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ON INDICATIONS FOR REPEAT LIVER TRANSPLANTATION

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Objective: to study the causes of graft loss and indications for repeat liver transplantation (rLT). **Materials and methods.** We studied the experience garnered from 250 orthotopic full-size cadaveric liver transplantations in 228 patients from 1998 to 2021. The severity of the patient's condition at the time of intervention was estimated according to the MELD scale. Repeat surgeries were performed in 22 cases in 19 patients (analyzed group). **Results.** Organ preservation parameters, length of stay in intensive care unit (ICU), severity of postoperative complications in primary transplantations in general and in the analyzed group did not differ significantly. The main causes of graft loss were graft arterial insufficiency (57.9%) and hepatic artery thrombosis (21%). Severe early allograft dysfunction (EAD) and primary nonfunction accounted for 10.5%, portal vein thrombosis occurred in 5%, and chronic graft rejection was noted in 5% of cases. **Conclusion.** Arterial insufficiency is one of the leading causes of graft loss after liver transplantation. Early correction of arterial and biliary complications help in preserving graft viability.

Keywords: liver transplantation, liver graft loss, early arterial complications.

INTRODUCTION

Repeat liver transplantations (rLT) are performed in 10–15% of patients with severe graft dysfunction [1]. The most common reason for graft loss is arterial insufficiency of the graft. Acute hepatic artery thrombosis (HAT) without early correction leads to organ necrosis and development of hepatic and then multiple organ failure, sepsis [2]. Chronic ischemia is realized in the formation of multiple biliary strictures (ischemic cholangiopathy, IsC) with a gradual loss of organ function, requiring rLT in the long term [3]. Recurrence of viral, autoimmune hepatitis, hepatocellular carcinoma, chronic rejection, are much less common, and can be conservatively treated over a long period [4, 5]. Primary nonfunction (PNF) of the liver graft remains a separate problem, when only rLT can save the patient.

Objective. To study the possible causes of graft loss and indications for rLT.

MATERIALS AND METHODS

We studied the experience garnered from 250 orthotopic full-size cadaveric liver transplantations (OLT) in 228 patients from 1998 to 2021. There were 104 males and 124 females; their ages ranged from 18 to 64 years (mean, 44.9 ± 7.7 years). The severity of condition of the 228 recipients was assessed using the MELD scale; it averaged 17 ± 6.3 points at the time of intervention (before 2006, OLT were calculated retrospectively). Indications for OLT are presented in Table 1.

Repeat surgeries were performed in 19 patients (analyzed group), *three of them underwent retransplantation afterwards*. Indications for primary OLT were cirrhosis resulting from chronic viral hepatitis (CVH) C (8 cases, 42%), CVH B (3, 15.8%), mixed hepatitis (2, 10.5%), and primary biliary cholangitis (2, 10.5%) respectively. Budd–Chiari syndrome, primary sclerosing cholangitis, unspecified cirrhosis, and alveococcosis were the reasons for primary OLT in 4 recipients. The mean age of the subsequently re-transplanted recipients at the time of primary OLT (9 women and 10 men, 19 to 58 years) was 44.0 ± 10.7 years, MELD severity averaged 17.8 ± 4.8 points, and did not differ significantly between all 228 patients (17.8 ± 4.8 vs 17 ± 6.3 points, $P > 0.05$).

Table 1

Indications for OLT in all recipients

Etiology	n
Hepatitis C cirrhosis	65
Hepatitis B cirrhosis	28
Mixed hepatitis cirrhosis	7
Autoimmune liver disease	22
Cholestatic liver disease	36
Malignant liver tumors	23
Unverified cirrhosis	24
Parasitic liver diseases	2
Budd–Chiari syndrome	4
Wilson–Konovalov disease	2
Toxic hepatitis/cirrhosis	9
Transplant dysfunction	20
Others	8
Total	250

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Statistical comparison of parameters between the groups was performed using Student's t-test; Mann–Whitney U test was used to assess differences. Binary regression was used to identify risk factors of graft loss.

Cold perfusion during organ harvesting was performed with 8–16 liters of custodiol (HTK "Custodiol", Kohler, Germany) cooled to 2–4 °C. If steatosis was suspected, the suitability of the organ for transplantation was reassessed at the end of cold perfusion; if in doubt, an emergency morphological examination of the biopsy sample was performed in 37 cases (15%); *in 12 cases, the quality of the donor organ was unsuitable for transplantation. In our Center (Granov Russian Research Center for Radiology and Surgical Technologies), liver transplantation with more than 50% steatosis diagnosed during an emergency biopsy was practically not performed. Planned histological examination of biopsy specimens of the harvested organ in the main and study groups showed no significant difference.*

OLT stages. After hepatectomy, caval reconstruction was performed in 11 cases according to the piggyback technique, in 5 cases according to the classical technique (inferior vena cava (IVC) resection), and cavostomy in 3 cases. Temporary venous shunting was used in three recipients. Portal vein anastomosis was performed end-to-end. Given the high variability of the arterial anatomy of the hepatic artery, its reconstruction in orthotopic liver transplantation was represented by different variants.

Most often, reconstruction was performed by forming an anastomosis between the recipient's common hepatic artery (CHA) and the donor's native hepatic artery (NHA), 64.4% (n = 161). The second most common variant was anastomosis between the recipient's and donor's native arteries, 22.8% (n = 57). In other cases, peculiarities of arterial revascularization – 12.8% (n = 32) – were caused by the variants of the right hepatic artery (RHA) origin, more rarely by the presence of a significant accessory left hepatic artery (LHA). When the RHA of the donor organ branches off a separate trunk (from the superior mesenteric artery), the reconstruction was performed by forming an anastomosis between the donor RHA and recipient RHA. In this case, the donor CHA anastomosis was performed using both the LHA and recipient CHA. In some cases, an anastomosis between the RHA and the donor's gastroduodenal artery (GDA) was performed for RHA reconstruction. This anastomosis was formed at the "back table" stage. As a rule, the recipient LHA was used to anastomose the donor's accessory LHA, while the recipient RHA was used to anastomose with the donor's CHA or NHA. Most arterial anastomoses were formed with continuous sutures (the parachute technique was used) using Prolen 6/0 thread. A small number of anastomoses were formed with separate knotty sutures using Prolen 7/0–8/0 thread.

Biliary reconstruction using a T-tube was performed in 9 cases, internal drainage in 6, and hepatic enteroanastomosis in 2 patients. In the remaining cases, the ducts were not drained. After OLT, all patients received standard immunosuppression according to the triple scheme: cyclosporine/tacrolimus, mycophenolate/azathioprine, prednisolone. Basiliximab was administered for induction before graft initiation into systemic circulation and on day 4 after the operation. The duration of preservation stages, volume of replacement hemotransfusion, stages of surgery, and length of stay in the ICU were recorded. The degree of graft dysfunction was assessed according to the criteria by P. Salvalaggio et al. (2012) [6], and the severity of general surgical complications was assessed according to the Clavien–Dindo classification (2004) [7, 8].

Arterial insufficiency, established intraoperatively by Doppler flowmetry, was corrected by heparinization of the graft vascular bed, revision or reconstruction of the anastomosis zone, ligation of the gastroduodenal and/or splenic arteries. In the postoperative period, the state of hepatic arterial blood supply was assessed by Doppler ultrasound (DU) and spiral CT scan; correction was based on direct angiography results. Balloon plasty and stenting were used. In cases of biliary complications, we drained the bile ducts, resected them with the formation of hepatic enteroanastomosis or cholangiostomy, and removed necrotized liver tissue.

RESULTS

Repeat transplantations were performed in 19 (8.3%) out of 228 patients, among whom retransplantation was performed twice in three of them. The reasons for rLT were arterial insufficiency of the organ in 11 (57.9%) and HAT in 4 recipients (21%). Cases of early allograft dysfunction (EAD) and PNF were noted in 2 (10.5%), portal vein thrombosis (5%), and chronic rejection (5%) in 1 case each, respectively (Table 2).

The length of ICU stay and the severity of postoperative complications in 19 recipients who subsequently underwent rLT were comparable to all primary 288 OLTs.

Morphological evaluation of native donor liver biopsy specimens was performed in all patients of the analyzed group during primary OLT.

The degree of diagnosed macrovesicular graft steatosis, which was not a contraindication for transplantation, in the analyzed group was also not significantly different from all observations (incidence, 18% vs 16%, $P > 0.05$). In one case, 50% macrovesicular steatosis was not an obstacle to rLT, as the organ was used in a patient with PNF.

Causes of dysfunction varied in the small rLT group.

In the first case, severe EAD was manifested by persistent hyperbilirubinemia (>200 μmol/L) and lack of bile production. Immunosuppression failure resulted in graft rejection in the second recipient. Recurrent portal vein thrombosis in the third case was complicated by late multiple intrahepatic biliary strictures. In cases 4,

5, 6, 8, 11 and 13, the cause of ischemic cholangiopathy was arterial insufficiency of the graft in the late postoperative period. Extra-hepatic biliary-ductal necrosis was detected in 3 patients (No. 7, 16, 18), but there was no pronounced disturbance of arterial blood supply to the liver. Acute HAT with the development of necrotizing cholangitis and liver abscesses was diagnosed in three recipients (No. 9, 14, 15). Splenic artery steal syndrome in the late postoperative period caused intrahepatic biliary strictures in 10 cases. Arterial insufficiency with the formation of early biliary strictures was noted in the twelfth recipient, right portal vein thrombosis led to a sharp deterioration in his condition. Late HAT with the development of ischemic cholangiopathy was diagnosed in the seventeenth case. PNF, severe abdominal compartment syndrome was noted in the last patient. When comparing conservation parameters and intraoperative data, the following results were obtained (Table 3).

As follows from Table 2, median preservation parameters, intraoperative data for primary transplants in the main and analyzed groups did not differ significantly; regression analysis revealed no signs/risk factors of graft

Table 2

Causes of graft dysfunction, ICU length of stay and severity of postoperative period

Patient	Cause of graft dysfunction	ICU (days)	Clavien–Dindo
1. S.	Early graft dysfunction	20	III a
2. I.	Violation of immunosuppression regime, rejection	22	I
3. Z.	Portal vein thrombosis. Cholangiopathy	15	III b
4. M.	Arterial insufficiency. Necrosis of donor part of ducts	10	III a
5. A.	Common iliac artery occlusion. Ischemic cholangiopathy	9	III b
6. K.	Ischemic cholangiopathy	7	III a
7. S.	Necrosis of donor part of ducts	9	III a
8. V.	Critical vertebral artery stenosis. Ischemic cholangiopathy	4	II
9. K.	Early hepatic artery thrombosis. Necrosis of the donor part of ducts	14	III b
10. M.	Late steal syndrome, ischemic cholangiopathy	8	II
11. G.	Vertebral artery stenosis. Ischemic cholangiopathy	5	II
12. O.	Portal vein thrombosis. Arterial insufficiency. Ischemic cholangiopathy	15	III b
13. M.	Arterial insufficiency. Ischemic cholangiopathy	6	II
14. K.	Early hepatic artery thrombosis. Necrosis of the donor part of ducts	25	III b
15. S.	Early hepatic artery thrombosis. Necrosis of the donor part of ducts	13	III a
16. V.	Necrosis of the donor donor part of ducts	6	III b
17. S.	Late hepatic artery thrombosis. Ischemic cholangiopathy	5	III a
18. S.	Necrosis of the donor portion of the ducts	5	III b
19. K.	Primary nonfunction, severe compartment syndrome	7	III b

Table 3

Median graft preservation parameters and intraoperative data for primary transplantation in the main (n = 209) and analyzed (n = 19) groups

Parameters	OLT (n = 209)	OLT (n = 19)	95% CI, P
Cold ischemia (min) IQR	382.5 306–485	375 300–435	P > 0.05
Warm ischemia (min) IQR	45 35–55	50 45–55	P > 0.05
Liverless period (min) IQR	75 60–95	75 60–80	P > 0.05
Arterial revascularization (min) IQR	35 25–50	40 28.75–61.25	P > 0.05
Systolic BP at the start of arterial blood flow	*>100 mmHg – 62%* *<100 mmHg – 38%*	*>100 mmHg – 32%* *<100 mmHg – 68%*	*P > 0.05*
Replacement hemotransfusion (ml) IQR	1193 615–2099	972 412–2519	P > 0.05
Operation duration (min) IQR	445 430–490	515 500–545	P > 0.05
Initial hemoglobin level (g/l) *IQR*	*101* *96–108*	*95* *90–102*	*P > 0.05*

IQR, interquartile range.

loss in both groups. The indicators of systolic blood pressure at the start of arterial blood flow are noteworthy: in the study group, most of the recipients (68%) had blood pressure below 100 mm Hg.

Analyzing bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels at day 0, 3 and 7 following OLT, it should be noted that there were higher values of cytolysis markers in the study group at day 0 and 3 after transplantation (Table 4); however, no significant difference was obtained (p > 0.05).

In the study group, 15 of 19 recipients with evident or latent arterial insufficiency of the graft developed biliary complications within 14 days to 37 months (mean 13.2 months). Before rLT, cholangiodrainage – percutaneous transhepatic drainage (n = 6) and endoscopic drainage (n = 1) – was performed in seven cases. Six patients required resection of necrotic ducts with the formation of an external cholangiostomy. Before rLT, the MELD score of the severity of patients' condition was 21.3 ± 4.6.

It should be noted that late HAT developed in 4 patients (not included in the analysis) after OLT. Regional thrombolysis, multilevel balloon angioplasty, recanalization attempts and arterial stenting were performed. All patients were included in the waiting list. However, the absence of a donor organ, a gradual increase in biliary and infectious complications led to sepsis and death in these patients. Inadequate arterial blood supply to the liver in the long-term period in the 228 OLT was observed in 32 cases, which accounted for 14% of all transplants. In 11 recipients with significant splenic artery steal syndrome, its embolization was performed, which led to a stable positive outcome in 8 cases. Two patients died from infectious complications, one from acute myocardial infarction. Successful correction of arterial insufficiency by balloon angioplasty and stenting was performed in 5 out of 8 cases of hepatic artery stenosis. Three recipients died of sepsis.

An example of an indication for repeat transplantation is a clinical observation where the fight against a series of arterial and biliary complications was a temporary success.

***Patient I.**, 57 years old. Her medical records show that cirrhotic transformation of the liver parenchyma was detected during laparoscopic cholecystectomy in 2014. In February and August 2021, endoscopic ligation was performed for bleeding esophageal varices. Considering the high risk of recurrent bleeding, the patient was hospitalized on September 06, 2021 at Granov Russian Research Center for Radiology and Surgical Technologies for the installation of a transjugular intrahepatic portosystemic shunt (TIPS). On September 8, 2021, the superior mesentericography was performed; celiacography. Conclusion: cirrhosis, portal hypertension, splenic vein thrombosis. Attempted TIPS installation was unsuccessful. Repeat TIPS surgery on September 13, 2021 was deemed technically impossible due to anatomical features.*

On September 18, 2021, the following surgeries were performed: laparotomy according to Dr. Starzl's technique, hepatectomy with preservation of the retrohepatic IVC, orthotopic piggy back liver transplantation, abdominal cavity drainage. Cold ischemia of the organ lasted for 4 hours 40 minutes, warm ischemia was 40 minutes.

Histological report No. 50622/2021 dated September 23, 2021: small nodular liver cirrhosis.

Doppler ultrasonography of the hepatic vessels, which was conducted on September 29, 2021, showed a significant decrease in the volumetric velocity of blood flow through the hepatic artery and increased inflow through the portal vein, signs of splenic artery steal syndrome. On September 29, 2021, superior mesentericography and celiacography were performed (Fig. 1).

The catheter was inserted into the distal part of the splenic artery trunk, six Cook steel coils with a coil dia-

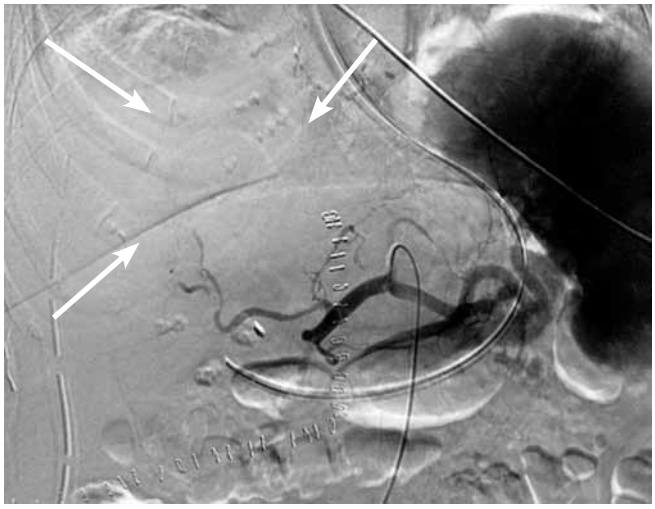

Fig. 1. Celiacography. Impoverishment of arterial architectonics at the segmental level is noted (arrows)

Table 4

Medians of bilirubin levels and cytolysis markers at day 0, 3 and 7 after OLT in primary transplantations in general and in the analyzed group

Indicators	Bilirubin (μmol/l)			ALT (IU/l)			AST (IU/l)		
Day after OLT	0	3	7	0	3	7	0	3	7
Main group (n = 209)	40.7	39.4	37.3	560	429	180	829	244	58
Study group (n = 19	41.7	44.4	36.7	822	585	158	1047	385	69

meter of 8 mm + hemostatic sponge were installed until blood flow was reduced (Fig. 2).

The splenic artery trunk was occluded with steel coils (black arrow). Arterial architectonics is traceable at the segmental level (white arrows).

DU of the hepatic vessels, which was conducted on September 30, 2021, shows a significant increase in the volumetric velocity of blood flow through the hepatic artery and decreased portal vein inflow.

Further control DU of the liver vessels conducted on October 26, 2021 (37 days after OLT) showed decreased linear velocity of blood flow in the native and right hepatic arteries in the absence of clinical and biochemical manifestations. Superior mesentericography and celiacography were performed, hemodynamically significant local narrowing of the native hepatic artery in the anastomotic area was visualized (Fig. 3).

A Medtronic Resolute 3.0 × 26 mm self-absorbable stent was placed coaxially to the stricture zone. Stenting was performed (Fig. 4).

According to the control DU of the hepatic vessels, which was conducted on October 27, 2021, there was a positive dynamics – acceleration of arterial blood flow in the NHA and the right branch of the hepatic artery. Free fluid between the left lobe of the liver and the stomach up to 300 ml was visualized. Ultrasound-guided puncture and catheter drainage of fluid accumulation was performed, 350 ml of the discharge with bile admixture was evacuated. The drainage yielded 400 ml of bile within a day. Magnetic resonance cholangiopancreatography conducted on October 28, 2021 visualized a defect in the common bile duct up to 5 mm with bile leakage into the abdominal cavity.

Relaparotomy, revision, irrigation of the abdominal organs, excision of the necrotic section of the common bile duct were performed. Hepatico-jejunal anastomosis was formed on a Roux-disconnected loop of small intestine, with Felker drainage of lobar bile ducts and Braun intestinal anastomosis.

Histological report #51548/2021 dated November 3, 2021: bile duct fragment with piecemeal necrosis, inflammatory infiltration.

Control fistulocholangiography that was conducted on November 08, 2021: adequate contrast enhancement of the bile ducts in both lobes of the liver. There are no leakages into the abdominal cavity.

Fig. 2. Control celiacography after splenic artery embolization

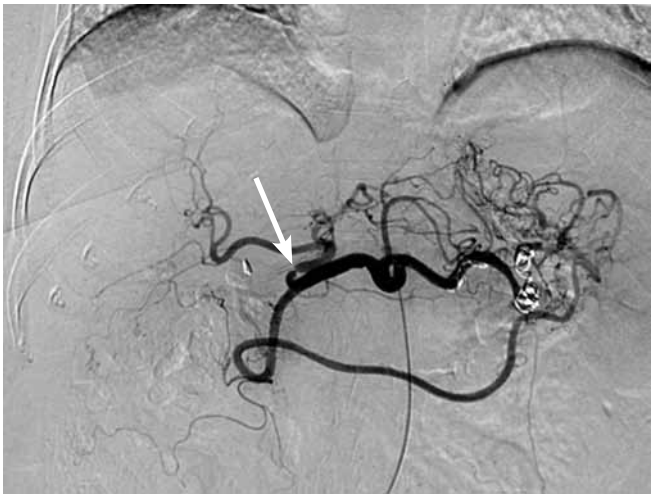

Fig. 3. Celiacography at day 37 after OLT. Hepatic artery stenosis (arrow) and impoverishment of the arterial pattern at the segmental level were revealed in comparison to the previous study

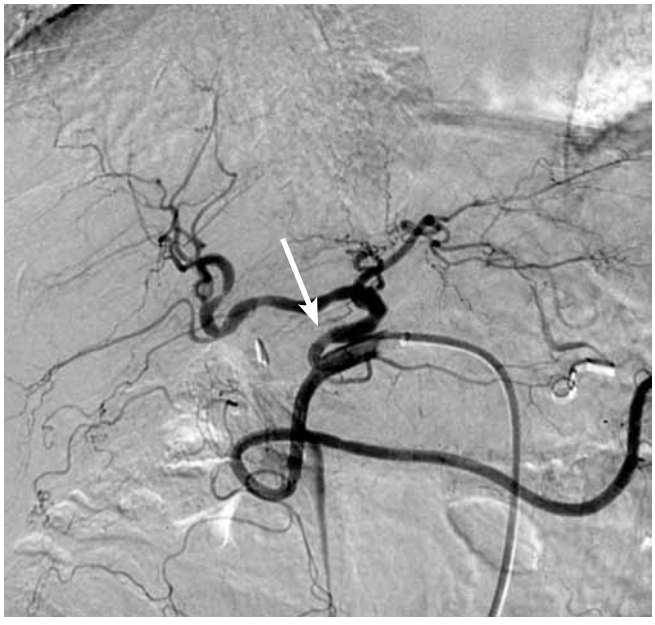

Fig. 4. Control hepatic arteriography. Hepatic artery stenting (arrow), stenosis eliminated, segmental arterial architectonics restored

DU that was conducted on November 12, 2021 showed there was a significant decrease in the volumetric blood flow through the hepatic artery.

Control celiacography and hepatic arteriography were performed. (November 12, 2021). GDA is found to be stealing hepatic blood flow, and there is decreased liver perfusion. In order to redistribute blood flow, the GDA was embolized – 4 Cook microcoils with a coil diameter of 6 mm were installed (Fig. 5).

Felker drains were removed on December 08, 2021. The patient was discharged on day 82 after OLT.

Blood tests at discharge: creatinine, 53.3 μmol/l; total bilirubin, 12.3 μmol/l; ALT, 7 units/l; AST, 12 units/l; albumin, 28 g/l. Tacrolimus concentration, 3.5 ng/ml. The patient had COVID-19 in February 2022 in a mild form with leukopenia 1.5–3.5 × 10^9/L, which required withdrawal of mycophenolic acid. In mid-March 2022, she noted jaundice. Liver DU conducted on March 29, 2022 showed no evidence of vascular complications in the graft, bile ducts were not dilated. Blood tests conducted on April 04, 2022: total bilirubin 470.4 μmol/L, ALT 1356 units/L, and AST 1172 units/L. Liver biopsy was carried out on April 5, 2022. Histological report #54845: liver tissue column with multiple piecemeal necrosis of hepatocytes. Diffuse lymphoplasmacytic infiltration of the stroma, most pronounced in the area of necrosis. Intracellular cholestasis. Protein degeneration of hepatocytes, areas of necrobiosis. Portal tracts were not revealed. Control celiacography, hepatic arteriography was performed (April 12, 2022). Decreased perfusion of the liver, distinct changes in the segmental arteries were noted (Fig. 6).

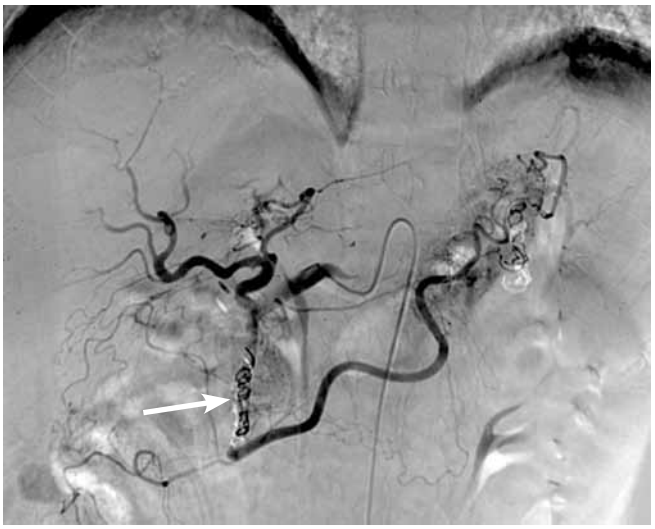

Fig. 5. Celiacography. Gastroduodenal artery occluded with metal coils (arrow). Obstruction of hepatic blood flow by the gastroduodenal artery was eliminated

Fig. 6. Celiacography. Segmental arteries are clearly altered (arrows), with no pulse wave

In dynamics, there was an increase in hyperbilirubinemia up to 508 μmol/l (April 19, 2022). In order to assess liver function, the patient was tested with indocyanine green, plasma elimination rate was 2.6% per 1 min. Without repeat transplantation, further treatment seems to be unpromising, the patient was waitlisted for liver transplantation.

Currently, 9 (47%) out of 19 patients who underwent rLT are alive. The follow-up period ranged from 17 to 138 months. Graft function in the majority of recipients was considered satisfactory.

DISCUSSION

According to the results of the study, the proportion of recipients with rLT was 8.3%, which corresponds to the data of published works by national and foreign authors [9, 10]. It should be noted that over the past decade, the proportion of causes, such as relapses of viral, autoimmune hepatitis, rejections, resulting in the need for rLT, has decreased significantly. The rationale for this is the use of modern effective antiviral therapy drugs and immunosuppression [11–13]. In PNF, the lack of a donor organ remains an unsolved problem due to its shortage, imperfect allocation system and distribution between regions.

After 19 primary OLTs in patients who subsequently underwent repeat transplantation, PNF and severe EAD were observed in 2 cases. Relatively stable condition of the recipient and absence of severe infectious complications allowed to perform repeat transplantation after 8 and 21 days, respectively.

Analyzing all cases of severe graft dysfunction (13 of 228, 5.7%), its relatively low proportion can be explained by a small number of harvested organs from marginal donors, weighted interpretation of the result of emergency morphological examination of a harvested organ in case of doubt about its suitability. It should be noted active management of patients in the waiting list, aimed at improving the functional status in preparation for rLT,

as well as correction of post-transplant complications. In part, this provision can be confirmed by the fact that the severity of the condition of patients before rLT is comparable to that of the recipients before primary OLT; according to our data, MELD score was 21.3 ± 4.6 vs 17.8 ± 4.8 (P > 0.05).

In the majority of our cases (79%), the causes of graft loss were HAT (n = 4) and arterial insufficiency (n = 11). These problems were manifested in the formation of donor bile duct necrosis in the early postoperative period and multiple intrahepatic biliary strictures in the long term. Complications required repeat interventions – duct resection with external bile drainage, cholangiodrainage with numerous sessions of balloon angioplasty and stenting. Unfortunately, patients with late HAT (n = 4), significant hepatic artery stenosis (n = 3) and splenic artery steal syndrome (n = 2) that were not in the analyzed group died from infectious complications without waiting for repeat transplantation or effective endovascular correction [14].

CONCLUSION

Arterial insufficiency of the liver graft, which involves HAT, hepatic artery stenosis, and splenic artery steal syndrome, is a negative predictor of liver graft loss. To preserve the viability of the transplanted organ, diagnosing it as early as possible is extremely important. Despite the fact that adequate arterial blood supply can not always be achieved, it is necessary to use all available methods of surgical and endovascular correction of blood flow. Therefore, early diagnosis of arterial insufficiency is one of the key links in predicting graft dysfunction.

In this regard, active control and correction of arterial and biliary complications greatly contribute to liver function stabilization and, consequently, to graft preservation.

The authors declare no conflict of interest.

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