

Significance of Portal Tract Histological Changes in Metabolic Dysfunction-Associated Steatohepatitis

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Abstract

Background: Metabolic dysfunction associated steatohepatitis (MASH) is a leading cause of advanced liver fibrosis globally. Current histological scoring (NAS-CRN) excludes portal-based features, despite emerging evidence suggesting their relevance. **Aim:** To study the prevalence of portal tract changes and their correlation with fibrosis in liver biopsies from patients with MASH.

Methods: In this retrospective and prospective cross-sectional study, 505 liver biopsies were analysed. Portal inflammation, interface hepatitis, ductular reaction, bile duct damage, and plasma cells were semi-quantitatively assessed. Fibrosis was quantified using whole slide digital images of Sirius red-stained slides, and hepatic progenitor cells (HPC) were measured by CK7 immunohistochemistry.

Results: Mean age was 45.1±12.5 years, with 65% males. Advanced fibrosis (F3–F4) was present in 69.1%. Portal inflammation was observed in 69.3% (predominantly mild). Moderate–severe portal inflammation, plasma cells, interface activity, ductular reaction, duct damage, and HPC were significantly associated with advanced fibrosis (all $p \leq 0.005$). Portal inflammation significantly correlated with ductular reaction, interface activity, plasma cell infiltration, bile duct damage, progenitor cells, and fibrosis fraction (all $p \leq 0.005$).

Conclusion: Portal inflammation and related features are strongly associated with advanced fibrosis in MASH, thereby suggesting multifactorial role in disease progression and supporting their inclusion in histological scoring systems and routine reporting. (*Acta gastroenterol belg.*, 2026, 89, 437-443).

Keywords: Metabolic dysfunction-associated steatohepatitis, Histological scoring, portal inflammation, fibrosis, portal features, quantification.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the leading cause of chronic liver disease worldwide, with a rapidly increasing global incidence and an estimated prevalence of 5–28% in the Indian population (1,2).

MASLD encompasses a spectrum of pathological changes ranging from simple steatosis to steatohepatitis, with variable degrees of fibrosis (3-5), and it may progress to cirrhosis, liver failure, and hepatocellular carcinoma. Differentiating metabolic dysfunction-associated steatohepatitis (MASH) from non-progressive hepatic steatosis is clinically important, and liver biopsy remains the gold standard for confirming or excluding MASH (5).

The diagnosis of MASH requires the presence of steatosis, lobular inflammation, and hepatocellular ballooning, with or without fibrosis (6,7). Liver biopsy is also essential for assessing disease severity and

staging fibrosis (8,9). The NASH Clinical Research Network (NASH CRN) histological scoring system is the most widely used system for evaluating MASH. The NAFLD Activity Score (NAS) is an un-weighted composite score that sums individual grades for steatosis (0-3), lobular inflammation (0-3), and hepatocellular ballooning (0-2), yielding a total score ranging from 0 to 8 and capturing the full histological spectrum of MASLD. Although portal inflammation was initially described as a relevant parameter, it was excluded from the NAS-CRN system. Fibrosis is staged using semi-quantitative scoring systems, most commonly the NAS CRN fibrosis staging system, which employs a five-tier scale (F0–F4) (6,7,10).

Fibrosis, a consequence of ongoing disease activity, is the strongest predictor of clinical outcomes in MASH (11). Some studies have demonstrated that more-than-mild portal inflammation is associated with advanced fibrosis and disease progression, suggesting its potential role as a marker of disease activity (11-13). A recently published position paper on histological grading and staging systems in MASH also recommends scoring and reporting portal inflammation (14). However, it is not currently included in standardized histological scoring systems.

In addition, portal-based features such as ductular reaction and periportal hepatic progenitor cell activation have been proposed to play a significant role in the progression to MASH and fibrogenesis (15-17).

Given that the prevalence and clinical significance of portal-based histological changes in MASH remain incompletely understood, this study was undertaken to evaluate the frequency and severity of portal inflammation, interface hepatitis, bile duct injury, and ductular reaction, and to assess their correlation with fibrosis in liver biopsies from patients with MASH.

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Methodology

Histopathological assessment

Liver biopsy specimens were formalin-fixed, paraffin embedded. The stains evaluated included hematoxylin and eosin (H&E) and Masson's trichrome for glass slide examination, and picrosirius red stain for digital quantification. All biopsy specimens were independently evaluated and scored by two liver pathologists (AR and NN). Any discrepancies were resolved by consensus through joint review using a multi-header microscope.

Histological grading and staging were performed using the NAS score developed by the NASH CRN. The NAS ranges from 0 to 8 and includes steatosis (0–3), lobular inflammation (0–3), and hepatocyte ballooning (0–2).

Fibrosis was staged according to the CRN staging system (F0–F4). The stages were defined as follows: Stage 0, no fibrosis; stage 1, perisinusoidal or portal fibrosis (1a: mild [delicate] zone 3 fibrosis; 1b: moderate [dense] zone 3 fibrosis; 1c: portal fibrosis only); stage 2, perisinusoidal and portal/periportal fibrosis; stage 3, bridging (septal) fibrosis; and stage 4, cirrhosis. Stage 3 fibrosis was further subclassified into 3a–3c (3a: a single definite fibrous bridge; 3b: few fibrous bridges without nodule formation; 3c: complex bridging with or without rare nodules). Stage 4 fibrosis (cirrhosis) was sub-classified using the Laennec system (4a, 4b, 4c) (18). Fig.1.

Portal tract-based histological features assessment

Portal inflammation was graded according to the

Goodman classification, based on the most severely affected portal tract and categorized as none, mild, moderate, or severe (grades 0–3) (5).

Ductular reaction and hepatic progenitor cells (HPCs) were assessed using CK7 immunohistochemistry (ready-to-use monoclonal antibody, clone EP16, rabbit, PathnSitu, CA, USA). Ductular reaction was graded on a scale of 0–3: 0, none; 1, mild (2–5 ductules); 2, moderate (6–9 ductules); and 3, severe (>10 ductules). Scores of 2–3 was considered positive for analysis.

Interface activity was graded using the Ishak scoring system (0–4). Plasma cell infiltration was also graded on a scale of 0 to 4 as follows: 0, none; 1, occasional and difficult to identify; 2, occasional but easily identified; 3, few; and 4, many. Fig.2.

Immunohistochemistry method

Immunohistochemical staining was performed using the peroxidase-labeled streptavidin-biotin (LSAB) detection method with a Polymer-HRP kit (Biogenex, San Ramon, USA), diaminobenzidine (DAB) as the chromogen, and Meyer's hematoxylin as the counter stain.

Sections mounted on poly-L-lysine-coated slides were deparaffinized. Endogenous peroxidase activity was blocked using 3 % hydrogen peroxide in distilled water for 10 minutes. Heat-induced antigen retrieval was performed in Tris buffer solution (TBS; pH 6.0), followed by application of a protein block to reduce background staining. Sections were incubated with the primary antibody for 1 hour, followed by secondary antibody for 20 minutes and tertiary (streptavidin) for 20 minutes, with TBS washes between each step.

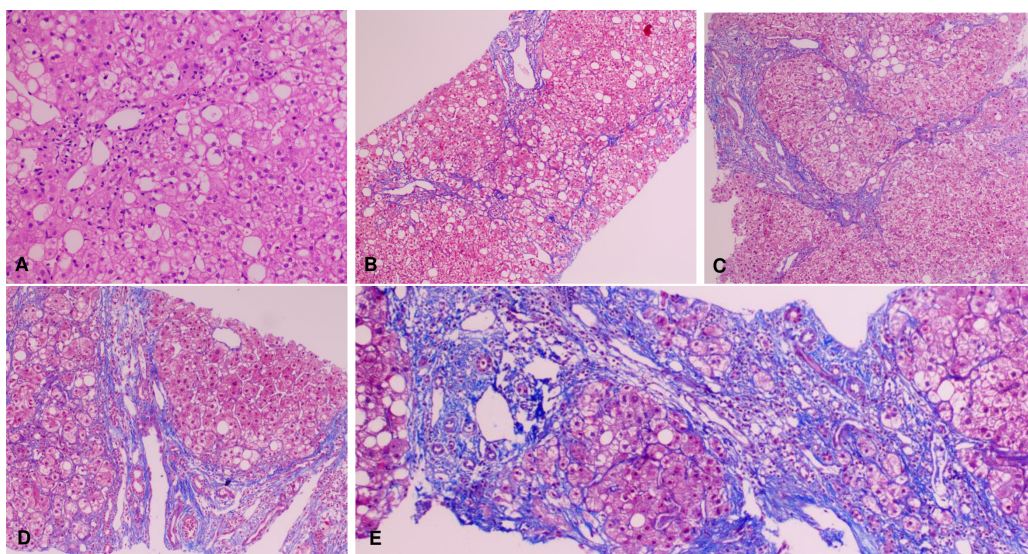


Figure 1. — Photomicrographs showing histological features of MASH (Steatosis, ballooning, lobular inflammation) (A; H&E stain); Masson's trichrome stain showing fibrosis spectrum and stages: F2 with increased periportal and zone 3 perisinusoidal fibrosis (B); F3C with complex fibrous bridges (C); F4B Broad curved septae partially enclosing regenerative parenchymal nodule with increased perisinusoidal fibrosis (D); F4C with micronodules surrounded by broad to very broad fibrous septae (E).

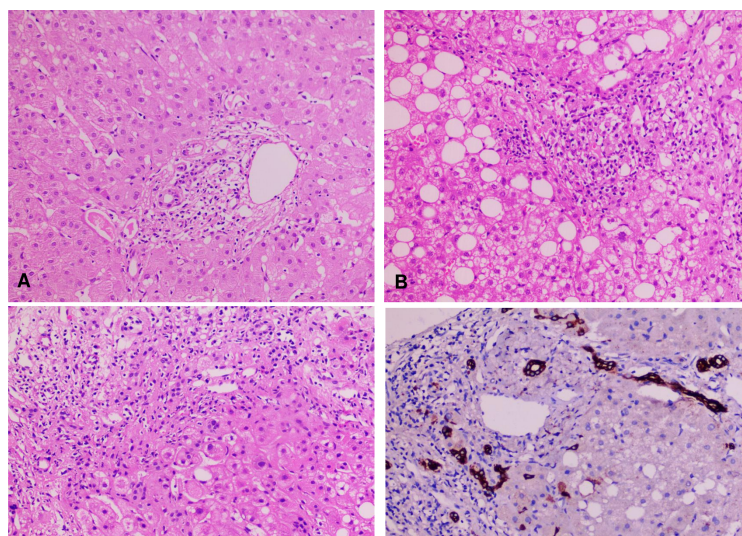


Figure 2. — Photomicrographs showing H&E stained liver biopsies of MASH with portal inflammation- mild (A), moderate (B); Interface activity (C), and ductular reaction onCK7 immunohistochemistry (D).

Sections were then treated with DAB for 10 minutes and counterstained with hematoxylin.

Bile duct structures served as internal positive controls, and ductular reaction in biopsies from cases of liver failure served as external positive controls. Negative controls were prepared by omitting the primary antibody.

Digital quantification of fibrosis and Hepatic progenitor cells (HPCs)

Quantitative assessment of fibrosis was performed using a Morpholens 6 digital slide scanner. The fibrosis fraction (collagen proportionate area) was calculated from digitised images of picrosirius red-stained liver sections and expressed as the percentage ratio of fibrotic area to total tissue area.

Hepatic progenitor cell (HPC) quantification was performed using ImageJ software on CK7-

immunostained images at 100× magnification. Images were converted to 8-bit format, followed by thresholding, binary mask creation with watershed segmentation, and numerical analysis. Fig.3.

Ethical Approval: The study was approved by the Institutional ethics committee (IEC)/ Institutional Review Board (IRB) [IEC/2024/115/MA17; 13 members participated & consented].

Statistical Analysis: Data was expressed as mean $\pm$ standard deviation (SD), median (range), or number (percentage), as appropriate. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Trends across fibrosis stages were assessed using the chi-square test for trend. A p-value of <0.05 was considered statistically significant. Data entry was performed using Microsoft Excel, and statistical analysis was conducted

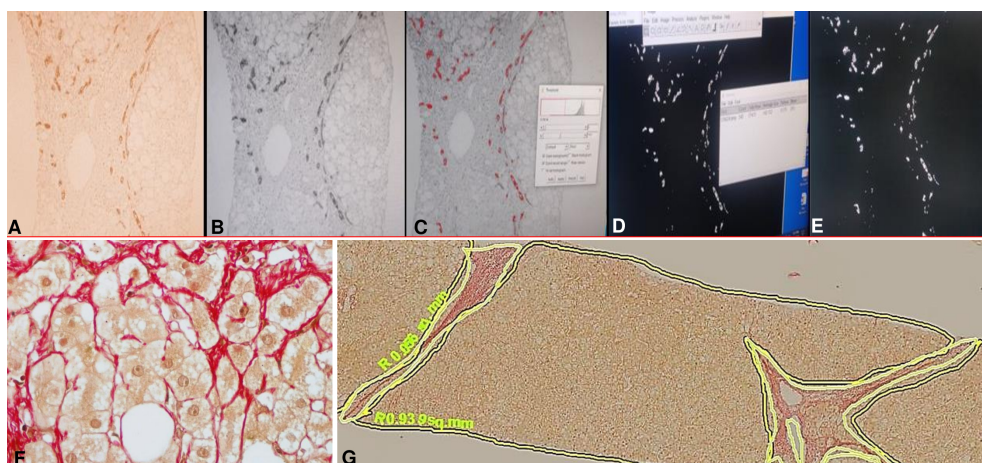


Figure 3. — Hepatic progenitor cell estimation by ImageJ image analysis software: CK7 immunostained image at 100x magnification (A); image conversion to 8-Bit (B); thresholding (C); process to make binary-making mask and watershedding (D); analyzing the number (E).

using the Statistical Package for the Social Sciences. (SPSS) software, version 21.0.

Results

Clinical characteristics

A total of 930 confirmed MASLD cases with liver biopsies were received in the Department of Pathology between June 2023 and May 2025. After excluding biopsies of suboptimal length, those lacking complete clinical details, and post-treatment or follow-up biopsies, 505 cases were included in the final study cohort.

The mean patient age was 45.1 ± 12.5 years, with a male predominance (65%). The mean serum total bilirubin level was 0.95 mg/dL (range: 0.29–8.5), alanine aminotransferase (ALT) was 40 U/L (range: 14–350), and aspartate aminotransferase (AST) was 39 U/L (range: 8–148). The mean serum triglyceride level was 142.03 ± 90.91 mg/dL, fasting blood glucose was 103.50 ± 25.10 mg/dL, and the mean body mass index (BMI) was 25.50 ± 5.20 kg/m².

Histopathological characteristics

The mean liver biopsy length was 2.0 ± 0.5 cm. Cirrhosis (F4) was present in 28.7% of cases, while significant fibrosis (F2–F4) was observed in 69.1%. The distribution of fibrosis stages was as follows: F0 (n = 37), F1 (n = 119), F2 (n = 87), F3 (n = 117), and F4 (n = 145). F3 stage was distributed as 3a (73), 3b (8), and 3c (36); similarly, stage 4 was further divided as 4a (95), 4b (32), and 4c (18).

The proportion of cases with a NAFLD Activity Score (NAS) ≥ 5 across fibrosis stages F0 to F4 was 21.62%, 25.21%, 36.78%, 47.86%, and 26.89%, respectively, indicating that higher disease activity is most prominent in stage F3 fibrosis ($p = 0.000$). The relatively lower NAS in cirrhosis (F4) likely reflects “burnt-out” disease, where necro-inflammatory activity may be reduced.

Portal inflammation was present in 69.3% of cases, with the majority (53.7%) showing mild inflammation. Moderate-to-severe portal inflammation ($p = 0.000$), plasma cell infiltration ($p = 0.000$), interface activity ($p = 0.002$), significant ductular reaction ($p = 0.000$), and bile duct damage ($p = 0.000$) were all significantly associated with advanced fibrosis stages (F3–F4). Table 1.

Digital image analysis demonstrated that high hepatic progenitor cell (HPC) counts (≥ 150) were present in 91.7% of F4 cases, compared to only 21.4% in F0–F1 stages. HPCs showed a significant association with advanced fibrosis ($p < 0.005$). Fig.4.

Portal inflammation showed strong correlations with ductular reaction ($p < 0.001$), interface activity ($p < 0.001$), plasma cell infiltration ($p < 0.001$), bile duct damage ($p = 0.002$), hepatic progenitor cells ($p < 0.005$), and fibrosis fraction ($p < 0.001$). Fig.5

No significant association was observed between portal inflammation and gender, serum ALT levels, or degree of steatosis ($p = 1.00$). However, portal inflammation demonstrated significant correlations with multiple histological parameters including interface activity, ductular reaction, bile duct damage, and plasma cell infiltration, particularly in cases with advanced fibrosis ($p < 0.005$).

Discussion

Metabolic dysfunction-associated steatohepatitis (MASH) represents an advanced stage within the spectrum of metabolic dysfunction-associated steatotic liver disease (MASLD), characterized by inflammation and fibrosis (10). Fibrosis is a key determinant of clinical outcomes, including cirrhosis, liver failure, and hepatocellular carcinoma (19). Therefore, identifying histological parameters that can predict fibrosis progression is of critical importance.

The diagnosis of MASH is established by the presence of a characteristic pattern of hepatosteatosis, lobular inflammation, and hepatocyte ballooning on liver biopsy, in the absence of significant alcohol

Table 1. — Correlation of Portal based features with CRN Fibrosis stages (F0-F4) in MASH patients (n=505).

Fibrosis	Significant PI	Significant Ductular reaction	Interface activity	Plasma cells	Duct damage	Activity>2
F-0 (N=37)	8.10% (3/37)	0%	2.70% (1/37)	24.32% (9/37)	13.51% (5/37)	21.62% (8/37)
F-1 (N=119)	2.52% (3/119)	0%	1.68% (2/119)	28.57% (34/119)	6.72% (8/119)	6.72% (8/119)
F-2 (N=87)	10.34% (9/87)	2.29% (2/87)	5.74% (5/87)	49.42% (43/87)	14.94% (13/87)	40.57% (44/87)
F-3 (N=117)	19.65% (23/117)	11.96% (14/117)	10.25% (12/117)	80.34% (94/117)	25.64% (30/117)	52.13% (61/117)
F-4 (N=145)	31.72% (46/145)	67.58% (98/145)	10.34% (15/145)	91.03% (132/145)	28.27% (41/145)	44.13% (64/145)
Total 505	P=0.000	P=0.000	P=0.002	P=0.000	P=0.000	P=0.000

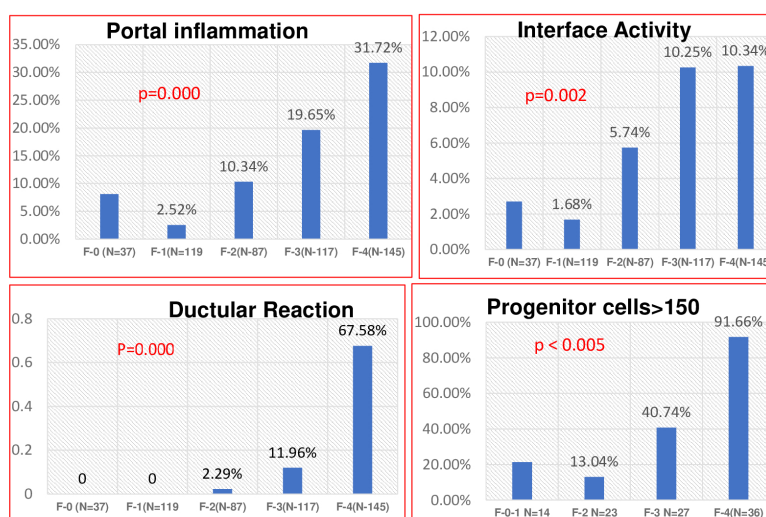


Figure 4. — Bar diagrams represent significant portal inflammation, interface activity, ductular reaction, and HPCs are associated with advance stages of fibrosis (n=505).

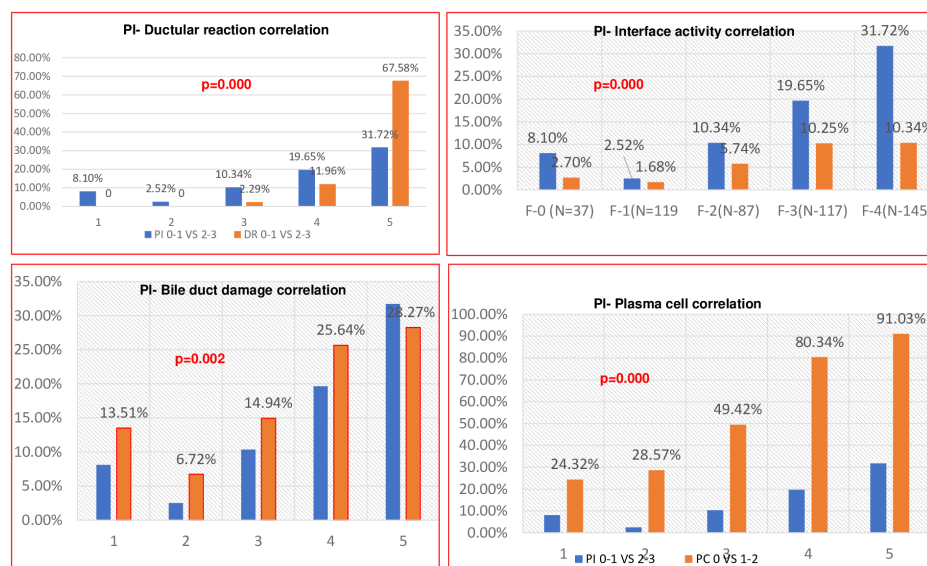


Figure 5. — Bar diagrams demonstrating correlation of portal inflammation with ductular reaction, interface activity, plasma cell infiltration, and bile duct damage.

consumption. Liver biopsy remains the gold standard for diagnosis, as it enables grading and staging while also providing prognostic information (20).

The NAS Score proposed by the NASH CRN, is widely used to grade disease activity. This scoring system incorporates steatosis, lobular inflammation, and hepatocyte ballooning; however, it does not include portal inflammation. This omission represents a limitation, particularly in predicting fibrosis progression and clinical outcomes. The relationship between portal-based changes and liver fibrosis in MASH has been relatively underexplored.

In our study, more-than-mild portal inflammation was strongly associated with advanced fibrosis (F3–F4). Notably, none of the F0 cases demonstrated more than mild portal inflammation, whereas a significant

proportion of F3–F4 biopsies exhibited moderate-marked portal inflammatory activity. These findings are consistent with prior studies, including those by Brunt et al., which demonstrated a significant correlation between portal inflammation and advanced fibrosis stages (12). A recent study also reported that portal inflammation, ductular reaction, and cholangiocyte injury are significantly associated with advanced fibrosis in MASH (13). Gadd et al. emphasised that although portal inflammation is generally mild across all stages of MASLD, it may precede portal fibrosis, suggesting a role in disease progression (21).

Chen et al. demonstrated that portal inflammation and ductular reaction are closely related during MASH and are independently associated with fibrosis (15). Published literature suggests that portal inflammatory

infiltrates may contribute directly to fibrogenesis and influence the fate of DR-associated hepatic progenitor cells (HPCs), thereby regulating the balance between liver repair and fibrosis (21). Our study similarly found a strong correlation between portal inflammation, disease severity (fibrosis stage) and DR, further supporting the role of portal-based changes in disease progression.

Ductular reaction involves the activation and proliferation of biliary epithelial cells and hepatic progenitor cells (HPCs), both of which are known to be profibrogenic. Recent studies have demonstrated a strong correlation between ductular reaction and advanced fibrosis, suggesting its potential role as a marker of fibrogenesis (2, 16). In our cohort, higher grades of ductular reaction and increased HPC counts (>100 and >150) were significantly associated with advanced fibrosis, reinforcing this mechanism.

We also observed a strong correlation between portal inflammation and interface activity. Interface hepatitis, defined as the extension of portal inflammatory infiltrates into periportal hepatocytes, reflects a more severe form of inflammatory injury. In MASH, this may indicate progressive portal-based damage and activation of fibrogenic pathways. Furthermore, the coexistence of plasma cell infiltration and bile duct injury with advanced fibrosis in our study suggests that portal immune responses may independently contribute to disease progression.

Another important finding was the significant correlation between portal inflammation and fibrosis fraction, quantified through digital morphometry using Sirius red staining. This objective assessment further strengthens the observed association between portal inflammation and fibrosis severity. To the best of our knowledge, such a correlation has not been previously reported. However, a very recent study has explored automated quantification of portal tracts in MASH and autoimmune hepatitis to improve reproducibility and accuracy (22).

The pathophysiological link between portal inflammation and fibrosis progression likely involves a complex interplay of inflammatory cytokines, activation of hepatic stellate cells, ductular reaction, and expansion of hepatic progenitor cells (17). Portal inflammatory aggregates may serve as a cellular niche that promotes signalling pathways leading to extracellular matrix deposition, thereby accelerating fibrosis and architectural distortion. A deeper understanding of the cellular composition of portal inflammatory infiltrate and HPCs-DR niche in MASLD will help guide future functional studies aimed at understanding the pathogenesis.

In summary, our findings reinforce growing evidence that portal inflammation and portal-based histological changes are closely associated with advanced fibrosis in MASH. Although the NAS-CRN system remains useful for grading disease activity, it does not incorporate portal parameters that appear to have important

prognostic significance. Portal-based features should therefore be routinely recorded in histopathological reports of patients with MASH. Incorporating portal inflammation into future histological scoring systems may improve risk stratification and disease monitoring.

Conclusion

This study demonstrates that portal-based histological changes including portal inflammation, ductular reaction, interface activity, bile duct injury, plasma cell infiltration, and hepatic progenitor cell expansion are highly prevalent in metabolic dysfunction-associated steatohepatitis (MASH) and show a strong, consistent association with advanced fibrosis.

The significant correlations observed between portal inflammation and multiple histological parameters, as well as with quantitatively assessed fibrosis, highlight the central role of portal compartment alterations in disease progression. Notably, portal inflammation appears to provide clinically meaningful information beyond conventional parameters such as steatosis grade and serum transaminase levels.

These findings underscore the importance of systematically evaluating and reporting portal-based features in routine histopathology. Incorporating portal inflammation and related changes into existing histological scoring systems may improve prognostic accuracy, risk stratification, and disease monitoring in patients with MASH.

Declarations

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Conflict of interest: None.

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