Differences in Pathology, Staging, and Treatment between HIV\(^+\) and Uninfected Patients with Microscopically Confirmed Hepatocellular Carcinoma

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ABSTRACT

**Background:** The incidence of hepatocellular carcinoma (HCC) is substantially higher among HIV-infected (HIV\(^+\)) than uninfected persons. It remains unclear if HCC in the setting of HIV infection is morphologically distinct or more aggressive.**Methods:** We evaluated differences in tumor pathology in a cohort of HIV\(^+\) and uninfected patients with microscopically confirmed HCC in the Veterans Aging Cohort Study from 2000 to 2015. We reviewed pathology reports and medical records to determine Barcelona Clinic Liver Cancer stage (BCLC), HCC treatment, and survival by HIV status. Multivariable Cox regression was used to determine the hazard ratio [HR; 95% confidence interval (CI)] of death associated with HIV infection after microscopic confirmation.**Results:** Among 873 patients with HCC (399 HIV\(^+\), 140 HIV\(^+\)) and 178 uninfected persons underwent liver tissue sampling and had microscopically confirmed HCC. There were no differences in histologic features of the tumor between HIV\(^+\) and uninfected patients, including tumor differentiation (well differentiated, 19% vs. 28%, P = 0.16) and lymphovascular invasion (6% vs. 7%, P = 0.17) or presence of advanced hepatic fibrosis (40% vs. 39%, P = 0.90). There were no differences in BCLC stage (P = 0.06) or treatment (P = 0.29) by HIV status. After adjustment for risk factors, risk of death was higher among HIV-infected than uninfected patients (HR = 1.37; 95% CI, 1.02–1.85).**Conclusions:** We found no differences in HCC tumor characteristics or background hepatic parenchyma by HIV status, yet HIV was associated with poorer survival. Of note, pathology reports often omitted these characteristics.**Impact:** Systematic evaluation of HCC pathology by HIV status is needed to understand tumor characteristics associated with improved survival.

Introduction

The incidence of hepatocellular carcinoma (HCC) has more than tripled in the United States over the last 3 decades, and HCC is one of the fastest growing causes of cancer-related death in the United States (1, 2). HCC typically develops in the setting of chronic liver disease or cirrhosis, particularly chronic viral hepatitis, alcohol abuse, or nonalcoholic liver disease (3–6). The prognosis after HCC diagnosis remains poor, with a 5-year survival of 17.7% (7–9).

Among HIV-infected patients (HIV\(^+\)), the prevalence of HCC has increased 12-fold between 1996 and 2009, particularly among those with hepatitis C virus (HCV) coinfection (10). Moreover, HIV\(^+\) individuals have a 2- to 4-fold higher risk of HCC compared with uninfected persons, largely due to the higher prevalence of chronic liver disease and increased longevity with antiretroviral therapy (ART; refs. 11–13). Prior estimates have suggested that the prevalence of chronic hepatitis B (HBV) and chronic HCV infection among HIV\(^+\) patients are 5% and 26%, respectively, which are approximately 16- to 29-fold higher compared with uninfected persons (14). Importantly, life expectancy among HIV\(^+\) patients on ART now approaches that of the general population (15). Consequently, the increased longevity of HIV\(^+\) patients on ART may result in increased duration of exposure to chronic viral hepatitis and cirrhosis, also increasing the risk of HCC.

Given the increased risk of HCC in persons living with HIV, evaluating the differences between HIV\(^+\) and uninfected persons in HCC pathology and stage, as well as treatment and survival, is needed. Understanding these differences may help to determine the potential mechanisms for the high rate of HCC among HIV\(^+\) persons. Such features may also inform treatment decisions at the time of HCC diagnosis that could improve morbidity and mortality associated with this malignancy.

We examined differences in characteristics of HCC tumor pathology, background liver parenchyma, HCC stage, treatment, and survival following microscopic confirmation of HCC between HIV\(^+\) and uninfected patients. We hypothesized that HIV\(^+\) patients would have more aggressive pathologic features of HCC, since prior reports have
suggested that HIV+ patients may present with more infiltrative HCC and a more advanced stage of this malignancy (16, 17). In addition, because previous studies observed a younger age at death among HIV+ patients, we hypothesized that HIV infection would be associated with reduced survival due to promotion of dysplasia and impaired immune surveillance (16–20).

Materials and Methods

Study design and setting

We performed a retrospective cohort study of patients with microscopically confirmed HCC within the Veterans Aging Cohort Study (VACS) between January 1, 2000 and September 30, 2015. The VACS consists of electronic medical record data from HIV+ patients receiving care at Veterans Health Administration (VA) medical facilities across the United States (21). At each VA site, HIV+ patients are matched on age, sex, and race/ethnicity to 2 uninfected patients. Data available within the VACS include hospital and outpatient diagnoses [recorded using International Classification of Diseases, Ninth Revision (ICD-9) codes], procedures [recorded using Current Procedural Terminology (CPT) codes], laboratory results, and dispensed inpatient or outpatient medications. Death dates are identified from the VA Vital Status file.

Study population

Potential HCC cases among VACS patients diagnosed between January 1, 2000, and September 30, 2015, were identified by relevant International Classification of Diseases for Oncology, Third Edition (ICD-O-3) topography (C22.0) and morphology (8170-8180) codes from the national VA Cancer Registry (22). Because of a lag in reporting in the cancer registry, we supplemented HCC case finding with ICD-9 diagnoses (155.0, 155.1, and 155.2) from medical claims in 2014 to 2015. ICD-O-3 and ICD-9 codes have been shown to match on age, sex, and race/ethnicity to 2 uninfected patients. Data were ascertained using inpatient or outpatient CPT codes (Supplementary Table S1). Use of sorafenib, the only FDA-approved systemic treatment of HCC during the study period, was defined by at least one 30-day outpatient prescription dispensed from a VA pharmacy within 365 days following HCC diagnosis (30).

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Additional data collected

Demographic and clinical data recorded at the date of HCC diagnosis included: age, sex, race/ethnicity, and current tobacco use as indicated by self-reported survey data from the VA’s Health Factors Dataset (32). Body mass index (BMI) recorded closest, but within 1 year prior, to HCC diagnosis was collected. We also collected history of alcohol dependence/abuse (defined by at least 1 hospital or 2 outpatient ICD-9 diagnoses; ref. 33) and diabetes mellitus (defined by ICD-9 diagnosis, antidiabetic treatment, or random glucose >200 mg/dL; ref. 34) ever recorded prior to HCC diagnosis.

Laboratory data included: HIV infection, chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count. HIV infection was determined by ICD-9 codes as previously detailed (21). Chronic HBV infection was defined by the presence of ≥2 of the following over ≥6 months: positive HBV surface antigen,
positive HBV e antigen, or detectable HBV DNA (35). Chronic HCV was defined by a positive HCV RNA on or prior to HCC tissue sampling. ALT, AST, and platelet count were collected from dates closest, but within 1 year prior, to the date of HCC diagnosis to calculate Fibrosis-4 Index for liver fibrosis (FIB-4), a noninvasive measure of hepatic fibrosis (36). FIB-4 >3.25 accurately identifies advanced hepatic fibrosis/cirrhosis. For HIV+ patients, HIV RNA and CD4+ cell count were collected within 1 year prior to HCC diagnosis and values closest to the date of HCC diagnosis were identified.

**Statistical analysis**

Demographic data, clinical characteristics, BCLC staging, and HCC therapies were compared by HCC diagnostic modality (i.e., microscopically confirmed versus other modality). Among patients with microscopically confirmed HCC, characteristics, including pathologic findings, were compared by HIV status. Differences between the groups were assessed using Chi-square tests for categorical data and Wilcoxon rank-sum tests for continuous data.

We compared survival following date of HCC diagnosis by diagnostic modality and between the HIV+ and uninfected cohorts. Individuals diagnosed with HCC at autopsy were excluded from this analysis. Patients were followed until death, last VA follow-up visit, or September 30, 2015. Kaplan–Meier curves were stratified by HIV status, and differences were assessed by log-rank tests (37). Multivariable Cox proportional hazards regression was used to determine the hazard ratio (HR) and 95% confidence interval (CI) of death associated with HIV infection after adjusting for variables known to be associated with survival after HCC diagnosis, including age, sex, race/ethnicity, alcohol abuse/dependence, chronic HBV infection, chronic HCV infection, FIB-4 (>3.25 vs. ≤3.25), BCLC stage, and HCC treatment (none or palliative vs. curative).

We performed 4 sensitivity analyses to assess the robustness of the above survival analysis results. First, we repeated our analysis after additionally adjusting for year of HCC diagnosis (prior to 2008 vs. 2008 or later), since sorafenib was approved in the United States in 2008 (30). Second, we repeated the survival analysis after excluding patients with any HCC treatment recorded within the VA prior to date of liver tissue sampling. Third, to evaluate the impact of missing tumor differentiation data on the association between HIV infection and death, missing values were replaced with a poorly-differentiated result for HIV+ patients, while missing values for uninfected patients were replaced with a well-differentiated result. Finally, to assess the variability in the magnitude of the HR of death associated with HIV infection with alternative methods of assessing advanced hepatic fibrosis, we repeated the survival analysis after replacing FIB-4 with 2 different measures of hepatic fibrosis defined by: (i) result from the clinical pathology report only, and (ii) a composite of either a pathologic definition of advanced hepatic fibrosis or FIB-4 >3.25 for those without pathologic data. Data were analyzed using Stata 14.1.

**Ethics**

This study was approved by the Institutional Review Boards of the University of Pennsylvania and Corporal Michael J. Crescenz VA Medical Center. The VACS was approved by the Institutional Review Boards of the VA Connecticut Healthcare System and Yale University.

**Results**

Among 873 patients (399 HIV+; 474 uninfected) diagnosed with HCC within the VACS between 2000 and 2015, 318 (36%) underwent liver tissue sampling and had confirmed HCC (Fig. 1). Patients who did not undergo liver tissue sampling and who were excluded were similar in baseline characteristics to those who underwent liver tissue sampling, except for age (median 59 vs. 58 years) and race/ethnicity (P = 0.01). Patients who did not undergo liver tissue sampling were more likely to have a baseline FIB-4 status >3.25 (68% vs. 59%, respectively; P = 0.02), more advanced BCLC stage (P < 0.01), and were less likely to receive curative treatment (P < 0.01; Supplementary Table S2).

Of the 318 patients with microscopically confirmed HCC included in the final sample (140 HIV+), 95% had underlying chronic liver
Table 1. Clinical characteristics of patients with microscopically confirmed HCC in the Veterans Aging Cohort Study (2000–2015), by HIV status.

| Characteristic                           | HIV– (n = 140) | HIV+ (n = 178) | P     |
|-----------------------------------------|----------------|----------------|-------|
| Age, median (IQR)                       | 58.1 (54.2, 62.5) | 58.6 (55.3, 62.7) | 0.34  |
| Male, n (%)                             | 139 (99%)      | 176 (99%)      | 0.71  |
| Race/ethnicity                          |                |                | 0.39  |
| White                                   |                |                |       |
| Black                                   | 47 (34%)       | 51 (29%)       |       |
| Hispanic                                | 10 (7%)        | 14 (8%)        |       |
| Other                                    | 3 (2%)         | 18 (10%)       |       |
| BMI, n (%)                              |                |                |       |
| <18.5 kg/m²                              |                |                | <0.01 |
| 18.5–24.9 kg/m²                          | 12 (9%)        | 4 (2%)         |       |
| 25.0–29.9 kg/m²                          | 58 (41%)       | 66 (37%)       |       |
| ≥30.0 kg/m²                              | 42 (30%)       | 55 (31%)       |       |
| Not reported                             | 7 (5%)         | 4 (2%)         |       |
| Alcohol dependence/abuse, n (%)         | 79 (56%)       | 125 (70%)      | 0.01  |
| Tobacco use, n (%)                      |                |                | 0.77  |
| None                                    | 22 (16%)       | 29 (16%)       |       |
| Current                                 | 99 (71%)       | 120 (67%)      |       |
| Former                                  | 19 (14%)       | 29 (16%)       |       |
| Diabetes mellitus, n (%)                | 17 (12%)       | 34 (19%)       | 0.09  |
| Chronic HBV infection, n (%)            | 20 (14%)       | 4 (2%)         | <0.01 |
| Chronic HCV infection, n (%)            |                |                | 0.17  |
| HCV RNA positive                        | 107 (76%)      | 144 (81%)      |       |
| HCV antibody negative                   | 21 (15%)       | 15 (8%)        |       |
| Other                                    | 12 (9%)        | 19 (11%)       |       |
| CD4+ cell count                         |                |                |       |
| Median (cells/mm³, IQR)                 | 389 (258, 581) |                |       |
| <200 cells/mm³, n (%)                   | 25 (18%)       |                |       |
| Not reported                             | 13 (9%)        |                |       |
| HIV RNA, n (%)                          |                |                |       |
| >400 copies/mL                          | 32 (23%)       |                |       |
| ≤400 copies/mL                          | 94 (67%)       |                |       |
| Not reported                             | 14 (10%)       |                |       |
| Baseline FIB-4d, n (%)                   |                |                | 0.30  |
| ≤3.25                                   | 55 (39%)       | 68 (38%)       |       |
| >3.25                                   | 85 (61%)       | 107 (60%)      |       |
| Not reported                             | 0 (3%)         |                |       |
| Year of HCC diagnosis                   |                |                | 0.03  |
| 2000–2003                               | 14 (10%)       | 15 (8%)        |       |
| 2004–2007                               | 48 (34%)       | 47 (26%)       |       |
| 2008–2011                               | 50 (36%)       | 53 (30%)       |       |
| 2012–2015                               | 28 (20%)       | 63 (35%)       |       |

Note: Bold P values are statistically significant P < 0.05 by Chi-square test and Wilcoxon rank-sum test for categorical variables and continuous variables, respectively. Abbreviation: IQR, interquartile range.

*Alcohol abuse/dependence defined by at least 1 hospital or 2 outpatient ICD-9 diagnoses (ICD-9: 303, 305.0).
*HBV infection defined by at least 2 of the following over >6 months: positive HBV surface antigen, e antigen, or HBV DNA.
*HCV infection defined by positive HCV RNA on or prior to HCC tissue sampling. Other HCV infection defined by HCV antibody positive with negative or unknown HCV RNA assay or unknown antibody status.
*FIB-4 calculated using alanine aminotransferase, aspartate aminotransferase, and platelet count obtained within 12 months prior to date of HCC diagnosis.

Table 2. Pathologic characteristics of HCC liver tissue sampling specimens, based on clinical pathologic reports, in the Veterans Aging Cohort Study (2000–2015), by HIV status.

| Characteristic                           | HIV– (n = 140) | HIV+ (n = 178) | P     |
|-----------------------------------------|----------------|----------------|-------|
| Biopsy, n (%)                           |                |                | 0.30  |
| Core                                    | 113 (81%)      | 135 (76%)      |       |
| Resection                               | 27 (19%)       | 43 (24%)       |       |
| Hepatic parenchyma, n (%)               |                |                | 0.90  |
| Hepatic fibrosis*                       | 56 (40%)       | 70 (39%)       |       |
| Nonadvanced                             | 12 (9%)        | 18 (10%)       |       |
| Not reported                            | 72 (51%)       | 90 (51%)       |       |
| Hepatic inflammation*                   |                |                | 0.27  |
| Present                                 | 28 (20%)       | 45 (25%)       |       |
| Absent                                  | 0 (0%)         | 0 (0%)         |       |
| Not reported                            | 112 (80%)      | 133 (75%)      |       |
| Hepatic steatosisc                      |                |                | 0.53  |
| Present                                 | 14 (10%)       | 18 (10%)       |       |
| Absent                                  | 1 (1%)         | 0 (0%)         |       |
| Not reported                            | 125 (89%)      | 160 (90%)      |       |
| Tumor characteristics, n (%)           |                |                | 0.16  |
| Differentiation                         |                |                |       |
| Well                                    | 26 (19%)       | 49 (28%)       |       |
| Moderate                                | 49 (35%)       | 53 (30%)       |       |
| Poor                                    | 10 (7%)        | 18 (10%)       |       |
| Not reported                            | 55 (39%)       | 58 (32%)       |       |
| Lymphovascular invasiond                |                |                | 0.17  |
| Present                                 | 9 (6%)         | 12 (7%)        |       |
| Absent                                  | 8 (6%)         | 21 (12%)       |       |
| Not reported                            | 123 (88%)      | 145 (82%)      |       |

*aAdvanced fibrosis defined by report of cirrhosis, Ishak score >4, or METAVIR score >2 as indicated on pathology report.
*Hepatic inflammation defined by presence of any hepatic inflammation or chronic hepatitis as indicated on pathology report.
*Hepatic steatosis defined by presence of any steatosis as indicated on pathology report.
*Lymphovascular invasion defined by presence of microvascular, macrovascular, or lymphovascular invasion indicated on pathology report.

abuse (Table 1). Among HIV+, 18% had a CD4+ cell count <200 cells/mm³, and 23% had an HIV RNA >400 copies/mL at the time of microscopic confirmation.

Strategies for microscopic confirmation did not differ by HIV status, and the majority underwent needle core biopsy (Table 2). Features of the hepatic parenchyma, including hepatic inflammation, presence of advanced fibrosis, and steatosis, were similar between the groups. Tumor morphology, including differentiation and presence of lymphovascular invasion, did not differ by HIV status. However, within the clinical pathology reports, tumor morphology was not described among 32% to 39% of reports, lymphovascular invasion was not commented upon in 82% to 88% of reports, and background parenchyma was not described in 51% of reports. These rates did not differ by HIV status (P > 0.15).

After medical record review, no significant differences were observed in BCLC stage between HIV+ and uninfected persons (Table 3). Most patients had stage A disease at microscopic confirmation. Treatment intent also did not differ between the groups (P = 0.29); however, uninfected patients were more likely to receive any HCC treatment prior to liver tissue sampling (P = 0.04).
Among the 318 patients in the sample, 4 received microscopic confirmation of HCC at autopsy. Of the remaining 314 patients, 251 (80%; 117 HIV+; 134 uninfected) died during follow-up. The median survival after HCC pathologic diagnosis was 0.96 years (95% CI, 0.72–1.32) among HIV+ persons and 1.54 years (95% CI, 1.03–1.83) among uninfected individuals (log-rank: $P = 0.09$; Fig. 2). After adjustment for known risk factors impacting survival after HCC diagnosis, the risk of death was significantly higher for HIV+ than uninfected individuals (HR = 1.37; 95% CI, 1.02–1.85; Table 4). Advanced hepatic fibrosis/cirrhosis measured by FIB-4, more advanced BCLC stage, palliative therapy, and lack of directed HCC treatment were also independently associated with poorer survival. In sensitivity analyses, HIV remained associated with an increased risk of death after: (i) additionally adjusting for HCC diagnosis before 2008 (Supplementary Table S3), (ii) addressing the impact of missing data on tumor differentiation (Supplementary Table S4), and (iii) adjusting for alternative methods of classifying advanced hepatic fibrosis (Supplementary Tables S5 and S6). In a sensitivity analysis excluding 30 patients who received HCC treatment prior to liver tissue sampling, HIV infection was associated with increased risk of all-cause mortality; however, statistical significance was attenuated due to the smaller sample size of this analysis ($P = 0.07$; Supplementary Table S7).

**Discussion**

In this national cohort study of US Veterans, 318 microscopically confirmed cases of HCC were identified from 2000 to 2015, representing one of the largest studies of HCC histopathology to date. However, among those with microscopic confirmation, important details were omitted in 32% to 89% of clinical pathology reports. Although we found no differences in HCC tumor characteristics or background hepatic parenchyma between HIV+ and uninfected patients, these findings are far from conclusive because pathology reports often did not indicate these characteristics. Further, on chart review of all microscopically confirmed cases, we found no differences by HIV status in BCLC stage or HCC treatments, yet HIV infection was associated with a 37% increased risk of death among those with microscopically confirmed HCC. This result was robust in sensitivity analyses.

Previous studies suggest that HCC in the presence of HIV infection may be more likely to be poorly differentiated at diagnosis and accompanied by lymphovascular invasion, possibly due to immunosuppression or weakened anti-tumor response (16, 20). Since 39% of HIV+ and 32% of uninfected persons’ reports did not comment upon
Table 4. Factors associated with all-cause mortality following liver tissue sampling among patients with microscopically confirmed HCC in the Veterans Aging Cohort Study (2000–2015).

| Characteristic                  | Unadjusted HR (95% CI) | Adjusted HR (95% CI) |
|--------------------------------|------------------------|----------------------|
| Age, per 10 years              | 0.99 (0.80–1.22)       | 1.04 (0.84–1.30)     |
| Male sex                       | 1.93 (0.27–13.77)      | 0.86 (0.12–6.34)     |
| Race/ethnicity                 |                        |                      |
| White                          | ref                    | ref                  |
| Black                          | 0.99 (0.75–1.31)       | 1.12 (0.82–1.52)     |
| Hispanic                       | 0.56 (0.32–0.97)       | 0.79 (0.44–1.41)     |
| Other                          | 0.98 (0.57–1.68)       | 0.96 (0.54–1.71)     |
| BMI <30.0 kg/m²                 | ref                    | ref                  |
| BMI ≥30.0 kg/m²                | 0.76 (0.55–1.04)       | 0.96 (0.68–1.35)     |
| Alcohol dependence/abuse<sup>a</sup> | 1.06 (0.82–1.39)   | 0.99 (0.74–1.33)     |
| HIV                            | 1.23 (0.96–1.58)       | 1.37 (1.02–1.85)     |
| Chronic HBV<sup>b</sup>        | 1.79 (1.14–2.80)       | 1.13 (0.66–1.94)     |
| Chronic HCV<sup>c</sup>        | 0.64 (0.47–0.85)       | 0.64 (0.46–0.89)     |
| Tumor differentiation          |                        |                      |
| Well                           | ref                    | ref                  |
| Moderate                       | 0.82 (0.58–1.17)       | 0.87 (0.60–1.31)     |
| Poor                           | 0.82 (0.49–1.37)       | 0.68 (0.40–1.14)     |
| Not reported                   | 1.34 (0.96–1.85)       | 0.79 (0.55–1.33)     |
| Baseline FIB-4<sup>d</sup>     |                        |                      |
| ≤3.25                          | ref                    | ref                  |
| >3.25                          | 1.23 (0.55–1.60)       | 1.51 (1.14–2.00)     |
| Barcelona Clinic Liver Cancer stage |                        |                      |
| Stage 0                        | 0.78 (0.36–1.69)       | 0.79 (0.35–1.76)     |
| Stage A                        | ref                    | ref                  |
| Stage B                        | 2.57 (1.89–3.49)       | 2.17 (1.55–3.04)     |
| Stage C                        | 3.67 (2.30–5.87)       | 2.58 (1.56–4.27)     |
| Stage D                        | 3.80 (2.62–5.51)       | 2.38 (1.53–3.72)     |
| Treatment intent               |                        |                      |
| Curative                       | ref                    | ref                  |
| Palliative                     | 2.05 (1.47–2.85)       | 2.00 (1.39–2.86)     |
| No directed therapy            | 5.41 (3.84–7.62)       | 4.33 (2.90–6.46)     |

<sup>a</sup>Alcohol abuse/dependence defined by at least 1 hospital or 2 outpatient International Classification of Diseases, Ninth Revision (ICD-9) diagnoses (ICD-9: 303, 305.0).

<sup>b</sup>HIV infection defined by at least 2 of the following over ≥6 months: positive HBV surface antigen, e antigen, or HBV DNA.

<sup>c</sup>Chronic HCV infection defined by detectable HCV RNA recorded on or prior to HCC tissue sampling.

<sup>d</sup>FIB-4 calculated using alanine aminotransferase, aspartate aminotransferase, and platelet count obtained within 12 months prior to date of HCC diagnosis.

Tumor differentiation, and because information on lymphovascular invasion was not included in 88% of HIV<sup>+</sup> and 82% of uninfected individuals’ reports, it is difficult to confirm the veracity of this observation in our analysis. The absence of reporting on tumor differentiation may be due to insufficient tissue sampling or lack of clinician request for this level of detail as it is not included in clinical staging systems. Further studies utilizing standardized evaluations of tumor pathology are needed to further elucidate the pathologic characteristics of HCC by HIV status.

Stage of background hepatic fibrosis was not described in 51% of the pathology reports for both HIV<sup>+</sup> and uninfected. Based on laboratory data, 39% of HIV<sup>+</sup> did not have advanced hepatic fibrosis/cirrhosis by FIB-4 at the time of microscopically confirmed HCC diagnosis, and this finding did not differ by HIV status. It has been previously demonstrated that chronic HBV infection and nonalcoholic fatty liver disease (NAFLD) can promote the development of HCC in the absence of advanced hepatic fibrosis (38, 39). Chronic HBV infection occurred in 14% of HIV<sup>+</sup> and 2% of uninfected patients in this sample, whereas risk factors for NAFLD, including obesity and diabetes, were each observed in 15% of HIV<sup>+</sup> and 28% of uninfected patients and 12% of HIV<sup>+</sup> and 19% uninfected patients, respectively. The overall lower prevalence of advanced hepatic fibrosis observed in this study compared with prior reports may be due, in part, to enrichment of chronic HBV and NAFLD in this patient sample. Of note, FIB-4 laboratory result fluctuations may occur in the setting of HCC (36). Further research is needed to determine the prevalence and determinants of HCC in the absence of advanced liver fibrosis in HIV and whether this differs from uninfected persons.

We found that the risk of death after microscopically confirmed diagnosis of HCC was increased with HIV infection after adjustment for BCLC stage, treatment, and other clinically relevant variables. HIV-related immunosuppression may allow for more aggressive tumor progression and impaired response (19, 40). HIV viremia may also adversely impact survival in patients with HCC by promoting hepatic dysfunction and decompensation (20, 25, 41–43). Although the association between HIV infection and increased risk of death after microscopically confirmed HCC was independent of initial treatment intent, equitable receipt of HCC treatment was not assessed nor were specific treatment modalities able to be determined. Factors such as patient management by multidisciplinary tumor boards (44), intensity and response to HCC treatment (45), and use of palliative therapy as a bridge to curative interventions are all factors that have the potential to further impact survival following HCC diagnosis. In our study, these data were not available. Further research is needed to identify the impact of these variables on survival among HIV<sup>+</sup> patients.

Our study demonstrates the current limitations of clinical pathology reports as a means of studying HCC among those with and without HIV infection. First, only a minority of those diagnosed with HCC had microscopical confirmation. Multiphasic computed tomography or magnetic resonance imaging can identify tumor characteristics previously validated for HCC diagnosis, thus microscopical confirmation of HCC is not required (46). The lack of required tissue diagnosis limits comprehensive evaluation of HCC pathology and prognosis and precludes development of novel, molecularly-targeted therapies. Patients with atypical or equivocal tumor features on such imaging studies often require liver sampling for diagnosis of HCC and, as a result, microscopical confirmation may reflect diagnostic and/or therapeutic uncertainty. Indeed, both HIV<sup>+</sup> and uninfected patients with radiographic diagnosis of HCC were more likely to have a more advanced BCLC stage (Supplementary Table S8). Patients who undergo microscopical confirmation may not be representative of all those with HCC (47). Although we found that those who underwent microscopical confirmation were, in most ways, demographically similar to those who did not, we found that patients with microscopically confirmed HCC were less likely to have advanced fibrosis as measured by FIB-4 > 3.25, less likely to have advanced BCLC stage, and more likely to have received curative treatment (Supplementary Table S2). Despite these differences, patients who had microscopical confirmation of HCC had an increased risk of all-cause mortality compared with those diagnosed by other modalities (Supplementary Table S9). This association cannot be explained by differences known to impact prognosis of HCC, including HCC stage, treatment, or advanced hepatic fibrosis, thus the increased risk of death among those with microscopically confirmed HCC may be due to factors not addressed...
in our study. Future work should further evaluate factors impacting survival by HCC diagnostic modality.

Second, HCC morphology, lymphovascular invasion, and background hepatic parenchyma were frequently not commented upon in the pathology reports. Nearly 90% of the microscopically confirmed HCC diagnoses were made within high-complexity clinical care settings (48), suggesting that lack of clinical experience is unlikely to explain the absence of histopathologic features. Instead, this likely reflects a clinical pathology focus on making the diagnosis rather than fully characterizing the HCC. This may be reasonable for patient management, yet it limits the utility of these reports for our research.

Third, data abstraction from pathology reports was conducted by a single abstractor, which could have led to misinterpretation in the trained abstractor. When not explicitly reported, histopathologic features were defined as “not reported.” Systematic and standardized reviews of liver tissue specimens by hepatopathologists are needed to further delineate differences in HCC histopathologic and prognostic features by HIV status. Future work is also needed to define molecular targets and histopathologic features that may allow for personalization and improved effectiveness of HCC treatments.

Fourth, although FIB-4 has been previously validated as an accurate measure of advanced hepatic fibrosis/cirrhosis, there remains the possibility that fibrosis/cirrhosis status was misclassified. However, the association between HIV infection and increased risk of death in our sample remained significant in sensitivity analyses using alternative definitions of advanced hepatic fibrosis/cirrhosis (36). Finally, our sample was comprised mainly of older men, limiting generalizability to women (49).

In conclusion, we found that information regarding tumor characteristics and background hepatic fibrosis was missing from clinical pathologic reports of microscopically confirmed HCC. Based on medical record review, we found no difference in HCC stage by BCLC criteria or treatment intent by HIV status. Finally, persons with HIV had a higher risk of death after microscopic diagnosis of HCC compared with uninfected patients. As the incidence of HCC continues to rise, understanding how HIV influences the pathology and prognosis of HCC are critically important to defining the mechanisms for the development of this malignancy and improving treatment response in HIV patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Differences in Pathology, Staging, and Treatment between HIV + and Uninfected Patients with Microscopically Confirmed Hepatocellular Carcinoma

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