Li *et al. Hepatoma Res* 2024;10:41
DOI: 10.20517/2394-5079.2024.63

Hepatoma Research

Review

Open Access

MASLD: an emerging factor in the pathophysiology and clinical management of ICC

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How to cite this article: Li ZL, Chen JL, Tang Y, Qin DL, Tang ZH. MASLD: an emerging factor in the pathophysiology and clinical management of ICC. *Hepatoma Res* 2024;10:41. https://dx.doi.org/10.20517/2394-5079.2024.63

Received: 30 Apr 2024 **First Decision:** 19 Jul 2024 **Revised:** 22 Aug 2024 **Accepted:** 20 Sep 2024 **Published:** 29 Sep 2024

Academic Editor: Matteo Donadon **Copy Editor:** Yu-Fei Wang **Production Editor:** Yu-Fei Wang

Abstract

This article explores the emerging role of metabolic dysfunction-associated steatotic liver disease (MASLD) in the pathophysiology of intrahepatic cholangiocarcinoma (ICC). Despite advances in public health, ICC incidence has risen, suggesting overlooked risk factors. Recent studies indicate a significant association between MASLD and ICC, though causality remains unproven. The article reviews current research, highlighting limitations such as retrospective designs and small sample sizes. It emphasizes the need for comprehensive investigations into MASLD's role in ICC pathogenesis, prognosis, and management. Future research should focus on integrating advanced methodologies to identify novel biomarkers and therapeutic strategies, aiming to improve patient outcomes and develop tailored prevention and treatment approaches.

Keywords: Metabolic dysfunction-associated steatotic liver disease, intrahepatic cholangiocarcinoma, risk factors, pathogenesis, progression, prognosis, treatment

INTRODUCTION

Previous studies have identified chronic inflammation caused by viruses, parasites, biliary obstruction, or stones as the most significant risk factor for intrahepatic cholangiocarcinoma (ICC). Despite advances in public health, living standards, medical technology, and vaccine distribution, the incidence of ICC has not only stabilized but has increased sharply by 140% over the past 40 years. This trend suggests that current research does not entirely elucidate the mechanisms underlying ICC and that some potential risk factors

may be overlooked.

Recent findings indicate that diabetes and obesity significantly elevate the risk of ICC, illustrating the critical role of metabolic diseases in its pathophysiology. Metabolic dysfunction-associated steatotic liver disease (MASLD), which is associated not only with hepatitis and liver fibrosis but also with various metabolic disorders, has seen a dramatic rise in prevalence, affecting over 30% of the global population. This suggests that MASLD may be an emerging factor in the pathophysiology of ICC.

There is currently a significant gap in research exploring the association between MASLD and ICC. Given MASLD's high prevalence and severity, overlooking its role in the pathogenesis of ICC could hinder early intervention efforts and worsen both ICC incidence and the global burden of liver disease. Therefore, thorough investigations into the relationship between MASLD and ICC are essential.

This study aims to provide a concise review of current research on MASLD and ICC while laying the groundwork for further exploration in this important area.

MASLD IS A LATENT RISK FACTOR

Research overview

The relevant research began in 2007. Welzel *et al.* identified an increasing incidence of ICC in the United States, contrasting with stable rates of extrahepatic cholangiocarcinoma (eCCA)[1]. This observation led to the hypothesis that unknown risk factors, potentially including MASLD, might contribute to ICC pathogenesis. Their subsequent investigations utilizing the SEER-Medicare database indicated a significant association, with an odds ratio (OR) of 3.0 (95%CI: 1.2-7.3). However, it is crucial to note that these findings, while suggestive, do not establish causation.

In 2016, Kinoshita *et al.* further explored this potential link, noting a higher prevalence of metabolic dysfunction-associated steatohepatitis (MASH) in ICC patients without known risk factors compared to those with liver metastatic carcinoma[2]. They formally proposed MASLD as a risk factor associated with ICC.

Meta-analyses and cohort studies, such as those by Wongjarupong *et al.* in 2017, have reinforced the hypothesis of an increased risk, reporting an OR of 2.22 (95%CI: 1.52-3.24) for cholangiocarcinoma (CCA)[3]. Similarly, Petrick *et al.*'s randomized controlled study suggested a more than threefold increase in risk (OR = 3.52, 95%CI: 2.87-4.32) for ICC[4]. Despite these findings, the absence of prospective data means that the role of MASLD as a risk factor remains speculative.

In addition to these studies, numerous scholars have investigated the relationship between MASLD and ICC in depth [Table 1]. In conclusion, while the current evidence indicates a potential link between MASLD and ICC, it is premature to draw definitive conclusions about causality.

Critical re-examination

Current research on the association between MASLD and the risk of ICC is constrained by several limitations, including retrospective designs, small sample sizes, and single-center cohort studies. These limitations contribute to weak evidence, potential biases, and significant heterogeneity in research outcomes, making it challenging to draw consistent conclusions. Several specific issues warrant further attention:

Table 1. Research on MASLD and the risk of ICC

Authors	Year of publication	Country	Related conclusions
Zhou *et al.*[5]	2009	China	MASLD may be a risk factor for ICC
Reddy *et al.*[6]	2013	USA	MASH may affect up to 20% of patients with resectable ICC
Nkontchou *et al.*[7]	2013	French	The incidence of MASH was higher (19%) in ICC patients with no other known risk factors
Chang *et al.*[8]	2013	Taiwan, China	MASLD increases the risk of CCA
Choi *et al.*[9]	2016	USA	MASLD is not a risk factor for CCA (OR = 1.40, 95%CI: 0.94-2.09)
Xiong *et al.*[10]	2018	China	Metabolic syndrome was significantly associated with a 1.86-fold increased risk of CCA
Sirica *et al.*[11]	2019	USA	MASLD and MASH are risk factors for HCC and ICC
De Lorenzo *et al.*[12]	2020	Italy	MASH is a risk factor for ICC, MASLD is not
Corrao *et al.*[13]	2021	Italy	MASLD is significantly correlated with the progress of ICC, not eCCA
Ghidini *et al.*[14]	2021	Italy	MASLD and MASH are associated with a high risk of CCA, especially ICC

MASLD: Metabolic dysfunction-associated steatotic liver disease; ICC: intrahepatic cholangiocarcinoma; MASH: metabolic dysfunction-associated steatohepatitis; CCA: cholangiocarcinoma; eCCA: extrahepatic cholangiocarcinoma.

(1) Temporal Relevance: The incidence of MASLD has increased dramatically over the past decade[15], yet many studies rely on data from the late 20th century. This temporal disconnect, coupled with inadequate control of confounding factors, compromises the accuracy of research findings. Future studies should utilize up-to-date, comprehensive datasets and account for time effects and potential confounders.

(2) Geographic and Ethnic Considerations: The influence of regional and ethnic factors cannot be overlooked. While MASLD was traditionally considered a Western disease[16], its prevalence in Asia, the Middle East, and North Africa has surged over the past three decades, with related mortality rates surpassing those in Europe and the United States[17]. The predominance of studies based on European and American populations may introduce bias due to genetic, environmental, and lifestyle differences across regions and ethnicities. Moreover, the current data inadequately represent the baseline characteristics and disease patterns of Asian populations, potentially leading to misinterpretation of the MASLD-ICC association in these groups.

(3) Metabolic Syndrome Features: A critical oversight in current research is the insufficient focus on the individual components of metabolic syndrome, namely obesity and diabetes, as these factors may play pivotal roles in the observed association between MASLD and ICC. Obesity, a proinflammatory state, can exacerbate liver pathology, possibly accelerating the progression from MASLD to ICC. Similarly, diabetes, through its systemic metabolic effects, might influence carcinogenic pathways, thereby increasing ICC risk. Future studies must employ a multifaceted approach to address this issue: (a) Comprehensive patient profiling: Researchers should conduct detailed metabolic assessments, including body mass index (BMI), waist circumference, lipid profiles, fasting glucose levels, and insulin resistance markers; (b) Stratified analysis: Studies should stratify patients based on the presence and severity of individual metabolic syndrome components to isolate their effects on ICC risk; (c) Longitudinal designs: Long-term follow-up studies are needed to track the progression of metabolic syndrome features and their temporal relationship with ICC development; (d) Molecular investigations: Research should explore potential molecular mechanisms linking specific metabolic abnormalities to cholangiocarcinogenesis, such as examining the role of adipokines, proinflammatory cytokines, and insulin signaling pathways; (e) Dose-response relationships: Investigations into whether the severity or duration of metabolic syndrome features correlates

with ICC risk could provide valuable insights.

By meticulously accounting for these factors, future research can more accurately evaluate the independent contribution of MASLD to ICC risk, potentially uncovering complex interactions between metabolic syndrome components and liver pathology in cholangiocarcinogenesis.

PATHOGENESIS OF MASLD-RELATED ICC

Research overview

Research on the pathogenesis of MASLD and ICC remains limited. To date, only two articles address this topic [Figure 1]. The first article[18] focuses on the genetic factors, offering an in-depth examination of the role of MASLD in the initiation and proliferation of ICC. The second article[19] analyzes the impacts of metabolic syndrome (MetS) and fibrosis on inflammation and the mechanism that promotes cholangiocyte cancer, framed within the context of systemic metabolism. Together, these studies not only provide valuable insights for future research but also underscore the pressing need for comprehensive investigations and expansions within this domain.

High expression of YAP1 and SOX9 promotes ICC progression

In 2020, Hu *et al.* reported that over 90% of ICC patients exhibited alterations in YAP1 and/or SOX9[18]. Utilizing dual tissue microarray chips and a preclinical ICC mouse model, their findings included: (a) Nuclear levels of SOX9 and YAP1 were elevated in over 90% of human CCA samples (n = 108). Additionally, the expression of p-AKT, SOX9, and YAP1 was significantly upregulated in the hepatic cells of mice with MASH or primary sclerosing cholangitis (PSC); (b) The deletion of either YAP1 or SOX9 alone led to ICC pathogenesis, which was characterized by high expression levels of the remaining gene. In contrast, concurrent deletion of both genes completely inhibited ICC pathogenesis; (c) YAP1 deficiency impeded the reprogramming of hepatic cells to biliary epithelial cells (BECs) and tumor cell proliferation. In contrast, SOX9 deficiency solely inhibited tumor cell proliferation. Based on these observations, the authors propose a model of MASLD-related ICC pathogenesis. This model suggests that steatohepatitis in MASLD patients promotes elevated expression of YAP1 and SOX9 in liver cells, facilitating the transdifferentiation of hepatic cells to BECs and subsequent tumor cell proliferation.

The biological heterogeneity of ICC significantly impacts the efficacy of surgical and chemotherapeutic interventions. This is primarily due to the diverse origins of ICC cells[20]. This study not only underscores the complex interplay between MASLD, HCC, and ICC but also advocates for a comprehensive approach to hepatobiliary diseases, avoiding isolated disease analyses. Furthermore, the study highlights common features of ICC heterogeneity, offering novel insights for the development of broad-spectrum therapeutic strategies for advanced ICC and improving prognosis.

Osteopontin overexpression is a prominent feature of ICC patients with MetS

In 2023, Cadamuro *et al.* highlighted recent epidemiological evidence suggesting that MetS is frequently associated with MASLD or MASH, positioning it as a potential risk factor for ICC[3,14,19]. Concurrently, studies have demonstrated that ICC typically involves the deposition and remodeling of a dense extracellular matrix (ECM)[21-23], with ECM remodeling identified as a critical mechanism underlying cardiovascular mortality in patients with MetS and MASLD[19]. Thus, the authors hypothesize that ECM remodeling driven by MetS is a key pathological mechanism in MASLD that may precipitate ICC.

In their study, Cadamuro *et al.* analyzed 44 ICC patients with MetS and 22 without, focusing on the levels of osteopontin (OPN), tenascin-C (TnC), and periostin (POSTN) within the ECM to assess changes in its

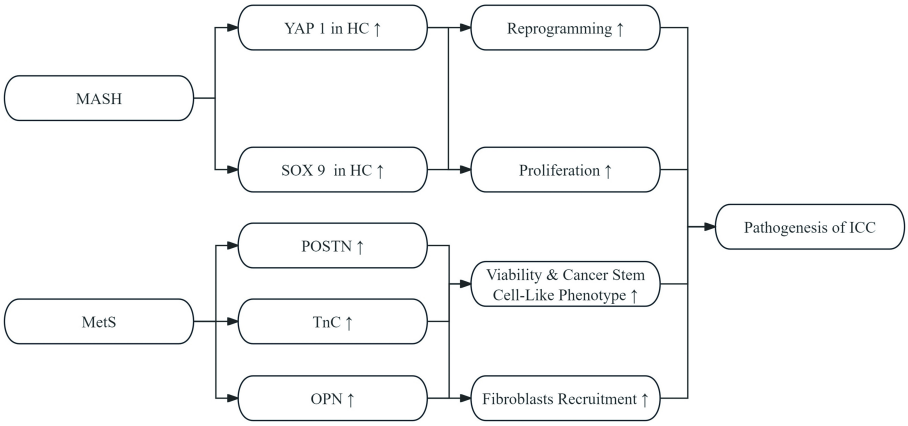

Figure 1. Potential pathogenesis of MASLD-related ICC. MASH: Metabolic dysfunction-associated steatohepatitis; MetS: metabolic syndrome; HC: hepatic cells; YAP 1: yes-associated protein 1; SOX 9: SRY-box transcription factor 9; OPN: osteopontin; TnC: tenascin-C; POSTN: periostin; ICC: intrahepatic cholangiocarcinoma.

composition and impact on ICC cell biology[19].

Their findings revealed that: (a) Enhanced deposition of OPN, TnC, and POSTN was observed in the tumors of the 44 ICC patients with MetS compared to adjacent non-tumorous tissue; (b) Significantly greater OPN accumulation was observed in MetS-afflicted ICC patients relative to those without MetS; (c) OPN, TnC, and POSTN markedly promoted cell viability and a cancer stem cell-like phenotype in human ICC cell lines; (d) Differences in the distribution and composition of fibrosis between MetS and non-MetS ICC patients are likely due to OPN-mediated recruitment of cancer-associated fibroblasts.

The study concluded that de novo expression of OPN, TnC, and POSTN was significantly associated with the promotion of motility of malignant cholangiocytes. At the same time, fibrosis can promote tumor progression. The overexpression of OPN is a significant feature of ICC with MetS and a key effector of fibrosis.

This investigation provides a foundational analysis of the pathophysiological links between MetS, ECM remodeling, and ICC, offering crucial insights for monitoring MetS and MASLD patients' risk of progressing to ICC. This work also establishes a theoretical basis for early prevention, precise diagnosis, and the development of novel ICC treatment strategies. However, further investigation is required to elucidate the specific roles and mechanisms of various OPN isoforms (including OPNa, OPNb, OPNc, OPN4 and OPN5) in ICC progression, suggesting substantial opportunities for future research in this domain.

Future perspective

MASLD-related ICC represents a complex disease trajectory originating from metabolic disorders and culminating in malignancy. Current research into its pathogenesis remains sparse, and existing studies fall short of providing a comprehensive understanding of the disease's overall mechanistic blueprint. However, revisiting the literature from the perspectives of origin and outcome offers valuable insights.

Origin perspective

From the origin standpoint, existing studies have delved into the mechanisms by which metabolic disorders such as diabetes and obesity contribute to CCA. These studies highlight key features such as hepatic steatosis, insulin resistance, and the subsequent upregulation of genes promoting cell turnover in the

pathogenesis of CCA [Table 2]. Given that MASLD shares commonalities with these metabolic disorders, it is anticipated that MASLD-related ICC will exhibit similar characteristics. Future research can build upon these findings by investigating:

(1) The specific molecular pathways linking MASLD to hepatic steatosis, insulin resistance, and altered gene expression in cholangiocytes.

(2) The potential synergistic effects of various metabolic derangements commonly observed in MASLD (e.g., dyslipidemia, hyperglycemia, and altered adipokine profiles) on ICC development.

(3) The role of genetic predisposition and epigenetic modifications in modulating the susceptibility of individuals with MASLD to ICC.

Outcome perspective

From the outcome perspective, the pathogenesis of ICC, including MASLD-related ICC, involves intricate physiological systems and metabolic processes. The convergence of pathological progression in ICC, regardless of the initial causative factors, suggests shared mechanisms that warrant further exploration. In general, the investigation of ICC pathogenesis can be divided into three main categories: (a) Studies of metabolic-related pathways: for instance, the association between the overexpression of ErbB family receptor tyrosine kinases in the bile of ICC patients and the origin of ICC[41]; (b) Investigations at the cellular and molecular levels, including mutations in PTEN, TP53, KRAS, CXCL12, and other genes in ICC cell lines and tissue[42-44], as well as the promoting effects of multiple uncontrolled miRNA expressions on the progression of ICC[45,46]; (c) Analysis of related signaling pathways: the potential roles of C-JNK, Wnt/β-catenin, and JAK-STAT signaling pathways in the proliferation and metastasis of ICC. Building on these established research foundations, we can delve deeper into the key genes and signaling pathways upstream or downstream of MASLD-related ICC to uncover its unique pathological processes and provide new insights for developing treatment strategies.

Inflammation as a central element

Inflammation is a critical factor linking MASLD to ICC, given its close association with hepatic steatosis. Extensive research has demonstrated the role of inflammation in ICC pathogenesis [Figure 2][47,48], with inflammatory mediators like IL-6 and TNFα activating pathways such as JAK-STAT, p38 MAPK, and Akt, which enhance cell growth, survival, and proliferation. The upregulation of COX-2 and Mcl-1 due to inflammation confers resistance to apoptosis, further promoting oncogenesis. Understanding the pivotal role of inflammation in the pathophysiological process of MASLD-related ICC is essential for unraveling its pathogenesis. Future studies should focus on delineating the inflammatory pathways and mediators that serve as critical links between MASLD and ICC, providing a foundation for targeted therapeutic strategies.

Additional insights and revelations

Recent studies have indicated that certain ICCs share a common progenitor cell origin as HCC[49,50]. This finding underscores the importance of adopting a holistic approach to hepatobiliary diseases and highlights the necessity of a unified metabolic interpretation. It also reveals a significant correlation between MASLD-related ICC and the broader spectrum of existing MASLD diseases. As research progresses, the MASLD disease spectrum may be refined, with eventual outcomes potentially extending beyond HCC to include ICC.

Table 2. Metabolic factors affect the pathophysiology of ICC

Metabolic factor	Proposed mechanism	Reference
Leptin	Overexpression enhances cholangiocarcinoma cell growth	[24]
Adipose tissue inflammation	Chronic hepatic inflammation and fibrosis due to IL-6 and TNFα release	[25]
Insulin resistance	Compensatory hyperinsulinemia and increased IGF-1 production, promoting cell proliferation and survival	[4,26-28]
Hyperinsulinemia	Direct stimulation of cholestatic cell proliferation; increased IGF-1 and insulin receptor expression in tumor cells	[29-33]
Hyperglycemia	STAT3 activation leading to aggressive CCA phenotypes; NF-κB glycosylation and nuclear localization promoting aggressive phenotype	[31,34,35]
Low APN levels	Reduced AdipoR expression leading to APN insensitivity; impaired activation of anti-neoplastic pathways (MAPK, mTOR, STAT-3, *etc.*)	[36-40]

IL-6: Interleukin-6; TNF-α: tumor necrosis factor alpha; IGF-1: insulin-like growth factor 1; STAT3: signal transducer and activator of transcription 3; CCA: cholangiocarcinoma; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; AdipoR: adiponectin receptor; APN: adiponectin; MAPK: mitogen-activated protein kinase; mTOR: mechanistic target of rapamycin.

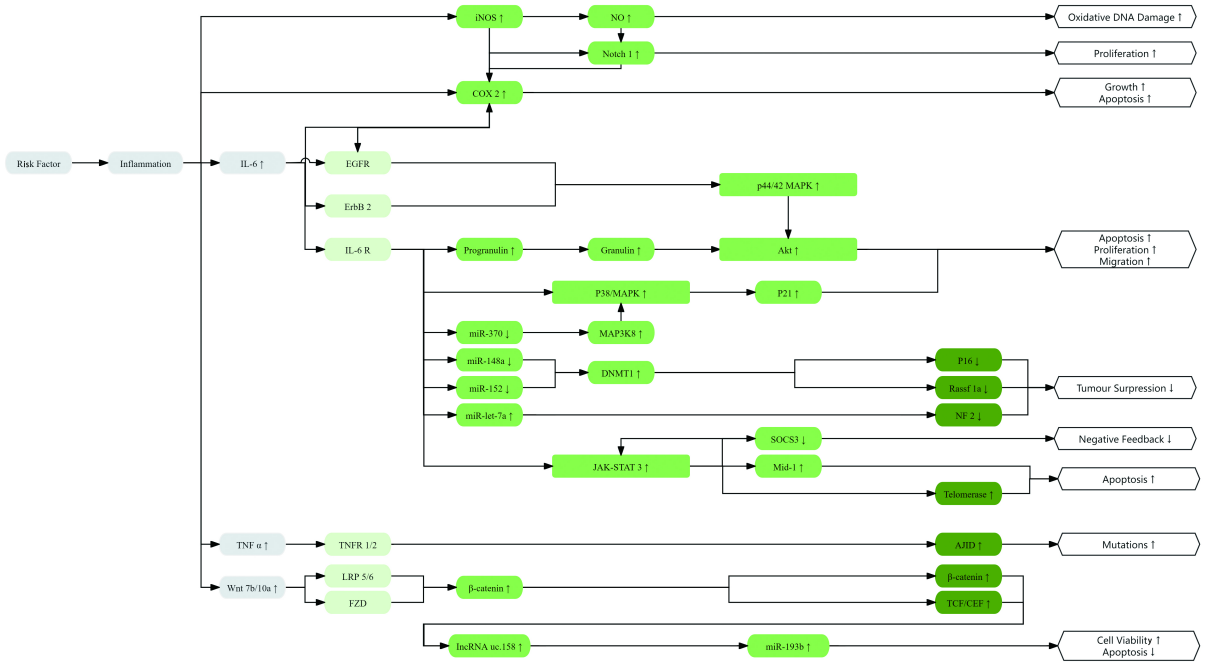

Figure 2. The molecular pathogenesis of ICC induced by inflammation. IL-6: Interleukin-6; TNF-α: tumor necrosis factor alpha; Wnt: wingless/integrated; EGFR: epidermal growth factor receptor; ErbB2: Erb-B2 receptor tyrosine kinase 2; IL-6R: interleukin-6 receptor; TNFR: tumor necrosis factor receptor; LPR: low-density lipoprotein receptor-related protein; FZD: frizzled; iNOS: inducible nitric oxide synthase; COX2: cyclooxygenase-2; miR: microRNA; lncRNA: long non-coding RNA; NO: nitric oxide; Notch: notch signaling pathway; p38: p38 mitogen-activated protein kinase; MAPK: mitogen-activated protein kinase; MAP3K8: mitogen-activated protein kinase kinase kinase 8; DNMT1: DNA methyltransferase 1; JAK-STAT3: janus kinase-signal transducer and activator of transcription 3; p44/42 MAPK: p44/p42 mitogen-activated protein kinase (also known as ERK1/ERK2); P21: cyclin-dependent kinase inhibitor 1; SOCS3: suppressor of cytokine signaling 3; Mid-1: midline 1; P16: cyclin-dependent kinase inhibitor 2A; RASSF1A: RAS-association domain family 1, isoform A; NF2: neurofibromatosis type 2; AJID: atypical junctional intercellular domain; TCF: T-cell factor; CEF: cell-free extract.

Furthermore, it is important that MASLD without cirrhosis has been associated with HCC or ICC[51,52]. This association suggests that certain elements of the MASLD disease progression may not always manifest as traditionally expected. Therefore, in investigating the pathogenesis of MASLD-related ICC, it is crucial to elucidate this phenomenon and transcend the limitations of conventional progression models in order to expand the scope of research perspectives.

PROGNOSIS OF MASLD-RELATED ICC

Research overview

The prognosis of patients is a critical factor in predicting the course of progression and provides an essential basis for treatment decisions by healthcare providers. Recent studies on the prognosis of MASLD-related ICC have primarily focused on differences between ICC patients with and without MASLD, yielding varied conclusions that warrant further investigation.

Reddy *et al.* reported no significant differences in tumor-free survival and overall survival between ICC patients with or without MASLD[6]. Conversely, De Lorenzo *et al.* found that the median survival of patients with MASLD (38.5 months) was significantly shorter than that of patients without traditional risk factors including HBV, HCV, alcohol, and environmental toxins (48.1 months, $P = 0.003$), and was comparable to that of patients with traditional risk factors (31.9 months, $P = 0.948$)[12]. Yu *et al.* observed that, in comparison to HBV-associated ICC, MASLD-related ICC patients exhibited a lower 5-year overall survival rate (24.0% *vs.* 48.9%), a higher 5-year recurrence rate (80.9% *vs.* 55.0%), and a higher early recurrence rate (58.5% *vs.* 30.0%) (all $P < 0.01$)[53].

In conclusion, the results of current cohort studies on the prognosis of MASLD-related ICC patients are inconclusive. Meta-analyses are challenging due to the limited number of studies and diverse research objectives. Further investigation is needed to elucidate the role of MASLD in the onset and progression of ICC and its impact on quality of life. A clear understanding of the prognosis of MASLD-related ICC patients can facilitate more accurate disease progression assessment and subsequent treatment adjustments, such as the introduction of new adjuvant therapies or postoperative radio-chemotherapy, with the aim of enhancing patient prognosis.

Critical re-examination

The prognosis of MASLD-related ICC patients is closely related to the treatment. Currently, the treatment strategy is mostly referred to the general ICC patients, but the surgical procedure has been updated in recent years. New adjuvant chemotherapies have been recommended as first-line treatments for locally advanced ICC[54-56]. Additionally, the role of lymph node dissection in surgery has gained focus[57,58], with the latest treatment guidelines advocating for its widespread application during surgical intervention[59].

However, due to the extensive time span of samples included in relevant studies, the underutilization of novel adjuvant chemotherapies and lymph node dissection in earlier cases may lead to a pessimistic prognosis assessment for MASLD-related ICC. Therefore, further studies are necessary to determine the prognosis and optimal treatment strategies for MASLD-related ICC patients.

CLINICAL MANAGEMENT

Early intervention

Malignant tumors, both intrahepatic and extrahepatic, rank as the second most common cause of death among patients with MASLD, following cardiovascular events. Large cohort studies[60] have identified a significant link between MASLD and an elevated cancer risk. Further investigations[61] have revealed that all histological stages of MASLD are significantly associated with increased overall mortality. This risk intensifies with the histological progression of MAFLD (HR = 1.71, 95%CI: 1.64-1.79 for simple steatosis; HR = 2.14, 95%CI: 1.93-2.38 for MASH; HR = 2.44, 95%CI: 2.22-2.69 for non-cirrhotic fibrosis; HR = 3.79, 95%CI: 3.34-4.30 for cirrhosis). Consequently, the early identification of MAFLD patients at high risk of malignancy and timely intervention to obstruct disease progression is crucial for optimizing the management of MAFLD-related ICC.

Key intervention[62] targets connecting MASLD and ICC include metabolic function, inflammation, insulin resistance, and liver fibrosis, making them essential focal points for early intervention strategies. Current research primarily focuses on evaluating the effects of pharmacological interventions on these aspects of MASLD. Two main approaches have emerged: one investigates the repurposing of existing drugs for other metabolic disorders (such as hyperlipidemia and diabetes) for use in MASLD[62,63] [Table 3]; the other concentrates on the development of new drugs specifically targeting MASLD. Recently, phase 3 clinical trial data for the new drug Rezdiffra demonstrated a significant improvement in liver fibrosis among MASH patients with moderate to severe non-cirrhotic fibrosis[64]. As a result, Rezdiffra was approved, marking a milestone as the first drug sanctioned for MASH treatment, effectively addressing a long-standing therapeutic gap.

Additionally, some scholars have argued[65] that new drug development should focus on the broader "metabolic dysfunction" rather than solely aiming to ameliorate inflammation and fibrosis pre- and post-liver biopsy. Reducing the risk of malignancy and improving patient quality of life should be key objectives in pharmacotherapy.

Looking ahead, the future of MASLD management is promising, with innovative approaches under exploration. These include targeting the gut-liver axis via microbiome modulation, leveraging incretin-based therapies, and investigating epigenetic modifications in disease progression[66]. Furthermore, precision medicine approaches utilizing genetic and metabolomic profiling may enable more personalized and effective interventions.

Treatment and challenges

Currently, the U.S. National Comprehensive Cancer Network's 2023 CCA Guidelines[59] do not specify distinct treatment protocols for patients with MASLD-related ICC. Consequently, these patients typically receive standard ICC treatments, which encompass a range of modalities depending on disease stage and patient factors.

For resectable tumors, surgical resection remains the gold standard, offering the best chance for long-term survival. However, only 30%-40% of patients are candidates for this approach at diagnosis[67]. Additionally, the presence of MASLD can complicate surgical outcomes due to impaired liver function and regenerative capacity.

For unresectable cases, systemic therapy is the mainstay of treatment. The current first-line regimen consists of gemcitabine plus cisplatin, which has shown improved overall survival compared to gemcitabine alone[68]. In addition, recent studies have proposed new regimens such as TOPAZ-1[69] and KEYNOTE-966[70], which can benefit patients more than traditional first-line regimens. Recent advancements in targeted therapies, such as FGFR2 inhibitors for FGFR2 fusion-positive ICC, have opened new avenues for personalized treatment[71]. However, the efficacy of these regimens in MASLD-related ICC is not well-documented, and the potential for increased toxicity due to underlying liver dysfunction warrants careful consideration.

Locoregional therapies play a crucial role in managing ICC, particularly for patients with limited hepatic disease[71,72]. These include radiofrequency ablation (RFA), microwave ablation (MWA), and transarterial chemoembolization (TACE). Stereotactic body radiation therapy (SBRT) has also shown promise in local tumor control. However, the radiosensitivity of MASLD-affected liver tissue and the risk of radiation-induced liver disease necessitate precise planning and dose management. In addition, the altered vascular

Table 3. Effects of drugs on hepatic steatosis, inflammation and fibrosis, and cardiovascular events

Drug	Liver	Cardiovascular system
Vitamin E	Improves non-T2DM fatty liver and hepatocyte ballooning/inflammation, does not improve fibrosis	Increases the risk of heart failure in T2DM patients
Obeticholic acid	Improves liver fibrosis, prevents the progression of NASH	No effect
Statins	Prevent the progression of MASLD, reduce the risk of HCC	Reduce cardiovascular risk
Metformin	Prevents the progression of MASLD, reduce the risk of HCC	No effect
Pioglitazone	Reduces liver fat content in DM patients, alleviates NASH	Reduces the risk of cardiovascular events in T2DM and NASH patients
GLP-1RA	The effect on improving fatty liver, liver enzyme levels, and liver fibrosis in NASH patients needs further research	Reduces the risk of cardiovascular events in T2DM patients
SGLT-2i	The effect on improving fatty liver in T2DM patients, and liver fibrosis in NASH patients needs further research	Reduces the risk of cardiovascular and kidney events in T2DM patients
DPP-4i	Cannot alleviate fatty liver and fibrosis in overweight T2DM patients	Reduces the risk of cardiovascular events in T2DM patients

T2DM: Type 2 diabetes mellitus; NASH: non-alcoholic steatohepatitis; MASLD: metabolic dysfunction-associated steatotic liver disease; HCC: hepatocellular carcinoma; DM: diabetes mellitus; GLP-1RA: glucagon-like peptide-1 receptor agonist; SGLT-2i: sodium-glucose co-transporter 2 inhibitor; DPP-4i: dipeptidyl peptidase-4 inhibitor.

architecture and regenerative limitations in MASLD may impact their effectiveness and safety.

Liver transplantation, while a potential curative option for select patients with MASH-related end-stage liver disease and early-stage ICC[66], poses significant challenges in the context of MASLD. The increased risk of postoperative complications, including the risk of developing recurrent or de novo MASLD, graft dysfunction, and cardiovascular events[73], highlights the need for stringent candidate selection and comprehensive perioperative management.

Despite these options, the unique pathophysiology of MASLD-related ICC presents distinct challenges. The altered hepatic microenvironment, chronic inflammation, and metabolic dysregulation associated with MASLD may influence treatment efficacy and tolerability. This underscores a significant gap in current oncological practice, highlighting the need for tailored approaches that consider the specific biological context of MASLD-related ICC.

Perioperative management

Recent studies[74] have demonstrated that patients with MetS, MASLD, or MASH face significantly increased risks of postoperative complications such as cardiovascular events, infections, and renal insufficiency following liver resection or transplantation. A meta-analysis by Meijer *et al.* indicated that both MASLD and MASH are independent risk factors for postoperative complications after hepatectomy, with risks escalating alongside disease severity[75]. Neal *et al.* suggested that only MASH was associated with increased complication risks, but the majority of studies highlight the need for intensive perioperative management due to elevated surgical risks in MASLD patients[76]. Mechanistic studies by Veteläinen *et al.* and McCuskey *et al.* have demonstrated that MASH can exacerbate postoperative inflammatory responses, impair hepatocyte function, diminish liver regenerative capacity, and lead to microvascular dysfunction[77,78]. Collectively, these factors reduce surgical tolerance and increase the risk of postoperative mortality in these patients.

Therefore, for patients with MASLD, irrespective of disease stage, enhanced perioperative management is crucial. Poon *et al.* recommend comprehensive preoperative liver function assessments, preoperative interventions such as portal vein embolization, and meticulous surgical techniques to minimize liver

injury[79]. Cauchy *et al.* and Reddy *et al.* noted that even patients with latent or mild MASLD are at increased risk of postoperative complications[80,81]. Cauchy *et al.* further emphasized that the reduced liver regenerative capacity associated with MASH necessitates combining tumor treatment with minimally invasive techniques during surgery[82].

In conclusion, detailed and comprehensive treatment and management strategies should be emphasized for MASLD-related ICC patients to mitigate surgical risks and reduce the incidence of complications regardless of their stage of MASLD. Additionally, specific treatment options for this subgroup have not received adequate attention, underscoring the need for further research to fundamentally improve prognosis for these patients.

DEFINITION UPDATE

MASLD represents a novel conceptualization of non-alcoholic fatty liver disease (NAFLD), establishing more precise diagnostic criteria. It is crucial to recognize that MASLD should not be viewed exclusively as the hepatic manifestation of metabolic syndrome. Instead, it encompasses a broader spectrum of intra- and extrahepatic complications, including insulin resistance and alcoholic liver disease[15]. The recent consensus to further rename NAFLD to MASLD underscores the pivotal role of metabolic cardiovascular risk factors in its pathogenesis[83]. This refinement in terminology allows for a more nuanced diagnosis: patients with fatty liver disease and a normal BMI without diabetes can be diagnosed with MASLD based on a single metabolic cardiovascular risk factor, while those with multiple risk factors require at least two for diagnosis.

These terminological shifts emphasize the need for a more comprehensive understanding of the disease, particularly highlighting the central role of metabolic dysfunction in its initiation and progression. This evolving conceptualization is crucial for developing more targeted therapeutic interventions. Moreover, it underscores the importance of categorizing MASLD alongside other metabolic disorders such as diabetes, chronic kidney disease, and cardiovascular disease, facilitating a more integrated approach to treatment and management.

The relationship between MASLD and NAFLD has been a subject of debate in recent literature. Some researchers argue that these should be considered distinct disease entities. In a meta-analysis involving 980,867 patients, Ayada *et al.* compared the definitions of the two diseases[84]. The study found that 79.9% of patients with fatty liver met the criteria for both conditions, 4.0% met only the NAFLD criteria, and 15.1% met the MASLD criteria. Notably, patients diagnosed with MASLD exhibited a higher prevalence of liver fibrosis progression than those with NAFLD or overlapping conditions. Alharthi *et al.* considered MASLD a superior name compared with NAFLD, and the transformation in name and definition from NAFLD to MAFLD represents an important milestone, which indicates significant tangible progress toward a more inclusive, equitable, and patient-centered approach to addressing the profound challenges of this disease[85].

However, other studies suggest a high degree of overlap between MASLD and NAFLD, indicating that they may be more similar than different. Younossi *et al.* found that only 5.29% of patients with NAFLD do not fulfill MASLD criteria in their database and the National Health and Nutrition Examination Survey of 6,429 patients[86]. Similarly, a study by Suzuki *et al.* reported that 96.7% of MASLD patients in their database met NAFLD criteria[87]. Zou *et al.* further corroborated these findings, suggesting that insights from NAFLD research remain largely applicable to MASLD[88]. These studies collectively argue that the clinical characteristics, diagnostic criteria, and research findings for NAFLD can be largely applied to MASLD, indicating a high degree of continuity between the two concepts.

In conclusion, while the shift from NAFLD to MASLD represents a significant advancement in our understanding of fatty liver disease, the high degree of overlap between these concepts suggests that much of our existing knowledge remains relevant. However, the more precise and inclusive nature of MASLD criteria may lead to better identification and management of patients at risk for metabolic liver disease. As we move forward, a balanced approach that acknowledges both the continuity and the refinements brought by the MASLD concept will be crucial for advancing our understanding and treatment of this increasingly prevalent condition.

LEAN MASLD

Obesity is a well-established risk factor and diagnostic criterion for MASLD. The increasing prevalence of MASLD over recent decades can largely be attributable to an obesogenic environment characterized by high-calorie food intake and physical inactivity[89,90]. However, it is important to note that obesity is not present in all MASLD patients. Global studies have identified that individuals with a normal BMI (18.5-25 kg/m^2) who present with at least two associated risk factors - such as increased waist circumference, hypertension, low HDL-C levels, hypertriglyceridemia, impaired fasting glucose, insulin resistance, and chronic subclinical inflammation - can also develop MASLD. These cases, often termed "lean MASLD," account for 15% to 50% of all MASLD cases[91].

While some studies suggest that lean MASLD patients may share similar morphological characteristics with their non-lean counterparts[92] or even exhibit better histological and metabolic profiles[93], long-term prognostic data often indicate worse outcomes. Meta-analyses have demonstrated that lean MASLD is associated with a higher risk of various extrahepatic complications[94] and increased all-cause mortality compared to non-lean MASLD patients[95-97]. Nonetheless, some studies report no significant survival differences between these groups. Despite the limited and somewhat conflicting prognostic data, outcomes for lean MASLD patients tend to be poorer than those of healthy individuals and may be similar to or worse than those of non-lean MASLD patients. Therefore, there is a critical need for targeted management strategies aimed at slowing disease progression and improving prognosis in lean MASLD patients.

Recent research has highlighted the role of metabolic adaptation in the pathogenesis of lean MASLD, which may explain why lean MASLD patients have similar or worse long-term outcomes compared to their non-lean counterparts. Initially, lean MASLD patients exhibit adaptive metabolic responses characterized by increased serum bile acids and elevated Farnesoid X Receptor (FXR) activity[98,99]. This adaptation appears to mitigate hepatic inflammation in the early stages of the disease. However, as the disease progresses, this adaptive response wanes, leading to a failure to attenuate hepatic inflammatory responses and contributing to disease progression. The impaired bile acid signaling, driven by alterations in the macrophage epigenome and increased expression of proinflammatory cytokines, underscores the complexity of lean MASLD pathophysiology.

Currently, no specific guidelines exist for managing lean MASLD due to a paucity of research evidence. Nevertheless, some studies indicate that weight loss can effectively mitigate fatty liver disease, with a dose-dependent relationship observed[100]. Additionally, poor diet quality is a principal modifiable risk factor for worsening metabolic health[101]. Therefore, it is important to provide all MASLD patients, particularly those with metabolically unhealthy profiles, with personalized dietary guidance and encourage physical activity (while reducing sedentary behavior) to optimize metabolic function and maintain cardiovascular health.

FUTURE INSIGHTS

The intricate interplay between metabolic dysregulation, chronic inflammation, and biliary carcinogenesis warrants further investigation. Our preliminary search on ClinicalTrials.gov using the terms "MASLD" and "intrahepatic cholangiocarcinoma" did not yield any ongoing or completed trials. Expanding the search to "metabolism" and "primary liver cancer" identified 13 relevant clinical trials, providing insights into the current research landscape on metabolic dysfunction and liver cancer.

These trials [Table 4] predominantly investigate the metabolic reprogramming of cancer cells, the impact of lifestyle factors such as diet and obesity on liver cancer, and the exploration of metabolic markers for early diagnosis and prognosis of HCC. For instance, trial NCT06278701 examines dietary interventions on liver function recovery post-hepatectomy, while NCT05794048 aims to identify metabolic markers for optimizing patient care. Trials such as NCT03663062 and NCT03356535 explore links between obesity, metabolic syndrome, and liver cancer risk, emphasizing the complex relationship between metabolic health and liver carcinogenesis.

Given that ICC and HCC both fall under PLC and share common progenitor cell origins, future clinical research on MASLD-related ICC should leverage insights from these existing studies. Looking ahead, we propose several key directions for MASLD-related ICC:

(1) Prospective Cohort Studies: Large-scale studies are needed to delineate the natural history and specific risk factors of MASLD-related ICC. Incorporating advanced imaging techniques, such as those in NCT05794048, may help identify early radiological signatures of ICC in MASLD patients.

(2) Metabolomic and Proteomic Approaches: Methods used in trials like NCT04371042 and NCT03356535 should be applied to ICC research to discover novel biomarkers for early detection and prognosis.

(3) Interventional Studies on Lifestyle Modifications: Adapt strategies from trials such as NCT06278701 (late-evening snack strategy) and NCT04649671 (mobile health-based exercise program) for MASLD patients at high risk of ICC.

(4) Innovative Therapeutic Approaches: Explore novel treatments like *p53* gene therapy investigated in NCT02561546 in the context of MASLD-related ICC to open new avenues for targeted therapy.

By addressing these priorities, we anticipate significant advancements in our understanding of MASLD-related ICC. Development of tailored screening protocols, identification of novel therapeutic targets, and ultimately improved outcomes for at-risk or diagnosed patients are expected. Interdisciplinary collaboration and integration of cutting-edge technologies will be pivotal in unraveling the complex interplay between metabolic dysfunction and cholangiocarcinogenesis, paving the way for personalized prevention and treatment strategies in the precision medicine era.

CONCLUSION

In general, it is evident that MASLD is an emerging factor in the pathophysiology of ICC. Despite the increasing prevalence of MASLD and its potential role in ICC progression, significant research gaps remain, particularly concerning the pathogenesis, prognosis, and optimal management strategies for MASLD-related ICC. Current studies are limited by retrospective designs, small sample sizes, and regional biases, necessitating large-scale, multicenter prospective cohort studies to elucidate the natural history and specific

Table 4. Clinical trials of metabolism and PLC

NCT number	Country	Focus	Objective
NCT06278701	China	Dietary intervention	Evaluate the effects of late-evening snacks on nutritional status, liver function recovery, complication rate, quality of life, and metabolic patterns in HCC patients post-hepatectomy
NCT05794048	France	Metabolic profiling	Characterize metabolic signatures of HCC and pancreatic tumors to identify prognostic and theranostic markers
NCT06315361	Italy	Diabetes and NAFLD	Investigate the clinical impact of NAFLD in diabetic patients and assess the applicability of non-invasive fibrosis scores in this high-risk population
NCT05623150	France	Alcohol-related liver disease and metabolic syndrome	Identify metabolic, immune, and imaging factors associated with HCC development in patients with alcohol-related liver disease or non-alcoholic steatohepatitis
NCT04371042	Italy	NAFLD and metabolic syndrome	Establish an observational cohort of NAFLD patients at different stages and a comparative cohort without NAFLD to characterize clinical phenotypes and collect biological samples for future omics-based studies
NCT03663062	UK	Obesity and liver disease	Assess the link between body weight, fatty liver disease, and colorectal adenomas in a UK population undergoing colonoscopy
NCT02730611	USA	Metabolic syndrome and bile acid metabolism	Investigate the relationship between bile acid profiles, metabolic syndrome, and the efficacy of vertical sleeve gastrectomy in obese patients, with a focus on HCC and cholangiocarcinoma risk
NCT03356535	France	Lifestyle and metabolic signatures	Identify metabolic signatures associated with healthy lifestyle behaviors and assess their relationship with HCC risk using data from a large European cohort
NCT01798173	France	Metabolic syndrome and HCC in cirrhosis	Identify metabolic signatures associated with healthy lifestyle behaviors and assess their relationship with HCC risk using data from a large European cohort
NCT01342705	France	Iron overload and HCC risk	Assess the effect of phlebotomy on HCC risk in patients with compensated alcoholic cirrhosis and hepatic iron overload
NCT04649671	China	Exercise and insulin resistance	Investigate the impact of a mobile health-based exercise program on insulin resistance in HCC patients
NCT02561546	China	Gene therapy and diabetes in HCC	Evaluate the preliminary efficacy of *p53* gene therapy in treating diabetes in patients with HCC
NCT06072287	UK	Psychological distress in chronic diseases	Develop and validate a new measure of illness-related distress for individuals living with long-term health conditions, including liver diseases

PLC: Primary liver cancer; HCC: hepatocellular carcinoma; NAFLD: non-alcoholic fatty liver disease.

risk factors of MASLD-related ICC. Additionally, the intricate interplay between metabolic disorders, inflammation, and genetic factors in ICC pathogenesis warrants further exploration. Future research should focus on integrating advanced imaging, metabolomic, and proteomic approaches to identify novel biomarkers for early detection and prognosis. Moreover, interventional studies on lifestyle modifications and targeted therapeutic strategies are crucial for improving patient outcomes. Addressing these gaps will not only enhance our understanding of MASLD-related ICC but also pave the way for more effective prevention and treatment paradigms.

DECLARATIONS

Authors' contributions

Conceptualized the review, conducted the literature review, and contributed to the writing and editing of the manuscript: Li ZL, Tang ZH

Assisted in the literature review: Chen JL, Tang Y, Qin DL

Availability of data and materials

Not applicable.

Financial support and sponsorship

National Natural Science Foundation of China (81772521); Hospital-level Clinical Research Cultivation Fund of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (17CSK06);

Multicenter Clinical Study of Shanghai Jiao Tong University School of Medicine (DLY201807).

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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