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Bilary anastomotic strictures after right lobe living donor liver transplantation: a single-center experience

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ABSTRACT

Objective. To determine the incidence of AS after right lobe living donor liver transplantation with various biliary reconstructions and to identify the predictors of this complication.

Material and methods. A retrospective and prospective analysis included 245 RLLDLTs for the period 2011—2018 at the Burnazjan Federal Medical Biophysical Center. The results of transplantations in 207 patients aged 19—68 years (median 43 years) were assessed. There were 82 men and 125 women. Follow-up period ranged from 10 to 98 months (median 35 months). We analyzed the relationship between surgical characteristics (preoperative data of recipients and donors, graft parameters, technical features of biliary reconstruction and features of post-transplantation period) and incidence of anastomotic strictures. A total of 58 parameters were analyzed.

Results. AS occurred in 20 (9.7%) recipients. Median AS-free period was 5 months (range 1—44). In 17 (85%) patients, AC developed within a year after surgery. Cumulative 1-, 2- and 5-year incidence of AS was 8.3%, 8.9%, and 11%, respectively. Significant predictors of AS were impaired arterial blood supply to the graft (HR 7.8, 95% CI 2.3—26.0, $p<0.001$), biliary leakage ISGLS class B or C (HR 5.0, 95% CI 2.0—12.8, $p<0.001$), early allograft dysfunction (HR 4.2, 95% CI 1.5—11.6, $p=0.006$) and female recipient (HR 3.2, 95% CI 1.1—9.9, $p=0.04$). In our sample, variant biliary anatomy of the graft and recipient liver, as well as technical features of biliary reconstruction did not affect the risk of AS.

Conclusion. Variant biliary anatomy of potential donor alone should not be considered as a contraindication for organ donation and right liver lobe transplantation. Precise surgical technique, high transplantation activity, as well as experience of reconstructive interventions on the bile ducts during other operations can significantly reduce the incidence of AS after RLLDLT up to 9.7%.

Keywords: *biliary anastomotic strictures, living donor liver transplantation, biliary complications of liver transplantation, early allograft dysfunction.*

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Background

Liver lobe transplantation from a living donor is an effective and safe alternative in the context of a deficit of postmortem donor organs. This method is successfully used in clinical practice, including adults. Right lobe living donor liver transplantation is the most common in these cases. Anatomic variability of the bile ducts of the right liver lobe determines certain technical difficulties of biliary reconstruction. There are various methods for reconstruction of the bile ducts depending on the number of bile ducts in the transplant, their mutual arrangement, diameter and characteristics of vessels, as well as anatomy of recipient's ducts, etiology of liver cirrhosis. These and other aspects require careful research analysis, since the incidence of biliary complications compromising postoperative outcomes is still high (18-37% after liver lobe transplantation from a living donor) [1, 2].

Influence of certain features of biliary reconstruction and other factors on the risk of anastomotic stricture (AS) is one of the most relevant issue in liver transplantation. In this regard, we have analyzed own results after liv-

er transplantation and determined the incidence and risk factors of AS in right liver lobe recipients.

Material and methods

There were 245 right lobe living donor liver transplantations for the period from January 1, 2011 to December 31, 2018. All interventions were carried out at the Burnazyan Federal Medical Biophysical Center. Exclusion criteria: transplant failure or death of recipient in early postoperative period ($n = 11$), redo liver transplantation ($n = 2$), follow-up period after transplantation < 10 months ($n = 21$), unavailable data required for analysis ($n = 4$). Thus, our sample included 207 recipients aged 19 — 68 years (median 43 years). There were 82 men and 125 women. Liver cirrhosis was the main indication for transplantation, viral etiology was noted in 94 (45.4%) patients. The follow-up period ranged from 10 to 98 months (median — 35 months). Median age of donors was 31 years (range 18 — 59). Men prevailed (n=119, 57.5%). With the exception of two cases, all donors were identical or compatible by ABO system with a recipient.

Right lobe living donor liver transplantation was carried out in accordance with the internationally accepted technical standards. We would like to distinguish the following technical features associated with the bile ducts. Cautery or energy instruments were not used for dissection of ducts and peribiliary tissues of the transplant, dissection was maximally precise. Prior to scheduled hepaticocholedochostomy, hepatectomy in recipient was associated with dissection of hepatoduodenal ligament, preservation of tissues around the common bile duct and arteries of the duct wall at 3 and 9 hours clockwise. The type and number of biliary anastomoses were determined intraoperatively considering anatomical features of transplant bile ducts, underlying disease of recipient, state of available ducts in recipient including adequacy of their blood supply. In case of multiple adjacent ducts without common wall segment for their ostia, we applied ductoplasty to reduce the number of anastomoses. Anastomosis was sutured in two fashions (continuous or interrupted seams with absorbable 6/0 or 7/0 suture) using optical magnification. The method of biliary anastomosis suturing depended on the bile duct wall structure, its diameter, use of ductoplasty, and localization of the transplant ducts throughout the Glisson's capsule.

AS was confirmed by clinical and laboratory signs of obstructive jaundice, ultrasound, MR cholangiopancreatography and direct percutaneous cholangiography. Biliary leakages were diagnosed and classified in accordance with ISGLS criteria [3]. Type A was excluded from analysis. Early graft dysfunction was recognized using Olthoff criteria [4].

Statistical analysis was carried out using RStudio 1.2.5019 software environment (RStudio Inc.). Quantitative variables are described as mean with standard deviation and 95% confidence interval, or median with interquartile range. Qualitative data are shown as absolute values and percentages. Student's t-test was applied as parametric method to compare quantitative variables in independent samples, Mann-Whitney U-test — as nonparametric test. Fisher's exact test or Pearson's $\chi 2$ test was used to compare qualitative variables. Spearman's rank correlation coefficients were applied in correlation analysis. Effects of predictors on the outcomes were assessed using Cox regression model. Selection of predictors for multivariate model was carried out using "random forest" algorithm after exclusion of predictors with missing data

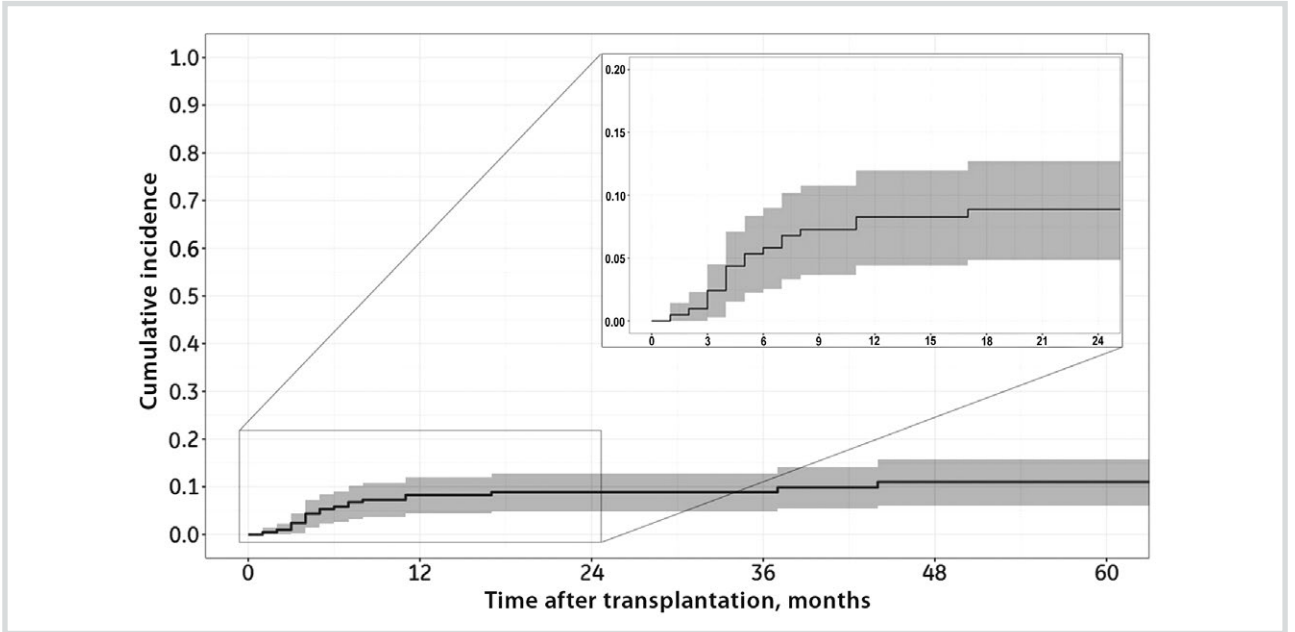


Fig. 1. **Overall incidence of biliary anastomotic strictures.**

and one of predictors with strong significant correlation in each pair. Differences were significant at p-value< 0.05.

Results

AS were diagnosed in 20 (9.7%) recipients in 5 months (range 1 — 44) after right lobe living donor liver transplantation. In most cases (n = 17, 85%), AS developed within a year after surgery. Overall incidence of AS after 1, 2 and 5 years was 8.3%, 8.9% and 11%, respectively **(Fig. 1)**.

We have divided our sample into 3 groups to assess the impact of own experience on the risk of AS: initial 70 operations, the next 70 and the last 67 procedures. In the first group, AS occurred in 7 cases, in the second group — 5 cases, in the third group — 8 recipients. No significant between-group differences were found (p = 0.6).

Baseline characteristics of donors and recipients, features of transplants, biliary reconstruction, early function of grafts, early postoperative complications and schemes of immunosuppressive therapy depending on AS are shown in **Tables 1 — 3**.

Univariate Cox regression models included predictors with p-value <0.2 in baseline between-group comparison. These models showed statistical significance of the following predictors: baseline INR (HR 2.5, 95% CI 1.27-4.88, p = 0.008), baseline MELD score (HR 1.1, 95% CI 1-1.16, p = 0.045), male donor (HR 0.377, 95% CI 0.15-0.95, p = 0.038), total bilirubin in 7 days after surgery (HR 1, 95% CI 1-1.01, p = 0.002), initial graft function on the 7th postoperative day (HR 4.8, 95% CI 1.83-12.5, p = 0.001), biliary leakage (HR 5.1, 95% CI 2.03-12.8, p = 0.0005), arterial complication in postoperative period (HR 8.2, 95% CI 2.94-22.8, p = 0.00005). Cumulative risk plot of a number of predictors based on univariate Cox models is shown in **Fig. 2**.

Initial multiple Cox proportional intensity model was constructed after eliminating the highly correlated variables and identifying a pool of ten the most significant variables using "random forest" algorithm. The variables were excluded from original multiple Cox model using reverse exclusion method to determine a descriptive model and identify cause-and-effect relationships. The parameters of the final descriptive Cox model are presented in **Table 4**.

Considering Cox proportional hazards model, the highest regression coefficients were noted for arterial complication and biliary leakage. Early graft dysfunction and female recipient were significant factors too. Likelihood ratio test showed statistical significance of the model (p <0.001).

Table 1. **Preoperative data of recipients, donors and grafts**

Variable	No AS, n=187	AS, n=20	*p-value*
Age, years	43 (19—68)	44.5 (23—59)	0.98
Female recipient, n (%)	112 (59.9)	13 (65)	0.84
Indication for transplantation, n (%)			0.76
Cirrhosis following viral hepatitis	82 (43.6)	11 (55)	
Cholestatic disease	40 (21.4)	3 (15)	
Cancer	16 (8.6)	2 (10)	
Other	49 (26.2)	4 (20)	
Body mass index	23.5 (14.4—38.3)	24.3 (15—30.8)	0.90
Albumin, g/l	33.3±6.5 (32.4; 34.2)	30.9±6.8 (27.7; 34.1)	0.12*
Total bilirubin, μmol / l	45.8 (5—682)	70.1 (10—502)	0.18*
INR	1.4 (0.9—3.9)	1.6 (1—2.9)	0.001*
Creatinine, μmol / l	68 (29—245)	64.5 (37—134)	0.47
MELD, score	14 (4.8—32.9)	16 (8.5—30.7)	0.03*
MELD-Na, score	16.3 (4—37.4)	18.3 (6.9—31.6)	0.15*
TELV, ml	1404.2 (798.5—2283.8)	1429.7 (1144.2—1789.0)	0.93
Age of donor, years	31 (18—59)	35.5 (21—55)	0.30
Age of donor >50 years	13 (7)	3 (15)	0.2
Female donor, n (%)	75 (40.1)	13 (65)	0.06*
“Female donor — male recipient” pair, n (%)	19 (10.2)	5 (25)	0.06*
Transplant volume, ml	830 (500—1475)	820 (560—1188)	0.70
GRWR, %	1.2 (0.7—2.3)	1.2 (0.8—1.8)	0.62
GV/TELV, %	57.6 (32.8—109.4)	56.3 (39.2—83.6)	0.57

Note. * — p <0.2; TELV — total estimated liver volume, GRWR — graft-to-recipient weight ratio, GV / TELV — ratio of graft volume to total estimated liver volume.

Table 2. **Technical features of biliary reconstruction during right lobe living donor liver transplantation**

Variable	No AS, *n*=187	AS, *n*=20	*p-value*
Number of graft ducts: *n* (%)			0.93
1	58 (31)	7 (35)	
2	97 (51,9)	10 (50)	
⩾3	32 (17,1)	3 (15)	
Number of anastomoses: *n* (%)			0.26
1	142 (75,9)	16 (80)	
2	38 (20,3)	2 (10)	
⩾3	7 (3,8)	2 (10)	
Type of anastomosis: *n* (%)			0.24
Hepaticohepaticostomy	115 (61,5)	16 (80)	
Hepaticojejunostomy	67 (35,8)	4 (20)	
Combined	5 (2,7)	0 (0)	
Ductoplasty, *n* (%)	24 (12,8)	4 (20)	0.49
External anastomosis drainage, *n* (%)	74 (39,6)	8 (40)	0.84
Use of recipient's high-grade ducts for anastomosis, *n* (%)	29 (15,5)	6 (30)	0.12*

Note. * — p <0.2.

Table 3. **Postoperative data**

Variable	No AS, *n*=187	AS, *n*=20	*p-value*
Biochemical blood test in 7 days after liver transplantation:			
Total bilirubin, μmol / l	40 (5—323)	60.7 (12—235)	0.03*
Max ALT in 7 days, U/l	321.5 (105—2163)	358.5 (145—818)	0.59
INR	1.2 (1—11)	1.3 (1—2,3)	0.15*
Early transplant dysfunction, *n* (%)	12 (6,4)	5 (25)	0.015*
Bile leakage (ISGLS type B or C), *n* (%)	47 (25,1)	13 (65)	<0.001*
Stenosis of occlusion of the transplant artery, *n* (%)	5 (2,7)	5 (25)	<0.001*
Features of immune suppression:			
Calcineurin inhibitors: *n* (%)			0.62
Tacrolimus (any form)	170 (90,9)	18 (90)	
Cyclosporin A	11 (5,9)	2 (10)	
No data	6 (3,2)	0	
Glucocorticosteroids, *n* (%)	103 (55)	10 (50)	0.72
Mycophenolates, *n* (%)	6 (3,2)	2 (10)	0.18*
mTOR-inhibitors, *n* (%)	7 (3,7)	0	>0.99

Note. * — p <0.2.

Discussion

Incidence of biliary complications and, in particular, anastomotic strictures, as well as associated risks for both recipient and donor is still high. Moreover, we can equate recipient transplant loss and donor liver lobe loss. According to modern foreign data, incidence of AS after right lobe living donor liver transplantation is 13 — — 31% [1,2]. Akamatsu et al. [5] included 2812 right lobe living donor liver transplantations into one of the largest meta-analyses. Incidence of biliary AS was 19%. In own sample, incidence of biliary AS was significantly lower (< 10%). This is probably due to predominant precise surgical technique of biliary reconstructions by the most experienced surgeons, as well as routine use of some well-known surgical techniques aimed at maintaining an adequate blood supply to the anastomosed ducts: maximum preservation of periductal tissues with choroid plexus during dissection, dissection of ducts without cautery, assessment of arterial blood flow in the duct considering bleeding along the dissection line, the use of microsurgical techniques [6–10].

Graft blood supply impairment occurs in 2-5% of recipients and is more common in early post-transplantation period. Possible adverse events following circulatory disorders are early dysfunction and/or loss of the graft if treatment is not ensured [11]. According to various researchers, arterial blood supply disturbances following arterial thrombosis or severe stenosis is a significant risk factor of AS [12]. In our sample, early and delayed arterial problems were observed in 10 (4.8%) patients. In all cases, these complications were successfully treated surgically (endovascular procedures). Despite successful treatment, arterial complication was the most significant risk factor of AS. Hazard ratio in multivariate Cox hazard model was 7.76 (95% CI 2.32 — 26.00) (p <0.001).

Bile leakage in post-transplantation period is the second common risk factor of AS after arterial complications [5]. According to our data, bile leakage ISGLS type B or C significantly increases the risk of AS (hazard ratio in multivariate regression model was 5.00 (95% CI 1.95 — 12.79, p <0.001)).

Primary liver graft dysfunction, caused by ischemic and reperfusion injury, can develop in 40% of cases and is subdivided into two types: early graft dysfunction (EGD) and primary non-function (PNF) [13]. PNF is an extreme and irreversible form of primary dysfunction, and redo transplantation is the only method to save the patient's life in this case. EGD is a reversible form. However, this event affects survival of patients and grafts and can potentially increase the risk of surgical complications including AS. This hypothesis was confirmed in this study. Indeed, EGD established in accordance with Olthoff criteria [4] showed statistical significance as a risk factor of AS in both univariate and multivariate regression analysis.

Right lobe living donor liver transplantation is one of the most difficult surgical interventions. This is largely due to difficulties in ensuring adequate and reliable bile outflow from the graft. Certain method of biliary reconstruction is often determined during surgery considering multiple factors: underlying disease in recipient, blood supply to the bile ducts, their number, diameter, location in the graft, etc. However, Chok et al. [14] showed that one can achieve the results comparable with "classical" biliary anatomy (including biliary complications) in any variants of donor biliary system anatomy and technically competent approach. That is, surgeon should be ready for any variant of graft biliary architecture during right lobe living donor liver transplantation.

Literature data on the influence of technical features of biliary reconstruction on the risk of AS are extremely contradictory. The following features are considered as risk factors: multiple ducts in the graft [1, 15], multiple anastomoses [16], their type [1, 2, 5], ductoplasty [15], high-grade ducts [17] and temporary transanastomotic external drainage [18, 19]. Equally, there are reports rejecting the effect of these factors on the risk of AS [14, 20–23].

We have analyzed all these factors. However, significant relationship with the risk of AS was not revealed for any predictor.

Influence of preoperative MELD score on the incidence of biliary complications is controversial. Some authors emphasize that baseline MELD score is a risk factor of biliary strictures [1,24], while others refute this thesis [12]. In our sample, there was a tendency to higher incidence of AS in patients with higher baseline MELD score. According to Cox univariate hazard model, augmentation of MELD score by one point increases the risk of stricture by 8% ($p = 0.045$). However, this parameter was not significant in multivariate regression model.

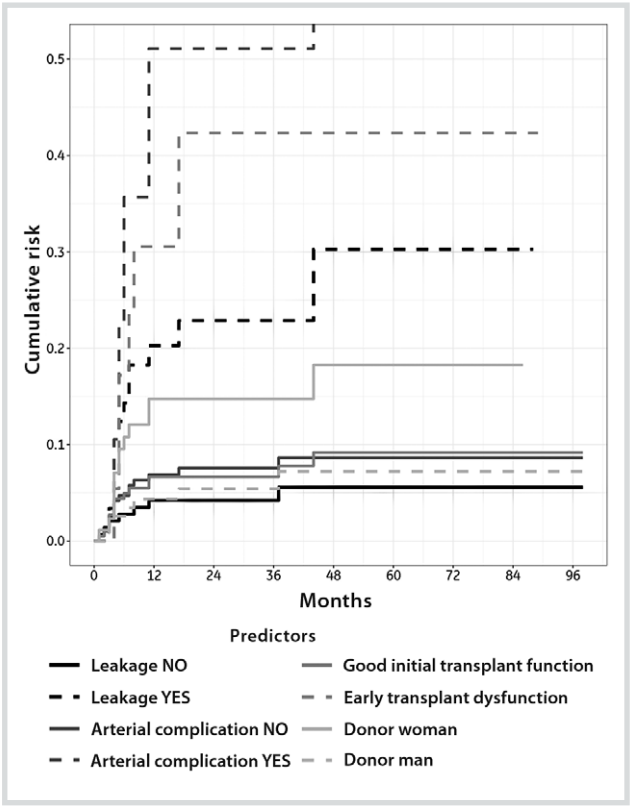


Fig. 2. **Cumulative risk plot of some predictors based on univariate Cox models.**

Incidence of AS was similar in male and female recipients ($p = 0.8$). At the same time, "random forest" algorithm and Cox multiple regression model revealed this factor as significant one. Egawa et al. [25] found similar data. The authors reported higher incidence of biliary strictures in female recipients (12.8% vs. 4.1%, $p = 0.015$). However, considering statistical data in between-group comparison and univariate analysis, this factor should be regarded as a confounder or relationship between gender and other variables should be sought. Further study with larger sample size is required to accurately assess significance of this factor.

Gender mismatch between donor and recipient is found in the literature as a risk factor of various complications, including biliary events. A higher incidence of complications is observed in a pair of female donor — male recipient [26]. We found higher incidence of AS for this pair in between-group comparison and univariate regression model. However, significance was absent in multiple regression analysis.

Table 4. **Multivariate analysis by Cox proportional hazards model**

Predictor	Final Cox proportional hazards model				*p-value*
	Coefficient	Coefficient bias	RR (95% CI)	Wald test	
Graft artery stenosis or thrombosis	2.049	0.6166	7.76 (2.32—26.00)	3.324	0.0009
Early graft dysfunction	1.433	0.5189	4.19 (1.52—11.59)	2.761	0.0058
Bile leakage	1.609	0.4793	5.00 (1.95—12.79)	3.357	0.0008
Female recipient	1.172	0.5741	3.23 (1.05—9.94)	2.041	0.0413

Own experience, regularity and annual number of transplantations (the so-called "learning curve") certainly affect the incidence of complications [27]. Incidence of AS was similar in all three groups (70, 70 and 67, $p = 0.6$). This is due to the fact that surgeons had advanced experience in complex liver resections and other hepatopancreatoduodenal interventions requiring vascular and biliary reconstructions by the moment of living donor liver transplantation program initiation.

Conclusion

The established risk factors of AS should be considered in the management of patients after right lobe living donor liver transplantation, especially within the first year after surgery.

Variant biliary anatomy of potential donor alone should not be considered as a contraindication for organ donation and right liver lobe transplantation.

Precise surgical technique, high transplantation activity, as well as experience of reconstructive interventions on the bile ducts during other surgeries can significantly reduce the incidence of AS after right lobe living donor liver transplantation up to 9.7%.

The authors declare no conflicts of interest.

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