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Liver resection of hepatocellular carcinoma in HIV-HCV co-infected patients: a retrospective case series

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Abstract

Introduction: Despite the effectiveness of new therapies and awareness campaigns, the number of seropositive patients is increasing every year. Recently, other causes of death, not directly related to HIV, have emerged, such as chronic liver disease. The risk of hepatocellular carcinoma (HCC) is seven times greater in HIV patients than in noninfected patients, and it is especially attributable to HCV infection. The aim of our study was to evaluate clinical outcomes of HCC in HIV-HCV co-infected patients after liver resection (LR).

Materials and methods: The current study was conducted on a prospective database and reviewed retrospectively. All consecutive patients with HCC treated by LR from January 2013 to March 2019 at the Luigi Sacco University Hospital in Milan were enrolled. We included patients older than 18 years of age with HCV-related HCC, and in this set of patients, we identified two groups based on the presence of HIV infection.

Results: We identified 16 patients with HCV infection and precisely five with HIV-HCV co-infection and eleven with HCV infection alone. All HIV patients were male against 72.7% in the non-HIV group ($p = 0.509$). All patients had optimal HIV virologic control and a normal CD4 T-cell count. The mean diagnosis-to-treatment interval was statistically different between the two groups (HIV versus non-HIV: 1.2 ± 0.55 months versus 2.39 ± 1.09 months, $p = 0.039$).

No other significant differences were found between HIV-HCV co-infected patients and HCV-infected patients. Long-term outcomes in terms of OS and RFS were similar between the two groups.

Conclusions: With a multidisciplinary approach and intensive support, LR can be a safe and efficacious procedure in HIV-HCV patients. For these reasons, we should not exclude potential patients merely on the basis of their HIV seropositivity.

Keywords: Liver cancer, Hepatocarcinoma, HCV, HIV, Liver surgery, Liver resection

Introduction

The human immunodeficiency virus (HIV) infection is considered a pandemic with 39 million infected people globally and 690,000 deaths for acquired immunodeficiency syndrome (AIDS) in 2019 [1]. Despite the effectiveness of new therapies and awareness campaigns, the number of seropositive patients is increasing every year. The highly active antiretroviral agent therapy (HAART) has reduced the risk of developing AIDS and the incidence of AIDS-defining malignancies (ADM), such as aggressive non-Hodgkin lymphoma, Kaposi's sarcoma, and invasive cervical cancer [2].

Nowadays, HIV patients can have an excellent quality of life and a long survival, but at the same time, an increased risk of many non-ADM tumors (NADM) has

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been observed. Malignant tumors in HIV patients result in higher mortality than tumors in non-HIV patients due to immunosuppression, delayed diagnosis, and unequal treatment. Recently, other causes of death, not directly related to HIV, have emerged, such as chronic liver disease [3, 4].

Liver disease is the most common non-AIDS-related cause of mortality in HIV-infected patients, and it is mainly related to the presence of HBV or HCV co-infection as well as to the hepatotoxicity of antiretroviral therapy and alcohol abuse. The risk of hepatocellular carcinoma (HCC) is seven times greater in HIV patients than in noninfected patients, and it is especially attributable to HCV infection [5].

In the last decades, the highest rate of HCV-HIV co-infection occurred parenterally with a rising incidence for intravenous drug users. The clinical course of HCC in HIV patients is not well defined, as most of the studies are made up of small sample, with different designs and containing patients who were not subjected to HAART [3, 6]. Complicating the picture is the inadequate or even no treatment used in HIV patients with HCC, although many of these patients were younger and in an earlier stage according to the Barcelona Clinic Liver Cancer classification (BCLC) [7].

Since some studies have shown a more aggressive course in co-infected patients [8], the early diagnosis of HCC is particularly relevant for their correct management. Effective medical treatment of both viruses is therefore recommended to achieve a favorable outcome in co-infected patients, with an indication to suppress viral HIV replication before starting anti-HCV treatment [9–11].

Although surgical procedures data for different types of cancer are reported [12], there are no universal guidelines for the management of HCC in HIV patients, and the literature has often given conflicting and unclear results. Only few main articles are reported on this topic, specifically on outcomes after liver transplantation (LT). Despite the different approaches, both these studies consider LT an effective option for selected HIV patients with no differences in survival and HCC recurrence [13–15].

The aim of our study was to evaluate clinical outcomes of HCC in HIV-HCV co-infected patients after liver resection (LR).

Materials and methods

The current study was conducted on a prospective database and reviewed retrospectively. All consecutive patients with hepatocellular carcinoma treated by liver resection from January 2013 to March 2019 at the Luigi Sacco University Hospital in Milan were enrolled. We included patients older than 18 years of age with HCV-related HCC, and in this set of patients, we identified two groups based on the presence of HIV infection. Our analysis focused on the study of the HIV+/HCV+ co-infected group; we therefore excluded patients with HCC related to other etiologies and prior operated.

Preoperative evaluation

The diagnosis of HCC was reached according to the European Association for the Study of the Liver (EASL) guidelines [16]. All patients were preoperatively investigated by both quadriphasic-computed tomography (CT) and magnetic resonance imaging (MRI) with liver-specific contrast agents, notably after the finding of a focal lesion > 1 cm on abdominal ultrasonography. Percutaneous liver biopsy was limited to doubtful cases with atypical nodules at imaging.

Patients were evaluated in a multidisciplinary board with hepatologists, oncologists, interventional radiologists, and general surgeons. The combination of CT and MRI was used to enhance sensitivity and specificity and to identify patients with multifocal disease, portal thrombosis, and extrahepatic dissemination. Radiological parameters of the number, site, and size of nodules were evaluated and used to define BCLC stage and potential inclusion in Milan criteria [16–20]. We analyzed liver global function and the presence of cirrhosis or steatosis through liver elastography, Child-Pugh score, and model for end-stage liver disease score (MELD) [21–24]. We assessed the presence of main comorbidities, and we used parametric scores to evaluate general clinical conditions like ECOG-PS [25], anesthesiologic risk like ASA score [26, 27], and the Charlson comorbidity index (CCI) [28] as overall comorbidity indicator.

Each patient was screened for the presence of hepatitis viruses and HIV. We considered a sustained virologic response (SVR) in HCV patients if viral RNA was undetectable in the blood for 6 months after completing antiviral treatment, and we assessed lymphocytes CD4 levels, adherence to HAART, and the presence of active viral replication specifically in HIV patients.

Before surgery, patients were controlled with serial laboratory tests: leucocytes, hemoglobin, platelets, liver transaminases, total bilirubin, serum albumin, sodium, creatinine, and prothrombin time. We routinely analyzed alpha-fetoprotein as an oncological marker.

Surgical technique and follow-up

Surgical resection was performed with laparoscopic or laparotomic approach, and the type of resection (anatomical or nonanatomical) was chosen preoperatively

considering liver function, tumor location, drainage tumor area, and technical difficulty of LR. The resections were carried out using a mixture of monopolar cautery, bipolar forceps, and ultrasonic dissection devices. Intraoperative ultrasonography (IOUS) was routinely performed for planning and for guiding the liver dissection. Intermittent Pringle maneuver was used with cycles of 15 min of inflow occlusion followed by 5 min of reperfusion when necessary. We evaluated surgical duration, the need for blood or plasma transfusion, and intraoperative complications.

In the postoperative course, patients were evaluated clinically and with blood tests to assess general and specific complication, like biliary complications (bile leaks), postoperative liver failure, and ascites. Postoperative complications were classified according to the Clavien-Dindo classification [29], and the assessment of patients' overall morbidity was based on comprehensive complication index (CCI) [30, 31]. In addition, we considered the length of hospital stay, the need of reintervention, and 30-day mortality.

Histological examination of the surgical specimens and parenchymal biopsy of an uninvolved site were performed to evaluate the general liver status. We analyzed pathologic parameters like Edmondson grading, numbers of lesions, dimension of major nodule, satellitosis, microvascular invasion, and resection margin distance and status.

After hospital discharge, a follow-up program was planned for all patients including clinical, laboratory, and imaging evaluation with periodic infectious and oncological follow-up. We focused on the eventual occurrence of recurrence, its characteristics, and its management. In patients deceased during the follow-up, we distinguished the causes of death based on the progression of the underlying liver disease, cancer progression, or other causes.

Statistical analysis

Categorical variables are reported as number of cases and percentages. Continuous variables are expressed as mean ± standard deviation (SD) or by median and range. Overall survival (OS) and recurrence-free survival (RFS) were evaluated using the Kaplan-Meier method and the compared with the log-rank test. Differences between HCV+/HIV+ and HCV+/HIV− groups have been assessed by Fisher exact test and the Freeman-Halton extension for categorical variables, by Student's *t*-test and Wilcoxon-Mann-Whitney test for continuous variables when appropriate. Statistical significance was set at $p < 0.05$. Statistical analysis was performed with IBM SPSS Statistics 25.0.

Results

Between January 2013 and March 2019, a series of 111 patients underwent liver surgery in our unit for either benign or malignant tumors, among these 40 for HCC. We identified 16 patients with HCV infection and precisely five with HIV-HCV co-infection and eleven with HCV infection alone.

General clinical features and preoperative data of the two groups are shown in Table 1. All HIV patients were male against 72.72% in the non-HIV group ($p = 0.509$); non-HIV patient tended to be older, but there was no statistical difference between the two groups (mean age 53.2 ± 4.66 versus 62.54 ± 10.27, $p = 0.076$). No differences in performance status (ECOG PS), ASA score, Charlson comorbidity index, and other organ-specific comorbidities were found. Child-Pugh and MELD score were similar between the two groups, and no statistically significant differences were observed in the alpha-fetoprotein levels ($p = 0.085$) and other preoperative biochemical parameters evaluated.

SVR was achieved by 80% and 90.9% of HIV-HCV co-infected patients, and HCV-infected patients, respectively ($p = 0.99$).

All patients had optimal HIV virologic control and a normal CD4 T-cell count (mean ± *SD* 600.2 ± 267.33 cells/mmc). The therapeutic management with HAART allowed a long-lasting HIV suppression before and after surgery (Table 2). Only one patient was classified at stage CDC-C according to the Centers for Disease Control and Prevention categories (CDC) for a previous HIV encephalopathy, and his specific therapies were incompatible with the anti-HCV ones.

No significant differences were found on number and size of HCC nodules (Table 1). All HIV patients had a single nodule compared to non-HIV group with number of nodules from 1 to 3 ($p = 0.244$), and all were at BCLC stage 0 or A ($p = 0.99$). Only one patient in the non-HIV group showed portal vein thrombosis (9.09%).

Table 3 summarizes surgical and histologic outcomes. The mean diagnosis-to-treatment interval was statistically different between the two groups (HIV versus non-HIV: 1.2 ± 0.55 months versus 2.39 ± 1.09 months, $p = 0.039$).

Laparoscopic resection was performed in 3 HIV patients (60%) and 3 (27.72%) non-HIV patients ($p = 0.299$). In our series, conversion to open surgery was never necessary. Within the non-HIV group, one patient underwent combined LR and radiofrequency ablation (9.09%). We did not find significant statistical difference between the two groups regarding type of resection (anatomical versus nonanatomical), Pringle maneuver, and intraoperative transfusions.

Histological examination confirmed HCC in all patients without other histotype combinations. The

Table 1 General clinical features of enrolled patients

	HIV+/HCV+	**HIV−/HCV+**	***p*-value**
Patients, *n*	5	11	
Sex, *n* (%)			
Male	5 (100)	8 (72.73)	0.509
Female	0	3 (27.27)	
Age (years)			
Mean ± SD (min; max)	53.2 ± 4.66 (49; 60)	62.54 ± 10.27 (48; 79)	0.076
Median (25°; 75°)	51 (50; 56)	62 (64; 70.5)	
ECOG PS, *n* (%)			
0	5 (100)	8 (72.72)	0.509
1	0 (0)	3 (27.27)	
Comorbidities, *n* (%)			
Diabetes	1 (20)	1 (9.09)	0.99
Heart failure	0	1 (9.09)	0.99
Chronic kidney disease	0	0	1
Respiratory insufficiency	0	3 (27.27)	0.509
Previous abdominal surgery	2 (40)	7 (63.63)	0.596
Charlson comorbidity index			
Mean ± SD (min; max)	4.8 ± 1.09 (4; 6)	5.36 ± 1.36 (3; 8)	0.447
Median (25°; 75°, %)	4 (4; 6)	5 (5; 6)	
< 7	6 (100)	9 (81.81)	0.515
≥ 7	0	2 (18.18)	
ASA score, *n* (%)			
1	0	1 (9.09)	0.99
2	4 (80)	8 (72.72)	
3	1 (20)	2 (18.18)	
Cirrhosis, *n* (%)	4 (80)	9 (81.81)	0.99
Child-Pugh class, *n* (%)			
A	4 (80)	11 (100)	
B	1 (20)	0	0.315
C	0	0	
MELD			
Mean ± SD (min; max)	9 ± 2.82 (6; 12)	9.18 ± 2.4 (7; 14)	0.895
Median (25°; 75°, %)	8 (7; 12)	8 (8; 10)	
AFP ng/mL, *n* (%)			
≤ 20	4 (100)	4 (40)	0.085
> 20	0	6 (60)	
HCV treatment response, *n* (%)			
SVR	4 (80)	10 (90.9)	0.99
Non-SVR	1 (20)	1 (9.09)	
Number of nodules at imaging, *n*	5	15	
Mean (range)	1 (1; 1)	1.36 (1; 3)	0.244
Largest nodule diameter at imaging (mm)			
Mean ± SD	26.4 ± 14.2	29.3 ± 11	0.57
Portal vein thrombosis, *n* (%)	0	1 (9.09)	0.99
BCLC stage, *n* (%)			
0-A	5 (100)	9 (81.81)	0.99
B-C	0	2 (18.18)	
Milan criteria, *n* (%)			
Out	0 (0)	2 (18.18)	0.99
In	5 (100)	9 (81.81)	

SD standard deviation; *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *ASA* American Society of Anesthesiologist classification, *MELD* model for end-stage liver disease, *AFP* alpha-fetoprotein, *SVR* sustained virologic response, *BCLC* Barcelona Clinic Liver Cancer

Table 2 Viro-immunological preoperative features of HIV-HCV co-infected patients

N°	Sex	Age (years)	MELD	Child	HCV RNA	HCV genotype	T-CD4 (cell/mmc)	HAART	HIV viral load	AIDS defining conditions	CDC	HIV diagnosis age
1	M	56	8	5	+	/	860	Yes	< 37	HIV-related encephalopathy	C1	34
2	M	50	7	5	-	1a	848	Yes	< 37	No	A1	28
3	M	49	12	5	-	/	353	Yes	109	No	A2	43
4	M	51	12	7	-	3a	294	Yes	< 37	No	A2	20
5	M	60	6	5	-	/	646	Yes	< 37	No	A1	29

CDC Centers for Disease Control and Prevention classification

Table 3 Surgery and pathology

	HIV+/HCV+	HIV−/HCV+	*p*-value
Diagnosis-to-treatment interval (months), mean ± SD	1.2 ± 0.55	2.39 ± 1.09	0.039
Type of procedure, *n* (%)			
Resection	5 (100)	10 (90.9)	0.99
Resection + ablation	0	1 (9.09)	
Surgical procedure, *n* (%)			
Open	2 (40)	8 (72.72)	0.299
Laparoscopy	3 (60)	3 (27.27	
Type of resection, *n* (%)			
Wedge resection	2 (40)	9 (81.81)	0.244
Segmentectomy	3 (60)	2 (18.18)	
Pringle maneuver, *n* (%)	1 (20)	3 (27.27)	0.99
Operative time (min), mean ± SD	244 ± 89	306 ± 50	0.232
Intraoperative transfusions, *n* (%)			
Red blood cells	1 (20)	4 (36.36)	0.99
Histological evaluation			
Number of nodules, *n*	5	14[a]	
Mean (range)	1 (1; 1)	1.27 (1; 2)	0.242
Largest nodule diameter (mm)	27 ± 14.83	30.7 ± 12.46	0.53
mean ± SD			
Edmondson-Steiner grading, *n* (%)			
1–2	4 (80)	7 (63.63)	0.99
3–4	1 (20)	4 (36.36)	
Microvascular invasion, *n* (%)	2 (40)	3 (27.27)	0.99
Satellitosis, *n* (%)	1 (20)	1 (9.09)	0.99
Residual tumor, *n* (%)			
R0	5 (100)	10 (90.91)	0.99
R1	0	1 (9.09)	
Surgical margin (mm), mean ± SD	6.25 ± 4.57	4 ± 3.57	0.473

[a] *SD* standard deviation, one nodule identified at imaging was treated with RFA

largest nodule diameter was 27 ± 14.83 mm in the HIV group and 30 ± 12.46 mm in the non-HIV group ($p = 0.53$). According to Edmondson-Steiner grading, low-grade HCC were found in 80% and 63.6% of HIV and non-HIV patients respectively ($p = 0.99$). Surgical margin was positive for cancer cells in a non-HIV patient (R1).

Postoperative course was substantially overlapping between the two groups (Table 4). Mean hospital stay was 9.6 ± 4.45 days in the HIV group and 10.81 ± 3.71 days in the non-HIV group ($p = 0.6$). The occurrence of postoperative complications was 40% in the HIV group and 72.7% in the non-HIV ($p = 0.299$). According to the Clavien-Dindo Classification and the Comprehensive Complication Index, there were not significantly differences between the two groups ($p = 0.594$ and $p = 0.815$, respectively). Ascites was described in two patients of the non-HIV group (18.18%), each of them responsive to diuretics and without further complication. Post-hepatectomy liver failure did not occur, and 30-day mortality rate was zero in both groups.

Long-term outcomes in terms of OS and RFS are similar between the two groups. The OS at 1 and 3 years was 100% and 75% for HIV-HCV patients and 90.9% and 53.3% for HCV patients respectively ($p = 0.351$; Fig. 1). The RFS at 1 and 3 years was 80% and 53.3% for HIV-HCV patients and 82.5% and 57.8% for HCV patients respectively ($p = 0.873$; Fig. 2).

All relapses were intrahepatic and precisely in the HIV group were distant intrahepatic; in the non-HIV group, two of them were local recurrence ($p = 0.467$). Treatment of HCC recurrence is shown in Table 4. One death was observed in the HIV group due to HCC progression, while in the non-HIV group, four deaths were described due to HCC recurrence and/or HCV exacerbation.

Discussion

Hepatocellular carcinoma has become one of the main malignant cancers affecting HIV patients (NADM) and one of the main causes of death in this category.

Liver transplant for HCC in HIV patients began to be considered from 2002 in an extremely limited number of centers on extremely limited numbers of patients. Only few important articles were published about the

Table 4 Outcomes and survival analysis

	HIV+/HCV+	HIV−/HCV−	*p*-value
Days of hospitalization			
°Mean ± SD	9.6 ± 4.45	10.81 ± 3.71	0.6
Complications, *n* (%)	2 (40)	8 (72.72)	0.299
Clavien-Dindo score, mean ± SD	1 ± 1.41	1.36 ± 1.2	0.594
°≤ 2	4 (80)	10 (90.91)	0.99
°> 2	1 (20)	1 (9.09)	
Comprehensive complication index			
°Mean ± SD (min; max)	12.8 ± 17.6 (0; 34)	12.7 ± 11.2 (0; 34)	0.815
°Median (25; 75° percentile)	0 (0; 30)	9 (4.5; 21.5)	
Postoperative ascites, *n* (%)	0	2 (18.18)	0.99
Overall survival (months)			
°Mean ± SE	36 ± 2.59	29.9 ± 3.49	0.443
°Death, *n* (%)	1 (20)	4 (36.36)	0.99
°OS at 1 year	100%	90%	
°OS at 3 years	75%	53.3%	
Recurrence-free survival (months)			
°Mean ± SE	27 ± 5.69	26.78 ± 4.41	0.873
°Relapse, *n* (%)	2 (40)	4 (36.36)	1
°RFS at 1 year	80%	80.8%	
°RFS at 3 years	53.3%	58.9%	
Type of relapse, *n* (%)			
°Extrahepatic, *n* (%)	0	0	
°Intrahepatic, *n* (%)	2	4	
°Local recurrence, *n* (%)	0	2 (50)	0.467
°Distant intrahepatic, *n* (%)	2 (100)	2 (50)	
Treatment of relapse, *n* (%)			
°Liver resection	0	0	
°Termoablation	0	1 (25)	
°Liver transplant	1 (50)	0	
°TACE	0	0	0.20
°Medical treatment	0	3 (75)	
°Palliative treatment	1 (50)	0	
°Other	0	0	

SD standard deviation, *SE* standard error

impact of HIV infection on liver transplantation for HCC [13–15], and no differences in survival and HCC recurrence were observed. DAAs therapy for HCV were not yet available in that time, and no other treatments were analyzed. In our study, we evaluated liver resection as first treatment for HIV-HCV co-infected patients, and we compared them to patients with HCV infection alone without significant outcomes differences.

In the present study, all HIV patients were at the early or very-early stage (BCLC 0 or A) with a single nodule, and LR was the first-choice treatment according to the main guidelines [16, 20]. It is important that all centers dealing with liver diseases and mainly HCC discuss with a multidisciplinary team, consider liver transplantation, and refer the patients to the specific centers before or soon after a bridge-to-transplant therapy, especially since donation from deceased HIV-infected donors to HIV-infected recipients is possible, at least in Italy [32].

In published literature, HIV-HCV patients tend to be young at the time of HCC diagnosis. Some authors suggest that seropositive patients develop neoplastic pathology almost 10 years earlier suggesting a rapid rate of progression to cirrhosis and a greater aggressiveness of HCC or possibly an earlier age of infection

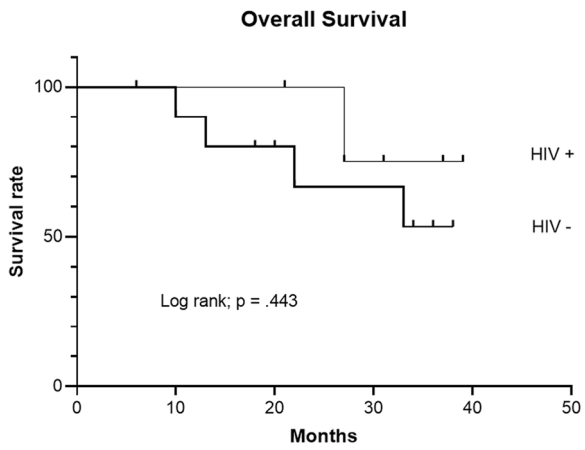

Fig. 1 Overall survival after liver resection in HIV-positive and HIV-negative patients

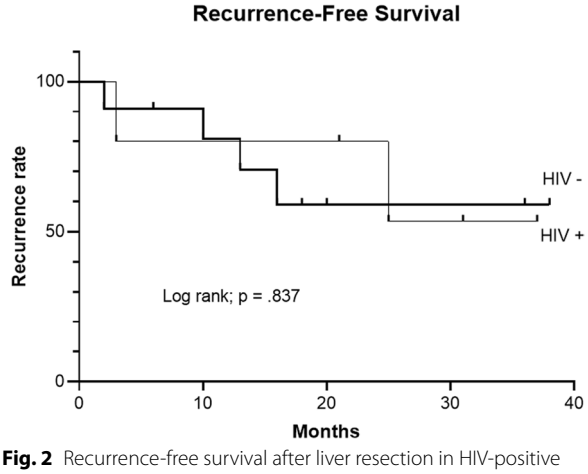

Fig. 2 Recurrence-free survival after liver resection in HIV-positive and HIV-negative patients

[33]. However, many papers pay attention on the correct management of HAART and how a suppression of the viral load can allow to HIV patients a better prognosis [3, 6]. At the same time, a SVR of HCV should be reached to expand the benefit [34], and the landscape is changing day by day due to DAA therapy.

Notably, a special attention must be paid to seropositive for an early diagnosis of HCC and a potentially curative treatment [35]. In this study, all HIV-HCV patients were strictly controlled by hepatologists in our Infectious Disease Clinic with an optimum treatment adherence; the diagnosis-to-treatment interval was indeed significantly shorter for HIV-positive patients ($p = 0.039$). There were no statistically significant differences in OS and RFS between the two groups. LR can reach similar short- and long-term oncological outcomes in patients with HCC whether they have HIV or not. Nonetheless, these results must be interpreted with caution due to several limitations and lack of prior papers on this topic. The present study is limited by its small sample and the retrospective design. Potential biases could be smoothed in the future with a bigger sample and a propensity score study.

Conclusions

In conclusion, our experience shows how a correct management of HAART therapy and an adequate treatment of hepatocellular carcinoma in these patients can allow for an overall survival rate similar to that of non-HIV patients. With a multidisciplinary approach and intensive support, LR can be a safe and efficacious procedure in HIV patients. For these reasons, we recommend the same approach for patients with HIV-HCV co-infection as HCV mono-infection.

Authors' contributions

FC and LB collected data, made the statistical analysis, and wrote the manuscript. MC, AT, and LP participated in the design of the study, the conceptualization of the study, and its coordination. AT helped writing the draft. MS helped collecting data and revising literature. DF supervised the whole project. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standard on human experimentation and with the Helsinki Declaration of 1964 and its later amendments. The study was approved by the local responsible committee (L. Sacco Hospital no. 00-28004). This article does not contain any studies with animal subjects performed by any of the authors.

Consent for publication

Informed consent was obtained from all patients for being included in the study.

Competing interests

The authors declare that they have no competing interests.

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