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Waiting list changes and follow-up of anti-HCV positive liver transplant recipients: an analysis of 400 cases out of 1000 transplantations

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Abstract

Background. *The terminal stages of chronic hepatitis C remain the main indication for liver transplantation in Russia and in the world.*

Aim. *To retrospectively evaluate the changes in the waiting list of liver transplantation that occurred during 22 years of work of the Department for Liver Transplantation at N.V. Sklifosovsky Research Institute for Emergency Medicine in relation to patients with anti-HCV+; and to study the survival rate of anti-HCV+ after liver transplantation, and peculiarities of the course of recurrent HCV infection and virological outcomes of modern antiviral therapy.*

Material and methods*. We analyzed the results of anti-HCV+ liver transplantations from a deceased donors (n=400) operated in the*

Department for Liver Transplantation at N.V. Sklifosovsky Research Institute for Emergency Medicine for 22 years. Changes in the Waiting List structure, recipient survival and antiviral therapy efficacy were studied.

***Results**. The proportion of anti-HCV+ recipients decreased from 44.3% (period from 2007 to 2019) to 34.1% (from 2020 to 2022, p=0.0027). Survival of anti-HCV+ recipients without HCC is currently comparable to survival of non-infectious non-HCC recipients. The 5-year survival of anti-HCV+ recipients without HCC at the time of liver transplantation was 84%, and the 10-year survival was 76%. The 3- and 5-year survival rates of recipients without HCC at the time of liver transplantation who had surgery before August 2016 were lower (80% and 77%, respectively) than the 3- and 5-year survival rates (91%) of liver transplant recipients operated on later than this date (p=0.01). Before August 2016, recurrence of HCV infection occurred in > 90% of anti-HCV+ recipients with known HCV RNA status after liver transplantation. Spontaneous clearance of HCV RNA after liver transplantation was observed in 2.1% of cases. In recent years, the incidence of recurrent HCV infection after liver transplantation has decreased significantly (~25% in 2021-22). The use of modern direct acting antiviral regimens results in >95% viral eradication after the 1st course. The emergence of drug resistance polymorphisms in patients who have had unsuccessful experience of direct acting antiviral before liver transplantation is not an obstacle to the success of direct acting antiviral treatment after liver transplantation.*

***Conclusion**. The possibility of a rapid and safe cure for HCV infection against the backdrop of a shortage of donor organs necessitates a revision of the documents regulating organ donation, which should make organs from donors with anti-HCV in the blood available for transplantation.*

Keywords: waiting list, liver transplantation, HCV antibody, recurrent hepatitis C, survival rate, follow-up

Conflict of interests Authors declare no conflict of interest

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ASUNA, asunaprevir

AVT, antiviral therapy

DAA, direct acing antiviral (drug)

DAC, daclatasvir

DLT, Department for Liver Transplantation of the N.V. Sklifosovsky Research Institute for Emergency Medicine

FCH, fibrosing cholestatic hepatitis

FLF, fulminant liver failure

GRAZO, grazoprevir

HCC, hepatocellular carcinoma

ETR, end-of-treatment response

LED, ledipasvir

LT, liver transplantation

NAFLD, non-alcoholic fatty liver disease

PEG-IFN, pegylated interferon

PI, protease inhibitor

RBV, ribavirin

SIM, simeprevir

SOF, sofosbuvir

SVR, sustained virological response

VELPA, velpatasvir

WL, Waiting List

Introduction

End-stage chronic hepatitis C remains the main indication for liver transplantation (LT) in Russia and in the world. HCV replication after LT recurs in all recipients in whom it was observed at the time of LT; and the disease progression speeds up significantly without antiviral therapy (AVT). With the advent of direct acing antivirals (DAAs) and their implementation into daily clinical practice, eradication of HCV infection has become possible and should be achieved in all recipients with recurrent hepatitis C [1]. In this regard, in most countries of the world, the pool of organs available for transplantation has expanded to include donors having anti-HCV in blood and minor liver damage [2, 3]. In the Russian Federation, LT from donors having anti-HCV is not yet permitted by law. Analysis of the work of the Department for Liver Transplantation (DLT) at the N.V. Sklifosovsky Research Institute for Emergency Medicine, which performed more than 1000 LT from posthumous donors over 22 years, seems to us to be relevant and necessary to justify the urgent changes.

The aim was to retrospectively trace the changes occurred in the Liver Transplant Waiting List in the Department for Liver Transplantation at the N.V. Sklifosovsky Research Institute for Emergency Medicine that have occurred over the 22 years of work in relation to patients having anti-HCV in blood; to study the survival of liver recipients with anti-HCV, typical features of the of recurrent HCV infection course, and virological outcomes with regard to currently used antiviral therapy.

Material and methods

From September 2000 to August 2022, 1000 liver transplantations (LT) from a posthumous donor were performed at our DLT of the

N.V. Sklifosovsky Research Institute for Emergency Medicine (DLT). Of these, 400 (40%) recipients had anti-HCV in their blood at the time of transplantation. One year after the 1000th surgery (in August 2023), we analyzed the characteristics of patients with anti-HCV on the LT WL who underwent LT; the recipient survival; the AVT efficacy in this group of recipients.

The χ-square test was used to compare frequencies in two unrelated groups. The analysis of recipient survival was carried out by Kaplan–Meier method using Statistica 12.0 software package (StatSoft, Inc., USA). Comparisons of survival curves were made using the log-rank test.

Results

I. Liver Transplant Waiting List Trend Analysis

Among the operated patients, 370 (92.5%) had signs of current or previous HCV monoinfection, 8 HCV patients had co-infection with the HBV virus (2%); 19 patients (4.75%) had infection with three viruses (HBV, HCV, and HDV). In 3 more patients, anti-HCV was detected against other liver diseases that were indications for LT (Wilson's disease, alveococcosis, and non-alcoholic fatty liver disease [NAFLD]). It is difficult to exactly assess the impact of chronic alcohol intoxication in liver damage in our patients. At the time of entering LT WL, we qualified the etiology of the disease as mixed (viral and alcoholic) in 30 patients (7.5%); but we suppose that in reality these figures are much higher.

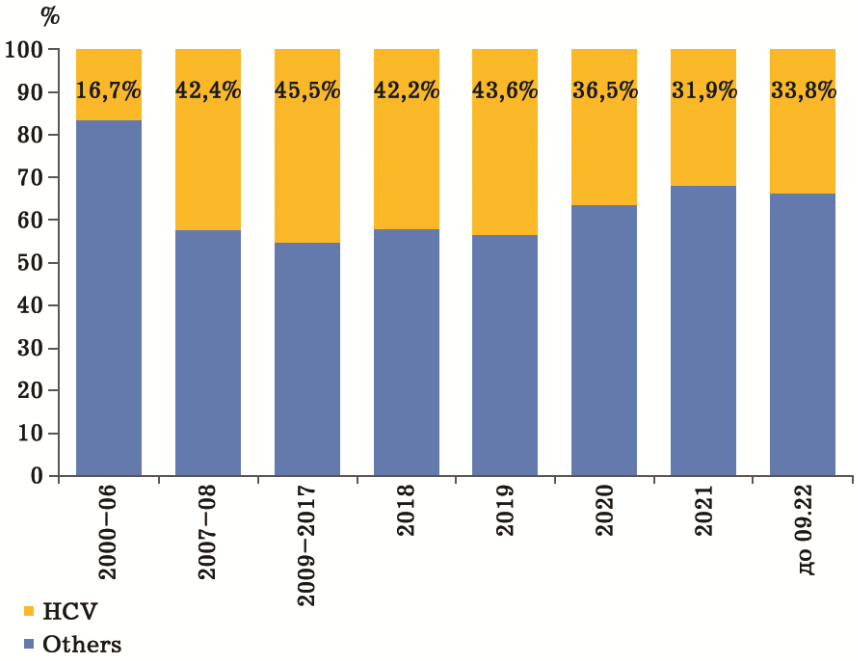

Fig. 1. Proportion of liver transplants performed in anti- HCV positive patients among all reasons for liver transplantation by year

Fig. 1 shows the proportion of liver recipients with anti-HCV in blood at the time of transplantation with regard to etiology and by year. In 2000–2006 it made 16.7%. During this initial period under the study, DLT performed 42 LTs (from 2 to 14 operations per year). Preference in performing LT was given to recipients with non-viral etiology of liver disease. In 2007–2008 the number of LTs increased to 29–30. The proportion of anti-HCV+ recipients increased to 42.4%. Subsequently, from 2009 to 2017, the number of liver transplants performed annually continued to increase, and the proportion of liver recipients with anti-HCV among all recipients was 45.5%. It remained virtually unchanged in 2018 (42.2%) and 2019 (43.6%). Starting from 2020, anti-HCV+ recipients made 36.5% (2020), 31.9% (2021) and 33.8% (2022) in the total structure of transplants. Starting from 2019, more than 100 LT procedures were performed at DLT annually (that is, as many as were performed in the first 9 years of studied period). Thus, the proportion of

anti-HCV+ recipients operated on from 2007 to 2019 was 42.2%–45.5% (44.3%, n=650), and the percentage of those operated on from 2020 to 2022 made 34.1% (n=308, p=0.0027).

General characteristics of recipients are given in Table 1.

It is interesting to note that there were significantly more male anti-HCV anti-HCV+ recipients than women (with ratio of approximately 4:1). With the increasing experience of doctors at DLT, the mean age of recipients tended to increase. On average, our recipients did not have significant obesity at the time of transplantation, which reduced the risk of concomitant fatty graft disease. Liver transplantation for fulminant liver failure (FLF) was performed in 25 (2.5%) of 1000 recipients at DLT of the Research Institute for Emergency Medicine. In no case was HCV the cause of the FLF development. Liver transplantation in all of our patients, except for the patient with alveococcosis, was performed for end-stage chronic liver disease (cirrhosis, hepatocellular carcinoma). The proportion of patients with hepatocellular carcinoma (HCC) against the background of cirrhosis varied significantly from year to year and overall amounted to 40.75% (Table 1).

Table 1. Characteristics of liver transplant recipients being anti-HCV positive at the time of liver transplantation

Years	2000–08	2009–11	2012–14	2015–16	2017	2018	2019	2020	2021	09.2022	Total
Number of recipients	32	50	50	41	43	35	44	42	39	24	400
Gender (m/f)	27/5	34/16	40/10	33/8	28/15	31/4	35/9	34/8	33/6	23/1	318/82
Age at the time of LT (Me (Q25;Q75)), years	48.5 (42.5;54.4)	49.9 (44.2;56.5)	48.7 (43.8;54.4)	51.6 (47.3;58.1)	52.8 (41.7;55.1)	55.2 (49.1;58.7)	53.1 (47.6;60.4)	57.6 (54.0;64.5)	55.5 (46.3;61.7)	53.7 (46.7;57.0)	52.8 (46.0;57.8)
Body mass index (Me (Q25; Q75)), kg/m^2	24.9 (22.6;29.4)	26.6 (22.7;29.1)	25.7 (23.2;29.8)	24.1 (22.2:28.4)	25.7 (22.3;27.1)	25.1 (22.2;29.1)	24.1 (20.9;25.7)	24.4 (21.6;28.9)	23.8 (22.1;26.0)	25.6 (21.5;26.6)	24.9 (22.2;28.0)
Number of patients with HCC, n (%)	16 (50)	10 (20)	16 (32)	13 (31.7)	14 (32.6)	16 (45.7)	19 (43.2)	25 (59.5)	22 (56.4)	12 (50)	163 (40.75)

The first recipient, who had the experience of receiving DAA therapy before LT, was operated on in August 2016. In order to analyze the survival and assess virological outcomes, we divided the studied period of DLT work into the “pegylated interferon (PEG-IFN) era” (until August 2016) and the “DAA era” (from August 2016–September 2022).

During the “PEG-IFN era,” 166 recipients were operated on, 141 of whom (84.9%) had HCV RNA in their blood. Data on HCV viremia after transplantation in 10 recipients was unavailable known; 9 died in the early post-transplantation period; one was not followed-up in our DLT, lost for follow-up. HCV RNA was not found in 15 recipients (9%), including 7 cases of co-infection with HBV/HCV/HDV. There were 4 cases of successful AVT with pegylated interferon (PEG-IFN) and ribavirin before the patient placement on the LT WL; and in one case, HCV RNA was absent in the recipient’s blood before LT without previous AVT. In 3 (2.1%) of 144 recipients, with HCV RNA detected in the blood at the time of LT, the spontaneous clearance of HCV RNA occurred after LT. Thus, recurrence of HCV infection after LT occurred in 141 (90.4%) of 156 anti-HCV+ recipients in whom the data on viremia after LT were available.

We retrospectively analyzed the experience of using DAAs before LT in the recipients operated on since 2017. In 10–15% of cases, the information on the conduct and nature of AVT before LT was not available. The proportion of recipients who did not receive DAAs before LT was 50% in 2017. By 2022, it had decreased to 30% (Fig. 2). Of particular interest are the patients who, despite the use of DAAs before LT, experienced recurrent hepatitis C after LT. Earlier, we published the first experience of analyzing this group of patients [4]. Of the 46 patients who received DAAs before LT, 14 (30%) resumed HCV replication after LT. Of these 14 patients, 12 (85.7%) had HCV genotype 3 and only two

(14.3%) had HCV genotype 1. Meanwhile, among the recipients operated on before August 2016, 65% had HCV genotype 1, and only 29% had genotype 3, which corresponded to the distribution of HCV genotypes in the Russian population [5]. Differences in the frequency of detecting HCV genotypes 1 and 3 between the patients with recurrent HCV infection operated on before and after August 2016 were statistically significant ($p<0.001$). A study of mutations associated with DAA resistance in the NS5A and NS5B loci of the viral genome was conducted in 11 of 12 recipients with recurrent HCV genotype 3 infection. The Y93H mutation was detected in 6 recipients; other mutations associated with drug resistance in NS5A (A30K, L31I) were found in 3 cases. Only 3 patients had no clinically significant drug resistance mutations.

At the time of this analysis, the HCV replication recurrence after LT was observed in 22 of 101 recipients who received DAA therapy before LT. That is, DAAs were ineffective in every fifth patient having an advanced stage of liver cirrhosis (21.8%). HCV genotype information was available for 19 of these 22 recipients. The ratio of genotypes 1 and 3 increased slightly (6 versus 13). Unfortunately, the study of drug resistance polymorphisms is currently not available to us.

After the implementation of DAAs into routine clinical practice, the percentage of patients in whom HCV RNA was detected in blood at the time of LT decreased from 60% in 2017 to 25% in 2021–22 (Fig. 3).

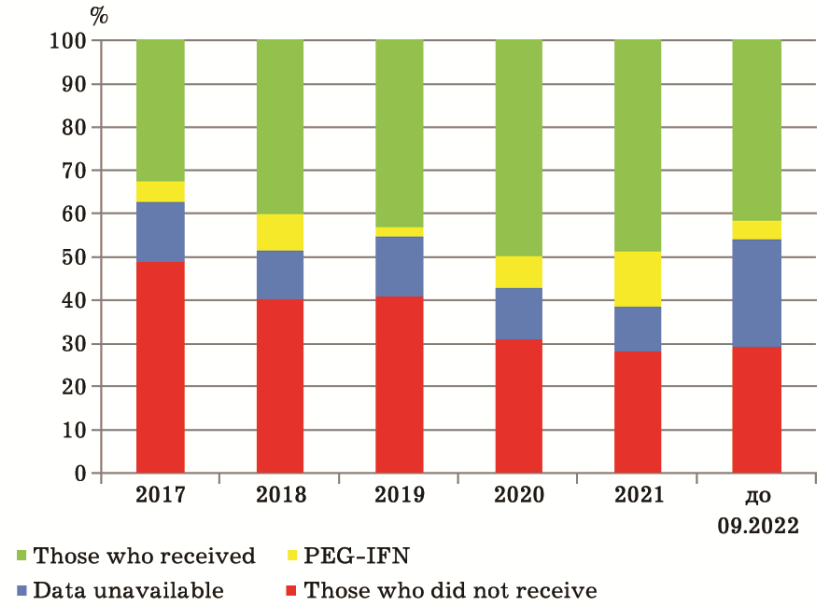

Fig. 2. Information on the use of direct-acting antiviral drugs in anti-HCV+ patients being on the Waiting List for liver transplantation (PEG-IFN - HCV aviremia as a result of pegylated interferon therapy)

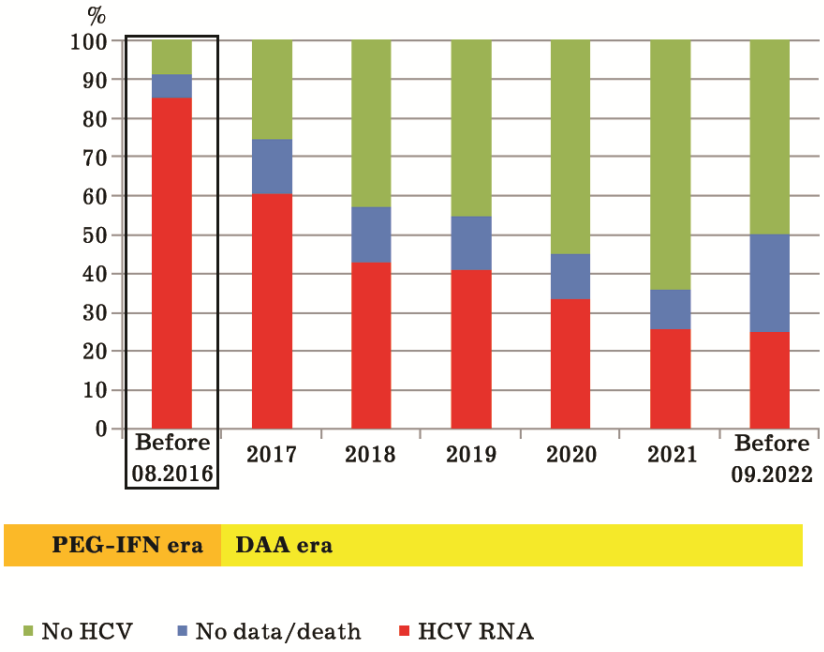

Fig. 3. The rates of HCV viremia (RNA+) at the time of liver transplantation among anti-HCV+ recipients before and after the implementation of direct-acting antiviral drugs into routine clinical practice (ND - no data)

II. Outcome and survival analyses of recipients who had anti-HCV in blood at the time of liver transplantation

At the time of analysis, 248 recipients were alive; 111 died (58 of them in the first year after LT); 41 recipients did not come for follow-up visits to DLT of the Sklifosovsky Institute for more than 12 months. The fate of these recipients is unknown.

The mortality causes among the recipients in the first year after LT and in the long-term period are presented in Table. 2. The most common cause of death was the HCC progression (31 patients). A detailed analysis of the HCC course after LT is beyond the scope of this study; however, above we have already note a relatively high proportion of patients with HCC at the time of LT. The second most common cause of death was graft pathology (27 patients). Nineteen of them did not survive 1 month after surgery; 4 patients died directly from HCV infection complications: 2 died from fibrosing cholestatic hepatitis (FCH) C in the early post-transplant period; and 2 others from graft cirrhosis in the long-term. Thus, mortality directly from HCV infection made 3.6% of all cause mortality, and 14.8% of non-neoplastic “hepatic” causes of death. Another 3 patients died from graft dysfunction of an unspecified origin (HCV RNA was detected in blood only in one case). One patient died from complications of decompensated graft cirrhosis of unspecified etiology; there was no HCV RNA in blood throughout the entire follow-up period (67 months).

Table 2. Causes of death in recipients in the first year after liver transplantation and in the long-term period

Cause of death	First year after LT	Long-term period (>12 months)
Graft pathology	21 (36.2%)	6 (11.3%)
including those HCV-associated	2 (FCH C)	2 (graft cirrhosis)
Progression of HCC	10 (17.2%)	21 (39.6%)
Infections other than COVID-19	14 (24.1%)	1 (1.9%)
COVID-19	4 (6.9%)	5 (9.4%)
Cardiovascular diseases	3 (5.2%)	4 (7.5%)
Oncology (except HCC)	1 (1.7%)	5 (9.4%)
Others	5 (8.6%)	11 (20.8%)
Total	**58**	**53**

In 12 cases, re-LT was performed. Nine recipients died (8 in the early postoperative period, 1 lived after re-LT for 22 months and died from complications of chronic alcohol intoxication). Three patients who underwent re-LT were alive at the time of analysis. Causes of graft loss were the following: a) complications of the early postoperative period (5 patients); b) recurrent cholangitis against multiple strictures (2); c) severe rejection refractory to corticosteroids (1); d) fibrosing cholestatic hepatitis C (1); e) HCC progression (1), f) graft cirrhosis as a result of autoimmune hepatitis (1). In one case, the cause of severe graft dysfunction was not specified.

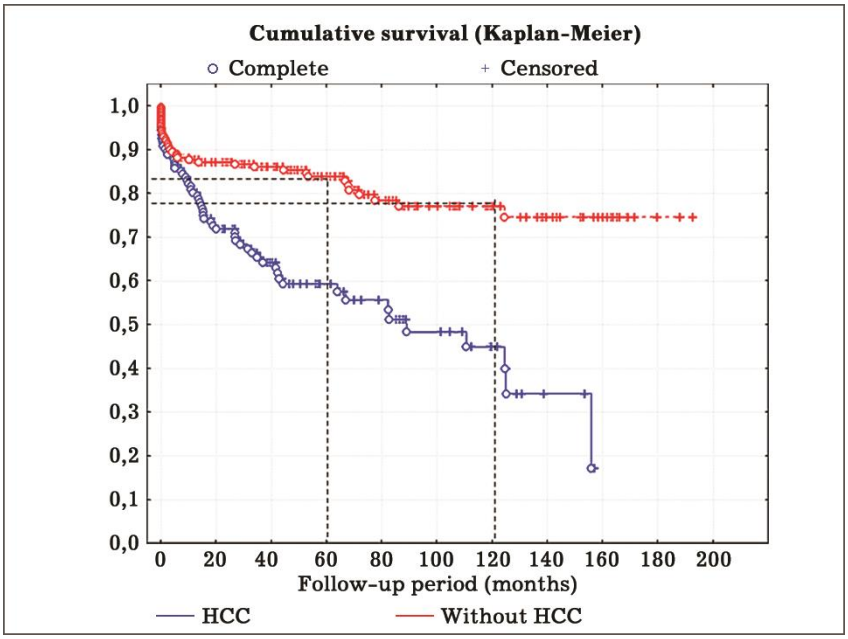

Fig. 4. Survival of anti- HCV+ recipients depending on the presence of hepatocellular carcinoma at liver transplantation

An overall 5-year recipient survival rate was 74%, and a 10-year survival rate was 65%, which was likely due to a high proportion of patients who progressed to HCC after LT. The 5-year survival rate of recipients who did not have HCC at the time of transplantation was 84%, and the 10-year survival rate was 76%. The survival rate of recipients is shown in Fig. 4 ($p<0.0001$).

The 3- and 5-year survival rates of recipients who underwent LT in the "DAA era" were higher (91%) than the 3- and 5-year survival rates of recipients who underwent LT in the "PEG-IFN era" (80% versus 77% respectively; $p=0.01$, Fig. 5).

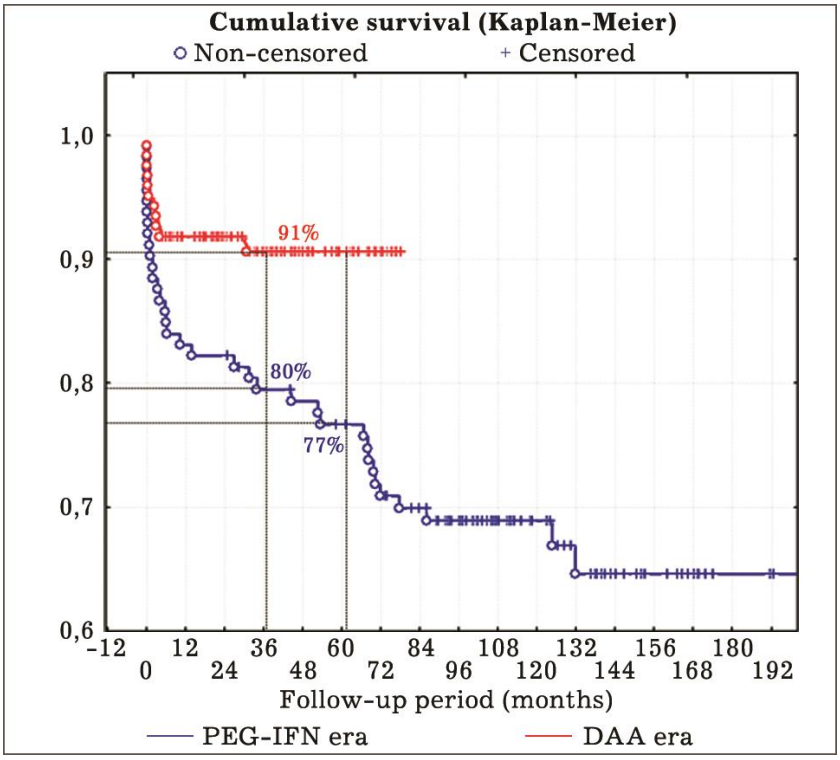

Fig. 5. Survival of anti-HCV+ recipients without hepatocellular carcinoma at liver transplantation depending on the "era": before 08.2016 and after 08.2016

III. AVT results in recipients being anti-HCV+ at the time of transplantation

HCV RNA was detected after LT after LT in 232 of 400 recipients with anti-HCV in blood (Fig. 6). In 182 cases (78.4%) the recipients received one or more courses of AVT. In 164 cases (90.1%), a sustained virological response (SVR) was obtained. Three more recipients were still receiving AVT or were being followed-up after completion of AVT course at the time of this analysis. A sustained virological response was achieved as a result of one or more PEG-IFN-containing AVT courses in 29 cases, after the DAA first course in 131 cases (some of the patients who did not respond to PEG-IFN were successfully treated with DAAs). In 6 recipients with recurrent hepatitis C, the first DAA course was ineffective. That is, the SVR rate after the first DAA course was 95.6% (131 of 137 patients). In 4 cases, SVR was achieved after the second

course of AVT containing DAAs and PEG-IFN (n=2) or containing only DAAs (n=2). Two more 2 recipients continue to be followed-up after completing a repeated course of DAAs.

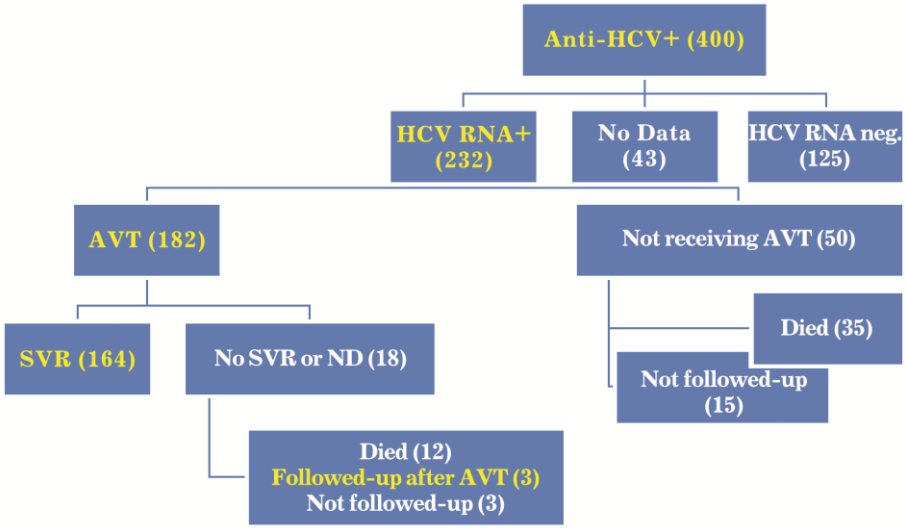

Fig. 6. Results of antiviral therapy and recipient outcomes

AVT regimens and treatment results for these patients are presented in Table. 3.

Table 3. Repeated courses of therapy with direct-acting antiviral drugs in liver transplant recipients

Patient, gender/age	HCV genotype	1st course of DAAs (drugs, duration (weeks))	DAA resistance mutations	2nd course of AVT, (drugs, duration (weeks)), year	Result
MAI, m/47	1	SOF/RBV 24 weeks	Not found	SOF/DAC/RBV, 24 weeks, 2016	SVR
PVA, f/60	1	SOF/SIM/RBV 12 weeks	NS3: T54 S, D168E	SOF/ICE, 24 weeks, 2016	SVR
VAV, m/41	1	SOF/DAC/RBV 24 weeks	NS5A: L31M, Y93H NS5B: C316N, S556G	SOF/PEG-IFN/RBV/ASUNA, 24 weeks, 2017	SVR
HHB, f/57	1	DAC/ASUNA 24 weeks	NS3: D168E NS5A: R30Q, L31M	SOF/PEG-IFN/RBV, 12 weeks, 2018	SVR
ShSS, m/40	3	SOF/VELPA 12 weeks	No data	SOF/VELPA, 24 weeks, 2022	ETR
IAT, m/50	3	SOF/DAC 12 weeks	No data	SOF/VELPA, 24 weeks, 2022	Aviremia due to AVT

Notes: SOF, sofosbuvir; RBV, ribavirin; DAC, daclatasvir; SIM, simeprevir; ASUNA, asunaprevir; GRAZO, grazoprevir; LED, ledipasvir; PEG-IFN, pegylated interferon; VELPA, velpatasvir; ETR, end-of-treatment response (at completion of the AVT course); SVR, sustained virological response

IV. Fibrosing cholestatic hepatitis as a specific course of recurrent HCV infection

Fibrosing cholestatic hepatitis (FCH) C was diagnosed in 6 (2.6%) of 232 recipients in whom HCV RNA was detected in blood after LT. In two cases it ended up fatally (without AVT in one case, and in unsuccessful treatment with PEG-IFN and ribavirin in the other). In one recipient, timely initiation of PEG-IFN monotherapy produced SVR. We reported this case in detail as a rare case of successful therapy for FCH C in those years [6]. Two more recipients were successfully treated with DAAs. Unfortunately, one of them subsequently died from HCC progression. Finally, of particular interest is the case where FCH therapy with PEG-IFN and ribavirin did not lead to a complete cure, but made it possible to change the course of the disease from FCH to classic chronic hepatitis. This gave our patient a reprieve, but led to the occurrence of graft cirrhosis. Subsequently, the virus eradication was achieved with triple therapy of PEG-IFN, ribavirin, and telaprevir [7] . There are reports in the literature on the changes in the hepatitis C course from its classical form to FCH [8]. Apparently, reverse transformation is also possible under the effect AVT. Interestingly, despite the overall significant predominance of men in the analyzed population, 5 of our 6 FCH C patients were women. Perhaps this observation is a coincidence. In literature on FCH C, we have not encountered a predominance of this gender-dependent variant of the hepatitis (for a review, see [9]). We would like to especially note that after 2017, we have not encountered such a course of recurrent HCV infection within the work of our DLT.

Discussion

Our analysis of the DLT at the Sklifosovsky Institute for Emergency Medicine over 22 years in relation to patients with end-stage chronic hepatitis C (mono- or co-infection) allowed us to identify trends associated with changes in the clinical and virological characteristics of both patients in the LT WL and liver recipients.

First, in recent years the proportion of anti-HCV+ recipients among the total number of liver recipients operated on at our DLT has decreased (from 44.3% before 2020 to 34.1% starting from 2020). We relate these changes to the consequences of the DAA implementation into the routine clinical practice of hepatologists, which led to a decreased proportion of HCV-associated cirrhosis of all liver cirrhosis cases comparable in severity. Foreign authors also noted similar changes in the structure of LT WL in earlier years, as well. Thus, G. Crespo et al. (2018), based on an analysis of 1483 patients, reported that the proportion of anti-HCV+ patients in LT WL decreased from 47% (2008–2013) to 35% (2014–2016), and also related these changes with the emergence of DAAs [10]. This explanation of the Spanish investigators seems to us only partly correct. Of course, DAAs became widespread in Europe earlier (~since 2014) than in Russia (~since 2016), but, in our opinion, it takes some time for the virological effects of their use in routine clinical practice to be converted into clinical effects. The same authors reported a simultaneous increase in the proportion from 4 to 7% among patients with liver cirrhosis as part of NAFLD (p=0.003). J. A. Flemming et al. (2017), based on the analysis of the North American Registry including 47,591 patients being on the LT WL, reported similar results. This group of investigators identified three “eras” for analysis: the “interferon era” (2003–2010), the “first generation protease inhibitor era” (PIs: 2011–2013), and the “DAA era” (2014–2015) [11]. The adjusted LT rate in

patients with anti-HCV+ decompensated liver cirrhosis decreased by 5% in the “PI era” ($p=0.004$) and by 32% in the “DAA era” ($p<0.001$) when compared with the “PEG-IFN era”. On the contrary, the frequency of including patients with NAFLD in LT WL increased by 41% in the “IP era”, and by 81% in the “DAA era” ($p<0.001$).

A similar division into “eras” is given in publication by L.S. Belli et al. (2018) presenting the analysis of data from the European Transplant Registry [12]. Of 60,527 LTs, more than half (36,382) were performed for end-stage viral hepatitis (HBV and HCV), alcoholic liver disease, and NAFLD. The proportion of LTs for HCV-related liver diseases decreased over time ($p<0.0001$), falling from 22.8% in the “PEG-IFN era” (2007–2010) to 17.4% in the “PI era" (2011–2013), while the proportion of LT in NAFLD increased significantly ($p<0.0001$). In the “DAA era” (2014 – June 2017), the proportion of LT for end stages of chronic hepatitis C decreased from 21.1% (I semester of 2014) to 10.6% (I semester of 2017 ($p<0.0001$)).

Thus, starting from 2014 in the world and from 2020 in Russia, there has been a clear trend towards a decrease in the proportion of anti-HCV+ patients with decompensated cirrhosis in the LT WL. In Western countries, this can be explained both by the population effect of current AVT and by the increased number of patients with end-stage NAFLD. In Russia, the increase in patients with NAFLD is not so evident, and more recent changes in the structure of the pool of liver recipients are most likely associated with the implementation of DAAs into the daily practice of hepatologists, which has contributed to the decreasing proportion of anti-HCV+ patients with decompensated cirrhosis in the LT WL.

The possibility of prescribing DAAs for decompensated cirrhosis has led to an increased number of patients with HCV aviremia who are placed on the LT WL, or receive DAAs and achieve aviremia while in the

LT WL. If before 2017, the majority of anti-HCV+ patients on LT WL had also the signs of current HCV infection, which recurred after LT in almost all recipients, then in the last two years only every 4th anti-HCV+ recipient had HCV RNA detected in blood. Similar results were reported by D. Goldberg et al. (2017), who found that the proportion of anti-HCV+ patients screened in 2013–14 who had detectable HCV RNA made 0.5 (95% CI [0.42;0.55]); this value was significantly lower than that reported in 2010 (0.64; 95% CI [0.59;0.73]) (p=0.03) [13].

On the other hand, the structure of this patient group according to virus genotypes had changed. If before the introduction of DAAs into clinical practice, HCV genotype 1 predominated among patients on LT WL and, accordingly, among liver recipients, then in recent years, recurrent hepatitis C after LT in the overwhelming majority of cases has been caused by virus genotype 3. Most patients who had experienced DAA therapy before LT had drug resistance mutations to NS5A inhibitors. We have already published these results obtained by analyzing a much smaller group of patients [4]. Subsequent experience of implementing up-to-date AVT regimens into routine clinical practice demonstrated low clinical significance of the identified polymorphisms. In all 12 patients analyzed in a previous study, the with recurrent hepatitis C was caused by virus genotype 3, regardless of the presence and nature of polymorphisms associated with drug resistance, achieved SVR based on the results of the first DAA therapy course LT. This information has been new to this work compared to the previous publication.

The 5-year (84%) and 10-year (76%) survival rates of our recipients who underwent LT for viral cirrhosis (without HCC) were unexpectedly high. At the same time, the survival rate of recipients operated on in the “PEG-IFN era” was lower than that in the “DAA era.” Similar results were reported by G. Crespo et al. (2018). During the study

period, 1,114 patients underwent LT: 753 in 2008–2013, and 361 in 2014–2016. The 3-year patient survival after LT increased significantly in the second period in the entire cohort (82% vs. 91%, p=0.002) due to better survival among anti-HCV+ recipients (76% vs. 91%, p=0.001), rather than among the recipients without anti-HCV (88% vs. 91%, p=0.359) [10]. It is possible that such high results in our cohort of patients without HCC operated on during the "DAA era" were associated with an early administration of DAAs, which was also accounted for a low (2.6%) incidence of FCH and no cases of post-transplant FCH since 2017.

The structure of mortality was dominated by causes associated with the HCC progression: 31 (27.9%) of 111 deaths. The results of analyzing the European Transplant Registry data confirm that in recipients who underwent LT for HCV-related HCC, the rate of HCC recurrence after LT remained at the same level throughout the entire analyzed period and was the main cause of death in anti-HCV+ liver recipients in whom SVO had been achieved [12]. In the "PEG-IFN era," recipients with HCV infection had a higher risk of graft loss and death than recipients operated on for non-HCV-related non-neoplastic reasons, according to an analysis of the United Network for Organ Sharing (UNOS) Registry. In the "DAA era", the differences in the risks of graft loss and death between recipients with and without anti-HCV have disappeared [14].

The SVR rate after the first DAA therapy course was 95.6%. The analysis included the patients receiving a variety of DAA regimens, including first-generation drug regimens (sofosbuvir/ribavirin, sofosbuvir/simeprevir, daclatasvir/asunaprevir). These regimens have lower efficacy than current pangenotypic drug combinations recommended for the treatment of recurrent hepatitis C [15]. For comparison, we can cite the modern publication of the treatment results obtained by Italian investigators in routine clinical practice in 136 liver

recipients with recurrent hepatitis C. In their study, 69% of recipients received low-efficacy DAA regimens (sofosbuvir/ribavirin, sofosbuvir/simeprevir). The incidence of SVR after the 1st course of therapy was 79%. The rate of SVR after the 2nd DAA therapy course was 96% [1-6].

According to recommendations currently used in Russia and other countries, all three classes of modern DAAs can be used in liver recipients. These are HCV protease inhibitors (glecaprevir), HCV polymerase inhibitors (sofosbuvir), and inhibitors of the NS5A fragment of the virus (daclatasvir, ledipasvir, velpatasvir). All these active ingredients are registered in the Russian Federation as independent components or fixed medicinal combinations. Drug interactions between these agents and immunosuppression components are not clinically significant. Since two of our recipients had not completed AVT at the time of the analysis, we cannot write about the 100% effectiveness of the 2nd course of DAA. But according to literature, hepatologists now have enough tools at their disposal to achieve 100% eradication of HCV.

In the present work, we focused on the virological outcomes in anti-HCV+ recipients. Analyses of the comorbidity in these recipients, extrahepatic morbidity, metabolic changes, and the effect of long-term use of immunosuppressants, as well as an analysis of HCC recurrence, were not the subject of our study.

Our study has a number of limitations. Thus, the conclusions we have made regarding the changes in the structure of the LT WL were based on the analysis of the structure of liver recipients, that is, after the LT was performed, rather than at the time the patient was included in the LT WL. We believe that this approach has brought no serious bias into the results and conclusions of our study, since LT is performed on non-nosological priority. That is, patients from LT WL with comparable

severity scores (MELD, Child–Pugh) have equal chances of receiving an organ, regardless of the liver disease etiology. Accordingly, the etiological structure of LT WL is proportional to the structure of the operated patients.

Another limitation of our study is its retrospective design, which resulted in the incomplete set of data necessary for analysis. A small number of recipients are followed-up outside our DLT. Others died long before the analysis, and the information we were interested in was missed in the medical records available to us. The share of such recipients was about 10% (Fig. 6). We believe that the absence of this information did not lead to significant deviations confounding the results of our studies.

The implementation of direct acting antiviral drugs into daily clinical practice has led to the possibility of eradicating HCV infection in 95–100% of cases in any clinical situation, including in liver transplant recipients. Liver transplant recipients with recurrent HCV infection are no longer a peculiar group of patients. Survival of anti-HCV+ recipients has now improved significantly and is comparable to that of recipients undergoing liver transplantation for non-infectious etiologies. The possibility of a quick and safe cure for HCV infection and given the shortage of donor organs in most world countries has led to the practice of organ transplantation from anti-HCV+ donors without significant liver damage. It seems to us that it is time for a certain revision of the documents regulating the organ donation in the Russian Federation so the organs from anti-HCV+ donors could be qualified suitable for transplantation.

Conclusions

1. The proportion of liver transplant recipients having anti-HCV in blood decreased from 44.3% (from 2007 to 2019) to 34.1% (from 2020 to 2022 p=0.0027).

2. In the “era of interferon” (until August 2016 as defined in the Department for Liver Transplantation of the N.V. Sklifosovsky Research Institute for Emergency Medicine), the recurrence of HCV infection after liver transplantation was reported in > 90% of anti-HCV+ recipients in whom the information about HCV viremia after liver transplantation was available. Spontaneous clearance of HCV RNA after liver transplantation was observed in 2.1% of cases. In recent years, the incidence of HCV viremia before transplantation in patients having anti-HCV in blood, and accordingly, of recurrent HCV infection after liver transplantation, has decreased significantly (to ~25% in 2021–2022)

3. All current antiviral therapy regimens can be successfully used at any time after liver transplantation, which leads to >95% eradication of the virus after the 1st course of therapy with direct acting antiviral drugs.

4. The emergence of drug resistance polymorphisms in patients who had unsuccessful experience with antiviral therapy before liver transplantation is not an obstacle to a successful antiviral therapy after liver transplantation.

5. A five-year survival rate of anti-HCV+ recipients without signs of hepatocellular carcinoma at the time of liver transplantation was 84%, and a 10-year survival rate was 76%. Mortality directly from HCV infection was 3.6% among all mortality causes, and 14.8% among non-neoplastic “hepatic” causes. The three- and five-year survival rates (80% and 77%, respectively) of the recipients without evidence of hepatocellular carcinoma at the time of liver transplantation who

underwent surgery before August 2016 were lower than the three- and five-year survival rates (91%) of the recipients operated on after this date (p=0.01).

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