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Metabolic dysfunction-associated steatotic liver disease: a key factor in hepatocellular carcinoma therapy response

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Abstract

The conceptual evolution of non-alcoholic fatty liver disease (NAFLD) to what, since 2023, is called metabolic dysfunction-associated steatotic liver disease (MASLD) not only represents a change in the classification and definition of the disease but also reflects a broader understanding of this heterogeneous condition, which still with many aspects to refine. Although the definition of NAFLD can be interchanged to a high percentage with the new MASLD concept in different aspects, MASLD has been proposed as a relevant factor that influences the response to new immunotherapeutic treatments in the management of MASLD-related hepatocellular carcinoma (HCC), compared to HCC of other etiologies. This indicates that the etiology of HCC plays a relevant role in the prognosis, highlighting the urgency of evaluating treatment regimens for this subgroup of patients in upcoming clinical trials. A better understanding of the pathophysiology of MASLD generates strategies that not only aid in its management but also provide strategies to directly intervene in the carcinogenesis of HCC.

Keywords: Hepatocellular carcinoma, NAFLD, MASLD, HCC therapy, immunotherapy

INTRODUCTION

In the last two decades, there has been a significant global increase in the prevalence of the entities associated with fatty deposits in the liver, as well as in the incidence of hepatocellular carcinoma (HCC), the most common primary liver neoplasia[1-7]. Although the heterogeneity of individuals affected by these diseases is complex, a deeper understanding of their pathophysiology has led to therapeutic advancements that have not only changed the treatments of choice but also foreseen a potential revolution in their management[8]. The conceptual shift from non-alcoholic fatty liver disease (NAFLD), essentially a diagnosis of exclusion, to metabolic dysfunction-associated steatotic liver disease (MASLD), which has occurred in recent years (2020-2023)[9-15], reflects the confrontation of scientific explanations with clinical reality.

BEYOND THE MASLD TERMINOLOGY CHANGE

In 2000, a nomenclature change from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed[9]. This change aimed to provide greater precision regarding the association with metabolic dysfunction while retaining the term "fatty", which many considered stigmatizing. Additionally, the MAFLD definition required the inclusion of individuals with at least two metabolic risk factors for its diagnosis.

In 2023, the conclusions of a multidisciplinary consensus (organized by the American Association for the Study of Liver Disease, AASLD; the European Association for the Study of the Liver, EASL; in collaboration with the Asociación Latinoamericana para el Estudio del Hígado, ALEH; and with the participation of other stakeholders, even patient representatives) were published[10]. Based on the Delphi methodology, the consensus aimed to evaluate a change in the nomenclature and/or definition of what was previously known as NAFLD. The consensus focused on five key areas, one of which was to help patients and health professionals better understand the disease. The term "steatotic liver disease" (SLD) was adopted as an umbrella term to encompass all conditions leading to hepatic steatosis, including NAFLD, alcoholic-associated liver disease (ALD), and other related liver conditions[16,17]. This consensus mainly reflects the intention to associate the presence of cardiovascular risk factors, which are indicators of insulin resistance, as central drivers of hepatic steatosis in the MASLD concept[10].

Since then, relevant communications have concluded that most of the data related to NAFLD or MAFLD remain valid within the context of the new definition of MASLD, despite the evolved concept indicating that they are not identical[11-14]. In nearly all studies that have compared the old and new terminologies, the percentage of agreement for classifying patients as NAFLD and MASLD exceeds 95%[15-17]. This high concordance suggests that existing data on the epidemiology, natural history, biomarkers, and clinical trials in the NAFLD population could be extrapolated to MASLD patients[17]. Although the MAFLD terminology is still in use and continues to fuel the debate on the change of nomenclature, it omits alcohol intake assessment in its definition, complicating the identification of high-risk populations. Emerging data suggest that there are notable differences, mainly in mortality rates and the risk of complications such as hepatic fibrosis, cardiovascular disease, and chronic kidney disease[18-21]. Pennisi *et al.* evaluated the prognostic impact of NAFLD and MAFLD on overall mortality, cardiovascular mortality, non-fatal cardiovascular events, risk of developing chronic kidney disease, and extrahepatic neoplasms. They reported higher overall mortality in the MAFLD population; however, it should be noted that the studies included in their analysis showed significant heterogeneity ($I^2 = 73\%$; $P < 0.01$) for overall mortality, with a 12%-15% higher mortality rate in MAFLD compared to NAFLD[22].

Additionally, metabolic dysfunction-associated steatohepatitis (MASH) has been proposed to replace non-alcoholic steatohepatitis (NASH) to describe patients with MASLD and active necroinflammation

characterized by the presence of lobular inflammation and hepatocyte ballooning[10,14,16]. A new definition was also included for patients with "non-abusive" alcohol consumption: metabolic dysfunction- and alcohol-associated liver disease (MetALD), which refers to individuals with moderate alcohol consumption (30-60 g per day or 210-420 g per week in men, and 20-50 g per day or 140-350 g per week in women)[10,14,16,17]. This conceptual refinement has improved the identification of subpopulations with distinct prognostic implications, such as the lean-MASLD variant[17]. Mortality rates for both MetALD and ALD are significantly higher compared to MASLD[17,23-28].

Cautions regarding the new terminology highlight the potential for overdiagnosis in the MetALD subtype. Indicators of metabolic dysfunction, such as hypertriglyceridemia and arterial hypertension, may reflect alterations associated with alcohol intake rather than with metabolic dysfunction itself, potentially affecting the assessment of complications risks[29]. Petrie *et al*., by studying an unselected North American population, pointed out the importance of considering the effects of arterial hypertension and triglycerides as associated with moderate alcohol consumption rather than as direct outcomes of increased insulin resistance or lipotoxicity. This distinction complicates the accurate characterization of the effects across different patient subtypes with fatty liver disease, especially when alcohol consumption is self-reported[29]. Ciardullo *et al.* reported different mortality rates by subgroup, with the MetALD subtype showing higher mortality rates compared to MASLD, across all causes of death, as well as in mortality associated with cardiovascular diseases and cancer[30].

In real-life settings, a variety of risk factors, beyond the classic metabolic ones or the high risk of alcohol consumption, can influence the prognosis in various ways[31-37]. García-Nieto *et al.* observed a substantially elevated prevalence of advanced fibrosis concomitant with SLD and MASLD among patients with immune-mediated inflammatory diseases (IMID) in comparison to controls, despite no significant differences in the prevalence of SLD and MASLD between the cohorts[37]. Therefore, these authors suggest that independent mechanisms or molecules could differentially drive the pathogenesis of IMID compared to control MASLD cases[37]. In this sense, the role of metabolic and immune-mediated comorbidities, as indicated by García-Nieto *et al*., highlights the need to evaluate these subgroups of patients, especially in relation to the development of primary hepatic neoplasms[37]. Notably, it is also important to recognize that type 2 diabetes mellitus (T2DM) is the risk factor with the greatest impact on the development of MASLD, fibrosis progression, and HCC[31-35,38].

The controversy surrounding the broader inclusive capacity of the new MASLD concept, specifically its failure to accurately reflect medium- and long-term complications, raises the possibility that the dimensions of metabolic dysfunction that involves conceptual changes may serve as indicators of deeper effects on the pathophysiology of these diseases, which are still being explored[39]. These effects are becoming increasingly apparent in the response to systemic treatments in the population with HCC associated with NAFLD/MAFLD/MASLD[32]. We could encompass these effects under what might be termed immune dysfunction associated with SLD, particularly concerning the tissue microenvironment (both tumor and non-tumor)[40].

CONCEPTUAL EVOLUTION OF CANCER BIOLOGY

From the earliest descriptions of neoplastic diseases in the Edwin Smith Papyrus[41] (breast tumors) and the Ebers Papyrus[42] (skin and uterine tumors, among others) to the identification of cancer hallmarks by Hanahan and Weinberg[43] at the beginning of the 21st century, the conceptual framework of tumor biology has evolved significantly[44,45]. Initially, grounded in the reductionist "clonal genetic model of cancer", which focused on the sum of mutations, our understanding has now expanded to encompass the intricate

interactions within the tumor microenvironment[43-45].

Despite intense research in the search for specific recurrent mutations that determine tumor progression, it has not been possible to determine an exclusive role for them[44]. Instead, changes in gene expression associated with tumor progression have been identified[44]. As noted by Feinberg *et al.* in 2006, genetic mechanisms were not the only pathway to genetic disruption in cancer[46]; this led to the proposal of the "epigenetic progenitor model of cancer". According to this model, the epigenetic disruption of progenitor cells is a critical event not only for the development of cancer, but also for tumor progression and late-stage heterogeneity observed in tumors derived from these cells[45]. In this way, four additional concepts were added to the cancer hallmarks in 2011: genomic instability, tumor-promoting inflammation, reprogramming of energy metabolism, and evasion of immune destruction[44]. These additions helped to shape the conceptual framework of the tumor microenvironment[44-45].

A better understanding of the influence of the different components of the tumor microenvironment has highlighted the fundamental role of the immune evasion mechanisms in tumor cells. In 2013, Chen and Mellman detailed what they termed the "cancer-immunity cycle", outlining the steps necessary to initiate, proceed, and expand the immune response for the effective elimination of tumor cells[47]. The influence of the tumor microenvironment on the cancer-immunity cycle can be affected by epigenetic changes that, in the case of HCC, may be determined by the etiological factors of the underlying liver disease[46-48]. The use of checkpoint inhibitors over the past 10 years has marked a turning point in cancer management strategies[48]. Anti CTLA-4 (Cytotoxic T-Lymphocyte-Associated protein 4) and anti PD-1 (programmed cell death protein 1)/anti PD-L1 (programmed death-ligand 1) therapies play crucial roles, mainly observed in the steps of priming and activation of T lymphocytes (CTLA-4), as well as in the inhibition of the immunostatic blockade (PD-1/PD-L1), respectively[47]. The fundamental strategy of initial systemic treatments against HCC has been to block tumor neoangiogenesis mechanisms[48].

TREATMENT OUTCOMES FOR MASLD-RELATED HCC

The treatment response rate of MASLD-related HCC has been evaluated based on the type of treatment received and compared with the response rate of non-MASLD-related HCC cases. Response rates have been analyzed in the contexts of liver resection (LR)[49-51], liver transplantation (LT)[52-59], locoregional therapy[60-62], and systemic therapy[63,64] of HCC.

Differences in overall survival (OS) have been observed in patients with MASLD-related HCC undergoing surgical resection compared to patients with HCC of different etiologies[49-51]. Molinari *et al.*, in a meta-analysis of 14 studies that included 7,226 patients, described an improvement in disease-free survival (DFS) and OS after LR in patients with MASLD-related HCC compared to those with HCC of other etiologies[49]. Chin *et al.*, in another meta-analysis of 9 studies evaluating 5,579 patients, also reported improvements in both DFS and OS[50]. It should be noted that in Molinari *et al.*'s study, the prevalence of cirrhosis in the two groups evaluated was similar, although the retrospective nature of the studies limits the assessment of adequate inclusion of patients with the metabolic comorbidities typical of MASLD[49]. Lin *et al.* evaluated the impact of the new MASLD concept on the OS and recurrence-free survival (RFS) in patients with HCC and chronic hepatitis B virus infection (HBV) at Barcelona Clinic Liver Cancer classification (BCLC) stage 0/A after liver resection[51]. They found no differences in RFS and OS between the MASLD and non-MASLD groups[51]. However, within the MASLD group, the lean-MASLD subgroup was identified as a risk factor for recurrence, suggesting that further analysis of the different MASLD subgroups is required[51].

In the context of LT, Wong *et al.* presented registry data from the United Network for Organ Sharing (UNOS) covering the period from 2002 to 2012[52]. The data revealed the prevalence of T2DM across different etiological groups: 12.6% for ALD, 13.6% for HCV, increasing to 24.0% in patients with HCC, and 35.5% in those with metabolic-associated steatohepatitis (MASH)[52]. Furthermore, patients with MASH had higher post-transplant survival [hazard ratio (HR) = 0.69; 95%CI: 0.63-0.77] and lower risk of graft loss (HR = 0.76; 95%CI: 0.69-0.83) compared with those with viral etiology or HCC, despite higher rates of body mass index (BMI), T2DM, and cardiovascular disease[52]. Conversely, data from the European Liver Transplant Registry presented in 2019 showed no significant difference in post-transplant survival (HR = 1.10; 95%CI: 0.97-1.24) or graft survival (HR = 1.02; 95%CI: 0.90-1.15) between MASH and other etiologies[53]. HCC was more common among recipients transplanted for MASH (39.1% *vs.* 28.9%, $P < 0.001$). This registry did not determine the prevalence of T2DM[53].

In addition, the characteristics of the donor should not be overlooked. Zamora-Olaya *et al.* from the Reina Sofía University Hospital (Córdoba, Spain) demonstrated that atheromatosis of the donor's hepatic artery is an independent risk factor for the development of hepatic artery thrombosis (OR = 17.79; $P = 0.008$)[54]. Evaluation of atherosclerosis is not usually performed routinely in donor assessments. Donors are usually older than transplant candidates, and their most frequent cause of death is cerebrovascular disease, which confers them an inherent adverse metabolic profile. In this series of patients[54], the prevalence of hepatic steatosis between donors with and without atherosclerosis of the hepatic artery was not different. However, if we consider hepatic artery atheromatosis as a surrogate marker of metabolic dysfunction, this subtype of dysfunction could be inferred. On the other hand, in this same series[54], the authors describe an unexpected protective factor of ALD against the development of hepatic artery thrombosis (OR = 0.24; 95%CI: 0.06-0.97; $P = 0.046$), in contrast to the absence of influence from the etiology of liver disease on the development of artery thrombosis. However, they point out that most of these studies were carried out before the redefinition of the MASLD/MetALD concepts, and this absence of association must be confirmed in prospective series.

Holzner *et al.* reported one of the largest single-center series of LT for MASH-related HCC (MASH-HCC) from Mount Sinai Medical Center[55]. They evaluated data from 2001 to 2017, comparing MASH-HCC ($n = 51$) with non-MASH-HCC ($n = 584$), and found no significant differences in OS and RFS. This case study analyzed the tumor risk characteristics of the explant and found no significant differences between MASH-HCC and non-MASH-HCC, except for a greater amount of viable tumor tissue in the MASH-HCC group (3 *vs.* 1, $P < 0.001$)[55]. This contrasts with previous reports[56,57], which noted fewer high-risk features associated with MASH-HCC in the histological study of the explant. High-risk tumor features included: more than 3 tumors, the largest tumor size greater than 5 cm, the presence of vascular invasion, the presence of metastases, and poor tumor differentiation. Although most reported series conclude that there are no significant differences in the post-transplant outcomes between MASH-HCC and non-MASH-HCC[52,53,55-57], these conclusions should be interpreted with caution. The metabolic morbidity associated with MASLD may influence post-surgical complications[58] or the type of tumor recurrence[59], particularly in the understaged subgroup (especially in cases where understaging occurs following treatment with checkpoint inhibitors).

Sadler *et al.*, evaluating a cohort of MASH-HCC *vs.* non-MASH-HCC patients at two reference centers, found that MASH status was a protective factor against recurrence in patients with tumors beyond Milan criteria (HR = 0.21; 95%CI: 0.05-0.86; $P = 0.029$)[59]. Although the difference in the proportion of patients with microvascular invasion between the MASH group (57.9%) and the non-MASH group (36.6%) was not statistically significant ($P = 0.07$), it highlights a difference in tumor biology[59]. Notably, in the MASH-HCC

subgroup, late recurrence (> 4 years post-transplant) was observed in 4 patients[59]. In contrast, Kern *et al.*, analyzing data from their center at Innsbruck Medical Centre (Austria), found that patients with MASH had a higher incidence of advanced HCC (beyond the Milan criteria) compared to those with ALD, HCV, and other indications (P = 0.034)[58]. Additionally, postoperative complications were significantly higher in the MASH cohort (P = 0.048). The study highlighted cofactors such as diabetes and infections, reporting a prevalence of T2DM in 40% of MASH patients, 31.7% of ALD patients, 14.6% of HCV patients, and 15.4% of patients with other etiologies[58]. However, no differences in OS were detected when transplant patients were stratified by the presence or absence of T2DM[58]. The accuracy of diagnosing MASH in registry studies has been heterogeneous across different research groups[63,64]. This variability is critical because it impacts patient outcomes due to the disease's characteristics and the effects of its comorbidities[32,36]. Accurate diagnosis is, therefore, essential for optimizing the treatments that patients will receive.

There are few reports on the evolution of MASH-HCC in response to locoregional therapies, with a small number of patients being studied[60-62]. These reports have not identified any significant differences in terms of progression time, radiological response, or complications compared to non-MASH-HCC[60-62]. The response rate to systemic treatments for HCC has not been very high[60,61]. However, in recent years, the use of checkpoint inhibitors and different combination strategies has increased the response rate, positively impacting OS. Despite these advances, the improvement in response rates has yet to exceed 35%[63,64].

MASLD-RELATED HCC IN NON-CIRRHOTIC PATIENTS

In the population with "non-cirrhotic" liver diseases, various events can trigger fibrogenesis, which may progress or regress at different rates[65-68]. This process can ultimately lead to established cirrhosis and its associated comorbidities[65-71]. In methodologically selected populations (such as review studies and meta-analyses based on paired biopsies), examining the different subtypes of NAFLD (NAFL, NASH), it was observed that the rate of fibrosis progression can vary even within each subtype, identifying both slow and rapid fibrosis progressors[72-75]. The rates of fibrosis progression and regression differ depending on whether the study is based on a population database or not, as well as whether it includes only histological diagnoses or non-invasive techniques. The rate of fibrosis progression is a recognized estimator of potential complications, including the development of HCC[76-79]. Estimates on the rates of fibrosis progression have been fundamental for predicting the future impact of these entities, facilitating efficient resource allocation across all areas involved in patient care[75,76]. As an independent prognostic marker of hepatic-related events (such as decompensation in the form of ascites, variceal digestive bleeding, encephalopathy, jaundice, and HCC), the development of significant or advanced liver fibrosis is established as a critical factor, regardless of the presence or absence of MASH. In addition, it correlates with an increased risk of cardiovascular events and extrahepatic cancer[74-79]. Sanyal *et al.*, in a cohort of patients with MASH and advanced fibrosis, confirmed that fibrosis is the key determinant of disease progression, consistent with findings from other significant MASH cohorts[80]. However, an interesting observation in their results was that 1 in 7 patients developed clinical complications (such as variceal gastrointestinal bleeding) despite having a hepatic venous pressure gradient (HVPG) of less than 10 mmHg. This challenges the commonly accepted threshold for clinically significant complications of portal hypertension, which is typically set at HVPG levels above 10 mmHg. These findings suggest that the inflammatory processes associated with MASH may overlap early with carcinogenic mechanisms, potentially bypassing the need for progression to cirrhosis.

Vitellius *et al.* recently reported on a French cohort of 354 cases of MASLD-related HCC, in which 35% occurred in non-cirrhotic patients[81]. These non-cirrhotic patients, despite having poor prognostic factors (such as advanced age and greater tumor burden), demonstrated better liver function, which allowed for a more aggressive treatment approach and, overall, better survival compared to patients with cirrhosis.

Reviewing the major series of reports[81-85] on MASLD-related HCC reveals that the proportion of non-cirrhotic cases ranges from 35%-55% [Table 1]. The heterogeneity in response rates to curative treatments in MASLD-related HCC may be attributed to various factors, including the fact that 72% of diagnoses are incidental[81]. This is largely because non-cirrhotic patients fall outside the target population for HCC screening programs. Nonetheless, the average percentage of MASLD-HCC cases in non-cirrhotic patients (40%) is higher than that observed for other causes in the published series. Tan *et al.*, in a systematic review and meta-analysis involving 13,577 individuals with MASLD-HCC, noted that non-cirrhotic patients were less likely to receive liver transplantation but more likely to undergo liver resection[85]. They had a similar likelihood of receiving ablation, and overall, patients with MASLD-related HCC were just as likely to receive curative therapies as those with HCC from other etiologies[85].

MASLD is a heterogeneous clinical and pathophysiological condition characterized by several subphenotypes, each with varying immunoregulatory effects that are just beginning to be understood in terms of their impact on the efficacy of new treatments for HCC[32,36]. An underlying genetic predisposition to MASLD has been established, particularly involving alterations in patatin-like phospholipase domain-containing 3 (PNPLA3) and transmembrane 6 superfamily member 2 (TM6SF2), with the p.I148M and p.E167K variants, respectively, being linked to MASLD[86-93]. Additionally, a genetic risk stratification has been developed for entities with metabolic dysfunction[90,91]. It should be mentioned that these polymorphisms have also been associated with the development of HCC in other liver diseases unrelated to MASLD, such as ALD and chronic hepatitis C virus infection (HCV)[91], although in this study, the MASLD population comprised around 12%. Bianco *et al.* demonstrated that the polygenic risk score (PRS) associated with alleles in four genes - PNPLA3, TM6SF2, membrane-bound O-acyltransferase domain-containing 7 (MBOAT7), and glucokinase regulatory protein (GCKR) - improves the accuracy of HCC detection and may aid in stratifying HCC risk in individuals with dysmetabolism, including those without severe liver fibrosis[92]. Thomas *et al.* also evaluated the PRS in an Asian population with NAFLD and assessed its association with the risk of HCC[93]. They concluded that genetically determined NAFLD may play a potential causal role in HCC development[93]. Chalasani *et al.*, evaluating data from nine centers in North America (MASH Clinical Research Network - MASH CNR - database), demonstrated the influence of the PNPLA3 polymorphism, along with other modifiable and non-modifiable risk factors (age, sex, diabetes, and advanced fibrosis), on the risk of developing a major adverse liver outcome (MALO) in MASLD[94]. They reported a HR of up to 7.78 (95%CI: 4.39-13.81; E value: 15.04; CI: 8.25) in patients with the PNPLA3 GG polymorphism and advanced fibrosis.

To identify phenotypes that may present worse outcomes in SLD subgroups, it is important to consider the lean-MASLD or non-obese MASLD subgroup[94-97]. Approximately 40% of MASLD patients are non-obese, with 20% categorized as lean. Among these, nearly 30% have MASH, and almost 30% have significant fibrosis[96,97]. These patients also share lower OS rates with the MetALD population and experience higher rates of extrahepatic events, such as cardiovascular mortality and cancer development[94-103]. Sripongpun *et al.* recently presented their data analyzing the NHANES III cohort (the third National Health and Nutrition Examination Survey that covers the years 1988-1994) with a follow-up of up to 27 years, showing an association of a 16% increase in mortality in patients with MASLD compared to people without SLD[104,105]. From their data, we highlight that the MetALD subgroup presented an increase of 33% but in ALD of up to 75%. The authors stratified the risk of developing complications using both FIB-4 (Fibrosis-4 index) and SAFE (steatosis-associated fibrosis estimator) scores (the latter designed to discriminate patients with non-advanced fibrosis). In its multivariate analysis, the SAFE score manages to differentiate an increase in mortality of 31% and 90% in the intermediate and high-risk groups, respectively, in contrast to the FIB-4, which only detects a significant increase in mortalityin the high-risk subgroup (FIB-4 > 2.26) of 53%. Therefore, robust

Table 1. MASLD-related HCC in people non-cirrhotic

Author	Year	Country	Total cases MASLD-HCC	Cirrhosis *n*, (%)	Non-cirrhosis *n*, (%)	Reference
Mittal *et al.*	2016	United States	107	70 (65.4%)	37 (34.6%)	[82]
Wong *et al.*	2017	United States	5898	2572 (43,6%)	3326 (56.4%)	[83]
Stine *et al.*	2018	Multiple*	1191	738 (62%)	453 (38%)	[84]
Tan *et al.*	2022	Multiple*	15377	9457 (61.5%)	5920 (38.5%)	[85]
Vitellius *et al.*	2024	France	354	230 (65%)	124 (35%)	[81]

*Systematic review and meta-analysis. MASLD: Metabolic dysfunction-associated steatotic liver disease; HCC: hepatocellular carcinoma.

epidemiological data on these subgroups, particularly regarding the interaction between various metabolic risk factors[39,106,107], remain an unmet medical need. An example of this was recently demonstrated by Burke *et al.*, pointing out that patients with non-viral liver disease are poorly represented in studies that evaluate predictive models for the development of HCC, especially in the subgroups of ALD and MASLD, which are the two dominant etiologies in the West associated with HCC[108].

CONSIDERATIONS IN THE PATHOPHYSIOLOGY OF MASLD-RELATED HCC

MASLD has been linked not only to the development of HCC, but also other hepatic (biliary), gastrointestinal (colorectal, esophagus, stomach, pancreas), and extra-digestive (breast, thyroid, prostate, gynecological, urinary system, and lung) malignancies[109]. While detailing the pathophysiological mechanisms of MASLD-related HCC is beyond the scope of this review, these mechanisms generally can be grouped into the following interacting factors: genetic predispositions, metabolic dysfunction, chronic inflammation and immune dysfunction, lipid metabolism alterations and oxidative stress (lipotoxicity), fibrosis/cirrhosis development, molecular signaling mechanisms, and the gut microbiome[109]. The pathophysiology connecting MASLD with extrahepatic malignancies likely follows similar interactions, though it may develop independently of liver fibrosis severity[80,109,110].

Since the first pathophysiological models for MASH (formerly NASH) framed its development as a succession of "two hits" events[111], knowledge on this topic has evolved significantly, now positioning tissue macrophages as central to the initiation and progression of inflammation and liver fibrosis[112,113]. Kupffer cell activation, in particular, has been linked to several signaling pathways: the gut-liver axis, where increased intestinal permeability and lipopolysaccharides (LPS) activate Toll-like receptors (TLRs); molecules associated with liver damage, such as histidine-rich glycoprotein (HRG) and danger-associated molecular patterns (DAMPs); free fatty acids (FFAs) acting through TLRs and adipokines; and cholesterol along with its metabolites via scavenger receptor A (SCA)[112].

A key milestone in understanding liver carcinogenesis was achieved in 2015 by Zucman-Rossi *et al.*, who conducted whole-exome sequencing and identified the main mutations in driver genes that participate in critical signaling pathways involved in hepatocarcinogenesis[114]. These signaling pathways include those involved in telomere maintenance, WNT/β-catenin signaling, p53 cell cycle regulation, epigenetic modifications, oxidative stress signaling, and phosphoinositide 3-kinases/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) and rat sarcoma virus/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase (RAS/RAF/MAPK) pathways. Based on these findings, they proposed two molecular subclasses of HCC: proliferative (mainly associated with HBV-related HCC) and non-proliferative (which includes HCCs associated with mutations in WNT signaling and those exhibiting immune response behaviors), the latter being the most frequent HCV- and alcohol-related HCC. One

limitation of this approach is that it is based on post-surgical HCC samples, which are typically from more advanced disease stages and primarily represent prevalent etiologies at the time (HBV, HCV, and alcohol). In a subsequent study published in 2017, Sia *et al.* analyzed samples from 956 patients with HCC and found that approximately 25% presented markers of inflammatory expression, which they termed the "Immune Class"[115]. Within this class, they identified two subtypes: one with active immune responses and another with exhausted immune responses. The immune-exhausted subtype showed marked activation of transforming growth factor-beta (TGF-β), which stimulates the polarization of macrophages toward the M2 type, and a significant methylation profile of immune-related genes, suggesting an important epigenetic effect in this group. It is worth noting that viral etiologies (HBV and HCV) predominated in this cohort, comprising around 80% of cases, while non-viral cases represented less than 18%.

In 2019, Jaitin *et al.*, using single-cell RNA-sequencing, evaluated the complete immune cell behavior in adipose tissue from obese mice and humans, identifying the lipid receptor triggering receptor expressed on myeloid cells 2 (TREM2) as a key regulator of immune responses at the tissue level[116]. Lipid-associated macrophages (LAMs), which develop in conditions of obesity from circulating monocytes and are located around adipocytes, are characterized by TREM2 receptor activation. In this regard, recent findings by Fredrickson *et al.* demonstrate that TREM2+ macrophages can facilitate MASH resolution independently of weight loss following bariatric surgery[117]. These findings highlight TREM2 as a key regulatory checkpoint in the regulation of macrophage activation in MASH and potentially in HCC.

Other relevant aspects of the role of macrophages in HCC were pointed out by Ding *et al.*, who analyzed 137 resected HCC samples (mostly from patients with HBV infection and in the cirrhosis stage), finding that high intratumoral macrophage density [tumor-associated macrophages (TAMs)] was associated with a poor prognosis[118]. In another study, Kuang *et al.*, analyzed the expression of PD-L1 in the peritumoral stromal tissue of 28 patients with HCC, demonstrating that these activated monocytes suppressed the activity of T lymphocytes, favoring tumor progression and linking proinflammatory states to tumor immunotolerance[119]. Furthermore, Wang *et al.*, using single-cell RNA-sequencing, identified nine cell types in HCC samples, with macrophages showing the highest rates of intercellular communication, and characterized macrophage subtypes associated with differing OS, TME infiltration, and response to immunotherapy[120]. These findings underscore the importance of molecular mechanisms that maintain hepatic immune homeostasis and influence macrophage polarization in the progression of both MASH and HCC.

On the other hand, the impact of the microbiome on the mechanisms associated with the development of MASLD and carcinogenesis is increasingly evident. Obesity due to overnutrition is very common, often driven by an excess intake of foods rich in fructose, which induces fructose-associated lipogenesis via microbiome-derived acetate, as demonstrated by Zhao *et al.*[121]. This suggests that different microbiome-derived substrates can influence hepatic lipid metabolism. Hu *et al.*, using murine models of HCC, demonstrated that modifying the intestinal microbiota using strains of *Lactobacillus reuteri* or the presence of short-chain fatty acids (SCFA) inhibits the production of IL-17A by innate lymphoid cells subtype 3 (ILC3), potentially modulating the antitumor efficacy of immune checkpoint therapies (e.g., anti-PD-1)[122]. However, it remains possible that additional intermediaries contribute to these immune response modifications.

INFLUENCE OF MASLD ON THE RESPONSE TO SYSTEMIC THERAPY FOR HCC

The use of immunotherapy in the last decade has revolutionized oncological treatments, significantly improving response rates compared to previous systemic treatment strategies[8,48]. As of the first half of 2024,

there are at least ten positive studies on the management of HCC using checkpoint inhibitors across various stages of BCLC (stage 0-early, intermediate, or advanced) [Table 2]. However, when reviewing the stratification by etiology in these trials, it becomes evident that specific subgroups of patients with NAFLD, MAFLD, or the current term MASLD have not yet been adequately considered. The relevance of this stratification was highlighted by Pfister *et al.* in a meta-analysis of three randomized phase III clinical trials involving over 1,600 patients with advanced HCC[136]. These trials tested inhibitors of PDL1 (programmed death-ligand 1) or PD1 and revealed that immune therapy did not improve survival in patients with non-viral HCC. Likewise, they found a shared gene-expression profile and increased abundance of unconventionally activated hepatic CD8+PD1+ T cells in human MASH tissue[136]. Subsequently, Llovet *et al.* extended the meta-analysis to five randomized clinical trials, confirming the same suboptimal outcomes in the MASH-HCC subpopulation[48].

Since HCC can develop in the MASH population without requiring progression to cirrhosis, this suggests distinct carcinogenic mechanisms compared to other etiologies. As previously mentioned, differences at the molecular level have been identified between MASH-HCC and HCC of other etiologies[86-93]. These findings indicate differences in key signaling pathways. However, we would like to highlight the role of immune dysfunction in these tumorigenesis processes. In this regard, Ma *et al.* demonstrated that MASLD leads to selective CD4+ T lymphocyte loss, promoting hepatocarcinogenesis[137]. Subsequently, Heinrich *et al.* showed in a murine model that the microenvironment in MASH-induced mice impairs the efficacy of immunotherapy in the management of liver neoplasms[138]. Dudek *et al.* detected hepatic accumulation of auto-aggressive CXCR6+ CD8 T cells in a mouse model of MASH[139,140]. Leslie *et al.*[141] provided compelling data showing that anti-CXCR2 treatment, which induces the accumulation of immature neutrophils, can mitigate the presence of auto-aggressive lymphocytes, potentially modifying the natural progression toward MASH and blocking the associated carcinogenesis process[142-148]. Most of the information regarding this immune dysfunction is based on three animal models[148]: (1) Genetically engineered mouse models (GEMMs) for MASH-HCC, GEMMs; (2) Carcinogen and high-fat diet (HFD)-induced MASH-HCC; and (3) the sleeping beauty (SB) transposon-induced MASH-HCC model. However, a detailed description of these models is beyond the scope of this review.

Additionally, a key role has also been proposed for other immune cell populations present in the liver, such as liver tissue macrophages, in the development of MASH-HCC. During macrophage expansion, there is a recruitment of Kupffer cells that express proinflammatory characteristics, which impair triglyceride storage and promote liver injury[148]. Within this heterogeneous population of monocytes, a subtype known as LAMs has been described[148]; these cells are involved in both MASH progression or regression phenomena, depending on their phenotype and spatial distribution[149]. TAMs with TREM2+ deficiency enhance the infiltration of CD8+ lymphocytes, thereby improving the response to anti-PD-L1 therapies[150].

An expanded meta-analysis with new phase III studies, excluding those with a predominant viral population, concluded that there are no differences in the effectiveness of checkpoint inhibitors between populations of viral and non-viral etiology. However, the same authors pointed out that the heterogeneity of the non-viral population may involve an amalgam of risk factors, the impact of which on the efficacy of HCC treatments cannot be precisely determined[151]. The need for adequate patient stratification in clinical trials focused on the HCC population must include a well-characterized MASLD-HCC group, particularly since it represents one of the main causes of HCC. This emphasizes that non-viral HCC etiology is not synonymous with MASLD-HCC etiology[152]. Furthermore, subspecialized treatment strategies still do not adequately consider the prognostic impact of this population on an individualized basis[153].

Table 2. Positive phase III clinical trials (First line)

BCLC stage	Identifier	Year	Trial	*n*	Investigational arm (s)	Control arm	Primary endpoints	Aetiology, %	Reference
Early-stage (BCLC A)	NCT04102098	2023	IMbrave 050	668	Atezolizumab + bevacizumab	Active surveillance	RFS (IRF)	HBV 62,28 HCV 10,78 Viral 73,06 Non-viral 12,42 Unknown 14,52	[123]
Intermediate-stage (BCLC B)	NCT03778957	2024	EMERALD-1	616	Durvalumab + bevacizumab + TACE	TACE + placebo	PFS (BICR)	HBV 36 HCV 23,40 Viral 59,40 Non-viral 59,40 Unknown 0	[124]
	NCT04246177	2024	LEAP-012	480	Lenvatinib + pembrolizumab + TACE	TACE + placebo	PFS (BICR), OS	Viral 72,08 Non-viral 27,92	[125]
Advanced-stage (BCLC C)	NCT00105443	2008	SHARP	602	Sorafenib	Placebo	OS	HBV 18,44 HCV 28,07 Viral 46,51 Non-viral 36,05 Unknown 17,44	[126]
	NCT00492752	2009	Asia-Pacific	226	Sorafenib	Placebo	OS	HBV 73,0 HCV 8,40 Viral 81,42 Non-viral 18,58 Unknown 0	[127]
	NCT01761266	2018	REFLECT	954	Lenvatinib	Sorafenib	OS	HBV 50,0 HCV 23,0 Viral 73,0 Non-viral 13,0 Unknown 14,0	[128]
	NCT03434379	2020	IMbrave150	501	Atezolizumab + bevacizumab	Sorafenib	OS, PFS-IRF (co-primary)	HBV 47,90 HCV 21,56 Viral 69,46 Non-viral 30,54 Unknown 0	[129]
	NCT03794440	2021	ORIENT-32	571	Sintilimab + bevacizumab biosimilar	Sorafenib	OS, PFS-IRRC (co-primary)	HBV 94,2 HCV 2,45 Viral 96,65 Non-viral 3,35 Unknown 0	[130]
	NCT03755791	2022	COSMIC-312*	837	Cabozantinib + atezolizumab	Sorafenib	PFS, OS (dual)	HBV 29,87 HCV 31,42 Viral 61,29 Non-viral 38,71 Unknown 0	[131]
	NCT03298451	2022	HIMALAYA	1171	Tremelimumab + durvalumab	Sorafenib	OS	HBV 30,74 HCV 27,41 Viral 58,20 Non-viral 41,80 Unknown 0	[132]
	NCT03412773	2023	RATIONALE-301	674	Tislelizumab	Sorafenib	OS	HBV 60,68 HCV 12,61 HBV + HCV 2,7 Viral 76,00 Non-viral 24,00 Unknown 0	[133]
	NCT03764293	2023	CARES-310	543	Camrelizumab + rivoceranib	Sorafenib	PFS, OS (dual)	HBV 74,59 HCV 9,40	[134]

							Viral 84,0 Non-viral 16,00 Unknown 0	
NCT04039607	2024	Check-Mate 9DW	668	Nivolumab + ipilimumab	Sorafenib or Lenvatinib	OS	HBV 34,30 HCV 27,80 Viral 62,10 Non-viral 36,40 Unknown 1,5	[135]

*Positive one of the dual endpoints. BCLC: Barcelona Clinic Liver Cancer classification; HBV: hepatitis B virus; HCV: hepatitis C virus; TACE: transarterial chemoembolization; OS: overall survival; PFS: progression-free survival; BICR: blinded independent central review; RFS: recurrence-free survival; IRF: independent review facility; IRRC: independent radiological review committee.

CONCLUSION

The conceptual shift from NAFLD to MASLD allows for a more comprehensive diagnostic and therapeutic framework for this chronic liver condition, emphasizing the importance of understanding the diverse subpopulations within MASLD and their specific prognostic implications. For instance, the identification of different phenotypes, such as MASLD in non-obese individuals and the lean-MASLD subgroup, highlights their interaction with different risk factors for disease progression, particularly concerning the development of HCC. This redefined framework also underscores the unmet need for treatments specifically evaluated in patients with HCC associated with MASLD. Advancements in understanding the pathophysiological mechanisms underlying both MASLD and HCC may reveal common links, mainly by emphasizing the immune dysfunction associated with metabolic dysregulation, which is central to the conceptual approach for the new terminology. This presents a significant challenge, given that the current screening recommendations for HCC mainly target populations with advanced fibrosis, even though cases of MASLD-related HCC are increasing among non-cirrhotic individuals. Therefore, personalized therapeutic strategies are essential to effectively address the unique characteristics and progression of MASLD-related HCC.

In conclusion, the transition from NAFLD to MASLD represents a significant step forward in MASLD-related HCC research and treatment. This shift could pave the way for more precise and individualized care, ultimately improving outcomes for patients suffering from this complex and multifaceted condition. Further research and clinical trials focused on MASLD-related HCC are imperative for developing targeted therapies that meet the specific needs of these patients.

DECLARATIONS

Authors' contributions

Conceptualization, investigation, writing - original draft, writing - review and editing: Llamoza-Torres CJ, Fuentes-Pardo M

Writing - review, editing, and supervision: Ramos-Molina B

Availability of data and materials

Not applicable.

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Conflicts of interest

Ramos-Molina B is a Junior Editorial Board member of the journal *Metabolism and Target Organ Damage*.

Ramos-Molina B was not involved in any steps of editorial processing, notably including reviewers' selection, manuscript handling and decision making. Llamoza-Torres CJ has received speaker and conference fees, travel expenses from EISAI, MSD and Roche. Fuentes-Pardo M declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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