

Review

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Review

Masld-Related Hepatocarcinoma: Special Features And Challenges

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Abstract: Metabolic Associated Steatohepatitis Liver Disease (MASLD) currently impacts a quarter of the global population and its prevalence is expected to increase in the future. As a result, the incidence of hepatocellular carcinoma associated with MASLD is also on the rise. Notably, hepatocellular carcinoma in this group does not always develop alongside liver cirrhosis, often leading to a more advanced stage at diagnosis. The challenge lies in accurately identifying patients who are at a higher risk of hepatocellular carcinoma to tailor screening processes effectively. Additionally, several therapeutic approaches are being explored to prevent hepatocellular carcinoma, although there are yet no universally accepted guidelines.

Keywords: NAFLD; NASH; cirrhosis; hepatocellular carcinoma; surveillance; prevention

1. Metabolic Dysfunction Associated Steatosis (MASLD)

1.1. Concept and Nomenclature

For decades, hepatic steatosis closely linked to obesity has been known as a cause of liver damage potentially leading to liver cirrhosis. In the 1980s, it was first recognized as an independent entity associated with liver damage and was named non-alcoholic steatohepatitis [1]. Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of chronic liver pathology from isolated non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), characterized by inflammation and tissue damage, with or without fibrosis [2,3].

Over the past few decades, research into this disease and its underlying mechanisms has led to its recognition as a multisystem disorder. Consequently, in 2020, its name was updated to Metabolic Associated Fatty Liver Disease (MAFLD). Diagnosing MAFLD requires histological proof, imaging tests, or biomarkers that demonstrate excessive fat accumulation in the liver, accompanied by at least one of the following: overweight or obesity, type 2 diabetes mellitus, or metabolic dysfunction [4–6]. This shift in nomenclature transitioned MASLD from an exclusionary diagnosis to an inclusive one [7]. In 2023, the term was revised once more to Metabolic Dysfunction Associated with Hepatic Steatosis (MASLD) to better represent the pathophysiological roots of the condition and its strong association with cardiometabolic changes [5,8]. Furthermore, the latest consensus on liver disease nomenclature has introduced a new subgroup known as MetALD [1]. This category includes patients with MASLD who consume alcohol at levels considered harmful, defined as 210 to 420 grams per week for men and 140 to 350 grams per week for women [9,10].

1.2. Epidemiology

The increasing incidence of Metabolic Associated Fatty Liver Disease (MASLD) mirrors the worldwide surge in obesity, which has nearly tripled over recent decades [11]. A meta-analysis

conducted by Younossi et al. indicates that MASLD affects approximately 30% of the global population [12]. This study identifies Latin America as having the highest prevalence at 44% (CI: 30.66% - 59%), followed by Western Europe with a prevalence estimated at 25.1% (20.55% - 30.28%) [11,12]. Moreover, available evidence suggests that nearly all patients diagnosed with Non-Alcoholic Fatty Liver Disease (NAFLD), ranging between 98 and 99%, also meet the criteria for MASLD [1,5].

1.3. Etiopathogenesis

MASLD exhibits a close association with metabolic syndrome [14]. Despite ongoing research, the precise etiopathogenic mechanisms underlying MASLD remain incompletely understood. The "multiple hits" hypothesis posits that MASLD arises in genetically predisposed individuals due to the interplay of various environmental factors, including lifestyle choices, dietary habits, and microbiota composition [5,11]. Key metabolic alterations in carbohydrate and lipid metabolism, alongside insulin resistance, play pivotal roles [5]. These alterations manifest as increased de novo hepatic lipogenesis, augmented release of fatty acids, and diminished fatty acid oxidation, culminating in lipotoxicity [5,11,14]. Lipotoxicity induces oxidative stress and initiates inflammatory cascades characterized by heightened production of cytokines and other pro-inflammatory mediators [5,11,14]. Prolonged inflammation within liver tissue leads to cellular damage and eventual fibrosis, impairing the function of Kupffer cells and stellate cells. Importantly, inflammation extends beyond the liver to encompass chronic low-grade systemic inflammation, predisposing individuals to long-term complications such as cardiovascular events or the development of neoplasias [5,11–14].

2. Masld-Related Complications

2.1. Cardiovascular Complications

Cardiovascular events pose a significant threat to the health and survival of MASLD patients, emerging as the primary cause of mortality within this demographic [11], particularly among those who have not advanced to cirrhosis.

The connection between MASLD and cardiovascular disease is profound. A national cohort study conducted in Japan, involving around 4 million individuals, revealed that the incidence of cardiovascular events was more than twofold higher in MASLD subjects compared to their healthy counterparts [15]. MASLD shares a close nexus with type 2 diabetes, obesity, and dyslipidemia—key cardiovascular risk factors [13]. Various mechanisms, including chronic low-grade inflammation, heightened oxidative stress, hepatic insulin resistance, disrupted lipid metabolism, and endothelial dysfunction, are believed to be implicated [13,16]. Typical dyslipidemia associated with MASLD is characterized by high LDL particle concentration and low HDL. This phenotype is atherogenic and is related to the increased cardiovascular disease risk observed in MASLD [13]. Despite the well-established association between MASLD and cardiovascular disease, standardized screening and primary prevention protocols for this population are yet to be established, necessitating further research.

2.2. Extrahepatic Neoplasms

The most frequent extrahepatic neoplasms in patients with MASLD are endometrial, breast, prostate, colorectal, and lung cancer [5]. To date, it has not been demonstrated that the risk increases in the presence of a higher degree of fibrosis or cirrhosis [5]. As the prevalence of MASLD is expected to increase in the coming decades, the incidence of its associated neoplasms is also expected to rise [5].

The most studied extrahepatic neoplasm associated with MASLD in the literature to date is colorectal cancer. In the pathogenesis of this cancer associated with MASLD, insulin resistance and chronic low-grade inflammation are thought to play a crucial role with a proliferative effect and inhibition of apoptosis, thus initiating the process of carcinogenesis [17,18]. MASLD has been recognized as an independent risk factor for the development of colon polyps. It has been shown that in this population, the risk of developing adenomatous colon polyps is three times that of the general

population. Moreover, they are more likely to be multiple, located in the right or transverse colon, and present high-grade dysplasia [17]. Hence, it is suggested that a more rigorous colorectal cancer screening protocol be implemented for MASLD patients, given that the right colon is the most common site for neoplasia in this group. Establishing the link between MASLD and other malignancies is more complex due to the lack of detailed understanding regarding how MASLD may impact their development. Obesity is a key factor in the onset of esophageal, pancreatic, breast, and thyroid cancers [17], potentially serving as the link between MASLD and these neoplasms. Further studies are imperative to identify patients at elevated risk for extrahepatic neoplasms and to devise effective screening strategies [17,18].

3. Hepatocellular Carcinoma and MASLD

3.1. Pathogenesis

As of now, the precise etiopathogenic pathways linking hepatocellular carcinoma (HCC) to MASLD remain elusive. Insulin resistance stands out as a pivotal factor in carcinogenesis. Insulin resistance and subsequent hyperinsulinemia contribute to elevated levels of insulin-like growth factor 1 (IGF-1), which, in turn, promotes cell survival, stimulates cell proliferation, and facilitates angiogenesis. Additionally, albeit to a lesser degree, IGF-2, which shares similar biological effects with IGF-1, is also elevated [4,19].

There is also an increase in oxidative stress, partly favored by hyperinsulinemia. Insulin promotes the deposition of lipids in the liver and increases the oxidation of free fatty acids, producing an increase in reactive oxygen species (ROS) [4]. This results in inflammation, necrosis, and activation of liver stellate cells that favor fibrogenesis and have a carcinogenic role [4,19,20]. In addition, the increase in ROS leads to an increase in the production of pro-inflammatory cytokines, including tumor necrosis factor alpha, which activates pro-oncogenic pathways [19].

The intestinal microbiota plays a fundamental role in the development of MASLD and its progression to HCC. In patients with MAFLD, there is an increase in intestinal permeability due to the decrease in intercellular junctions between enterocytes [4,8,21]. This increase in permeability results in bacterial translocation and other products that promote inflammation [4,21]. The microbiota interacts with the immune system through the liver-intestine axis. Patients with MASLD experience a reduction in microbial species diversity within the gut microbiota [20]. Moreover, those with HCC related to MASLD exhibit an elevation in pathogenic genera, primarily *Bacteroides* and *Ruminococcaceae*. A reduction in protective genera such as *Akkermansia* and *Bifidobacterium* has also been seen, which in murine models seem to favor the integrity of the intestinal barrier and reduce hepatic inflammation [21]. In addition to contributing to perpetuating chronic inflammation, the greater conversion of primary to secondary bile acids affects the antitumor response of natural killer lymphocytes and produces an increase in fibroblast growth factor (FGF)-19, involved in the proliferation of hepatocytes [4,20–22].

Research into genetic factors contributing to the pathogenesis of HCC associated with MASLD is ongoing. Currently, the genetic variant most strongly linked to an increased risk of HCC progression is the single nucleotide polymorphism rs738409 of the "patatin-like phospholipase-3" (*PNPLA3*) gene, resulting in the I148M isoform of its encoded protein [4]. The frequency of this variant ranges from 17 to 49% across different ethnicities and geographic regions, with higher prevalence observed in Hispanic populations [23]. The protein, adiponutrin, encoded by the *PNPLA3* gene, plays a role in lipid export from the liver and the nucleotide substitution (isoleucine to methionine) disrupts protein function, leading to enhanced fat accumulation in hepatocytes and stellate liver cells, thereby promoting carcinogenesis [4,19]. Carriers of this variant face an elevated risk of developing cirrhosis and hepatocellular carcinoma, with homozygotes facing an even higher risk [4,19,23]. Additionally, ongoing investigations involve other genes such as human telomerase reverse transcriptase (*hTERT*). The shortening of telomeres in peripheral blood and the presence of *hTERT* mutations correlate with the risk of HCC development in MASLD subjects, though further research is warranted in this area [4].

3.2. Epidemiology

Primary liver neoplasms are the sixth most common type of cancer and rank third among the most frequent causes of cancer-related mortality [11]. HCC is the most common primary liver neoplasm, representing between 75 and 85% of all cases [8,24]. The highest incidences are recorded in Asia and Africa, with Mongolia having the highest incidence rate worldwide [24]. In these countries, HCC is associated with the hepatitis B virus.

Among MASLD patients, an estimated 20-30% progress to steatohepatitis associated with metabolic dysfunction (MASH), with 10-20% of MASH patients advancing to liver cirrhosis [24]. In MASLD-induced cirrhosis cases, the incidence of HCC ranges from approximately 0.5% to 2.6% [8,21]. With MASLD affecting more than a quarter of the global population and its prevalence rapidly rising alongside obesity rates, MASLD is poised to become the leading cause of liver disease. Consequently, an increase in MASLD-related HCC cases is anticipated [8,11,21]. Conversely, other etiologies of HCC, such as hepatitis B and C viruses, are declining due to vaccination and treatment strategies [7,25].

The primary risk factor for HCC development in MASLD patients is the presence of liver cirrhosis, though it can occur even without cirrhosis [8]. Risk is higher in patients with decompensated cirrhosis compared to those without prior decompensations [26]. Additionally, the emergence of HCC is closely linked to metabolic syndrome, with obesity—particularly central obesity—identified as an independent risk factor [8]. Type 2 diabetes mellitus exacerbates liver disease progression and HCC development by perpetuating chronic inflammation and oxidative stress. Notably, diabetes poses a higher HCC risk in men than in women and elevates risk with longer disease duration [8,24,27].

In a prospective study by Chen et al., the risk of HCC development was compared among patients with steatosis due to MASLD, MetALD, and alcohol-induced liver disease versus those with cirrhosis but without steatosis or other cardiovascular risk factors. The findings revealed a higher HCC risk in patients with steatosis, particularly in the MetALD subgroup (Hazard ratio: 2.91, CI: 2.11-4.03) compared to non-SLD without cardiometabolic risk factors [9,10].

3.3. Clinical Presentation

In various studies investigating HCC related to MASLD, age, sex, and comorbidities emerge as significant factors. Typically, MASLD-related HCC is diagnosed at an older age, with an average age of 73 years, compared to 66 and 70 years for hepatitis C and B, respectively [21]. In a meta-analysis conducted by Hao Tan et al., encompassing 61 studies and a total of 94,636 HCC patients (15,377 with MASLD-related HCC and 79,259 with HCC from other causes), no significant gender differences were noted [25]. However, other research indicates a higher prevalence in men [8,24,28]. MASLD-related HCC patients often exhibit a higher burden of comorbidities, notably hypertension, diabetes, and dyslipidemia, and are more likely to present with cardiovascular pathology at the time of diagnosis [11,25]. Additionally, they tend to have a higher body mass index, frequently demonstrating overweight or obesity [11,25,29].

Moreover, HCC related to MASLD manifests with larger lesions, with an average difference of 0.67cm (95% CI 0.35-0.98, $p=0.0087$). Additionally, lesions are more commonly uninodular [25]. Lastly, in an observational study in Italy involving 6,882 HCC patients diagnosed between 2002 and 2019, MASLD emerged as the leading cause of HCC. Despite being diagnosed at a more advanced stage compared to other causes, MASLD-related HCC exhibited lower mortality, suggesting a comparatively less aggressive disease course [7].

3.4. HCC without Cirrhosis

A notable feature of HCC related to MASLD is that approximately one-third of cases occur in patients without liver cirrhosis, setting it apart from HCC related to other liver diseases like viral hepatitis or autoimmune conditions [8,21,24].

In a meta-analysis comprising 19 studies and 168,571 patients, the prevalence of HCC related to MASLD without cirrhosis was 38%, whereas the prevalence of HCC without cirrhosis from other etiologies (e.g., alcohol or viral hepatitis) was 14.2% [21,30]. One plausible explanation for this clinical presentation is that, in a non-cirrhotic liver, there's less resistance to tumor expansion. Moreover, individuals with MASLD but without liver cirrhosis aren't typically included in HCC screening programs, potentially leading to delayed lesion detection [8,11,25].

3.5. Screening

The aim of screening for HCC is twofold: to reduce mortality attributed to HCC and to facilitate early detection of the neoplasia. To achieve these goals, accurate identification of the at-risk population is crucial [4,8]. Presently, guidelines recommend HCC screening via abdominal ultrasound every 4 to 6 months for all patients with liver cirrhosis, regardless of etiology [31,32]. Abdominal ultrasound offers the advantage of being non-invasive and radiation-free. However, its efficacy is contingent upon operator skill, and in individuals with significant central obesity, its sensitivity may be compromised. For patients with challenging ultrasound evaluations, alternative imaging techniques may be considered [3,8].

A particularity of HCC related to MASLD that differentiates it from other etiologies is that up to 40% of the cases develop in the absence of liver cirrhosis. The occurrence of HCC in MASLD patients without cirrhosis is relatively rare. Given the rapid increase in MASLD cases, screening all MASLD patients would be financially prohibitive. Therefore, at present, there is no justification for universal screening in all cases [3,4].

Today's challenge lies in identifying, within the subset of patients lacking liver cirrhosis, those at high risk and optimizing screening systems [33]. While obesity and type 2 diabetes are established risk factors for HCC development, their role in non-cirrhotic patients remains unclear [4]. Liver fibrosis severity correlates with an increased risk of HCC and mortality, prompting the development of tools to detect advanced fibrosis [26,33]. However, the nonlinear evolution of liver fibrosis complicates assessment. Liver biopsy, the gold standard for fibrosis determination, is invasive and prone to adverse effects and inter-observer variability, making non-invasive markers preferable for screening [26,33].

Several non-invasive tests, utilizing blood or serum markers or ultrasound techniques, are currently accessible and progressively employed for assessing liver fibrosis. Among those based on blood markers, alpha-fetoprotein (AFP) is widely studied as a HCC tumor marker, but its efficacy for early detection is debated due to varying sensitivities and potential false positives. While European guidelines recommend biannual ultrasound screening without AFP, American guidelines advocate combined screening to enhance ultrasound efficiency [32,34,35]. The Fibrosis-4 index (FIB-4) offers a simple, cost-effective tool for identifying high-risk HCC patients, showing good predictive ability for HCC in MASLD populations. The Non-Alcoholic Fatty Liver Disease (NAFLD) fibrosis score demonstrates superior predictive capability for HCC compared to other fibrosis indices [4,26,33,35,36]. The GALAD score, also based in blood markers along with age and sex, exhibits promising diagnostic capacity for HCC, providing specificity compared to AFP.

Hepatic elastography, such as Controlled Transient Elastography (VCTE), offers valuable fibrosis assessment, but interpretation can be challenging within indeterminate risk zones [3,33,36–39]. Unfortunately, both serological markers and elastographic tests have a gray area of indeterminate risk that further complicate decision-making [26]. Recently, the liquid biopsy has emerged as a potential tool for early HCC detection, with circulating tumor DNA, cells, and extracellular vesicles showing promise compared to serum AFP levels [4]. On the other hand genetic studies for high-risk patient detection currently lack sensitivity, specificity, and cost-effectiveness [4,40].

The latest guideline from the European Association for the Study of the Liver (EASL) suggests evaluating inclusion in hepatocarcinoma screening programs for patients with advanced fibrosis (F3) or cirrhosis identified through biopsy or elastography, irrespective of etiology. In contrast, the American society proposes initiating screening upon confirmation of advanced fibrosis by two non-invasive methods. These methods are categorized into three groups: imaging techniques (e.g., VCTE

or magnetic resonance imaging), point-of-care tests combining demographic and analytical parameters (e.g., FIB-4 or NAFLD fibrosis score), and specific blood tests (e.g., Enhanced Liver Fibrosis panel or Fibrospect 2). Additionally, the American guideline specifies that tests utilized should belong to different groups [4,31–33].

3.6. Prevention

Weight loss interventions have shown promise in mitigating the progression of MASLD, potentially reducing steatosis, steatohepatitis, and fibrosis. Evidence suggests that weight loss medications like orlistat and GLP-1 receptor agonists such as liraglutide, as well as bariatric surgery, are associated with a decreased incidence of HCC [26]. Moreover, dietary interventions play a crucial role in HCC prevention, with the Mediterranean diet often recommended due to its rich fiber, unsaturated fats, and vitamin content. Higher adherence to this diet has been linked to a reduced risk of HCC. Additionally, the Mediterranean diet offers added benefits in improving comorbidities associated with MASLD [26,41,42].

Physical activity has emerged as another protective factor against HCC. In the EPIC study, regular physical activity was associated with a 45% reduction in HCC risk, independent of other risk factors [8,43]. Furthermore, lifestyle modifications such as cessation of alcohol and tobacco consumption are essential for HCC prevention in MASLD patients [26,41,44].

Managing glycemic control is also of paramount importance in MASLD and metabolic syndrome. Oral antidiabetic medications, particularly metformin, have shown promise in reducing HCC risk, potentially through the reduction of IGF-1 levels. However, insulin or sulfonylureas may pose a higher risk [21,36,41,45]. Likewise, the treatment of dyslipidemia with statins appears to decrease the risk of HCC, particularly lipophilic statins like atorvastatin and simvastatin. This risk reduction is believed to be dose-dependent and attributed to their anti-inflammatory, antiangiogenic, and antiproliferative properties [21,36,42,44,46]. On the other hand, regular aspirin use, commonly employed for cardiovascular prevention, may also reduce HCC risk due to its anti-inflammatory effects and inhibition of COX-2. Studies have shown a significant reduction in HCC risk with regular aspirin use [21,41,42].

Considering the microbiome's role in HCC pathogenesis, the use of pre- and probiotics for prevention in MASLD has been proposed [41]. These supplements potentially decrease inflammation, improve intestinal barrier integrity, and modulate immune response, with minimal adverse effects. However, further research is needed to identify the most beneficial species for this condition [26,41].

3.7. Treatment of HCC Related to MASLD

To date, the therapeutic options for HCC related to MASLD are the same as for other etiologies, including locoregional and systemic therapies. However, the characteristics of this group of patients, both due to the usual presence of multiple cardiovascular risk factors and the diagnosis at older ages, may contraindicate some treatments. In some series, it is described that these patients have a higher use of liver resection, which may be related to a non-negligible proportion of HCC in the absence of underlying cirrhosis. Liver transplantation is a less used option in this group, mainly due to the larger tumor size at diagnosis, advanced age, and comorbidities. Moreover, the mortality on the waiting list is higher, mainly due to FCRVs related to MASLD. Also, obesity, especially when it comes to morbid obesity (with a BMI greater than 40 kg/m²), may contraindicate transplantation. The available evidence suggests that immunotherapy treatments may exhibit reduced efficacy in patients with MASLD-HCC [47]. However, these findings may be influenced by biases, as most studies compare patients with HCC of viral etiology with those of other etiologies, including MASLD, as well as alcohol consumption and autoimmune causes. This discrepancy could stem from the immune alterations present in MASLD patients. Notably, the microbiota is thought to play a critical role, with some authors even proposing investigating fecal microbiota transplantation as a potential treatment for MASLD-HCC [47]. Despite these challenges, there is a consensus among researchers regarding

the necessity of ongoing research to identify new therapeutic targets and develop more tailored treatments [20,45,47].

4. Discussion

The etiology of liver diseases has changed over the last few decades. Previously, viral hepatitis predominated, but currently, we are facing an exponential growth of liver disease related to the metabolic syndrome, in line with the global obesity pandemic. Its new nomenclature, MASLD, better reflects the relationship with this syndrome and its systemic consequences [5,7].

The current guidelines of the main scientific societies of hepatology are not specific for MASLD. These patients have some particularities compared to other etiologies, mainly older age, higher prevalence of cardiovascular pathology, and metabolic syndrome [3]. It is worth noting that according to some studies, up to 40% of the cases of HCC related to MASLD develop in patients who do not have liver cirrhosis [25]. In the analysis conducted by Hao Tan et al, in the cases of HCC in the group of patients with MASLD, only 33% were enrolled in screening programs, while in other pathologies it reached 56% [25]. This significant disparity prompts the question: should all MASLD patients undergo HCC screening, even in the absence of cirrhosis? As of now, the answer is no. There is consensus that efforts should focus on developing tools to identify those at higher risk of developing HCC. Thus, current research focuses on the development and validation of various tests and indices to detect advanced fibrosis, as it is known that the risk of HCC parallels liver fibrosis. To date, FIB-4, NFS, and GALAD are laboratory-based scores that provide good specificity and sensitivity in predicting hepatocarcinoma [3,4,26,33]. However, they are currently considered complementary tools and are not incorporated into algorithms due to the limited validation studies available.

The current guidelines from major hepatology societies worldwide recommend screening only in cases of advanced fibrosis, with minor variations between them and without differentiation based on etiology. As stated above, those guidelines, originally developed for viral hepatitis, which historically dominated liver disease worldwide, may need to adapt to the increasing prevalence of MASLD or include specific recommendations for this patient group, given its unique characteristics.

Various pharmacological and non-pharmacological strategies have been proposed for preventing hepatocarcinoma related to MASLD. However, large-scale controlled prospective studies are necessary to establish general recommendations [36]. While exercise stands out among non-pharmacological measures, specific guidelines are lacking. Regarding chemoprophylaxis, metformin, aspirin, and statins are prominent options, deemed safe drugs with potential to reduce HCC incidence. Nevertheless, prospective controlled studies are required to assess their risk-benefit profile for this indication, considering that many MASLD patients already receive these medications due to their common comorbidities [26,35,41]. Although numerous interventions are under investigation for hepatocarcinoma prevention in this population, it may be more cost-effective to prioritize primary prevention efforts for MASLD.

5. Conclusions

The prevalence of MASLD is on the rise, leading to an expected increase in hepatocarcinoma cases linked to MASLD. This condition more commonly affects older individuals who often have multiple comorbidities and typically present with larger lesions at diagnosis. Research is advancing on therapeutic strategies aimed at preventing hepatocarcinoma across various populations and demographics. However, up to 40% of hepatocarcinoma cases associated with MASLD occur in patients without liver cirrhosis, making them unsuitable for conventional ultrasound screening. Efforts are underway to develop non-invasive serological and imaging indices to identify high-risk individuals and tailor hepatocarcinoma screening for those without cirrhosis.

6. Future Directions

Developing risk stratification systems for hepatocarcinoma in MASLD patients without liver cirrhosis is essential. It is also equally crucial the validation of non-invasive risk prediction tools and the development of specific screening algorithms for MASLD. Additionally, further research is needed to understand the etiopathogenesis of hepatocarcinoma in MASLD to identify targeted therapeutic options.

References

1. Rinella, M.E.; Lazarus, J.V.; Ratziu, V.; Francque, S.M.; Sanyal, A.J.; Kanwal, F.; et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology*. 2023,78,1966–1986.
2. Han, S.K.; Baik, S.K.; Kim, M.Y. Non-alcoholic fatty liver disease: Definition and subtypes. *Clin Mol Hepatol*. 2023, 29, S5-S16.
3. Anstee, Q.M.; Reeves, H.L.; Kotsiliti, E.; Govaere, O.; Heikenwalder, M. From NASH to HCC: current concepts and future challenges. *Nat Rev Gastroenterol Hepatol*. 2019, 16, 411-428.
4. Valle Tovo, C.; de Mattos, A.Z.; Coral, G.P.; Sartori, G.D.P.; Villela Nogueira, L.; Both, G.T.; et al. Hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis. *World J Gastroenterol*. 2023, 29, 343–356.
5. Targher, G.; Byrne, C.D.; Tilg, H. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. *Gut*. 2024, 73, 691-702.
6. Eslam, M.; Newsome, P.N.; Sarin, S.K.; Anstee, Q.M.; Targher, G.; Romero-Gomez, M.; et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *J Hepatol*. 2020, 73,202–209.
7. Vitale, A.; Svegliati-Baroni, G.; Ortolani, A.; Cucco, M.; Riva, G.V.D.; Giannini, E.G.; et al. Epidemiological trends and trajectories of MAFLD-associated hepatocellular carcinoma 2002-2033: the ITA.LI.CA database. *Gut*. 2023, 72,:141–152.
8. Motta, B.M.; Masarone, M.; Torre, P.; Persico, M. From Non-Alcoholic Steatohepatitis (NASH) to Hepatocellular Carcinoma (HCC): Epidemiology, Incidence, Predictions, Risk Factors, and Prevention. *Cancers*. 2023, 22, 5458.
9. Chen, Y.T.; Chen, T.I.; Yang, T.H.; Yin, S.C.; Lu, S.N.; Liu, X.R. Long-term risks for cirrhosis and hepatocellular carcinoma across steatotic liver disease subtypes. *Am J Gastroenterol*. 2024.
10. Stauffer, K.; Stauber, R.E. Steatotic liver disease: metabolic dysfunction, alcohol, or both? *Biomedicines*. 2023, 8, 2108.
11. Phoolchund, A.G.S.;Khakoo, S.I. MASLD and the Development of HCC: Pathogenesis and Therapeutic Challenges. *Cancers*. 2024, 16, 259.
12. Younossi, Z.M.; Golabi, P.; Paik, J.M.; Henry, A.; Van Dongen, C.; Henry, L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology*. 2023,4,1335–1347.
13. Zhou XD, Targher G, Byrne CD, Somers V, Kim SU, Chahal CAA, et al. An international multidisciplinary consensus statement on MAFLD and the risk of CVD. *Hepatol Int*. 2023, 17, 773-791.
14. Ghazanfar, H.; Javed, N.; Qasim, A.; Zacharia, G.S.; Ghazanfar, A.; Jyala, A.; Shehi, E.; Patel, H. Metabolic dysfunction-associated steatohepatitis and progression to hepatocellular carcinoma: a literature review. *Cancers*. 2024, 16, 1214.
15. Yoneda, M.; Yamamoto, T.; Honda, Y.; Imajo, K.; Ogawa, Y.; Kessoku, T.; et al. Risk of cardiovascular disease in patients with fatty liver disease as defined from the metabolic dysfunction associated fatty liver disease or nonalcoholic fatty liver disease point of view: a retrospective nationwide claims database study in Japan. *J Gastroenterol*. 2021,56, 1022–1032.
16. Zhou, X.D.; Cai, J.; Targher, G.; Byrne, C.D.; Shapiro, M.D.; Sung, K.C.; et al. Metabolic dysfunction-associated fatty liver disease and implications for cardiovascular risk and disease prevention. *Cardiovasc Diabetol*. 2022, 21, 270.
17. Sanna, C.; Rosso, C.; Marietti, M.; Bugianesi, E. Non-alcoholic fatty liver disease and extra-hepatic cancers. *Int J Mol Sci*. 2016, 17, 717.
18. Mitsala, A.; Tsalikidis, C.; Romanidis, K.; Pitiakoudis, M. Non-Alcoholic Fatty Liver Disease and Extrahepatic Cancers: A Wolf in Sheep's Clothing? *Curr Oncol*. 2022, 29, 4478–4510.
19. Streba, L.A.M.; Vere, C.C.; Rogoveanu, I.; Streba, C.T. Nonalcoholic fatty liver disease, metabolic risk factors, and hepatocellular carcinoma: An open question. *World J Gastroenterol*. 2015, 21, 4103-4110.
20. Loomba, R.; Friedman, S.L.; Shulman, G.I. Mechanisms and disease consequences of nonalcoholic fatty liver disease. *Cell*. 2021, 184, 2537–2564.
21. Huang, D.Q.; El-Serag, H.B.; Loomba, R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol*. 2021, 18, 223–238.

22. Behary, J.; Amorim, N.; Jiang, X.T.; Raposo, A.; Gong, L.; McGovern, E.; et al. Gut microbiota impact on the peripheral immune response in non-alcoholic fatty liver disease related hepatocellular carcinoma. *Nat Commun.* 2021, 12,187.
23. Kanda, T.; Goto, T.; Hirotsu, Y.; Masuzaki, R.; Moriyama, M.; Omata, M. Molecular mechanisms: Connections between nonalcoholic fatty liver disease, steatohepatitis and hepatocellular carcinoma. *Int J Mol Sci.* 2020, 21, 1525.
24. McGlynn, K.A.; Petrick, J.L.; El-Serag, H.B. Epidemiology of Hepatocellular Carcinoma. *Hepatology.* 2021, 73, 4-13.
25. Tan, D.J.H.; Ng, C.H.; Lin, S.Y.; Pan, X.H.; Tay, P.; Lim, W.H.; et al. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. *Lancet Oncol.* 2022, 23, 521–530.
26. Cernea, S.; Onişor, D. Screening and interventions to prevent nonalcoholic fatty liver disease/nonalcoholic steatohepatitis-associated hepatocellular carcinoma. *World J Gastroenterol.* 2023, 29, 286-309.
27. Jarvis, H.; Craig, D.; Barker, R.; Spiers, G.; Stow, D.; Anstee, Q.M.; et al. Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies. *PLoS Med.* 2020, 17, e1003100.
28. Petrick, J.L.; Florio, A.A.; Znaor, A.; Ruggieri, D.; Laversanne, M.; Alvarez, C.S.; et al. International trends in hepatocellular carcinoma incidence, 1978–2012. *Int J Cancer.* 2020, 147, 317–330.
29. Yasui, K.; Hashimoto, E.; Komorizono, Y.; Koike, K.; Arii, S.; Imai, Y.; et al. Characteristics of Patients With Nonalcoholic Steatohepatitis Who Develop Hepatocellular Carcinoma. *Clin Gastroenterol Hepatol.* 2011,9, 428–433.
30. Stine, J.G.; Wentworth, B.J.; Zimmet, A.; Rinella, M.E.; Loomba, R.; Caldwell, S.H.; et al. Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. *Aliment Pharmacol Ther.* 2018, 48, 696-703.
31. Loomba, R.; Lim, J.K.; Patton, H.; El-Serag, H.B. AGA clinical practice update on screening and surveillance for hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: expert review. *Gastroenterology.* 2020, 158, 1822-1830.
32. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol.* 2018, 69, 182-236.
33. Taru, M.G., Lupsor-Platon, M. Exploring Opportunities to Enhance the Screening and Surveillance of Hepatocellular Carcinoma in Non-Alcoholic Fatty Liver Disease (NAFLD) through Risk Stratification Algorithms Incorporating Ultrasound Elastography. *Cancers.* 2023, 15, 4097.
34. Verdelho Machado, M. The growing landscape of NAFLD-Associated hepatocellular carcinoma and its impact in surveillance. *GE Port J Gastroenterol.* 2023, 31, 14-23.
35. Alexander, M.; Loomis, A.K.; Van Der Lei, J.; Duarte-Salles, T.; Prieto-Alhambra, D.; Ansell, D.; et al. Risks and clinical predictors of cirrhosis and hepatocellular carcinoma diagnoses in adults with diagnosed NAFLD: Real-world study of 18 million patients in four European cohorts. *BMC Med.* 2019, 17.
36. Shah, P.A.; Patil, R.; Harrison, S.A. NAFLD-related hepatocellular carcinoma: The growing challenge. *Hepatology.* 2023, 77, 323-338.
37. Cagnin, S.; Donghia, R.; Martini, A.; Pesole, P.L.; Coletta, S.; Shahini, E.; Boninsegna, G.; Biasiolo, A.; Pontisso, P.; Giannelli, G. Galad score as a prognostic marker for patients with hepatocellular carcinoma. *Int J Mol Sci.* 2023, 24, 16485.
38. Guan, M.C.; Zhang, S.Y.; Ding, Q.; Li, N.; Fu, T.T.; Zhang, G.X.; He, Q.Q.; Shen, F.; Yang, T.; Zhu, H. The performance of GALAD score for diagnosing hepatocellular carcinoma in patients with chronic liver diseases: a systematic review and meta-analysis. *J Clin Med.* 2023, 12, 949.
39. Berhane, S.; Toyoda, H.; Tada, T.; Kumada, T.; Kagebayashi, C.; Satomura, S.; et al. Role of the GALAD and BALAD-2 Serologic Models in Diagnosis of Hepatocellular Carcinoma and Prediction of Survival in Patients. *Clin Gastroenterol Hepatol.* 2016, 14, 875-886.
40. Chen, V.L.; Xu, D.; Wicha, M.S.; Lok, A.S.; Parikh, N.D. Utility of liquid biopsy analysis in detection of hepatocellular carcinoma, determination of prognosis, and disease monitoring: a systematic review. *Clin Gastroenterol Hepatol.* 2020, 18, 2879-2902.
41. Lange, N.F.; Radu, P.; Dufour J.F. Prevention of NAFLD-associated HCC: Role of lifestyle and chemoprevention. *J Hepatol* 2021, 75,1217–1227.
42. Geh D, Anstee QM, Reeves HL. NAFLD-Associated HCC: Progress and Opportunities. *J Hepatocell Carcinoma.* 2021 Apr;Volume 8:223–39.
43. Baumeister, S.E.; Schlesinger, S.; Aleksandrova, K.; Jochem, C.; Jenab, M.; Gunter, M.J.; et al. Association between physical activity and risk of hepatobiliary cancers: A multinational cohort study. *J Hepatol.* 2019,70, 885–892.
44. Ahmad, M.I.; Khan, M.U.; Kodali, S.; Shetty, A.; Bell, S.M.; Victor, D. Hepatocellular Carcinoma Due to Nonalcoholic Fatty Liver Disease: Current Concepts and Future Challenges. *J Hepatocell Carcinoma.* 2022, 9, 477–496.

45. Marengo, A.; Rosso, C.; Bugianesi, E. Liver cancer: Connections with obesity, fatty liver, and cirrhosis. *Annu Rev Med.* 2016, 67,103–117.
46. Islam, M.M.; Poly, T.N.; Walther, B.A.; Yang, H.C.; Li, Y.C. Statin use and the risk of hepatocellular carcinoma: A meta-analysis of observational studies. *Cancers.* 2020, 12, 671.
47. Pinter, M.; Pinato, D.J.; Ramadori, P.; Heikenwalder, M. NASH and Hepatocellular carcinoma: immunology and immunotherapy. *Clin Cancer Res.* 2023, 29, 513-520.

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