

Original paper

Liver transplantation in Central Europe

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Abstract

Introduction: Transplant hepatologists convened in Warsaw on 20-21 November 2015 at a meeting of the Initiative Group for Central European Hepatologic Collaboration to exchange their experience in liver transplantation in their respective countries.

Material and methods: The description is based on narration of individual country representatives, supplemented by data from additional queries, and from publicly accessible sources.

Results: Liver transplantation programs were launched, in the Czech Republic in 1983, in Poland in 1990 (paediatric) followed by the adult program 1994; the first liver transplant in Hungary was performed in 1995, with Slovakia launching its liver transplantation program in 2008. Currently, there are 2 centres for liver transplantation in Slovakia, 1 centre in Hungary, 6 centres in Poland, and 2 centres in the Czech Republic. The rates of liver transplantation correspond to the number of cadaveric donations being the highest in the Czech Republic (15.8 per million population) and the lowest in Slovakia (4.2 per million population) (2014 data). Live donation is utilized systematically in Poland. Indications vary from country to country, but the 3 most frequent ones include hepatitis C and B cirrhosis, alcoholic cirrhosis, and cholestatic liver disorders. There is a growing incidence of hepatocellular carcinoma among adult liver transplant recipients. Biliary atresia and hereditary diseases are the most frequent indications among children. Hungary became a member of Eurotransplant, other countries are not a part of any international organization for organ sharing.

Conclusions: Despite some differences, liver transplant programs seem to be compatible honouring the same values and principles universal to liver transplant programs in most parts of the world.

Key words: liver transplantation, organ donation, Central Hepatologic Collaboration, Visegrád Four.

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Introduction

Representatives of transplant hepatology delegated by national societies of study of liver from the Czech Republic, Hungary, Poland, and Slovakia (in the alphabetical order) convened on 20-21 November 2015 in Warsaw at the Meeting of the Initiative Group for Central European Hepatologic Collaboration to exchange their experience in liver transplantation in their respective countries and to start a new era of scientific

cooperation in this field. This was the first meeting with such an aim.

Central European countries, at least their part making up the Visegrad Four (V4) have close local relationships at many levels and share similar historical heritage of the socialist era of the post Second World War period. They have also withstood the great challenges of socioeconomic changes of the post-Soviet era. Despite their well-developed health care services in general, the limited cultural contacts with

the West (including exchange in medical science) caused a substantial delay in the development of liver transplantation programs considered a very complex medical program project at that time. Consequently, liver transplant programs were formed after this procedure had become a well-established standard treatment method in all West European countries and many other places worldwide.

With the exception of the pioneering achievement of the team at the Centre for Cardiac and Transplant Surgery, Brno, former Czechoslovakia, 1983, all attempts to start a viable liver transplantation program in the 1980s failed. It was not earlier than the mid-1990s that liver transplantation programmes actually became a reality.

Currently, there are well-established transplant programmes in all V4 countries serving most of the population needs and achieving standard results of patient and graft survival. The transplantation rate is highly dependent on the capacity of cadaveric donor programs in each country with the exception of Poland with the most active paediatric live donor program. Despite historical parallels, there are local differences in the organization of transplantation programs. Except for Hungary, a member of Eurotransplant, no other Central European country is a part of any international transplantation network for organ sharing. National transplantation agencies in each country organize their waiting lists on the national level, and programs are highly dependent on local organ donation even for highly urgent cases. While there is some limited exchange of organs between Slovakia and the Czech Republic, no systematic organ sharing is practised with the other V4 countries.

Regardless of the differences, liver transplant programs seems to be compatible honouring the same values and principles. In fact, the V4 countries are not any exception to the worldwide transplantation endeavour. Liver transplantation is practiced in a much unified way throughout the Western hemisphere as the programs evolved directly or indirectly from roots set by Thomas Starzl (Denver, Colorado) in the United States, and Sir Roy Calne (Cambridge, UK) in Europe, who pioneered liver transplantation programs in the 1960s [1].

Material and methods

The description of development in liver transplantation in each country is based on narration of individual country representatives, supplemented by data from additional queries from the author (PT), and from publicly accessible sources [2-4]. The respective

countries are listed in the alphabetical order. Survival rates are presented as Kaplan-Meier survival analysis.

Results

Liver transplantation in the Czech Republic

The first liver transplantation in the Czech Republic was performed in the Centre for Cardiovascular and Transplantation Surgery (CKTCH) Brno, former Czechoslovakia, in 1983 by Václav Kořístek [5]. The second liver transplantation program was launched 12 years later, in April 1995, at the Prague-based Institute for Clinical and Experimental Medicine (IKEM) in its transplant centre where heart, pancreatic, and kidney transplantations have been routinely performed since 1966. The Transplant Centre at IKEM has since become the country's largest liver transplant centre performing more than two thirds of liver transplantations and the only one for paediatric cases. A third liver transplantation centre opened in Ostrava in 1996 to be closed only 4 years later. An attempt to start a paediatric liver transplant program was undertaken in Prague's largest University Hospital in Motol in 2004, but only one case was actually performed. Recently, 169 liver transplantations were done in the Czech Republic in two centres in 2014 (119 in IKEM Prague, and 50 in CKTCH Brno). In total, 1695 liver transplantations were registered in the country as of 31 December 2014 [2].

The most frequent indication for liver transplantation is alcoholic liver cirrhosis (22%), followed by cholestatic liver disease (primary biliary cirrhosis [PBC] or primary sclerosing cholangitis [PSC]; 15%), hepatitis C cirrhosis (10%), hepatocellular carcinoma (8%), and cryptogenic cirrhosis or non-alcoholic steatohepatitis (NASH) (7%). There is a growing number of hepatocellular carcinomas among liver transplant recipients (16% in 2014). Biliary atresia and metabolic disorders are the most frequent indications for LTx in the paediatric population.

Most of these procedures were performed as a whole cadaveric liver transplantation with preservation of the retro-hepatic vena cava, only in few (paediatric) cases, a live donor graft (mostly left lateral segment) was used, first in 2003 by Miroslav Ryska at IKEM. Over the last two years, splitting of the graft was a common policy at IKEM; 29 splits were performed in 2014, even as a split for two adults. Three livers were split as early as 1998. Two cases of auxiliary liver transplantation were done in 2015, both for fulminant liver failure. As the donor liver is supplied from an area with a population of 10 million only, a protocol for ABO-incompatible liver was developed for highly urgent recipients.

Among these, Wilson's disease (39%), fulminant hepatitis B (18%), autoimmune hepatitis (14%), and toxic lesions (12.5%) were the most common indications. The first multivisceral transplantation (including liver and intestine) was performed in 2014 (Jiri Fronek).

The survival rates after liver transplantation are similar in both transplant centres and exceed the average post-transplant survival rates reported by the European Liver Transplant Registry: the Kaplan-Meier estimated 1-year patient survival was 92.2%, 5-year 85%, and 10-year 75.3%. Eighty-three patients were awaiting transplantation nationwide as of 21 December 2015.

All recipients are followed up indefinitely by hepatologists at transplant centres, and protocol biopsies are performed routinely.

Liver transplantation in Hungary

There are four kidney transplant centres in Hungary, two centres for simultaneous kidney and pancreas transplantations, two centres for heart transplant, but only one liver transplant centre. The liver transplant program in Hungary was started on 5 January 1995 by Ferenc Perner, who successfully transplanted a liver into a female patient becoming the longest survivor among Hungarian patients. Since then, 756 orthotopic liver transplantations (OLT) have been performed until 2015 in patients with acute and chronic liver failure. More than 500 of these patients are on regular follow-up.

Three periods can be distinguished during development of the Hungarian transplant program. The first period coincided with the start of the learning curve. The first 150 liver transplantations were performed during this time interval with a sizeable mortality rate. In the second period, intensive care management was changed, with considerable attention paid to anaesthesia pre-assessment (patient evaluation and monitoring, better assessment of extrahepatic comorbidities), continuous improvement of homeostasis, and haemostasis care during surgery. Our Hungarian colleagues used early renal replacement therapy in the intensive care unit, Pentaglobin administration was introduced, and recipients were closely monitored (indocyanine green [ICG] test, frequent laboratory testing, ultrasound).

Recently, the programme entered a third period: the number of transplantations has increased while the results have been continuously improving. Liver transplantations without transfusions have become more common.

The most frequent indications for liver transplantation in adults are hepatitis C cirrhosis (31.8%),

cholestatic liver disease (17.3%), alcoholic liver disease (14.8%), fibrosis hepatitis (5.7%), and autoimmune hepatitis (5.52%), while hereditary disorders (Alagille syndrome, mucoviscidosis, Gierke's disease, α -1-antitrypsin deficiency) (39%), acute liver failure (26%), polycystic liver and kidney disease, CKLT (8.6%), primary sclerosing cholangitis (8.6%), and cryptogenic cirrhosis (8.6%) are the leading indications among paediatric recipients.

Survival of recipients is very good, with only 13% of patients transplanted between 1 January 2009 and 31 December 2015 (396 cases) lost.

In 2012, a preliminary cooperation agreement with the Eurotransplant Foundation was signed, with Hungary becoming a full member in 2013. The number of transplantations has increased since then, which, fortunately, did not have a negative effect on survival rates in the program [6].

Liver allocation is based on the Model for End-Stage Liver Disease (MELD) score taking into account the waiting time. Patients with liver cancer are given an additional 24 points.

Liver transplantation in Poland

The era of liver transplants in Poland began on 12 March 1987, when a surgical team led by Stanislaw Zielinski from the Department of Surgery of the Medical University in Szczecin made the first – failed – attempt at liver transplantation. The first successful transplantation in a child was performed on 10 December 1990. The procedure was undertaken by Piotr Kaliciński at the Children's Memorial Health Institute in Warsaw-Międzylesie. Successful transplantation in adults was performed in 1994 by two surgeons: Bogdan Michałowicz and Jacek Pawlak at the Central Clinical Hospital, Medical University of Warsaw. In 1999, the first successful transplantation from a living-related donor was performed by Marek Krawczyk and Piotr Kaliciński in Warsaw [7, 8].

Currently, there are 6 active liver transplant centres in Poland: Warsaw (3 hospitals), Szczecin, Wrocław, and Katowice. One of the transplant centres in Warsaw specializes in paediatric patients.

In 2014, there were a total of 570 people on the waiting list, including 437 new submissions. Livers were transplanted to 366 recipients, and 29 patients died on the active waiting list. The number of individuals waiting for liver transplantation is double the number of transplants. Currently (as of 30 October 2015), there are 171 people on the active waiting list, including two patients scheduled for simultaneous kidney and liver transplantation.

Each year, more than 330 liver transplants from deceased donors and around 30 transplants of liver segments from living donors are performed. The number of transplantations has doubled over the last 10 years. In total, from 1987 through October 2015, 3756 transplantations (284 from living donors) were performed. The utilization rate of harvested livers is almost 60%. Over 70% of all transplants took place in Warsaw-based centres. Ninety-four percent of the procedures in the whole group are the first transplantations.

The majority of transplantations from living donors were performed in paediatric recipients. In 88% of cases, II + III segments were transplanted, and II + III + IV segments in 11%, with the right lobe in 2 cases.

The most common indication for the first transplantation in adults was cirrhosis [58%, mainly because of hepatitis C virus (HCV) infection, 24%, alcoholic liver disease (14%), autoimmune hepatitis (AIH) (8%) or hepatitis B virus (HBV) (7%)]. Cholestatic disease (PSC, PBC) was diagnosed in 16%, cancer (mainly hepatocellular carcinoma; HCC) in 8%, metabolic diseases (mainly Wilson's disease) in 5%, and acute liver failure in 5% of recipients. The most common indications for transplantation in children included congenital biliary tract diseases (38%), liver cirrhosis (14%), and metabolic diseases (10%). Acute hepatic failure, usually after poisoning by *Amanita phalloides*, was diagnosed in 7% of liver transplants in children. Six percent of transplantations were performed for cancer (mainly hepatoblastoma, 3%).

The outcomes of liver transplantation in Poland are very good and do not differ from the European average. Data collected by POLTRANSPLANT show a 70% 5-year survival rate of grafts from deceased donors (recipient survival, 74%), an 82% 5-year graft survival from living donors, and an 86% survival of recipients. Ten-year results show survival rates of 57% for grafts and 63% for patients receiving liver from deceased donors, as well as 79% and 80% from living donors, respectively.

Liver transplantation in Slovakia

The first liver transplantation in Slovakia was performed in 1998 in Banská Bystrica by Ludovít Laca; it took another 10 years until liver transplantation became standard of care in the country's two transplant centres: Bratislava and Banská Bystrica. Instrumental in the development of the program has been tutorship from IKEM Prague and from others.

Since there are no studies on the prevalence of end-stage liver disease (ESLD) in Slovakia, the real need for LTx per million inhabitants per year (as compared to

the current 4.5) is difficult to determine. Judging from the mortality rates of ESLD in general (Slovakia ranks among top 5 countries in Europe) and 20% waiting list mortality in particular, it might be inferred that the rate of liver transplants should increase.

From 2008 to 2015, 196 liver transplantations were performed (on average 25 per year). In the analysed cohort of 132, the median age of patients was 50.7 years, 58% were men. The most common indications included alcoholic liver disease (42%), hepatocellular carcinoma (10%), autoimmune hepatitis and related syndromes (9%), hepatitis C and B cirrhosis (8% and 2%, respectively), NASH (8%), and other (21%). There is evidence suggesting the real contribution of non-alcoholic fatty liver disease (NAFLD)/NASH to the cohort is underestimated; and that the incidence of HCC in Slovakia is on a steep increase. Median waiting time was 24.5 weeks, and one in five patients had died while on the waiting list. Median donor age was 41.3. One-, three-, and five-year patient survival rates were 91%, 90%, and 88%, respectively.

The main challenges for the V4 LTx programs in 2016 are to tackle organ shortage, provide interferon-free therapy for all liver transplant recipients with hepatitis C, and for selected patients on the waiting list (with focus on unmet needs in preventing futility), to determine the real burden of NASH, and to address the increased incidence of HCC by improving early diagnosis and treatment.

Main results are summarized in Table 1 and Figure 1.

Discussion

In contrast to our previous publication [9], this article presents the situation of liver transplant programs run by the V4 countries: the Czech Republic, Hungary, Poland, and Slovakia (in the alphabetical order) mostly from 2 decades since the first transplantations were undertaken. This paper focuses on the current status and prospects rather than the past.

Despite a similar history during the second part of the 20th century, there were different traditions earlier in development of the health care system in each country that may have helped shape the transplantation services. Organizational principles of all transplant medicine were always, particularly in the Euro Atlantic region, similar and liver transplantation is practiced in a most uniform way using procedures conceived by a few internationally fully accepted authorities. Although the V4 countries have almost the same level of socioeconomic development as measured by World Bank indexes (Human Development Index – HDI, GDP per capita) and the region enjoys similar eco-

Table 1. Liver transplantation in the V4 countries in 2014

Country	Population ¹ (million)	HDI ²	Number of deceased donors, pmp ³	Number of transplant centres for liver	Number of liver transplants ³ (2014) Total and pmp
Czech Republic	10.7	0.870	24.4	2	169/15.8
Hungary	9.9	0.828	20.5	1	75/7.6
Poland	38.2	0.843	15.5	6	366/9.6
Slovakia	5.5	0.844	11.6	2	23/4.2

¹World Bank Report 2014

²Source: United Nations Human Development Reports 2014, <http://hdr.undp.org/en/composite/HDI>

³Council of Europe Newsletter Transplant

HDI – Human Development Index, pmp – per million population

conomic growth, still there are noticeable differences in transplantation rates, possibly due to the traditionally more effective deceased donor program in the Czech Republic and utilization of live donation in Poland.

The number of centres for liver transplantation has evolved quite reasonably in the region. In theory, in all V4 countries with the exception of Slovakia, where two centres cater to a population of 5 million, each transplant program serves populations from 5 to 9.9 million, on average. As claimed on several times that the centres performing less than 20 liver transplantations a year could have problems with quality and efficacy of their services [10, 11], the current distribution pattern seems to be very sound. Moreover, larger teams are essential for employing more advanced surgical techniques (splitting, live donor program). Thus, quite logically, larger centres will always have an advantage over smaller programs. This tendency for asymmetrical growth is seen in the Czech Republic (IKEM does 2/3 of the country's volume), in Poland (with Warsaw-based centres performing 70% of all liver transplantations in Poland), and, even in Slovakia, a substantial majority of procedures was performed by the team in Banska Bystrica. While this process helps to concentrate experience and fosters advanced surgical techniques, it could potentially cause some logistic problems if a large geographical area is being served.

Until recently, only Hungary was a part of an international organization of organ sharing, with the other three countries depending solely on their own areas to supply livers for their recipients on the waiting list. While this could work well for Poland with its sizeable population of almost 40 million, even for highly urgent candidates, patients in the other two countries with fulminant liver failure (or primary graft non-function after engraftment) are endangered by delayed graft arrival resulting in patient loss. Technical solutions as ABO incompatible and split liver could decrease the risk of death but also carry additional complications.

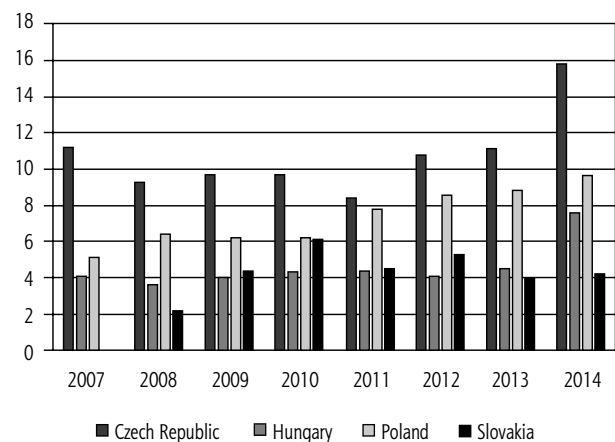


Fig. 1. Liver transplantation rate (per million population) in the V4 countries (2008–2014). Source: Council of Europe Newsletter Transplant 2008–2015

Thus, some administrative arrangements could help by creation of an international network to provide liver for highly urgent recipients within the region. Our Group for Central European Hepatologic Collaboration could serve well the idea.

Disclosure

Authors report no conflict of interest.

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