

# Clinical Profile, Risk Factors, and Treatment of Hepatocellular Carcinoma in Nepal: A Single Centre Experience

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## Abstract

Background Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Liver cancer is one of the commonest cancers worldwide in terms of incidence and mortality. Viral hepatitis, alcohol abuse, and autoimmune hepatitis are the common causes of HCC. Usually patients present at advanced stages where curative treatment is no longer possible. This study aims to analyze the demographic, clinical, and radiological profiles and treatment patterns of HCC patients. Methods We studied patients with HCC from March 2020 to August 2022 and analyzed their risk factors, clinical characteristics, and treatment modalities. Patients with at least one clinical, radiological, or biochemical evidence of HCC were considered for the study. Data were collected using predetermined proformas. Results Our study included 54 patients with a mean age of 57.17 years, and male: female ratio of 5:1. Of them, 68.52% consumed alcohol and 74.07% smoked cigarettes. At the time of diagnosis, 88.89% of them were symptomatic, weight loss (64.81%) being the most common symptom. The majority of the participants belonged to Barcelona Clinic Liver Cancer (BCLC) terminal stage (38.89%) and had more than three liver lesions (35.19%) involving the right lobe (55.56%). Only four patients underwent curative surgical resection. As most were in the terminal stage (BCLC D), supportive care was provided. Conclusion Alcohol-related liver cirrhosis is the most common cause of HCC in Nepal. Despite the significant progress in diagnostic methods, most of the patients are diagnosed at advanced and terminal stages. These patients are unsuitable for curative treatment and are treated with supportive methods. Keywords Autoimmune hepatitis, hepatitis, hepatocellular carcinoma, treatment.

## Clinical Profile, Risk Factors, and Treatment of Hepatocellular Carcinoma in Nepal: A Single Centre Experience

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## ETHICAL APPROVAL STATEMENT

The study was approved by the Institutional Review Committee of the Institute of Medicine (reference number: 132/ (6-11) E<sup>2</sup>/076/077), and informed consent was taken from each patients.

## ABSTRACT

### Background

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Liver cancer is one of the commonest cancers worldwide in terms of incidence and mortality. Viral hepatitis, alcohol abuse, and autoimmune hepatitis are the common causes of HCC. Usually patients present at advanced stages where curative treatment is no longer possible. This study aims to analyze the demographic, clinical, and radiological profile and treatment patterns of HCC patients.

### Methods

We studied patients with HCC from March 2020 to August 2022 and analyzed their risk factors, clinical characteristics, and treatment modalities. Patients with at least one clinical, radiological, or biochemical evidence of HCC were considered for the study. Data were collected using predetermined proformas.

### Results

Our study included 54 patients with a mean age of 57.17 years, and male: female ratio of 5:1. Of them, 68.52% consumed alcohol and 74.07% smoked cigarettes. At the time of diagnosis, 88.89% of them were symptomatic, weight loss (64.81%) being the most common symptom. The majority of the participants belonged to Barcelona Clinic Liver Cancer (BCLC) terminal stage (38.89%) and had more than three liver lesions (35.19%) involving the right lobe (55.56%). Only four patients underwent curative surgical resection. As most were in the terminal stage (BCLC D), supportive care was provided.

### Conclusion

Alcohol-related liver cirrhosis is the most common cause of HCC in Nepal. Despite the significant progress in diagnostic methods, most of the patients are diagnosed at advanced and terminal stages. These patients are unsuitable for curative treatment and are treated with supportive methods.

### Keywords

Autoimmune hepatitis, hepatitis, hepatocellular carcinoma, treatment.

## INTRODUCTION

Liver cancer is one of the commonest cancers worldwide which occupies fifth and seventh ranks in terms of incidence among males and females respectively, and fourth position in overall mortality.<sup>1</sup> The higher age-standardized rates (ASR) of incidence of liver cancer i.e. 22.2 and 7.2 per 100,000 population among males and females respectively in South East Asia suggest that this tumor is more prevalent in the developing world where the prevalence of viral hepatitis B and hepatitis C is higher. As per the same report, the estimated mortality of liver cancer in this region is 21.4 and 6.8 per 100,000 for males and females respectively.<sup>2</sup> According to the National Cancer Registry of Nepal (2013), the incidence of liver cancer in Nepal in men

and women is 0.8 and 0.9 per 100,000 population respectively. However, the mortality rates of cancer are not recorded in the registry.<sup>3</sup>

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, the other less common types being intrahepatic cholangiocarcinoma (ICC), angiosarcoma, hemangiosarcoma, and hepatoblastoma in the descending order of their occurrence.<sup>4, 5</sup>

Liver cirrhosis is the most common cause of HCC accounting for 80% of cases.<sup>6</sup> The commonest risk factors for HCC are viral hepatitis (hepatitis B and hepatitis C infection), excessive alcohol use, occupational exposure, nonalcoholic fatty liver disease (NAFLD), and autoimmune hepatitis (AIH).<sup>6</sup> These factors lead to liver cirrhosis which is also considered as a premalignant state. The cirrhotic cells are more likely to undergo dysplasia and may lead to HCC development.<sup>6</sup> The patients with hepatic cirrhosis and those with suspected HCC are investigated with noninvasive modalities like multiphasic contrast-enhanced computed tomography (CECT), contrast-enhanced magnetic resonance imaging (CE-MRI) of the abdomen to verify the presence of HCC (diagnosis) and to determine its extent (radiological staging).<sup>7</sup>

The Barcelona Clinic Liver Cancer (BCLC) algorithm is the most widely used staging system. Patients with a single liver tumor or as many as three nodules of less than 3 cm diameter are classified as having very early-stage (BCLC stage 0) or early-stage (BCLC stage A) cancer. These patients benefit from curative treatment modalities like resection, transplantation, or ablation. Those with a greater tumor burden, confined to the liver, but are free of symptoms are considered to have intermediate-stage (BCLC stage B) cancer. If their liver function is intact, they can be benefitted from chemoembolization. Those with symptoms of HCC and/or vascular invasion and/or extrahepatic cancer are considered to have advanced-stage (BCLC stage C) and terminal-stage (BCLC stage D) cancer. These patients could benefit from treatment with the kinase inhibitor, sorafenib.<sup>8</sup>

Though the cancer registry began in Nepal in 2003, the registry is not comprehensive, and there are very limited studies conducted on liver cancers in Nepal.<sup>9</sup> In this single center-based study, we have analyzed clinical, etiological, and radiological data and treatment patterns of patients with liver cancer visiting the outpatient department (OPD) or admitted to the Department of Gastroenterology in Tribhuvan University Teaching Hospital (TUTH).

## METHODS

This is a descriptive cross-sectional study. Fifty-four patients with HCC who either visited the OPD or were admitted to the TUTH under the Department of Gastroenterology from March 2020 to August 2022 were considered for the study. These patients had at least one clinical, radiological, or biochemical evidence of HCC. We analyzed the risk factors, clinical characteristics, and treatment modalities in patients with HCC. The diagnosis of HCC was made by detailed clinical examination, imaging modality (dynamic CT scan or MRI of the abdomen) which show early arterial enhancement and venous washout of the lesion, or with the biopsy of the lesion whenever necessary. Predetermined proforma was used as a tool for data collection. The study was approved by the Institutional Review Committee of the Institute of Medicine (reference number: 132/ (6-11) E<sup>2</sup>/076/077).

### Statistical Analysis

The data obtained from the above study were tabulated in Microsoft Excel 2016. The statistical analysis was done using SPSS (Statistical Package for the Social Sciences) version 21. Results on continuous variables were expressed as mean  $\pm$  standard deviation (SD) and results on categorical variables were expressed in number (%).

## RESULTS

We enrolled and analyzed 54 patients who had hepatocellular carcinoma. The youngest patient in our study was 28 years old, the oldest was of 81years, and the mean age was 57.17 years. Of them, 46 (85.18%) were male and 8 (14.82%) were female. The majority of the patients in the study followed Hinduism (75.93%).

Of the total participants, 37 (68.52%) consumed alcohol and a majority of them were smokers (74.07%). Comorbidity in the form of diabetes mellitus was present in five patients (9.26%), hypertension in six patients (14.81%), and both diabetes and hypertension were present in eight patients (11.11%) (Table 1).

We also analyzed all the patients to determine the possible etiologies of HCC. The study depicted that, alcohol abuse was the commonest cause of HCC (38.89%) followed by chronic viral hepatitis B (CHB) infection (11.11%). In addition, 12 patients (22.22%) had a history of both significant alcohol consumption as well as CHB infection (Table 2).

At the time of diagnosis, most of the patients were symptomatic (88.89%). The commonest presenting symptoms were weight loss (64.81%), abdominal distension (61.11%), anorexia (61.11%), and abdominal pain (50.0%). Ascites was present in more than half of the patients (59.26%) and hepatic encephalopathy was found in only four patients (7.41%) (Table 3).

All patients underwent imaging by either triple phase CT scan or an MRI of the abdomen. The HCC most commonly involved the right lobe of liver (55.56%) followed by the bilobar involvement (29.63%). The left lobe was involved in eight patients (14.78%). Multicentric HCC with more than three lesions was the most common radiological pattern (35.19%) followed by the single lesion (27.78%). Vascular involvement of the porto-splenic axis was seen in nearly half of the patients (44.44%). Extrahepatic spread of the tumor was seen in eight patients (14.81%). Four patients (7.41%) had regional periportal lymph node involvement, two (3.70%) had metastasis to the lung, and the remaining two (3.70%) had metastasis to the peritoneum. On detailed evaluation, 42 patients (77.78%) were found to have underlying liver cirrhosis. The majority of cirrhotic patients had already progressed to the decompensated stage (80.95%).

Child-Turcotte-Pugh (CTP) status was calculated in all patients. The analysis depicted that 23 (42.59%) patients had CTP A, 14 (25.93%) had CTP B, and 17 (31.48%) had CTP C. Functional status was assessed by using Eastern Cooperative Oncology Group (ECOG) performance status, and most common performance status was ECOG 0 (37.04%) followed by ECOG 2 (20.37%) and ECOG 3 (20.37%). Based on tumor characteristics, CTP score, and ECOG performance status, BCLC (Barcelona Clinic Liver Cancer (BCLC) staging was done. The analysis showed that the majority of the participants belonged to the terminal stage (BCLC category D) (38.89%) followed by the advanced stage (BCLC category C) (35.19%). None of our patients was detected in the very early stage (BCLC category 0). (Table 4)

The evaluation of laboratory parameters among the participants demonstrated that the serum alpha-fetoprotein was elevated in 44 patients (81.48%) with a mean value of  $525 \pm 37$  ng/ml. The majority of the patients were anemic with a mean value of hemoglobin of  $10.9 \pm 2.7$  g/dl. The mean values of serum sodium level, AST, and ALT were within normal limits, however, mean serum alkaline phosphatase (ALP) was raised as shown in Table 5. The mean values of CTP score, Model for End-Stage Liver Disease (MELD) score, and MELD-Na score were also calculated. (Table 5)

Most of the patients (92.59%) underwent non-surgical treatment and only four patients underwent surgical treatment i.e., tumor resection. Among non-surgical treatment modalities, only 2 patients underwent therapy with curative intent in the form of microwave ablation. As most of our patients were in the terminal stage (BCLC D), they were provided with the best supportive care. Some patients received transarterial chemoembolization (TACE) (50.0%) and chemotherapy with sorafenib (31.48%) as palliative therapeutic measures. (Table 6)

## DISCUSSION

This is the largest study in Nepal of this type where we analyzed the clinical, etiological, and radiological profile of 54 patients with HCC visiting the OPD or admitted to the ward under the Department of Gastroenterology. Previous studies have shown that the incidence of HCC increases with age such that its occurrence before 40 years of age is minimal in the Western world.<sup>10</sup> The age distribution of patients with HCC in this study is similar to a study by Kumar R. et al. in India which has shown the maximum incidence of HCC in the sixth decade.<sup>10</sup> Regarding the sex-wise distribution of HCC, our study showed that there is a

male preponderance in the prevalence of HCC in our study with a male: female ratio of 5:1. Similar finding with a higher preponderance of HCC in male is shown in other previous studies with the male: female ratios ranging from 3:1 to 10:1.<sup>9-11</sup> This suggests that older age and male sex are the risk factors for liver cancer. However, the higher incidence of HCC in males might be because of the higher tendency of males in seeking medical treatment in comparison to females.

The current study demonstrated that most of the patients (88.89%) were symptomatic at the time of presentation, and the most common presentations were abdominal discomfort/pain, abdominal distention, and anorexia. This finding corresponds with other similar studies where only 16.81% of total patients were asymptomatic and the rest presented with similar complaints.<sup>11, 12</sup> This reflects the late presentation of the patients with HCC to the medical facility when the tumor is no longer resectable with complaints like abdominal pain and abdominal distension.

Non-cirrhotic HCC accounted for 22.22% of all patients in our study, while the majority (77.78%) had liver cirrhosis. Most of the patients with cirrhosis (80.95%) had decompensated disease in various forms. A multinational cross-sectional study by Yang J.D et al. in Africa revealed that all the patients with HCC in Egypt (100%) and around two-thirds in other African nations (66%) had cirrhosis. The findings in our study and other similar studies suggest that hepatic cirrhosis is also a strong risk factor for HCC.<sup>13</sup>

The etiological factors for HCC vary in different geographical regions. The majority of our patients with HCC had alcohol abuse as a cause of cirrhosis, and HBV as the sole cause of cirrhosis was seen only in 11% of patients. These findings contradict the outputs of other studies conducted in India which found HBV as the most common cause of HCC.<sup>10,12</sup> However, a similar study conducted by Egypt showed HBV infection in only 22.4% of total cases of HCC.<sup>14</sup> Similarly, another study by Aljumah A. et al. indicated HCV infection as the most common cause of HCC affecting 46.80% of the total cases.<sup>6</sup> This could be due to the fact that there is a very low prevalence of HBV and HCV in Nepal, and alcohol-related cirrhosis is quite common in our country.<sup>15-17</sup>

We also analyzed the tumor markers of these patients. Serum AFP level was elevated in 81.48% of our patients and median AFP level was 286ng/ml. In a study by Bhatti et al., the median AFP level among patients with HCC was only 43.6ng/ml. This difference could be because most of the patients presented with advanced HCC in our study. Though serum AFP measurement is used as a screening tool for HCC, the rise in its levels in serum is neither sensitive nor specific to HCC.<sup>18, 19</sup>

We observed that most of our patients presented either with advanced stage (BCLC stage C) (35.19%) or terminal stage (BCLC stage D) (38.89%) HCC despite the fact that the majority (42.59%) of them had Child-Turcotte-Pugh (CTP) score A. This is in contrast to the study by Aljumah A. et al. where BCLC combined stages A and B comprise nearly 70% of total cases, with the majority having preserved liver function, CTP score class A.<sup>6</sup> Moreover, macrovascular invasion and metastases were seen in 44.44% and 14.81% of patients respectively, which is in accordance with the study, by Masunuri et al., where portal vein thrombosis (PVT) was seen in 40.4% of patients.<sup>11</sup> However other similar studies found PVT in less than 20% of total cases only.<sup>6, 14</sup> Since, tumor cells are more likely to disseminate via portal circulation to distant organs, presence of PVT in a HCC is a critical issue leading to early deterioration of hepatic function and worse prognosis.<sup>6</sup> Thus, PVT was the major reason that more than one-third of the patients in our study belonged to the advance stage HCC despite being in a good functional status. Notably, potentially curative therapies were underutilized i.e. only 7.41% received surgical and 3.70% received non-surgical curative services. Because of the presence of poor prognostic factors and aggressive behavior of HCC, 38.89% of them received only the best supportive care for their symptoms. However, the treatment approaches for patients with HCC in Africa varied compared to our setting. For example, 35% of total HCC patients in Egypt and less than 1% in other African countries received curative treatment.<sup>13</sup>

In this study, though we tried to include all the patients with HCC at a tertiary care center in Nepal, and analyzed their clinical, etiological, and radiological profile, there are certain limitations. Being a single-center study, it does not reflect the actual scenario of HCC in Nepal and therefore the results are not generalizable.

Being a tertiary care center, most cases we received were at advanced stages, therefore, we could not analyze the actual outcomes of the treatment in all the stages. In addition, we did not follow up on these patients to evaluate the outcomes of the treatment.

## CONCLUSION

In summary, our study depicted that, older age, male gender, excess alcohol intake, viral hepatitis, and liver cirrhosis were the common risk factors for liver cancer in Nepal. Since most of the patients are asymptomatic in the initial stage of cancer, it is already late when they become symptomatic and present to us when curative treatment is no longer possible. Being a single-center study, the findings are not generalizable to all the Nepalese population. Therefore, we suggest a multicenter study to draw a clearer picture of the prevalence, risk factors, clinical presentation, and treatment modalities of HCC in Nepal.

## ABBREVIATIONS

AIH: Autoimmune Hepatitis

ASR: Age-standardized Rates

Barcelona Clinic Liver Cancer (BCLC)

CECT: Contrast-Enhanced Computed Tomography

CE-MRI: Contrast-Enhanced Magnetic Resonance Imaging

CHB: Chronic Viral Hepatitis B

CTP: Child-Turcotte-Pugh

ECOG: Eastern Cooperative Oncology Group

g/dl: Gram per deciliter

g/l: Gram per liter

HCC: Hepatocellular Carcinoma

ICC: Intrahepatic Cholangiocarcinoma

IU/L: International Unit per Liter

MELD: Model for End-Stage Liver Disease

MELD-Na: Model for End-Stage Liver Disease Sodium

meq/l: Milliequivalent per liter

NAFLD: Nonalcoholic Fatty Liver Disease

ng/ml: Nanogram per milliliter

OPD: Outpatient Department

## AUTHOR CONTRIBUTIONS

**Arun Gnawali:** Conceptualization, data collection, data analysis, manuscript writing, and editing the draft

**Rahul Pathak:** Conceptualization, data analysis, supervision, and editing the draft

**Dinesh Koirala:** Data analysis, supervision, and editing the draft

**Rajesh Pandey:** Data analysis, and editing the draft

**Rabin Hamal:** Data collection, data analysis, and editing the draft

**Anurag Jha:** Data collection, data analysis, and editing the draft

**Brindeswari Kafle Bhandari:** Data collection, data analysis, and editing the draft

**Siddinath Gyawali:** Manuscript writing, data analysis, and editing the draft

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### CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest.

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**Table 1.** Demographic profile of the patients (n = 54)

Patient characteristics	Patient characteristics	Number (%)
Age wise distribution (in years)	[?]40	6 (11.11)
	40-49	8 (14.81)
	50-59	14 (25.92)
	60-69	13 (24.07)
	[?]70	13 (24.07)
Gender	Male	46 (85.18)
	Female	8 (14.82)
Religion	Hindu	41 (75.93)
	Buddhist	13 (24.07)
HCC diagnosis	Symptomatic	48 (88.89)
	Incidental	6 (11.11)
Co-morbidities	HTN	5 (9.26)
	DM	8 (14.81)
	DM+HTN	6 (11.11)
Alcohol use	Alcohol use	37 (68.52)
Smoking	Smoking	40 (74.07)

**Table 2.** Etiology of HCC (n = 54)

Etiology	Number (%)
Alcohol	21 (38.89)
HBV	6 (11.11)
NAFLD	2 (37.03)
Alcohol + HBV	12 (22.22)
Alcohol + HCV	4 (7.41)
Cryptogenic	6 (11.11)
Hereditary hemochromatosis	3 (5.56)

**Table 3.** Clinical features of patients with HCC (n = 54)

Clinical features	Number (%)	Number (%)	Number (%)
Pain abdomen	27 (50.0)	27 (50.0)	27 (50.0)
Abdominal distention	33 (61.11)	33 (61.11)	33 (61.11)
Anorexia	33 (61.11)	33 (61.11)	33 (61.11)
Weight loss	35 (64.81)	35 (64.81)	35 (64.81)
Jaundice	8 (14.81)	8 (14.81)	8 (14.81)
UGI bleed	6 (11.11)	6 (11.11)	6 (11.11)

Clinical features	Number (%)	Number (%)	Number (%)
Altered sensorium	2 (37.04)	2 (37.04)	2 (37.04)
Ascites	32 (59.26)	Grade I	5 (15.63)
		Grade II	4 (12.50)
		Grade III	23 (71.88)
Hepatic encephalopathy	4 (7.41)	4 (7.41)	4 (7.41)

**Table 4.** Malignancy characteristics of HCC (n = 54)

Malignancy characteristics	Malignancy characteristics	Malignancy characteristics	Number (%)
No. of lesion	1	1	15 (27.78)
	2	2	8 (14.81)
	3	3	12 (22.22)
	>3	>3	19 (35.19)
Lobe of liver	Right	Right	30 (55.56)
	Left	Left	8 (14.81)
	Both	Both	16 (29.63)
CTP status	A	A	23 (42.59)
	B	B	14 (25.93)
	C	C	17 (31.48)
ECOG performance status	0	0	20 (37.04)
	1	1	8 (14.81)
	2	2	11 (20.37)
	3	3	11 (20.37)
	4	4	4 (7.41)
BCLC Staging	0	0	0
	A	A	8 (14.81)
	B	B	6 (11.11)
	C	C	19 (35.19)
	D	D	21 (38.89)
Distant metastasis	Yes	Yes	8 (14.81)
	No	No	46 (85.19)
Portal vein thrombosis	Yes	Yes	24 (44.44)
	No	No	30 (55.56)
AKI	Yes	Yes	8 (18.81)
	No	No	46 (85.19)
AFP elevated	Yes	Yes	44 (81.48)
	No	No	10 (18.52)
Liver status	Cirrhotic	Decompensated	34 (62.97)
		Compensated	8 (14.81)
	Non-cirrhotic	Non-cirrhotic	12 (22.22)

**Table 5.** Laboratory parameters of patients with HCC (n = 54)

Parameters	Mean value	Normal references used
Hemoglobin (g/dl)	10.9±2.7	12.5-15 gm%
Total bilirubin (micromole/l)	60.6±13	5-21 µMol/L
Serum albumin (g/l)	32.2±4	34 to 54 g/L

Parameters	Mean value	Normal references used
Sodium (meq/l)	135±4	135-146 meq/L
AST (IU/L)	114±20	0-35 U/L
ALT (IU/L)	52±11	0-35 U/L
ALP (IU/L)	525±44	30-120 U/L
AFP level (ng/ml)	525±37	0 ng/mL to 40 ng/mL
CTP score	7.7±1.6	-
MELD score	12.78±3	-
MELD-Na score	14.19±4.2	-

**Table 6.** Management modality of the patients with HCC. (n = 54)

Management Modality	Management Modality	Management Modality	Number (%)
Surgical	Surgical	Surgical	4 (7.41)
Non-surgical	Potentially curative (micro-ablation)	Potentially curative (micro-ablation)	2 (3.70)
	Palliative	TACE	10 (18.52)
		Sorafenib	17 (31.48)
	Best supportive	Best supportive	21 (38.89)