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RISK FACTORS IN DECEASED DONOR LIVER TRANSPLANTATION: A SINGLE CENTRE EXPERIENCE

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Deceased brain-dead donor liver transplantation (LT) is a high-risk intervention. The outcome depends on a large number of modifiable and non-modifiable factors. **Objective:** to analyze our own experience and identify preoperative and perioperative prognostic factors for poor outcomes in LT. **Materials and methods.** The study included 301 liver transplants performed between January 2016 and December 2021. Donor and recipient characteristics, intraoperative data, perioperative characteristics including laboratory test data, and the nature and frequency of complications were used for the analysis. **Results.** The 1-, 3- and 5-year recipient survival rates were 91.8%, 85.1%, and 77.9%, respectively; graft survival rates were 90.4%, 83.7%, and 76.7%, respectively. The most significant predictors of poor outcome of LT on the recipient side were biliary stents (HR 7.203, $p < 0.01$), acutely decompensated cirrhosis (HR 2.52, $p = 0.02$); in the postoperative period, non-surgical infectious complications (HR 4.592, $p < 0.01$) and number of reoperations (HR 4.063, $p < 0.01$). Donor creatinine level (HR 1.004, $p = 0.01$, one factor analysis; HR 1.004, $p = 0.016$, multivariate analysis) was the only reliable prognostic negative factor. **Conclusion.** LT taking into account established risk factors will improve surgery outcomes and help personalize the therapy for each patient.

Keywords: liver transplantation, deceased donor, expanded criteria donor, risk factors.

INTRODUCTION

LT is a high-risk operation [1]. A large number of conditions accompanying the complicated course of liver cirrhosis determine a more severe initial status of a recipient with increased early and long-term mortality [2, 3]. With the emergence of better surgical techniques, surgical contraindications to LT, such as portal vein thrombosis, are decreasing in number [4]. Progressive development of transplantation oncology also brings a large number of patients, previously considered non-transplantable, to the liver transplant waiting list [5]. Expansion of LT indications is increasing the disproportion between number of patients waiting for LT and number of donor organs available, and, as a consequence, increasing waitlist mortality [2, 6]. In an effort to maximize the use of available donor organs, many centers go beyond the traditional "ideal" donor and include expanded donor organ eligibility criteria [7]. The peculiarities of donor organs have an impact on both immediate and long-term outcomes of LT [8]. The above-mentioned peculiarities determine the continuing relevance of evaluation and reassessment of risk factors of adverse outcomes of LT in order to stratify recipients and perform the operation with optimal results for each patient.

Allocation of organs, which takes into account both donor and recipient risk factors, helps to reduce the risk of graft loss and postoperative mortality [9, 10].

MATERIALS AND METHODS

The study included deceased, brain-dead LT in adult recipients, performed at Shumakov National Medical Research Center of Transplantology and Artificial Organs Moscow (Shumakov Center) from January 2016 to December 2021.

The following recipient data were collected and analyzed: demographic characteristics, anthropometry, liver disease severity index (MELD), and concomitant characteristics affecting the severity of liver disease. In addition, we analyzed intraoperative data of LT performed, the presence of postoperative complications, the dynamics of laboratory parameters in the postoperative period, as well as recipient and graft survival rates.

To assess the quality of graft received, we used donors' anthropometric and demographic indicators, laboratory data, amount of vasopressor support, type of graft obtained, and results of histological examination (microscopy of zero-hour biopsies).

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Liver harvesting technique

Our center uses a modification of the rapid liver extraction method with exclusively arterial perfusion of the liver [11]. Graft suitability was assessed on the basis of a preliminary clinical assessment of the donor, a comprehensive abdominal ultrasound examination, and visual assessment of graft. The results of "time-zero" liver allograft biopsies were retrospectively considered.

Table 1

Characteristics of liver recipients (n = 301)

Indicator	Median (min–max)
Age, years	43 (18–72)
Male, n (%)	148 (49.2)
BMI, kg/m^2	24 (15–40)
Associated conditions, n (%)	
Thrombophilia	7 (2.3)
Previous surgeries	29 (9.6)
TIPS	5 (1.7)
Biliary drains/stents	4 (1.3)
Severity of liver disease	
MELD	18 (7–40)
Fulminant liver disease, n (%)	7 (2.3)
Acutely decompensated cirrhosis, n (%)	22 (7.3)
Hepatorenal syndrome, n (%)	88 (29.2)
Waiting time, months	5 (0–48)

Table 2

Characteristics of deceased liver donors (n = 301)

Indicator	Median (min–max)
Male, n (%)	203 (67.4)
Age, years	48 (18–73)
BMI, kg/m^2	26 (17–48)
Graft type, n (%)	
Whole liver	284 (94.3)
Extended right lobe split	17 (5.6)
DRI	1.45 ± 0.28
Steatosis, n (%)	(n = 229)
Mild	181 (79)
Moderate	19 (8.3)
Severe	29 (12.7)
Fibrosis, n (%)	**(n = 229)***
F = 0	152 (66.4)
F = 1	60 (26.2)
F = 2	17 (7.4)
Laboratory indicators	
Alanine aminotransferase (ALT)	28 (1–436)
Aspartate aminotransferase (AST)	35 (8–1099)
Total bilirubin	11 (1–96)
Creatinine	101 (6–720)
Sodium	145 (124–176)

*, 229 biopsies were included in the analysis.

Liver implantation technique

The peculiarities of the surgical technique adopted in our center during deceased donor liver transplant (DDLT) are described in detail in previous works [12, 13]. The choice of caval reconstruction technique was determined by intraoperative characteristics of the recipient's hemodynamics [14].

In the postoperative period, immunosuppressive therapy was prescribed according to accepted protocols, depending on the underlying disease [15]. Patients were followed up for 1 to 3 months by transplant surgeons, with subsequent transfer to a hepatologist for long-term follow-up.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics 23 package. Quantitative variables were expressed as median and range values, qualitative variables as numbers and percentages. Patient and graft survival were determined by the Kaplan–Meier method. Multivariate Cox regression (proportional hazards model) was used to determine risk factors. Hazard Ratio (HR) with 95% confidence interval (CI) value was used to estimate the chances of graft loss/recipient death. The level of significance was considered significant at $p < 0.05$.

RESULTS

From January 2016 to December 2021, 304 DDLT in adult recipients were performed at Shumakov Center. Histological examination of explants in 3 cases verified tumor thrombosis of the portal vein in hepatocellular carcinoma (HCC). Patients who exceeded the UCSF criteria for LT in HCC were excluded from the study.

The general characteristics of recipients are shown in Table 1.

Donor characteristics

The main parameters used in the evaluation of brain-dead donors are shown in Table 2.

The relatively high Disease Risk Index (DRI) is noteworthy. According to the original article by Feng et al., the one-year survival of recipients with DRI from 1.4 to 1.5 is 79.7% [16].

Perioperative parameters

The time characteristics of the surgery, blood loss volume, the need for blood transfusions, and laboratory values reflecting liver function on days 1, 5, and 30 of the postoperative period were analyzed. The data are summarized in Table 3.

Complications and survival

In order to determine negative prognostic events in the postoperative period, we performed a comprehensive assessment of complications with calculation of the Comprehensive Complication Index. The data are summarized in Table 4.

The actuarial recipient and graft survival after transplantation was analyzed using the Kaplan–Meier method (Fig.).

Table 3

Perioperative characteristics of recipients

Indicator	Median (min–max)
Time, min	347 (185–805)
Cold ischemia, min	288 (105–744)
Warm ischemia, min	30 (12–80)
Biliary ischemia, min	31 (10–400)
Blood loss, ml	1000 (200–10000)
Fresh frozen plasma, doses	6 (1–28)
RBC mass, doses	2 (0–11)
Classic caval reconstruction, n (%)	283 (94)
Laboratory indicators	
Day 1 after surgery	
ALT	493 (23–6919)
AST	481 (28–21280)
Total bilirubin	46 (11–874)
Creatinine	81 (26–576)
International normalized ratio (INR)	2 (1–4)
Day 5 after surgery	
ALT	195 (29–4260)
AST	88 (6–4435)
Total bilirubin	40 (6–477)
Creatinine	82 (28–382)
INR	1 (1–2)
Day 30 after surgery	
ALT	30 (1–694)
AST	23 (3–809)
Total bilirubin	19 (2–292)
Creatinine	90 (34–537)
INR	1 (1–3)

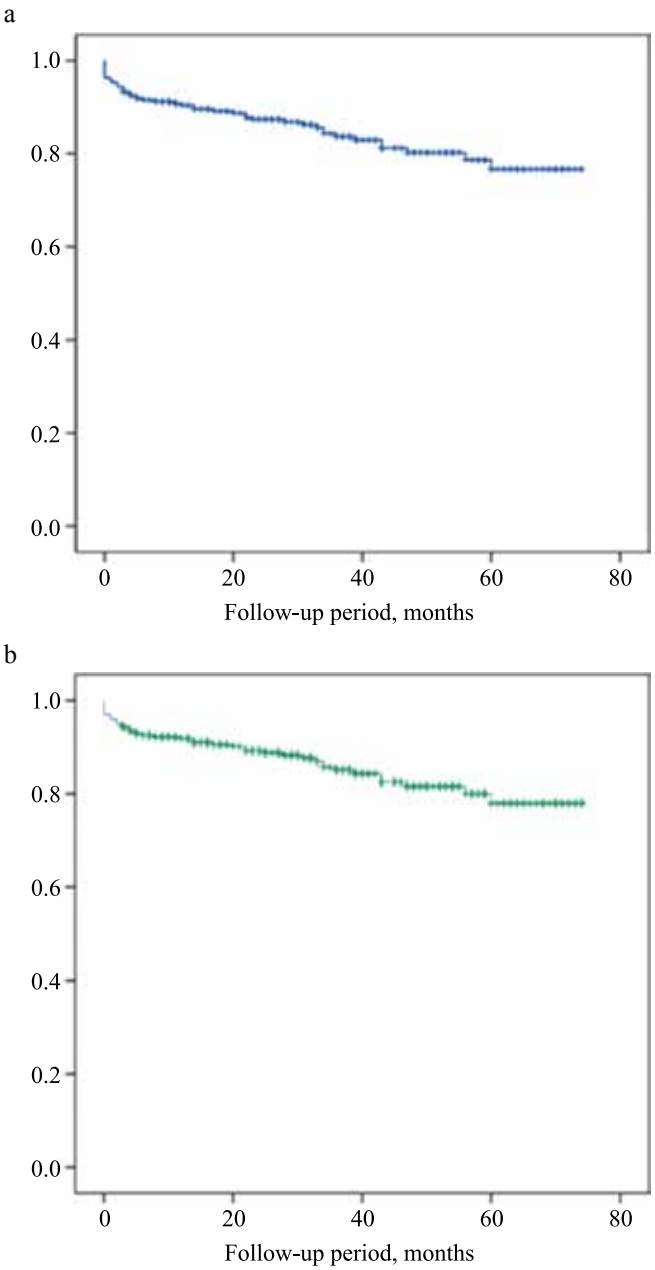
Table 4

Postoperative complications

Indicator	n (%)
Bleeding	25 (8.3)
Arterial complications	
Obstruction	4 (1.32)
Stenosis	4 (1.32)
Thrombosis	7 (2.32)
Biliary complications	
Early stricture	13 (4.3)
Late stricture	8 (2.7)
Fistula	4 (1.32)
Wound infection	26 (8.6)
Re-interventions	60 (19.9)
Rejection	24 (8)
Non-surgical infectious complications	42 (14)
CCI (median, min–max)	0 (0–100)
Bed-day (median, min–max)	17 (1–177)
Retransplantation	5 (1.7)

Identification of risk factors

Based on the data obtained, statistical analysis was performed using single-factor and multifactor Cox regression analysis (Table 5, 6).



n = 301	Month 12	Month 36	Month 60
Graft survival, % (n)	90.4 (227)	83.7 (129)	76.7 (38)
Recipient survival, % (n)	91.8 (231)	85.1 (130)	77.9 (38)

Fig. Survival after liver transplantation. a, graft survival; b, recipient survival

Male gender (HR 0.55; CI 0.3–0.98; p = 0.04) reduced the risk of poor outcome. Carrying drains, intraductal stents, significantly increased recipient mortality (HR 7.203; CI 1.699–30.534; p < 0.01). Acutely decompensated cirrhosis more than doubled the risk (HR 2.52; CI 1.128–5.631; p = 0.02). Creatinine level was the only one of the assessed donor criteria that significantly influenced transplant outcome.

Time characteristics of liver transplantation, magnitude of blood loss, and greater need for transfusion media significantly reduced recipient and graft survival. In the analysis of postoperative laboratory indices, reliability was determined for almost all of the studied values. Among the identified risk factors, the INR has the greatest influence on LT outcomes. A number of postoperative complications also increased the risk of graft loss. Biliary fistulas, non-surgical infectious complications, number of repeated operations, and graft artery thrombosis had the greatest negative prognostic significance.

Based on identified risk factors, a multivariate analysis was performed using the Cox regression model.

According to multivariate analysis, liver donor creatinine levels had a significant effect on LT outcomes (HR 1.004; CI 1.002–1.007; p = 0.016).

DISCUSSION

The association between gender and mortality was shown in a recent large study by Serrano et al.

Table 5

Risk factors (univariate analysis)

Indicator	HR	95% CI	p
Recipient factors			
Age	1.025	0.99–1.05	0.06
Male	0.55	0.3–0.98	**0.04**
BMI	0.96	0.89–1.04	0.37
Thrombophilia	1.631	0.223–11.938	0.63
Portal vein thrombosis	1.424	0.723–2.792	0.31
Disseminated portal vein thrombosis	1.448	0.519–4.039	0.48
Previous surgeries	1.379	0.617–3.083	0.43
TIPS	1.452	0.2–10.554	0.71
Biliary drains/stents	7.203	1.699–30.534	**<0.01**
MELD	1.027	0.992–1.063	0.13
Fulminant liver disease	0.917	0.126–6.65	0.93
Acutely decompensated cirrhosis	2.52	1.128–5.631	**0.02**
Hepatorenal syndrome	1.589	0.885–2.854	0.12
Waiting time	0.91	0.853–0.972	**<0.01**
Donor factors			
Age	0.994	0.97–1.018	0.62
Male	0.873	0.467–1.632	0.67
BMI	1.004	0.952–1.06	0.88
Graft type	0.385	0.053–2.975	0.35
DRI	0.654	0.228–1.871	0.43
DRI >1.7	0.781	0.349–1.746	0.55
ALT	0.996	0.988–1.004	0.36
AST	1	0.997–1.003	0.91
Creatinine	1.004	1.002–1.006	**0.01**
Bilirubin	0.988	0.957–1.021	0.48
Sodium	1.002	0.971–1.034	0.91
Norepinephrine	1	1.0–1.001	0.16
Dopamine	0.941	0.788–1.123	0.5
Steatosis	0.939	0.56–1.573	0.81
Fibrosis	0.675	0.369–1.237	0.2
Intraoperative factors			
Surgery duration	1.005	1.003–1.007	**<0.01**
Preservation time	1.002	1.0–1.005	0.06
Secondary warm ischemia	1.002	0.995–1.008	0.62
Biliary ischemia	1.009	1.004–1.013	**<0.01**
Type of caval reconstruction	0.046	0–13.463	0.29
Blood loss	1	1.0–1.0	**<0.01**
Fresh frozen plasma	1.11	1.055–1.168	**<0.01**
RBC mass	1.28	1.164–1.409	**<0.01**
Postoperative indicators			
Day 1			
ALT	1	1.0–1.001	**<0.01**
AST	1	1.0–1.0	**<0.01**
Bilirubin	1.003	1.001–1.01	**<0.01**
Creatinine	1.004	1.001–1.007	**0.03**
INR	1.998	1.201–3.324	**<0.01**
Day 5			
ALT	1	1.0–1.001	0.29
AST	1	0.999–1.001	0.9
Bilirubin	1.005	1.003–1.008	**<0.01**
Creatinine	1.005	1.001–1.009	**0.01**
INR	4.228	1.392–12.838	**0.01**
Day 30			
ALT	1.001	0.999–1.004	0.28
AST	1.002	0.999–1.004	0.19
INR	4.196	1.564–11.255	**<0.01**
Creatinine	1.004	1.001–1.008	**0.02**
Bilirubin	1.012	1.008–1.017	**<0.01**
Complications			
Re-operations	4.063	2.267–7.823	**<0.01**
Non-surgical infection	4.592	2.526–8.346	**<0.01**
Wound infection	1.722	0.838–3.538	0.14
Rejection	1.04	0.416–2.603	0.93
Bleeding	3.64	1.746–7.591	**<0.01**
Arterial complications (any)	1.967	0.705–5.489	0.2
Arterial graft thrombosis	3.682	1.136–11.93	**0.03**
Biliary complications (any)	2.57	1.199–5.508	**0.015**
Biliary stricture (any duration)	2.067	0.877–4.875	0.1
Biliary fistula	5.619	1.354–23.328	**0.017**
CCI	1.04	1.03–1.049	**<0.01**

Table 6

Risk factors (multivariate analysis)

Indicator	HR	95% CI	p
Recipient factors			
Male	1.665	0.821–3.376	0.157
Biliary stents/drains	0.923	0.318–2.682	0.88
Acutely decompensated cirrhosis	0.179	0.03–1.068	0.06
Donor factors			
Donor creatinine	1.004	1.002–1.007	**0.016**
Intraoperative factors			
Surgery duration	1.001	0.997–1.005	0.61
Biliary ischemia	1.001	0.993–1.008	0.89
Blood loss	1	1.0–1.0	0.53
Fresh frozen plasma	1.037	0.938–1.147	0.47
RBC mass	1.062	0.873–1.292	0.55
Postoperative indicators			
Day 1			
ALT	1	0.999–1.001	0.9
AST	1	1.0–1.0	0.23
Bilirubin	1.001	0.996–1.006	0.65
Creatinine	0.999	0.993–1.005	0.75
INR	1.623	0.756–3.484	0.21
Day 5			
Bilirubin	1	0.994–1.007	0.95
Creatinine	1	0.992–1.008	0.94
INR	0.397	0.069–2.269	0.3
Day 30			
Bilirubin	1.003	0.995–1.011	0.48
Creatinine	1.001	0.995–1.007	0.75
INR	0.589	0.109–3.186	0.54
Complications			
Bleeding	2.067	0.715–5.972	0.18
Arterial graft thrombosis	0.522	0.112–2.429	0.41
Biliary complications (any)	0.62	0.228–1.69	0.35
Biliary fistula	2.762	0.373–20.457	0.32

Male patients are characterized by lower early mortality with higher overall and long-term mortality [17]. Prolonged wearing of conventionally sterile implants increases the risk of infectious complications [18]. Due to the high frequency of inpatient treatment, multiresistant hospital microflora predominate in such recipients [19], which, combined with post-transplant immunosuppressive therapy, causes a high risk of infectious complications with potential generalization [20]. Acute decompensation of liver cirrhosis also increased the risk of recipient death >2.5-fold. Organ dysfunction against the background of existing chronic liver disease is characterized by significant increase in patient mortality [21].

The association of donor creatinine with LT outcomes is reflected, in particular, in the SOFT prognostic scale [22]. However, the mechanism of this effect has not been reliably established. Creatinine level, according to Rogers et al., may reflect the degree of secondary ischemic damage to donor liver parenchyma. However, the authors caution against allocating organs taking into account this factor, emphasizing the need for further research [23]. The lack of influence of DRI on LT outcomes in our study is consistent with later works [24, 25]. Thus, it is possible to raise the question of switching to more modern scales for assessing the quality of organs from brain-dead donors for a more precise allocation depending on recipient's characteristics [22].

Large amount of blood loss and a need for intraoperative blood transfusion are associated with a higher incidence of infectious complications, renal dysfunction and worse survival after LT [26].

The Rostved study showed the prognostic value of MELD in the early post-transplant period to determine the risk of liver graft loss during the first year [27]. The INR value largely reflects the severity of impairment of synthetic function of the graft, which is associated with higher postoperative mortality [28]. The severity of coagulopathy indirectly reflects the degree of multiple organ dysfunction, which is most relevant for patients with septic status [29, 30]. Thus, a higher INR level can serve as a negative prognostic criterion in LT [28, 31].

CONCLUSION

We have identified prognostic risk factors for poor outcome of DDLT. Performing liver transplantation taking into account the data obtained would improve surgery outcomes and help personalize the treatment strategy for each patient.

The authors declare no conflict of interest.

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