DOI: 10.15825/1995-1191-2022-2-23-30

LIVER TRANSPLANT PROGRAM AT BOTKIN HOSPITAL. EXPERIENCE OF 100 SURGERIES

A.V. Shabunin[1, 2], I.P. Parfenov[2], M.G. Minina[1], V.V. Bedin[1, 2], P.A. Drozdov[1], O.N. Levina[1], G.S. Mikhayliants[2], I.V. Nesterenko[1], D.A. Makeev[1], O.S. Zhuravel[1], N.A. Ongoev[1]

[1] Botkin City Clinical Hospital, Moscow, Russian Federation

[2] Russian Medical Academy of Continuous Professional Education, Moscow, Russian Federation

Objective: to present an analysis of the results of 100 cadaveric liver transplants performed at Botkin Hospital from July 2018 to October 2021. **Materials and methods.** From July 2018 to October 2021, 100 orthotopic liver transplantation (LTx) from a deceased donor were performed at the surgical clinic of Botkin Hospital. The recipients were 58 males (58%) and 42 females (42%). The mean age of the recipients was 48.73 ± 8.56 (24–66) years, while their mean MELD was 19.54 ± 4.35 (15–33). The main indications for LTx were cirrhosis resulting from chronic viral hepatitis (CVH) C (52%), nutritional-toxic cirrhosis (20%), autoimmune liver and bile duct disease (18%), CVH B (7%), and hepatocellular carcinoma (HCC) (3%). During the period under study, 119 potential liver transplant donors were evaluated. The mean age of the donors was 44.2 ± 11.12 (21–63) years. Median levels of sodium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin were 141 (138–146) mmol/L, 27 (20.7–47.4) units/L, 25 (17–41.5) units/L, and 9.65 (6.42–13.7) μmol/L, respectively. The median graft hepatic steatosis was 10% (5–15). LTx was performed using the piggyback technique (99/100 cases) and classic technique with inferior vena cava resection (1/100). End-to-end porto-portal vein anastomosis was performed (99/100 cases). Anastomosis of the donor organ's portal vein with the recipient's left gastric vein due to occlusive thrombosis of the recipient's portal vein was carried out (1/100). In all cases, a continuous end-to-end arterial anastomosis was formed. End-to-end choledochocholedochal anastomotic strictures (95/100) and end-to-side hepaticojejunostomy (5/100) were formed. **Results.** Median cold ischemia time was 312.5 minutes (280–380). Mean operative time was 488.91 ± 65.34 (95% CI: 475.9–501.9) minutes, median intraoperative blood loss was 1000 (600–1500) mL. Thirty-day mortality was 2% (Clavien–Dindo class V). Early postoperative complications (Clavien–Dindo class IIIa–IVa) developed in 12/100 patients (12%). Graft arterial thrombosis occurred in 3 cases (3%), biliary anastomotic strictures in 6 (6%), and subhepatic hematoma in 2 (2%). The average intensive care unit (ICU) bed day was 2.34 ± 1.67 (1–8). Total postoperative bed-day was 14.63 ± 5.35 (10–39). During case follow-up, a prolonged form of calcineurin inhibitor (CNI) was administered as immunosuppressive therapy in mono regimen (85 patients), in combination with mycophenolic acid derivatives (7), and in combination with everolimus (6). Of the 93 patients, 46 patients (49.46%) had the new coronavirus infection (COVID-19) before or after transplantation; in no case did COVID-19 lead to death. Six patients (13.04%) were hospitalized due to COVID-19. To date, 33/93 (25.48%) patients have been vaccinated, resulting in 75 (75%) liver transplant recipients immune to COVID-19. The overall 1-year survival rate was 95% and the 3-year survival rate was 91%. **Conclusion.** Introduction of LTx in multidisciplinary hospitals allows to, already at the start of the program, achieve immediate and long-term treatment outcomes (in decompensated diffuse liver disease) that are comparable to those of leading transplantation centers.

Keywords: liver transplantation, Botkin Hospital, survival rate.

INTRODUCTION

A little more than half a century has passed since the first successful LTx by the great surgeon Thomas Starzl (USA, 1967). Since then, LTx has become a standard procedure for patients with end-stage liver disease. To date, more than 80,000 LTx operations have been performed worldwide [1]. According to the 2020 European Liver Transplant Registry (ELTR), the 1-, 5-, 10- and 20-year patient survival are 90%, 72%, 61% and 40%, respectively [2]. Along with active development in surgical and anesthesiological techniques, similar results were achieved due to development and introduction of modern immunosuppressive drugs, preservative solutions, perfusion devices, etc. Despite shortages in donor organs, the indications for LTx are expanding, and the progress of medical science allows to identify more and more candidates for LTx. Therefore, development of organ donation is a priority for transplant surgeons around the world.

The Russian Federation is not among the world leaders in terms of donor activity and number of liver

Corresponding author: Pavel Drozdov. Address: 15/8, Brusilova str., Moscow, 117148, Russian Federation. Phone: (962) 985-04-41. E-mail: dc.drozdov@gmail.com

transplant surgeries per million population. However, the situation has significantly improved over the past 10 years. Every year, due to the enormous demand for this type of medical care, more and more LTx programs are opening in multidisciplinary hospitals in different regions of the country [3].

The first LTx at Botkin Hospital was performed in July 2018. Over the 3 years of existence of the transplant program, we have managed to implement an algorithm by which patients receive quality medical care at all stages: from examination and inclusion in the waiting list to discharge from the hospital with a functioning transplant and subsequent regular outpatient follow-up [4]. A large flow of patients with end-stage liver disease, active development of organ donation in Moscow, and coordinated work by a multidisciplinary team of specialists have all allowed us to cross the threshold of 100 operations as of October 2021. In this paper, we have summarized and analyzed the experience of 100 cadaveric liver transplants performed at Botkin Hospital from July 2018 to October 2021.

MATERIALS AND METHODS

From July 2018 to October 2021, 100 orthotopic liver transplants from a deceased donor were performed in the surgical clinic of Botkin Hospital. The recipients included 58 men (58%) and 42 women (42%). The mean age of the recipients was 48.73 ± 8.56 (24–66) years. The mean MELD of the recipients was 19.54 ± 4.35 (15–33). Among the etiological factors that led to cirrhosis, chronic viral hepatitis C prevailed, 52% (Fig. 1).

During the period described, 119 potential liver transplant donors were evaluated. To assess the suitability of a liver transplant, we evaluated the donor's laboratory parameters, ultrasound findings with the assessment of echogenicity of the liver parenchyma, visual assessment of the graft before and after cold perfusion, and emergency histological examination. Grafts with the presence of hepatic steatosis of more than 50% of the liver parenchyma were considered unsuitable for transplantation. Predictors of this condition were: elevated levels of AST, ALT, total bilirubin in the donor, increased echogenicity of the liver during ultrasound examination (Fig. 2), and jaundice coloration of the liver after cold perfusion (Fig. 3). The final decision on the suitability of the organ for transplantation was made on the basis of histological examination (Fig. 4). 100/119 liver grafts were found suitable for transplantation.

The mean age of the donors was 44.2 ± 11.12 (21–63) years; 85 donors (85%) had vasopressor support at the time of explantation. Median sodium, AST, ALT, and bilirubin levels were 141 (138–146) mmol/L, 27 (20.7–47.4) units/L, 25 (17–41.5) units/L, and 9.65 (6.42–13.7) mmol/L, respectively. The median time spent by the donor in the hospital was 48 (26–78.5) hours, and the median percentage of hepatic steatosis was 25 (15–30).

LTx was performed using the piggyback method (99/100 cases) and classic technique with inferior vena cava resection (1/100) due to HCC invasion. Separation of the end-to-side splenorenal anastomosis at the stage of hepatectomy (2/100 cases) and the side-to-side mesocaval anastomosis (1/100) were done. These anastomoses were previously formed to prevent portal hypertension complications. End-to-end porto-portal vein anastomosis (99/100 cases) was formed, in two of them against the background of partially recanalized thrombosis of the main portal vein trunk. Anastomosis of the donor organ's portal vein with the recipient's left gastric vein (1/100) was formed due to occlusive thrombosis of the recipient's portal vein. In 21 cases (21%), given the

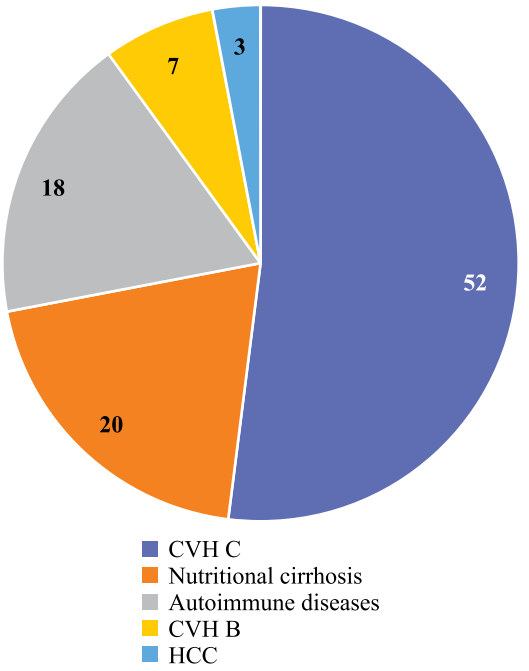


Fig. 1. Etiological structure of indications for LTx at Botkin Hospital (%)

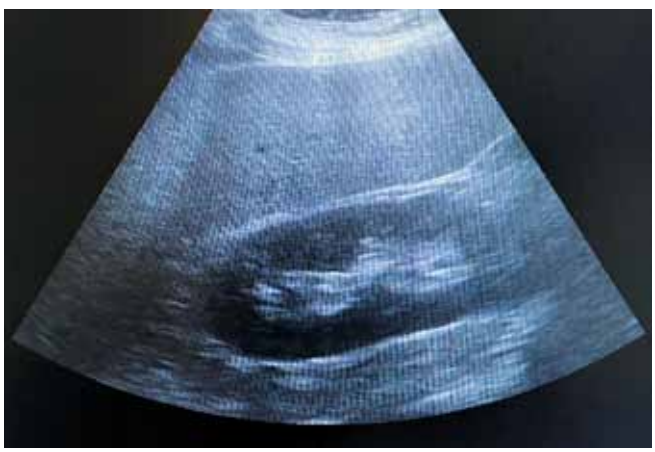


Fig. 2. Liver ultrasound in a potential donor. Increased liver echogenicity

specific arterial anatomy of the donor liver, a back-table vascular reconstruction was required (Figs. 5 and 6).

A continuous end-to-end arterial anastomosis was formed in all cases. Nodal end-to-end choledochocholedochal anastomosis was formed in 92 cases, continuous end-to-end choledochocholedochal anastomosis in 3 cases, nodal end-to-end hepaticojejunal anastomosis was formed in 5 cases in patients with autoimmune liver disease and common bile duct involvement.

RESULTS

Median cold ischemia time was 312.5 (280–380) minutes. Median operative time was 488.91 ± 65.34 (95% CI: 475.9–501.9) minutes, median intraoperative blood loss was 1000 (600–1500) mL. Thirty-day mortality was 2% (Clavien–Dindo class V). One death occurred from lightning-fast septic condition on postoperative day 3, another death resulted from acute heart failure on postoperative day 4. In addition, there were 12 complications (12%) that did not lead to death in the early postoperative period (Table). In 6 cases, the complications were managed by minimally invasive treatment, while relaparotomy was required in the other 6 cases (6%). So, there were postoperative complications in 14% of cases.

The average ICU bed-day was 2.34 ± 1.67 (1–8); total postoperative bed-day was 14.63 ± 5.35 (10–39). The long-term period had an immunological complication – acute humoral rejection with graft dysfunction, which was stopped by increasing immunosuppressive therapy, cascade plasmapheresis sessions with administration of immunoglobulins and rituximab.

Fig. 3. Intraoperative photo. Liver after cold perfusion. Jaundice coloration as a sign of hepatic steatosis

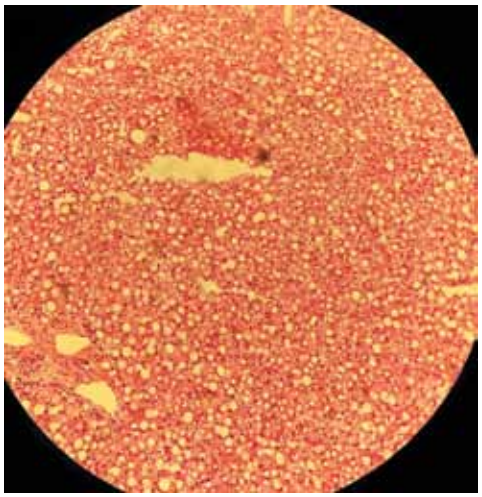


Fig. 4. Emergency histological examination. Over 80% hepatic steatosis. Organ unsuitable for transplantation

Fig. 5. Intraoperative photo, back-table stage. Graft arterial anatomy (Michels type III) – replacing the right hepatic artery originating from the superior mesenteric artery

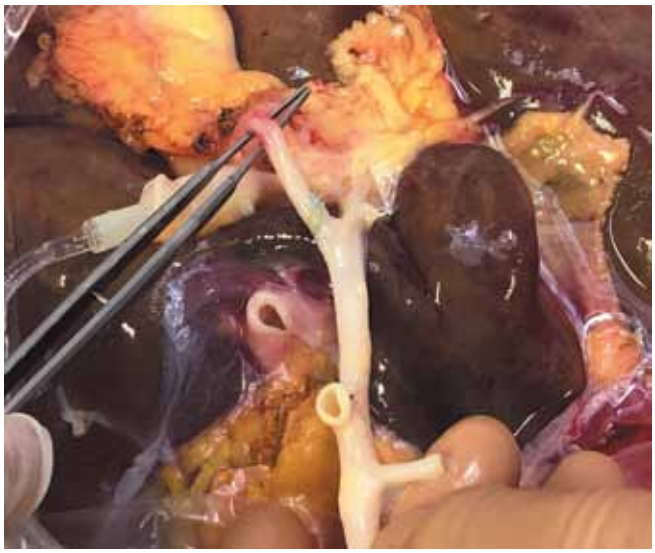


Fig. 6. Intraoperative photo, back-table stage. Vascular reconstruction of the hepatic graft. Anastomosis between the gastroduodenal artery and right hepatic artery

During case follow-up, a prolonged form of calcineurin inhibitor (CNI) was administered as immunosuppressive therapy in mono regimen (85 patients), in combination with mycophenolic acid derivatives (7), and in combination with everolimus (6).

In the long-term period, there were 5 deaths between month 3 and 21 after surgery. The overall 1-year and 3-year survival rates were 95% and 91%, respectively (Fig. 7).

Of the 93 patients under case follow-up, 46 recipients (49.46%) had COVID-19 before or after transplantation; in no case did COVID-19 lead to death after LTx. Six patients (13.04%) were hospitalized due to COVID-19. A total of 33/93 (25.48%) patients were vaccinated, of which 9/46 (19.5%) were vaccinated after the disease. The number of liver transplant recipients immune to COVID-19 was 75 (75%).

DISCUSSION

Liver transplantation is the gold standard of treatment for end-stage diffuse liver disease. Increasing the availability of transplantation care for this category of patients is an important step towards improving long-term treatment outcomes in this group of patients. Over the last few years, the number of effective donors in Moscow has doubled, reaching 20.9 per million population in 2020, which correlates with figures obtained by leading European countries. The opening of a new transplantation center at Botkin Hospital was a reasonable step for Moscow health care following the dramatic increase in the number of donor organs [5].

The multidisciplinary nature of the hospital was the key factor that made it possible to successfully start and actively develop the LTx program.

Table

Postoperative complications after orthotopic LTx at Botkin Hospital

Complication	Number, %	Clavien–Dindo	Correction method
Ascitic leak	1 (1%)	IIIa	Abdominal drainage
Arterial thrombosis	1 (1%)	IIIa	Endovascular balloon dilatation with stenting
Subhepatic hematoma	2 (2%)	IIIb	Relaparotomy, stopping bleeding
Ischemic cholangiopathy	1 (1%)	IIIb	Bilateral retrograde stenting with plastic stents
Hepaticojejunostomy stricture	1 (1%)	IIIb	Hepaticojejunostomy reconstruction
Biliary anastomotic stricture	3 (3%)	IIIb	Stricture stenting with a nitinol stent
Biliary anastomotic stricture	1 (3%)	IIIb	Hepaticojejunostomy formation
Arterial thrombosis	2 (2%)	IVa	Retransplantation
Heart failure	1 (1%)	V	
Sepsis	1 (1%)	V	
Total:	14 (14%)		

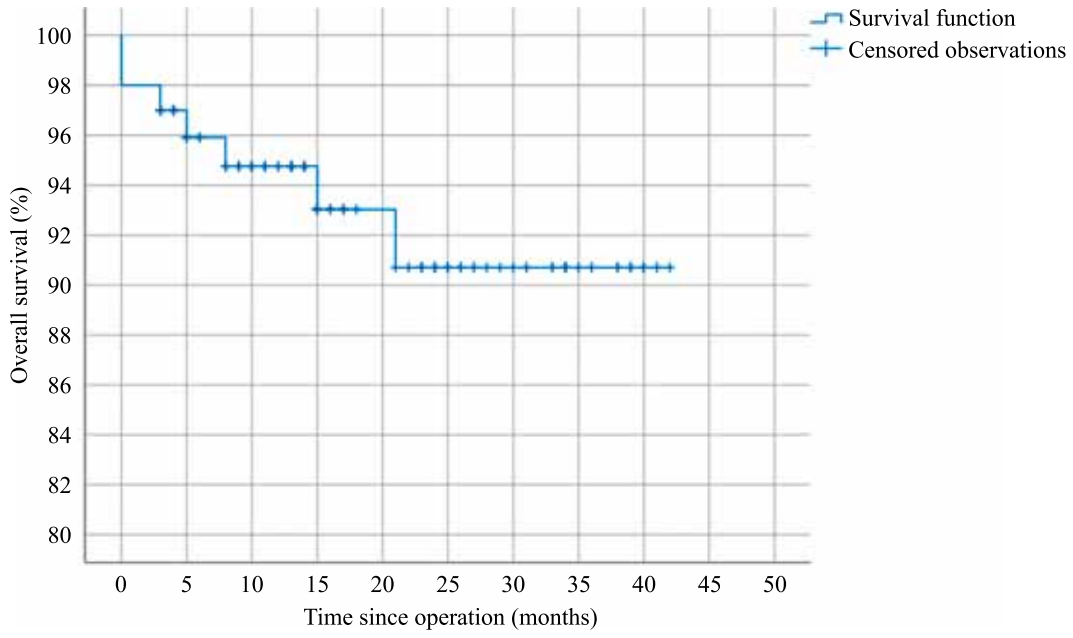


Fig. 7. Overall liver transplant survival rate

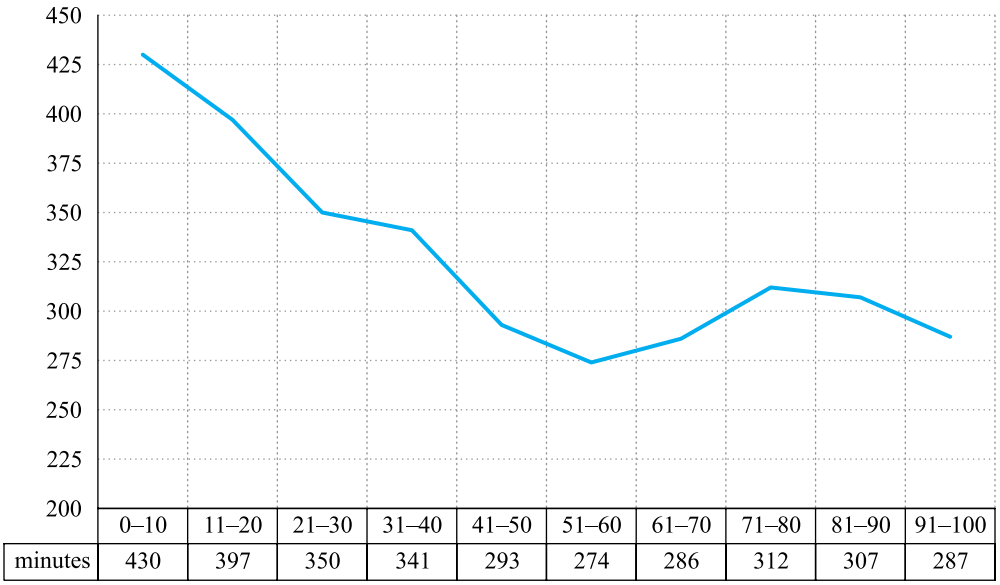
LTx is an emergency surgical intervention. At the time of surgery, transplant surgeons have sufficient information about the anatomy and functional state of the recipient's liver, but the team receives information about the anatomy and functional state of the liver graft only at the stage of explantation, and any deviations from the norm require informed, weighted, but quick decisions.

To assess the time of acquiring stable skills by the medical team providing liver transplantation medical care, we chose the cold ischemia time as an indicator, as it depends on the work of the organ explantation team, anesthesiologists, operating nurses, teams performing pre-transplant preparation of the liver transplant and hepatectomy (Fig. 8).

It can be seen from the graph that by the 40th operation, the average cold ischemia time had decreased to 293 minutes, which is slightly less than 5 hours, and then did not change significantly. This suggests that the surgical team acquires stable skills by the 40th operation.

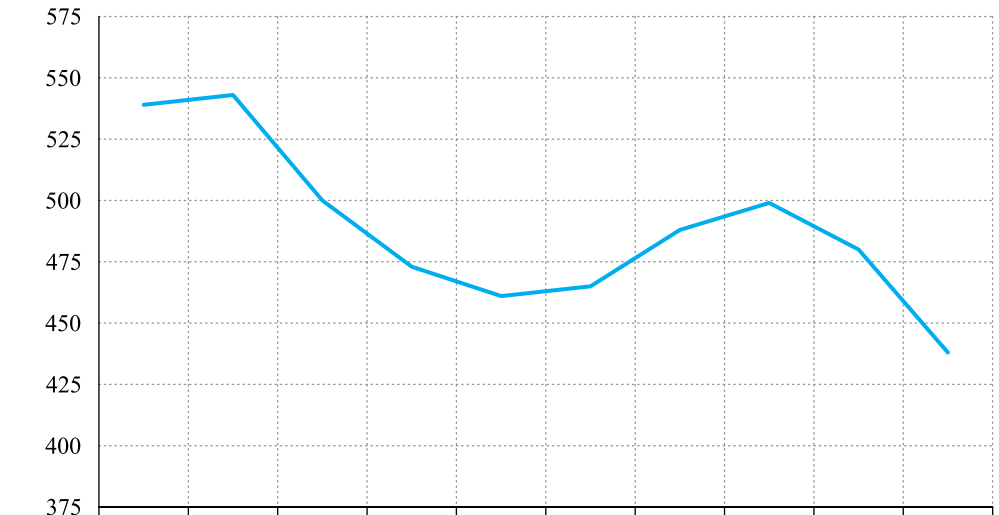
The surgical team directly encounters so many non-standard situations, which cannot be predicted at the preoperative stage: the severity of fibrous adhesions between the liver and the retrohepatic segment of the inferior vena cava, the level and diameter of the arterial junction, the nature of biliary reconstruction – biliary-biliary anastomosis, hepaticojejunal anastomosis.

We evaluated surgeons' learning curve for a new surgical intervention at the time of surgical intervention in the recipient (Fig. 9).



	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100
minutes	430	397	350	341	293	274	286	312	307	287

Fig. 8. Learning curve for liver transplant care teams



	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100
minutes	539	543	500	473	461	465	488	499	480	438

Fig. 9. Learning curve for transplant surgeons

The graph shows that by the 30th transplantation, the average time decreased to 473 minutes, then there was a second rise in the average operation time, which characterized the training of the second liver transplantation surgical team; it began to decrease also by the 30th operation. Thus, the learning curve of the liver transplantation surgical team was 30 operations.

Analysis of postoperative complications shows that the main part of them are complications of arterial and biliary anastomosis – 9/14 (64%). Development of the liver transplantation program in the multidisciplinary hospital allowed to stop most of these complications (5/9 (55.5%)) by minimally invasive treatment methods. The use of a coated nitinol stent with a short insertion time, a technique developed and first introduced in the Russian Federation in the surgical clinic of Botkin Hospital, demonstrated its safety and efficiency in the treatment of anastomotic bile duct strictures after orthotopic LTx [6]. The only experience of X-ray endovascular treatment of arterial thrombosis did not demonstrate its effectiveness in the long-term period regarding the condition of intrahepatic bile ducts. That is why in 2 patients where this complication reoccurred, LTx was performed with good long-term outcomes.

Case follow-up of liver transplant recipients is an important function of the transplant center. According to our data, liver transplant recipients compared to kidney recipients have a low risk of immunological complications in the long-term period. However, despite this, the transplantation center should have all the necessary laboratory, instrumental and drug support to stop graft rejection in this group of patients in order to prevent graft loss. A multidisciplinary hospital with the involvement of a multidisciplinary case conference certainly offers an advantage in the treatment of this type of complications as well.

Long-term survival rates are comparable to those in leading transplantation centers in Russia and the world [7–9], which is primarily due to the possibility of involving a multidisciplinary team for post-transplant management.

Our center has recently been focusing on educating patients before and after LTx on the importance of vaccination against COVID-19. Currently, 75% of our recipients are immune to SARS-Cov-2. None of our post-transplant recipients who have been vaccinated have had side effects. Meanwhile, the efficacy of various vaccines in liver transplant recipients needs to be investigated in the future. Currently, 88% of Botkin Hospital patients on the waiting list for cadaveric liver transplantation are immune to COVID-19.

CONCLUSION

Introduction of LTx in multidisciplinary hospitals allows to, already at the start of the program, achieve immediate and long-term treatment outcomes (in decompensated diffuse liver disease) that are similar to those of leading transplantation centers.

The authors declare no conflict of interest.

REFERENCES

1. The European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. 2018. https://doi.org/10.1016/j.jhep.2018.03.024.
2. European Liver Transplant Registry (http://www.eltr.org/).
3. *Gautier SV, Khomyakov SM.* Donorstvo i transplantatsiya organov v Rossiyskoy Federatsii v 2019 godu. XII soobshchenie registra Rossiyskogo transplantologicheskogo obshchestva. *Vestnik transplantologii i iskusstvennykh organov*. 2020; 22 (2): 8–34. https://doi.org/10.15825/1995-1191-2020-2-8-34.
4. *Shabunin AV, Parfenov IP, Minina MG, Drozdov PA, Nesterenko IV, Makeev DA, Zhuravel' OS.* Programma transplantatsii Botkinskoy bol'nitsy: opyt 100 transplantatsiy solidnykh organov. *Vestnik transplantologii i iskusstvennykh organov*. 2020; 22 (1): 55–58. https://doi.org/10.15825/1995-1191-2020-1-55-58.
5. *Shabunin AV, Parfenov IP, Minina MG, Drozdov PA, Levina ON.* V Botkinskoy bol'nitse startovala programma po transplantatsii pecheni. *Effektivnaya farmakoterapiya*. 2019; 15 (2): 50–53.
6. *Shabunin AV, Korzheva IYu, Chechenin GM, Lebedev SS, Drozdov PA, Zhuravel' OS, Astapovich SA*. Pervyy opyt primeneniya pokrytykh samorasshiryayushchikhsya nitinolovykh stentov dlya lecheniya anastomoticheskikh striktur zhelchnykh protokov posle ortotopicheskoy transplantatsii pecheni. *Al'manakh klinicheskoy meditsiny*. 2020; 48 (3): 171–176. https://doi.org/10.18786/2072-0505-2020-48-044.
7. *Porkhanov VA, Kosmacheva ED, Pashkova IA*. Opyt transplantatsii solidnykh organov v Krasnodarskom krae. *Transplantologiya*. 2018; 10 (2): 98–104. https://doi.org/10.23873/2074-0506-2018-10-2-98-104.
8. *Gautier SV, Moysyuk YaG, Poptsov VN, Kornilov MN, Yaroshenko EB, Pogrebnichenko IV i dr.* Otdalennye rezul'taty transplantatsii trupnoy pecheni. *Vestnik transplantologii i iskusstvennykh organov*. 2014; 16 (3): 45–53. https://doi.org/10.15825/1995-1191-2014-3-45-53.
9. *Sarkar M, Watt KD, Terrault N, Berenguer M.* Outcomes in liver transplantation: does sex matter? *Journal of hepatology*. 2015; 62 (4): 946–955.

The article was submitted to the journal on 18.04.2022