ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Assessment of HCV-Induced Insulin Resistance in Egyptian HCV End-Stage Cirrhotic Patients before and After Living Donor Liver Transplantation (LDLT).

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ABSTRACT

HCV virus has been shown to induce insulin resistance (IR) itself. The aim of this work: was to evaluate HCV-induced IR in Egyptian HCV cirrhotic patients after LDLT and correlate the occurrence of IR with the level of HCV-RNA viremia and the status of HCV disease recurrence post LDLT. 67 patients had received LDLT from November 2010 to November 2012. 17 of them were included in this prospective research by the following criteria :1) Patients with HCV related End Stage Liver Disease , who were eligible for liver transplantation . 2) Patients with an estimate of IR using HOMA-IR level more than or equal 2 +/- [impaired fasting plasma glucose (FPG) and/or impaired oral glucose tolerance test (OGTT)] .Patients were followed up with the following schedule : FPG , OGTT and HOMA were routinely done 3 , 6 and 12 months post LDLT. HCV RNA level by PCR was performed 1 , 6 and 12 months to follow up the level of viremia post LDLT . Protocol liver biopsies were taken 6 and 12 months post LDLT. The median HOMA value showed reduction during the first year post LDLT , which was not significant at 3 months post LDLT (p value = 0.055) , was highly significant at 6 months post LDLT (p value =0.002) and was again significant at 12 months post LDLT (p value = 0.028) . Recurrence of HCV-disease was documented histologically in 9 patients (52.9%) at 6 months and 10 patients (58.8%) 1 year post LDLT. There was no statistically significant relation between median HOMA values and either level of HCV-RNA viremia or histological recurrence of HCV 6 and 12 months post LDLT. To our knowledge , this is the first study of HCV-induced IR that was conducted on LDLT recipients. HCV-induced insulin resistance is improved 1 year after after LDLT.

Keywords: insulin Resistance IR, Liver transplantation LT.

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ISSN: 0975-8585

INTRODUCTION

Hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease [1]. Egypt has the highest worldwide prevalence with 9% countrywide and up to 50% in certain rural areas, due to specific modes of infection [2]. HCV is currently the most frequent indication for liver transplantation, comprising approximately 40-50% of all case[4,5]. In Egypt , the use of diseased organ donors is still prohibited, and as a result, some patients seek liver transplant abroad. Thus living-donor liver transplant (LDLT) is the only possible option for patients with end-stage liver disease in Egypt [5]. In Egyptian patients who have undergone LDLT, hepatitis C virus related end-stage liver disease is the main indication for liver transplantation [6,7]. Unfortunately, liver transplantation doesn't cure HCV-infected recipients, but reinfection of HCV universally occurs and disease progression is accelerated [8]. HCV recurrence after liver transplantation is also associated with insulin resistance and PTDM [9] are risk factors for fibrosis progression in HCV-positive liver transplant recipients [10].

Aim of the Work

To evaluate the HCV-induced IR in Egyptian HCV cirrhotic patients after LDLT and to correlate the occurrence of IR with the level of HCV-RNA viremia and the status of HCV disease recurrence post LDLT.

MATERIALS AND METHODS

Study Design and Sampling: from November 2010 to November 2012, 67 patients with HCV positive-end stage liver disease (ESLD), aged 18-60 years old and who were eligible for liver transplantation had received LDLT in Ain Shams Center for organs transplantation (ASCOT); Ain Shams University. Seventeen of them were included in this prospective research by the following inclusion criteria :

- Accepting participation in the current study and signing a written consent.
- Patients with Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) level more than or equal 2 and\or (impaired fasting plasma glucose (FPG) and\or impaired oral glucose tolerance test (OGTT).

HOMA-IR = fasting plasma glucose (mmol/L) x fasting serum insulin [FSI] (micro U/mL)/22.5. Typically, a HOMA-IR value > 2 is used as a significant indicator of IR [11].According to the definitions of categories with increased risk for diabetes (pre-diabetes stage)[12]. Impaired Fasting Plasma glucose level=Fasting blood glucose level of 100-125 mg/dl (5.5-6.8 mmol/L) and impaired glucose tolerance [2h plasma glucose during an OGTT]= 140 mg/dl (7.8 mmol/l) to 199 mg/dl (11 mmol/l). All included patients recruited during the study period (2 years) were followed up for one more year.

Exclusion criteria

- Patients who refused to be enrolled in the study or refused to sign the consent.
- Known diabetic patients, and/or those who are on oral antidiabetic drugs or insulin therapy pre transplantation.
- Those with confirmed diagnosis of metabolic syndrome [a state of insulin resistance that is not due to HCV].
- Presence of any indication other than HCV for LDLT: e.g. HBV, HCC (hepatocellular carcinoma), autoimmune hepatitis…., etc.

Patients were subjected to : FPG, OGTT and an estimate of IR using HOMA-IR equation that were routinely done 3, 6 and 12 months post LDLT. HCV RNA level by PCR was performed 1, 6 and 12 months post LDLT. All biobsy specimens were scored using Metavir score.

Statistical Analysis

Descriptive statistics

- Quantitative data : Mean, standard deviation (+/-SD)
- Qualitative data: frequency and percentage.

Analytical statistics

Quantitative data : paired t test , Mann-Whitny test , Wilcoxon Signed Ranks test and Kruskall-Wallis test. Qualitative data: ChiSquare test.Levels of significance:P >0.05 = non-significant (NS), P <0.05 = significant (S).P <0.01 = highly significant (HS) , andP <0.001 = very highly significant (VHS).

RESULTS

His study was conducted on seventeen patients with HCV-ESLD who underwent LDLT intervention. They included 14 males (82.4%) and 3 females (17.6%) with a mean age of 45.29 +/- 9.16 years (range 19-58years). Pre LDLT, the studied patients were included 12 patients (70.5%) with impaired tolerance, among them 3 patients had impaired FPG (fasting plasma glucose: 5.6 – 6.9 mmole/L) and 9 patients had impaired glucose tolerance (2-h plasma glucose in 75-g OGTT (7.8-11 mmole/L). The main maintenance immune-suppression in our study was cyclosporine A that was given to14 patients (82.3%) all through the 1st year post LDLT. Three patients had an indication to be shifted to tacrolimus due to development of acute cellular rejection at different times during the 1st year post LDLT. Mycophenolatemoeftil was added to cyclosporine A in 12 patients to prevent rejection of the graft. mTOR inhibitor(Sirolimus) was needed in 2 patients as they had renal impairment and so to minimize the dose of calcinurin inhibitors.

The mean FPG showed statistically significant increase 3, 6 and 12 months post LDLT with p value <0.05 . However, the mean (2h-PP-OGTT) showed drop after LDLT value to reach the lowest value at the end of the 1st year post LDLT , impaired OGTT was improved (9/17) (52.9%) patients with IGT pre LDLT versus 2/17 (11.7%) patients one year post LDLT, p value =0.02), Only 2 out of 3 patients who had IFG pre LDLT and 1 out of 9 patients who had IGT developed NODMAT (New onset diabetes mellitus after transplantation) 1 year post LDLT. So the incidence of NODM 1 year post LDLT in our cohort was 11.7%.

This study showed statistically significant reduction of the median FSI after LDLT to reach the lowest value at 6 months (highly significant reduction, p value 0.01) and modest increase at 12 months (however, still highly significant reduction, p value < 0.01) post LDLT, indicating an improvement of fasting hyperinsulinemia during the first year post LDLT.

The median HOMA value showed a significant reduction and so improvement during the first year post. This reduction was not significant at 3 months post LDLT (p value = 0.055) was highly significant at 6 months post LDLT (p value = 0.028).

The median HCV-viral load showed overall increase in the first year post LDLT. This increase was highly significant at 6 (p value = 0.001) and 12 months post LDLT (p value = 0.002). There was no statistically significant relation between median HOMA values and HCV viral load at 6 months post LDLT.

Regarding the outcome protocol biopsies that were done at 6 and 12 months for our patient, at 6 months post LDLT there were nine patients with confirmed histological recurrence of HCV-disease (Metavir score A1F1-mild hepatitis), two without morphological abnormalities, four cases that had lost follow up and two patients with other diagnosis on liver biopsy.

At 1 year post LDLT. There were ten patients with confirmed histological recurrence of HCV-disease (nine with Metavir score A1F1-mild hepatitis and one Metavir score A2F2-moderate hepatitis), one case who had lost up, two patients were on standard treatment for HCV-disease recurrence , three patients who had other diagnoses and one with no morphological abnormalities on liver biopsy-figure (2).

ISSN: 0975-8585

Figure (1): Shows comparison between the median HOMA value pre LDLT and median HOMA values at 3, 6, 12 months post LDLT

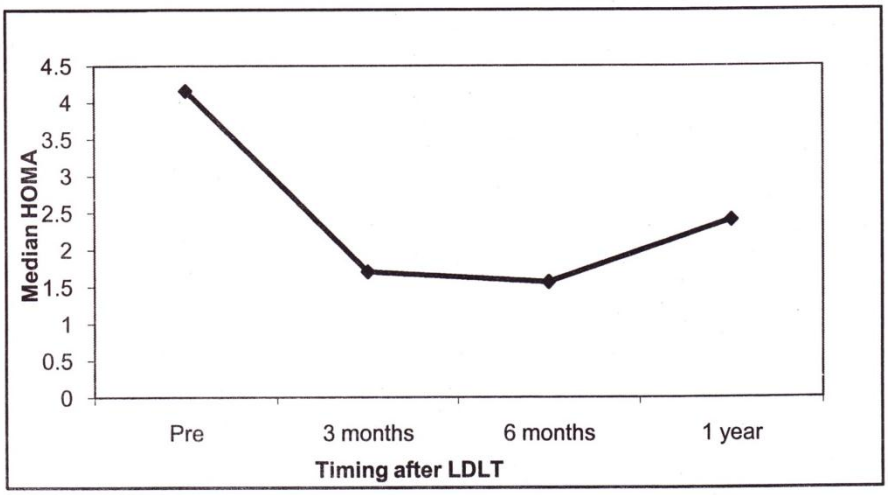
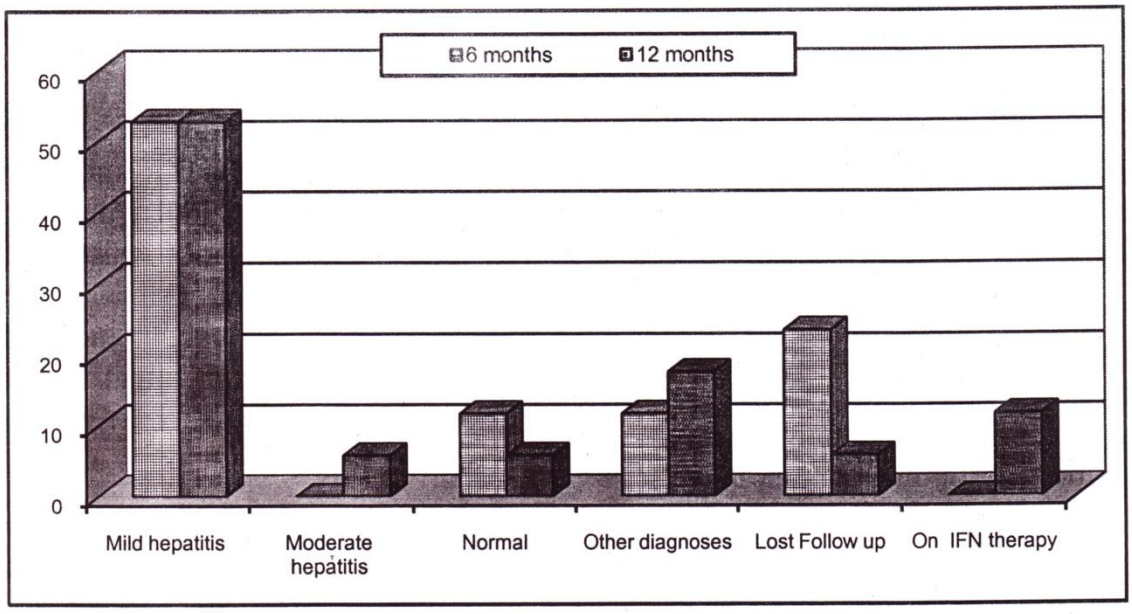


Figure (2): Outcome of protocol biopsy at 6 and 12 months post LDLT.



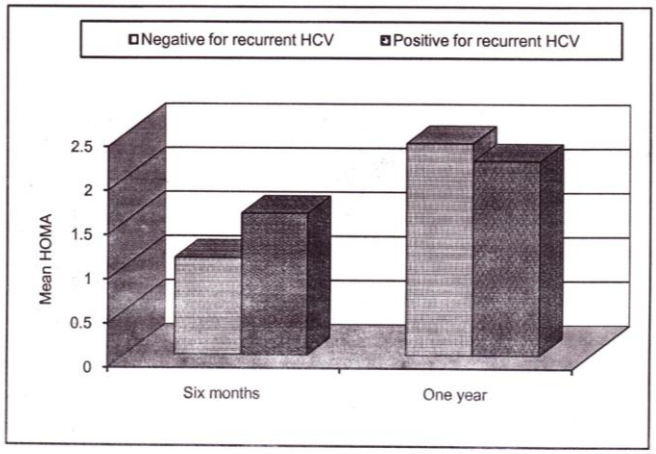
Collectively, early recurrence of HCV-disease post LDLT was documented in our results at 6 months (52.9%) and at 1 year (58.8%) .

All of our patients protocol biopsies exhibited mild histopathological recurrence except one at 1 year that showed moderate HCV-disease recurrence.

There was no statistically significant relation between median HOMA values and histological recurrence of HCV among studied patients during the first year post LDLT, Figure (3).

ISSN: 0975-8585

Figure (3): Relation between median HOMA and histological recurrence of HCV at 6 and 12 months post LDLT



Symptoms and signs before	No	%
Abd enlargement	20	100
Abd pain	16	80
Hepatomegaly	15	75
Splenomegaly	11	55
Jaundice	9	45
dilated veins	8	40
LL edema	7	35
Tender liver	6	30
Encephalopathy	3	15
GI bleeding	1	5
pleural effusion	1	5

Table (2): Laboratory investigations before intervention, during and at the end of follow up (at 1, 3, 6, 12 months):

PT (seconds)	PTT (seconds)	Bilirubin (mg/dL)	ALT (mg/dL)	AST (mg/dL)	S.alb (g/dL)	
Mean±SD	Mean±SD	Median (IQR)	Median (IQR)	Median (IQR)	Mean±SD	Time
14.9±4.8	40.5±10.2	1.9 (1.3–3.8)	33.0 (20.3–42.8)	39.5 (23.0–74.0)	3.2±0.7	Before
21.0±8.0*	50.3±11.6	1.8 (1.3–3.6)	27.0 (19.0–39.5)	42.0 (31.5–63.5)	3.2±0.8	1 m
23.7±5.1*	51.3±8.1	1.9 (1.3–3.9)	27.0 (18.0–45.0)	50.0 (35.0–65.0)	3.2±0.8	3 m
24.1±5.8*	48.8±14.1	1.3 (1.0–2.4)	28.5 (20.0–41.3)	45.0 (35.0–64.8)	3.5±0.8	6 m
22.3±8.3*	45.4±9.9	1.7 (1.0–2.2)	26.5 (17.8–35.5)	37.5 (27.8–65.0)	3.8±0.8	12 m

Table (3): Esophageal varices before intervention, during and at the end of follow up

Time	Total	Positive cases		P^
		N	%	
Before	20	12	60.0	
1 month	17	3	17.6	0.016*
3 months	15	3	20.0	0.031*
6 months	12	1	8.3	0.031*
12 months	10	0	0.0	<0.001*

Table (4): Quality of life scores before intervention, during and at the end of follow up:

Time	N	Median (IQR)	Range	Z^	P
Before	20	10.9 (8.8–11.9)	5.4–14.6		
1 month	17	15.6 (7.8–47.9)	3.5–48.5	-1.917	0.055
3 months	15	88.0 (8.6–88.6)	3.5–88.6	-2.386	0.017*
6 months	12	90.8 (15.8–94.7)	8.6–96.3	-2.824	0.005*
12 months	10	90.8 (15.8–94.7)	8.6–96.3	-2.824	0.005*

Intervention details: 29 patients were candidates for TIPS. The need of revision was 47% (7 out of 17 patients).

Figure (1) Shows frequency of complications post intervention (N=20). The duration of follow up was ranging from days-2 years. One year survival rate was 65% due to death of 7 patients, 2 of them died hours post intervention, 1 died after 3 days all 3 due to intra-abdominal hemorrhage, one died after 1 month due to septic shock, 3 others died at 3,5 months due liver cell failure and hematemesis.

At one year of follow up, only 2 patients of 10 (20%) had occluded shunts. Patients with occluded shunts showed no improvement regarding their clinical manifestations, laboratory profile, upper GI endoscopy and HRQoL. On the contrary, patients with patent shunts (8 of 10 ; 80%) showed marked improvement as shown in tables (2, 3 , and 4).

DISCUSSION

Our cohort study included 17 patients who were having HCV-induced insulin resistance (HOMA≥/=) and in the pre-diabetes stage before LDLT.

Regarding the progression of FPG during the 1st year post LDLT in the current study , this was not consistent with the early study that was conducted by Merli etal[13]. on 6 patients including 3 patients with HCV related cirrhosis and 3 patients with other indications for liver transplantation. The authors found that Fasting glucose levels were not significantly modified after LT. Before LT, OGTT showed a diabetic pattern in five patients and normal glucose tolerance in one patient. After LT, all patients had a normal glucose tolerance.

Collectively in our results, impaired OGTT was improved 9/17 (52.9%) patients with IGT pre LDLT versus 2/17 (11.7%) patients one year post LDLT, (p-value=0.02). These results were consistent with an early study of glucose tolerance that was conducted by Shetty et al[14].before and after liver transplantation on 5 patients with IGT after orthotopic liver transplantation, 4 of them had 2 hours blood glucose value in an OGTT improved, so their study concluded that liver transplantation could reverse cirrhosis associated glucose tolerance.

Also, our results were consistent with Tietge et al[15], who stated that some patients with IGT may improve after OLT. However, the major risk factor for IGT or diabetes after OLT was preexisting IGT or diabetes.

In our study and going hand in hand with other studies [16],NODATwas assessed at one year post LDLT to exclude patients with transient hyperglycemia related to the stress of surgery and effect of corticosteroids.

Only 2 out of three patients who had IFG pre LDLT and 1 out of 9 patients who had IGT developed NODMAT 1 year post LDLT. So the incidence of NODM 1 year post LDLT in our cohort was 11.7%

These results go hand in hand with Honda et al[17] who stated that the incidence of NODM was 13.7% in a retrospective study was performed on 161 adult patients without diabetes who had been followed up for more than three months after LDLT with a mean follow up of 49.8 months. The improvement of FSI during the first year post LDLT in our results was consistent with Merli etal [13] who stated that after LT, insulin and C-peptide levels decreased significantly and became similar to those of healthy controls.

Several cross-sectional and longitudinal studies have convincingly established the relationship between chronic hepatitis C infection and IR/type 2diabetes mellitus.

However, to our knowledge, no prospective studies are available to follow up the outcome of the HCV induced insulin resistance measured by HOMA in LDLT recipient's cohort. Our study was the first study that was conducted on patients who underwent LDLT to study prospectively the fate of HCV induced IR at different time points during the 1st year post LDLT.

Our results revealed that the median HOMA value showed significant improvement during the 6 and 12 months post LDLT. These results could be attributed to strict inclusion criteria and also to that most of our patients received cyclosporine A as the main maintenance immunosuppression during the 1st year post LT, taking in consideration the more diabetogeniceffect of the tacrolimus than Cyclosporine A**[9].**

Regarding the recurrent HCV infection post LDLT in our results, the median HCV viral load showed overall increase during the 1st year post LDLT, This increase was highly significant at 6 (p value = 0.001) and 12 months post LDLT (p value =0.002).

In our results, there was no statistically significant relation between median HOMA values and HCV viral load at 6 months post LDLT.

This was contradictory to Delgado-Borrego et al[18]. who stated that subjects with higher mean integrated HCV RNA levels (defined as mean integrated HCV RNAs from month 1 post-LT to the time at which high HOMA-IR was attained) reached high HOMA levels significantly earlier than subjects with lower HCV RNA levels. They found a hazard ratio of 5.2 (p- 0.03) when evaluating integrated mean HCV RNA levels as a function of time.

Delgado-Borrego et al[18].categorized HCV RNA levels as low (<600 IU/mL and >60 IU/mL , i.e.,undetectable by quantitative but detectable by qualitative assay), medium range (>/=600 IU/mL and </=500000 IU/mL), or high (>500000 IU/mL). Subjects with high integrated HCV RNA levels (>/=500000 IU/mL) reached high HOMA-IR 5.2 times earlier than those with medium integrated HCV RNA levels (</=600 and >/=500000 IU/mL) and these in turn reached high HOMA IR 5.2 times earlier than those with low integrated HCV RNA levels (>60 and <600 IU/mL).

Also in contrast to our results, in multivariate linear regression analysis, a dose-response relationship was observed between the log10 HCV RNA level and the presence of IR. IR was positively correlated HCV RNA[19]. However this study was conducted on patients with chronic hepatitis C who didn't undergo liver transplantation.

In agree with our results, Tsochatzis et al[19]. Who studied 275 nondiabetic treatment-native chronic hepatitis C patients.Histological model assessment for insulin resistance (HOMA-IR).Tsochatzis et al[19]results showed that HOMA greater than 3.0 and HCV-RNA levels was found. However these results again were not validated in transplant recipients.

Collectively, early recurrence of HCV-disease post LDLT was documented in our results at 6 months (52.9%) and at 1 year (58.8%). All of our patients' protocol biopsies exhibited mild histopathological recurrence except one at 1 year that showed moderate HCV-disease recurrence.

Our results go hand in hand with the study that was conducted by Yosry et al [7].in which seventy-four adult hepatitis C virus positive subjects were monitored for 36 months after LDLT. In this study, recurrent hepatitis C virus infection was diagnosed on the basis of viral replication revealed by polymerase chain reaction after transplant, elevated levels of transaminases, and the results of liver biopsy. Hepatitis C virus recurrence was identified in 31.1% of the patients studied. Histopathologic recurrence was mild, and 91% of the subjects had a fibrosis score of less than or equal F2 using ishak modification of the Knodell classification.

In our study, there was no statistically significant relation between median HOMA values and histological recurrence of HCV. These results might be attributed to multiple factors including small total number of the studied patients, short follow up duration that was only 1 year, all patients except one recurrence of HCV-disease had mild disease recurrence, absence of HCV (-ve) control group and finally improvement of HCV-induced IR as estimated by HOMA equation in our results.

This was contradictory to Veldt et al[10]. who investigated whether the (HOMA-IR) can be used to identify insulin-resistant patients at risk for rapid fibrosis progression after liver transplantation for chronic

hepatitis C. in that study, one hundred sixty patients were included; 25 patients (16%) were treated for diabetes mellitus and 36 patients (23%) were pre-diabetic, defined as HOMA-IR greater than 2.5. the evaluation of HOMA-IR was done at 4 months post transplant. This still early enough for patients not having developed significant graft fibrosis and it is late enough for the largest acute effects of the transplantation procedure on homeostasis to have resolved. Liver biopsies were routinely performed at 1, 3 and 5 years after transplantation on a protocol basis regardless of biochemical profile and also when clinically indicated.Liver biopsies were scored by experienced pathologists, using the Knodell fibrosis score. The study showed that insulin resistance (hazard ratio (HR) 2.07; confidence interval (CI) 1.10-3.91, P=0.024) was significantly associated with a higher probability of developing advanced fibrosis, i.e. Knodell fibrosis stage 3 or 4.

Also there was no difference in progression to advanced fibrosis between patients with pre-transplant diabetes mellitus and patients who developed diabetes mellitus within 4 months of transplantation : hazard ratio (HR) 0.87 (Confidence interval (CI) 0.25-3.00,p=0.83)

In that sequence, Veldt et al, concluded that not only patients treated for diabetes mellitus, but also prediabetic patients with an elevated HOMA-IR are at risk for rapid fibrosis progression after liver transplantation for hepatitis C.

The strength of this study was in long duration of follow up using protocol biopsies at 1, 3 and 5 years. Veldt et al, stated that although insulin resistance was an important predictor of more advanced fibrosis stage, this didn't translate into an association of insulin resistance and poorer graft survival in our study (5-year survival 85.5% vs 78.1% log rank p=0.37).

CONCLUSION

To our knowledge, this is the first study of HCV-induced IR that was conducted on LDLT recipients. HCV-induced insulin resistance is improved 1 year after LDLT. Liver transplantation could reverse HCV related cirrhosis- associated glucose tolerance Neither level of HCV- viremia nor histological recurrence of HCV was significantly related to HCV-induced IR.

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