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Review

An updated overview on hepatocellular carcinoma in patients with Metabolic dysfunction-Associated Steatotic Liver Disease: Trends, pathophysiology and risk-based surveillance

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ABSTRACT

Hepatocellular carcinoma (HCC) is a relevant complication occurring in individuals with advanced Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD). Recent epidemiological data suggest an alarming increase in the HCC burden worldwide, with a relevant proportion attributable to MASLD (up to 38 %), either in cirrhotic or non-cirrhotic livers. In view of the changing landscape of metabolic syndrome as "silent pandemic", this narrative review aims to provide an updated picture of the burden of HCC in individuals with MASLD. In the complex pathophysiological pathways linking insulin resistance to MASLD and cardiometabolic syndrome, metabolic inflammation appears a relevant driver of systemic as well as organ-specific complications. Novel insights from the field of immunology, gut-derived liver damage, and association with extra-hepatic cancers will be discussed. Finally, strategies for risk-based HCC surveillance (circulating biomarkers, prognostic models and polygenic risk scores) will be provided and the potential impact of novel drug targeting fibrosing Metabolic dysfunction-Associated Steatohepatitis (MASH) on incident HCC will be discussed.

1. Introduction

Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) is the leading chronic liver disease, affecting over 30 % of adults [1]. MASLD is tightly linked to metabolic syndrome, especially obesity and type 2 diabetes, contributing significantly to healthcare costs [2–5]. The recent updates in disease nomenclature shift from the term NAFLD (Non-Alcoholic Fatty Liver Disease) to MASLD, emphasizing its connection to cardiometabolic health [6,7]. MASLD is a complex, heterogenous disease, driven by insulin resistance in tissues like visceral fat, skeletal muscle, and the pancreas, resulting in liver fat build-up due to increased free fatty acids and pro-inflammatory adipokines [8,9]. The progressive form, metabolic dysfunction-associated steatohepatitis (MASH), escalates liver damage, potentially leading to cirrhosis and increasing the risk of hepatocellular carcinoma (HCC) [10–12].

The risk of HCC is independent of portal hypertension and is mostly dependent on the architectural subversion of regenerative cirrhotic nodules. Identification of fibrosis stage is crucial to assess the severity of MASH and its progression to cirrhosis. Currently, diagnosis of MASH relies on liver biopsy, but non-invasive tests (NITs) like liver stiffness measurement (LSM) and Fibrosis-4 (FIB-4) can be used as surrogates for the identification of severe fibrosis/early cirrhosis [13,14]. HCC risk is

Abbreviations: MASLD, Metabolic dysfunction-Associated Steatotic Liver Disease; T2DM, type 2 diabetes mellitus; MASH, metabolic dysfunction-associated steatohepatitis; HCC, hepatocellular carcinoma; US, United States; MELD, Model for End-Stage Liver Disease; NAFLD, Non-Alcoholic Fatty Liver Disease; HR, hazard ratio; OR, odds ratio; PAMPs, pathogen-associated molecular patterns; LPS, lipopolysaccharide; PPAR, peroxisome-proliferator-activated receptor; PKC1, protein kinase C1; MRI, magnetic resonance imaging; CTP, Child Turchotte Pugh; AFP, α-fetoprotein; BMI, Body Mass Index; PIVKA-II, Protein induced by vitamin K absence or antagonist II; DCP, Des-γ- carboxy-prothrombin; AUC, area under the curve; NITs, Non-invasive Tests; FIB-4, fibrosis-4 score; NFS, Non-Alcoholic Fatty Liver Disease Score; LSM, liver stiffness measurement; GWAS, genome-wide association studies; SNP, single nucleotide polymorphisms; PNPLA3, Patatin-like phospholipase domain-containing protein 3; TM6SF2, Transmembrane 6 superfamily member 2; MBOAT7, Membrane bound O-acyltransferase domain containing 7; GCKR, Glucokinase Regulator; HSD17B13, Hydroxysteroid 17-Beta Dehydrogenase; PRS, polygenic risk score.

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also notable, even before cirrhosis onset, particularly in those with advanced fibrosis (F3 stages). Thus, there is a critical need for early HCC prediction tools and personalized surveillance. The increasing prevalence of metabolic risk factors further underscores MASLD's silent progression and the importance of vigilant management to prevent severe liver outcomes. This review describes the current clinical impact of HCC in MAFLD and discusses the most important unmet needs for its effective management.

2. Epidemiology of HCC in MASLD: prevalence, incidence and trajectories

HCC is the fourth cause of death from cancer worldwide and the fifth cause of cancer-related disability [15,16] and will increase by 2030 in most countries. MASLD is projected to be the leading cause of HCC in Caucasian as well as Asian countries, in parallel with a modelled increase in MASH incidence of >50 % over the next ten years [17,18].

A US study from medical registries including almost 5000 HCC cases from 2004 to 2009 (Surveillance, Epidemiology and End Results [SEER]-Medicare databases) found a 14 % prevalence of MASLD-HCC, with a 9 % annual increase [19]. Recent data from Asia report a prevalence of MASLD-HCC of 12 %–30 % across countries, with a significant burden in non-obese individuals, suggesting strong genetic drivers of HCC [20]. The discrepancies in HCC prevalence are partially explained by the inclusion criteria of the studies (e.g. definition of MASLD or histological evidence of MASH), heterogeneity in numbers, and limited body of evidence coming from population-based studies as compared to case-control studies.

The annual HCC incidence in cirrhotic MASLD is reported to be 0.7–2.6 % [21], with an increase burden in older men, in subjects with T2DM and with concomitant alcohol intake [22–24]. A recent meta-analysis of 1.377.466 individuals with MASLD found an incidence rate of HCC of 3.39 per 1000 person-years, with a higher occurrence in patients with MASH, when compared to non-MASH ($p = 0.043$) [25]. A population-matched Swedish study of nearly 9000 biopsy-proven individuals with MASLD from 1966 to 2016 found a higher incidence of MASLD-HCC versus other aetiologies (adjusted hazard ratio [aHR] 17.08, 95 % CI 11.56–25.25), with a stepwise increase across disease stage (higher incidence in cirrhosis, 6.2 per 1000 person/years) and amplified by the presence of T2DM [26]. In one prospective study of 247 European, US and Australian patients with biopsy-proven MASLD-cirrhosis, the incidence of HCC was 2.4 % after a mean follow up of 85 months [27].

A Swedish population-based longitudinal study found 2.245 incident cases of HCC in the time frame 2003–2018, of which 22 % attributable to MASLD (by ultrasound-based steatosis and metabolic co-factors), 26 % to HCV, and 19 % to alcohol-related liver disease [28].

Currently, MASLD-related HCC accounts for 1 % to 38 % of total HCC burden across countries [29]. In a large retrospective study involving 14 countries from 2005 to 2012 (the BRIDGE study), MASLD etiology accounted for 12 % of the total HCC cases in North America, 10 % in Europe, 1 % in China, 5 % in Taiwan, 6 % in South Korea, and 2 % in Japan [30]. In agreement with the previous evidence of MASLD as the fastest growing cause of liver transplant for HCC in the US [31] and the leading cause of liver transplant among the elderly [32], the updated US Scientific Registry of Transplant Recipients (SRTR 2013–2022) revealed a significant reduction of HCC burden due to hepatitis C virus (from 60 % to 27 %) and a greater increase in the HCC burden due to MASLD (from 10 % to 31 %) [33]. Currently, MASLD-HCC in US appears to be the second leading cause for liver transplant in males and the first cause in females [34].

A recent multicentric Italian study of 6882 patients with HCC consecutively enrolled from 2002 to 2019 (ITA.LI.CA database), attributed to MASLD (by ultrasound-based steatosis and metabolic co-factors) 68.4 % of cases; MASLD-related HCCs were larger, often with extra-hepatic metastases, and with a more advanced liver disease [35].

Diagnosis of MASLD-HCC occurs at an older age and usually at a later stage than viral-related HCC, with a higher risk of HCC-related death [36]. This is consistent with the lack of awareness of this liver disease in either primary care or non-hepatological specialty settings. Data obtained from the US multicenter HCC transplant consortium from 2002 to 2013 pointed out that adult liver transplant recipients with MASLD were less likely to receive pre-transplant locoregional therapy (63.3 % versus 72.9 % non-MASLD, $p < 0.001$) and had higher MELD values (15 versus 13, $p < 0.001$). Additionally, patients with MASLD undergoing liver transplant were more likely to have incidental HCC on the explanted liver (19.4 % versus 10.4 %, $p < 0.001$), although not affecting the cumulative incidence of HCC recurrence between MASLD and non-MASLD transplanted patients [37].

2.1. Impact of moderate alcohol consumption on the risk of HCC in subjects with cardiometabolic risk factors

Following the introduction of the metALD subtype (Metabolic dysfunction-Associated Steatotic Liver Disease with Increased Alcohol Intake - 30-60 g/day for men and 20–50 g/day for women) in the new classification of steatotic liver disease [6], the impact of small daily alcohol intake in the HCC onset has been recently investigated. In a recent Korean nationwide study, 0.9 % developed primary liver cancer during a median follow up of 3.227.176 person-years, of which 1.1 % in individuals with MASLD and 1.3 % in those with metALD. Both types of steatotic liver disease (defined by Fatty Liver Index ≥60) were significantly associated with HCC incidence: HR for MASLD 1.65 (95 % CI 1.44–1.88), and HR for metALD 1.87 (95 % CI 1.52–2.29) [38]. In a health screening program performed in Taiwan from 1997 to 2013, 1392 cases of HCC were found out of 332.175 participants. The HRs for HCC risk in individuals with MASLD, metALD and alcohol-related liver disease (ALD) (all defined by ultrasound-based steatosis) were 1.92 (95 % CI 1.51–2.44), 2.91 (95 % CI 2.11–4.03) and 2.59 (95 % CI 1.93–3.48), respectively, highlighting the synergic harmful impact of alcohol and metabolic dysfunction [39].

2.2. HCC in non-cirrhotic MASLD

The evidence about HCC occurring in non-cirrhotic MASLD is less robust, in particular for the non-standardized surveillance for this population [40], but available data suggest that the risk is limited to subject with severe (F3) fibrosis only. The presence and severity of metabolic co-factors, especially T2DM, is a further risk factor. Overall, observational studies of non-cirrhotic MASLD have reported an incidence of HCC 0.1–1.3 per 1000 patient/year [41]. A recent nationwide real-world US study of >750.000 non-cirrhotic patients with MASLD found an incident rate of 0.05 per 1000 person-years over more than one million person-years of follow up [42]. According to a recent population-based US study of 392.000 patients with MASLD (defined by imaging-based steatosis and presence of T2DM), age > 65 years, increased transaminases, male gender, T2DM and smoking habit were independent predictors of HCC in non-cirrhotic MASLD (ORs 3.4 [95 % CI 2.47–4.59], 2.7 [95 % CI% 2.14–3.37], 2.6 [95 % CI 1.88–3.49], 1.56 [95 % CI1.15–2.11], and 1.7 [95 % CI 1.23–2.49], respectively) [43]. Further data from a recent multicentric Indian study of 5798 patients found that MASLD etiology was more frequently found in non-cirrhotic HCC (48.2 % of the overall HCC attributable to MASLD). When considering the metabolic co-factors, T2DM was found in 50.5 % of all non-cirrhotic HCC, as compared to 35.2 % of HCC in cirrhosis [44]. This is reported also in smaller, single-centre studies, where additional slight alcohol intake (210 g/week for men and 140 g/week for women) was an independent predictor (OR 4.9; 95 % CI 95%CI: 1.92–12.44) for non-cirrhotic HCC in MASLD [45]. Interestingly, a Swedish study of 1592 MASLD-HCC found HCC nodes in 37 % of non-cirrhotic subjects, larger and more prone to undergo liver resection rather than liver transplant compared to HCC nodes in cirrhotic livers (35 % versus 8 % liver

resection and 0 % versus 11 % liver transplant, all $p < 0.05$). In this study, T2DM was independently associated with increased mortality in both cirrhotic and non-cirrhotic HCC [46].

Taken together, these data mirror the alarming increase in MASLD and MASH burden across countries, highlighting once again the challenge of surveillance in both cirrhotic or at-risk cases (non-cirrhotic) on one side and the need for an effective MASLD treatment on the other side. In particular, the burden of metabolic co-factors, especially T2DM, and concomitant alcohol intake are synergic risk factors for pre-cirrhotic HCC. While waiting for definite approval of drug therapy for treating "fibrosing MASH", non-invasive tests to identify advanced fibrosis or cirrhosis are crucial. Early detection enables risk assessment for pre-cirrhotic or cirrhotic HCC, monitors treatment response, and reduces the likelihood of liver-related complications [47,48].

3. Pathophysiology

MASLD represents a unique entity across liver diseases, due to the connection between the liver and other organs or tissues in determining metabolic derangements [49].

Insulin resistance in key insulin-sensitive tissues (adipose tissue, skeletal muscle, pancreas) is a major determinant of liver disease onset and progression. In particular, visceral adipose tissue elicits intra- and inter-adipocyte inflammatory pathways, interfering with insulin metabolism. The resulting excessive delivery of free fatty acids to the liver, on one side cause steatosis by re-esterification into triglycerides in lipid droplets, and on the other enhances gluconeogenesis, worsening hyperglycaemia and compensatory hyperinsulinemia [50,51]. In addition, the excessive intake of industrialized fructose, one typical feature of the "Westernized" diet, is conveyed toward de novo lipogenesis in the liver, furtherly aggravating steatosis. In parallel, the excessive visceral adiposity promotes a systemic, low-grade "metabolic inflammation" through the release of proinflammatory cytokines from activated macrophage, which affects multiple organs and worsens insulin resistance [52]. The excess of free fatty acids in the liver causes lipotoxicity and oxidative stress that disrupt the physiological function of the endoplasmic reticulum, increase oxygen reactive species and exacerbate inflammation [53,54]. Lipid intermediates (e.g. ceramides, diacylglycerols) further interfere with glucose uptake and insulin sensitivity [9,55].

3.1. Metabolic inflammation and immune system impairment

Inflammation is one of the main drivers toward hepatic fibrogenesis, cirrhosis and portal hypertension (via capillarization of sinusoids). Chronic inflammation is sustained by the activation of the innate immune system and increase in cytokines levels including Interleukin-6 (IL-6), Interleukin-17 (IL-17) and Tumour necrosis factor-α (TNF-α). Oncostatin M, a pleiotropic cytokine of the IL-6 family, is selectively increased in MASLD-HCC in both murine models and in human-affected liver specimens [56]. Chronic inflammation is an early marker of MASH and a driver of hepatocyte DNA damage, whereas the adaptive immune system, raising in the context of active fibrogenesis and progressive disease, plays a role in the advanced MASH and in a major susceptibility to HCC. Apart from the above-mentioned mechanisms, a derangement in the adaptive immune system is also observed in MASH with advanced fibrosis, which favour carcinogenesis. [57–60]. This activation is of crucial relevance for intrahepatic immune surveillance, a key step in the development and propagation of early cancers. For example, $CD4^+$ T cells are responsible for senescence surveillance of pre-malignant hepatocytes and an impaired $CD4^+$ T-cell activity is relevant in promoting cancer in mouse models [61]. Conversely, data from pre-clinical models of MASH-induced HCC suggest that an immunotherapy-induced increase in CD8 T-cells did not lead to tumour regression, indicating an impairment in the tumour immune surveillance [62].

3.2. The role of gut-liver axis and bile acids composition

More recently, the emerging role of the gut-liver axis and the bile acid metabolism have shed light on potential liver disease and tumour drivers. Dysbiosis, commonly seen in patients on a "Westernized" diet, raises from the inflamed gut and impacts on the diversity and relative abundance of intestinal bacterial strains. In particular, a reduction in *Firmicutes* and relative increase in *Proteobacteria* (*Lachnospiraceae* and *Enterobacteriaceae* species) are associated with MASLD [63,64]. Dysbiosis in MASLD is connected with impaired gut barrier (the so-called "leaky gut") [65], considered an early event in MASH pathogenesis [66]. A dysfunctional gut barrier allows translocation of pathogen-associated molecular patterns (PAMPs) from dysbiosis. In mice fed with a high-fat diet, an increased translocation of lipopolysaccharide (LPS), a structural component of the Gram-negative bacterial stains, can boost liver inflammation and fibrosis by binding Toll-like receptors and subsequent cytokine production [67]. In a recent study, 5:2 intermittent feeding in MASH mice improved liver inflammation and halted HCC development via positive modulation of liver nuclear receptors (namely PPAR - peroxisome-proliferator-activated receptor, and PKC1 - protein kinase C1), corroborating the intersection between dietary/environmental factors and liver disease progression [68].

Bile acid composition and turnover are modulated by gut microbiota leading to marked differences in the bile acid pool [69]. High levels of bile acids, in particular deoxycholic acid and lithocholic acid, have been shown to induce HCC through direct DNA damage. Other bile acids, including cholic acid and chenodeoxycholic acid, can activate Farnesoid-X receptor (FXR). FXR is bile-activated nuclear receptor located in multiple tissues (liver, ileum, kidney, white and brown adipose tissue). It is involved in bile acid synthesis and modulation, as well as in key metabolic pathways (lipid metabolism, insulin and glucose homeostasis, and immune responses) [70,71], but its role in tumorigenesis is still controversial. An impaired FXR signalling can promote dysbiosis in obesity [72]. In mouse models with depleted *FXR*, spontaneous HCC development was observed after 15 months, while intestinal FXR activation could improve bile acid pool and metabolism, protecting against tumorigenesis [73]. In humans, FXR agonism has been shown to exert antifibrotic effects in the liver in a large, phase 3 randomized trial with high-dose obethicolic acid, following pre-clinical evidence on the suppression of FXR agonism-dependent bile acid reduction [74].

An overview of the main mechanisms involved in carcinogenesis in MASLD/MASH is reported in Fig. 1.

4. Risk-based surveillance of HCC

Patients with MASLD at risk of HCC should undergo personalized surveillance strategies according to their individual risk of HCC development [75] (Fig. 2). The EASL current guidelines recommend semi-annual abdominal ultrasound as the primary strategy for HCC surveillance while the risk in patients without cirrhosis is not deemed sufficiently high to justify a similar approach [75]. Nevertheless, the identification of a high-risk group of patients who must absolutely receive HCC surveillance and a low-risk group who may not need HCC surveillance at all would allow optimizing resources allocation, improving early HCC detection, and thus patients' survival. This approach holds true both in patients with cirrhosis and in subjects with severe (F3) fibrosis, where the risk is low but not negligible.

One main limitation of ultrasound-based surveillance is poor visualization of HCC nodules in a fatty, "foggy" liver. Cross-sectional MRI abdominal imaging is increasingly used for HCC surveillance in clinical practice, supported by the results of a recent meta-analysis including 15 studies (comprising 2807 patients, 917 with HCC) showing a pooled per-patient sensitivity and specificity of 86 % (95 % CI 84–88 %) and 94 % (95 % CI 91–96 %), respectively; in comparison to ultrasound, the sensitivity of abbreviated MRI was significantly higher (53 % vs. 82 %) [76,77]. However, the implementation in clinical practice of an

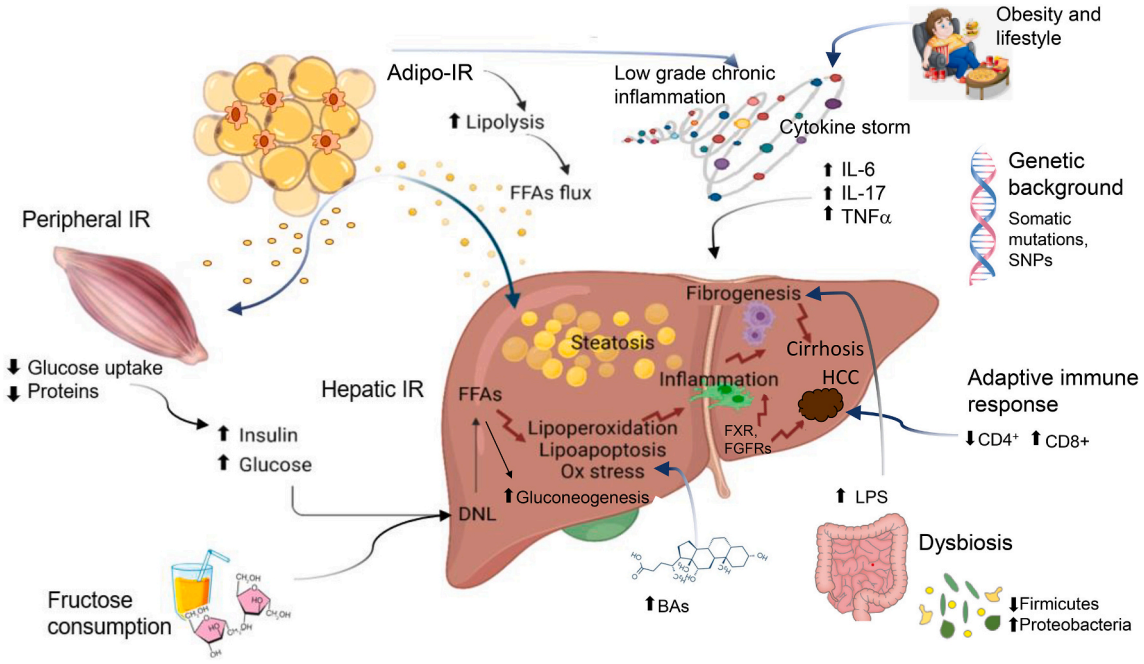

Fig. 1. Key pathophysiological steps in the development of Metabolic dysfunction-Associated Steatohepatitis (MASH) and hepatocellular carcinoma (HCC). Low-grade chronic metabolic inflammation in the setting of insulin resistance creates a fertile soil for HCC growth in MASLD. The cytokine storm induced by an inflamed adipose tissue promotes hepatic inflammation that in turn enhances fibrogenesis. High-fat diets and high carbohydrate intake (mainly fructose) can worsen the cytokine pattern and increase hepatic DNL, promoting lipoperoxidation. IR state leads to hyperglycaemia and compensatory hyperinsulinism establishing a vicious cycle that aggravates metabolic derangement.

An impaired adaptive immune response characterized by the decrease in $CD4^+$ T-cells, may favour carcinogenesis by blocking the inactivation of the oncogene Myc, thus favouring senescence and angiogenesis pathways. Moreover, $CD4^+$ T cells cooperate with the other innate immune cells (mainly new recruited monocytes but not resident-macrophage) in killing pre-malignant senescent hepatocytes. Conversely, an immunotherapy-induced increase in CD8 T-cells does not lead to tumour regression, indicating an impairment in the tumour immune surveillance. Changes in the gut microbiota composition, mainly in obese subjects, contribute to hepatic inflammation by increasing intestinal permeability, bacterial components translocation such as LPS, and activation of the toll-like receptors. Deoxycholic acid, a secondary BA predominantly produced by the gram-positive bacteria, can disrupt BA homeostasis, enhancing liver inflammation, fibrogenesis, and ultimately contributing to the development of HCC through DNA damage. Genetic background contributes to increase the risk of HCC, mainly through the *PNPLA3* rs738409 variant.

Abbreviations: Adipo-IR, adipose tissue insulin resistance; Bas, bile acids; DNL, de novo lipogenesis; FFAs, free fatty acids; FGFRs, fibroblast growth factor receptors; FXR, farnesyl X receptor; HCC, hepatocellular carcinoma; IL, interleukin; Hep-IR, hepatic insulin resistance; HSC, hepatic stellate cells; IR, insulin resistance; LPS, lipopolysaccharides; NKs, natural killer cells; Ox stress, oxidative stress; SNPs, single nucleotide polymorphisms; TNFα, tumour necrosis factor alpha.

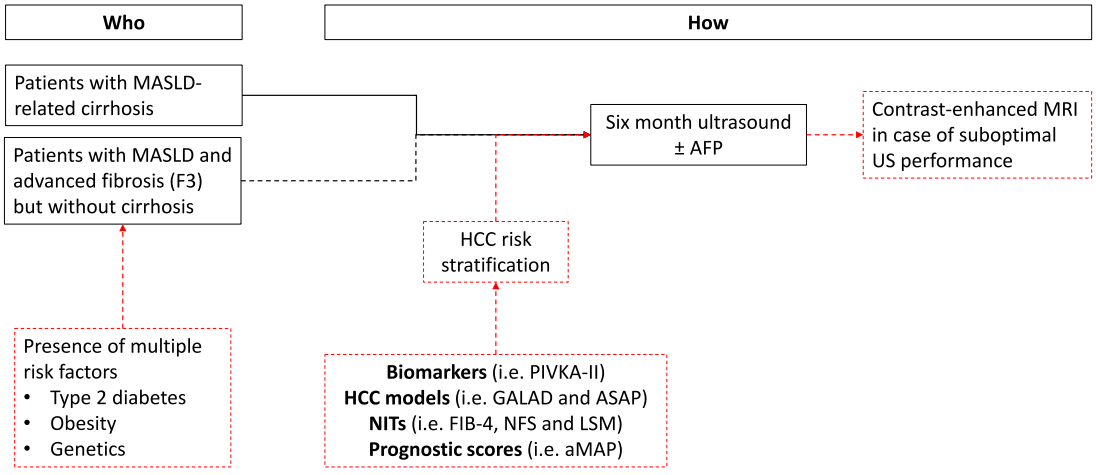

Fig. 2. Surveillance of patients with Metabolic-dysfunction Associated Steatotic Liver Disease (MASLD) at risk for hepatocellular carcinoma (HCC). In red, suggested tools for risk-based surveillance. Abbreviations: AFP: alpha-fetoprotein; FIB-4: Fibrosis-4 score; LSM: liver stiffness measurement; MRI: magnetic resonance imaging; NFS: Nonalcoholic Fatty Liver Disease Fibrosis Score; NITs: Non-Invasive Tests; PIVKA-II: Protein induced by vitamin K absence-II. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

abbreviated MRI surveillance strategy could be cost-effective only on selected high-risk patients. [75].

4.1. Biomarkers for risk-based surveillance of HCC

The effectiveness of serological markers of HCC for risk stratification in patients with MASH-cirrhosis is unclear. Alpha-fetoprotein (AFP) is the only biomarker approved for its use in clinical practice in combination with ultrasound. In a meta-analysis of 13,367 individuals, the combined use of AFP and ultrasonography was reported to increase the sensitivity for the detection the early-stage HCC from 45 % to 63 % ($p = 0.002$) [78]. The use of a combination of US with AFP has been recommended by some international guidelines [79,80] particularly in settings where MRI is not available. Several others biomarkers and prognostic scores are under investigation for the prediction and risk stratification of HCC development, although most are in early phases of evaluation, and still require validation in large phase III/IV biomarker cohort studies.

Data on HCC predictiveness are reported in Table 1 [81 – 110].

Overall, different biomarkers already showed promising results as novel potential tools for HCC-risk detection; serologic biomarkers such as OPN, GPC-3, Golgi protein 73 and SCCA showed good performance with summary AUC (sAUC) between 0.78 and 0.82 [111 – 114] as well as epigenetic biomarkers such as microRNAs with sAUC up to 0.92 [115]. However, most studies have been carried out mainly in patients with liver disease of viral etiology and data available in patients with MASLD mostly derive from phase II validation studies (case-control studies). In addition, the lack of standardized methods for biomarkers measurements currently hampers the application of most of these biomarkers in clinical practice.

PIVKA-II, also known as des-γ- carboxy-prothrombin (DCP), is one of the few biomarkers that underwent phase II and early phase III validation. PIVKA-II showed superior performance compared to AFP for the discrimination between cirrhotic patients with and without HCC [116,117], but mostly in patients with cirrhosis of viral etiology [118 – 122], while results from studies including patients with MASLD are ongoing [123]. PIVKA-II is characterized by excellent stability in blood samples and can be measured by fully automated and standardized methods, thus being a valid candidate for future implementation into clinical practice.

Noteworthy are the results from studies investigating the performance of biomarkers combination. The GALAD model, that combines gender, age, AFP, AFP-L3%, and PIVKA-II has been evaluated in a case-control multicentre study of cirrhotic patients with MASLD and it was found to have an excellent diagnostic performance (Area Under the Curve [AUC] 0.93) for the discrimination between patients with and without HCC [124]. In the same study, the authors observed that GALAD scores above −0.63 identified patients with MASH who developed HCC approximately 200 days before diagnosis [124]. The ASAP score, that combines age, sex, AFP, and PIVKA-II, is a more recent diagnostic model derived from GALAD; among 248 HCC patient and 722 patients with chronic liver disease, the ASAP model outperformed GALAD independently of liver disease etiology (AUC 0.886 vs. 0.853; $p < 0.001$) [125]. Considering the good performance of ASAP model despite using one less laboratory variable, a head-to-head comparison with GALAD model in Phase III studies is eagerly awaited.

4.2. Biomarkers for risk of severe fibrosis/cirrhosis

As stated previously, severe fibrosis/cirrhosis is the soil for the development of HCC, hence NITs for the prediction of severe liver fibrosis may be helpful and have been also tested for longitudinal HCC prediction in patients with advanced liver disease. FIB-4 is the NITs that showed the most promising results. In a cohort of 122 consecutive cirrhotic individuals with MASLD (median follow-up of 5.9 years), baseline FIB-4 (<1.45, 1.45–3.25, >3.25) was significantly and independently associated with an increased risk of HCC occurrence (HR 6.40, 95 % CI 1.71–24.00, $p = 0.006$), with the highest risk for FIB-4 > 3.25 at baseline [126]. Furthermore, longitudinal changes in FIB-4 values can be even more informative; in patients within the full histologic spectrum of MALSD, high FIB-4 (>2.67) at baseline and 3 years was associated to >50-fold higher risk of HCC than persistently low FIB-4 (<1.45) values [127].

The aMAP score (age, male, albumin-bilirubin, and platelet count) has been recently developed and validated as a universal HCC risk score to predict the HCC development for patients with chronic hepatitis. The performance for HCC prediction of aMAP score in the Japanese non-viral hepatitis cohort ($n = 720$) was 0.82 (95 % CI 0.79–0.90) and 0.61 (95 % CI 0.49–0.73) in the entire cohort and in the subset of cirrhotic patients, respectively [128]. The model has been independently validated in an external cohort of 1389 patients who had a histological diagnosis of MASLD or MASH and underwent regular surveillance for HCC [129]. The C-index of aMAP score was 0.887, and the HRs for HCC development in the intermediate and high-risk groups were 21.0 (95 % CI 3.6–402.0) and 110.3 (95 % CI, 16.3–2251.4), respectively [129]. The combination of inexpensive NITs (i.e. FIB-4) or prognostic scores (i.e. aMAP) with oncologic biomarkers (i.e. AFP and/or PIVKA-II) may improve overall performance and lead to highly performing, but still low-cost, prognostic models able to reflect multiple parameters involved in HCC occurrence.

Finally, it is worth mentioning that liver stiffness measurement (LSM) by vibration controlled transient elastography may be useful for the prediction of liver-related events, including HCC. A retrospective analysis of consecutive patients with MASLD and advanced liver disease ($n = 1039$; F ≥ 3 and/or LSM >10 kPa) with at least 6-months follow-up showed that the change of LSM values overtime was significantly and independently associated with HCC development (HR 1.72, 95 % CI 1.01–3.02; $p = 0.04$) [130]. Additionally, in a recent large retrospective multicentric cohort study of >16,000 patients followed up for median 51 months, LSM achieved a time-dependent AUC of 0.89 for the prediction of long-term liver-related events and HCC, starting from a low cut-off value of 10 kPa [131].

4.3. Genetic susceptibility and polygenic risk scores for HCC risk stratification

The heritability of different traits associated with MASLD (obesity, metabolic syndrome, insulin resistance) ranges from 30 % to 75 % [132,133]. However, genetic variants characterizing certain traits (i.e. hepatic steatosis) are not uniformly associated with other such as fibrosis or insulin resistance, suggesting the presence of a high genetic heterogeneity within pathways influencing these traits [133]. Furthermore, host genetic and environmental modifiers may synergize with metabolic traits, thus driving the onset and progression of MASLD [134] (Fig. 2).

Germline pathogenic variants have been identified in 11 %–15 % of patients with a diagnosis of HCC. In addition, a number ranging from 50 to 70 somatic mutations acquired during the stage of cirrhosis are characteristic hallmarks of HCC. These mutations may affect “driver genes” that regulate pathways involved in the maintenance of telomere, cell cycle, epigenetic regulation, chromatin remodeling and oxidative stress, as described by Schulze et al. [135] (Fig. 3).

In the past 15 years, genome-wide association studies (GWAS) led to the identification of several single nucleotide polymorphisms (SNPs) that are associated with MASLD progression and complications such as HCC-related MASH. [136]. Overall, the largest fraction of genetic predisposition can be greatly explained by the rs738409 C > G SNP encoding the patatin-like phospholipase domain-containing 3 (PNPLA3) I148M protein variant [137]. A meta-analysis on 2503 cirrhotic patients from European ancestry showed that the carriage of the *PNPLA3* rs738409 G risk allele was strongly associated with incident HCC independent of obesity, particularly in alcoholic hepatitis [138,139].

Table 1
Performance of novel biomarkers and tools from representative phase II and phase III validation studies including patients with MASLD.

Biomarker	Type	Study	Country	Patients' characteristics	Performance	Reference
PIVKA-II	Circulating biomarker	50 HCC vs. 41 cirrhosis (ALD+MASLD) - MASLD diagnosis: liver biopsy	UK	HCC: mean age 68 ± 12 years; M = 80 %; MASLD = 40 % Cirrhosis: mean age 54 ± 10 years; M = 32 %; MASLD = 20 %	PIVKA-II: AUC = 0.810 (95%CI 0.715–0.886) AFP: AUC = 0.710 (95%CI 0.610–0.800)	Beale et al. 2008
		Case-control MASLD cohort 125 HCC vs. 231 CLD - MASLD diagnosis: liver biopsy or presence of metabolic syndrome and absence of other causes of liver disease	Germany	HCC: median age 71 (64 to 75) years; M = 67 %; T2DM = 72 %; cirrhosis = 76 %; BCLC A = 23 % CLD: median age 52 (44 to 59) years; M = 52 %; T2DM = 39 %; cirrhosis = 21 %	Overall cohort: PIVKA-II: AUC = 0.87 (95%CI 0.82–0.91) AFP: AUC = 0.88 (95%CI 0.84–0.92) Cirrhotics only: PIVKA-II: AUC = 0.83 (95%CI 0.76–0.90) AFP: AUC = 0.79 (95%CI 0.72–0.86)	Best et al. 2020
		72 HCC vs. 119 CLD - MASLD diagnosis: liver biopsy or US evidence of steatosis without other causes of liver disease	Italy	HCC: median age 67 (IQR 62–70) years; M = 79 %; cirrhosis = 88 %; T2DM = 60 %; median ALT 32 (24–41) U/l; BCLC 0/A = 65 % CLD: median age 58 (IQR 49–66) years; M = 54 %; cirrhosis = 55 %; T2DM = 57 %; median ALT 53 (31–72) U/l	PIVKA-II: AUC = 0.853 (95%CI 0.794–0.900) AFP: AUC = 0.763 (95%CI 0.696–0.821)	Caviglia et al. 2021
		139 HCC vs. 345 CLD - MASLD diagnosis: liver biopsy or US evidence of steatosis without other causes of liver disease	China	HCC: mean age 61 ± 11 years; M = 76 %; cirrhosis = 34 %; BCLC 0/A = 43 % CLD: mean age 56 ± 12 years; M = 64 %; cirrhosis = 17 %	Overall PIVKA-II: AUC = 0.869 (95%CI 0.846–0.898) AFP: AUC = 0.763 (95%CI 0.723–0.801) early HCC (BCLC0/A) PIVKA-II: AUC = 0.851 (95%CI 0.812–0.884) AFP: AUC = 0.752 (95%CI 0.707–0.793)	Guan et al. 2022
		248 HCC vs. 722 CLD various etiology	China	Overall population HCC: mean age 55 ± 12 years; M = 88 %; cirrhosis = 62 %; BCLC0/A = 62 % CLD: mean age 54 ± 11 years; M = 77 %; cirrhosis = 37 %	PIVKA-II: AUC = 0.812 (95%CI 0.793–0.843) AFP: AUC = 0.750 (95%CI 0.721–0.777)	Sun et al. 2023
		MASLD only: 39 HCC vs 147 CLD - MASLD diagnosis: liver biopsy or US evidence of steatosis without other causes of liver disease		MASLD subgroup HCC: mean age 60 ± 10 years; M = 74 %; cirrhosis = 33 %; BCLC0/A = 95 % CLD: mean age 57 ± 13 years; M = 63 %; cirrhosis = 15 %	PIVKA-II: AUC = 0.785 (95%CI 719–0.841) AFP: AUC = 0.732 (95%CI 0.662–0.794)	
AFP-L3	Circulating biomarker	Case-control MASLD cohort 125 HCC vs. 231 CLD - MASLD diagnosis: liver biopsy or presence of metabolic syndrome and absence of other causes of liver disease	Germany	HCC: median age 71 (64 to 75) years; M = 67 %; T2DM = 72 %; cirrhosis = 76 %; BCLC A = 23 % CLD: median age 52 (44 to 59) years; M = 52 %; T2DM = 39 %; cirrhosis = 21 %	Overall cohort: AFP-L3: AUC = 0.86 (95% CI 0.82–0.90) AFP: AUC = 0.88 (95%CI 0.84–0.92) Cirrhotics only: AFP-L3: AUC = 0.75 (95% CI 0.68–0.86) AFP: AUC = 0.79 (95%CI 0.72–0.86)	Best J et al. 2020
		139 HCC vs. 345 CLD - MASLD diagnosis: liver biopsy or presence of metabolic syndrome and absence of other causes of liver disease	China	HCC: mean age 61 ± 11 years; M = 76 %; cirrhosis = 34 %; BCLC 0/A = 43 % CLD: mean age 56 ± 12 years; M = 64 %; cirrhosis = 17 %	Overall AFP-L3: AUC = 0.689 (95%CI 0.646–0.730) AFP: AUC = 0.763 (95%CI 0.723–0.801) early HCC (BCLC0/A) AFP-L3: AUC = 0.660 (95%CI 0.612–0.706) AFP: AUC = 0.752 (95%CI 0.707–0.793)	Guan et al. 2022
		248 HCC vs. 722 CLD various etiology	China	Overall population HCC: mean age 55 ± 12 years; M = 88 %; cirrhosis = 62 %; BCLC0/A = 62 % CLD: mean age 54 ± 11 years; M = 77 %; cirrhosis = 37 %	AUC = 0.687 (95%CI 0.657–0.716)	Sun et al. 2023
		MASLD only: 39 HCC vs 147 CLD - MASLD diagnosis: liver biopsy or US evidence of		MASLD subgroup HCC: mean age 60 ± 10 years; M = 74 %; cirrhosis = 33 %;	AUC = 0.594 (95%CI 0.520–0.665)	

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Table 1 (*continued*)

Biomarker	Type	Study	Country	Patients' characteristics	Performance	Reference
		steatosis without other causes of liver disease		BCLC0/A = 95 % CLD: mean age 57 ± 13 years; M = 63 %; cirrhosis = 15 %		
GPC-3	Circulating biomarker	50 HCC vs. 41 cirrhosis (ALD+MASLD) - MASLD diagnosis: liver biopsy	UK	HCC: mean age 68 ± 12 years; M = 80 %; MASLD = 40 % Cirrhosis: mean age 54 ± 10 years; M = 32 %; MASLD = 20 %	GPC-3: no difference between patients with cirrhosis and those with HCC AFP: AUC = 0.710 (95%CI 0.610–0.800)	Beale et al. 2008
		72 HCC vs. 119 CLD - MASLD diagnosis: liver biopsy or US evidence of steatosis without other causes of liver disease	Italy	HCC: median age 67 (IQR 62–70) years; M = 79 %; cirrhosis = 88 %; T2DM = 60 %; median ALT 32 (24–41) U/l; BCLC 0/A = 65 % CLD: median age 58 (IQR 49–66) years; M = 54 %; cirrhosis = 55 %; T2DM = 57 %; median ALT 53 (31–72) U/l	GPC-3: AUC = 0.759 (95% CI 0.691–0.817) AFP: AUC = 0.763 (95%CI 0.696–0.821)	Caviglia et al. 2021
OPN	Circulating biomarker	25 HCC vs. 25 CLD-MASLD - MASLD diagnosis: not specified	Egypt	HCC: mean age 50 ± 8 years; M = 72 %; mean ALT 32 ± 5 IU/l CLD-MASLD: mean age 48 ± 10 years; M = 64 %; mean ALT 49 ± 6 IU/l	Mean OPN values: HCC: 401 ± 72 ng/ml CLD-MASLD: 106.7 ± 35 ng/ml	Fouad et al. 2015
		86 HCC vs. 86 cirrhosis mixed etiology - MASLD diagnosis: liver biopsy or US evidence of steatosis without other causes of liver disease	Australia	HCC: mean age 62 ± 11 years; M = 87 %; T2DM = 41 %; MASLD etiology = 19 % cirrhosis: mean age 59 ± 10 years; M = 87 %; T2DM = 34 %; MASLD etiology = 12 %	Overall population OPN: AUC = 0.65 (95%CI 0.57–0.73) AFP: AUC = 0.83 (95% CI0.77–0.89) MASLD only OPN: AUC = 0.66 (95%CI 0.44–0.88) AFP: AUC = 0.76 (95 % CI 0.58–0.95)	Vongsuvanh et al. 2016
LC-SPIK	Circulating biomarker	62 HCC vs. 58 cirrhosis-MASLD - MASLD diagnosis: liver biopsy or US evidence of steatosis without other causes of liver disease	Italy	HCC: median age 66 (IQR 62–70); M = 79 %; T2DM = 58 %; median ALT 34 (IQR 25–45) U/l; BCLC 0/A = 61 % cirrhosis: median age 63 (IQR 57–69); M = 50 %; T2DM = 69 %; median ALT 41 (IQR 25–64) U/l	Overall LC-SPIK: AUC = 0.841 (95%CI 0.763–0.901) AFP: AUC = 0.719 (95%CI 0.630–0.797) early HCC (BCLC0/A) LC-SPIK: AUC = 0.832 (95%CI 0.744–0.899) AFP: AUC = 0.651 (95%CI 0.539–0.735)	Caviglia et al. 2022
MDK	Circulating biomarker	86 HCC vs. 86 cirrhosis mixed etiology - MASLD diagnosis: liver biopsy or US evidence of steatosis without other causes of liver disease	Australia	HCC: mean age 62 ± 11 years; M = 87 %; T2DM = 41 %; MASLD etiology = 19 % cirrhosis: mean age 59 ± 10 years; M = 87 %; T2DM = 34 %; MASLD etiology = 12 %	Overall population MDK: AUC = 0.70 (95%CI 0.63–0.76) AFP: AUC = 0.83 (95% CI0.77–0.89) MASLD only MDK: AUC = 0.86 (95%CI 0.72–1.00) AFP: AUC = 0.76 (95 % CI 0.58–0.95)	Vongsuvanh et al. 2016
sCD163	Circulating biomarker	Prospective cohort of 243 MASLD patients; 13 HCC de novo during FU - MASLD diagnosis: liver biopsy	Japan	At baseline: mean age 53 ± 14; M = 49 %; histologic cirrhosis = 8 %; median ALT 56 (10–281) IU/l Median FU 4.8 (1–14.1) years	AUC = 0.83 5- and 10- year HCC incidence rate of 2 % and 11 % for baseline sCD163 < 800 ng/ml 5- and 10-year HCC incidence rate of 4.7 % and 42 % for baseline sCD163 ≥ 800 ng/ml	Kawanaka et al. 2023
SCCA	Circulating biomarker	499 HCC vs. 462 cirrhosis mixed etiology - MASLD diagnosis: not specified	Italy	HCC: mean age 67 ± 10 years; M = 81 %; MASLD≈8 % cirrhosis: mean age 61 ± 12 years; M = 93 %; MASLD≈8 %	SCCA: AUC = 0.656 (9 %% CI 0.625–0.686) AFP: AUC = 0.724 (95%CI 0.695–0.752)	Giannelli et al. 2007
		50 HCC vs. 41 cirrhosis (ALD+MASLD) - MASLD diagnosis: liver biopsy	UK	HCC: mean age 68 ± 12 years; M = 80 %; MASLD = 40 % Cirrhosis: mean age 54 ± 10 years; M = 32 %; MASLD = 20 %	SCCA: no difference between patients with cirrhosis and those with HCC AFP: AUC = 0.710 (95%CI 0.610–0.800)	Beale et al. 2008
SCCA IgM	Circulating biomarker	499 HCC vs. 462 cirrhosis mixed etiology - MASLD diagnosis: not specified	Italy	HCC: mean age 67 ± 10 years; M = 81 %; MASLD≈8 % cirrhosis: mean age 61 ± 12 years; M = 93 %; MASLD≈8 %	SCCA IgM: AUC = 0.675 (9 %%CI 0.645–0.705) AFP: AUC = 0.724 (95%CI 0.695–0.752)	Giannelli et al. 2007

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Table 1 (*continued*)

Biomarker	Type	Study	Country	Patients' characteristics	Performance	Reference
		Prospective cohort of 141 patients with cirrhosis of various etiology - MASLD diagnosis: not specified	Spain	Validation cohort: mean age 59 ± 9 years; M = 73 %; MASLD≈10 %; CTP A = 79 %; mean ALT 35 ± 25 IU/ml 2y cumulative HCC incidence: 14/141 5y cumulative HCC incidence: 34/141	2y SCCA IgM: AUC = 0.706 (95%CI 0.588–0.827) 5y SCCA IgM: AUC = 0.706 (95%CI 0.623–0.788) 2y AFP: AUC = 0.748 (95%CI 0.617–0.880) 5y AFP: AUC = 0.646 (95%CI0.548–0.734)	Gil-Gomez et al. 2021
fAIM	Circulating biomarker	141 MASH vs 26 MASH-HCC - MASLD diagnosis: liver biopsy	Japan	MASH-HCC: mean age 73 ± 9 years; M = 46 %; mean ALT 42 ± 28 IU/ml; liver cirrhosis = 85 % MASH: mean age 59 ± 14 years; M = 47 %; mean ALT 90 ± 62 IU/ml; liver cirrhosis = 6 %	fAIM: AUC = 0.929	Koyama et al. 2018
		II cohort study of 199 patients with MASLD; 24 incident HCC - MASLD diagnosis: liver biopsy	Japan	At baseline: median age 62 (range 51–70) years; M = 46 %; median ALT 65 (range 41–105) IU/mL; cirrhosis = 9 %; Median FU 7.4 years	Risk of HCC development AFP ≥ 10 ng/ml: HR = 4.02 (95%CI 1.31–12.29) fAIM ≥1.6 μg/ml: FR = 2.82 (95%CI 1.03–7.73)	Okanoue et al. 2022
GALAD	Biomarker-based model Gender + Age + AFP-L3% + AFP + DCP	Case-control MASLD cohort 125 HCC vs. 231 CLD - MASLD diagnosis: liver biopsy or presence of metabolic syndrome and absence of other causes of liver disease	Germany	German cohort HCC: median age 71 (64 to 75) years; M = 67 %; T2DM = 72 %; cirrhosis = 76 %; BCLC A = 23 % CLD: median age 52 (44 to 59) years; M = 52 %; T2DM = 39 %; cirrhosis = 21 %	Overall German cohort: AUC = 0.96 (95%CI 0.94–0.98) Cirrhotics only: AUC = 0.93 (95%CI 0.88–0.97)	Best et al. 2020
		Prospective cohort of 389 MASLD patients; 28 HCC de novo during FU - MASLD diagnosis: US evidence of steatosis without other causes of liver disease	Japan	Japanese cohort → median FU of 167 months HCC: median age 62 (54 to 68) years; M = 81 %; T2DM = 81 %; cirrhosis = 81 %; BCLC not available CLD: median age 68 (59 to 74) years; M = 50 %; T2DM = 39 %; cirrhosis = 20 %	Median GALAD values in prospective cohort: HCC: −0.60 (−1.49–0.72) No HCC: −3.24 (−4.21–-2.20)	
		248 HCC vs. 722 CLD various etiology	China	Overall population HCC: mean age 55 ± 12 years; M = 88 %; cirrhosis = 62 %; BCLC0/A = 62 % CLD: mean age 54 ± 11 years; M = 77 %; cirrhosis = 37 %	AUC = 0.853 (95%CI 0.829–0.875)	Sun et al. 2023
		MASLD only: 39 HCC vs 147 CLD - MASLD diagnosis: liver biopsy or US evidence of steatosis without other causes of liver disease		MASLD subgroup HCC: mean age 60 ± 10 years; M = 74 %; cirrhosis = 33 %; BCLC0/A = 95 % CLD: mean age 57 ± 13 years; M = 63 %; cirrhosis = 15 %	AUC = 0.859 (95%CI 0.800–0.906)	
ASAP	Biomarker-based model Age + Sex + AFP + PIVKA-II	248 HCC vs. 722 CLD various etiology	China	Overall population HCC: mean age 55 ± 12 years; M = 88 %; cirrhosis = 62 %; BCLC0/A = 62 % CLD: mean age 54 ± 11 years; M = 77 %; cirrhosis = 37 %	AUC = 0.886 (95%CI 0.864–0.905)	Sun et al. 2023
		MASLD only: 39 HCC vs 147 CLD - MASLD diagnosis: liver biopsy or US evidence of steatosis without other causes of liver disease		MASLD subgroup HCC: mean age 60 ± 10 years; M = 74 %; cirrhosis = 33 %; BCLC0/A = 95 % CLD: mean age 57 ± 13 years; M = 63 %; cirrhosis = 15 %	AUC = 0.876 (95%CI 0.820–0.920)	
APAC	Biomarker-based model Age + sPDGFRβ + AFP + creatinine	122 HCC vs. 145 cirrhosis various etiology - MASLD diagnosis: not specified	Germany	HCC: median age 66 (IQR 60–72) years; M = 78 %; median ALT 42 (IQR 30–73) IU/ml; MASLD = 21 %; BCLC 0/A = 22 % Cirrhosis: median age 54 (IQR 47–60) years; M = 68 %; median ALT 35 (IQR 25–64) IU/ml; MASLD = 23 % Training cohort: 70 % of the entire study cohort Validation cohort: 30 % of the entire study cohort	Overall APAC: AUC = 0.950 (95% CI 0.926–0.945) AFP: AUC = 0.883 (95%CI 0.803–0.962) Training cohort APAC: AUC = 0.941 (95% CI 0.892–0.989) AFP: AUC = 0.848 (95%CI 0.792–0.904) Validation cohort APAC: AUC = 0.951 (95% CI 0.920–0.981) AFP: AUC = 0.848 (95%CI 0.792–0.904)	Lambrecht et al. 2021

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Biomarker	Type	Study	Country	Patients' characteristics	Performance	Reference
FIB-4[a]	Non-invasive test Age + AST + ALT + Platelet count	7068 patients with MASLD-cirrhosis; 407 incident HCC - MASLD diagnosis: T2DM or BMI $\geq$ 30 kg/m^2 without other causes of liver disease	USA	Mean age 67 ± 10 years: M = 96 %; T2DM = 78 % Mean FU 3.7 (range 1–6) years	C-index = 0.701	Ioannou et al. 2019
		1168 MASLD patients; 17 HCC de novo during the FU - MASLD diagnosis: liver biopsy	Italy, Spain, UK	Median age 49 (IQR 38–57) years; M = 65 %; T2DM = 28 %; median ALT 59 (IQR 41–88) IU/ml; F3/4 = 24 % Median FU 81 (IQR 62–110) months	C-index = 0.783 ± 0.029	Yunes et al. J 2021
		81,108 patients (77.2 % with metabolic risk factors, 21.7 % MASLD, and 1.1 % MASH); 275 HCC during the FU - MASLD diagnosis: not specified (ICD codes from electronic medical records)	USA	Median age 62.0 (IQR 14) years; M = 49.6 %; obesity = 73 %; T2MD = 34 % Median FU 34.8 (IQR 12.2) months	Risk of HCC development FIB-4 < 1.3: 1 Ref. FIB-4 1.3–2.66: aHR = 1.18 (95%CI 0.89–1.58) FIB-4 $\geq$ 2.67: aHR = 3.66 (95%CI 2.71–4.94)	Vieira Barbosa et al. 2022
		996 patients with MASLD; 26 HCC de novo during the FU - MASLD diagnosis: liver biopsy or CAP by VCTE	Spain	Median age 60 years; M = 49 %; T2DM = 42 %; liver cirrhosis = 10 % Median FU 2.5 (IQR 1.9–3.6) years	AUC = 0.87 (95%CI 0.78–0.96)	Pons et al. 2022
		121 patients with MASLD - MASLD diagnosis: liver biopsy	Portugal	F $\geq$ 3 = 22 %	AUC = 0.88	Rigor et al. 2022
		1389 MASLD patients; 37 HCC de novo during the FU - MASLD diagnosis: liver biopsy	Japan	Median age 57 (IQR 45–65); M = 43 %; T2DM = 36 %; median ALT 73 (IQR 47–110) IU/ml; cirrhosis = 2 % Median FU 4.61 years (IQR, 2.52–10.20) years	Overall: C-index = 0.878 (95%CI 0.829–0.927) F3-F4 only: C-index = 0.714 (95%CI 0.551–0.877)	Toyoda et al. 2023
		364 MASLD patients; 9 HCC de novo during the FU - MASLD diagnosis: liver biopsy	Japan	Patients with FIB-4 $\geq$ 1.255 *n* = 177; mean age 61 ± 9 years; M = 47 %; mean ALT 97 ± 66 IU/ml; liver cirrhosis = 3 % Patients with FIB-4 < 1.255 *n* = 176; mean age 44 ±12 years; M = 48 %; mean ALT 86 ± 73 IU/ml; liver cirrhosis = 0 % Mean FU 2716 ± 1621 days	AUC = 0.848	Kamada et al. 2022
		122 consecutive patients with MASLD-cirrhosis; 13 HCC de novo - MASLD diagnosis: liver biopsy or US evidence of steatosis without other causes of liver disease	Italy	Median age 62 (IQR 51–67) years; M = 52 %; obesity = 57 %; T2DM = 57 %; median ALT 42 (IQR 24–61) IU/ml Median FU 5.9 (3.2–9.3) years	HCC cumulative incidence FIB-4 < 1.45 = 0 % FIB-4 1.45–3.25 = 10.3 % FIB-4 > 3.25 = 19.4 % aHR = 6.40, *p* = 0.006	Armandi et al. 2023
		202,319 MASLD patients; 473 HCC during the FU. - MASLD diagnosis: $\geq$2 elevated ALT values without other causes of liver disease	USA	Mean age 55 ± 13 years; M = 94 %; obesity = 58 %; T2DM = 20 % Mean FU 8.2 ± 2.8 years	HCC risk according to FIB-4 variation from baseline to 3y FU Stable FIB-4 > 2.67; aHR = 57.7	Cholankeril et al. 2023
		47,165 patients with MASLD Non-cirrhosis, *n* = 37,325; 139 HCC during the FU - MASLD diagnosis: not specified (ICD codes from electronic medical records)	USA	Mean FU: 3.4 years	Annual HCC incidence in patients without cirrhosis: FIB >2.67 = 2.8/1000 PY FIB <1.30 = 0.7/1000 PY	Behari et al. 2023
		1338 patients with MASLD-cirrhosis; 157 HCC during the FU - MASLD diagnosis: not specified (ICD codes from electronic medical records)	U.S.	Median age 57 (IQR 48–64) years; M = 43 %; T2DM = 26 %; mean ALT 70 ± 239 IU/ml Median FU 3.7 (IQR 0.7–7.9) years	Risk of HCC development FIB-4 < 1.45: 1 Ref. FIB-4 1.45–3.25: aHR = 1.22 (95%CI 0.67–1.86) FIB-4 > 3.25: aHR = 1.93 (95%CI 1.22–3.05)	Albhaisi et al. 2023
		16,603 patients with MASLD; 139 HCC during the FU - MASLD diagnosis: liver biopsy or US evidence of steatosis without other causes of liver disease	U.S., Europe, Asia	Mean age 53 ± 14 years; M = 58 %; T2DM = 35 %; median ALT 37 (IQR 23–62) IU/ml Patients from U.S. or Europe = 18 % Patients from Asia = 82 % Median FU 51.7 (IQR, 25.2–85.2) months	iAUC = 0.77 (95%CI 0.71–0.83)	Lin et al. 2024
NFS[a]	Non-invasive test Age + AST + ALT +	1168 MASLD patients; 17 HCC de novo during the FU	Italy, Spain, UK	Median age 49 (IQR 38–57) years; M = 65 %; T2DM = 28 %; median ALT 59 (IQR 41–88) IU/	C-index = 0.901 ± 0.030	Yunes et al. J 2021

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Biomarker	Type	Study	Country	Patients' characteristics	Performance	Reference
	PLT + BMI + Alb + IFG/T2DM	- MASLD diagnosis: liver biopsy		ml; F3/4 = 24 % Median FU 81 (IQR 62–110) months		
		121 patients with MASLD - MASLD diagnosis: liver biopsy	Portugal	F ≥ 3 = 22 %	AUC = 0.88	Rigor et al. 2022
		16,603 patients with MASLD; 139 HCC during the FU - MASLD diagnosis: liver biopsy or US evidence of steatosis without other causes of liver disease	U.S., Europe, Asia	Mean age 53 ± 14 years; M = 58 %; T2DM = 35 %; median ALT 37 (IQR 23–62) IU/ml Patients from U.S. or Europe = 18 % Patients from Asia = 82 % Median FU 51.7 (IQR, 25.2–85.2) months	iAUC = 0.77 (95%CI 0.70–0.83)	Lin et al. 2024
LSM[a]	Non-invasive test Derived scores: Agile 3+ LSM + AST + ALT + PLT + Age+ Sex + T2DM	2245 consecutive patients with MASLD - MASLD diagnosis: US evidence of steatosis without other causes of liver disease	France, Hong Kong	Median age 59 (IQR 51–66) years; M = 53 %; T2DM = 61 %; median ALT 33 (IQR 22–57) IU/ml Median FU 27 (IQR 25–38) months	HCC incidence: LSM <12 kPa: 0.32 %; LSM: 12–18 kPa: 0.58 %; LSM: 18–38 kPa: 9.26 % LSM >38 kPa: 13.3 %	Shili-Masmoudi S et al. 2020
	Agile 4 LSM + AST + ALT + PLT + Sex + T2DM	Training cohort 2666 patients with MASLD; 22 incident HCC - MASLD diagnosis: CAP evidence of steatosis without other causes of liver disease	Korea	Median age 52 (IQR 41–61) years; M = 57 %; T2DM = 39 %; median ALT 41 (IQR 24–68) IU/ml Mean FU 28.2 ± 20.8 months	Risk of HCC development LSM ≥ 9.3 kPa: aHR = 13.76 (95%CI 2.83–66.96)	Lee et al. 2021
		1039 patients with cACLD-MASLD; 35 HCC de novo during the FU - MASLD diagnosis: liver biopsy	Italy, Canada, Spain, Hong Kong, France; Switzerland	Mean age 60 ± 11 years; M = 56 %; obesity = 66 %; T2DM = 61 %; mean ALT 63 ± 50 IU/ml Median FU 35 (IQR 19–63) years	HCC risk according to: Baseline LSM: HR = 1.03 (95%CI 1.00–1.04) ΔLSM during FU: HR = 1.72 (95%CI 1.01–3.02)	Petta et al. 2021
		996 patients with MASLD; 26 HCC de novo during the FU - MASLD diagnosis: liver biopsy or CAP by VCTE	Spain	Median age 60 years; M = 49 %; T2DM = 42 %; liver cirrhosis = 10 % Median FU 2.5 (IQR 1.9–3.6) years	Overall: AUC = 0.85 (95%CI 0.77–0.93)	Pons et al. 2022
		MASLD cohort: 13,629 patients; 42 HCC during the FU - MASLD diagnosis: not specified (ICD codes from electronic medical records)	U.S.	LSM <12.5 kPa: n = 10,970; mean age 56 ± 14 years; M = 89 %; T2DM = 35 % LSM ≥12.5 kPa: *n* = 2659; mean age 62 ± 11 years; M = 93 %; T2DM = 64 % Median FU 1.1 years	Risk of HCC development LSM <9.5 kPa: 1 Ref. LSM 9.5–12.4 kPa: aHR = 3.87 (95%CI 0.95–14.68) LSM 12.5–14.4 kPa: aHR = 9.99 (95%CI 2.45–38.15) LSM ≥14.5 kPa: aHR = 15.74 (95%CI 6.45–47.25)	Davitkov et al. 2023
		403 patients with MASL; 7 HCC de novo during the FU - MASLD diagnosis: liver biopsy	Japan	Median age 60 (IQR 47–68) years; M = 40 %; T2DM = 47 %, median ALT 69 (IQR 42–102) IU/ml; F3/4 = 17 % Median FU 2.7 (range, 0.0–12.5) years	Agile 3+: C-index = 0.833 Agile 4: C-index = 0.890	Miura et al. 2023
		16,603 patients with MASLD; 139 HCC during the FU - MASLD diagnosis: liver biopsy or US evidence of steatosis without other causes of liver disease	U.S., Europe, Asia	Mean age 53 ± 14 years; M = 58 %; T2DM = 35 %; median ALT 37 (IQR 23–62) IU/ml Patients from U.S. or Europe = 18 % Patients from Asia = 82 % Median FU 51.7 (IQR, 25.2–85.2) months	LSM: iAUC = 0.76 (95%CI 0.69–0.82) Agile 3+: iAUC = 0.80 (95%CI 0.73–0.87) Agile 4: iAUC = 0.80 (95% CI 0.73–0.86)	Lin et al. 2024
aMAP	Prognostic score Age + Sex + Alb + TBil + PLT	Japanese non-viral hepatitis cohort: 720 MASLD patients; 19 HCC de novo during the FU - MASLD diagnosis: not specified	Japan	Median age 65 (IQR 57–72) years; M = 47 %; concomitant excessive alcohol intake = 11 % Median FU 60 (IQR 51–62) months	Overall: C-index = 0.85 (95%CI 0.79–0.90) Cirrhotics only: C-index = 0.61 (95%CI 0.49–0.73)	Fan et al. 2020
		1389 MASLD patients; 37 HCC de novo during the FU - MASLD diagnosis: liver biopsy	Japan	Median age 57 (IQR 45–65); M = 43 %; T2DM = 36 %; median ALT 73 (IQR 47–110) IU/ml; cirrhosis = 2 % Median FU 4.61 years (IQR, 2.52–10.20) years	Overall: C-index = 0.887 (95%CI 0.848–0.926) F3-F4 only: C-index = 0.754 (95%CI 0.648–0.860)	Toyoda et al. 2023
THRI	Prognostic score Age + Etiology + Sex + PLT	Derivation cohort: 2079 patients with cirrhosis of various etiology; 226 incident HCC	Canada	Median age 54 (range 15–93) years; M = 60 %; MASLD = 5.3 % Median FU 5.4 (range 0.5–18.6) years	10-y HCC incidence: low-risk (<120) = 3 % medium-risk (120–240) = 10 % high-risk (>240) = 32 %	Sharma et al. 2017

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Table 1 (*continued*)

Biomarker	Type	Study	Country	Patients' characteristics	Performance	Reference
		- MASLD diagnosis: not specified				
		7068 patients with MASLD-cirrhosis; 407 incident HCC - MASLD diagnosis: T2DM or BMI $\geq$ 30 kg/m^2 without other causes of liver disease	U.S.	Mean age 67 ± 10 years: M = 96 %; T2DM = 78 % Mean FU 3.7 (range 1–6) years	C-index = 0.669	Ioannou et al. 2019
		2187 patients with cirrhosis of various etiology; 304 incident HCC - MASLD diagnosis: BMI $\geq$ 30 kg/m^2 or BMI $\geq$ 25 kg/m^2 + T2DM, without other causes of liver disease	Sweden	HCC: mean age 61 ± 9 years; M = 73 %; T2DM = 31 %; MASLD = 49 %; mean FU 3.3 ± 2.3 years No HCC: mean age 59 ± 11 years; M = 65 %; T2DM = 24 %; MASLD = 58 %; mean FU 3.7 ± 3.1 years	C-index = 0.69	Astrom et al. 2021
HCC risk	Prognostic score Age + Sex + PLT + Alb + AST + ALT available at: www.hccrisk.com	7068 patients with MASLD-cirrhosis; 407 incident HCC - MASLD diagnosis: T2DM or BMI $\geq$ 30 kg/m^2 without other causes of liver disease	U.S.	Mean age 67 ± 10 years: M = 96 %; T2DM = 78 % Mean FU 3.7 (range 1–6) years	Derivation cohort, C-index = 0.749 Validation cohort, C-index = 0.718	Ioannou et al. 2019
HEDS score	Prognostic score Sex + Years of cirrhosis + Age + Obesity + AST + AFP + Alb	1325 patients with cirrhosis of various etiology; 95 incident HCC - MASLD diagnosis: not specified	U.S.	Median age 60 (IQR 54–65) years; M = 53 %; obesity = 51 %; MASLD = 25 % Median FU 2.2 (range 0–8.7) years	C-index = 0.73	Reddy et al. 2023
Iron status	Serum iron Transferrin saturation Serum ferritin	18,568 patients with MASLD; 244 incident HCC - MASLD diagnosis: not specified (ICD codes from electronic medical records)	U.S.	Incident HCC: mean age 66 ± 11 years; M = 49 %; T2DM = 65 % HCC free: mean age 60 ± 12 years; M = 38 %; T2DM = 47 %	Risk of HCC development Serum iron >175 μg/dl: HR = 2.91 (95%CI 1.34–6.30) Transferrin saturation > 35 %: HR = 2.02 (95%CI 1.22–3.32) Serum ferritin >30 μg/dl for M and > 20 μg/dl for F: HR = 1.03 (95%CI 0.75–1.42)	Yu et al. 2022
		1474 patients with MASLD; 25 incident HCC - MASLD diagnosis: liver biopsy	Italy, UK, Spain, Germany. Sweden, Australia	Median age 48 (SEMed 0.6) years; M = 65 %; T2DM = 27 %; median ALT 62 (SEMed 1.4) IU/ml MASH = 61 %; F3/4 = 20 %	Serum ferritin: C-index = 0.859 ± 0.01	Armandi et al. 2024
Epigenetics and cfDNA	circulating microRNAs cfDNA mutations	26 MASH-HCC vs 26 MASH-cirrhosis - MASLD diagnosis: US evidence of steatosis without other causes of liver disease	Malaysia	HCC: median age 72 (58–88) years; M = 69 %; T2DM = 89 %; BCLC 0/A = 77 % Cirrhosis: median age 61 (45–69) years; M = 77 %; T2DM = 92 %	HCC vs. cirrhosis EV miR-182: +1.77 (±0.13), $p = 0.045$ EV miR-301: +2.52 (±0.26), $p = 0.016$ EV miR-373: +1.67 (±0.22), $p < 0.001$	Muhammad Yusuf et al. 2020
		36 MASLD HCC vs. 21 MASLD - MASLD diagnosis: liver biopsy	Japan	MASLD HCC: median age 71 (range 41–87) years; M = 31 %; T2DM = 67 %; median ALT 34 (range 12–105) iU/ml; BCLC 0/A = 83 % MASLD: median age 67 (range 44–79) years; M = 90 %; T2DM = 24 %; median ALT 32 (range 8–232) IU/ml	MASLD HCC: TERT C228T positive 23/36 MASLD: TERT C228T positive 1/21 p < 0.001	Akuta et al. 2021
		70 non-viral HCC vs. 70 MASLD vs. 35 HC - MASLD diagnosis: liver biopsy or US evidence of steatosis without other causes of liver disease	Thailand	HCC: mean age 69 ± 11 years; M = 77 %; mean ALT 35 ± 18 IU/ml; BCLC0/A = 36 % MASLD: mean age 51 ± 10 years; M = 43 %; mean ALT 43 ± 43 IU/ml HC: mean age 53 ± 5 years; M = 11 %	HCC vs. non-HCC EV miR-19-3p: AUC = 0.82 (95%CI 0.75–0.88) EV miR-16-5p: AUC = 0.74 (9 %%CI 0.67–0.82) EV miR-223-3p: AUC = 0.65 (95%CI 0.56–0.73) EV miR-30d-5p: AUC = 0.72 (95%CI 0.64–0.80) EV miR451a: AUC = 0.70 (95%CI 0.61–0.78)	Boonkaew et al. 2023

Abbreviations: ALD, alcoholic liver disease; ALT, alanine aminotransferase; AFP, α-fetoprotein; AFP-L3, AFP isoform L3; Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; BMI, body mass index; cACLD, compensated advanced chronic liver disease; CAP, controlled attenuation parameter; cfDNA, circulating free DNA; CLD, chronic liver disease; CTP score, Child-Turcotte-Pugh score; DCP, des-γ-carboxy prothrombin; EV, extracellular vesicles; F, female; fAIM, IgM free apoptosis inhibitor of macrophage; FU, follow-up; GPC-3, glypican-3; HCC, hepatocellular carcinoma; HEDS, Hepatocellular Carcinoma Early Detection Strategy; HC, healthy controls; HR, hazard ratio; iAUC, integrated area under the curve; ICD, International Classification Diseases; IQR, interquartile range; LC-SPIK, liver cancer-specific isoform of serine protease inhibitor Kazal; LSM, liver stiffness measurement; M, males; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, Metabolic dysfunction-Associated Steatotic Liver Disease; MDK, midkine; NFS, NAFLD fibrosis score; OPN, osteopontin; PLT, platelet count; PY, person-years; SCCA, squamous cell carcinoma antigen; SEMed, standard error of the median; sPDGFRβ; soluble platelet-derived growth factor receptor beta;T2DM, type 2 diabetes mellitus; THRI, Toronto HCC risk index; TBil, total bilirubin; US, ultrasound; VCTE, vibration controlled transient elastography.

[a] Biomarkers/tools originally developed for the non-invasive prediction of liver fibrosis.

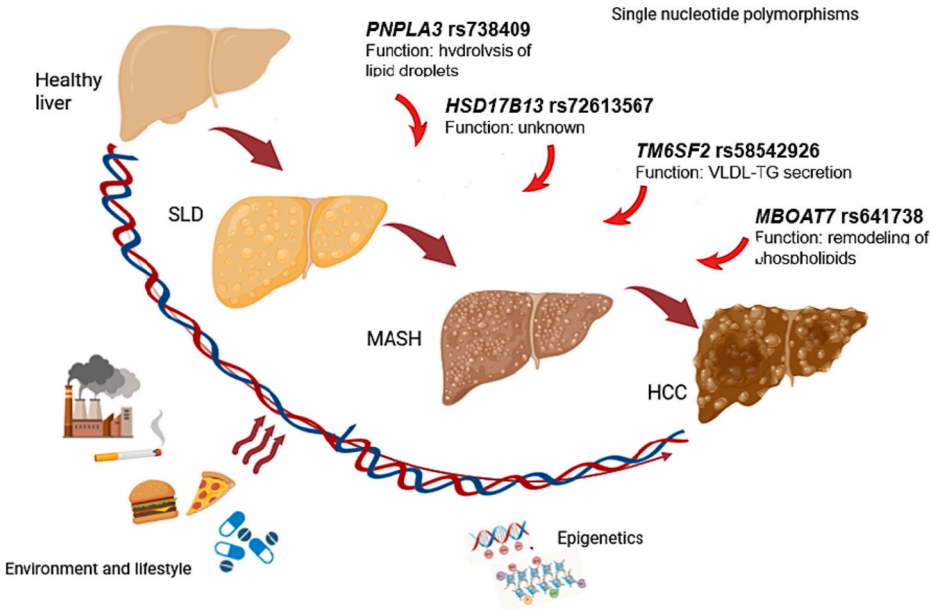

Fig. 3. Impact of genetic background and genetic modifiers on the onset and progression of MASLD. The interplay between host factors (genetic predisposition), environment (pollution, smoke) and unhealthy lifestyle may play an important role in the onset and progression of steatotic liver disease. Abbreviations. GCKR, glucokinase regulatory protein; HCC, hepatocellular carcinoma; HSD17B13, 17β-hydroxysteroid dehydrogenase type 13; MASH, metabolic-dysfunction associated steatohepatitis; MASLD, metabolic-dysfunction associated steatotic liver disease; MBOAT7, membrane-bound O-acyltransferase 7; PNPLA3, patatin-like phospholipase domain-containing 3; SLD, steatotic liver disease; TM6SF2, transmembrane 6 superfamily member 2.

Furthermore, non-obese biopsy-proven MASLD women older than 50 years carrying the GG risk homozygosis are more prone to develop liver-related events during follow-up, including HCC [140].

Other SNPs in genes encoding for proteins involved in lipids metabolism, like *TM6SF2* rs58542926 and *MBOAT7* rs641738, are associated with HCC, with variations in susceptibility across populations [141 – 143]. Recently, the protective variant rs72613567:TA in the *HSD17B13* gene has been associated with a reduced risk of HCC in the UK Biobank cohort [144]. Since the use of single SNPs in the clinical setting is less useful in terms of diagnostic accuracy, their combination into polygenic risk score (PRS) can improve risk stratification [145]. A PRS can be created through the sum of the risk alleles carried by an individual, representing the "individual's genetic predisposition to develop a disease or a relevant-associated outcome" [146]. The PRS based on *PNPLA3*, *TM6SF2* and *HSD17B13* genetic variants was associated with a 12-fold and 29-fold increased risk of non-viral liver cirrhosis and HCC, respectively, in a large cohort of European descent [147]. Another PRS based on *PNPLA3-TM6SF2-GCKR-MBOAT7* SNPs, was able to increase by 3-fold the risk of developing HCC with a good specificity, and to accurately identify a subgroup of dysmetabolic patients at high risk of developing HCC [147,148].

Next-generation exome sequencing technique can enhance PRS accuracy by identifying rare variants with strong pathogenic potential [149]. However, this technology is not yet widely used in clinical practice due to the high costs and technical expertise requirements. Increase knowledge on the biological mechanistic role of SNPs associated with MASLD and liver disease progression can be of great importance for the development of new safe and effective targeted therapies.

5. Potential role of the novel MASH therapies in preventing MASH-related HCC

The promising drugs currently tested in phase III trials for the treatment of at-risk MASH [150,151] might reduce the burden of HCC by reducing the progression to fibrosing MASH and cirrhosis. However, we still do not have data on the long-term impact of the drugs currently in Phase III trials, necessary for obtaining a definite approval from FDA and EMA.

Resmetirom, the first drug to treat fibrosing MASH to gain FDA provisional approval based on histology improvement, is a thyroid hormone analogue acting selectively on the liver beta-thyroid hormone receptor. Resmetirom is among the "liver-centred" therapies for MASH, since it maintains liver homeostasis by controlling de novo lipogenesis, fatty acid oxidation, mithocondrial biogenesis, and cholesterol and carbohydrate metabolism. In phase 2 and phase 3 studies, Resmetirom significantly improved MASH and fibrosis, mainly acting upon mitochondrial health [152,153].

Another promising drug target is PPARs. Lanifibranor, a pan-PPAR agonist has shown to increase fatty acid oxidation, to improve dyslipidaemia, and to modulate adipose tissue and skeletal muscle insulin sensitivity. Additionally, in a phase 2 study Lanifibranor showed to resolve MASH and improve liver fibrosis, and is currently under investigation in a large phase 3 study [154].

In general, engineered, long-lasting incretins represent a cornerstone of the treatment of type 2 diabetes, obesity and their complications. [155]. Incretins include glucagon-like peptide 1 receptor agonists (GLP-1RAs) but also other small peptides secreted by the small intestine (mainly duodenum and jejunum), including Gastric Inhibitor Peptide (GIP), as well as glucagon-receptor (GLG-R) agonists. Incretins significantly induce weight loss through pleiotropic mechanisms (positive modulation of the emotional approach to food and satiety, liver and pancreas homeostasis) and exert cardiovascular protection [156].

Semaglutide is a GLP-1RA that is currently being investigated in a phase 3 study after the positive results on MASH resolutions in the previous phase 2 study [157]. Tirzepatide (dual GIP and GLP-1 receptor agonist) and sorvodutide (dual GLG-R and GLP-1 receptor agonist) have shown a positive impact on obesity and a successful effect on MASH resolution (but not on fibrosis regression) in phase 2b studies [158,159].

Recent investigation assessed the long-term liver-related outcomes in diabetic cohorts treated by GLP-1 RA versus non-treated. A systematic review and meta-analysis of 579.256 diabetic patients showed that GLP1-RAs were associated with reduced risk of HCC (HR 0.74, 95%CI 0.56–0.96) as well as liver decompensation (HR 0.68, 95%CI 0.65–0.72) [160]. In a population-based Swedish study of diabetic patients with any chronic liver disease, the use of GLP-1RAs was associated with a reduced risk of major adverse liver outcomes including HCC (10-year per-protocol risk estimates were 7.4 % in GLP-1RA users versus 14.4 % in non-users; (RR = 0.51, 95%CI 0.14–0.88) [161]. Finally, a retrospective cohort study of >1 million diabetic individuals who were prescribed either GLP-1RA or other non-GLP-1RA medications and follow up for 5 years, showed that GLP-1RAs were associated with lower risk of incident HCC (HR 0.20, 95%CI 0.14–0.31), as compared to other medications (insulin, sulfonylureas, and metformin) [162].

Among the diabetic medications, metformin does not exert a meaningful impact on histologic features of MASH, despite a positive effect on insulin resistance [163,164]. However, diabetic patients with advanced MASLD or MASLD-cirrhosis under treatment with metformin have longer transplant-free survival and reduced overall mortality [165,166].

The optimization of treatment of metabolic co-factors may also have a positive effect on the risk of HCC. Statins represent a necessary treatment to prevent cardiovascular events in subjects with MASLD. Statin use has been associated with reduced risk of MASH and fibrosis, as well as liver-related mortality, liver decompensation and HCC in patients with cirrhosis of any etiology [167–172].

6. MASLD and extra-hepatic cancers

Extrahepatic cancers represent the second cause of death in MASLD [173]. Both hepatic and extra-hepatic mechanisms contribute to a higher incidence of malignancies in individuals with MASLD [174]. Visceral obesity produces pro-inflammatory cytokines, including Nuclear Factor-kappaB (NF-kB), which is a potent driver of carcinogenesis [175]. In addition, the inflamed liver is a source of reactive oxygen species and enhanced Insulin-like Growth Factor-1 synthesis, which can activate inflammatory pathways and induce carcinogenesis. On the other side, visceral obesity is characterized by a reduced production of adiponectin, which exerts anti-inflammatory and anti-proliferative activity via Mitogen-activated protein kinase (MAPK)-mammalian Target of Rifamicin (mTOR) pathway, as shown by pre-clinical models of colorectal cancer (CRC). In fact, CRC is characterized by lower level of adiponectin, and this aspect may mechanistically link MASLD and obesity with extra-hepatic malignancies [176,177].

A Swedish population-based study of 10.568 individuals with biopsied MASLD, found that over median 14.2 years of follow up, extra-hepatic cancers represented the most frequent cause of mortality (incidence 4.5 per 1000 person-year, HR 2.16, 95 % CI 95 % CI 2.03–2.30) [178]. In a meta-analysis of 64 observational studies including 41.027 patients with MASLD, the extra-hepatic cancer incidence rate was 10.58 per 1000 person-years (2288 incident cases), and the most frequent were CRC (1.43 per 1000 person-years), prostate (1.44 per 1000 person-years), and lung (1.35 per 1000 person-years), Notably, extra-hepatic cancers were >8-fold more frequent than HCC [179]. Another meta-analysis of 10 cohort studies including 182.202 individuals (24.8 % with MASLD) and 8485 incident cases of extra-hepatic malignancies, found that MASLD was associated with almost 1.5-fold increased risk to develop gastrointestinal cancers (oesophagus, stomach, CRC, pancreas) after a median follow up of 5–8 years. In addition, MASLD was associated with 1.2-fold to 1.5-fold increase in lung, breast, gynaecological or urinary cancers. Notably, the association was independent from metabolic risk factors, including age, sex, smoking, obesity and T2DM [180]. A nationwide Korean cohort study including >5 million individuals age 20–39, found that during 38.8 million person-year follow up the cumulative incidence of extra-hepatic cancers was higher in individuals with MASLD (defined by Fatty Liver Index ≥60). In particular, MASLD was associated with gastrointestinal cancers (overall aHR 1.16 [95 % CI 1.10–1.22]; aHR for CRC 1.14 [95 % CI 1.06–1.22; aHR for pancreas 1.23 [95 % CI 1.09–1.40). The association was independent from age, sex, smoking habit and alcohol intake, suggesting a role for MASLD in early cancer onset [181]. Finally, a meta-analysis of 56.745 MASLD individuals (of which 11 % lean) and 704 cases of incident gastrointestinal cancers, found that lean MASLD was significantly associated with higher risk of HCC (relative risk [RR] 1.77 [95 % CI 1.15–2.73), pancreatic cancer (RR 1.97 [95 % CI 1.01–3.86) and CRC (RR 1.53 [95 % CI 1.12–2.09) [182].

7. Conclusions

In MASLD, hepatocellular carcinoma (HCC) presents a major challenge, often under-recognized due to limited awareness of MASLD's progression. Genetic and environmental factors contribute to metabolic inflammation, immune disruption, and intrahepatic fibrosis, creating varied individual HCC risks. MASLD is also a risk factor for non-liver cancers, particularly gastrointestinal, partly independent of traditional factors like age and obesity. Surveillance is challenging, as HCC can arise even in non-cirrhotic livers, and US-based protocols perform poorly in MASLD patients. Biomarker-based, risk-driven management of MASLD-HCC remains undeveloped. Current research prioritizes non-invasive fibrosis staging and personalized HCC risk tools, including gene polymorphisms, for better detection and treatment. With the approval of the first MASH drug and new therapies in phase 3 trials, combining "metabolic" and "liver-centered" approaches may enhance fibrosis regression and prevent HCC.

CRediT authorship contribution statement

Angelo Armandi: Writing – original draft, Conceptualization. **Chiara Rosso:** Writing – original draft, Conceptualization. **Gian Paolo Caviglia:** Writing – original draft, Conceptualization. **Elisabetta Bugianesi:** Writing – review & editing, Supervision, Conceptualization.

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Declaration of competing interest

Authors declare no conflict of interest.

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