Review

Challenges and Solutions in the Management of Hepatocellular Carcinoma Associated with Non-Alcoholic Fatty Liver Disease

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Challenges and Solutions in the Management of Hepatocellular Carcinoma Associated with Non-Alcoholic Fatty Liver Disease

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Abstract: Non-alcoholic fatty liver disease (NAFLD) has gained attention in the last few years due to its increasing prevalence worldwide thus becoming a global epidemic. The increasing incidence of NAFLD has been associated with an increase in the number of hepatocellular carcinoma (HCC) cases. HCC has several risk factors, of which NAFLD and its associated metabolic disturbances—type 2 diabetes mellitus, obesity, and dyslipidemia—are of great interest due to their pandemic rise in incidence worldwide. This review aims to discuss the latest recommendations regarding the diagnosis and treatment of NAFLD-associated HCC and the remaining challenges. Thus, there is a high amount of data derived from basic and clinical studies that reveal the molecular pathways that drive NAFLD-associated hepatocellular carcinoma (HCC). Based on these findings, new prevention, surveillance, and treatment strategies are emerging. However, current data on treatment modalities in NAFLD-associated HCC are still scarce, but based on subgroup analysis, results from non-NAFLD HCC studies are promising and could provide a basis for a future research agenda to address NAFLD/NASH patients. Conclusion: Due to the pandemic proportions that NAFLD gained in the last few years, there is a high amount of data derived from basic and clinical studies that revealed the molecular pathways that drive NAFLD-associated HCC. Based on these findings, new prevention, surveillance, and treatment strategies could be developed at the individual level. Clinicians should carefully assess all the clinical and imagistic parameters and establish a prognosis based on BCLC classification and discuss in a multidisciplinary team the treatment strategy. It should be taken into consideration the specific factors associated with NAFLD-associated HCC which can have a negative impact on survival even in patients with early HCC, such as cardiovascular disease, type 2 diabetes and obesity.

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1. Introduction

The global prevalence of non-alcoholic fatty liver disease (NAFLD) is 25%, registering an alarming increase in recent years (from 15% in 2005 to 25% in 2010) as a consequence of the dramatic change in lifestyle that mainly includes an increased level of sedentarism and a hypercaloric diet [1,2]. NAFLD occurs secondary to the accumulation of excess triglycerides in the liver in the absence of excessive alcohol intake, which can lead to the appearance of non-alcoholic steatohepatitis (NASH)

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in approximately 30% of patients, which evolves in 10–20% of cases to liver cirrhosis [3,4]. Currently, the definition of NAFLD is based on the amount of alcohol intake. Although there is no consensus on the threshold of alcohol consumption to exclude NAFLD, a level of 30 g/day for men and 20 g/day for women is commonly used (easl). However, light (1.0–9.9 g/day) or moderate (10.0–29.9 g/day; 10.0–19.9 g/day for women) alcohol consumption in patients with NAFLD is not uncommon [5].

Considering that a major aspect of establishing the diagnosis of NAFLD is to rule out alcohol consumption which is often underestimated, in recent years efforts have been made to change the current nomenclature of the disease, many researchers relying on a widely accepted, inclusive name, an umbrella term to facilitate rapid diagnosis using noninvasive diagnostic techniques and therapeutic opportunities based on the control of changes in metabolic parameters. An important change has been brought at the at EASL Congress in 2023, where the multinational liver societies leaders from La Asociación Latinoamericana para el Estudio del Hígado (ALEH), American Association for the Study of Liver Diseases (AASLD), and European Association for the Study of the Liver (EASL) as well as the co-chairs of the NAFLD Nomenclature Initiative, announced that steatotic liver disease (SLD) was chosen as an umbrella term to encompass the various aetiologies of steatosis.

However, it has been decided that steatohepatitis should be retained further as an important term in the spectrum of steatotic liver diseases. NAFLD will be further metabolic dysfunction-associated steatotic liver disease (MASLD) which includes individuals patients who have hepatic steatosis and have at least one of five cardiometabolic risk factors (central obesity, or increased waist circumference, raised triglycerides, reduced HDL-cholesterol, high blood pressure, raised fasting plasma glucose.). Furthermore, the experts decided to develop a new category of patients named MetALD which encompasses patients with MASLD who have greater intake of alcohol units per week (140 g/week and 210 g/week for females and males respectively). Those with no metabolic parameters and no known cause have cryptogenic SLD. Metabolic dysfunction-associated steatohepatitis (MASH) is the replacement term for nonalcoholic steatohepatitis (NASH). This new nomenclature is meant to be a common lexicon for hepatologists worldwide and should ease the diagnostic workup. Due to its recent release, the new nomenclature is still on debate, thus we will discuss further referring to MASLD as NAFLD.

The increasing incidence of NAFLD has been associated with an increase in the number of hepatocellular carcinoma (HCC) cases in developed countries, with most data coming from studies conducted in the USA, where 10–20% of HCC cases are attributed to NAFLD [6–8]. The asymptomatic clinical setting of NAFLD results in a delayed diagnosis with negative implications for HCC surveillance strategies. Studies investigating the incidence of HCC in patients with liver cirrhosis of different etiologies reported that NAFLD cirrhosis was diagnosed much later in the course of the disease compared to the other etiologies [9,10]. NAFLD may act synergistically with chronic HCV infection or excessive alcohol consumption, leading to HCC progression [11].

Over the past few decades, liver cancer incidence and death have both been steadily increasing. With a total of 905,677 new cases reported in 2020, liver cancer constituted the sixth most prevalent cancer globally. Liver cancer still has a poor prognosis despite recent improvements. In terms of cancer-related deaths in 2020, liver cancer came in third with 830,180 fatalities. HCC has several risk factors, of which NAFLD and its associated metabolic disturbances—type 2 diabetes mellitus, obesity, and dyslipidemia—are of great interest due to their pandemic rise in incidence worldwide.

The pathophysiology, surveillance, and treatment of NAFLD-HCC are discussed in this review based on the latest research. It also identifies current difficulties brought on by this condition and offers recommendations for how to deal with them.

2. From NAFLD to HCC

In most cases, the initiation, promotion, and progression of hepatocarcinogenesis take place in the presence of a microenvironment characterized by severe liver fibrosis, in which the presence of a permanent cycle of inflammation, necrosis, and fibrosis leads to the accumulation of genetic and epigenetic alterations, the dysregulation of signaling pathways, and the activation or inadequate suppression of proto-oncogenes and tumor suppressor proteins. Thus, in more than 80% of HCC

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cases, liver cirrhosis is present, with a cumulative 5-year risk of 5–30%, depending on the etiological agent of the liver disease, geographic area, ethnic group, and liver cirrhosis stage [12].

It is well known that immune pathways that act as both promoters and accelerators of carcinogenesis modulate liver tumorigenesis in NAFLD. For instance, in a murine model of NASH induced by a choline-deficient high-fat diet (CDHFT), a significant acceleration of tumorigenesis occurred as a consequence of CD8+ T and natural killer T cell activation [13]. Furthermore, it seems that a high level of CD8+PD1+ T cells in the liver parenchyma has a negative impact on immune system surveillance, which consequently triggers tumorigenesis in NASH [14]. On the other hand, CD4+ T cells are key factors for efficient immune surveillance, which decreases the risk of hepatocyte malignant transformation [15]. Thus, a murine study that evaluated the effects of decreased CD4+ T cells in a MYC oncogene transgenic mouse model fed with a methionine-choline-deficient diet demonstrated that it subsequently drives HCC development [16]. Furthermore, NAFLD-driven chronic inflammation leads to the suppression of cytotoxic CD8+ T lymphocytes by IgA+ cells, thereby disrupting immune surveillance and promoting HCC development [17]. Immune checkpoint inhibitors (ICIs) are thought to restore tumor immune surveillance by targeting the programmed cell death-1 receptor (PD1; nivolumab, pembrolizumab) on exhausted CD8+ T cells or the programmed cell death-1 ligand 1 (PDL1, atezolizumab) [18–21]. In addition, there is growing evidence that the gut microbiome plays a key role in the pathogenesis of NAFLD [22]. NAFLD-related cirrhosis and NAFLD-HCC are both characterized by unique gut microbiome signatures, which could be used in future diagnostic strategies and improve the outcome of these patients [23].

3. Diagnosis of NAFLD-Associated HCC

Alpha-fetoprotein (AFP) is the most commonly used biomarker for the diagnosis of HCC. AFP is a 70-kD glycoprotein with a structure similar to albumin, produced in the first trimester of pregnancy by the fetal liver and yolk sac [24]. Data from recent research shows that for the threshold value of 20 ng/mL at a prevalence of HCC of 5%, the positive predictive value (PPV) is 25% and the negative predictive value (NPV) is 97.7%, and at a prevalence of 20%, VPP is 61% and VPN is 90% [25]. Thus, APASL and AASLD recommend AFP as a serologic marker for HCC to be determined semi-annually along with US, whereas EASL does not support its use due to its low cost-efficiency index [5,26,27]. Considering that HCC surveillance strategies should be based on the most available, non-invasive, and cost-efficient technique, which at the same time needs to have high sensitivity and specificity, US is the most appropriate tool recommended by all current guidelines. Regarding the performance of US for detecting HCC, a systematic review demonstrated an excellent sensitivity of 94% for any stage but a poor sensitivity of 63% for early tumors [28]. Once the nodule is identified, a more sensitive imaging method is recommended for establishing the diagnosis: CT, MRI, or contrast-enhanced ultrasound (CEUS). In a meta-analysis that compared the accuracy of MRI *versus* CT in diagnosing HCC, MRI had better sensitivity and specificity than CT (82% *vs.* 66% and 92% *vs.* 91%, respectively), with significantly higher sensitivity for HCCs smaller than 1 cm (46% vs. 69%) [29]. Still, there are several shortcomings that limit the use of MRI on a daily basis in clinical practice, such as low availability, high costs, time consumption, and image quality variability. Regarding CEUS, a meta-analysis showed a sensitivity and specificity of 85% and 91%, but it should be noted that operator- and patient-related factors decrease the accuracy of CEUS, which limits its use in favor of CT or MRI [30,31]. The LiRADS criteria encompass tumor features observed on CT, MRI, and CEUS, such as tumor size, arterial hyperenhancement, wash-out, threshold growth, and capsule, and represent a common lexicon meant to increase the rates of HCC diagnosis.

According to current guidelines, the diagnostic algorithm for HCC is mainly based on the size of the nodule identified by the US. Thus, after the identification by US of a nodule larger than 1cm, the diagnosis is confirmed by a more sensitive method such as CT or MRI, and if the result is inconclusive, the next imaging method is used, the biopsy being reserved for the uncertain cases at two successive imaging techniques [25,26].

After a diagnosis is established, HCC needs to be further evaluated by a staging system. The purpose of using malignant neoplasia staging systems is to eliminate ambiguity thus contributing to

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the correct placement of patients in the appropriate therapeutic strategy, to estimate the prognosis and also to evaluate the response to treatment. The situation of patients with HCC is a particular one compared to other cancers considering the presence of liver cirrhosis in most cases. Thus, the prognosis of patients depends on the stage of the two conditions, HCC and liver cirrhosis. In order to overcome this short come, numerous HCC staging systems have been proposed over the years, the most well-known being the BCLC (Barcelona Clinic Liver Cancer), Okuda, CLIP (Cancer of the Liver Italian Program) score, CUPI (Chinese University Prognostic Index), TNM and JIS (Japan Integrated Staging) score. The most widely used classification is the BCLC classification.

4. Management of Hepatocellular Carcinoma Associated with NAFLD

The therapeutic management of HCC is complex and, according to the recommendations of current guidelines, it requires a multidisciplinary team consisting of hepatologists, oncologists, and surgeons specialized in liver surgery and transplantation, and radiologists. However, data from the literature show that only half of patients diagnosed with HCC are subsequently evaluated by a multidisciplinary team. Currently, the treatment recommendations for HCC are based on the BCLC classification and do not differ from one etiology to another, but do take into consideration the presence of liver cirrhosis and consequently the liver function [32]. Placing patients in a specific therapeutic strategy depends on the classification of BCLC. There is scarce data regarding both treatment modalities and long-term survival in NAFLD-HCC, taking into consideration that these patients frequently have several comorbidities such as type 2 diabetes mellitus, cardiovascular disease, and obesity.

4.1. Hepatic Resection

In patients with HCC without liver cirrhosis and impaired liver function, hepatic resection represents the first option for treatment [25,26]. However, despite progress has been made in the last years in improving the survival rate in those with liver resection, the recurrence rate did not record major changes. There are several studies that assessed the overall survival (OS) and recurrence-free survival (RFS) in patients with NAFLD-associated HCC, with optimistic results (Table 1). It appears that OS at 5 years after liver resection for NAFLD-associated HCC ranges from 51.5% to 97%, whereas RFS at 5 years ranges from 36.3% to 66% [33–39]. However, there is an ongoing debate regarding the outcomes after resection in patients with NAFLD-associated HCC *versus* other liver diseases. It appears that the presence of metabolic and cardiovascular comorbidities, which are often found in patients with NAFLD, has a negative impact on the OS after liver resection for HCC [40]. A meta-analysis that aimed to evaluate the outcome after hepatic resection for HCC in NAFLD *versus* other liver diseases in approximately 7200 patients found a better RFS and OS in those with NAFLD [41]. Furthermore, a lower RFS was found in a study that compared NAFLD-associated HCC with HCV-related HCC (44.6% versus 62.5%) [37]. Still, it is important to acknowledge that the high post-surgical mortality in patients with NAFLD is mainly due to the metabolic comorbidities, which should be carefully diagnosed and managed.

Table 1. Overall survival (OS) and recurrence-free survival (RFS) in patients with NAFLD-associated HCC after iver resection.

Ref.	Type of Study	Patient (n) and Characteristics	Overall Survival Rate *	Recurrence-Free Survival **
Koh et al. [33]	Retrospective	N=996 HCC patients, of which 844 with nonNAFLD HCC, 152 with NAFLD HCC	70.1%	45.4%
Reddy et al. [34]	Retrospective	N=214 HCC patients, of which 52 with NASH, 162 with HCV or ALD	59%	48%

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Liang et al. [35]	Retrospective	N=177 HCC patients, of which 75 with NASH , 102 with alcoholic or viral hepatitis	87%	51%
Vigano et al. [36]	Retrospective	N=192 HCC patients, of which 96 with NASH, 96 with HCV	65,6%	37%
Billeter et al. [37]	Retrospective	N=365 HCC patients, of which 62 with NASH, 303	71.3%	36.3%
Yang et al. [38]	Retrospective	N=1483 HCC patients, of which 96 with NAFLD HCC, 1387 with HBV HCC	51,4%	38,8%
Wakai et al. [39]	Retrospective	N=225 HCC patients, of which 17 with NAFLD HCC, 61 with HBV and 147 with HCV	59%	66%

* 5-year overall survival rate. ** 5-year recurrence free survival.

4.2. Ablation

Radiofrequency ablation (RFA) is a non-surgical treatment method that is currently recommended in patients with stage 0 (tumors smaller than 2 cm) or A according to the BCLC classification, with OS rates similar to resection [32]. Regarding NAFLD-associated HCC, a recent study that evaluated the OS rates in patients treated with RFA for HCC in NAFD and other liver diseases reported no significant differences [35]. However, data from another study shows that the presence of type 2 diabetes impairs the outcome after RFS, but metformin therapy has a positive impact on OS [42]. Despite the good efficacy and safety of microwave ablation of HCC, there is no data regarding the outcome in patients with NAFLD.

4.3. Liver Transplantation

According to the European Liver Transplant Registry, the survival rate at 10 years after liver transplantation for HCC is 51%, irrespective of underlying etiology [43]. The current guidelines recommend liver transplantation as the first choice in patients with HCC who do not meet the eligibility criteria for liver resection but are within the Milan criteria [25–27]. There are several studies regarding long-term outcomes after liver transplantation in NAFLD-associated HCC (Table 2). The OS and RFS rates range from 59% to 88% and 48% to 68%, respectively [34,44–48]. Although some studies reported similar outcomes after liver transplantation for HCC in NAFLD and other etiologies [34,49], there are some studies that raised concerns regarding worse OS in those with NAFLD. For instance, a comprehensive analysis from the European Transplant Registry, which included patients with liver transplantation for different etiologies, reported lower OS in NAFLD-HCC compared to alcoholic liver disease-related HCC [44]. On the other hand, the same authors found no difference in terms of OS rates at 10 years when compared to chronic HCV infection and cryptogenic cirrhosis (73%). In contrast with these results, an American study found no difference in OS rates after liver transplantation in NAFLD-associated HCC versus alcoholic liver disease-associated HCC [34]. Thus, it seems that NAFLD has no significant impact on OS after liver transplantation for HCC compared to other causes of liver disease, but it needs to be taken into consideration due to the high complication rates after surgery due to metabolic syndrome-associated comorbidities.

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Table 2. Overall survival (OS) and recurrence-free survival (RFS) in patients with NAFLD-associated HCC after liver transplantation.

Ref.	Type of Study	Patient (n) and Characteristics	Overall Survival Rate *	Recurrence-Free Survival
Reddy et al. [34]	Retrospective	N=214 HCC patients, of which 52 with NASH and 162 patients with HCV or ALD	59%	48% at 5 years
Haldar et al. [44]	Retrospective	N=68950 recipients, of which 1071 with NASH-HCC and 19134 with HCC of other etiologies	68.6%	n/a
Wong C.R. et al. [45]	Retrospective	N=17644 HCC patients, of which 406 patients with NAFLD, 1854 with HCV, 1342 with HBV, 1024 with ALD	60%	n/a
Rajendran et al. [46]	Retrospective	N=20672 HCC patients, of which 2071 with NASH HCC and 18601 with HCC of other etiologies	76.3%	n/a
Sadler et al. [47]	Retrospective	N=929 HCC patients, of which 60 with NASH and 869 had other etiologies	80%	68%
Malik et al. [48]	Retrospective	N=17 NASH HCC patients	88% at 2.5 years	n/a

4.4. Neoadjuvant and Adjuvant Therapies

Currently, there is no recommendation for adjuvant and neoadjuvant therapies use in HCC management because of the low efficacy and poor safety profile of the agents studied until now. Although HCC has very high rates of recurrence after resection or ablation (up to 70% at 5 years after curative treatment), there has been no therapy able to modify the outcome in these patients. There are several ongoing phase III randomized controlled trials that are evaluating the efficacy as adjuvant therapies after curative treatment of nivolumab, pembrolizumab, atezolizumab + bevacizumab, and durvalumab [50].

4.5. Transcatheter Arterial Chemoembolization

In patients with unresectable HCC and preserved liver function with no evidence of vascular invasion or extrahepatic spread, categorized as BCLC class B, the first-line treatment is transcatheter arterial chemoembolization (TACE). The classic method for TACE, consisting of the administration of an anticancer-in-oil emulsion followed by embolic agents, has been replaced in the last few years with a more efficient alternative that offers the possibility to introduce an embolic drug-eluting bead (DEB), thus providing a better efficacy and safety profile [51]. Data from several studies that assessed the pharmacokinetic profile of DEB loaded with doxorubicin reported excellent features with lower systemic drug exposure and significantly reduced liver toxicity compared with conventional TACE [52–54].

In NAFLD-associated HCC, data about TACE efficacy is still scarce, with few studies mentioning its feasibility [55,56]. In a recent study, Young et al. retrospectively compared the median OS in patients with HCC and NAFLD versus other etiologies after TACE and found that there were no significant differences [58]. In contrast with these results, another study conducted by Wu et al., which included 57 patients with HCC of different etiologies who had performed 100 TACE procedures, reported a negative impact of obesity on post-therapy residual disease and the time-to-progression interval [59]. Consequently, the low scientific evidence for TACE in NAFLD-associated

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HCC does not currently sustain a clear recommendation for including this procedure in the treatment strategy.

4.6. Systemic Therapy

The first agent for systemic therapy in HCC was sorafenib, which was introduced in 2007 based on the excellent results from the SHARP trial and has been used as a first-choice therapy for advanced stage HCC (BCLC C) for over 10 years [60]. Data from the SHARP phase III trial showed that the efficacy of sorafenib varied depending on the etiology of HCC, being more effective in those with chronic HCV infection [61]. Interestingly, it has been recently demonstrated by a cohort study that included HCC patients with several etiologies of liver disease that the efficacy of sorafenib was similar in NAFLD patients when compared to other etiologies [62].

Recent advances in the field of immunotherapy for HCC have introduced new agents in the management of advanced-stage HCC, with promising results. The REFLECT trial demonstrated an improved OS of Lenvatinib compared to Sorafenib (13.6 versus 12.3 months) [63]. Interestingly, Lenvatinib showed an improvement of 1.5 months in terms of progression-free survival in patients with NAFLD-associated HCC compared to viral-related HCC [64]. Regorafenib has been recently recommended based on the improved survival rates in viral and non-viral HCC when compared to placebo (10.6 versus 7.8 months), but due to the low incidence of NAFLD patients in the pivotal trial, there is no data regarding the efficacy of the drug in this cohort [65]. Similarly, the trials that evaluated cabozantinib and ramucirab, which, along with Lenvatinib, are recommended as second-line choices when sorafenib fails, did not offer any data on their efficacy in NAFLD patients [66,67].

5. Remaining Challenges

As the pool of patients with viral-related HCC is decreasing worldwide due to efficient antiviral therapy and vaccination, NAFLD-associated HCC is gaining more attention. Thus, effective strategies for prevention and treatment are needed.

The goal of all therapy strategies is to increase efficacy while maintaining a good safety profile. Patients with NAFLD-associated HCC have a unique profile that is characterized by the presence of metabolic disorders, cardiovascular disease, and type 2 diabetes mellitus. These features could impair the outcome after surgery (resection and transplantation) or lower the efficacy of TACE and systemic therapy. Thus, the treatment strategy should be individualized based on the patient's characteristics. Furthermore, it is important to acknowledge the high chance of developing HCC in non-cirrhotic patients with NAFLD, which is more frequent than in patients with viral or alcoholic etiologies, which implies that a more aggressive surveillance strategy is needed in order to diagnose early HCC. The question remains if such strategies are cost-efficient due to the low prevalence of HCC in non-cirrhotic NAFLD patients.

Regarding systemic therapies, there is scarce data about the efficacy and safety profile of local and systemic therapies due to the low proportion of NAFLD-associated HCC patients in the trials. Thus, considering that most treatment modalities are influenced by the underlying etiologies, there is an urgent need for randomized controlled trials that are focused on these patients.

6. Conclusion

Due to the pandemic proportions that NAFLD gained in the last few years, there is a high amount of data derived from basic and clinical studies that revealed the molecular pathways that drive NAFLD-associated HCC. Based on these findings, new prevention, surveillance, and treatment strategies could be developed at the individual level. Current data on treatment modalities in NAFLD-associated HCC are still scarce, but based on subgroup analysis, results from non-NAFLD HCC studies are promising and could provide a basis for a future research agenda to address NAFLD/NASH patients. Clinicians should carefully assess all the clinical and imagistic parameters and establish a prognosis based on BCLC classification and discuss in a multidisciplinary team the treatment strategy. It should be taken into consideration the specific factors associated with NAFLD-

associated HCC which can have a negative impact on survival even in patients with early HCC, such as cardiovascular disease, type 2 diabetes and obesity.

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