DOI: 10.15825/1995-1191-2021-1-15-23

OUTCOMES OF LIVER TRANSPLANTATION IN THE ERA OF MODERN ANTIVIRAL THERAPY FOR HEPATITIS C

K.Yu. Kokina, Yu.O. Malinovskaya, Ya.G. Moysyuk

Vladimirsky Moscow Regional Research Clinical Institute, Moscow, Russian Federation

The emergence of direct-acting antivirals (DAAs) has become the basis for a new potential treatment for chronic hepatitis C (CHC) in patients with decompensated cirrhosis, who previously had no other alternative than liver transplantation (LT). However, optimal timing of antiviral therapy (AVT) remains an issue. **Objective:** to present a spectrum of clinical outcomes in LT waitlisted patients with HCV-related cirrhosis, who received and did not receive DAA therapy. **Materials and methods.** Enrolled for the study were 49 waitlisted patients with HCV-related end-stage liver diseases. The patients were divided into 2 groups: Group 1 included 40 patients who received DAA therapy before LT, while Group 2 consisted of 9 patients who did not receive antiviral treatment while on the LT waiting list. **Results.** The sample was represented in most cases by patients who had MELD/Na score <20. Only six had MELD/Na score >20, but <25. At the time of analysis, 38 patients had reached 12 weeks post AVT. Of these, 35 (92.1%) had sustained virologic response (SVR). Of these, 51.4% (n = 18) of cases showed decreased MELD/Na. There were no changes in 22.9% (n = 8). Increased MELD/Na was noted in 25.7% (n = 9). In 42.8% (n = 15) of cases, sustained elimination of HCV infection led to delisting. Among patients without SVR, increased MELD/Na was observed in all cases (n = 3). In the non-AVT group, one patient showed improved liver function (11.1%); in the rest, MELD/Na either remained stable or continued to increase – 44.5% (n = 4). A comparison of the frequency of deaths depending on AVT showed statistically significant differences ($p < 0.001$, $V = 0.728$). Among the non-AVT patients, the likelihood of waitlist death increased 66.5 times (95% CI: 7.99–554). **Conclusion:** DAA therapy carries significant advantages for waitlisted patients with MELD/Na score <25.

Keywords: waiting list, liver transplantation, antiviral therapy, direct-acting antivirals.

INTRODUCTION

For decades, chronic hepatitis C (CHC) has remained the most common indication for orthotopic liver transplantation worldwide [1]. The emergence of direct-acting antivirals (DAAs) for the treatment of hepatitis C virus (HCV) infection has revolutionized the field of liver transplantation (LT). The main achievements in modern antiviral therapy (AVT) regimens are high efficacy and a favorable safety profile for both patients with decompensated cirrhosis (Child–Turcotte–Pugh (CTP) classes B and C) and those in the post-transplant period [2]. However, a new subject of discussion now centers on the choice of optimal timing of DAA therapy in LT waitlisted patients [3].

Every year, new evidence emerges indicating that sustained virologic response (SVR) in patients with decompensated cirrhosis (CTP classes B and C) can lead to stabilization or relative compensation of liver function, which suggests that post-transplant outcomes can be improved and the need for liver transplantation may be reduced in this large patient cohort [4].

However, CHC treatment in LT candidates is recommended if the MELD (Model for End-stage Liver Disease) score does not exceed 20. The choice of AVT regimens in this patient cohort is limited by contraindications for protease inhibitors. In the Russian Federation, clinicians are limited to three AVT regimens: sofosbuvir/daclatasvir, sofosbuvir/ledipasvir, and sofosbuvir/velpatasvir with or without ribavirin. While for liver recipients, there are no limits to therapeutic possibilities within DAAs regimens [5].

There is also contradictory evidence on antiviral treatment in patients with hepatocellular carcinoma (HCC). Since for this group of patients, the indications for orthotopic liver transplantation (OLT) are often not associated with the functional state of the liver, achievement of SVR will therefore not affect prognosis. Moreover, there are opinions that DAAs promote HCC progression and recurrent tumor process in the postoperative period [6, 7].

An important factor affecting the efficiency of a transplant center is the state of the donor resource. Often, a shortage in donor organs can lead to higher waiting times for liver transplantation and more critical decompensation and deaths before operation. Therefore, a successful AVT can become an integral tool for improving waitlist survival [8].

While discussions continue, clinical practice is expanding our knowledge of the impact of AVT on liver

Corresponding author: Kseniia Kokina. Address: 61/1, Shchepkina str., Moscow, 129110, Russian Federation. Phone: (985) 814-36-34. E-mail: kseniaur@yandex.ru

tissue functionality and developing individual approaches to navigate these competing issues.

MATERIALS AND METHODS

From March 2016 to April 2020, indications for OLT were established in 153 patients at the transplant center of Vladimirsky Moscow Regional Research Clinical Institute. Enrolled for the study were 49 (32%) OLT waitlisted patients with CHC-related end-stage liver diseases. The patients were divided into 2 groups: Group 1 included 40 patients who received DAA therapy in the LT waiting list, while Group 2 consisted of 9 patients who did not receive antiviral treatment while in the waiting list. In the study group, the following outcomes were observed: liver transplantation, delisting, dropout (delisting due to contraindications to transplantation), death.

The studied medical documentation fully met the requirements of the study: it contained the necessary information about patient's physical status, data from laboratory and imaging examinations to assess the dynamics of liver function and complications of cirrhosis during the observation period in the waiting list and in the post-transplant period.

The dynamics of liver function was assessed by calculating the MELD-Na score at inclusion in the OLT waiting list and at the time of outcome. The difference between these indicators shows the dynamics of the state and is represented by Δ MELD-Na. Patients were delisted at our center with a stable MELD-Na <15 for 6 months.

The AVT on the waiting list was performed according to current guidelines for the treatment of CHC in patients with cirrhosis. For decompensated liver cirrhosis (CTP classes B and C), the treatment regimen was sofosbuvir + daclatasvir, and three patients with compensated cirrhosis and HCC were prescribed protease inhibitor regimens (ombitasvir/ritonavir/paritaprevir + dasabuvir or glecaprevir/pibrentasvir). The following virologic response criteria have been adopted to assess the efficacy of antiviral treatment:

– SVR – the HCV RNA PCR test came out negative 12 weeks after the end of AVT;
– recurrence – HCV RNA PCR test came out positive 12 weeks after the end of AVT [9].

Since all waitlisted patients had different periods up to the moment of outcome, we used the person-years index to standardize the indicators of certain events in the study groups. This indicator was introduced by the professional community of specialists in the field of organ donation and organ donor transplantation and is used in the Scientific Registry of Transplant Recipients (SRTR), USA to assess waiting list outcomes. The person-years index was calculated by dividing the number of days spent by each candidate on the waiting list by 365.25 (average number of days in a year). The coefficient of the outcome of interest was determined by dividing the number of cases by the sum of person-years in the study group and multiplied by 100 (expressed in units – the number of cases per 100 person-years) [10].

$$\text{Person-years index} = \frac{\text{Waiting list time}}{365.25}$$

$$\text{Outcome coefficient} = \frac{\text{Number of outcome cases}}{\text{Sum of "person-years" indices in the study group}} \times 100$$

This makes it possible to compare the true waitlist mortality at different periods of the program and between transplant centers, regardless of the absolute number of patients standing on the list and the waiting time of each candidate. So, if there were 100 waitlisted candidates between January 1 to December 31, 25 of them were observed in the list for 90 days from this period, while 75 were observed for 80 days, then the sum of the person-years indices will be (90/365.25) × 25 + (180/365.25) × 75 = 43.12. If at the same time, 30 patients died, then the outcome rate would be 30/43.12 × 100 = 69.5 deaths per 100 person-years. In other words, this indicator characterizes outcomes on the waiting list, where 100 people were observed within one year.

Data analysis was carried out using statistical software Statistica 13 and the Jamovi program (The jamovi project, 2020). To characterize the studied cohort for all statistical parameters, descriptive statistics were used, which was determined by the type of statistical parameter. Indicators with normal distribution are represented by the following values: mean value of the sample and standard deviation. To describe quantitative parameters with abnormal distribution, the median, 25 and 75 quartiles, were used. To assess the normal distribution of quantitative data, the Shapiro–Wilk test, skewness and kurtosis indicators were used. Frequency and percentage were used when describing qualitative parameters or quantitative characteristics that take only a very small number of values.

Statistical comparison of mean values of quantitative continuous variables between two independent groups was carried out using Student's t-test (for indicators distributed approximately normally). The Mann–Whitney U test and the Kruskal–Wallis test were used to compare independent populations in cases where there were no signs of normal data distribution or to compare by ordinal indicator. The equality of variances was assessed using the Levene's test. Analysis of variance was also used to compare several independent populations.

Spearman rank-order correlation was used to study the relationship between the phenomena represented by quantitative data, whose distribution differed from the normal. Contingency tables were constructed to compare

groups by a binary trait expressing clinical outcome. Fisher's exact test was used to compare the distribution of qualitative variables. Assessment of the strength of the connection between the signs was carried out using the Cramer V criterion. Standardized residuals were calculated for each cell in the contingency table to determine the contribution of different populations to the formation of the factor relationship indicator. Version 4.0.0 of the R program was used to create a graph to visualize the strength of interrelationship between the populations of the contingency table. The survival function of patients was assessed using the Kaplan–Meier method and compared statistically using the log rank test, which implies predicting the risk of death for patients on the waiting list depending on their AVT status. Risk is viewed as a function of time. Differences in indicators were considered statistically significant at $p < 0.05$ significance level.

RESULTS

The analysis included 49 patients with CHC-related cirrhosis waitlisted for liver transplantation. The median age was 52 [46; 59]. A comparison of the AVT and non-AVT patient cohorts revealed no significant differences in gender composition, in the initial stage of cirrhosis decompensation and in the time of onset of the outcome after being listed (Table 1). All deaths and dropouts were due to critical decompensated cirrhosis.

Characteristics of patients who received DAA therapy

At inclusion in the waiting list, 36 patients had MELD-Na score <20, while for 4 candidates (10%, 4/40), the score ranged between 21 and 25. At the time of analysis, 38 patients had reached the endpoint of antiviral treatment efficacy evaluation – 12 weeks after the end of AVT (Fig. 1). Of these, 92.1% (n = 35/38) had SVR. In 45.7% (n = 16/35) of cases, persistent elimination of HCV infection was accompanied by significant improvement in liver function with subsequent disappearance of indications for liver transplantation (delisting). The median follow-up time after delisting at the time of analysis was 36 [27; 41] months. In 15 patients (94%), compensated liver function was preserved, only one

Table 1

Comparison of the initial characteristics of the study groups

Indicators	Group 1. AVT + n = 40	Group 2. AVT – n = 9	Intergroup differences (p)
Women/men	17/23	2/7	0.451
Median age (years)	50 [45.5; 58.3] (36–69)	56 [55; 60] (46–67)	0.093
Initial MELD/Na score	16 [13; 18]	15 [14; 17]	0.876
Person-years median	0.5 [0.25; 0.83]	0.25 [0.25; 0.5]	0.514
HCC: yes/no	6/33	1/7	1.0
GFR	59 [47; 79]	59 [43; 72]	0.959

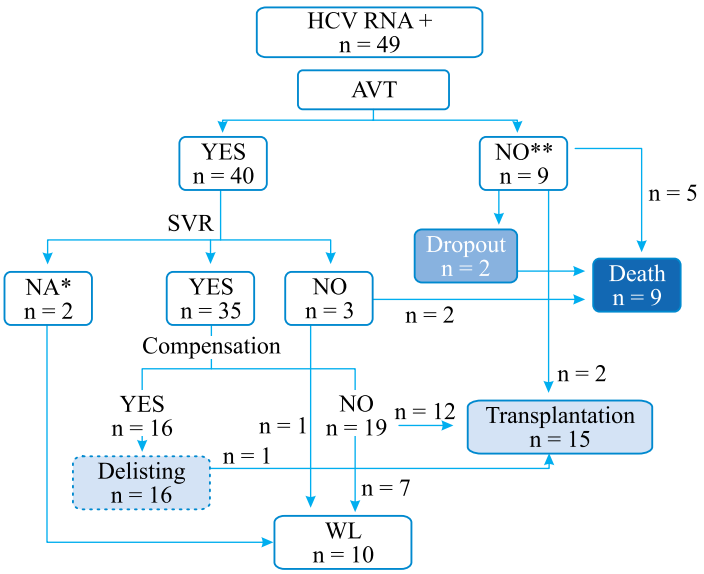

Fig. 1. Outcomes in waitlisted patients with or without AVT DAA.
* – patients underwent a course of antiviral treatment, but have not reached the deadline for evaluating the effectiveness of the SVR therapy yet; ** – therapy was not prescribed because DAAs were not available

patient (6%, 1/16), six months after delisting, had clinical progression of cirrhosis, manifested by edematous-ascitic syndrome and hepatic encephalopathy of grade 2. In this regard, after re-listing, the patient underwent liver transplantation. Favorable results were also observed among the remaining patients who achieved SVR: 12 patients (34.3%, 12/35) had liver transplantation and 7 patients (20%, 7/35) without significant progression of the disease are on the OLT waiting list. Persons who received AVT on the waiting list and achieved SVR had no recurrence of HCV infection in the post-transplant period. Statistical analysis showed no relationship between delisting and demographics and between delisting and baseline MELD-Na. However, a statistically significant positive correlation was found between Δ MELD-Na and the patient's age (Spearman's rs = 0.419, p = 0.015), that is, the older the patient was, the more often there was higher MELD-Na score, despite successful treatment outcomes.

Four of the patients who received AVT were diagnosed with HCC (10%, 6/40), with tumor spread based on the Milan criteria. Simultaneously with etiotropic treatment, the patients underwent locoregional therapy based on indications. At the time of analysis, one patient had not reached the endpoint of the AVT efficacy assessment and in one case (20%, 1/5), there was a relapse of HCV infection. Four patients (80%, 4/5) had SVR: three of them underwent liver transplantation and one patient is on the waiting list.

Let us separately consider the outcomes in three patients (7%, n = 3/38) who had a relapse after DAA therapy. Two of them were placed on the waiting list for decompensated cirrhosis with baseline MELD-Na score of 14 and 17. They were 52 and 41 years old at the time of inclusion on the waiting list. The first patient died as a result of occlusive portal vein thrombosis with subsequent development of acute liver failure and type 1 hepatorenal syndrome. The other patient continues to be followed up on the waiting list. The third case of post-AVT relapse was reported in a patient with HCC. During the follow-up period, oncological process did not progress. However, the patient died due to complications after an episode of bleeding esophageal varices. To exclude factors that could affect outcomes in patients who did not achieve SVR, we compared the groups in terms of time of outcome, person-years index level, baseline MELD-Na scores, age, gender, and Δ MELD-Na. However, no statistically significant differences were found.

Characteristics of patients who did not receive DAA therapy on the OLT waiting list

At the time of listing, two patients (22%, 2/9) had MELD-Na scores of 21 and 24. In other cases, the MELD-Na score did not exceed 20. One patient (11%, 1/9) was diagnosed with HCC on the background of cirrhosis. Prevalence of the process was within the Milan criteria. Patients were not given etiotropic treatment due to the unavailability of suitable AVT regimens. The observed difference in the outcome spectrum in these patients in comparison with group 1 turned out to be interesting: the majority of patients had an adverse outcome – only two patients from this group survived. All adverse outcome cases (death and dropout) were due to complications of cirrhosis.

Analysis of differences in outcomes between patient cohorts with and without AVT

When studying the dynamics of the functional state of the liver in the waiting list, which was determined by the change in the MELD-Na score, patients with SVR in 51.4% (n = 18/35) cases had a decrease in this indicator. There were no changes in 22.9% (n = 8/35), while an increase in MELD-Na score was noted in 25.7% (n = 9/35). All patients without SVR (n = 3) had an increased MELD-Na score. In the non-AVT group, only one patient had liver function compensation (11.1%, n = 1/9), progression or stable MELD-Na score was the same – 44.5% (n = 4/9). In the group of patients with SVR, the median decrease in the MELD-Na score was –4 [–7; –2] (–11…–1), and the median increase in MELD-Na was +3 [1; 4] (1–7). A more significant increase in the MELD-Na score was observed in persons who did not reach SVR: median +5 [3.5; 18] (2–30), which was comparable to the indicators for patients who did not receive AVT: median +6 [5.75; 7.5] (5–12).

Curious were the results of the dynamics of the functional status of the liver in patients with baseline MELD-Na score >25 (n = 6). Of these, four patients received AVT, and SVR was observed in all cases. None of them showed disease progression, and the median decrease in MELD-Na was –10 [–10.5; –9.5]. According to two medical records in the non-AVT group, disease progression with Δ MELD-Na +6 was observed in one case; in the other case, the patient's condition was stable. A statistically significant relationship between a decrease in MELD-Na and the presence of SVR and age was determined. Gender, presence of HCC, and baseline MELD-Na score were found to have no influence on the dynamics of the functional status of the liver (Table 2).

Despite the fact that the difference in time to outcome in the two groups was statistically insignificant, the death rate in the group of patients who did not receive AVT (24 cases per 100 person-years) was significantly higher than that for patients with AVT (7 cases per 100 person-years). Thus, the emergence of DAAs had a significant positive impact on the efficiency of the transplant center.

Statistically significant differences ($p < 0.001$) were obtained by comparing the death rate depending on AVT. With no AVT, the chances of dying on the waiting list increased 66.5 times (95% of CI: 7.99–554). There was

a strong association between the compared signs (V = 0.728). Fig. 1 shows the relationship between DAA treatment in the waiting list and the presence and absence of death. In our study, we found a strong positive correlation between death and absence of AVT in waitlisted patients (st. res = 4.1, $p < 0.05$) and a strong negative correlation between death and favorable outcome (st. res = –1.97, $p < 0.05$). During AVT, there was a strong negative correlation with death (st. res = –1.97, $p < 0.05$). Thus, in the absence of antiviral therapy, the patient is more likely to die than to survive.

Analysis of the probability of death by Kaplan–Meier method using the log rank test also found statistically significant differences in survival between groups ($p < 0.001$). Moreover, in the group of patients treated with antiviral therapy, we observed a long "plateau" period in patient survival 7 months after listing, which may be a manifestation of persistent stabilization of liver function in patients who had successful AVT outcomes.

DISCUSSION

Thanks to successful therapy in patients with advanced liver disease, we see the benefits of AVT in terms of further prognosis and reduced need for liver transplantation. According to published data, successful treatment of CHC improved liver function in the short term in 60% of patients. This was accompanied by decreased MELD scores, while 17% had no changes, and 23%, on the contrary, recorded an increase in MELD scores [11]. The results described are very close to the data obtained

Table 2

Characteristics of patients with different MELD/Na dynamics

Indicators	Reduction MELD/Na n = 20	No reduction MELD/Na n = 29	Intergroup differences (p)
Male	14	16	0.454
Median age (years)	46.5 [41.8; 51.3]	56 [50.0; 60.0]	**0.002**
Initial MELD/Na score	16.0 [15.5; 18.3]	15.0 [13.0; 17.0]	0.127
HCC: yes/no	1/19	6/23	0.216
GFR	59.0 [59.0; 66.8] (47.0–79.0)	59.0 [56.5; 68.0] (48.0–77.0)	0.512
SVR: yes/no	18/0	17/12	0.024

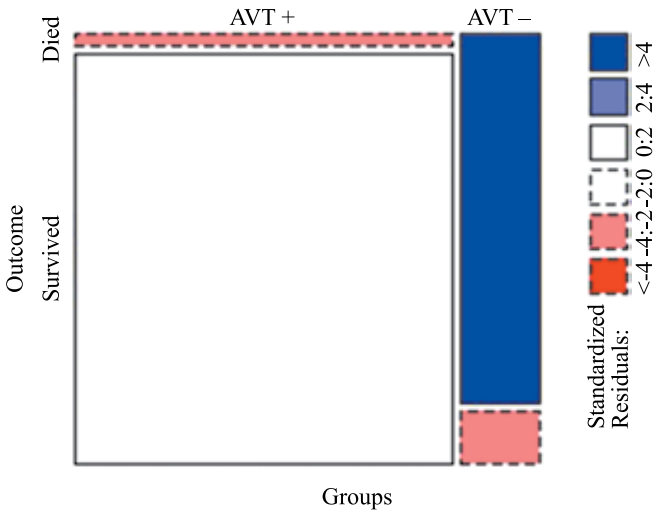

Fig. 2. Impact of AVT in the waiting list with and without fatal outcomes. Standardized Residuals. This graphical representation of contingency tables (made in the R program) allows to evaluate the contribution of different factor combinations to the formation of the relationship indicator. The sizes of the rectangles show the proportions of observations, while the color is for the value of the standardized residual, which reflects the statistical significance of the deviation of the indicator from the expected value. A standardized residual of more than 1.96 indicates a statistically significant positive relationship between the indicators, while values less than –1.96 indicate a negative relationship

in our study: 51.4%, 22.9% and 25.7%, respectively. The decrease in MELD after effective AVT in decompensated cirrhosis in large studies varies with a mean of –2, while in a small proportion of patients, the MELD continued to deteriorate with a median of +1 [12]. These changes were more pronounced in our sample: the median decrease in the MELD-Na score was 4, and the median increase in MELD-Na was +3. Some difference in the results may be due to the use of a more accurate MELD-Na index.

It was noted that 15 patients (42%) with decompensated cirrhosis were delisted for liver transplantation due to persistent clinical improvement after achieving SVR. The delisted patients showed either complete regression or improvement in hepatic decompensation. At the time of writing this paper, the median follow-up time after delisting was 36 months. According to a study by the European Liver and Intestine Transplant Association (ELITA), 20.4% of patients were delisted after effective AVT and 33% were inactivated from the transplant list [13]. These results provide grounds for optimism on the reduction in the need for liver transplantation in almost one third of patients in this large population.

Improvement in liver function and quality of life can be achieved after successful therapy, but not in all patients. Predictors of improvement or inability to compensate have been identified earlier, but at present they

are not reliable enough to be widely applied in clinical practice. According to analysis of data drawn from the Scientific Registry of Liver Transplant Recipients of the USA, the following algorithm was proposed for CHC treatment in liver transplant candidates: for patients with MELD score <20, DAA therapy is carried out with the aim of possible delisting and prevention of reinfection in the post-transplant period, with a MELD score of 20 to 27 and a GFR >30 mL/min/1.73 m^2, the decision to use AVT should be individualized, depending on the availability of OLT and presence of related conditions, with a MELD score >27 and/or GFR <30 mL/min/1.73 m^2, AVT should be postponed until the post-transplant period [14]. At our center, we found no clear correlation between baseline MELD and the likelihood of delisting. This is primarily due to the fact that our sample consists mostly of patients with MELD <20, only six had MELD >20, while not exceeding 25. Also, there were no significant GFR deviations at the time of listing and the start of AVT. However, out of 4 patients with a MELD score of 20 to 25 who received AVT, 2 (50%) showed sustained clinical improvement for which they were delisted. Besides, the recommendation to prioritize liver transplantation in a patient with high MELD, followed by AVT, is valid for countries with a national MELD-based organ allocation system, where waiting times can be reduced to hours and days if clinically necessary. Given the shortage of donor organs in our country Russia, the use of such a resource as AVT can reduce the risks of waitlist mortality for this complex patient category. In this regard, we also believe that DAA therapy cannot be limited by the recommended MELD threshold of 20 and should be considered individually.

When examining the effect of DAAs on outcomes in patients with HCC, we did not observe any significant deterioration among this patient cohort. Also, data from recent meta-analyzes report that a high level of HCC progression was associated with predominant use of DAAs in elderly people with concomitant disorders and/or significant complications of cirrhosis [15–17]. This gives grounds to assert that the presence of HCC is not a determining factor for not assigning DAAs. The solution to the issue must be comprehensive with an assessment of the prevalence of the tumor process, the functional state of the liver and further prognosis.

Since there were not enough patients with graft reinfection at our center, we cannot draw conclusions on the outcome of AVT in CHC patients in the post-transplant period. According to published data from clinical practice, the frequency of SVR in patients undergoing DAA therapy varies from 93% to 100%. At the same time, DAA therapy is characterized by a good safety profile. Only one study reported mild liver transplant rejection in 2.7% of cases (n = 1), which was stopped by high-dose pulse glucocorticoid therapy with positive clinical effect, without further functional graft disorders

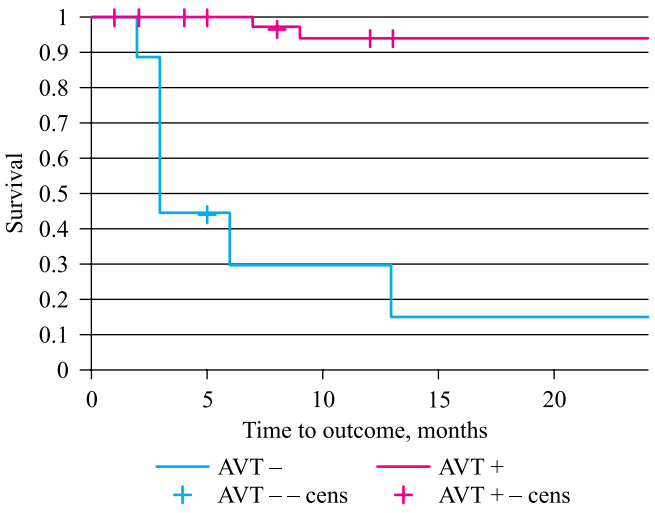

Fig. 3. Kaplan–Meier waitlist survival analysis. Censored were cases of being dropped from the waiting list due to liver transplantation

[18–20]. However, recurrence of HCV infection after liver transplantation is associated with graft dysfunction. There is evidence that lack of effective AVT in the post-transplant period leads to cirrhosis in about one third of patients within 5 years after OLT [21]. In our center, all patients who received AVT before liver transplantation did not have a recurrence of viral hepatitis C in the graft. This may become an additional factor that can improve long-term outcomes in liver transplantation.

It should be noted that most patients with decompensated cirrhosis may have OLT limitations due to issues with availability of donor organs or presence of relative contraindications for OLT. Therefore, these patients should be considered for CHC treatment with the hope that successful DAA therapy may have benefits at varying degrees. At our center, the death rate decreased by almost 3.5 times based on the calculation of the number of cases per 100 person-years.

CONCLUSION

For several years since the first interferon-free AVT regimens appeared, dozens of patients have been able to receive treatment at our center. We see a significant advantage of safe and effective treatments for OLT candidates who face immediate complication risks under persistent infection. Most modern scientific research is aimed at identifying predictors of disease regression after DAA therapy. However, the positive effects of therapy, such as reduced inflammatory activity, slower disease progression and prevention of graft reinfection, are no less relevant under organ shortages. From our study, we conclude that for all waitlisted candidates with HCV infection, DAA therapy in the preoperative period is preferable if there are no contraindications for the treatment.

The authors declare no conflict of interest.

REFERENCES

1. *Thrift AP, El-Serag HB, Kanwal F.* Global epidemiology and burden of HCV infection and HCV-related disease. *Nat Rev Gastroenterol Hepatol*. Epub 2016 Dec 7. doi: 10.1038/nrgastro.2016.176.
2. Internet: AASLD-IDSA. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. http://www.hcvguidelines.org/. Accessed February 13, 2017.
3. *Aronsohn A.* Timing Is Everything: Managing Hepatitis C Virus in Liver Transplant Candidates. *Transplantation*. 2017 May; 101 (5): 898–899. doi: 10.1097/TP.0000000000001703.
4. *Verna EC.* The dynamic landscape of liver transplant in the era of effective hepatitis C virus therapy. *Hepatology*. 2017; 65 (3): 763–766.
5. Hepatitis C Guidance 2018 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Clin Infect Dis*. 2018 Oct 30; 67 (10): 1477–1492. doi: 10.1093/cid/ciy585.
6. *Yang JD, Aqel BA, Pungpapong S et al.* Direct acting antiviral therapy and tumor recurrence after liver transplantation for hepatitis C-associated hepatocellular carcinoma. *J Hepatol*. 2016; 65: 859–860.
7. *Reig M, Mariño Z, Perelló C et al.* Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol*. 2016; 65: 719–726.
8. *Toniutto P, Zanetto A, Ferrarese A et al.* Current challenges and future directions for liver transplantation. *Liver Int*. 2017; 37: 317–327.
9. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. *J Hepatol*. 2018. https://doi.org/10.1016/j.jhep.2018.03.026.
10. Internet: Scientific registry of transplant recipients: [www.srtr.org]. URL: https://www.srtr.org/faqs/for-transplant-center-professionals/#ptyearsformula.
11. *Perricone G, Duvoux C, Berengue M, Cortesi PA et al.* Delisting HCV-infected Liver Transplant Candidates Who Improved After Viral Eradication: Outcome 2 Years After Delisting. *Liver Int*. 2018 Dec; 38 (12): 2170–2177. doi: 10.1111/liv.13878.
12. *Bunchorntavakul C, Reddy KR.* Treat chronic hepatitis C virus infection in decompensated cirrhosis – pre- or post-liver transplantation? the ironic conundrum in the era of effective and well-tolerated therapy. *J Viral Hepat*. 2016; 23: 408–418.
13. *Belli LS, Berenguer M, Cortesi PA, Strazzabosco M et al.* Delisting of Liver Transplant Candidates With Chronic Hepatitis C After Viral Eradication: A European Study. *J Hepatol*. 2016 Sep; 65 (3): 524–531. doi: 10.1016/j.jhep.2016.05.010.
14. *Verna EC.* The dynamic landscape of liver transplant in the era of effective hepatitis C virus therapy. *J Hepatology*. 2017; 65 (3): 763–766. https://doi.org/10.1002/hep.29054.
15. *Waziry R, Hajarizadeh B., Grebely J. et al.* Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression. *J Hepatol*. 2017 Dec; 67 (6): 1204–1212. doi: 10.1016/j.jhep.2017.07.025.
16. *Rutledge SM, Zheng H, Li DK, Chung RT.* No evidence for higher rates of hepatocellular carcinoma after direct-acting antiviral treatment: a meta-analysis. *Hepatoma Res*. 2019; 5: 31. doi: 10.20517/2394-5079.2019.19.
17. *Piñero F, Boin I, Chagas A, Quiñonez E.* Direct-Acting Antivirals and Hepatocellular Carcinoma: No Evidence of Higher Wait-List Progression or Posttransplant Recurrence. *Liver Transpl*. 2020 May; 26 (5): 640–650. doi: 10.1002/lt.25744.
18. *Maluf DG, Archer KJ, Villamil F, Stravitz RT, Mas V.* Hepatitis C Virus Recurrence After Liver Transplantation: Biomarkers of Disease and Fibrosis Progression. *Expert Rev Gastroenterol Hepatol*. 2010 Aug; 4 (4): 445–458. doi: 10.1586/egh.10.39.
19. *Tsiroulnikova OM, Umrik DV, Miloserdov IA, Egorova ET, Latypov RA.* The efficacy and safety of antiviral drugs of direct action in liver recipients with recurrence of chronic hepatitis C genotype 1 after transplantation. *Russian Journal of Transplantology and Artificial Organs*. 2018; 20 (4): 61–68. (In Russ.). https://doi.org/10.15825/1995-1191-2018-4-61-68.
20. *Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R et al.* Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. *Hepatology*. 2016. 631: 493–505.
21. *Wu SH, Loong CC, Chu CJ, Su CW, Lin CC, Hsia CY et al.* Highly effective treatment response and well tolerability by all oral direct acting antivirals for chronic hepatitis C patients post organ transplantation. *J Chin Med*. 2020; 83/1: 18–24.

The article was submitted to the journal on 22.06.2020