

Incidence and Risk Factors of HCV Recurrence after Living Donor Liver Transplantation

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Abstract: Hepatitis C virus (HCV) is the most common indication for liver transplantation worldwide. Recurrence of HCV post transplantation is one of the major challenges which is associated with poor graft and patient survival. The aim of this study was to assess the frequency of clinical HCV recurrence after liver transplantation (LT) and identify possible factors affecting it. The study was conducted on 122 recipients of living donor liver transplantation (LDLT) due to HCV related liver cirrhosis. Clinical HCV recurrence was diagnosed by elevated liver enzymes, increased viral load and confirmed by histopathology of liver biopsy. Several factors related to recipients, donors, operative and postoperative period were analyzed for their relation to recurrent HCV. Our results showed that the clinical HCV recurrence was diagnosed in 22.7 % (28 patients) of LDLT recipients with 75% of them (21 patients) diagnosed in the first year post transplantation. Less graft recipient weight ratio (GRWR) and rejection episodes following surgery were the only factors significantly related to the development of recurrent disease.

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1. Introduction

Egypt has high prevalence of hepatitis C virus (HCV) infection. It is estimated that 90% of cases of HCV in Egypt are infected by genotype 4 [1]. The high prevalence of HCV infection has led to increasing numbers of Egyptian patients suffering from chronic liver disease, cirrhosis, and hepatocellular carcinoma; all are associated with high morbidity and mortality [2].

Liver transplantation (LT) is the only effective curative treatment for end-stage liver disease [2]. Cadaveric organ transplantation is still not applied in Egypt [3] and LT from living donor is the only hope for Egyptian patients with end stage liver disease.

The outcome of LT has been improved over the past years due to advances in perioperative management, a better understanding of the course and prognosis of several liver disease, improved immunosuppressive therapy and more effective postoperative care [4]. However, complications are common in the early and long term period and contribute to significant morbidity and mortality [4].

Recurrence of original disease, especially HCV recurrence, remains to be one of the major problems which are associated with poor long term outcome [5]. Unfortunately, the recurrence of HCV post transplant is almost universal [6] and early recurrence of HCV disease is recognized as a poor prognostic indicator with lower subsequent graft and patient survivals [7].

Recognition of recipients who are at risk for recurrent HCV disease would be useful when considering organ allocation and prophylactic antiviral treatment [8].

Aim of the study:

This study was done to estimate the incidence of HCV recurrence among a sample of Egyptian patients who underwent living donor liver transplantation (LDLT). It also aimed to analyze different variables related to recipients, donors, operative and post operative period that may increase the risk for HCV recurrence after LT.

2. Patients and Methods:

This study included all patients who underwent adult LDLT in Ain Shams Specialized Hospital and Egypt Air Hospital transplantation centers in the period from May 1st, 2009 to September 1st, 2011.

Inclusion criteria:

Adult recipients who underwent LDLT due to HCV related ESLD and meeting the transplantation criteria of the centers (Child Pugh score ≥ 7 [9] or presence of HCC limited to the Milan criteria [10] irrespective to Child score).

Exclusion criteria:

Cases with early post operative mortality (death within the first three months) and cases transplanted for causes other than HCV related liver cirrhosis.

Study design:

During the study duration, a total of 144 LDLT surgeries were done. Twenty-two cases were excluded from the study either because of early postoperative mortality (12 patients) or because the diagnosis of cirrhosis was due to HBV infection (5 patients), cryptogenic liver disease (3 patients), Wilson disease (one patient) and Budd chiari syndrome (one patient). The remaining 122 patients matched the inclusion criteria and they were all enrolled. Included patients were divided in two groups; group with clinical HCV recurrence and group without recurrence of HCV.

In both centers, LDLT surgeries were performed by the same surgical team. The study protocol was approved by the scientific and ethical committee of Ain Shams University. A written consent was obtained from all subjects for data documentation and analysis.

Diagnosis of clinical HCV recurrence:

Diagnosis of HCV recurrence was based on the presence of elevated liver enzymes, evidence of viremia by quantitative assessment of HCV RNA using PCR technique and confirmed by liver biopsy for assessment of necro-inflammation and histopathological grading. All biopsies were examined by a single expert pathologist.

Risk factors for recurrent hepatitis C:

The following risk factors for hepatitis C recurrence were analyzed; **Recipients' factors:** Age, sex, Child-Pugh score, MELD score, presence of HCC and evidence of Schistosomal infection (presence of positive antibelharzial antibodies in the serum and/or presence of living or dead belharzial ova in rectal snip). In addition to HBc Ab (total) status and preoperative level of HCV PCR. **Donors' factors:** Age, sex, presence of blood relationship to the recipient and graft steatosis (steatosis is accepted in donor's liver biopsy up to 20% according to the centers' protocol).

Operative factors:

Cold ischemia time, warm ischemia time, actual graft weight and graft recipient weight ratio (GRWR). **Postoperative factors:** Type of immunosuppression (either cyclosporine based or tacrolimus based), severe rejection episode (required additional immune suppressive agent rather than increasing the dose of the patient's basic immunosuppression drugs), biliary complications and CMV infection.

Statistical analysis:

Analysis of data was performed by using the 15th version of Statistical Package for Social Science (SPSS). Description of all data in the form of mean (M) and standard deviation (SD) for all quantitative variables was done. Frequency and percentage was

done for all qualitative variables. Comparison between quantitative variables was done using t-test to compare two groups. Comparison of qualitative variables was done using the Chi-square test. Significant level measured according to *P* (probability) value, $P > 0.05$ is insignificant, $P \leq 0.05$ is significant and $P \leq 0.01$ is highly significant. Relative risk (Risk ratio) of HCV disease recurrence for each qualitative variable was calculated.

Incident rate was calculated by the following formula:

$$\text{Incidence rate} = \frac{N}{\text{Time}} = \frac{\text{Number of individuals developing disease}}{\text{Total time experienced by population at risk}}$$

3. Results:

Of 122 recipients met the inclusion criteria of the study; 53 (43.4%) of them had concomitant HCC and 3 (2.4%) cases had HBV co-infection. The mean follow-up period was 14.62 ± 8.87 months (range 4 months to 32 months). Most recipients were men ($n=108$ [88.5%]).

Table (1): Preoperative characteristics of recipients and donors

Preoperative characters of recipients	
Gender (total number =122) male/female	108/14*
Age (mean \pm SD in years)	48.95 \pm 7.447
Child Class A/B/C	7/51/64*
MELD Score (mean \pm SD)	15.41 \pm 5.134
Preoperative HCV PCR	
Undetectable /Low / Moderate/ High	7/87/27/1*
HCC yes/no	53/69*
Evidence of Schistosomal infestation yes/no	66/56*
HBc Ab (total) status positive/negative	71/51*
Preoperative characters of donors	
Gender (total n=122) male/female	89/33*
Age (mean \pm SD in years)	29 \pm 6.499
Blood relation to recipient yes/no	51/71*
Graft steatosis (up to 20%) positive/negative	34/88*

*number of cases

The mean recipients' age was 48.95 ± 7.4 years. Table (1) summarizes the main preoperative characteristics of recipients and donors.

Clinical recurrence of HCV:

In the study population (122 recipients) who had LDLT due to HCV related liver cirrhosis; there were 28 (22.7%) recipients diagnosed with recurrent HCV. The remaining 94 (77.3%) patients had no evidence of recurrent disease (Figure 1). The calculated incidence rate of HCV recurrence was 17.4 per 100 person-years.

From the total number of cases (28 cases) with recurrent HCV; 21 recipients (75%) were diagnosed within the first year post transplantation and 7 patients (25%) were diagnosed in second year

(Table 2). The diagnosis was made in 9 patients were (32.14%) within 6 months of transplantation and in 12 patients (42.86%) between 6 and 12 months after

transplantation. The highest number of cases diagnosed was between the 6th and the 9th months post transplantation (Figure.2).

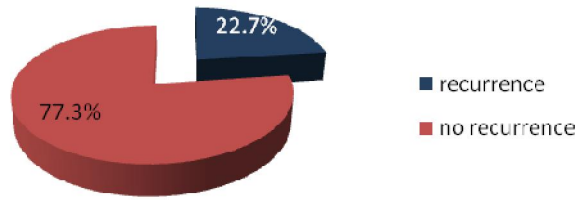


Figure (1): HCV recurrence rate in the study group

Table (2): Timing of HCV recurrence post LDLT

Interval from LDLT surgery	Number of recurrent HCV cases
0 - 6 months	9/28 (32.14%)
6 - 12 months	12/28 (42.86%)
12 - 18 months	6/28 (21.43%)
18 - 24 months	1/28 (3.57%)

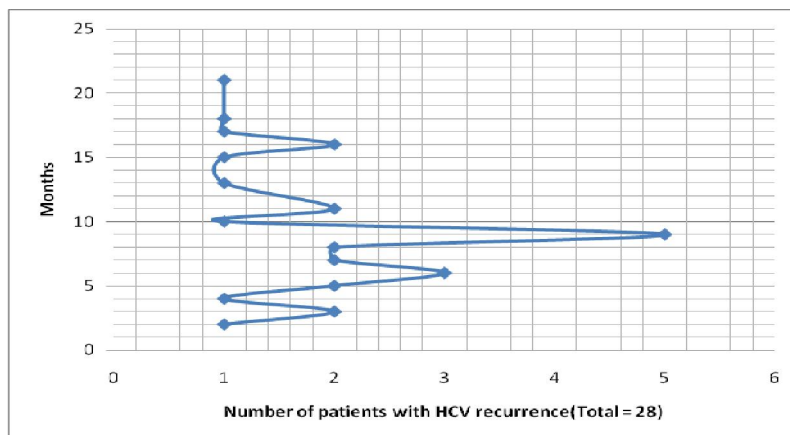


Figure (2): Timing of HCV recurrence

Risk Factors for Recurrent HCV:

Preoperative recipients' factors:

- **Gender and age of recipients**

Most recipients were males either in the group with recurrent HCV post transplantation or in the group without HCV recurrence. The male to female ratio was 8.3:1 in the first group and 7.55:1 in the second group respectively. The mean age of patients who had clinical recurrent hepatitis C virus infection after transplantation was (47.14 ± 6.89 years) and the mean age of patients who had no recurrence was (49.49 ± 7.55 years). Both gender and age of recipients did not affect the development of HCV recurrence (Table 3).

- **Child Pugh class and MELD score**

There was no statistically significant relationship between the preoperative Child-Pugh Class of patients and development of HCV recurrence

after transplantation. The mean MELD score at time of transplantation was 14.25 ± 5.51 in the group with HCV recurrence and 15.76 ± 4.99 in none recurrence group. The mean MELD score was not significantly associated with the development of clinically recurrent hepatitis C virus after LT (Table 3).

- **Preoperative HCV RNA level**

There was no significant effect of the preoperative HCV PCR level in the recipients and the incidence of hepatitis C recurrence post operative (P = 0.134) (Table 3).

- **Other recipient clinical and laboratory data**

The total number of recipients with hepatocellular carcinoma was 53 patients; 12 of them developed recurrent HCV and 41 patients didn't develop recurrence. The presence of HCC did not significantly affect the incidence of HCV recurrence (P = 0.934) (Table 3). The presence of positive HBc

Ab and the evidence of schistosomiasis infestation preoperative were not associated with increased incidence of recurrence of hepatitis C post LDLT as shown in table (3).

Preoperative donors' factors:

- **Gender and age of donors**

The gender of the donor did not affect the risk of HCV recurrence as well as the mean donors' age. P was 0.836 and 0.15 respectively (Table 3).

- **Presence of blood relationship to recipients and presence of graft steatosis**

The presence of donor recipient blood relationship and the presence or absence of mild graft steatosis (between 5% up to 20% according to the centers' protocol) were not significant factors affecting the incidence of HCV recurrence as shown in table (3). Risk ratio for both factors was <1.

Operative factors:

There was no effect of cold ischemia time, warm ischemia time or actual graft weight on HCV recurrence. The risk of HCV recurrence postoperative was **significantly higher** with **less mean GRWR** ($P = 0.02$) (Table 4).

Table (3): Correlation between preoperative recipients' and donors' factors and HCV recurrence

Variables	Cases with HCV recurrence (Total=28)	Cases without HCV recurrence (Total=94)	Risk ratio	P
Recipients' Factors				
Gender Male	25/28 (89.3%)	83/94 (88.3%)	1.011	0.886
Female	3/28 (10.7%)	11/94 (11.7%)		
Age (years) (mean±SD)	47.14 ± 6.89	49.49 ± 7.55	-	0.14
Child Pugh Class A	2/28(7.14%)	5/94(5.32%)	-	
B	16/28(57.14%)	35/94 (37.23%)	-	0.128
C	10/28(35.72%)	54/94 (57.45%)	-	
MELD Score (mean±SD)	14.25 ± 5.51	15.76 ± 4.99	-	0.17
HCC	12/28 (42.85%)	41/94 (43.62%)	0.76	0.934
Schistosomiasis infestation	16/28 (57.15%)	50/94 (53.19%)	1.074	0.713
HBc Ab (total) status	19/28 (67.86%)	52/94 (55.32%)	1.226	0.238
Preoperative HCV PCR				
Undetectable	0/28 (0%)	7/94 (7.44%)	-	
Low viremia	20/28 (71.43%)	67/94(71.28%)	-	0.134
Moderate viremia	7/28 (25%)	20/94 (21.28%)	-	
High viremia	1/28 (3.57%)	0/94 (0%)	-	
Donors' Factors				
Gender Male	20/28 (71.43%)	69/94 (73.4%)		0.973
Female	8/28 (28.75%)	25/94 (26.6%)		
Age (years) (mean±SD)	27.46 ± 5.28	29.46 ± 6.77		0.15
Blood relation to recipient	11/28 (39.29%)	40/94 (42.55%)	.923	.758
Graft steatosis (maximum 20%)	5/28 (17.86%)	29/94 (30.85%)	.578	.178

Table (4): Relation between operative and postoperative factors and recurrence of HCV

Variables	Cases with HCV recurrence (Total=28)	Cases without HCV recurrence (Total=94)	Risk ratio	P
Operative factors (mean ± SD)				
Cold ischemic time (min)	49.11 ±25.28	45.51 ±26.77	-	0.62
Warm ischemic time (min)	56.63± 23.56	51.61 ±14.85	-	0.314
Actual Graft weight (gm)	861.05 ±141.58	886.77 ±172.92	-	0.561
GRWR (%)	1.08 ±0.15	1.17 ±0.27	-	0.02*
Postoperative factors				
CMV infection	4/28 (14.29%)	10/94 (10.64%)	1.342	0.595
Biliary complication	4/28 (14.29%)	28/94 (29.79%)	0.479	0.102
Rejection episodes	5/28 (17.86%)	5/94 (5.32%)	3.357	0.034*
Immunosuppression				
Cyclosporine	11/28 (39.29%)	35/94 (37.23%)	1.055	0.844
Tacrolimus	17/28 (60.71%)	59/94 (62.77%)		

* Significant

Postoperative factors:

Patients with postoperative CMV infection had a 1.34 fold risk of recurrence but it was statistically not significant ($P = 0.595$). Development of biliary complications postoperative did not increase

the risk of HCV recurrence. There was a **significant relation** between **rejection episodes** and recurrence of hepatitis C ($P = 0.034$) with a **3.3 fold greater risk** to develop recurrent HCV **in patients who experienced rejection**. The type of calcineurin inhibitor used for

immunosuppression did not significantly affect the development of clinically recurrent hepatitis C virus after transplantation.

4. Discussion

In the present study, HCV recurrence post-transplantation was diagnosed in 22.7% of recipients (28 patients out of 122 cases) during mean duration of follow up 14.62 ± 8.87 months. The incidence rate of HCV recurrence was 17.4 per 100 person-years.

In Egypt, *Ezat et al.* reported that 33.7 % recipients with HCV genotype 4 developed post transplantation HCV recurrence [11]. Similarly, *Yosry et al.* found 31.1% of recipients developed HCV (genotype 4) recurrence [6]. The mean duration of follow up in their studies was 29.76 ± 16.86 month and 36 months respectively. The relatively lesser percentage reported in our study maybe due to shorter follow up duration.

Although *Paik et al.* found only 14% of patients had clinical evidence of recurrent HCV [12], many studies showed clinical and/or histological HCV recurrence ranging from 40% to 66% of patients [13-16]. This discrepancy may be explained by difference in HCV genotypes in those studies and/or different studies durations. Additionally some studies considered protocol liver biopsy following surgery which was not routinely done in our included centers (currently protocol liver biopsy is done routinely after 6 months of transplantation). Other factors related to different centers (advanced donor age, graft steatosis and high MELD score especially in deceased donor liver transplantation (DDLT)) may have played a role in the difference of the percentage of HCV recurrence as will be discussed later.

We diagnosed 32.14% (9 cases) of patients with recurrent hepatitis C within the first 6 months post transplantation and a total of 75% of cases with recurrent HCV were diagnosed within the first year after transplantation (21 out of 28 cases) (Table 2). Similarly *Ezat et al.* found 79.3% of cases with recurrence occurred in the first year of follow up [11]. Other study showed 61.1% of HCV recurrence diagnosed within the first year post transplantation [13]. These figures suggested that highest rate of HCV recurrence occurs in the first year following transplantation. We found that the most common time for recurrence to be diagnosed was between the 6th and 9th months post surgery. The time of diagnosis of HCV recurrence is crucial. It was found that HCV recurrence within 6 months of LT is associated with high risk of disease progression compared to recurrence later than 6 months. Moreover, HCV recurrence within 1 year post transplantation was significantly associated with decreased 5-year patient

and graft survival rates compared with patients with recurrence after 1 year [13].

In this study, recipients and donors gender were not correlated with disease recurrence. This agreed with other reports which had similar findings [6, 8].

Our study showed that neither recipients nor donors ages affected HCV recurrence. A finding that came in accordance with many studies [6, 11, 16, 17]. On the other hand, *Cameron et al.* found that advancing recipient age (>40) and older donor age (>50) are significant predictors for HCV recurrence [8]. The fact that centers that undergo LDLT (as in our centers) rather than DDLT have younger donors may explain this discrepancy.

The mechanisms that might explain advancing donor age as risk factor for HCV recurrence is not completely understood. The process of liver aging and associated pathological changes (more lipofuscin, more steatosis, iron overload, and also fibrosis and inflammation without any known cause) may explain the aggressive course of HCV recurrence in recipients receiving elderly liver graft [18].

We also reported that both Child class and MELD scores did not significantly affect the incidence of HCV recurrence. This was in agreement with other local reports [6, 11]. On the other hand, *Cameron et al.* reported that elevated recipient MELD score above 27 gave a 1.6-fold greater risk of HCV recurrence and considered it as a significant predictor for HCV recurrence [8]. In our work most patients included in had their MELD score much lower (mean MELD score was 15.41 ± 5.134). This explains the absence of significant effect of MELD score on recurrent HCV cases.

Ezat et al. reported that patients with high pre transplantation viral load had a significant risk for HCV recurrence [11]. In our study, the pre-transplant HCV viral load had no significant effect on the incidence of HCV recurrence. However, all patients who developed recurrent disease had viremia before transplantation and none of them had undetectable virus before surgery. *Yosry et al.* agreed that the pre-transplant HCV viral load is not a significant risk factor for recurrent disease [6].

In a univariate analysis, the presence of preoperative hepatocellular carcinoma had a significant predictive value on HCV recurrence [17]. However, in the current work hepatocellular carcinoma was not associated with recurrent HCV after transplantation.

We found no significant association between recipients with positive HBc antibody pre-transplantation and the development of recurrent hepatitis C virus. Both *Ezat et al.* and *Yosry et al.* reported significant risk of HCV recurrence in

recipients with positive HBc Ab [6, 11]. On the other hand, *Rizzetto et al.* reported that preoperative HBV-HCV co-infection is not a significant risk factor for HCV recurrence post transplantation compared to recipients with only HCV [19].

Schistosomiasis infestation is common in Egypt. So, we analyzed its effect on HCV recurrence and we found that evidence of schistosomiasis infestation had no significant correlation on post LDLT HCV recurrence. This agreed with *Ezat et al.* as they reported non-significant difference between recipients with positive and negative anti schistosomiasis antibodies [11].

In this study, we found that blood related donors did not increase the risk of HCV recurrence post transplantation. This agreed with *Ezat et al.* [11]. In addition, *Herrero et al.* found no significant relation between HLA donor-recipient compatibility and HCV recurrence [17]. However, some studies showed that HLA donor-recipient compatibility increased the risk of HCV recurrence and the risk of progression to bridging fibrosis [20, 21]. A recent work demonstrated a significant relationship between the individual scores of HLA mismatches (HLA-A3, HLA-B35, HLA-DR3, HLA-DR7, HLA-DQ2, HLA-DQ2-0) and the recurrence of HCV rather than the total score of HLA mismatches [22].

It was found that HCV recurrence is more frequent and occurs earlier in recipients of moderately and severely steatotic livers [23]. The frequency and severity of HCV recurrence increase markedly when donor graft steatosis is higher than 30% [24]. In our study, no significant liver steatosis was present in the grafts because of the donor selection criteria and this explains why graft steatosis in our study was not associated with higher risk of HCV recurrence.

In the current work we agreed with *Cameron et al.* [8] that cold ischemia and warm ischemia times are non predictive for HCV recurrence while *Botha et al.* stated that prolonged cold ischemia time increases the relative risk of HCV recurrence [25]. This conflict may be related to the type of donor as cold ischemia time in DDLT may exceed 8 hours while it doesn't usually exceed 2 hours in LDLT.

As regard the mean estimated actual graft weight, we found it had no significant correlation to the development of clinically recurrent hepatitis C virus infection so as reported by others [6, 11].

However, we found that the lower mean GRWR was associated with a higher incidence of HCV recurrence. Such association was not present in *Ezat et al. and Yosry et al.* studies [6, 11].

Humara and his co-investigators showed that CMV infection after LT was not associated with increased HCV recurrence rate or HCV viral load but may be associated with more severe forms of

recurrence. We also found that CMV infection post LT was not a significant risk factor for recurrent HCV [26].

Regarding post operative biliary complications, it didn't affect the development of HCV recurrence in the current study. Similarly, no correlation was reported by *Katz and his colleagues* between recurrent HCV disease and biliary complications [27].

Immunosuppression is a major factor responsible for the accelerated recurrence as they are associated with significantly increased hepatitis C viral load compared to the values of the same patients pretransplantation [28]. We compared the effect of initial immunosuppression agent used on the incidence of HCV recurrence. The two most frequently used basic immunosuppressive drugs in the included centers were cyclosporine and tacrolimus. We did not find significant correlation between type of calcineurin inhibitors used and incidence of HCV recurrence. Our results are in accordance with many published studies which also found no effect of either type of calcineurin inhibitors on the induction or severity of recurrent hepatitis in HCV infected patients after LT [6, 11, 12, 29].

Martin et al. had different finding. They reported that the rate of HCV recurrence was more among recipients treated by cyclosporine after one year of follow up [30].

In the current work, although the basic immunosuppressive agent didn't affect recurrence of HCV infection, we found strong relation between HCV recurrence and rejection episodes in recipients. This finding was highlighted in many studies that reported more frequent recurrence of hepatitis C in patients who had previous episodes of allograft rejection. Moreover, rejection episodes were associated with higher histological activity grades [31-33] and a more rapid progression to graft cirrhosis [34]. *Prieto et al.* explained such association by the following reasons: 1) Increased HCV viremia caused by immunosuppression. 2) Generalized up-regulation of the immune system by rejection episodes so that recognition of viral antigens as well as HLA antigens is enhanced. 3) An overlap of histological findings between cellular rejection and recurrent hepatitis C [35].

As cadaveric organ donation has been prohibited in Egypt, comparison between LDLT and DDLT regarding hepatitis C virus recurrence could not be studied. In this regards, *Guo et al.* reported no difference in the cumulative incidence of histological recurrence of HCV between recipients of DDLT and LDLT [36]. Many reports showed no difference in graft survival or fibrosis progression between recipients of LDLT compared with DDLT [37-39]. On

the contrary, recent study illustrated better survival rate and low fibrotic score for LDLT recipients [40].

As discussed above, several factors may affect the incidence of recurrent HCV following OLT. However, no universal agreement on many of these factors in the published studies. The difference in findings reported may be attributed to difference in HCV genotype between studies, different size of study population, different durations of follow up and lack of uniform criteria for the diagnosis of recurrent hepatitis C (biochemical markers versus histological diagnosis and application of protocol biopsies in some studies). In addition, the difference in some factors related to the graft between DDLT and LDLT such as (donor's age, presence of graft steatosis and the graft volume) may contribute to this paradigm.

The liver enzymes levels are poor markers for detection of HCV recurrence and bad indicators of the histological disease severity, a characteristic already observed in immunocompetent patients [35]. This emphasizes the importance of performing protocol liver biopsies in the follow-up of patients with HCV infection after they receive liver transplantation for early detection of histological HCV recurrence. Protocol liver biopsy is best to be considered after six months of transplantation. Without a protocol biopsy post-OLT, it could be claimed that the time of recurrence could be falsely prolonged because of delayed diagnosis. Early identification of patients at risk for developing HCV recurrence after LT may allow better patient management through early diagnosis and administration of antiviral treatment.

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