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Comparative analysis of models predicting the risks of early poor outcome of deceased-donor liver transplantation: a retrospective single-center study

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Abstract

Rationale. *The risk of early graft loss determines the specifics and plan of anesthesiological assistance, intensive therapy, and overall the feasibility of liver transplantation. Various prognostic models and criteria have become widespread abroad; however, Russian transplant centers have not yet validated them.*

Objective*. To evaluate the applicability and accuracy of the most common models predicting the risks of early adverse outcomes in liver transplantation from deceased donors.*

Material and methods. *A retrospective single-center study included data on 131 liver transplantations from deceased donors performed between May 2012 and January 2023. For each observation, DRI, SOFT, D-*

MELD, BAR, MEAF, L-GrAFT, and EASE indices were calculated, and compliance with an early allograft dysfunction criteria was verified. Depending on the possibility of calculating the indicators and their values relative to known cutoff points, the study groups were formed, and 1-, 3-, 6-, and 12-month graft survival rates were calculated. The forecast was compared with the actual outcomes, and sensitivity, specificity, F1-score, and C-index were calculated.

Results. *When assessing the risk of 1- and 3-month graft loss, models using only preoperative parameters demonstrated relatively low prognostic significance: DRI (F1-score: 0.16; C-index: 0.54), SOFT (F1-score: 0.42; C-index: 0.64), D-MELD (F1-score: 0.30; C-index: 0.58), and BAR (F1-score: 0.23; C-index: 0.57). Postoperative indices of MEAF (F1-score: 0.44; C-index: 0.74) and L-GrAFT (F1-score: 0.32; C-index: 0.65) were applicable in 96%, those of ABC (F1-score: 0.29; C-index: 0.71) in 91%, and EASE (F1-score: 0.26; C-index: 0.80) in 89% of cases. The relative risk of 30-days graft loss in case of EAD was 5.2 (95% CI: 3.4-8.1; p<0.0001), F1-score: 0.64, and C-index: 0.84. Using locally established cutoff values for SOFT (11 points) and L-GrAFT (-0.87) scores increased their prognostic significance: F1-score: 0.46 and 0.63, C-index: 0.69 and 0.87, respectively.*

Conclusion. *The analyzed models can be used to assess the risks of early liver graft loss; however, their prognostic significance is not high. Developing a new model in a multicenter Russian study, as well as searching for new objective methods to assess the state of the donor liver are promising directions for future work.*

Keywords: liver transplantation, graft survival, prognostic models, early allograft dysfunction, primary non-function graft

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ALT, alanine aminotransferase

AST, aspartate aminotransferase

CVA, cerebrovascular accident

EAD, early allograft dysfunction

GGT, gamma-glutamyl transpeptidase

MLV, mechanical lung ventilation

PBC, primary biliary cholangitis

PNF, primary non-function

PSC, primary sclerosing cholangitis

RR, relative risk

Introduction

Transplantation for many patients with severe liver diseases is an effective treatment method that allows to increase both the life expectancy [1, 2], and the quality of life [3]. At the same time, an individual prognosis is determined by a wide range of factors, their combinations, mutual effects, and their significance that varies depending on the stage of the peritransplantation process [4–6].

The predominant number of patients in need of transplantation over the number of available donor organs is an objective reality and determines the importance of the optimal use of a limited donor resource [7]. The global goal is *to simultaneously* minimize mortality among those waiting for transplantation and maximize the recipient survival rates [8, 9].

Over the recent decade, the number of liver transplants annually performed from deceased donors in the Russian Federation has more than tripled: from 139 operations in 2012 to 455 in 2021, which naturally led to an expansion of waiting lists: from 488 to 2272 patients for the same time period [10]. Thus, the tasks of evaluating the suitability of a potential deceased donor liver for transplantation, choosing a patient from the waiting list for whom transplantation of a particular organ will be associated with the best risk-benefit ratio, predicting the immediate outcomes of operations, and quickly diagnosing the initial function of the graft are becoming increasingly important.

Over the recent 10–15 years, there have been developed the calculation indices that have been actively used in clinical practice to possibly establish individual preoperative risks of liver transplantation:

- Donor Risk Index (DRI) [11],
- Survival Outcomes Following Liver Transplantation (SOFT) [12],
- D-MELD [13],
- Balance of Risk (BAR) [14],
- Eurotransplant Donor Risk Index (ET-DRI) [15].

The models have also been proposed that predict the direct outcomes of transplantations taking into account data on the course of the short-term (3–10 days) post-transplantation period:

- Model for Early Allograft Function Scoring (MEAF) [16],
- Liver Graft Assessment Following Transplantation risk score (L-GrAFT) [17],
- Early Allograft Failure Simplified Estimation score (EASE) [18],
- AST, Bilirubin & Coagulation factor (ABC) [19].

Widespread in research are the proposed by K. Olthoff et al. Early Allograft Dysfunction (EAD) criteria for early liver graft dysfunction

[20]. In developing these criteria, in contrast to the above prognostic models, a fundamentally different methodological approach was used. The authors revised the definition of early liver allograft dysfunction in the era of using the MELD score for donor organ allocation. As a combination of variables that made up the criteria, the previously known objective post-transplant parameters were selected reflecting the main components of the dysfunction: cytolysis (AST), cholestasis (total bilirubin) and coagulopathy (INR). No new cut-off values were set either. That is, when formulating these criteria, statistical methods, for example, regression analysis, were not used. The results of the multicenter study showed that the EAD development was associated with a statistically significantly increased risk of graft loss (RR=7.4; 95% CI [3.4;16.3]; $p<0.0001$) and death of recipients (RR=10, 7; 95% CI [3.6;31.9]; $p<0.0001$) at 6 months after surgery. This determined the expedience of studying the applicability and predictive value of the EAD criteria in our own cohort of liver transplant recipients.

Despite the fact that Russian authors, when characterizing individual series of operations, sometimes give the values of some indices (most often, DRI, and EAD incidence), the question of their predictive value and, in general, the adequacy of their use has not been studied.

The aim was to assess the applicability and accuracy of the existing models predicting the risks of early adverse outcomes in liver transplantation from a post-mortem donor.

Material and methods

Study Design

The single center retrospective study included information on 131 deceased-donor liver transplants consecutively performed between May 2012 and January 2023. Particulars relating to the characteristics of

donors, recipients, post-transplantation period, and outcomes of operations were obtained from the local Registry of liver transplantations. Loss of the liver graft was considered as the end point (outcome), and the day of death or retransplantation was considered as the date of outcome.

The analysis is divided into two parts: the first deals with preoperative models: DRI, SOFT, D-MELD, BAR; the second part deals with postoperative ones: MEAF, L-GrAFT, EASE, ABC. As far as the criteria for early allograft dysfunction (EAD) were initially proposed as a “soft” endpoint for clinical trials, their prognostic value was analyzed separately. The ET-DRI index [15] was not calculated, since this model takes into account the donor gamma-glutamyl transpeptidase (GGT) level, and information about this laboratory parameter, which is not included in the list of routine examinations, was available in less than half of the cases.

If the calculated values exceeded the cut-off values, the cases were classified as having a high probability of an unfavorable early outcome; if they were lower, then the risk of early graft loss was considered (conditionally) low. For this, the known and(or) previously used cut-off points for each of the models were chosen:

- DRI $\geq$ 1.8 [11, 21],
- SOFT $\geq$ 16 [12, 22],
- D-MELD $\geq$ 1600 [13, 23],
- BAR $\geq$ 18 [14, 23, 24],
- MEAF > 8 [16, 24],
- L-GrAFT > 1.3 [17, 24],
- EASE > 0 [18, 24],
- ABC $\geq$ 2[24].

Next, the model-calculated prognoses were compared with the actual outcomes. The cases were assigned to the third group that was designated as "N/A" if the calculation of one or another index was impossible due to the graft loss earlier the expiry of the data collection period.

Study (validation) cohort of patients

The period of registering the outcomes was limited to one year after transplantation. By the time of the analysis, more than 3 months had passed from the date of 131 operations (100%); 126 operations (96%) were more than 6 months old; 120 operations (92%) were one year old or more. The number of lost and functioning grafts for individual time points during the first year is shown in Fig. 1.

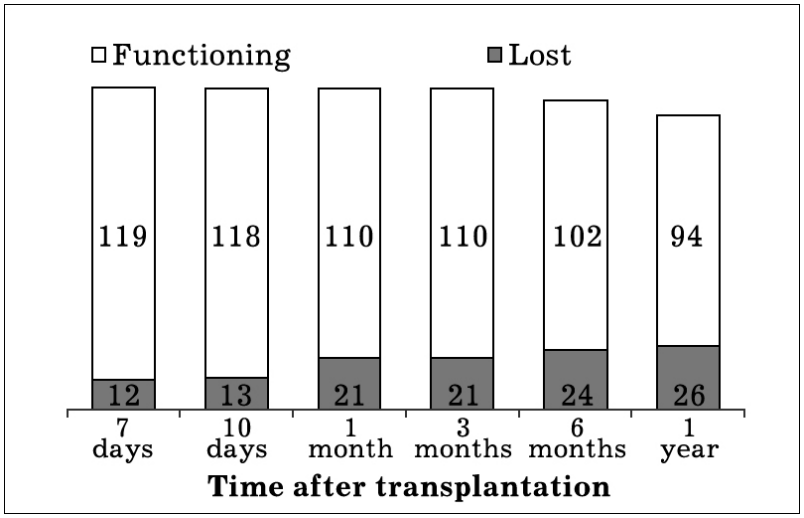

Fig. 1. Numbers of functioning and lost liver grafts according the time after transplantation

Of the 26 grafts lost in the first year after transplantation, 21 (81%) losses occurred within the first month. Due to the fact that no losses were registered from the 31st to the 90th day, the results of all calculations

made for a period of 1 month were similar to those for a period of 3 months.

The structure of causes that led to the graft loss during the first month after surgery was highly heterogeneous. However, all cases could be distributed into four groups:

1*) Primary non-function (PNF) (n=5).* In all cases, a typical clinical and laboratory pattern was observed: critical hemodynamic instability after reperfusion, severe coagulopathy, massive diffuse bleeding, anuria, lactate acidosis, hypoglycemia, an increase in the level of aminotransferases above 3000 U/L. In 4 cases, death occurred on the 1st–3rd day after the surgery; in one case, successful retransplantation was performed on the 3rd day.

2) Retransplantation in patients with high MELD (n=6). Amid the severe dysfunction of a previously transplanted liver (scored from 27 to 40 by MELD), in 3 cases when retransplantation was performed early after the primary surgery, the condition of the patients was further aggravated by the recent surgical injury, acute kidney injury, accompanied by the need for prolonged mechanical lung ventilation (MLV) and vasopressor support. In 3 patients operated on in the long term, retransplantations were associated with technically complicated hepatectomy, which led to a significant increase in the surgery duration and the need for massive transfusion of blood components. Deaths in this group occurred in the range from 2 to 20 days due to progressive multi-organ failure.

3) *Massive intraoperative blood loss (n=3)*. All patients of this group had a history surgical interventions and, as a result, a pronounced adhesive process in the upper abdominal cavity (“*frozen abdomen”*), which, combined with portal hypertension and a large number of venous collaterals, made hepatectomy extremely difficult. Graft reperfusion

occurred under suboptimal hemodynamic conditions. Two recipients died a day after the surgery, the clinical signs being consistent with PNF; however, it was the “primary” etiology of the non-functioning that seemed extremely unlikely. In the 3rd patient, unresolved graft dysfunction was complicated by the development of sepsis; death occurred on the 24^{th} day.

4) *Progressive multiple organ failure and sepsis against the severe graft dysfunction (n=7).* Despite the presence of initially severe graft dysfunction in patients of this group, the liver failure was not directly life-threatening, however, it determined the need for prolonged mechanical ventilation and vasopressor support, transfusions of large volumes of fresh frozen plasma. In all cases, progressive acute renal injury was noted, often requiring sessions of veno-venous hemodiafiltration. Pneumonia was a universal complication. The escalation of antimicrobial therapy and regular toilet bronchoscopy were ineffective, which led to the generalization of the infectious process and the aggravation of multiple organ failure that became the cause of deaths that occurred in the range from 7 to 30 days after surgery.

Statistical data processing

Quantitative variables were presented as medians additionally specifying either the minimum and maximum values when exactly they represented clinical significance, or the interquartile range. For qualitative parameters, the absolute frequencies and relative frequencies expressed as in percentage were given. The significance of differences in quantitative and qualitative variables in two independent samples was determined using the nonparametric two-tailed Mann-Whitney test and two-tailed Fisher's exact test, respectively. Differences were considered statistically significant at $p<0.050$. Survival was calculated using the Kaplan–Meier

method. Differences in survival between two independent groups were assessed using the Log-rank test and were considered statistically significant at $p<0.050$.

To assess the adequacy of the prognostic models, their parameters were calculated: sensitivity, specificity, F1-score and C-index. To search for new optimal cut-off points for the analyzed cohort of cases, ROC-analysis was performed with the maximization by F1-score.

Calculations were performed using Statistica 12 statistical software package (StatSoft Inc., USA) and Jamovi version 2.3.21.0 (Jamovi project, https://www.jamovi.org) with additional modules "Survival", "meddecide" and "PPDA".

Results

Characteristics of the validation cohort as a whole, as well as groups of cases formed with regard to reaching the end point within a month after transplantation, are shown in Table. 1.

Table 1. Characteristics of the validation cohort and the study groups formed with regard to surgery outcomes

Parameter	All cases (n=131)	Functioning grafts (n=110)	Graft loss within the first month (n=21)	p
Recipient characteristics				
Age, years	49 [40;57] (20–72)	51 [41;57] (24–72)	44 [40;52] (20–66)	0.194
Males, n(%)	86 (66)	69 (63)	17 (81)	0.135
Main indications for surgery, n (%)				
Liver cirrhosis of viral etiology	38 (29)	34 (31)	4 (19)	0.431
Hepatocellular carcinoma	29 (22)	25 (23)	4 (19)	1.000
PBC/PSC	15 (12)	11 (10)	4 (19)	0.507
Retransplantation	12(9)	6 (6)	6 (29)	**0.004**
Urgent	7 (5)	2 (2)	5 (24)	**0.001**

transplantation, n (%)				
MELD, score	14 [11;19] (6–46)	14 [11;18] (6–46)	17 [14;26] (7–40)	**0.014**
MELD-Na, score	17 [12;21] (6–46)	16 [11;20] (6–46)	19 [16;28] (7–40)	**0.013**
Characteristics of donors and grafts				
Age, years	48 [37;58] (18–67)	48 [37;58] (18–65)	47 [37;56] (20–67)	0.948
Males, n (%)	81 (61.8)	69 (62.7)	12 (57.1)	0.455
CVA being the cause of donor's death, n (%)	104 (79.4)	86 (78.2)	18 (85.7)	0.564
Sodium, mmol/L	148 [142;154] (124–178)	147 [142;154] (124–178)	152 [145;158] (136–163)	0.156
AST, U/L	31 [20;55] (7–426)	31 [20;47] (7–200)	47 [25;68] (18–426)	0.061
ALT, U/L	27 [18;40] (6–278)	27 [18;40] (6–183)	35 [19;64] (11–278)	0.329
MLV duration, days	2 [1;3] (1−9)	2 [1;3] (1–9)	2 [2;3] (1–6)	0.905
Cold ischemia time, hours	8.5 [7.1;10.0] (1.9-15.0)	8.3 [7.1;9.7] (1.9–13.5)	9.0 [7.5;11.0] (3.0-15.0)	0.115
Surgery peculiarities				
Intervention duration, hours	7.5 [6.5;8.0] (3.0-16.5)	7.0 [6.5;8.0] (3.0-12.5)	8.0 [7.0;9.9] (4.0-16.5)	**0.033**
Warm ischemia time, min	45 [38;50] (14–70)	45 [38;50] (14–70)	45 [33;48] (22–57)	0.531
Blood transfusion, mL	1180 [720;1830] (0–11644)	1017 [685;1581] (0–5500)	2460 [1190;3471] (300–11644)	**<0.001**
Reperfusion syndrome*, n (%)	19 (15)	11 (10)	8 (38)	**0.003**

Notes: *, drop in mean arterial pressure by more than 30% below the baseline level, exceeding one minute in duration and developing within the first 5 minutes after liver allograft reperfusion; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MLV, mechanical lung ventilation; CVA, cerebrovascular accident; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis

In the group of recipients who lost grafts in the early postoperative period, retransplantations were performed statistically significantly more often, surgeries were urgent, and the condition of patients before surgery was more severe when assessed by MELD and MELD-Na scores. The characteristics of donors and grafts were comparable between the groups.

The need for large volumes of blood transfusion, an increase in surgery duration, as well as a more frequent development of reperfusion syndrome were associated with a subsequent graft loss.

Preoperative models (DRI, SOFT, D-MELD, BAR)

The values of the parameters required for the calculation of preoperative prognostic indices were available for all cases. With the exception of DRI, the absolute values of the calculated indices differed statistically significantly between groups (Fig. 2).

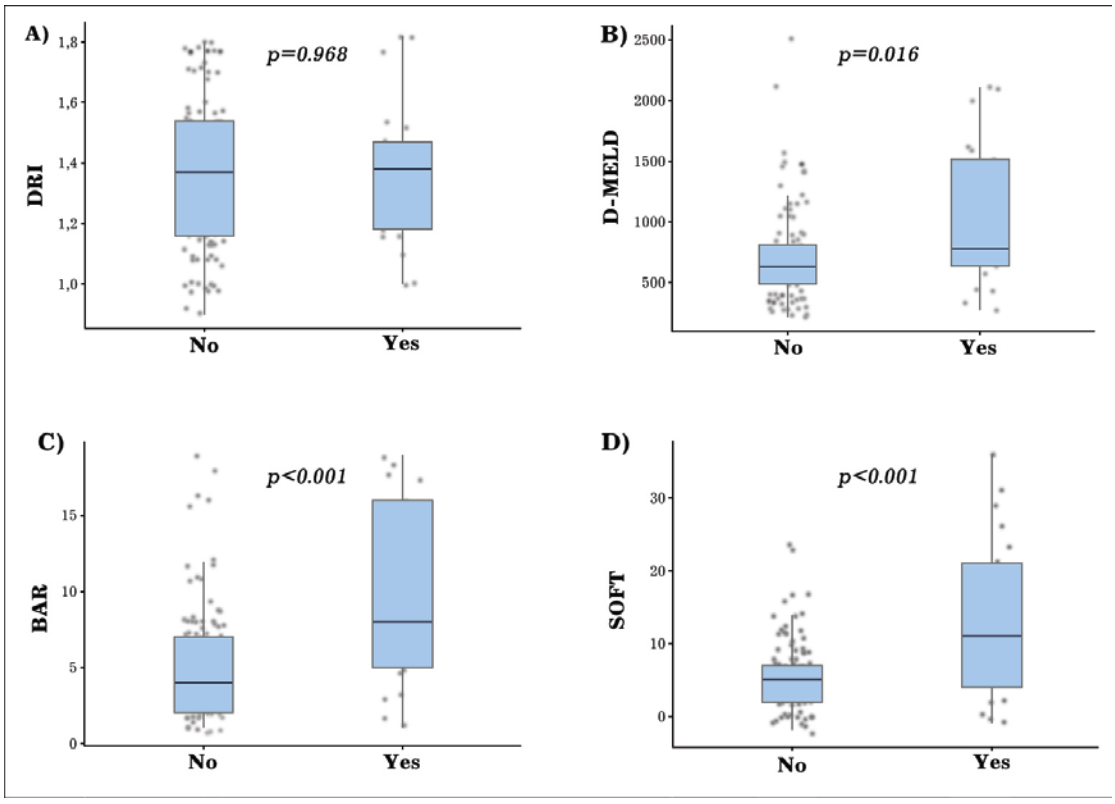

Fig. 2. The values of preoperative indices: (A) DRI, (B) D-MELD, (C) BAR, and (D) SOFT calculated with regard to the liver transplantation outcome: "No" denotes the graft functioning for more than 1 month, "Yes" denotes the graft lost within the first month

When comparing the groups by the rate of cases, for which the calculated indices exceeded the accepted cut-off values, the same picture was observed: for all models except DRI, statistically significant differences were seen (Table 2).

Table 2. The frequency of exceeding the DRI, D-MELD, BAR and SOFT cut-off values with regard to the 30-day outcome of liver transplant

Parameter	All cases (n=131)	Functioning grafts (n=110)	Graft loss within the first month (n=21)	p
DRI ≥ 1.80, n (%)	4 (3.1)	2 (1.8)	2 (9.5)	0.120
D-MELD ≥ 1600, n (%)	6 (4.6)	2 (1.8)	4 (19.0)	**0.006**
BAR ≥ 18, n (%)	5 (3.8)	2 (1.8)	3 (14.3)	**0.029**
SOFT ≥ 16, n (%)	12 (9.2)	5 (4.5)	7 (33.3)	**<0.001**

An analysis of the graft survival in the groups formed with regard to the values of preoperative indices showed that all the studied models, except for DRI, can be used to assess the risk of a transplanted liver loss within 12 months (Fig. 3).

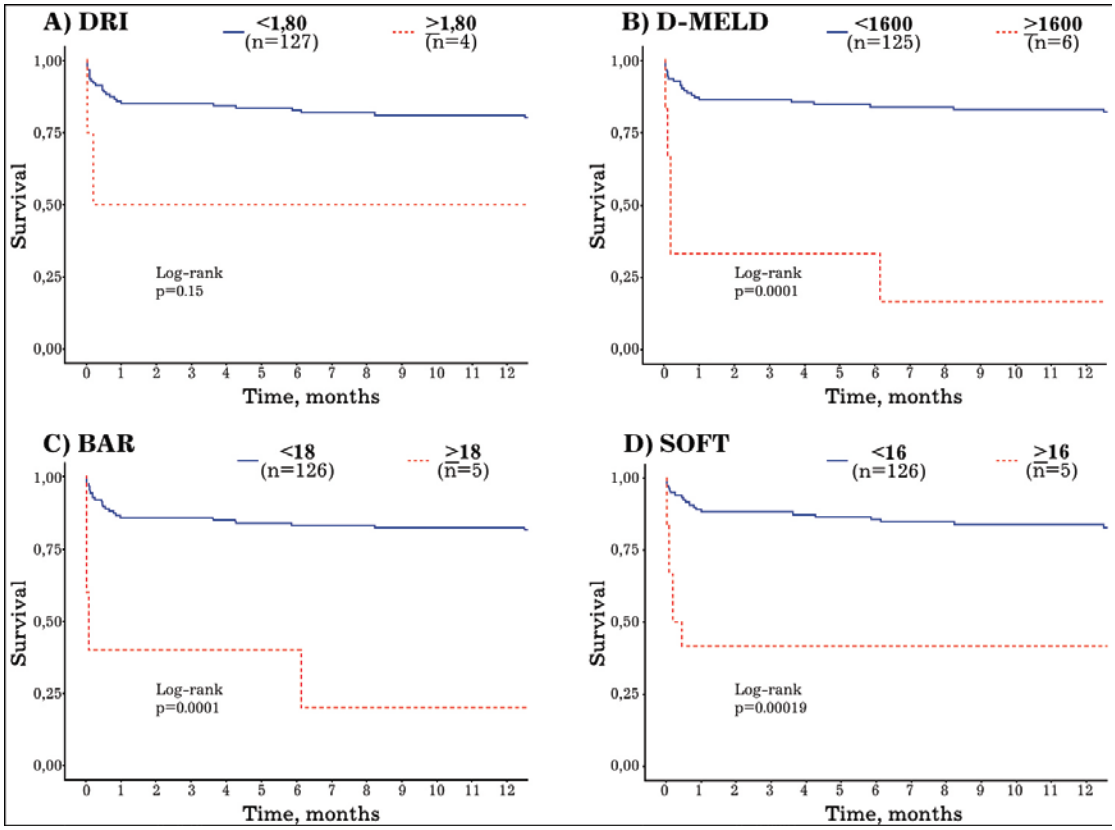

Fig. 3. Liver graft survival as a function of (A) DRI, (B) D-MELD, (C) BAR and (D) SOFT values. Blue solid curves mean "below the cut-off value"; red dotted curves mean "above the cut-off value"

Postoperative models (MEAF, L-GrAFT, EASE, ABC)

The calculation of postoperative prognostic indices requires the results of laboratory tests performed no earlier than 24 hours after the completion of surgery up to 3 (MEAF), 7 (L-GrAFT, ABC) or 10 (EASE) days. This limits the applicability of these models in case of graft loss earlier than the indicated dates. Due to that, the MEAF and L-GrAFT values could not be calculated for 7, ABC for 12, and EASE for 14 cases.

The values of all postoperative indices in the group of patients who lost grafts in the early postoperative period turned out to be statistically significantly higher than in the cases where the transplanted liver functioned for one month or longer (Fig. 4).

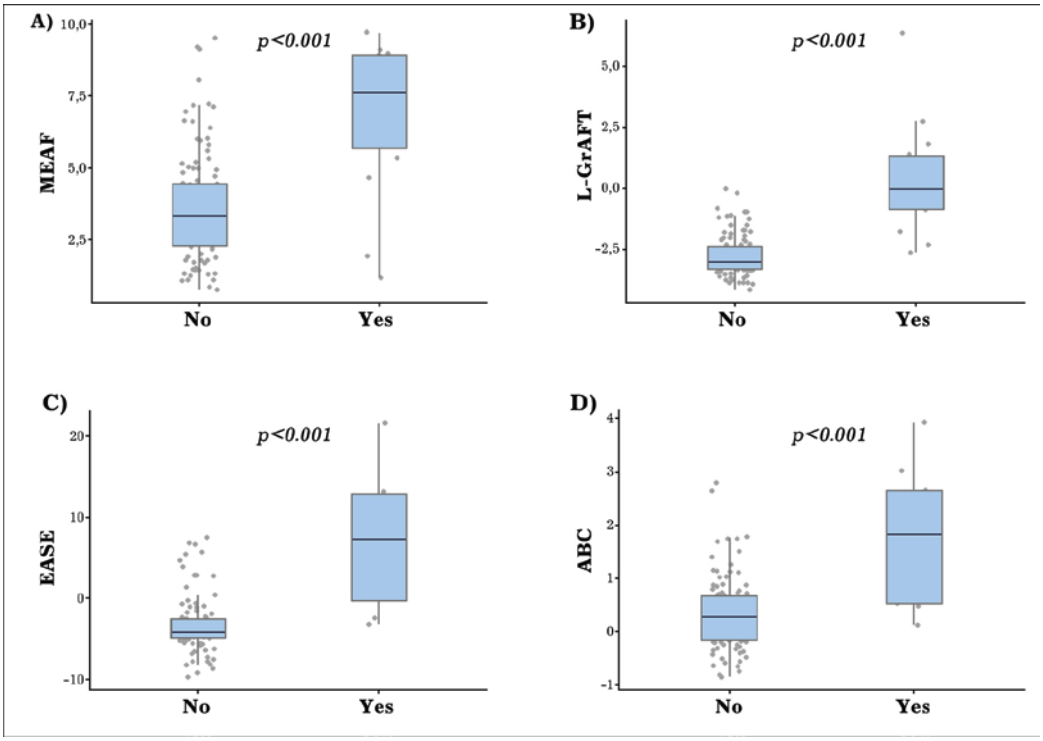

Fig. 4. The values of postoperative indices: (A) MEAF, (B) L-GrAFT, (C) EASE, and (D) ABC calculated with regard to the liver transplantation outcome: "No" denotes the graft functioning for more than 1 month, "Yes" denotes the graft lost within the first month

When analyzing the frequency of exceeding the established cut-off values with regard to reaching the end point, the EASE model (in contrast to the other three ones) did not show statistically significant differences (Table 3).

Table 3. The frequency of exceeding the MEAF, L-GrAFT, EASE and ABC cut-off values with regard to the outcome of liver transplantation

Parameter	All cases (n=131)	Functioning grafts (n=110)	Graft loss within the first month (n=21)	p
MEAF > 8, n (%)	15 (11.5)	7 (6.4)	6 (28.6)	**0.007**
EASE > 0, n (%)	17 (13.0)	12 (10.9)	5 (23.8)	0.149
L-GrAFT > 1.3 n (%)	4 (3.1)	0 (0.0)	4 (19.0)	**<0.001**
ABC ≥ 2, n (%)	6 (4.6)	2 (1.8)	4 (19.0)	**0.006**

Differences in the estimated graft survival when divided into groups with regard to reaching the cut-off for all postoperative models turned out to be statistically significant (Fig. 5). Meanwhile, expectedly, the worst values were in the group of cases, where it was impossible to calculate the index values (N/A).

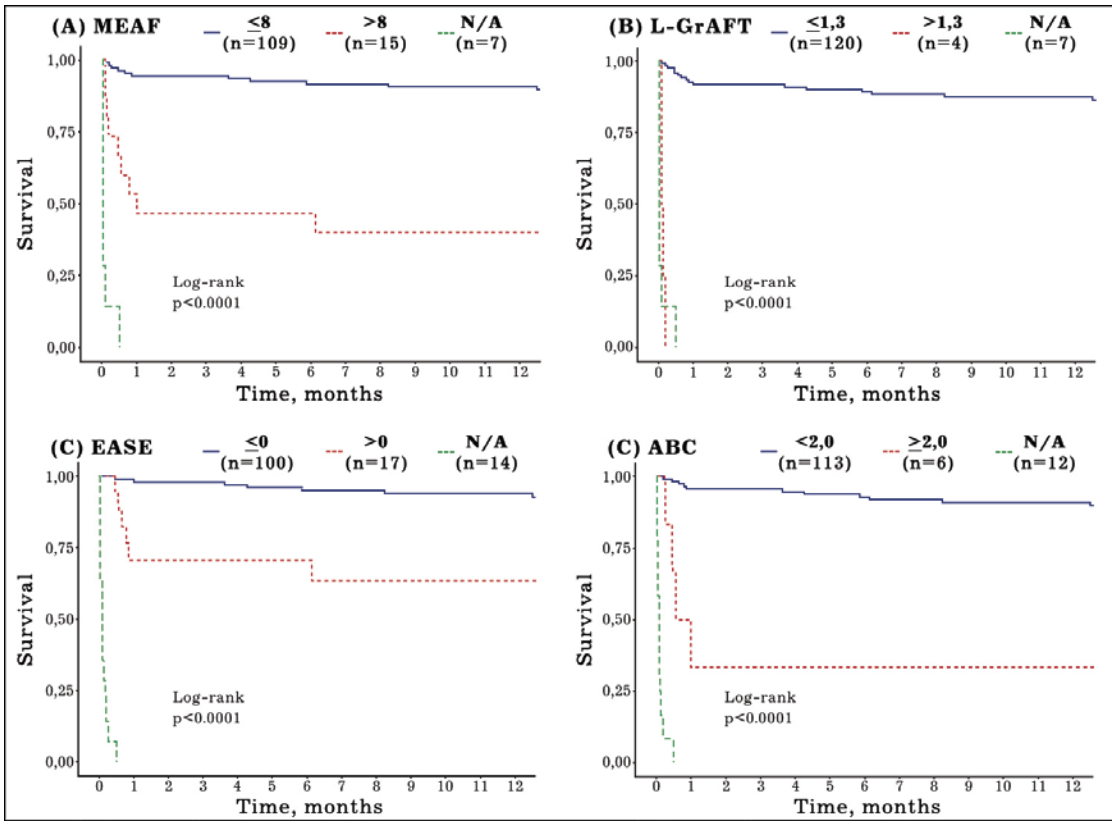

Fig. 5. Liver allograft survival as a function of (A) MEAF, (B) L-GrAFT, (C) EASE and (D) ABC values. Blue solid curves mean "below the cut-off value"; red dotted curves mean "above the cut-off value"; Green dotted curves denote the cases for which predictive indices cannot be calculated

Prognostic value of early graft dysfunction based on Olthoff et al. criteria (EAD)

EAD was diagnosed in 38 recipients (29.0%): in 90.5% of cases (19/21) in the group of early graft losses, in 17.3% of cases (19/110) in

the group with the allograft functioning for more than a month. The relative risk of graft loss during the first month with the EAD development was 5.2 (95% CI [3.4;8.1]; p <0.0001).

Graft survival with regard to the EAD development is shown in Fig. 6.

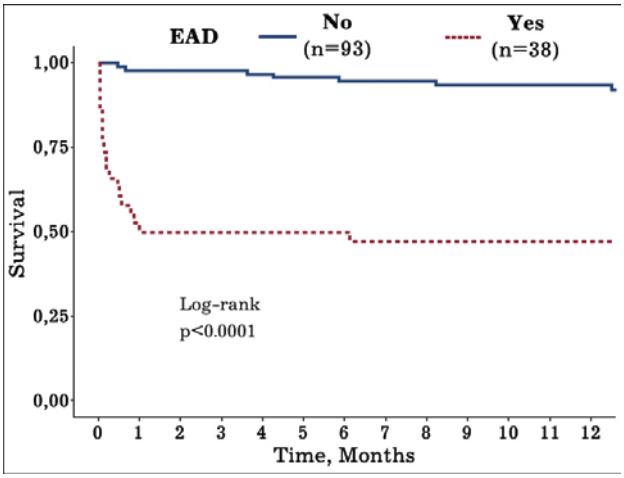

Fig. 6. Liver allograft survival as a function of meeting the early allograft dysfunction criteria. Blue solid curves denote those not meeting the early allograft dysfunction criteria, Red dotted curves denote those meeting them

Comparative analysis of applicability and predictive value of preoperative, postoperative models, and EAD criteria

The data required to calculate preoperative model values were available in all cases. The proportions of cases for which it was possible to calculate postoperative indices are shown in Fig. 7A (for the entire cohort) and in Fig. 7B (separately for the early graft loss group).

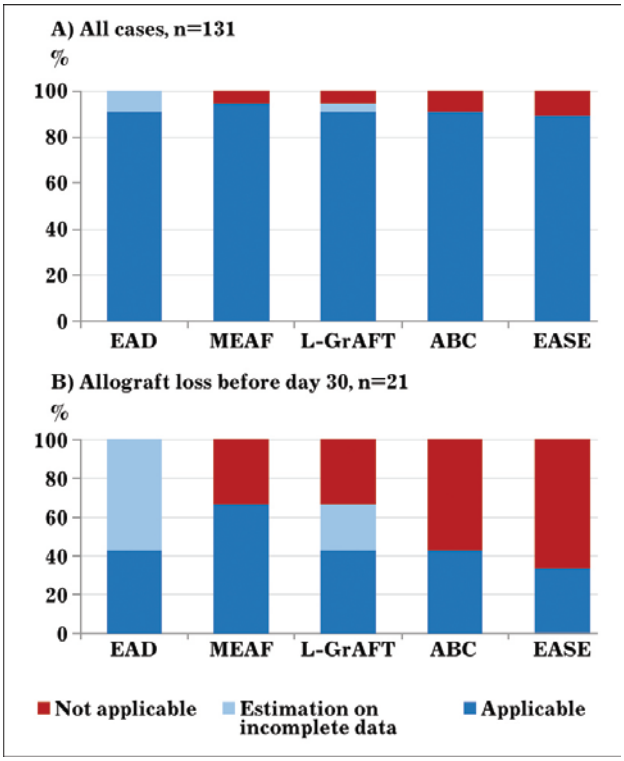

Fig. 7 Applicability of postoperative prognostic models and early allograft dysfunction criteria: (A) to the entire study cohort; (B) for graft loss cases within the first 30 days

Test for meeting the EAD criteria could be performed for all cases. Meantime, for 12 recipients (9% of the entire cohort and 57% of the cases from the early graft loss group), only the AST/ALT level was taken into account.

Although the L-GrAFT model uses laboratory results as obtained between the 1st and the 7th postoperative days, thanks to the possibility of making calculations from incomplete data, the applicability of this index was similar to the MEAF model, which requires only a three-day follow-up period.

The risk assessment by using ABC and EASE models was not possible for 12 and 14 recipients, respectively: all patients, except for one, lost grafts before the 10th day after transplantation, one case lacked

the necessary data for the calculation, this recipient died on the 14th postoperative day.

Thus, for the entire cohort of patients, the MEAF and L-GrAFT indices were applicable for 96% of cases, ABC and EASE were applicable for 91% and for 89%, respectively. For the group where the graft loss occurred during the first month: MEAF and L-GrAFT were applicable for 67%, ABC for 43%, EASE for 33%.

The results of calculating the metrics of assessing the predictive value of models and criteria are shown in Table. 4.

Table 4. Sensitivity, specificity, F1-score, C-index of preoperative (DRI, SOFT, D-MELD, BAR), postoperative (MEAF, L-GrAFT, EASE, ABC) models and early allograft dysfunction criteria for predicting liver allograft loss at timepoints of 1, 3, 6 and 12 months after surgery

	DRI	SOFT	D-MELD	BAR	EAD	MEAF	L-GraFT	EASE	ABC
Cut-off value	≥ 1.80	≥ 16	≥ 1600	≥ 18		>8	> 1.3	> 0	≥ 2
1 (3) month(s)									
Sensitivity/ Specificity, %	10/98	33/96	19/98	14/98	91/83	38(57)/94	19(29)/100	24(71)/89	19(44)/98
F1-score	0.16	0.42	0.30	0.23	0.64	0.44 (0.55)	0.32 (0.44)	0.26 (0.42)	0.29 (0.53)
C-index	0.54	0.64	0.58	0.57	0.84	0.74	0.65	0.80	0.71
6 months									
Sensitivity/ Specificity, %	8/98	29/95	17/98	13/98	79/82	33 (47)/93	17 (24)/100	21 (50)/90	17 (33)/98
F1-score	0.14	0.39	0.27	0.21	0.62	0.41 (0.50)	0.29 (0.38)	0.26 (0.40)	0.27 (0.44)
C-index	0.53	0.62	0.57	0.56	0.79	0.69	0.62	0.70	0.65
12 months									
Sensitivity/ Specificity, %	8/99	27/95	19/99	15/99	77/84	35 (47)/94	15 (21)/100	23 (50)/90	15 (29)/98
F1-score	0.14	0.37	0.31	0.26	0.66	0.44 (0.53)	0.27 (0.35)	0.29 (0.44)	0.25 (0.40)
C-index	0.53	0.61	0.58	0.57	0.79	0.70	0.61	0.70	0.63

Note: Sensitivity, specificity, C-index values shown in parentheses exclude the cases for which it was not possible to calculate the prognostic index

The sensitivity of all preoperative models for the periods of 1, 3, 6 and 12 months after transplantation did not exceed 33%, the F1-score was less than 0.5, and the C-index ranged from 0.53 to 0.64. The obtained values of the metrics indicate a low predictive value of the models being studied.

Comparable values of sensitivity, specificity, F1 were obtained for postoperative models, when all cases were analyzed. Exclusions from the calculations of graft losses that occurred earlier than 3 days (for MEAF), earlier than 7 days (for L-GrAFT and ABC), and earlier than 10 days (for EASE) were associated with an increase in sensitivity and F1: the values are presented in parentheses in Table. 4. Provided that the graft loss did not occur before the end of the data collection period, the prediction accuracy can be considered satisfactory for all postoperative models.

The prognostic value of the development of the early liver graft dysfunction meeting the K.M. Olthoff et al criteria turned out to be significantly higher compared to other postoperative models.

To achieve the maximum possible local predictive value of the models, an additional search for new cut-off values was performed: ROC analysis with maximization by F1-score. The following values were obtained: DRI $\geq$ 1.16, SOFT $\geq$ 11, D- MELD $\geq$ 1424, BAR $\geq$ 14, MEAF $\geq$ 6.7, L-GrAFT $\geq$ -0.87, EASE $\geq$ 7, ABC $\geq$ 1.83. A significant improvement in metrics was obtained for SOFT, BAR, MEAF and L-GrAFT (Table 5).

Table 5. Sensitivity, specificity, F1-score, C-index of preoperative (SOFT, BAR), and postoperative (MEAF, L-GrAFT) models for predicting liver allograft loss at timepoints of 1, 3, 6, and 12 months after surgery using new cut-off values

	SOFT	BAR	MEAF	L-GraFT
Cut-off value	≥ 11	≥ 14	≥ 6.7	≥ -0.87
1 (3) month(s)				
Sensitivity/ Specificity, %	52/86	38/96	48 (71)/93	52 (79)/97
F1-score	0.46	0.47	0.51 (0.63)	0.63 (0.79)
C-index	0.69	0.66	0.81	0.87
6 months				
Sensitivity/ Specificity, %	46/86	33/95	42 (59)/92	46 (65)/97
F1-score	0.45	0.43	0.48 (0.57)	0.58 (0.71)
C-index	0.65	0.64	0.75	0.80
1 year				
Sensitivity/ Specificity, %	46/86	35/96	42 (58)/93	42 (58)/97
F1-score	0.47	0.46	0.50 (0.60)	0.55 (0.67)
C-index	0.65	0.64	0.74	0.77

Thus, SOFT became the best of the preoperative models with a selected cut-off point of 11, and L-GrAFT with a cut-off value of -0.87 was the best among postoperative models. Comparable prognostic value was demonstrated by the EAD criteria with their advantage of possibly establishing the dysfunction diagnosis before the end of the 7-day observation period as soon as by the end of the first postoperative day based on the level of aminotransferases.

Discussion

The use of predictive models in organ transplantation, in particular the liver, has two practical goals:

1) Selecting the patient from the waiting list who will benefit from transplantation of a particular donor organ most of all other candidates;

2) Pre- and postoperative identification of patients with an increased risk of adverse transplant outcome and in need of a change in the standard tactics of treatment and follow-up.

In liver transplantation, there are two objective conditionally insurmountable circumstances that determine the initial choice of patients for transplantation: the incompatibility of the blood types of the donor and the candidate for transplantation and the anthropometric discrepancy (excess) of the donor liver size to the size of the upper abdominal cavity. Once these situations have been ruled out, patient selection is based on the individual risk of death if surgery is not performed and if an organ from an available actual or effective post-mortem donor is used. The time depth of the assessment of these risks does not exceed one year and, as a rule, makes 1-3 months. Surgery is considered appropriate provided that it does not at least worsen the patient's prognosis.

Predicting clinical outcomes is a non-trivial multiparametric problem, the solution of which lies in the plane of comparing the characteristics of transplant candidates and the donor to a retrospective cohort of cases with known characteristics and outcomes. Technically, this can be implemented using various statistical methods, machine learning algorithms, and artificial neural networks.

The most common and validated on a large number of cases model that predicts the probability of death in patients with liver cirrhosis is MELD [25], as well as its later modifications MELD-Na [26] and MELD 3.0 [27]. In many countries, including Russia, MELD is a key indicator for liver transplant prioritization. The severity of the patient's condition before transplantation will have a direct impact on its outcome. No less, and in many cases a significantly greater contribution, will be made by the parameters of the donor organ, which should also be taken into account when predicting the transplant result.

Often a judgment about the suitability of an organ for transplantation is made in isolation, i.e. without taking into account data on candidates for transplantation. This approach is acceptable and aimed at excluding cases when, during the operation, regardless of the recipient characteristics, an unfavorable outcome is inevitable or will occur with a very high probability. However, there remains a non-zero probability of non-functioning or primary (donor related) severe dysfunction for organs deemed suitable for transplantation. An attempt to grade this probability led to the emergence of categories: “ideal donor”, “standard donor”, “suboptimal donor”, “expanded criteria donor”, “marginal donor”, etc. The list of parameters and their cut-off values used for categorization are often chosen empirically or based on statistical calculations that are insufficient in power.

The concept of a Donor Risk Index (DRI) proposed by S. Feng et al. [11] in 2006 to assess the probability of an adverse outcome of liver transplantation based on donor characteristics, made it possible to move from taking into account individual factors to a quantitative risk assessment, which is determined by their various combinations. The authors emphasize that, ultimately, the decision to take the risk of transplantation or to continue waiting remains with the doctors and their patients, and DRI is a tool to make this decision rationally.

The SOFT [12], D-MELD [13], and BAR [14] models combine both transplant candidate risk factors and donor organ risk factors and, in general, have similar predictive value. It is important to note that all of them were developed on the basis of data on liver transplants performed in the USA and accumulated by UNOS: SOFT (February 1, 2002–August 1, 2006; n=21,673), D-MELD (01.01.2003–12.31.2006; n=17,942), BAR (December 27, 1987–September 30, 2010; n=37,255). Probably, it is this circumstance that can affect the accuracy of prediction when using these

models in other regions and countries, being actualized as a “country effect”, similar in essence to the well-known “center effect” [28, 29].

Assessing the predictive value of preoperative models on their own cohort of cases, including after searching for new cut-off values, showed that the best accuracy can be expected when using SOFT (C-index 0.69; F1-score 0.46; cut-off values, value ≥ 11 points) and BAR (C-index 0.66; F1-score 0.47; cut-off value ≥ 14 points) (Fig. 8).

The relevance of predicting the outcome of transplantation remains after the surgery completion. Features of the intraoperative period, the events of the next postoperative hours and days can radically change the initial ideas about the risk of a poor outcome. This should determine the tactics of intensive care, subsequent treatment and follow-up, as well as the making a timely decision on retransplantation, if other options for saving the life of the recipient have been exhausted.

The key value in determining the prognosis is not the absolute values of any parameters at a particular moment, but their dynamics or maximum value over a certain period of time. The models we considered require a period of follow-up and data collection from 3 days (MEAF [16]) to 10 days (EASE [18]) after transplantation. On the one hand, an increase in this period helps to refine the prognosis, and on the other hand, it limits the applicability of the model due to the impossibility of obtaining an assessment in situations where pathophysiological processes proceed so quickly that they lead to a graft loss or death in the coming days after surgery. This shortcoming is clearly demonstrated by our own data. In 21 cases of an early graft loss that occurred within the first month after surgery, at least one of the prognostic indices could be calculated for only 2/3 of the cases.

L-GrAFT index should be singled out separately [17]. Despite the fact that its calculation requires data on daily values of AST, total bilirubin, INR, and platelet count during the first postoperative week, the

model is designed in such a way that a preliminary result can be obtained as soon as on the 2nd day, and further data entry will refine the prognosis.

This also concerns the EAD criteria [20]: for establishing the fact of dysfunction, at least one of three conditions is required: the level of AST/ALT is more than 2000 U/L in the interval from the 1st to the 7th day, the total bilirubin is above 10 mg/dL (171 μmol/L) on day 7, INR ≥ 1.6 on day 7. Thus, the level of aminotransferases, which exceeds the cut-off value, as soon as one day after transplantation, makes it possible to establish the diagnosis of EAD.

It should be noted that it was the EAD criteria, which in essence are not a predictive model and were developed not as such, in the studied cohort of cases most accurately assessed the risk of graft loss at various times, up to 1 year after surgery. Similar predictive value was demonstrated by the L-GrAFT model when using a locally established cut-off value, of -0.87 (Fig. 8).

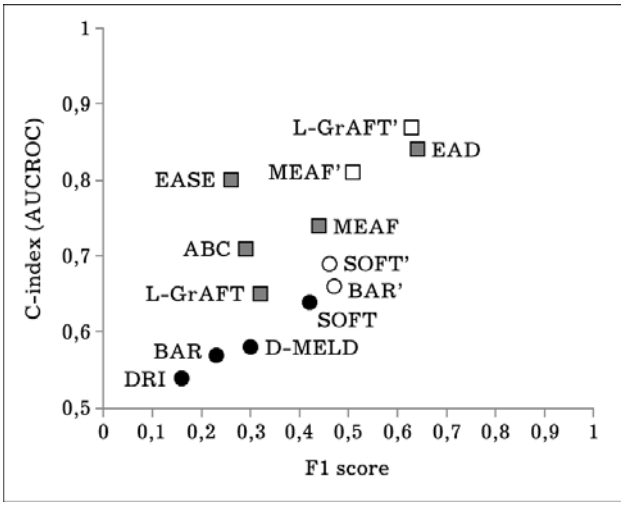

Fig. 8. F1-score and C-index values for preoperative (round markers) and postoperative (square markers) models using known (black markers) and established by the study local (white markers) cut-off values when predicting a graft loss in the first 1(3) month(s) after liver transplantation

The undertaken analysis of applicability and predictive value of the most common models for risk assessment of early adverse outcome of liver transplantation is the most detailed analysis ever conducted in Russia. The results obtained correspond to foreign studies similar in design [21–24, 30–32].

It is important to note that the problem of predicting complications and outcomes of patients in need of transplantation and liver transplant recipients is relevant and is in the focus of attention of Russian transplantation centers, which is confirmed by the topics of publications and dissertations.

In his study, I.V. Pogrebnichenko (2014) proposed clinical and morphological criteria for the suitability of a deceased-donor liver of for transplantation, and the assessed the contribution of donor factors to the development of an early graft dysfunction [33]. V.A. Gulyaev (2016) developed the system for assessing the quality of a donor liver, which was designed to predict its function after transplantation, reduce the rate of unmotivated refusals from transplantation, and improve clinical results when suboptimal quality allografts were used [34]. K.K. Gubarev (2022) clarified the eligibility criteria and risks of liver transplantation, taking into account the predicted duration and route of donor organ transportation [35]. M.G. Minina et al. (2022) studied a nine-year evolution of the characteristics of effective liver donors, and identified prospects for further expanding the criteria for liver suitability for transplantation [36].

The role of factors of candidates for transplantation and recipients of the liver determining the prognosis was also studied. V.L. Korobka et al. studied the informative value of the MELD, Child-Turcotte-Pugh and

Charlson indices for assessing liver function and predicting deterioration in the condition of patients on the waiting list [37], established predictors and exclusion criteria for liver failure recompensation [38], and also proposed their own predictive model for evaluating the mortality risk during the period of waiting for surgery and, based on it, the criteria for choosing a candidate for transplantation [39].

Ya.G. Moisyuk et al. were the first in Russia to validate the EAD criteria, and to determine the effects of the donor and recipient factors, and the surgery characteristics on the initial function of grafts and long-term prognosis [40]. Having made a multivariate analysis, S.I. Zubenko et al. [41] obtained interesting, but at the same time controversial data, according to which plasma creatinine of a deceased donor is the only factor that statistically significantly affects the outcome of liver transplantation. The same study showed no effect of DRI on surgical outcomes, which was consistent with our results.

Despite the possible increase in the accuracy of newly created prognostic models based on deep machine learning algorithms [41], the search for additional, objective methods for assessing the condition of donor organs seems to be no less promising approach. M.S. Novruzbekov et al. [42] proposed a "Method for selecting a donor organ for liver transplantation" based on the assessment of the indocyanine green clearance in brain-dead donors. In an experiment on the isolated liver of a laboratory pig O.N. Reznik et al. [43] and A.E. Skvortsov et al. [44] using a human liver unsuitable for clinical transplantation tested samples of the first domestic device for normothermic perfusion. D.A. Granov et al. [45] proposed a “Method for Predicting the Risk of Early Cadaveric Liver Transplant Dysfunction,” based on measuring the ratio of potassium to glucose concentrations in the physiological solution flowing from the donor liver used to wash it from the preservation agent. Aimed at

predicting and immediately diagnosing EAD, our group conducted the studies in 2018–2022, that are still under way to monitor the parameters of interstitial glucose metabolism in the liver of a deceased donor during preservation and after transplantation using microdialysis technology [46].

An analysis of the applicability and accuracy of widely accepted models for assessing the risk of early adverse outcome of deceased-donor liver transplantation demonstrated their relatively low significance. This raises the question of the adequacy of their routine use in clinical practice and at the same time determines the relevance of developing new models based on update machine learning algorithms. The optimal format for such work seems to be a multicenter study. The search for new objective predictors of poor initial function of allografts, including the liver, is a promising scientific and clinical trend in the field of organ donation and transplantation.

Conclusions

1. The most common preoperative models for assessing the risk of poor outcome after deceased-donor liver transplantation have a relatively low prognostic value: DRI (F1-score: 0.16; C-index: 0.54), SOFT (F1-score: 0.42; C-index: 0.64), D-MELD (F1-score: 0.30; C- index: 0.58), BAR (F1-score: 0.23; C-index: 0.57).

2. The use of postoperative prognostic models involves the collection of data on the recipient during the first 3-10 days after transplantation. This significantly limits their applicability, especially in the group of patients where a poor outcome occurred within the next few days.

3. For some models, a local increase in the prediction accuracy can be achieved by searching for new cut-off values. For example, the transition from cut-off 1.30 to (-0.87) when calculating L-GrAFT score was accompanied by an increase in F1- score from 0.32 to 0.63, and C-

index from 0.65 to 0.87. Such “tuning”, in addition to a confident knowledge of statistical analysis skills, requires the availability of the most complete set of data on at least several dozen of previously performed transplantations.

4. Criteria for early allograft dysfunction proposed and validated by K. M. Olthoff et al. demonstrated both high applicability (100%) and accuracy (F1-score: 0.64; C-index: 0.84) for postoperative risk prediction of early liver allograft loss.

5. The annually increasing number of liver transplants performed in Russia determines the increasing attention of transplantation centers to the problem of predicting the surgery outcomes, high relevance, and most importantly, the possibility of creating new models based on their own data. The optimal format for such future work should be considered a multicenter study.

6. The development of new objective methods for predicting and diagnosing the initial function of the donor liver and other organs is difficult, requires significant material resources and time costs, but is the most promising in terms of expected results.

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