DOI: 10.15825/1995-1191-2020-3-26-35

PRIORITIZATION FOR LIVER TRANSPLANTATION

V.L. Korobka[1, 2], M.Y. Kostrykin[1], V.D. Passetchnikov[1, 3], E.S. Pak[1, 2]

[1] Rostov Regional Clinical Hospital, Rostov-on-Don, Russian Federation
[2] Rostov State Medical University, Rostov-on-Don, Russian Federation
[3] Stavropol State Medical University, Stavropol, Russian Federation

Objective: to determine the threshold MELD scores when prioritizing for liver transplantation. **Materials and methods.** We conducted a cohort study of 350 patients who were waitlisted for liver transplantation between 2015 and 2020. **Results.** A logistic regression model was used to identify the independent predictors of liver transplantation waitlist mortality. MELD scores and serum albumin at the time of listing were significant predictors of mortality ($p = 0.001$ and $p = 0.004$, respectively). Their predictive values were confirmed using ROC (Receiver Operating Characteristic) analysis. The area under the ROC curve (AUC) was 0.883 [95% confidence interval (CI) 0.828–0.939; $p < 0.001$] for MELD, and 0.841 [95% CI 0.775–0.907; $p < 0.001$] for serum albumin. Mortality odds ratio was 3.7778, 95% CI (1.619–7.765) provided that the listing MELD score was ≥25. Mortality odds ratio was 2.979 (95% CI 1.63–5.95) provided that the listing serum albumin concentration was ≤30.1 g/L. With a threshold MELD score of 25, there were significant differences between patient survival when comparing patient cohorts with MELD ≥25 and with MELD ≤25 (Log-rank, $p < 0.0001$). **Conclusion.** The MELD model has a high predictive ability in prioritization of waitlisted candidates for liver transplantation. The threshold MELD score and mortality predictors were determined. There were significant differences between patient survival among patient cohorts with MELD ≥25 and with MELD ≤25.

Keywords: liver transplant waiting list, MELD threshold, patient survival, prioritization for liver transplantation.

INTRODUCTION

Since the first liver transplant was performed by an American surgeon Thomas Earl Starzl [1], the operation has radically changed the treatment of severe liver diseases, significantly improving the survival of patients.

Currently, liver transplantation (LT) is a choice therapy for terminal liver diseases, fulminant hepatic failure and some types of hepatocellular carcinoma (GCC) [2]. The increased indications, the higher number of patients included in the waiting list (WL) for liver transplantation caused a severe shortage of donor livers in almost all countries [3–5].

In the Russian Federation, the need for LT in patients with various severe liver diseases far exceeds the resources of transplant centers. In 2018, according to the national register, 1,830 people were waitlisted, and in the same year LT was performed in 505 patients, thus reaching 3.4 per 1 million population [6].

Thus, the continued worldwide growth in the number of patients waitlisted for LT challenges healthcare organizers and transplant experts to determine the best ways to prioritize patients in need of this treatment. Many countries of the world have started the institutions to promptly regulate the distribution of donor organs for patients with the highest mortality risk. In the United States, such donor organs distribution tactics is performed by The United Network for Organ Sharing (UNOS) NGO [7].

The optimal time for LT has not yet been determined, as it is not clear at what stage of liver cirrhosis the need to perform this operation arises [8]. Besides, in conditions of significant excess of donor liver demand exceeding the supply, the primary task is not only to determine the timing of organ transplantation, but also to consider the correct selection of recipients [8, 9].

When the LT was just developing, such methods as the time in the WL, the disease severity, MELD score, etc. were used to prioritize patients [10, 12–14]. However, the transplant community has not yet come to consensus on what the ideal organ donation rate for LT should be. For example, some suggest that the prioritization of patients with LT should base on the difference between the survival rate after liver transplantation and the survival rate of patients that are still in WL [11].

An ideal indicator for organ allocation would help identify a relatively narrow group of patients, e. g., one similar in size to the number of available donors and adhere to the principle of prioritization according to medical needs. When prioritizing waitlisted patients, the MELD threshold above which LT will be most beneficial in reducing patient mortality should be considered.

Objective: to determine the threshold MELD scores when prioritizing the patients for liver transplantation.

Corresponding author: Victor Passetchnikov. Address: 21, Aviatsionnaya str., Stavropol, 355017, Russian Federation. Phone: (962) 447-75-13. E-mail: passetchnikov@mail.ru

MATERIALS AND METHODS

In the course of the cohort study of patients observed at the Center for Surgery and Donor Coordination of the Rostov Regional Clinical Hospital, 350 patients – candidates for LT were included in WL from 2015 to 2020. The study was approved by the Ethics Committee of the Rostov Regional Clinical Hospital.

Inclusion criteria

The absolute criteria for waitlisting the patients with terminal liver diseases was the lack of the effect of conservative therapy in the previous stages. Additional indications were the following: ascites or hepatic hydrothorax development, antibiotic relief of spontaneous bacterial peritonitis (SBP) in the disease history, the presence of cholestasis, hepatic encephalopathy (HE) and / or gastrointestinal varicose bleeding. The condition for inclusion in WL of the patients with alcoholic liver disease (ALD) was the abstinence for at least 3 months confirmed by the conclusions of experts in narcology and psychiatrists. At waitlisting, in the dynamics of the disease course and the development of any outcomes, the following indicators were calculated: the original and improved indices, MELD [14] and MELD-Na [15] as well as the Charlson comorbidity index (CCI) and Child-Turcotte-Pugh (CTP). The patients were waitlisted at MELD ≥16.

Exclusion criteria

Patients with severe pulmonary heart disease and those continuing alcohol ingestion at the time of the study were excluded. The study did not include HCC patients, the patients waitlisted due to decompensation and delisted due to reasons other than recompensation. The study excluded patients waitlisted for reasons other than decompensation (recurrent cholangitis at primary sclerosing cholangitis), as well as waitlisted patients for the following reasons: widespread thrombosis of portal vein and its main arteries; Budd-Chiari syndrome, sinusoidal obstruction syndrome; polycystic liver disease, and amyloidosis. The patients waitlisted for regrafting or with previous transplants of other organs and patients with acute liver failure were to be excluded from the study.

Diagnostic testing

At waitlisting, the patients underwent clinical examinations, laboratory tests of blood and urine, biochemical and hemostasis parameters studies. HBV and HCV screening and diagnosis were based on enzyme-linked immunosorbent assay (ELISA) for the corresponding markers and qualitative and quantitative determination of viruses in blood by polymerase chain reaction (PCR). All patients underwent elastography and in some cases, liver biopsy followed by morphological examination. Ascitic fluid analysis was made in some patients.

Therapy

Conservative therapy in the waitlisted patients was performed by syndromes, with non-selective β-blockers, diuretics, L-ornithine-L-aspartate combined with lactulose and rifaximin per os (if the overt or latent hepatic encephalopathy was present). Some patients underwent extracorporeal hemocorrection (plasma adsorption and prolonged veno-venous hemodiafiltration). If HCV and HBV infections were diagnosed, all patients received antiviral therapy, which included direct antiviral (HCV) drugs and nucleoside reverse transcriptase inhibitors (HBV). In patients with autoimmune diseases, therapy included immunosuppressants and glucocorticosteroids.

In connection with recurrent varicose bleeding, some patients received transjugular portosystemic shunts (TIPS) and azigo-portal disconnection (APD) surgery according to the original technique (RF patent 2412657) [16]. Orthotopic liver transplantation (OLT) was performed in 59 patients.

Study design

Depending on the disease outcome, the patients waitlisted at the Center for Surgery and Donor Coordination of the Rostov Regional Clinical Hospital were divided into 4 cohorts. The first cohort included 51 patients with LC recompensation due to the therapy. The criteria for the diagnosis of liver cirrhosis (LC) recompensation were the absence of ascites and / or hepatic hydrothorax; absence of peripheral edema (at diuretics discontinuation); absence of PE (without drugs aimed at stopping it); decrease in the MELD (≤15) and CTP for at least 6 months with confirmed steady compensation of liver function [17]. The second cohort (liver function subcompensation) consisted of 153 patients who failed to achieve CP recompensation and remained in WL. The third cohort included 87 patients with lethal outcomes. The fourth cohort consisted of 59 patients who underwent OLT.

The **primary endpoint** was a survival study for the waitlisted patients. The **secondary endpoint** of the study was the definition of the MELD threshold values to prioritize the selection of LT candidates.

Statistical data processing

The data was analyzed using the IBM SPSS Statistics software (v. 21). The type of distribution of the obtained data and the subsequent choice of parametric or nonparametric analysis was determined with Kolmogorov–Smirnov test. In case of normal distribution of samples, the data were represented by arithmetic means (M) and standard deviation (SD) with 95% confidence interval (CI). The statistical significance of the diffe-

rences between the compared parameters with normal distribution was determined by Student's t-test. If the sample showed the absence of the normal distribution, nonparametric tests were used: Wilcoxon for paired comparisons of dependent variables, Mann–Whitney (U test), Pearson's Chi-square for comparison of independent variables. Quantitative indicators in samples with a distribution other than normal were presented in the form of a median and an interquartile range (IQR), the interval between the 25th and 75th percentiles. Frequencies and proportions (%) were calculated to assess the qualitative data. Differences between the compared parameters were considered statistically significant with the error rate less than 0.05 ($p < 0.05$).

Mortality predictors were defined through regression analysis (logistic regression). The odds ratio was calculated for significant mortality predictors with 95% CI. To assess the quality of the regression model (predictive power of the model), ROC curves (Receiver Operating Characteristic) were plotted, and the AUC (Area Under Curve) was calculated. The statement that the AUC ROC does not differ from 0.5 [18] was taken as a null hypothesis.

The survival rate was assessed by Kaplan–Meier, the mean and median survival times were determined by criteria of Log-Rank (Mantel-Cox), Breslow, and Tarone-Ware.

RESULTS

In Kolmogorov–Smirnov test, patients' age, body mass index (BMI), leukocyte count, albumin concentration, MELD, MELD-Na at the time of waitlisting corresponded to the normal distribution and were analyzed with parametric statistics methods.

Such parameters as the severity of hepatic encephalopathy, alkaline phosphatase activity, Na, creatinine and bilirubin concentrations, INR, CCI and CTP at the time of waitlisting did not correspond to the normal distribution, and nonparametric statistical methods were used for their subsequent analysis (Mann–Whitney, U-test, Chi-square).

Tables 1 and 2 show demographic parameters, the results of clinical, laboratory studies, BMI, MELD, MELD-Na, CCI, and CTP in cohorts of patients with LC recompensation (n = 51), LC subcompensation (n = 153), the patients who died during their stay in WL (n = 87) and those who underwent OLT (n = 59).

Fig. 1 shows the MELD of the waitlisted patients of all cohorts. The MELD index in the group of patients with lethal outcomes significantly differed from the parameters of other compared cohorts. Patients with LC recompensation and lethal outcomes were subjected to regression analysis (logistic regression). MELD and blood plasma albumin ($p = 0.001$ and $p = 0.004$, respectively) were significant mortality predictors.

AUCs were calculated for MELD scores and albumin concentrations, and ROC curves for these parameters were plotted (Fig. 2).

AUC ROC for MELD was 0.883 [95% CI 0.828–0.939; $p < 0.001$]. AUC ROC for albumin concentration was 0.841 [95% CI 0.775–0.907; $p < 0.001$].

The odds ratio (OR) for the development of mortality, provided that at waitlisting MELD score ≥25, was 3.778, 95% CI (1.619–7.765). The OR for the development of mortality, provided that at waitlisting the concentration of plasma albumin ≤30.1 g/L, was 2.979 (95% CI 1.63–5.95).

The survival was analyzed depending on MELD scores with Kaplan–Meier and Log-rank (Mantel-Cox), Breslow, and Tarone-Ware criteria. The study showed that the survival rate of waitlisted patients depended on the MELD score. There were significant differences between patient survival when comparing cohorts of patients with MELD scores ≥25 and ≤25 (Log-rank, $p < 0.0001$; Breslow, $p < 0.0001$; Tarone-Ware, $p < 0.0001$). According to the developed model, the function of survival was identified with the development of mortality at certain times for specific patients (Fig. 3).

Table 1

Comparative characteristics of patient indices in study cohorts with normal distribution of the data sample

Parameters at waitlisting	Cohorts of patients			
	1 (n = 51) M ± SD	2 (n = 153) M ± SD	3 (n = 87) M ± SD	4 (n = 59) M ± SD
Age, years	48.35 ± 9.93*	51.85 ± 9.32	50.98 ± 11.35^{e}	45.02 ± 11.94^{a}
BMI, kg/m^2	27.72 ± 4.47	26.80 ± 4.46	24.50 ± 4.18^{e}	25.29 ± 4.13^{ad}
WBC, ×10^9/l	3.75 ± 0.49*	3.34 ± 0.69^{e}	2.69 ± 0.74^{m}	3.22 ± 0.70^{cd}
Plasma albumin, g/l	37.76 ± 4.73	33.27 ± 6.79	28.39 ± 7.67^{m}	31.69 ± 5.18^{acd}
MELD-Na	18.33 ± 1.93*	20.59 ± 4.46^{e}	25.97 ± 8.30^{m}	20.93 ± 5.64^{cd}

Note. 1 – LC recompensation; 2 – LC subcompensation; 3 – died in WL; 4 – OLT; * – $p < 0.05$ comparison between groups 1 and 2; ^{a} – $p < 0.05$ comparison between groups 2 and 4; ^{c} – $p < 0.05$ comparison between groups 3 and 4; ^{d} – $p < 0.05$ comparison between groups 1 and 4; ^{e} – $p < 0.05$ comparison between groups 2 and 3; ^{m} – $p < 0.05$ comparison between groups 1 and 3.

Table 2

Comparative characteristics of patient indices in study cohorts in the absence of normal distribution of the data sample

Parameters at waitlisting	Cohorts of patients			
	1 (n = 51) Median (IQR) or %	2 (n = 153) Median (IQR) or %	3 (n = 87) Median (IQR) or %	4 (n = 59) Median (IQR) or %
Male gender, %	64.7	50.3	55.2	57.6
Hepatic encephalopathy severity	2.0 (1.0–2.0)*	2.0 (2.0–2.0)^{e}	2.0 (3.0–3.0)^{m}	2.0 (2.0–3.0)^{d}
CCI	7.0 (5.0–8.0)*	9.0 (7.5–11.0)	14.0 (13.0–14.0)^{m}	9.0 (7.0–11.0)^{d}
CTP	14.0 (13.0–14.0)	14.0 (12.0–14.0)	14.0 (13.0–14.0)	14.0 (13.0–14.0)^{a}
PLT, $\times 10^9$/l	94.0 (78.0–126.0)*	67.0 (49.0–96.0)^{e}	45.0 (32.0–72.0)^{m}	43.0 (58.0–86.0)^{cd}
ALP, U/l	243.0 (167.0–365.0)	273.0 (148.5–383.5)^{e}	387.0 (286.0–500.0)^{m}	287.0 (217.0–401.0)^{c}
Na, mmol/l	139.0 (137.0–141.0)*	138.0 (136.0–140.0)^{e}	137.0 (136.0–139.0)^{m}	138.0 (136.0–140.0)^{cd}
Creatinine, μmol/l	109.0 (93.0–120.0)	112.0 (86.0–132.5)^{e}	139.0 (111.0–187.0)^{m}	120.0 (96.0–143.0)^{acd}
Bilirubin, μmol/l	79.0 (61.0–103.0)*	72.0 (51.0–95.0)^{e}	93.0 (58.0–198.0)^{m}	72.0 (48.0–96.0)^{cd}
IHR	1.4 (1.4–1.6)*	1.8 (1.6–2.0)^{e}	2.0 (1.6–2.5)^{m}	1.6 (1.4–1.8)^{ad}

Note. 1 – LC recompensation; 2 – LC subcompensation; 3 – died in WL; 4 – OLT; * – $p < 0.05$ comparison between groups 1 and 2; ^{a} – $p < 0.05$ comparison between groups 2 and 4; ^{c} – $p < 0.05$ comparison between groups 3 and 4; ^{d} – $p < 0.05$ comparison between groups 1 and 4; ^{e} – $p < 0.05$ comparison between groups 2 and 3; ^{m} – $p < 0.05$ comparison between groups 1 and 3.

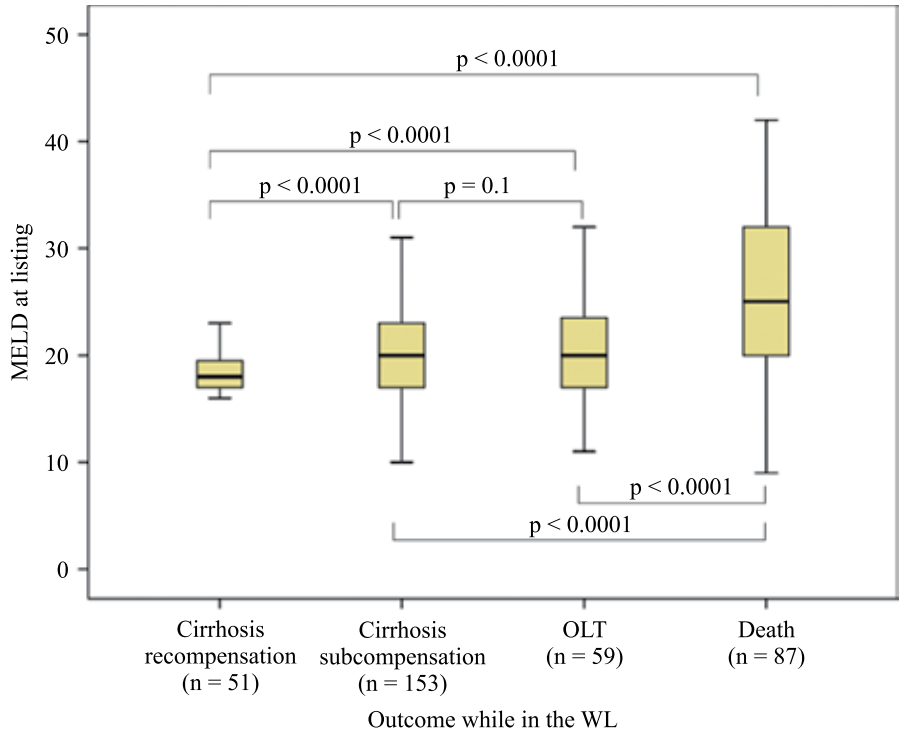

Fig. 1. MELD score in compared patient cohorts. Vertical bar on the box plot, the median; upper line, 75% of the quartile; lower line, 25% of the quartile; range, 95% CI; p, statistical significance of differences

DISCUSSION

LC is featured by high morbidity and mortality rates, reaching more than 48 thousand annually worldwide, or 2.4% of the total number of deaths. For 27 years in Russia, the number of patients with decompensated LC has almost doubled [19]. Decompensated LC is associated with poor prognosis and poor quality of life for patients. For the majority of patients with decompensated LC, LT remains the only treatment method [20], but in some patients there is a possibility of LC recompensation (stabilization of liver function) with subsequent delisting of patients [17, 21].

We found that in patients with LC recompensation, the level of leukocytes and the concentration of albumin were significantly higher in comparison with other stu-

died cohorts. At the same time, in this group, INR, the severity of hepatic encephalopathy, bilirubin, Na levels, platelets, MELD, MELD-Na, and CCI were significantly lower than in other cohorts.

Recompensation of terminal liver disease (TLD) of various etiologies is possible at a combination of factors. First, the preserved liver reserves and the presence of a "point of return" of the lost function after the damaging factors discontinue, which is confirmed by the better parameters of liver function in comparison with other cohorts during the listing, and second, the better response to the therapy.

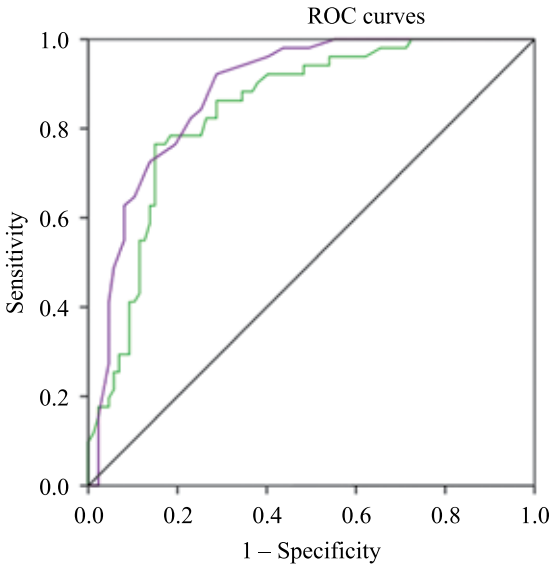

Fig. 2. ROC-curve for MELD and albumin in blood of the patients at waitlisting as mortality predictors. Diagonal segments are formed by matches. Curve source: green, albumin concentration at waitlisting; red, MELD at waitlisting; black, baseline

In 57% of cases, patients with LC recompensation underwent etiological and pathogenetic therapy (azathioprine for patients with autoimmune LC etiology, direct antiviral (HCV) drugs, sofosbuvir + daclatasvir and sofosbuvir/ledipasvir). In 71% of cases, patients received a non-selective β-blocker (carvedilol), in 100% of cases, diuretics and in 84% of cases, hepatic encephalopathy therapy (L-ornithine-L-aspartate intravenously in combination with lactulose and rifaximin per os). In addition to drug therapy, 31% of patients underwent APD, 47%, single endoscopic varicosity ligation, 22%, repeated ligations. Extracorporeal hemocorrection was performed in 16% of cases.

From the point of view of relieving the factors causing LC progression and complications development, significant advancements have been made recently. The use of vasopressors, antibiotics, and minimally invasive surgery techniques have significantly improved the prognosis for patients with acute variceal bleeding [22, 23]. The use of modern antimicrobial therapy has reduced the number of deaths from sepsis and septic shock [24]. Combined treatment of HRS with albumin and vasopressors also led to significant improvements in the outcome in TLD. Successful and timely HCV eradication with a subsequent decrease in LH and fibrosis can lead to the development of LC recompensation, thus making it possible to signi-

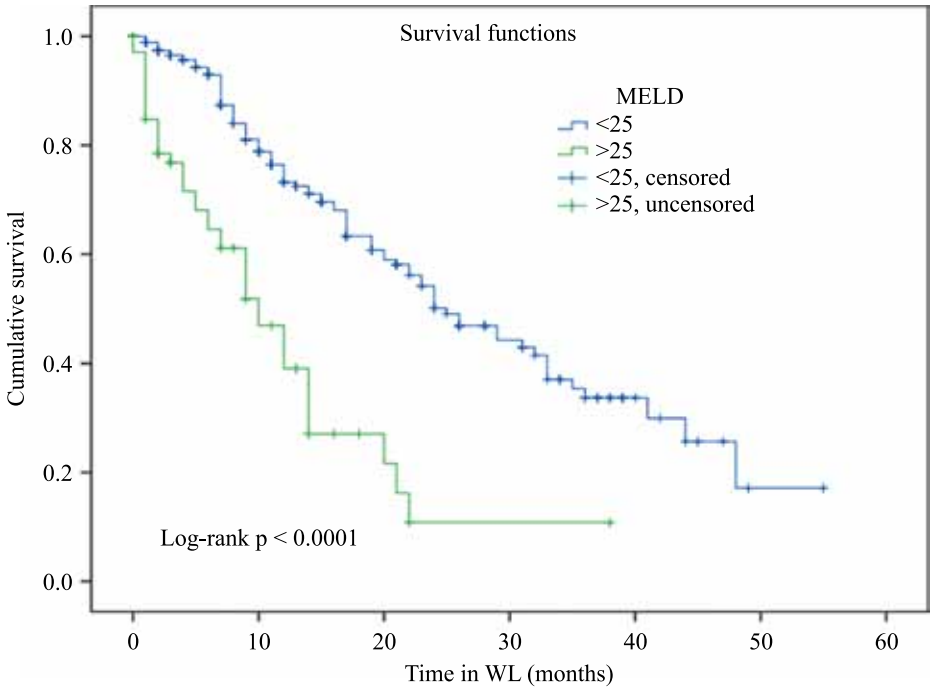

Fig. 3. Comparison of survival curves of patients with different MELD scores by log-rank. The time to death (time from waitlisting to death) is shown

ficantly "unload" WL, which is important in conditions of organ deficiency [21, 25, 26].

Antiviral therapy, AIH treatment with azathioprine and TIPS are counted as probable factors causing the development of LC recompensation with subsequent delisting of patients [17]. We believe that the development of recompensation in patients who left WL in the present study was determined by such factors as successful HCV antiviral therapy, the use of immunosuppressants in autoimmune diseases, treatment of hepatic encephalopathy, prescription of diuretics and nonselective β-blockers. Surgical treatment seems to have also made a certain contribution to the results of conservative treatment of the patients.

When prioritizing the waitlisted patients, it is worth relying on the CTP index, which was originally used to assess the severity of liver disease and predict the outcome of LC and has recently been used to stratify LC patients [20, 27].

In the present study, in all four cohorts, CTP did not significantly differ, thus showing its limited capabilities due to the subjectivity of ascites and hepatic encephalopathy indicators, frequent discrepancies between the clinical picture and the actual data of ultrasonography, psychometric testing, and electroencephalography [20, 28].

Other considered prognostic indices (MELD and its modification MELD-Na), in contrast to CTP, had significant differences in their values in the studied cohorts of patients: LC and OLT recompensation; LC recompensation and death; LC subcompensation and death; OLT and death. MELD and MELD-Na did not significantly differ between the cohorts of patients with LC and OLT subcompensation.

One of the most serious concerns for CRD patients awaiting transplantation is mortality the risk while in WL. In the present study, special attention was paid to the cohort of patients with LC subcompensation, since the therapy here did not allow achieving compensation of liver function in most cases. The patients in this group can move to other cohorts. Due to fluctuations in such laboratory parameters as creatinine and bilirubin, which inevitably occur during the treatment of LC patients, for example, with diuretic therapy or if the patient has sepsis or hemolysis, the use of the MELD index may be limited. A significant drawback of the clinical use of the index is its ability to predict only the short-term survival of LC patients, while the time spent in the LT WL in 63% of cases can be as long as one year; thus, when assessing a period of more than 3 months, the predictive accuracy of MELD significantly decreases [12, 14, 29, 30].

Despite its specificity in assessing the severity of LC, MELD does not take into consideration a number of other equally important clinical, instrumental and laboratory parameters, thus reduces the diagnostic value of the method and not providing full trust in the indicator when assessing an unfavorable outcome of the disease for a period of more than three months. The progress of TLD while in the WL can be unpredictable, and mortality grows exponentially [31] due to the development of an acute decompensating event (e. g., SBP and bleeding from esophageal varices) [30].

Thus, patients can live with a low MELD score (and therefore a low predicted mortality risk) for months or even years without realizing that a sudden breakdown in the SBP course may happen any time.

In our study, a fatal outcome occurred in 30% of the waitlisted patients. In this cohort of patients, the median WL stay was 10.8 ± 9.8 months. The MELD-Na index varied and exceeded 16 points in 84% of cases, averaging 25.97 ± 8.30. Significant predictors of mortality in regression analysis were MELD and blood plasma albumin at the time of inclusion in the WL ($p = 0.001$ and $p = 0.004$, respectively). The chosen model had high predictive power, sensitivity and specificity, as evidenced by AUC for both independent variables (0.883 and 0.841, respectively) and the ROC curves. This is confirmed by the OR calculation, which showed that in patients with MELD ≥25 at the time of inclusion in the WL, the probability of mortality increases by 3.778 times.

Despite the functioning system of patient prioritization with the MELD score [29] and the donor organ distribution system (UNOS), one in five patients (20%) in WL do not live to see this operation [30]. It can be assumed that the cause of death of these patients was the failure to perform LT due to improper stratification and / or deficiency of the donor organs, as well as the sudden TLD decompensation [30, 31]. This may indicate that the fate of the patient depends both on the correct tactics and the competence of the specialists managing the LT WL.

In the present study, hypoalbuminemia was another independent mortality predictor. This condition is a known independent risk factor for mortality in TLD patients as a malnutrition marker, and an increase in albumin concentration in blood plasma predicts the patient recompensation [17, 26]. This was confirmed by calculating the OR for the mortality development. If the concentration of blood plasma albumin at the time of waitlisting was ≤30.1 g/l, the probability of mortality increased by 2.979 times.

Noteworthy is our analysis of survival with Kaplan–Meier method and Log-rank (Mantel-Cox), Breslow, and Tarone-Ware criteria depending on MELD. It was found that the survival rate of patients in the WL is determined by MELD value, namely, its threshold value of 25 points, since there were significant differences between patient survival when comparing cohorts of patients with MELD ≥25 and MELD ≤25 (Log-rank, $p < 0.0001$).

Which of the patients in the LT WL should be given priority? This is an exceedingly difficult question, and many factors must be considered to answer it. For

the purposes of this study, we have shown that priority should be given to patients with MELD ≥25.

Adaptation of the MELD index to determination of the disease severity and prioritization of the patients access to LT made it possible to distribute donor organs to the most severe patients, regardless of the time of their inclusion in WL [14]. This approach has reduced mortality in patients awaiting LT in many countries [32]. Nevertheless, there are still limitations in the use of the MELD indicator, in particular in patients with cholestatic liver diseases [14, 15]. In this category of patients, until the latest TLD stages, MELD remains low due to the normal values of its constituent parts, i. e., IHR and creatinine level. Patients with refractory ascites, hepatopulmonary syndrome, and even chronic hepatic encephalopathy maintain liver function for a long time [32]. Thus, in these patients, in addition to MELD, other indicators must be considered for the timely implementation LT [33].

In the present study, mortality after OLT was 15% (9 deaths within 2 years after surgery). The average MELD score in this category of patients was close to but did not exceed 21. Merion et al. [9] showed that in patients with MELD scores of 18–20 after LT, the risk of mortality decreased by 38% compared to those patients who remained in WL. At the same time, in patients with MELD score of 15–17, the mortality risk was higher (21%) after LT than in patients remaining in the WL. This comparison highlighted the lack of LT efficacy at low MELD scores, despite the fact that in general, these patients had 79% lower mortality risk compared to those remaining in the WL [8]. The variability in assessing the results of LT has shown the need for additional requirements for selection of the patients and organs for LT to ensure its maximum efficacy [8, 34]. For this, it is proposed to use prioritization based not only on MELD, but also the deceased-donor risk index (DRI). It has been established that an organ with a high DRI index provides good survival of recipients after LT with high, not low MELD scores [35, 36]. Beal et al. [11] showed that at MELD <15, LT did not produce the expected effect. The present study also showed that LT was most effective with MELD scores of 21 or less.

CONCLUSION

Prioritizing certain patients on the waiting list as candidates for liver transplantation is a difficult choice for transplant surgeons. Our study showed that one approach to solving this problem, which would satisfy the set goals – to reduce the mortality of patients awaiting liver transplantation and are on a long-term waiting list, is to determine the threshold value of MELD. The MELD model turned out to be predictive in terms of mortality in patients in WL liver transplantation: significant predictors of mortality in regression analysis were MELD and plasma albumin at waitlisting ($p = 0.001$ and $p = 0.004$, respectively). The predictive value of the chosen model is confirmed by the AUC calculation for both independent variables (0.883 and 0.841, respectively) and ROC curves, as well as OR, which showed that in patients with MELD ≥25 at waitlisting, the probability of mortality increased by 3.778 times. The odds ratio for the mortality, provided that the plasma albumin concentration at waitlisting was ≤30.1 g/L, was 2.979 (95% CI 1.63–5.95).

MELD threshold score was 25, since there were significant differences between survival when comparing cohorts of patients with MELD ≥25 and MELD ≤25 (Log-rank, $p < 0.0001$).

The authors declare no conflict of interest.

REFERENCES

1. *Starzl TE, Marchioro TL, Vonkaulla KN et al.* Homotransplantation of the liver in humans. *Surg Gynecol Obstet*. 1963; 117: 659–676.
2. *Lee J, Lee JG, Jung I et al.* Advisory Committee on Improving Liver Allocation. Development of a Korean Liver Allocation System using Model for End Stage Liver Disease Scores: A Nationwide, Multicenter study. *Sci Rep*. 2019; 16; 9 (1): 7495. doi: 10.1038/s41598-019-43965-2.
3. Rapport médical et scientifique de l'Agence de la biomédecine 2017 n.d. https://www.agence-biomedecine.fr/Le-rapport-annuel-medical-et?lang=fr.
4. Organ Procurement and Allocation Transplant Network. National Data. Overall by Organ. Current U.S. Waiting List. Based on OPTN data as of December 7, 2017. https://optn.transplant.hrsa. gov/data/view-data-reports/national-data/#.
5. Organ Procurement and Allocation Transplant Network. National Data. Transplants by Donor Type. U.S. Transplants Performed January 1, 1988 – October 31, 2017. Based on OPTN data as of December 7, 2017. https://optn.transplant.hrsa.gov/data/viewdata-reports/national-data/#.
6. *Gautier SV, Khomyakov SM*. Organ donation and transplantation in Russian Federation in 2018. 11th report of National Register. *Russian Journal of Transplantology and Artificial Organs*. 2019; 21 (3): 7–32. [In Russ, English abstract]. doi: 10.15825/1995-1191-2019-3-7-32.
7. United Network for Organ Sharing / Organ Procurement and Transplantation Network Standard Transplant Analysis and Research Database; 2017. http://optn.transplant.hrsa.gov/data/about/OPTNDatabase.asp.
8. *Merion RM, Schaubel DE, Dykstra DM et al.* The survival benefit of liver transplantation. *Am J Transplant*. 2005; 5 (2): 307–313.
9. *Kim WR, Lake JR, Smith JM et al.* OPTN/SRTR 2013 Annual Data Report: liver. *Am J Transplant*. 2015; 15 Suppl 2: 1–28.
10. *Freeman RB, Wiesner RH, Edwards E et al.* Results of the first year of the new liver allocation plan. *Liver Transpl*. 2004; 10 (1): 7–15.

11. *Beal EW, Akateh C, Tumin D et al.* Defining a Liver Transplant Benefit Threshold for the Model for End-Stage Liver Disease-Sodium Score. *Exp Clin Transplant*. 2019 May 2. doi: 10.6002/ect.2018.0346. [Epub ahead of print] PubMed PMID: 31050611.
12. *Malinchoc M, Kamath PS, Gordon FD et al.* A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology*. 2000; 31 (4): 864–871.
13. *Kamath PS, Wiesner RH, Malinchoc M et al.* A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001; 33 (2): 464–470.
14. *Wiesner R, Edwards E, Freeman R et al.* Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology*. 2003; 124 (1): 91–96.
15. *Leise MD, Kim WR, Kremers WK, Larson JJ et al.* A revised model for end-stage liver disease optimizes prediction of mortality among patients awaiting liver transplantation. *Gastroenterology*. 2011; 140: 1952–1960.
16. *Korobka VL, Shapovalov AM, Danil'chuk OYa, Korobka RV.* Sposob khirurgicheskogo lecheniya i profilaktiki retsidiva krovotecheniy pri varikoznom rasshirenii ven pishchevoda i kardial'nogo otdela zheludka. Patent RF № 2412657. http://www.freepatent.ru/images/patents/48/2412657/patent-2412657.pdf.
17. *Aravinthan AD, Barbas AS, Doyle AC et al.* Characteristics of liver transplant candidates delisted following recompensation and predictors of such delisting in alcohol-related liver disease: a case-control study. *Transpl Int*. 2017; 30: 1140–1149. https://doi.org/10.1111/tri.13008.
18. *Zweig MH, Campbell G.* Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clinical Chemistry.* 1993; 39: 561–577.
19. GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2020; 5 (3): 245–266. doi: 10.1016/S2468-1253(19)30349-8.
20. *Christensen E.* Prognostic models including the Child-Pugh MELD and Mayo risk scores-where are we and where should we go? *J Hepatol*. 2004; 41: 344–350.
21. *Perricone G, Duvoux C, Berenguer M et al.* Delisting HCV-infected liver transplant candidates who improved after viral eradication: Outcome 2 years after delisting. *Liver Int*. 2018; 38: 2170–2177.
22. *de Franchis R.* Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol*. 2015; 63: 743–752. https://doi.org/10.1016/j.jhep.2015.05.022.
23. *Carbonell N, Pauwels A, Serfaty L et al.* Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. *Hepatol Baltim Md*. 2004; 40: 652–659. https://doi. org/10.1002/hep.20339.
24. *Galbois A, Aegerter P, Martel-Samb P et al.* Improved prognosis of septic shock in patients with cirrhosis: a multicenter study. *Crit Care Med*. 2014; 42: 1666–1675.
25. *Roberts S, Gordon A, McLean C et al.* Effect of sustained viral response on hepatic venous pressure gradient in hepatitis C-related cirrhosis. *Clin Gastroenterol Hepatol*. 2007; 5: 932–937.
26. *Belli LS, Berenguer M, Cortesi PA et al.* Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: A European study. *J Hepatol*. 2016; 65: 524–531.
27. *Pugh R, Murray-Lyon I, Dawson J.* Transsection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973; 60: 646–649.
28. *Durand F, Valla D.* Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. *J Hepatol*. 2005; 42 (Suppl): S100–S107.
29. *Freeman RB, Wiesner RH, Edwards E et al.* Results of the first year of the new liver allocation plan. *Liver Transpl*. 2004; 10: 7–15.
30. *Lai JC, Covinsky KE, Hayssen H et al.* Clinician assessments of health status predict mortality in patients with end-stage liver disease awaiting liver transplantation. *Liver Int*. 2015; 35 (9): 2167–2173. doi: 10.1111/liv.12792.
31. *Massie AB, Segev DL.* MELD trajectory prior to death on the liver transplant waitlist. *American journal of transplantation*. 2013; 13: 89–90.
32. *Samuel D, Coilly A.* Management of patients with liver diseases on the waiting list for transplantation: a major impact to the success of liver transplantation. *BMC Med*. 2018; 16: 113.
33. *Northup PG, Intagliata NM et al.* Mortality on the liver transplant waiting list: unintended policy consequences and model for end stage liver disease (MELD) inflation. *Hepatology*. 2015; 61: 285–291.
34. *Su F, Yu L, Berry K et al.* Aging of liver transplant registrants and recipients: trends and impact on waitlist outcomes, posttransplantation outcomes, and transplant-related survival benefit. *Gastroenterology*. 2016; 150 (2): 441–453.
35. *Schaubel DE, Sima CS, Goodrich NP et al.* The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. *Am J Transplant*. 2008; 8 (2): 419–425.
36. *Feng S, Goodrich NP, Bragg-Gresham JL et al.* Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant*. 2006; 6 (4): 783–790.

The article was submitted to the journal on 30.06.2020