The impact of HIV infection on clinical presentation and mortality among persons with hepatocellular carcinoma in Kampala, Uganda

Sara K. Nsibirwa[1,2*], Jim Aizire[1,3], Julie Nabweteme Mugerwa[1], David L. Thomas[1,3], Ponsiano Ocama[1,4] and Gregory D. Kirk[1,3]

Abstract

Background HIV infection is associated with more rapid progression of some comorbidities. This study assessed the impact of HIV-infection on the presentation and outcome of HCC.

Methods HCC patients attending the Mulago National Referral Hospital in Uganda were enrolled into a natural history study of HCC between March 2015 and February 2019. Standardized methods were used to collect clinical, ultrasound and laboratory data at enrolment. HCC cases were confirmed and enrolled based on a combination of clinical, ultrasound, tumor marker and pathology data. Follow-up contact was made at one, three, six, and twelve months post-enrolment to determine vital status. Symptoms and signs at diagnosis and subsequent survival were compared by HIV status. Kaplan Meier curves were used to assess HCC survival.

Results Of 441 persons with HCC, 383 (87.0%) died within 12 months following HCC diagnosis. The median (IQR) survival was 42 (20, 106) days. HIV infection was present in 79 (18%) cases. After adjusting for baseline demographic and clinical characteristics, HIV infection was associated with increased mortality but only among those with severe HIV-associated immunosuppression (CD4 count < 200 cells per cubic milliliter), aHR (95% C) = 2.12 (1.23–3.53), p = 0.004, and not among PLWH with ≥ 200 CD4 cells per cubic milliliter, aHR (95% C) = 1.15 (0.82–1.60), p = 0.417.

Conclusion Among relatively young Ugandans, HCC is a devastating disease with rapid mortality that is especially rapid among people living with HIV(PLWH). HIV was associated with slightly higher mortality, notably among PLWH with lower CD4 cell counts. As a substantial majority of PLWH diagnosed with HCC were engaged in HIV care, further investigation should determine the effectiveness of incorporating screening and early identification of HCC among high-risk individuals into existing HIV care programs. Concurrent with growing access to curative localized treatment for HCC in sub-Saharan Africa, leveraging HIV care infrastructure affords opportunities for earlier HCC intervention.

Keywords Hepatocellular carcinoma (HCC), Mortality, Human immunodeficiency virus, Sub-saharan Africa

*Correspondence:
Sara K. Nsibirwa
snsibirwa@idi.co.ug
[1]HIV and HCC in Uganda (H²U) Consortium, Kampala, Uganda
[2]Infectious Diseases Institute (IDI), Makerere University, Kampala, Uganda
[3]Johns Hopkins University, Baltimore, MD, USA
[4]Makerere University College of Health Sciences, Kampala, Uganda

Nsibirwa *et al. BMC Infectious Diseases*   (2023) 23:216

Page 2 of 9

Introduction

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide [1]. It is one of the least curable malignancies with the number of new cases reported (905,677) approximating the number of deaths (830,180) worldwide in 2020 [1, 2]. HCC has the amongst the shortest survival time of any cancer, [3] with an even poorer prognosis among patients in lower-income countries which disproportionately bear a higher burden of primary risk factors and of HCC [4]. With the advent of effective combination antiretroviral therapy (cART), people living with HIV infection (PLWH) have had dramatically improved survival [5, 6]. While the rates of many AIDS-defining cancers have declined, non-AIDS defining cancers including HCC are increasing in incidence [7, 8]. Previous studies looking at incidence of HCC during the cART-era have shown an increase in HCC incidence in HIV-infected persons, compared with the general population [9, 10]. Trends in North America have demonstrated increased HCC incidence rates among PLWH coinciding with increased uptake and efficacy of ART [11]. These data raise the question of the impact that this transition may have in sub-Saharan Africa (SSA) which accounts for more than 70% of the global HIV burden, where cART is being widely rolled out and where the median survival for PLWH is increasing [12]. Further, compared to more developed regions, SSA has higher underlying HCC incidence rates and greater burden of HCC risk factors (e.g., endemic hepatitis B virus (HBV) infection, broad aflatoxin exposure) which may substantially influence the burden of HCC among PLWH in this region.

In more developed regions, PLWH with cancer experienced higher cancer-specific mortality than HIV-uninfected patients, independent of cancer stage or receipt of cancer treatment [13]. General estimates of cancer survival in Uganda have shown a poor prognosis for patients with a 2.3% 5-year survival rate [14]. Earlier studies conducted on a cohort of Ugandan HCC patients showed a median survival of 1 month among untreated patients [15]. However, these data are over 30 years old and predate the current situation of substantial HIV prevalence of 6.5% [16] among adults. As a result, there are a paucity of data in Uganda on the impact of HIV infection on the clinical presentation and subsequent survival of HCC cases.

The objective of this study was therefore to analyze data on the clinical presentation at HCC diagnosis and characterize survival in a contemporary cohort of patients diagnosed with HCC in Uganda, emphasizing any differences attributable to HIV infection.

Methods

Study population

As part of a hospital-based case-control study, HCC patients were prospectively recruited from the gastrointestinal and oncology wards of Mulago National Referral Hospital in Kampala, Uganda between March 2015 and February 2019. Potential participants were deemed eligible if they were 12 years of age or older and spoke and comprehended English or Luganda, the languages in which consenting materials were administered. All adult participants provided written informed consent; assent and parental/guardian consent were obtained prior to enrolling 12-17-year-old individuals. The study was approved by the Makerere University School of Medicine Research and Ethics committee, Uganda National Council for Science and Technology and the Johns Hopkins University Institutional Review Board.

Study procedures

All enrolled participants underwent standardized interview, clinical, and ultrasound examination. Questionnaires were administered by trained staff and collected data on socio-demographic, behavioral and clinical factors, and the duration and type of presenting symptoms. Patients self-reported their initial symptom(s) and indicated their duration. Further, interviewers assessed symptoms commonly occurring in HCC at time of enrollment utilizing a standardized questionnaire previously used in HCC studies from west Africa [17, 18]. Clinical examination assessed physical signs reflective of HCC or advanced liver disease including jaundice, wasting, hepatosplenomegaly, abdominal tenderness, ascites, collateral veins, hepatic bruit and asterixis. These data were collected by study physicians who underwent standardized training using uniform data collection instruments.

Laboratory testing was performed at a single laboratory (Makerere University- Johns Hopkins University Core Laboratory; Kampala, Uganda) for hepatitis B surface antigen (HBsAg), anti-hepatitis B core antibodies (anti-HBc), anti-hepatitis B surface antibodies (anti-HBS), anti-hepatitis C antibodies (anti-HCV), HIV antibody, alpha-fetoprotein (AFP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, international normalized ratio (INR), and a complete blood cell count. Urine was tested for circulating cathodic antigen (CCA) for diagnosis of active *Schistosomiasis* infection.

Ultrasound was performed by trained radiographers/radiologists with data collected on a standardized ultrasound form, as previously described [17, 19]. For this analysis, characterization of tumor number and size were incorporated.

Nsibirwa *et al. BMC Infectious Diseases*   (2023) 23:216

Page 3 of 9

HCC case definition

Participants with a clinical presentation compatible with HCC were confirmed by a standardized ultrasound examination showing space-occupying lesions with either an AFP level≥100 ng/ml or liver biopsy documenting histologically-confirmed HCC. Study staff facilitated the completion of diagnostic assessments and almost uniformly, the initial diagnostic confirmation of HCC was made following study enrollment. No HCC cases were identified as part of routine HCC surveillance but were evaluated due to clinical symptoms.

Survival follow-up

Contact information of both the patient and of secondary contacts was obtained at enrollment and used for participant tracing, primarily by telephone, to ascertain vital status at 1,3, 6 and 12 months after study enrolment. For individuals that were not reachable following three attempted telephone contacts, field tracing was carried out using address information. Using these follow-up procedures, vital status was verifiable for >95% of HCC cases, resulting in 419 HCC cases analyzable at three months or beyond for survival outcomes. Additional information obtained included whether the patient was hospitalized or not, date of death and reported cause of death obtained from death certificates if available to informant. Vital status and cause of death information was also determined by reviewing hospital records for those who were hospitalized.

Statistical analysis

Pearson chi-squared (χ [2]) and Wilcoxon rank-sum (Mann-Whitney) tests were used to compare baseline categorical and continuous variables (e.g., demographics, symptoms, signs), respectively, stratified by HIV status. The primary outcome measure in this analysis was mortality risk following HCC diagnosis (study enrolment was used as a proxy). Kaplan-Meier methods were used to compare survival curves by key factors of HIV status and HIV-associated markers. Cox-proportional hazards regression was used to estimate the crude and adjusted hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) for mortality risk. The multivariable model assessed the association between HIV status and mortality risk controlling for potential confounders defined *a priori* including age, sex, education, history of alcohol use, history of cigarette smoking, HBsAg, anti-HCV, and urine *Schistosomiasis* CCA. All *p*-values were based on a two-sided hypothesis test with a type-1 error (α=0.05). Stata 13.0 (College Station, TX) was used for statistical analysis.

Results

Characteristics of 441 HCC cases are shown in Table 1, overall and stratified by HIV status (N=79, 18.0% were HIV-infected). Two-thirds of HCC cases were male, and the median age was 42 years (inter-quartile range, [IQR] 31–55 years). Almost half reported a history of alcohol intake, while 82 (19.0%) reported history of cigarette smoking. Of the 195 (44%) participants who reported prior alcohol use, over two-thirds reported regular consumption of either beer or local brew with the majority reporting alcohol use initiation below the age of 20 years. Co-infections were common: 192 (43.9%) were HBsAg positive, 30 (6.9%) were anti-HCV positive, and 214 (52.8%) were urine CCA positive for active *Schistosomiasis* infection. Overall, 219 (50.3%) of cases had elevated AFP concentrations≥100 IU/ml), while 344 (78.2%) had serum AST levels above 45 U/l, 244 (55.4%) had serum ALT levels above 40 U/l, and INR was raised above the upper limit of normal (1.15) among 351 (82.2%) of cases, and three-quarters of cases had multifocal disease by ultrasound. Histopathology diagnosis of HCC was only present in 106 (24%) of all the HCC cases.

HIV-associated HCC cases were a median of three years older (45 vs. 42 years, P=0.62) although their age range was notably more restricted with almost half between 36 and 50 years of age compared to non-HIV HCC cases with an equal proportion in the extremes of age (P=0.001). HIV-associated HCC cases were less educated, reported more prior alcohol use and cigarette smoking, and had higher AST levels at diagnosis. Among the HIV-associated cases, 69 (87.3%) had been diagnosed with HIV prior to study enrollment. The median (IQR) CD4 count was 308 (5-1244) cells/ml^3 among all HIV-associated cases, 316 (25-1244) among those with known HIV infection prior to HCC diagnosis, and was 262 (5-1005) among those not receiving cART. Of the 69 cases with known HIV infection, 58 (84.1%) were on some form of cART and 32 (58.2%) of these reported consistent use of cART in the month prior to study enrolment. Overall, 51 (64.6%) had an HIV viral load less than 200 copies /ml while among those receiving ART 45 (77.6%) were virally suppressed at this cutoff.

Clinical presentation

Figure 1 A - Symptoms reported by patients at HCC diagnosis, stratified by HIV infection. Figure 1B- Clinical signs exhibited by patients on examination at time of diagnosis; stratified by HIV infection. Patients were examined for clinical signs of liver disease and HCC.

Survival among HCC cases

Through 12 months follow-up post-HCC diagnosis with an accumulated 1,209 person-months at risk, vital status was verifiable for all but 22 (5.0%) HCC cases; 4 (5.0%)

Nsibirwa *et al. BMC Infectious Diseases*   (2023) 23:216

Page 4 of 9

Table 1 Characteristics of HCC cases at diagnosis, stratified by HIV status

Characteristics	Overall* N = 441	HIV positive n = 79 (18.0%)	HIV negative n = 361 (82.0%)	p-value
Socio-Demographic				
Age (years)§, median (IQR)	42 (31–55)	45 (37–52)	42(30–56)	0.463[a]
Age groups, n (%)				
20 years or younger	16 (3.6)	1 (1.3)	15 (4.2)	**0.001[b]**
21–35 years	133 (30.2)	16 (20.3)	117 (32.4)	
36–50 years	142 (32.3)	40 (50.6)	102 (28.3)	
Older than 50 years	150 (34.0)	22 (27.9)	127 (35.2)	
Males, n (%)	295 (67.1)	51 (64.6)	244 (67.6)	0.600[b]
Education attained				
Primary or less	233 (53.0)	52 (65.8)	181 (50.1)	**0.034[b]**
Secondary	139 (31.6)	20 (25.3)	119 (33.0)	
Tertiary	68 (15.4)	7 (8.9)	61 (16.9)	
Alcohol consumption, n (%)	194 (44.1)	48 (60.8)	146 (40.4)	**0.001[b]**
Cigarette smoking, n (%)	82 (19.0)	22 (28.0)	60 (17.0)	**0.025[b]**
Clinical				
Physical activity, Karnofsky score, < 50, n (%)	44 (10.1)	10 (12.7)	34(9.5)	0.39 [b]
Hand grip strength, > 45 pounds, n (%)	188 (47.0)	31 (41.3)	157 (48.2)	0.310[b]
Laboratory				
HBsAg positive, n (%)	192 (43.9)	35 (44.9)	157 (43.6)	0.900[b]
Anti-HCV positive, n (%)	30 (6.9)	2 (2.5)	28 (7.8)	0.137[b]
Active *Schistosomiasis* (Urine CCA) positive, n (%)	214 (52.8)	37 (50.0)	177 (53.5)	0.610[b]
AST (U/l), > 45, n (%)	344 (78.2)	69 (87.3)	275 (76.2)	**0.035[b]**
ALT (U/l), > 40, n (%)	244 (55.5)	48 (60.8)	196 (54.3)	0.319[b]
INR > 1.15, n (%)	351 (82.2)	66 (86.8)	285 (81.2)	0.321[b]
AFP (IU/mL), ≥ 100, n (%)	218 (50.2)	39 (50.0)	179 (50.3)	1.000[b]
AFP (IU/mL), ≥ 400, n (%)	199 (45.9)	33 (42.3)	166 (46.6)	0.532[b]
HIV load (copies/ml) [c]				
<200	--	51(64.6)	--	
≥200	--	28(35.4)	--	
CD4 cell count (cells/mm3) [d]				
<200				
≥200				
<200	--	21(26.6)	--	
≥200	--	58(73.4)	--	
Ultrasound imaging				
Multifocal disease, n (%)	316 (73.6%)	61(77.2)	255 (72.9%)	0.730[b]

Key: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; anti-HCV, hepatitis C virus antibody; AST, aspartate aminotransferase; CCA, circulating cathodic antigen, a urine-based, point-of-care test for active *Schistosomiasis* diagnosis; HBsAg, hepatitis B surface antigen; INR, international normalized ratio, a measure of how long it takes blood to form a clot; IQR, interquartile range; [a] p-value from Wilcoxon rank-sum test; [b] p-value from Fisher's exact test. Highlighted p-values are statistically significant. [c] HIV viral suppression defined as less than 200 copies of HIV per millilitre of blood. [d] HIV severe disease defined as less than 200 CD4 cells per cubic millilitre). § Ages ranged from 13–92 years. *Missing data: AFP (n=6); anti-HCV (n=2); AST (n=1); grip strength (n=39 (8.8%)); HBsAg (n=2); HIV (n=1); INR (n=13); Multifocal disease (n=11)

of which were HIV-infected. There were no significant differences between the participants whose vital status was ascertained at 12 months post HCC diagnosis versus those who were lost to follow-up regarding the distribution of baseline characteristics.

Kaplan-Meier risk curves overall and by HIV status and severity of immunosuppression at diagnosis are depicted in Fig. 2. The overall median observed survival time was only 42 days (IQR, 20, 106) after HCC diagnosis. In comparison of HIV-associated HCC to non-HIV HCC, the median survival was 29 days (IQR, 16, 85)

and 45 days (IQR, 20, 112), respectively. Overall, cumulative risk of death by 1, 3, 6 and 12 months was 42.6%, 72.7%, 84.7% and 90.7%, respectively; which was higher in the HIV versus non-HIV groups at earlier timepoints: 54.4% vs. 44.6% at 1 month (P 0.13), 75.9% vs. 70.1% at 3 months (P 0.47), and 84.8% vs. 81.7% at 6 months (P 0.77), respectively.

Figure 2 shows Kaplan-Meier curves depicting probability of death within 12 months after HCC diagnosis, (A) overall, (B) by HIV-infection status (p=0.21), (C) by HIV-infection status and CD4 cell categories (HIV-uninfected
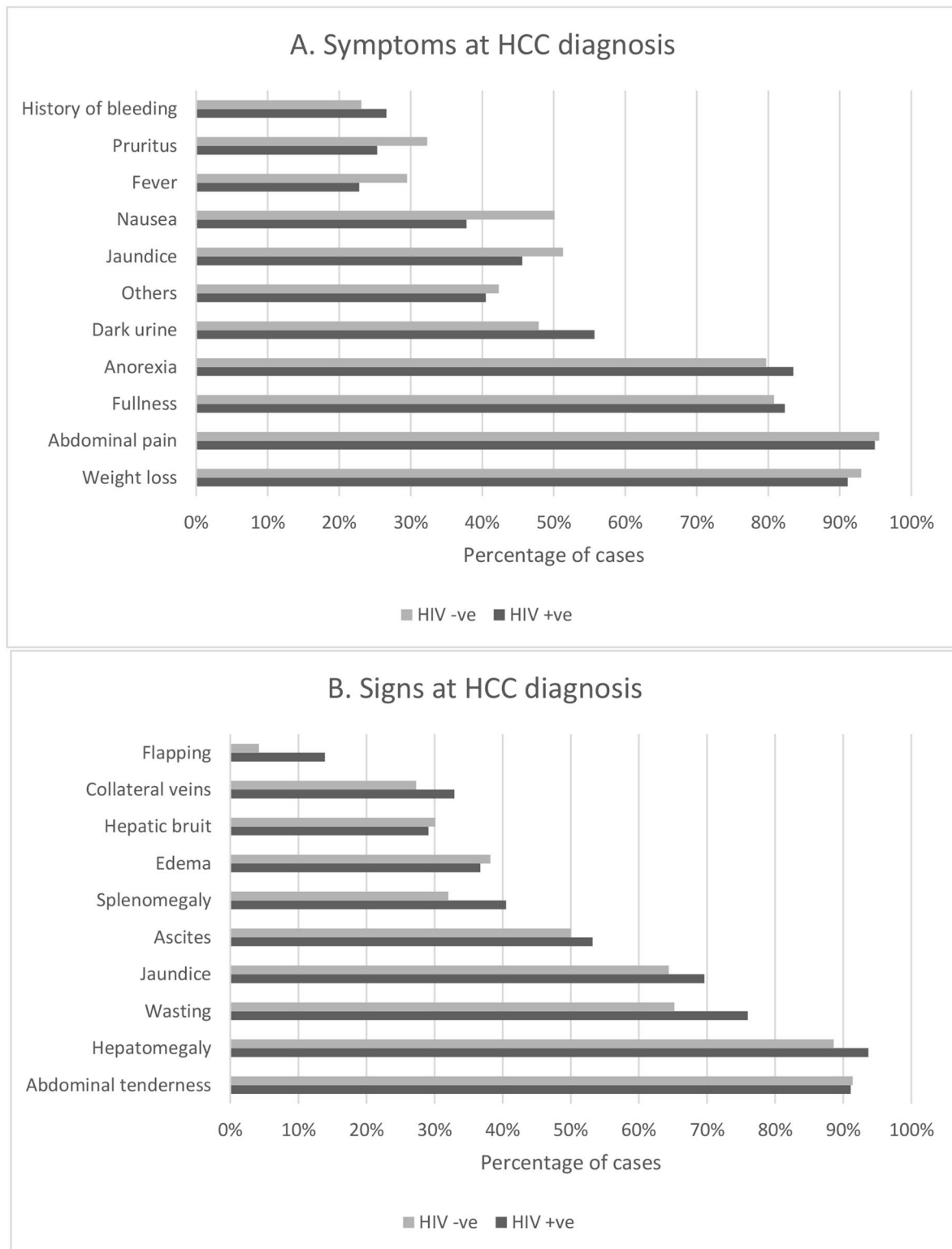
Fig. 1 Symptoms (A) and signs (B) of liver diseases at hepatocullar carcinoma diagnosis stratified by HIV infection status
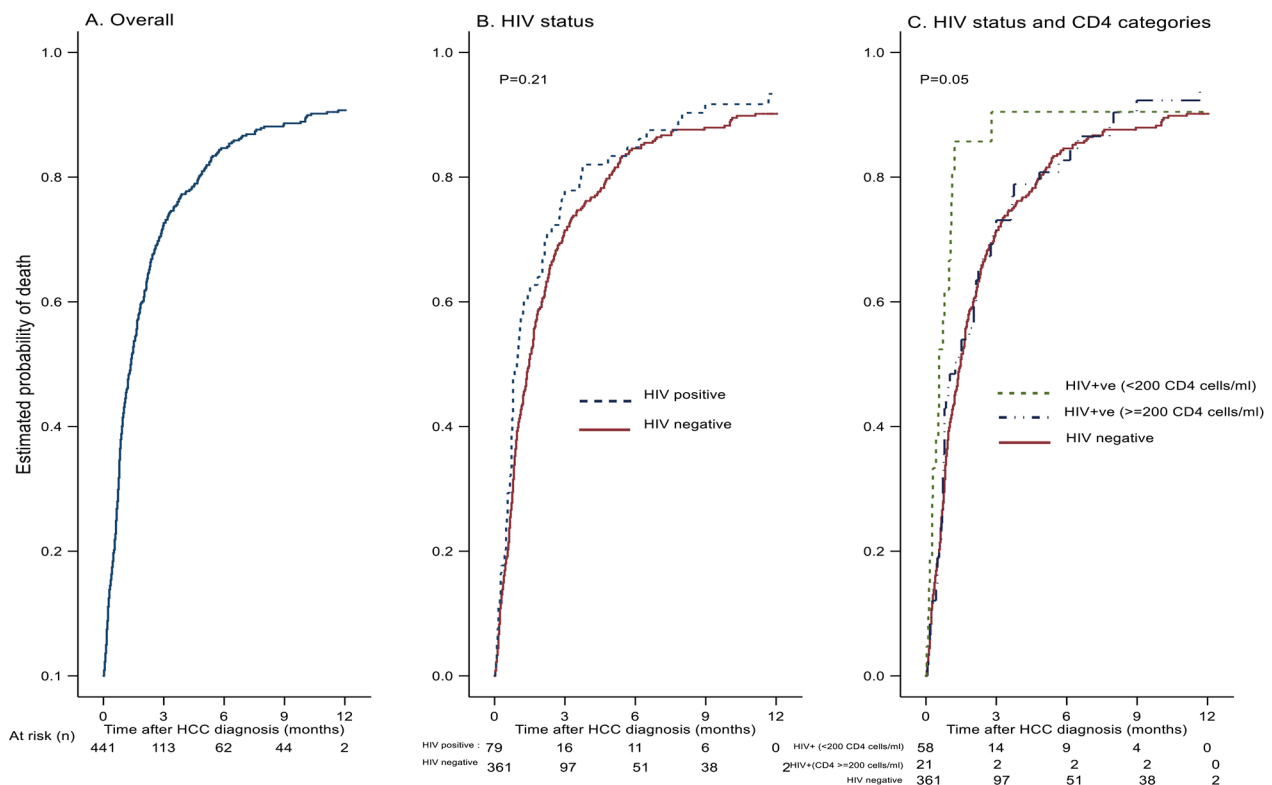
Fig. 2 Survival after hepatocullar carcinoma diagnosis, overall, by HIV status, and by HIV and CD4 cell category

versus HIV-infected with ≥200 CD4 cells/ml versus HIV-infected with <200 CD4 cells/ml (p=0.05), and comparison of HIV-infected group with <200 CD4 cells/ml versus others (HIV-infected with ≥200 CD4 cells/ml or HIV-uninfected), (p=0.02). [a] p-value from non-parametric Log-rank test, a global test to compare if the survival between two or three independent groups, B and C respectively, are identical (overlapping) or not.

The crude hazard ratio (HR) and corresponding 95% confidence intervals (CI) of death after HCC diagnosis associated with HIV infection was 1.20 (0.93–1.56), p=0.16. In multivariable analysis adjusting for age, sex, education, alcohol and smoking history, HBsAg, anti-HCV and urine schistosomiasis CCA, HIV infection was associated with increased mortality risk although this difference did not achieve statistical significance, aHR (95% C)=1.30 (0.97–1.74), p=0.081. Compared with HIV-uninfected counterparts, the higher mortality risk observed among HIV-infected individuals was significant among those with more severe HIV-disease (less than 200 CD4 cells per cubic milliliter), aHR (95% C)=2.12 (1.23–3.53), p=0.004, but not among individuals with 200 or more CD4 cells per cubic milliliter, aHR (95% C)=1.15 (0.82–1.60), p=0.417. In a similar trend of increased mortality risk associated with more advanced HIV disease albeit not statistically significant,

compared to non-HIV HCC cases, higher mortality risk was observed among PLWH with detectable HIV viremia [aHR (95% C)=1.47 (0.94–2.30) with VL≥200 copies/ml", p=0.095] than observed among those with current viral suppression [aHR (95% C)=1.23 (0.87–1.73), p=0.243].

Discussion

This investigation reveals the exceptionally high mortality associated with the diagnosis of HCC in SSA. While there were no major differences detected in how HCC presented in PLWH, mortality was exceptionally fast in those with advanced HIV. Collectively, these data contribute to the urgency to identify and deploy new methods to prevent, detect and cure HCC worldwide.

HCC in SSA, and particularly in Uganda, is one of the most common causes of cancer and of cancer-attributable death. Previously, we leveraged Kampala Cancer Registry data to identify an increasing trend in HCC incidence rates in Uganda which predated widespread availability of cART [20]. Our suspicion, similar to what has been observed in more developed settings, is that HCC incidence rates are likely to continue to increase as PLWH survive into older ages in a setting with substantive chronic HBV infection and aflatoxin exposure. While this study does not calculate population-level HCC incidence rates, we do note that almost one in five HCC

cases were HIV-infected, which is among the highest HIV prevalence reported of any prior non-targeted HCC study [21–23].

Survival in patients with untreated advanced HCC is poor, although varying 1-year survival rates and prognostic factors have been reported depending on demographic and clinical characteristics, different timing of referral and diagnostic criteria, underlying cause of liver disease, severity of the underlying cirrhosis, and tumor burden [24–26]. The short median survival after HCC diagnosis observed in this study is consistent with an Uganda study from three decades ago which characterized similar survival among untreated HCC patients [15]. Studies looking at survival in which participants received treatment for HCC disease have reported a relatively longer median survival beyond 10 months [26–28]. Unfortunately, a recent review from SSA indicates that only 3% of 1315 HCC cases underwent any HCC specific therapy [29]. Today, HCC in SSA represents an advance diagnosis with minimal treatment options with limited advancement over decades.

Despite the limited survival time, we observed an HIV effect towards more rapid mortality. This effect was generally observed by HIV status, but was accentuated when evaluating markers of more advanced HIV disease, notably CD4 count less than 200 cells/ml. Theoretically, PLWH engaged in a well-developed, HIV care delivery system in Uganda and achieving viral suppression should potentially be more readily identified at earlier HCC stages. Our data do not support this hypothesis however. Almost 80% of HCC cases in our study had multifocal liver lesions at diagnosis, irrespective of HIV status. The clinical signs, symptoms and laboratory studies of HCC cases also were very similar by HIV status. Despite this, PLWH with more advanced immunosuppression had up to 30% more rapid time to death. We are unable to establish the underlying mechanism for advanced HIV disease resulting in earlier mortality, and advanced liver cirrhosis itself may contribute to changes in CD4 counts [30].

To our knowledge, this is the first African study to report the impact of HIV infection on survival after HCC diagnosis. Data from other regions are mixed; a study by Yopp et al. from a single European institution reported that HIV infection was not associated with HCC survival [31]. In contrast, other European studies [32, 33] showed a worse survival outcome among HIV-infected HCC patients; these studies were relatively small retrospective studies from tertiary care academic centers with possible biases of patient selection and treatment options. Despite several analyses of large-scale HIV and cancer datasets from the US that excluded HCC, [34] inferences from national data did find that PLWH with HCC presented at more advanced stages and had worse survival compared to non-HIV HCC even after accounting for a variety of health associated factors. In what purports to be among the largest international studies of the HIV effect on HCC survival (N=132 HIV associated HCC cases) from four continents (excluding SSA), the authors estimated around the 25% increased mortality risk associated with HIV, despite appropriate ART and viral suppression [35].

For 15% of HIV-associated HCC cases, the diagnosis of HCC prompted the initial identification of HIV infection. The small proportion of HCC cases who were unaware of their HIV status prior to study enrolment is consistent with data that has shown that Uganda has high rates of HIV testing and treatment [36, 37]. Around 77% of HIV-infected cases on cART had undetectable HIV viral loads which is similar to findings by Byonabye et al. [38] that have shown that PLWH in Uganda in care achieve high levels of viral suppression. Notably, these higher levels of viral suppression occurred despite only 57% of persons with advanced HCC disease reporting optimal ART adherence, emphasizing the potency of current ART regimens despite less-than-perfect adherence.

The prevalence of 53% for active Schistosomiasis mansoni infection is similar to that shown by different studies done within Uganda showing prevalence ranging from 25 -60% [39, 39] in the more endemic areas and age groups; irrespective of their HIV status. For Uganda as an endemic country, this implies that screening and prevention strategies against Schistosomiasis should be considered nationwide.

This study had both strengths and limitations. Many prior investigations of HCC in SSA have been limited by the relatively small size and the reliance on convenience sampling or compilation of sporadic cases without standardized assessment of symptoms, clinical and laboratory findings or ultrasonographic features. Leveraging our standardized data collection procedures, we report uniformly-collected interview, clinical, laboratory, and ultrasonographic data among a large number of highly-characterized HCC cases systematically enrolled in a hospital-based study in Kampala, Uganda. The study was large with complete registration of participants, and though it was hospital-based, it was within a referral hospital with patients coming from several regions around the country with limited options for diagnosis and treatment for HCC. Despite the relatively large size for an HCC study from SSA, the numbers of cases were limited when evaluating stratified analyses by CD4 count or viral suppression status. We also had limited data on duration in care and time on cART for the PLWH. Data collected on the time of first symptoms of disease was participant-reported and therefore may not have fully characterized the natural history and survival of HCC. Our study was also limited by the fact that only a few of the patients with suspected HCC had a confirmatory histopathologic diagnosis and the possibility that other cancers such as

cholangio-carcinoma or unspecified types being diagnosed as HCC is plausible, however we limited misclassification of liver metastases as HCC by noting the differing ultrasonographic patterns and use of AFP, generally not elevated with metastases. Further, HCC accounts for approximately 70–90% of primary liver cancers [20, 41, 42] in Uganda and in SSA .

Although HCC cases with earlier stage symptoms can be identified, it remains unclear if more aggressive diagnostic approaches can identify earlier-stage HCC and improve survival. It is also important to start surveillance for HCC in high-risk patients including those with HIV infection in endemic SSA countries to ensure early diagnosis and thereafter linkage to localized curative treatments in order to modify the statistics caused by this lethal disease.

Conclusions

Prognosis for HCC in SSA is dismal and has largely remained the same over the last few decades [15, 43] Similar to the nihilism confronting HIV care delivery in SSA prior to the widespread scale up of ART programs, substantial skepticism exists on whether HCC can be identified in earlier stages and curative treatments be provided to impact this current situation. However, global efforts have identified viral hepatitis elimination as a primary goal and increasingly, locally curative therapies and tumor resection (without transplantation) for earlier stage disease may become increasingly available. Within the past two years, the first liver resections for HCC have been performed in Uganda.

Advanced HIV disease appears to accelerate mortality among HCC patients with this already highly lethal disease. However, the existing HIV care infrastructure in SSA where patients are engaged over long periods of time, advanced diagnostic testing is available, and antivirals can be successfully delivered provides a framework on which to leverage HCC surveillance programs. Leveraging this human and infrastructure capacity, resources should be invested to develop and evaluate the integration of active HCC surveillance programs within HIV care delivery systems, targeting both PLWH and high-risk, HIV uninfected persons, to identify patients with limited HCC amenable to locally available curative therapies.

Authors' contributions
SN conceived the presented research idea and took the lead in writing the draft manuscript. AJ contributed to creating the final study dataset, reconstruction of study variables and took the lead in data analysis. GK, AJ and PO provided overall supervision and guidance of statistical analysis and contributed to revisions of the manuscript. GK,PO and DT conceptualized the study on which this manuscript is based, were the lead investigators and contributed to revisions of the manuscript. JNM contributed to revisions of the manuscript. All authors have read and approved the final manuscript.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All methods were performed in accordance with the relevant guidelines and regulations of the regulatory bodies. This study was approved by the Institutional Review Boards of Makerere University School of Medicine and Johns Hopkins University. Written informed consent was obtained from all patients before participation in the study. For individuals aged 17 years and below, both written assent from the individuals and informed consent from their parents/legal guardians were obtained prior to enrollment.

Consent to publish
Not applicable.

Competing interests
None of the authors has financial, consultant, institutional or other relationships that might lead to a bias or conflict of interest.

References
1. Sung H, Ferlay J, Siegel RL et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. 2021;71(3):209–249.
2. Ferlay J, Colombet M, Soerjomataram I et al. Cancer statistics for the year 2020: An overview. International Journal of Cancer. 2021.
3. Kew MC. Epidemiology of chronic hepatitis B virus infection, hepatocellular carcinoma, and hepatitis B virus-induced hepatocellular carcinoma. Pathol Biol. 2010;58(4):273–7.
4. Kew MC. Hepatocellular carcinoma in developing countries: Prevention, diagnosis and treatment. World J Hepatol. 2012;4(3):99–104.
5. Trickey A, May MT, Vehreschild J-J et al. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. 2017;4(8):e349-e356.
6. IeDEA COHERE, EuroCoord Cohort C, Jarrín I, Egger M, Del Amo JJA. All-cause mortality after ART initiation in HIV-positive women from Europe. Sub-Saharan Afr Americas. 2020;34(2):277–89.
7. Marcus JL, Chao C, Leyden WA, et al. Survival among HIV-infected and HIV-uninfected individuals with common non-AIDS-defining cancers. Cancer Epidemiol biomarkers prevention: publication Am Association Cancer Res cosponsored Am Soc Prev Oncol. 2015;24(8):1167–73.
8. Wang C-CJ, Silverberg MJ, Abrams DI. Non-AIDS-Defining malignancies in the HIV-Infected Population. Curr Infect Dis Rep. 2014;16(6):406–6.
9. Shiels MS, Cole SR, Kirk GD, Poole C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr. 2009;52(5):611.

Nsibirwa *et al. BMC Infectious Diseases*   (2023) 23:216

Page 9 of 9

10. Mutyaba I, Phipps W, Krantz EM, et al. A Population-Level evaluation of the Effect of Antiretroviral Therapy on Cancer incidence in Kyadondo County, Uganda, 1999–2008. J Acquir Immune Defic Syndr. 2015;69(4):481–6.

11. Sun J, Althoff KN, Jing Y, et al. Trends in Hepatocellular Carcinoma incidence and risk among persons with HIV in the US and Canada, 1996–2015. JAMA Netw open. 2021;4(2):e2037512.

12. UNAIDS. Global AIDS Update Geneva: Joint United Nations Programme on HIV/AIDS., 2016.;2016.

13. Coghill AE, Shiels MS, Suneja G, Engels EA. Elevated Cancer-specific mortality among HIV-Infected patients in the United States. J Clin Oncol. 2015;33(21):2376–83.

14. Gondos A, Brenner H, Wabinga H, Parkin DM. Cancer survival in Kampala, Uganda. Br J Cancer. 2005;92(9):1808–12.

15. Primack A, Vogel CL, Kyalwazi SK, Ziegler JL, Simon R, Anthony PP. A staging system for hepatocellular carcinoma: prognostic factors in ugandan patients. Cancer. 1975;35(5):1357–64.

16. Uganda population-based. HIV impact assessment UPHIA 2016–2017. 2017; https://www.scribd.com/document/356607702/UPHIA-Uganda-Factsheet.

17. Kirk GD, Lesi OA, Mendy M, et al. The Gambia Liver Cancer Study: infection with hepatitis B and C and the risk of hepatocellular carcinoma in West Africa. Hepatology. 2004;39(1):211–9.

18. Umoh NJ, Lesi OA, Mendy M, et al. Aetiological differences in demographical, clinical and pathological characteristics of hepatocellular carcinoma in the Gambia. Liver international: official journal of the International Association for the Study of the Liver. 2011;31(2):215–21.

19. Mendy ME, Welzel T, Lesi OA, et al. Hepatitis B viral load and risk for liver cirrhosis and hepatocellular carcinoma in the Gambia, West Africa. J Viral Hepatitis. 2010;17(2):115–22.

20. Ocama P, Nambooze S, Opio CK, Shiels MS, Wabinga HR, Kirk GD. Trends in the incidence of primary liver cancer in Central Uganda, 1960–1980 and 1991–2005. Br J Cancer. 2009;100(5):799–802.

21. Estevez J, Yang JD, Leong J, et al. Clinical features Associated with Survival Outcome in African-American patients with Hepatocellular Carcinoma. Am J Gastroenterol. 2019;114(1):80–8.

22. Tassachew Y, Abebe T, Belyhun Y, et al. Prevalence of HIV and its co-infection with Hepatitis B/C Virus among Chronic Liver Disease Patients in Ethiopia. Hepatic Med. 2022;14:67–77.

23. Otedo A, Simbiri KO, Were V, Ongati O, Estambale BA. Risk factors for liver Cancer in HIV endemic areas of western Kenya. Infect Agents Cancer. 2018;13(1):41.

24. Cabibbo G, Enea M, Attanasio M, Bruix J, Craxì A, Cammà C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology. 2010;51(4):1274–83.

25. Kim YA, Kang D, Moon H, et al. Survival in untreated hepatocellular carcinoma: a national cohort study. PLoS ONE. 2021;16(2):e0246143.

26. De Toni EN, Schlesinger-Raab A, Fuchs M, et al. Age independent survival benefit for patients with hepatocellular carcinoma (HCC) without metastases at diagnosis: a population-based study. Gut. 2020;69(1):168.

27. Bruix J, Llovet JM. Major achievements in hepatocellular carcinoma. The Lancet. 2009;373(9664):614–6.

28. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–90.

29. Yang JD, Mohamed EA, Aziz AOA, et al. Characteristics, management, and outcomes of patients with hepatocellular carcinoma in Africa: a multicountry observational study from the Africa Liver Cancer Consortium. Lancet Gastroenterol Hepatol. 2017;2(2):103–11.

30. Claassen CW, Diener-West M, Mehta SH, Thomas DL, Kirk GD. Discordance between CD4 + T-Lymphocyte Counts and Percentages in HIV-Infected persons with liver fibrosis. Clin Infect Dis. 2012;54(12):1806–13.

31. Yopp AC, Subramanian M, Jain MK et al. Presentation, treatment, and clinical outcomes of patients with hepatocellular carcinoma, with and without human immunodeficiency virus infection. Clinical Gastroenterology and Hepatology. 10(11):1284–1290.

32. Berretta M, Garlassi E, Cacopardo B, et al. Hepatocellular carcinoma in HIV-infected patients: check early, treat hard. Oncologist. 2011;16(9):1258.

33. Bräu N, Fox RK, Xiao P, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a US–Canadian multicenter study. J Hepatol. 2007;47(4):527–37.

34. Coghill AE, Suneja G, Rositch AF, Shiels MS, Engels EA. HIV infection, Cancer Treatment Regimens, and Cancer Outcomes among Elderly adults in the United States. JAMA Oncol. 2019;5(9):e191742–2.

35. Pinato DJ, Allara E, Chen T-Y et al. Influence of HIV Infection on the Natural History of Hepatocellular Carcinoma: Results From a Global Multicohort Study. 2019;37(4):296–304.

36. Opito R, Mpagi J, Bwayo D, Okello F, Mugisha K, Napyo A. Treatment outcome of the implementation of HIV test and treat policy at the AIDs Support Organization (TASO) Tororo clinic, Eastern Uganda: a retrospective cohort study. PLoS ONE. 2020;15(9):e0239087–7.

37. Uganda MoH. *Uganda Population-based HIV Impact Assessment (UPHIA) 2016–2017* Kampala:Ministry of Health; July 2019 2019.

38. Byonanebye DM, Semitala FC, Katende J, et al. High viral suppression and low attrition in healthy HIV-infected patients initiated on ART with CD4 above 500 cells/μL in a program setting in Uganda. Afr Health Sci. 2020;20(1):132–41.

39. Exum NG, Kibira SPS, Ssenyonga R, et al. The prevalence of schistosomiasis in Uganda: a nationally representative population estimate to inform control programs and water and sanitation interventions. PLoS Negl Trop Dis. 2019;13(8):e0007617.

40. Sanya RE, Muhangi L, Nampijja M, et al. Schistosoma mansoni and HIV infection in a ugandan population with high HIV and helminth prevalence. Trop Med Int Health. 2015;20(9):1201–8.

41. Bosch FX, Ribes J, Díaz M, Cléries R. Primary liver cancer: worldwide incidence and trends. Gastroenterology. 2004;127(5 Suppl 1):5–S16.

42. Kew MC. Epidemiology of hepatocellular carcinoma in sub-saharan Africa. Ann Hepatol. 2015;12(2):173–82.

43. Tognarelli J, Ladep NG, Crossey MM, et al. Reasons why West Africa continues to be a hotbed for hepatocellular carcinoma. Nigerian Med journal: J Nigeria Med Association. 2015;56(4):231–5.

Publisher's note