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Hepatic decompensation is the major driver of mortality in Hepatocellular Carcinoma patients treated with Atezolizumab plus Bevacizumab: the impact of successful antiviral treatment

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Conflicts of interest

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Authors' contributions

Study concept and design: CiC, GC, CaC, DJP. Analysis and interpretation of data: CiC. Statistical analyses: SB, CiC. Supervision: GC, CaC, DJP. Drafting of the manuscript: CiC, DJP. All the authors were involved in data acquisition and critical revision of the manuscript and they all approved the final version of the manuscript.

Data Availability Statement

Data, analytic methods and study materials will be made available to other researchers upon reasonable request.

Graphical Abstract

GA1

Abstract

Background&aims. Unlike other malignancies, hepatic functional reserve competes with tumour progression in determining the risk of mortality from hepatocellular carcinoma (HCC). However, the relative contribution of hepatic decompensation over tumour progression in influencing overall survival (OS) has not been assessed in combination immunotherapy recipients.

Approach&Results From the AB-real observational study(n=898), we accrued 571 patients with advanced/unresectable HCC, Child-Pugh A class treated with frontline atezolizumab+bevacizumab(AB). Hepatic decompensation and tumour progression during follow-up were studied in relationship to patients' OS using time-dependent Cox model. Baseline characteristics were evaluated as predictors of decompensation in competing risks analysis.

During a median follow-up of 11.0 months (95%CI 5.1-19.7), 293 patients(51.3%) developed tumour progression without decompensation and 94(16.5%) developed decompensation. In multivariable time-dependent analysis, decompensation(hazard ratio[HR] 19.04, 95%CI 9.75-37.19), HCC progression(HR 9.91, 95%CI 5.85-16.78), albumin-bilirubin(ALBI) grade 2/3(HR 2.16, 95%CI 1.69-2.77) and number of nodules>3(HR 1.63, 95%CI 1.28-2.08) were independently associated with OS. Pre-treatment ALBI grade 2/3(subdistribution HR [sHR] 3.35, 95%CI 1.98-5.67) was independently associated with decompensation, whereas viral aetiology was protective(sHR 0.55, 95%CI 0.34-0.87). Among patients with viral aetiology, effective antiviral treatment was significantly associated with lower risk of decompensation (sHR 0.48, 95%CI 0.25-0.93).

Conclusions. Hepatic decompensation identifies patients with the worst prognosis following AB and is more common in patients with baseline ALBI>1 and non-viral aetiology. Effective antiviral treatment may protect from decompensation, highlighting the prognostic disadvantage of patients with non-viral aetiologies and the importance of multi-disciplinary management to maximise OS.

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Keywords: HCC, decompensation, immunotherapy, atezolizumab, bevacizumab.

Introduction.

More than 90% of cases of hepatocellular carcinoma (HCC) arise on a background of cirrhosis or chronic liver disease, often characterised by its own independent clinical course (1). It is universally recognised that the prognosis of HCC, unlike most solid tumours, is not exclusively related to cancer progression and its associated complications, but also to the degree of liver dysfunction (2, 3).

The occurrence of clinical events of decompensation, including ascites, variceal bleeding, hepatic encephalopathy, and jaundice, dramatically changes overall survival (OS) from a median of approximately 12 years in compensated patients to about 2 years for decompensated patients (4, 5). However, little is known with regards to the impact of hepatic decompensation in patients with active or previously treated HCC, a knowledge gap of greater consequence given the rapidly changing treatment landscape of HCC (6). In patients with HCV-related cirrhosis and HCC successfully treated with curative resection or ablation, early hepatic decompensation emerged as a much stronger determinant of OS compared to tumour recurrence (7). With active anti-cancer therapy being strongly dependent upon the presence of an adequately preserved liver function at the point of recurrence, early decompensation remains an often-irreversible barrier prejudicing the achievement of long-term survivorship in patients whose HCC has relapsed after radical therapy. Similar evidence have been obtained in patients with advanced HCC treated with sorafenib, showing that patients whose liver function decompensated during sorafenib experienced a significantly worse prognosis compared to those who discontinued for adverse events or for HCC progression (8).

The advent of combination immunotherapy has led to survival outcomes previously unseen in advanced disease, with median OS approaching 2 years in patients treated with immune checkpoint inhibitors (ICIs) (9-13). However, prevalence and clinical impact of hepatic decompensation events on the survival of patients treated in the cancer immunotherapy era are fundamentally unknown, and these data are not readily available from randomised clinical trial datasets. OS benefit across treatment arms is in fact captured without differentiating mortality due to cancer-related progression from that attributable to hepatic decompensation.

In this study we estimated the prevalence and prognostic role of hepatic decompensation against oncological disease progression by comparatively weighting the impact of these two evolutionary events on patients' OS. To achieve this aim, we analysed a cohort of advanced or unresectable HCC

patients treated with first-line atezolizumab plus bevacizumab in the context of the AB-real observational study.

Materials and Methods.

Patients.

Consecutive patients with unresectable HCC who received atezolizumab plus bevacizumab as part of routine clinical care in 25 tertiary care centres across Europe, USA and Asia from January 2019 to June 2023 were enrolled in a prospectively maintained database(14, 15). Patients included had: 1) evidence of radiologic and/or histological diagnosis of HCC according to international guidelines (16); 2) unresectable HCC defined according to BCLC classification as stage B or C not amenable to resection or with evidence of progression after loco-regional treatments; 3) history of cirrhosis or compensated advanced chronic liver disease; 4) received atezolizumab plus bevacizumab as first-line systemic treatment with available data on liver decompensation during follow-up. Patients with Child-Pugh class B or C cirrhosis at the time of atezolizumab plus bevacizumab initiation and patients who received atezolizumab plus bevacizumab as second- or further-line of systemic treatment were excluded.

Demographic, clinical and biochemical characteristics, including age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), Barcelona Clinic Liver Cancer (BCLC) stage, history of previous decompensation, previous or ongoing treatment with beta-blockers, aetiology of liver disease, baseline presence of ascites, hepatic encephalopathy, presence of high-risk oesophageal varices (i.e. varices of medium/large size or small varices with red spot signs), Child-Pugh score, Model for End-Stage Liver Disease (MELD), and alpha-fetoprotein (AFP) levels were recorded at the time of treatment initiation.

Viral aetiology was defined in presence of HCV and/or HBV infection. Non-viral aetiology was defined in presence of metabolic dysfunction-associated steatotic liver disease (MASLD) or MetALD or alcohol-related liver disease in absence of HCV or HBV infection.

Diagnosis of MASLD was made in patients with steatotic liver disease, associated with the presence of at least one cardiometabolic risk factor and self-reported alcohol intake less than 20 g/day for women or 30 g/day for men (previously known as non-alcoholic fatty liver disease)(17). Diagnosis of MetALD was made in patients with steatotic liver disease, associated with the presence of at least one cardiometabolic risk factor (previously defined as non-alcoholic fatty liver disease) and self-reported alcohol intake higher than 20 g/day for women and 30 g/day for men (17).

Diagnosis of alcohol-related liver disease was based on the history of a self-reported regular alcohol intake of more than 20 g/day for women and 30 g/day for men, according to international guidelines (18).

We documented prior treatment of underlying aetiologic factors for viral aetiology of chronic liver disease. Successful treatment was defined in case the following conditions were met before the first cycle of treatment with atezolizumab plus bevacizumab: achievement of a sustained virologic response (SVR) in HCV patients; evidence of undetectable HBV-DNA within 1 month from initiation of systemic therapy in HBV patients.

Atezolizumab and bevacizumab were administered following a multidisciplinary assessment of the patient and according to the local practice of each participating institution.

Outcomes and follow-up

Overall survival (OS), defined as the time lapsing from the first administration of atezolizumab plus bevacizumab to death (by any cause) or last clinical follow-up, was elected as the primary study endpoint to assess the differential impact of radiological HCC progression and hepatic decompensation.

Radiologic HCC progression was defined by RECIST criteria v1.1 on multiphasic CT or MRI, performed every 9–12 weeks as part of periodic restaging and assessed by each investigator. Radiological patterns of progression were categorised as previously described (19): new extrahepatic lesion (i.e. the development of new lesion(s) outside the liver, including new macrovascular invasion); new intrahepatic lesion (i.e. the development of new liver lesion(s) if the tumour was inside the liver); extrahepatic growth (i.e. ≥20% growth in the target tumour outside the liver); intrahepatic growth (i.e. ≥20% growth in the target tumour inside the liver).

Hepatic decompensation was defined according to international guidelines as the occurrence of new or worsening ascites, variceal bleeding, hepatic encephalopathy or jaundice(20). In patients with pre-existing grade 1 ascites (i.e. mild ascites only detectable by radiological examinations)(21) or grade 1-2 hepatic encephalopathy (22), decompensation was defined as worsening to grade 2-3 ascites(i.e. moderate-refractory ascites) or to grade 3-4 hepatic encephalopathy, respectively. The occurrence of hepatic decompensation was verified by each investigators every 3 weeks through the review of medical history and physical examination.

As secondary aims, we compared the clinical outcomes of patients who developed HCC progression or hepatic decompensation by describing the proportion of patients who received second-line post-progression treatments, treatment discontinuation rates and post-treatment discontinuation survival

and we identified baseline predictors of hepatic decompensation. Post-treatment discontinuation survival was defined as the time from the last administered dose of atezolizumab plus bevacizumab to death or last follow-up visit.

Statistical analysis.

The impact of HCC progression and hepatic decompensation on OS was evaluated by including them as time-dependent covariates in a time-dependent multivariable Cox regression model (23).

The cumulative incidence function (CIF) of hepatic decompensation was computed by competing risks analysis, with HCC progression as competing event (24). Gray's test was used to test the differences in the CIF of hepatic decompensation between patients with viral and non-viral aetiology. In patients with viral aetiology, the CIF of hepatic decompensation was compared according to the presence or not of successfully treated aetiology.

A multivariable Fine-Gray subdistribution hazard model was fitted to estimate the effect of baseline covariates on hepatic decompensation (25).

Covariates were entered in the multivariable analysis of predictors of OS and predictors of hepatic decompensation by a backward stepwise selection. The best-fit multivariable models for OS and for hepatic decompensation were selected according to the minimum Akaike information criterion (AIC) values. The full list of the variables screened for multivariable models for OS and for hepatic decompensation are reported in Supplementary Table S1, http://links.lww.com/HEP/I569 and Supplementary Table S2, http://links.lww.com/HEP/I569 respectively. All the continuous variables were included in their continuous form, except for AFP levels, that were dichotomized as higher or lower 400 ng/mL.

Additional analyses of predictors of OS and hepatic decompensation were performed with imputation of missing data by Hotdeck imputation method (26). Hot.deck function from hot.deck library was used.

The predicted probability of developing hepatic decompensation was computed for hypothetical patients identified by a combination of prognostic factors.

In a Fine and Gray framework, patients who experienced HCC progression as competing event prior to decompensation remain in the risk set indefinitely without decompensation (or vice versa). The performance of Fine and Gray model was evaluated by splitting the dataset into a training (75%) and a test (25%) set. The model's performance for predicting hepatic decompensation was assessed in terms of discrimination and calibration. Discrimination was assessed by time-dependent

area under the receiver operating characteristic (ROC) curve. To estimate the time-dependent ROC curves in the presence of censoring and different time- points, we used the Score function of the R package *riskRegression*, specifying the plots option as "ROC" (27). Calibration was evaluated through the comparison, at different time-points, between the predicted and observed event rates, specifying the plots option as "Calibration" in the R package *riskRegression*, following the approach by Gerds et al (28). We also calculated the Brier score as a calibration measure, that is defined as the expected squared distance between the observed status at that time and the predicted probability. Thus, the smaller the Brier score, the more calibrated the model.

The Kaplan-Meier method was used to estimate post-treatment discontinuation survival. Log-rank testing was used to assess the differences in survival.

For all analyses, p values<0.05 were considered statistically significant. All p values were two-tailed, and all confidence intervals(CIs) were 95%. Analyses were performed using the R-studio software, R Core Team(2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Ethical considerations

The study was conducted according to the ethical standards stipulated within the Declaration of Helsinki. Ethical approval to conduct this study was granted following review of the study protocol by the Imperial College Tissue Bank (Reference Number R16008) and locally by the ethical committee of each participating site. Written informed consent was obtained for all patients.

Results.

Baseline.

At the time of data cut-off, 898 patients treated with atezolizumab plus bevacizumab were accrued to the AB-real study. After removing patients not meeting the inclusion criteria(Supplementary Figure S1, http://links.lww.com/HEP/I569), 571 patients were retained for analyses.

Table 1 shows the baseline characteristics of patients meeting inclusion criteria: mean age was 66.9±11.6 years and 453 patients(79.2%) were male. Viral aetiology was present in 350(61.3%) of patients. Among these 350 patients, aetiology was successfully treated before the initiation of atezolizumab plus bevacizumab in 263(75.1%)patients(143 HBV, 115 HCV, 5 HBV/HCV co-infected patients), while viral aetiology was not treated in the remaining 87 patients (24.9%)(35 HBV, 46 HCV, 6 HBV/HCV co-infected).

Prior history of hepatic decompensation was present in 108 patients(20.5%). At the time of treatment initiation, 163 patients(34.9%) had oesophageal varices, 55 patients(11.8%) had varices needing treatment and 84 patients(14.7%) had grade 1 ascites. Eighy-nine patients(19.9%) were receiving treatment with beta-blockers(propranolol or carvedilol) at the time of study inclusion. Child-Pugh score was 6 in 201(35%) patients, mean MELD score was 6.6 and 300 patients(52.5%) were classified as ALBI grade 2 or 3.

Evolutionary events during follow-up and impact on OS

During a median follow-up of 11.0 months(95%CI 5.1-19.7), 184 patients(32.2%) developed neither progression nor decompensation. In total, 293 patients(51.3%) developed radiological HCC progression in absence of hepatic decompensation and 94 patients(16.5%) developed hepatic decompensation. Baseline characteristics of patients stratified according to the development of progression and decompensation during follow-up are reported in **Table 1**.

Cumulative incidence of HCC progression and hepatic decompensation by competing risks analysis are showed in **Figure 1**.

Rates of HCC progression at 3-, 6- and 12-month were 23%(95%CI 19-26%), 34%(95%CI 30-38%) and 48%(95%CI 43-52%), respectively, by competing risks analysis. Radiological patterns of progression are reported in Supplementary Table S3, http://links.lww.com/HEP/I569.

Rates of hepatic decompensation at 3-, 6- and 12-month were 7%(95%CI 3-11%), 10%(95%CI 7-13%) and 14%(95%CI 11-17%), respectively, by competing risks analysis.

Among 94 patients who developed hepatic decompensation during follow-up, 45 patients(47.9%) developed hepatic decompensation as isolated event, while the remaining 49 patients(52.1%) also developed HCC progression during follow-up. Particularly, in 49 patients who developed both events during follow-up, decompensation occurred before progression in 39 patients(79.6%), with a median time-lag between decompensation and progression of 1.6 months(95%CI 0.7-2.0).

During follow-up, 141 patients died(40.7%) and median OS in the overall cohort was 17.4 months(95%CI 15.4-20.7).

Univariate analysis of predictors of OS is reported in Supplementary Table S1, http://links.lww.com/HEP/I569.

The time-dependent multivariable Cox regression analysis showed that hepatic decompensation(HR 19.04, 95% CI 9.75-37.19, p<0.001) and HCC progression(HR 9.91, 95%CI 5.85-16.78, p<0.001) were independent predictors of death, as well as ALBI grade 2/3(HR 2.16, 95%CI 1.69-2.77, p<0.001) and number of nodules higher than 3(HR 1.63, 95%CI 1.28-2.08, p<0.001)(**Figure 2**).

Similar results were obtained when ALBI was included in the multivariable model for OS as a continuous variable, as showed in Supplementary Table S4, http://links.lww.com/HEP/I569.

Among pattern of progression, only intrahepatic growth and extrahepatic growth, assessed as time-dependent variables, were significantly associated with death by univariate analysis (Supplementary Table S5, http://links.lww.com/HEP/I569). Similar results were observed when hepatic decompensation was evaluated against the radiological pattern of progression by time-dependent multivariable Cox model, as showed in Supplementary Table S6, http://links.lww.com/HEP/I569.

After imputation of missing data, the results of multivariable analysis of predictors of OS were not significantly different than those obtained with the original data(Supplementary Table S7, http://links.lww.com/HEP/I569).

Management of systemic therapy after HCC progression or hepatic decompensation.

Figure 3 depicts the impact of HCC progression or hepatic decompensation on subsequent therapeutic management, described in terms of receipt of second-line systemic treatments and treatment discontinuation.

Among 293 patients who developed HCC progression in absence of hepatic decompensation, 179 patients(61.1%) received second-line systemic treatments, most commonly tyrosine kinase inhibitor(TKI) monotherapies(n=123) or ICI-based regimens(n=46). Atezolizumab plus bevacizumab treatment was still ongoing at the time of data cut-off despite progression in 15 patients(5.1%), while the remaining 99 patients(33.8%) discontinued atezolizumab plus bevacizumab treatment without receiving a second-line treatment. The main reasons of treatment discontinuation in these patients are reported in **Figure 3A**.

Among 94 patients who developed hepatic decompensation, atezolizumab plus bevacizumab treatment was permanently discontinued for this reason in 75 patients(79.8%), after a median time of 1.3 months(95%CI 0.9-2.5) from decompensation. Only 13 patients(13.8%) received a second-line systemic treatment(TKI monotherapy in 11 patients and ICI-based regimens in 2 patients),

while the remaining patients received best supportive care after atezolizumab plus bevacizumab discontinuation(**Figure 3B**).

Median survival after atezolizumab plus bevacizumab discontinuation was significantly longer in patients who discontinued for HCC progression(7.5 months, 95%CI 6.0-9.6) compared to those who discontinued due to decompensation(2.2 months, 95%CI 1.6-3.0, p<0.001, **Figure 4**).

Clinical characteristics and predictors of hepatic decompensation

Among 94 patients who developed hepatic decompensation, ascites was the most common feature of worsening liver dysfunction, occurring as isolated event in 66 patients(70.2%). In the remaining patients, decompensation events were represented by jaundice in 8 patients(5.8%), variceal bleeding alone in 6 patients, variceal bleeding plus ascites in 6 patients, hepatic encephalopathy alone in 6 patients(6.4%) each, hepatic encephalopathy plus ascites, and hepatic encephalopathy plus variceal bleeding in 1 patient(1.0%) each.

Univariate analysis of predictors of hepatic decompensation by competing risks analysis is reported in Supplementary Table S2, http://links.lww.com/HEP/I569.

Cumulative incidence of hepatic decompensation at the end of follow-up was 13%(95%CI 9-17%) in patients with viral aetiology, and 23%(95%CI 17-30%) in patients with non-viral aetiology(p-value=0.014 by Gray's test)(**Figure 5)**.

Multivariable competing risks analysis(**Figure 6A)** showed that viral aetiology was independently associated with a lower risk of hepatic decompensation (sHR[subdistribution hazard ratio]0.55, 95%CI 0.34-0.87, p=0.01), while ALBI grade 2/3(sHR 3.35, 95%CI 1.98-5.67, p<0.001) was independently associated with a higher risk of hepatic decompensation. The full competing risks model with sHRs for HCC progression is reported in Supplementary Table S8, http://links.lww.com/HEP/I569.

Similar results were obtained when ALBI was included in the competing risks multivariable model for hepatic decompensation as a continuous variable, as showed in Supplementary Table S9, http://links.lww.com/HEP/I569.

After imputation of missing data, the results of multivariable competing risks analysis of predictors of hepatic decompensation were the same of those obtained with the original data.

In order to refine the prognostic prediction of hepatic decompensation at individual patient-level, we combined the two independent predictors(ALBI grade and aetiology of liver disease) to identify two different risk profiles**(Figure 6B**). Patients with the worst profile(i.e. ALBI grade 2/3 and non-viral aetiology) showed a predicted probability of hepatic decompensation of 16%(95%CI 11-22%) at 3 months, 23%(95%CI 16-32%) at 6 months and 31%(95%CI 22-40%) at 12 months. Conversely, patients with the best profile(i.e. ALBI grade 1 and viral aetiology) showed a probability of hepatic decompensation of only 3%(95%CI 1-4%) at 3 months, 4%(95%CI 2-7%) at 6 months and 6%(95%CI 3-9%) at 12 months.

Time-dependent AUROCs of the model were 0.77(95%CI 0.64-0.90) at 3 months, 0.76(95%CI 0.65-0.87) at 6 months and 0.74(95%CI 0.64-0.85) at 12 months(Supplementary Figure S2, http://links.lww.com/HEP/I569**).** Calibration plots for hepatic decompensation are showed in Supplementary Figure S3, http://links.lww.com/HEP/I569 respectively.

In patients with viral aetiology(n=350), successful aetiological treatment was significantly associated with lower risk of hepatic decompensation(sHR 0.48, 95% CI 0.25-0.93, p=0.029). Cumulative incidence of hepatic decompensation at the end of follow-up was 10%(95%CI 7-14%) in patients with successful aetiological treatment and 23%(95%CI 12-33%) in patients with untreated viral aetiology(p-value=0.026 by Gray's test) (**Figure 7**).

No significant differences in the cumulative incidence of hepatic decompensation at the end of follow-up were observed between patients with not treated viral aetiology(23%, 95%CI 12-33%) and patients with MASLD(30%, 95%CI 18-42%) (p-value=0.250 by Gray's test).

Discussion

Evaluation of efficacy from systemic therapy strongly relies on OS extension: an endpoint that in patients with HCC reflects two disease entities – cirrhosis and cancer – with distinctive clinical features and an often-independent course. Decompensation of chronic liver disease is a relevant driver of mortality in patients with cirrhosis irrespective of the presence of HCC.

Unfortunately, decompensation events are not routinely reported as an event of interest in phase III RCTs evaluating systemic treatments and worsening of liver function is often reported as an adverse event associated with various degree of causality to the exposure to systemic therapy as opposed to tumour progression (29). Dedicated post-registration studies can shed light on prevalence and

clinical impact of liver decompensation: a clinically relevant event whose reporting is universally neglected in RCTs.

In this global multicentre study drawing on a repository of about 900 patients with unresectable/advanced HCC we provide, for the first time to our knowledge, data on the incidence, characteristics, and clinical relevance of hepatic decompensation during first-line therapy with atezolizumab plus bevacizumab for advanced/unresectable HCC.

We showed that approximately 17% of patients who started systemic treatment with preserved liver function developed a decompensation event during follow-up, mostly represented by ascites build-up in about 70% of cases. In these patients, decompensation occurred early during treatment, highlighting the existence of a population who is at risk of early adverse outcome irrespective of the achievement of tumour control. Previous real-world studies have assessed the frequency of hepatic decompensation during treatment with sorafenib identifying it as the main reason of treatment discontinuation in up to 23% of patients (8). Similarly, in patients treated with lenvatinib, real-world data showed that hepatic decompensation occurs in about 23% of patients and about 55% of patients experience a decline in ALBI grade on treatment (30).

Whilst direct comparison of decompensation risk across different systemic treatment modalities is beyond the scope of this study, the overall decompensation risk of 17% emerging from our data is the lowest ever reported in observational studies and might contribute to explain at least in part the superior survival outcomes achieved in the context of combination immunotherapy compared to molecularly targeted therapies.

Compared to patients who did not develop tumour progression or decompensation, in our study decompensating patients experienced a 19-fold increase in mortality, a significantly higher risk compared to the 9-fold increase observed in patients who progressed without decompensation. The strongly detrimental effect of liver decompensation emerges as an independent predictor of survival when progression and decompensation are considered as time-dependent covariates in multivariable analysis: a finding already observed after curative treatments in early-stage disease (7). Pre-treatment ALBI grade and number of HCC nodules were additional independent predictors of OS. These results indicate that a time-dependent model, accounting for early changes during the course of the disease, is able to adequately express the complexity of interactions between tumour features and degree of liver failure during follow-up.

The detrimental effect of hepatic decompensation on OS is not only mediated by its intrinsic lethality and poor reversibility, but also by the impact on the ability to continue active anti-cancer treatments for HCC.

Unfortunately, early functional decompensation appears to be an irreversible phenomenon in up to 80% of patients, leading to permanent discontinuation of treatment and initiation of best supportive care. Only up to 14% patients who survived initial decompensation were deemed eligible for second-line therapy in case of concomitant progression, after recovering from decompensation. These figures are in deep contrast with outcomes of patients who developed HCC progression without hepatic decompensation. Over 60% of patients in this group were in fact able to receive a second-line systemic treatment, an aspect that is accountable for the clear difference in survival outcomes post-progression.

This study highlights how the clinical significance of hepatic decompensation profoundly differs from that of treatment-related increase in transaminases (i.e. immunotherapy-related liver injury), with the latter being proven not to affect the outcomes of patients with HCC in terms of survival, response rates and treatment discontinuation (31).

Long-term stability of liver function has been long term recognised as a key reason for attrition between first and subsequent lines of treatment. Survival after sorafenib discontinuation is significantly worse in patients with hepatic decompensation, compared to those who discontinue for toxicity or for cancer progression (8). Post-hoc analyses of phase III RESORCE trial further reinforces the concept that patients who remain within Child-Pugh A liver function criteria at the time of sorafenib discontinuation can hope for a median OS of up to 26 months from commencement of systemic therapy (32) and similar results were observed also for cabozantinib (33).

With liver dysfunction being recognised as a key factor to influence prognosis in patients with advanced/unresectable HCC, early identification of patients at higher risk of hepatic decompensation during atezolizumab plus bevacizumab treatment is a highly desirable aim in order to implement all available therapeutic measures to prevent decompensation.

Multivariable competing risks analysis of pre-treatment patient characteristics identified worse ALBI grade as independent predictors of hepatic decompensation, suggesting that a pre-treatment ALBI grade>1 can further refines the prognostic prediction of patients with HCC particularly within Child-Pugh A criteria (34). Although our model demonstrated a good discriminatory ability and calibration for 3-month prediction, the overall performance decreased at 6 and 12 months,

particularly regarding calibration. This suggests that while the model is reliable for short-term prediction, its use for long-term predictions should be approached with caution.

A key question for future research is whether use of simple biochemical parameters including bilirubin and albumin may optimise the provision of disease-modifying agents such as beta-blockers, rifaximin, statins or parenteral albumin administration as a measure to reverse the risk of future decompensation in high-risk patients. Whilst thought-provoking, the role of enhanced management of cirrhosis in high-risk patients requires prospective testing in patients with advanced HCC. In patients with compensated advanced chronic liver disease, the PREDESCI trial has demonstrated the benefit of beta-blockers in reducing the risk of decompensation and death (35). Unfortunately, the same evidence is lacking in patients with HCC

Aside from evaluation of baseline unmodifiable risk factors for decompensation, our study provides novel and clinically important evidence to show that, compared non-viral aetiology (metabolic and alcohol-related liver disease), viral aetiology (HBV and/or HCV infection) is independently associated with a lower risk of hepatic decompensation and that effective antiviral treatment before the start of systemic treatment is significantly associated with a decreased risk of hepatic decompensation during atezolizumab plus bevacizumab.

To our knowledge, this is the first time that treatment of underlying viral aetiology is confirmed to improve outcomes from combination immunotherapy for HCC, with previous evidence being restricted to the beneficial role of HCV eradication in early-stage HCC (36, 37).

However, adequate control of underlying aetiologic factors for chronic liver disease is not equally achievable for all patients. Whilst HCV eradication or HBV-DNA suppression can be achieved through highly effective antiviral treatments, alcohol abstinence and reversal of complex metabolic dysfunction including diabetes and malnutrition are often difficult to achieve (38, 39). Therefore, it can be hypothesized that the lack of effective aetiological treatments in the subgroup of patients with “non-viral” HCC could led to ensuing higher risk of liver decompensation compared to viral patients, that can conversely benefit from the protective effect of highly effective therapies such as anti-viral agents.

The high lethality of early decompensation events emerging from our study sheds new light to the ongoing debate concerning aetiology of chronic liver disease as an immunotherapy effect modifier (40). One might in fact postulate that the influence of aetiology on survival might not be exclusively linked to aetiology-related differences in the immune microenvironment but linked to the

disadvantage of patients suffering with MASLD and alcohol-related liver disease in receiving effective aetiological treatments and be protected from liver decompensation (41).

It should be also considered that while viral eradication efforts are underway, a proportion of patients is diagnosed with active viremia at the time of starting systemic treatment, and it is therefore relevant to refer these patients for antiviral treatment. Likewise, it is necessary to encourage abstinence in patients with alcohol-related cirrhosis. All in all, this reinforces the importance of a multidisciplinary management that should not just solely be focused on tumour, even in patients with advanced stage HCC.

Although we have identified a group with a high risk of decompensation at 1 year of about 30% (i.e. those with ALBI grade > 1 and non-viral aetiology), we believe that atezolizumab plus bevacizumab should not be denied in these patients, given that this treatment significantly reduces the risk of progression, that is another significant determinant of death, as confirmed by our analysis.

Amongst key limitations of our study, it should be acknowledged that despite accurate attribution of decompensation versus progression outcomes by experienced multi-disciplinary teams in the context of high-volume referral centres for the care of HCC, decompensation and tumour progression often coexist and may be causally interlinked. Therefore, we cannot exclude that progression could have been the main determinant of decompensation in some patients or that radiological schedule of follow-up could have hampered the documentation of progression before the occurrence of decompensation. However, none among tumour-related covariates was able to significantly predict the risk of hepatic decompensation in multivariable analysis, to suggest that for most cases the trajectory of decompensation was independent of tumour progression. A second common hurdle that this study shares with other retrospective observational studies is that the quality of data registration is lower than randomised controlled studies. Particularly, the alcohol-related aetiology may not have been sufficiently accurate in absence of validated questionnaires to assess alcohol consumption and it was only based on self-reported alcohol abuse, as well as the recent introduction of the new nomenclature of steatotic liver disease could have introduced a bias in the correct identification of metabolic aetiology. Moreover, we lack reproducible data on the timing of antiviral treatments before atezolizumab plus bevacizumab initiation – a factor that could have a significant impact on the risk of decompensation during systemic therapy. While demonstrating the importance of successful treatment of viral aetiology of underlying liver disease before initiation of atezolizumab plus bevacizumab can be valuable, the impact of antiviral

treatment during systemic therapy remains unclear, due to the lack of data on the intake of antiviral treatments after initiation of atezolizumab plus bevacizumab. Therefore, this hypothesis needs to be confirmed by prospective studies with pre-planned definition of treatments for different aetiologies of liver disease, both before and after the start of atezolizumab plus bevacizumab.

In conclusion, our study demonstrates that up to 10% of patients can develop hepatic decompensation within six months from atezolizumab and bevacizumab initiation, leading to early mortality.

A pre-treatment ALBI >1 and non-viral aetiology predict for the risk of decompensation, whereas effective antiviral treatment for HBV and HCV infections protects from decompensation.

Taken together, our findings highlight the need for continuous integrated care for cancer and chronic liver disease in advanced HCC management to optimise the handling of complications related to the underlying liver disease and to improve patient outcomes.

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Figure 1. Cumulative incidence of HCC progression and hepatic decompensation in 571 patients with unresectable hepatocellular carcinoma treated with atezolizumab plus bevacizumab as first-line systemic therapy.

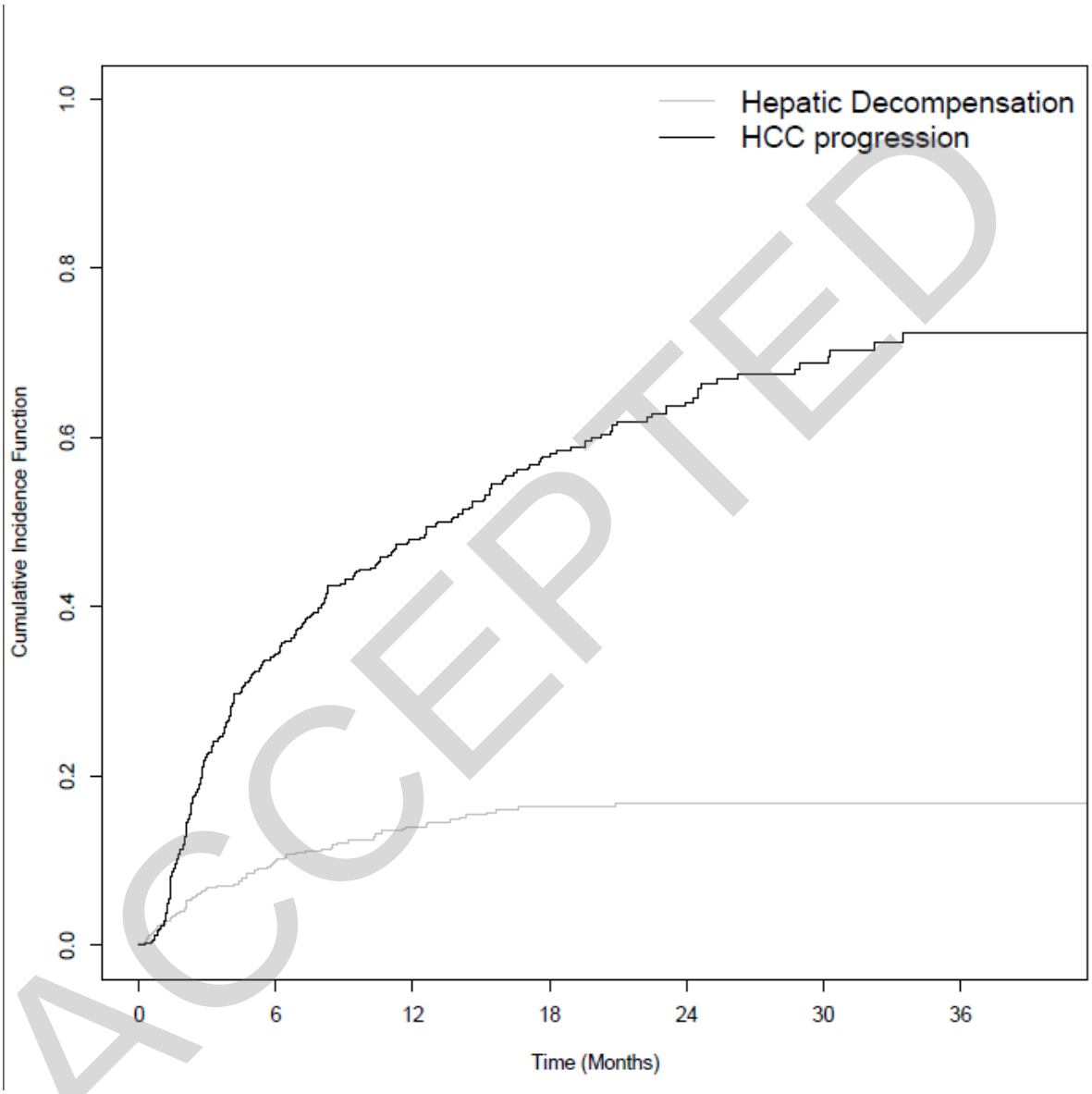


Figure 2. Predictors of death in 571 patients with unresectable hepatocellular carcinoma treated with atezolizumab plus bevacizumab as first-line systemic therapy by multivariable Cox regression analysis.

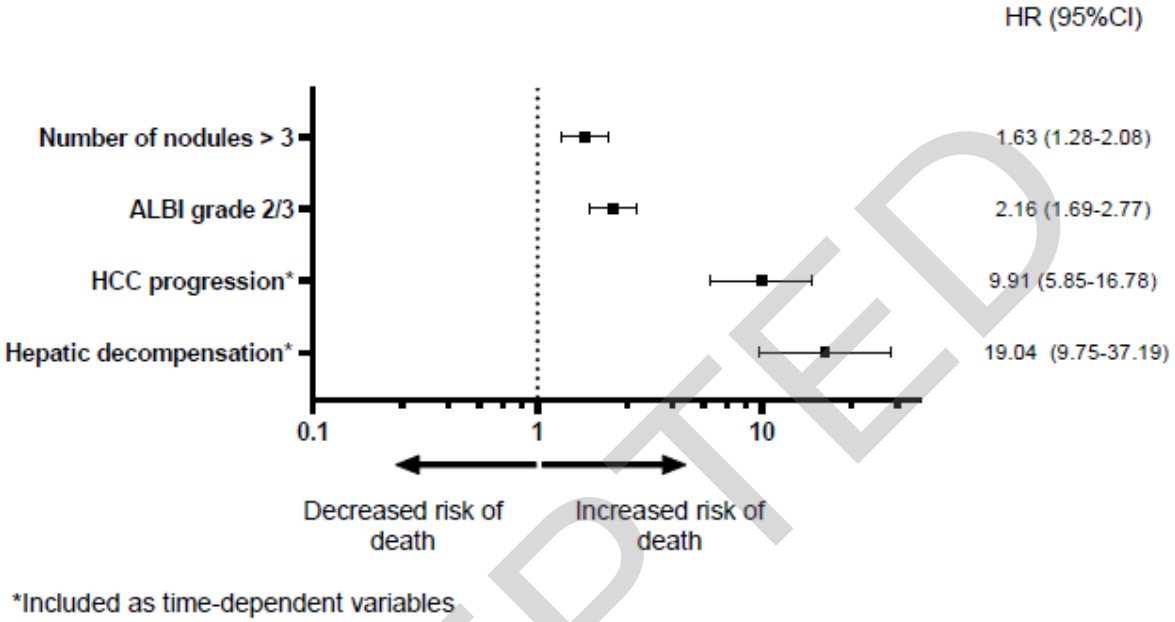


Figure 3. Impact of tumour progression (Panel A) or hepatic decompensation (Panel B) on therapeutic management of 571 patients with unresectable hepatocellular carcinoma treated with atezolizumab plus bevacizumab as first-line systemic therapy.

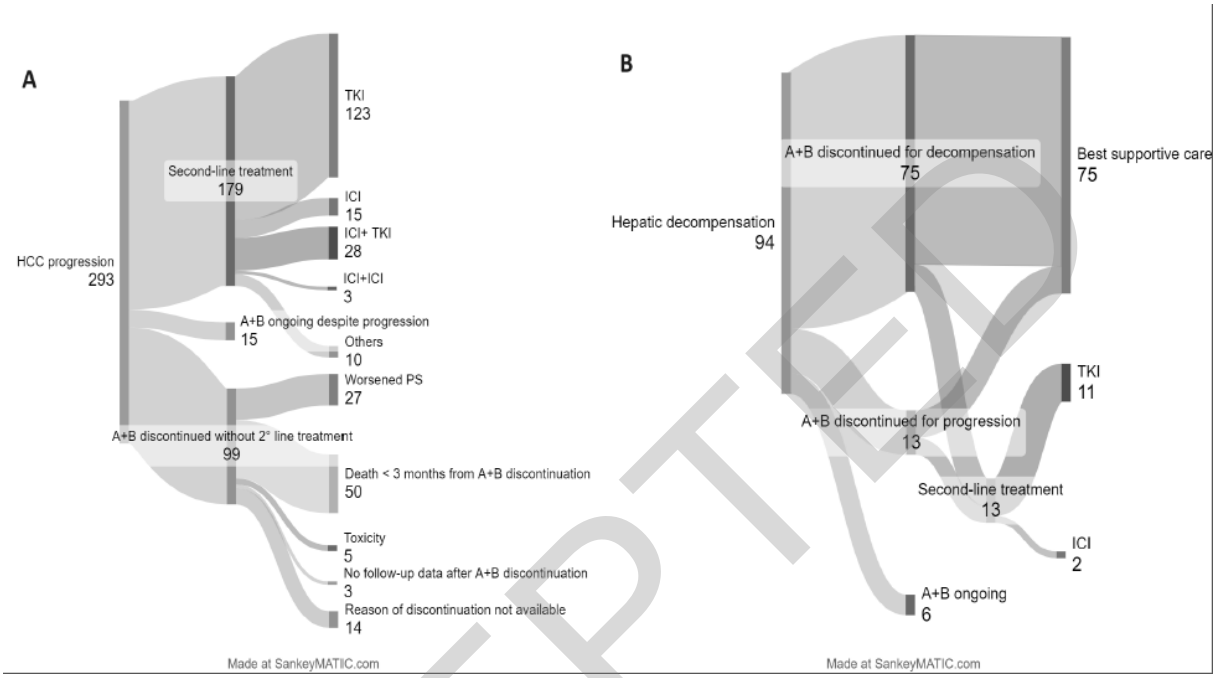


Figure 4. Survival after discontinuation of atezolizumab plus bevacizumab stratified according to the reason of treatment discontinuation (tumour progression versus hepatic decompensation).

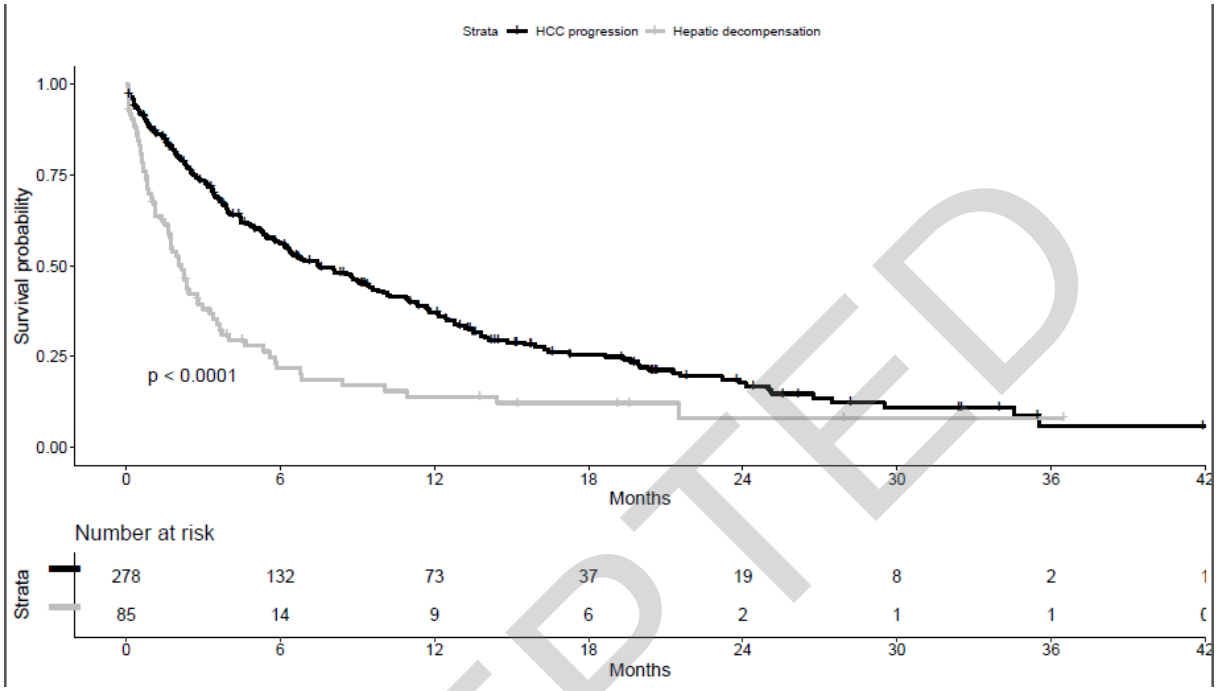


Figure 5. Cumulative incidence function of hepatic decompensation in patients with viral and non-viral aetiology of liver disease by competing risks analysis.

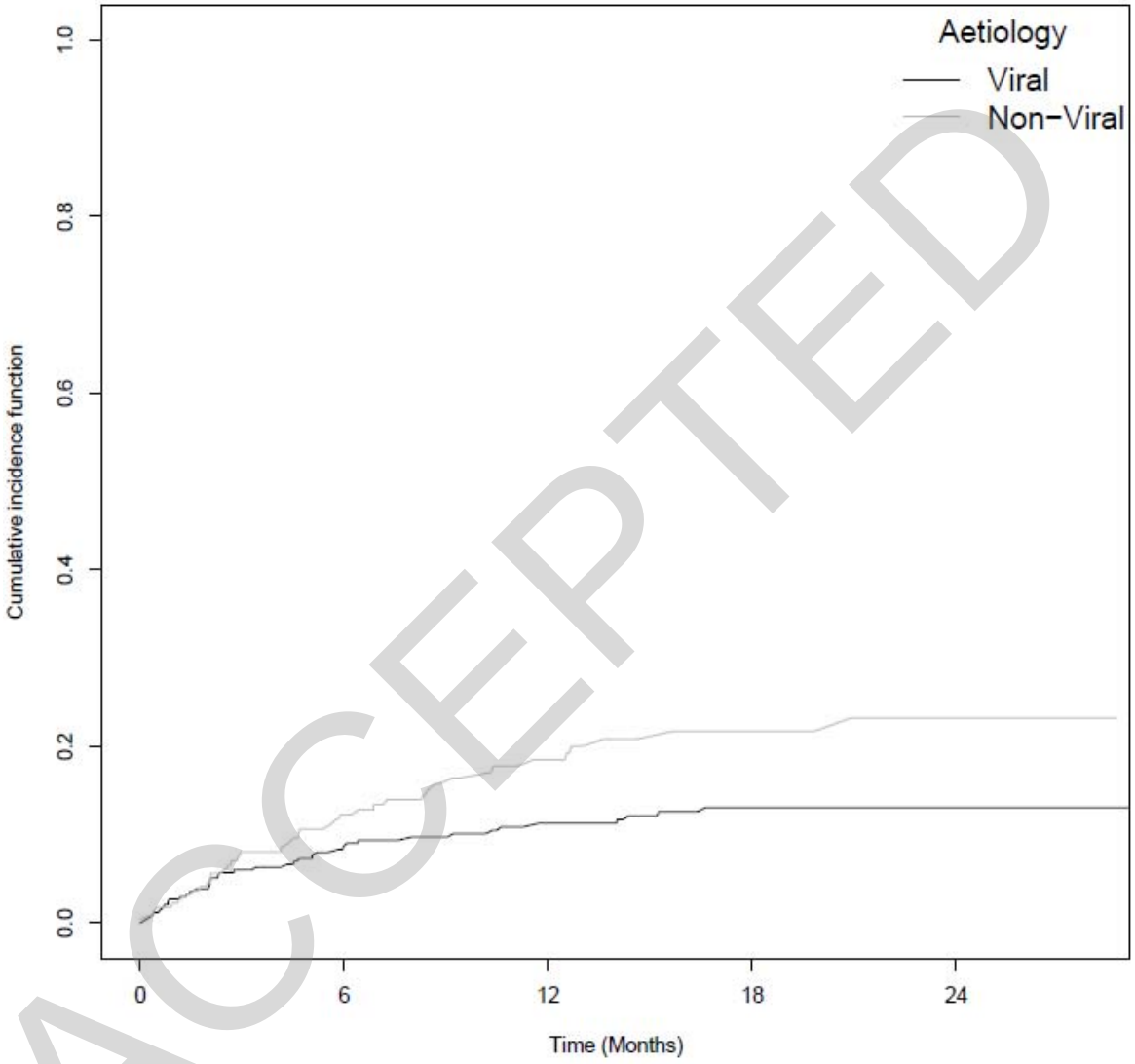
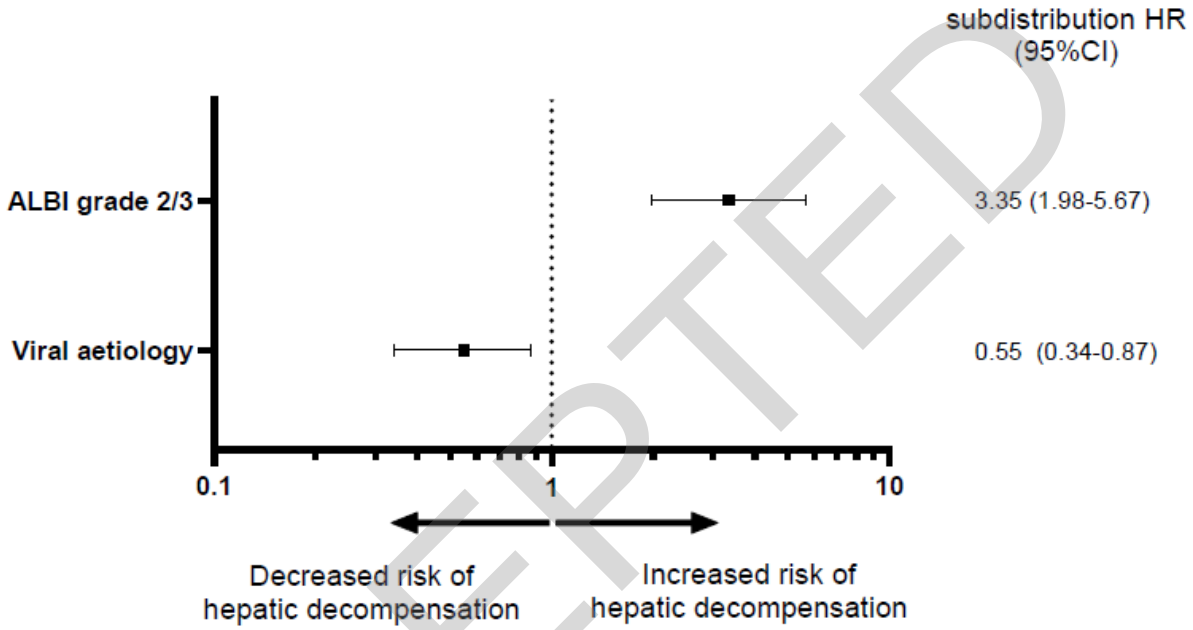


Figure 6. Predictors of hepatic decompensation during atezolizumab plus bevacizumab treatment. Panel A: Forest plot summarising the multivariable competing risks analysis of predictors of hepatic decompensation with subdistribution Hazard Ratios (sHR) and 95% confidence intervals. Panel B: Predicted probabilities of hepatic decompensation according to the combination of significant predictors by multivariable competing risks analysis in two different patient profiles. (Low risk profile: ALBI grade 1, viral aetiology; high risk profile: ALBI grade 2/3, non-viral aetiology).



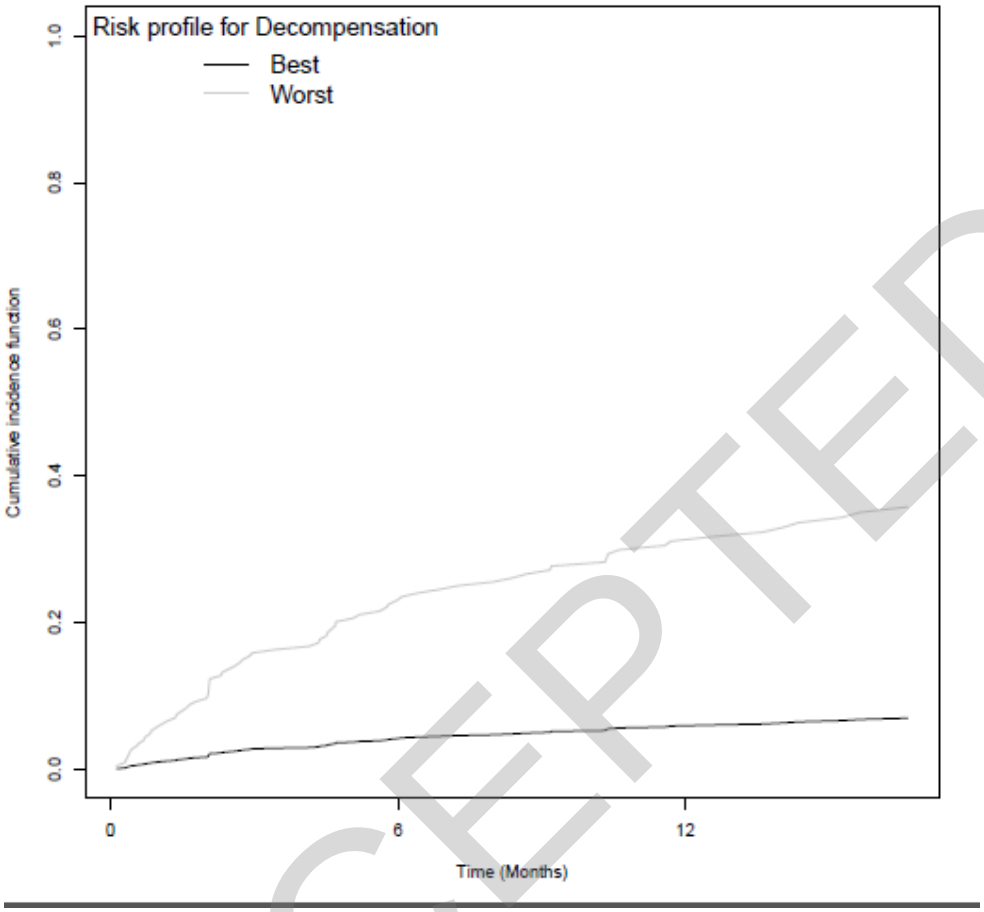


Figure 7. Cumulative incidence function of hepatic decompensation in patients with viral aetiology according to the presence of treated or not treated aetiology.

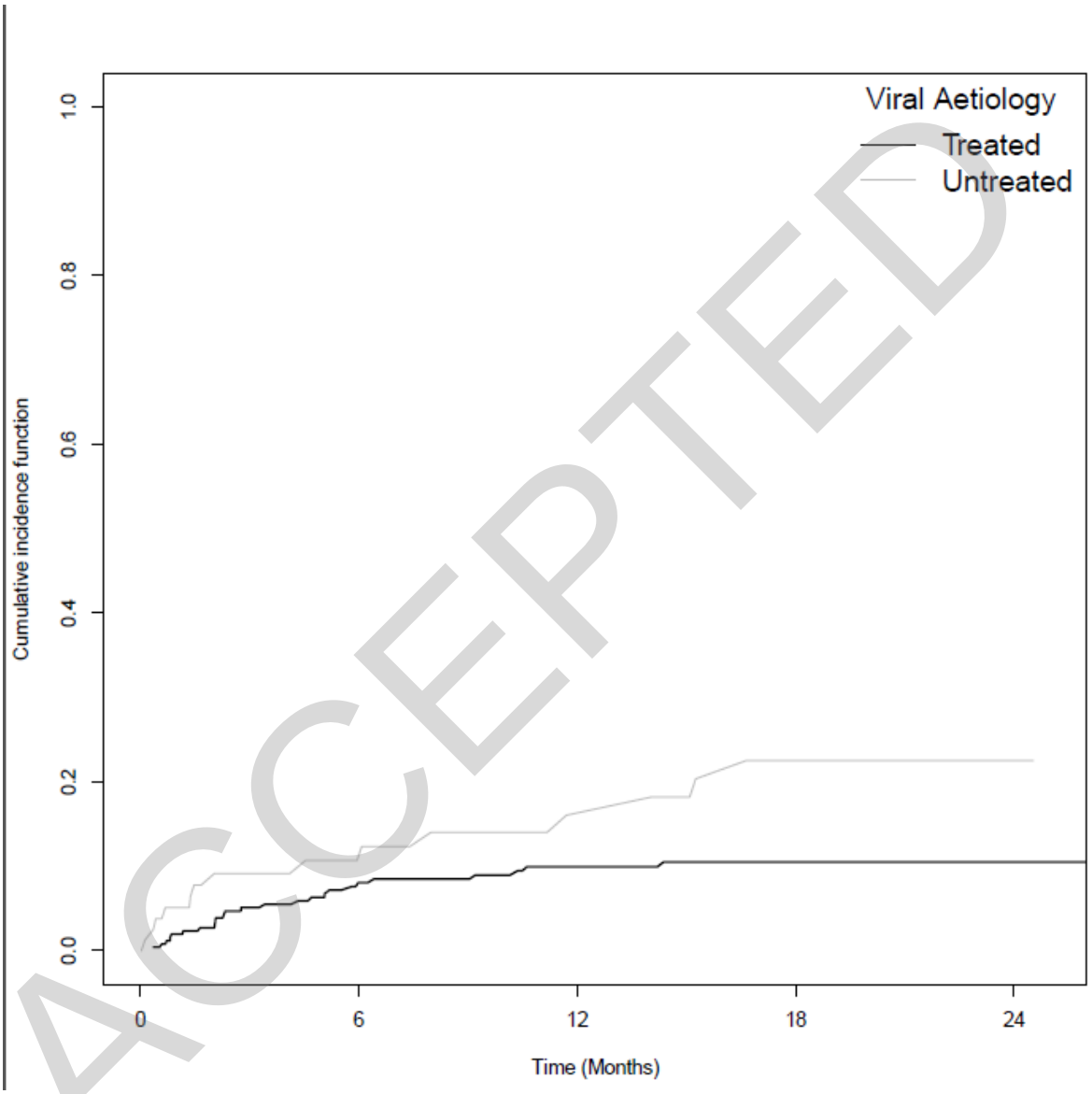


Table 1. Baseline characteristics of 571 patients with unresectable/advanced hepatocellular carcinoma (HCC) treated with Atezolizumab plus Bevacizumab as first-line systemic therapy, stratified according to evolutionary events during follow-up (no HCC progression or decompensation; HCC progression without decompensation; hepatic decompensation with or without HCC progression).

	Overall (N=571)	**No progression or decompensation (n=184, 32.2%)**	**HCC progression without hepatic decompensation (n=293, 51.3%)**	**Hepatic decompensation (n=94, 16.5%)**
Age (years)	66.9±11.6	68.7±11.2	65.5±12.1	67.5±10.6
Male sex	453 (79.2)	144 (78.3)	230 (78.5)	79 (84.0)
Aetiology of liver disease				
HCV alone	122 (21.4)	44 (23.9)	51 (17.4)	27 (28.7)
HBV alone	161 (28.2)	33 (17.9)	111 (37.9)	17 (18.1)
Alcohol alone	78 (13.7)	31 (16.8)	30 (10.2)	17 (18.1)
MASLD alone	72 (12.6)	24 (13.0)	31 (10.6)	17 (18.1)
HCV+alcohol	34 (6.0)	13 (7.1)	18 (6.1)	3 (3.2)
HBV+alcohol	17 (3.0)	5 (2.7)	11 (3.8)	5 (2.7)
HCV+HBV	11 (1.9)	7 (3.8)	3 (1.0)	1 (1.1)
HCV+MASLD	5 (0.9)	1 (0.5)	1 (0.3)	3 (3.2)
MetALD	6 (1.1)	3 (1.6)	2 (0.7)	1 (1.1)
Cryptogenic	65 (11.4)	23 (12.5)	35 (11.9)	7 (7.4)
History of hepatic decompensation	108 (20.5)	31 (18.9)	52 (18.9)	25 (29.1)
NA	45 (7.9)	20 (10.9)	17 (5.9)	8 (8.5)
Grade 1 ascites	84 (14.7)	19 (10.3)	48 (16.4)	19 (20.2)
Oesophageal varices	163 (34.9)	52 (34.4)	69 (28.9)	42 (54.5)
High-risk varices	55 (11.8)	15 (9.9)	23 (9.6)	17 (22.1)
NA	104 (18.2)	33 (17.9)	54 (18.4)	17 (18.1)
Previous treatment with beta-blockers				
Carvedilol	30 (6.7)	10 (7.8)	10 (4.1)	10 (13.3)
Propranolol	59 (13.2)	21 (16.3)	24 (9.9)	14 (18.7)
NA	124 (21.7)	55 (29.9)	50 (17.1)	19 (20.2)
PLT count (10^9/L)	188±101	189±95	193±103	171±109
Albumin (g/L)	38.3±5.1	38.4±4.9	39.2±5.0	35.7±4.8
Bilirubin (mg/dL)	0.9±0.5	0.8±0.5	0.9±0.5	1.1±0.5
INR	1.1±0.2	1.1±0.2	1.1±0.2	1.1±0.1

Creatinine (mg/dL)	0.9±0.3	0.9±0.4	0.8±0.4	1.0±0.7
Child-Pugh score 5 6	 370 (64.8) 201 (35.2)	 125 (67.9) 59 (32.1)	 203 (69.3) 90 (30.7)	 42 (44.7) 52 (55.3)
MELD score	6.6±1.2	6.4±0.9	6.5±1.1	7.1±1.5
ALBI grade 1 2 3	 271 (47.5) 290 (50.8) 10 (1.8)	 87 (47.3) 93 (50.5) 4 (2.2)	 162 (55.3) 126 (43.0) 5 (1.7)	 22 (23.4) 71 (75.5) 1 (1.1)
ALBI score	-2.53±0.52	-2.53±0.56	-2.61±0.48	-2.25±0.44
ECOG-PS 0 1	 332 (58.1) 239 (41.9)	 120 (65.2) 64 (34.8)	 151 (51.5) 142 (48.5)	 61 (64.9) 33 (35.1)
Alphafetoprotein > 400 ng/mL NA	197 (35.9) 23 (4.0)	48 (27.4) 9 (4.9)	113 (40.1) 11 (3.7)	36 (39.6) 3 (3.2)
Major nodule size	6.3±4.4	6.0±4.3	6.4±4.4	6.9±4.2
Number of nodules > 3	306 (53.5)	82 (44.6)	176 (60.0)	48 (51.1)
Neoplastic portal invasion NA	171 (30.6) 13 (2.3)	43 (23.9) 4 (2.2)	93 (32.5) 7 (2.4)	35 (38.0) 2 (2.2)
Extrahepatic disease NA	234 (41.6) 9 (1.6)	72 (40.0) 4 (2.2)	137 (47.2) 3 (1.0)	25 (27.2) 2 (2.1)
BCLC stage A/B C	 150 (26.3) 421 (73.7)	 51 (27.7) 133 (72.3)	 67 (22.9) 226 (77.1)	 32 (34.0) 61 (66.0)

HCC, hepatocellular carcinoma. HCV, hepatitis C virus. HBV, hepatitis B virus. MASLD, metabolic dysfunction-associated steatotic liver disease. MetALD, PLT, platelet. INR, international normalised ratio. MELD, model for end-stage liver disease. BCLC, Barcelona Clinic Liver Cancer. ECOG-PS, Eastern Cooperative Oncology Group-Performance Status. NA, not available.