https://doi.org/10.12659/AOT.931786
UDC 616-089.843; 616.3
IRSTI 76.29.46; 76.29.34

Liver Transplantation: A 10-year Low-volume Transplant Center Experience in Kazakhstan

Running title: Liver transplantation program in Kazakhstan

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Abstract

Background. Liver transplantation is the best available treatment option for patients with end-stage liver disease. The organ transplantation program in Kazakhstan started in 2010. Here we present 10-year experience of liver transplantation in a low-volume transplant center in Kazakhstan.

Material and Methods. Clinical data of the 64 consecutive liver transplantations from deceased and living donors between 2010 and 2020 were collected from electronic records. All data were retrospectively analyzed.

Results. Among 64 liver transplantations, 11 from deceased and 53 from living donors have been performed in our center from 2010 to 2020. The mean age of the recipient was 44 y.o.; 53% female; 47% male. Hepatitis B + hepatitis D infection was the most common cause of end-stage liver disease (21 cases; 32,8%). The overall patient survival rates for 1, 3, 5 years were 75%; 69,5%; 59,6% respectively for liver transplant recipient from a living donor and 54,5%; 45,5%; and 39% for the liver recipient from a deceased donor

Conclusions. Our clinical outcomes showed a high rate of biliary and vascular complications that led to the low survival rate of the recipients. Starting the transplant program in Kazakhstan faced various challenges. In the early period, most transplantations were performed in collaboration with or under the guidance of transplant teams of Russia, Turkey, and South Korea.

We believe that improving surgical techniques and protocols of pre- and post-transplantation management can diminish the complications after transplantation.

Keywords: Liver transplantation; end-stage liver disease; living donors

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Oncology.kz 2021; 1 (1): 11-17
Recieved: 04-12-2021
Accepted: 08-12-2021

This is a republishing of this article.
Link for citation: Saparbay J, Spatayev J, Sharmenov A, Aytbayev S, Uristenova A, Mukazhanov A, Zhexembayev A. Liver Transplantation: A 10-Year Low-Volume Transplant Center Experience in Kazakhstan. Ann Transplant. 2021 Jul 6;26:e931786. doi: 10.12659/AOT.931786. PMID: 34226437; PMCID: PMC8272395

Introduction

Liver transplantation is the best available treatment option for patients with end-stage liver disease [1]. According to the RCCT ("Republican Center for the Coordination of Transplantation" of the Ministry of Health of the Republic of Kazakhstan), 127 adults and 8 children were registered on the waiting list for liver transplantation [2]. The first successful deceased donor liver transplantation in Kazakhstan was performed in 1996. However, due to the lack of trained transplant surgeons, immunologists, and mainly the absence of deceased donation, the first case was the only case for almost 10 years. Asian countries have the lowest rate of liver transplantation from a deceased donor. By 2010 deceased organ donation comprised 0,05-6,0 per million of the population, whilst in the USA it was 33,9 per million of the population [3]. Currently, organ transplantation program in Kazakhstan is in its early decade. Similar to other eastern countries, developing transplant service meet a variety of obstacles. The common absence of education regarding importance of organ donation and transplantation, lack of governmental support, poorly developed health care system, altogether this factors is a barrier for deceased organ donation development [4-6]. Thus, a visible discrepancy between the availability of organs and the patients awaiting liver transplantation exist in Kazakhstan. Living donation is the most attractive option in solving the organ shortage problem [7]. In Kazakhstan, the first successful liver transplantation from a living donor was performed in 2011 in collaboration with the transplant team from Belarus [8]. Since 2013, liver transplantation numbers are steadily increasing in transplant centers of Kazakhstan (Figure 1). In Kazakhstan, LDLT comprised 80% of the total number of liver transplantation cases in 2019. Here we present a 10-year single-center experience of liver transplantation in the low-volume transplant center in Kazakhstan.

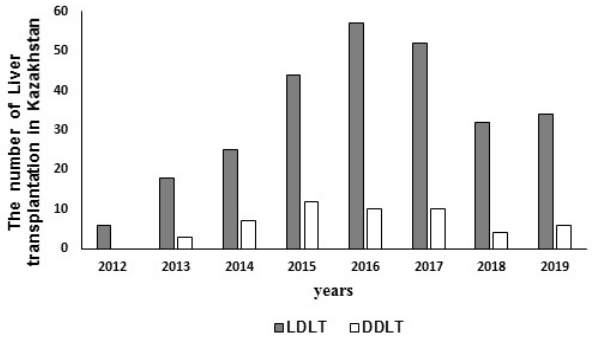

Figure 1. The total cases of LDLT and DDLT between 2012 and 2019 in Kazakhstan

Patients and Methods

This retrospective study was conducted in compliance with the principles of the Declaration of Helsinki. The Local Ethical Committee of National Research (permit number #7) approved this study.

Total 64 liver transplantations were performed in our center between 2011 January, when the transplant program started in Kazakhstan, and October 2020. Among them 11 liver transplantation from deceased donors and 53 from living donors. All data, concerning recipients and donors, were retrieved from electronic data. We have reviewed the course of the recipients; the follow-up period was more than 1 year in all cases. All recipients, who received liver transplantation from a deceased or living donor, were listed in the National Waiting List of the Republic of Kazakhstan.

Almost all grafts from living donors were right lobe hepatectomy, except one left hepatectomy. In all right hepatectomy cases, the middle hepatic vein was left in the donor remnant liver. Remnant liver volume, evaluated by computed tomography, was more than 35%, GRWR> 0,8 was acceptable in our center. An interposition synthetical graft was used for venous drainage of segments 5 and 8. Biliary reconstruction was completed either with duct-to-duct anastomoses or with hepaticojejunostomy.

Basiliximab (anti-interleukin 2 receptor antagonist) was used for induction therapy. For mainstay therapy, a calcineurin inhibitor-based immunosuppressive regimen was used in our center. Three-component therapy involved tacrolimus, steroid, and mycophenolate mofetil.

Oral nucleoside analogs were used in recipients with HBV- associated ESLD prior to liver transplantation and continued after liver transplantation as prophylaxis against recurrence.

All data were retrospectively analyzed. Descriptive statistics were used to describe the characteristics of participants. Data for categorical variables are expressed as numbers and percentages. For continuous variables, data are reported as the median with range. Chi-square test was used to define whether there is a statistically significant difference in categorical variables between groups. The significance level was set at 0,05 (a=0,05). The Kaplan-Meier survival estimate was used to determine patient and graft survival rates in two groups. All analyses were performed using STATA software version 14.0.

Results

Among 64 liver transplantations, 11 liver grafts were from deceased donors and 53 from living donors (50 donors were relatives of to the recipient, 3 from living unrelated donors). There was one LDLT from an AB0-incompatible donor. The major causes of liver cirrhosis were hepatitis B+D in 21 (32,8%) cases; hepatitis B – 9 (14%); primary biliary cirrhosis – 9 (14%); autoimmune hepatitis – 7 (10,9%); hepatitis C – 4 (6,3%); NASH in 3 cases; hepatitis B+C+D – 1 (1,5%). In 2 cases hepatocellular carcinoma was an indication for liver transplantation. Cryptogenic

cirrhosis (6,3%) and Chanarin-Dorfman syndrome (1,6%) were the rare indications for liver transplantation.

The mean age of transplant recipient was 44 years (range 15-63), with a slight majority of the female recipient (53%) compare to male (47%). The mean hospital stay was 40±25 days (range 11-196). Demographic and clinical characteristics of the liver recipient are shown in Table 1.

Table 1. Demographic and Clinical Characteristics of the Liver recipients

Variable	Mean (SD)	Median (range)	N (%)
Age	43.9 (11.2)	15-63	64
Gender (male/female)			30(47)-34(53)
Cause of ESLD			
PBC			9 (14)
HCV			4 (6.35)
HBV			9 (14)
AIH			7 (10.9)
HCC			2 (3.17)
HBV+HDV			21 (32.8)
HBV+HDV+HCV			1(1.6)
Cryptogenic cirrhosis NASH			4(6.3) 3(4.7)
Others			4 (6.3)
MELD (points)	16(6)	6-34	64
Child-Pugh classification			
A			5
B			31
C			28
Bilirubin (μmol/l)	135.01(141.6)	(14.4-434)	64
Creatinine (μmol/l)	62.69 (22.8)	(30-143.75)	64
ALT	69.69 (84.05)	(11.6-193.5)	64
AST	78.44(46.95)	(11.7-180.9)	64
PVT			7(11.86)

BMI: Body Mass Index; ESLD: End-Stage Liver Disease; PBC: Primary biliary cirrhosis; HCV: Hepatitis C virus; HBV: Hepatitis B virus; AIH: Autoimmune hepatitis; HCC: Hepatocellular carcinoma; MELD Model of End-Stage Liver Disease; ALT: Alanine aminotransferase; AST: Aspartate transaminase; PVT: Portal vein thrombosis

The mean age of liver donors was 31,5 years (range 19-54). The gender ratio was male 45 (70,35%) and female – 19 (29,7%). All living donors survived the procedure. Among living related donors, in 12 cases (22,6%) the donor was a parent of the recipient; 17 cases (32,0%) – offspring; 21 cases (39,6%) – sibling; all unrelated living donors were the spouse of the recipient 3 (5,67%). No major complications were experienced in living donors. Demographic and clinical characteristics of the liver donors are shown in Table 2.

Table 2. Demographic and Clinical Characteristics of Liver donors

Variable	Mean (SD)	Median (range)	N (%)
Age	32.5 (9.26)	(22-54)	64
Gender (male/female)			45(70.35%)/19(29.7%)
Living/Cadaveric			53(82.8%)/11(17.2%)
Living related			
Parent			12 (22.6%)
Offspring			17 (32.0 %)
Sibling			21 (39.6%)
Living unrelated			
Spouse			3 (5.67%)
Bilirubin (μmol/l)	15.14(10.7)	(3.61-31.1)	64
Creatinine (μmol/l)	59.6(13.9)	(47-81)	64

BMI: Body Mass Index; ALT: Alanine aminotransferase; AST: Aspartate transaminase

The mean cold ischemic time was 234.2±153 minutes, ranging from 330 to 830 minutes. The mean operation time was 555±114 minutes. The mean bleeding volume was 1835±1226 ml, ranging from 600 to 8000 ml (Table 3).

Table 3. Postoperative complications and operational data

Variable	Mean (SD)	Median (range)	N (%)
Operation time (minute)	555(114)	(330-830)	64
CIT (minute)	234.3(153.4)	(60-630)	
Bleeding volume (ml)	1835.7(1226.5)	(600-8000)	
Postoperative complication			
Bleeding			18(28.57%)
Biliary complications			21(32.8%)
Bile leakage			9 (42.8%)
Biliary stricture (anastomotic)			8 (38 %)
Biliary stricture (non-anastomotic)			1(4.8%)
Cholangitis			3(14.4%)
PVT			7(10.93%)
Infection			18 (28.57%)
HAT			3 (4.68%)

CIT: Cold ischemic time; HV: hepatic vein; HAT: Hepatic artery thrombosis; PVT: Portal vein thrombosis

Most of the recipients experienced biliary complications – 21 cases (32,8%), among them anastomotic biliary stricture 8 (38%), bile leakage 9 (42,8%), and non-anastomotic biliary stricture 1 (4,8%), cholangitis – 3 (14,4%). Bile leakage was treated conservatively in cases 3 (33,3%) and reoperation was performed in cases 5 cases (55,5%) to remove the biloma or reanastomosis. Anastomotic biliary stricture needed reoperation with Roux-en-Y hepaticojejunostomy. In recipients, when high bilirubinemia persisted even after reanastomosis; percutaneous transhepatic draining of the bile ducts was performed.

Portal vein thrombosis occurred in 7 recipients, hepatic artery thrombosis in 4 cases, all after LDLT.

Acute rejection was observed in 7 patients (10,9%) after LTx, 1 case (9%) after DDLT and 6 cases (11,3%) after LDLT. There was a significant association between donor type (living/deceased) and rejection rate (p=0,004) (Table 3). All patients with acute rejection were treated with steroid therapy. We did not observe any steroid-resistant rejection.

The overall patient survival rates for 1, 3, 5 years were 75%; 69,5%; 59,6% respectively for liver transplant recipient from a living donor and 54,5%; 45,5%; and 39% for a liver recipient from a deceased donor (Fig 2).

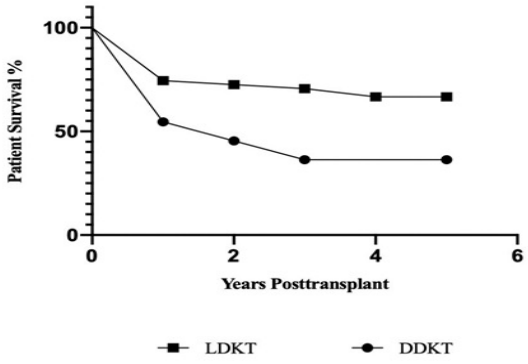

Figure 2. Liver recipients overall survival rate

Discussion

National Research Oncology Center is one of the few transplant centers in the largest country of central Asia - Kazakhstan. In this study, we analyzed the outcome of 64 liver transplantations performed in our center since 2010. Clinico-demographical characteristics of donors, recipients, and outcomes were described in this paper. Our data showed that the main cause of ESLD among our patients was HBV that is similar to the systematic review, where Kazakhstan showed the highest prevalence of HBV in central Asia [9]. Among a total of 64 LT, 53 recipients got the liver graft from living donors. Worldwide, LDLT has developed significantly, with the highest distribution in Asian countries [10]. The main disadvantage of the living donation is the donor hepatectomy that can lead to various complications [11]. We made a strict selection of so-called ideal donors, the volume of remnant liver varied from 35% to 40%, liver steatosis less than 10%, and the mean age was 32,5 years. In our study, living donors did not experience any major complications.

The liver transplant procedure itself is technically complicated; partial liver transplantation is a more challenging procedure. Numerous perioperative complications occurred in our case series. Biliary and vascular complications are the major cause of morbidity and mortality after liver transplantation. The most common complication in our study comprised of biliary complications. The incidence of biliary complications in liver recipients varies from 10-15% in DDLT; 15-30% in DDLT [12]. The rate of biliary complications in our study was 32,8%. Most of the biliary stenosis were treated with reoperation and hepaticojejunostomy or transhepatic draining. Hepaticojejunostomy often led to chronic cholangitis and biliary cirrhosis of the liver graft.

Our data revealed that DDLT patients had fewer episodes of AR (9% vs. 11,3%), which is not similar to other transplant centers' data. We suggest that a higher rate of AR in LDLT recipients might be due to a higher rate of HAT after LDLT.

Despite the high rate of AR in LDLT patients, OS was significantly higher in LDLT recipients than in DDLT (p-value <0,05).

This study is limited due to small-size cohort and its retrospective character. Longer observation period and increasing the number of LTx, improving donor and recipient selection is necessary for further work.

Conclusion

For developing countries, starting the liver transplant program is a challenge due to many factors, such as insufficient financial support and lack of opportunity to train surgeons and other specialists, which is essential for complicated procedure of liver transplantation and efficient follow-up. Improving surgical technique, prevention of biliary and vascular complications, overcoming the organ shortage problems remains to be refined.

In conclusion, in Kazakhstan, similar to other developing countries, settlement of transplantation program is essential for healthcare system improvement.

Conflict of Interest. No potential conflict of interest relevant to this article was reported.

Acknowledgments. We would like to thank the transplant team of National Research Oncology center for their great work throughout 10 years.

Funding: The authors received no financial support

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Бауыр трансплантациясы: Қазақстандағы трансплантология орталығының бірінің 10 жылдық тәжірибесі

Қазіргі атауы: Қазақстандағы бауыр трансплантациясы бағдарламасы

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Түйіндеме

Бауыр трансплантациясы бауыр жеткіліксіздігі бар науқастарды емдеудің ең жақсы әдісі болып саналады. Қазақстанда бауыр трансплантациясы бағдарламасы он жыл бұрын құрылған. Бұл зерттеуде біз Қазақстандағы бауыр трансплантациясы бойынша шағын трансплантология орталығының тәжірибесін талдадық.

Материалдар мен әдістер. 2010 жылдан 2020 жылға дейінгі кезеңде қайтыс болған және тірі донорлардан 64 рет бауыр трансплантациясы туралы клиникалық деректер электрондық жазбалардан алынды. Барлық деректер ретроспективті түрде талданды.

Нәтижелер. Барлығы 2010 жылдан бастап 2020 жылға дейін біздің орталықта 64 бауыр трансплантациясы, қайтыс болғандардың 11-і және тірі донорлардың 53-і өткізілді. Реципиенттердің орташа жасы 44 жасты; әйелдің 53%-ын; ерлердің 47%-ын құрады. В гепатитінің + D гепатитінің инфекциясы бауыр ауруының терминалдық сатысының ең көп таралған себебі болды (21 жағдай; 32,8%). 1, 3, 5 жыл ішінде науқастардың жалпы өмір сүру деңгейі тірі донордан алынған бауыр реципиенттері үшін тиісінше 75 %; 69,5 %; 59,6% және қайтыс болған донордан алынған бауыр реципиенті үшін 54,5 %; 45,5 %; және 39% құрады.

Қорытынды. Біздің клиникалық нәтижелеріміз билиарлы және тамырлы асқынулардың жоғары жиілігін көрсетті, бұл реципиенттердің өмір сүруінің төмендеуіне әкелді. Қазақстанда трансплантаттау бағдарламасының іске қосылуы түрлі қиындықтарға тап болды. Ерте кезеңде трансплантациялардың көпшілігі Ресей, Түркия және Оңтүстік Кореядағы трансплантация бригадаларының басшылығымен немесе ынтымақтастығымен жүзеге асырылды.

Біз хирургиялық әдістер мен трансплантациядан кейінгі хаттамаларды жетілдіру трансплантациядан кейінгі асқынуларды азайтуы мүмкін деп санаймыз.

Түйін сөздер: Бауыр трансплантациясы; соңғы сатыдағы бауыр ауруы; тірі донорлар.

Трансплантация печени: 10-летний опыт одного центра трансплантологии Казахстана

Текущее название: Программа трансплантации печени в Казахстане

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Резюме

Трансплантация печени считается лучшим доступным методом лечения пациентов с печеночной недостаточностью. В Казахстане программа трансплантации печени была создана десять лет назад. В этом исследовании мы проанализировали опыт небольшого центра трансплантологии по пересадке печени в Казахстане.

Материалы и методы. Клинические данные о 64 последовательных трансплантациях печени от умерших и живых доноров в период с 2010 по 2020 год были получены из электронных записей. Все данные были ретроспективно проанализированы

Результаты. Всего с 2010 по 2020 г. в нашем центре было проведено 64 трансплантации печени, 11 от умерших и 53 от живых доноров. Средний возраст реципиентов составил 44 года; 53% женщины; 47% мужчин. Инфекция гепатита В + гепатита D была наиболее частой причиной терминальной стадии заболевания печени (21 случай; 32,8%). Общая выживаемость больных в течение 1, 3, 5 лет составила 75 %; 69,5 %; 59,6% соответственно для реципиентов печени от живого донора и 54,5 %; 45,5 %; и 39 % для реципиента печени от умершего донора.

Выводы. Наши клинические результаты показали высокую частоту билиарных и сосудистых осложнений, что привело к низкой выживаемости реципиентов. Запуск программы трансплантации в Казахстане столкнулся с различными трудностями. В ранний период большинство трансплантаций выполнялось в сотрудничестве или под руководством трансплантационных бригад России, Турции и Южной Кореи.

Мы считаем, что совершенствование хирургических техник и протоколов пред- и пост-трансплантационного ведения может уменьшить осложнения после трансплантации.

Ключевые слова: трансплантация печени; терминальная стадия заболевания печени; живые доноры.