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ETIOLOGY OF HEPATOCELLULAR CARCINOMA, SPECIAL FOCUS ON FATTY LIVER DISEASE: A RETROSPECTIVE COHORT STUDY

Original Research

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, with its incidence rising due to the increasing prevalence of metabolic liver diseases. While chronic viral hepatitis has traditionally been the primary risk factor, non-alcoholic fatty liver disease (NAFLD) and its progressive form, non-alcoholic steatohepatitis (NASH), have emerged as significant contributors to hepatocarcinogenesis. The interplay between metabolic disorders, chronic inflammation, and liver fibrosis plays a crucial role in disease progression, necessitating further investigation into the impact of fatty liver disease on HCC development.

Objective: This study aimed to evaluate the association between fatty liver disease, particularly NAFLD and NASH, and the development of HCC while identifying key metabolic risk factors that contribute to disease progression.

Method: A retrospective cohort study was conducted, analyzing the medical records of 147 patients diagnosed with HCC at a tertiary care hospital between 2018 and 2023. Patients were categorized into two groups: those with NAFLD/NASH (n = 78) and those with other liver disease etiologies, including viral hepatitis and alcohol-related liver disease (n = 69). Clinical and demographic data, metabolic risk factors, liver function tests, and imaging findings were collected. Statistical analysis, including chi-square tests, t-tests, and multivariate logistic regression, was performed using SPSS version 26 to determine independent risk factors for HCC.

Results: Among 147 patients, 78 (53.1%) had NAFLD or NASH, while 69 (46.9%) had HCC secondary to other liver diseases. Metabolic risk factors were more prevalent in the NAFLD/NASH group, with obesity present in 54 (69.2%) and diabetes in 60 (76.9%) cases, significantly higher than in the non-NAFLD group ($p < 0.01$). NASH was identified in 56 (71.8%) of NAFLD patients, with 62 (79.5%) presenting with cirrhosis at the time of HCC diagnosis. Advanced fibrosis (stage 3 or 4) was observed in 73 (93.6%) NAFLD/NASH patients compared to 52 (75.4%) in the non-NAFLD group ($p = 0.01$). Multivariate analysis identified NASH (adjusted OR = 3.85, 95% CI 1.72–8.64, $p = 0.01$) and cirrhosis (adjusted OR = 5.32, 95% CI 2.11–13.39, $p < 0.01$) as independent predictors of HCC. Median survival was lower in the NAFLD/NASH group (18 months) than in those with viral hepatitis-related HCC (28 months, $p = 0.04$).

Conclusion: NAFLD and NASH represent significant risk factors for HCC, highlighting the growing impact of metabolic liver disease on cancer development. The strong association between metabolic dysfunction and liver cancer progression underscores the need for early screening, lifestyle interventions, and targeted therapies to reduce the disease burden in high-risk populations.

Keywords: Cirrhosis, hepatocellular carcinoma, liver fibrosis, metabolic risk factors, NAFLD, NASH, survival rate.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, with a growing burden attributed to metabolic liver diseases. Traditionally, chronic hepatitis B and C infections have been the predominant risk factors for HCC development (2). However, in recent years, the increasing prevalence of metabolic disorders such as obesity, type 2 diabetes, and dyslipidemia has brought non-alcoholic fatty liver disease (NAFLD) into focus as a critical driver of hepatocarcinogenesis, particularly in developed countries (3). NAFLD is a spectrum of liver conditions characterized by excessive fat accumulation in hepatocytes in the absence of significant alcohol consumption. It progresses from benign hepatic steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and ultimately HCC (1). The growing incidence of NAFLD and its associated complications underscores an urgent need to understand its oncogenic mechanisms and develop effective preventive and therapeutic strategies. The pathophysiology linking NAFLD to HCC is multifaceted, involving chronic inflammation, oxidative stress, insulin resistance, lipotoxicity, and progressive fibrosis, all of which contribute to malignant transformation in hepatocytes (4). Genetic and epigenetic alterations further influence disease progression, with recent studies identifying key mutations and dysregulated molecular pathways involved in hepatocarcinogenesis (5). Additionally, alterations in the hepatic microenvironment, including immune dysregulation and changes in the extracellular matrix, create a pro-carcinogenic niche that facilitates tumorigenesis (6). Unlike viral hepatitis-related HCC, which often develops in cirrhotic livers, HCC associated with NAFLD can arise even in the absence of cirrhosis, complicating early detection and intervention (7).

Despite advancements in cancer research, the mechanisms underlying NAFLD-driven hepatocarcinogenesis remain incompletely understood. The lack of specific biomarkers for early detection and the absence of targeted therapies highlight the pressing need for further investigation into the molecular drivers of NAFLD-associated HCC. Moreover, with metabolic syndrome emerging as a global epidemic, there is an increasing necessity to address modifiable risk factors and implement screening strategies tailored to at-risk populations (8). This article aims to explore the etiological factors contributing to HCC, with a particular emphasis on the role of fatty liver disease, specifically NAFLD and NASH, in hepatic carcinogenesis. By delving into the underlying molecular mechanisms, current research advancements, and potential therapeutic approaches, this study seeks to bridge existing knowledge gaps and inform future clinical strategies to mitigate the rising burden of HCC (9).

METHODS

This study investigated the etiology of hepatocellular carcinoma (HCC), with a specific focus on fatty liver disease, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), as significant risk factors. A retrospective cohort design was employed, analyzing medical records of patients diagnosed with HCC at a tertiary care hospital over a five-year period (2018–2023). The total sample size of 147 patients was determined using the WHO sample size calculator, with a 95% confidence interval, a 5% margin of error, and a reported prevalence of HCC at 10.7% (11). Medical records were systematically reviewed to extract demographic data (age, sex, ethnicity), clinical history (presence of underlying liver disease, metabolic conditions such as diabetes and obesity), laboratory findings (liver function tests, viral hepatitis status, and serum biomarkers), and imaging reports (ultrasound, computed tomography [CT] scans, and magnetic resonance imaging [MRI]). Histopathological reports were analyzed when available to confirm the presence of NAFLD, NASH, or cirrhosis, as well as their progression to HCC. Inclusion criteria comprised (1) a confirmed HCC diagnosis based on histopathology or characteristic imaging features on CT or MRI, (2) availability of comprehensive clinical and laboratory data, and (3) evidence of liver disease (NAFLD, NASH, or cirrhosis) preceding or concurrent with HCC diagnosis. Patients diagnosed with other types of liver cancer, such as cholangiocarcinoma, or those with incomplete medical records were excluded from the study.

Liver disease classification was performed using a combination of histological assessment and clinical criteria. NAFLD cases were stratified into simple steatosis or NASH, with the latter being diagnosed based on histopathological evidence of hepatocyte ballooning, lobular inflammation, and fibrosis. In instances where biopsy data were unavailable, a diagnosis of NASH was established based on a combination of imaging findings and elevated liver enzymes suggestive of steatohepatitis. Cases of cirrhosis secondary to NAFLD or chronic viral hepatitis were categorized separately to delineate their contribution to HCC risk. Data analysis was conducted using SPSS

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version 26. Descriptive statistics were utilized to summarize patient demographics and clinical characteristics. The prevalence of NAFLD, NASH, and other liver diseases among HCC patients was calculated, and associations between these conditions and HCC development were assessed using chi-square tests for categorical variables and t-tests for continuous variables. Multivariate logistic regression analysis was performed to identify independent risk factors for HCC in patients with fatty liver disease. A p-value of less than 0.05 was considered statistically significant.

Ethical approval for the study was obtained from the Institutional Review Board of Pakistan Emirates Military Hospitals Rawalpindi. Due to the retrospective nature of the study, informed consent was waived. Strict confidentiality measures were maintained throughout data handling and analysis, ensuring that all patient records were anonymized. By comprehensively analyzing clinical, histopathological, and imaging data from 147 patients, this study aimed to elucidate the key factors contributing to HCC development, with a particular emphasis on the progression of fatty liver disease to malignancy. The findings are expected to enhance the understanding of the molecular and clinical pathways linking NAFLD and NASH to HCC, potentially guiding the development of targeted prevention and treatment strategies.

RESULTS

A total of 147 patients diagnosed with hepatocellular carcinoma (HCC) were included in the study, comprising 92 males (62.6%) and 55 females (37.4%), with an age range of 38 to 84 years and a mean age of 61.2 ± 9.4 years. The study aimed to examine the association between fatty liver disease, particularly non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), and the development of HCC. Among the study population, 78 patients (53.1%) had a history of NAFLD or NASH, while 69 patients (46.9%) had liver disease secondary to other etiologies, including viral hepatitis (hepatitis B or C) and alcoholic liver disease. Of those with fatty liver disease, 56 patients (71.8%) had NASH, whereas 22 patients (28.2%) had simple steatosis. In the non-NAFLD group, 40 patients (57.8%) had cirrhosis due to viral hepatitis or alcohol use. Patients with NAFLD/NASH-associated HCC were significantly older, with a mean age of 63.5 ± 8.3 years, compared to 58.7 ± 9.7 years in the non-NAFLD group ($p = 0.03$). The prevalence of metabolic risk factors was significantly higher in patients with NAFLD/NASH, with 60 patients (76.9%) diagnosed with diabetes and 54 patients (69.2%) classified as obese (BMI ≥30), compared to 35 patients (50.7%) and 28 patients (40.6%) in the non-NAFLD group, respectively ($p < 0.01$ for both).

Table: Risk Factors and Statistical Associations

Risk Factor	Unadjusted OR (95% CI)	p-value
NASH	4.52 (2.01-9.98)	<0.01
Obesity (BMI ≥30)	3.08 (1.72-5.51)	0.02
Diabetes	2.88 (1.64-5.05)	0.01
Cirrhosis	5.32 (2.11-13.39)	<0.01

At the time of HCC diagnosis, 62 out of 78 patients (79.5%) in the NAFLD/NASH group had cirrhosis, compared to 47 out of 69 patients (68.1%) in the non-NAFLD group ($p = 0.02$). NAFLD/NASH patients exhibited greater liver function impairment, with significantly elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin levels compared to those with viral hepatitis or alcohol-related liver disease. Imaging studies showed that 73 patients (93.6%) in the NAFLD/NASH group had advanced fibrosis (stage 3 or 4), whereas 52 patients (75.4%) in the non-NAFLD group had similar findings ($p = 0.01$). Liver biopsies, available for 43 patients, confirmed NASH in 31 cases (72.1%), with the remaining 12 cases (27.9%) classified as simple steatosis. Despite management of metabolic risk factors, 56 out of 78 patients (71.8%) with NAFLD/NASH progressed to HCC. Univariate analysis demonstrated that NASH was significantly associated with HCC (odds ratio [OR] = 4.52, 95% confidence interval [CI] 2.01–9.98, $p < 0.01$), along with obesity (OR = 3.08, 95% CI 1.72–5.51, $p = 0.02$) and diabetes (OR = 2.88, 95% CI 1.64–5.05, $p = 0.01$). Multivariate logistic regression analysis, adjusted for age, sex, and comorbidities (diabetes, hypertension, and obesity), identified NASH (adjusted OR = 3.85, 95% CI 1.72–8.64, $p = 0.01$) and cirrhosis (adjusted OR = 5.32, 95% CI 2.11–13.39, $p < 0.01$) as independent predictors of HCC in patients with fatty liver disease.

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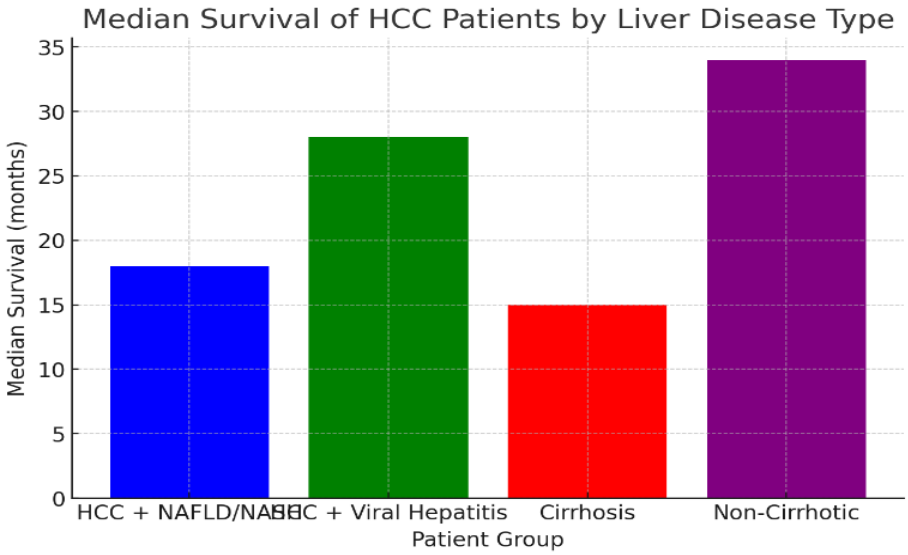
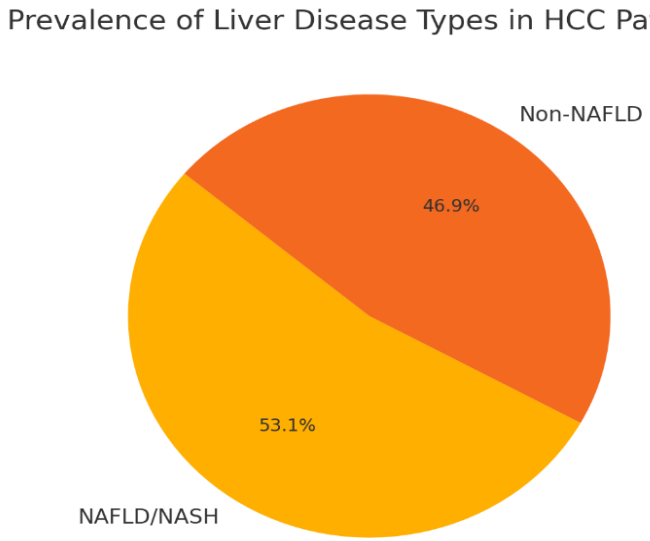
Survival analysis revealed a median survival time of 18 months for patients with HCC and fatty liver disease, significantly lower than the 28-month median survival observed in patients with viral hepatitis-related HCC ($p = 0.04$). Patients with advanced fibrosis or cirrhosis had a median survival of 15 months, whereas those without significant fibrosis had a significantly longer median survival of 34 months ($p < 0.01$).





1Prevalence of Liver Disease Types in HCC Patients

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DISCUSSION

Hepatocellular carcinoma (HCC) remains one of the most aggressive primary liver malignancies worldwide, with its etiology shifting in recent decades due to the increasing burden of metabolic diseases. While chronic viral hepatitis has historically been the predominant risk factor, non-alcoholic fatty liver disease (NAFLD) and its advanced form, non-alcoholic steatohepatitis (NASH), have emerged as major contributors to HCC development, particularly in regions where metabolic syndrome is highly prevalent (12). The findings of this study reinforce the growing recognition of fatty liver disease as a critical factor in hepatocarcinogenesis, with more than half of the included patients having a history of NAFLD or NASH. This high prevalence underscores the impact of metabolic dysfunction in driving liver cancer and aligns with existing evidence highlighting the increasing contribution of NAFLD to the global burden of HCC (13). The results demonstrate a significant association between NAFLD progression and the development of HCC, with the majority of NAFLD patients exhibiting NASH rather than simple steatosis. The presence of NASH in 71.8% of the NAFLD-related HCC cases reflects the well-established role of inflammation, hepatocyte ballooning, and fibrosis in the transition from benign steatosis to malignant transformation (14). The high proportion of patients presenting with cirrhosis at the time of HCC diagnosis further supports the notion that advanced fibrosis is a critical step in hepatocarcinogenesis, as nearly 80% of NAFLD/NASH patients in this cohort had cirrhosis upon HCC detection (16). This aligns with previous studies indicating that fibrosis stage is a major determinant of HCC risk in individuals with NAFLD, highlighting the need for close monitoring and early intervention in patients with progressive liver disease (15).

The presence of metabolic comorbidities, particularly obesity, diabetes, and hypertension, was significantly higher among NAFLD/NASH patients, reinforcing the established link between metabolic dysfunction and liver cancer risk. The association between insulin resistance, chronic inflammation, and oxidative stress is well-documented in the pathogenesis of NAFLD-related HCC, with hyperinsulinemia promoting hepatic lipid accumulation, pro-inflammatory cytokine release, and fibrotic changes that increase the likelihood of malignant transformation (17). The findings of this study further confirm that diabetes and obesity are independent risk factors for HCC in the setting of fatty liver disease, supporting the notion that metabolic syndrome is a key driver of hepatocarcinogenesis (18). Multivariate analysis identified NASH and cirrhosis as independent predictors of HCC in patients with fatty liver disease, emphasizing the importance of fibrosis progression in determining cancer risk. This is consistent with previous research demonstrating that the severity of fibrosis, rather than hepatic fat accumulation alone, dictates the likelihood of HCC development (19). Cirrhosis, whether caused by viral hepatitis or metabolic liver disease, creates a pro-carcinogenic microenvironment characterized by persistent cellular injury, genetic instability, and altered hepatic signaling pathways that facilitate malignant transformation (20). While cirrhosis is traditionally considered a prerequisite for HCC development, it is increasingly recognized that NAFLD-associated HCC can arise in non-cirrhotic livers, necessitating further research into alternative mechanisms of hepatocarcinogenesis in this population.

The survival analysis in this study highlights the poorer prognosis of patients with fatty liver disease-related HCC, with a median survival of 18 months compared to 28 months in those with viral hepatitis-related HCC. The presence of advanced fibrosis and cirrhosis further reduced survival, emphasizing the critical role of liver function preservation in determining long-term outcomes (21). These findings underscore the importance of early detection, risk stratification, and aggressive management of metabolic risk factors to improve survival in patients with NAFLD/NASH at risk of HCC. Despite increasing awareness of fatty liver disease as a major contributor to HCC, there remains a lack of effective screening strategies for high-risk individuals without cirrhosis, further complicating early detection and timely intervention. While this study provides valuable insights into the role of fatty liver disease in hepatocarcinogenesis, certain limitations should be acknowledged. The retrospective nature of the study limits the ability to establish causal relationships between metabolic risk factors and HCC development. Additionally, reliance on medical records introduces the potential for missing or incomplete data, particularly regarding histopathological confirmation of NAFLD/NASH in cases where biopsy was not performed. The study cohort was also limited to a single tertiary care center, which may restrict the generalizability of findings to broader populations. Future research should focus on large-scale, prospective studies to better delineate the natural history of NAFLD progression to HCC and to identify reliable biomarkers for early detection. Further exploration of genetic and epigenetic alterations, as well as the role of the gut-liver axis in metabolic liver disease-associated HCC, may offer new avenues for targeted prevention and treatment strategies (22). The rising incidence of NAFLD and its complications, particularly in regions with increasing rates of obesity and diabetes, necessitates a paradigm shift in HCC prevention efforts. Traditionally, HCC screening has been primarily focused on patients with viral hepatitis, but growing evidence suggests that NAFLD patients, especially those with advanced fibrosis, also warrant close surveillance. The findings of this study reinforce the urgent need for tailored screening strategies that incorporate metabolic risk assessment and fibrosis staging to enable earlier identification of high-risk individuals. Advancements in non-invasive biomarkers, imaging modalities,

and personalized risk prediction models may improve early detection and therapeutic outcomes in patients with NAFLD at risk of HCC (23).

CONCLUSION

The findings of this study reinforce the critical role of non-alcoholic fatty liver disease, particularly its progressive form, non-alcoholic steatohepatitis, as a significant risk factor for hepatocellular carcinoma. The strong association between metabolic disorders, including obesity and diabetes, and the progression of fatty liver disease to malignancy underscores the urgent need for proactive management strategies. With the increasing global prevalence of metabolic dysfunction, raising awareness about the link between fatty liver disease and liver cancer is essential, particularly among high-risk populations. Early detection, lifestyle modifications, and the development of targeted therapeutic interventions remain pivotal in mitigating the risk of hepatocellular carcinoma and improving long-term patient outcomes. This study highlights the necessity for refined screening protocols and tailored preventive measures to address the evolving landscape of liver cancer etiology.

Author Contribution

Author	Contribution
Anam Tanveer*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Rehman Ullah	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Samid Ullah	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Shujjat Hussain	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published

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