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Research Article

Nonalcoholic Fatty Liver Disease Is Correlate With Cryptogenic Hepatocellular Carcinoma: A Case-Control Study

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Abstract

Background: Fatty liver is the most frequent chronic liver disease. Fatty liver-related hepatocellular carcinoma may be the origin of cryptogenic liver cancer. We aimed to perform the correlation between fatty liver and steatohepatitis in cryptogenic hepatocellular cancer. **Methods:** We retrospectively analyzed the records of 2086 primary hepatic carcinoma (HCC) patients in the District, Lahore from 2007 to 2020. A total of 330 cases were screened out with pathologic reports. Among the 330 cases, 183 cases of hepatitis B, 14 cases of hepatitis C, 33 cases of alcoholic liver, 20 cases of cholangiocarcinoma, 15 cases of metastatic carcinoma, 2 cases of autoimmune liver disease were ruled out, and **63** cases without definite etiology were inclusion analysis. **49** patients diagnosed with intrahepatic cholangiocarcinoma (CC) during the same period were also included as a comparison group. A total of **112** cases were included in this study. We delved into the demographic, clinical, and pathological characteristics of patients. Liver pathological films were interpreted by a pathologist（LLL）and a hepatologist who knows liver pathology (ZYT）. The pathological films around liver cancer were scored by the NAS method. The standard NAS score ≥5 was classified as steatohepatitis and non-alcoholic simple fatty liver disease was defined as those without intralobular inflammation, ballooning degeneration, and fibrosis but with hepatic steatosis>5%. The differences between the two groups were analyzed. **Results:** Pathological slides were not found in 2 of 112 cases (both in the HCC group). Among the pathological slides of 110 patients, 12 had no normal tissue around the tumor (10 HCC, 2 CC). Of the remaining 98 cases（51 HCC,47 CC）, 31 (26.7%) had a fatty liver background, including 24 patients with HCC (48%, 24/50) and 7 patients with CC (14.58%, 7/48), with statistically significant differences ($P < 0.001$). There were 16 cases of steatohepatitis, 14 cases in the HCC group (28 %, 14/50), and 2 cases in the CC group (4.17%,2/48), with statistically significant differences ($P < 0.001$). NAS score in the non-tumor liver was a statistically significant difference in HCCs and CCs groups ($p < 0.0001$), A statistically significant difference in NAS score between HCCs

and CCs was observed in the non-tumor liver ($p < 0.0001$), with HCC being more prevalent in those with higher grades of steatosis. 88% of the 50 cases had no cirrhotic background in HCC. **Conclusions:** Fatty liver-related hepatocellular carcinoma is one of the possible causes of Cryptogenic HCC. Cirrhosis-free is more common in cryptogenic HCCs. We recommend that NAFLD patients with advanced fibrosis accept early detection of HCC.

Keywords: Fatty liver-related hepatocellular carcinoma, steatohepatitis, cirrhosis, intrahepatic cholangiocarcinoma

Introduction

Globally, hepatocellular carcinoma is a major healthcare concern, with viral hepatitis and alcohol still being significant risk factors [1,2]. However, Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming the primary source of hepatocellular carcinoma (HCC) in the United States, France, and the United Kingdom [3]. The serious condition of fatty liver, such as HCC [4], has been largely neglected in Lahore, despite NAFLD becoming a more frequent cause of chronic liver disease.

The criteria for NAFLD necessitated the exclusion diagnosis of Cryptogenic HCC [5], which was based on the following: (1) no serologic or clinical proof of HBV or HCV infection; (2) alcohol consumption of less than 20 g/day for men and less than 10 g/day for women; and (3) no other causes of chronic liver illness such as autoimmune hepatitis, drug-induced hepatitis, hemochromatosis, Wilson's disease, or intestinal bypass surgery. Primary biliary cirrhosis, Budd-Chiari syndrome, and primary sclerosing cholangitis - are the afflictions.

We endeavored to ascertain if NAFLD had any connection to hepatocellular carcinoma without a definite cause by contrasting the demographic, clinical, and histopathological features of HCC with intrahepatic cholangiocarcinoma (CC) in a group of patients.

Materials and Methods

Electronic Medical Records (Software—) were reviewed to identify all patients (N=2086) with an International Classification of Diseases (ICD)-10 code corresponding to HCC at any time from 1 January 2007 to 31 May 2020 in the district Lahore . The Patients were excluded due to a lack of hepatic pathology. Excluding all patients with hepatitis B and/or C, alcohol abuse, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, cholangiolithiasis, hemochromatosis, alpha-1-antitrypsin deficiency, and Wilson disease, we screened the remaining cases in accordance with Cryptogenic HCC [5].

We compared the group of patients diagnosed with intrahepatic cholangiocarcinoma (CC), who underwent partial hepatectomy during the study period as seen in (Figure 1) with a flowchart of patient inclusion. Histologic data on fibrosis stage (0-4) and the presence of NASH (present or absent) from non-tumorous tissue were also recorded. Additionally, primary liver tumors which had elements of both HCC and CC (combined hepatocellular cholangiocarcinoma) were excluded, as the study was comparing HCC and CC. The institutional review boards gave their approval to the study protocol after it had been reviewed.

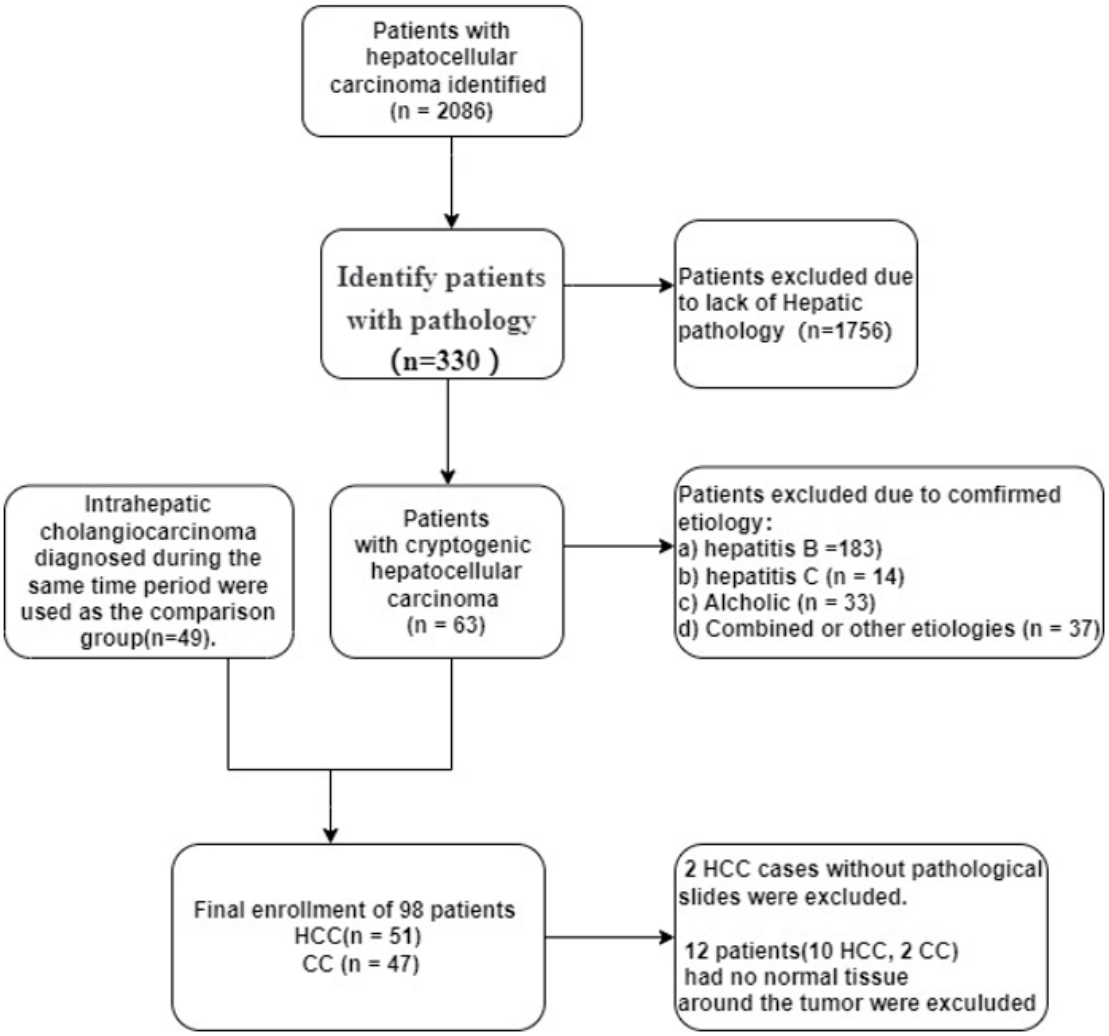

Figure 1: Flowchart of patient inclusion.

A pathologist specializing in liver pathology (LLL) and a hepatologist who comprehends pathology (ZYT) reviewed hematoxylin and eosin-stained slides of the liver parenchyma, distant from the tumor. Steatohepatitis, characterized by steatosis, lobular inflammation, and ballooned hepatocytes in the non-tumor liver, was diagnosed using the NASH Clinical Research Network (NASH CRN) and graded semi-quantitatively according to the Multiactivity Score (NAS) [6]. Classifying involvement of less than 5% as grade 0, 5%-33% as grade 1, 34%-66% as grade 2, and >66% as grade 3 was done according to NASH CRN [5]. A microscopic examination of each case was conducted without any knowledge of the demographic or clinical characteristics of the patients. We reviewed slides from HCC tumors to determine if intra-tumor steatosis was present and the steatohepatitis morphology of hepatocellular carcinoma（SH-HCC）, which was characterized by steatosis, ballooning of HCC cells, inflammation, Mallory-Denk bodies, and pericellular fibrosis. Additionally, we examined the available clinical data, including demographic characteristics and metabolic syndrome features from medical records (Table 1).

We compared the clinical and histopathological characteristics of HCC with intrahepatic CC and those of cases with and without non-tumor steatosis and those with and without SH-HCC. Data for continuous variables were recorded as means with standard deviations, while those for categorical variables were recorded as counts with percentages. Fisher's exact test and $\chi 2$ test were used to compare categorical variables. Two-sample t-tests were employed to contrast the means of continuous variables. To gauge the intensity of the correlation between binary variables and HCC, non-tumor steatosis, and SH-HCC, an odd ratio was calculated. Free Statistic 1.7.1 and Prism 9.3.0 were utilized for all statistical analyses, with a P-value of less than 0.05 being deemed statistically significant.

Ethical considerations

The ethics committee approved the study in the District, Lahore (reg no 2023/1772-31/2). Because of the retrospective nature of the data collection process and because there was no direct contact with any of the patients' informed consent was waivered by the committee.

Results

We identified 2086 patients with HCC. 1756 patients were excluded due to a lack of Pathology information. A total of 330 HCC cases with pathological reports were screened out, including 183 cases of hepatitis B, 14 cases of hepatitis C, 33 cases of alcoholic liver disease, 20 cases of cholangiocarcinoma, 15 cases of metastatic carcinoma, and 2 cases of autoimmune liver disease. We identified 63 cases without definite etiology (Figure 1). 49 patients diagnosed with intrahepatic cholangiocarcinoma (CC) during the same period were also included as a comparison group. A total of 112 cases were included in this study. Pathological slides were not found in 2 of the 112 cases (both in the HCC group). Among the pathological slides of 110 patients, 12 had no normal tissue around the tumor (10 HCC, 2 CC),. Out of the total of 98 cases, 51 patients were diagnosed with HCC and 47 patients were diagnosed with CC. Patients diagnosed with Cryptogenic HCC were more common in men (Table 1).

Variables	Total (n = 98)	HCC (n = 51)	CC (n = 47)	p
Sex （male）	64 (65.3)	40 (78.4)	24 (51.1)	0.004
Age, Mean ± SD	58.9 ± 10.1	60.4 ± 10.5	57.3 ± 9.5	0.133
BMI, Mean ± SD	23.0 ± 4.0	23.3 ± 3.7	22.7 ± 4.4	0.45
HTN, n (%)	23 (23.5)	14 (27.5)	9 (19.1)	0.333
DM, n (%)	24 (24.5)	17 (33.3)	7 (14.9)	0.034
HPL, n (%)	23 (23.5)	12 (23.5)	11 (23.4)	0.988
HUA, n (%)	18 (18.4)	11 (21.6)	7 (14.9)	0.394
FBG, Mean ± SD	5.8 ± 2.2	6.2 ± 2.6	5.4 ± 1.4	0.065
TC, Mean ± SD	4.0 ± 1.1	4.0 ± 1.0	4.0 ± 1.2	0.77
TG, Mean ± SD	1.5 ± 1.5	1.7 ± 2.0	1.4 ± 0.7	0.422
Significant steatosis in non-tumor liver, n (%)	31 (31.6)	24 (47.1)	7 (14.9)	< 0.001
NASH in non-tumor liver	13 (13.3)	11 (21.6)	2 (4.3)	0.012

Table 1: Comparison of the demographic, clinical, and histopathological features of HCC and CC.

31 patients (26.7%) had a fatty liver background, including 24 patients with HCC (47.1%, 24/51) and 7 patients with CC (14.9%, 7/47), with statistically significant differences ($P < 0.001$). Patients with HCC were more likely to have diabetes($p=0.034$). The stages of fibrosis in the background were distributed as stage 0 (43.13%), stage 1 (17.64%), stage 2 (5.88%), stage 3 (11.76%), and stage 4 (21.57%) in the HCC group, and stage 0 (82.97%), stage1 (8.51%), stage 2 (5%), stage 3 (4.25%) and stage 4 (4.25%) in the CC group.

When grouped according to the NAS grade of steatosis in the non-tumor liver, there was a statistically significant difference in HCCs and CCs groups ($p < 0.0001$), HCC being more prevalent in cases with higher grades of steatosis: HCC was present in 27 out of 67 (40.29%) patients with grade 0 steatosis, 12 of 17 (70.58%) patients with grade 1 steatosis, 7 out of 8 (87.5%) patients with grade 2 steatosis, and 5 out of 6 (83.33%) patients with grade 3 steatosis (Figure 2).

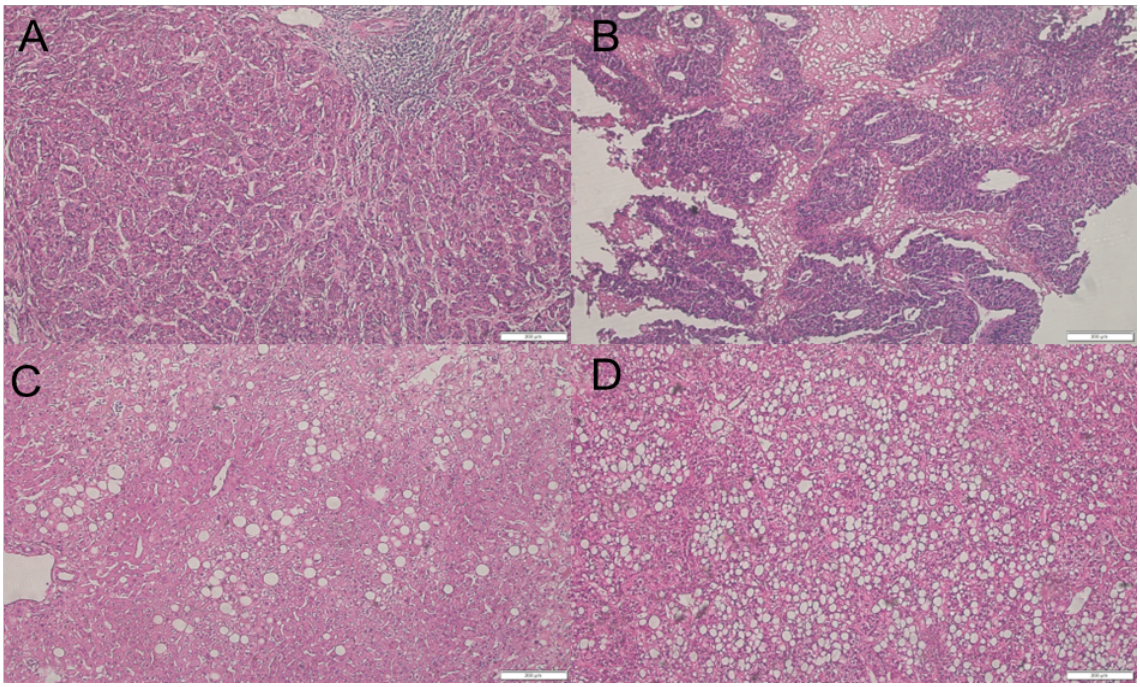

Figure 2: The histomorphology of HCC in the background of the fatty liver shows the typical trabecular (A, hematoxylin and eosin stain, 100X magnification) and pseudo glandular (B, hematoxylin and eosin stain, 100X magnification) pattern. Additionally, certain HCCs demonstrate fatty change within the tumor (C, hematoxylin and eosin stain, 100X magnification). A considerable number of the cases demonstrate the steatohepatitis HCC form, exhibiting a conglomeration of steatosis, inflammation, ballooning degeneration, and intrasinusoidal fibrosis within the tumor (D, hematoxylin and eosin stain, 100X magnification).

A statistically significant relationship between steatosis in the non-tumor liver and obesity was observed in a cohort of patients with HCC. Moreover, those with HCC with significant steatosis in the non-tumor liver were more likely to have a higher BMI (Table 2). Similarly, a statistically significant association between steatosis in the non-tumor liver and obesity was also found in the cohort of patients with CC (Table 3).

Variables	Total (n = 51)	HCC with significant steatosis in non- tumor liver (n = 24)	HCC without significant steatosis in non-tumor live (n = 27)	p
Sex(male), n (%)	40 (52.1)	21 (87.5)	19 (70.4)	0.138
BMI, Mean ± SD	23.3±3.7	24.7±4.0	22.0±3.0	0.008
Hypertension, n (%)	9 (18.8)	8 (33.3)	6 (25)	0.375
Diabetes, n (%)	12 (23.5)	6 (22.2)	6 (25)	0.074
Hyperlipidemia, n (%)	11 (22.9)	10 (22.7)	1 (25)	0.815
Hyperuricemia, n (%)	7 (14.6)	6 (13.6)	1 (25)	0.214
Total. cholesterol, Mean ± SD	3.9 ± 1.2	4.3 ± 1.1	3.8 ± 0.9	0.204
Triglycerides, Mean ± SD	2.1 ± 2.7	1.2 ± 0.7	1.4 ± 1.0	0.85

Table 2: Comparison of the demographic, clinical and histopathological characteristics of cases of HCC with and without significant steatosis in non-tumor liver

Variables	Total (n = 47)	CC with significant steatosis in non- tumor liver (n = 7)	CC without significant steatosis in the non-tumor liver (n = 40)	p
Age, Mean ± SD	57.3 ± 9.5	58.3 ± 6.0	57.1 ± 10.1	0.77
BMI, Mean ± SD	22.7 ± 4.4	26.1 ± 3.5	22.1 ± 4.3	0.025
HTN, n (%)	9 (19.1)	2 (28.6)	7 (17.5)	0.605
DM, n (%)	7 (14.9)	1 (14.3)	6 (15)	1
HPL, n (%)	11 (23.4)	3 (42.9)	8 (20)	0.33
HUA, n (%)	7 (14.9)	3 (42.9)	4 (10)	0.057
TC, Mean ± SD	4.0 ± 1.2	3.2 ± 1.1	4.1 ± 1.2	0.07
TG, Mean ± SD	1.4 ± 0.7	1.6 ± 0.9	1.4 ± 0.7	0.41
FBG, Mean ± SD	5.4 ± 1.4	5.5 ± 0.9	5.4 ± 1.5	0.821

Table 3: Comparison of the demographic, clinical, and histopathological traits of CC cases with and without significant steatosis in non-tumor liver

The HCC cohort exhibited a much higher prevalence of background steatohepatitis (21.6%, compared to 4.3%, P =0.012) - defined as the presence of steatosis, lobular inflammation, and ballooned hepatocytes in the non-tumor liver. Diabetes was more likely in those with background steatohepatitis (p=0.034), yet no statistically significant relationship was found between it and hypertension, hyperuricemia, fasting blood glucose, total cholesterol, or triglyceride. The distribution of fibrosis stages in the background steatohepatitis cases was as follows: stage 0 (19.35%), stage 1 (32.26%), stage 2 (6.45%), stage 3 (19.35%), and stage 4(22.58%).

In the study of HCC patients, 79% exhibited the typical trabecular HCC pattern (Figure 2A), 18% had the typical pseudo glandular HCC pattern (Figure 2B), and 3% had a combination of both (Figure 2C). Intratumoral steatosis was seen in 40% of the cases, but it had no significant correlation with non-tumor steatosis. In 8(15.68%) cases the steatohepatitic morphology of hepatocellular carcinoma (SH-HCC morphology) featuring a blend of steatosis, ballooning degeneration, lobular inflammation, and perivenular/pericellular fibrosis (Figure 2D), was identified. A statistically significant difference in the proportion of cases with SH-HCC (p=0.019) was observed when classified by the grade of steatosis in the non-tumor liver; SH-HCC became more frequent in cases of higher grades of steatosis, with 12.5% of HCC cases having grade 0 steatosis, 37.5% grade 1 steatosis, 25% grade 2 steatosis, and 37.5% grade 3 steatosis (Figure 3) exhibiting SH-HCC (Table 4).

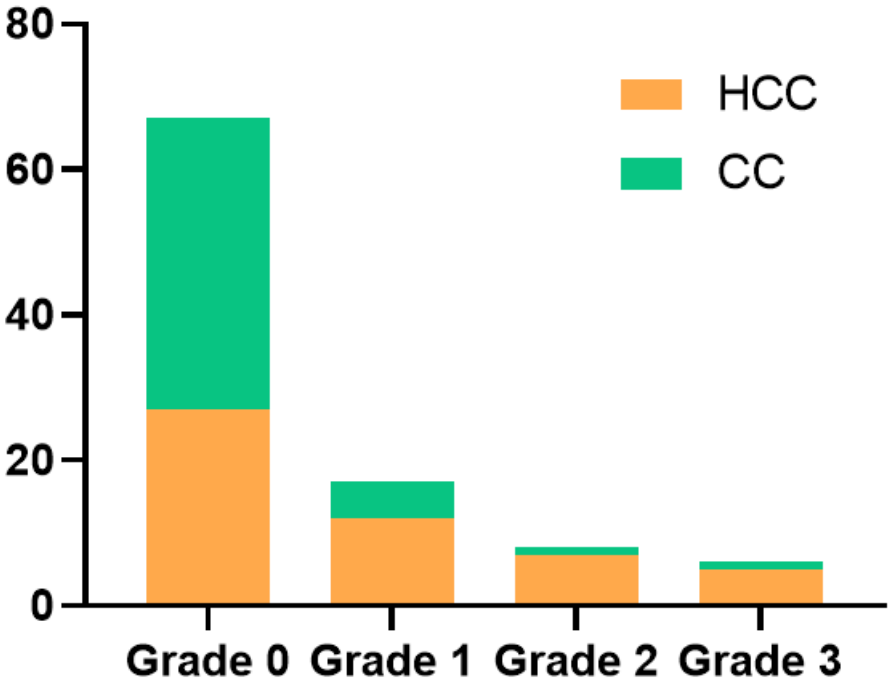

Figure 3: NAS grade of steatosis in the non-tumor liver

Variables	Total (n = 51)	HCC with SH-HCC Morphology (n =43)	HCC without SH-HCC Morphology (n = 8)	p
Sex（male）	40 (78.4)	7 (87.5)	33 (76.7)	0.668
Age, Mean ± SD	60.4 ± 10.5	67.6 ± 11.2	59.0 ± 9.9	0.032
BMI, Mean ± SD	23.3 ± 3.7	24.8 ± 4.9	23.0 ± 3.4	0.203
HTN, n (%)	14 (27.5)	4 (50)	10 (23.3)	0.192
DM, n (%)	17 (33.3)	5 (62.5)	12 (27.9)	0.099
HPL, n (%)	12 (23.5)	2 (25)	10 (23.3)	1
HUA, n (%)	11 (21.6)	2 (25)	9 (20.9)	1
FBG, Mean ± SD	6.2 ± 2.6	6.8 ± 2.1	6.1 ± 2.7	0.515
TC, Mean ± SD	4.0 ± 1.0	4.2 ± 1.1	4.0 ± 1.0	0.594
TG, Mean ± SD	1.5 ± 1.5	1.4 ± 0.7	1.7 ± 2.0	0.422
Significant steatosis in non-tumor liver, n (%)	24 (47.1)	7 (87.5)	17 (39.5)	0.019
NASH in non-tumor liver	11 (21.6)	5 (62.5)	6 (14)	0.008

Table 4: Comparison of the demographic, clinical, and histopathological traits of HCC cases with and without steatohepatitis (SH-HCC) morphology.

11 cases had a cirrhotic background in HCC and 40 cases without cirrhotic background (78.43%, 40/51) (Figure 4).

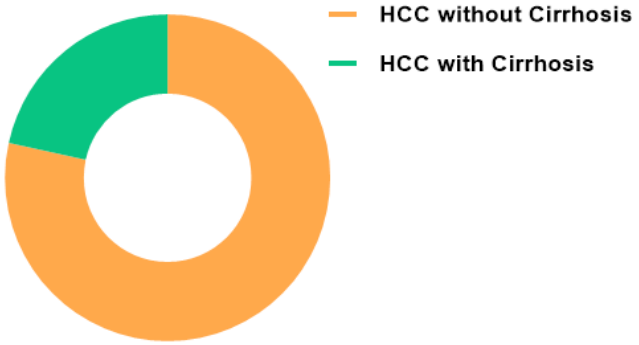

Figure 4: Background cirrhosis portion of HCC

Discussion

Our research uncovered a significant correlation between cryptogenic HCC and both steatosis and steatohepatitis in the non-tumor liver. Furthermore, a statistically significant association between steatosis and steatohepatitis in the non-tumor liver and the SH-HCC morphology was observed. In the HCC cohorts, hepatic steatosis was linked to obesity and diabetes, and hepatic steatosis was linked to SH-HCC morphology. The hypothesis that hepatic steatosis could be the cause of hepatocarcinogenesis in Cryptogenic HCCs is bolstered by these observations, indicating a potential connection between the two [7].

The majority of cryptogenic HCC cases had non-cirrhotic backgrounds. Cirrhosis oftentimes brings about HCC as a backdrop [8]. There were about 20% of cases can develop in a non-cirrhotic liver [9,10]. NAFLD-related HCC is also well known to develop in the absence of liver cirrhosis, unlike liver diseases of other aetiologies such as alcohol-related and autoimmune liver disease [11,12]. A meta-analysis of 19 studies and 168,571 individuals with NASH reported that the prevalence of NAFLD-related HCC in patients with NASH but without cirrhosis is approximately 38% compared with 14% for other liver diseases [13]. The absence of HCC screening protocols in patients with NAFLD but without cirrhosis contributes to the late diagnosis and management [12,14]. The EASL guidelines [15] recommend that patients with liver disease (not only NAFLD but any other etiology) with advanced fibrosis (F3) should be monitored for HCC through an individual risk assessment, whereas the APASL clinical practice guidelines [16] do not offer a specific recommendation for surveillance in those without cirrhosis of NAFLD [17]. The danger of HCC in those without advanced fibrosis is too slight to suggest a regular examination [18]. So, patients with NAFLD should recommend advanced fibrosis surveillance.

This study has several drawbacks, such as its retrospective design, case-control design with incomplete clinical data, lack of histopathological background liver information, and no longitudinal follow-up. Moreover, the hospital-based nature of the study means that the cohort of patients may not accurately reflect the true population of those with HCC, due to the unavoidable referral bias. Thirdly we did not assess for occult HBV infection, which is defined as HBV DNA in the liver of a person with negative HBsAg, occult HBV infection may be linked to "cryptogenic" HCC. Fourthly, the use of CC patients as the comparison group could be seen as a restriction of this study. The potential carcinogenic effect of hepatic steatosis on the pathogenesis of CC renders it an unsuitable control, potentially resulting in a misjudgment of its carcinogenic effect on HCC. Nevertheless, this study does present proof of a correlation between hepatic steatosis and HCC, yet it does not prove causation. Observational studies like this can only demonstrate an association, not causation. A burgeoning corpus of empirical data implies a probable causal link between hepatic steatosis and HCC [19,20], as previously discussed.

Conclusion

To conclude, this study offers morphological proof of the connection between hepatic steatosis and cryptogenic HCC and implies a potential role in the emergence of HCC in those with NAFLD who had little awareness of the condition. Moreover, due to the ever-increasing global prevalence of NAFLD, even a slight rise in the risk of HCC in hepatic steatosis is likely to lead to a considerable number of cases of HCC in the following decades. It should be intervened and prevented in the early stage of fatty liver. It is suggested that those with NAFLD and advanced fibrosis should be alerted to HCC early on, and further research is necessary to understand the pathophysiologic processes linked to HCC associated with steatosis.

Reference

1. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A (2022) Hepatocellular carcinoma. Lancet. 400:1345-1362.
2. Shah PA, Patil R, Harrison SA (2023) NAFLD-related hepatocellular carcinoma: The growing challenge. Hepatology. 77:323-338.
3. Huang DQ, El-Serag HB, Loomba R (2021) Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 18: 223-238.
4. Zhou J, Zhou F, Wang W, Zhang XJ, Ji YX, et al. (2020) Epidemiological Features of NAFLD From 1999 to 2018 in Lahore. Hepatology. 71:1851-1864.
5. Lee SS, Jeong SH, Byoun YS, Chung SM, Seong MH, et al. (2013) Clinical features and outcome of cryptogenic hepatocellular carcinoma compared to those of viral and alcoholic hepatocellular carcinoma. BMC Cancer 13:335.

6. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, et al. (2005) Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 41: 1313-21.

7. Lee DH, Lee JM (2017) Primary malignant tumours in the non-cirrhotic liver. Eur J Radiol. 95:349–361.

8. Liu S, Chan KW, Wang B, Qiao L (2009) Fibrolamellar hepatocellular carcinoma. Am J Gastroenterol. 104:2617–24.

9. Stine JG, Wentworth BJ, Zimmet A, Rinella ME, Loomba R, et al. (2018) Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. Aliment Pharmacol Ther. 48: 696–703.

10. Desai A, Sandhu S, Lai J-P, Sandhu DS (2019) Hepatocellular carcinoma in non-cirrhotic liver: a comprehensive review. World J Hepatol. 11:1–18.

11. Huang DQ, El-Serag HB, Loomba R (2021) Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 18 :223-238.

12. Epub 2020 Dec 21. European Association for the Study of the Liver (2021) EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol. 75: 659-689.

13. Stine JG, Wentworth BJ, Zimmet A, Rinella ME, Loomba R, et al. (2018) Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. Aliment Pharmacol Ther. 48: 696–703.

14. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, et al. (2018) The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 67: 328–357.

15. European Association for the Study of the Liver (2018) EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 69: 182–236.

16. Omata, M, Cheng AL, Kokudo N, Kudo M, Lee JM, et al. (2017) Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 11: 317–370.

17. Plaz Torres MC, Bodini G, Furnari M, Marabotto E, Zentilin P, et al. (2020) Surveillance for Hepatocellular Carcinoma in Patients with Non-Alcoholic Fatty Liver Disease: Universal or Selective? Cancers (Basel). 12:1422.

18. Kanwal F, Kramer JR, Mapakshi S, Natarajan Y, Chayanupatkul M, et al. (2018) Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. Gastroenterology. 155: 1828–1837.e2.

19. Thuluvath PJ, Kantsevoy S, Thuluvath AJ, Savva Y (2018) Is cryptogenic cirrhosis different from NASH cirrhosis? J. Hepatol, 68: 519–525.

20. Alexander M, Loomis AK, Fairburn-Beech J, van der Lei J, Duarte-Salles T, et al. (2018) Real-world data reveal a diagnostic gap in non-alcoholic fatty liver disease. BMC Med. 16: 130.