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MASLD-Related HCC: Trends, Pathogenesis and Current Treatment Options

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Abstract: Hepatocellular carcinoma (HCC) is a late-stage complication in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). Recent epidemiological studies indicate that as the global burden of HCC continues to rise alarmingly, the proportion of MASLD-related HCC cases both in cirrhotic and non-cirrhotic populations has been steadily increasing. This review aims to provide an update on the HCC burden in individuals with MASLD, exploring its association with insulin resistance, metabolic inflammation, and gut-derived liver injury. Finally, we will outline risk-based HCC surveillance strategies and discuss the potential impact of novel targeted therapies for metabolic dysfunction-associated steatohepatitis (MASH) related fibrosis on HCC incidence.

Keywords: Hepatocellular carcinoma; Metabolic-dysfunction associated steatotic liver disease; metabolic dysfunction-associated steatohepatitis; Metabolic syndrome; Biomarkers

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1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most common chronic liver disease globally, replacing non-alcoholic fatty liver disease (NAFLD). MASLD is defined by hepatic steatosis in the presence of at least one cardiometabolic risk factor, with alcohol consumption excluded as a contributing factor. The global prevalence of MASLD is approximately 30%, with the highest rates observed in the Middle East and South America. About 20% of MASLD cases progress to metabolic dysfunction-associated steatohepatitis (MASH), and the incidence of MASLD is projected to rise to over 55% in the next decade. MASH exacerbates liver injury and can lead to cirrhosis and hepatocellular carcinoma (HCC).

HCC is one of the leading causes of cancer-related deaths worldwide. While liver cancer often arises from cirrhosis

due to various etiologies, MASH patients exhibit a significantly increased risk of HCC even in the absence of cirrhosis. The development of HCC is associated with structural changes in regenerative cirrhotic nodules. However, the precise mechanisms by which MASH progresses to HCC remain unclear. Current treatment strategies primarily focus on weight normalization, physical activity and diabetes management, with limited additional therapeutic options available.

The histopathological features of MASH include steatosis, inflammation and fibrosis, ultimately leading to cirrhosis, HCC, or end-stage liver disease. Therefore, early determination of fibrosis stage is crucial for assessing MASH severity and its progression to cirrhosis. Currently, the diagnosis of MASH relies on invasive liver biopsy, though non-invasive methods such as liver stiffness measurement (LSM) and the Fibrosis-4 (FIB-4) index are available for detecting advanced fibrosis and early cirrhosis. This review explores the global epidemiology, predictive factors and risk factors of MASLD-related HCC and proposes preventive strategies to address this growing public health challenge.

2. Epidemiology of HCC in MASLD

Primary liver cancer ranks as the sixth most common cancer globally and the third leading cause of cancer-related deaths, with HCC accounting for approximately 75–85% of cases. The main etiologies of HCC include hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease and non-alcoholic steatohepatitis (NASH). Over the past decade, HBV and HCV-related HCC has declined due to increased vaccination and antiviral therapies, while alcohol consumption and rising obesity rates have contributed to the growing burden of MASLD-related HCC. According to WHO, as of 2022, over 2.5 billion adults aged ≥ 18 were overweight, including more than 890 million with obesity. With increasing obesity rates, MASLD-related liver disease progression to cirrhosis and HCC has led to a significant rise in liver-related morbidity and mortality. A Global Burden of Disease Study projected annual HCC deaths to surge from 800,000 in 2020 to 1.3 million by 2040 [1], with predictive models suggesting MASLD will become the leading cause of HCC in Asia.

Globally, MASLD-HCC prevalence and incidence are rising, particularly among older men, individuals with T2DM and overweight populations. A meta-analysis of 1,377,466 MASLD patients found an HCC incidence of 3.39 per 1,000 person-years, with higher rates in MASH patients ($p = 0.043$) [2]. A cohort study by Simon *et al.* involving nearly 9,000 biopsy-confirmed MASLD cases demonstrated significantly higher HCC risk in MASLD compared to other etiologies (aHR 17.08, 95% CI 11.56–25.25), with diabetes further elevating risk [3]. Current annual HCC incidence ranges from 0.5–2.6% in MASH cirrhosis patients versus 0.01–0.13% in non-cirrhotic MASLD.

Growing evidence shows HCC can develop in MASH patients without cirrhosis. A meta-analysis revealed 14.2% of HCC cases occurred in non-cirrhotic patients ($P < 0.001$), with non-cirrhotic NASH patients having 2.61-fold higher HCC risk (OR 2.61, 95% CI 1.27–5.35, $P = 0.009$) [4]. U.S. liver transplant data showed HCV-related HCC declined from 60% (2013) to 27% (2022), while MASH-HCC increased from 10% to 31% ($p = 0.62$) [5]. Similarly, European transplant registries (2002–2016) reported MASH-related transplants rising from 1.2% to 8.4% [6]. Although cardiovascular disease remains the leading cause of death in MASLD patients, particularly among women, its high prevalence has made it the top indication for HCC and liver transplantation in the U.S.

3. Pathogenesis of HCC in MASH

The mechanisms of HCC development in MASLD remain unclear but involve several pathways. Hyperinsulinemia,

insulin resistance, and hepatic lipid accumulation create chronic inflammation and oxidative stress, promoting tumorigenesis. Excess free fatty acids induce lipotoxicity, ER stress, ROS production, and mitochondrial dysfunction, triggering cell death and senescence. In MASH, imbalanced cytokines (TNF-α, IL-6, IL-4) promote HCC proliferation. Insulin resistance activates key pathways (PI3K/AKT/mTOR, JAK2/STAT3, MAPK, Wnt/β-catenin) [7].

The gut-liver axis plays a critical role. Dysbiosis increases intestinal permeability, allowing PAMPs and bacteria to translocate to the liver, driving inflammation. Akkermansia and Bifidobacterium species enhance gut barrier function and reduce hepatic inflammation in animal models [8,9]. Gut microbiota also modulates bile acid metabolism via FXR, which regulates lipid metabolism and immune responses. Elevated bile acids (e.g., deoxycholic acid) induce DNA damage and HCC.FXR-deficient mice develop spontaneous HCC at 15 months [10].

Genetic variants (PNPLA3, TM6SF2, HSD17B13) influence HCC risk. The PNPLA3 rs738409 GG genotype is an independent risk factor (OR 5.05, 95% CI 1.47–17.29, $P = 0.01$) [11], while TM6SF2's role remains controversial [12]. These genetic and epigenetic alterations activate oncogenic signaling cascades.

4. HCC surveillance in MASLD/MASH

Given the rising MASLD-HCC incidence, early detection is crucial. AASLD recommends ultrasound ± AFP every 6 months for high-risk groups (e.g., cirrhosis). For F3 fibrosis, individualized surveillance is advised. Ultrasound alone has 63% sensitivity for early HCC, increasing to 45% with AFP [13].

Non-invasive tests (NITs) like FIB-4 and LSM predict HCC risk. In a NAFLD cirrhosis cohort ($n = 122$), FIB-4 > 3.25 was independently associated with HCC (HR 6.40, 95% CI 1.71–24.00, $P = 0.006$) [14]. LSM changes also correlate with HCC development (HR 1.72, 95% CI 1.01–3.02, $P = 0.04$) [15]. PIVKA-II outperforms AFP in differentiating HCC from cirrhosis. The GALAD score (age, sex, AFP, AFP-L3, DCP) combined with ultrasound improves detection (AUC 0.98 vs. 0.82 for ultrasound alone)[16].

Liquid biopsies (CTC, ctDNA) show promise. ctDNA can detect HCC-associated mutations (TP53, Wnt/β-catenin, KEAP1/NFE2L2) [17] ,enabling personalized management.

5. Treatment of MASH-related HCC

Lifestyle modification remains the cornerstone. Weight loss (5–10%) reduces hepatic fat and fibrosis [18]. Mediterranean diet is recommended, and bariatric surgery lowers HCC risk (0.05% vs 0.34%, $P = 0.03$). Metabolic syndrome management is critical.GLP-1RAs (e.g., semaglutide) reduce HCC risk and improve fibrosis [19]. Metformin inhibits mTOR and tumor growth. Although no drugs are specifically approved for MASLD, resmetirom (a THR-β agonist) shows promise in phase 2/3 trials [20]. Lanifibranor (a pan-PPAR agonist) improves fibrosis in phase 2 [21]. Statins may reduce HCC risk via anti-inflammatory effects. Gut microbiota modulation (probiotics, FMT) improves insulin sensitivity and reduces hepatic inflammation. Combined lifestyle, pharmacotherapy, and surveillance strategies are essential for HCC prevention.

6. Conclusion

HCC is a severe complication of MASLD, often diagnosed late due to asymptomatic early stages. Genetic and

environmental factors drive metabolic inflammation, fibrosis, and HCC risk. Lifestyle interventions are crucial for risk reduction, while advanced fibrosis patients require HCC surveillance. Emerging biomarkers and targeted therapies (e.g., resmetirom) offer hope for personalized prevention. Integrating metabolic and liver-focused approaches may enhance fibrosis regression and HCC prevention.

Disclosure statement

The author declares no conflict of interest.

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