Establishing hepatic decompensation as a meaningful clinical outcome during systemic therapy for hepatocellular carcinoma

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Summary

Unlike other solid tumours, the prognosis of patients with advanced hepatocellular carcinoma (HCC) is dually influenced by tumour progression and liver dysfunction. Accumulating evidence suggests that clinically evident hepatic decompensating events impact on the prognosis of patients with HCC more profoundly than tumour progression. This observation is particularly relevant in the new era of highly effective immunotherapy, that can also be administered to patients with impaired hepatic function (i.e., higher albumin-bilirubin (ALBI) grade) and/or with clinical signs of portal hypertension that both indicate a high risk of hepatic decompensation. Thus, it is of utmost clinical importance in HCC patients to develop practical strategies for prevention and management of decompensation that including a rigorous diagnostic workup and treatment of the underlying liver disease etiology – which may allow for cirrhosis recompensation and to ensure the use of non-selective beta-blockers in those with portal hypertension. We propose that future trials should incorporate hepatic decompensation as a clinically meaningful and prognostically relevant intermediate endpoint to investigate the competing effects of decompensation and tumour progression on overall survival – the gold standard endpoint for the regulatory approval of systemic HCC therapy. Clinical practice should adopt an integrated and multifaceted treatment approach that addresses both the underlying liver disease and the superimposed cancer to optimise overall patient outcomes in the context of expanding therapeutic options.

Introduction

Hepatocellular carcinoma (HCC) arises in the context of chronic liver disease, which has most often progressed to cirrhosis, representing its typical pre-neoplastic niche in the vast majority of incident cases. Unlike other tumours, patient survival is affected not only by tumour burden but also by the severity of underlying liver dysfunction and portal hypertension (PH). Understanding their detrimental effect on liver-related morbidity and mortality is crucial, while the efficacy of aetiologic therapies and PH-directed treatments holds promise to prevent complications and improve overall survival (OS) in patients with HCC, both in clinical research and routine practice.

The therapeutic landscape for advanced/unresectable HCC has evolved dramatically over the past 5 years, transitioning from the era of single-agent tyrosine kinase inhibitors (TKIs) to the remarkable efficacy of immune checkpoint inhibitor (ICI)-based combinations. By reprogramming the tumour microenvironment and reversing immune tolerance, these combinations have achieved unprecedented response rates and survival benefits in the first-line setting. The availability of sequential therapeutic options now enables a significant proportion of

patients to achieve long-term disease control. This paradigm shift has made the preservation of liver function increasingly critical, as patients need to maintain adequate hepatic reserve not only to endure the initial therapy but also to remain on active treatment for as long as possible or to be eligible for subsequent lines of treatment in case of cancer progression.[1]

So far, liver dysfunction has been evaluated as a static predictor of outcome in trials of systemic therapy; in fact, only patients fulfilling Child-Turcotte-Pugh (CTP) class A are generally enrolled in clinical studies due to the concern that more advanced liver dysfunction could confound a balanced estimation of cancer treatment-mediated OS extension. Nevertheless, some patients may derive benefit from immunotherapy even beyond restrictive CTP A criteria.[2] Despite several alternative markers, such as the albumin-bilirubin (ALBI) grade, being proposed as stage-independent surrogates of hepatic functional reserve, it is recognised that liver function may dynamically change during treatment.[3]

Recent evidence suggests that hepatic decompensation, which may occur earlier than tumour progression, may be a

key determinant of patient outcome and OS not only in early stage HCC,[4] but also in advanced stage disease treated with systemic therapies.[5] This highlights the need for careful monitoring of liver function alongside tumour response and the importance of developing strategies to prevent decompensation or achieve effective recompensation.

Landscape of systemic therapies for advanced/unresectable HCC

In the last 5 years, the benefit of immunotherapy has been unequivocally established for HCC and it is now the first-line treatment in patients who do not carry contraindications. ICI-based combinations, particularly those targeting programmed cell death protein 1 or its ligand (PD-L1), have been tested in combination with anti-vascular endothelial growth factor (VEGF) agents, cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) blockade, or TKIs. Overall, five phase III randomized controlled trials (RCTs) demonstrated positive results of ICI-based combinations on OS[6–10] and three combinations are currently approved for first-line treatment by regulatory agencies: atezolizumab plus bevacizumab, durvalumab plus tremelimumab, and nivolumab plus ipilimumab.

The IMbrave150 phase III trial represented the turning point trial, combining a PD-L1 inhibitor (atezolizumab) together with a VEGF inhibitor (bevacizumab) in a phase III worldwide trial of 501 patients.[6] With a median follow-up duration of 15.6 months, treatment with atezolizumab plus bevacizumab reduced the risk of death by 44% compared with sorafenib, achieving an OS of 19.2 months and an unprecedented overall response rate (ORR) of 30%. It should be noted that although landmark phase III RCTs share similar inclusion and exclusion criteria, only IMbrave150 also included patients with invasion of main portal trunk (14% of patients). The presence of portal vein tumour thrombosis (PVTT), particularly the invasion of the main portal trunk (Vp4), represents a well-established adverse prognostic factor in patients with HCC. This condition defines a cohort with more advanced tumour burden and exacerbated PH, consequently leading to increased risk of clinical decompensation and reduced survival, as demonstrated in a post hoc analysis of the IMbrave150 trial.[5]

Also, combinations of dual immunotherapies have succeeded in demonstrating robust antitumour activity.[7,10] The combination of durvalumab with a single priming dose of tremelimumab showed, in the STRIDE arm of the HIMALAYA phase III trial, an OS hazard ratio (HR) for STRIDE vs. sorafenib of 0.78, an ORR of 17.5% and a challenging tolerability profile (25.8% grade 3/4 AEs with STRIDE vs. 36.9% with sorafenib).[7] Nivolumab plus ipilimumab was initially approved as second-line treatment after sorafenib, following the results of CheckMate-040 trial[11] and it has recently been approved as a first-line option, following the results of CheckMate 9DW trial, where the combination showed a median OS of 23.7 months (HR 0.79 vs. lenvatinib or sorafenib) and an ORR of 36%.[10]

Of note, despite being excluded from most of the pivotal trials involving immunotherapy in advanced HCC, Vp4 portal invasion remains a well-established negative prognostic factor. By altering hepatic haemodynamics it is responsible for worsening PH and increasing the risk of decompensation. Therefore, despite limited direct evidence and pending the availability of real-world data on decompensation during dual

immunotherapy, we firmly believe that the relationship between portal invasion, risk of decompensation, and survival remains relevant across all systemic HCC therapies.

The role of liver function and hepatic decompensation during systemic therapies: what is already known?

Baseline assessment of liver function has been explored as a potential predictor of outcomes in patients with HCC undergoing systemic therapy. CTP class A is an established key inclusion criterion for clinical trials on systemic therapies, as it minimises the potential noise related to hepatic decompensation, that may in turn obscure the effect of cancer therapy. Therefore, several post hoc analyses of clinical trials[12] have provided valuable insights into the role of baseline liver function –assessed by ALBI grade – a prognostic score that can capture subtle differences in hepatic reserve even within patients with CTP A cirrhosis. Consistent trends for shorter survival in patients with pre-treatment ALBI grade 2 compared to ALBI grade 1 have been observed, with a stronger signal for OS compared to progression-free survival.

Post hoc analyses of the REFLECT[12] and IMbrave150[13] trials confirmed baseline ALBI grade as prognostic for OS across treatment arms, with grade 1 patients consistently showing longer median OS. When evaluating ALBI grade as a treatment effect modifier, patients with pre-treatment ALBI grade 2 demonstrated slightly higher HRs compared to grade 1, indicating a potentially reduced benefit from experimental treatments. In IMbrave150, the significant survival benefit of atezolizumab plus bevacizumab vs. sorafenib was confirmed in patients with ALBI grade 1 but not 2, suggesting that treatment differences diminish with more advanced baseline liver dysfunction. Recent data, however, indicate that the benefit of durvalumab plus tremelimumab appears independent of baseline ALBI grade.[14] This discrepancy remains unexplained. On the one hand, the post hoc exploratory nature of the analyses performed on ALBI subclassification in the IMbrave150 and HIMALAYA trials limits definitive conclusions around efficacy in these subgroups. Whilst anti-CTLA-4- vs. anti-VEGF-containing regimens may have differing effects on liver function through distinct impacts on the cirrhotic liver milieu, inherent differences in trial eligibility criteria (inclusion of Vp4 in IMbrave150 trial) confound the assessment of a causal relationship between therapeutic modality and risk of decompensation.

While a thorough baseline liver function assessment is essential, the dynamic course of hepatic (dys)function during treatment should not be neglected. Progression of cirrhosis and PH (independently from cancer progression), liver toxicity from systemic therapies or other concomitant drugs, insufficient treatment of underlying liver disease (both aetiological or not aetiological) or cancer progression can lead to liver function worsening during treatment. Conversely, a strong and rapid tumour response can improve liver function.[15] Thus, we advocate for a dynamic re-assessment of liver function on top of a thorough baseline assessment. Moreover, while ALBI grades are useful for static (semiquantitative) classification, the continuous ALBI score allows for dynamic and more granular monitoring of liver function during treatment. Following this line of reasoning, a post hoc analysis of IMbrave150 proposed time to deterioration of the ALBI score (defined as a 0.5-point

increase maintained over two visits) as an endpoint to assess changes in liver function. The analysis revealed that atezolizumab plus bevacizumab was associated with a longer median time to ALBI deterioration compared to sorafenib, suggesting that the combination therapy may better preserve liver function during treatment.[13]

While ALBI grade offers advantages of objectivity and ease of measurement, it has several important limitations. First, serum albumin levels can be confounded by systemic inflammation, nutritional status[16,17] or by intravenous supplementation. Most importantly, the ALBI score does not capture clinical events of decompensation related to PH such as ascites, upper gastrointestinal bleeding, and hepatic encephalopathy.[18] This is a crucial limitation since these complications, while absent at baseline in patients with CTP A cirrhosis starting on systemic therapies, can develop during treatment and potentially impact survival as much as, if not more than, tumour progression. Therefore, while ALBI grade represents a valuable tool for baseline risk stratification, its utility for monitoring liver function during treatment has to be complemented by careful assessment of clinically evident decompensating events. As for now, decompensation events have not been included as pre-defined endpoints in clinical trials and are registered only as adverse events (AEs) and graded according to Common Terminology Criteria for Adverse Events (CTCAE).

In the absence of such data from clinical trials, some real-world studies have recently been published (Table 1).[19–23] Among them, Celsa et al.[18] demonstrated that patients developing clinical decompensation were at significantly higher risk of death than those with tumour progression in the absence of decompensation, when analysing decompensation and progression by using competing risk analysis to differentiate decompensation from progression. The study also identified pre-treatment ALBI grade and viral aetiology as independent predictors of decompensation risk, with successful antiviral treatment being protective and patients with metabolic dysfunction-associated liver disease (MASLD) being disfavoured by the lack of specific aetiological treatment, which prevented achievement of "aetiologic cure". This study suggests that the availability of disease-modyfing agents (e.g. effective antiviral therapies for HBV/HCV) represents a significant advantage that may potentially not only modify the course of the disease but also improve adherence to therapies. Conversely during immunotherapy, the lack of specific treatments targeting the underlying pathophysiology of MASLD may contribute to a poorer outcome. This contrast underscores the critical importance of addressing aetiological factors of cirrhosis as an integral component of comprehensive HCC management, particularly when considering immunotherapeutic approaches. In this context, disease-modifying interventions warrant careful consideration for cirrhosis recompensation, including non-selective beta-blockers (particularly carvedilol), rifaximin, albumin administration and proactive infection prevention and management. These strategies may contribute to sustained treatment delivery in patients with HCC receiving immunotherapy-based regimens, translating into improved survival outcomes.

However, all the aforementioned studies are affected by some limitations, mainly related to their retrospective designs and the lack of a rigorous standardised protocol for clinical, biochemical and radiological follow-up, which precludes an accurate assessment of evolutionary events and time-to-event endpoints, such as progression-free survival or time-to-progression.

In light of the limitations of real-world studies and in the absence of RCTs with a pre-planned definition of hepatic decompensation, the post hoc analysis of IMbrave150 by Cabibbo et al. provides the first comprehensive assessment of clinical hepatic decompensation from a phase III RCT.[5] Given the close interplay between HCC progression and decompensation, in this analysis early clinical hepatic decompensation was defined as the first occurrence of ascites, variceal bleeding, hepatic encephalopathy, or jaundice occurring within the first 3 months, provided there was no documented neoplastic progression. Similarly, early radiological progression of HCC occurring within the first 3 months was defined as the first oncological event, occurring in the absence of clinical hepatic decompensation. This approach ensured a conservative classification, thereby minimising the likelihood that the observed clinical hepatic decompensation would be inappropriately attributed to HCC progression. Using time-dependent analysis, early decompensation carried a 7.5-fold increased risk of death, higher than the impact of radiological progression (HR 5.9). This post hoc analysis of the IMbrave150 trial highlights that, although hepatic decompensation may represent a direct consequence of neoplastic progression, early decompensation events (occurring within 3 months from treatment initiation and in the absence of tumour progression) exert a profound independent prognostic impact on survival.

Hepatic decompensation: opportunities and challenges for prevention, early detection and effective management

Considering the evidence generated in previous studies, demonstrating the role of liver decompensation as a driver of poor outcomes in patients with HCC, the development of practical approaches to prevent and detect decompensation early, and facilitate recompensation in patients with HCC undergoing systemic therapy, represent an urgent unmet medical need (Fig. 1; Table 2). The implementation of these approaches is particularly relevant given that hepatic decompensation events may require a delay or interruption of systemic therapy (pending resolution of hepatic encephalopathy, ascites, or variceal bleeding), thereby adversely affecting prognosis in patients with HCC due to potential interim tumour progression during treatment interruption.

According to Baveno VII consensus,[18] non-selective beta blockers, preferably carvedilol, should be used to prevent variceal bleeding[24] and treat clinically significant portal hypertension (CSPH) in order to prevent both bleeding and non-bleeding decompensation.[25] In fact, while acknowledging that the pathophysiology of bleeding may be considerably different in HCC (i.e. due to portal vein invasion or transtumoral arterioportal blood shunting), and that there is no direct evidence supporting the use of carvedilol to prevent decompensation in the HCC setting, it appears reasonable to assume that – similar to observations in patients with cirrhosis but without HCC – the use of carvedilol in patients with CSPH may lead to improved survival by preventing decompensation.[26] Therefore, given the paucity of robust data in patients with HCC and CSPH, and while waiting for HCC-specific evidence to emerge, cautious

Table 1. Characteristics of studies assessing the impact of hepatic decompensation on outcomes of patients with advanced/unresectable hepatocellular carcinoma receiving systemic therapies.

First name (year of publication)	Number of patients	Systemic treatment	Baseline CTP class A	Baseline ALBI grade 1/2/3	Definition of decompensation	Incidence of decompensation	Impact of decompensation on overall survival	Impact of decompensation on subsequent treatments	Predictors of decompensation
Celsa et al. (2024)[19]	571	Atezolizumab plus bevacizumab: 100%	100%	1: 47.5% 2/3: 52.5%	Ascites, variceal bleeding, hepatic encephalopathy or jaundice	16.5%	HR 19.04 (95% CI 9.75-37.19) of decompensation for death*	Permanent treatment discontinuation: 79.8%	ALBI grade 2/3; non-viral aetiology
Pinero et al. (2023)[20]	188	Atezolizumab plus bevacizumab: 17.5%	NR	NR	Worsening on CTP score ≥2 points	14.4%	HR 2.9 (95% CI 1.64-5.29) of decompensation for death	NR	NR
Sultanik et al. (2024)[21]	200	Atezolizumab plus bevacizumab: 100%	71%	1: 33% 2/3: 68%	Variceal bleeding, ascites.	Variceal bleeding: 12%. Ascites: 22%	HR 1.81 (95% CI 1.03–3.17) of variceal bleeding for death. HR 2.29 (95% CI 1.52–3.45) of ascites for death*	NR	Variceal bleeding: presence of OV, portal vein invasion, history of variceal bleeding <6 months. Ascites: baseline radiological ascites; spleen >12 cm
De Castro et al. (2024)[22]	207	Atezolizumab plus bevacizumab: 100%	76.8%	1: 36.7% 2: 54.6% 3: 7.2%	Ascites; hepatic encephalopathy	Severe ascites: 11.6%.	HR 1.55 (95% CI 1.29–1.89) of worsening ascites for death. HR 1.82 (95% CI 1.37-2.42) of worsening hepatic encephalopathy for death	NR	ALBI grade 2
Stella et al. (2025)[23]	247	Atezolizumab plus bevacizumab: 100%	77.4%	1: 35.2% 2: 57.1% 3: 7.7%	Ascites, variceal bleeding, hepatic encephalopathy or jaundice	25.5%	HR 2.86 (95% CI 2.02-4.49) of treatment interruption after decompensation for death*	Permanent treatment discontinuation: 58.7%	ALBI grade 2/3; portal hypertension; grade ≥3 treatment-related adverse events
Cabibbo et al. (2025)[5]	401	Atezolizumab plus bevacizumab: 66%	100%	1: 53% 2: 47%	Ascites, variceal bleeding, hepatic encephalopathy or jaundice	7.0%	HR 7.56 (95% CI 4.47–12.80) of early decompensation for death*	NR	ALBI grade 2/3; INR; portal vein invasion

Hazard ratios are computed by Cox proportional hazards model.
ALBI, albumin-bilirubin; CTP, Child-Turcotte-Pugh; HR, hazard ratio; INR, international normalised ratio; NR, not reported; OV, oesophageal varices.
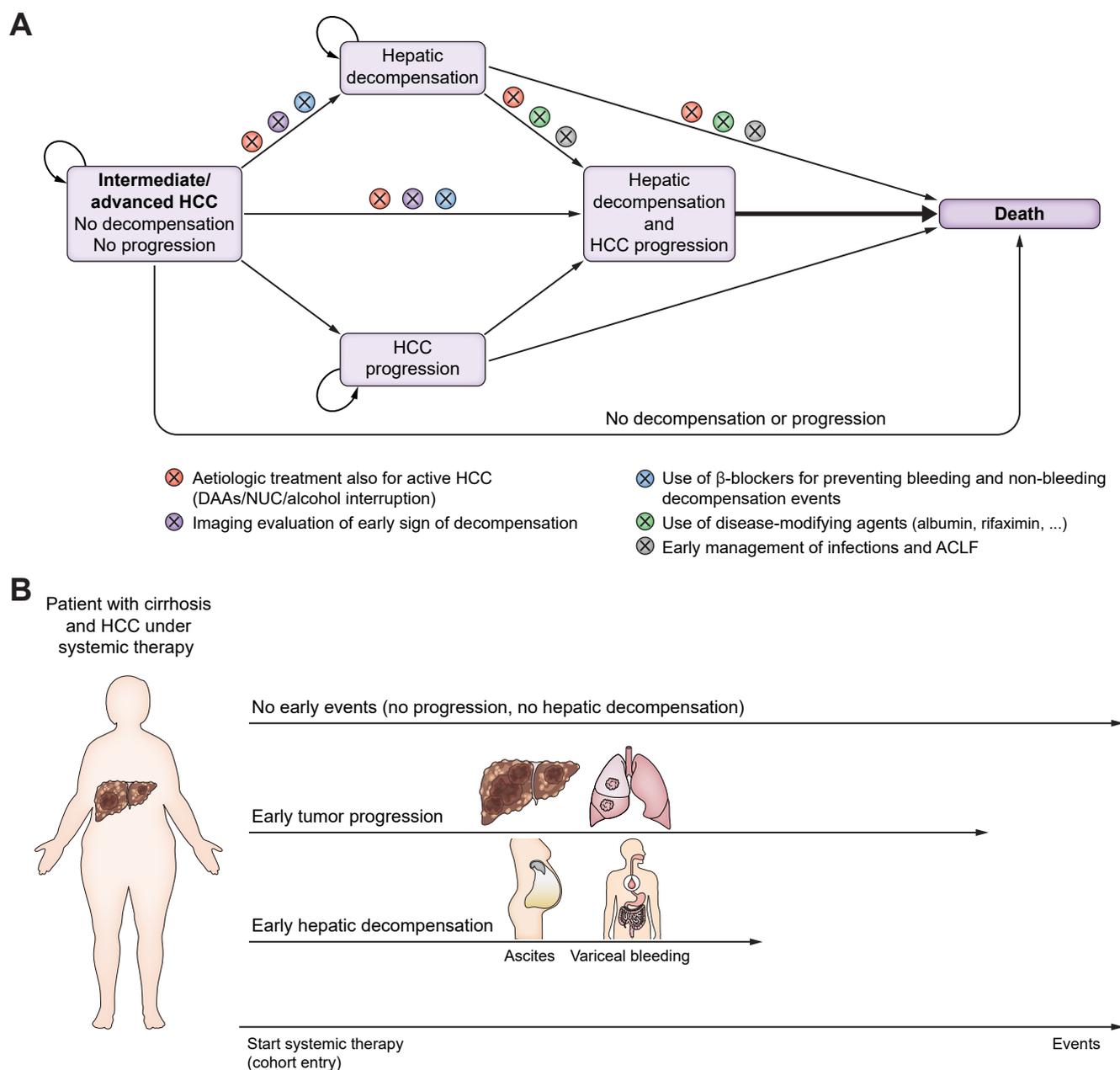*Assessed by time-dependent Cox model.

Fig. 1. Competing risk factors for survival during systemic therapy and different hypothetical scenarios. (A) Competing risk factors in survival during systemic therapy for hepatocellular carcinoma and measures to prevent and treat hepatic decompensation in patients. Modified from Reig M. & Cabibbo G. J Hep 2021 (https://doi.org/10.1016/j.jhep.2021.01.046).[1] (B) Different hypothetical scenarios of a patient with HCC and cirrhosis under systemic therapy, according to occurrence of early hepatic decompensation or early HCC progression.

adaptation of established cirrhosis management guidelines currently represents the most reasonable approach in this setting.

The most effective way to avoid progression of liver disease is to treat the underlying liver disease, *i.e.* to achieve aetiologic cure. While cirrhosis was traditionally regarded as an irreversible stage of liver disease, effective antiviral therapies have resulted in cirrhosis regression in patients with hepatitis B treated with nucleosides analogues[27] and in those with hepatitis C achieving sustained virologic response (SVR).[28] Maintained alcohol abstinence has also been demonstrated as the

key factor influencing clinical outcomes in patients with alcohol-related cirrhosis.[29] Thus, underlying liver disease aetiology should also be addressed in patients with HCC, and their clinical management should not be focused only on cancer.

However, some patients with cirrhosis with cured/treated viral hepatitis[30] and/or alcohol abstinence remain at risk of developing HCC or hepatic decompensation. Thus, in the context of HCC surveillance or monitoring, any imaging conducted in patients with cirrhosis should focus on early signs of hepatic decompensation, such as mild (perihepatic) ascites,

Table 2. Practical approach to manage decompensation and recompensation in patients with HCC receiving systemic therapies.

Prevention of decompensation	Early identification of decompensation	Treatment of decompensation/recompensation
Use of carvedilol (not only to prevent variceal bleeding, but also other non-bleeding decompensation events)	Evaluate all imaging (also with ultrasound scan) conducted for HCC follow-up/monitoring for early signs of decompensation (mild/perihepatic ascites) also during outpatient visits	Aetiologic treatment of underlying liver disease (antiviral therapy for HBV/HCV, alcohol abstinence)
Treatment of underlying liver disease (achieve aetiologic cure) also in patients with active HCC	Radiological and ultrasound monitoring (also during outpatient visits) for risk factors such as porto-systemic shunts	Role for disease-modifying agents? (albumin, rifaximin…)
Alcohol abstinence	Endoscopic surveillance for oesophageal varices	
Address metabolic comorbidities		

HCC, hepatocellular carcinoma.

progressive collateralization,[31] or the development of varices. This would allow for preventive or early therapeutic interventions to be implemented, such as initiation of non-selective beta blocker therapy, which has been reported to decrease mortality in patients with HCC.[32]

Unfortunately, the late-stage presentation of HCC in patients with decompensated cirrhosis is a relatively common clinical scenario. While immunotherapy may be a safe and effective option for selected patients with decompensated CTP B cirrhosis,[2] those with decompensated CTP C cirrhosis should receive best palliative end of life care per EASL guidance.[33]

However, more recently, effective aetiologic therapies have changed the evolution of cirrhosis, with encouraging evidence for a prognostically relevant clinical phenomenon of cirrhosis recompensation.[34] While clinical improvement and effective control of ascites or prevention of rebleeding or of recurrent encephalopathy have been observed with non-aetiological therapies, primary aetiological therapies go one step beyond and represent the "true cure".[35] In patients with HCV-related cirrhosis, SVR has been found not just to prevent liver decompensation but also to restore hepatic function to a level comparable to that of a patient with CTP class A cirrhosis. Achieving all these criteria: (i) cure/control of the primary aetiologic factor, (ii) absence of decompensation events without prophylactic medications, and (iii) restoration of hepatic function to a level similar to that of a patient with CTP-A cirrhosis, defines recompensated cirrhosis.[18] Following the example of HCV-SVR, patients with HBV achieving long-term virological suppression[36] and patients achieving long-term abstinence from alcohol[37] may be able to functionally recompensate.

From a practical perspective, all patients with HCC should be evaluated for underlying liver disease(s) and receive aetiologic therapy(ies) – as this will not only prevent decompensation or promote recompensation but also improve outcomes and survival – as demonstrated for patients with cured viral hepatitis receiving atezolizumab/bevacizumab.[19] Importantly, patients with HCC and CSPH should be treated with beta-blockers to prevent both bleeding and non-bleeding events, which are known to significantly impact morbidity and mortality. Furthermore, metabolic comorbidities should be addressed in patients with HCC, as weight loss could improve CSPH[38] and thus lower the risk of decompensation. Of note, weight loss in overweight patients with cancer may not provide the same benefits observed in cancer-free individuals and should always be accompanied by measures to prevent malnutrition and nutritional deficiencies. Although statins could be effective in lowering portal pressure, and thereby lowering the risk of decompensation, specific evidence from the clinical context of HCC are lacking. Prospective studies specifically including patients with HCC are needed to prove the safety and effectiveness of statins in this subgroup of patients.

Alcohol abstinence should be encouraged for all patients with HCC – not only in those with alcohol-related liver disease but also in those with decompensated cirrhosis (whatever the aetiology), as abstinence is associated with a significant reduction in the risk of liver-related complications. Finally, when ICI treatment is used for HCC in patients with CTP B cirrhosis, some patients – particularly those with radiologic tumor response – may show functional liver improvement.[39] Thus, the use of ICIs – in contrast to locoregional therapies – may allow for sufficient time to initiate measures and therapies aimed at recompensation of cirrhosis, thereby optimising clinical outcomes and OS. The growing evidence for novel and effective therapies for MASLD will likely contribute to a further improvement in the outcomes of patients with HCC in the near future.

Hepatic decompensation as a clinical endpoint in clinical trials

According to the previously discussed evidence, we propose that clinical hepatic decompensation, defined as the occurrence of ascites, variceal bleeding, hepatic encephalopathy or jaundice, should be incorporated as a clinical endpoint in HCC trials. We acknowledge that the interpretation of hepatic decompensation in this setting can be challenging given that this event can: 1) reflect the natural progression of liver disease in the absence of tumor progression; 2) occur concomitantly with progression (i.e. occurrence of ascites as a result of extension of PVTT); 3) occur as a treatment-related AE. For these reasons, the measurement and analysis of hepatic decompensation require rigorous trial conduct with stringent and precise time assessments.[40,41] Time-to-event analyses must account for the competing risk between tumor progression and decompensation, focusing on the first event to occur in order to minimise confusion arising from the close interplay between the two. It is important to note that early decompensation events (within 3 months of treatment initiation), as opposed to late events, may reflect the inclusion of patients with more advanced liver disease (e.g. ALBI grade 2/3, PVTT,
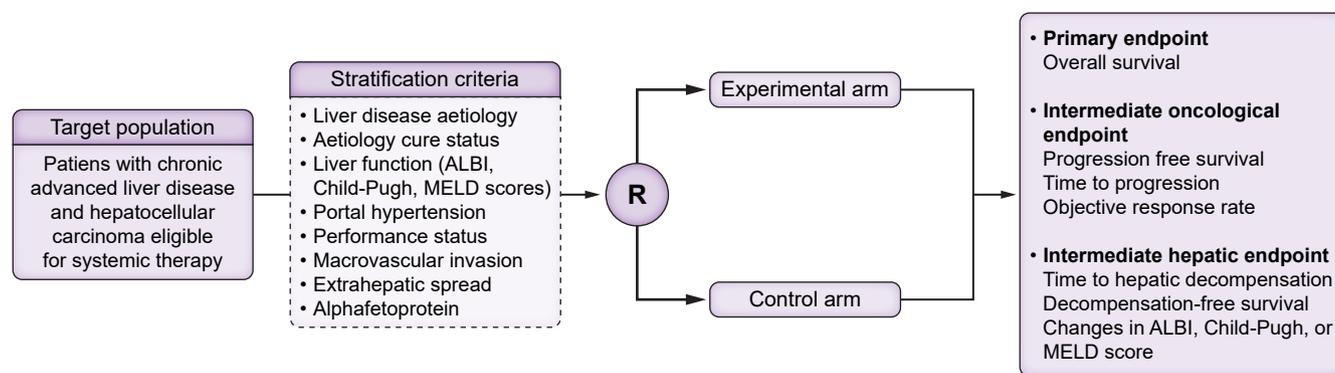
Fig. 2. A proposal for phase III randomized controlled trials including hepatic decompensation as an intermediate endpoint. Modified from Cabibbo G. *et al.* Hepatology 2023 (DOI: 10.1097/HEP.0000000000000205).[40]

or untreated underlying aetiology), even within an apparently homogeneous group of pre-treatment compensated patients.

Decompensation-related endpoints (time to decompensation, decompensation-free survival, decompensation rate) should represent secondary endpoints in phase III trials, similarly to traditional radiology-based oncological endpoints (PFS, time-to-progression, ORR), with potential elevation to primary outcomes in phase IIIb or IV studies. Ideally, future RCTs should prospectively define hepatic decompensation as a protocol-specified endpoint (Fig. 2). In the meantime, despite the limitations of retrospective analyses, a reasonable approach to assess the prognostic role of decompensation in ongoing or past studies could be the use of CTCAE or MedRA (Medical Dictionary for Regulatory Activities) terminology. This approach was used in a *post hoc* analysis of the IMbrave study, where clinical hepatic decompensation was defined as the onset of ascites, variceal bleeding, hepatic encephalopathy or jaundice (grade ≥2, per CTCAE).[5] Considering the emerging evidence, we suggest that future RCTs should be stratified according to independent predictors of hepatic decompensation. The stratification for liver disease aetiology could be challenging, given the potential for mixed aetiologies in the same patient. A simplified and thus more straightforward approach may involve stratification according to ALBI grade or the presence of CSPH in order to improve the interpretability and comparability of trial results.

Conclusions

Hepatic decompensation represents a crucial determinant of survival in patients with HCC receiving systemic therapy, having an even more profound impact than tumour progression itself. Optimal management of the underlying liver disease may not only extend survival but also substantially improve quality of life outcomes.

The available evidence highlights the need to improve clinical phenotyping of patients at risk of significant decompensation and to address the underlying liver disease aetiology in order to enhance recompensation. A multifaceted integrated approach considering anticancer therapies and liver disease management, including the full *armamentarium,* will ultimately result in improved patient outcomes. Implementation of proactive strategies to prevent or detect decompensation early, and facilitate recompensation through aetiologic treatments, cirrhosis disease-modifying agents and the careful selection of the systemic therapy associated with the lowest risk of decompensation is urgently warranted. So too are adjusted trial designs that include hepatic decompensation as a predefined (intermediate) endpoint (Fig. 2). A multidisciplinary approach focusing on both hepatological and oncological aspects of care will enable more patients to benefit from the expanding therapeutic options for advanced HCC, ultimately improving survival outcomes.

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Abbreviations

AE, adverse event; ALBI, albumin-bilirubin; CSPH, clinically significant portal hypertension; CTCAE, common terminology criteria for adverse events; CTLA-4, cytotoxic t-lymphocyte–associated protein 4; CTP, child–turcotte–pugh; EASL, european association for the study of the liver; HCC, hepatocellular carcinoma; HR, hazard ratio; ICI, immune checkpoint inhibitor; MASLD, metabolic dysfunction-associated steatotic liver disease; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; PH, portal hypertension; PFS, progression-free survival; PVTT, portal vein tumour thrombosis; RCT, randomized controlled trial; STRIDE, single tremelimumab regular interval durvalumab; SVR, sustained virologic response; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; Vp4, invasion of the main portal trunk.

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Authors' contributions

All authors contributed equally to this Expert Opinion article. Giuseppe Cabibbo: Conceptualization, supervision, validation, investigation, methodology, writing–original draft, project administration, writing– review and editing; Ciro Celsa: supervision, validation, investigation, methodology, writing–original draft, project administration, writing– review and editing; Sherrie Bhoori: supervision, validation, investigation, methodology, writing–original draft, project administration, writing– review and editing; Thomas Reiberger: supervision, validation, investigation, methodology, writing–original draft, project administration, writing– review and editing; David James Pinato: supervision, validation, investigation, methodology, writing–original draft, project administration, writing– review and editing; Calogero Cammà:: supervision, validation, investigation, methodology, writing–original draft, project administration, writing– review and editing.

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Author names in bold designate shared co-first authorship

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