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Title page

Early post-liver transplant surgical morbidity in HIV infected recipients: risk factor for overall survival? A nationwide retrospective study.

Running title: relaparotomy in HIV transplanted patients

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ABSTRACT

Aim. 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.

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Methods. Retrospective study on a nationwide multicenter cohort of 157 HIV patients submitted to liver transplantation in 6 Italian Transplant Units between 2004-2014.

Results. An early relaparotomy was performed in 24.8% of cases and the underlying clinical causes were biliary leak(8.2%), bleeding(8.2%), intestinal perforation(4.5%) and suspect of vascular complications(3.8%). No differences in terms of prevalence for either overall or cause-specific early relaparotomies were noted when compared to a non-HIV control group, matched for MELD, recipient age, HCV-RNA positivity and HBV prevalence. While in the control group an early relaparotomy appeared a negative prognostic factor, such impact on OS was not noted in HIV recipients. Nonetheless increasing number of relaparotomies were associated with decreased survival. In multivariate analysis, preoperative refractory ascites and Roux-en-Y choledochojejunostomy reconstruction were significant risk factors for early relaparotomy.

Conclusions. In HIV liver transplanted patients, 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 increased risk of early relaparotomy.

Key words:HIV, Human Immunodeficiency Virus, liver transplantation, relaparotomy, complications

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Footnote Page

List of abbreviations:

BMI: body mass index,

C-ART: combined antiretroviral therapy;

CT: computed tomography,

HAART: highly active antiretroviral therapy,

HBV: hepatitis B virus,

HCC: hepatocellular carcinoma,

HCV: hepatitis C virus,

HDV: hepatitis D virus,

IQR: interquartile range;

LT: liver transplantation,

MELD: Model for end-stage liver disease,

MR: magnetic resonance,

OR: odds ratio,

OS: overall survival;

POD: postoperative day

SD: standard deviation,

UNOS: united network of organ sharing

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MAIN TEXT

INTRODUCTION

Since the introduction of highly active antiretroviral therapy (HAART) the life expectancy of HIV-positive patients has significantly improved [1-4]. Consequently, other non-AIDS-related complications have progressively emerged, in particular end-stage liver disease (ESLD) [5]. The pathogenesis of ESLD among HIV-infected patients is multifactorial, although the frequent HCV and/or HBV co-infection, alcohol abuse, and antiretroviral therapy-related toxicity appear to play a major role. Liver failure currently represents the most frequent cause of non-AIDS-related deaths in this patient population[1-4]. Liver transplantation has been demonstrated to be a feasible and effective treatment for ESLD HIV-positive patients, even in presence of HCC diagnosis, reaching outcomes comparables to non-HIV patients [1,5]. However, these results are necessarily conditioned by restrictive preoperative patients' selection criteria [5]. Furthermore, some specific subgroups such as HIV/HCV coinfected patients still have a poor prognosis and clinical series of unselected HIV patients submitted to overall abdominal surgical procedures report an high incidence of postoperative complications (25%-41%) [2-4], with HIV positive status being identified as an independent risk factor for postoperative sepsis [3,4].

Surgical complications after orthotopic liver transplantation requiring re-laparotomy are currently identified as negative prognostic factors for the patient and graft survival in the overall liver recipients population [6].

The aim of the present study was to analyze the risk factors for a liver transplanted HIV positive patient of developing an early postoperative complication requiring a re-laparotomy and the related impact on overall survival. To strengthen the clinical

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significance of the results, a comparison with a matched control group of non-HIV recipients was performed.

MATERIAL AND METHODS

This is a nationwide retrospective study on a multicenter cohort of 157 HIV patients listed and submitted to primary liver transplantation at 6 Italian Transplant Units between 2004-2014. Inclusion criteria for liver transplantation were the followings [5]:

- Absolute CD4 T cell count above 200 cells/mmc, if history of opportunistic infections or AIDS-defining malignancies;

- Absolute CD4 T cell count above 100 cells/mmc if absence of previous documented opportunistic infections;

- Undetectable HIV-RNA in blood for patients on combined antiretroviral therapy (C-ART); if not on C-ART, previous documentation of efficacious therapy or genotypic/phenotypic resistance test documenting available post-LT C-ART options; no active (< 1 yr) opportunistic infections, no wasting syndrome or severe malnutrition, compliance to therapies and to follow-up visits;

- Absence of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis (>1 month duration); Lymphoma or otherneoplasms, unless an adequate disease-free period is documented.

Demographic and clinical data of the recipients, intraoperative and postoperative outcomes were reviewed from the local electronic database.

Liver cirrhosis was diagnosed based on clinical and radiologic criteria and its severity was assessed by medical MELD score, Child-Pugh score and clinical signs of portal

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hypertension. The virological status was investigated for possible HCV, HBV, HDV co-infection.

In case of HCC, the diagnosis was performed by preoperative imaging (CT or MRI scan) and α-fetoprotein serum level, or by liver biopsy when requested.

Demographic and clinical data of the donors were reviewed from the electronic database of the Hospitals where the graft procurement was performed.

Antimicrobial perioperative prophylaxis was given according to international guidelines [7]. Immunosuppression was based on tacrolimus twice daily plus steroids and eventual MMF introduction for renal sparing, not differently from the non-HIV population; however, due to the multicenter nature of the study and the heterogenicity of the cohort, individual data on immunosuppressive regimen were not collected. Standard post-transplant management for clinical surveillance over postoperative complications was based on daily laboratory tests including full blood count, liver and kidney function for the first 10 PODs and thereafter as needed according to the clinical course. Hepatic US with echocolordoppler was routinely performed every day up to POD 7 and thereafter when clinically indicated. A CT scan and/or angiography or cholangiography were used as the second level investigation in case of clinical or laboratory/US scan suspicion of occurring complications.

Early relaparotomy was defined as an urgent or planned surgical procedure within 30 days after LT. The identified possible clinical indications were the followings:

- intraoperative poorly controlled bleeding requiring intra-abdominal packing or continuous postoperative bleeding causing hemodynamic instability

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- surgical attempts to correct vascular complications in case of unfeasibility or failure of radiological interventions

- gastrointestinal perforation

- biliary leak in case of unfeasibility or failure of endoscopic/radiological interventions

The overall number of relaparotomies per patient represented the number of required reoperations after LT due to complications within POD 30. This was evaluated as a continuous variable with 0 identifying no reoperation. Cases of re-transplantation within 30 days were excluded.

In order to adequately evaluate the rate and impact of early surgical morbidity requiring laparotomy on outcome, a control group of non-HIV recipients was identified. These patients were submitted to LT in the same transplant centers, during the same time period and were matched with 1:1 ratio according to the recipient age and the clinical variables which were shown to have a significant impact on OS in the HIV study group (MELD, HBV, HCV-RNA positivity).

Statistical analysis

Categorical variables and frequencies were expressed by percentage, while continuous variables were expressed by mean ± standard deviation (SD) or median [IQR], as appropriate. For categorical variables, cross-tabulations were generated, and chi-square or Fisher exact test was used to compare distributions.

Overall survival (OS) was defined as the time (months) from liver transplantation to either death or last observation. OS was described using the Kaplan-Meier approach. Comparisons between survival distributions were performed using Log-

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rank test. Analysis of survival was done using Cox proportional hazard models, after the proportional hazards assumption had been verified.

Among patients with 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 $p \leq 0.10$ in univariate analysis. Retention in the stepwise model required the variables being significant at $p \leq 0.05$ in a multivariate analysis.

RESULTS

Patient characteristics

A total of 160 HIV positive patients were submitted to primary LT during the study period. Three patients were excluded due to re-transplantation within 30 days, thus the final study population comprised 157 recipients. The demographic, clinical data and surgical details are summarized in Table 1. Virologic status comprised 90.5% HCV co-infection, 19.1% HBV and 12.1% HCV-HBV. The median MELD score was 18 (12-26.5). HCC was present in 37.8% of cases. The piggyback technique, with caval preservation, was used most frequently (59.2% of cases). End-to-end anastomosis and duct-to-duct anastomosis both with interrupted suture were used as standard technique for hepatic artery and bile duct reconstruction respectively. An aortohepatic jump became necessary for reconstruction in 6.4% and Roux-en-Y choledochojejunostomy in 7% of cases.

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Early relaparotomies features, related risk factors and impact on survival

During the postoperative course, 39 patients (24.8%) were submitted to an early re-laparotomy on a median POD 5 [1-12]. The clinical indications were bleeding in 13 (8.2%) cases, biliary leak in 13 (8.2%), intestinal perforation in 7 (4.5%) and concerns for vascular compromise in 6 (3.8%). No cases of negative re-exploration were recorded. The median total number of relaparotimes within the first 30 days post-LT among patients who had at least one reoperation was 1 [1-2]. Within the first year after LT, additional relaparotomies were required just in 6 cases, establishing an overall 1 year reoperation rate of 28.6%. Overall the median length of hospital stay was 18 days [12-27]. The median follow up after hospital discharge was 25.4 months [5.7-70.7]. Eleven patients died within POD 30. The median MELD score of these patients was 29 [14-31]. During the postoperative course, 45.4% (5/11) required at least one early relaparotomy. Among these, 3 patients required multiple reinterventions (2 relaparotomies for 2 patients, and 4 for 1 patient). The underlying surgical complications were a vascular complication in 5 cases, major bleeding in 3 and gastrointestinal perforation in 1. The causes of patients' death were the following: sepsis (4 pts, 36.4%) hemorrhagic shock (2 pts, 18.3%) due to massive bronchial bleeding and intraoperative bleeding respectively, cerebral oedema in patients transplanted due to fulminant hepatitis (2 pts, 18.3%), primary dysfunction (1pt, 9%), fulminant graft hepatitis due to adenovirus infection (1pt, 9%), acute myocardial infarction (1pt, 9%).

146 patients survived more than 30 days after LT and within this patients group the risk factors for early relaparotomy were investigated among variables regarding pre-transplant clinical status, donor and graft characteristics and surgical procedure details (Tab 2). In univariate analysis, preoperative refractory ascites (OR 3.32,

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p<0.01) and Roux-en-Y choledochojejunostomy reconstruction (OR 16.15, p<0.01) resulted significant risk factor for early relaparotomy. Both variables maintained significance even at multivariate analysis.

The OS at 1, 3, 5 years was 74.3%, 68.0% and 60.0% respectively. A graft failure due to HCV recurrence represented the leading death cause, accounting for 56.4% cases (31 pts). Early relaparotomy was not associated with an increased mortality (p=0.117). Nevertheless the number of early relaparotomies per patient did actually demonstrate a significant prognostic value (HR=1.400, p=0.011) as well as an index early relaparotomy due to vascular complications (HR=2.920, p=0.04). Additionally HCV RNA positivity, HBV positivity (protective), Child-Pugh score and MELD score were also identified as significant determinants of OS(Tab 3). In multivariate analysis, MELD score maintained significance (HR=1.048, p=0.003).

Comparison with a non-HIV control group

The non-HIV control group (n=157) and the HIV group were homogeneous in terms of age (non-HIV vs HIV, 49.8±7.3 years vs 49.2±5.4 years, p=0.518), sex (female sex 19.1% vs 13.4%, p=0.168), HCV infection (87.9% vs 90.4%, p= 0.467), HCV-RNA positivity (67.5% vs 68.8%, p=0.808), HBV infection (18.4% vs 19.1%, p=0.885), HCC diagnosis (41.4% vs 37.8%, p=0.460), MELD score (17 [12-25] vs 18 [12-26], p=0.478). Twenty-eight non-HIV recipients (17.8%) required an early relaparotomy post-LT. No differences in terms of prevalence for either overall or cause-specific early relaparotomies were noted when compared to the non-HIV group (Tab. 2). Thirty-days and 90-days mortality post-LT were also comparable between the groups (Tab. 2). However, in the non-HIV control group, early relaparotomy (HR 5.482, 95%-IC 2.915-10.309, p<0.001), number of early

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relaparotomies (HR 2.944, 95%-IC 2.024-4.283, p<0.001), index early relaparotomy due to biliary leak (HR 5.482, 95%-IC 2.915-10.309, p<0.001), vascular complication (HR 13.347, 95%-IC 3.110-57.272, p<0.001) and bleeding (HR 3.975, 95%-IC 1.824-8.664, p=0.001), were all identified as significant risk factors for poor overall survival. Intestinal perforation did appear to have only a marginal impact on the outcome (HR 3.171, 95%-IC 0.975-10.316, p=0.055).

DISCUSSION

Limited data are available regarding the postoperative 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 co-morbidities, an highly invasive surgical procedure, an emergency operation and high bacterial contamination [8]. Highly active antiretroviral therapies (HAART) have significantly decreased the risk for bacterial infections, improved nutritional status and overall life expectancy [1-4]. Furthermore, the application of restrictive LT inclusion criteria aimed at minimizing the risk of immunodeficiency related complications even under immunosuppressant therapies have guaranteed a relatively low incidence of de-novo opportunistic infections and neoplasms post-LT [1, 9]. The most frequently reported risk factors for OS in HIV liver recipients comprise a pre-LT low BMI, high MELD score, low GFR or need of combined kidney-liver transplantation, higher donor age or donor risk index and HCV co-infection [9-12]. These results were confirmed even by the present investigation which identified HCV-RNA positivity, HBV positivity (protective), Child-Pugh score, MELD score as significant factors. HCV RNA positivity showed the highest HR (2.262). It has been demonstrated that HIV enhances HCV replication and recurrence on the graft, with

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accelerated liver damage and rapid progression of fibrosis [5,13]. As a result, HCV co-infection is identified as the most severe determinant of a poor prognosis [13]. Both the HIV and the non-HIV groups of the present study belonged to the pre-Directly Acting Antivirals (DAAs) era, and this aspect may have probably affected the patient survival. Indeed the leading cause of patient death among HIV patients was a graft failure due to recurrent HCV infection. The implementation of DAAs in routine clinical practice is expected to control and remove such negative effect of HCV on the LT outcome, with significant improvement of both patient and graft survival [11, 13, 14]. Therefore investigating on surgical morbidity in HIV liver recipients may soon become of even greater relevance. So far HIV infection has been associated with a pro-thrombotic state and with a related concern of increased risk of vascular complications [15]. However the data are conflicting without possibility to draw definitive conclusion [11], as also demonstrated by our previous report which did not identify any significantly higher prevalence of hepatic artery complications in HIV compared to non-HIV recipients [16]. Furthermore, in the present study, HIV patients did not show a significantly different prevalence of either overall or cause-specific early relaparotomies, compared to matched controls.

A re-laparotomy after LT causes a major physical stress for the patient. It represents a risk factor for postoperative infections and is associated with increased mortality in the overall liver transplanted population [6,17-23]. In the clinical series of 1620 deceased donor LT patients (median MELD score 29) recently reported by Norcia et al. [6], the reoperation rate was 29% over a median follow-up time of 3.4 years. Median time to reoperation was 2 days. Intra-abdominal bleeding was the most common indication for reoperation (17.3%), followed by delayed biliary reconstruction in recipients who required intra-abdominal packing (6.2%),

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retransplantation for early graft failure (5.2%), biliary complications (4.1%), intra-abdominal infection (4.0%), and concern for vascular compromise (2.3%). Patients with reoperative complications had significantly increased mortality rates (74%, 66%, 63% vs 88%, 75%, 73%; $p<0.001$). An analogue negative impact on patient survival was recorded even just focusing on early postoperative bleeding requiring urgent re-exploration [24,25]. Even in the non-HIV control group of the present investigation, the negative impact of early surgical morbidity on patient outcome was evident. As a matter of fact, it showed that the invasiveness of the surgical procedure itself was a significant determinant of a poor survival, besides the underlying specific clinical indications which, as expected, were identified as risk factors. Certainly, during the early postoperative period the patient is more fragile and reinterventions due to complications occurring during this time frame may severely and irreversibly compromise the patient capability to recover [24-26]. Differently from the non-HIV control group in which even a single relaparotomy was identified as a risk factor, the survival of HIV recipients was negatively affected by the increasing number of reinterventions rather than by a single event. Under this perspective, it may be speculated that the inclusion criteria for LT indication in HIV positive patients, although based only on immuno-infective parameters, may have selected patients with an higher performance status which guaranteed an higher endurance to the surgical stress [14, 27]. Nonetheless, the risk factors for an early re-laparotomy identified for HIV recipients by the present investigation were coherent with the overall recipients population, as reported in literature. The major predictors appear to correlate with the recipient illness acuity (pretransplantation mechanical ventilation, earlier major abdominal operation, MELD), donor quality (donor length of hospital stay, serum sodium), and operative factors (cold ischemia time, warm ischemia time,

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intraoperative blood transfusion) [6,24]. Accordingly, in the present study, preoperative refractory ascites, defined as ascites that does not respond to sodium restriction and high-dose diuretic treatment (400 mg/day spironolactone and 160 mg/day furosemide) or that recurs rapidly after therapeutic paracentesis, and Roux-en-Y choledochojejunostomy, as risk factors for early re-laparotomy, may reflect a severe portal hypertension (recipient status) and a difficult hilar dissection/biliary tree reconstruction (operative factors), respectively.

The only other study [1] which investigated the impact of relaparotomy on outcome in a clinical series of 125 HIV liver transplanted patients reported a significant association with increased mortality [HR: 2.8; 95% CI: 1.2-6.5; p=0.01] in univariate but not in multivariate analysis and marginal association with higher risk of graft loss [HR: 2.8; 95% CI: 1.0-8.4; p=0.06] in multivariate analysis. Unfortunately, no detailed information about the patient clinical characteristics were provided by Harbell et al.[1], thus it is difficult to speculate on the partial heterogeneity of the results.

The present study has several limitations: data heterogeneity and unavailability of details for some clinical information such patient performance status, inherent to a multicenter national database and retrospective modality of data analysis.

CONCLUSIONS

Very limited data are available about LT surgical morbidity in HIV positive recipients, probably because HCV coinfection has represented so far the most crucial and severe determinant of post-LT outcome. According to our experience, an early relaparotomy due to surgical complications does not affect the OS, possibly thanks

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to the restrictive preoperative patients' selection criteria. However, increasing number of early relaparotomies per patient and an index early relaparotomy due to vascular complications are associated with higher mortality rates. Recipients with pretransplant severe portal hypertension causing refractory ascites and those requiring a Roux-en-Y choledochojejunostomy are associated with increased risk of early relaparotomy due to complications. The highest incidence of post-LT relaparotomies occurs within the first post-LT month, thus within this time frame and in the identified high risk patients a closer clinical surveillance with possibly a scheduled abdominal CT scan may be advisable. Further studies are required anyway to draw definitive conclusions.

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Table 1. Demographic and clinical data, graft characteristics and surgical details

Gender [M:F]	136:21
Age [years]	49.2±5.4
BMI	23.7±3.8
HCV positivity (%)	142 (90.5%)
HCV-RNA serum positivity (%)	108 (73.0%)
HBV positivity (%)	30 (19.1%)
HCC diagnosis (%)	59 (37.8%)
MELD score	18 [12-26.5]
Child-Pugh score - A - B - C	 29 (19%) 57 (37.3%) 67 (43.8%)
INR	1.7±0.6
Bilirubin serum level [mg/dL]	3.8 [1.5-12.5]
Creatinine serum level [mg/dL]	1 [0.89-1.2]
Sodium serum level [mEq/L]	137.5 [135-140]
Albumin plasm level [mg/dL]	3.1 [2.6-3.7]
Refractory ascites (%)	73 (46.5%)
Portosystemic encephalopathy (%)	53 (37.1%)
Pretransplant portal thrombosis (%) - partial - complete	 16 (10.3%) 0
Previous abdominal surgery (%)	23 (14.7%)
Time in waiting list [months]	3.73 [1.02-9.72]
Donor age [years]	53.8±17.5 years
Donor gender [M:F]	86:71
Donor BMI	25.5 ±3.8
Mild graft steatosis (0-30%) (%)	22 (14.6%)
Type of graft (%): - whole liver - split liver	 147 (93.6%) 10 (6.4%)
Total ischemia time [min]	481.3 ±143.0

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Combined transplantation (%)	9 (5.7%)
Operative time [min]	415.6±99.0
Packed blood cells transfusion, [UI]	4 [1-8]
Frozen fresh plasma transfusion, [ml]	800 [0-2000]
Kehr tube placement (%)	60 (38.2%)
Roux-en-Y choledochojejunostomy (%)	11 (7.0%)
Aorto-hepatic jump (%)	10 (6.4%)
Outflow reconstruction type (%): - Piggy-back - Caval replacement - Side-to-side cavocavostomy	 93 (59.2%) 65 (41.4%) 3 (1.9%)

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Table 2. Early surgical morbility in HIV group and non-HIV control group

	HIV group (n=157)	Non-HIV group (n=157)	p
Early relaparotomy	39 (24.8%)	28 (17.8%)	0.130
Number of early relaparotomies per patient, (in complicated cases only)	1 [1-2]	1 [1-2]	0.405
Causes of index early relaparotomies			
- Bleeding	13 (8.3%)	13 (8.3%)	1
- Biliary leak	13 (8.3%)	9 (5.7%)	0.377
- Intestinal perforation	7 (4.5%)	5 (3.2%)	0.556
- Vascular complication	6 (3.8%)	2 (1.3%)	0.152
30-days mortality post-LT	11 (7.0%)	8 (5.1%)	0.477
90-days mortality post-LT	22 (14%)	22 (14%)	1

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Table 3. Univariate and multivariate analysis of risk factors for early re-laparotomy in recipients with a survival >30days

	Univariate analysis			**Multivariate analysis**		
Factors	**OR**	**95% Conf. Interval**	**p-val**	**OR**	**95% Conf. Interval**	**p-val**
Sex - female - male	 1 .894	 .274-2.916	 0.853			
Age	1.018	.947-1.093	0.620			
BMI	1.007	.911-1.113	0.878			
HCV positivity	.767	.224-2.618	0.672			
HCV-RNA serum positivity	1.088	.453-2.610	0.849			
HBV positivity	1.011	.390-2.616	0.981			
HCC diagnosis	.586	.256-1.339	0.205			
MELD score	1.022	.977-1.070	0.329			
Child-Pugh score	1.196	.7125-2.010	0.497			
INR	1.745	.949-3.209	0.073			
Bilirubin serum level	1.015	.979-1.051	0.406			
Creatinine serum level	.944	.645-1.384	0.771			
Sodium serum level	.995	.912-1.084	0.910			

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Albumin plasm level	.719	.462-1.119	0.144			
Refractory ascites	3.322	1.479-7.458	**0.004**	2.769	1.185-6.470	**0.019**
Portosystemic encephalopathy	1.328	.586-3.009	0.496			
Pretransplant portal thrombosis	1.448	.417-5.027	0.560			
Previous abdominal surgery	.275	.061-1.244	0.094			
Time in waiting list	.993	.938-1.051	0.821			
Donor age	1.018	.994-1.042	0.138			
Donor gender - female - male	 1 1.389	 .648-2.977	 0.397			
Donor BMI	.951	.856-1.056	0.349			
Graft steatosis	.527	.144-1.93	0.334			
Type of graft: - whole liver - split liver	 1 2.258	 .598-8.512	 0.229			
Total ischemia time	1.000	.997-1.002	0.914			
Combined transplantation	1.640	.388-6.933	0.501			
Operative time	.999	.995-1.003	0.968			
Packed blood cells transfusion	1.012	.926-1.106	0.789			

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Frozen fresh plasma transfusion	1.000	.999-1.000	0.554			
Kehr tube placement	.825	.372-1.828	0.636			
Roux-en-Y choledochojejunostomy	16.148	3.241- 80.443	**0.001**	12.712	2.471-65.385	**0.002**
Aorto-hepatic jump	1.284	.238- 6.933	0.771			
Piggy-back outflow reconstruction	.553	.256-1.190	0.130			
Side-to-side cavocavostomy outflow reconstruction	3.235	.197-53.116	0.411			
Caval replacement outflow reconstruction	1.739	.808-3.741	0.157			

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Table 4. Prognostic factors for recipient OS in univariate and multivariate analysis

	Univariate analysis			**Multivariate analysis**		
Factors	**HR**	**95% Conf. Interval**	**p-val**	**HR**	**95% Conf. Interval**	**p-val**
Gender - Female - Male	 1 1.124	 .530-2.382	 0.760			
Age	.974	.926-1.024	0.313			
BMI	.986	.918-1.059	0.711			
HCV positivity	1.518	.547-4.205	0.422			
HCV-RNA serum positivity	2.262	1.019-5.024	**0.045**			
HBV positivity	.403	.171-.944	**0.036**			
HCC diagnosis	.643	.358-1.154	0.140			
MELD score	1.046	1.015-1.079	**0.004**	1.048	1.015-1.081	0.003
Child-Pugh score	1.550	1.044-2.300	**0.030**			
INR	1.402	.945-2.080	0.092			
Bilirubin serum level	1.013	.991-1.036	0.223			
Creatinine serum level	1.027	.827-1.275	0.806			
Sodium serum level	1.004	.941-1.072	0.887			
Albumin plasm level	1.064	.790-1.434	0.680			
Refractory ascites	1.186	.695-2.025	0.530			
Portosystemic encephalopathy	1.467	.811-2.654	0.205			
Pretransplant portal thrombosis	1.199	.512-2.807	0.675			
Previous abdominal surgery	1.201	.566-2.547	0.633			
Time in waiting list	.979	.938-1.022	0.342			

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Donor age	1.008	.992-1.023	0.292			
Donor gender - female - male	 1 1.339	 .785-2.286	 0.283			
Donor BMI	.985	.919-1.056	0.683			
Graft steatosis	1.764	.922-3.378	0.086			
Graft type - whole liver - split liver	 1 .208	 .028-1.508	 0.120			
Total ischemia time	1.000	.998-1.002	0.615			
Combined transplantation	.839	.261-2.693	0.769			
Operative time	.999	.997-1.002	0.856			
Packed blood cells transfusion	1.022	.971-1.077	0.392			
Frozen fresh plasma transfusion	1.000	.999-1.000	0.266			
Kher tube placement	1.667	.977-2.846	0.061			
Roux-en-Y choledochojejunostomy	.0714	.222-2.289	0.571			
Aorto-hepatic jump	1.77	.708-4.467	0.220			
Piggyback outflow reconstruction	.932	.541-1.605	0.801			
Early relaparotomy	1.583	.891-2.813	0.117			
Number of early relaparotomies per patient	1.400	1.079-1.817	**0.011**			
Causes of index early relaparotomy						
Bleeding	1.909	.862-4.228	0.111			
Biliary leak	.648	.202-2.080	0.467			
Vascular complication	2.920	1.051-8.110	**0.040**			
Intestinal perforation	1.316	.410-4.222	0.644			
Lenght of hospital stay	1.000	.986-1.015	0.951			

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