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REVIEW

Current challenges and future perspectives in treating patients with NAFLD-related cirrhosis

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Abstract

Despite the slow, progressive nature of NAFLD, the number of patients with NAFLD-related cirrhosis has significantly increased. Although the management of patients with cirrhosis is constantly evolving, improving the prognosis of patients with NAFLD-related cirrhosis is a challenge because it is situated at the crossroads between the liver, the metabolic, and the cardiovascular diseases. Therefore, the therapeutic interventions should not only target the liver but also the associated cardiometabolic conditions and should be adapted accordingly. The objective of the current review is to critically discuss the particularities in the management of patients with NAFLD-related cirrhosis. We relied on the recommendations of scientific societies and discussed them in the specific context of NAFLD cirrhosis and the surrounding cardiometabolic milieu. Herein, we covered the following aspects: (1) the weight loss strategies through lifestyle interventions to avoid sarcopenia and improve portal hypertension; (2) the optimal control of metabolic comorbidities in particular type 2 diabetes aimed not only to improve cardiovascular morbidity/mortality but also to lower the incidence of cirrhosis-related complications (we discussed various aspects related to the safety of oral antidiabetic drugs in cirrhosis); (3) the challenges in performing bariatric surgery in patients with cirrhosis related to the portal hypertension and the risk of cirrhosis decompensation; (4) the particularities in the diagnosis and management of the portal hypertension and the difficulties in managing patients awaiting for liver transplantation; and (5) the difficulties in developing drugs and conducting clinical trials in patients with

Abbreviations: ALD, alcohol-associated liver disease; BS, bariatric surgery; c-ACLD, compensated advanced chronic liver disease; CLD, chronic liver disease; CSPH, clinically significant portal hypertension; CV, cardiovascular; DPP-4i, dipeptidylpeptidase-4 inhibitors; EFX, efruxifermin; ELF, enhanced liver fibrosis; EMA, European Medical Agency; EPOS: elucidating pathways of steatohepatitis; FDA, Food and Drug Administration; FGF, fibroblast growth factor; FIB4, Fibrosis-4 score; FXR, farnesoid X receptor; GB, gastric bypass; GLP1 RA, glucagon-like peptide-1 receptor agonists; HSP47, Heat shock protein 47; LOXL2, lysyl oxidase homolog 2; LSM, liver stiffness measurement; LT, liver transplantation; NSBBs, nonselective beta-blockers; OCA, obethicolic acid; PHT, portal hypertension; RYGB, Roux-en-Y gastric by-pass; SAF, steatosis-activity-fibrosis; SG, sleeve gastrectomy; SGLT2i, sodium-glucose cotransporter 2 inhibitors; siRNA, small interfering ribonucleic acid; SO, sarcopenic obesity; T2DM, type 2 diabetes mellitus; TEE, total energy expenditure; TZD, thiazolidinediones.

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NAFLD-related cirrhosis. Moreover, we discussed the emerging options to overcome these obstacles.

INTRODUCTION

The etiology of chronic liver disease (CLD) has substantially changed over the last decade, and NAFLD has become the most frequent cause of liver disease worldwide[1] following the increasing prevalence of type 2 diabetes mellitus (T2DM) and obesity and the recent advances in treating viral hepatitis. Although most of the patients have mild to moderate disease ranging from isolated steatosis to NASH and moderate to significant (F2–F3) fibrosis, 10% to 20% of patients still progress to cirrhosis[2,3] and its complications—HCC and end-stage liver disease. The prevalence of NAFLD-related cirrhosis more than doubled in the United States[4] and significantly increased in Europe,[5] resulting in increasing rates of decompensated cirrhosis (168%), HCC (137%), liver transplantation (LT) (59%), and liver-related death (178%).[5] There are several explanations for these trends. First, the fibrosis regression rate is low unless there is a significant improvement in metabolic comorbidities or a specific pharmacological treatment. However, for most of the patients, it is difficult to implement and maintain lifestyle changes to allow significant improvement of comorbidities. On the other hand, the increasing prevalence of NAFLD in children and adolescents results in a longer exposure to metabolic risk factors and a time-dependent fibrosis progression rate that explains both the increasing prevalence of "severe" NAFLD and its occurrence at a younger age.[6]

It should be noted that in patients with NAFLD/NASH, the fibrosis pattern is predominantly pericentral, resulting in a more genuinely perisinusoidal portal hypertension, while the post-necrotic fibrosis pattern usually seen in viral hepatitis more commonly results in arterialization of sinusoids, with early porto-central shunting.[7] The divergent patterns of fibrosis across etiologies also explain differences in the development of clinically significant portal hypertension (CSPH) and outcomes. It should be also noted that the development of cirrhosis requires not only changes in the composition and turnover of the extracellular matrix but also specific vascular changes with sinusoidal remodeling and increased angiogenesis, which further contributes to the CSPH.[8] Once compensated cirrhosis stage is reached, patients with NAFLD spend on average 4 years in this state until the first decompensation occurs. However, after the first decompensating event, the prognosis of patients with NAFLD cirrhosis is grim, and the time to progression to further decompensation or LT is on an average 2 years.[9] In more advanced stages of Child B and C, the prognosis of NAFLD-related cirrhosis is at least comparable to other etiologies of CLD.[10,11] Ascites and renal failures are the main drivers of mortality in decompensated stages in NAFLD-related cirrhosis. Because of the significant morbidity and mortality (liver and not liver related)[12] and substantial health-related costs[13] associated with NAFLD, there is an ongoing effort to develop effective therapies. Despite accelerated approval pathways, promising results of phase IIb studies, and several molecules being in phase III clinical trials, none of these drugs have gotten the Food and Drug Administration (FDA) or European Medical Agency (EMA) approval at this time. Cirrhosis regression occurs in less than 20% of patients in the absence of efficacy-proven treatment as shown by published negative trials in cirrhotic NAFLD.[14] Therefore, managing patients with NAFLD-related cirrhosis is a real challenge in clinical practice because of the lack of a specific treatment to prevent progression/the occurrence of liver-related events and because of the presence of concomitant metabolic comorbidities requiring a multidisciplinary approach. Cirrhosis regression, or the prevention of progression to decompensated cirrhosis, is a meaningful clinical end point and possibly results in the reduction of liver-related complications, the need for LT, and improved overall survival.[14] In the context of these unmet needs, we propose here a critical review of several essential aspects in managing patients with NAFLD-related cirrhosis (Figure 1): (i) difficulties in implementing lifestyle changes (ii) and managing of sarcopenia; (iii) how to ensure the optimal control of the metabolic comorbidities; (iv) the role of bariatric surgery (BS); (v) the challenges in developing drugs and conducting clinical trials in NAFLD-related cirrhosis; and (vi) finally, we will provide some reflections on how to optimize the access to LT.

Lifestyle interventions to correct the nutritional status in NAFLD-related cirrhosis

Lifestyle interventions are the cornerstone in the management of NAFLD and are recommended across all the severity spectrum of the disease.

The main objectives attainable through lifestyle interventions are weight loss with preserved muscle mass and optimized control of cardiometabolic risk factors with the goal to prevent the progression or induce regression of the liver lesions and therefore avoid the occurrence of adverse clinical outcomes. Studies have shown that in non-cirrhotic NASH, 7% to 10% weight loss is associated with significant histological improvement—clearance of NASH and fibrosis

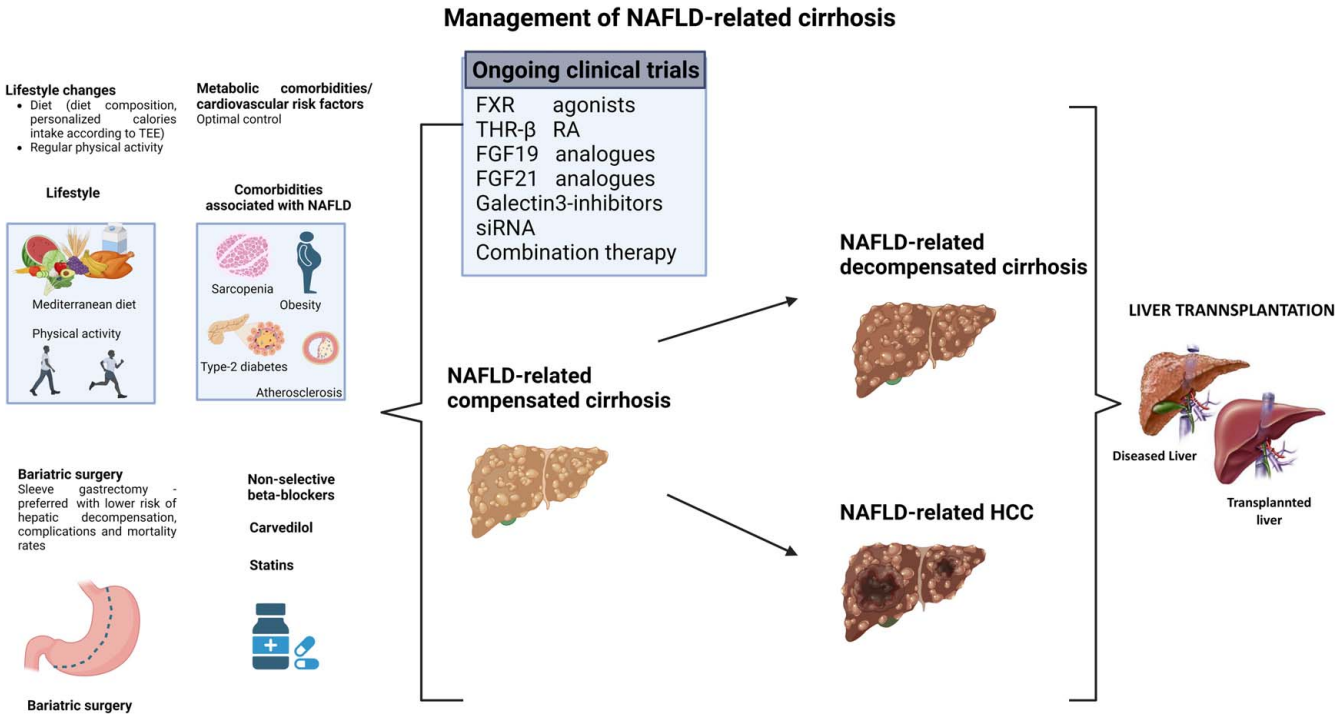

FIGURE 1 Proposal for a multidisciplinary approach in the management of NAFLD-related cirrhosis combining lifestyle interventions (diet and physical activity), optimal control of metabolic comorbidities associated with NAFLD/NASH, bariatric surgery, management of portal hypertension, and liver transplantation. Created with BioRender.com. Abbreviation: FXR, farnesoid X receptor; FGF, fibroblast growth factor; TEE, total energy expenditure; siRNA, small interfering ribonucleic acid.

regression.[15,16] However, in more advanced stages (bridging fibrosis or cirrhosis), there is no threshold for the magnitude of weight loss expected to significantly improve liver lesions. Data from BS cohorts suggest that advanced fibrosis may persist in almost half of the patients despite significant weight loss of >20%.[17] In patients with cirrhosis, 5% to 10% weight loss through lifestyle interventions is associated with a significant reduction in portal hypertension (PHT).[18] Nevertheless, lessons from non-cirrhotic NASH cohorts have shown that diet composition and micronutrient, as well as physical activity, have beneficial effects on liver lesions even in the absence of significant weight loss.[16] While a large amount of data support the benefits of the Mediterranean diet in non-cirrhotic NAFLD, there are few or no data on patients with cirrhosis. Instead, the role of dietary composition in preventing the occurrence of HCC (in the presence or absence of liver cirrhosis) is well-established, and adherence to the Mediterranean diet is associated with significantly lower HCC risk.[19] In the European Prospective Investigation into Cancer and Nutrition cohort, the risk of liver cancer increased by 43% per 50g/day of total sugar and was reduced by 30% per 10 g/ of total fiber.[20] A recent meta-analysis has shown that HCC risk decreased by 8% for every 100 g/day increase in vegetable intake.[21]

The major aspects that should be considered when counseling for dietary and physical activity in patients with NAFLD-related cirrhosis are the presence of sarcopenia-/sarcopenic obesity (SO) and the severity of liver disease (as determined by the Child-Pugh or MELD scores).

Both sarcopenia (age-related loss of muscle mass and functional impairment)[22] and frailty (defined in the geriatric population as a decrease in physical reserve and increase in vulnerability to stress)[23] are prevalent conditions commonly associated with chronic diseases such as cancer, cardiometabolic comorbidities (in particular T2DM and obesity), and CLD. Sarcopenia is associated with NAFLD independent of insulin resistance. As many as 40% to 70% of patients with compensated advanced CLD are sarcopenic,[24,25] with variations according to the definition used. In cirrhotic stages, the annual rate of skeletal muscle loss increases with the severity of the liver disease, from 1.3% compensated stages (Child A) to 6% in Child C patients.[26] Therefore, among different etiologies of CLD, patients with NAFLD-related cirrhosis are expected to have an increased risk of sarcopenia because of the additive effect of insulin resistance and systemic inflammation.[27]

The prevalence of frailty has also been reported to increase with the severity of the liver disease with higher rates (38%–68%) in hospitalized patients[28,29] versus outpatients with compensated liver disease (range from 17% to 43%)[30–32] and to significantly impact outcomes.

A particularity of patients with NAFLD is the high prevalence (18% to 77%) of SO. Obesity is frequently observed in cirrhosis (20%–40%), regardless of the

etiology of liver disease; patients with cirrhosis may develop simultaneous loss of skeletal muscle and gain of adipose tissue, culminating in the condition of SO (high fat and low muscle mass) because repeat exposure to restrictive dietary interventions concomitant with lack of physical activity.[24,33] In an analysis of 678 patients with cirrhosis (mostly patients with Child-Pugh B), sarcopenia, SO, and myosteatosis were present in 43%, 20%, and 52% of patients, respectively.[24]

Both sarcopenia/SO and frailty are independent predictors of survival especially in patients with decompensated cirrhosis, regardless of the MELD score or PHT.[34–36] A single unit increase in the frailty index is associated with a 45% increase in mortality on the waiting list.[30] Because of the significant impact on strong clinical outcomes, Baveno VII consensus advises to evaluate sarcopenia and frailty in all patients with cirrhosis using available standardized tools.[37] Specific dietary and physical activity recommendations are made by both American and European Societies[38–40] and should target all the determinants of sarcopenia/frailty in cirrhosis: the etiology of the liver disease, the impaired intake of macronutrients or micronutrients (because of early satiety, anorexia, nausea, malabsorption, etc.), cirrhosis-related factors and altered protein metabolism in particular branch chained amino acids, systemic inflammation, and endocrine factors, as well as environmental and organizational factors. The goals of these interventions should be to preserve muscle mass and function and to prevent the occurrence of adverse health outcomes. These interventions are complex and require a dedicated platform and a multidisciplinary team, where the primary care provider, the hepatologist, the dietician, and the physical therapist should work together.

The calorie intake should be personalized for each patient and should consider the total energy expenditure, which includes resting energy expenditure, food thermogenesis, and physical activity expenditure. Whether these general recommendations need to be specifically tailored in patients with NAFLD-related cirrhosis has to be determined; 1 study suggested that resting energy expenditure is 17% higher in severely obese males with metabolic syndrome and NAFLD[41]; in another study, resting energy expenditure was not different between patients with similar BMI (NAFLD: 27.7 kg/m^2 vs. controls 25.3 kg/m^2), (77.4 $\pm$ 1.4 vs. 75.6 $\pm$ 1.0 J/kg free fat mass/min) after adjustment for free fat mass.[42]

The amount of physical activity advised by the American Heart Association is at least 30 minutes of moderate aerobic activity, at least 5 days/week, for a total of 150 minutes/week, or at least 25 minutes of vigorous aerobic activity, at least 3 days/week, for a total of 75 minutes/week combined with moderate to high-intensity muscle strengthening for at least 2 days/week. However, only one-third of US adults meet these recommendations, and more than half of the patients with NAFLD are inactive.[43] There are multiple barriers to regular physical activity in NAFLD: older age, metabolic comorbidities, mechanic complications of obesity, patients' motivation, and environmental and socio-economic factors. Moreover, patients with cirrhosis have decreased aerobic capacity, which aggravates the severity of the liver disease.[44,45] After adjusting for age and MELD, patients with low aerobic endurance, as assessed by the 6-minute walk test of <250 m have a 2-fold increase in mortality for every 100 m decrease in walking distance.[46] Other obstacles to physical activity in cirrhosis reported by earlier studies are the increase in portal pressure and muscle ammonia production. However, more recent data support the beneficial effect of physical activity on portal pressure: 24% to 42% of patients had a 10% to 20% decrease in HVPG depending on the amount of weight loss in the SPORT-Diet study.[47] Although intuitively, the increase in abdominal pressure with resistance exercises should be avoided in patients with PHT, there are no clear recommendations regarding the best exercise type and duration of the physical activity program in cirrhosis. The European Prospective Investigation into Cancer and Nutrition cohort study has shown that performing 2 hours of vigorous activity per week significantly decreases the risk of HCC independently of body weight and other risk factors.[20] A Japanese study suggested that in patients with compensated cirrhosis, $\geq$5000 steps/day combined with an energy intake of 30 kcal/kg of ideal body weight would prevent sarcopenia.[48] Other beneficial effects of physical activity observed in patients with cirrhosis are a significant improvement in the peak VO_2,[49] in the 6-minute walk test,[50] anthropometric changes (increase in muscle mass and decrease in fat mass),[51] and some improvement in the quality of life.[52] However, it should be noted that most of these studies have a short duration of 8 to 16 weeks and a limited number of patients. Even less data are available in patients with decompensated cirrhosis. Probably, any type and amount of physical activity should be encouraged; the physical activity program should be tailored based on the baseline assessments of physical performances and the motivation of each patient. A safety assessment should also be performed: disease-related safety issues, cardiopulmonary safety, and the impact of associated comorbidities.[53] Accompanying these patients and providing personalized and assisted programs with a gradual approach is particularly important to increase adherence, which is otherwise low.

Optimal control of metabolic comorbidities associated with NAFLD

The management of metabolic comorbidities is particularly important in patients with NAFLD-related

cirrhosis, whether end-stage liver disease is on the waiting list for LT. While age is not a modifiable risk factor, efforts should be made to achieve optimal control of the modifiable risk factors, obesity, T2DM, and cardiovascular disease.

Diabetes mellitus in patients with liver cirrhosis

Glucose metabolism is altered in patients with cirrhosis because of the loss of parenchymal liver cells by apoptosis and the development of porto-systemic shunts leading to decreased hepatic insulin metabolism and increased systemic insulin levels. Not surprisingly, both glucose intolerance and T2DM are frequent conditions (range from 30% to 50%) in patients with cirrhosis; only one-third of patients with cirrhosis have normal glucose metabolism.[54] The prevalence of T2DM is even higher (>60%) in patients with NAFLD-related or cryptogenic cirrhosis compared to viral hepatitis.[55] T2DM is associated with fibrosis progression and poor outcomes in patients with NAFLD.[56] In patients with cirrhosis, T2DM is a major risk factor for cirrhosis-related complications (infection, ascites, renal function impairment, and HE) and death, which outperforms the risk of diabetes-related complications.[57–60] Retrospective BS series identified T2DM as an important predictor for the persistence of advanced fibrosis and cirrhosis despite massive weight loss.[17] Although long-term prospective longitudinal studies are missing, these data support the hypothesis that the optimal control of T2DM might be beneficial and improve outcomes, in particular, the occurrence of cirrhosis-related complications.

Nevertheless, several aspects should be considered when prescribing antidiabetic medication in patients with NAFLD-related cirrhosis. First, because of dysregulated glucose metabolism in patients with CLD, hypoglycemia is more frequent and occurs in 12% to 16% of patients with both diabetes and cirrhosis. In addition, recent data suggest that NAFLD itself is an independent risk factor for hypoglycemia,[61] potentially explained by the downregulation of hepatic glucagon receptors, increased oxidative stress, and external factors—alcohol or antidiabetic medication, in particular sulphonylureas and insulin. Beyond the immediate risk, hypoglycemia should be avoided because it increases gluconeogenesis, which further favors and aggravates sarcopenia. For these reasons, less stringent glycemic targets (<8%) are accepted in cirrhotic patients.[62,63] Second, glycosylated hemoglobin is an unreliable tool[64,65] to monitor glycemic control in patients with CLD and should be avoided in particular in patients with decompensated cirrhosis and concomitant anemia for whom self-monitoring of capillary blood glucose should be preferred.[66] It is recommended that in patients with decompensated cirrhosis, fasting capillary blood glucose should be maintained between 5 and 11 mmol/l. Finally, the choice of antidiabetic medication in NAFLD-related cirrhosis should consider the mechanism of action, the pharmacokinetics and the metabolic pathways of the selected drug, the severity of the liver disease, the risk of hypoglycemia, and the potential effect on NAFLD and liver-related outcomes. Based on these considerations, the use of some antidiabetic drugs is either strongly recommended (both safe in patients with cirrhosis and potentially beneficial in patients with NAFLD), neutral (safe in cirrhosis but not established benefit in NAFLD), or strongly discouraged (especially for safety concerns in cirrhosis) (Table 1).

Among the newly developed antidiabetic drugs, glucagon-like peptide-1 receptor agonists are strongly recommended in patients with cirrhosis as they are not metabolized in the liver, and there is no risk of hypoglycemia. These recommendations are particularly relevant in patients with NAFLD as glucagon-like peptide-1 receptor agonists showed promising results on liver fat content, liver enzymes, and resolution of NASH without worsening of fibrosis concomitant with significant weight loss and improvement in glycemic control.[67,68] However, limited data are available on patients with cirrhosis. A small study reported that semaglutide exposure is not affected by hepatic impairment, suggesting that the drug can be safely administered and no dose adjustment is required in patients with mild to moderate liver dysfunction.[69] Dual agonists [glucagon-like peptide-1 receptor agonists ((GLP1)/gastric inhibitory peptides or GLP1-glucagon)] are now being tested in patients with T2DM, and preliminary results also support their usefulness in NAFLD,[70,71] but no safety or efficacy data are available in cirrhosis. Similar to GLP1-RAs, dipeptidylpeptidase-4 inhibitors can be safely administered in patients with compensated cirrhosis, but should be avoided in patients with severely impaired liver function. Dipeptidylpeptidase-4 inhibitors are neutral on NASH progression.[72] The other antidiabetic drugs (except pioglitazone) either have no proven efficacy in patients with NASH or available data are insufficient. Metformin use has been for a long time discouraged in patients with cirrhosis because of the risk of lactic acidosis. Although there is no effect of metformin on the histological lesions of NASH, data have shown that metformin use in patients with cirrhosis with T2DM is safe and associated with improved survival by 57%.[73] The beneficial effect of metformin on hepatic decompensation rate has not been confirmed in a more recent study after adjusting for confounders.[74] Most of the antidiabetic drugs (except metformin, dipeptidylpeptidase-4 inhibitors, and GLP1-RAs) are metabolized in the liver and should not be used in patients with moderately/severely impaired liver function (Table 1). Dose reduction should be considered for antidiabetic drugs that are metabolized in the liver. Insulin therapy is safe in

TABLE 1 Benefits and safety of antidiabetic drugs in patients with NASH-related cirrhosis

Antidiabetic drug	Steatosis	NASH	Fibrosis	Metabolism	Safety in patients with cirrhosis	
					Compensated	Decompensated
Metformin	Neutral	Neutral	Neutral	Not metabolized in the liver; limited passive diffusion through the membranes of hepatocytes. Renal excretion; and dose adjustment to the renal function.	Metformin can be used in patients with cirrhosis and preserved/ slightly impaired liver function. Dosage should be adapted to renal function.	Metformin should be discontinued in patients with cirrhosis and severely impaired liver function because of the risk of lactic acidosis.
DDP-4i	Neutral/improved	Not studied	Not studied	Generally, not substrate for cytochrome P450— except for saxagliptin, that is, metabolized using CYP 3A4/A5. Renal excretion, except for linagliptin, whose metabolism in the liver appears to be predominant.	Can be used in patients with cirrhosis and slightly/moderately impaired liver function.	Not recommended in patients with cirrhosis and severely impaired liver function.
	—	—	—	—	Vildagliptin should not be used in patients with cirrhosis and impaired liver function.	—
GLP1-RA[a]	Improved	Improved	Neutral	Not metabolized in the liver. Exenatide is primarily eliminated by the kidney, whereas liraglutide and dulaglutide are totally degraded within the body via the action of DPP-4.	Can be used in patients with cirrhosis and preserved/slightly impaired liver function[b].	Caution in patients with cirrhosis and moderately impaired liver function.
TZD (pioglitazone)[c]	Improved	Improved	Neutral/Improved	Pioglitazone is metabolized in the liver mainly by CYPC28	Pioglitazone can be used in patients with cirrhosis and preserved/ slightly impaired liver function	Should be avoided in patients with moderately/severely impaired liver function because of the risk of fluid retention.
SGLT2i	Neutral/improved	Not studied	Not studied	Hepatic metabolism mainly by glucuronidation; small amounts of metabolite are eliminated through the renal route	Extensive hepatic metabolism mainly by glucuronidation. Although there are insufficient data, pharmacological studies suggest increasing accumulation with decreasing liver function.	
Sulfonylurea	Not studied	Not studied	Not studied	Metabolized in the liver into active and inactive metabolites through cytochrome P450 (CYP450) enzymes; extensively bound to serum proteins and excreted mainly through the renal pathway.	Sulfonylureas are metabolized in the liver into active and inactive metabolites through cytochrome P450 (CYP450) enzymes. Can be used in patients with preserved/slightly impaired liver function but at lower doses.	Contraindicated in patients with moderately/severely impaired liver function.
Insulin	Not studied	Not studied	Not studied		Insulin can be used in any patient with cirrhosis regardless of the level of liver function impairment.	

[a]None of these drugs has been tested in patients with cirrhosis. A phase 2 randomized controlled trial with semaglutide is ongoing in cirrhotic patients.
[b]concerns Liraglutide, dulaglutide and semaglutide. Not enough data for exenatide and lixisenatide.
[c]not commercialized in Europe.
Abbreviations: DDP-4i, dipeptidylpeptidase-4 inhibitors; GLP1-RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitors; TZD, thiazolidinediones.

patients with cirrhosis, regardless of the level of liver function impairment, and should be preferred as first-line therapy, especially in patients with decompensated Child-Pugh C cirrhosis. Although patients with cirrhosis might have significant insulin requirements because of insulin resistance, hyperglucagonemia, and decreased hepatic clearance of portal glucose, the insulin doses should be carefully adapted and should be lower compared to non-cirrhotic patients because of decreased neoglucogenesis.[75,76]

Management of cardiovascular risk and statin therapy

Because of the high prevalence of cardiovascular (CV) disease and atherogenic dyslipidemia, patients with NAFLD are often indicated to statin therapy to lower the CV risk and to prevent adverse clinical outcomes. However, despite several studies showing clinical benefit,[77] statins are underprescribed in patients with NAFLD, and only half of eligible patients are on statins.[78,79] Safety concerns are the main reason for the suboptimal use of statins[80]—for both health care providers and patients—and reflect the gap between clinical practice and recommendations from guidelines. Numerous studies have shown that statins are safe in patients with NAFLD,[81,82] normalize liver enzymes,[83] and improve histological lesions[84] through various mechanisms.

Statins present beneficial effects in cirrhosis. Data from experimental models show that statins reduce collagen production by Rho kinase inhibition in HSC.[85] In addition, by upregulating the activity of endothelial nitric oxide synthase and increasing nitric oxide availability, statins improve endothelial dysfunction and lower portal pressure.[86,87] In humans, statins significantly decrease the risk of cirrhosis decompensation and mortality.[88] By lowering portal pressure, statins improve liver perfusion and liver function, an additive and independent effect of beta-blocker treatment. This has been demonstrated in a randomized controlled trial showing that simvastatin reduced HVPG by ≥10% and ≥20% in 40% and 32% of patients, respectively.[89] It has been shown that simvastatin decreases intrahepatic vascular resistance by upregulating endothelial nitric oxide production and thus reduces HVPG without modifying hepatic blood flow.[86] The beneficial effects of statins on intrahepatic vascular resistance further encouraged statin use in addition to standard prophylaxis to prevent variceal bleeding. The BLEPS trial, a large randomized controlled trial that assessed the effects of statins in cirrhosis, showed a significant improvement in survival in patients with cirrhosis who recover from acute variceal bleeding after treatment with simvastatin, without significant effects on other cirrhosis complications.[90] In addition, a large study including veterans from the United States Veterans Health Administration database showed that statins have the potential to reduce morbidity and mortality caused by infections in patients with cirrhosis.[91] More recently, a retrospective study of 84,963 US veterans with cirrhosis showed that binary statin exposure resulted in 38% reduced hazard of developing acute-on-chronic liver failure in a dose-dependent manner. Importantly, in this cohort, among patients on statins at baseline or initiated to statins, 41% and 20%, respectively, had NAFLD-related cirrhosis.[92] The beneficial effects observed in this study were not found for other lipid-lowering drugs than statins, suggesting a class effect and thus, at least an indirect causal relationship. Although data are controversial, it seems that statin exposure might also reduce infection-related mortality in the context of acute-on-chronic liver failure.[93,94]

Finally, besides the positive effect on cirrhosis decompensation and mortality, statins also have a dose-dependent chemopreventive effect with a 25% reduction in HCC risk.[95] Altogether, these data support the Baveno VII recommendations that encourage the use of statins in patients with cirrhosis if indicated. A lower dose (eg, simvastatin 20 mg/day) is recommended in patients with Child-Pugh B and C cirrhosis to minimize the risk of liver and muscle toxicity.[37]

The risk of adverse reactions could be linked to the dose used, the interactions with other drugs inhibiting the cytochrome P450 isoenzyme system, the reduced statin metabolism affecting statin pharmacokinetics in patients with cirrhosis, and the genetic variability. The single nucleotide polymorphism in the SLCO1B1 gene influences hepatic uptake by the liver and increases plasma levels of statins and the risk of adverse events.[96]

CV risk assessment needs particular attention in LT candidates with NAFLD who are at higher risk for CV morbidity and mortality both while on the waiting list and following LT.[97] This questions the usefulness of more aggressive approaches for CV risk assessment to identify high-risk patients amenable to specific interventions aimed to optimize the access to LT and post-LT outcomes.[98,99] The classical noninvasive tools have limited performance to evaluate the CV risk in LT candidates because (1) inability to perform exercice testing as a consequence of malnutrition and sarcopenia associated with end-stage liver disease (2) the failure to achieve the target heart rate during exercise testing or dobutamine stress echocardiography because of the frequent use of beta-blockers.[99,100] Coronary angiography has been used as a primary investigation by most of the LT centers,[101–103] but this more aggressive approach is now questioned by studies reporting 50% posttransplant mortality in revascularized

patients. Coronary angiography also underestimates the nonobstructive plaques and the microvascular dysfunction ,which further limits its usefulness as first-line test.[104] Whether routine stress testing and coronary angiography should be preferred versus a case-by-case multidisciplinary approach in patients with silent coronary disease needs further validation.

Particularities in the diagnosis and management of portal hypertension in NAFLD-related cirrhosis

PHT and HVPG $\geq$5 mm Hg and CSPH and HVPG $\geq$10 mm Hg are major complications of cirrhosis associated with adverse clinical outcomes (cirrhosis decompensation, ascites, variceal bleeding, encephalopathy, etc.).

Several particularities should be considered in the assessment and management of PHT in compensated patients with NAFLD-related cirrhosis in relationship with the presence of associated comorbidities—obesity and cardiovascular disease.

First, specific prognostic HVPG thresholds need further validation by prospective longitudinal studies in patients with NAFLD-related cirrhosis. Although a HVPG cutoff of 10 mm Hg is strongly correlated with significant clinical outcomes, recent studies have shown that in patients with NAFLD, cirrhosis decompensation may occur even at an HVPG < 10 mm Hg. Furthermore, for a given liver function, patients with NAFLD had lower HVPG but higher decompensation rates than viral-related cirrhosis.[105] Despite a similar HVPG, patients with decompensated NAFLD cirrhosis have a worse liver function and more clinical signs of PHT, suggesting a more advanced liver disease than cirrhosis of other etiologies. These data align with older studies demonstrating that in decompensated stages, the prognosis of patients with NAFLD is at least comparable with HCV-related cirrhosis.[11]

Second, Baveno VII recommendations put forward the concept of treating CSPH rather than preventing variceal bleeding in compensated patients. In other words, nonselective beta-blockers (NSBBs) should be prescribed not only in patients with large varices but also in patients with a high probability of displaying CSPH to decrease the occurrence of cirrhosis decompensation, especially ascites, and since the conclusions of the PREDESCI trial.[106] Off-notes, the PREDESCI trial included mainly patients with viral cirrhosis and very few patients with metabolic syndrome alone. Hence, whether the conclusions of this trial can be derived to patients with NAFLD remains to be proven. This is of major importance for patients with NAFLD, as the concept itself implies to decrease drastically the number of upper endoscopies in patients with cirrhosis. Upper endoscopy is now reserved for patients for whom the CSPH status is not known (see below). However, patients with NAFLD are more prone to gastroesophageal complications outside PHT-related ones, like reflux, as well as esophagitis, and the idea of restricting upper endoscopies in those patients is debatable.

Moreover, Baveno VII conference allows the use of noninvasive tools (a composite of the liver stiffness — liver stiffness measurement (LSM) and platelet counts) to assess CSPH and predict compensated advanced chronic liver disease (c-ACLD). These recommendations first included patients with viral-related cirrhosis and have now been expanded to patients with NAFLD-related cirrhosis. The ANTICIPATE model used to predict CSPH has now been adapted for NAFLD cirrhosis by adding BMI and adjusting the weight of platelet count in the model.[107] The model has been externally validated[108] and can be used in non-obese patients with NAFLD-related CLD: patients with LSM > 25 kPa are considered to display CSPH and patients with LSM between 20 and 25 kPa and a platelet count < 150 G/L or LSM between 15 and 20 kPa and a platelet count < 110 G/L have at least 60% risk of CSPH (Figure 2). There is a need to further validate and refine the noninvasive tools for the diagnosis of CSPH in obese patients with NAFLD-related cirrhosis.[37]

Finally, NSBBs are the standard of care in patients with CSPH,[2] and Baveno VII recommendations state that carvedilol is the preferred NSBBs to prevent decompensation in patients with CSPH and compensated cirrhosis. Owing to its intrinsic alpha adrenergic vasodilatory effect, carvedilol is more effective in reducing HVPG compared to propranolol in both primary[109] or secondary prophylaxis.[110] Besides the doubts raised by the applicability of this recommendation to patients with NAFLD (see before), the use of carvedilol in patients with NAFLD-related cirrhosis must be balanced in a relationship with the competing risk derived from associated comorbidities, in particular CV disease. Differences in the effect of beta-blockers are based on their affinity for β1 or β2 receptors and the presence of additional properties (α1-receptor inhibition-mediated vasodilatation or L-arginine/nitric oxide-mediated vasodilatation). Older studies suggest that carvedilol used for the treatment of chronic heart failure in patients optimally treated with diuretics and angiotensin-converting enzyme inhibitors, has a significantly greater beneficial effect on survival than metoprolol.[111,112] These data potentially encourage the use of carvedilol in patients with NAFLD-related cirrhosis and heart failure. Nevertheless, a sizeable proportion of the patients with NAFLD are already on selective beta-blockers for CV disease (either ischemic heart disease or heart failure) with well-established benefits on short-term and long-term mortality.[113] In this context, the switch to NSBBs to prevent variceal bleeding or c-ACLD should be considered on a case-by-case basis for these patients.

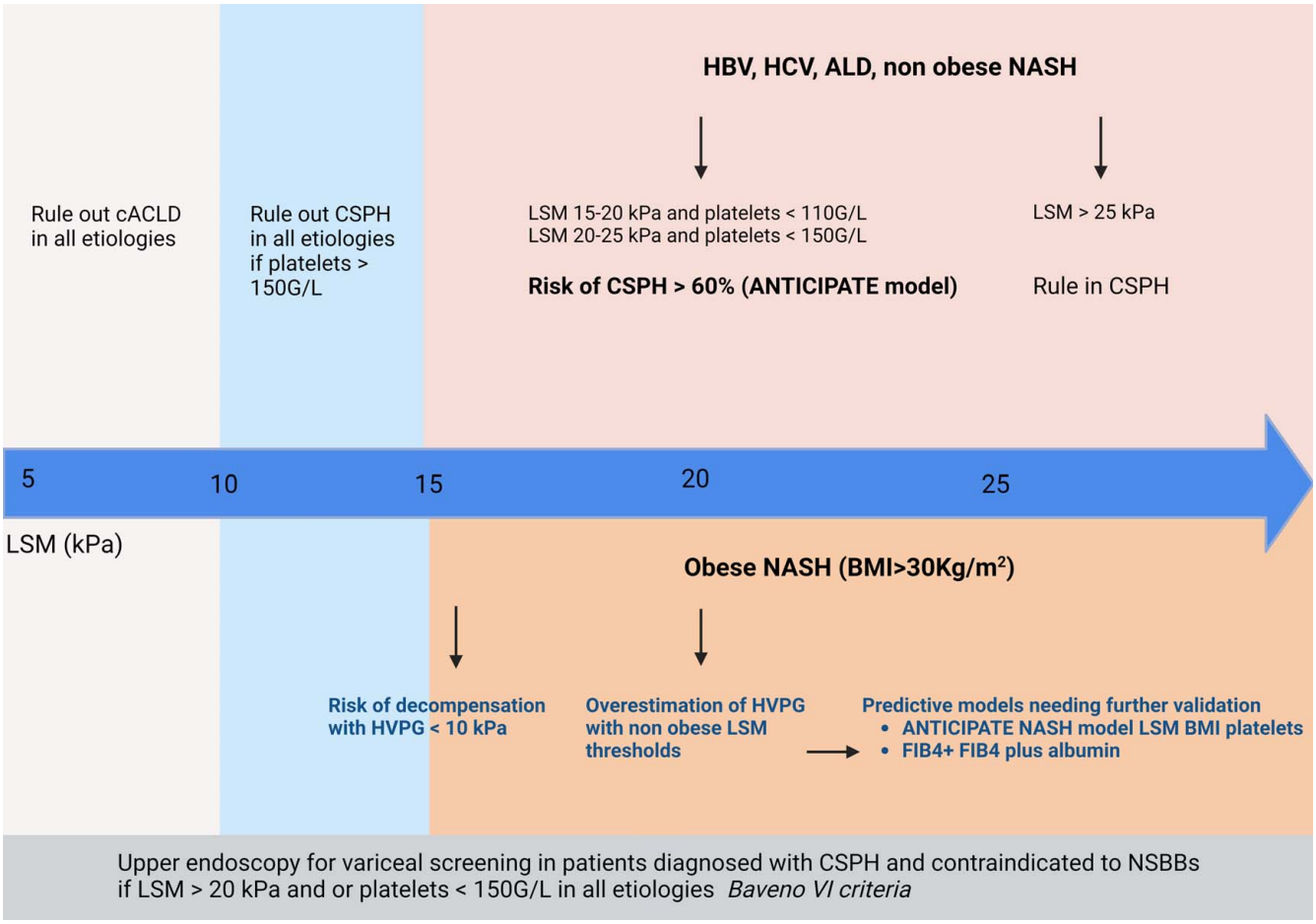

FIGURE 2 Algorithm to predict CSPH in obese patients with NASH (adapted from Baveno VII recommendations). Created with BioRender.com. Abbreviations: ALD, alcohol-associated liver disease; c-ACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; FIB4, Fibrosis-4 score; LSM, liver stiffness measurement; NSBBs, nonselective beta-blockers.

Benefits and risks of bariatric surgery in patients with NAFLD-related cirrhosis

Bariatric surgery has been shown to have substantial benefits in reducing overall mortality and to improve the cardiometabolic condition, insulin resistance, and low-grade inflammation in morbidly obese patients.[114] These metabolic and systemic effects of BS result in significant improvement in liver lesions, particularly in those patients with mild disease.[115] The effect of BS in patients with advanced fibrosis or cirrhosis is insufficiently assessed because of the limited number of patients with advanced liver disease included in most of the BS series.[116] Among BS studies with available liver biopsy at baseline and follow-up, only 7 studies included patients with cirrhosis (Table 2).

At least two aspects should be considered in cirrhotic patients: first, which are the benefits expected in terms of fibrosis/cirrhosis regression and how these translate in terms of survival benefit, and second, which are the acceptable risks related to PHT and to cirrhosis decompensation following the surgery.

The regression of liver fibrosis is very common in very early stages, which lacks extracellular matrix crosslinking and marked angiogenesis. In cirrhotic stages, which are characterized by significant distortion of liver parenchyma and blood flow changes, fibrosis regression is less certain and might take a longer time.[117,118] Furthermore, longer prospective follow-up studies should be performed to determine whether the histological improvement following BS translates into an improvement in overall survival.

We and others have recently shown that almost half of the patients with advanced fibrosis who underwent BS still had bridging fibrosis or cirrhosis more than 5.5 years after surgery.[17,119] Persistent advance fibrosis/cirrhosis was concomitant with lower rates of diabetes remission (21% vs. 60% in most of the BS series)[120] and less (although significant, 10 ± 6 kg/m^2) weight loss. These results raise important concerns on the impact of weight loss on cirrhosis reversal and allow us to emphasize that the mechanisms involved in fibrosis regression following BS are possibly procedure dependent. BS induces significant changes in the gut-liver axis—increase in

TABLE 2 Histological outcomes of bariatric surgery in patients with cirrhosis[a]

References, country	Study design	Surgery type	Follow-up period (mo)	BMI reduction, %	Baseline biopsy	Follow-up biopsy	Histopathological scoring	Overall fibrosis regression (≥ 1 stage), %	Baseline cirrhosis (N)	Cirrhosis regression
Dixon, 2004[1], US, Australia	Retrospective	GB	25.6	27.6	36	36	Dixon	70	3	No, but reduction in necroinflammatory lesions. Two additional patients developed cirrhosis
Mattar 2005[2], US	Prospective	RYGB, SG, GB	15 ± 9	30	70	70	Brunt	20	2	No, but improvement in steatosis and inflammation
Lassailly, 2015[115], France	Prospective	RYGB, SG, GB	12	24	109	82	Brunt, NASH CRN, METAVIR	38 (Metavir) 46 (Kleiner)	5	One patient
Taitano, 2015[3], US	Retrospective	RYGB, GB	20	36.5	160	160	Brunt	56	1	No One patient with bridging fibrosis progressed to cirrhosis
Lassailly, 2020[119], France	Prospective	RYGB, SG, GB	60	25	180	64	Brunt, Kleiner	70	3	Cirrhosis regressed in 2 patients to stage 3 fibrosis. One patient progressed from bridging fibrosis to cirrhosis
Kaul, 2020[4], India	Retrospective	SG, RYGB	34.5	30.6	20	12	NASH CRN	75	4	Cirrhosis regressed in 3 patients: 2 to bridging fibrosis and one to F0
Pais, 2022[17], France	Retrospective	RYGB, SG	66	25.6	196	66	SAF, Kleiner, EPOS 7 tiers	70	14	Cirrhosis regression in 11 patients: 7 regressed to bridging fibrosis and 3 to ≤ F3. None developed cirrhosis during the follow-up

[a]Only studies with histologically documented cirrhosis at baseline and available follow-up biopsies are presented.

Abbreviations: EPOS, elucidating pathways of steatohepatitis; GB, gastric bypass; RYGB, Roux-en-Y gastric bypass; SAF, steatosis-activity-fibrosis; SG, sleeve gastrectomy.

[1]Dixon JB, Bhathal PS, Hughes NR, O'Brien PE. Nonalcoholic fatty liver disease: Improvement in liver histological analysis with weight loss. Hepatology 2004;39:1647-1654.

[2]Mattar SG, Velcu LM, Rabinovitz M, Demetris AJ, Krasinskas AM, Barinas-Mitchell E, Eid GM, et al. Surgically-Induced Weight Loss Significantly Improves Nonalcoholic Fatty Liver Disease and the Metabolic Syndrome. Transactions of the ... Meeting of the American Surgical Association 2005;123:304-314.

[3]Taitano AA, Markow M, Finan JE, Wheeler DE, Gonzalvo JP, Murr MM. Bariatric surgery improves histological features of nonalcoholic fatty liver disease and liver fibrosis. J Gastrointest Surg 2015;19:429-436; discussion 436-427.

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circulating bile acids, FGF-19, and farnesoid X receptor signaling,[121–123] as well as significant changes in the richness and composition of gut microbiota.[124] All these mechanisms might conceptually affect the liver histology independently of the weight loss.[125–128] Therefore, an important question is whether one BS technique should be preferred versus another. Studies have shown that although fibrosis regression rate seems to be lower in patients undergoing sleeve gastrectomy (SG),[17] this procedure is preferred in almost half of the patients with cirrhosis because of a lower risk of hepatic decompensation compared to malabsorptive procedures and the need to preserve the normal gastrointestinal continuity in the eventuality of LT.[129] Overall, SG has significantly lower complication (17% vs. 29%) and mortality rates (0.45% vs. 3%) compared to Roux-en-Y gastric by-pass, but similar rates of liver decompensation (~4%).[129] The mortality rates significantly increase (up to 16%) in patients with decompensated cirrhosis, suggesting that carefully selected patients with Child-Pugh A cirrhosis will benefit the most from BS.[130] Based on these data, both the American Association of Clinical Endocrinology[131] and the European Society for Clinical Nutrition (ESPEN)[40] advocate the benefits of BS in patients with compensated cirrhosis, but because of limited evidence and potential for harm, they do not recommend BS in patients with decompensated cirrhosis unless in highly experimented centers within carefully structured programs.[132] A thorough analysis is mandatory to determine if the postoperative risk and complications are offset by the benefits of BS. The major limits of the BS studies performed in patients with cirrhosis are the retrospective design; the small sample size; the patient selection criteria, with most of the studies including carefully selected patients with Child-Pugh A cirrhosis (>90%); and the heterogeneity in the diagnosis of cirrhosis and measures of liver disease severity.[129] Another important limit for BS in patients with cirrhosis is the presence of CSPH, which increases the mortality risk. Several small pilot studies reported that decreasing portal pressure with TIPS may improve outcomes in patients undergoing abdominal surgery,[133,134] but no data are available for TIPS placement before BS.

Finally, BS may also serve as a bridge to increase the eligibility for LT in morbidly obese patients with cirrhosis.[135] Most LT centers apply specific BMI thresholds (BMI $\leq$ 40 kg/m2) for performing transplantation because of higher rates of peritransplant complications (infections, longer stay in intensive care units) in patients with severe obesity.[136,137] Several options should be considered[135]: (1) BS before LT, but with a risk of 35% of cirrhosis decompensation; (2) BS concomitant to LT, but this would increase the time and the complexity of the procedure; and (3) BS after LT, but this will still not give the access to LT of patients with BMI $\geq$ 40 kg/m2 and will not modify the risk of short complications.

The BS procedure is decided on an individual basis upon the technical feasibility for each patient. SG is preferred by most of the transplant centers for several reasons: (1) the technique does not require intestinal anastomosis and (2) it allows the endoscopic access to the biliary system to manage biliary posttransplant complications; (3) the intestinal absorption of drugs and nutrients is not altered, which allows to maintain adequate immunosuppression and prevent malnutrition; and (4) the metabolic benefit beyond the weight loss—higher glucagon-like peptide-1—serum levels, lower ghrelin, increased postprandial release of cholecystokinin and peptide YY, and accelerated gastric emptying.[138] Finally, BS not only facilitates the access to LT in obese patients but also prevents weight gain and the occurrence/worsening of metabolic syndrome after LT.[132] A small case series from Mayo Clinics demonstrated that 3 years after transplant, only 29.4% of patients in the LT-lifestyle measure cohort maintained >10% loss in total body weight loss, whereas 100% of the combined LT and SG patients did. Patients in the combined LT and SG group also had a lower prevalence of hypertension, insulin resistance, and hepatic steatosis.[139] Endoscopic balloon placement might be an alternative to BS as a bridge to LT, but the experience is even scarce and limited to a small number of cases.[140]

Clinical trials in *NAFLD-related cirrhosis*

Several drugs have been tested in clinical trials for NAFLD/NASH, but none of them have gotten the FDA or EMA approval despite positive results for some of them. In contrast to non-cirrhotic NASH, most of the molecules tested in patients with NAFLD-related cirrhosis showed negative results (Table 3), underlying the difficulties to develop drugs and to conduct clinical trials in patients with NAFLD in general and in patients with NAFLD-related cirrhosis in particular.[141] Challenges in conducting clinical trials in patients with cirrhosis have been addressed by regulatory agencies, multiple stakeholders, and academics and involve both patients' selection criteria and clinical trial end points.[142–146]

Patients' heterogeneity is a major challenge in conducting clinical trial in NASH and impact both patients' selection and outcomes assessment. First of all, the dichotomous patients' classification in compensated and decompensated cirrhosis based on the portal pressure and the occurrence of clinical events does not reflect the continuum of fibrosis progression.[147] On the other hand, patients' selection based on stringent histological criteria with a requirement of a NAS score of $\geq$4 and at least 1 point for each component might be difficult to fulfill at a cirrhotic stage because of the regression of steatosis and inflammatory lesion ("burned-out" NASH) and thus leads to high rates of screen failure.[146] Furthermore, it is likely

TABLE 3 Selected studies of drugs tested in patients NASH cirrhosis that failed in phase II/III clinical trials

Agent	NCT identifier	Mechanism of action	Phase	No of patients	Primary outcome	Results
Simtuzumab	NCT01672879.	Humanized monoclonal antibody against LOXL2	IIb	Simtuzumab 200 mg, N = 87 Simtuzumab 700 mg, N = 86 Placebo, N = 85	The difference in the mean change from baseline in HVPG at week 96 between each simtuzumab arm and placebo	No significant reduction in HVPG vs. placebo
Selonsertib	NCT03053063	Inhibitor of apoptosis signal-regulating kinase 1	III	Selonsertib 18 mg, N = 354 Selonsertib 6 mg, N = 351 Placebo, N = 172	≥1-stage fibrosis improvement without worsening of NASH and the time to first clinical event	No significant improvement in fibrosis Similar rates of liver-related events
Emricasan	NCT02960204.	Pan-caspase inhibitor	III	Emricasan 5 mg, N = 65 Emricasan 25 mg, N = 65 Emricasan 50 mg, N = 66 Placebo, N = 67	Change in HVPG from baseline to week 24 between emricasan and placebo.	No significant differences in ΔHVPG for any emricasan dose vs. placebo. Significant decrease in patients with baseline HVPG ≥ 16 mm Hg.
Emricasan	NCT03205345.	Pan-caspase inhibitor	II	Emricasan 5 mg, N = 73 Emricasan 25 mg, N = 71 Placebo, N = 70	All-cause mortality; new decompensation event; MELD-Na increase of ≥4 points from baseline.	No significant difference in the event rates No significant effect on MELD-Na
Belapectin	NCT02462967	Inhibitor of Galectin-3	IIb	Belapectin 2 mg/kg, N = 54 Belapectin 8 mg/kg, N = 54 Placebo, N = 54	Change in HVPG from baseline to 1 y	No significant reduction in HVPG Subgroup analysis of patients without esophageal varices, 2 mg/kg belapectin did reduce HVPG and development of varices
Pegbelfermin	NCT03486912	Polyethylene glycol (PEG)-conjugated recombinant analog of human FGF21	IIb	Pegbelfermin 10 mg, N = 25 Pagbelfermin 20 mg, N = 25 Pegbelfermin 40 mg, N = 25 Placebo, N = 25	Fibrosis improvement without worsening of NASH	Ineffective for fibrosis improvement
Cilofexor and Firsocostat	NCT03449446	Cilofexor: nonsteroidal FXR agonist Firsocostat is a liver-targeted, small-molecule allosteric inhibitor of acetyl-CoA carboxylase	IIb	Cilofexor/Firsocostat, N = 78 Cilofexor/Selonsertib, N = 77 Firsocostat/selonsertib, N = 79 Cilofexor, N = 40 Firsocostat, N = 40 Selonsertib, N = 39 Placebo, N = 39	≥1-stage improvement in fibrosis without worsening of NASH between baseline and 48 wk	No significant difference between any of the treatment arms and placebo
Semaglutide	NCT03987451	Semaglutide: GLP1-RA	IIb	Semaglutide once-weekly dose escalation to 2.4 mg, N = 47 Placebo, N = 24	≥1-stage improvement in fibrosis without worsening of NASH between baseline and 48 wk	Semaglutide did not significantly improve fibrosis or achievement of NASH resolution versus placebo. No safety concerns

Abbreviations: FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP1-RA, glucagon-like peptide-1 receptor agonists; LOXL2, lysyl oxidase homolog 2.

that even patients who fulfill these histological criteria are different despite "looking the same" under the microscope. As an example, in the simtuzumab trial, baseline alpha-smooth muscle actin and changes in alpha-smooth muscle actin from baseline better correlated with regression or progression to cirrhosis and with the outcome when compared with liver histology.[148] These data suggest that different fibrogenic drivers are involved in patients with compensated cirrhosis that otherwise look the same, and these markers could potentially be used for better patient selection. A possible approach to overcome patient heterogeneity and to optimize the therapeutic response would be to stratify patients according to the severity and prognostic of cirrhosis (eg, HVPG),[149] the relevant metabolic comorbidities (eg, T2DM—which might interfere with drug efficacy either directly or through concomitant medication),[150] the genetic background,[151] or a combination of these.[152] Efforts have been made to build machine learning algorithms using clinical predictors to improve the prediction of NASH and at-risk NASH.[153] Finally, the increased accuracy in the case definition of NAFLD-related cirrhosis would result in a decrease in the rate of screen failure. Platform trials appear as an alternative to reduce the screen failure rate[154] using a common screening platform to identify all interventions/drugs for which a patient might be eligible. Master protocols and platform trials are now considered in the NAFLD drug development pipeline for non-cirrhotic NAFLD, but their usefulness in NAFLD-related cirrhosis is questioned.[155]

The second lesson learned from negative trials in NAFLD-related cirrhosis is to choose the right end point. It is, therefore, challenging to determine which is the best end point that would be feasible to achieve in a relatively short time frame in a clinical trial setting to prove the efficacy of a drug and fulfill the clinicians' expectations. Ultimately, what is relevant for clinicians is to improve survival and to prevent death from cirrhosis and its complications. However, the conduction of clinical trials with such hard clinical end points is challenging because of the slow disease progression[3] and the low event rates (3%–4% y), which would require a significant time period to demonstrate drug efficacy. Past and ongoing studies in patients with cirrhosis have a relatively weak, short-term surrogate primary end point concomitant with stronger, long-term, primary end point like 5-year mortality and liver-related mortality. A classic example of a composite long-term outcome would include all-cause mortality and liver-related clinical outcomes at the time to accrue a pre-specified number of adjudicated events, which is estimated to be 5 years. However, some of the drugs tested will probably obtain approval before if their primary (surrogate, short-term) end point is reached. Hence, this will be very difficult for investigators to keep patients included in the placebo group, and all these studies will probably terminate before evaluating stronger clinical end points. Population-based estimates in patients with NAFLD have shown that based on a progression rate to decompensated cirrhosis of 10% per year and subsequent risk of liver events and death of 32% per year, trials in compensated cirrhosis would require at least 2886 subjects followed up for ≥ 2 years to detect a significant decrease of $\geq 15\%$ in liver-related events.[9] This last pitfall is probably the most important one in the development of new therapies.

To support accelerated approval, FDA and EMA proposed surrogate histological end points (NASH resolution without worsening of fibrosis and ≥ 1-point fibrosis regression without worsening of NASH) that are believed to best correlate with such significant clinical outcomes.[156,157] While this is true for non-cirrhotic NASH, some uncertainties persisted related to fibrosis regression and improvement in clinical outcomes in patients with cirrhosis. Recently, it has been shown that histological regression of cirrhosis is associated with a 6-fold decrease in the risk of liver-related events, which further supports the regulatory acceptance of surrogate histological end points for drug approval.[14] Nonetheless, it is not clear to which extent cirrhosis is truly reversible in terms of histological, architectural, biological, and clinical aspects, and the "point of no return" has to be further refined. It is, therefore, important to distinguish between fibrosis regression and reversal of cirrhosis. Histological regression of fibrosis might be sometimes difficult to capture with the actual NASH-Clinical Research network staging system and requires either a quantitative or semi-quantitative measure of fibrosis (morphometry, hepatic collagen, and alpha-smooth muscle actin expression) or a more granular staging system able to distinguish between incomplete cirrhosis with nascent regenerative nodules and annular fibrosis with complete nodulation.[158] For this reason, EMA requires that histological regression of cirrhosis is associated with improved or at least similar prognosis as in non-cirrhotic patients. Even less consensus exists concerning the end points to be considered in phase II clinical trials in NAFLD-related cirrhosis; several surrogate end points have been proposed: HVPG measures, enhanced liver fibrosis score, alpha-smooth muscle actin expression, etc. Finally, data from cirrhotic as well as non-cirrhotic NAFLD clinical trials have clearly shown the limits of the liver biopsy in terms of sampling, interobserver and intraobserver variability, which affects patients' selection and drug efficacy and explain the high response rate in the placebo arms.[159,160] Particularly, the regression to the mean applies in patients with NASH and advanced fibrosis/cirrhosis and is seen as apparent fibrosis regression at follow-up biopsy.[161,162]

Several options can be considered to overcome the shortcoming of liver biopsy. First, the histological assessment of NASH and fibrosis can be improved using novel approaches like machine learning-based assessment of key histological lesions associated with

TABLE 4 Ongoing trials in patients with NASH cirrhosis

Molecule	NCT Identifier	Mechanism of action	Phase	Treatment arms	Primary outcome	Estimated enrolment and completion date
Obethicolic acid (OCA)	NCT03439254	FXR agonist	III	OCA 10 mg OCA 10 mg titrated up to 25 mg Placebo	≥1-stage improvement in fibrosis without worsening of NASH	N = 919, August 2022
Resmetiron	NCT05500222	Liver-directed, orally active, selective thyroid hormone receptor-β agonist	III	Resmetiron 80 mg Placebo	Incidence of adjudicated composite clinical outcome event. Any event of all-cause mortality, liver transplant, ascites, HE, gastroesophageal variceal hemorrhage, and confirmed increase of MELD score from <12 to. >/= 15 due to liver disease	N = 700, November 2025
Aldafermin	NCT04210245	Fibroblast growth factor 19 analog	II/3	Aldafermin 03 mg, 1 mg, 3 mg vs. placebo	≥1-stage improvement in fibrosis without worsening of NASH	N = 160, March 2023
Belapectin	NCT04365868	Inhibitor of galectin-3	IIb/3	Belapectin 2 mg/kg/2 wk 18 mo ? switch to optimal dose Belapectin 4 mg/kg/ /2 wk 18 mo ? switch to optimal dose Placebo	Prevention of variceal varices	N = 1010 pts, December 2023
Efruxifermin (EFX)*	NCT05039450	Fc-FGF-21 fusion protein	IIb	EFX 28 mg (main study) EFX 50 mg (main study) Placebo (main study) EFX 50 mg (cohort D) Placebo (cohort D)	Change from baseline in fibrosis with no worsening steatohepatitis	N = 200 pts, April 2024
Semaglutide ± Cilofexor/Firsocostat	NCT04971785	Semaglutide: GLP1-RA Cilofexor: nonsteroidal FXR agonist Firsocostat is a liver-targeted, small-molecule allosteric inhibitor of acetyl-CoA carboxylase	II	SEMA + CILO/FIR FDC SEMA + Placebo-To-Match (PTM) CILO/FIR PTM SEMA + CILO/FIR FDC	≥1-stage improvement in fibrosis without worsening of NASH	
BMS-986263	NCT04267393	siRNA designed to degrade HSP47 mRNA	II	2 experimental doses of BMS- 986263	≥1 stage improvement in liver fibrosis without worsening of NASH	N = 270 pts, July 2024
BI 685509 ± Empagliflozin	NCT05282121	BI 685509: Substrate of the drug transporters P-gp and Organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1/OATP1B3) Empagliflozin: inhibiteurs du co-transporteur de sodium-glucose de type 2 - SGLT2	II	Experimental doses of HBV, HCV, and NASH cirrhosis	Percentage change in HVPG from the baseline	N = 80, July 2023

Note: Encouraging results in a phase 2a study: ≥ 1-stage improvement in fibrosis without worsening of NASH in 33% of EFX-treated patients (N = 12) vs 0% in placebo arms (N = 5).
Abbreviations: EFX, efruxifermin; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP1-RA, glucagon-like peptide 1 receptor agonist; HSP47, heat shock protein 47; OCA, obethicolic acid; SGLT2, sodium-glucose cotransporter-2; siRNA, small interfering ribonucleic acid.

NASH or second-harmonic generated images on unstained-paraffin-embedded sections. When applied to patients with advanced fibrosis and cirrhosis included in clinical trials (STELLAR-3[NCT03053050], STELLAR-4[NCT03053063], ATLAS [NCT03449446], and FLIGHT- farnesoid X receptor [NCT02855164]), both techniques had a high degree of concordance to central pathology reading, higher sensitivity to capture subtle fibrosis changes, minimized the reported placebo response, and added prognostic information.[163,164] In particular, the machine learning-derived DELTA-Liver fibrosis score revealed a significant antifibrotic effect of the association cilofexor + firsocostat that has not been observed with conventional pathological staging.[163,165] Second, past trials in NAFLD-related cirrhosis suggest that noninvasive tests (NITs) could be leveraged to assess the treatment response.[148] noninvasive tests are now used in ongoing trials, including those in the cirrhotic population (NCT05500222 and NCT03439254).

The third lesson learned from past trials in patients with NAFLD-related cirrhosis is that targeting only the final step of cell death signaling might not be enough if the downstream targets (metabolic and inflammatory pathways) are still active. This has been shown in the Emricasan clinical trial (NCT02960204), which despite relevant physiopathological background to decrease PH[166] and good target engagement, as shown by the significant decrease in caspase and other relevant biomarkers along with the improvement in aminotransferases, failed to achieve the primary end point.[149] However, in patients with higher HVPG at baseline (≥16 mm Hg), Emricasan was associated with a clinically significant reduction in PHT. Similarly, selonsertib did not meet the primary end point (fibrosis regression without progression of NASH) in the phase III clinical trial despite significant target engagement, as shown by the dose-dependent reduction in p38 phosphorylation.[167] These negative results suggest that the redundancy of downstream pathways requires a more precise target identification and encourages either the use of drugs with pleiotropic effects or the combination therapy hitting both upstream and downstream pathways. Several new molecules and combination therapy approaches are now tested in patients with NAFLD-related cirrhosis with some encouraging preliminary and safety results (Table 4).

CONCLUSION

The increasing prevalence of NAFLD and NAFLD-related cirrhosis has revealed new challenges for hepatologists. It is of paramount importance that the management of these patients should involve a multidisciplinary team, including dieticians, diabetologists, and physical exercise trainers. Lifestyle recommendations are the cornerstone in the management of NAFLD but are difficult to implement in patients with cirrhosis. These recommendations should be personalized for each patient according to both the presence of associated comorbidities—CV disease, diabetes, sarcopenia, or SO—and the severity of portal hypertension and liver disease (Child or MELD scores). Diabetes care and statin therapy are part of a multifaceted approach to lower cardiac and metabolic morbidity and mortality and prevent NAFLD progression. New data concerning the safety and beneficial effects of statins and antidiabetic drugs must be taken into consideration. Because a sizeable proportion of patients with NAFLD are already on BB for CV disease, the use of carvedilol and NSBB in patients with NAFLD-related cirrhosis must be balanced in relationship with the competing risk derived from associated comorbidities. There is also a need to further validate and refine the noninvasive tools for the diagnosis of CSPH in obese patients with NAFLD-related cirrhosis. Restricting upper endoscopies in these patients is debatable. BS in obese patients should be discussed as part of the therapeutic strategy of NAFLD but is limited by the presence of PHT. It seems of particular interest to consider BS before the onset of cirrhosis to target fibrosis regression, which is otherwise less likely to occur in cirrhotic stages. Nevertheless, those patients with NAFLD and BMI less than 35 kg/m^2 could not benefit from bariatric surgery regardless of the severity of the liver damage. Although some of the NAFLD drugs under development showed promising results in phase IIb or III clinical trials, none of them met all the requirements of regulatory agencies (EMA and FDA) for approval. A better stratification of patients included in NAFLD-related cirrhosis trials according to metabolic comorbidities and/or the severity of portal hypertension will hopefully demonstrate the efficacy of candidate drugs in specific subgroups of patients with NAFLD (eg, diabetics, obese patients, portal hypertension, or CSPH). Finally, the growing population of patients with NAFLD with decompensated cirrhosis and HCC has led to an increase in the number of patients with NAFLD awaiting LT. The cumulative effect of older age and cardiovascular and liver-specific complications should be considered to improve morbidity and mortality risk assessment before and after LT.

KEY POINTS

(1) Sarcopenia and SO are key points that should be considered when counseling diet and physical activity interventions in patients with NAFLD-related cirrhosis.
(2) The choice of antidiabetic medication in NAFLD-related cirrhosis should consider the mechanism of action, the pharmacokinetics and the metabolic pathways of the selected drug, the severity of the

liver disease, the risk of hypoglycemia (because of altered glucose metabolism), and the potential effect on NAFLD/NASH and liver-related outcomes.
(3) Specific prognostic HVPG thresholds need further validation by prospective longitudinal studies in patients with NAFLD-related cirrhosis; the use of carvedilol in patients with NAFLD-related cirrhosis must be balanced in relationship with the competing risk derived from associated comorbidities, in particular CV disease.
(4) Although bariatric surgery could be an attractive option in carefully selected patients with compensated cirrhosis, further longitudinal studies are needed to evaluate the benefit/risk ratio in patients with decompensated liver disease.

AUTHOR CONTRIBUTIONS

Maxime Mallet, Cristina Alina Silaghi, Dominique Thabut, and Raluca Pais: conception and design, drafting the article, revising the article for intellectual content, and final approval of the version to be published. Philippe Sultanik, Filomena Conti, Marika Rudler, and Vlad Ratziu: drafting the article, revising the article for intellectual content, and final approval of the version to be published.

CONFLICTS OF INTEREST

Dominque Thabut is on the speakers' bureau for AbbVie, Gilead, and Gore. Vlad Ratziu consults and received grants from Intercept. He consults for Boehringer-Ingelheim, Enyo, Madrigal, NGM Bio, North Sea, Novo-Nordisk, Pfizer, Poxel, Sagimet, and Terns. He received grants from Gilead. The remaining authors have nothing to report.

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