

Review

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Review

Metabolic Dysfunction-Associated Steatotic Liver Disease and Acute Cholangitis; Hepatobiliary Diseases Are in a Relation

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Abstract: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is defined by hepatic fat accumulation unrelated to significant alcohol use and is strongly associated with metabolic disorders. It progresses from simple steatosis to inflammation and fibrosis, increasing the risk of cirrhosis and hepatocellular carcinoma. In contrast, acute cholangitis (AC) is a severe biliary infection usually caused by bile duct obstruction—often due to gallstones, strictures, or tumors—and presents with symptoms such as fever, jaundice, and abdominal pain. While both conditions affect liver health, their causes differ. There is pieces of evidence from clinical and experimental studies that shows there could be a relationship between MASLD and AC. It has been demonstrated that MASLD significantly increases AC risk, with worse clinical outcomes, including higher mortality, prolonged hospitalization, and severe complications such as sepsis and acute kidney injury. A piece of evidence has been provided mechanistic insights, showing that MASLD exacerbates cholangitis through chronic inflammation, ductular proliferation, and fibrosis, driven by bile acid (BA) dysregulation and gut-liver axis dysfunction. Studies highlighted BA metabolism disruptions in MASLD, while other studies emphasized the role of metabolic comorbidities and dysbiosis in amplifying biliary inflammation. Collectively, these studies underscore MASLD as a critical risk factor for AC, mediated by metabolic, inflammatory, and biliary pathways. This review aims to explain these connections, offering insights into preventive strategies and therapeutic targets to mitigate AC risk and improve outcomes in MASLD patients.

Keywords: NAFLD; Cholangitis; Hepatobiliary; Hepatic steatosis; liver fibrosis

Introduction

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is characterized by hepatic fat accumulation in the absence of significant alcohol consumption, closely linked to metabolic disorders such as obesity, insulin resistance, and type 2 diabetes. It encompasses a spectrum from simple steatosis to inflammation and fibrosis, posing risks for cirrhosis and hepatocellular carcinoma [1,2]. In contrast, acute cholangitis (AC) is a life-threatening biliary infection typically caused by bile duct obstruction—often due to gallstones, strictures, or tumors—leading to symptoms like fever, jaundice, and abdominal pain [3]. While both conditions impact liver health, their etiologies differ: MASLD arises from metabolic dysregulation, whereas cholangitis stems from biliary obstruction and subsequent bacterial overgrowth[1,4].

Emerging evidence suggests potential intersections between MASLD and AC[5]. MASLD-related metabolic dysfunction may predispose individuals to gallstone formation—a key cholangitis risk factor—through cholesterol metabolism alterations[6]. Chronic inflammation and fibrosis in MASLD could also impair biliary motility or immune responses, exacerbating cholangitis severity [2,7]. Moreover, cholangitis might worsen MASLD progression by inducing systemic inflammation or hepatobiliary injury[8]. Despite these hypotheses, the bidirectional relationship remains

underexplored, with limited clinical data clarifying whether MASLD independently increases cholangitis susceptibility or influences its outcomes.

This study aims to review existing evidence on the connection between MASLD and AC, reviewing pathophysiology, and clinical correlations. By evaluating epidemiological data, pathways, and clinical outcomes, it pursues to explain the significance of MASLD and cholangitis relation or severity and vice versa.

Pathophysiological and Clinical Links Between MASLD and Acute Cholangitis

Epidemiological Association

The epidemiological link between MASLD and AC is increasingly supported by large-scale clinical studies. Patel et al.[9] conducted a pivotal retrospective analysis using the U.S. National Inpatient Sample (2016–2019), comparing 1,550 AC patients with MASLD to 1,550 propensity-matched non-MASLD controls. MASLD patients exhibited a 2.33-fold higher odds ratio for AC (95% CI: 1.81–3.0, $p < 0.001$), alongside prolonged hospitalization (4 vs. 3 days) and higher mortality (1.6% vs. 0%). Notably, MASLD patients suffered more complications, including acute kidney injury (24.2% vs. 17.7%), sepsis (3.2% vs. 1.6%), and portal vein thrombosis (3.2% vs. 0%), suggesting systemic metabolic and inflammatory derangements amplify AC severity. These findings align with Sbeit et al.'s [5] multicenter study of 811 patients with common bile duct (CBD) stones, where MASLD prevalence was nearly double in AC patients (15.5% vs. 8.3%, $p = 0.01$). Even after adjusting for age, MASLD remained independently associated with AC (OR 2.15, $p = 0.005$). This association may reflect MASLD's role in promoting gallstone formation—a key AC trigger—through dyslipidemia and bile acid (BA) dysregulation.

Greco et al. [8] further contextualized these findings, noting that MASLD's global prevalence (~25%) parallels rising rates of gallstone-related complications. MASLD patients often exhibit obesity, insulin resistance, and dyslipidemia, which collectively drive cholesterol supersaturation in bile. Patel et al.[9] found MASLD patients had a 3.7-fold higher risk of concurrent acute cholecystitis (OR 3.70, 95% CI: 3.19–4.29), underscoring shared pathways in biliary disease. Mechanistically, MASLD-induced chronic inflammation may impair biliary motility and immune responses, facilitating bacterial colonization during CBD obstruction. Sbeit et al. [5] also observed elevated inflammatory markers (CRP, neutrophils) in MASLD-AC patients, reflecting systemic immune activation. These studies highlight MASLD not merely as a hepatic condition but as a multisystem disorder that primes the biliary tract for infection. However, gaps remain: most data are retrospective, and causality is inferred. Prospective studies are needed to confirm whether MASLD directly increases AC risk or serves as a marker of metabolic dysfunction.

Cholesterol Metabolism and Gallstone Formation

MASLD-driven metabolic dysregulation, including insulin resistance and altered cholesterol homeostasis, may predispose individuals to gallstone formation—a primary trigger for AC. Patel et al. [9] noted that MASLD patients had higher risk of concurrent acute cholecystitis, suggesting shared pathways in cholesterol saturation and biliary stasis. Sbeit et al. [5] further highlighted that MASLD's pro-inflammatory state may exacerbate bile duct inflammation during CBD stone episodes, increasing AC susceptibility.

MASLD's disruption of cholesterol homeostasis is a critical pathway linking it to gallstone formation and subsequent AC. Insulin resistance, a hallmark of MASLD, upregulates hepatic de novo lipogenesis while reducing cholesterol excretion via ABCG5/G8 transporters, leading to cholesterol-supersaturated bile. Patel et al. [9] observed that MASLD patients had a 3.7-fold higher risk of acute cholecystitis, a gallstone-related condition, emphasizing this metabolic nexus. Similarly, Sbeit et al. [5] found MASLD doubled the risk of AC in CBD stone patients, suggesting cholesterol-rich stones are more prevalent or inflammatory in MASLD.

Gottlieb and Canbay [10] highlighted BA dysregulation in MASLD, including reduced bile-salt export pump (BSEP) expression, which impairs canalicular BA secretion. This stagnation promotes hydrophobic BA accumulation, damaging biliary epithelia and fostering bacterial overgrowth—key steps in AC pathogenesis. Maeda et al.'s [11] murine models corroborated this: high-fat diet (HFD)-fed mice with E-cadherin deficiency (a MASLD mimic) exhibited exacerbated cholangitis, ductular proliferation, and elevated Sox9+/CD44+ progenitor cells, indicating chronic biliary injury. These mice also developed cholangiocellular carcinoma (CCC), suggesting MASLD accelerates malignant transformation in inflamed bile ducts.

MASLD-driven dyslipidemia further exacerbates gallstone risk. Greco et al. [8] noted that hypertriglyceridemia and low HDL-C—common in MASLD—promote cholesterol crystallization. Additionally, MASLD-associated gut dysbiosis alters BA metabolism, reducing secondary BAs like deoxycholic acid, which normally inhibit cholesterol nucleation. This creates a permissive environment for stone formation. Clinically, Patel et al. [9] reported higher rates of mechanical ventilation (3.2% vs. 0%) and percutaneous cholecystostomy (3.2% vs. 1.6%) in MASLD-AC patients, reflecting severe, refractory infections likely tied to viscous, stone-laden bile.

Inflammation and Fibrosis Exacerbate Cholangitis

The relationship between inflammation, fibrosis, and cholangitis in MASLD patients is a critical area of study, as chronic hepatic inflammation and fibrotic remodeling significantly exacerbate biliary disease. Maeda et al. [11] provided mechanistic insights using liver-specific E-cadherin knockout mice fed a high-fat diet (HFD), a model mimicking MASLD. These mice exhibited severe periportal inflammation, ductular reactions, and fibrosis, with increased F4/80+ macrophages and Sox9+/CD44+ progenitor cells. The HFD cohort also showed elevated serum alkaline phosphatase (ALP) and bile acids, markers of biliary injury, suggesting that MASLD-induced inflammation amplifies cholangitis severity. The ductular reaction, characterized by proliferation of bile ductules and progenitor cells, was irreversible even after switching to a normal diet, indicating persistent biliary damage. This suggests MASLD-related hepatic injury amplifies cholangitis by impairing biliary integrity and promoting ductular proliferation.

In humans, MASLD-associated systemic inflammation, driven by adipokines, cytokines (e.g., TNF- α , IL-6), and oxidative stress, likely primes the biliary tract for infection. Patel et al. [9] reported higher rates of sepsis (3.2% vs. 1.6%) and portal vein thrombosis (3.2% vs. 0%) in MASLD-AC patients, reflecting systemic immune dysregulation. Sbeit et al. [5] also noted elevated inflammatory markers (CRP, neutrophils) in MASLD-AC patients, further supporting the role of chronic inflammation in AC pathogenesis (Table 1).

Table 1. This table summarizing the key findings and details from the articles you provided. The table includes columns for Authors, Study Type, Population/Model, Key Findings, Mechanisms/Pathways, Clinical Outcomes, Therapeutic Implications, and Limitations.

Authors	Study Type	Population/Model	Key Findings	Mechanisms/Pathways	Clinical Outcomes	Therapeutic Implications	Limitations
Patel et al.[9]	Retrospective cohort	1,550 AC patients with MASLD vs. 1,550 without	MASLD associated with 2.33x higher AC risk; longer hospital stays, higher costs, and increased mortality (1.6% vs. 0%). Higher rates of sepsis, acute kidney injury, and portal vein thrombosis.	Cholesterol metabolism, bile stasis, systemic inflammation.	Increased complications (sepsis, acute kidney injury, and portal vein thrombosis), higher mortality, and resource utilization.	Nothing explicitly is introduced as modifications to reduce MASLD severity.	Retrospective design; causality not established.
Maeda et al.[11]	Experimental (mice)	HFD-fed E-cadherin knockout mice	MASLD exacerbates cholangitis, ductular proliferation, and fibrosis. Increased Sox9+/CD44+ progenitor cells and F4/80+ macrophages. Irreversible ductular reactions post-diet reversal.	BA dysregulation, chronic inflammation, ductular reaction, and fibrosis.	Severe cholangitis, increased tumorigenesis (HCC and CCC).	Targeting ductular reactions (e.g., Sox9/CD44 pathways) and BA metabolism.	Mouse model may not fully replicate human disease.
Gottlieb & Canbay [10]	Review	NAFLD/NASH patients	BA dysregulation (reduced BSEP expression) and altered BA composition in MASLD. FXR activation may protect against NAFLD progression.	BA metabolism, gut-liver axis, FXR signaling.	Increased cholestasis, inflammation, and fibrosis.	FXR agonists (e.g., obeticholic acid) to improve BA homeostasis and reduce inflammation.	Limited clinical trial data on FXR agonists in MASLD-AC patients.
Sbeit et al.[5]	Retrospective	811 patients with CBD stones (161 with AC)	MASLD independently associated with AC (OR 2.15). Higher inflammatory markers (CRP, neutrophils) in MASLD-AC patients. No association with cholangitis severity.	Cholesterol gallstones, systemic inflammation, and gut dysbiosis.	Increased AC risk, higher inflammatory markers, but no impact on severity.	Lifestyle modifications and weight loss to reduce MASLD and AC risk.	Retrospective design; missing data on cholangitis severity in some patients.

Greco et al.[8]	Narrative review	MASLD and biliary disease patients	MASLD linked to AC through metabolic comorbidities (obesity, T2DM), dysbiosis, and BA dysregulation. Shared pathways include insulin resistance, inflammation, and gut-liver axis disruption.	Dysbiosis, BA metabolism, systemic inflammation, and metabolic syndrome.	Increased AC risk, prolonged hospitalization, and higher morbidity.	Probiotics, antibiotics, and BA modulators to target dysbiosis and BA metabolism.	Limited evidence on probiotics/antibiotics for AC prevention in MASLD.
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Fibrosis, a hallmark of advanced MASLD, exacerbates cholangitis by impairing biliary motility and immune surveillance. Maeda et al. [11] observed increased α -smooth muscle actin (α -SMA) staining in HFD-fed mice, indicating fibrotic remodeling. This fibrosis disrupts the biliary architecture, promoting bile stasis and bacterial colonization. Additionally, MASLD-related gut dysbiosis may exacerbate biliary inflammation through bacterial translocation and endotoxemia, as proposed by Greco et al [8].

Therapeutic strategies targeting inflammation and fibrosis, such as FXR agonists or antifibrotic agents, may mitigate cholangitis severity in MASLD patients. However, Maeda et al.'s [11] findings suggest that early intervention is crucial, as advanced fibrosis and ductular reactions may be irreversible. Future research should explore biomarkers of biliary inflammation in MASLD and evaluate anti-inflammatory therapies in high-risk populations.

Bile Acid Dysregulation

Gottlieb and Canbay [10] emphasized BA metabolism disruptions in MASLD, including reduced BSEP expression and altered BA composition. These changes may impair bile flow, increasing cholestasis and bacterial overgrowth—key drivers of AC. Maeda et al. [11] also observed elevated serum ALP and BA in HFD-fed mice, linking BA retention to cholangitis progression.

Bile acid (BA) dysregulation is a central feature of MASLD that contributes to cholangitis pathogenesis. Gottlieb and Canbay [10] highlighted that MASLD disrupts BA homeostasis, reducing bile-salt export pump (BSEP) expression and impairing canalicular BA secretion. This leads to BA retention, hepatocyte injury, and cholestasis, creating a permissive environment for bacterial overgrowth and biliary inflammation. Maeda et al. [11] observed elevated serum bile acids in HFD-fed mice, correlating with exacerbated cholangitis and ductular reactions. These findings suggest that BA dysregulation is a key link between MASLD and AC.

MASLD-associated gut dysbiosis further exacerbates BA dysregulation. Dysbiosis alters the gut microbiome's ability to metabolize primary BAs into secondary BAs, reducing protective BAs like deoxycholic acid, which inhibit cholesterol nucleation and bacterial growth. Greco et al. [8] proposed that dysbiosis-driven BA changes promote bile stasis and bacterial translocation, increasing AC risk. Sbeit et al. [5] noted that MASLD patients with AC had higher levels of inflammatory markers, likely reflecting BA-induced hepatobiliary injury.

BA dysregulation also impairs the gut-liver axis, a critical regulator of metabolic and immune homeostasis. Gottlieb and Canbay [10] emphasized that BA signaling through the farnesoid X receptor (FXR) modulates lipid metabolism, inflammation, and fibrosis. In MASLD, reduced FXR activity exacerbates hepatic lipogenesis and inflammation, further impairing BA secretion and promoting cholestasis. Maeda et al. [11] demonstrated that HFD-fed mice with E-cadherin deficiency exhibited increased ductular reactions and fibrosis, likely driven by BA retention and FXR dysregulation.

Clinical Outcomes and Complications

MASLD worsens AC outcomes. Patel et al. [9] reported higher rates of sepsis, acute kidney injury, and portal vein thrombosis in MASLD patients, with a 1.6% mortality rate versus 0% in non-MASLD. Sbeit et al. [5] noted elevated inflammatory markers (C-reactive protein (CRP), neutrophils) in MASLD-AC patients, reflecting systemic inflammation. These findings highlight MASLD's role in amplifying AC severity through metabolic and immune dysregulation (Table 1).

The clinical outcomes of AC in patients with MASLD are notably worse compared to those without MASLD, reflecting the interplay of metabolic, inflammatory, and biliary dysfunction. Patel et al. [9] demonstrated that MASLD patients hospitalized with AC experienced significantly higher rates of severe complications, including acute kidney injury (24.2% vs. 17.7%), sepsis (3.2% vs. 1.6%), and portal vein thrombosis (3.2% vs. 0%). These complications are likely driven by MASLD-associated systemic inflammation, insulin resistance, and impaired immune responses, which

exacerbate the severity of biliary infections. Furthermore, MASLD patients required more invasive interventions, such as mechanical ventilation (3.2% vs. 0%) and percutaneous cholecystostomy tube insertion (3.2% vs. 1.6%), highlighting the refractory nature of AC in this population.

Sbeit et al. [5] corroborated these findings in their retrospective study of 811 patients with CBD stones, where MASLD was independently associated with AC (OR 2.15, $p = 0.005$). MASLD patients with AC also exhibited higher levels of inflammatory markers, including CRP and neutrophil counts, suggesting a heightened systemic inflammatory response. This inflammatory milieu may contribute to the increased morbidity observed in MASLD-AC patients, as chronic inflammation impairs tissue repair and increases susceptibility to infections. Additionally, MASLD patients with AC had higher total bilirubin levels, reflecting more severe cholestasis and biliary obstruction, which further complicates clinical management.

Greco et al. [8] emphasized that MASLD's association with metabolic comorbidities, such as obesity, type 2 diabetes, and dyslipidemia, exacerbates AC outcomes. These conditions not only increase gallstone formation but also impair immune function, making MASLD patients more vulnerable to severe infections. The study highlighted that MASLD patients with AC often present with more advanced disease, requiring prolonged hospitalization and intensive care, which aligns with Patel et al.'s findings of increased length of stay and inpatient mortality in this population[9].

Gut-Liver Axis and Dysbiosis

Greco et al. [8] and Gottlieb and Canbay [10] proposed that MASLD-associated gut dysbiosis may prime the liver for AC. Dysbiosis promotes bacterial translocation and endotoxemia, exacerbating biliary inflammation. Sbeit et al. [5] linked MASLD's systemic inflammatory state to cholangitis susceptibility, suggesting gut-derived pathogens exploit disrupted biliary motility in MASLD patients.

Genetic and Molecular Interactions

Maeda et al. [11] identified E-cadherin loss as a genetic factor amplifying HFD-induced cholangitis and cholangiocarcinoma in mice. This aligns with human studies showing E-cadherin downregulation in cholestatic diseases. While Greco et al. [8] noted no direct links between MASLD-associated genes (e.g., PNPLA3) and cholangitis, epigenetic modifications in metabolic pathways may synergize with biliary injury.

Role of Metabolic Comorbidities

Obesity and diabetes, common in MASLD, independently increase gallstone risk and impair immune responses. Patel et al. [9] and Sbeit et al. [5] found hypertension and hyperlipidemia correlated with AC, suggesting metabolic syndrome components collectively drive biliary inflammation. HFD-induced insulin resistance in Maeda's [11] model further underscores metabolic dysregulation as a bridge between MASLD and AC.

Therapeutic Implications

FXR agonists, which improve BA homeostasis, are promising for MASLD and cholestatic diseases [10]. Maeda et al.'s [11] findings suggest targeting ductular reactions (e.g., Sox9/CD44 pathways) may mitigate cholangitis progression. Greco et al. [8] proposed probiotics to modulate dysbiosis, though clinical evidence remains limited.

FXR agonists, such as obeticholic acid, enhance BSEP expression, reduce BA synthesis, and improve insulin sensitivity. Greco et al. [8] suggested that probiotics or BA sequestrants may modulate dysbiosis and BA metabolism, though clinical evidence is limited. Future studies should explore whether FXR agonists or BA modulators reduce AC incidence in MASLD patients, addressing a critical gap in preventive hepatology.

Conclusions

In summary, there is valuable data on the bidirectional relationship between MASLD and AC, shared pathways in cholesterol metabolism, inflammation, BA dysregulation, and gut-liver interactions. By integrating clinical data with mechanistic insights from previous studies, there is pieces of evidence that show MASLD predisposes to AC and influences its outcomes. Future research should explore targeted therapies, such as FXR agonists or anti-inflammatory agents, to disrupt this pathogenic interplay and improve patient care.

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References

1. Sotoudeheian M. Galectin-3 and Severity of Liver Fibrosis in Metabolic Dysfunction-Associated Fatty Liver Disease. *Protein and Peptide Letters*. 2024;31:290-304.
2. Sotoudeheian Mj. Value of Mac-2 Binding Protein Glycosylation Isomer (M2BPGi) in Assessing Liver Fibrosis in Metabolic Dysfunction-Associated Liver Disease: A Comprehensive Review of its Serum Biomarker Role. *Current protein & peptide science*. 2025;26:6-21.
3. Cozma M-A, Găman M-A, Srichawla BS, Dhali A, Manan MR, Nahian A, et al. Acute cholangitis: a state-of-the-art review. *Annals of Medicine and Surgery*. 2024;86:4560-74.
4. Zimmer V, Lammert F. Acute bacterial cholangitis. *Visceral Medicine*. 2015;31:166-72.
5. Sbeit W, Sbeit M, Kalisky I, Katz L, Mari A, Khoury T. The possible association of non-alcoholic fatty liver disease with acute cholangitis: a retrospective multicenter cohort study. *Life*. 2021;12:35.
6. Sogabe M, Okahisa T, Kagawa M, Sei M, Kagemoto K, Tanaka H, et al. Association of metabolic dysfunction-associated fatty liver disease with gallstone development: A longitudinal study. *Journal of Gastroenterology and Hepatology*. 2024;39:754-61.
7. Pinto C, Giordano DM, Maroni L, Marzioni M. Role of inflammation and proinflammatory cytokines in cholangiocyte pathophysiology. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*. 2018;1864:1270-8.
8. [Greco S, Campigotto M, D'Amuri A, Fabbri N, Passaro A. Dyslipidemia, Cholangitis and Fatty Liver Disease: The Close Underexplored Relationship: A Narrative Review. *Journal of Clinical Medicine*. 2024;13:2714.
9. Patel P, Inayat F, Ali H, Afzal A, Taj S, Rehman AU, et al. Association of nonalcoholic fatty liver disease with acute cholangitis: a nationwide propensity-matched analysis from the United States. *Baylor University Medical Center Proceedings: Taylor & Francis*; 2023. p. 600-7.
10. Gottlieb A, Canbay A. Why bile acids are so important in non-alcoholic fatty liver disease (NAFLD) progression. *Cells*. 2019;8:1358.
11. Maeda S, Hikiba Y, Fujiwara H, Ikenoue T, Sue S, Sugimori M, et al. NAFLD exacerbates cholangitis and promotes cholangiocellular carcinoma in mice. *Cancer Science*. 2021;112:1471-80

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