Comprehensive Analysis of Imaging Features, Immunohistochemistry and Prognosis of Hepatocellular Carcinoma Patients with Human Immunodeficiency Virus

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Research article

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Abstract

Background: This study aims to provide clues for the preoperative and prognostic assessment of hepatocellular carcinoma (HCC) patients with human immunodeficiency virus (HIV) by comparing the imaging characteristics, immunohistochemistry and prognosis of HCC patients with and without HIV infection.

Methods: The study reviewed two databases, one for HIV-HCC patients and the other for HCC patients who were not infected with HIV. The inclusion criteria were surgically resected and pathologically diagnosed hepatocellular carcinoma patients from October 2013 to August 2016. This study collected 11 HIV-HCC patients (11 men; median age 45 years old, age range 33~71 years) and 11 HCC patients without HIV infection (11 men; median age 50 years old, age range 42~61 years). The image characteristics of HCC were analysed by computed tomography (CT) imaging. In addition, samples were obtained from resected specimens for immunohistochemical analysis, and the expression of glypican-3 (GPC-3), CD34 and Ki-67 were measured. The independent-samples t test, Fisher exact test and Wilcoxon test were used for comparisons. Kaplan-Meier plots were used for postoperative recurrence-free survival analysis.

Results: The median diameter of the largest nodule was significantly larger in the HIV-HCC patients than in the HCC group (P=0.027). In addition, the HIV-HCC patients presented significantly higher CD34 and GPC-3 expression than the HCC patients (P=0.031, 0.007, respectively). Moreover, the postoperative recurrence-free survival time was significantly shorter in the HIV-HCC patients than in the HCC patients (Log-Rank test, c2=6.076, P=0.014), with respective median durations of 4 months and 28 months, respectively. Multivariate Cox model analysis revealed that GPC-3 expression and tumour size were independent prognosis factors in the HCC patients (HR = 4.506, 95% CI :1.247-16.278, P= 0.022; HR = 1.479, 95% CI :1.137-1.923, P = 0.022, respectively).

Conclusion: Compared to HCC patients with non-HIV infection, HIV-HCC patients frequently present a larger tumour size and high expression of CD34 and GPC-3, which result in shorter postoperative recurrence-free survival. Observing the tumour expression of CD34, GPC-3, and Ki-67 and imaging characteristics could be helpful in providing a basis for the choice of treatment strategies and the prognosis evaluation of patients.

Background

Due to infection with human immunodeficiency virus (HIV), the CD40 counts of patients decrease, and immune function also decreases, eventually leading to acquired immunodeficiency syndrome (AIDS) [1]. Currently, HIV infection and AIDS remain among the most important infectious diseases worldwide [2]. Since the era of treatment using highly active antiretroviral therapy (HAART) began in 1996, the opportunistic infections of AIDS have been effectively controlled. Patients have achieved a longer survival advantage, but malignancies have become an important cause of mortality in the HIV-infected

and AIDS population [3, 4]. HIV-related cancer types can be divided into AIDS-defining cancers (ADCs) and non-AIDS-defining cancers (NADCs) [5–7]. With their increasing incidence, NADCs are being diagnosed at a younger age [8–10]. A study of the risk of non-AIDS-defined cancers in Asian HIV-infected individuals showed that liver cancer has an elevated risk among the HIV-infected patients [11]. Most patients with hepatocellular carcinoma (HCC) have the basis of viral hepatitis, alcohol hepatitis, nonalcoholic steatohepatitis, and other risk factors. It usually takes decades for most patients to experience the process of "fibrosis, cirrhosis and HCC" [12, 13]. However, this progression would be accelerated in HIV-infected patients [14]. This study was conducted to explore the effect of HIV complicated with HCC in terms of HCC imaging characteristics, immunohistochemistry and postoperative recurrence-free survival prognosis and to provide more information for the preoperative and prognostic assessment of HIV-HCC patients.

Methods

Patients

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Guangzhou Eighth People's Hospital (Guang dong, China). Because of the retrospective nature of the study, patient consent for inclusion was waived. We conducted a retrospective case control study between October 2013 and August 2016. Two databases were included: one for HIV-HCC patients and the other for HCC patients without HIV. The inclusion criteria were surgically resected and pathologically diagnosed HCC during the period of the study. Eleven HIV-HCC patients (11 men; median age, 45 years old [age range 33–71 years]) were found to meet the criteria and included in our study. The HCC patients without HIV in our study were obtained in the same way. To have comparable groups in power analysis, we limited the database of this study to the first 11 patients with pathological diagnosis and CD 34, glypican-3 (GPC-3), and Ki-67 immunohistochemical staining for HCC (11 men; median age, 51 years old [age range, 42–61 years]).

All the included patients were speculated of having HCC according to the CT examination or elevated α-fetoprotein (αFP) levels (> 200 ng/mL) [14]. All cases underwent tumour resection and pathological confirmation. The expression of CD34, GPC-3 and Ki-67 were detected by immunohistochemical techniques for further analysis.

The clinical data were analysed as follows: age, sex, previous smoking or drinking, previous intravenous drug injection, type of hepatitis virus infection, liver background, CD4 + cell count, αFP levels, postoperative recurrence and date of death.

Image Acquisition

The HIV-HCC patients and HCC patients underwent computed tomography (CT) examination before surgical resection. The CT system that we used (Mx8000, Philips Medical Systems) was set at 240 mA

and 120 kV, and the minimum section thickness was 6.5 mm. All of the patients received nonionic iodinated contrast agent injections (iohexol, 300 mg I/l; 2 mL/kg at 2.5–3.0 mL per second). The examinations included unenhanced and contrast enhanced dynamic imaging with three-phase imaging after contrast agent injection (late arterial phase, 25–30 seconds; portal venous phase, 65–70 seconds; delayed phase, 3–5 minutes).

Image Analysis

All of the images were analysed by two senior abdominal radiologists with 15–20 years of experience in a consistent and nonblinded manner. The image analysis focused on the largest lesion features of each patient as follows: (a) largest diameter; (b) the type of HCC, massive or nodular – the massive type characterized by single, multiple or merged into blocks with a diameter ≥ 5 cm, and the nodular type characterized by single or multiple nodules with a diameter ≤ 5 cm; (c) the attenuation level on unenhanced and contrast-enhanced CT images with reference to the adjacent hepatic parenchyma; (d) necrosis, defined as unenhanced areas; and (e) a venous- and/or portal-obstructing tumour, defined as distention of the hepatic and/or portal vein lumen by thrombus enhancement [15].

Immunohistochemistry

Paraffin-embedded tissues were sectioned, and the stained tissue sections (4 μm) were deparaffinized in xylene, dehydrated and rehydrated in ethanol, and subjected to steamer antigen retrieval. The sections were processed with the following primary antibodies: mouse anti-human CD34 (clone no., QBEnd/10; dilution, 1:100; Zhongshan Jinqiao Biotechnology Co., Ltd., Beijing, China), mouse anti-human GPC-3 (clone no., 1G12, dilution, 1:100; Zhongshan Jinqiao Biotechnology Co., Ltd., China), and mouse anti-human Ki-67(clone no., UMAB107, dilution, 1:200; Zhongshan Jinqiao Biotechnology Co., Ltd., China).

Evaluation Of Immunohistochemical Staining

CD34 and GPC-3 immunostaining was evaluated semiquantitatively, and the positive immunostaining was assessed in tumour cells for the HCC samples. Staining intensity was scored as 0, negative; 1, weak; 2, moderate; or 3, strong. The degree of staining was scored based on the percentage of positive cells as follows: 0, 0–5%; 1, 6–25%; 2, 26–50%; 3, 51–75%; and 4, 76–100%. When there was any doubt about the score to be assigned, the highest score was chosen. The sum of the intensity and the degree of the staining scores were used to produce a final overall score as follows: 0–1, negative; 2–3, weak; 4–5, moderate; and 6–7, strong. HCC tissue samples strongly graded were judged to have high CD34 or GPC-3 expression, while those graded negative, weak, or moderate were regarded to have non-high CD34 and GPC-3 expression, and the proliferation index Ki-67 was calculated based on the percentage of positive cells.

Statistical analysis

The independent-samples t test and Wilcoxon test were used to compare the distribution of continuous variables between the groups (HIV-HCC patients and HCC patients). The Fisher exact test was used to compare the frequencies of categorized variables. Mitigation times were calculated from the date of hepatectomy to recurrence or death or were censored at the date of the last follow-up for those patients who were non-recurrent. Kaplan-Meier estimates were obtained according to different predictive group stratifications and compared using the Log-Rank test. Predictive death factors were detected using a Cox proportional hazards regression model. We used SPSS statistical software (version 13.0, Chicago, IL, USA). P values of 0.05 or less were required to indicate a statistically significant difference.

Results

Patient characteristics

The median age of the HIV-HCC patients was substantially but not significantly younger than that of the HCC group (P = 0.355), but they were not statistically significantly different (Table 1). In both groups, almost of the all included patients had cirrhosis backgrounds with hepatitis virus infection, mostly hepatitis B virus infection. The HIV-HCC patients were all men (11 patients) who were addicted to intravenous drugs (4 patients). The median CD4 + cell count was 310 cells per cubic millimetre (range, 4-455 cells per cubic millimetre), and five of the 11 HIV-HCC patients had a CD4 + level less than 200 cells per cubic millimetre. The median αFP value was 164.4 ng/mL (range, 1.6-17791.0 ng/mL) in the HIV-HCC patients and 44.6 ng/mL (range, 2.0-9572 ng/mL) in the HCC patients, which was not significantly different (P = 0.812).

Table 1
Clinical characteristics of the 22 male patients studied

Parameter	Patients with HIV-HCC (n = 11)	Control patients with HCC (n = 11)	P value
Median patient age (y)	45 (33–71)	50 (42–61)	0.355
Smokers	3/11 (27.3)	4/11 (36.4)	> 0.99
Alcohol users	1/11 (9.1)	1/11 (9.1)	> 0.99
Previous intravenous drug users	4/11 (36.4)	ND	ND
Hepatitis virus infected			
HBV	6/11 (54.5)	10 /11(90.9)	0.149
HCV	1/11 (9.1)	0	> 0.99
HBV and HCV	3/11 (27.3)	0	0.214
HBV and HDV	0	1 /11(9.1)	> 0.99
Hepatic background of cirrhosis	9/11 (81.8)	10/11 (81.8)	> 0.99
Median CD4 + cell count	310 (4-455)	ND	ND
CD4 + < 200/mm3	5/11 (45.5)	ND	ND
Median αFP No. of αFP > 200 ng/mL	164.4 (1.6-17791.0) 5/11 (45.5)	44.6 (2.0-9572) 5/11 (45.5)	0.812 > 0.99

Imaging Findings

Massive HCC was found in 5 patients with HIV-HCC and 2 patients with HCC, which was not significantly different. The remaining HCCs were nodular. The size of the largest lesions in the HIV-HCC patients ranged from 15 mm to 92 mm (median, 45 mm), and the size of the largest lesions in the HCC patients ranged from 12 mm to 57 mm (median, 20 mm). The median diameter of the largest nodule was statistically larger in the HIV-HCC patients than in the HCC group.

The lesions displayed arterial hyperenhancement with washout in the venous or delayed phase in all but one of the cases. Consistent with the diagnostic criteria applied, arterial hyperenhancement of tumours was seen in all of the HIV-HCC patients. Similarly, arterial hyperenhancement of tumours was also seen in all but one HCC patients. There were no significant differences between the two groups in terms of the presence of intralesion necrosis (Table 2). A portal-obstructing tumour was found in 2 of 11 (18.2%) HIV-HCC patients and none of the HCC patients.

Table 2
Imaging characteristics

Parameter	Patients with HIV-HCC (n = 11)	Control patients with HCC (n = 11)	P value
Type of HCC			
Massive	5/11 (45.5)	2/11 (18.2)	0.361
Nodular	6/11 (54.5)	9/11 (81.8)	0.361
Median diameter of the largest tumour (mm)	45 (15–92)	20 (12–57)	0.027
Unenhanced CT Hypoattenuation Iso- to hyperattenuation	11/11 (100) 0/11(0)	10/11 (90.9) 1/11 (9.1)	0.317 … …
Arterial phase imaging Hypervascular Isovascular Hypovascular	11/11 (100) 0/11 (0) 0/11 (0)	8/11 (72.7) 1/11 (9.1) 2/11 (18.2)	0.069 … … …
Portal phase imaging Hypervascular Isovascular Hypovascular	1/11 (9.1) 0/11 (0) 10/11 (90.9)	1/11 (9.1) 1/11 (9.1) 9/11 (81.8)	0.582 … … …
Delayed phase imaging Hypervascular Isovascular Hypovascular	0/11 (0) 0/11 (0) 11/11 (100)	0/11 (0) 1/11 (9.1) 10/11 (90.9)	0.317 … … …
Portal-obstructing tumours Intralesion necrosis	2/11(18.2) 3/11 (27.3)	0/11(0) 1/11 (9.1)	0.476 0.586

Immunohistochemistry Evaluation

The HIV-HCC patients presented significantly higher expression of CD34 and GPC-3 than that of the HCC patients (P = 0.031, 0.007, respectively) (Table 3). The median percentage of Ki-67 positive rate in the HIV-HCC patients was higher than that in the HCC group, but the difference was not significant (P = 0.138).

Table 3
Results of immunohistochemical staining

Parameter	Patients with HIV-HCC (n = 11)	Control patients with HCC (n = 11)	P value
CD34 negative weak moderate strong	0/11 (0) 0/11 (0) 6/11 (54.5) 5/11 (45.5)	0/11 (0) 2/11 (18.2) 8/11 (72.7) 1/11 (9.1)	0.031 … … … …
GPC-3 negative weak moderate strong	0/11 (0) 1/11 (9.1) 6/11 (54.5) 4/11 (36.4)	0/11 (0) 6/11 (54.5) 5/11 (45.5) 0/11 (0)	0.007 … … … …
Ki-67 (median percentage of positive cells) (%)	40 (5–80)	20 (10–80)	0.138

Prognosis

For curative treatments, all of the patients underwent liver tumour resection. Recurrence-free survival time was significantly shorter in the HIV-HCC patients than in the HCC patients (Log-Rank test, $\chi^2 = 6.076$, P = 0.014), with respective median durations of 4 months versus 28 months (Fig. 1), respectively.

Single factor analysis indicated that CD34 expression, GPC-3 expression, Ki-67 expression and tumour size were the primary factors influencing the prognosis of HCC patients (Table 4). Multivariate Cox model analysis revealed that GPC-3 expression and tumour size were independent prognostic factors for HCC patients (hazard ratio (HR) = 4.506, 95% confidence interval (CI) :1.247–16.278, P = 0.022; HR = 1.479, 95% CI :1.137–1.923, P = 0.022, respectively).

Table 4
Univariate and multivariate Cox regression analysis for the prediction of survival of HCC patients

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI of HR	p value	HR	95% CI of HR	p value
CD34	3.726	1.109–12.519	0.033	0.950	0.196–4.592	0.949
GPC-3	3.935	1.136–13.629	0.031	4.506	1.247–16.278	0.022
Ki-67	1.022	1.001–1.043	0.037	1.001	0.970–1.033	0.954
Tumour size	1.418	1.113–1.805	0.005	1.479	1.137–1.923	0.004

Discussion

The results of this study demonstrated that most of the patients had a background of cirrhosis with hepatitis virus infection, and some of these patients had the habit of smoking and drinking for years. Just as Tsuchiya et al [16] reported, hepatocellular carcinoma (HCC) most often occurs in patients with cirrhosis, mainly resulting from chronic alcohol abuse, nonalcoholic steatohepatitis (NASH), or hepatitis virus infection. Moreover, the included HCC patients in the two groups mostly had infections of hepatitis C virus and/or hepatitis B virus, and this finding is consistent with a recent report [17]. In addition, HIV can attack the body's immune system, decrease CD4 + cell counts, and cause immunosuppression. As a consequence, people living with HIV are more susceptible to hepatitis virus infection. Moreover, research showed that the incidence of HCC in HIV-infected people increased by approximately 5 to 6 times, compared with the general population [18]. In our study, approximately half of the included patients with HIV had a CD4 + reduction of less than 200/mm^3, so we suspected that the decrease in CD4 + might be an HCC risk factor. Similar results were also observed by Kramer et al [19], who concluded that patients with CD4 + cell counts less than 200 had a 71% increased risk of developing HCC.

Most of the cases demonstrated the characteristic features of hepatocellular carcinoma – hyperenhancement on arterial phase images and washout quickly on portal venous or delayed phase images – except for one patient in the HCC group. There were no significant differences in HCC types between the two groups, which manifested as massive and nodular. Since all of the patients underwent surgical resection, there were no infiltrative types in our study, and portal-obstructing tumours were only found in 2 HCC-HIV patients, with none in the HCC patients. In addition, the tumours in the HCC-HIV group were significantly larger than in the HCC group. Just what was reported by Lewin et al [15], portal-obstructing tumours were only found in the HIV-HCC patients compared with the HCC patients on diagnostic imaging. Choi et al [20] also revealed that T-cells can inhibit the process of hepatocellular carcinoma invading the portal vein and spreading throughout the liver. Since HIV can attack and decrease human T-cells, cancer cells were more likely to invade the vessels due to the immunosuppression of HIV-infected patients, which could cause the tumours to become more aggressive and grow rapidly.

In our study, only 2 cases in the HIV-HCC group showed recurrence-free survival at 5 years after resection. The recurrence-free survival was significantly reduced in patients with HIV-HCC compared to patients with HCC ($P = 0.014$), and the median durations of recurrence-free survival were 4 months versus 28 months, respectively. Our results are consistent with those reported previously [21] [22]. A recent study determined that the recurrence of HCC within 5 years accounted for 70%, manifesting as intrahepatic metastases or multicentric recurrence, and 25% after liver transplantation [21]. Another study also found that the median survival of HIV-infected patients with HCC was approximately 7 months [22]. Lewin et al [15] speculated that HIV-HCC patients frequently demonstrate portal-obstructing tumours compared with hepatitis HCC, which might be the reason for shortened survival. Unlike other research methods, our diagnosis of HIV-HCC depends not only on imaging characteristics but also on immunohistochemistry. The expression levels of CD34, GPC-3 and Ki-67 were observed, providing us with more information.

After the evaluation of immunohistochemical staining, we found that the positive rate of CD34 and GPC-3 in the HIV-HCC patients was statistically higher than in the HCC group. It is known that CD34 is a transmembrane glycoprotein with high glycosylation, and it is useful in differentiating benign from malignant liver lesions [23, 24]. CD34 protein expression decreases as cells mature [25], but abnormal capillaries of HCCs are diffusely CD34 positive [26]. A study reported that the wild-type CD34 gene might be involved in the occurrence and development of HCC [27]. The increased expression of CD34 in the HIV-HCC patients could indicate an increase in new abnormal capillaries. Thus, the tumours were more invasive and grew faster, which also explained why the hepatocellular carcinomas in the HIV-HCC patients were significantly larger than those in the HCC group.

Multivariate Cox regression analysis showed that GPC-3 is an independent risk factor for recurrence-free survival probability (P = 0.022). GPC-3 is a type of membrane-associated heparan sulphate proteoglycan that can be specifically detectable in HCC but not in benign hepatocellular lesions [28, 29]. A study concluded that increased expression of GPC-3 could indicate the malignant transformation of hepatocytes [28]. We found that the HIV-HCC patients presented a significantly higher GPC-3 positive rate and a shorter recurrence-free survival time than the HCC patients. Our results are consistent with those of Liu [30]. Consequently, over-expressed GPC-3 could indicate poor prognosis. Thus, the evaluation of GPC-3 could play an important role in the choice of treatment for HIV-HCC patients.

In our study, the median Ki-67 positive rate in the HIV-HCC patients was higher than that in the HCC group, but the difference was not significant. Ki-67 is a nuclear antigen, which is associated with cell proliferation activity, and it is widely used as a proliferation associated markers in cancer cells [31]. A previous study determined that proliferation status was closely linked to cancer biological behaviour, tumour invasiveness and high mortality, which could predict treatment efficacy and prognosis [32]. Luo et al proved that increased expression of Ki-67 was related to poor disease-free survival, relapse-free survival and overall survival in patients with hepatocellular carcinoma [33], while in our study, Cox regression analysis showed that Ki-67 was a primary but not an independent risk factor for recurrence-free survival probability. We speculate that this finding is due to the small number of cases in this study, and we will increase the sample size in future research.

Our study had two main limitations. First, very few HIV-HCC patients underwent surgical treatment, only 11 HIV-HCC patients and 11 HCC patients were included in our study. Thus, we will increase the sample size to render the research results more credible. Second, all of the patients underwent only CT examinations, but MRI examination data were incomplete. Therefore, this article did not describe the MRI imaging manifestations of patients with HIV-HCC. In future research, we will combine CT with MRI examinations to analyse the image characteristics of the HIV-HCC patients and to provide more imaging information to the clinic.

Conclusion

In conclusion, compared to HCC patients without HIV infections, HIV-HCC patients frequently present with larger tumour sizes and high expression of CD34 and GPC-3, resulting in shorter free-recurrence survival. Observing the tumour expression of CD34, GPC-3, and Ki-67 and imaging characteristics can provide us with more tumour information and could help in devising strategies to provide appropriate and effective treatment for patients with HIV-HCC.

Abbreviations

HCC: Hepatocellular Carcinoma; HIV: Human Immunodeficiency Virus CT: Computed Tomography; GPC-3: Glypican-3; AIDS: Acquired Immunodeficiency Syndrome; HAART: Highly Active Antiretroviral Therapy; ADCs: AIDS-Defining Cancers; NADCs: Non-AIDS-Defining Cancers; αFP: α-fetoprotein; HR: Hazard Ratio; CI: Confidence Interval

Declarations

Acknowledgements

Not applicable.

Authors' contributions

JL, LL, XX designed the study, QG drafted the article, XX was a major contributor in writing the manuscript, LZ, DH and CY revised it critically for important intellectual content. All authors have read and approved the manuscript.

Availability of data and materials

The data used in the study are available from the corresponding author on reasonable request.

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Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Guangzhou Eighth People's Hospital (Guang dong, China). Because of the retrospective nature of the study, patient consent for inclusion was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

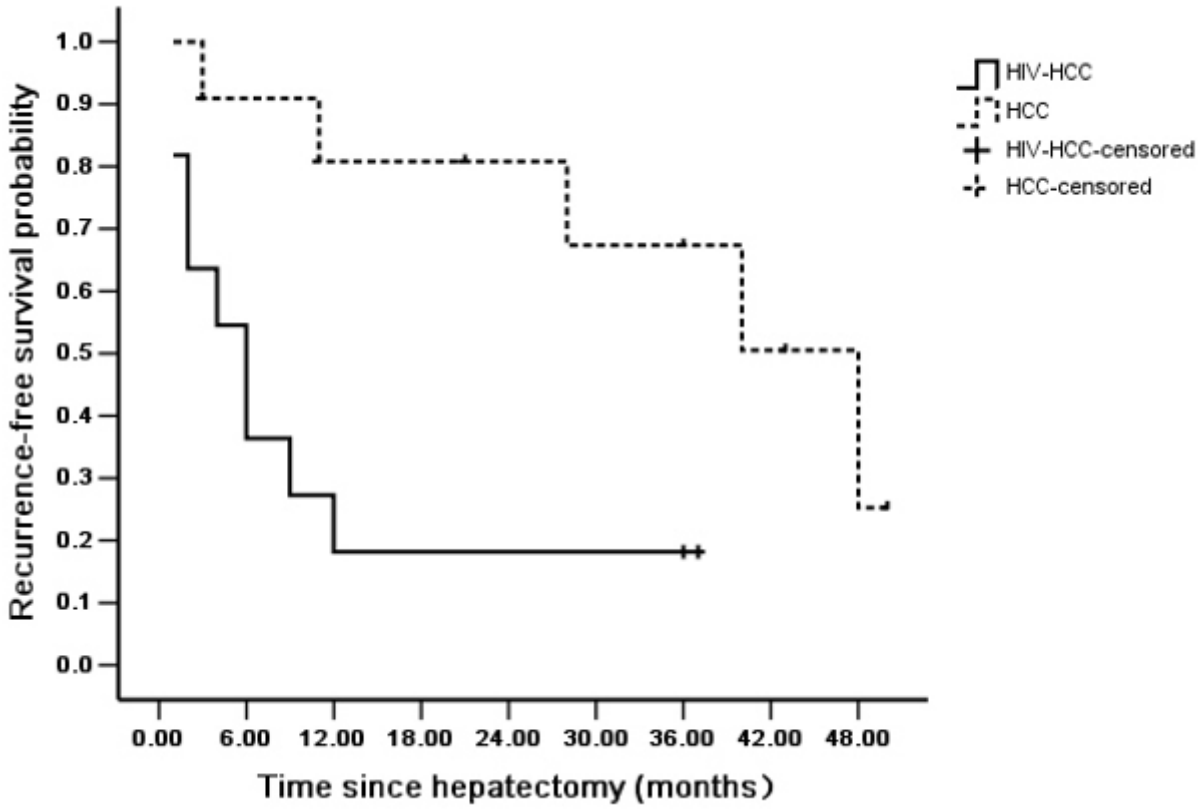

Figure 1

Kaplan-Meier survival curves demonstrating recurrence-free survival in the HIV-HCC group versus the HCC group.

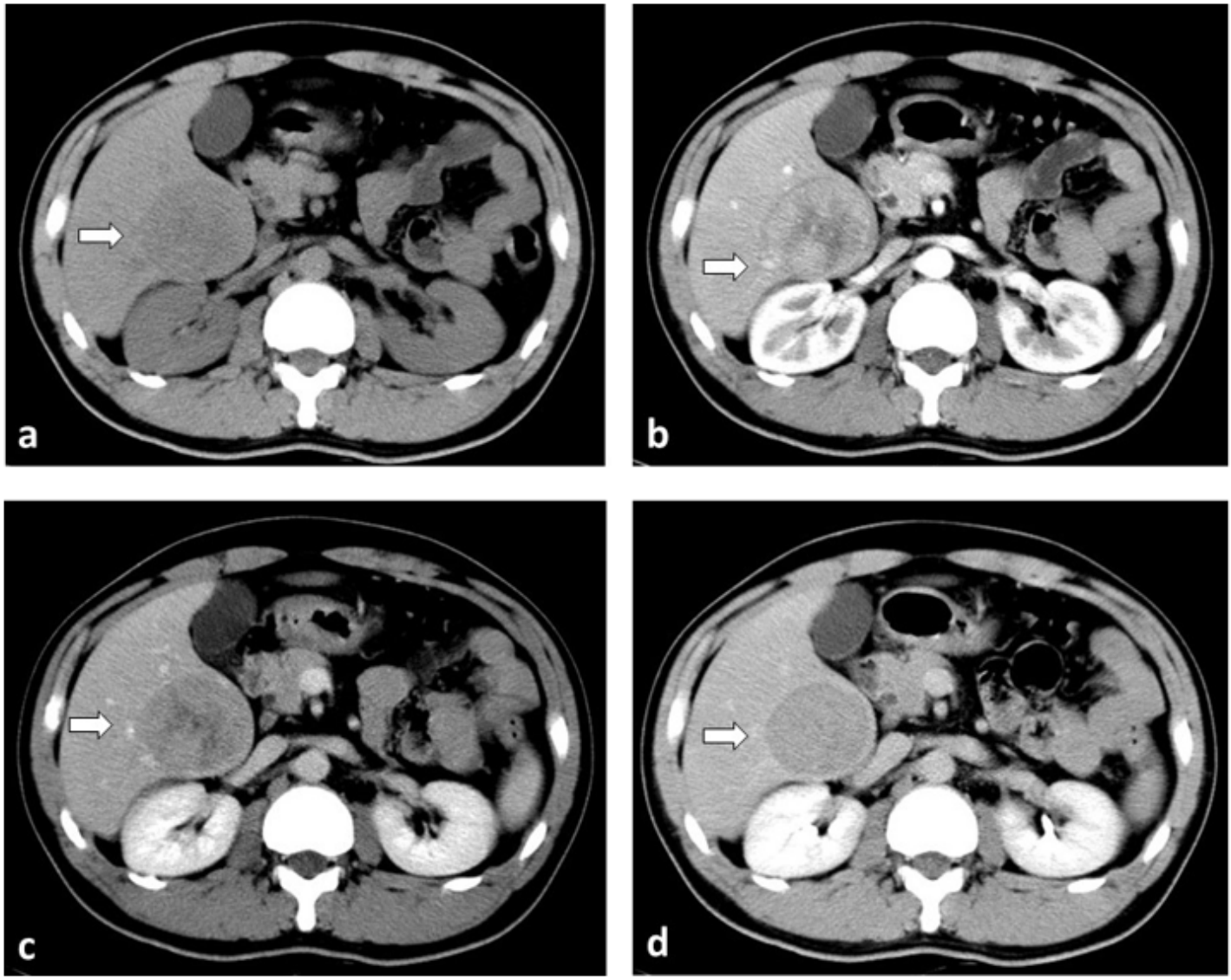

Figure 2

Nodular-type HCC in a man with HIV-HCC. (a) Axial unenhanced CT scan shows a hypoattenuating mass (arrow). (b) Axial arterial-phase CT scan from a multiphase study shows hyperenhancement of the mass (arrow). (c) Axial portal venous and (d) delayed phase CT scan demonstrate washout of the hyperenhancement seen in the arterial phase (arrow).

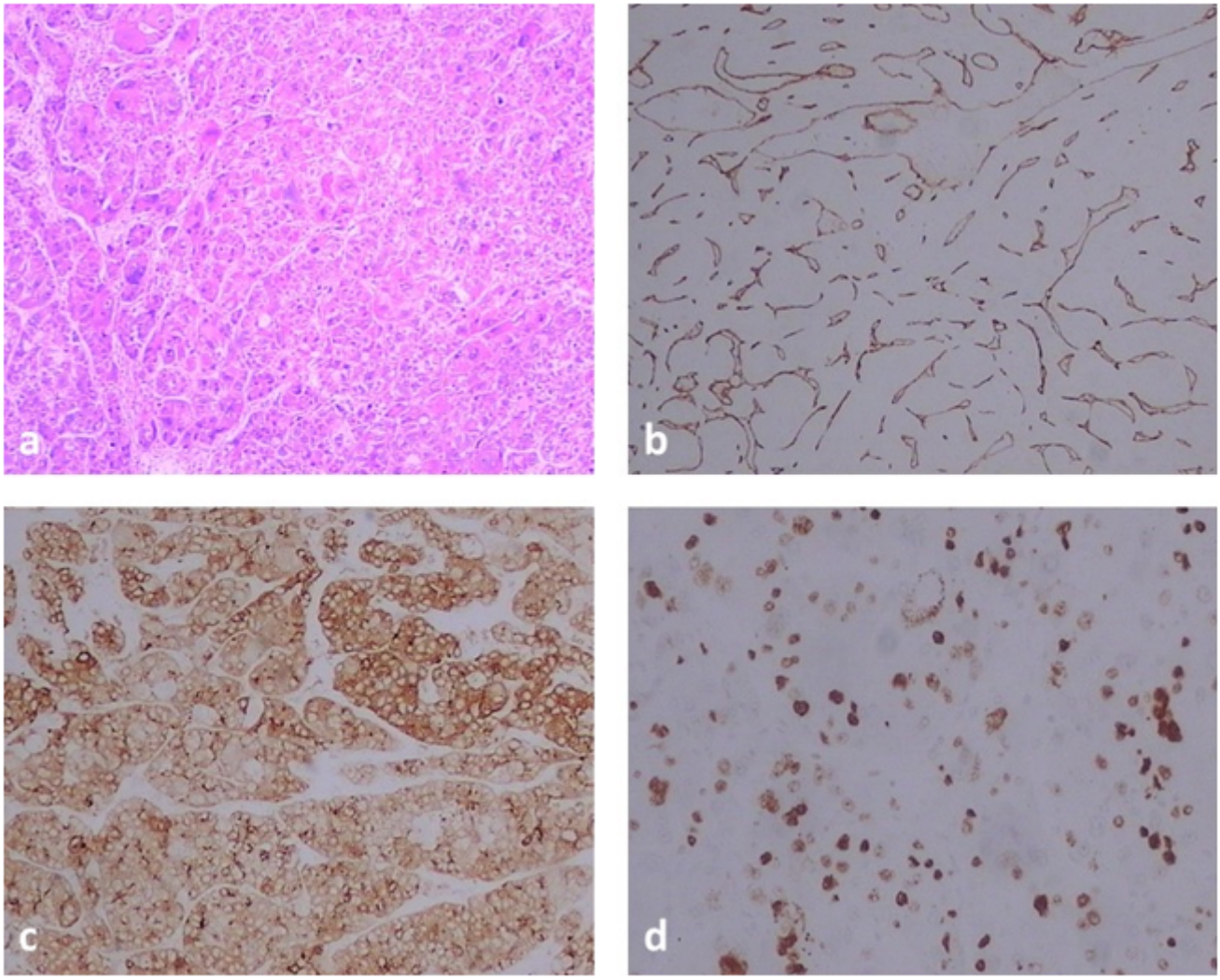

Figure 3

Same patient as in Figure 2. (a) HE staining in hepatocellular carcinoma and adjacent non-tumour tissue (× 200); (b) CD34 shows liver blood vessels in the marginal tissue of HCC (× 200); (c) Hepatocellular carcinoma shows diffuse positive cytoplasmic GPC-3 immunostaining (× 200); (d) Cells positive for Ki-67 in hepatocellular carcinoma (× 200).