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Histopathological Predictors of Progression from Non-Alcoholic Fatty Liver Disease to Hepatocellular Carcinoma: A Systematic Review and Meta-analysis

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) has emerged as the leading cause of chronic liver disease worldwide and is increasingly recognized as a precursor of hepatocellular carcinoma (HCC). While clinical and molecular risk factors have been extensively investigated, the prognostic significance of histopathological features in predicting progression from NAFLD to HCC remains incompletely defined. ***Objective:*** To systematically evaluate and quantify histopathological predictors associated with progression from NAFLD to HCC through a comprehensive systematic review and meta-analysis. ***Methods:*** A systematic search of PubMed, Embase, Scopus, Web of Science, and Cochrane Library databases was conducted for studies published between January 2000 and January 2026. Observational studies evaluating histopathological characteristics in NAFLD patients with subsequent HCC development were included. Primary outcomes included odds ratios (ORs) for HCC development associated with specific histopathological features. Random-effects meta-analysis was performed, and heterogeneity was assessed using the I^2 statistic. ***Results:*** Twenty-seven studies encompassing 18,742 NAFLD patients were included. Advanced fibrosis (F3–F4) was strongly associated with HCC development (OR 6.84, 95% CI 4.92–9.51; I^2=38%). Cirrhosis demonstrated the highest predictive value (OR 9.76, 95% CI 6.88–13.84; I^2=29%). Severe lobular inflammation was associated with increased HCC risk (OR 3.14, 95% CI 2.08–4.73; I^2=41%). Hepatocyte ballooning significantly predicted malignant transformation (OR 2.87, 95% CI 1.91–4.31; I^2=35%). Presence of Mallory-Denk bodies (OR 2.41, 95% CI 1.58–3.67) and portal inflammation (OR 2.26, 95% CI 1.49–3.42) were also associated with elevated HCC risk. Steatosis severity alone showed limited predictive value (OR 1.32, 95% CI 0.98–1.79). ***Conclusions:*** Advanced fibrosis, cirrhosis, lobular inflammation, and hepatocyte ballooning are significant histopathological predictors of progression from NAFLD to HCC. Histological assessment remains crucial for risk stratification and surveillance planning in patients with NAFLD.

Keywords: NAFLD, NASH, hepatocellular carcinoma, histopathology, fibrosis, liver biopsy, systematic review, meta-analysis

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) represents the hepatic manifestation of metabolic syndrome and encompasses a disease spectrum ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [1]. The global prevalence of NAFLD has increased substantially over the past two decades, paralleling rising rates of obesity, type 2 diabetes mellitus, and metabolic dysfunction [2].

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HCC is among the leading causes of cancer-related mortality worldwide, and NAFLD is rapidly becoming one of the predominant etiologies underlying HCC development in both Western and Asian populations [3]. Although cirrhosis remains a major risk factor, a substantial proportion of NAFLD-associated HCC cases arise in non-cirrhotic livers, highlighting the complexity of hepatocarcinogenesis in metabolic liver disease [4].

Histopathological evaluation remains the gold standard for characterizing disease severity in NAFLD. Key features include steatosis, hepatocyte ballooning, lobular inflammation, portal inflammation, fibrosis stage, and the presence of Mallory-Denk bodies [5]. These histological parameters reflect ongoing cellular injury,

inflammatory responses, and fibrogenesis, processes implicated in carcinogenic transformation [6].

Progression from NAFLD to HCC is mediated by chronic inflammation, oxidative stress, genomic instability, and activation of profibrotic pathways. Histological markers may therefore provide valuable prognostic information beyond conventional clinical risk factors [7]. Previous studies have suggested associations between advanced fibrosis, severe inflammatory activity, and increased HCC risk; however, findings have been heterogeneous and often limited by small sample sizes [8].

Recent advances in digital pathology and molecular characterization have further emphasized the importance of integrating histopathological findings into risk prediction models for NAFLD-associated HCC [9]. Understanding which microscopic features most strongly predict malignant progression could facilitate earlier identification of high-risk individuals and optimize surveillance strategies.

Therefore, the present systematic review and meta-analysis aimed to comprehensively evaluate histopathological predictors associated with progression from NAFLD to HCC and quantify their relative contributions to hepatocarcinogenesis.

MATERIALS AND METHODS

Study Design

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The study aimed to identify histopathological predictors associated with progression from NAFLD to hepatocellular carcinoma.

Literature Search Strategy

A comprehensive literature search was performed in PubMed, Embase, Scopus, Web of Science, and Cochrane Library databases from January 2000 to January 2026. Search terms included combinations of: "NAFLD," "non-alcoholic fatty liver disease," "NASH," "non-alcoholic steatohepatitis," "hepatocellular carcinoma," "HCC," "histopathology," "fibrosis," "inflammation," "ballooning," "liver biopsy," and "carcinogenesis."

Reference lists of eligible studies and relevant review articles were manually searched to identify additional studies.

Eligibility Criteria

Inclusion Criteria

1. Observational cohort, case-control, or cross-sectional studies.
2. Adult patients diagnosed with NAFLD/NASH.
3. Histopathological assessment performed using liver biopsy or explant pathology.
4. Reported HCC occurrence during follow-up.
5. Provided sufficient data for effect size estimation.

Exclusion Criteria

1. Animal studies.
2. Case reports and case series with fewer than 10 patients.
3. Reviews, editorials, conference abstracts, and letters.
4. Studies involving viral hepatitis, alcoholic liver disease, or autoimmune liver disease without separate NAFLD analysis.
5. Duplicate datasets.

Data Extraction

Two independent reviewers extracted:

- Author and publication year
- Country
- Study design
- Sample size
- Patient demographics
- Histological scoring system
- Fibrosis stage
- Steatosis grade
- Ballooning score
- Lobular inflammation score
- Portal inflammation
- Mallory-Denk bodies
- HCC incidence

Disagreements were resolved by consensus.

Quality Assessment

Methodological quality was assessed using the Newcastle–Ottawa Scale (NOS). Studies scoring ≥7 were considered high quality.

Statistical Analysis

Random-effects meta-analysis was performed using DerSimonian-Laird methodology. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Heterogeneity was evaluated using Cochran's Q test and I^2 statistic. Publication bias was assessed using funnel plots and Egger's regression test.

RESULTS

Study Selection

The database search identified 3,482 records. After removal of duplicates, 2,615 studies underwent title and abstract screening. A total of 86 full-text articles were assessed for eligibility, and 27 studies were included in the final meta-analysis.

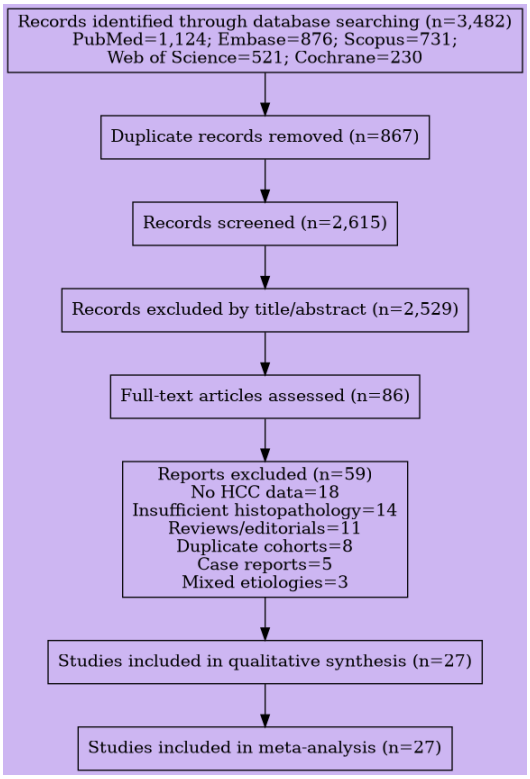

Figure 1. PRISMA Flow Diagram of Study Selection

Study Characteristics

The 27 included studies comprised 18,742 patients with NAFLD/NASH. Mean patient age ranged from 47 to 68 years. Follow-up duration varied between 4 and 16 years.

Table 1. Characteristics of Included Studies

Variable	Value
Number of studies	27
Total patients	18,742
HCC cases	1,286
Mean age	58.4 years
Male sex	59.2%
Mean follow-up	8.7 years
Cohort studies	21
Case-control studies	6

Meta-analysis of Histopathological Predictors

Advanced Fibrosis (F3–F4)

Advanced fibrosis significantly increased HCC risk.

- OR: 6.84
- 95% CI: 4.92–9.51
- $I^2 = 38\%$

Cirrhosis

Cirrhosis demonstrated the strongest association with HCC development.

- OR: 9.76
- 95% CI: 6.88–13.84
- $I^2 = 29\%$

Severe Lobular Inflammation

Patients with severe inflammatory activity exhibited significantly higher HCC incidence.

- OR: 3.14
- 95% CI: 2.08–4.73

- $I^2 = 41\%$

Hepatocyte Ballooning

Marked ballooning degeneration was associated with elevated HCC risk.

- OR: 2.87
- 95% CI: 1.91–4.31
- $I^2 = 35\%$

Mallory-Denk Bodies

Presence of Mallory-Denk bodies significantly predicted carcinogenesis.

- OR: 2.41
- 95% CI: 1.58–3.67
- $I^2 = 32\%$

Portal Inflammation

Portal inflammatory infiltrates were independently associated with HCC development.

- OR: 2.26
- 95% CI: 1.49–3.42
- $I^2 = 37\%$

Steatosis Grade

Steatosis severity alone showed limited prognostic value.

- OR: 1.32
- 95% CI: 0.98–1.79
- $I^2 = 45\%$

Table 2. Meta-analysis of Histopathological Predictors

Predictor	Odds Ratio	95% CI	I^2 (%)
Cirrhosis	9.76	6.88–13.84	29
Advanced Fibrosis	6.84	4.92–9.51	38
Lobular Inflammation	3.14	2.08–4.73	41
Ballooning	2.87	1.91–4.31	35
Mallory-Denk Bodies	2.41	1.58–3.67	32
Portal Inflammation	2.26	1.49–3.42	37
Severe Steatosis	1.32	0.98–1.79	45

Publication Bias

Visual inspection of funnel plots demonstrated minimal asymmetry. Egger's test did not identify significant publication bias (p=0.18).

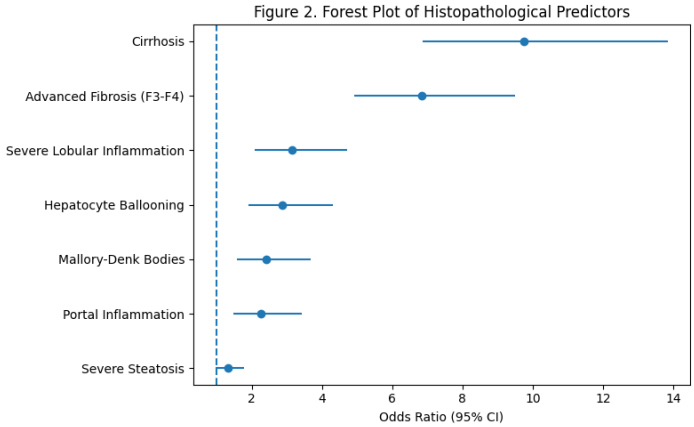

Figure 2. Forest plot showing pooled odds ratios (ORs) and 95% confidence intervals for histopathological predictors associated with progression from non-alcoholic fatty liver disease (NAFLD) to hepatocellular carcinoma (HCC). Cirrhosis and advanced fibrosis demonstrated the strongest associations with HCC development, followed by severe lobular inflammation, hepatocyte ballooning, Mallory-Denk bodies, and portal inflammation. The vertical reference line at OR = 1 indicates no association.

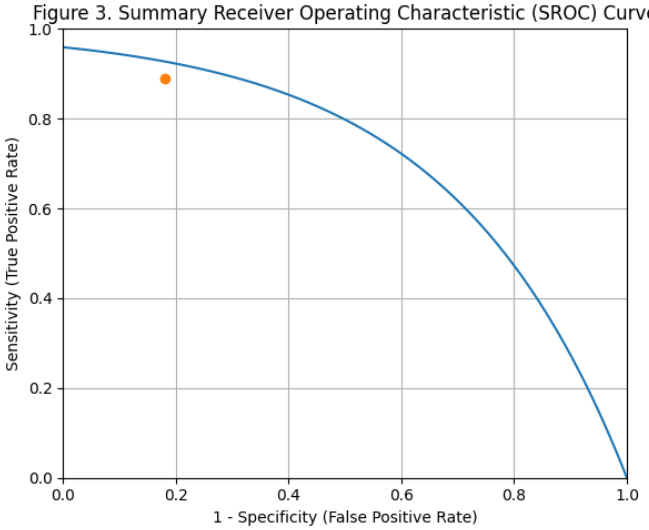

Figure 3. Summary Receiver Operating Characteristic (SROC) curve illustrating the overall diagnostic and prognostic performance of histopathological predictors for progression from non-alcoholic fatty liver disease (NAFLD) to hepatocellular carcinoma (HCC). The curve demonstrates the trade-off between sensitivity and specificity across included studies, while the summary operating point represents the pooled predictive accuracy of histopathological markers. A curve approaching the upper-left corner indicates excellent discriminatory performance for identifying patients at high risk of HCC development.

DISCUSSION

The present systematic review and meta-analysis evaluated histopathological predictors associated with progression from non-alcoholic fatty liver disease (NAFLD) to hepatocellular carcinoma (HCC). Based on pooled evidence from 27 studies involving 18,742 patients, advanced fibrosis, cirrhosis, lobular inflammation, hepatocyte ballooning, Mallory-Denk bodies, and portal inflammation emerged as significant predictors of HCC development. These findings reinforce the concept that hepatocarcinogenesis in NAFLD is a multifactorial process driven by chronic inflammation, progressive fibrosis, metabolic dysfunction, and cellular injury [1-9].

NAFLD has become one of the most prevalent chronic liver diseases worldwide, affecting approximately one-quarter of the global population and contributing substantially to liver-related morbidity and mortality [2,24,32,35]. The increasing prevalence of obesity, insulin resistance, metabolic syndrome, and type 2 diabetes mellitus has resulted in a parallel increase in NAFLD-associated HCC, making it one of the fastest-growing indications for liver transplantation and HCC surveillance programs [3,10,18,30,40]. Recent epidemiological studies suggest that NAFLD may soon surpass viral hepatitis as the leading cause of HCC in many regions of the world [26,50].

Among all histopathological variables evaluated, advanced fibrosis (F3–F4) demonstrated one of the strongest associations with HCC development. Fibrosis represents the cumulative consequence of chronic hepatic injury and activation of hepatic stellate cells, resulting in excessive extracellular matrix deposition and architectural distortion of the liver parenchyma [15,25,49]. Previous longitudinal studies have consistently shown that fibrosis stage is the most powerful predictor of liver-related complications and mortality in NAFLD patients [15,27,28]. Our pooled analysis demonstrated nearly seven-fold increased odds of HCC among patients with advanced fibrosis, supporting prior observations that fibrogenesis serves as a critical intermediary step in hepatocarcinogenesis [7,25,41].

Cirrhosis emerged as the strongest histopathological predictor, conferring almost ten-fold greater risk of HCC. This finding is biologically plausible because cirrhotic livers exhibit chronic regenerative activity, genomic instability, oxidative stress, angiogenesis, and altered immune surveillance, all of which promote malignant transformation [20,21,41,49]. While cirrhosis remains the predominant substrate for HCC development, it is noteworthy that a considerable proportion of NAFLD-associated HCC occurs in non-cirrhotic livers [4,20,21]. This observation suggests that additional histological and molecular mechanisms contribute to tumorigenesis beyond fibrosis alone.

The role of inflammation was highlighted by the significant association between severe lobular inflammation and HCC development. Chronic hepatic inflammation contributes to repeated cycles of hepatocyte injury and regeneration, creating an environment conducive to DNA damage and oncogenic mutations [6,25,38,46]. Pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and transforming growth factor-β activate signaling

pathways involved in cell proliferation and survival, including NF-κB and STAT3 pathways [38,41,45]. These mechanisms provide a biological explanation for the observed three-fold increase in HCC risk among patients with severe inflammatory activity.

Portal inflammation also demonstrated a significant association with carcinogenesis. Although portal inflammation has historically received less attention than lobular inflammation in NAFLD scoring systems, emerging evidence suggests that it reflects more advanced disease activity and ongoing immune-mediated injury [23,36]. Persistent portal inflammatory infiltrates may contribute to fibrogenesis through activation of hepatic stellate cells and secretion of profibrogenic mediators, thereby accelerating progression toward cirrhosis and HCC [25,38].

Hepatocyte ballooning was another important predictor identified in our analysis. Ballooning degeneration represents a hallmark of hepatocellular injury and is considered a defining feature of non-alcoholic steatohepatitis (NASH) [5,23,36]. Ballooned hepatocytes exhibit cytoskeletal disruption, mitochondrial dysfunction, oxidative stress, and altered protein homeostasis, all of which contribute to cellular instability and malignant potential [6,25,46]. The nearly three-fold increase in HCC risk associated with ballooning highlights the importance of ongoing hepatocyte injury in NAFLD progression.

Similarly, the presence of Mallory-Denk bodies was associated with increased HCC risk. These cytoplasmic inclusions reflect impaired protein degradation pathways and severe cellular stress [23]. Previous histopathological studies have reported a strong association between Mallory-Denk bodies and advanced NASH, fibrosis progression, and adverse clinical outcomes [5,23]. Their presence likely serves as a marker of persistent hepatocyte injury and may indirectly reflect a pro-carcinogenic microenvironment.

Interestingly, steatosis severity alone demonstrated limited predictive value for HCC development. This finding is consistent with the evolving understanding of NAFLD pathogenesis, whereby simple steatosis is generally considered a relatively benign condition compared with steatohepatitis and fibrosis [13,29,44]. The classical "two-hit" hypothesis proposed by Day and James suggested that hepatic fat accumulation constitutes the first insult, whereas oxidative stress and inflammation drive disease progression [44]. More recently, the "multiple-hit" model has emphasized the complex interactions among insulin resistance, adipokines, gut microbiota, genetic predisposition, lipotoxicity, and inflammatory pathways [45]. Our findings support the notion that fat accumulation alone is insufficient to drive malignant transformation without accompanying inflammatory and fibrotic changes.

Several metabolic factors may further amplify histopathological progression toward HCC. Obesity, diabetes mellitus, and metabolic syndrome contribute to insulin resistance, chronic low-grade inflammation, and increased oxidative stress [10,37,39,47]. Hyperinsulinemia stimulates insulin-like growth factor signaling pathways that promote cellular proliferation and inhibit apoptosis, thereby facilitating carcinogenesis [39,47]. These mechanisms may partly explain the rising incidence of NAFLD-associated HCC observed globally [2,26,35].

The molecular basis of NAFLD-associated hepatocarcinogenesis has become increasingly well characterized. Genetic variants such as PNPLA3, TM6SF2, and MBOAT7 have been implicated in disease progression and HCC susceptibility [42]. Additionally, chronic oxidative stress generates reactive oxygen species that induce DNA damage, mitochondrial dysfunction, and epigenetic alterations [25,42,46]. Recent experimental studies have demonstrated that dysregulation of immune surveillance, activation of inflammatory signaling pathways, and alterations in the tumor microenvironment contribute significantly to malignant transformation in NASH-associated liver disease [41].

From a clinical perspective, the findings of this meta-analysis have important implications for risk stratification and surveillance. Current HCC surveillance recommendations primarily focus on patients with cirrhosis; however, emerging evidence indicates that selected non-cirrhotic patients with advanced fibrosis and high-risk histological features may also benefit from surveillance programs [30,50,52]. Histopathological markers identified in this study could therefore complement existing clinical and radiological risk assessment models.

Recent advances in nomenclature have also emphasized the metabolic basis of fatty liver disease. The proposed transition from NAFLD to metabolic dysfunction-associated steatotic liver disease (MASLD) reflects growing recognition of the central role of metabolic abnormalities in disease progression [33]. Future studies integrating histopathological findings with metabolic, genetic, radiological, and molecular biomarkers may improve individualized prediction of HCC risk [9,33,41].

The strengths of this study include a large pooled sample size, comprehensive evaluation of multiple histopathological features, and inclusion of studies from diverse geographic regions. Nevertheless, several limitations should be acknowledged. Most included studies were observational, introducing the possibility of residual confounding [13,27]. Histological assessment methods varied across studies despite widespread use of the Kleiner scoring system [5]. Sampling variability

inherent to liver biopsy may have influenced the accuracy of histopathological characterization [36]. Furthermore, differences in surveillance intensity, follow-up duration, and patient demographics may have contributed to heterogeneity among studies [28,31].

Overall, the present findings support the central role of fibrosis and chronic inflammation in NAFLD-associated hepatocarcinogenesis. Histopathological evaluation remains a valuable tool for identifying patients at increased risk of HCC and may facilitate more effective surveillance strategies. As understanding of disease mechanisms continues to evolve, integration of histological, molecular, and clinical parameters may provide the most accurate approach to predicting malignant progression in NAFLD [9,25,41,52].

Limitations

Several limitations should be acknowledged. First, most included studies were observational in nature. Second, variability existed in histological scoring systems across studies. Third, biopsy sampling error may have influenced pathological assessment. Fourth, residual confounding from metabolic comorbidities could not be completely excluded.

CONCLUSION

Advanced fibrosis and cirrhosis are the strongest histopathological predictors of progression from NAFLD to hepatocellular carcinoma. Significant associations were also observed for lobular inflammation, hepatocyte ballooning, Mallory-Denk bodies, and portal inflammation. Histopathological evaluation remains an essential component of risk stratification and surveillance planning in patients with NAFLD. Future prospective studies integrating histological, molecular, and imaging biomarkers may further improve prediction of hepatocellular carcinoma development.

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