and HCC worldwide (5). However, the impact of cirrhosis etiology on the stage at which HCC is diagnosed is not fully understood.

Alcohol-related cirrhosis is associated with multiple clinical and socioeconomic factors that may contribute to delayed diagnosis, including the absence of routine surveillance, more frequent decompensation events that mask tumor-related symptoms, and differences in healthcare-seeking behavior (6). Understanding whether ALD-related cirrhosis predisposes patients to a later-stage diagnosis of HCC is critical for improving surveillance strategies and optimizing patient outcomes.

The **aim** of this study is to assess the stage at which HCC is diagnosed and to determine whether cirrhosis etiology, particularly alcohol-related cirrhosis, influences the likelihood of an advanced-stage presentation at the time of diagnosis.

MATERIAL AND METHODS

Patients. We conducted a retrospective observational study of patients diagnosed with hepatocellular carcinoma (HCC) at a tertiary reference center over a two-year period (January 2022 – December 2023). Eligible patients were identified from the hospital's electronic medical records and included if they had a confirmed diagnosis of HCC based on imaging criteria (contrast-enhanced computed tomography or magnetic resonance imaging) and/or histopathological confirmation.

Methods. We collected demographic data, including age, sex, and relevant clinical history. The etiology of liver cirrhosis was recorded for each patient and classified as alcohol-related cirrhosis, viral hepatitis (HBV with or without HDV, and HCV), MASLD, or other less common causes (including autoimmune etiology, hereditary hemochromatosis, Wilson's disease, and other rare etiologies).

The stage of HCC at the time of diagnosis was determined using the 2022 Barcelona Clinic Liver Cancer (BCLC) classification system (7). This system classifies patients into five stages (one of them comprising three substages) based on tumor burden, liver function, and performance status (Table I).

For this study, patients were categorized into two groups based on the feasibility of curative treatment: those with ***curative stages at diagnosis***, defined as BCLC 0-A and selected BCLC B1 cases eligible for liver transplantation, and those with ***non-***

curative stages at diagnosis, comprising BCLC B2-B3, C, and D.

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional ethics committee. Informed consent was waived due to the retrospective nature of the study.

TABLE I.
BCLC staging (7)

BCLC Stage	Characterization
0 (Very Early Stage)	Single, small tumors without vascular invasion and good liver function, suitable for curative treatment (e.g., surgical resection or ablation)
A (Early Stage):	Single or multiple tumors with good liver function, candidates for curative treatment (e.g., resection, liver transplantation, or ablation)
B1 (Intermediate Stage, Subgroup 1)	Multiple tumors with a low tumor burden and good liver function, potentially eligible for liver transplantation
B2 (Intermediate Stage, Subgroup 2)	Multiple tumors with a higher tumor burden, but with preserved liver function and no signs of advanced liver disease
B3 (Intermediate Stage, Subgroup 3)	Multiple tumors associated with moderate hepatic dysfunction (e.g., ascites or varices), without signs of advanced liver failure
C (Advanced Stage)	Large or multinodular tumors with vascular invasion, or extrahepatic spread, with poor liver function, typically treated with systemic therapies
D (End-Stage)	Extensive tumor burden with decompensated liver disease, managed with palliative care

Statistical analysis was performed using the *SPSS version 17.0 software* (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarize patient characteristics. Comparisons between groups were made using the chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

Patients' characteristics

A total of 152 patients with hepatocellular carcinoma (HCC) were analyzed (Table II). Among them, 54 patients (35.53%) had alcohol-related liver cirrhosis (LC), while 96 patients (63.16%) had a viral etiology: 30 with hepatitis B virus (HBV), 6 with both HBV and hepatitis C virus (HCV), 8 with both HBV and hepatitis D virus (HDV), and 52 with hepatitis C virus (HCV) alone. Additionally, one patient (0.66%) had metabolic dysfunction-associated steatotic liver disease (MASLD), and one (0.66%) had autoimmune-related cirrhosis.

HCC staging

According to the BCLC classification, 10 patients were diagnosed at the early stage (A), 33 at the intermediate stage (B) (5 in B1, 11 in B2, and 17 in B3), 39 at the advanced stage (C), and 70 at the terminal stage (D). Notably, no cases were detected at a very early stage (BCLC 0).

Curative treatment eligibility

When grouped by treatment eligibility, 28 patients (18.4%) were diagnosed at a curative stage (BCLC A or selected B1 cases eligible for liver transplantation), while 124 (81.6%) were diagnosed at a non-curative stage (BCLC B2-B3, C, or D). This distribution highlights a significant predominance of late (especially advanced-stage and end-stage diagnosis), limiting therapeutic options for most patients.

TABLE II.

Patients' clinical characteristics, cirrhosis etiology and stage at diagnosis

Characteristics	Total number of patients = 152
Age (years), mean +/- SD	65 +/- 10
Range (years)	44-86
Sex, male, n (%)	96 (63.2%)
Etiology of cirrhosis, n (%)	
- Alcohol-related	54 (35.53%)
- HBV	30 (19.74%)
- HBV+HCV	6 (3.95%)
- HBV+HDV	8 (5.26%)
- HCV	52 (34.21%)
- MASLD	1 (0.66%)
- Autoimmune	1 (0.66%)
Diagnostic stage, n (%)	
- Curative	28 (18.4%)
- Non-curative	124 (81.6%)

Staging by etiology

We subsequently analyzed patients based on etiology, comparing those with alcohol-related cirrhosis to those with viral hepatitis-related cirrhosis (tab. III). Due to the small numbers, we excluded the two patients with other etiologies (one with autoimmune cirrhosis and one with MASLD). Among patients with alcohol-related cirrhosis, only 4 (7.4%) were diagnosed at a curative stage, while 50 (92.6%) were diagnosed at a non-curative stage. In contrast, among patients with viral hepatitis-related cirrhosis, 23 were diagnosed at a curative stage (24%), while 73 (76%) were diagnosed at a non-curative stage. Comparative analysis using the chi-square method revealed that the proportion of patients diagnosed at a curative stage was significantly lower among those with alcohol-related cirrhosis compared to those with viral hepatitis-related cirrhosis ($p = 0.01$). This finding underscores the challenges faced by patients with alcohol-related cirrhosis in accessing timely and effective treatment options.

TABLE III.

Stage at diagnosis according to cirrhosis etiology

	Alcohol-related cirrhosis (n=54)	Viral hepatitis-related cirrhosis (n=96)	p-value
BCLC stage, n (%)			
Potentially curable stages	**4 (7.4%)**	**23 (24%)**	
0 (very early)	0	0	
A (early)	2 (3.7%)	8 (8.3%)	
B1 (intermediate 1)	2 (3.7%)	15 (15.6%)	
Stages not eligible for curative treatment	**50 (92.6%)**	**73 (76%)**	p = 0.01
	4 (7.4%)	7 (7.3%)	
B2 (intermediate 2)	2 (3.7%)	3 (3.1%)	
B3 (intermediate 3)	18 (33.3%)	19 (19.8%)	
C (advanced)	26 (48.2%)	44 (45.8%)	
D (terminal)			

DISCUSSION

A striking finding of our study is the exceptionally high proportion of patients diagnosed at non-curative stages (81.6%), with no cases identified in the very early stage and only 18.4% diagnosed at curative stages, highlighting a critical gap in early detection and intervention.

Moreover, nearly half of the patients in both alcohol-related and viral cirrhosis groups were diagnosed at the terminal stage (BCLC D). According to the current staging system, patients with severely impaired liver function are automatically classified as Stage D, regardless of tumor burden (7). This could be seen as a limitation of the actual staging system, because this means that even patients with small, potentially treatable tumors may be excluded from curative or life-prolonging interventions, because of end-stage liver disease. Nevertheless, while this classification reflects the poor overall prognosis in such cases, it also raises concerns about missed therapeutic opportunities, particularly in centers where liver transplantation is accessible. Given the evolving landscape of HCC management, with improvements in locoregional therapies and transplant eligibility criteria, a more nuanced approach that considers individual patient profiles-beyond hepatic function alone-could be beneficial in refining treatment decisions.

At the same time, most hospitalized patients fall into this D category, while very few have preserved liver function-these patients may be evaluated in outpatient settings and possibly managed directly by surgery, oncology, or interventional radiology without requiring admission to the gastroenterology department. This could partly explain the exceptionally high proportion of patients diagnosed at Stage D.

Our study demonstrates that patients with hepatocellular carcinoma (HCC) who have alcohol-related cirrhosis are significantly more frequently diagnosed at non-curative stages compared to those with viral hepatitis-related cirrhosis. This finding highlights critical disparities in disease surveillance, healthcare engagement, and modifiable risk factors between these two groups.

One of the most plausible explanations for this discrepancy is the reduced adherence of patients with alcohol-related liver disease to regular medical follow-up and surveillance programs. Chronic alcohol consumption is often associated with poor healthcare-seeking behavior, lower compliance with medical recommendations, and social or psychological factors that further hinder early diagnosis. Unlike patients with viral hepatitis, who are often identified through screening programs and may receive structured follow-up care, patients with alcohol-related cirrhosis may not seek medical attention until they develop symptoms, by which time the disease has often progressed to an advanced stage. Furthermore, alcohol use disorder is frequently accompanied by socioeconomic challenges, mental health comorbidities, and stigma (8), all of which contribute to delayed presentation and reduced access to curative interventions.

Another key factor in this disparity is the availability of antiviral therapies that can effectively suppress or even eliminate viral hepatitis, reducing the risk of HCC development and improving liver function. The advent of direct-acting antivirals (DAAs) for hepatitis C virus (HCV) and nucleos(t)ide analogs for hepatitis B virus (HBV) has significantly changed the natural history of viral cirrhosis (9,10). By decreasing viral replication, these treatments slow fibrosis progression, decrease inflammation, and, in some cases, lead to

fibrosis regression, thereby mitigating the oncogenic potential of chronic hepatitis (11). In contrast, alcohol-related liver disease remains a challenging entity with no pharmacologic intervention capable of reversing liver injury or eliminating the carcinogenic risk. Abstinence is the primary intervention, but its success depends heavily on patient motivation, psychological support, and access to addiction treatment services-factors that are highly variable and difficult to sustain in the long term.

Our findings emphasize the urgent need to enhance HCC surveillance in patients with alcohol-related cirrhosis. Given that current guidelines recommend biannual ultrasound screening for high-risk individuals (12,13), strategies to improve adherence among this population are critical. Potential solutions include integrating hepatology care with addiction services, implementing patient navigation programs, and leveraging digital health tools for appointment reminders and follow-up (14). Additionally, targeted public health interventions that address alcohol dependence and promote awareness of HCC risk may help shift the current paradigm of late-stage diagnosis in this vulnerable group.

Another aspect that deserves attention is the underutilization of liver transplantation in patients with alcohol-related cirrhosis. Despite being a well-established curative option for selected patients with HCC (15), access to transplantation remains limited for those with alcohol-related liver disease due to concerns regarding relapse and post-transplant adherence to medical care. While current selection criteria emphasize sustained abstinence (16), emerging evidence suggests that some patients with alcohol-related HCC may achieve excellent outcomes even with shorter pre-transplant sobriety periods, provided they receive appropriate psychosocial support (17). Expanding transplantation eligibility in carefully selected patients could improve survival rates and offer curative potential in a subset of patients who are otherwise classified as non-curative due to liver dysfunction.

Finally, the disparities observed in our study highlight the need for targeted public health interventions to improve HCC screening and early detection, particularly in high-risk populations. Patients with alcohol-related cirrhosis may benefit from enhanced surveillance strategies that integrate hepatology with addiction medicine, patient navigation programs to facilitate adherence, and digital health tools such as automated reminders for screening appointments. Additionally, raising awareness about HCC risk among primary care providers and implementing outreach programs for underserved populations could help bridge the gap in early diagnosis and improve outcomes in this vulnerable group.

CONCLUSIONS

The significantly higher proportion of non-curative stage diagnoses among patients with alcohol-related cirrhosis underscores the need for improved screening strategies, better patient engagement, and integrated approaches to alcohol use disorder management. Unlike viral hepatitis, where antiviral therapies can modify disease progression and reduce HCC risk, alcohol-related liver disease continues to pose unique challenges that demand a more proactive and multidisciplinary approach.

Our findings reinforce the urgent need for a more proactive, multidisciplinary approach to the detection and management of HCC in patients with alcohol-related cirrhosis. Addressing disparities in surveillance and access to care, refining staging criteria, and optimizing treatment pathways could

significantly improve outcomes for these high-risk patients. Future research should focus on identifying effective interventions to bridge these gaps and reduce the burden of advanced-stage HCC diagnoses.

CONFLICT OF INTEREST AND FUNDING

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