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Original Research Article

Etiology of hepatocellular carcinoma- Indian scenario - A changing landscape

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Abstract

Background: Recent studies from both India and abroad have shown a change in the etiological profile of hepatocellular carcinoma (HCC).
Aims-We aim to analyze the etiological spectrum and changing trends of HCC etiology in India at our tertiary centre
Materials and Methods: The records of all patients diagnosed with HCC between May 2012 and November 2024 were extracted from the hospital-based electronic database. Medical records were reviewed for 430 patients who received treatment for HCC. Patient characteristics and demographics were recorded. Data was captured and analysed for the patients who recieved radiation therapy.
Results: Total number of patients analysed were 429 who were diagnosed as HCC. There was a male preponderance of 90.6%. HBV/HCV cases initially increased from 22.2% (2012-2015) to 42.2% (2016-2019) but later dropped to 35.6% (2020-2024). In contrast, NASH/Alcohol cases steadily increased from 13.8% (2012-2015) to 24.5% (2016-2019) and then sharply rose to 61.6% (2020-2024), making it the leading cause in recent years. The Chi-square value (27.517) and p-value (<0.001) indicate a statistically significant association between disease type and time interval.
Conclusions: Rising HCC incidence rate is a cause for concern in India with viral hepatitis being the main cause. However, the increased incidence of non-viral HCC, particularly NASH-related, has been involved in the changing etiologies of HCC. Globally Nonalcoholic fatty liver disease (NAFLD) is swiftly becoming the most important cause of HCC. Effective strategies are needed to improve surveillance and early diagnosis in patients with high risk of developing hepatocellular cancer. NAFLD preventive strategies are an urgent need for public health in India.

Keywords: HCC, SBRT, PVTT, Nash, hepatitis B virus, hepatitis C virus

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1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer (~ 75–86% of liver cancers), the sixth most common cancer worldwide, and the third leading cause of cancer mortality[1-3] among patients with chronic liver disease. The prevalence and etiological factors of HCC vary greatly across nations indicating geographical variations worldwide. Earlier, the most common causes of HCC in Asia were chronic liver disorders associated to the hepatitis B and hepatitis C viruses. But in recent years, alcohol abuse and non-alcoholic fatty liver disease (NAFLD) have emerged as the main causes of cirrhosis and HCC.[4] The incidence of HCC related to hepatitis B is showing a downtrend, while those related to alcohol and NASLD are rising

Across all continents, the incidence rates of HCC linked to alcoholic fatty liver disease (AFLD) and nonalcoholic fatty liver disease (NAFLD) have sharply increased due to societal shifts, the growing preference for western diets, and a lifestyle with little to no physical exercise.[27,28] The clinical spectra of liver injury in supporting the development of HCC in NAFLD and AFLD share identical molecular mechanisms, despite their different pathogenic origins. Additionally, ethanol and a high-calorie diet work synergistically to cause hepatocarcinogenesis at multiple stages.[29]

Curative resection or liver transplant are the optimal treatments for patients with localized HCC. Several treatment options are available for patients who are ineligible for surgery, including transarterial chemoembolization (TACE), transarterial radioembolization (TARE), hepatic arterial infusion chemotherapy (HAIC), radiofrequency ablation (RFA), percutaneous ethanol injection therapy, and radiation therapy (RT). Selection of treatment modality depends on the tumor size, number, vascular invasion, and the patient's

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performance status. External beam radiotherapy (EBRT) can be performed in various circumstances, from curative to palliative. Compared to conventional EBRT, stereotactic body radiotherapy (SBRT) delivers a high conformal dose with a lower dose to the normal liver and is included in the National Comprehensive Cancer Network guidelines as a curative option.[6] SBRT for HCC has shown high rates of local control, ranging from 87% to 100% at 1 to 3 years in prospective clinical trials.[7]

In light of the evolving epidemiology and etiological spectrum of HCC in India, an updated evaluation of the existing literature and databases is therefore required. In addition to previous Indian research, the study includes data from the Global Burden of Diseases, Injuries, and Risk Factors Study and the National Cancer Registry Program emphasises that the present incidence (2.15 per 100,000), prevalence (2.27 per 100,000), and mortality (2.21 per 100,000) rate of HCC in India remain lower compared to the global data. In the Indian population males have a greater current incidence, prevalence, and mortality rate from HCC, although females have a higher yearly rate of change. Campaigns for awareness, targeted therapies, and public health activities are all required to combat these changes, especially in regions with high incidence rates.[5]

2. Materials and Methods

This was a retrospective study. Clinical data of patients diagnosed with hepatocellular carcinoma (HCC) between May 2012 and November 2024 were extracted from the hospital's electronic medical records system.

Step-by-Step Data Collection Process*:*

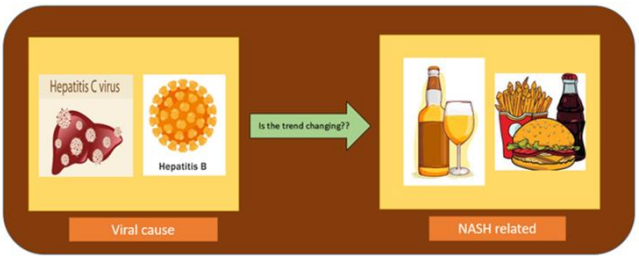
1. Patient identification: All patients with a confirmed diagnosis of HCC were identified using ICD coding and departmental oncology logs.
2. Inclusion criteria**:** Patients with histologically or radiologically confirmed HCC, with or without extrahepatic spread, and who received treatment (especially radiation therapy) at our center during the study period.
3. Data abstraction**:** A structured data abstraction form was used to collect:
    a. Demographics (age, gender)
    b. Clinical data (ECOG performance status, BCLC stage, Child-Pugh Score)
    c. Laboratory values (AFP, PIVKA-II)
    d. Imaging reports
    e. Etiology of chronic liver disease (HBV, HCV, NASH, alcohol, cryptogenic)
    f. Prior treatments (TACE, TARE, surgery)
    g. Radiation details (SBRT dose and technique)
4. Data Entry and Validation**:** Data were entered into a secure spreadsheet. Two reviewers independently cross-verified a 10% random sample for accuracy.

Handling of Missing Data: Missing values for non-critical variables were reported as "not available" and excluded from specific analyses using pairwise deletion. Incomplete cases for key variables (e.g., diagnosis, treatment received, outcome) were excluded from the final analysis. No imputation was performed. The number of observations (n) included for each variable is indicated in tables wherever applicable.

Child Turcot Pugh (CTP) score was assessed and staged as per BCLC criteria. Baseline alpha feta protein (AFP) and Protein induced by vitamin K antagonist II (PIVKA II) values were recorded. History of prior treatment ie TACE/ TARE were recorded and patients were taken up for SBRT depending upon the multidisciplinary tumour board decision. The total dose prescription was individualized as per the tumor volume, location, relation with OARs, and other clinical conditions. Data was captured and analysed for these patients who were treated with radiation therapy.

2.1. Statistical methods

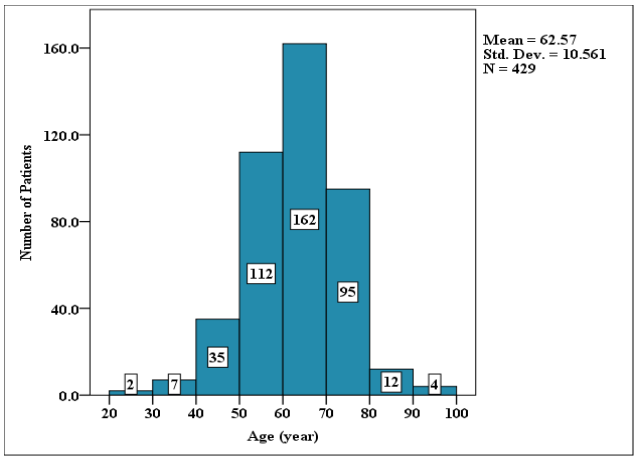
The analysis includes profiling of patients on different demographic, clinical and radiological findings. Descriptive analysis of quantitative parameters were expressed as means and standard deviation. Categorical data were expressed as absolute number and percentage. Cross table was generated and Chi square test was used for testing of associations. All analysis were done using SPSS software, version 24.0.



3. Results

Total number of patients analysed were 429 who were diagnosed as HCC.

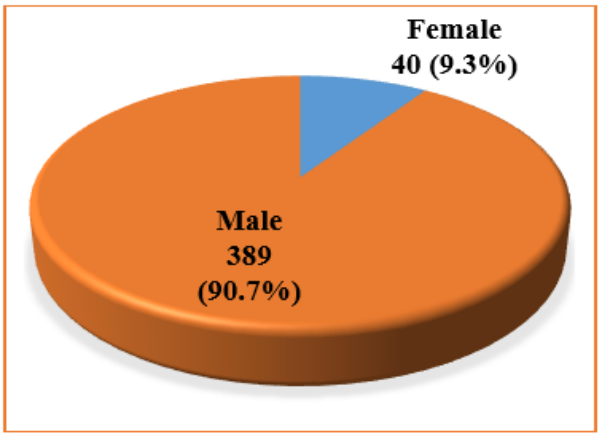
We calculated age standardized incidence rates as shown in **Graph 1**. Out of which there was a male preponderance of 90.6% **Graph 2**. Other baseline patient characteristics and demographics are tabulated in **Table 1**. Treatment characteristics summarized in **Table 2**



Graph 1: Distribution of age (years)

Table 1: Baseline characteristics of patients

	Number of Patients (n = 429) (%)
Age (years)	
Mean ± SD (Range)	62.6 ± 10.6 (25 - 95)
Median (IQR)	64 (56 - 70)
Gender	
Female	40 (9.3%)
Male	389 (90.7%)
BCLC	
A	42 (9.8%)
B	57 (13.3%)
C	316 (73.7%)
D	14 (3.3%)
ECOG	
0	96 (22.4%)
1	225 (52.4%)
2	94 (21.9%)
3/4	14 (3.3%)
Diagnosis	
HCC with PVTT	231 (53.8%)
Metastatic HCC	86 (20%)
HCC	81 (18.9%)
Multicentric HCC	8 (1.9%)
Metastatic HCC with PVTT	5 (1.2%)
Multifocal HCC	5 (1.2%)
Multifocal HCC with PVTT	5 (1.2%)
HCC post-transplant	4 (0.9%)
HCC with IVCTT	3 (0.7%)
Multicentric HCC with PVTT	1 (0.2%)
CLD Cause	
HBV	143 (33.3%)
Nash	136 (31.7%)
HCV	124 (28.9%)
Alcohol/ethanol related	22 (5.1%)
Cryptogenic	2 (0.5%)
HBV/HCV	1 (0.2%)
HBV/nash	1 (0.2%)
Child Pugh Score (CPS) (n = 64)	
A	31 (48.4%)
B	28 (43.8%)
C	5 (7.8%)
AFP (ng/dl)	
Median (Range)	174 (4 - 27533)
PIVKA-II (mAU/ml)	
Median (Range)	2778 (23.8 - 385454)



Graph 2: Distribution of gender

Table 2: Treatment characteristics

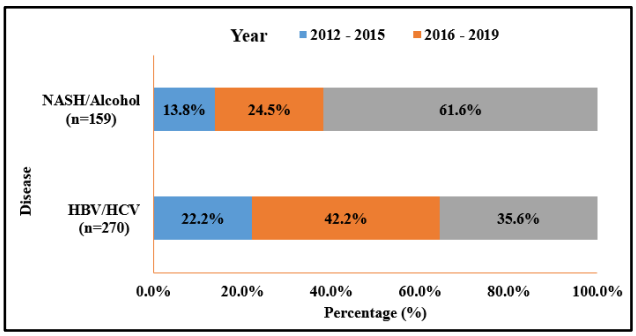
Prior treatment	
Yes	298 (69.5%)
No	131 (30.5%)
Treatment (n = 298)	
Tare	186 (62.4%)
Tace	99 (33.2%)
Both	13 (4.4%)
SBRT dose Gy (Median range)	35Gy (25-40Gy)

The mean age of patients is 62.6 years, with a standard deviation of 10.6 years, ranging from 25 to 95 years. The median age is 64 years (IQR: 56 - 70) with a male preponderance (90.7). The largest group of patients falls under BCLC stage C (73.7%), indicating advanced disease. Smaller proportions are in BCLC stage A (9.8%), B (13.3%), and D (3.3%). Majority patients have an ECOG status of 1 (52.4%), reflecting mild symptoms. 22.4% have an ECOG score of 0 indicating no symptoms. More severely affected patients with ECOG 2 (21.9%) and 3/4 (3.3%) are in the minority. 69.5% of patients had received prior treatment while 30.5% were treatment-naïve. Considering the diagnosis distribution, most common diagnosis was HCC with PVTT (53.8%). Other notable subtypes were metastatic HCC (20%), HCC without vascular invasion (18.9%), less common diagnoses included multicentric HCC (1.9%), HCC post-transplant (0.9%) and HCC with IVCTT (0.7%). The overall most common etiology for HCC were HBV (33.3%)

followed by NASH (31.7%) and HCV (28.9%). Alcohol-related liver disease accounted for 5.1%, while cryptogenic and dual infections were rare. Highlighting the liver function in terms of Child-Pugh Score (CPS) -Among 64 (n) patients assessed for CPS 48.4% had CPS A indicating well-compensated liver function. 43.8% had CPS B representing moderate impairment. 7.8% had CPS C reflecting severe liver dysfunction. Regarding the tumor markers the median value of AFP (Alpha-fetoprotein) was 174 ng/dl with a wide range (4 to 27,533 ng/dl) reflecting variable tumor burden. Similarly, the median level for PIVKA-II (Protein Induced by Vitamin K Absence-II) was 2778 mAU/ml ranging from 23.8 to 3,85,454 mAU/ml suggesting significant variability in disease severity. Among 298 treated patients 62.4% underwent TARE (Transarterial Radioembolization), 33.2% received TACE (Transarterial Chemoembolization): 33.2% and patients who underwent both TARE and TACE were 4.4%.

Table 3: Association of disease proportion with time interval

Year	HBV/HCV (n=270)	NASH/ Alcohol (n=159)	Total (n = 429)
2012-2015	60 (22.2%)	22 (13.8%)	82 (19.1%)
2016 - 2019	114 (42.2%)	39 (24.5%)	153 (35.7%)
2020 - 2024	96 (35.6%)	98 (61.6%)	194 (45.2%)

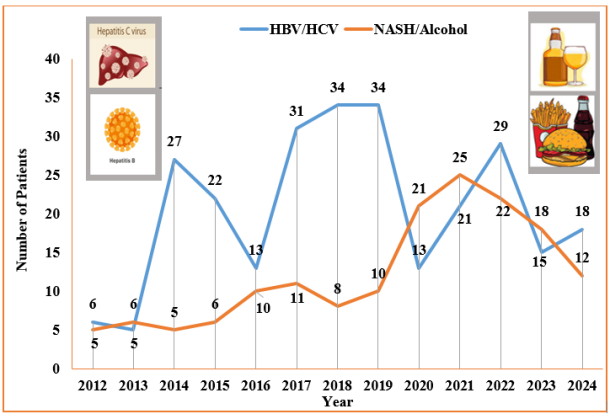


Chi-square value = 27.517; p-value < 0.001*

Graph 3: Association of disease proportion with time interval

The table 3 shows how the proportion of HBV/HCV and NASH/Alcohol-related liver disease has changed over time from 2012 to 2024 in a study of 429 patients (270 with HBV/HCV and 159 with NASH/Alcohol).

HBV/HCV cases initially increased from 22.2% (2012-2015) to 42.2% (2016-2019) but later dropped to 35.6% (2020-2024) **Graph 3**.



Graph 4: Distribution of number of patients of both group in different years

In contrast, NASH/Alcohol cases steadily increased from 13.8% (2012-2015) to 24.5% (2016-2019) and then sharply rose to 61.6% (2020-2024), making it the leading cause in recent years as in **Graph 4**.

The total number of cases has grown over time, with NASH/Alcohol now being more common than HBV/HCV. The Chi-square value (27.517) and p-value (<0.001) indicate a statistically significant association between disease type and time interval.

This shift suggests that metabolic and alcohol-related liver disease is becoming more prevalent, likely due to lifestyle factors, and highlights the need for stronger public health measures focused on prevention, alcohol control, and lifestyle changes.

4. Discussion

According to multiple studies, HBV infection accounts for around 70% to 80% of all occurrences of HCC in India, while HCV causes just 15% of cases.[10] The risk of developing HCC is 100 times higher for those with an HBV infection.[11] In India, there are about 40 million HBV carriers, and the prevalence of hepatitis B surface antigen ranges from 3.2% to 4.2%.[9]

The transmission of HBV infection through the fecal-oral route has been facilitated by inadequate waste management and drainage systems, inadequate education, and inadequate basic sanitation facilities.[12] Furthermore, India has inadequate hepatitis B birthdose vaccination. Commercial sex workers, injecting drug abusers, those with HIV infection or other sexually transmitted diseases and people receiving regular blood transfusions all had higher prevalence rates.[13]

The following are some factors that raise the risk of needle stick injuries and the spread of HBV and HCV: Inadequate hepatitis B immunization among healthcare professionals, excessive and unnecessary injection use,

unsafe injection procedures, and inappropriate disposal of sharp objects.[14] In patients with chronic liver disease caused by HBV or HCV, the risk of HCC is increased if they also have coexistent obesity, diabetes mellitus, HIV, aflatoxin exposure, or chronic drinking. [15]

An Indian multicentric research that examined data from hospital-based records at 11 participating centres between January 2017 and August 2022 under the supervision of the WHO Collaborative Center states that NAFLD is the most prevalent aetiology (35.5%), followed by hepatitis B (21.2%), hepatitis C (18%) and alcohol (13.9%).

Surgical resection is a treatment that has the potential to be curative.[22] The number and location of tumors, hepatic reserve, the expected volume of resection, and the underlying liver function are the factors that need to be considered to determine if a lesion is resectable.[21] Few studies have even shown that HCC patients with PVTT can achieve acceptable survival with LDLT after successful downstaging. There was a trend toward better overall survival in downstagiiing+ LDLT group versus non-downstaging + LDLT group (5-y OS/RFS—48%/40%).[15]

Local ablation can be used to try to cure patients who are not a good candidate for surgical resection, or it can be used to lessen the tumor burden[4]. Common ablation techniques include radiofrequency ablation (RFA), microwave ablation, and intra-arterial therapies such as transarterial chemoembolization (TACE).[23] SBRT has been recognized as an alternative therapy for patients for whom standard modalities such as surgery (resection or transplantation) or ablation are deemed unsuitable.[24] Retrospective studies have suggested the safety and efficacy of SBRT for the treatment of HCC [25,26] which is supported by the results of several prospective studies. Ultimately, future discoveries may facilitate the use of individualized therapy in patients with HCC.

It has been noticed that the etiology of HCC has changed in the recent years. A decrease in HBV infections, stability in HCV infections, and rising incidence of alcohol and nonalcoholic steatohepatitis (NASH) were observed as risk factors for HCC over the past few decades.[16] A total of 122 patients (4.6%) had either co-infection of hepatitis B and C, hepatitis associated with hazardous alcohol use, or both.[17]

It appears that NAFLD is now the most frequent cause of HCC, surpassing hepatitis B.[18] 51% of patients in a 3-year observational research at a tertiary care centre in India had NAFLD/cryptogenic as their primary cause of HCC, followed by hepatitis B (17.4%) and hepatitis C (5.8%).In individuals with both cirrhotic and noncirrhotic HCC, it is probably going to emerge as the most common causative cause. [19]

Indians are prone to obesity, type 2 diabetes, and physical inactivity, all of which are influenced by their increasing consumption of energy-dense foods and raise their risk of developing NAFLD. [20] While cirrhosis develops in around 3%–15% of obese NASH patients, HCC is acquired by approximately 4%–27% of NASH patients with cirrhosis. .[18] Early detection of HCC is therefore crucial, especially in individuals with noncirrhotic NAFLD.

5. Conclusion

In India, viral hepatitis has been the primary cause of HCC since the beginning. However, the evolving aetiologies of HCC in India have been related to the rising frequency of non-viral HCC, especially NASH-related HCC. It is crucial to look at how the aetiology of HCC has changed in order to drive future research and policy development. These shifting patterns and emerging trends suggest that in order to lower the incidence of HCC, more attention needs to be paid to addressing obesity and diabetes and putting in place more efficient policies to control alcohol use.

6. Abbreviations

HCC: Hepatocellular carcinoma; SBRT: Stereotactic body radiation therapy; NASH: Non-alcoholic Steatohepatitis; PVTT: portal vein tumor thrombosis; IVCTT: inferior vena cava tumor thrombosis; AFP: alpha feto protein; CPS: Child Pugh score; TARE: Transarterial radioembolisation; TACE: Transarterial chemoembolization.

7. Source of Funding

None.

8. Conflict of Interest

None.

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