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REVIEW

Novel approaches in the medical management of compensated cirrhosis

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ABSTRACT

Introduction: Classically, clinical practice guidelines and expert recommendations have focused on the management of decompensated cirrhotic patients, so we focused this review on improving care for compensated cirrhotic patients who are followed up in outpatient clinics.

Areas covered: We reviewed the current methods for establishing liver function, the diagnosis and management of advanced chronic liver disease and clinically significant portal hypertension as well as the prevention of its complications, with special attention to covert hepatic encephalopathy, we also paid attention to the extrahepatic complications of cirrhosis and the palliative care. All this from the perspective of evidence-based medicine and trying to empower precision medicine. The literature search was undertaken by PubMed with 'cirrhosis,' 'advanced chronic liver disease,' 'liver function,' 'portal hypertension,' 'covert hepatic encephalopathy,' 'minimal hepatic encephalopathy,' 'palliative care' as MeSH terms.

Expert opinion: We must offer compensated cirrhotic patients specific care and measures to prevent the progression of the disease and the appearance of its complications beyond the calculation of liver function and imaging screening for hepatocellular carcinoma that we perform every six months. Entities that have typically received little attention, such as covert hepatic encephalopathy, extrahepatic complications and symptoms of cirrhosis, and palliative care, must come to the spotlight.

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Liver cirrhosis; advanced chronic liver disease; compensated cirrhosis; recompensated cirrhosis; decompensated cirrhosis; portal hypertension; hepatic encephalopathy; palliative care

1. Introduction

Medical management of patients living with compensated cirrhosis is a major issue with a lot of implications in clinical practice. Chronic liver diseases affect 1.5 billion people around the world, and the incidence of cirrhosis and its related mortality continued growing in recent years despite overall mortality due to cardiovascular events and neoplasms was decreasing [1]. Liver-related mortality rates by country are shown in Figure 1 [2]. The three pillars supporting cirrhosis management are: a) detecting causes (etiology), b) stratifying risk of progression (adding new methods and techniques), and c) personalized medicine.

All causes of chronic liver diseases could progress to liver cirrhosis, from viral hepatitis to alcohol-related and metabolic-associated fatty liver disease (MAFLD), together with uncommon causes like autoimmune hepatitis, primary biliary cholangitis, metabolic disorders such as hemochromatosis, Wilson's Disease, alpha-1 deficiency, or porphyria. Precision medicine could help to diagnosis exceptional cases of idiopathic cirrhosis. Indeed, whole exome analysis did allow to identify a quarter of cases of idiopathic liver diseases [3]. Etiology-directed therapy could modify the natural history of liver cirrhosis and avoid progression, as has been demonstrated with the success of the direct antiviral drugs against hepatitis C virus.

Liver ultrasound showing nodularity of the liver surface together with the bluntness of the liver edge and/or the coarseness of the parenchyma, together with increased spleen diameter or spleen area, have been strongly linked to cirrhosis diagnosis [4]. Nevertheless, in the last Baveno VII consensus [5], transient elastography (TE) emerged as a powerful method with high diagnostic accuracy for liver cirrhosis, compensated advanced chronic liver disease (cACLD) and clinically significant portal hypertension (CSPH). So, although liver biopsy and measurement of hepatic venous pressure gradient remain the standard for the diagnosis of liver cirrhosis and portal hypertension (PHT), in everyday clinical practice liver ultrasound and transient elastography are the most available techniques.

Liver dysfunction should be monitored by bilirubin level, prothrombin ratio and albumin concentration. Model for end-stage liver disease (MELD) and Child-Pugh-Turcotte (CPT) score have been commonly utilized to monitoring liver dysfunction. MELD was accepted as a criterion to be included in a waiting list for liver transplantation when higher than 15 points. Patients in stage 1 cirrhosis (no ascites no varices) and patients in stage 2 (with varices but not ascites), which means compensated cirrhosis, show a very good prognosis at five years in comparison with patients in stage 3 and 4, which means decompensated cirrhosis, who suffer a dramatically declines in survival rate over the first 3 years (within this last

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Article highlights

- This review focuses on improving care for compensated cirrhotic patients who are followed up in outpatient clinics.
- Attention to the appearance and management of extrahepatic manifestations of cirrhosis, as well as the use of the most effective and safe drugs, are essential to offer quality care to these patients.
- Transient elastography is the most useful method for noninvasive assessment of both compensated advanced chronic liver disease and clinically significant portal hypertension.
- Pharmacologic therapy for portal hypertension decreases the need for endoscopic surveillance, so beta-blockers should be always taken into account and considering the temporal window of opportunity for them.
- Carvedilol could improve the prognosis of cirrhosis by preventing the first decompensation event.
- Minimal hepatic encephalopathy is associated with a higher risk of development of overt hepatic encephalopathy, faster progression of cirrhosis, higher risk of hospitalization and of mortality. The detection and treatment of minimal hepatic encephalopathy can potentially decrease the risk of meeting these outcomes.
- Adopting the principles of palliative care has the potential to decrease symptom burden, improve their quality of life, and save resources. This approach may be chosen even when targeted and curative treatments, including the possibility of liver transplant, are still underway.

group, patients with variceal bleeding but otherwise no complication have the better long-term prognosis). CPT and MELD scores together with cirrhosis stage help to figure out the risk of progression or decompensation. As just mentioned, cirrhotic patients are considered to be suffering from decompensated cirrhosis after the first decompensation with ascites, variceal bleeding or hepatic encephalopathy (HE). However, a selected group of patients, with decompensated cirrhosis could recover liver function and keep free of complications for many years, so the term recompensated cirrhosis has been proposed [6]. The prognosis implication of this concept remains elusive, and further studies should be addressed.

Extrahepatic manifestations, PHT, and even HE and palliative care (PC) in patients with compensated cirrhosis are all addressed in the current review.

2. Management of hepatic insufficiency and extrahepatic manifestations

Liver insufficiency implies the liver's own inability to perform its metabolic functions; namely, those of synthesis, excretion, and detoxification.

2.1. Liver dysfunction evaluation

To determine the severity of the illness and to predict its short-term prognosis, we should establish the degree of hepatic dysfunction and etiology. The Child-Turcotte score became the most widespread method for the evaluation of cirrhosis prognosis since 1964, including five parameters (albumin, bilirubin, ascites, HE, and nutritional status), with nutritional status being later replaced by international normalized ratio (INR), which originated the CPT score [7,8]. The MELD scale has been established as a model for assigning a position on the liver transplant waiting list, as it involves parameters that are easily measurable and comparable, such as creatinine, bilirubin, and INR [9]. Sodium was added in 2003, which originated

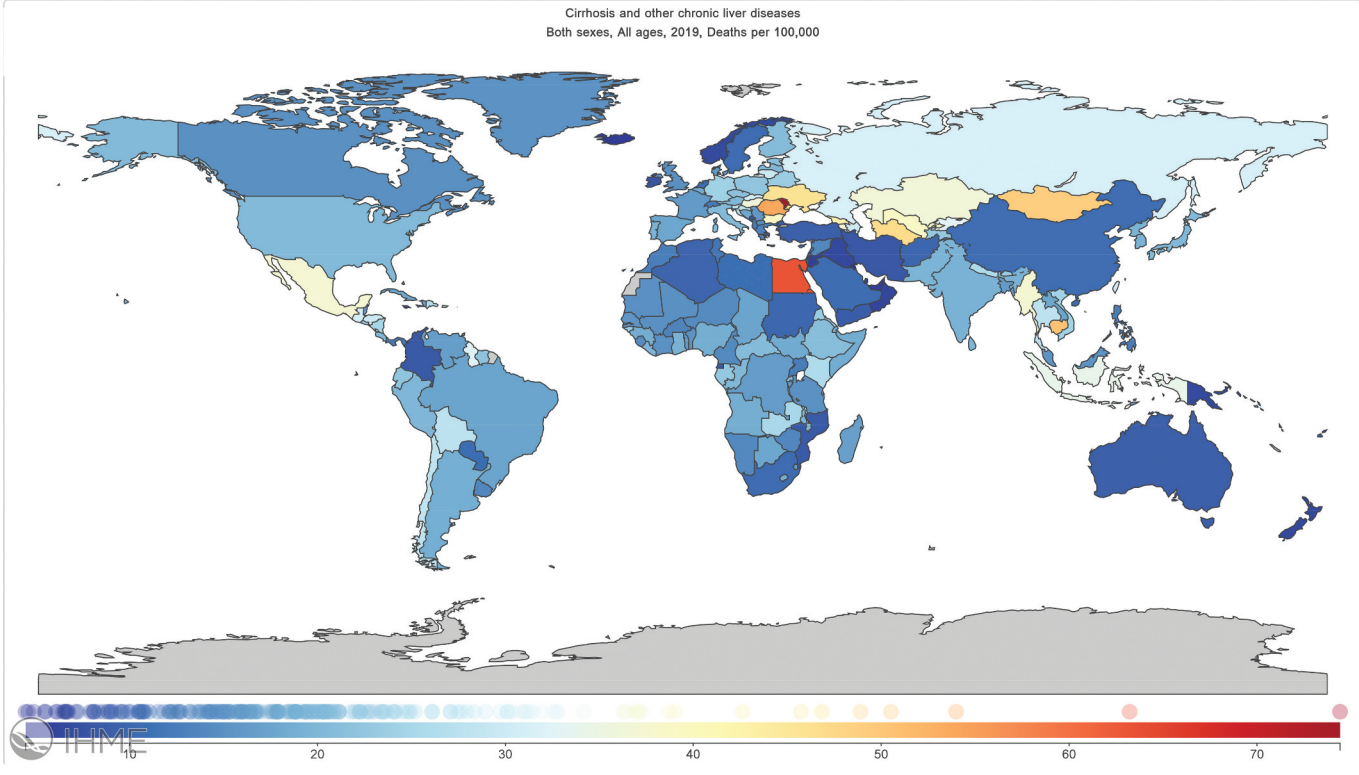

Figure 1. Deaths per 100,000 due to cirrhosis in both sex around the world. Taken from Institute for Health Metrics and Evaluation (IHME), University of Washington (October 10th, 2023). https://vizhub.healthdata.org/.

the MELD-Na scale, as hyponatremia was observed to be a significant predictive factor regarding mortality [10]. On the other hand, serum creatinine can underestimate renal function and the risk of mortality in women patients compared to men with the same level of creatinine. That is the reason why Kim et al. proposed a new update of the MELD scale, named MELD 3.0, including gender and serum albumin and diminishing the upper limit of creatinine to 3 mg/dL [11]. After determining the degree of liver dysfunction, we must establish its treatment based on the etiology of the liver disease, and if acute worsening of liver dysfunction has occurred we must establish its treatment based on the precipitant factor too. An acute worsening of liver dysfunction could be precipitated for several reasons including alcohol consumption, infections, reactivations or viral hepatitis or new viral infections together with intrinsic disease progression. The most frequent precipitant factors are infections, particularly spontaneous bacterial peritonitis (SBP) or pneumonia, with their early diagnosis being of utmost importance to provide adequate antibiotic treatment. Furthermore, several factors causing the liver disease may precipitate the acute dysfunction too, such is the case of viral, alcoholic or autoimmune hepatitis [12–14].

2.2. Sarcopenia and osteopenia/osteoporosis

It is essential to actively look out for malnutrition in cirrhotic patients, as well as screening for osteopenia/osteoporosis. Malnutrition (BMI <18.5 Kg/m^2) is present in 20–50% of cirrhotic patients [15]. Sarcopenia (loss of muscle mass) is associated with a higher rate of complications and lower survival. Multiple tools can be used for its diagnoses, such as the Royal Free Hospital Index, computed tomography (CT), or dual-energy x-ray absorptiometry (DEXA) [16]. Of all of them, the most used are hand grip and anthropometric measurements such as the muscle circumference of the middle of the arm [17]. Another widely used measure is the lumbar skeletal muscle index at the level of L3 using CT to measure the total cross-sectional area (cm2) of the abdominal skeletal muscles at L3. An L3 muscle area < 50 cm2/m2 in men and < 39 cm2/m2 in women have been proposed as cutoff points for sarcopenia [18]. It is recommended to provide at least 35 Kcal/kg/day with a protein intake of 1.5 g/kg to avoid the loss of muscle mass, and also avoiding overnight fasting [19]. Protein intake should not be restricted to avoid catabolism and gluconeogenesis. Nutritional supplements rich in proteins are recommended in decompensated cirrhotic patients. Nutritional supplements rich in vegetable proteins or branched-chain amino acids should be of choice in patients with HE if others supplements are not well tolerated. Deficiencies of B vitamins and fat-soluble vitamins (A, E, D) should be corrected. Physical exercise should also be recommended to prevent sarcopenia. It is recommended that it consist of resistance exercises such as use of weights, squats and elastic band, divided into 3 phases: 1) warm-up (5–10 min); 2) main phase or physical conditioning (20–60 min) and 3) cool down and stretching (10 min) [20,21].

In osteopenia, vitamin D deficiency should be treated with vitamin D2 800 IU/day or calcifediol 266 µg every 15 days associated with calcium 1000–1500 mg/day [22]. If osteoporosis is present, bisphosphonates (weekly alendronate or etidronate, monthly ibandronate), which increase bone mass and reduce the incidence of fractures, or denosumab (one subcutaneous vial every 6 months), should be used [23]. There is evidence that treatment with alendronate (10 mg/day) or etidronate (400 mg/day) for 14 days every 3 months in women with primary biliary cholangitis and osteoporosis results in an improvement in bone mineral density after approximately two years of treatment [24]. In the case of bisphosphonates, it is recommended not to lie down or eat within 30 minutes of taking them, especially in patients who have undergone recent banding.

2.3. Sexual dysfunction

It is not unusual for sexual dysfunction to appear in cirrhotic patients, both males and females, particularly in diabetic, malnourished, or decompensated patients. Its clinical spectrum varies from male impotence and decreased libido to early amenorrhea in women. Its etiology is usually multifactorial (malnutrition, drugs toxic ingestion, pharmacological, hormonal, psychiatric) and they usually go unnoticed during clinical practice. Validated questionnaires (International Erectile Function Index or Female Sexual Function Index) should be used for its detection. It is advisable to stop smoking and consuming alcohol, to search for potential depression and/or anxiety and hormonal deficiencies. There are several phosphodiesterase inhibitors that can be used to treat impotence, with demonstrated efficiency in clinical trials: such is the case of tadalafil (10 mg/day), which improved erectile dysfunction, anxiety, and quality of life after 12 weeks, in patients with a CPT score up to C10, showing good tolerance and no significant side effects on the portal pressure gradient [25]. Other drugs studied are sildenafil, vardenafil, and avanafil. Side effects include headache, hot flashes, and dyspepsia, all subsiding around 48 hours after discontinuation. Although a negative impact on erectile function was reported in the case of propranolol, a large meta-analysis and a randomized clinical trial ruled out this association [26]. An interesting experimental study with rats observed that the association of a phosphodiesterase-5 inhibitor (udenafil) with propranolol reduced portal pressure and liver resistance without systemic side effects [27]. Spironolactone can cause decreased libido, as well as gynecomastia, and should be replaced by eplerenone.

2.4. Pruritus

Pruritus is a common symptom in patients with advanced liver diseases. In the absence of biliary obstruction therapy should be addressed step by step starting with a chelate of biliary salts like cholestyramine (4–16 g/d), second-line rifampicin (150–300 mg/d), third-line naltrexone 50 mg/d, fourth line sertraline (100 mg/d). Regarding fibrates, a randomized placebo-controlled clinical trial that included 24 cirrhotic patients (16 CPT A cirrhosis and 8 CPT B cirrhosis), showed that bezafibrate 400 mg per day achieved a statistically significant reduction of pruritus (45% vs 11%). Topic approaches including ultraviolet B therapy could be useful in some patients [28,29]. New

approaches are in development, including the selective blockade of the enterohepatic cycle by ileal bile acid transporter (IBAT) inhibitors including odevixibat, linerixibat, and maralixibat. Clinical trials evaluating IBAT inhibitors are currently underway with inconclusive preliminary results [30].

2.5. Muscle cramping

More than half of patients with liver cirrhosis reported painful muscle cramps resulting in low-quality sleep and impaired quality of life. Many drugs have been tested to avoid muscle cramps without success including oral zinc, vitamin D, vitamin E, branched-chain amino acids, l-carnitine, eperisone hydrochloride, intravenous albumin and quinidine [31]. In a randomized controlled trial comparing taurine 2 g per day versus placebo, in a per-protocol analysis, patients receiving oral taurine experienced a statistically significant reduction in cramp frequency (7 cramps fewer/fortnight), duration of cramps (89 minutes less/fortnight), and severity (1.4 units less on Likert scale) compared to placebo, supporting that a supplementation of taurine could be useful to address this painful comorbidity [32]. Baclofen 30 mg per day is also an effective, safe and well-tolerated therapeutic alternative, as was seen in a clinical trial in which CPT A5-B9 cirrhotic patients were included, observing that after 3 months the muscle cramps completely disappeared in 72%, they were reduced in 20% and there were no changes in 8% of patients. Its adverse effects include headache, drowsiness, nausea and vertigo, but these were minimized by gradually increasing the dose to the full dose or taking it with food [33]. In a recent placebo-controlled clinical trial, methocarbamol 400 mg 2 times a day for 1 month showed superiority in reducing cramps and being well-tolerated [34].

2.6. Fatigue

Even though fatigue is a major issue, there is currently no specific drug therapy approved for fatigue in cirrhosis [35].

2.7. Use of drugs in cirrhosis

Drugs should be used with caution when treating liver cirrhosis, as some are contraindicated, usually due to reduced metabolism of cytochrome P450, as well as the existence of portal-systemic shunts, hypoalbuminemia, and cholestatic states. Statins should be avoided in decompensated patients with elevated total bilirubin; however, their beneficial effect in lowering the risk of hepatocarcinoma has been demonstrated and should be kept in mind. Non-steroidal anti-inflammatory drugs (NSAIDs) should also be avoided due to the risk of renal toxicity entailed by the decrease in the natriuretic effect together with enhanced risk of bleeding [36]. Paracetamol is safe in patients with compensated cirrhosis at doses up to 3–4 g per day for short periods of time but a reduced dose of 2–3 g daily is recommended for long-term use (>14 days). Making recommendations is difficult in decompensated cirrhosis because of the lack of data, likely a maximum dose of 2–3 g per day may be safer in these patients, particularly if patients are malnourished [37–39]. Carbamazepine should also be avoided during the treatment of neuropathic pain, due to potential hepatoxicity. Esomeprazole is the proton pump inhibitor with the best pharmacokinetic profile. As for antibiotics, azithromycin and amoxicillin should be used with caution, given their potential risk of hepatoxicity; it is therefore recommended to monitor the hepatic profile of the patient beforehand. Aminoglycosides could be used with caution in compensated cirrhosis but they are formally contraindicated in decompensated cirrhosis as long as other options are available [40]. A meta-analysis has shown the usefulness of direct-acting oral anticoagulants (DOACs) in non-tumor portal thrombosis, 79.5% of patients under treatment with DOACs achieved complete or partial recanalization and 9.80% experienced an hemorrhagic event. DOACs were superior to low molecular weight heparins, warfarin and placebo in achieving complete recanalization. The risk of bleeding and mortality were similar compared with other treatments. DOACs are contraindicated in CPT B-C cirrhosis and CPT A cirrhosis with untreated high-risk esophageal varices or without prophylaxis with beta-blockers, with apixaban being the worst positioned due to its hepatic metabolism [41,42].

2.8. Coagulopathy

Coagulopathy appears as a consequence of unstable hemostatic balance. The liver plays a key role in hemostasis, as the primary site of synthesis for most of the factors involved in coagulation and fibrinolysis. Cirrhosis has traditionally been considered a hemorrhagic coagulopathy, based on the quantification and correction of basic laboratory tests, such as INR and platelet counts [43]. However, the paradigm in regard to hepatic coagulopathy has been changing lately, as there are alterations in all phases of hemostasis, which places the cirrhotic patient in an unstable hemostatic balance called 'the hemostatic rebalance' [44]. This balance is frailer than the one in healthy individuals, which can give place to fast changes in states of hyper- and hypo-coagulation depending on the clinical context, which explains the appearance of hemorrhagic and thrombotic complications in cirrhotic patients [45]. Routine laboratory tests do not help evaluate hemostasis in cirrhotic patients, as they do not evaluate prothrombotic and fibrinolytic changes. Viscoelastic tests, such as thromboelastography or rotational thromboelastography, are more efficient, as they describe the interaction between different components of the hemostatic system and evaluate the kinetic and viscoelastic characteristics of the clot in real time, although they still show important shortcomings since they do not assess the increase in the Von Willebrand factor, protein C deficiency and procoagulant deficiencies [46]. Given the alterations, it is necessary to individualize the management of coagulopathy based on the aforementioned techniques, always being aware of their deficiencies.

2.9. Thrombocytopenia

Cirrhotic patients with severe thrombocytopenia (platelets <50,000 $\times 10^3/\mu L$) could develop hemorrhagic complications while undergoing invasive diagnostic or therapeutic procedures (variceal banding, transjugular intrahepatic portosystemic shunt [TIPS], thoracocentesis, liver biopsy, endoscopic polypectomy or surgery), for which reason they were usually subjected to prophylactic platelet transfusion. Nowadays,

there are oral treatments that can be used before carrying out this type of procedures on a scheduled basis, consequently saving blood products, and avoiding their potential side effects. Thrombopoietin receptor agonists have been authorized for the treatment of severe thrombocytopenia in patients with cACLD who must undergo scheduled, non-urgent invasive procedures. Several clinical trials have shown how oral lusutrombopag (3 mg/day) or avatrombopag (40–60 mg/day) achieved an increase in platelet count after 1 week of therapy in 68–79% of cases, allowing them to undergo invasive procedures between days 9 and 14 post-treatment [47,48]. However, they cannot be used in emergency situations, such as gastrointestinal bleeding or urgent surgery, in which case it would be advisable to request an urgent thromboelastogram to determine whether intravenous (iv) fibrinogen or other clotting factor are required [49].

2.10. Diabetes approaches

Insulin resistance and diabetes mellitus are two of the most frequent extrahepatic manifestations of cirrhosis (15–37%). It is advisable to avoid antidiabetic drugs in decompensated patients, such as repaglinide, sulphonylureas, and pioglitazone. Metformin, semaglutide (glucagon-like peptide-1 -GLP-1- agonist) and canagliflozin, dapagliflozin and empagliflozin (sodium-glucose cotransporter 2 -SGLT-2- inhibitors) are encouraged due to beneficial effects preventing cirrhosis related-outcomes from hepatic encephalopathy to liver cancer [50,51]. However, it should be taken into account that all antidiabetic drugs should be given with caution in CPT C cirrhosis and metformin is contraindicated in CPT B-C cirrhosis and in patients who continue to drink alcohol due to the risk of lactic acidosis [52]. The use of coffee is also recommended [53].

2.11. Bacterial infections

There is a higher risk of pulmonary, urinary, and cutaneous infections in cirrhotic patients, which may trigger events with high morbimortality. The negative impact of bacterial infections on morbidity and mortality in cirrhotic patients is observed in both the compensated and decompensated phases of the disease [54]. In fact, while mortality associated with other complications of cirrhosis has decreased in recent years, mortality associated with infection has increased. This could be related to the increasing spread of multidrug-resistant (MDR) bacteria and the lack of effective antibiotics, as shown a worldwide study of hospitalized cirrhotic patients which found that the global prevalence of MDR bacteria was 34% [55]. Furthermore, bacterial infections are common in hospitalized patients with cirrhosis and these patients are frequently readmitted within 30 days from discharge (35%) [56]. So, in cirrhotic patients with signs of infection it is essential to perform an active search for the focus, to order cultures, as well as empiric antibiotic treatment considering the rate of MDR bacteria in our area, as soon as possible. In case of severe community-acquired pneumonia, intravenous use of ceftriaxone or cefotaxime associated with levofloxacin is recommended throughout the following 7 days. In the case of *Pseudomonas*, cefepime associated with levofloxacin it is a better option. In community urinary tract infections, ceftriaxone is recommended; however, in nosocomial community urinary tract infections, meropenem or piperacillin-tazobactam should be used, and adding vancomycin if *Enterococcus* is suspected. In the case of cellulitis, ceftriaxone associated with oxacillin are recommended, but if nosocomial cellulitis, meropenem associated with oxacillin it is a better option. In the case of a MDR strain, carbapenem or tigecycline should be used [57].

2.12. Vaccinations in cirrhotic patients

Use of vaccinations in cirrhotic patients avoid severe infectious diseases and decompensation of the liver disease allowing a decrease of morbidity and mortality [58].

Vaccination against hepatitis B virus (HBV) is strongly recommended in non-immunized patients [58–61]. The cirrhotic-related immunosuppression state is associated with a decrease in the efficiency of vaccination [62]. To avoid the decrease in the immunogenicity, there are different strategies, such as to use higher doses during vaccination and/or additional doses in non-responders [63–65]. The hepatitis B surface antibody (anti-HBs) titer should be measured in 1–2 months after the last dose [66]. Vaccination with recombinant HBs antigen vaccine at 0-1-6 months is the classical vaccination schedule [58]. However, accelerated cycles of vaccination (0-1-2 months) with double doses (40 µg), with a similar fourth dose at 6th month, especially in non-responder patients, could be used [67–69]. A recent open-label randomized clinical trial has shown that the revaccination of non-responders to the first cycle (0-1-2 months), with three additional 40 µg doses, achieved significantly better response rates to those obtained with an isolated 40 µg booster dose [70]. In spite of this, the vaccinating during the early stage of the disease is the most important [71]. In any case, the anti-HBs titer could decreases up to non-protective levels in responder-patients, so it should be determined annually to check if a booster dose is necessary [72,73]. A new hepatitis B vaccine (CpG-adjuvanted hepatitis B vaccine) shows better response in ACLD compared to the traditional three-dose vaccine [74].

Vaccination against hepatitis A virus (HAV) is strongly recommended in non-immunized patients [58,64]. An initial dose of an inactivated virus vaccine followed by a booster at 6th month is recommended [58]. There is a combined bivalent vaccine against HBV and HAV which is highly immunogenic and very protective, and it is also very comfortable for patients. For this vaccine, an alternative program of four doses administered in one month followed by a booster at 12 th month could be used [75].

Annual vaccination against flu is strongly recommended [54]. A similar humoral immune response in both cirrhotic patients and healthy individuals has been observed [76].

Vaccination against pneumococcal infection is strongly recommended [54]. An initial dose of 15-valent or 20-valent pneumococcal conjugate vaccine (PCV 15 or PCV 20) followed by pneumococcal polysaccharide vaccine (PPSV23) at 12 th month, with a second dose of PPSV23 five years after the first dose, and a third dose after 65 years of age, it is

recommended. However, if PPSV23 is the initial vaccine, it must be followed by a PCV 15 or 20 vaccine after one year [64,77].

Vaccination against SARS-CoV-2 should be considered [58]. Cirrhotic patients have five-fold higher risk to develop a severe infection with a three-fold higher risk of mortality [78]. A boosting dose is necessary to get a better response [79,80]. There are two options: COVID-19 BNT162b2 mRNA vaccine at time 0 and after 21 days or COVID-19 mRNA-1273 vaccine at time 0 and after 28 days [58].

A summary of the management of extrahepatic manifestations of compensated liver cirrhosis is shown in the attached Figure 2.

3. Management of portal hypertension in the era of transient elastography

The confirmation of both liver cirrhosis and PHT classically requires a liver biopsy and a measurement of the hepatic venous pressure gradient (HVPG), respectively [81]. Both procedures are invasive and show additional drawbacks: liver biopsy could be limited due to limited representativeness, whereas an elevated HVPG does not always accurately means true underlying PHT, as has been demonstrated in some etiologies as nonalcoholic fatty liver disease (NAFLD) [82,83]. TE is a useful alternative diagnostic tool due to its simplicity and reproducibility. From a technical point of view, the physical quality measured by TE is liver stiffness measurement (LSM) in kilopascal (kPa), a phenomenon influenced primarily, but not exclusively, by fibrosis [84]. Individuals at risk of advanced fibrosis (metabolic syndrome, harmful use of alcohol, viral hepatitis) should be evaluated order to stratify their baseline risk of liver-related complications and mortality [85]. Two novel definitions have emerged under the umbrella of TE: a) cACLD, which includes patients with known causes of liver disease and advanced fibrosis, and identifies those who benefit from further specialized evaluation, screening strategies, and preventive treatments. The TE cutoff point of 10 kPa, which would exclude cACLD below and highly suggestive of this entity when higher should be taken cautiously. Never interpreting the point data categorically, but rather as a continuum that attempts to encompass the entire spectrum of patients who are still asymptomatic, but with increased risk of developing PHT-related complications; b) CSPH, classically with HVPG >10 mmHg [86,87]. A TE value of 25 kPa is highly indicative of CSPH, and therefore it identifies patients at risk of developing esophageal varices. When the TE shows a value between 20 and 25 kPa, the platelet count should be lower than 150,000 $\times 10^3$/μL to label the patient as having CSPH, whereas when liver stiffness is between 15 and 20 kPa, the platelet count must be lower than 110,000 $\times 10^3$/μL. On the contrary, values lower than 20 kPa together with a platelet count higher than 150,000 $\times 10^3$/μL are associated with negligible risk of developing varices, especially large ones. The exclusion of this risk situation is very relevant from a clinical point of view, as it makes endoscopy unnecessary

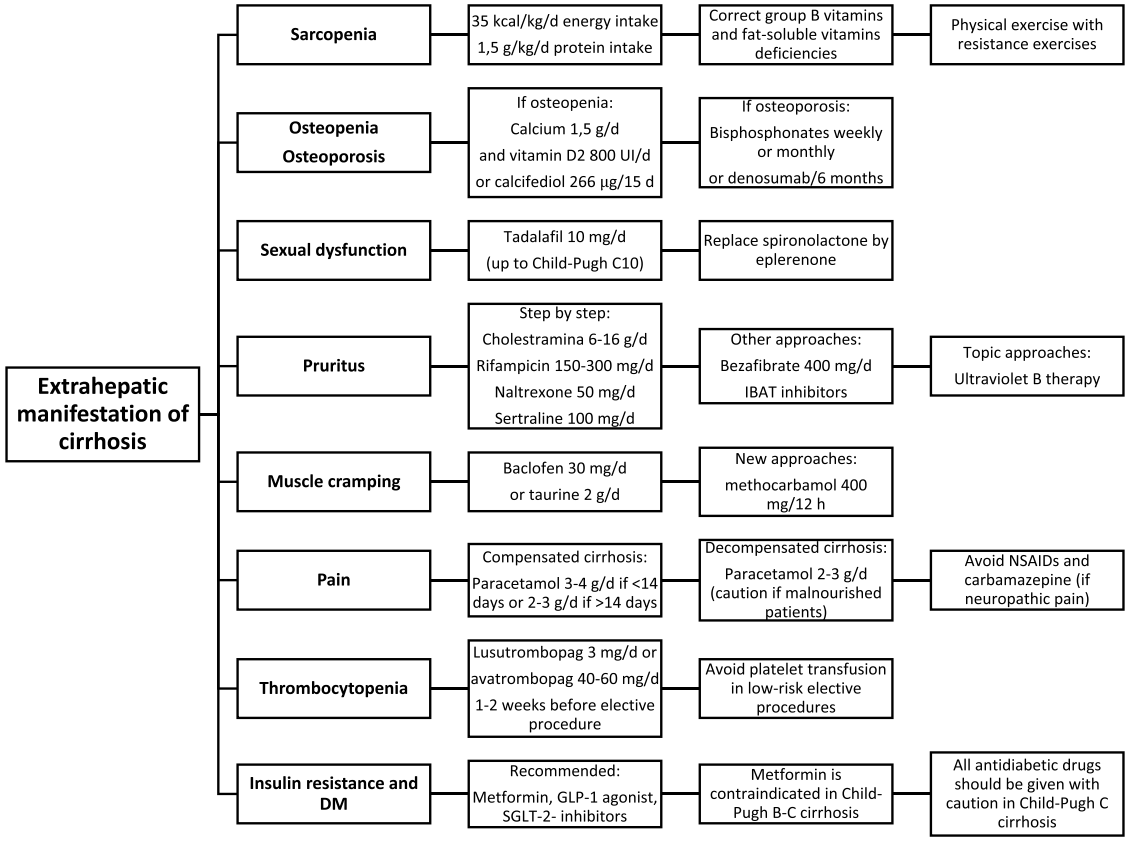

Figure 2. Management of extrahepatic manifestations of compensated advance chronic liver disease. DM: diabetes mellitus. GLP-1: glucagon-like peptide-1. SGLT-2: sodium-glucose cotransporter 2. IBAT: ileal bile acid transporter. NSAIDs: non-steroidal anti-inflammatory drugs.

when it comes to searching for serious endoscopic manifestations of PHT [88,89]. However, it should be noted at this point that the LSM figure varies depending on the etiology, and that the above algorithms leave a large number of patients in a gray area [90]. Repeated evaluations (for example, annually), can eventually categorize those patients who appear to be initially unclassifiable. Likewise, splenic TE is a promising technique that may diminish confusion and help in decision-making in some cases, although it is still pending validation in several clinical scenarios [91–93]. Finally, all the assessments are simply not necessary in patients who show unequivocal data of CSPH, such as collateral circulation on imaging tests, or those who show the existence of decompensated data.

A schematic view of the noninvasive assessment of cACLD and CSPH is shown in the attached Figure 3.

3.1. Natural history of portal hypertension and liver cirrhosis could be modified

The paradigm of fibrosis progression to cirrhotic nodules to CSPH and to decompensation as a unidirectional and irreversible event, shifted to a more dynamic and bidirectional process [94]. The best procedure to modify the natural history of advanced liver disease is supported by the removal of the etiological cause of the disease. Indeed, abstinence in alcohol-related decompensated liver cirrhosis or direct antiviral agents in hepatitis C to promote sustained virological response, or hepatitis B promoting stable viral replication suppression, was linked to clinically significant improvement in liver stiffness and PHT, although not in a direct and parallel way [95–99]. On the other hand, MAFLD-related cirrhosis is strongly associated with metabolic dysfunction like type 2 diabetes, obesity, arterial hypertension and dyslipidemia, all these factors playing a deleterious effect on the natural history of both MAFLD-related cirrhosis and cACLD from other etiologies. So, the optimal timeframe for subsequent LSM assessment seems reasonable to be between 1–3 years depending on baseline stage, etiology and metabolic cofactors. In patients with cACLD at diagnosis, annual repeated LSM can be used to refine the residual risk once etiological factor has been removed [45]. Screening of esophageal varices is a major task in the management of cACLD. Regarding this issue, in the last BAVENO consensus recommendations were based on both removal of etiological factors and the presence of drivers of progression, such as obesity and type 2 diabetes [100].

Two new concepts have recently emerged in the management of liver cirrhosis: recompensated cirrhosis and PHT resolution. Recompensated cirrhosis which included patients in a stable condition after being decompensated for more than one year, including lack of ascites or HE without the use of diuretics or non-absorbable disaccharides or rifaximin and free of bleeding events (beta-blockers use was allowed) and preserved liver function [101]. PHT resolution was considered when patients with recompensated cirrhosis did not show esophageal varices and liver stiffness was lower than 12 kPa [102]. Both events happened in patients in which it was possible to remove the etiological cause of the disease, such as alcohol consumption or viral hepatitis clearance. MAFLD-related cirrhosis remains out of this concept, waiting for effective therapies able to cure the disease. Recompensated status reduces the risk of developing further liver-related clinical events, leading to a CPT A stage and, finally, delisting patients as transplant candidates [103]. The effects of treatments for reducing PTH and the role of metabolic comorbidities in the

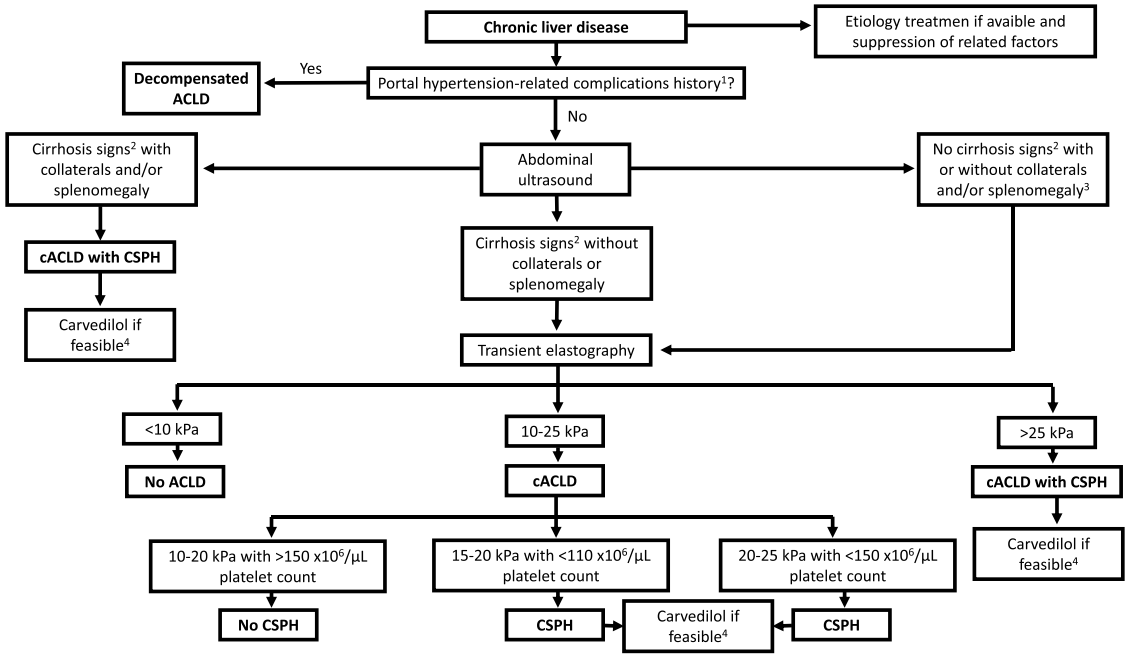

Figure 3. Noninvasive assessment of compensated advance chronic liver disease and clinically significant portal hypertension. 1. Ascites, variceal bleeding, hepatic encephalopathy. 2. Nodularity of the liver surface together with the bluntness of the liver edge and/or the coarseness of the parenchyma. 3. Collateral circulation and/or splenomegaly do not always means true underlying advanced chronic liver disease with clinically significance portal hypertension, as has been observed in nonalcoholic fatty liver disease. 4. Endoscopic surveillance if beta-blockers are contraindicated or the patient refuses them. ACLD: advanced chronic liver disease. cACLD: compensated advanced chronic liver disease. CSPH: clinically significant portal hypertension.

long-term follow-up in this setting need to be explored. Risk of hepatocellular carcinoma seems to be reduced but not completely attenuated, so routine screening programs in recompensated patients should be continued. Nevertheless, future studies are required to fully elucidate the natural history of these patients [104].

3.2. A customized treatment for personalized medicine

Non-cardio selective beta-blockers (NSBB) are the cornerstone of the medical treatment of PHT. Historically, the goal of NSBB was the prevention of the first (or successive) hemorrhage. Classically, the indication for NSBB in primary prophylaxis was limited to patients at high hemorrhagic risk, which was established according to endoscopic findings (large varices and/or red dots) and liver function (CPT C) [105]. This reduced view of the benefits of NSBB required multiple endoscopies, first for screening and later for surveillance [106]. However, it has been shown recently that NSBB can succeed in preventing the first decompensation (not only the hemorrhage itself, but also and primarily, ascites) once CSPH develops (and probably not before), even if the varices are not yet at risk. In fact, it is in patients with small varices that NSBB appear to be more beneficial [107,108]. Ascites could be avoided by the HVPG reduction but also by the ability to decrease systemic inflammation (diuretics, including spironolactone or furosemide, are not recommended in compensated cirrhosis) [109]. The recommended drug is carvedilol, over propranolol, due to its better tolerability, as well as its greater potency and more notable impact on survival [110,111]. This view of the indication of NSBB in cACLD, which is much more generous, will undoubtedly allow an ostensible saving in endoscopic explorations, with a notorious secondary impact in economic terms and on the patient's quality of life [112]. The appearance of an episode of variceal hemorrhages implies in itself a high risk of a new episode. This event, particularly if it occurs under previous treatment with NSBB, is probably likelier in selected patients with a more advanced stage of the disease, which justifies the recommendation of associating banding to prophylaxis with NSBB, even though its contribution in terms of increased survival is quite scarce [113]. The use of carvedilol has recently been accepted in secondary prophylaxis.

However, NSBB is the best example of a treatment that can be effective and safe at an early stage but dangerous at a later one [114]. This apparent contradiction is due to the sum of multiple mechanisms, both hemodynamic and non-hemodynamic, related to the drug itself, as well as to the complex systemic circulatory disorders that occur successively throughout the different stages of cirrhosis [115]. The associated vasodilator effect of carvedilol (alpha-adrenergic blocker) may worsen the prognosis in patients with severe ascites and/or associated systemic circulatory dysfunction, which are indicative of a more advanced liver disease [116,117]. In this scenario, propranolol (with pure beta-blocking effect) is the drug of choice [118]. Therefore, in end-stage liver disease, NSBB lose their efficacy and, more importantly, are no longer applicable due to a question of tolerance, thus considering the window of opportunity for their use closed.

4. An approach to the management of hepatic encephalopathy in compensated cirrhosis

HE should not be understood as an all-or-nothing phenomenon, but as a continuous spectrum academically divided into a preclinical stage of alteration in specific cognitive functions that are not clinically manifested by themselves (minimal HE), then moving toward a clinical stage that may go unnoticed (grade I HE), and finally reaching a stage with evident clinical manifestations, defined by the appearance of disorientation and/or flapping that may lead to a coma (grades II, II and IV HE) [119–123]. The patient may fluctuate through this spectrum in both directions, thus making HE a phenomenon of a dynamic nature. Therefore, the approach to HE in compensated cirrhotic patients should be that which establishes their susceptibility to develop overt HE, which entails a decreased quality of life (altered social and familial relationships, decreased work productivity, increased risk of falls and traffic accidents, need for medical care or repeated hospitalization), and decreased survival regardless of the severity of liver dysfunction (40% through the first year and 25% in three years) [99,124–128]. Once this susceptibility has been identified, strategies should be implemented to reduce it and even improve the patient's quality of life, which may have already been maimed in comparison with an imperceptible preclinical or hardly perceptible subclinical phase of HE.

4.1. Risk factors for the development of hepatic encephalopathy

The definition of HE points toward the consequences of cirrhosis (liver failure and/or portosystemic shunts); however, certain etiologies of cirrhosis and comorbidities may cause preclinical (simulating minimal HE) and clinical (simulating grade I HE) neuropsychiatric disturbances, leading to a much more difficult differential diagnostic. They may also lower the threshold through which the cirrhotic patient faces the precipitating factors leading to overt HE, such as the increment in their susceptibility to it. In the case of minimal HE, they may cause preclinical cognitive deficits verifiable through psychometric and/or neurophysiological tests: alcohol (chronic direct neurotoxicity and malnutrition), MAFLD (peripheral vasculopathy, oxidative stress, urea cycle dysfunction, neuroinflammation), hepatitis C virus (brain replication, neuroinflammation), primary biliary cholangitis (neuroinflammation) [129–135]. The comorbidities or concomitant factors are as follows: renal dysfunction, hyponatremia, obesity, diabetes mellitus, and advanced age [136–140]. Age is particularly relevant in patients over 60 years of age, who present a 20% prevalence of mild cognitive impairment; in contrast to minimal HE, it is associated with an inferior impairment of socio-occupational performance [141]. It also tends to be constant rather than fluctuating, and ultimately does not respond to therapeutic measures aimed at HE [142]. However, even though several patients show the same etiology of cirrhosis, liver function, concomitant factors, and exposure to precipitating factors, they still suffer from a different range of susceptibility in the development of HE. This could be explained through individual genetic factors. The existence of long microsatellites (≥14 GCA

tandem repeats) in the promoter region of the glutaminase gene is associated with a higher risk of HE at 2 and 4 years, as it conditions the overexpression of said enzyme, which cleaves glutamine into glutamate and ammonium, with the subsequent increase in ammonemia, a key element in the pathogenesis of HE [143]. Polymorphisms of the SLC1A3, SLC1A5, FUT2, and TLR9 genes are also associated with an increased risk of HE [144–146].

A HE development risk score has been created to add the predictive capacity of clinical-analytical and genetic factors, combining previous episodes of HE, bilirubin, albumin, glutaminase gene microsatellites, and gene polymorphisms related to HE pathophysiology. The total score is associated with a low, intermediate, or high risk of HE at 1, 3, and 5 years [147]. Despite its potential, genotyping may not be available in routine clinical practice.

In such a scenario, individual metabolic factors may be investigated by means of an oral glutamine challenge (OGC), which consists in the determination of the basal concentration of ammonia in venous blood, the oral administration of 10 g of glutamine, and its re-determination 60 minutes later. It was at first considered that a post-ingestion concentration above 128 mg/dl defined an alteration of ammonium metabolism predictive of HE [148]. It has since been redefined to take into account the baseline glutamine concentration (pathological if >78 mg/dl) and the increase in its concentration after overload (pathologic if >32 mg/dl), given that the combination of both elements has a greater predictive capacity for the development of HE than the isolated use of the threshold of 128 mg/dl. Low-, intermediate-, and high-risk groups are defined depending on whether neither, one or both elements are altered, respectively. The high-risk group shows a cumulative incidence of HE four times higher than the low-risk group, which is also associated with different precipitants (which allows individualized decision-making) [149]. In spite of these considerations, OGC it is not routinely used because of the need of time and qualified professionals, and the complicated processing of the blood samples necessary for determination of ammonia concentration.

4.2. Minimal hepatic encephalopathy as a prognostic tool and therapeutic target

In the absence of genotyping and the OGC, susceptibility to the development of overt HE can be established through the diagnosis of the cognitive alterations that define minimal HE, with an estimated prevalence of 30–70% [150,151]. Minimal HE is associated with a higher risk of development of overt HE (33% per year), as well as a faster progression of cirrhosis, higher risk of hospitalization and of mortality [36,152–157]. The detection and treatment of minimal HE can potentially decrease the risk of meeting these outcomes. Taking limited resources into account, a subgroup of patients at higher risk of minimal HE, or those for whom it may have significant consequences, may be selected, and subjected to psychometric and/or neurophysiological tests. This may include patients with several clinical-analytical risk factors, nonspecific complaints in their socio-occupational performance, nonspecific complaints from those living with them, frequent falls, or professional drivers [158,159]. Another approach is to submit all patients to a psychometric test that does not require specific material, thus making it feasible in the outpatient clinic; this approach, referred to as the *animal naming test*, assesses how many animals the patient is able to name in 1 minute [160]. If the patient does not manage to name at least 15 animals, they should undergo further testing to exclude the presence of minimal HE. This diagnostic process has been compared with other more established tests, having obtained good results; however, it should be avoided if the patient shows confounding factors (previous neuropsychiatric disorders, use of psychotropic drugs, active alcoholism), which would difficult the interpretation of nonspecific HE test results [161]. Regarding routine clinical practice, it has been established that obtaining a pathological result in a psychometric or neurophysiological test in comparison with the country's normality tables is sufficient for the diagnosis of minimal HE [162]. The *pencil and paper test* or *psychometric HE score* (PHES; pathological if a score <-4 is obtained after performing its five subtests) has shown good external validity among the psychometric tests, as well as the *critical flicker frequency* (CFF; pathological if a light spot needs to flicker at a frequency ≤39 Hz in order for the patient to detect that it is flickering) [32,43,163–165]. In the event of receiving a negative result for the test performed, one may choose to perform the other test and/or wait 6 months to repeat it, due to the multidimensional and fluctuating nature of cognitive impairment [166,167]. In any case, the selected tests should always be validated in their target population and carried out by trained staff [44,168].

The value of the diagnosis of minimal HE lies not only in its predictive capacity for overt HE, but also in its ability to make nutrition-related recommendations, as well as preventing the risk of falls and while driving (which is particularly relevant in professional drivers), as well as establishing a treatment with the potential to improve the patient's quality of life by treating cognitive alterations that could eventually impair their social and familial relationships or their work performance [49,52,159,169–171]. This would also change the natural history of the disease by reducing the risk of developing overt HE (decompensation) and the mortality associated with it [172]. Lactulose, rifaximin, and probiotics have all been evaluated with good results [173]. The short duration and variability of the studies, as well as the different diagnostic criteria for minimal HE and what is considered clinically significant improvement, did not allow recommendations to be made in the 2014 European Association for the Study of the Liver (EASL) guideline. It was then suggested that each case should be assessed individually after establishing the potential repercussions of untreated minimal HE, and that approved treatments for overt HE should be used [95]. However, the 2022 revision of these guidelines does recommend treatment with nonabsorbable disaccharides (and/or rifaximin) after the detection of minimal HE; however, this recommendation is not supported by the publication of new trials [127]. Probiotics and L-onithine L-aspartato (LOLA) have been mentioned in the literature as an alternative or additional agent to treat overt HE without response to conventional therapy. Therefore, they both could be an option in the treatment of

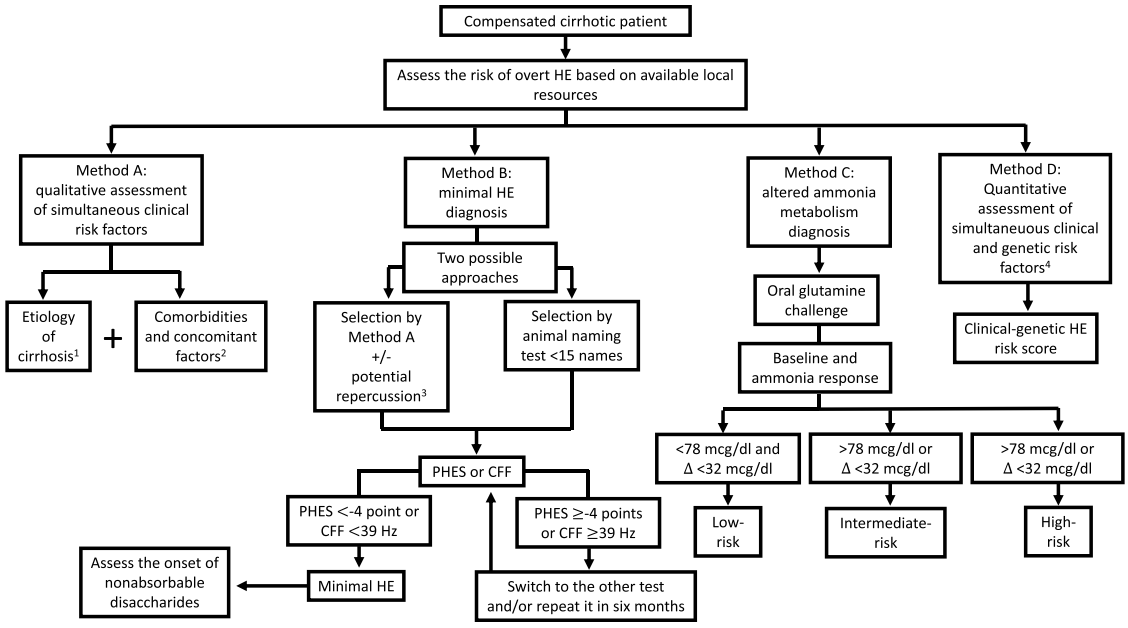

Figure 4. Algorithm for predicting the risk of overt hepatic encephalopathy in compensated cirrhotic patients. Four predictive strategies are presented in increasing order of complexity (from method a to D) in terms of the need for available resources. 1. Alcohol abuse, Metabolic associated fatty liver disease, hepatitis C, primary biliary cholangitis. 2. Kidney failure, hyponatremia, obesity, diabetes, age. 3. Professional drivers. 4. previous episodes of overt hepatic encephalopathy, bilirubin, albumin, microsatellite in the promoter region of the gene *GLS*, single nucleotide polymorphisms of the genes *FUT2, TRL9, SLC1A3 y SLC1A5*. HE: hepatic encephalopathy. PHES: psychometric hepatic encephalopathy score. CFF: critical flicker frequency.

minimal HE. However, limitations in the current literature do not allow recommendations to be made. The quality of evidence on the use of other products, such as glycerol phenylbutyrate, acetyl-L-carnitine or AST-120, is even lower [174].

4.3. Usefulness of imaging tests in establishing the risk of developing hepatic encephalopathy

Imaging tests have been developed, mostly in the form of magnetic resonance (MR) imaging techniques, with the aim of detecting structural or biochemical brain alterations associated with HE [175]. MR spectroscopy stands out for having been the most validated one [176,177]. It has been suggested that these alterations could precede clinical expression, serving as prognostic markers of overt HE, although none of them manifests sufficient specificity for their detection to be incorporated into routine clinical practice at present time. For the time being, they are reserved for research [178].

An algorithm for predicting the risk of overt HE in compensated cirrhotic patients is shown in the attached Figure 4.

Table 1 offers a schematic view of expanded indications of drugs typically used in decompensated cirrhosis to compensated cirrhosis.

Table 1. Expanded indications of drugs typically used in decompensated cirrhosis to compensated cirrhosis. 1. Variceal bleeding even if the varices are not yet at risk, but also, and primarily, ascites (the recommended drug is carvedilol). 2. In patients at high risk according to endoscopic findings (large varices or red dots) and liver function (Child-Pugh stage C) (the recommended drug is carvedilol). 3. The recommended drug is carvedilol (propranolol is the drug of choice if severe ascites and/or associated systemic circulatory dysfunction). 4. For purposes of differential diagnosis and to prevent overt HE. 5. As an adjunct to lactulose following one or more additional episodes of overt HE within 6 months of the first one. 6. In patients with previous episodes of overt HE. cACLD: compensated advanced chronic liver disease. CSPH: clinically significant portal hypertension. HE: hepatic encephalopathy. TIPS: transjugular intrahepatic portosystemic shunt.

Non-cardio selective beta-blockers	Prevention of first decompensation in cACLD with CSPH[1]. Prevention of first variceal bleeding[2]. Prevention of recurrent variceal bleeding[3].
Nonabsorbable disaccharides	Treatment of covert HE[4]. Treatment of overt HE. Prevention of recurrent overt HE. Prevention of overt HE after gastrointestinal bleeding.
Rifaximin	Treatment of covert HE[4]. Prevention of recurrent overt HE[5]. Prevention of overt HE after TIPS[6].

5. Palliative care in the cirrhotic patient

PC is defined as specialized, multidisciplinary medical care that puts the needs of the patient and their caregiver at its center, rather than the disease, encompassing physical psychological, social, and spiritual aspects [179]. This approach may be chosen in the course of a severe illness, even when targeted and curative treatments, including the possibility of organ transplantation, are still underway [180]. It has even been proposed that the concept of 'supportive care,' which can be integrated within curative care planning, is better than 'palliative care' [181]. PC can be offered by two groups of professionals: one made up of doctors and nurses specializing in PC, and the other made up of doctors and nurses who are part of the patient's usual care [182]. Cirrhosis is a serious, progressive illness, often without offering any options toward curative treatment, with great repercussion on the patient and their caregivers caused by the development of complications, and for whom life expectancy can be predicted using prognosis

indexes, often leading toward a span of time lower than a year or even 6 months [183–185]. Despite this, it is infrequent for the cirrhotic patient and their caregiver's needs to be properly evaluated throughout diagnosis or its progression [186,187]. This leads to a more 'aggressive' management compared to other serious diseases, and this is also heightened in the case of patients evaluated for liver transplantation [188,189]. Hepatologists would be included among the professionals expected to provide basic PC. Given the limited resources, the complexity of the diseases that lead the patient to a terminal situation, and the need for continuous care, board-certified PC providers and hepatologists should not be understood as mutually exclusive, but rather as mutually participant in patient care. This is important because adopting the principles of PC during the treatment of cirrhotic patients has the potential to decrease symptom burden, improve their quality of life, and save resources [190,191].

Following the PC approach, the role of the hepatologist could be summarized in three aspects: advance care planning (ACP), assessment and management of symptoms according to the patient's preferences, and referral to specialized care or home hospitalization [192]. Given that this revision focuses mainly on the compensated cirrhotic patient, the only one of the aforementioned aspects to be developed will be ACP, which consists in a process of decision-making taken between the doctor, the patient, and the caregivers, with the goal of ensuring that the patient's preferences and values are taken into account when it comes to deciding between treatments in the context of a disease that significantly diminishes their survival [193]. This process should be completed ahead of events and updated periodically [194]. Writing it down and ideally drawing up an advance directives document can be an efficient way of synthesizing it, as well as making sure that the patient's preferences are always available for the various health professionals involved in their care to respect them [195]. When such communication takes place in an appropriate way, the assistance provided to the cirrhotic patient toward the end of their life becomes significantly better, as it is consequent with their preferences [196]. A recently published single-center clinical trial shows that PC integrated into the hepatology unit more frequently achieves that ACP is established with the patient [197]. Likewise, a pilot randomized controlled trial of an ACP video decision tool for patients with transplant-ineligible ACLD showed that 81% of patients felt very comfortable watching the video, they had higher mean knowledge scores about their disease, and they were less likely to prefer to receive cardiopulmonary resuscitation [198]. Despite the aforementioned, there is no evidence available regarding the benefit of ACP in patients with cACLD, and it is unlikely to be a favorable scenario for its implementation considering that the life expectancy of these patients may exceed 10 years. However, and although it may seem contradictory, we bring this topic to the spotlight of this review to raise awareness about the importance and potential benefits of establishing ACP immediately after transitioning to decompensated disease, in the same way as treatment or prophylaxis of complications, or evaluation for liver transplantation are initiated. It is important to do so before the patient loses their ability to clearly express their will, which may happen in HE [199]. In fact, informing the cirrhotic patient of the risk of HE is a rather efficient way of introducing them to the conversation.

The management of life-limiting illnesses, as ACLD, must to be evidence-based, so well-designed clinical trials are necessary to offer high quality PC. A recently published review analyzes current clinical trials in ACLD addressing barriers and facilitators for the provisions of PC, and offering recommendations for designing and conducting interventional trial in cirrhotic patients [141]. The outcomes of the multicenter clinical trial PAL-LIVER are awaited with great interest, which compares PC provided by the patient's hepatologist after successfully completing a PC course versus by a board-certified PC provider [200]. REDUCe 2 is another clinical trial whose outcomes are awaited as it could change the palliative management of patients with refractory ascites, it compares home versus hospital drainage of ascites [201]. This clinical trial is based in a smaller one, REDUCe, from the same research group, which showed that long-term abdominal drain (home drainage) was acceptable to patients an clinical staff [202].

6. Conclusion

Novel management of liver cirrhosis is supported by the well-established paradigm of liver cirrhosis as a dynamic, systemic, and reversible disease strongly related to the availability of etiological therapy. Precision medicine could help identify the cause of cryptogenic cirrhosis; and it could also predict the risk of decompensation, like in cases of HE with the development of genetic risk scores. New methods to monitor PTH based on liver and spleen stiffness measurement by TE together with ultrasound-guided portal pressure measurement could modify the landscape of PTH management in patients living with cirrhosis. Evidence-based medicine supports the usefulness of NSBB (mainly carvedilol) to improve survival rates in cirrhotic patients irrespectively of variceal bleeding risk, as well as to prevent complications and the first decompensation of liver cirrhosis. Decompensated cirrhosis could be recompensated by the etiological therapy and the use of NSBB, as has been demonstrated in patients suffering from hepatitis C-related cirrhosis. The diagnosis and treatment of minimal HE have the potential to improve the patient's quality of life and also change the natural history of the disease by reducing the risk of developing overt HE (decompensation) and the mortality associated with it. PC improvement is an unmet need that should be addressed in the next decade as a priority.

7. Expert opinion

Increased awareness of the need to diagnose ACLD as well as the etiologies that lead to it, with special emphasis on viral hepatitis elimination programs and diagnose of metabolic syndrome, has increased the number of patients diagnosed with cirrhosis in early, compensated phase, and who are followed up in outpatient clinics for years while they remain in this situation. In addition to our current capacity to get decompensated patients back to a recompensated phase.

During this compensated phase, we must offer patients specific care and measures to prevent the progression of the disease and the appearance of its complications beyond the calculation of liver function and imaging screening for hepatocellular carcinoma that we perform every six months. Entities that have typically received little attention, such as covert HE or extrahepatic complications and symptoms of cirrhosis, without forgetting the comprehensive care offered by the vision of PC, must come to the spotlight along with the search for ascites or risk of bleeding due to PHT, problems that usually focus attention and which already have been issues of multiple clinical practice guidelines. All this emphasize the need to generate research that standardizes the care offered to compensated patients through different health centers. In this sense, compensated cirrhosis offers a perfect scenario for investment in precision medicine research, which will allow establishing medical care based on risk groups defined by clinical and genetic factors, thus being able to establish different recommendations and prevention measures so that each patient obtains the greatest benefit assuming the least drawbacks. Several areas of research have developed significantly in recent years: the noninvasive diagnosis and management of cirrhosis and PTH (with the concepts of cACLD and CSPH, and the modification of natural history of the disease with etiology treatment and NSBB), the characterization and monitoring of liver function (with new scores), and the approach to symptom management and PC. Regarding cACLD and CSPH, it is important to find the best cutoff points both in serological scores and in hepatic and splenic TE for each etiology of cirrhosis to avoid loss of patients due to false negatives as well as unnecessary follow-up for years of false positives. Likewise, the periodic application of these noninvasive methods must be established given the dynamic nature of the disease, which may have a potential application in the distribution of resources, establishing subgroups that require more or less close monitoring. Regarding the monitoring of liver function, the scores we usually use are weighed down by the influence of other comorbidities, which is especially important considering that metabolic syndrome-related cirrhosis is increasing, a pathology in which the heart and kidney are frequently affected concomitantly, affecting the concentrations of surrogate markers such as creatinine and serum proteins. In relation to the latter and the need for attention to symptoms and PC, the interaction between hepatologists and other specialists should be strengthened to meet the needs of these patients. This care should not be independent, since the systemic nature of cirrhosis requires the hepatologist to modulate the approach from other specialists to liver disease to avoid actions by excess or by default in the context of a misinterpretation of the situation of the liver disease. All this requires that the health resources be adapted so that quality care is possible for patients who have been increasing in number in recent years and this trend is expected to continue in the coming years.

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