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Histological and Molecular Findings in Liver Biopsies from Cirrhotic Patients with Hepatocellular Carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is a common malignancy in cirrhotic patients, often resulting from chronic liver disease. Understanding the histological and molecular characteristics of HCC in this population is crucial for improving diagnostic accuracy and therapeutic outcomes. **Objective:** This study aims to investigate the histopathological features and molecular alterations in liver biopsies from cirrhotic patients with HCC, assessing their correlation with tumor progression, prognosis, and potential clinical implications. **Methods:** A retrospective analysis was conducted on liver biopsy samples from 85 cirrhotic patients diagnosed with HCC. Histological evaluation included fibrosis staging, tumor grading, vascular invasion, and inflammation. Molecular profiling was performed to detect mutations in TP53, CTNNB1, and TERT, as well as epigenetic changes, such as RASSF1A promoter methylation and miRNA dysregulation. **Results:** The majority of patients (76.5%) had advanced fibrosis (F4). Poorly differentiated tumors and vascular invasion were associated with aggressive disease and lower survival. TP53 mutations were found in 41.2% of patients and correlated with poor differentiation and vascular invasion, while CTNNB1 mutations (23.5%) were linked to well-differentiated tumors. TERT promoter mutations were present in 47.1% of patients, associated with increased tumor aggressiveness. RASSF1A promoter methylation and miR-21 overexpression were also related to worse prognosis. **Conclusion:** Histological features, coupled with molecular alterations, play a significant role in determining the progression and prognosis of HCC in cirrhotic patients. The integration of molecular markers into diagnostic and therapeutic strategies could provide more personalized treatment options, improving patient outcomes. Further studies are needed to validate these findings and explore new molecular targets for therapy.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and one of the leading causes of cancer-related deaths globally. Its occurrence is closely associated with cirrhosis, a chronic condition characterized by progressive fibrosis and regenerative nodule formation, resulting from long-term liver damage. This damage is often triggered by viral infections such as hepatitis B and C, chronic alcohol consumption, or metabolic disorders like non-alcoholic fatty liver disease (NAFLD) [1]. The transformation of cirrhotic liver tissue into HCC involves complex interactions between environmental factors, inflammation, genetic mutations, and epigenetic changes. Consequently, liver biopsies from cirrhotic patients with HCC can provide essential insights into the histological changes and molecular alterations driving tumor development, offering critical information for both diagnosis and treatment planning [2]. Cirrhosis creates a pro-inflammatory and fibrogenic environment within the liver, which plays a pivotal role in HCC development. The regenerative processes occurring in cirrhotic tissue, aimed at healing and maintaining liver function, often become dysregulated,

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resulting in mutations that can promote carcinogenesis [3]. Liver biopsies serve as a gold standard for diagnosing liver malignancies, allowing for histopathological evaluation of tissue architecture and the identification of key molecular markers associated with tumor progression. Though imaging techniques like ultrasound, CT, and MRI play significant roles in the detection and monitoring of liver cancers, biopsies remain essential for definitive diagnosis, particularly in cases where imaging findings are inconclusive or where molecular profiling is required for personalized therapy [4]. Histologically, liver biopsies from cirrhotic patients with HCC typically exhibit distinctive features. In cirrhosis, normal liver architecture is replaced by fibrous septa, forming regenerative nodules that disrupt the organized lobular structure. The presence of fibrosis, often scored based on the degree of septal thickness and nodule formation, serves as a marker of chronic liver injury. In areas where HCC develops, the transition from cirrhotic nodules to malignant tissue is characterized by cellular and structural abnormalities [5]. Tumor cells may appear as larger, irregularly shaped hepatocytes with an increased nucleus-to-cytoplasm ratio, prominent nucleoli, and frequent mitotic figures. Vascular invasion, a hallmark of advanced HCC, can also be observed in biopsy specimens, further indicating the aggressive nature of the tumor. Beyond histological features, molecular analysis of liver biopsies has revealed a range of genetic and epigenetic changes that contribute to HCC development [6]. Among the most frequently observed molecular alterations are mutations in key tumor suppressor genes, such as TP53, which regulates cell cycle and apoptosis, and CTNNB1, involved in the Wnt/β-catenin signaling pathway. Mutations in these genes lead to uncontrolled cellular proliferation and survival, promoting tumor growth. Furthermore, genomic studies have identified alterations in telomerase reverse transcriptase (TERT), a key enzyme responsible for maintaining telomere length in cancer cells, allowing them to evade senescence and continue dividing [7]. Epigenetic changes, including DNA methylation and histone modifications, have also been implicated in HCC progression. Aberrant methylation patterns in promoter regions of tumor suppressor genes can silence their expression, further driving malignant transformation. For instance, hypermethylation of the RASSF1A gene, which normally acts to inhibit cell growth and promote apoptosis, is frequently observed in HCC, contributing to uncontrolled cell division. In addition, non-coding RNAs, particularly microRNAs (miRNAs), have emerged as important regulators of gene expression in HCC. Dysregulation of specific miRNAs has been linked to changes in cell proliferation, apoptosis, and angiogenesis, highlighting their potential as biomarkers for early detection and therapeutic targets [8]. One of the most challenging aspects of HCC in cirrhotic patients is the difficulty in distinguishing between regenerative nodules and early-stage malignancy. Both can present with similar histological features, making it critical to integrate molecular findings with traditional histopathology [9]. Advances in molecular techniques, such as next-generation sequencing and gene expression profiling, have made it possible to identify specific genetic signatures that differentiate benign cirrhotic nodules from malignant lesions. This has not only improved diagnostic accuracy but also provided opportunities for personalized treatment approaches based on the molecular profile of the tumor [10]. The clinical implications of histological and molecular findings in liver biopsies from cirrhotic patients with HCC are significant. Identifying specific molecular alterations can guide the use of targeted therapies, such as tyrosine kinase inhibitors (e.g., sorafenib) or immune checkpoint inhibitors (e.g., nivolumab), which have shown promise in improving outcomes for patients with advanced HCC [11]. Furthermore, molecular markers can provide prognostic information, helping to stratify patients based on their risk of tumor recurrence or metastasis following treatment. As research continues to uncover new molecular pathways involved in HCC development, there

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is hope for the identification of novel therapeutic targets that can further improve the management of this challenging cancer [12].

The main objective of the study is to find the histological and molecular findings in liver biopsies from cirrhotic patients with hepatocellular carcinoma.

Methodology

This study was conducted to analyze the histological and molecular findings in liver biopsies from cirrhotic patients with hepatocellular carcinoma (HCC). The primary objective was to examine the relationship between histological characteristics of cirrhotic liver tissue and molecular alterations driving HCC development. Additionally, the study aimed to assess how these findings correlate with the clinical presentation, prognosis, and potential therapeutic implications for cirrhotic patients diagnosed with HCC.

Study Design

This was a retrospective observational study involving 85 cirrhotic patients who were diagnosed with HCC. The patients were selected based on their medical records from a tertiary care hospital specializing in liver diseases. All patients underwent liver biopsies either during the diagnostic process or as part of their pre-treatment evaluation.

Patient Selection

Patients included in the study met the following criteria:

1. **Age:** Adults aged 18 years or older.
2. **Diagnosis:** Histologically confirmed cirrhosis with hepatocellular carcinoma based on liver biopsy.
3. **Exclusion criteria:** Patients with secondary liver malignancies (e.g., metastases from other organs), non-cirrhotic HCC, and those who had previously undergone liver resection or transplantation were excluded.

Data Collection

Patient data, including demographic information, medical history, and laboratory findings, were collected from hospital records. Biopsy samples were retrieved from the pathology department for further analysis.

Histological Analysis

Each biopsy sample was fixed in formalin and embedded in paraffin. Hematoxylin and eosin (H&E) staining was performed on the sections for routine histopathological evaluation. The histological parameters assessed included:

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- **Fibrosis staging:** Fibrosis was staged according to the METAVIR scoring system, ranging from F0 (no fibrosis) to F4 (cirrhosis).
- **Tumor grading:** Tumor cells were graded based on nuclear atypia, mitotic activity, and cellular differentiation.
- **Inflammation:** Degree of inflammatory cell infiltration in cirrhotic and tumor tissue was recorded.
- **Vascular invasion:** Presence of microvascular or macrovascular invasion was noted.
- **Nodule formation:** The presence of regenerative nodules versus malignant nodules was evaluated.

Molecular Analysis

Molecular profiling of the liver biopsy samples was conducted to identify genetic mutations, epigenetic alterations, and expression of key oncogenes and tumor suppressor genes. The following molecular markers were analyzed:

- **TP53 gene mutation:** Associated with loss of tumor suppressor function, leading to uncontrolled cell growth.
- **CTNNB1 gene mutation:** Linked to the activation of the Wnt/β-catenin signaling pathway, promoting tumor progression.
- **TERT promoter mutations:** Known for their role in telomere maintenance, enabling cancer cells to evade senescence.
- **RASSF1A promoter methylation:** Investigated for its epigenetic silencing, contributing to uncontrolled cell division.
- **MicroRNA (miRNA) expression profiles:** Specific miRNAs were examined for their role in regulating gene expression involved in cell proliferation, apoptosis, and angiogenesis.

DNA extraction from the biopsy tissues was followed by sequencing using next-generation sequencing (NGS) technology. Epigenetic analyses were conducted using bisulfite sequencing to identify methylation patterns. miRNA profiles were assessed using quantitative PCR (qPCR).

Statistical Analysis

Data were analyzed using statistical software to determine the significance of correlations between histological features, molecular findings, and clinical outcomes. Continuous variables, such as age and liver function tests, were compared using t-tests or Mann-Whitney U tests. Categorical variables, such as fibrosis stage and the presence of vascular invasion, were

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compared using chi-square or Fisher's exact tests. Kaplan-Meier survival analysis was performed to evaluate the prognostic value of specific histological and molecular markers.

Results

This section presents the findings of the study, based on histological and molecular analyses of liver biopsies from 85 cirrhotic patients diagnosed with hepatocellular carcinoma (HCC). The results are divided into histological findings, molecular alterations, and correlations with clinical outcomes. Hypothetical data are used to illustrate these results.

Patient Demographics

The study included 85 patients, with the following characteristics:

- **Mean age:** 58.4 years (range: 42–74 years)
- **Gender:** 60 males (70.6%) and 25 females (29.4%)
- **Etiology of cirrhosis:**
  - Hepatitis B: 35 patients (41.2%)
  - Hepatitis C: 30 patients (35.3%)
  - Alcoholic liver disease: 10 patients (11.8%)
  - Non-alcoholic fatty liver disease (NAFLD): 10 patients (11.8%)

Histological Findings

The liver biopsy samples were examined for fibrosis stage, tumor grade, inflammation, vascular invasion, and the presence of malignant versus regenerative nodules.

- **Fibrosis Staging (METAVIR):**
  - F3 (Severe fibrosis): 20 patients (23.5%)
  - F4 (Cirrhosis): 65 patients (76.5%)
- **Tumor Grading:**
  - Well-differentiated HCC: 20 patients (23.5%)
  - Moderately differentiated HCC: 45 patients (52.9%)
  - Poorly differentiated HCC: 20 patients (23.5%)
- **Inflammation:**
  - Mild inflammatory infiltration: 25 patients (29.4%)
  - Moderate infiltration: 45 patients (52.9%)
  - Severe inflammation: 15 patients (17.7%)
- **Vascular Invasion:**
  - Microvascular invasion: 30 patients (35.3%)
  - Macrovascular invasion: 10 patients (11.8%)
  - No invasion: 45 patients (52.9%)
- **Nodule Formation:**
  - Regenerative nodules: 40 patients (47.1%)
  - Malignant nodules: 45 patients (52.9%)

Patients with vascular invasion (particularly macrovascular) were found to have more aggressive tumor phenotypes and were primarily in the moderately to poorly differentiated HCC categories.

Molecular Findings

The molecular profiling of the biopsy samples revealed several key genetic mutations and epigenetic alterations.

- **TP53 Mutation:**
  - Present in 35 patients (41.2%)

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  - TP53 mutations were significantly associated with poorly differentiated tumors ($p < 0.05$).
- **CTNNB1 Mutation:**
  - Present in 20 patients (23.5%)
  - This mutation was more common in well-differentiated tumors ($p < 0.01$).
- **TERT Promoter Mutations:**
  - Detected in 40 patients (47.1%)
  - TERT mutations were found in both moderately and poorly differentiated tumors, with a higher incidence of vascular invasion ($p < 0.05$).
- **RASSF1A Promoter Methylation:**
  - Hyper-methylation detected in 25 patients (29.4%)
  - Patients with RASSF1A methylation had an increased risk of tumor recurrence after treatment ($p < 0.01$).
- **miRNA Dysregulation:**
  - Overexpression of miR-21 (35 patients, 41.2%) was associated with increased angiogenesis and poorer survival outcomes ($p < 0.05$).
  - Downregulation of miR-122 (40 patients, 47.1%), a liver-specific miRNA, was observed in patients with more advanced disease and greater tumor burden.

Correlation Between Histological and Molecular Findings

- **TP53 mutations** were strongly correlated with poorly differentiated tumors and the presence of vascular invasion, highlighting their role in tumor aggressiveness and metastasis potential.
- **CTNNB1 mutations** were predominantly found in well-differentiated tumors and were associated with a slower rate of tumor progression.
- **TERT promoter mutations** and **RASSF1A promoter methylation** were significantly associated with increased fibrosis, suggesting their role in both cirrhosis progression and carcinogenesis.
- **miR-21 overexpression** and **miR-122 downregulation** were linked to more aggressive tumor phenotypes and poorer survival outcomes, indicating their potential as prognostic biomarkers.

Prognostic Outcomes

The overall survival (OS) and disease-free survival (DFS) of the patients were analyzed based on histological and molecular markers.

- **Overall Survival (OS):**
  - Patients with **well-differentiated HCC** had a median OS of 48 months.
  - Patients with **moderately differentiated HCC** had a median OS of 30 months.
  - Patients with **poorly differentiated HCC** had a median OS of 18 months.
- **Disease-Free Survival (DFS):**
  - Patients with **no vascular invasion** had a median DFS of 36 months.
  - Patients with **microvascular invasion** had a median DFS of 24 months.
  - Patients with **macrovascular invasion** had a median DFS of 12 months.

The presence of **TP53 mutations** and **TERT promoter mutations** was associated with poorer OS and DFS, while **CTNNB1 mutations** correlated with better survival outcomes.

Table 1: Patient Demographics and Etiology of Cirrhosis

Characteristic	Number of Patients (n=85)	Percentage (%)

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Age (mean)	58.4 years	-
Gender		
Male	60	70.6%
Female	25	29.4%
Etiology of Cirrhosis		
Hepatitis B	35	41.2%
Hepatitis C	30	35.3%
Alcoholic liver disease	10	11.8%
NAFLD	10	11.8%

Table 2: Histological Findings in Liver Biopsies

Histological Feature	Number of Patients (n=85)	Percentage (%)
Fibrosis Stage (METAVIR)		
F3 (Severe fibrosis)	20	23.5%
F4 (Cirrhosis)	65	76.5%
Tumor Grading		
Well-differentiated HCC	20	23.5%
Moderately differentiated HCC	45	52.9%
Poorly differentiated HCC	20	23.5%
Inflammation		
Mild	25	29.4%
Moderate	45	52.9%
Severe	15	17.7%
Vascular Invasion		
Microvascular invasion	30	35.3%
Macrovascular invasion	10	11.8%
No invasion	45	52.9%
Nodule Formation		
Regenerative nodules	40	47.1%
Malignant nodules	45	52.9%

Table 3: Molecular Findings in Liver Biopsies

Molecular Marker	Number of Patients (n=85)	Percentage (%)
TP53 Mutation	35	41.2%
CTNNB1 Mutation	20	23.5%
TERT Promoter Mutations	40	47.1%
RASSF1A Promoter Methylation	25	29.4%
miR-21 Overexpression	35	41.2%
miR-122 Downregulation	40	47.1%

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Table 4: Survival Outcomes Based on Tumor Differentiation and Vascular Invasion

Survival Outcome	Median OS (months)	Median DFS (months)
Tumor Differentiation		
Well-differentiated HCC	48	36
Moderately differentiated HCC	30	24
Poorly differentiated HCC	18	12
Vascular Invasion		
No vascular invasion	48	36
Microvascular invasion	30	24
Macrovascular invasion	18	12

Discussion

The findings from this study provide valuable insights into the histological and molecular landscape of hepatocellular carcinoma (HCC) in cirrhotic patients. By integrating histopathological features with molecular alterations, the study enhances our understanding of the mechanisms driving HCC progression and highlights important correlations between specific genetic changes, tumor differentiation, and clinical outcomes. Liver biopsies from the 85 cirrhotic patients showed the characteristic features of cirrhosis, including fibrosis, regenerative nodules, and in some cases, malignant transformation into HCC. The majority of patients (76.5%) presented with advanced fibrosis (F4 stage), consistent with the well-established link between cirrhosis and HCC development [12]. Notably, well-differentiated tumors, which were present in 23.5% of patients, appeared to be associated with a slower progression of disease and better survival outcomes, as evidenced by a median overall survival (OS) of 48 months [13]. In contrast, poorly differentiated HCC, observed in 23.5% of patients, was linked to more aggressive disease and a significantly lower median OS of 18 months. The presence of vascular invasion, particularly macrovascular invasion, was another key histological indicator of aggressive tumor behavior. Patients with macrovascular invasion had a median OS of 18 months, underscoring its strong association with poor prognosis. Microvascular invasion, present in 35.3% of patients, also negatively impacted survival, although to a lesser extent than macrovascular invasion [14]. These findings emphasize the importance of assessing vascular invasion in liver biopsies, as it provides crucial prognostic information that can guide treatment decisions. The molecular analysis of the liver biopsy samples revealed several important genetic and epigenetic alterations that are known to play a role in HCC development. Among the most frequently observed mutations was **TP53**, found in 41.2% of patients. The **TP53** mutation is a well-known driver of carcinogenesis, associated with the loss of tumor suppressor function, leading to uncontrolled cell growth and proliferation. In this study, **TP53** mutations were predominantly found in poorly differentiated tumors and were strongly associated with vascular invasion, particularly macrovascular invasion [15]. This suggests that **TP53** mutations are linked to more aggressive tumor phenotypes and may serve as a predictor of poor prognosis in HCC patients. Mutations in **CTNNB1**, a key regulator of the Wnt/β-catenin signaling pathway, were present in 23.5% of patients. Interestingly, these mutations were more commonly found in well-differentiated tumors and were associated with better survival outcomes, suggesting that **CTNNB1** mutations may be indicative of a less aggressive tumor biology. This finding aligns with previous research indicating that **CTNNB1**-mutated HCC often follows a more indolent course compared to **TP53**-mutated HCC [16]. As such, **CTNNB1** mutations may serve as a potential biomarker for identifying patients with a more favorable prognosis, which could influence therapeutic

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strategies. In addition to genetic mutations and epigenetic changes, **microRNAs (miRNAs)** played a significant role in HCC progression. Overexpression of **miR-21**, found in 41.2% of patients, was associated with increased angiogenesis and poorer survival outcomes. Conversely, downregulation of **miR-122**, a liver-specific miRNA, was observed in 47.1% of patients with more advanced disease. These findings support the growing body of evidence that miRNAs can serve as both diagnostic and prognostic biomarkers in HCC, as well as potential therapeutic targets [17]. The combination of histological and molecular data provides a comprehensive view of HCC in cirrhotic patients and has several important clinical implications. First, the presence of specific molecular alterations, such as **TP53**, **TERT**, and **CTNNB1** mutations, can aid in risk stratification and help identify patients who may benefit from more aggressive treatment strategies. For example, patients with **TP53** or **TERT** mutations, particularly those with vascular invasion, may be candidates for systemic therapies, including targeted therapies or immune checkpoint inhibitors, to improve outcomes. Additionally, the identification of miRNA dysregulation, such as **miR-21** overexpression or

Conclusion

This study offers a comprehensive evaluation of the histological and molecular findings in liver biopsies from cirrhotic patients with hepatocellular carcinoma (HCC), providing critical insights into the mechanisms of tumor progression and potential clinical implications. The combination of advanced fibrosis, tumor differentiation, and the presence of vascular invasion in histological assessments was strongly associated with poorer survival outcomes, emphasizing the importance of these markers in prognostic evaluations.

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