The albumin-bilirubin grade uncovers the prognostic relationship between hepatic reserve and immune dysfunction in HIV-associated hepatocellular carcinoma.

David J. Pinato[1,2], Rohini Sharma[1,2], Caitlin Citti[2], Heather Platt[2], Meritxell Ventura-Cots[2], Elias Allara[2], Ting-Yi Chen[2], Alessia Dalla Pria[2], Mamta Jain[2], Beatriz Mínguez[2], Luciana Kikuchi[2], Erica Kaufman West[2], Marco Merli[2], David E. Kaplan[2], Hamid Hasson[2], Kristen Marks[2], Mark Nelson[2], Marina Núñez[2], Ayse Aytaman[2], Mark Bower[2], Norbert Bräu[2,3,4]

1. Department of Surgery & Cancer, Imperial College London, Hammersmith Hospital, Du Cane Road, London, United Kingdom.
2. The Liver Cancer in HIV Study Group.
3. James J. Peters Veterans Affairs Medical Center, Bronx, NY, United States.
4. Divisions of Infectious Diseases & Liver Diseases, Mount Sinai School of Medicine, New York, NY, United States.

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To whom correspondence should be addressed:

Dr David James Pinato, MD MRes MRCP (UK) PhD

NIHR Academic Clinical Lecturer in Medical Oncology, Imperial College London Hammersmith Campus, Du Cane Road, W12 0HS, London (UK)

E mail: david.pinato@imperial.ac.uk

Abstract.

Background: Hepatocellular carcinoma (HCC) is a leading cause of liver-related mortality in people living with HIV, where co-infection with hepatotropic viruses accelerates the course of chronic liver disease.

Aims: In this study, we hypothesized whether the albumin-bilirubin (ALBI) grade, a more accurate marker of liver dysfunction in HCC, might identify patients with progressive liver dysfunction in the context of HIV/hepatitis co-infection.

Methods: Using uni- and multivariable analyses, we studied the ALBI grade as a predictor of overall survival (OS) in a large, multi-center cohort of patients with HIV-associated HCC recruited from 44 centres in 9 countries within the Liver Cancer in HIV study group. Patients who underwent liver transplantation were excluded.

Results: A total of 387 patients, predominantly HCV co-infected (78%) with balanced representation of all Barcelona Clinic Liver Cancer (BCLC) stages (A=33%, B=18%, C=37%, D=12%) were recruited. At HCC diagnosis, 84% had been on anti-retrovirals for a median duration of 8.8 years. The ALBI grade identified significant differences in median survival of 97 months for grade 1 (95%CI 13-180 months), 17 months for grade 2 (95% CI 11-22 months) and 6 months for grade 3 (95%CI 4-9 months, $p<0.001$). A more advanced ALBI grade correlated with lower CD4 counts (464/373/288 cells/mm^3 for grades 1/2/3) and higher HIV viraemia (3.337/8.701/61.845 copies/ml for grades 1/2/3, $p<0.001$).

Conclusions: In this large, multi-center retrospective study, the ALBI grade highlights the interplay between liver reserve and immune dysfunction as prognostic determinants in

HIV-associated HCC.

Introduction.

Liver-related morbidity and mortality is rapidly expanding in people living with HIV, as a result of shared transmission modalities between HIV and Hepatitis B (HBV) and C virus (HCV) as well as alcohol abuse, which is associated with HIV risk behaviors[1]. Over the past few decades, the consolidated use of combined antiretroviral therapy (cART) has dramatically changed the pattern of mortality of people living with HIV, where the proportion of deaths from opportunistic infections related to uncontrolled HIV replication has reduced in favor of chronic pathologies including cancer[2].

Hepatocellular carcinoma (HCC), the third most lethal malignancy, most frequently arises in the context of liver cirrhosis, a highly prevalent condition in patients co-infected with HIV and hepatitis[3]. Liver cirrhosis is not merely a predisposing factor but also a key prognostic determinant in patients with HCC, where impairment of liver reserve strongly influences treatment decisions[4].

The most widely adopted system to estimate hepatic impairment in HCC patients is the Child-Turcotte-Pugh classification, which combines objective biosynthetic parameters including circulating albumin, bilirubin and coagulation profile with more subjective prognostic traits including the presence and severity of ascites and encephalopathy[5]. Whilst originally devised as a prognostic tool to estimate post-surgical mortality in cirrhotic patients without HCC[6], the Child-Turcotte-Pugh classification has been subsequently incorporated as a biomarker of liver functional reserve in the vast majority of staging systems for HCC including the Barcelona Clinic Liver Cancer algorithm

(BCLC), the Cancer of the Liver Italian prognostic score (CLIP) and many others[7].

Recent evidence has highlighted potential limitations in the prognostic accuracy of the Child-Turcotte-Pugh classification as a biomarker of liver function. On one hand, it has been argued that the clinical assessment of ascites and encephalopathy might suffer from lack of reproducibility between clinicians[8]. Secondly, the use of pre-determined cut-off values applied to laboratory variables might artificially reduce the ability to capture more subtle changes in liver function that may be of prognostic significance[9].

To overcome these limitations, which can influence optimal treatment allocation in patients with HCC, a novel marker of liver functional reserve based exclusively on circulating albumin and bilirubin levels, the albumin-bilirubin (ALBI) grade, has been proposed as an alternative to the Child-Turcotte-Pugh class[10]. Originally derived from large patients cohorts of HCC patients and cirrhotic controls, the ALBI grade has subsequently been validated in patients of diverse geographical origin and aetiology of chronic liver disease[11-14] and integrated with currently available prognostic algorithms in HCC[15, 16].

However, there is no evidence to support the clinical utility of the ALBI grade in patients diagnosed with HIV-associated HCC, a patient population where the progression of liver fibrosis is characterized by an accelerated course[17].

The aim of this study was therefore to independently validate the prognostic value of the ALBI grade in the setting of a large collaborative study including patients with HIV-associated HCC derived from Liver Cancer in HIV study cohort.

Patients and Methods.

This retrospective study identified all patients diagnosed with HCC on a background of HIV infection in 44 referral centres providing specialist multidisciplinary care for HIV and HCC across 9 countries including United States, Canada, Brazil, Argentina, Germany, Spain, United Kingdom, Italy and Australia (**Supplementary Table 1**). Consecutive referrals in the period between 1992 and 2016 were collected in a joint database as part of an international research consortium using electronic case report forms. Methodology of data collection and clinical outcomes pertaining to a proportion of the patients was published in 2007[18]. All patients had a diagnosis of HCC either on imaging or by histologic criteria according to international guidelines[19]. To avoid incurring in the confounding effect stemming from a fully restored liver function in the prognosis of transplant recipients, patients who underwent liver transplantation were excluded (n=33), leaving a total of 387 patients eligible for analysis.

Medical records at each participating institution were searched to derive complete demographic, staging and treatment data. All the clinical variables were obtained at baseline, defined as the time of HCC diagnosis. HCC staging followed computerized tomography and/or magnetic resonance imaging criteria as clinically required to derive extent of intra and extra-hepatic spread. Computation of the Child-Turcotte-Pugh functional class and BCLC stage followed standard pre-published methodology[20]. The ALBI grade was calculated using the following equation: linear predictor = ($\log_{10}$ bilirubin × 0.66) + (albumin × -0.085), where bilirubin is in µmol/L and albumin in g/L. The continuous linear predictor was further categorised into 3 different grades for prognostic stratification purposes: grade 1 (inferior to -2.60), grade 2 (between -2.60 and -1.39)

and grade 3 (above -1.39) as previously described[10].

The primary clinical endpoint of the study was overall survival (OS), calculated from the date of diagnosis to patients' death and/or last follow-up.

Statistical Analysis.

Continuous variables were presented as median and range, with associations being tested using Mann-Whitney, Kruskal Wallis or Student's t test as appropriate. Categorical variables were presented as frequencies and tested for associations using Chi-square or Fisher's exact test as appropriate. Kaplan-Meier statistics followed by stepwise backward Cox regression was used for uni- and multivariable analyses of survival[21]. We utilised Harrel's concordance index (c-index) method to rank the different prognostic traits according to their predictive ability of discriminating patients according to outcome, comparing actual survival outcomes of usable pairs of patients with the values of their estimated prognostic indices from the corresponding Cox regression model. We adjusted for the overoptimism produced by modelling via comparison with 150 bootstrap samples. For all analyses, the levels of statistical significance accepted was $p<0.05$. Statistical analyses were performed using SPSS package version 20.0 (IBM Inc., USA), R Statistical Computing Environment (R Foundation, Vienna, Austria) and GraphPad PRISM (GraphPad software inc., La Jolla, CA, USA).

Results.

Baseline Patient Characteristics.

Baseline features of the study cohort are presented in **Table 1**. Median OS was 96

months (95%CI 44-150 months) for patients who received potentially curative therapies for HCC (surgical resection, radio-frequency ablation or percutaneous ethanol injection; n=121, 31%) compared to 15 months (95%CI 11-19 months) of patients who exclusively received non-curative treatments (chemo or radioembolisation, systemic therapies; n=123, 32%) and 3.2 months (95%CI 2.4-3.9 months) of patients who received best supportive care (n=143, 37%). The majority of patients had a performance status (PS) of 0 (n=210, 56%) and classified within Child-Turcotte-Pugh class A criteria (n=214, 56%). The mean and median follow-up period was 20 and 12 months respectively, with 216 patients (56%) having died at the time of analysis.

Nearly all patients had virally-induced chronic liver disease (n=377, 97%) with HCV being the leading risk factor in 305 patients (78%). HCV genotype was available in 190 patients (51%), 153 of whom (78%) were of genotype 1. HCV RNA levels at the time of HCC diagnosis were available in 238 patients (74%), with 203 (66%) displaying evidence of detectable viraemia. In the 83 patients with HBV-associated HCC (21%), 44 (53%) had evidence of detectable HBV DNA levels at HCC diagnosis.

The majority of patients were on cART (n=322, 83%) with a median duration of treatment of 8.8 years prior to the diagnosis of HCC. Most patients had undetectable HIV viral load at the time of HCC diagnosis (n=240, 65%) and CD4 counts >200 cells/mm^3 (n=265, 69%). The most prevalent risk factor for HIV infection was intravenous drug use (n=211, 55%).

The prognostic performance of the ALBI grade in HIV-associated HCC.

The ability of the ALBI grade to stratify patients according to OS amongst all patients

(n=387) is shown in **Figure 1**. The median OS in patients with ALBI grade 1 (n=64, 17%) was 97 months (95%CI 13-180 months) compared to 17 months (95% CI 11-22 months) of ALBI grade 2 (n=182, 48%) and 6 months (95%CI 4-9 months, of ALBI grade 3 patients (n=141, 35% p<0.001). Hazard ratios for mortality considering ALBI grade 1 as reference prognostic category was 2.0 (95%CI 1.3-3.3, p=0.002) for ALBI grade 2 and 4.7 (95%CI 2.3-7.5, p<0.001) for ALBI grade 3 (**Figure 1A**).

When stratified according to Child-Turcotte-Pugh class, OS worsened from 27 months (95%CI 14-40) in patients within functional class A (n=215, 56%) to 8 months (95%CI 5-10 months) in B (n=127, 32%) and 2.6 months (95%CI 0.9-4.3 months) in C (n=45, 12%), with HRs for mortality of 2.4 (95%CI 1.8-3.3 p<0.001) for the comparison between class B versus A and 4.3 (95%CI 2.9-6.4, p<0.001) for class C versus A (**Figure 1B**).

We further characterized the prognostic potential of the ALBI grade in patients fulfilling Child-Turcotte-Pugh A criteria (n=215), where median OS ranged from 97 months (95%CI 13-180 months) in ALBI 1 patients to 23 months (95%CI 13-32 months) in ALBI 2 and 8 months in ALBI 3 patients (95%CI 2-14 months, p<0.001, **Figure 1C**). We evaluated the prognostic role of the ALBI grade in relationship to the type of treatment received, confirming its ability to predict for OS in patients receiving radical therapies (n=121) where median OS was 96 months (95%CI 13-179 months) in ALBI 1, 53 months in ALBI 2 (95%CI 30-75 months) and 15 months in ALBI 3 (95%CI 1-31 months, Log rank p<0.001). The ALBI grade preserved its stratification potential in patients receiving palliative treatments for HCC (n=123), where median OS was 10 months (95%CI 8-12 months) in ALBI 1, 7.7 months (95%CI 4.9-10.4 months) in ALBI 2 and 4.5

months (95%CI 3.1-5.8 months) in ALBI 3 patients (Log rank p<0.001).

We verified the value of a number of established prognostic factors in our patient population. The BCLC stage accurately predicted for patients' survival with median OS of 41 months in stage A (95%CI 25-57), 11 months in stage B (95%CI 8-15), 9 months in stage C (95%CI 6-13) and 3 months in stage D (95%CI 0.8-5 months, p<0.001, **Figure 1D**). Other prognostic factors included AFP>400 ng/ml (median OS 27 vs. 5 months, HR 3.2, 95%CI 2.5-4.3, p<0.001), extrahepatic spread (median OS 16 vs. 4 months, HR 2.6, 95%CI 1.9-3.6, p<0.001), CD4 count <200 cells/mm^3 (median OS 5 vs. 17 months, HR 2.0, 95%CI 1.5-2.7, p<0.001), detectable HIV RNA (median OS 7 vs. 18 months, HR 1.8 95%CI 1.4-2.5, p<0.001), detectable HBV DNA (median OS 6 vs. 29 months, HR 2.0 95%CI 1.1-3.7, p=0.015) and provision of active anticancer treatment (median OS 33 vs. 3 months, HR 6.3 95%CI 4.7-8.4, p<0.001).

To establish their independent prognostic value, ALBI grade and Child-Turcotte-Pugh class were tested in multivariable Cox regression models adjusted for BCLC stage. This confirmed the independent ability of the ALBI in predicting for patients' OS **(Table 2)**.

We subsequently investigated the predictive ability of the ALBI grade alone and following adjustment for BCLC stage of the disease using Harrel's c-index. ALBI grade and Child-Turcotte-Pugh class achieved similar predictive accuracy with c-index scores of 0.65 (95%CI 0.61-0.68) and 0.66 (95%CI 0.62-0.69) respectively, whereas BCLC stage achieved higher accuracy in predicting for OS with a c-index value of 0.70 (95%CI 0.66-0.74). Combination of BCLC stage with the ALBI grade improved the prognostic accuracy of the model, with a resulting c-index of 0.73 (95%CI 0.70-0.76).

The relationship between ALBI grade and clinicopathologic features of the disease.

In light of the established relationship between HIV-related immune dysregulation and the progression of chronic liver disease[22], we verified the presence of a correlation between ALBI grade and HIV viraemia and CD4 counts at HCC diagnosis. In 371 patients with evaluable ALBI and HIV RNA levels we found a statistically significant difference in HIV viral load within each ALBI grade with median HIV RNA values of 3337 (95%CI 170-6505) in ALBI 1; 8701 (95%CI 2554-14847) in ALBI 2; and 61845 (95%CI 10723-112968) copies/ml in ALBI 3 patients (Kruskal-Wallis Chi-square 14.2, DF=2, p<0.001, **Figure 2A**). Similarly, we found an inverse correlation between ALBI grade and CD4 counts, with worsening median CD4 cells across patients graded as ALBI 1 (median 464, 95%CI 402-515), ALBI 2 (median 373, 95%CI 339-407) and ALBI 3 (median 288, 95%CI 250-325, Kruskal-Wallis Chi-square 32.4, DF=2, p<0.001, **Figure 2B**). We found no correlation between ALBI grade and HCV RNA levels (p=0.08) or HBV DNA levels (p=0.06) at HCC diagnosis. The ALBI grade maintained its ability in predicting OS in patients with detectable (n=44, median OS not reached, 5.9 months and 2.5 months for ALBI 1, 2 and 3) and undetectable HBV DNA levels (n=39, median OS not reached, 27 months and 10 months for ALBI 1, 2 and 3, Log rank p=0.005).

Discussion.

The incidence of HCC is seven times higher in PLHIV compared to the general population[23]. Despite progressive improvements in the multidisciplinary management of both HIV infection and liver cancer, the burden of HCC has been steadily increasing, having seen a 23-fold prevalence rise in HCV-co-infected patients over the past 20 years[24]. This has been unfortunately mirrored by a consensual increase in mortality, where HCC now accounts as a leading cause of death in this patient group, being responsible for up to 40% of liver-related events[25].

The tumor-promoting properties of HIV exist by virtue of a synergistic oncogenic effect with hepatitis mediated by a faster progression of fibrosis in the context of immune-depression[26], which can be further exacerbated by other co-existing *noxae* including alcohol consumption, cART-induced hepatotoxicity and the presence of an underlying metabolic syndrome[27]. All these factors might not just shape the risk of HCC, but also have a direct impact on the tumour microenvironment once HCC is diagnosed, imposing an additional toll on residual liver function compared to HIV-negative patients.

Building on our observation in large cohorts of patients with HCC of various aetiology and stage[28], we designed this large, collaborative, study to verify whether the prognostic role of the ALBI grade, a novel biomarker of liver function, might extend to patients with concurrent HIV infection, where HCC has been often depicted as carrying a more adverse clinical course[29].

In our consecutive, multi-institutional patient cohort with balanced representation of all

the BCLC stages of the disease, we found that the ALBI grade could effectively stratify patients according to clinically meaningful differences in median OS ranging from 6 to 97 months. Previous studies have established that the key advantage of the ALBI grade stands in an improved prognostic characterization of patients clustering within the better end of the liver functional spectrum. Our results are in support of this view by confirming the capacity of the ALBI grade to sub-stratify individuals within Child-Turcotte-Pugh class A criteria, where an ALBI score of 1 identifies a subset of patients with median survival times of 97 months, a figure that is 4-fold greater compared to that of unselected patients fulfilling class A criteria whose median OS is 27 months.

The improved stratification potential we observed for the ALBI grade holds important ramifications in the management of HIV-associated HCC, where the preserved prognostic ability of the ALBI in patients undergoing curative and palliative therapies confirms the wide clinical applicability of this biomarker. The prognostic dissection of patients fulfilling Child-Turcotte-Pugh class A criteria has been proposed to further optimize management decisions across the various stages of HCC including early stage disease, where ALBI more carefully predicts for post-operative complications[30], as well as in advanced cases, where the ALBI grade correlates with longer survival and increase likelihood to access second-line therapy after sorafenib failure[31].

Whilst it is recognized that HIV status adds a further layer of complexity to the clinical management of patients with HCC[32], previous studies have been inconsistent in addressing the sources of clinical heterogeneity that characterize this special patient population where cancer is often diagnosed at an earlier age[18] due to a shorter interval between infection with HIV/hepatitis and advanced fibrosis[3]. Initial studies comparing

survival outcomes in series of HCC patients matched by HIV status had originally reported a significantly shorter survival in HIV-infected patients, with higher intra and extra-hepatic disease burden and poor liver function emerging as adverse prognostic factors[33]. However, with the diffusion of standardized screening and treatment strategies including adoption of the BCLC staging algorithm from the early 2000s[20], HIV status vanished as an independent prognostic determinant in subsequent studies, where optimal control of HIV infection no longer precluded access to active anticancer treatment in the cART era[34].

Despite not stemming from a comparative case-control study with HIV-negative patients, our results provide an important contribution to the clinico-pathologic characterization of patients with HIV-associated HCC, corroborating the finding that liver functional reserve, as measured by the ALBI grade, is a key prognostic determinant in this patient population.

To further substantiate the leading role of liver functional reserve in dictating patients' survival we evaluated the relationship between the ALBI grade and common quantitative parameters reflecting HIV infection control. Strikingly, we found a highly significant correlation between worsening ALBI grade, higher HIV viraemia and lower peripheral CD4 counts, a finding that highlights the important connection between the progression of HIV infection and that of underlying liver dysfunction in patients with co-existing hepatitis and HCC[35].

Such relationship is of greater consequence in co-infected patients, in whom the poorer survival figures emerged in comparison to HIV-negative controls cannot be solely

explained by the underlying neoplastic disease burden at presentation, which in fact seems to be consistently lower in HIV-positive cases, possibly as a result of different adherence to screening[18, 29]. In the absence of robust molecular biomarkers to predict the prognosis of HCC in the context of HIV infection, our study provides compelling evidence that a routinely available, inexpensive and externally validated biomarker may help clinicians to optimize the prognostic assessment of patients with HCC based on an improved evaluation of liver functional reserve.

Unfortunately, our study lacks longitudinal evaluation of the ALBI grade, which might have been useful to detect prospective treatment-related changes in liver functional reserve. Another important limitation of this study is the lack of longitudinal data on HBV and HCV viraemia and the absence of information about subsequent treatment for HCV in patients who presented with detectable HCV RNA levels. The recent advent of direct-acting antiviral therapies characterized by HCV eradication rates >90%[36] strengthens the importance of evaluating the dynamic changes of the ALBI grade in relationship to antiviral therapy in this patient group, an aim that should be explored in future studies[37].

It is conceivable that the relatively wide recruitment times that characterize our patient cohort might have influenced patients' survival. However, the median OS reported according to BCLC stage and type of treatment reflect survival rates reported in clinical guidelines[38]. Furthermore, in our study, we verified the value of a number of prognostic factors indicative of tumor burden, liver function and HIV infection, confirming a close similarity to previously published patient cohorts[27], to suggest our patient sample to be fully representative of the entire population of HIV-associated HCC. The retrospective design should also be acknowledged as a limitation to our work. However, this study is

- to our knowledge - the largest to report survival outcomes in HIV-associated HCC, where the multi-centre accrual of consecutive, unselected referrals limits the chances of systematic bias.

In conclusion, this study supports the role of the ALBI grade as a prognostic predictor in HIV-associated HCC and warrants prospective validation in future studies. Its prognostic ability spans across all the BCLC stages of the disease and its discriminative power in predicting patients' mortality is equal to routinely available liver functional staging systems such as the Child-Turcotte-Pugh class, with the advantage of relying exclusively on two objective biochemical parameters. The ALBI grade suitably integrates with the BCLC staging algorithm to improve its prognostic ability and is able to reflect hepatocellular damage relating to HIV-related immune dysfunction and active HIV replication, establishing an appealing prognostic relationship between the control of HIV infection and progressive liver dysfunction in patients with cirrhosis and superimposed HCC.

Due to its robust pathophysiological foundations and optimal stratifying features, the ALBI grade deserves verification as a novel prognostic biomarker in prospective clinical studies in a view to potentially incorporate it in routine clinical practice.

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Guarantor of the Article: David James Pinato

Authors Contribution:

Study concept and design: DJP, NB, MB.

Acquisition of data: DJP, CC, HP, MVC, TC, ADP, MJ, BM, LK, EKW, MM, DK, KM, MN, MN, AA, NB.

Analysis and interpretation of data: DJP, EA.

Drafting of the manuscript: DJP

Critical revision of the manuscript for important intellectual content: All the authors.

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Study supervision: DJP, RS, MB, NB.

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Figure Legends.

Figure 1. Kaplan Meier curve analysis showing the effect of the albumin-bilirubin (ALBI) grade as predictor of overall survival in the entire patient cohort of patients with HIV-associated HCC (**Panel A**), in comparison with the Child-Turcotte Pugh (CTP) class (**Panel B**). **Panel C** shows the difference in survival according to the ALBI grade in a subset of patients with Child-Turcotte Pugh class A cirrhosis (n=215). **Panel D** illustrates the prognostic classification of patients according to the Barcelona Clinic Liver Cancer (BCLC) staging system.

Figure 2. The relationship between the albumin-bilirubin (ALBI) grade and HIV RNA levels measured at HCC diagnosis (**Panel A**). **Panel B** illustrates median CD4 cell count at HCC diagnosis categorized according to ALBI grade. An asterisk (*) marks a level of $p<0.05$.

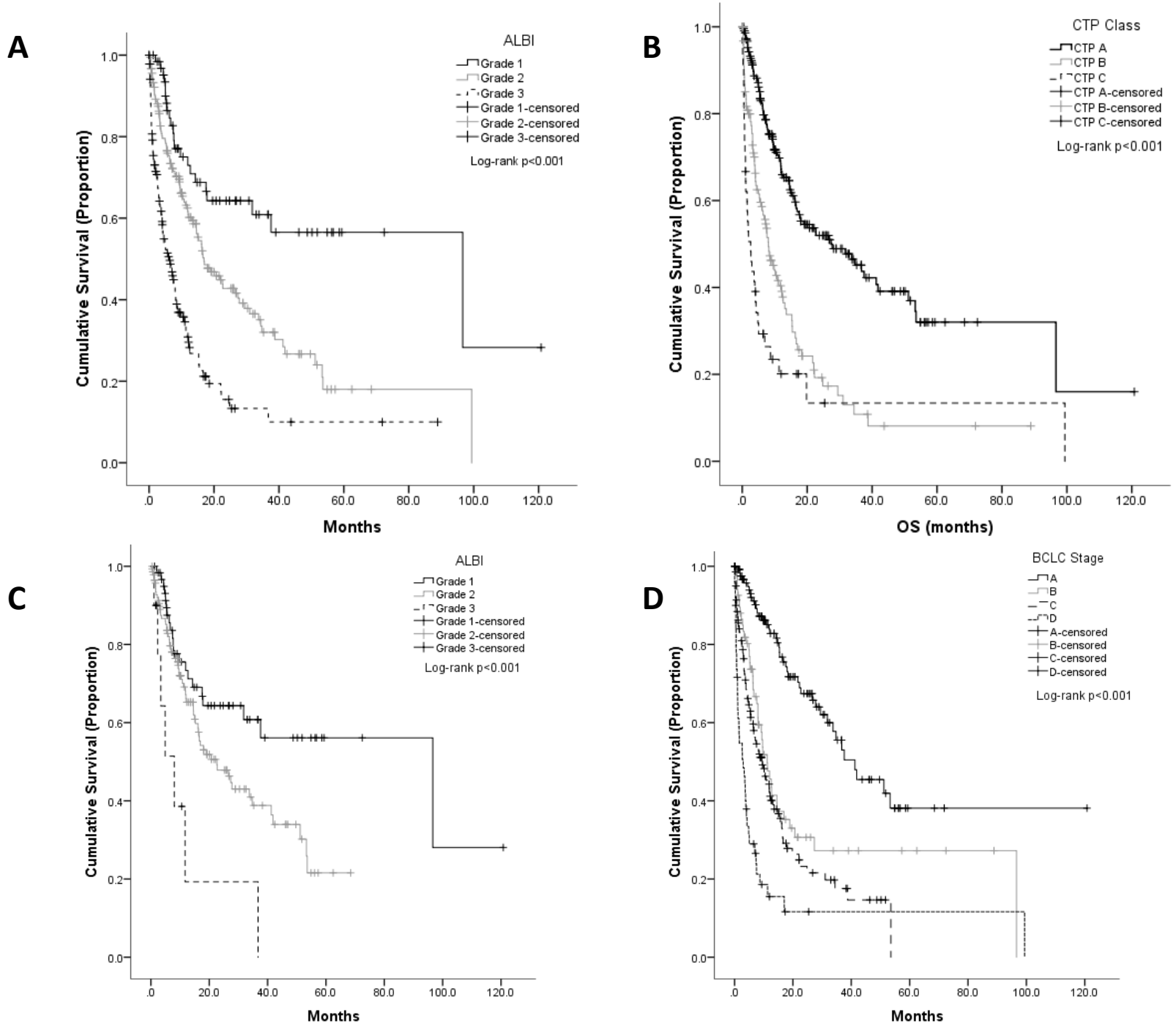
Characteristic	N=387 (%)
Age in years, median (range)	54 (28-74)
Gender	
Male	355 (92)
Female	32 (8)
Geographical Origin	
North and South America	290 (75)
Europe	96 (24)
Australia	1 (1)
Viral etiology of liver disease	
Hepatitis B virus infection	83 (21)
Hepatitis C virus infection	305 (78)
Alcohol Excess	
Absent	289 (75)
Present	98 (25)
AFP	
<400 ng/ml	239 (65)
>400 ng/ml	141 (34)
Albumin, g/L Median (range)	35 (3-52)
Bilirubin, umol/L Median (range)	18 (4-643)
AST* (IU/L) Median (range)	81 (12-623)
ALT (IU/L) Median (range)	55 (9-299)
INR Median (range)	1.1 (0.9-2.4)
Platelet count, Median (range)	127 (15-635)
Child-Turcotte Pugh Score	
A	215 (56)
B	127 (32)
C	45 (12)
Albumin-bilirubin Grade	
1	64 (17)
2	182 (48)
3	141 (35)
Intrahepatic spread	
Unifocal	199 (51)
Multifocal (< 50% of liver replacement)	105 (27)
Massive (>50% of liver replacement)	83 (21)
Maximum diameter of largest lesion (cm) Median (range)	4.0 (1-20)
Extrahepatic spread	
Absent	327 (85)
Present	60 (15)
Portal Vein Involvement	
Absent	306 (80)
Present	81 (20)
**Performance Status ** **	
0	210 (56)
1	98 (26)
2	43 (11)
>2	22 (6)

BCLC Stage	
A	126 (33)
B	68 (18)
C	143 (37)
D	50 (12)
CLIP Score	
0-1	179 (46)
≥2	208 (54)
Number of treatment lines for HCC	
0	140 (37)
1	187 (48)
≥2	58 (15)
Type of treatments for HCC	
Surgical resection	59 (14)
Radiofrequency Ablation	58 (14)
Percutaneous Ethanol Injection	14 (4)
Transarterial chemoembolization	130 (34)
Radioembolization	9 (2)
Sorafenib	40 (10)
Other systemic therapies	7 (2)
Risk factor for HIV	
Intravenous drug use	211 (55)
MSM contact	52 (13)
Heterosexual contact	48 (13)
Blood products	14 (4)
Unknown	63 (16)
On cART at HCC diagnosis	
Yes	322 (84)
No	52 (13)
Missing data	13 (3)
Duration of HIV treatment in years, median (range)	8.8 (0-27)
HIV RNA	
Undetectable	240 (62)
Detectable	131 (34)
Missing data	16 (4)
CD4 count, cells/mm^3	
Median (range)	330 (5-1423)

*AST available on 361 patients.

** PS available on 373 patients.

Figure 1.


A
ALBI
Grade 1
Grade 2
Grade 3
Grade 1-censored
Grade 2-censored
Grade 3-censored
Log-rank p<0.001
Cumulative Survival (Proportion)
Months
B
CTP Class
CTP A
CTP B
CTP C
CTP A-censored
CTP B-censored
CTP C-censored
Log-rank p<0.001
Cumulative Survival (Proportion)
OS (months)
C
ALBI
Grade 1
Grade 2
Grade 3
Grade 1-censored
Grade 2-censored
Grade 3-censored
Log-rank p<0.001
Cumulative Survival (Proportion)
Months
D
BCLC Stage
A
B
C
D
A-censored
B-censored
C-censored
D-censored
Log-rank p<0.001
Cumulative Survival (Proportion)
Months