original report

Influence of HIV Infection on the Natural History of Hepatocellular Carcinoma: Results From a Global Multicohort Study

David J. Pinato, MD, PhD[1]; Elias Allara, MD[1,2]; Ting-Yi Chen, MD, MPH[3]; Franco Trevisani, MD[4]; Beatriz Minguez, MD, PhD[5]; Marco Zoli, MD[4]; Marianne Harris, MD[6]; Alessia Dalla Pria, MD[7]; Nicolás Merchante, MD, PhD[8]; Heather Platt, MD[9]; Mamta Jain, MD, MPH[10]; Eugenio Caturelli, MD[11]; Luciana Kikuchi, MD[12]; Juan Pineda, PhD[8]; Mark Nelson, MBBS[7]; Fabio Farinati, MD[13]; Gian Ludovico Rapaccini, MD[14]; Ayse Aytaman, MD[15]; Michael Yin, MD[16]; Chee-Kiat Tan, MBBS[17]; Mark Bower, MD, PhD[7]; Edoardo G. Giannini, MD, PhD[18]; Norbert Bräu, MD, MBA[19,20]; and the Liver Cancer in HIV and ITA.LI.CA Study Groups

abstract

PURPOSE Conflicting evidence indicates that HIV seropositivity may influence the outcome of patients with hepatocellular carcinoma (HCC), a leading cause of mortality in people with HIV. We aimed to verify whether HIV affected the overall survival (OS) of patients with HCC, independent of treatment and geographic origin.

PATIENTS AND METHODS We designed an international multicohort study of patients with HCC accrued from four continents who did not receive any anticancer treatment. We estimated the effect of HIV seropositivity on patients' OS while accounting for common prognostic factors and demographic characteristics in uni- and multivariable models.

RESULTS A total of 1,588 patients were recruited, 132 of whom were HIV positive. Most patients clustered within Barcelona Clinic Liver Cancer (BCLC) C or D criteria (n = 1,168 [74%]) and Child-Turcotte-Pugh (CTP) class B (median score, 7; interquartile range [IQR], 3). At HCC diagnosis, the majority of patients who were HIV-positive (n = 65 [64%]) had been on antiretrovirals for a median duration of 8.3 years (IQR, 8.59 years) and had median CD4$^+$ cell counts of 256 (IQR, 284) with undetectable HIV RNA (n = 68 [52%]). OS decreased significantly throughout BCLC stages 0 to D (16, 12, 7.5, 3.1, and 3 months, respectively; $P < .001$). Median OS of patients who were HIV-positive was one half that of their HIV-uninfected counterparts (2.2 months [bootstrap 95% CI, 1.2 to 3.1 months] *v* 4.1 months [95% CI, 3.6 to 4.4 months]). In adjusted analyses, HIV seropositivity increased the hazard of death by 24% ($P = .0333$) independent of BCLC ($P < .0001$), CTP ($P < .0001$), α-fetoprotein ($P < .0001$), geographical origin ($P < .0001$), and male sex ($P = .0016$). Predictors of worse OS in patients who were HIV-positive included CTP ($P = .0071$) and α-fetoprotein ($P < .0001$).

CONCLUSION Despite adequate antiretroviral treatment, HIV seropositivity is associated with decreased survival in HCC, independent of stage, anticancer treatment, and geographical origin. Mechanistic studies investigating the immunobiology of HIV-associated HCC are urgently required.

J Clin Oncol 37:296-304. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third-largest cause of cancer-related mortality on a global scale.[1] As a recognized complication of liver cirrhosis, which predates the onset of cancer in more than 80% of incident cases, HCC is characterized by a wide prognostic heterogeneity because of the combined influence of etiology and severity of underlying chronic liver disease and the extent of spread of malignancy.[2] In people living with HIV (PLHIV), the high prevalence of coinfection with hepatitis B virus (HBV) and C virus (HCV) has made HCC a rapidly increasing cause of morbidity and mortality, currently accounting for more than 40% of liver-related deaths.[3]

The relative contribution of HIV to the pathogenesis and prognosis of HCC has been the focus of intense debate. Mechanistic evidence suggests that HIV-mediated impairment of antiviral CD4$^+$ and CD8$^+$ T-cell responses facilitates an accelerated progression of chronic liver disease to fibrosis and ultimately malignancy.[4] However, more recent evidence has highlighted how other factors, including increased oxidative stress from combination antiretroviral therapy (cART),[5] HIV-associated gut dysbiosis,[6] and the high prevalence of excessive alcohol intake in this patient population,[7] might exert a synergistic carcinogenic role independent of the achievement of immune reconstitution by optimal HIV control.

Clinical studies have been fairly inconsistent in addressing the question of whether HIV infection might worsen the clinical course of HCC, with some providing null results and others suggesting evidence of association.[8-10] The reasons behind the nonuniform conclusions regarding this prognostic relationship are to be found in the low quality of the available evidence,

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on November 4, 2018, and published at jco.org on December 18, 2018: DOI https://doi.org/10.1200/JCO.18.00885

mostly flawed by the retrospective, single-center design of the majority of studies.[11] An important source of bias affecting the currently available evidence emerges from the geographic diversity in the provision of active anticancer treatment, which can, in turn, lead to profound differences in clinical outcomes.

The marked heterogeneity in survival outcomes within each Barcelona Clinic Liver Cancer (BCLC) stage is a renowned feature of HCC[12,13] and is even broader in PLHIV, where attainment of long-term HIV control, polypharmacy, and socioeconomic factors might influence access and eligibility to treatment, hence influencing patients' survival independent of any true immunobiologic effect of HIV.[14] Understanding whether HIV carries an independent effect on the clinical history of HCC irrespective of treatment is an important unmet need, with significant ramifications in the definition of screening, diagnosis, and treatment algorithms personalized to the needs and clinical features of this patient population.[11]

To address this issue and to overcome the limitations of previous studies, we designed this large collaborative global study to include patients from cohorts from four continents. As a primary objective, we aimed to estimate the effect of HIV status on the overall survival (OS) of untreated patients with HCC while accounting for common prognostic factors. As a secondary objective, we aimed to characterize prognostic factors among a subset of patients who were HIV-positive with untreated HCC.

PATIENTS AND METHODS

Study Population

We established a global consortium of tertiary referral centers located in North and South America and Europe to access prospectively collected cohorts of patients who were HIV-positive and HIV-negative with untreated HCC (Fig 1). This multicenter effort led to the accumulation of more than 1,500 patients, resulting in, to our knowledge, the largest observational investigation conducted to date into the effect of HIV infection among patients with HCC.

Consecutive patient data were collected as part of routine clinical care. Patients who were clinical trial participants were not selected. HCC diagnosis was based on imaging or on histologic criteria according to international guidelines.[15]

The Liver Cancer in HIV data set study identified all patients diagnosed with HCC on a background of HIV infection in 44 referral centers providing specialist multidisciplinary care for HIV and HCC across nine countries: the United States, Canada, Brazil, Argentina, Germany, Spain, the United Kingdom, Italy, and Australia. Consecutive referrals in the period between 1992 and 2016 were collected using electronic case report forms in a joint database as part of an international research consortium. At the last database update, a total of 387 patients who were HIV-positive were identified[16]; this data set was merged with a separate data set of 226 HIV-negative controls from four centers in the United States.[17]

The Italian Liver Cancer (ITA.LI.CA.) data set is a multicenter Italian collaborative network that has, to date, curated and prospectively maintained data on more than 5,000 consecutive patients evaluated in 24 tertiary referral centers for the assessment and treatment of HCC between the years 1988 and 2012. Before statistical analysis, the consistency of the data was checked by the ITA.LI.CA. study coordinator (F.T.). Outcomes pertaining to a proportion of the patients presented here were published in

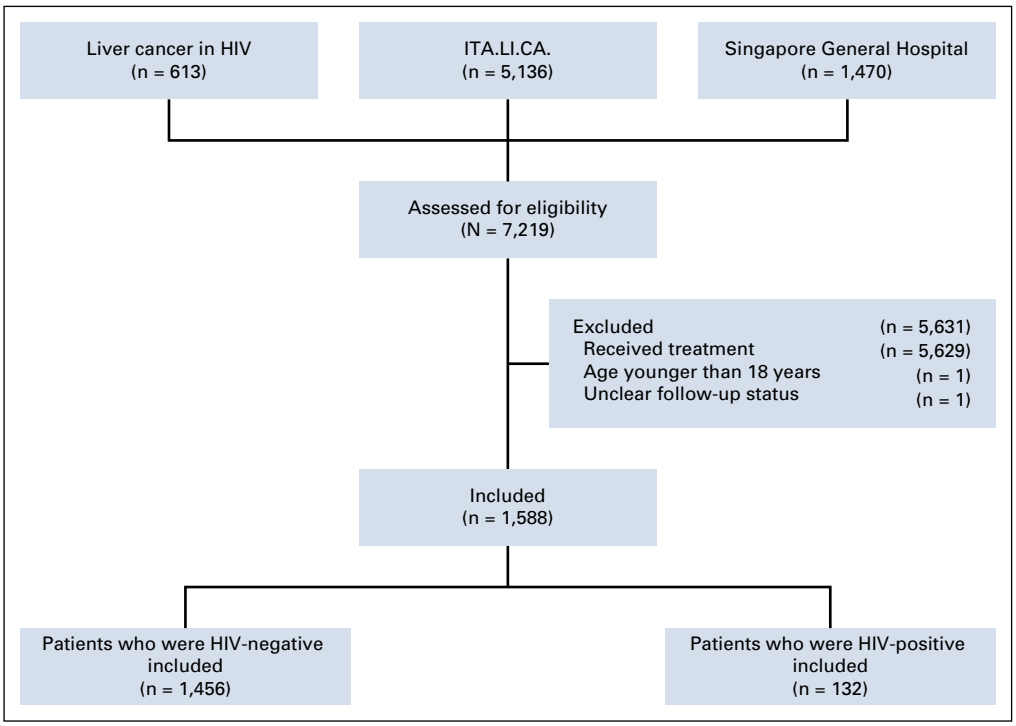

FIG 1. Patient accrual to the study. ITA.LI.CA., Italian Liver Cancer.

2015.[18] As a separate cohort, we assessed for eligibility 1,470 patients with HCC who were diagnosed at the Department of Gastroenterology and Hepatology in the Singapore General Hospital, a tertiary-level medical center in Singapore and were listed in a prospectively maintained HCC registry starting in January 1988.[19]

The primary clinical end point of the study was OS, calculated from the date of diagnosis to the date of death and/or last follow-up. Of the initial sample of 1,590 patients, we removed one patient with unclear follow-up status and one patient who was younger than 18 years of age.

For the full data set of 1,588 patients, we reconstructed demographic data, complete blood count including liver function tests, α-fetoprotein (AFP), and the international normalized ratio value for prothrombin time from electronic medical records. We staged patients using computerized tomography and/or magnetic resonance imaging as clinically required to derive the number of focal hepatic lesions and maximum tumor diameter detected during contrast enhancement. Computation of Child-Turcotte-Pugh (CTP) functional class and BCLC stage followed standard prepublished methodology.[20]

We further characterized the subset of 132 patients who were HIV-positive in terms of prior antiretroviral treatment, time from HCC to cART initiation, $CD4^+$ T-cell count, HIV viral load, hepatitis antigens and antibodies, and risk factors for HIV infection. The study protocol was approved by the institutional review board or ethics committee in each participating institution and was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

We explored the distribution of continuous variables with median and interquartile ranges and tested differences in medians using Mann-Whitney tests. We tabulated categorical variables and tested for differences in proportions using Pearson's χ^2 tests. We plotted the OS function by HIV status and potential prognostic factors using Kaplan-Meier curves. Before conducting Cox regression analyses, we checked the proportional hazards assumption with log-likelihood ratio tests of relevant predictors over time bands. There was no evidence of violation at the 5% level of the proportional hazards assumption for the main predictor (HIV status; $P = .0870$). For the predictors for which the proportional hazards assumption did not hold, we explicitly accounted for time-dependent effects by adding interaction terms with time bands in all regression analyses.[21] We imputed missing data using a multiple imputation with chained equations approach, assuming that the data were missing at random. Details are included in the Data Supplement.

To select the main prognostic factors, we applied a backward selection algorithm to the imputed data sets (Data Supplement). In the full data set (N = 1,588), backward selection identified the following prognostic factors associated with OS at the 5% significance level: HIV, sex, BCLC stage, CTP class, log-transformed AFP, and continent (a binary variable coded as North or South America and Asia *v* Europe). In the subset of patients who were HIV-positive (n = 132), two prognostic factors were associated with OS: CTP class and log-transformed AFP. We re-added common prognostic factors for HCC and HIV so that the final model for the subset of patients who were HIV-positive included CTP class, log-transformed AFP, BCLC stage, log-transformed HIV viral load, $CD4^+$ concentration, and continent.

All reported *P* values are two sided. We performed all analyses in R v.3.4.4, with the following packages: survival v.2.42, mice v.3.0.0, and ggplot2 v.2.2.1.

RESULTS

Baseline Patient Characteristics

A total of 132 patients who were HIV-positive and 1,456 who were HIV-negative were included in the study. Baseline features of the study cohort, stratified according to HIV seropositivity, are presented in Table 1. On average, patients who were HIV-positive were younger (52.9 *v* 66 years, $P < .0001$), were more commonly male (94.7% *v* 81.9%, $P = .0003$), and had a higher prevalence of HCV-related chronic liver disease (78% *v* 37.1%, $P < .0001$) compared with patients who were HIV-negative. Staging by BCLC criteria ($P = .93$) and liver functional reserve by CTP class ($P = .34$) was not different across groups; however, patients who were HIV-positive had lower albumin (31 *v* 29 g/L, $P < .0001$) and higher ALT (56 *v* 47, $P = .0014$) and AST (128 *v* 95, $P = .0005$) levels. The majority of patients had a performance status of 1 (n = 534 [33.6%]) and were classified within CTP class B criteria across HIV negativity and HIV positivity (median score, 7; interquartile range, 3). None of the patients infected with HCV from the ITA.LI.CA. or Singapore General Hospital data sets had previously been treated successfully for HCV. In terms of anti-HBV treatment, 17 HBV carriers (2.4%) from Singapore and all the Italian patients with chronic HBV (16% of the ITA.LI.CA. data set) were receiving nucleoside analog therapy.

In the HIV-positive subset, 103 patients (78%) had HCV infection. Three patients (2.9%) had received treatment with interferon-based regimens before HCC diagnosis, and all were nonresponders. HCV genotype was available in 53 patients (40.2%), 45 of whom (84.9%) were of genotype 1, three (5.7%) of genotype 2, and five (9.4%) of genotype 3. HCV RNA levels at the time of HCC diagnosis were available in 60 patients (45.5%), with 52 (86.7%) showing evidence of detectable viremia. In the 33 patients with HBV-associated HCC (25%), 12 (36.4%) had evidence of detectable HBV DNA levels at HCC diagnosis, and 13 (39.4%) had received treatment for HBV infection. The majority of patients with HIV were receiving cART (n = 85 [64.4%]), with a median duration of treatment of 8.3 years before the

TABLE 1. Clinicopathologic Features of Patients With Untreated Hepatocellular Carcinoma

Characteristics	HIV− (n = 1,456)	HIV+ (n = 132)	*P*
Age, years, median (IQR)	66.0 (15.79)	52.9 (10.88)	< .0001*
Male sex	1,193 (81.9)	125 (94.7)	.0003†
Continent: North or South America and Asia	861 (59.1)	97 (73.5)	.0017†
Viral etiology of liver disease			
HBV	665 (45.7)	33 (25.0)	< .0001†
HCV	540 (37.1)	103 (78.0)	< .0001†
Alcohol etiology of liver disease	370 (25.4)	45 (34.1)	.9112 †
AFP, μg/L, median (IQR)	351.0 (6,878.00)	660.0 (9,949.50)	.1116 *
Albumin, g/L, median (IQR)	31.0 (9.00)	29.0 (10.00)	< .0001*
Bilirubin, μmol/L, median (IQR)	27.4 (32.49)	26.4 (42.75)	.7675*
ALT, IU/L, median (IQR)	47.0 (44.00)	56.0 (56.75)	.0014*
AST, IU/L, median (IQR)	95.0 (100.00)	128.0 (111.00)	.0005*
Platelets, 10^9 cells/L, median (IQR)	149.0 (138.75)	129.0 (149.50)	.0675*
Performance status			
0	431 (29.6)	55 (41.7)	.0048†
1	502 (34.5)	32 (24.2)	
2	292 (20.1)	18 (13.6)	
3	116 (8.0)	14 (10.6)	
4	29 (2.0)	5 (3.8)	
BCLC stage			
0	15 (1.0)	2 (1.5)	.9323†
A	158 (10.9)	17 (12.9)	
B	191 (13.1)	16 (12.1)	
C	699 (48.0)	62 (47.0)	
D	372 (25.5)	35 (26.5)	
CTP score, median (IQR)	7.0 (3.00)	7.0 (3.00)	.4245*
CTP class			
A	499 (34.3)	40 (30.3)	.3435†
B	610 (41.9)	59 (44.7)	
C	288 (19.8)	33 (25.0)	
Maximum diameter of largest lesion, cm, median (IQR)	4.8 (5.00)	5.5 (5.25)	.0493 *
Extrahepatic disease	604 (41.5)	37 (28.0)	.0035†
Portal vein thrombosis	536 (36.8)	47 (35.6)	.3940†
Multinodular disease	738 (46.5)	67 (50.8)	.6947†
On antiretroviral treatment	—	85 (64.4)	—
Duration of antiretroviral treatment, years, median (IQR)		8.3 (8.59)	
Antiretroviral regimen			
PI	—	35 (26.5)	—
NNRTI	—	25 (18.9)	—
NRTI	—	16 (12.1)	—
INI	—	5 (3.8)	—
NNRTI + INI	—	1 (0.8)	—
INI + PI	—	1 (0.8)	—

(continued on following page)

TABLE 1. Clinicopathologic Features of Patients With Untreated Hepatocellular Carcinoma (continued)

Characteristics	HIV− (n = 1,456)	HIV+ (n = 132)	P
Risk factor for HIV			
Intravenous drug use	—	66 (50.0)	—
Heterosexual contact	—	14 (10.6)	—
Homosexual contact	—	10 (7.6)	—
Blood products	—	3 (2.3)	—
Unknown	—	25 (18.9)	—
CD4+ cell count, cells/μL, median (IQR)	—	256.0 (284.00)	—
Undetectable HIV viral load	—	68 (51.5)	—
Undetectable HBV DNA	—	6 (4.5)	—
Undetectable HCV RNA	—	8 (6.1)	—
HCV genotype			
1	—	45 (34.1)	—
2	—	3 (2.3)	—
3	—	5 (3.8)	—

NOTE. Values are No. (%) unless otherwise indicated. The sum of percentages may be less than 100% owing to missing data.

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV+, HIV positive; HIV−, HIV negative; INI, integrase inhibitor; IQR, interquartile range; NNRTI, nonnucleoside reverse transcription inhibitor; NRTI, nucleoside reverse transcription inhibitor; PI, protease inhibitor.

*Mann-Whitney test.

†Pearson's χ^2 test.

diagnosis of HCC. Most patients had an undetectable HIV viral load at the time of HCC diagnosis (n = 68 [51.5%]) and CD4 counts greater than 200 cells/μm (n = 71 [53.8%]). The most prevalent risk factor for HIV infection was intravenous drug use (50%).

Relationship Between HIV and Survival of HCC

Kaplan-Meier curves (Fig 2) revealed strong evidence of unadjusted lower survival for patients who were HIV-positive compared with HIV-negative participants in the full sample of 1,588 patients with HCC (log-rank $P < .0001$). Median OS for the whole study cohort was 4 months (bootstrap 95% CI, 3.8 to 4.1 months), with BCLC stage-specific median survivals of 16, 12, 7.5, 3.1, and 3 months for stages 0, A, B, C, and D, respectively. At the time of analysis, 1,428 patients (89.9%) had died. In the HIV-positive cohort, no deaths could be attributed to HIV infection.

After adjustment for common prognostic factors and multiple imputation of missing data, HIV infection was independently associated with a 24% greater hazard of death (95% CI, 2% to 52%; $P = .0333$; Table 2). Other prognostic factors independently associated with OS were male sex ($P = .0016$), BCLC stage, CTP class, AFP, and geographical origin (all $P < .0001$). As expected, the adjusted effects estimated in complete-case analyses (Data Supplement) were similar in size and direction to the multiple imputation analysis.

Prognostic Factors for OS in HIV-Associated HCC

In the subset of 132 patients with HIV infection, multivariable analyses after multiple imputation revealed two prognostic factors to be independently associated with OS: AFP (hazard ratio, 1.18 [95% CI, 1.09 to 1.28]; $P < .0001$) and CTP class C versus A (hazard ratio, 2.78 [95% CI, 1.31 to 5.91]; $P = .0079$). There was no evidence of association with OS for BCLC stage, CTP class B versus A, CD4 count, viral load, or geographical origin. These results were in line with those obtained from complete-case analyses (Data Supplement).

DISCUSSION

Existing epidemiologic evidence suggests a seven-fold increase in the incidence of HCC in people affected by HIV and hepatitis compared with HIV-negative controls.[22] The excess risk associated with HIV infection has been explained traditionally by the immunomodulatory effects of the virus, leading to a faster progression of liver fibrosis.[23] Consistent with this view, people with HIV-associated HCC present at a younger age, suggesting a shorter latency of hepatocarcinogenesis compared with their HIV-negative counterparts.[8]

Once cancer is diagnosed, however, the question as to whether HCC arising in the context of HIV is biologically different from other etiologies has remained unanswered. In the absence of evidence to demonstrate potential differences at a molecular level, clinical studies evaluating HIV for its prognostic role in HCC have led to controversial conclusions, with some studies demonstrating HIV to adversely influence the clinical behavior of HCC and others refuting this prognostic association.[8-10,17]

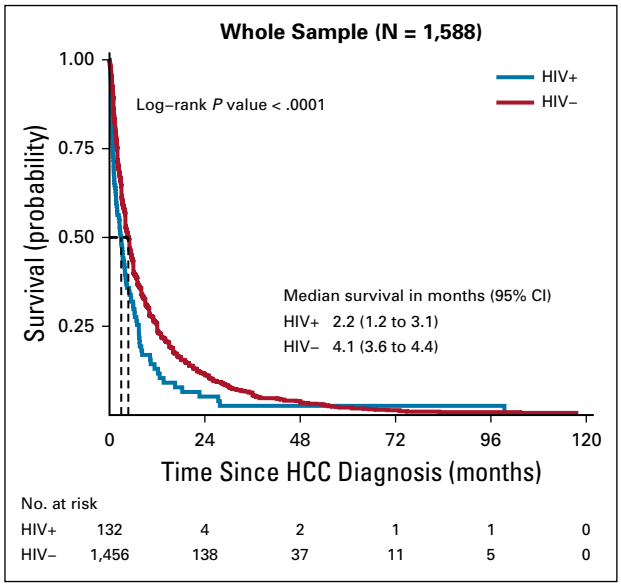

FIG 2. Kaplan-Meier curves illustrating the prognostic relationship of HIV seropositivity in influencing the overall survival of patients with untreated hepatocellular carcinoma (HCC). HIV+, HIV positive; HIV−, HIV negative.

In this global collaborative study, to our knowledge the largest study to date to have evaluated the clinicopathologic impact of HIV in patients with HCC, we demonstrate that HIV infection adversely influences the clinical course of HCC, leading to a 24% increase in the hazard of death in patients who did not receive any active anticancer treatment. A precise estimate of the relationship between HIV and survival in patients with untreated HCC is essential to gain insight into the natural history of the disease and to gather basic information on patients' prognosis that can be used as a point of reference for future mechanistic and clinical studies. By specifically selecting patients who did not receive any effective anticancer treatment for HCC, we intended to rule out the documented confounding effect imposed by the heterogeneity in the provision of radical and palliative therapies for HCC and to improve the quality of evidence supporting the clinical characterization of HIV-associated HCC.

Several previously published studies have confirmed the provision of treatment as a key prognostic factor in this population. In the cross-sectional study by Puoti et al,[9] one of the first to document a negative prognostic role of HIV in HCC, 60% of the patients with HIV-associated HCC received best supportive care compared with 38% of the HIV-negative controls ($P = .02$), highlighting that the adverse prognostic role of HIV status might have been at least in part dictated by the diverse treatment allocation across groups. Treatment imbalance is also a feature of the study by Berretta et al,[8] in which a significantly higher proportion of patients who were HIV-positive received active anticancer treatment (85.6% *v* 65.4%, $P < .001$). However, despite the high proportion of

TABLE 2. Effects of HIV+ Status and Common Prognostic Factors on Overall Survival in Multiply Imputed Data Sets

	Univariable Models		Multivariable Models	
Predictor	**Hazard Ratio (95% CI)**	***P***	**Hazard Ratio (95% CI)**	***P***
Full sample of patients with HCC (n = 1,588)				
HIV+ status	1.49 (1.22 to 1.82)	< .0001	1.24 (1.02 to 1.52)	.0333
Male sex	1.62 (1.36 to 1.94)	< .0001	1.34 (1.12 to 1.61)	.0016
BCLC stage C or D *v* 0, A, or B	3.06 (2.57 to 3.65)	< .0001	1.76 (1.44 to 2.13)	< .0001
CTP class				
B *v* A	1.69 (1.45 to 1.97)	< .0001	1.76 (1.50 to 2.06)	< .0001
C *v* A	2.44 (2.04 to 2.93)	< .0001	2.42 (1.98 to 2.95)	< .0001
Log AFP level, ng/dL	1.18 (1.16 to 1.21)	< .0001	1.15 (1.12 to 1.17)	< .0001
Continent: Americas/Asia *v* Europe	2.59 (2.24 to 3.00)	< .0001	1.92 (1.63 to 2.25)	< .0001
Patients with HIV and HCC (n = 132)				
BCLC stage C or D *v* 0, A, or B	1.58 (1.01 to 2.46)	.0441	1.38 (0.82 to 2.31)	.2226
CTP class				
B *v* A	1.67 (0.86 to 3.26)	.1331	1.43 (0.72 to 2.86)	.3048
C *v* A	3.45 (1.72 to 6.92)	.0005	2.78 (1.31 to 5.91)	.0079
Log AFP level, ng/dL	1.20 (1.11 to 1.31)	< .0001	1.18 (1.09 to 1.28)	< .0001
$CD4^+$ cell count (× 100)	0.93 (0.83 to 1.04)	.1914	0.96 (0.85 to 1.08)	.4689
Log HIV viral load, copies/mL	1.02 (0.96 to 1.08)	.6126	0.99 (0.92 to 1.06)	.7124
Continent: Americas/Asia *v* Europe	1.09 (0.70 to 1.69)	.7154	0.90 (0.55 to 1.46)	.6666

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV+, HIV positive.

patients qualifying for radical treatments in both groups (44.5% *v* 51.1%, $P = .66$), patients who were HIV-positive seem disadvantaged by the inferior likelihood of receiving treatment at recurrence (61% *v* 86.2%, $P < .001$).

Our study cohort, which included patients from multiple centers across Europe, America, and Asia, reproduced a balanced distribution of liver functional reserve classes and BCLC stages, showing, perhaps unsurprisingly, that the majority of patients who, on the basis of the opinion of the treating multidisciplinary team, qualified solely for best supportive care, clustered within the more advanced BCLC stages of the disease (C and D stages [approximately 75%]). In attempting to determine the prognostic interaction between HIV and the basic clinicopathologic features of HCC, we produced a multivariable regression model of survival to adjust our prognostic estimate for key confounders including BCLC stage, CTP class, sex, AFP levels. and geographical origin of the patients.

Interestingly, our results show that the effect of HIV seropositivity influences the survival of patients with HCC independent of a number of established staging parameters, including BCLC stage. We also document the protective effect of female sex[18,24] in the prognosis of advanced HCC, as well as the inherent differences in survival among Western and Eastern populations, results that find a strong resonance in the HCC literature.[25] Taken together, these results suggest our patient cohort to be fully representative of the broader, contemporary population of patients with HCC. From an HIV infection standpoint, it is worthy of note that the majority of the patients who were HIV-positive considered for this study were HCV coinfected and receiving cART at the time of diagnosis and had evidence of acceptable CD4 counts and suppressed HIV RNA levels.

This is in line with previous studies reporting on the incidence and mortality of HCC in PLHIV, where HCV coinfection is demonstrated as the predominant risk factor for HCC,[26] causing a significant increase in liver-related mortality even in patients achieving long-term control of the underlying HIV infection.[3] In our study, patients had been receiving cART for a median duration of 8.3 years. However by choosing cART initiation as a measure of duration of HIV infection, we are likely to have underestimated the true latency period between HIV–hepatitis coinfection and HCC diagnosis, which typically ranges from 10 to 20 years.[27]

As a likely consequence of good HIV control, none of the parameters indicative of severity of HIV infection (CD4 counts, HIV RNA) were revealed to be prognostic in our cohort of patients with HIV-associated HCC, where liver functional reserve and AFP levels emerged as the only indicators of worse survival. We believe this finding to have important ramifications regarding the clinical management of patients with HIV-associated HCC. Clinical practice has evolved to support an equal-access, unbiased environment for the management of HCC in PLHIV.[10] Although patients with HCC and well-controlled HIV should face no barriers in the provision of active anticancer treatment compared with HIV-negative individuals, the inferior probability of survival that accompanies patients with HIV deserves to be taken into account in patient counseling and therapeutic decision making.

Our study emphasizes the predominance of tumor-related factors and hepatic reserve over parameters relating to the severity of HIV infection in influencing survival. Several studies have highlighted the complex and multifactorial pathogenesis of accelerated hepatic fibrosis in patients with HIV and hepatitis. Besides viral factors, enhanced gut permeability, metabolic dysregulation of the liver microenvironment, and a high prevalence of concurrent liver-specific noxae including alcohol and drug use are factors that might explain the accelerated course of the disease.[28] In our study, patients who were HIV-positive were significantly younger at HCC diagnosis and had evidence of poorer synthetic function and more severe portal hypertension as demonstrated by higher ALT and AST levels and lower albumin and platelet counts; this suggests that the prognostic imbalance observed might be caused by the superadded burden of HIV infection in deteriorating patients' liver functional reserve.[16] In keeping with this view, the balance in tumor staging features and circulating AFP levels observed across the two patient subgroups further emphasizes the pathophysiologic relevance of the cirrhotic microenvironment over tumor-specific features in justifying the excess mortality seen in HIV-associated HCC,[29] where decompensation of cirrhosis is more common and predicts significantly shorter survival.[30]

It has been shown that, particularly in the context of HIV and HCV coinfection, patients with HCC often present with infiltrative pattern of growth associated with a faster course of progression and an inferior likelihood of long-term survival.[27] Whether HIV infection preconditions the efficiency of antitumor immunity, an emerging prognostic and therapeutically actionable domain in the progression of HCC, is currently unknown and should be investigated in future studies.

Our study acknowledges a number of limitations. First, the patient population selected for this study consisted mostly of patients with advanced-stage HCC, whose natural history is fundamentally different from that of patients with early-stage disease.[31] However, as far as the primary end point of the study is concerned, BCLC stage was balanced across cases and controls and was accounted for in all survival analyses. Interestingly, the survival outcomes reported in the current study consolidate recent evidence suggesting that the prognosis of untreated early and intermediate-stage HCC might be significantly poorer than reported previously. In the study by Khalaf et al,[32] median OS for patients with BCLC 0/A and B was in fact 13 and 9 months, respectively, significantly shorter than the 38-, 25-, and 10-month median survival probabilities reported previously by Giannini et al[18] for BCLC 0, A, and B stages of HCC.

Such wide interstudy variability is perhaps unsurprising if one considers the number of potential unreported factors that might have influenced survival estimation, including comorbidities, socioeconomic factors, and patient preferences. However, these factors are difficult, if not impossible, to fully account for in a global multicenter study, where access to care, availability and adherence to screening programs, and quality of palliative care support after diagnosis can be highly heterogeneous across health care systems. Because we are unable to reconstruct the clinical reasons as to why patients did not receive effective anticancer treatment, we cannot adjust our analysis for the competing effect of liver-unrelated predictors of survival. In particular, because of limitations in sample size, we were unable to study the prognostic contribution of efficacious treatment of HCV or HBV on the survival estimates we reported, a point that should be addressed in future studies. However, the effect of comorbidities and prior antiviral treatment is likely to be fairly small in reality, because the dominant factor affecting the mortality of this patient population is tumor progression.[33]

In addition, although our study was affected by missing data, we explicitly addressed this issue using multiple imputation, an approach that relies on the assumption that the data are missing at random; that is, that the missing data mechanism does not depend on unobserved data. The considerable amount of information available in the data set (> 80 variables) and the large sample size (> 1,500 patients) enabled us to include in the imputation models all variables associated with missing data, rendering the missing-at-random assumption likely to hold.

To conclude, in our global, multicenter collaborative study, we have provided confirmatory evidence to show that HIV infection is associated with worse prognosis in a population of patients with HCC, where survival estimates were not biased by the effect of treatment. The median OS of patients with HIV-associated HCC of 2.2 months reflects the natural history of untreated patients seen in routine clinical practice and should be considered a reference point for future studies. Follow-up research should explore the prognostic impact of socioeconomic factors and comorbid conditions, two aspects that might be unevenly distributed across patients who were HIV-positive and HIV-negative and might relate to the difference in survival observed in our study. In parallel, mechanistic studies on clinical samples evaluating the immunopathologic features of HIV-associated HCC in comparison with HIV-negative controls are urgently required.

AFFILIATIONS

[1]Imperial College London, London, United Kingdom
[2]University of Cambridge, Cambridge, United Kingdom
[3]VA Central Texas Health Care System, Austin, TX
[4]Università di Bologna, Bologna, Italy
[5]Hospital Universitario Vall d'Hebron, Vall d'Hebron Institut of Research, CIBERehd, Universitat Autonoma de Barcelona, Barcelona, Spain
[6]St. Paul's Hospital, Vancouver, British Columbia, Canada
[7]Chelsea and Westminster Hospital and Imperial College London, London, United Kingdom
[8]Universidad de Sevilla, Seville, Spain
[9]Merck Sharp & Dohme, Kenilworth, NJ
[10]University of Texas Southwestern Medical Center, Dallas, TX
[11]Ospedale Belcolle, Viterbo, Italy
[12]Universidade de São Paulo, São Paulo-SP, Brazil
[13]Università di Padova, Padova, Italy
[14]Policlinico Universitario A. Gemelli, Rome, Italy
[15]VA New York Harbor Healthcare System, Brooklyn, NY
[16]Columbia University, New York, NY
[17]Singapore General Hospital, Singapore
[18]Università di Genova, Genova, Italy
[19]James J. Peters Veterans Affairs Medical Center, Bronx, NY
[20]Icahn School Medicine at Mount Sinai, New York, NY

CORRESPONDING AUTHOR

David J. Pinato, MD, MRes, PhD, Imperial College, London Hammersmith Campus, Du Cane Rd, W12 0HS, London, UK; e-mail: david.pinato@imperial.ac.uk.

EQUAL CONTRIBUTION

D.J.P. and E.A. contributed equally to this work.

SUPPORT

Supported by the National Institute for Health Research (D.J.P.) and by a Chelsea and Westminster NHS Foundation Trust Joint Research Committee Research Grant awarded on behalf of a joint collaboration between CW+ and Westminster Medical School Research Trust (Grant Code JRC SG 009 2018-19) (D.J.P.).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.120010.1200/JC0.18.00885.

AUTHOR CONTRIBUTIONS

Conception and design: David J. Pinato, Elias Allara, Alessia Dalla Pria, Juan Pineda, Mark Nelson, Mark Bower, Norbert Bräu

Financial support: David J. Pinato

Administrative support: David J. Pinato

Provision of study materials or patients: Ting-Yi Chen, Marianne Harris, Alessia Dalla Pria, Mamta Jain, Mark Nelson, Gian Ludovico Rapaccini, Mark Bower, Edoardo G. Giannini

Collection and assembly of data: David J. Pinato, Ting-Yi Chen, Franco Trevisani, Beatriz Minguez, Marco Zoli, Marianne Harris, Alessia Dalla Pria, Nicolás Merchante, Heather Platt, Mamta Jain, Eugenio Caturelli, Luciana Kikuchi, Mark Nelson, Fabio Farinati, Gian Ludovico Rapaccini, Ayse Aytaman, Chee-Kiat Tan, Mark Bower, Edoardo G. Giannini, Norbert Bräu

Data analysis and interpretation: David J. Pinato, Elias Allara, Franco Trevisani, Alessia Dalla Pria, Mark Nelson, Michael Yin, Chee-Kiat Tan, Mark Bower, Edoardo G. Giannini, Norbert Bräu

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359-E386, 2015
2. Pinato DJ, Sharma R, Allara E, et al: The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol 66:338-346, 2017
3. Rosenthal E, Roussillon C, Salmon-Céron D, et al: Liver-related deaths in HIV-infected patients between 1995 and 2010 in France: The Mortavic 2010 study in collaboration with the Agence Nationale de Recherche sur le SIDA (ANRS) EN 20 Mortalité 2010 survey. HIV Med 16:230-239, 2015
4. Joshi D, O'Grady J, Dieterich D, et al: Increasing burden of liver disease in patients with HIV infection. Lancet 377:1198-1209, 2011
5. Soriano V, Puoti M, Garcia-Gascó P, et al: Antiretroviral drugs and liver injury. AIDS 22:1-13, 2008
6. Vujkovic-Cvijin I, Dunham RM, Iwai S, et al: Dysbiosis of the gut microbiota is associated with HIV disease progression and tryptophan catabolism. Sci Transl Med 5:193ra91, 2013
7. Marcellin P, Pequignot F, Delarocque-Astagneau E, et al: Mortality related to chronic hepatitis B and chronic hepatitis C in France: Evidence for the role of HIV coinfection and alcohol consumption. J Hepatol 48:200-207, 2008
8. Berretta M, Garlassi E, Cacopardo B, et al: Hepatocellular carcinoma in HIV-infected patients: Check early, treat hard. Oncologist 16:1258-1269, 2011
9. Puoti M, Bruno R, Soriano V, et al: Hepatocellular carcinoma in HIV-infected patients: Epidemiological features, clinical presentation and outcome. AIDS 18: 2285-2293, 2004
10. Lim C, Goutte N, Gervais A, et al: Standardized care management ensures similar survival rates in HIV-positive and HIV-negative patients with hepatocellular carcinoma. J Acquir Immune Defic Syndr 61:581-587, 2012
11. Gelu-Simeon M, Sobesky R, Haïm-Boukobza S, et al: Do the epidemiology, physiological mechanisms and characteristics of hepatocellular carcinoma in HIV-infected patients justify specific screening policies? AIDS 28:1379-1391, 2014
12. Pinato DJ, Howell J, Ramaswami R, et al: Review article: Delivering precision oncology in intermediate-stage liver cancer. Aliment Pharmacol Ther 45: 1514-1523, 2017
13. Pinato DJ: Breaking Kuhn's paradigm in advanced hepatocellular carcinoma. Hepatology 67:1663-1665, 2018
14. Dika IE, Harding JJ, Abou-Alfa GK: Hepatocellular carcinoma in patients with HIV. Curr Opin HIV AIDS 12:20-25, 2017
15. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer: EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56:908-943, 2012
16. Pinato DJ, Sharma R, Citti C, et al: The albumin-bilirubin grade uncovers the prognostic relationship between hepatic reserve and immune dysfunction in HIV-associated hepatocellular carcinoma. Aliment Pharmacol Ther 47:95-103, 2018
17. Bräu N, Fox RK, Xiao P, et al: Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: A U.S.-Canadian multicenter study. J Hepatol 47: 527-537, 2007
18. Giannini EG, Farinati F, Ciccarese F, et al: Prognosis of untreated hepatocellular carcinoma. Hepatology 61:184-190, 2015
19. Li JW, Goh BG, Chang PE, et al: Barcelona Clinic Liver Cancer outperforms Hong Kong Liver Cancer staging of hepatocellular carcinoma in multiethnic Asians: Real-world perspective. World J Gastroenterol 23:4054-4063, 2017
20. Pinato DJ, Stebbing J, Ishizuka M, et al: A novel and validated prognostic index in hepatocellular carcinoma: The inflammation based index (IBI). J Hepatol 57: 1013-1020, 2012
21. Cox DR: Regression models and life-tables. J R Stat Soc Series B Methodol 34:187-220, 1972
22. Pinato DJ, Dalla Pria A, Sharma R, et al: Hepatocellular carcinoma: An evolving challenge in viral hepatitis and HIV coinfection. AIDS 31:603-611, 2017
23. Bräu N, Salvatore M, Ríos-Bedoya CF, et al: Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy. J Hepatol 44:47-55, 2006
24. Wang M, Gao Y, Feng H, et al: A nomogram incorporating six easily obtained parameters to discriminate intrahepatic cholangiocarcinoma and hepatocellular carcinoma. Cancer Med 7:646-654, 2018
25. Choo SP, Tan WL, Goh BKP, et al: Comparison of hepatocellular carcinoma in Eastern versus Western populations. Cancer 122:3430-3446, 2016
26. Ioannou GN, Bryson CL, Weiss NS, et al: The prevalence of cirrhosis and hepatocellular carcinoma in patients with human immunodeficiency virus infection. Hepatology 57:249-257, 2013
27. Lewin M, Gelu-Simeon M, Ostos M, et al: Imaging features and prognosis of hepatocellular carcinoma in patients with cirrhosis who are coinfected with human immunodeficiency virus and hepatitis C virus. Radiology 277:443-453, 2015
28. Mastroianni CM, Lichtner M, Mascia C, et al: Molecular mechanisms of liver fibrosis in HIV/HCV coinfection. Int J Mol Sci 15:9184-9208, 2014
29. Gramenzi A, Tedeschi S, Cantarini MC, et al: Outcome of hepatocellular carcinoma in human immunodeficiency virus-infected patients. Dig Liver Dis 45:516-522, 2013
30. Gelu-Simeon M, Lewin M, Ostos M, et al: Prognostic factors of survival in HIV/HCV co-infected patients with hepatocellular carcinoma: The CARCINOVIC Cohort. Liver Int [epub ahead of print on June 27, 2018]
31. Bruix J, Gores GJ, Mazzaferro V: Hepatocellular carcinoma: Clinical frontiers and perspectives. Gut 63:844-855, 2014
32. Khalaf N, Ying J, Mittal S, et al: Natural history of untreated hepatocellular carcinoma in a US cohort and the role of cancer surveillance. Clin Gastroenterol Hepatol 15:273-281.e1, 2017
33. Chang YS, Huang JS, Yen CL, et al: The Charlson comorbidity index is an independent prognostic factor for treatment-naïve hepatocellular carcinoma patients with extrahepatic metastases. Hepatogastroenterology 62:1011-1015, 2015

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Influence of HIV Infection on the Natural History of Hepatocellular Carcinoma: Results From a Global Multicohort Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

David J. Pinato
Research Funding: MSD, Bristol-Myers SquibbFranco Trevisani
Consulting or Advisory Role: Bayer AG, Alfasigma, Bristol-Myers Squibb
Speakers' Bureau: Bayer AG
Research Funding: Bayer AG (Inst)
Travel, Accommodations, Expenses: Bayer AG

Beatriz Minguez
Consulting or Advisory Role: Bayer AG
Travel, Accommodations, Expenses: Bayer AG, Gilead Sciences

Marianne Harris
Honoraria: ViiV Healthcare, Merck, Gilead Sciences
Consulting or Advisory Role: ViiV Healthcare (Inst), Merck (Inst), Gilead Sciences (Inst)
Speakers' Bureau: ViiV Healthcare, Merck, Gilead Sciences
Research Funding: Gilead Sciences (Inst), Amgen (Inst)

Nicolás Merchante
Honoraria: Merck Sharp & Dohme, Gilead Sciences
Consulting or Advisory Role: Gilead Sciences, Merck Sharp & Dohme
Research Funding: Gilead Sciences, Merck Sharp & Dohme
Travel, Accommodations, Expenses: Gilead Sciences, Merck Sharp & Dohme, Janssen-Cilag, AbbVie

Heather Platt
Employment: Merck
Stock and Other Ownership Interests: Merck

Mamta Jain
Consulting or Advisory Role: GlaxoSmithKline (Inst), Gilead Sciences (Inst), Merck Sharp & Dohme (Inst), GlaxoSmithKline (Inst), Janssen Pharmaceuticals (Inst), ViiV Healthcare (Inst), Theratechnologies
Travel, Accommodations, Expenses: GlaxoSmithKline

Luciana Kikuchi
Employment: Bayer AG, Servier (I)
Honoraria: Bayer AG
Travel, Accommodations, Expenses: Servier (I)

Mark Nelson
Honoraria: MSD, Gilead Sciences, Bristol-Myers Squibb, AbbVie, ViiV Healthcare, GlaxoSmithKline, Hetero, Mylan, Janssen Pharmaceuticals
Consulting or Advisory Role: MSD, Gilead Sciences, Bristol-Myers Squibb, AbbVie, ViiV Healthcare, Janssen Pharmaceuticals
Speakers' Bureau: MSD, Gilead Sciences, Bristol-Myers Squibb, AbbVie, ViiV Healthcare, GlaxoSmithKline, Hetero, Mylan, Janssen Pharmaceuticals
Research Funding: MSD, Gilead Sciences, AbbVie, ViiV Healthcare
Travel, Accommodations, Expenses: MSD, Gilead Sciences, AbbVie, ViiV Healthcare, Hetero, Mylan

Fabio Farinati
Speakers' Bureau: Alfasigma
Research Funding: Gilead Sciences (Inst)

Michael Yin
Consulting or Advisory Role: Gilead Sciences, ViiV Healthcare

Chee-Kiat Tan
Consulting or Advisory Role: Gilead Sciences, Bayer AG, MSD, Gilead Sciences, Bayer AG
Travel, Accommodations, Expenses: Bristol-Myers Squibb, Bayer AG, Gilead Sciences, MSD

Mark Bower
Honoraria: ViiV Healthcare, Gilead Sciences, Bristol-Myers Squibb, MSD, Janssen Pharmaceuticals, Johnson & Johnson

Norbert Bräu
Honoraria: AbbVie, Gilead Sciences, Merck
Consulting or Advisory Role: AbbVie, Gilead Sciences, Merck
Speakers' Bureau: AbbVie, Gilead Sciences, Merck
Research Funding: Gilead Sciences (Inst), AbbVie (Inst)
Travel, Accommodations, Expenses: AbbVie, Gilead Sciences

No other potential conflicts of interest were reported.