Review

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The Role of Extrahepatic Features on the Development and Management of Hepatocellular Carcinoma in Steatotic Liver Disease

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As the most common type of primary liver cancer, hepatocellular carcinoma (HCC) is reportedly the third leading cause of cancer-related death globally. Advanced steatotic liver disease (SLD) emerges as the most prominent contributor to HCC worldwide. In this paper, we review the extrahepatic features of metabolic dysfunction-associated SLD that exacerbate the risk for HCC, including insulin resistance, obesity-related factors such as physical inactivity and dietary patterns, as well as influences of genetics, ethnicity, gender-specific hormonal differences, alcohol-associated liver disease (ALD), smoking habits, and alterations in gut microbiota. Additionally, the mechanisms underlying how these extrahepatic features contribute to the development, as well as the detection and surveillance of HCC, are elaborated. With a better understanding of these factors, targeted interventions can be designed to prevent HCC development or ameliorate its clinical outcomes.

Keywords: steatosis; metabolic syndrome; alcoholic liver disease; insulin resistance; hepatocellular carcinoma; obesity; abbreviated magnetic resonance imaging (aMRI); ultrasound

Introduction

As the most common type of primary liver cancer, hepatocellular carcinoma (HCC) is reportedly the third most frequent cause of cancer-related mortality worldwide [1], representing a significant global health challenge. Liver cirrhosis is the primary cause of HCC development. There has been a growing research interest in the role of extrahepatic features in the development, prognosis, and management of liver disease and cancer due to their central role in the development of these diseases which is further complicated by the challenges in surveillance and slowdown of disease progression. This paper aims to review the role of extrahepatic features of HCC specifically in the context of steatotic liver disease (SLD) (Fig. 1).

Multiple etiologies of SLD are implicated in the development of HCC, including hepatitis C virus infection; however, this paper will specifically focus on the role of alcohol- and metabolic dysfunction-associated SLD in HCC development, mainly driven by the relative weight of the extrahepatic contributions to carcinogenic processes and inspired by the move to adopt a wider perspective in the evaluation of the multifaceted etiologies of HCC, which is conducive for the designing of a holistic management approach. Such an approach offers substantial benefits by facilitating early identification and multitargeted interventions. Understanding and integrating extrahepatic features such as lifestyle factors, genetic predispositions, and metabolic conditions into comprehensive management strategies can enhance risk stratification, tailor patient education, and refine surveillance methodologies. This approach not only reduces HCC risk but also improves overall patient outcomes by addressing the complex interplay of systemic health determinants that contribute to liver carcinogenesis.

Definitions

In 2023, the leading multinational liver societies, including the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL) and La Asociación Latinoamericana para el Estudio del Hígado (ALEH), had reached a consensus on adopting a new set of nomenclature for fatty liver disease that reflects its metabolic etiology and heterogeneity [2]. The term “steatotic liver disease” (SLD) was adopted as an umbrella term for all forms of liver steatosis, regardless of the etiologies. The term “nonalcoholic fatty liver disease” (NAFLD) was phased out for usage and is replaced by “metabolic dysfunction-associated steatotic liver disease” (MASLD), which is used to describe patients having hepatic steatosis and one or more of the following five cardiometabolic risk factors: obesity, type 2 diabetes, hy-

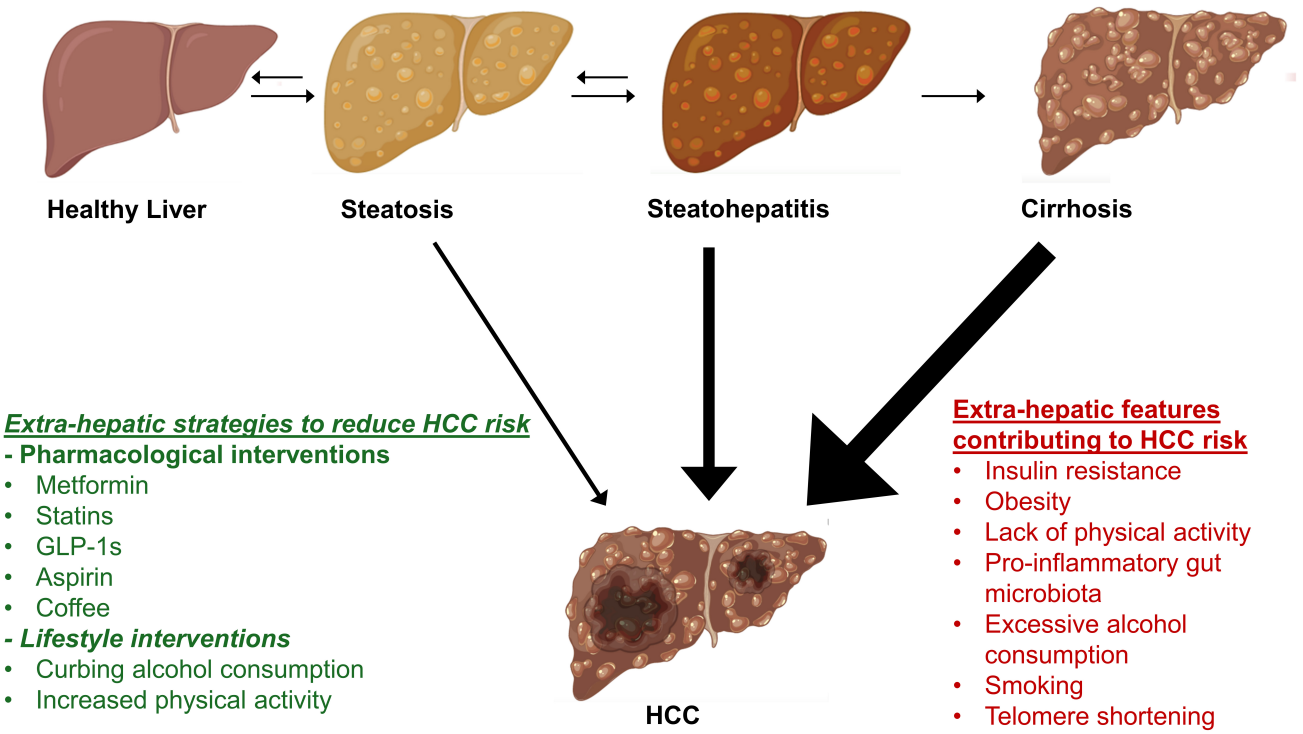

Fig. 1. Contributing extrahepatic factors associated with hepatocellular carcinoma development in steatotic liver disease, as well as potential pharmacological and non-pharmacological strategies for controlling cancer development. A standard image license has been granted by Shutterstock for the use of the images in this figure, https://www.shutterstock.com. HCC, hepatocellular carcinoma; GLP-1, glucagon-like peptide-1.

pertension, dyslipidemia, or metabolic syndrome. A new category, termed mixed metabolic and alcohol-associated steatotic liver disease (MetALD), was created to describe subjects with MASLD who consume a significant amount of alcohol per week (140 g/week and 210 g/week for females and males, respectively) [2]. Drawing from studies utilizing both sets of criteria for defining NAFLD and MASLD, this review seeks to describe the complex relationship between SLD and HCC.

Epidemiology

Globally, liver disease accounts for around 2 million deaths annually, or 3.5% of all deaths globally [3], with SLD being the leading cause of chronic liver disease [4,5]. MASLD affects an estimated 30% of the global population, increasing rapidly in parallel to the obesity pandemic [6]. The global prevalence of metabolic liver disease increased from 25% in 1990–2006 to 38 % in 2016–2019 (a 50.4% increase) [6]. Several epidemiological studies have found that the risk of HCC is increased by 1.5–2.0 fold in those with metabolic syndrome (MetS) [7–9], notably with several extrahepatic components of MetS that are independently related to the development of HCC. Alcohol-associated liver disease (ALD) is the major cause of cirrhosis in both industrialized Western countries and Asia [10], and appears to be on the rise in comparison to other causes. For example, in a retrospective study analyzing the evolution of cirrhotic etiologies in Eastern India from 2005 to 2017, the proportion of alcohol-associated cirrhosis increased by 26% during this period of time [11].

Extrahepatic Mechanisms of Hepatocarcinogenesis in Steatotic Liver Disease

Insulin Resistance

Insulin resistance and type 2 diabetes have been determined to be independent risk factors for HCC in patients with NAFLD [12,13]. In a population-based case-control study utilizing SEER-Medicare records [14], analysis of 2061 patients with HCC revealed that out of 2061 patients diagnosed with HCC, 43% had concurrent diabetes, a significantly higher proportion compared to the 19% in the non-cancer control group. This association persisted even when accounting for other known HCC risk factors such as hepatitis C and B infections, ALD, and hemochromatosis, with diabetes imparting a threefold increase in the risk for HCC. A study conducted at the Mayo Clinic in 2020 [15] aimed at further understanding the link between diabetes and HCC risk. Out of 354 patients with Non-alcoholic steatohepatitis (NASH) and cirrhosis treated between 2006 and 2015, 71% struggled with diabetes. In the same study, diabetes was found to be a significant independent factor for the increased likelihood of HCC development, with a hazard ratio (HR) of 4.2 and a 95% confidence interval

(CI) of 1.2–14.2 ($p = 0.02$). Additionally, each decade increase in age (HR = 1.8; 95% CI 1.2–2.6; $p < 0.01$) and a lower level of serum albumin (HR = 2.1; 95% CI 1.5–2.9; $p < 0.01$) were associated with higher HCC risk. However, other metabolic factors such as body mass index (BMI), hyperlipidemia, and hypertension did not show a significant association with the risk of HCC.

Obesity, Diet and Physical Activity

The connection between obesity and cancer deaths, including HCC, is well-established. A previous study found that individuals with BMI between 30.0 and 34.9 had a 1.90 times higher risk (95% CI 1.46–2.47) of developing liver cancer, which increased to 4.52 times (95% CI 2.94–6.94) for those with BMIs between 35.0 and 39.9 [16]. The connection between obesity, liver cancer, and the impact of lifestyle interventions on liver cancer risk has been further investigated in both animal and human studies. A study pointed out that mice fed a high-fat diet (HFD) for nine months developed significantly more liver tumors than those on a regular, standard diet [17]. These tumors appeared larger in size, a phenotypic outcome linked to higher levels of proinflammatory cytokines interleukin (IL)-6 and tumor necrosis factor (TNF), as well as activation of the cancer-related STAT3 transcription factor [17]. A separate study explored whether the consumption of certain nutrients, specifically sugar or fat, could promote the development of HCC, regardless of the presence of obesity [18]. The findings indicated that mice on a high-sugar diet exhibited a higher incidence of liver tumors but fat consumption did not seem to correlate with tumor development, indicating the potential role that sugar metabolism exclusively plays in the development of diet-induced liver tumors [18]. In contrast, physical activity appears to have a protective effect in the HCC context. An animal study attempted to explore the impact of physical activity on tumorigenesis, assigning mice on a standard diet containing 10% fat content to either a sedentary regimen or an exercise regimen that involved treadmill running for an hour daily [19]. Increased physical activity markedly reduced both the number of tumors per liver and the total volume of tumors in animals on the exercise regimen at the end of 32 weeks. While exercise did not alter steatosis or the histological NAFLD activity score (NAS), it did suppress tumor cell growth and activated the 5' adenosine monophosphate-activated protein kinase (AMPK) pathway, leading to reduced mechanistic target of rapamycin (mTOR) kinase activity. These findings are supported by evidence from human epidemiological studies. By analyzing data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study, which included over 467,000 participants from 10 countries followed for an average of 14.9 years, researchers observed that participants who were physically active had an HR of 0.55 (95% CI 0.38–0.80) for developing HCC compared to their sedentary counterparts [20]. Waist circumference and BMI appeared to account for approximately 40% and 30%, respectively, of the link between physical activity and HCC risk. More pronounced effects were noted in those who engaged in vigorous physical activity for more than two hours weekly, with an HR for HCC of 0.50 after adjusting for confounders. Overall, individuals with high levels of physical activity had a 45% reduced risk of HCC, and those who consistently performed vigorous exercise had a decreased risk of 50%.

Gut Microbiota

Dysbiosis in the gut has been correlated with the development of obesity and SLD across numerous studies [21–31]. Emerging evidence has lent increasing support to a microbiome component in liver cirrhosis, which correlates with liver disease severity [32,33]. There is also burgeoning evidence indicating that the gut microbiota plays a role in the development of HCC. Dysbiosis contributes to chronic liver inflammation, provokes immune system dysregulation by altering immune cell function and triggering cytokine production, and induces metabolic disruptions that collectively create a hepatic pro-carcinogenic niche [34,35]. Significant differences are seen in microbial populations between non-cirrhotic individuals and those with cirrhosis, and further distinctions are seen in cirrhotic patients with HCC, suggesting a potential stepwise alteration in gut flora in pace with liver disease progression [36,37]. For example, in a study comparing the gut microbiota of 61 patients divided into NAFLD-related cirrhosis and HCC group, NAFLD-related cirrhosis without HCC group, and healthy controls, the researchers found that patients with HCC showed increased levels of fecal calprotectin [36]. Additionally, the HCC group exhibited higher quantities of *Bacteroides* and *Ruminococcaceae*, but with lower levels of *Bifidobacterium* [36]. Moreover, a murine model study illuminated that disrupting the gut microbiota balance using antibiotics and gut sterilization could significantly reduce the likelihood of HCC development in obese mice, indicating a preventive but not therapeutic effect of these approaches on established tumors [34]. Therapeutic strategies aimed at modifying the gut microbiota present a novel avenue harnessing the modulation of the gut-liver axis for HCC management. Probiotic, prebiotic, and synbiotic interventions, designed to restore a healthy microbiome balance, have the potential to attenuate hepatic inflammation and modulate the immune response, thereby reducing oncogenic stimuli in the liver [38,39]. Furthermore, fecal microbiota transplantation is emerging as a potential therapy, with studies suggesting its efficacy in dysbiosis correction, which subsequently imparts positive effects on liver function and inflammation modulation [40].

Ethnicity

According to multiple studies, the occurrence and severity of MASLD vary across different racial or ethnic groups [41,42]. A study by Huang *et al.* [43], based on the National Health and Nutrition Examination Survey (NHANES) which is a cross-sectional study conducted by the US National Center for Health Statistics, showed that the prevalence of NAFLD was the highest in the Hispanic population (37.0%) and lower in the non-Hispanic Black population (24.7%) [43].

A systemic meta-review by Rich *et al.* [41] attempted further analysis of the comparative risk of NAFLD across different racial groups, effectively calculating the NAFLD likelihood ratios of one racial group to another. This analysis revealed a pooled relative risk (RR) of 1.47 (95% CI 1.35–1.61) for the Hispanic population, which has a higher susceptibility to NAFLD. Conversely, for high-risk individuals, such as those with diabetes or obesity, the Black population demonstrated a lower risk of developing NAFLD compared to the White population, with a pooled RR of 0.85 (95% CI 0.75–0.97) [41]. These observed ethnic differences in NAFLD prevalence may be explained by lifestyle, dietary habits, comorbidity profiles, as well as genetic factors. For example, the Hispanic population in the United States has a higher prevalence of the *PNPLA3* I148M mutation, which is known to increase liver disease and cancer development risk, and a low prevalence of *HSD17B13* predicted loss-of-function variants, which is known to reduce liver disease risk [44].

Gender

Estradiol is the most common type of estrogen found in the bloodstream, primarily produced and released by the ovaries in women before menopause [45]. Research has consistently linked the reduction of estradiol, resulting from natural or surgical menopause, with a heightened risk of cardiovascular diseases and hyperlipidemia, insulin resistance, glucose intolerance, hypertension, and visceral fat accumulation [46,47]. All of these conditions are associated with MASLD [48]. The prevalence of NAFLD appears to be higher in men than in women during their reproductive age, while the prevalence of NAFLD among women after menopause is superior to that of men [49]. Furthermore, it has been found that women with Turner's syndrome (thus lacking endogenous estrogen production) have a higher risk of NAFLD than healthy controls [50]. Recent studies have shown that the risk of developing HCC in NAFLD patients is higher in postmenopausal women than in premenopausal women and men, suggesting an important role of estrogen in slowing cancer development [49,51]. However, a population study in western Switzerland seems to contradict these loosely established perception as the proportion of NAFLD- and MAFLD-HCC in the region has increased significantly over the past 25 years, particularly in women, driving an increase in overall HCC incidence [52]. This possibly suggests that the gender effect is much more complex than previously thought, owing to the potential HCC incidence rise among women [52]. However, these studies are epidemiological in nature, without providing mechanistic evidence on the potential protective action of estrogen in liver.

Alcohol

Alcohol is an independent risk factor for HCC development [53,54], with an RR of 2.07 for heavy drinkers compared to non-drinkers. Prolonged excessive alcohol consumption causes steatosis, steatohepatitis, and cirrhosis. Several mechanisms are implicated in the process of alcohol-mediated hepatocarcinogenesis. As a crucial ingredient in most alcoholic drinks, ethanol is converted by alcohol dehydrogenase from acetaldehyde, a substance that is toxic to proteins, causes irreversible DNA damage, and influences methyl transfer. Ethanol results in DNA hypomethylation, which is linked to changes in gene expression, impacting the activity of oncogenes and tumor suppressor genes [54,55]. Additionally, oxidative stress resulting from the buildup of reactive oxygen species (ROS) further destroys cellular components by lipid peroxidation and contributes to DNA mutations through the creation of adducts and the disruption of DNA repair mechanisms [55]. This is compounded by the iron and lipid accumulation seen in ALD which further participates in ROS accumulation and potentiates the oxidative stress [54]. Alcohol promotes inflammation via the translocation of gut bacteria and lipolysaccharides, which trigger the pro-inflammatory immune cascade [56]. Alcohol also causes alterations in immune responses, promotes chronic inflammation, and disrupts the transfer of methyl groups, thereby affecting gene expression [54,55]. Individual genetic differences may influence how susceptible a person is to developing HCC in the context of ALD [54].

Smoking

Although smoking is not traditionally considered a direct risk factor for MASLD, emerging evidence suggests that it may exacerbate the progression of MASLD to HCC [57]. Smoking is associated with systemic inflammation, oxidative stress, and insulin resistance, all of which are underlying mechanisms implicated in the pathogenesis of MASLD and may synergistically interact with other risk factors of HCC, such as obesity, diabetes, and alcohol consumption, further increasing the overall risk in susceptible individuals. In a study using data from the Korean nationwide health screening database spanning from 2001 to 2015 which analyzed 283,088 subjects, including 110,863 MAFLD patients and 172,225 controls, active smokers among the MAFLD patients were found to exhibit a 24% increased risk of HCC compared to non-smokers (95% CI 1.08–1.41) [57]. In the control group, the increased risk associated with smoking was lower, with a 7% increase

in HCC risk (95% CI 0.89–1.30). Interestingly, the study found that male smokers had increased incidences of both HCC and CVD, while female smokers showed an increased risk of CVD only.

Telomere Shortening

Telomeres are repeated DNA sequences that function as protective caps at the ends of chromosomes to protect essential DNA from shortening during cell division, particularly in most adult cells, because of the inactivation of the *TERT* gene, which encodes telomerase [58,59]. Shorter telomere length appears to be correlated with more severe fibrosis in NAFLD patients, independently of age [58,60]. Telomere dysfunction not only contributes to the progression of SLD but also plays a crucial role in hepatocarcinogenesis. Shortened telomeres can result in chromosomal instability, genomic aberrations, and activation of oncogenic pathways, ultimately fostering the transformation of hepatocytes into cancerous cells [59]. In HCC cell lines, the use of antisense oligonucleotides effectively silenced *TERT* expression, particularly in cells that were rapidly divided and poorly differentiated. Administering treatment over a period of 3 to 16 weeks halted cell proliferation due to telomere shortening, DNA damage, and the initiation of apoptosis [59]. These therapeutic effects were recapitulated in a xenograft mouse model, supporting the potential of telomerase-targeted interventions as a promising strategy for HCC therapy [59].

Potential Extrahepatic Strategies to Reduce HCC Risk in Patients with SLD

Pharmacological Interventions

Currently, the pharmacological strategies for patients with alcohol use disorder (AUD), the main precipitating factor for ALD, remain limited. Naltrexone is considered the first-line treatment for patients with moderate or severe AUD, but it is not recommended in patients with acute hepatitis or hepatic failure, with its usage limited to patients with advanced alcoholic liver disease [61]. Acamprosate is a reasonable alternative first-line treatment in patients who have a contraindication to naltrexone. A 2010 Cochrane database systematic review analyzing 24 randomized controlled trials with 6915 participants found that compared to placebo, acamprosate significantly reduced the risk of drinking (RR = 0.86, 95% CI 0.81–0.91) and increased the cumulative abstinence duration (mean deviation [MD] = 10.94, 95% CI 5.08–16.81). However, the impact on secondary outcomes such as heavy drinking, which is directly linked to increased liver toxicity and HCC risk, did not reach statistical significance [62]. Another mainstay drug, disulfiram, may also be used in alcohol cessation, but clinical studies have shown mixed outcomes regarding the effectiveness of disulfiram in maintaining alcohol abstinence, due to a low adherence rate among patients [63].

Statin use has been associated with a decreased HCC risk in several studies [64]. A recent observational study in Denmark employing data from the Danish National Health Registry found that the use of statins for 5 years reduced the risk of HCC by 33%, as well as a decreased incidence of death in patients without HCC by 31% [65]. While the study is limited by its observational nature, and likely possesses an unidentified confounder in its analysis, it demonstrates the considerable potential of statins, prompting randomized controlled trials to validate and standardize their prophylactic use for HCC in ALD.

The pharmacological landscape for MASLD also remains limited (Table 1, Ref. [20,64,66–69]), with most available drugs targeting features of metabolic syndrome. Findings from several studies support the protective effect of statins in individuals at elevated risk for HCC [70,71], especially those carrying the *PNPLA3* I148M genetic variant [72]. In individuals without this variant, statin usage exhibited a correlation with lower incidences of steatosis, steatohepatitis, and significant fibrosis, exhibiting a dose-response relationship. This aligns with prior studies indicating statins may decrease HCC risk in diabetic patients, potentially due to their anti-inflammatory properties through Janus kinase (JAK) inhibition pathways [73].

Despite the widespread use of glucagon-like peptide-1 (GLP-1) receptor agonists in obese patients, phase 3 clinical trials showing their hepatoprotective effects in these patients are still underway [74]. A murine study has demonstrated the potential of GLP-1 receptor agonists in preventing the development of HCC in mice with diabetes and NASH [67]. In this study, mice with streptozotocin- and high-fat diet-induced diabetes and NASH were subcutaneously treated with liraglutide or saline (control) for 14 weeks. Herein, liraglutide was found to completely suppress hepatocarcinogenesis in the mouse population, whereas HCC was observed in all control mice (average tumor count, 5.5 $\pm$ 3.87; average tumor size, 8.1 $\pm$ 5.0 mm) [67]. An interesting study utilizing human recombinant transforming growth factor alpha (TGF-α) found that GLP-1Ra, via cAMP production, elicits suppressive impact on TGF-α- and Hepatocyte growth factor (HGF)-induced migration of HCC cells through the inhibition of Stress-activated protein kinases (SAPK)/Jun amino-terminal kinases (JNK) signaling pathway [75]. Interestingly, semaglutide also appears to reduce alcohol intake and prevent relapse-like drinking in a murine study. Semaglutide attenuates the ability of alcohol to cause hyperlocomotion and to elevate dopamine in the nucleus accumbens in mice [76], representing a potentially promising therapeutic approach for patients with MetALD and ALD, although human studies to validate these results are still underway.

The potential of aspirin in preventing various cancers, including HCC, is also under investigation. Aspirin may inhibit liver disease progression and the onset of HCC by suppressing cyclooxygenase-2, influencing bioactive lipids,

Table 1. Overview of key studies assessing the potential of extrahepatic strategies to reduce HCC risk in patients with SLD.

Intervention	Setting	Type of study	Effect size	Reference
Metformin	Systematic review of four population-based and four hospital-based populations	Eight observational studies, four case-control studies, four cohort studies, two retrospective cohorts and two prospective cohorts	OR 0.468; 95% CI 0.275–0.799, ($p = 0.0053$)	Cunha *et al.* [66]
Statins	Systematic review and meta-analysis	All studies were observational (2 nested case-control studies, 11 cohort studies)	HR = 0.57; 95% CI 0.52–0.62, $I^2 = 42\%$ ($\chi^2 = 20.67$, df = 12, $p < 0.06$)	Wong *et al.* [64]
GLP-1Ra	Murine study	Experimental study	Mean lesion number in liraglutide vs control group: 5.5 ± 3.9, $p < 0.01$; mean lesion size, 8.1 ± 5.0 mm, $p < 0.05$	Kojima *et al.* [67]
Aspirin	National population-based retrospective study	Cohort study	HR 0.69; 95% CI 0.62–0.76, ($p < 0.001$)	Simon *et al.* [68]
Coffee	Meta-analysis	8 case-control studies	RR 0.65; 95% CI 0.59–0.72	Kennedy *et al.* [69]
Increased physical activity	Pan-European prospective study	Cohort study	HR 0.50; 95% CI 0.33–0.76, ($p < 0.001$)	Baumeister *et al.* [20]

Abbreviations: OR, Odds ratio; CI, confidence interval; RR, relative risk; df, degrees of freedom; SLD, steatotic liver disease; HR, hazard ratio; GLP-1Ra, glucagon-like peptide-1 receptor agonist.

and impacting platelet degranulation [77]. Utilizing data from the Taiwan's National Health Insurance Research Database, a study that compared the incidence of HCC in 33,484 NAFLD patients who took aspirin daily for at least 90 days with that in 55,543 NAFLD patients who did not receive antiplatelet therapy [78], found a significantly lower 10-year cumulative incidence of HCC in the aspirin-treated group compared to the untreated group (0.25% [95% CI 0.19–0.32%] vs. 0.67% [95% CI 0.54–0.81%]; $p < 0.001$). This reduction in HCC risk was especially pronounced in high-risk patients aged 55 or older with elevated serum alanine aminotransferase levels (3.59% [95% CI 2.99–4.19%] vs. 6.54% [95% CI 5.65–7.42%]; $p < 0.001$). The protective role of aspirin for HCC in NAFLD patients reflects a similar benefit demonstrated in viral hepatitis patients [68].

Increased coffee consumption may also be linked to a decreased risk of HCC development. In a meta-analysis by Kennedy *et al*. [69], data from over 2 million participants showed that an additional two cups of coffee per day were linked to a 35% reduction in HCC risk, with a weaker association observed in higher-quality cohort studies compared to case-control studies. This reduction in HCC risk was evident regardless of liver disease stage. However, due to other limitations and a dearth of randomized controlled trials, supporting evidence in this respect remains scanty.

A growing line of evidence suggests that metformin usage among individuals with diabetes is linked to a lower occurrence of HCC [79–83]. This protective effect of metformin is believed to stem from the activation of AMPK, a mechanism that is also involved in the positive impact of physical exercise on HCC prevention [84]. A recent systematic review analyzing metformin's role in protecting against HCC in diabetic patients found a correlation between metformin use and a decreased incidence of HCC when contrasted with therapies excluding metformin [66]. Specifically, a meta-analysis of the case-control studies revealed an odds ratio of 0.468 with a 95% CI of 0.275–0.799, highlighting the inverse relationship between metformin usage and the risk of developing HCC. Conversely, the use of insulin was found to correlate with a higher incidence of HCC.

Role of Bariatric Surgery

Bariatric surgery is the current most effective NASH intervention demonstrating significant clinical improvement across studies, as well as being the only medical treatment option offering significant histological improvement [85–87]. Several studies also support the role of bariatric surgery in HCC prevention [88,89]. In a comprehensive analysis of 3410 bariatric surgery patients and 46,873 matched obese controls, a significantly lower rate of new-onset NASH and HCC in the surgery group (0.05% vs 0.34%, $p = 0.03$) after an average of 7.1 years was noted [88]. A retrospective cohort study including 98,090 patients in which 34.1% received bariatric surgery found that patients who underwent bariatric surgery had a 25% lower risk of obesity-related cancer compared to those who did not undergo surgery [90]. Additionally, among patients who underwent surgery, those with cirrhosis had significantly lower risks for both cancers of any origins and obesity-related cancer compared to those without cirrhosis. Using fully adjusted models focusing on specific cancer types, researchers found the significantly lower risk of HCC (by 52%) among patients who underwent surgery compared to those who did not.

Improving Risk Stratification and Screening for HCC in SLD Patients

Risk Stratification for HCC in MASLD

The occurrence of HCC among patients with non-cirrhotic NAFLD is relatively uncommon, with an incidence rate estimated at 0.03 per 100 person-years [51]. The vast majority of NAFLD-HCC cases develop in the context of advanced fibrosis [91], which has driven the currently adopted framework of HCC surveillance designed to target these patients [92]. However, NAFLD remains the predominant risk factor of HCC in the absence of cirrhosis [93–95] and given the high prevalence of NAFLD, even the small proportion of NAFLD patients that develop to HCC translates to a large overall at-risk population. Thus, there remains a critical issue in identifying individuals with NAFLD who have a heightened risk of HCC and who should be included in more rigorous surveillance protocols. Non-invasive tools such as the FIB-4 index and the NAFLD fibrosis score, which utilize standard laboratory tests and clinical information, hold promise in HCC risk assessment [96,97]. Advancements in genetics and metabolomics have also underscored the importance of utilizing genetic indicators in risk determination. Integrating single nucleotide polymorphism (SNP) data such as *PNPLA3*, *TM6SF2*, and *HSD17B13* into a risk assessment tool has gained traction in predicting the likelihood of HCC development. A specific mutation in the *MBOAT7* gene has been associated with an increased risk of HCC in non-cirrhotic individuals with NAFLD [73]. Gene expression profiles have also demonstrated potential, with liver tissue-based signature that is indicative of HCC onset in NAFLD patients being a prominent example utilizing this concept. This has led to the development of a serum panel that predicts HCC risk independently of clinical risk factors [98].

Extrahepatic Elements Influencing Radiological Aspects of HCC Surveillance

Early detection of HCC is a critical factor influencing prognosis, as numerous studies have shown that HCC screening leads to enhanced survival rates in cirrhotic patients [99]. Professional guidelines consistently recommend ultrasound, either alone or in combination with alpha-fetoprotein (AFP) detection, as the primary approach for HCC screening in individuals with cirrhosis. However, one

significant critique of ultrasound-based screening for HCC is its inconsistent sensitivity, which can vary widely from 32% to 89% when utilized alone [100]. Several studies have examined the factors that pose severe limitations to this modality. In a retrospective study including 941 patients aiming to identify the variables contributing to ultrasound quality, ultrasound results from 20% of the patients were inadequate to rule out HCC, particularly in the case of obesity and/or alcohol-related cirrhosis [101]. A retrospective cohort study including over 2000 cirrhotic patients confirmed these results [102], demonstrating that obesity and excessive alcohol consumption are directly correlated to a limited ultrasound visualization for HCC nodules; such as patients with elevated alcohol consumption (OR 2.69, 95% CI 1.50–4.83), or patients with obesity class II (OR 4.57, 95% CI 2.06–10.1) or class III (OR 9.00, 95% CI 4.21–19.2) [102]. Contrast-enhanced computed tomography has been proposed as an alternative for HCC screening [99]; however, its utilization is constrained by several limitations, such as radiation exposure, contrast media risks, and limited accuracy in patients who may end up with poor-quality ultrasound results. Magnetic resonance imaging (MRI) represents the gold-standard alternative, featuring significantly higher sensitivity compared to ultrasound in early screening of HCC (96% vs 63 %) [103] and better visualization of liver parenchyma in MASLD-related cirrhosis (OR = 9.00, $p = 0.04$) [104]. For these reasons, the implementation of MRI has been recommended in patients with inadequate surveillance on ultrasound due to obesity in order to yield more comprehensive [99] and sensitive assessments [105]. However, MRI remains a costly and less available option, feasible only in few resource-rich countries [99].

Multiple studies have also shown promising results on the use of abbreviated magnetic resonance sequences (aMRI), which may be a useful alternative to liver ultrasound in selected population with extrahepatic features such as obesity that can diminish the sensitivity of routine screening procedures to a large extent. Indeed, aMRI exhibits a multifaceted range of benefits. This approach is a cost-effective alternative to ultrasound given the lower cost involved and shorter examination time required as compared to traditional MRI, while demonstrating a high sensitivity in HCC detection [103,106–111].

Discussion

In this review, we discuss some of the significant challenges in early HCC detection, particularly among patients with SLD. The limitations of current screening modalities, such as variable ultrasound sensitivity and the barriers to accessing advanced imaging techniques such as MRI, highlight the critical need for improved diagnostic strategies. This necessitates further research into non-invasive, cost-effective, and widely accessible screening tools that can accommodate the complexities of SLD-related HCC surveillance.

Despite the significant strides made in understanding and managing HCC within the context of SLD, more research into novel, effective prevention and treatment strategies are still warranted due to the ever-growing disease burden. Addressing the modifiable risk factors of metabolic syndrome through lifestyle interventions, among others, presents a promising pathway to curtail the rising tide of HCC. Similarly, enhancing early detection through improved risk stratification and screening methodologies remains paramount in improving HCC prognosis and patient outcomes.

Conclusions

The mounting global prevalence of SLD and particularly MASLD, paralleling the obesity epidemic, signifies an exigency for addressing the modifiable risk factors to mitigate the increasing HCC incidence. Of note, the heterogeneity of HCC risk across different demographic groups underscores the complex interplay between genetics, lifestyle, and environmental factors in disease development. Adding to the intricacies of the multifaceted nature of HCC risk are contributing factors such as insulin resistance, obesity, diet, physical activity, and gut microbiota composition, each playing distinct roles in hepatocarcinogenesis. Particularly notable is the differential risk posed by metabolic conditions across racial and ethnic groups, suggesting the potential influence of genetic predispositions and socio-cultural lifestyle patterns on disease susceptibility.

The evolving understanding of extrahepatic mechanisms in HCC development, such as the role of gut-liver axis and systemic metabolic dysregulation, has spawned the formulation of novel therapeutic avenues and preventative strategies. For instance, the manipulation of gut microbiota through dietary interventions, probiotics, or fecal microbiota transplantation opens new avenues for reducing oncogenic stimuli in the liver. Additionally, the protective effects of physical activity against HCC, as well as the nuanced impacts of gender and hormonal status on disease risk, underscore the importance of personalized and holistic approaches to HCC prevention and management.

Availability of Data and Materials

Data supporting the findings of this study are available within the paper.

Author Contributions

LZ: conception and design, writing of the manuscript and is the article guarantor. JF: conception and design, cowriting of the manuscript and critical revision of the manuscript for important intellectual content. NVV: conception and design, cowriting and revision of the manuscript for important intellectual content. NG: concep-

tion and design, cowriting and revision of the manuscript for important intellectual content. All authors contributed significantly to editorial changes of important content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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