Surgical Complications Requiring an Early Relaparotomy in HIV-Infected Liver Transplant Recipients: Risk Factors and Impact on Survival

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ABSTRACT

Aim. We aimed to analyze the risk factors for early surgical complications requiring relaparotomy and the related impact on overall survival (OS) in HIV-infected patients submitted to liver transplantation.

Methods. We performed a retrospective study on a nationwide multicenter cohort of 157 HIV-infected patients submitted to liver transplantation in 6 Italian transplant units between 2004 to 2014.

Results. The median preoperative model for end-stage liver disease score was 18 (interquartile range 12-26.5). An early relaparotomy was performed in 24.8% of patients, and the underlying clinical causes were biliary leak (8.2%), bleeding (8.2%), intestinal perforation (4.5%), and suspected vascular complications (3.8%). The OS at 1, 3, and 5 years was 74.3%, 68.0%, and 60.0%, respectively, and an early relaparotomy was not a prognostic factor itself, but an increasing number of relaparotomies was associated with decreased survival (hazard ratio = 1.40, 95% confidence interval [CI] 1.07-1.81, $P = .01$). In the multivariate analysis, preoperative refractory ascites (odds ratio 3.32, 95% CI 1.18-6.47, $P = .02$) and Roux-en-Y choledochojejunostomy reconstruction (odds ratio 12.712, 95% CI 2.47-65.38, $P \leq .01$) were identified as significant risk factors for early relaparotomy.

Conclusions. In HIV-infected liver transplant recipients, an increasing number of early relaparotomies due to surgical complications did negatively affect the OS. Preoperative refractory ascites reflecting a severe portal hypertension and a difficult biliary tract reconstruction requiring a Roux-en-Y choledochojejunostomy were associated with an increased risk of early relaparotomy.

LIVER transplantation (LT) has been demonstrated to be a feasible and effective treatment for HIV-positive patients with end-stage liver disease, even in the presence of hepatocellular carcinoma (HCC), reaching outcomes comparable to non-HIV patients [1,2]. However, these results

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are necessarily conditioned by restrictive preoperative patient selection criteria [2]. Furthermore, some specific subgroups such as HIV/hepatitis C virus (HCV)-coinfected patients still have a poor prognosis, and clinical series of unselected HIV patients submitted to overall abdominal surgical procedures were reported to have a high incidence of postoperative complications (25%-41%) [3,4], with HIV-positive status being identified as an independent risk factor for postoperative sepsis [4]. The aim of the present study was to analyze the risk factors of a liver-transplanted, HIV-positive patient for developing an early postoperative complication requiring a relaparotomy and the related impact on overall survival (OS).

MATERIALS AND METHODS

This was a nationwide, retrospective study on a multicenter cohort of 157 HIV patients listed for and submitted to primary LT at 6 Italian transplant units between 2004 to 2014. The national protocol for LT inclusion criteria was applied as described elsewhere [2]. Early relaparotomy was defined as an urgent or planned surgical procedure within 30 days after LT, when endoscopic and radiologic interventions were inappropriate, unfeasible, or unsuccessful. The overall number of relaparotomies per patient was evaluated as a continuous variable, with 0 identifying no reoperation. Patients with retransplantation within 30 days were excluded.

Statistical Analysis

Categorical variables and frequencies were expressed by percentage, while continuous variables were expressed by mean ± standard deviation or median (interquartile range [IQR]), as appropriate. OS was defined as the time (months) from LT to either death or last observation. Analysis of survival was done using Cox proportional hazard models, after the proportional hazards assumption had been verified. The variables included in the analysis were the patients characteristics (age, sex, body mass index [BMI], Model for End-Stage Liver Disease [MELD] score, Child-Pugh, HCV positivity, HCV-RNA serum positivity, hepatitis B virus [HBV] positivity, HCC diagnosis, international normalized ratio [INR], bilirubin, creatinine, sodium and albumin plasma level, presence of refractory ascites, portosystemic encephalopathy and/or pretransplant portal thrombosis, previous abdominal surgery, and time in waiting list), donors characteristics (age, sex, and BMI), graft characteristics (steatosis, type, and total ischemia time), transplant details (combined kidney-liver, urgent LT, operative time, packed blood cells transfusion, frozen fresh plasma transfusion, Kehr tube placement, use of Roux-en-Y choledochojejunostomy, aortohepatic jump, and type of outflow reconstruction), early relaparotomy, number of early relaparotomies per patient, and length of hospital stay. Among patients with an OS longer than 1 month, univariate and multivariate logistic regression were used to explore predictive factors for early relaparotomy after LT. Multivariate stepwise analyses included all variables significant at $P \leq .10$ in univariate analysis. Retention in the stepwise model required the variables being significant at $P \leq .05$ in a multivariate analysis. Analogue clinical variables as for OS analysis were considered.

RESULTS

A total of 160 HIV-positive patients underwent primary LT during the study period (Table 1). Three patients were excluded because of retransplantation within 30 days, thus the final study population consisted of 157 recipients. The male-to-female ratio was 136:21, with a mean age at LT of 49.2 ± 5.4 years. Virologic status was 90.5% HCV co-infection, 19.1% HBV, and 12.1% HCV-HBV. HCC was present in 37.8% of patients. The median MELD score was 18 (12-26.5). LT was undertaken in urgent setting in 26.8%. An aortohepatic jump became necessary for reconstruction in 6.4% and Roux-en-Y choledochojejunostomy in 7% of patients. During the postoperative course, 39 (24.8%) patients underwent an early relaparotomy on a median postoperative day 5 (1-12) (Table 1). The clinical indications for the index relaparotomy were bleeding in 13 (8.2%) patients, biliary leak in 13 (8.2%), intestinal perforation in 7 (4.5%), and concern for vascular compromise in 6 (3.8%). No cases of negative re-exploration were recorded. The median total number of relaparotomies within the first 30 days post-LT among patients who had at least 1 reoperation was 1 (1-2). Within the first year after LT, additional relaparotomies were required just in 6 patients, establishing an overall 1 year reoperation rate of 28.6%. Overall, the median length of hospital stay was 18 days (12-27 days). The median follow-up after hospital discharge was 25.4 months (5.7-70.7 months).

One hundred and forty-six patients survived more than 30 days after LT, and within this patient group, the risk factors for early relaparotomy were investigated. In univariate analysis, preoperative refractory ascites (odds ratio [OR] 3.32, 95% confidence interval [CI] 1.479-7.458, $P < .01$) and Roux-en-Y choledochojejunostomy reconstruction (OR 16.15, 95% CI 3.241- 80.443, $P < .01$) were identified as significant risk factor for early relaparotomy. Both variables maintained significance even in multivariate analysis (ascites: OR 3.32, 95% CI 1.185-6.470, $P = .02$; Roux-en-Y choledochojejunostomy reconstruction: OR 12.712, 95% CI 2.471-65.385, $P < .01$).

The OS at 1, 3, and 5 years was 74.3%, 68.0%, and 60.0%, respectively. Early relaparotomy was not associated with an increased mortality ($P = .117$), but the number of relaparotomies per patient due to surgical complications within the first month post-LT did actually demonstrate a significant prognostic value (hazard ratio [HR] = 1.400, 95% CI 1.079-1.817, $P = .011$) as well as HCV-RNA positivity (HR = 2.262, 95% CI 1.019-5.024, $P = .045$), HBV positivity (HR = .403, 95% CI 171-.944, $P = .036$), Child-Pugh score (HR = 1.550, 95% CI 1.044-2.300, $P = .030$), MELD score (HR = 1.046, 95% CI 1.015-1.079, $P = .004$), and urgent LT (HR = 2.007, 95% CI 1.137-3.541, $P = .016$). In multivariate analysis, the MELD score maintained significance (HR = 1.048, 95% CI 1.015-1.081, $P = .003$)

DISCUSSION

An early relaparotomy after LT represents a major physical stress for the patient and is associated with increased post-LT mortality in the overall liver transplanted population [5,6]. Limited data are available regarding the postoperative

Table 1. Demographic and Clinical Data, Graft Characteristics, and Surgical Details

	Total (N = 157)	No Early Relaparotomy Group (n = 118)	Early Relaparotomy Group (n = 39)
Recipient sex, M:F	136:21	102:16	34:5
Recipient age, mean ± SD, y	49.2 ± 5.4	49.1 ± 5.8	49.4 ± 4.2
Recipient BMI, mean ± SD, kg/m^2	23.7 ± 3.8	23.5 ± 3.7	23.9 ± 3.9
HCV positivity, no. (%)	142 (90.5)	108 (91.5)	34 (87.1)
HCV-RNA serum positivity, no. (%)	108 (73.0)	79 (66.9)	29 (74.4)
HBV positivity, no. (%)	30 (19.1)	23 (14.49)	7 (17.9)
HCC diagnosis, no. (%)	59 (37.8)	47 (39.8)	12 (30.7)
MELD score, median (IQR)	18 (12-26.5)	18 (12-25)	18 (13-29)
Child-Pugh score, no. (%)			
A	29 (19)	22 (19.3)	7 (17.9)
B	57 (37.2)	45 (39.5)	12 (30.7)
C	67 (43.8)	47 (41.2)	20 (51.3)
INR, mean ± SD	1.7 ± 0.6	1.6 ± 0.5	1.8 ± 0.7
Bilirubin serum level, median (IQR), mg/dL	3.8 (1.5-12.5)	3.3 (1.4-13.5)	4.5 (2.3-12)
Creatinine serum level, median (IQR), mg/dL	1 (0.89-1.2)	1 (0.89-1.21)	1 (0.85-1.18)
Sodium serum level, median (IQR), mEq/L	137.5 (135-140)	138 (135-140)	137 (134-140)
Albumin plasm level, median (IQR), mg/dL	3.1 (2.6-3.7)	3.2 (2.6-3.7)	3.0 (2.2-3.6)
Refractory ascites, no. (%)	73 (46.5)	47 (39.8)	26 (66.6)
Portosystemic encephalopathy, no. (%)	53 (37.1)	38 (32.2)	15 (38.4)
Pretransplant partial portal thrombosis, no. (%)	16 (10.3)	11 (9.3)	5 (12.8)
Previous abdominal surgery, no. (%)	23 (14.7)	21 (17.8)	2 (5.1)
Time in waiting list, median (IQR), mo	3.73 (1.02-9.72)	4 (1.43-9)	3 (0.76-10)
Donor age, mean ± SD, y	53.8 ± 17.5	52.4 ± 18.13	58.2 ± 14.9
Donor sex, M:F	86:71	19:20	67:51
Donor BMI, mean ± SD, kg/m^2	25.5 ± 3.8	25.6 ± 3.7	25.1 ± 4.2
Mild graft steatosis (0%-30%), no (%)	22 (14.6)	17 (14.4)	5 (12.8)
Type of graft, no. (%)			
Whole liver	147 (93.6)	112 (94.9)	35 (89.7)
Split liver	10 (6.4)	6 (5.1)	4 (10.2)
Total ischemia time, mean ± SD, min	481.3 ± 143.0	477.5 ± 138.1	492.5 ± 158.1
Urgent transplantation, no. (%)	42 (26.8)	28 (23.7)	14 (35.9)
Combined transplantation, no. (%)	9 (5.7)	6 (5.1)	3 (7.7)
Packed blood cells transfusion, mean (IQR), UI	4 (1-8)	4 (0-8)	4 (2-9)
Frozen fresh plasma transfusion, mean (IQR), mL	800 (0-2000)	800 (0-1800)	1300 (0-3000)
Kehr tube placement, no. (%)	60 (38.2)	46 (40.0)	14 (35.9)
Roux-en-Y choledochojejunostomy, no. (%)	11 (7.0)	3 (2.5)	8 (20.5)
Aortohepatic jump, no. (%)	10 (6.4)	6 (5.1)	4 (10.2)
Outflow reconstruction type, no. (%)			
Piggyback	93 (59.2)	73 (61.8)	20 (51.3)
Caval replacement	61 (38.9)	43 (36.5)	18 (46.1)
Side-to-side cavocavostomy	3 (1.9)	2 (1.7)	1 (2.6)

BMI, body mass index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; M:F, male-to-female ratio; SD, standard deviation.

course of HIV-infected liver recipients in terms of surgical complications. In non-transplant setting, the reported factors associated with increased operative morbidity and mortality in HIV/AIDS patients are a compromised performance status and associated severe comorbidities, a highly invasive surgical procedure, an emergency operation, and high bacterial contamination [7]. The most frequently reported risk factors for OS in HIV recipients consist of a pre-LT low BMI, MELD score, low glomerular filtration rate or need of combined kidney-liver transplantation, higher donor age, or donor risk index [8–10]. However, the most validated and severe factor for a poor prognosis is surely an HCV co-infection. These results were confirmed even by the present investigation. Nonetheless, the advent of the directly acting antivirals is expected to control and remove the negative effect of HCV on LT outcome in the near future [10]. Therefore, investigation of surgical morbidity in HIV-infected liver recipients may soon become of even greater relevance. So far, HIV infection has been associated with a prothrombotic state and with a related concern of increased risk of vascular complications [11]. However the data are conflicting without possibility to draw definitive conclusion [10], as also demonstrated by our previous report [12]. In the only other clinical series of 125 HIV-infected liver-transplanted patients investigating the impact of relaparotomy on outcome [1], re-exploration

without any time limit after LT was required in 11% of patients. It was significantly associated with increased mortality [HR: 2.8; 95% CI: 1.2-6.5; $P = .01$] at univariate analysis and marginally associated with higher risk of graft loss [HR: 2.8; 95% CI: 1.0-8.4; $P = .06$] at multivariate analysis. Conversely, in the present study, early relaparotomy itself did not represent a negative prognostic factor, but the overall number of early relaparotomies due to complications per patient did have a negative impact on the patients' OS. Severe portal hypertension and biliary reconstruction by Roux-en-Y choledochojejunostomy were associated with increased risk of early relaparotomy.

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