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DELISTING OF LIVER TRANSPLANT CANDIDATES FOLLOWING RECOMPENSATION OF CHRONIC LIVER DISEASES – PATIENT CHARACTERISTICS AND PREDICTORS OF DELISTING: A PROSPECTIVE STUDY

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Objective: to identify predicting factors at the listing stage that could be associated with recompensation followed by patient's delisting. **Materials and methods.** A prospective case-control study was conducted. The "case" cohort included 19 adult patients who initially were wait-listed as a result of decompensated liver diseases of various origin, but later were delisted due to recompensation. The "control" cohort consisted of 61 patients who were listed during the same period for decompensation and died in the waiting list. **Results.** A logistic regression model was used to determine independent predictors of delisting following recompensation. Plasma albumin concentration and white blood cell count at listing became significant predictors of recompensation ($p = 0.024$ and $p = 0.019$, respectively). ROC (Receiver Operating Characteristic) curve analysis was used to compare the predictability of identified predictors. The area under the ROC curve (AUC) for plasma albumin concentration was 0.938 [95% confidence interval (CI) 0.882–0.995; $p < 0.001$]. The AUC for the white blood cell count was 0.924 [95% CI 0.865–0.982; $p < 0.001$]. The odds ratio for recompensation outcome, if the plasma albumin concentration at listing was $\geq 3.1 \times 10^9$/L, was 14.639 (95% CI 2.16–99.12). The odds ratio for recompensation outcome, if the plasma albumin concentration at listing was ≥39.1 g/L, was 3.06 (95% CI 1.58–5.95). **Conclusion.** Liver injury could be reversed after the factors leading to decompensation have ceased to exist. Independent predictors of recompensation and subsequent delisting of patients were: white blood cell count $\geq 3.1 \times 10^9$/L and plasma albumin concentration ≥39.1 g/L at listing for liver transplantation.

Keywords: liver transplant waiting list, delisting following recompensation of liver function, predictors of delisting.

INTRODUCTION

Liver transplant (LT) is the only option leading to higher survival of patients with end-stage liver disease when all other treatment methods are unsuccessful [1, 2]. The LT has a successive outcome due to the lack of alternative therapy and good survival rates of patients in the post-transplant period (90% and 80% in the first year and for the following five years, respectively) [3]. An important component of the LT procedure is the patients' selection and their inclusion in the waiting list (WL). After the LT candidates were wait listed, specialists monitored the somatic status and provided for the dynamic clinical and laboratory control, carried out pathogenetic and / or symptomatic therapy, and in the case of life-threatening complications, surgical treatment [3, 4]. The LP waiting list may include three main types of patients [1, 2]. The first group comprises patients with acute liver failure, who in most European centers are included in the so-called LT emergency waiting list. These patients have priority over all other liver recipients and receive a transplant within a few hours or days [5]. The second group in the LT waiting list are patients with decompensated liver cirrhosis (LC). The LT timing is determined by the MELD (Model for End Stage Liver Diseases) index. Priority is given to patients with a very high MELD, in which the LT terms are from several days to several weeks. The LT timing for patients with moderate to low MELD levels varies from several months to several years (1). The third group in the liver waiting list consists of patients with hepatocellular carcinoma (HCC) on the background of compensated LC. Lack of donor organs is a limiting factor in the LT development both in various countries and globally [6], which, in turn, contributes to the mortality of the wait

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listed patients or a critical deterioration in liver function leading to negative outcomes in the perioperative period and in the long term [7]. Nevertheless, in everyday clinical practice the liver function occasionally improves and the recompensation develops, even among the wait listed patients [8]. In particular, a change in the paradigm of liver decompensation and the development of recompensation became possible after modern antiviral agents were introduced into clinical practice. The use of drugs with direct antiviral effect (DAE) in patients with HCV cirrhosis awaiting LT showed a significant clinical improvement leading to their delisting [9–11]. It was possible to identify recombination predictors through analysis of the wait listed patients with alcoholic liver disease (ALD). In this, at listing, MELD <20 and serum albumin ≥32 g/l are predictors of the recompensation development in the ALD patients and their subsequent delisting [12]. In this regard, the present work was aimed at identifying, at the listing stage, the predictive factors (predictors) which could be associated with recompensation development followed by patient's delisting.

MATERIALS AND METHODS

From 2015 to 2019, 198 LT candidate patients have been included in the WL. Of these, 39 patients underwent orthotopic LT (OLT). The data obtained during a prospective case-control study of 80 LT candidate patients observed at the Center for Surgery and Donor Coordination of the Rostov Regional Clinical Hospital were analyzed. The case cohort included 19 adults with decompensated liver diseases of various etiologies included in the WL and subsequently delisted due to recompensation. The control cohort consisted of patients (n = 61) with decompensated liver diseases who were wait listed at the same time interval and died during the decompensation period.

Exclusion criteria were severe cardiopulmonary pathology; continued alcohol intake at the time of the study; hepatocellular carcinoma; patients included in the WL due to decompensation and delisted due to reasons other than recompensation; patients included in the WL for reasons other than decompensation (recurrent cholangitis with primary sclerosing cholangitis); patients included in the WL for advanced thrombosis of the portal vein and its stems, the Budd Chiari syndrome, sinusoidal obstruction syndrome, polycystic liver disease, amyloidosis; patients included in the WL for transplant or with other organs' transplants in history; patients with acute liver failure.

The demographic and clinical data were obtained from the continuously updated electronic database of the Center for Surgery and Donor Coordination of the Rostov Regional Clinical Hospital.

At listing and with the development of recompensation, all patients were measured for the original and updated indices: MELD [13, 14], MELD-Na [15] and Charlson comorbidity index [16].

The study was approved by the Ethics Committee at the Rostov Regional Clinical Hospital. The primary endpoint of the study was the identification of the at-listing factors associated with subsequent delisting of the patients due to recompensation, i.e., possible recombination predictors identification.

The reasons for listing the patients with liver function decompensation were failure of all previous therapeutic measures, development of ascites or hepatic hydrothorax, indications for antibiotic relief of spontaneous bacterial peritonitis, jaundice, presence of hepatic encephalopathy (HE) and / or varicose gastrointestinal bleeding, MELD ≥16. In all ALD patients included in the WL, withdrawal symptoms persisted for at least 3 months as evidenced by the narcologists and psychiatrists.

The clinical diagnosis of recompensation of patients included in WL due to decompensation of liver function was based on the absence of ascites, "hepatic" hydrothorax, and peripheral edema despite the cessation of diuretics, the absence of hepatic encephalopathy and the need for its preventive therapy, MELD <15. All patients with recombination have been followed-up for six months to confirm a stable "recompensation status" confirmed by examinations by specialists and the subsequent decision on delisting.

All patients in the WL passed clinical blood and urine tests, biochemical analyses, studies of hemostasis parameters, HBV and HCV screening and diagnostics, liver elastography and biopsy. Some patients underwent ascitic fluid analysis.

The patients in both cohorts with HCV and HBV infection received antiviral therapy, including direct antiviral drugs (HCV) and nucleoside reverse transcriptase inhibitors (HBV). In the patients with autoimmune diseases, the therapy included immunosuppressants, glucocorticosteroids. All patients underwent pathogenetic therapy with non-selective β-blockers and diuretics. The HE patients got L-ornithine-L-aspartate intravenously in combination with lactulose and rifaximin per os. In some patients, extracorporeal hemocorrection (plasma sorption and CVVHDF) was applied.

Some patients in both cohorts underwent surgery for recurrent varicose bleeding: transjugular intrahepatic portosystemic shunt (TIPS) and azygoportal disconnection (APD, RF patent No. 2412657) by the original procedure [17].

The statistical analysis of data was made with the IBM SPSS Staticrics version 21. To check the normality of distribution of the obtained data, Kolmogorov–Smirnov test was used. Sample data with a normal distribution are represented by arithmetic means (M) and standard deviation (SD) with 95% confidence interval (CI). The statistical significance of the differences between the compared parameters in the normal distribution was determined by Student t-test. Without normal data distribution, non-parametric tests were used, Wilkoxon for

paired comparisons of dependent variables, Mann–Whitney U test, Pearson's chi-squared test for comparison of independent variables. Quantitative indicators in samples with a distribution beyond normality were presented as the median and interquartile range (between the 25th and 75th percentiles). For qualitative data, frequencies and fractions (%) were calculated. Differences between the compared parameters were considered statistically significant provided the error less than 0.05 ($p < 0.05$). Regression analysis (logistic regression) was used to determine the recombination predictors. The odds ratio for significant outcome predictors was calculated by recompensation with 95% CI. To assess the quality of the constructed regression models (predictive ability of the model), ROC (Receiver Operating Characteristic) curves were built and the area under the AUC (Area Under Curve) was calculated. The AUC ROC not differing from 0.5 [18] was taken as a zero hypothesis. Survival was assessed by Kaplan–Meier technique.

RESULTS

Characteristics of the case group patients (recompensation)

The group of the patients with recompensation included 10 men (52.63%) and 9 women (47.37%) with a mean age at the time of inclusion in the WL 48.4 ± 10.3 years. BMI 25.5 ± 3.3 kg/m^2. The average stay in WL was 31.7 ± 12.1 days. At the time of listing, MELD-Na was <20 in 21.1% of cases, =20 in 63.2% of cases, and 21–30 in 15.7% of cases. The hepatorenal syndrome (HRS) was diagnosed in 21.05% of patients. Expressed HE was diagnosed in 84.21% of cases, latent HE in 15.69% of cases. By etiology, patients with end-stage liver disease were distributed as follows: LC in the outcome of chronic hepatitis C – 9 patients (47.37%), LC in the outcome of ALD – 5 patients (26.33%), primary biliary cirrhosis (PBC) – 1 patient (5.26%), PBC and autoimmune hepatitis (AIH) – 1 patient (5.26%), cryptogenic LC – 3 patients (15.79%). Eleven LC patients (57.89%) had class C and 8 patients (42.11) – class B by the Child–Pugh score. Charlson comorbidity index was 9.05 ± 2.48.

57.9% of patients in this group were treated casually, 89.5% of patients received non-selective β-blockers, 100% of patients received diuretics and HE therapy (intravenous administration of L-ornithine-L-aspartate in combination with lactulose and rifaximin per os). Besides the drug therapy, patients got azygoportal disconnection by the original technique (31.6% of cases), a single endoscopic esophagus veins ligation (10.5% of cases) and extracorporeal hemocorrection (plasma absorption combined with CVVHDF) (5.3% of cases).

Characteristics of the control group patients (fatal cases with liver function decompensation development)

The group of the patients with fatal cases included 36 men (59.02%) and 25 women (41.98%) with a mean age at the time of inclusion in the WL 48.2 ± 11.3 years, BMI 25.3 ± 6.6 kg/m^2. The average stay in WL was 9.8 ± 8.4 days. At the time of listing, MELD-Na was <18 in 3.3% of cases, 19–25 in 42.6% of cases, 26–35 in 34.4% of cases, >35 in 19.7% of cases. Hepatorenal syndrome (HRS) was diagnosed in 65.6% of patients. Expressed HE was diagnosed in 95.1% of cases, latent HE in 4.9% of cases. By etiology, patients with end-stage liver disease were distributed as follows: LC in the outcome of chronic hepatitis B – 2 patients (3.3%), LC in the outcome of chronic hepatitis B+D – 2 patients (3.3%), LC in the outcome of chronic hepatitis C – 17 patients (27.8%), LC in the outcome of ALD – 16 patients (26.2%), primary biliary cirrhosis (PBC) – 5 patients (8.2%), AIH – 2 patients (3.3%), primary sclerosing cholangitis (PSC) – 5 patients (8.2%), cryptogenic LC – 9 patients (14.7%). Sixty LC patients (98.4%) had class C, one patient (1.6%) – class B by the Child–Pugh score. Charlson comorbidity index was 9.11 ± 2.66.

31.2% of patients in this group were treated casually, 91.9% of patients received non-selective β-blockers, 100% of patients received diuretics and HE therapy (intravenous administration of L-ornithine-L-aspartate in combination with lactulose and rifaximin per os). Besides the drug therapy, patients got azygoportal disconnection by the original technique (4.92% of cases), TIPS (4.92% of cases), a single endoscopic esophagus veins ligation (13.11% of cases). Thirty patients got laparocentesis (49.18% of cases).

Comparison of parameters in the case and control groups

When checking the distribution of the obtained data with the Kolmogorov–Smirnov test, the age parameters of the patients, the number of leukocytes and platelets at the time of inclusion in WL, the albumin concentration at the time of inclusion in WL, MELD, MELD-Na, and Charlson corresponded to the normal distribution. Those were analyzed by parametric statistics. All other parameters (HE degree, alkaline phosphatase activity, Na concentrations, creatinine and bilirubin at the time of inclusion in WL, INR and BMI at the time of inclusion in WL) did not correspond to the normal distribution and nonparametric statistical methods (Mann–Whitney test, U-test, Chi-square) were used for their analysis.

Tables 1 and 2 show the demographic, clinical, laboratory parameters, BMI, comorbidity, MELD, MELD-Na in the groups of patients with recompensation (n = 19) and fatal cases in the period of stay in the WL (n = 61).

Table 1

Comparative characteristics of parameters of patients with recompensation (delisting) and deaths in the period of stay in the waiting list – listing (normal distribution)

Parameter	Recompensation (n = 19) M ± SD	Deaths (n = 61) M ± SD	p value
Age	48.42 ± 10.32	48.23 ± 11.26	0.57
WBC at the time of inclusion in the waiting list, $\times 10^9$/l	3.66 ± 0.38	2.55 ± 0.68	0.026
PLT at the time of inclusion in the waiting list, $\times 10^9$/l	84.37 ± 31.31	53.02 ± 33.37	0.912
Plasma albumin at the time of inclusion in the waiting list, g/l	39.21 ± 3.36	27.74 ± 6.33	0.015
MELD at the time of inclusion in the waiting list	15.73 ± 3.56	25.12 ± 8.43	<0.001
MELD-Na at the time of inclusion in the waiting list	15.77 ± 3.55	25.45 ± 8.44	<0.001
Charlson index at the time of inclusion in the waiting list	9.05 ± 2.48	9.11 ± 2.67	0.864

Table 2

Comparative characteristics of parameters of patients with recompensation (delisting) and deaths in the period of stay in the waiting list – listing (lack of normal distribution)

Parameter	Recompensation (n = 19) Median (25^{th}–75^{th} percentile) or quantity (%)	Deaths (n = 61) Median (25^{th}–75^{th} percentile) or quantity (%)	p value
Male gender	10 (52.6%)	36 (59%)	0.623
HE degree	2 (2-2)	3 (2-3)	<0.001
ALP at the time of inclusion in the waiting list, U/l	265.0 (180.0–300.0)	389.0 (296.5–500.5)	0.001
Na at the time of inclusion in the waiting list, mmol/l	139.0 (138.0–141.0)	136.0 (135.5–138.5)	0.001
INR at the time of inclusion in the waiting list	1.4 (1.3–1.5)	1.8 (1.6–2.35)	<0.001
Creatinine at the time of inclusion in the waiting list, μmol/l	114.0 (86.0–120.0)	148.0 (111.5–202.5)	<0.001
Bilirubin at the time of inclusion in the waiting list, μmol/l	49.0 (38.0–72.0)	82.0 (55.0–142.5)	0.001
BMI at the time of inclusion in the waiting list, kg/m^2	24.8 (23.6–28.3)	24.5 (20.6–27.9)	0.459

The patients with respective outcomes (recompensation/death) were subjected to regression analysis (logistic regression). Significant recompensation predictors were the parameters of albumin in blood plasma and leukocyte levels at the time of inclusion in the waiting list ($p = 0.024$ and $p = 0.019$, respectively).

Odd ratio (OR) for the recompensation outcome (delisting) provided the WBC count at the time of inclusion in the waiting list was $\geq 3.1 \times 10^9$/l, was 14.639; 95% CI 2.16–99.12. OR for the recompensation outcome (delisting) provided the albumin content in blood plasma at the time of inclusion in the waiting list was ≥39.1 g/l, was 3.06 (95% CI 1.58–5.95).

The AUC were calculated for albumin concentration and leukocyte level at the time of inclusion in the waiting list; the ROC curves were built for these parameters (Fig. 1). AUC ROC for albumin concentration was 0.938 [95% CI 0.882–0.995; $p < 0.001$]. AUC ROC for leukocyte levels was 0.924 [95% CI 0.865–0.982; $p < 0.001$].

The development of patient recompensation was analyzed by Kaplan–Meier technique. The survival function in the model was identified with the recombination development at certain times for specific patients. Figure 2 shows the waiting time for the recompensation development for patients (the period from inclusion in WL to the recompensation development and delisting).

DISCUSSION

It was shown that in the group of patients with developed recompensation of liver function at the time of inclusion in WL the leukocytes level, albumin concentration in plasma, Na in blood appeared significantly higher than in the group of deceased patients with decompensation. In the group of patients with recompensation at the time of inclusion in WL INR, HE degree, alkaline phosphatase, creatinine, bilirubin, MELD and MELD-Na were also significantly lower than in the group of the patients deceased at the decompensation stage.

The recompensation development in patients with LC of various etiologies is associated with a number of plausible factors. Fibrosis and portal hypertension have been shown to decrease after successful antiviral therapy of HCV-associated LC [18–21]. In particular, a significant decrease in the hepatic venous pressure gradient (HVPG) was established after achieving a stable virologic response resulted from HCV antiviral therapy in patients with decompensated LC and portal hypertension [20, 21]. A multicenter European study showed that recompensati-

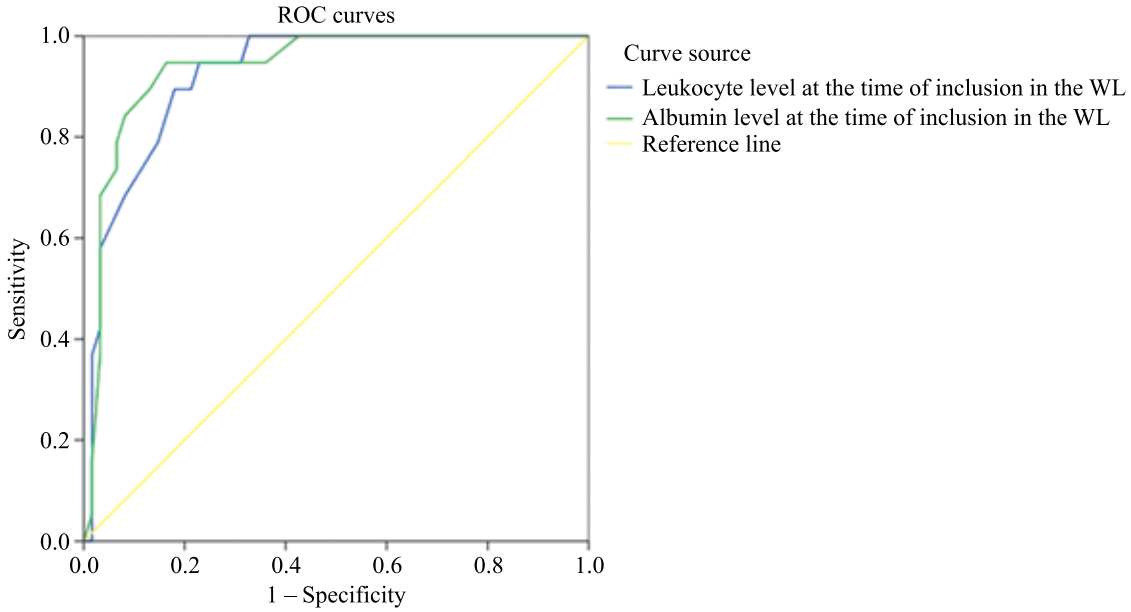

Fig. 1. ROC curve for leukocyte and albumin levels in the blood of patients at the time of inclusion in the waiting list as predictors of the development of recompensation

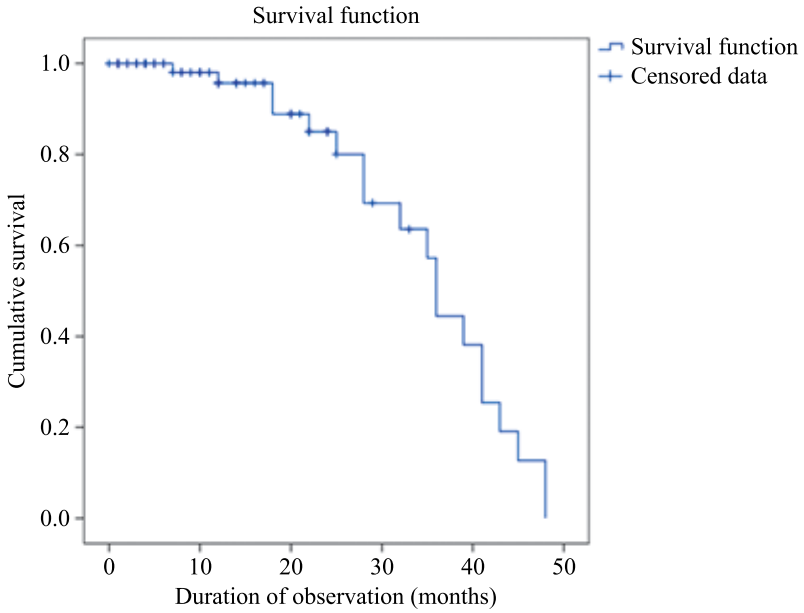

Fig. 2. The waiting time for the recompensation development (survival function) in the analysis of the survival rate by Kaplan–Meier

on due to antiviral therapy caused delisting of patients (19.2% of cases) who were previously included in WL due to decompensated LC in the outcome of chronic hepatitis C [22]. The authors came to an important conclusion that treatment of patients included in WL with direct antiviral agents before transplant, causing recompensation and delisting, can significantly reduce the LT number, which is important against the background of organ deficiency and high prevalence of HCV-associated liver diseases.

Another study showed that in 30.9% of cases, patients with successful antiviral therapy for HCV-associated decompensated LC develop recompensation followed by delisting [23]. However, in two years after delisting, four patients were re-included in WL (relisted). In one case, the patient developed HCC, in three cases ascites developed.

As a result of antiviral therapy in patients with HBV infection, the potential for the reverse development of not only compensated, but also decompensated LC was demonstrated [24–26]. Jang et al. [27] found antiviral therapy of LT candidates with HBV-associated decompensated LC to cause recombination followed by delisting in about $^{1}/_{3}$ of patients.

Candidate patients for LT with LC due to the development of obesity and progression of non-alcoholic steatohepatitis (NASH) got bariatric surgery [28]. In 33.3% of patients, a regression of the disease developed followed by delisting. However, subsequently, as the follow-up period increased to 7 years, the authors noted the development of sarcopenia and malnutrition in 71.4% of cases in patients with delisting.

Aravinthan et al. [12] found that of 77 LT candidate patients who developed recompensation with subsequent delisting, 61% had ALD, 16% – HCV-associated LC, 5% – ALD/HCV-associated LC. In the remaining patients, recombination followed by delisting in 4% of cases was associated with HBV-induced LC, in 5% of cases with AIH, in 4% of cases with NASH, in 1% of cases with PSC, in 1% of cases with cryptogenic LC, in 3% of cases with sarcoidosis. The authors suggest the application of TIPS, antiviral therapy of HCV and HBV infection, and treatment of AIH with azathioprine as probable factors that caused the development of recompensation in the patients [12].

In our study, the factors for the development of recompensation followed by delisting of patients are likely successful antiviral therapy of HCV-associated LC, immunosuppressive therapy of autoimmune liver diseases, HE therapy, administration of diuretics and non-selective β-blockers. Probable factors also include the application of TIPS, azygoportal disconnection by the original technique, and endoscopic ligation of the esophagus veins.

Using logistic regression, it was found that leukocytes level and albumin concentration at the time of inclusion in WL are independent predictors of the disease recompensation and patient delisting. The model has high predictive ability, sensitivity and specificity, as evidenced by AUC for both independent variables (0.924 and 0.938, respectively) and ROC curves.

Decrease in the leukocyte level in LC patients can presumably be associated with portal hypertension. For instance, spleen enlargement in LC patients is often accompanied by the development of hypersplenia that serves as the main cause of cytopenia and thrombocytopenia [29]. The exact effector mechanisms associated with splenomegaly and hypersplenia remain unclear. Nevertheless, the most probable causes of these phenomena are hemodynamic disturbances due to portal hypertension, damage to spleen tissue, and the inflammation-induced release of signaling molecules [30, 31]. The recompensation development, as our data show, is associated with a significant difference between the leukocyte levels in the compared groups at the time of inclusion in WL, which probably reflects a lesser degree of hypersplenia, and, accordingly, portal hypertension. This assumption is confirmed by the OR calculation, which showed that in patients with leukocyte levels $\geq 3.1 \times 10^9$/l at the time of inclusion in WL, the probability of developing recompensation (delisting) increases by 14.639 times.

Our data show that the second independent predictor of the recompensation development with subsequent delisting was the concentration of albumin in the blood plasma at the time of inclusion in WL. Belli et al. [22] in a multicenter European study found that the recompensation predictors for patients with HCV-associated LC due to successful antiviral therapy were MELD and serum albumin concentration at the time at the time of inclusion in WL. Aravinthan et al. [12] showed that in patients with ALD (decompensated LC), both of these indicators at the time of inclusion in WL turned out to be independent predictors of the recompensation development and subsequent delisting.

Hypoalbuminemia is an independent risk factor for patient mortality as a marker of malnutrition [32–34], and an increase in plasma albumin concentration is a predictor of patient recompensation [12, 22]. By calculating OR, we showed that in patients with albumin concentration ≥39.1 g/l at the time of inclusion in WL, the probability of recompensation developing (delisting) increases by 3.06 times.

We found that at the time of inclusion in WL, MELD and MELD-Na were significantly lower in the group of patients with recompensation than in the group of patients who died due to decompensation. At the time of inclusion in WL, low MELDs increased the likelihood of recompensation development, and high MELDs, on the contrary, were negative predictors for patients with decompensated HCV cirrhosis who received antiviral therapy and decompensated LC of the alcoholic etiology [12, 22].

Recompensation of patients with decompensated diseases is a clinical conclusion not corresponding to the concept of "recovery". There are various points of view specialists have on the definitions of this condition: "recompensation", "access to transplant", "avoidance of additional complications", etc. [36]. Regression of fibrosis after elimination of the HCV virus is a lengthy but probably proven process [37, 38]. However, despite the eradication of the HCV virus, fibrosis can not only avoid regress, but progress. Perhaps this is due to the fact that it the line between the "return and no return points" are very difficult to find, especially if we take into account that the elimination of liver damage factors (eradication of the HCV virus, withdrawal symptoms in the case of ALD) do not lead to normalization of vasculature alterations in LC patients [36].

CONCLUSION

The present study showed that the reversibility of liver damage (recompensation) after the cessation of factors causing its decompensation is a likely process. It should be emphasized that the concept of "recompensation" is a clinical conclusion that is not synonymous with the concept of "recovery" and requires physicians to continuously monitor patients and make proper decisions

(reinclusion in WL, relisting) if the condition worsens. It seems possible that there exists a "critical point of no return" after which the decompensation of liver function becomes irreversible. When candidates for LT are included in the WL, independent predictors of the liver recompensation development and subsequent delisting of patients are the number of blood leukocytes $\geq 3.1 \times 10^9$/l and the concentration of plasma albumin ≥39.1 g/l.

The authors declare no conflict of interest.

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