

Cirrhosis, portal hypertension and hepatocellular carcinoma: a stage-based approach

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Abstract

Cirrhosis and hepatocellular carcinoma (HCC) are interconnected outcomes of chronic liver disease, with portal hypertension playing a key part in cirrhosis decompensation, and influencing HCC prognosis and treatment. Despite their overlap, current guidelines address portal hypertension and HCC separately, leading to suboptimal risk stratification and treatment selection. This Review proposes a stage-based, integrated approach to HCC management that incorporates the prognostic stages of cirrhosis and emphasizes clinically significant portal hypertension (CSPH) as a key stratifying factor in compensated cirrhosis. CSPH is associated with an increased risk of cirrhosis decompensation, and its presence often limits the feasibility of curative treatments such as surgical resection. Although CSPH is strictly defined as hepatic venous pressure gradient (HVPG) of ≥ 10 mmHg, non-invasive tools (liver stiffness and platelet count) have largely replaced HVPG in cirrhosis; in patients with HCC, emerging data suggest that these non-invasive tests are poised to replace HVPG and its traditional surrogates, imaging and endoscopy. We explore the management of both cirrhosis and HCC across all cirrhosis stages – compensated (with or without CSPH), decompensated, and further decompensated – in relation to all HCC stages (very early, early, intermediate and advanced). Future research should validate non-invasive CSPH assessment in HCC and support outcome trials stratified by cirrhosis and HCC stage to guide personalized therapy and improve outcomes.

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Key points

- Cirrhosis has two main complications: portal hypertension and hepatocellular carcinoma (HCC).
- Cirrhosis has two major prognostic stages: compensated and decompensated.
- The onset of decompensation, driven largely by clinically significant portal hypertension, represents a pivotal clinical milestone associated with a marked decrease in survival; in turn, HCC also encompasses distinct prognostic stages.
- Existing guidelines address portal hypertension and HCC separately, rarely accounting for their coexistence.
- Effective management requires integrating cirrhosis stage and clinically significant portal hypertension with HCC to guide prognosis and treatment decisions.
- Clinical trials of HCC therapies should incorporate stratification by the stage of underlying cirrhosis in both study design and outcome analyses.

Introduction

Cirrhosis represents the end-stage of chronic liver disease and is primarily characterized by two major complications: portal hypertension (PH) and hepatocellular carcinoma (HCC).

Cirrhosis is initially asymptomatic ('compensated') but can progress to a symptomatic ('decompensated') stage characterized by the development of complications, specifically ascites, variceal haemorrhage (VH), hepatic encephalopathy (HE) or jaundice. A stage of 'further decompensation' has been described; this stage is when an additional decompensating event develops in a patient with decompensated cirrhosis or when 'complications' of a previous decompensating event occur (for example, when ascites becomes refractory to diuretics or is associated with hepatorenal syndrome–acute kidney injury (HRS-AKI), or when VH and HE become recurrent)^{1,2} (Fig. 1). Each stage is associated with decreased survival.

PH is a central driver of cirrhosis decompensation. The gold standard for measuring portal pressure is the hepatic venous pressure gradient (HVPG), obtained invasively by catheterizing the hepatic vein, and measuring the free hepatic venous pressure (balloon deflated) against the wedged or occluded hepatic venous pressure (balloon inflated). A normal HVPG is in the range 3–5 mmHg, whereas an HVPG of >5 mmHg indicates the presence of PH. Portosystemic collateral vessels (including gastro-oesophageal varices) only develop once this gradient equals or exceeds 10 mmHg. Studies across various aetiologies of cirrhosis have demonstrated that an HVPG of 10 mmHg or higher also predicts cirrhosis decompensation^{3–5}. Thus, this HVPG value of 10 mmHg or greater defines an entity known as 'clinically significant portal hypertension' (CSPH), which correlates with collateral vessel development and cirrhosis decompensation but also with an increased mortality in cirrhosis and increased mortality after HCC resection^{1,2}.

The histological categories of advanced liver fibrosis and cirrhosis have largely been replaced in clinical practice by the non-invasive concept of compensated advanced chronic liver disease (cACLD),

defined by a liver stiffness measurement (LSM) of ≥ 15 kPa. Likewise, in patients without HCC, CSPH is now diagnosed non-invasively according to Baveno criteria: LSM ≥ 25 kPa; LSM >20 kPa with platelet count $<150 \times 10^9/l$; or LSM >15 kPa with platelet count $<110 \times 10^9/l$ ^{1,2}. In addition, the endoscopic presence of oesophageal or gastric varices or radiological detection of portosystemic collateral vessels (peri-oesophageal varices, recanalization of the umbilical vein or splenoportal shunt) strongly suggests CSPH, as these findings typically occur when HVPG exceeds 10–12 mmHg. A spleen stiffness of >50 kPa has also emerged as a useful adjunct in the identification of CSPH¹. Establishing the presence of CSPH is clinically important in compensated cirrhosis because lowering portal pressure by the use of non-selective β -blockers (NSBBs) has been shown to prevent decompensation^{6,7}. Although non-invasive tests can reliably determine the presence of CSPH in patients without HCC, their diagnostic performance is less reliable in patients with HCC. Guidelines recommend starting NSBBs (carvedilol is preferred) once CSPH is identified in patients with compensated cirrhosis with the objective of preventing decompensation (ascites, VH or HE)^{1,2}. In the absence of CSPH, patients with compensated cirrhosis should be screened annually for its development^{1,2}.

HCC is a major cause of cancer-related mortality, with cirrhosis being its principal risk factor. It can occur at any stage of cirrhosis and is often the first liver-related event occurring in these patients^{1,8,9} (Fig. 2). Given the substantial risk of HCC associated with cirrhosis, routine surveillance for HCC is essential¹⁰. Current guidelines recommend liver ultrasonography and serum α -fetoprotein (AFP) measurements every 6 months in all patients with cACLD (non-invasive assessment) and/or cirrhosis (histological assessment)^{8,9,11}. Emerging risk stratification models aim to identify low-risk individuals who can forego surveillance and high-risk groups who will benefit from 'intensified' surveillance.

CSPH and HCC are strongly inter-related. In early HCC, CSPH (defined by HVPG ≥ 10 mmHg or by clinical surrogates such as varices, thrombocytopenia or splenomegaly) is present in ~35–52% of patients^{12–15}. Among individuals with advanced HCC, the prevalence of CSPH remains substantial at ~50% in real-world cohorts^{16,17}. Portal pressure can be even higher with tumoural invasion of the portal vein. On the other hand, indicators of PH (platelet count, varices, HVPG) predict HCC independently of the stage of cirrhosis and HVPG ≥ 10 mmHg is associated with a roughly sixfold increase in the incidence of HCC¹⁸. NSBBs can reduce HCC risk through antiangiogenic, antiproliferative and anti-inflammatory mechanisms^{19–21}, and a meta-analysis of randomized trials for variceal bleeding prophylaxis showed a lower rate of HCC among patients receiving NSBBs than in control groups²². Statins can also lower HVPG and improve hepatic endothelial function^{23,24} and in observational studies they have been associated with decreases in the incidence of HCC^{25,26}. However, evidence from ongoing randomized controlled trials is still lacking. Although statins are not contraindicated in patients with compensated cirrhosis, they are currently not approved for the management of PH or for HCC prevention. Low-dose aspirin has also been associated with a reduced risk of HCC, with evidence of dose–response and duration–response effects^{15,27}; however, aspirin has no demonstrated effect on portal pressure, and its use must be balanced against the potential risk of bleeding. Conversely, HCC can increase the HVPG through intratumoral arteriovenous shunting, architectural distortion and portal vein invasion, leading to both decompensation or further decompensation. Portal vein invasion, in particular, exacerbates PH and increases the risk of acute variceal bleeding²⁸.

Although PH and HCC have been mostly evaluated separately, there is a close interaction between them and management of one

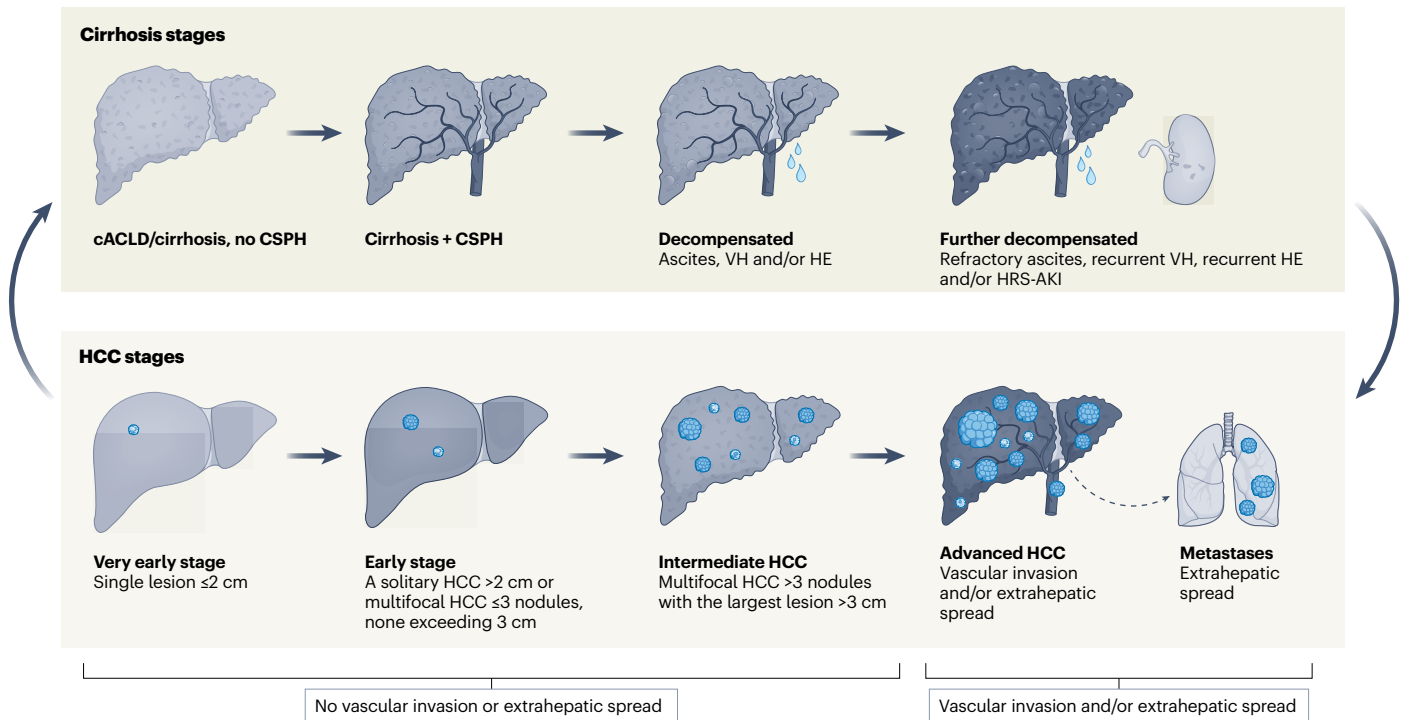


Fig. 1 Stages of cirrhosis, portal hypertension and hepatocellular carcinoma. The different definitions and stages of cirrhosis, portal hypertension and hepatocellular carcinoma (HCC) as the conditions progress. cACLD, compensated

advanced chronic liver disease; CSPH, clinically significant portal hypertension; HE, hepatic encephalopathy; HRS-AKI, hepatorenal syndrome–acute kidney injury; VH, variceal haemorrhage.

condition affects the outcomes of the other. The objectives of this Review are to evaluate staging of cirrhosis and PH in the setting of HCC and HCC treatment decisions based on the stages of cirrhosis and PH.

Management of HCC and PH according to staging Patients with very early HCC

Screening for CSPH in compensated cirrhosis and very early HCC. In patients with compensated cirrhosis and very early HCC, defined as a single lesion of ≤ 2 cm without vascular invasion or extrahepatic spread, either surgery or ablation is preferred⁹. Patients with CSPH (determined by either HVPG ≥ 10 mmHg or the presence of collateral vessels or splenomegaly) have a higher risk of morbidity and mortality after liver resection²⁹. Thus, patients in whom resection is considered should be screened for CSPH (Table 1). Although, ideally, the presence of CSPH should be determined by HVPG, finding varices on endoscopy or collateral vessels on imaging may be utilized as an alternative method (Table 2).

Studies using LSM in patients with very early or early HCC have focused on its correlation with postoperative decompensation rather than on the presence of CSPH³⁰. Indeed, the cut-off values proposed to predict postoperative complications in Asian and European populations are >14.3 kPa and >11.3 kPa, respectively³⁰. HCC can markedly influence both LSM and platelet count, potentially resulting in an overestimation of PH^{31,32}. This aspect raises questions about the applicability of non-invasive criteria to determine the presence of CSPH in patients with HCC. In a cohort of patients with Child–Pugh A (compensated) and ‘potentially resectable’ HCC, LSM was feasible in 88% of patients, and the correlation between LSM and HVPG was weaker

than in patients without HCC, suggesting that tumour-related factors such as size and location might affect LSM accuracy³³. Nevertheless, LSM <13.6 kPa reliably excluded CSPH, and LSM ≥ 21.2 kPa had a high specificity in the prediction of CSPH. The definition of ‘resectable’ HCC has included both very early and early HCC³³. Thus, in patients with compensated cirrhosis and very early HCC, where tumour burden is lowest, there are data to support screening for CSPH with LSM (alone or in combination with other parameters using the same cut-off values as for patients with cirrhosis and no HCC).

Compensated cirrhosis without CSPH and very early HCC. In patients with very early HCC, surgery or ablation is preferred^{8,9,11,34}, with ablation being more cost-effective^{35–37} (Table 1). The choice between liver resection or ablation should always consider patient comorbidities and the extent of the hepatectomy (that is, a major hepatectomy might be unreasonable when a very early HCC can be treated by ablation) and the location of the tumour (that is, ablation in high-risk areas, such as near the gallbladder, when surgery might be a better alternative). In patients without CSPH, there is no indication for NSBBs^{1,2} (Table 2).

Compensated cirrhosis with CSPH and very early HCC. The presence of CSPH is crucial in determining the choice between ablation and liver resection as CSPH is associated with an increased risk of postoperative liver failure^{29,38}. In these cases, ablation is generally preferred over resection^{8,9,11} (Table 1), although advances in minimally invasive surgical laparoscopic techniques have allowed resection in well-selected patients with CSPH^{39,40}. Laparoscopic resection can be feasible in the setting of CSPH, but the decision should be considered

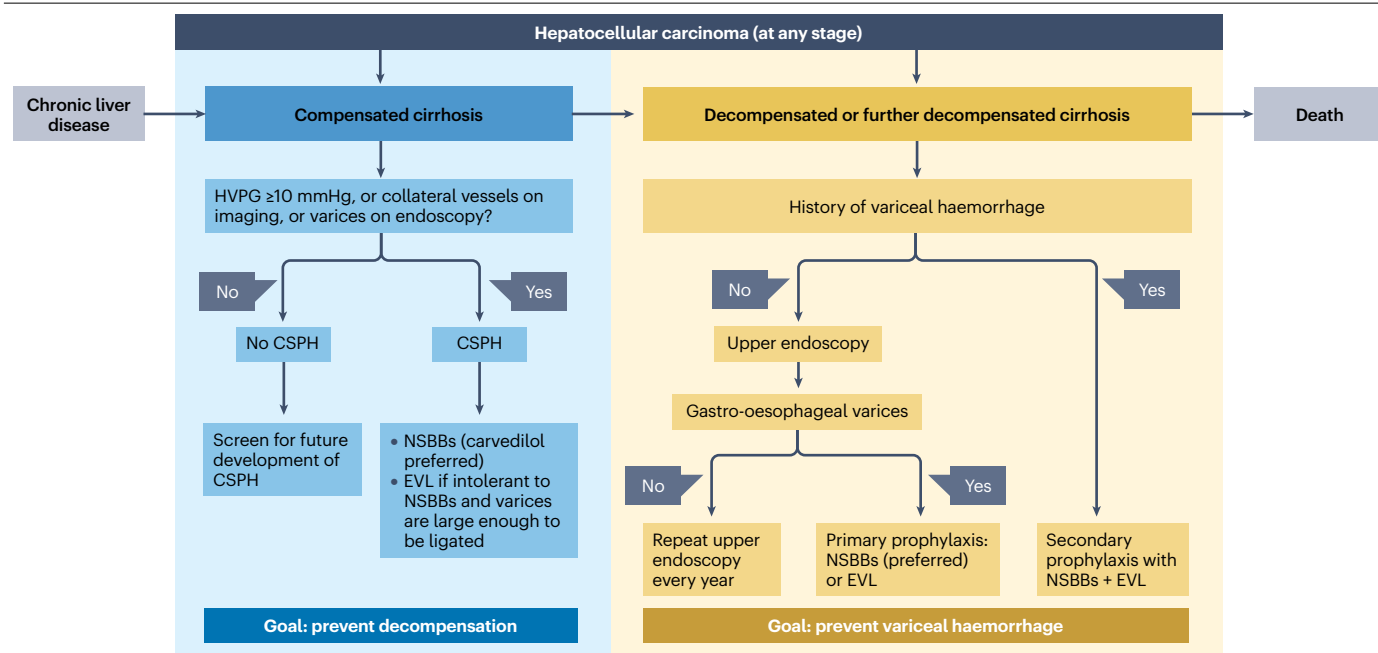


Fig. 2 | Suggested stepwise management of portal hypertension in patients with cirrhosis and hepatocellular carcinoma. Proposed clinical algorithm for managing portal hypertension in patients with cirrhosis and hepatocellular carcinoma based on current available evidence and expert opinion. The approach is stratified by disease stage (compensated, decompensated or further decompensated cirrhosis) and the presence of clinically significant portal hypertension (CSPH), defined by hepatic venous pressure gradient (HVPG) of >10 mmHg, presence of varices on endoscopy, or collateral vessels on imaging. HVPG would be indicated mostly in potential surgical candidates. Although

non-invasive tests can reliably determine the presence of CSPH in patients without HCC, their diagnostic performance is less reliable in patients with HCC. The algorithm emphasizes the role of non-selective β -blockers (NSBBs), with carvedilol as the preferred agent for primary prophylaxis, and endoscopic variceal ligation (EVL) in combination with NSBBs as secondary prophylaxis of variceal haemorrhage. For patients who cannot tolerate NSBBs, EVL is recommended if high-risk varices are present. Key management goals at different stages are also highlighted: prevention of decompensation in compensated cirrhosis and prevention of variceal haemorrhage in decompensated stages.

in the context of extent of hepatectomy, volume of the liver remnant, performance status and underlying liver function⁴¹. The presence of CSPH should be regarded as an absolute contraindication for major resection (more than two segments)^{8,9,11}.

Placement of a transjugular intrahepatic portosystemic shunt (TIPS) can be used selectively in the perioperative management of HCC to reduce CSPH-related risk⁴². However, HCC remains a relative contraindication for TIPS, particularly for centrally located tumours, given the risk of the TIPS crossing the tumour with possible rupture, bleeding or tumoural seeding. When venous anatomy is difficult to visualize, real-time ultrasonography guidance for portal vein puncture is recommended to avoid crossing the tumour⁴². Evidence for preoperative TIPS in HCC is limited to small series, but is encouraging^{43,44}. Accordingly, when technically feasible, TIPS should be reserved for carefully selected patients following individualized, multidisciplinary, case-by-case assessment.

Currently, few data are available regarding NSBB prophylaxis in patients with very early HCC, and no dedicated subgroup studies have been conducted. Thus, owing to the low burden of HCC in these patients, management of cirrhosis and/or PH should be the same as in those without very early HCC and follow the same guidelines as for patients with cirrhosis, with carvedilol being preferred in the setting of CSPH to prevent cirrhosis decompensation, or endoscopic variceal ligation (EVL) to prevent VH in patients with high-risk oesophageal varices who cannot tolerate NSBBs^{1,2} (Table 2).

Decompensated cirrhosis and very early HCC. The presence of decompensated cirrhosis also influences HCC treatment selection, as both ablation and resection carry higher risks of morbidity and mortality in this population^{45–47}. In carefully selected patients, ablation can be the preferred first-line option over surgery. However, some evidence suggests that appropriately selected patients with decompensated cirrhosis, particularly those with a Child–Pugh score B7 undergoing minimally invasive resection, might achieve good postoperative results^{48–50}. To guide treatment strategy, a nomogram to predict postoperative overall survival (OS) after resection in patients with Child–Pugh B cirrhosis has been proposed⁴⁸. This nomogram considers the presence of comorbidities, the Child–Pugh score, preoperative AFP levels, the number and size of lesions, and previous HCC treatments. Accurate estimation of surgical risk in these challenging patients could identify those whose perioperative mortality would be lower than 3% and morbidity lower than 20%^{8,9,11}. However, the decision to recommend liver resection or ablation in patients with decompensated cirrhosis should be carefully balanced against possible therapeutic alternatives, and liver transplantation should be strongly considered over other treatments owing to the risk of postoperative cirrhosis decompensation^{8,9,11} (Table 1).

In patients with decompensated cirrhosis, the goal of treatment for PH would be to prevent VH; endoscopy is recommended for variceal screening. The use of NSBBs would be recommended in patients with varices of any size and would have the advantage of reducing further decompensation^{1,2}. EVL would be reserved for patients with medium

or large varices who cannot tolerate NSBBs^{1,2} (Table 2). In the presence of VH, HCC is associated with a much worse prognosis, with a median survival of only 5 months, compared with 38 months in patients with cirrhosis without HCC. The 6-week mortality after VH also worsens with advancing Barcelona Clinic Liver Cancer (BCLC) stages: median survival is 17.3 months in patients with BCLC stage 0, A or B, decreasing to just 1.5 months in those with stage C or D⁵¹. The management of VH can be particularly challenging in the presence of HCC, leading to suboptimal outcomes. Although specific data are still limited, patients who meet Milan criteria have been included in studies on pre-emptive TIPS, suggesting that pre-emptive TIPS (that is, TIPS placed within 72 h and ideally within 24 h of initial upper endoscopy for VH) should be considered when feasible⁵². Similarly, although data on salvage TIPS in patients with HCC and VH are lacking, it might be an option based on individual prognosis, as suggested by available retrospective series⁵³. TIPS placement should, therefore, be considered earlier in patients with HCC and VH, with decisions made on a case-by-case basis, considering the specific characteristics of the HCC and being mindful of avoiding TIPS placement across the tumour⁴². For secondary prophylaxis of VH, the current recommended approach, as in patients without HCC, remains the combination of NSBBs and EVL^{1,2} (Table 2).

Further decompensated cirrhosis and very early HCC. In patients with further decompensated cirrhosis, liver transplantation remains the only viable curative treatment option (Table 1). Notably, patients with acute-on-chronic liver disease (alcohol-related hepatitis being the hallmark) are not candidates for HCC therapy while the disease is in its acute phase. In patients with refractory ascites that impedes tumour access, TIPS might facilitate HCC treatment and should be considered on a case-by-case basis, particularly in transplant candidates facing delays in graft availability. In a propensity-matched cohort of 4,484 of 42,843 transplant candidates with HCC, TIPS was associated with

improved survival on the waiting list⁵⁴. Moreover, studies have shown improvement in Child–Pugh score and ascites after TIPS in patients with HCC, increasing eligibility for local therapy^{43,44,54,55} (Table 2).

The use of NSBBs would be recommended only in those with gastro-oesophageal varices of any size (to prevent VH), and therefore screening for varices is recommended¹. In patients with refractory ascites, the dosage of traditional NSBBs should be reduced or the medication discontinued if persistently low blood pressure (systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg) and/or HRS-AKI occur¹. TIPS, if feasible, should be considered in patients with refractory ascites and recurrent VH or in those who cannot tolerate NSBBs^{1,2} (Table 2).

Patients with early HCC

Screening for CSPH in compensated cirrhosis and early HCC. Early HCC is defined by a solitary HCC of >2 cm or multifocal HCC with up to three nodules, none exceeding 3 cm, without vascular invasion or extrahepatic spread⁹. The use of non-invasive methods such as LSM and platelet count is more complex in early HCC, as their results can be confounded in the presence of up to three lesions in different liver segments. Several retrospective studies, summarized in Table 3, have evaluated the performance of Baveno criteria in patients with HCC^{56–58}. Some of these studies were somewhat flawed in that they included patients with decompensated cirrhosis and compared LSM performed before surgery with endoscopy performed after surgery. In the study that included only patients with Child–Pugh A disease⁵⁶, the investigators observed an unacceptably high rate of false-negative results for the diagnosis of both high-risk varices and CSPH using LSM alone or together with platelet count^{1,59}. In patients with early HCC, Baveno criteria are not reliable for determining the presence of CSPH⁵⁶, but unpublished data from the recent Baveno VIII conference (held in March 2026) suggest that they are useful in ruling out CSPH. Ongoing

Table 1 | Management of HCC based on the stage of cirrhosis and portal hypertension

HCC features ^a	Stage of cirrhosis ^b			
	cACLD + no CSPH	cACLD + CSPH	Decompensated	Further decompensated
Very early stage	Ablation over liver resection	Ablation over liver resection	Ablation or liver resection to be discussed case by case Consider LT (preferred)	Consider LT
Early stage	Liver resection over locoregional therapies (ablation, EBRT, TACE, TARE) Consider LT	Locoregional therapies (ablation, EBRT, TACE, TARE) over liver resection Consider LT	Locoregional therapies (ablation, EBRT, TACE, TARE) or liver resection to be discussed case by case Consider LT (preferred)	Consider LT
Intermediate	Locoregional therapies (EBRT, TACE, TARE) or systemic therapies according to HCC burden Consider downstaging for LT and extended LT criteria	Locoregional therapies (EBRT, TACE, TARE) or systemic therapies according to HCC burden Consider downstaging for LT and extended LT criteria	Locoregional therapies (EBRT, TACE, TARE) or systemic therapy to be discussed case by case Consider downstaging for LT and extended LT criteria (preferred)	Consider extended LT criteria
Advanced	Systemic therapies	Systemic therapies	Systemic therapy to be discussed case by case, with immune checkpoint inhibitor combinations preferred in patients with history of VH	Best supportive care

cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; EBRT, external beam radiation therapy; HCC, hepatocellular carcinoma; LT, liver transplantation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; VH, variceal haemorrhage. ^aVery early stage: single lesion of ≤2 cm without vascular invasion or extrahepatic spread. Early stage: a solitary HCC of >2 cm or multifocal HCC (up to three nodules, with the largest nodule being <3 cm) without vascular invasion or extrahepatic spread. Intermediate HCC: multifocal HCC (more than three nodules) without vascular invasion or extrahepatic spread. Advanced HCC: vascular invasion and/or extrahepatic spread. ^bcACLD + CSPH: hepatic venous pressure gradient (HVPG) of ≥10 mmHg, collateral vessels or varices on endoscopy. Decompensated cirrhosis: presence of ascites, history of VH and/or hepatic encephalopathy (HE). Further decompensated: recurrent VH or HE, refractory ascites or hepatorenal syndrome–acute kidney injury (HRS-AKI).

Table 2 | Management of cirrhosis or portal hypertension based on the stage of HCC

Stage of cirrhosis ^a	HCC features ^b			
	Very early stage	Early stage	Intermediate stage	Advanced stage
cACLD: preventing cirrhosis decompensation	Evaluate for CSPH ^c If no CSPH present: no specific therapy for PH If CSPH present: start NSBBs (preferred carvedilol) If NSBBs are not tolerated or are contraindicated: EVL if high-risk oesophageal varices present	Evaluate for CSPH ^c If no CSPH present: no specific therapy for PH If CSPH present: start NSBBs (preferred carvedilol) If NSBBs are not tolerated or are contraindicated: EVL if high-risk oesophageal varices present	Evaluate for CSPH ^c If no CSPH present: no specific therapy for PH If CSPH present: start NSBBs (preferred carvedilol) If NSBBs are not tolerated or are contraindicated: EVL if high-risk oesophageal varices present	Evaluate for CSPH ^c If no CSPH present: no specific therapy for PH If CSPH present: start NSBBs (preferred carvedilol) If NSBBs are not tolerated or are contraindicated: EVL if high-risk oesophageal varices present
Decompensated cirrhosis: preventing VH	Upper endoscopy If varices present: NSBBs (preferred) or EVL in patients who have never bled; NSBBs + EVL in patients with history of VH	Upper endoscopy If varices present: NSBBs (preferred) or EVL in patients who have never bled; NSBBs + EVL in patients with history of VH	Upper endoscopy If varices present: NSBBs (preferred) or EVL in patients who have never bled; NSBBs + EVL in patients with history of VH	Upper endoscopy If varices present: NSBBs (preferred) or EVL in patients who have never bled; NSBBs + EVL in patients with history of VH
Further decompensated cirrhosis	If varices present: NSBBs (preferred) or EVL in patients who have never bled; NSBBs + EVL in patients with history of VH If refractory ascites: consider TIPS as a bridge to HCC treatment and to prevent further decompensation	If varices present: NSBBs (preferred) or EVL in patients who have never bled; NSBBs + EVL in patients with history of VH If refractory ascites: consider TIPS as a bridge to HCC treatment and to prevent further decompensation	If varices present: NSBBs (preferred) or EVL in patients who have never bled; NSBBs + EVL in patients with history of VH If refractory ascites: consider TIPS as a bridge to HCC treatment and to prevent further decompensation	If varices present: NSBBs (preferred) or EVL in patients who have never bled; NSBBs + EVL in patients with history of VH If refractory ascites: no TIPS owing to poor HCC outcome

cACLD, compensated advanced chronic liver disease; EVL, endoscopic variceal ligation; NSBBs, non-selective β -blockers; PH, portal hypertension; TIPS, transjugular intrahepatic portosystemic shunt. ^acACLD+CSPH: HVPG of ≥ 10 mmHg, collateral vessels or varices on endoscopy. Decompensated cirrhosis: presence of ascites, history of variceal haemorrhage (VH) or hepatic encephalopathy (HE). Further decompensated: recurrent VH or HE, refractory ascites or hepatorenal syndrome–acute kidney injury (HRS-AKI). ^bVery early stage: single lesion of ≤ 2 cm without vascular invasion or extrahepatic spread. Early stage: a solitary hepatocellular carcinoma (HCC) of > 2 cm or multifocal HCC (up to three nodules, none exceeding 3 cm) without vascular invasion or extrahepatic spread. Intermediate HCC: multifocal HCC (more than three nodules) without vascular invasion or extrahepatic spread. Advanced HCC: vascular invasion and/or extrahepatic spread. ^cIn very early or early stages, evaluation for clinically significant portal hypertension (CSPH) entails measuring hepatic venous pressure gradient (HVPG) (≥ 10 mmHg indicates CSPH) or with finding varices on endoscopy or collateral vessels on abdominal imaging; in intermediate or advanced stages, evaluation for CSPH entails finding varices on endoscopy or collateral vessels on abdominal imaging, as HVPG does not correlate well with the presence of oesophageal varices in advanced HCC.

larger studies could help clarify the role of non-invasive methods in identifying CSPH in this patient population. Notably, in a survey published in 2023, 20% of physicians managing HCC were still using Baveno criteria for CSPH screening in these patients⁶⁰. Thus, when liver resection is being considered, the presence of CSPH should be determined by an HVPG of ≥ 10 mmHg, the presence of portosystemic collateral vessels on imaging and/or the presence of varices on endoscopy.

Compensated cirrhosis without CSPH and early HCC. For solitary tumours of < 3 cm, ablation is generally preferred given its less invasive nature and lower cost. However, resection might be preferred for larger tumours or those in high-risk locations where ablation is less effective^{8,9,11}. In patients with multifocal disease within the Milan criteria, there is no clear evidence favouring either resection or locoregional therapies such as ablation or transarterial chemoembolization (TACE)^{61–63}. Resection requires a multiparametric approach and, if concerns arise about the adequacy of the future liver remnant, pre-operative portal vein embolization can be utilized to increase the size of the contralateral hepatic lobe, facilitating safer resection⁶⁴. Transarterial radioembolization (TARE) with yttrium-90 is now recognized as a potential treatment for solitary unresectable HCC, and growing evidence supports its use to enhance the liver remnant, potentially enabling surgical resection^{65–67}. External beam radiation therapy (EBRT) is an alternative to ablation for tumours within the Milan criteria that are unsuitable for resection or liver transplantation^{68,69}. This approach could be proposed when there is a substantial risk of recurrence after

ablation owing to tumour size (> 3 cm) or challenging location (that is, in contact with large vessels). However, the risk of HCC recurrence remains notable in patients with multifocal disease, and liver transplantation should always be considered as a potential option (Table 1). Given the negative results of the eagerly awaited randomized IMbrave 050 trial⁷⁰, additional data are needed to determine whether adjuvant therapy can be an effective treatment in patients with early-stage high-risk HCC.

NSBBs are not recommended in this patient population as they are associated with a low risk for cirrhosis decompensation^{1,2} (Table 2).

Compensated cirrhosis with CSPH and early HCC. As in very early HCC, the presence of CSPH substantially influences the treatment approach. Ablation or other locoregional therapies are generally preferred and liver transplantation should always be considered^{8,9,11} (Table 1). In patients with PH features, EBRT has been associated with development of ascites, and therefore it should be used cautiously in patients with CSPH⁷¹. No data are available regarding the role of NSBBs in preventing cirrhosis decompensation in patients with CSPH and early-stage HCC. Regarding prevention of VH, a randomized controlled trial including 144 patients with cirrhosis and HCC with medium or large varices, showed that, compared with propranolol ($n = 72$), EVL ($n = 72$) was associated with a significant decrease in both VH ($P < 0.001$) and mortality ($P = 0.003$) in patients with BCLC A or B stage disease. These results are difficult to interpret, as patients with different prognostic stages (BCLC A to D) and Child–Pugh stages (A to C) were included in

the trial, creating uncertainty regarding subgroups that would have benefited from one or the other therapy⁷². Based on data from patients without HCC, NSBBs (carvedilol preferred) would have the advantage of not only preventing VH but also preventing cirrhosis decompensation in patients with CSPH. Thus, NSBBs would be first-line therapy in this patient population to prevent cirrhosis decompensation. EVL could be considered in patients with high-risk oesophageal varices to prevent VH, particularly in patients who cannot tolerate NSBBs^{1,2} (Table 2).

Decompensated cirrhosis and early HCC. In patients with decompensated cirrhosis and early HCC, treatment decisions should be made on a case-by-case basis owing to the risk of liver dysfunction after treatment. Locoregional therapies (ablation, TACE, TARE or EBRT) should be preferred over resection, and liver transplantation should always be considered as a first option^{8,9,11} (Table 1).

As in patients with very early HCC, NSBBs are indicated for the prevention of VH and this approach requires periodic endoscopic

screening. In patients with high-risk varices who cannot tolerate NSBBs, EVL would be used to prevent VH^{1,2}. In 2024, the CAVARLY trial demonstrated that, in patients with Child–Pugh B or C cirrhosis and high-risk varices, the combination of carvedilol and EVL is more effective than either therapy alone for primary prophylaxis of variceal bleeding. Comparable data from patients with HCC are lacking, warranting prospective investigation⁷³. TIPS placement should be considered in the setting of VH although the combination of NSBBs and EVL remains the standard of care in the prevention of rebleeding^{1,2} (Table 2).

Further decompensated cirrhosis and early HCC. In patients with further decompensated cirrhosis and early HCC, liver transplantation remains the only viable treatment option^{8,9,11} (Table 1). In cases where the presence of refractory ascites restricts access to HCC therapies, particularly in those on liver transplantation waiting lists, TIPS might be considered as an interim measure. Research indicates that TIPS can

Table 3 | Studies evaluating the performance of Baveno criteria in patients with hepatocellular carcinoma

Features	Allaire et al. ⁵⁶	Wu et al. ⁵⁷	Wu et al. ⁵⁸
Characteristics of the patients	185 patients, retrospective study Patients who underwent LSM, EGD and HVPG 6 months before HCC treatment	673 patients Patients underwent LSM examination before resection, and received at least one EGD afterwards.	200 patients Patients underwent LSM before treatment, and received at least one EGD afterwards at least 6 months prior to or up to 1 month after systemic therapy initiation
HCC stage	46% BCLC O or A 28% BCLC B 26% BCLC C	67% BCLC O or A 17% BCLC B 15% BCLC C	13% BCLC A 14% BCLC B 62% BCLC C
Liver function	100% Child–Pugh A	47% Child–Pugh A 53% Child–Pugh B 2% Child–Pugh C	67% Child–Pugh A 32% Child–Pugh B 1% Child–Pugh C
PH features	0% ascites 56% no oesophageal varices 21% small oesophageal varices 23% large oesophageal varices 50% platelet count <150/mm ³ 26% LSM <15 kPa 49% LSM ≥25 kPa	Ascites NA 88% no oesophageal varices 4% small oesophageal varices 8% large oesophageal varices 42% platelet count <150/mm ³ 66% LSM <15 kPa 21% LSM ≥25 kPa	Ascites NA 75% no oesophageal varices 2% small oesophageal varices 23% large oesophageal varices 38.5% platelet count <150/mm ³ 30% LSM <15 kPa 66% LSM ≥25 kPa
Performance of ‘favourable Baveno VI criteria’ (LSM <20 kPa, platelet count >150×10 ³ /mm ³) in ruling out the presence of large varices	21% favourable Baveno VI criteria 8% not correctly classified ^a in the whole cohort 11% not correctly classified ^a in BCLC O or A 0% not correctly classified ^a in BCLC B 10% not correctly classified ^a in BCLC C	2% favourable Baveno VI criteria 4% not correctly classified ^a in the whole cohort 3% not correctly classified ^a in BCLC O or A 6% not correctly classified ^a in BCLC B 12% not correctly classified ^a in BCLC C	41% favourable Baveno VI criteria 17% not correctly classified ^a in the whole cohort No data according to BCLC stage
Performance of ‘favourable Baveno VII criteria’ (LSM ≤15 kPa, platelet count ≥150×10 ³ /mm ³) in ruling in the absence of CSPH (defined by HVPG ≥10 mmHg)	16% favourable Baveno VII criteria 23% not correctly classified ^b in the whole cohort 25% not correctly classified ^b in BCLC O or A	No data regarding HVPG measurement	No data regarding HVPG measurement
Performance of LSM ≥25 kPa in ruling in the presence of CSPH	32% LSM ≥25 kPa 35% not correctly classified ^c in the whole cohort 27% not correctly classified ^c in BCLC O or A	No data regarding HVPG measurement	No data regarding HVPG measurement

BCLC, Barcelona Clinic Liver Cancer; EGD, oesophagogastroduodenoscopy; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; PH, portal hypertension. ^aLarge oesophageal varices in patients with favourable Baveno VI criteria. ^bClinically significant portal hypertension (CSPH) with favourable Baveno VII criteria. ^cNo CSPH with liver stiffness measurement (LSM) ≥25 kPa.

improve Child–Pugh score, diminish refractory ascites, and enable eligibility for intrahepatic local treatments^{42–44,54,55}.

As in patients with very early HCC, NSBBs are indicated for the prevention of VH in patients with decompensated cirrhosis and early HCC, which requires periodic endoscopic screening. In patients with high-risk varices who cannot tolerate NSBBs, EVL would be used to prevent VH^{1,2}. Consideration of pre-emptive or rescue TIPS is also advised when indicated and if feasible. For secondary prophylaxis, the combination of NSBBs and EVL remains the standard approach^{1,2} (Table 2).

Patients with intermediate HCC

Screening for CSPH in compensated cirrhosis without CSPH and intermediate HCC. Intermediate HCC is defined by multifocal tumours that exceed the criteria for early stages of HCC, but without vascular invasion or extrahepatic spread⁹. Given the burden of disease, Baveno criteria do not apply in this patient population to rule in CSPH⁵⁶. The presence of CSPH is therefore determined by the presence of collateral vessels on imaging or varices on endoscopy. Notably, repeated TACE has been associated with a substantial long-term increase in HVPG⁷⁴, although similar data for TARE and EBRT are missing. Thus, in patients undergoing repeated locoregional therapies who are not on NSBBs, screening for varices and determining volume of collateral vessels every 12 months, or earlier if there is HCC progression, is advisable. NSBBs would be recommended in patients who develop varices and/or experience growth in collateral vessels.

Compensated cirrhosis without CSPH and intermediate HCC.

Given the variability in tumour burden among patients with intermediate HCC, several subgroup classifications have emerged over the past few decades. The BCLC classification system designates patients with multinodular HCC as BCLC B if they have preserved liver function and no cancer-related symptoms⁹. This group is further divided into three subgroups⁹. The first subgroup includes patients with well-defined HCC tumours who are eligible for liver transplantation using extended criteria. The second subgroup encompasses patients who cannot undergo liver transplantation, for whom TACE is often considered the treatment of choice^{8,9,11}. However, research indicates that TACE might not be effective in some patients and can lead to a deterioration in liver function^{75,76}. This deterioration is an issue as liver function is a critical prognostic factor for systemic therapy^{8,9,11} and deterioration owing to repeated TACE might reduce access to systemic therapy. In addition, bilobar tumours with over 50% liver involvement, infiltrative or poorly defined nodular tumours, and large vessel vascular invasion have been associated with reduced effectiveness of TACE⁷⁵. These patients fall into the third BCLC B subgroup, which includes those with diffuse, infiltrative, and extensive HCC, and these patients should be considered for systemic therapy instead. Depending on the tumour burden, selective internal radiation therapy or EBRT alone or in combination with other locoregional therapy might be more appropriate than TACE in those with intermediate HCC. These therapies, along with TACE, can be considered as waiting and downstaging strategies for patients who might potentially qualify for liver transplantation^{8,9,11} (Table 1).

Emerging treatments for intermediate HCC combine locoregional therapies with systemic therapies, such as immune checkpoint inhibitors (ICIs). The Emerald-01 study showed promising results. After a median follow-up of 17.4 months, the combination of TACE with durvalumab and bevacizumab demonstrated superior

progression-free survival (PFS) than TACE plus placebo, with a hazard ratio for PFS of 0.77 (95% CI 0.61–0.98). The median PFS was 15 months versus 8.2 months. Long-term OS data are still pending⁷⁷. In the LEAP-012 study, the combination of TACE with lenvatinib and pembrolizumab resulted in a significant and clinically meaningful improvement in PFS. Specifically, the hazard ratio was 0.66 (95% CI 0.51–0.84; one-sided $P = 0.0002$), with a median PFS of 14.6 months in patients with unresectable, non-metastatic HCC, compared with 10 months with TACE plus placebo⁷⁸. However, combination approaches in these trials were associated with higher toxicity than TACE alone. In the EMERALD-1 trial, grade 3 or 4 adverse events occurred in 45% of patients treated with durvalumab, bevacizumab and TACE, compared with 23% of those receiving TACE alone⁷⁷, whereas in the LEAP-012 trial, grade ≥ 3 treatment-related adverse events were reported in 71% of participants receiving lenvatinib plus pembrolizumab versus 32% in the TACE arm⁷⁸. Although the results for combination of TACE with systemic therapy are encouraging, their clinical adoption should be tempered by the higher toxicity profile and the need for data on survival outcomes.

Additional phase III trials are ongoing for TACE, but also investigating combinations with other locoregional therapies and systemic therapies such as ICIs. Encouraging results have been observed in phase II trials combining TARE and ICIs. The NASIR-HCC trial, which included 42 patients unsuitable for TACE, reported an objective response rate (ORR) of 38%, a median time to progression of 8.8 months (95% CI 7.0–10.5 months), and a median OS of 20.6 months (95% CI 17.3–24.0 months)⁷⁹. Similarly, the CA 209-678 trial, which involved 36 patients mostly with BCLC C tumours (36% with extrahepatic spread), showed an ORR of 31%, a median time to progression of 5.6 months (95% CI 2.1–8.8 months), and a median OS of 16.9 months (95% CI 8.1–27.6 months)⁸⁰. Thus, combined therapy could be included in the treatment strategy for intermediate HCC and might enable more patients to access curative strategies such as resection or liver transplantation. Careful patient selection is essential. The optimal sequencing, concurrent versus sequential (for example, TACE with ICIs initiated at progression), remains under-studied. Importantly, treatment planning should avoid compromising access to subsequent systemic options in the event of progression after TACE plus ICI, including the potential for reduced efficacy of ICIs following prior exposure. There is no need to start NSBBs in patients without CSPH^{1,2} (Table 2).

Compensated cirrhosis with CSPH and intermediate HCC.

To date, the presence of CSPH (or not) does not affect the choice of locoregional therapy for intermediate HCC. In fact, as mentioned previously, management of HCC could lead to CSPH in a patient without CSPH through loss of hepatic parenchyma after surgery or ablation, vascular alterations, and cell death following locoregional therapies^{74,81}. Interestingly, whereas HVPG does not change shortly (within 3 days) after TACE⁸¹, repeated TACE has been linked to a substantial increase in HVPG at 6 months (median 16 mmHg (interquartile range (IQR) 11–19 mmHg)) compared with baseline (median 10 mmHg (IQR 5–12 mmHg); $P = 0.007$)⁷⁴. In patients without cirrhosis but with HCC, indirect evidence of worsening PH (increase in splenic volume and in portal vein diameter) was observed after treatment with TARE using yttrium⁸². Evidence of PH (for example, varices, VH, spleen size) with subsequent development of ascites has also been observed after EBRT⁷¹. Additional research is necessary to identify patients at greater risk of cirrhosis decompensation following HCC treatment,

particularly with repeated procedures. This investigation is crucial, as cirrhosis decompensation would preclude subsequent HCC treatments. There are currently limited data on the effect of NSBBs in preventing cirrhosis decompensation in patients with intermediate-stage HCC. However, in a study published in 2024 that included 109 patients, the incidence of PH complications within 12 months of TACE was 18%, with ascites occurring in 16%, VH in 3% and HE in 6% of patients. These complications were associated with markedly increased mortality at 12 months with an OS of 68% in those with PH complications versus 86% ($P = 0.001$). Notably, 54% of these patients did not receive NSBBs despite having varices identified on upper endoscopy, which was associated with the development of PH-related complications after TACE, and precluded further HCC treatment in 78% of affected patients. TARE, another treatment option for this subgroup of patients with HCC, should be used cautiously as it could also lead to cirrhosis decompensation, potentially precluding subsequent treatments. The influence of NSBBs in this setting should be explored. NSBBs would be first-line therapy for this patient population to prevent cirrhosis decompensation. EVL could be considered in patients with high-risk oesophageal varices to prevent VH, particularly in patients who cannot tolerate NSBBs^{1,2} (Table 2).

Decompensated cirrhosis and intermediate HCC. In patients with decompensated cirrhosis, treatment decisions should be made on a case-by-case basis, carefully weighing the risks and benefits while also considering the potential for liver transplantation following successful downstaging^{8,9,11} (Table 1). Systemic therapy might be better tolerated than locoregional approaches that can substantially worsen liver function, especially in the presence of elevated bilirubin levels^{8,9,11}.

In these patients, the goal of therapy for PH is to prevent VH. Therefore, periodic endoscopic screening for gastro-oesophageal varices is indicated. In patients with varices who have not bled, NSBBs are recommended. Among patients who cannot tolerate NSBBs, EVL would be recommended in those with high-risk varices to prevent VH^{1,2}. TIPS placement should be considered in the setting of VH and the combination of NSBBs and EVL remains the standard of care for secondary prophylaxis^{1,2} (Table 2).

Further decompensated cirrhosis and intermediate HCC. Among patients with further decompensation, liver transplantation remains the only viable treatment option in those meeting extended liver transplantation criteria, and best supportive care (symptom management) is typically recommended in patients ineligible for liver transplantation^{8,9,11} (Table 1).

In these patients, the goal of therapy is to prevent VH; therefore, periodic endoscopic screening for gastro-oesophageal varices is indicated. In patients with varices who have not bled, NSBBs are recommended to prevent VH^{1,2}. Among patients who cannot tolerate NSBBs, EVL would be recommended in those with high-risk varices to prevent VH^{1,2}. The combination of NSBBs and EVL remains the standard of care for secondary prophylaxis (that is, in the prevention of recurrent VH). Pre-emptive and salvage TIPS should be considered on a case-by-case basis in the setting of VH, when indicated, as long as the tumour does not interfere with stent placement^{1,2} (Table 2).

Patients with advanced HCC

Screening for CSPH in patients with intermediate HCC. Advanced HCC is defined by the presence of vascular invasion and/or extrahepatic spread⁹. Given the burden of disease (infiltration, vascular invasion),

Baveno criteria do not apply in this patient population⁵⁶. Thus, the presence of CSPH is determined by the presence of collateral vessels on imaging or varices on endoscopy.

Cirrhosis without CSPH and advanced HCC. For macroscopic vascular invasion in the absence of extrahepatic disease, locoregional options including SBRT and TARE can be proposed, with selection guided by HCC burden^{8,11}. Systemic therapy is indicated in patients with advanced HCC not amenable to locoregional treatment, or in patients with progression after such treatments^{8,9,11} (Table 1). Systemic therapy is also utilized in certain patients with infiltrative forms of intermediate HCC or HCC with diffuse and bilobar involvement, as discussed previously⁹. Systemic therapies for HCC are categorized into two main groups: anti-angiogenic targeted therapies and ICIs. Anti-angiogenic targeted therapies include tyrosine kinase inhibitors (TKIs) such as sorafenib, lenvatinib, cabozantinib and regorafenib, as well as anti-angiogenic monoclonal antibodies such as ramucirumab and bevacizumab. ICIs include anti-PD1 agents (such as pembrolizumab and nivolumab), anti-PDL1 agents (such as durvalumab and atezolizumab) and anti-CTLA4 agents (such as tremelimumab and ipilimumab).

For many years, only TKIs were available for the treatment of advanced HCC^{83–86}. However, positive outcomes from studies involving ICIs have substantially changed the management of HCC, making ICIs the standard treatment for advanced stages of the disease. The phase III IMbrave150 trial randomly assigned 501 patients to receive either a combination of atezolizumab and bevacizumab (336 patients) or sorafenib (165 patients)^{87,88}. Atezolizumab plus bevacizumab was associated with a superior OS compared with sorafenib (HR 0.58, 95% CI 0.42–0.79; $P < 0.001$) and longer PFS (HR 0.59, 95% CI 0.47–0.76; $P < 0.001$)^{87,88}. The phase III HIMALAYA trial compared the combination of tremelimumab and durvalumab (the STRIDE regimen; 393 patients) with sorafenib (389 patients). The primary end point of significantly longer OS for STRIDE versus sorafenib was met, with STRIDE associated with a superior OS (median OS 16.43 vs. 13.77 months; HR 0.78, 95% CI 0.65–0.93; $P = 0.0035$)⁸⁹. Another trial conducted in China assessed the combination of the PD1 inhibitor sintilimab and a bevacizumab biosimilar (IBI305) compared with sorafenib in an open-label randomized phase II–III study⁹⁰. A total of 595 patients were enrolled in the study. Of these, 24 were included in the phase II safety run-in cohort, and 571 were subsequently randomly assigned in a 2:1 ratio to receive either sintilimab plus bevacizumab biosimilar ($n = 380$) or sorafenib ($n = 191$). This study met its primary end point, demonstrating that sintilimab plus the bevacizumab biosimilar provided superior OS compared with sorafenib (HR 0.57, 95% CI 0.43–0.75; $P < 0.0001$). An interim analysis of the CheckMate 9DW trial (NCT04039607; including 668 patients) found that nivolumab plus ipilimumab ($n = 335$) was superior to lenvatinib or sorafenib ($n = 333$), with significantly longer OS (median 23.7 months (95% CI 18.8–29.4 months) versus 20.6 months (95% CI 17.5–22.5 months); HR 0.79 (95% CI, 0.65–0.96); $P = 0.018$)⁹¹. These trials strengthen the evidence supporting ICI-based combination therapies as first-line treatment options in advanced HCC. If ICIs are contraindicated or not tolerated, TKIs remain the treatment of choice (Table 1).

In the absence of CSPH, prophylaxis with NSBBs is not necessary (Table 2). However, owing to the potential presence of vascular invasion leading to CSPH, as well as the infiltrative nature of the disease with vascular invasion in some patients, endoscopic screening to detect varices and/or imaging screening for collateral vessels should

Box 1 | Research priorities in cirrhosis and HCC

Screening and non-invasive tools

Optimal strategies to assess clinically significant portal hypertension (CSPH) in patients with hepatocellular carcinoma (HCC) remain undefined. As hepatic venous pressure gradient and endoscopy are invasive, validation of alternatives (such as collateral vessels on imaging, liver and/or spleen stiffness measurements and multimodal approaches) is needed to improve screening and management.

Clinical research

Prospective trials in HCC should stratify patients by both HCC stage and cirrhosis and/or portal hypertension stage, and should include portal hypertension-related complications as key end points to reduce heterogeneity and enhance reliability.

Treatment of portal hypertension

Whether non-selective β -blockers prevent decompensation in patients with compensated cirrhosis and advanced or intermediate HCC receiving immunotherapy or combination treatments should be determined.

Therapeutic decision making

Beyond liver function, CSPH must be recognized as a central determinant in the management of HCC.

be performed every 12 months or more frequently if there is HCC progression. Anticoagulation in the setting of macroscopic vascular invasion remains undefined. Notably, real-world cohort data have not shown an increased risk of VH with anticoagulation⁹².

Cirrhosis with CSPH and advanced HCC. Limited data are available regarding the effects of PH on systemic therapies and vice versa because patients with CSPH, such as those with a recent history of VH, have been excluded from phase III studies²⁸. In the IMBrave150 study, bleeding events were more frequently reported with the combination of bevacizumab and atezolizumab compared with sorafenib (25.2% versus 17.3%), including instances of VH (2.4% versus 0.6%)^{87,88}. Importantly, patients with a history of VH within the previous 6 months or without effective VH prophylaxis have been excluded from study participation. Real-world data indicate that 14% of patients experience VH whilst on bevacizumab–atezolizumab^{17,93}, and therefore some clinicians might be reluctant to start this therapy in patients with high-risk varices or in those on anticoagulation therapies⁶⁰. However, more recent studies have not demonstrated an increased risk of VH in these situations, except in patients with a history of VH in the previous 6 months^{17,93–95}. Thus, the presence of CSPH without a history of VH should not influence the choice of first-line treatment (Table 1).

A French survey found that clinicians more often initiated EVL alone or combined with NSBBs to prevent bleeding in patients with advanced HCC before starting systemic therapy, despite a lack of supporting evidence⁶⁰. In the randomized trial comparing EVL, with propranolol across all stages of HCC, no differences in VH or survival were seen in 144 patients (72 EVL, 72 propranolol) with advanced disease⁷², although the analysis did not account for cirrhosis stage, and

propranolol, not carvedilol, was used. EVL might also delay systemic therapy and carries a risk of post-banding ulcer bleeding. It is therefore recommended to reserve EVL for patients with advanced HCC who cannot tolerate NSBBs^{1,2} (Table 2). Emerging data suggest that NSBBs might reduce decompensation risk in patients with oesophageal varices receiving atezolizumab–bevacizumab⁹⁶, an important consideration given that decompensation is a major cause of death^{97,98}. The benefit of NSBBs in patients with vascular invasion remains unknown and is probably limited.

Decompensated cirrhosis and advanced HCC. Rather than large oesophageal varices or anticoagulation, a history of VH is the main risk factor for VH in patients treated with combination atezolizumab–bevacizumab. Combination ICIs might be preferred in patients with a history of VH, even though data from trials are not available given that patients with CSPH have been excluded from participation^{8,9,11}. Systemic therapies are usually indicated in patients with compensated cirrhosis, but case-by-case discussion can be considered based on safety and efficacy outcomes that have been observed in patients with decompensated cirrhosis with ascites^{17,99,100} (Table 1). A retrospective study that included 47 patients suggested that adding albumin to atezolizumab–bevacizumab infusions might help reduce the incidence of ascites during treatment, but does not affect OS¹⁰¹. Ongoing phase II trials are focusing on patients with Child–Pugh B disease to better define the efficacy and safety of ICIs in this specific population^{102,103}.

In patients with decompensated cirrhosis and advanced HCC, the primary role of NSBBs remains the prevention of VH. Screening for collateral vessels on imaging or varices via endoscopy is recommended. In patients with varices that have not bled, NSBBs are recommended. Among patients who cannot tolerate NSBBs, EVL would be recommended in those with large varices to prevent VH^{1,2}. TIPS placement should be considered in the setting of VH based on location and/or size of HCC. The combination of NSBBs and EVL remains the standard of care for secondary prophylaxis^{1,2} (Table 2).

Further decompensated cirrhosis and advanced HCC. In patients with further decompensated cirrhosis and advanced HCC, the prognosis is poor and management should be individualized, taking into account patients' performance status, specific decompensating events and stage of HCC. Palliative care should be an integral part of the overall treatment approach (Tables 1 and 2).

Unmet needs

Screening and management of PH in the context of HCC are emerging as critical research areas (Box 1), driven by advances in HCC treatment, including immunotherapy and other novel therapies that have extended patient survival. However, because HCC occurs most frequently in the setting of cirrhosis and the stages of cirrhosis have been further refined, substantial data gaps remain regarding the interplay between PH and HCC.

Traditional methods for cirrhosis stratification such as HVPG measurement and endoscopy are invasive, underscoring the need for non-invasive alternatives. The presence of collateral vessels on imaging can serve as a straightforward indicator of CSPH, potentially guiding the use of NSBBs in patients in whom HVPG or endoscopy is not feasible. Although LSM can be unreliable for ruling in CSPH in the presence of HCC, particularly when advanced, spleen stiffness measurement is a promising non-invasive tool in patients with cirrhosis and HCC. A multimodal approach integrating multiple non-invasive techniques

could enhance screening accuracy by accounting for both PH-specific and HCC-specific factors influencing PH progression. Importantly, future prospective studies should stratify or include patients with comparable stages of both HCC and cirrhosis and/or PH. This strategy would minimize heterogeneity and improve data reliability. Given that therapeutic interventions for HCC can precipitate hepatic decompensation in previously compensated patients with cirrhosis, a critical research question is whether NSBBs might mitigate this risk. This issue is particularly important in the context of emerging immunotherapies and combination regimens that can lead to decompensation.

Clinical trials investigating novel HCC therapies should specify the stage of underlying cirrhosis and, if compensated, stratify participants according to the presence of CSPH. Furthermore, trial end points should encompass not only HCC outcomes but also cirrhosis outcomes. Although hepatic functional reserve remains a central determinant in current HCC treatment algorithms, PH should be similarly recognized as a pivotal factor influencing therapeutic selection and prognosis. Because HCC rarely develops in the absence of cirrhosis and frequently coexists with its haemodynamic and structural complications, a comprehensive evaluation of these interdependent processes is essential to advancing personalized and effective treatment strategies for patients with HCC and cirrhosis. As decompensation is known to occur with HCC therapy in compensated patients, a key question is to determine whether NSBBs can prevent such decompensation, particularly given that new immunotherapies and combination therapies might increase this risk.

Clinical trials of new HCC therapies must specify the stage of cirrhosis and identify those at high risk of developing PH-related complications. Furthermore, end points in these trials should include not only HCC outcomes but also PH outcomes. Although liver function is already a cornerstone of HCC treatment algorithms, we advocate for PH to be recognized as a pivotal factor in therapeutic decision making. A comprehensive evaluation of these interconnected factors is essential for developing personalized and effective treatment strategies for patients with cirrhosis and HCC.

Conclusions

Cirrhosis and HCC are closely linked, with PH playing a pivotal part in disease progression, treatment eligibility, and outcomes. Despite this connection, the stages of cirrhosis and PH are often under-recognized in HCC management, leading to suboptimal therapeutic decisions. Integrating the different stages of cirrhosis and PH into treatment algorithms for HCC, through invasive or non-invasive assessment, is essential for guiding HCC and PH treatment strategies. This aspect is particularly relevant in patients with compensated cirrhosis and HCC for whom the presence of varices and/or collateral vessels remains the prevailing method to assess the presence or CSPH. Future research (Box 1) should validate non-invasive tools in this population, clarify the role of β -blockers in preventing treatment-induced decompensation, and promote stage-stratified care. A unified approach that accounts for tumour burden, stage of cirrhosis and PH, can improve patient selection, reduce complications and enhance clinical outcomes.

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