## ORIGINAL ARTICLE

# ORIGINAL DISEASE RECURRENCE AFTER ADULT TO ADULT LIVING DONOR LIVER TRANSPLANTATION (A-ALDLT), SINGLE CENTER EXPERIENCE

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### Abstract

**Background and Aim:** The recurrence of the original disease affects liver transplantation (LT) outcome. Recurrence of viral and non-viral liver disease results in graft failure. This study aimed to analyze the factors responsible for disease recurrence after A-A LDLT and the effect of disease recurrence and its management on the outcome of LT.

**Subjects and Methods:** After exclusion of 6 months mortality and pediatrics, thirty one alive transplanted patients were enrolled in the analysis in the follow up duration from 6 months to 60 months post transplantation. Univariate analysis and then multivariate analysis were done to detect the relationship between (demographic, preoperative, intraoperative and postoperative data) and overall recurrence and between recurrence variables and total survival in the follow up period.

**Results:** Sixty nine patients underwent LDLT in our institute from April 2003 until the end of December 2009. The present retrospective study included 31 patients in the follow up duration and the incidence of recurrence was 15/31(48.4%) of patients (10 hepatitis C virus (HCV), 3 hepatocellular carcinoma (HCC) and 2 primary sclerosing cholangitis (PSC)). On univariate analysis, there was no statistically significant predictors of recurrence regarding (demographic, Preoperative, intraoperative and postoperative data). The overall 1-, 3- and 5- year survivals of patients were 90.3%, 87.1% and 83.9% respectively, while the overall 1-, 3- and 5- year survivals of patients with and without recurrence were 86.7%, 80% and 73.3% and 93.8%, 93.8% and 93.8% respectively.

**Conclusion:** Recurrence of primary disease after LDLT is confirmed in our study with the highest incidence in HCV patients. On the other hand HCV recurrence was higher in the following patients (Cytomegalovirus (CMV) infections and with acute rejection). While HCC recurrence was higher in the following patients (Beyond Milan, with Alfa feto protein (AFP) >200 and patients with moderate tumor differentiation). Recurrence of primary disease after liver transplantation decreases post transplantation Survival. However its effective management improves survival.

**Keywords:** Living donor liver transplantation, Hepatitis C virus recurrence, HCC recurrence.

## INTRODUCTION

Living related liver transplantation (LRLT) is a well-accepted therapeutic option for patients with end-stage liver disease caused by variable diseases like, chronic viral hepatitis, HCC and PSC.[1]

With improvement of surgical techniques, monitoring and immunosuppression, mortality and morbidity rates decreased after liver transplantation.[2] Recent studies indicated that 5-year survival after liver transplantation for HCV and HCC reached 60%[2] and for PSC reached 65%.[3]

Further, the recent development of LRLT decreased patients in waiting list and widened the spectrum of indications of LT with comparable results of cadaver LT.[4]

However, recurrence of primary disease is still a problem. Recent reports show that 99% recurrent viremia occur after transplantation for HCV and hepatitis B virus (HBV).[5] 46% clinical HCV recurrence occur after transplantation for HCV progressing rapidly to cirrhosis due to immunosuppressive,[6,7] less than 10% recurrence occur after transplantation for HCC[8] and between 10% and 27% recurrence occur after transplantation for (PSC).[9,10]

Many reports applied show that factors favoring HCV recurrence are coincident diseases destroying liver parenchyma; a high activity of the inflammatory process in the native liver, acute organ rejection, hepatocyte dysplasia[11] and CMV infection[12] and factors for tumor recurrence are pathological features, namely vascular invasion, more than three nodules, size larger than 5 cm and moderately to poorly differentiated tumors.[8] However treatment options of recurrent disease vary widely according to severity of recurrent disease and its effect on the recipient and his graft.[13]

The aim of this study was to analyze the factors responsible for disease recurrence after LDLT and the effect of disease recurrence and its management on the outcome of LT.

## MATERIAL AND METHODS

After approval of institutional review board (IRB) and obtaining written informed conscent from both donors and recipients, we retrospectively analyzed liver transplanted patients in the department of hepatopancreatobiliary (HPB) surgery, National Liver Institute (NLI), University of Menoufiya in the period from April 2003 to December 2009. During the period, 69 patients underwent LDLT. After exclusion of early death (6 months mortality) and pediatrics, 31 alive transplanted adult patients were enrolled in the current analysis in the follow up duration from 6 months to 60 months. They were analyzed for the following data:

**A- Preoperative variables:**

Donor's variables: (Age, gender, blood group and body mass index (BMI), donor to recipient relation). Recipient´s variables: A- Demographic findings: (Age, gender, blood group and BMI) B- Indication of liver transplantation (primary disease). C- Scoring systems including:1- model for end stage liver disease (MELD) score[14] 3- Child-Pugh scoring system[15] 4- Milan criteria for HCC cases.[16] These criteria are a single tumor of less than 5 cm in diameter or, in patients with multiple tumors, no more than three tumors each of them less than 3 cm in diameter, no vascular invasion and no distant metastases. b- University criteria of San Francisco (UCSF) criteria (extended Milan criteria):[17] A solitary tumour less than 6.5 cm or with two or three nodules, the largest being less than 4.5 cm and a totaling 8 cm, no vascular invasion and no distant metastases. D- Pre transplant intervention therapy: 1- Medical: a- Supportive treatment specific to the primary disease - Antiviral (Ribavirine, immunoglobulines and interferones).[18] 2- Intervention:a- Endoscopic:- Endoscopic sclerotherapy or band ligation for haematemesis or melena or endoscopic treatment of PSC (19. b- Radiological: - Radiofrequency, alcohol injection or chemoembolisation for tumors. E- Co-morbidity (cardiac, DM, HTN,....) F- CMV co infection.

**B- Intraoperative variables:**

Duration of the operation per hours, graft weight (actual intraoperative weight), actual graft recipient weight ratio (GRWR), cold ischemia time per minute, warm ischemia time per minute and blood transfusion per unit.

**C- Postoperative variables:**

**1- Immunosuppression protocol:** the standard is combination of 3 drugs (calcineurin inhibitors (CNIs), steroids and mycophenolate mofetil (MMF). Tacrolimus (FK506) was prescribed at an initial dose of 0.05–0.1 mg/kg/day divided every 12 hours (9 a.m. and 9 p.m.) and adjusted over time to maintain levels of 10–15 ng/mL at 0–14 days, 6–10 ng/mL at 14–28 days, and 5–8 ng/mL thereafter. MMF was given at an oral dosage of 250-500 mg twice a day to be stopped 6 months later. The initial methylprednisolone dose was 500 mg intraoperatively with a brief taper of prednisone from 240 to 40 mg/d over 6 days followed by 5–20 mg/d maintenance treatment, with complete withdrawal at the end of 3rd month post LDLT. Cyclosporine (CsA) was used when neurotoxicty or nephrotoxicity developed with Tacrolimus. It was given at an oral dosage of 8-10mg/kg/day, where blood trough levels were maintained between 150 and 250 ng/ml in the 1st 6 months and between 100 and 150 ng/ml thereafter. When CNIs were contraindicated or their side effects halted their use, sirolimus (SRL) was given at an initial dose of 3 mg/m2 and adjusted over time to achieve blood trough levels of approximately 5–8 ng/mL.

Biopsy-proven acute rejection episodes were treated with steroid pulses (IV methylprednisolone 200 to 500 mg/d for 3 days), which were tapered over several days to the baseline dose.

**2- Postoperative follow up protocol to detect recurrent disease:** The follow up was done monthly during the 1st 6 months, then every 3 months till the end of the 1st year, then every 6 months till the end of follow up (60 months). (N.B. We have no backup (LRLT grafts or Cadaveric grafts) for those who had recurrence of the original pathology (cause for transplantation) and the plane for those who developed disease recurrence will be mentioned with each disease recurrence).

**A- HCV recurrence:**

**a- Diagnosis:** 1- Laboratory results ( elevated alanine transaminase (ALT), aspartate transaminase(AST)) ≥2-fold over the normal upper limit. 2- Positivity of serum HCV RNA by reverse-transcription polymerase chain reaction (RT-PCR) 3- Core liver biopsies (The biopsy was performed with ultrasonographic guidance and a conventional automatic 16-gauge Tru-cut needle) to assess: a- Fibrosis: evaluated according to The METAVIR[20] and/or Ishak[21] scores. The fibrosis score was measured from 1 to 6 (Trichrome stain was used). b- The inflammatory grading (18 points) (infiltration of the portal tract with mononuclear inflammatory cells, interface hepatitis, spotty necrosis, confluent necrosis). c- The histological activity index (HAI): The sum of spotty necrosis score (from 1 to 4), a confluent necrosis score (from 0 to 6), interface hepatitis score (from 0 to 4) and a portal inflammation score (from 0 to 4) N.B. Other possible diagnoses (particularly cellular rejection was excluded by the followings: a- Absence of endothelialitis and centrilobular tissue damage. b- biopsies from patients with HCV infection contain macro or microvesicular steatosis, irregular limiting plates, lobular inflammations, hepatocyte necrosis and reactive changes of hepatocytes. C- The liver biopsy was analyzed by two expert pathologists to avoid inter-observer variation.

**b- Treatment:** Criteria for treatment of recurrent HCV were: staging >1 and grading >4. All treated patients received Pegelated interferon (PEG-IFN-α-2b) (PEG-Intron, Schering Plough, Kenilworth, NJ, USA) that was administered subcutaneously at a weekly dose of 1 μg/kg of body weight plus Ribavirin (Rebetol, Schering Plough, Kenilworth, NJ, USA) that was administered orally at the starting daily dose of 400–800 mg/day. Planned duration of treatment was 48 weeks. Patients who were HCV RNA-positive after 12 weeks of treatment were considered as non-responders and treatment was stopped. All patients were monitored monthly during and after therapy. Complete blood count, AST, ALT, bilirubin, creatinine and prothrombin time were checked monthly or more frequently if needed. Serum HCV RNA levels were checked by RT-PCR before therapy, at 12 and 24 weeks and at the end of therapy (Quantitative test: HCV Monitor; sensitivity >600 UI/mL.[12,18,22]

**B- HCC recurrence:**

**a- Diagnosis:** 1- Clinical findings: Abdominal pain, mass (hepatic recurrence), chest complaint (pulmonary recurrence), bone aches and fracture (bone recurrence). 2- Laboratory findings: persistent elevation of AFP, anaemia,….. 3- Radiology: Ultra sonography (Number, site and size of tumour, lymph nodes, …. ), tri phasic C.T abdomen (Number, site and size of tumour and assessment of lymph nodes), metastatic work up ( Bone scan, C.T chest, C.T brain and PET scan).

**b- Treatment:** The surgical treatment of recurrent HCC was the 1st option and the non-surgically fit patients were treated by palliative treatment in the form of radiotherapy for bone metastases, medical supportive treatment or administration of tyrosine kinase inhibitor (Sorafeneb) which also was given as adjuvant chemotherapy after resection.[23-26]

**C- PSC recurrence:**

**a- Diagnosis:** 1- Clinical: Jaundice, fever,….. 2- Laboratory findings: ''cholestatic'' liver tests (elevated gama glutamate transeferase (GGT), alkaline phosphatase (ALP) and bilirubin). 3- Radiological: The diagnosis of recurrent PSC was made primarily by showing multiple intra and extrahepatic biliary strictures with exclusion of other causes of nonanastomotic strictures (biliary infection, ischemia, hepatic artery thrombosis, ABO-incompatible graft, reperfusion injury). These strictures were shown by magnetic resonance cholangiopancreaticography (MRCP).[17] 4- Liver biopsy (fibro-obliterative cholangitis).

**b- Treatment:** Medical: Ursodeoxycholic acid at high doses (15-20 mg/kg/day) was the treatment of choice followed by endoscopic treatment of biliary strictures, symptomatic treatment of itching and radiotherapy, chemotherapy for cholangiocarcinoma.[27,9,10,25]

**Statistical analysis:** All data were tabulated and processed with SPSS software (Statistical Product and Service Solutions, version 21, SSPS Inc, Chicago, IL, USA) and Windows XP (Microsoft Corporation, Redmond, Washington, USA). Qualitative data were expressed in frequency and percentage and analyzed with the chi-square test. Quantitative data were expressed as the mean and standard deviation and were compared with the t test. The previous (preoperative, intraoperative and

postoperative) variables were descriptively studied. Univariate analysis and then multivariate analysis were done to detect the relationship between the previous data and (HCV and HCC) recurrence and between recurrence variables (Occurrence of recurrence and its management) and survival of patients in the follow up period after LDLT. The Kaplan–Meier method was applied for survival analysis and compared using log-rank tests. In all tests, a P value of <0.05 was considered significant.

## RESULTS

**I- Characteristics of patients and their donors:**

They were classified as 27 (87.1%) males, and 4 (12.9%) females. Their mean age was 47.84years ±5.07. Their donors were classified as 22 (71%) males and 9 (29%) females; their mean age was 24.39 years ±6.44. They were classified according to Child-Pugh score into 2 (6.5%) class A, 9 (29%) class B, and 20 (64.5%) class C, and their mean MELD score was 15.5±4.4. (54.8%) of them had co morbidity in the form of Hypertension and DM, while the incidence of CMV infection was (16.1%) in them (N.B. CMVIgG was positive in all donors and recepients, 2 patients developed CMV viremia and invasive CMV. Both had elevation of the liver enzymes, bilirubin plus GIT symptoms e.g. nausea, vomiting, colics and diarrhea. One of them responded to 4 weeks ganciclovir IV therapy and the second unfortunately died with graft failure 6 months postoperatively). (87.1%) of them were given regimen including FK, MMF and steroids (2 patients were not given FK and another 4 patients were not given MMF). (19.4%) were given regimen including Cyclosporine, MMF and steroids (18 patients were switched from FK to cyclosporine and 2 patients were given cyclosporine from the start) and (16.1%) were given regimen including sirolomus, MMF and steroids (5 patients were shifted from FK to sirolomus and 1 patient was switched from cyclosporine to sirolomus). Acute rejection episodes occurred in 9 (29%) of patients and treated with single steroid bolus in 7 (77.8%) and multiple boluses in 2 (22.2%). (Table 1).

**II- Indications of LT:** The commonest indication for transplantation in adults was post HCV cirrhosis which represented 54.8% of indications. (Fig. 1).

**III- Recurrence rate, timing, management and outcome**

The incidence of recurrence was 15/31(48.4%) of patients. It was distributed according to the aetiology as follow: 10/17(58.8%) had recurrent HCV, 3/8(37.5%) had HCC recurrence and 2/2 (100%) had PSC recurrence. It was diagnosed at a mean of 17.44±12.9 months post transplantation. The recurrence in HCV patients was at the following months post LT (5, 6, 6, 7.8, 9, 12, 16.6, 18, 26, 40) and HCC recurrence was at (17, 19, 29 months post LT), while recurrent PSC was at (3.1, 44 months post LT).

The treatment in adults was as follow: 3/15 (20%) had no treatment, 10/15(66.6%) were treated medically and 2/15(13.3%) were treated surgically.

**1- The medical treatment was distributed as follow:**

**a-** Seven HCV patients were treated with peg-interferone, and viracure, they completed the course of treatment with SVR

**b-** Two sclerosing cholangitis: The 1st one had recurrent sclerosing cholangitis at 3.1 monthes post LT and treated with medical treatment (UDCA). The patient developed multiple cholangectitic abscesses and has been treated with pigtail drainage then followed by surgical drainage but did not improve and died. The 2nd one had recurrent sclerosing cholangitis at 44 months post LT, complicated with intrahepatic cholangiocarcinoma with intraabdominal LN metastasis and was treated with medical treatment (UDCA), radiotherapy and chemotherapy for cholangiocarcinoma but he did not improve and he is still a live.

**c-** One HCC patient: The patient had bone recurrence at 19 months post LT and was treated with radiotherapy but he did not improve and he is still a live.

**2-** The surgical treatment included 2 patients with HCC: The 1st one had hepatic recurrence at 17 months post LT, associated with intraabdominal L.N metastases, with a large L.N. in porta hepatis and died intraoperative from massive P.V.bleeding. The 2nd one had pulmonary and hepatic recurrence at 29, 35 months respectively and was treated with pulmonary lobectomy and resection of hepatic F.L, then he underwent adjuvant chemotherapy in the form of Nexavar but he did not improve after treatment and died. (Fig. 2) and (Table 2).

**IV- Predictors of HCV recurrence:**

On univariate analysis, it was found that HCV recurrence was higher with CMV infections and acute rejection but without statistical significance. (Table 3).

**V- Predictors of HCC recurrence:**

On univariate analysis, it was found that HCC recurrence was higher in the following patients (beyond Milan, with AFP >200 and patients with moderate tumor differentiation) but without statistical significance. (Table 4).

**VI- Outcome of patients:** 1-, 3- and 5- years survival of patients were 90.3%, 87.1% and 83.9% respectively, while 1-, 3- and 5- years survival of patients with and without recurrence were 86.7%, 80% and 73.3% and 93.8%, 93.8% and 93.8% respectively. (Table 5), (Fig. 3).

**Table 1. Characteristics of patients and their donors.**

| | |
|---|---|
| **Number of patients** | 31(100%) |
| **Donor age(years) (Mean±SD)** | 24.39±6.44 |
| **Recipient age(years) (Mean±SD)** | 47.84±5.07 |
| **Donor gender** | |
| Males | 22 (71%) |
| females | 9 (29%) |
| **Recipient gender** | |
| males | 27 (87.1%) |
| females | 4 (12.9%) |
| **Child class** | |
| A | 2 (6.5%) |
| B | 9 (29%) |
| C | 20 (64.5%) |
| **MELD score (Mean±SD)** | 15.5±4.4 |
| **Co morbidity** | 17 (54.8%) |
| **CMV infection** | 5 (16.1%) |
| **Actual Graft weight (Mean±SD)** | 880.8±124.4 |
| **Actual GRWR(Mean±SD)** | 1.09±0.15 |
| **Cold ischemia time (min) (Mean±SD)** | 91.6±66.7 |
| **Warm ischemia time (min) (Mean±SD)** | 58.03±22.3 |
| **Duration of operation (hours) (Mean±SD)** | 13.8±2.7 |
| **Immunosuppression and steroid regimen** | |
| FK, MMF, steroids | 27 (87.1%) |
| Cyclosporine, MMF, steroids | 6 (19.4%) |
| sirolomus, MMF, steroids | 5 (16.1%) |
| Acute rejection episodes | 9 (29%) |
| **Bolus steroids number-** | |
| Single | 7 (77.8%) |
| Multiple | 2 (22.2%) |

**MELD:** Model for End stage Liver Disease, **CMV:** Cytomegalovirus, **GRWR:** Graft Recipient Weight Ratio, **MMF:** Mycophenolate mofetil.

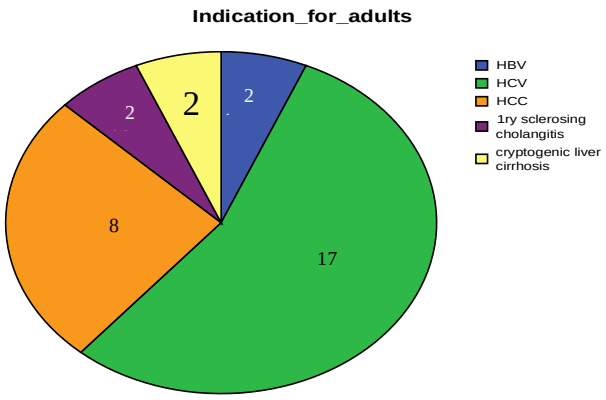
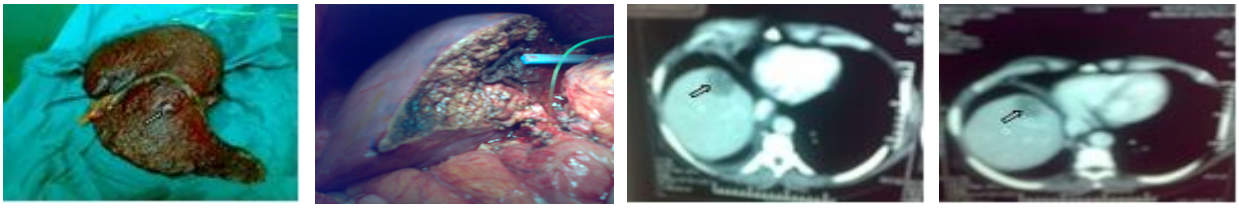



**Fig 1. Indications of LT.**



A B C D

**Fig. 2. (A)- picture of a native liver of HCC patient (1 FL, 3.5 cm, within Milan), (B)- The picture of the graft after implantation to the patient.(C)- Triphasic CT abdomen of the previous patient, with HCC recurrence, in the form of hepatic recurrence, 35 months, post transplantation, he underwent surgical exploration. (D)- Another triphasic CT abdomen of the patient.**

**Table 2. Recurrence, rate, timing, management and outcome.**

| Aetiology | Frequency | Recurrence rate (%) No (%) | Mean±SD | Management of recurrence | Outcome of recurrence treatment |
|---|---|---|---|---|---|
| HCV | 17 | 10 (58.8%) | 14.64±11.2 | No 3/10 (30%) Medical 7/10 (70%) | Improved 7/10 (70%) No improvement 3/10 (30%) |
| HCC | 8 | 3 (37.5%) | 21.66±10.5 | Medical 1/3 (33.3%) Surgical 2/3 (66.6%) | Improved 0 No improvement 3/3 (100%) |
| HBV | 2 | 0 | 0 | ---------- | ---------- |
| PSC | 2 | 2 (100%) | 23.55±6.7 | Medical 2/2 (100%) | Improved 0 No improvement 2/2 (100%) |
| Cryptogenic cirrhosis | 2 | 0 | 0 | ---------- | ---------- |
| Total number | 31 | 15 (48.4%) | 17.44±12.9 | No 3/15( 20%) Medical 10/15 (66.6%) Surgical 2/15 (13.3%) | Improved 7/15 (46.6%) No improvement 8/1(53.3%) |

**HCV:** Hepatitis c virus, **HCC:** Hepatocellular carcinoma, **HBV:** Hepatitis B virus, **PSC:** Primary sclerosing cholangitis.

**Table 3. Recipient and donor risk factors as predictors of HCV recurrence.**

| Characteristic | Recurrence No (%) | p-value |
|---|---|---|
| Number of patients | 10 / 17 (58.8%) | |
| Child class | | > 0.05 |
| - A | 0 | |
| - B | 1 / 2 (50%) | |
| - C | 9 / 15 (60%) | |
| MELD score group | | > 0.05 |
| - < 16 | 4 / 8 (50%) | |
| - 16 – 24 | 6 / 8 (75 %) | |
| CMV infection | 3 / 3 (100%) | > 0.05 |
| Actual Graft weight Mean ± SD | 935.5 ± 97.7 | > 0.05 |
| Actual GRWR | | > 0.05 |
| - 0.8 – 1 | 3 / 4 (75%) | |
| - > 1 | 7 / 13 (53.8%) | |
| Cold ischemia time per min. Mean ± SD | 93.7 ± 30.9 | > 0.05 |
| Warm ischemia time per min. Mean ± SD | 59 ± 14.5 | > 0.05 |
| Immunosuppresion and steroid regimen | | > 0.05 |
| FK, MMF, steroids | 8 / 13 (61.5%) | |
| cyclosporine, MMF, steroids | 1 / 3 (33.3%) | |
| sirolomus, MMF, steroids | 2 / 2 (100.0%) | |
| Acute rejection episodes | 6 / 7 (85.7%) | > 0.05 |
| Bolus steroids number | | > 0.05 |
| Single | 4 / 5(80%) | |
| Multiple | 2 / 2 (100%) | |

**Table 4. Recipient and donor risk factors as predictors of HCC recurrence.**

| Characteristic | Recurrence No (%) | p-value |
|---|---|---|
| **Number of patients** | **3/8 (37.5%)** | |
| Milan criteria | | > 0.05 |
| - Within | 1 / 6 (16.6%) | |
| - Beyond | 2 / 2 (100%) | |
| Comorbidity | 3 / 8(37.5%) | > 0.05 |
| CMV infection | 1 / 2 (50%) | > 0.05 |
| AFP | | > 0.05 |
| - ≤ 200 | 1 / 4 (25%) | |
| - > 200 | 2 / 4 (50%) | |
| Actual Graft weight | 833.3 ± 76.4 | > 0.05 |
| Actual GRWR | | > 0.05 |
| - 0.8 – 1 | 2 / 2 (100%) | |
| - > 1 | 1 / 6(16.6%) | |
| Cold ischemia time per min. (Mean ± SD) | 73.3 ± 28.9 | > 0.05 |
| Warm ischemia time per min. (Mean ± SD) | 66.7 ± 20.8 | > 0.05 |
| Immunosuppresion and steroid regimen | | > 0.05 |
| FK, steroids MMF | 3 / 7 (42.8%) | |
| cyclosporine, MMF, steroids | 1 / 3(33.3%) | |
| sirolomus, MMF, steroids | 1 / 4 (25%) | |
| Tumor differentiation | | > 0.05 |
| - Well | 1 / 3(33.3%) | |
| - Moderate | 2 / 5 (40%) | |

**Table 5. Outcome.**

| Characteristic | All recipients | Non recurrent | Recurrent |
|---|---|---|---|
| | **31 (100%)** | **16 (100%)** | **15 (100%)** |
| **Survival** | | | |
| 1 year | 28 (90.3%) | 15 (93.8%) | 13 (86.7%) |
| 3 years | 27 (87.1%) | 15 (93.8%) | 12 (80%) |
| 5 years | 26 (83.9%) | 15 (93.8%) | 11(73.3%) |
| **Disease specific survival** | | | |
| HCV | 16 / 17 (94.1%) | 7 / 7 (100%) | 9 / 10 (90%) |
| HCC | 5 / 8 (62.5%) | 4 / 5 (90%) | 1 / 3 (33.3%) |
| PSC | 1 / 2 (50%) | 0 | 1 / 2 (50%) |
| **Disease free survival** | | | |
| 1 year | 22 (71%) | - | - |
| 3 years | 17 (54.8%) | - | - |
| 5 years | 15 (48.4) | - | - |

**HCV:** Hepatitis c virus, **HCC:** Hepatocellular carcinoma, **PSC:** Primary sclerosing cholangitis.

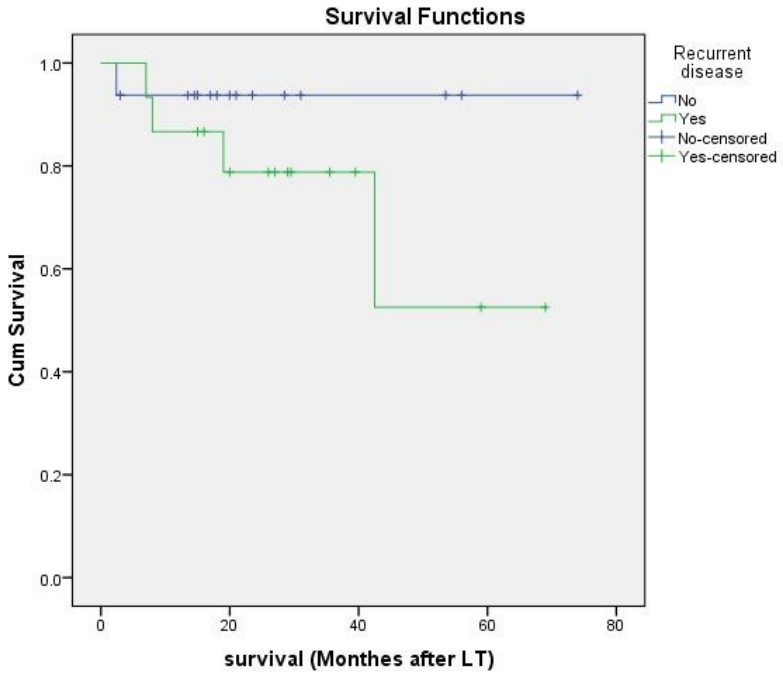



**Fig 3. Kaplan-Meier survival curve of recurrent and non-recurrent patients: Log Rank test= .215 p- value: > 0.05.**

## DISCUSSION

The incidence of recurrence in the present study was (48.4%), while Abdullah and colleagues in 2005[28] detected (25%) recurrence of primary disease in their study. On the other hand, Tsochatzis, and others in 2007[29] found recurrence of the primary disease in (29.5%) of patients. The recurrence of our HCV patients was (58.8%), however, in a study by Francisco and colleagues in 2006,[30] histological recurrence was 92%. in contrast, in the studies by Yosry and colleagues in 2009[31] and Raffaella and colleagues in 2010,[32] HCV recurrence was found in (31.1%) and (46.2%) respectively.

On the other hand, the recurrence in HCC patients was (37.5%) (1/6 within Milan and 2/2 beyond Milan criteria) however, in literature studies, HCC recurrence develops in 8%–20% of patients.[33] As in the studies by Valdivieso and colleagues in 2010[34] and Kornberg and colleagues in 2010[23] who found 12.5% and (26.6%) recurrence of HCC respectively.

Regarding predictors of recurrence, we studied predictors of HCV and HCC recurrence.

**I- HCV recurrence:**

Cytomegalovirus (CMV) infection has been strongly associated with increased severity of HCV recurrence.[35,36] Inversely, in the current study there was no significant association between CMV infection and recurrence. Similarly, Doris and associates in 2010[37] concluded that CMV had no impact on HCV recurrence.

The current study did not show any significant correlation between graft size and GRWR and HCV recurrence, similarly Yosry and associates in 2009[31] did not find significant association between the graft volume or between GRWR of <1% or >1% and HCV recurrence despite the larger graft volume (836± 142 g) in non-recurrent group in their study.

Immunosuppressant is considered a main factor in the severity of recurrent HCV infection,[35,6,36] because of its effect on viral replication and its suppression of the systemic immune responses, both of which can lead to accelerated hepatocellular damage and fibrosis.[38] So, modifying immunosuppressant are the main means of preventing disease progression.[31] Doris and associates in 2010[37] found that patients in the Calcineurin inhibitors group showed a significant trend towards HCV recurrence as compared to patients on SIR therapy during their follow up period. Similarly, in the study done by Kornberg and associates in 2010,[23] there was significant association between tacrolomus based immunosuppression and HCC recurrence. In contrast in the current study, the regimen of immunosuppressant (tacrolomus based, cyclosporine based or sirolomus based) was not significantly associated with disease recurrence. The possible explanation for that finding is that steroids were administered to the study subjects for only 3 months and monotherapy was the standard immunosuppressive regimen in our center and the sample size was small.

While,[30,31] found no significant correlation between the regimen of immunosuppression, and HCV recurrence. Also, in the study done by Balbi and colleagues in 2009[38] and Jiménez-Pérez and colleagues in 2010,[39] there was no significant association between tacrolomus based, or cyclosporine based immunosuppressant, and SVR after treatment for recurrent HCV infection after LT.[30] found significant correlation between MMF and low HCV recurrence. On the other hand, several authors reported that MMF administration was not associated with low HCV recurrence.[40] Similarly, in the present study we did not show significant correlation between MMF administration and disease recurrence. Treatment with steroids for acute cellular rejection episodes has been reported to be a risk factor for the severity of HCV recurrence.[41] In the studies by Francisco and colleagues in 2006[30] and Doris and colleagues in 2010[37] there was significant correlation between pulse steroids and HCV recurrence. In contrast we did not find a significant association between acute rejection episodes and recurrence despite the trend towards recurrence, similarly,[31] found no significant correlation between the administration of pulse steroid therapy and the development of clinically recurrent HCV.

**II- HCC recurrence:**

Concerning Milan criteria as a predictor of HCC recurrence, it was found that patients beyond Milan criteria had a higher recurrence (100%) with a trend towards significant recurrence, similarly, Marco and colleagues in 2005,[42] Marubashi and colleagues in 2006[43] and Kiyici and colleagues in 2008[44] did not find significant association between Milan and HCC recurrence. Inversely, Satoru and Hiroyuki, 2004[45] and Kornberg and colleagues in 2010[23] found significant association between Milan out status and recurrence.

An increase in AFP concentration might reflect tumor aggressiveness including differentiation degree and vascular invasion and consequently lead to a higher risk of tumor recurrence.[46] Hwang and colleagues in 2007,[47] Kondili and colleagues in 2007[48] and Kornberg and colleagues in 2010[23] found significant correlation between high AFP and HCC recurrence. Inversely, AFP >200 was not a significant predictor of HCC recurrence in the present study.

We found no association between tumor differentiation and HCC recurrence, similarly, Kiyici and colleagues in 2008[44] and Marubashi and colleagues in 2006[43] found no correlation between differentiation and recurrence, inversely Kondili and colleagues in 2007,[48] Hwang and colleagues in 2007[47] and Kornberg and colleagues in

2010[23] found correlation between poor differentiation and HCC recurrence.

In the present study overall adults survival was 83.9%, similarly, in the studies by Abdullah and colleagues in 2005[28] and Gruttadauria and colleagues in 2007,[49] the overall patient survival rate at 3 years was 85%. In our study, non-recurrent and recurrent adults survival were 93.7%, and 73.3% respectively, also, in study by[28] that included 20 patients, non-recurrent and recurrent patients survivals were (86.8%) and (80%) respectively.

Antiviral treatment in transplant patients is feasible and does not induce severe immunological effects, so, it is recommended in recurrent HCV to use antiviral in the form of PEG plus RBV with good SVR and survival.[38] In the current study, we found that survival was better (100%) in patients who underwent management of their recurrent HCV (Peg-interferone and viracure) than who did not undergo management (66.6%) with trend towards significant survival, Also in a study by Raffaella and colleagues in 2010,[32] it was found that long term maintenance RBV monotherapy was associated with reduced fibrosis progression in recurrent HCV patients and better survival.

The survival rate of recurrent HCC patients in this study was 33.3% while in Kiyici and colleagues in 2008,[44] Kornberg and colleagues in 2010[23] and Valdivieso and colleagues in 2010[34] studies the 5-years survival rates in their recurrent HCC patients were 25%, 41.7% and 48% respectively. In contrast, survival of our non-recurrent HCC patients was 90% that was similar to survivals in non-recurrent HCC patients in (Kornberg and colleagues in 2010[23] and Valdivieso and colleagues in 2010[34] studies where they were 89.3%, and 83.5% respectively.

In a study by Marubashi and colleagues in 2006,[43] surgical treatment was done in 3/9 of their recurrent HCC patients with good survival also, in Kornberg and colleagues in 2010[23] study, the surgical treatment of their recurrent HCC was the 1st option, and it was independent predictor of post recurrence survival and the non-surgically fit patients were treated by palliative treatment in the form of radiotherapy for bone metastases, administration of tyrosine kinase inhibitor (Sorafeneb) or medical supportive treatment. While, in Valdivieso and colleagues in 2010[34] study, surgical resection was performed in 11/23 patients, Sorafeneb in 2/23 and medical supportive treatment in 10/23, they found that surgical treatment prolonged survival. On the other hand, in the present work, surgical treatment of recurrent HCC was our 1st option where 2/3 of patients were treated surgically, and one of them was given adjuvant therapy in the form of Sorafeneb, but none of them survived and the 3rd non surgically fit patient (bone metastases) was given radiotherapy and he is still a live. The survival of PSC patients (recurrence (100%)) was 50%, however, Jeyarajah and associates in 2000[50] reported 5-year graft survival rate of 65% in recurrent PSC and 76% in non-recurrent. On the other hand, Alonso and associates in 2002(51) detected 1-, and 5-year survivals of their PSC patients of 85% and 70% respectively.

In Conclusion: Recurrence of primary disease after LDLT is confirmed in our study with the highest incidence in HCV patients. On the other hand HCV recurrence was higher in the following patients (CMV infections and with acute rejection). While HCC recurrence was higher in the following patients (beyond Milan, with AFP >200 and patients with moderate tumor differentiation). Recurrence of primary disease after liver transplantation decreases post transplantation Survival. However its effective management improves survival.

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