

Original Article

Liver Transplantation Status in Iran: A Multi-center Report on the Main Transplant Indicators and Survival Rates

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Abstract

Background: Iran's experience with liver transplantation (LT) began more than two decades ago. The purpose of this article is to present the status of LT in Iran, review specific characteristics of the programs, their outcomes, and their growth to become one of the largest LT programs in the world.

Methods: A questionnaire, asking for data on the number of transplants performed and specifics of the recipients and type of donors with focus on indications and outcomes was sent to LT programs.

Results: During a period of 23 years, 4,485 LTs were performed at 6 centers in the country. Of these, 4106 were from deceased donors and 379 were from living donors. There were 3553 adults and 932 pediatric recipients. Hepatitis B and biliary atresia were the most common etiologies in adult and pediatric patients, respectively. Overall survival rates at 1, 5, and 10 years were 85%, 77%, and 71% for adults and 76%, 67% and 56% for pediatric patients, respectively.

Conclusion: Approval of the brain death law in Iran and coordinated efforts by the transplant centers to build comprehensive LT programs has resulted in the ability to procure more than 700 deceased donors per year with acceptable long-term survival.

Keywords: Deceased organ donation in Iran, Liver transplantation, Organ transplantation in Iran

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Introduction

Since the successful performance of the first liver transplant in 1967 by Dr. Thomas E. Starzl, liver transplantation (LT) has advanced to become a routine procedure around the world.¹ LT is often the only treatment option for patients with acute or chronic hepatic failure of various etiologies. Advances in surgical techniques as well as immunosuppression have increased patient survival and improved overall quality of life. International data indicate that 27759 liver transplants were performed around the world in 2015 (21% from living donors); 10343 of which were performed in the Region of the Americas and 9545 were performed in Europe. This data suggests a 6.1% increase in global

liver transplant activities in 2014.^{2,3} In addition, trends from various countries show a rise in the number of LT performed year after year.^{4,5}

The Iranian LT experience began over 20 years ago at the Shiraz Organ Transplantation Center (SOTC) which is the leading transplant center in the country today, having performed over 3000 transplants from deceased and living donors. Nearly a decade after SOTC began its work, Iran's second transplantation center, at the Imam Khomeini Hospital Complex (IKHC), followed Shiraz's lead in the capital city of Tehran. Soon thereafter, several other hospitals commenced LT programs in different regions of the country. Although adult and pediatric LTs are now successfully being performed at different

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transplant centers in Iran, no report, to date, has captured this experience as a whole. Therefore, the purpose of this article is to present the LT status in Iran, addressing its main indications as well as survival rates. The primary objective in this report is to demonstrate that in a region noted for a relative lack of donation and transplantation, coordinated efforts at the societal, institutional and governmental levels can bring LT services to rank amongst the highest in the world.

Materials and Methods

Each Iranian liver transplant program maintains its own electronic data collection system, which is a modification of the liver transplant data system designed by the Digestive Disease Research Institute (DDRI) in Tehran. Programs known to have performed at least one LT were identified and asked to contribute to this report. A questionnaire was sent to each program asking for information on the total number of transplants performed distinguishing between deceased donor LTs (DDLTs) and living donor LTs (LDLTs), date of transplantation, age of recipients at the time of their transplant, the corresponding transplant indications, disease severity of the recipient at the time of listing and transplantation based on model for end-stage liver disease (MELD) and pediatric end-stage liver disease (PELD) scores, type of graft used (living, whole organ, split) as well as graft and patient outcomes. Data was collected from the inception of each program until December 2016 in order to have at least 6 months of follow-up. All data were sent to the DDRI after confirmation for accuracy within each LT center.

Statistics

All statistical analyses were performed at the DDRI. STATA (version 12, StataCorp, College Station, TX, USA) was used for analysis. Data are presented as numbers and percentages (%). Graft and patient survivals were calculated and the characteristics of each program were examined over time. Time from the first transplant to death or re-transplant was used to obtain life table and

Kaplan-Meier graft survival estimations.

Results

Six transplant centers in five different cities of Iran were identified and invited to participate; two of them were located in Tehran (the capital city). As of December 2016, 4485 transplants were performed at the following transplant centers: Shiraz (n = 3663), Tehran's first center (n = 527), Tehran's second center (n = 100), Mashhad (n = 125), Kerman (n = 48) and Esfahan (n = 22). Out of these transplants, 4106 were performed using DDLT and 379 were LDLT (Table 1). The growth of these programs over time is shown in Figure 1.

The top ten indications for adult LT were similar amongst the different centers. Hepatitis B-related cirrhosis (n = 816), followed by cryptogenic (n = 686) and primary sclerosing cholangitis (PSC) (n = 601) were the most common indications for adult LT in Iran. Top three transplant indications in pediatric patients included biliary atresia (n = 142), Wilson's disease (n = 126) and progressive familial intrahepatic cholestasis (n = 115) (Table 2 and Figure 2). Acute fulminant liver failure was the cause of LT in 57 (1.6%) adults and 18 (1.9%) pediatric cases. Fifty-four percent of patients were between ages 26–55 at the time of their transplant, while 932 pediatric and 56 elderly patients (65 and older) were also transplanted (Table 3 and Figure 3). Overall, MELD and PELD score medians were 20 and 16, respectively (All MELD/PELD scores are presented as medical/chemical scores) (Table 4). Survival of adult patients at 1, 5, and 10 years were 85%, 77%, and 71%; while pediatric cases had survival rates of 76%, 67% and 56%, respectively (Figure 4). In general, over a period of 20 years, 77.4% of the transplanted patients stayed alive up to June 2017.

All programs follow the same candidate selection process for listing. They all have a multidisciplinary candidate selection committee to review each patient for approval to enter the liver transplant list. Patients with an MELD score less than 15 are not usually listed for transplantation unless they show major complications

Table 1. Demographics of the Different Transplant Centers in Iran (alphabetical order)

Transplant Programs	Date of First Transplant	Total Number of Transplanted Patients (by December 2016)			DDLT	LDLT	Re-Transplants	Expired Patients
		Adult	Pediatric	Total				
Esfahan	7/2011	22	0	22	22	0	0	0
Kerman	12/2009	45	3	48	48	0	1	19
Mashhad	5/2013	115	10	125	125	0	0	13
Shiraz	5/1993	2762	901	3663	3284	379	65	831
Tehran 1	12/2002	511	16	527	527	0	24	117
Tehran 2	1/2009	98	2	100	100	0	4	31
Total	—	3553	932	4485	4106	379	94	1011

Abbreviations: DDLT, deceased-donor liver transplant; LDLT, living-donor liver transplant.

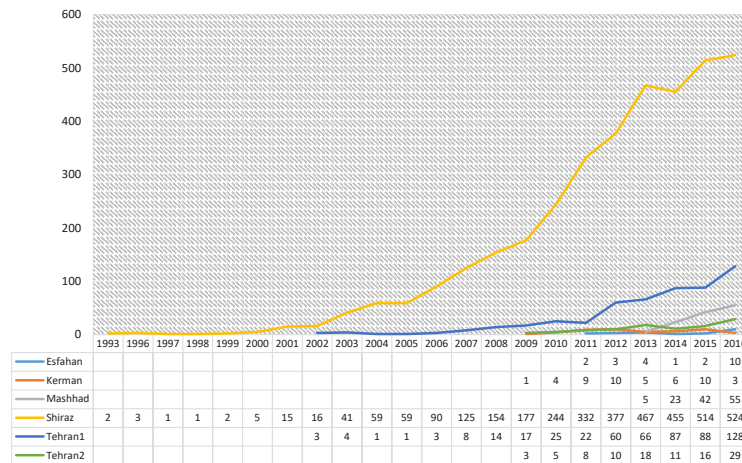


Figure 1. Liver Transplants Performed Each Year at Transplant Centers and Trend in Growth of the Programs.

Table 2. Top 10 Indications for Adult and Pediatric Transplantations

Adults Transplantations			Pediatric Transplantations		
Rank	Indications	No. (%)	Rank	Indications	No. (%)
1	Hepatitis B virus (HBV)	816 (22.93)	1	Biliary atresia	142 (15.28)
2	Cryptogenic	686 (19.28)	2	Wilson's disease	126 (13.56)
3	Primary sclerosing cholangitis (PSC)	601 (16.89)	3	Progressive familial intrahepatic cholestasis (PFIC)	115 (12.38)
4	Autoimmune hepatitis (AIH)	574 (16.13)	4	Cryptogenic	93 (10.01)
5	Hepatitis C virus (HCV)	198 (5.56)	5	Tyrosinemia	92 (9.90)
6	Hepatocellular carcinoma (HCC)	197 (5.54)	6	Autoimmune hepatitis	90 (9.69)
7	Wilson's disease	164 (4.61)	7	Crigler-Najjar syndrome	76 (8.18)
8	Budd-Chiari	120 (3.37)	8	Hypercholesterolemia	37 (3.98)
9	Non-alcoholic steatohepatitis (NASH)	90 (2.53)	9	Neonatal hepatitis	32 (3.44)
10	Primary biliary cirrhosis (PBC)	73 (2.05)	10	Primary sclerosing cholangitis (PSC)	18 (1.94)

of portal hypertension and cirrhosis, or they have hepatocellular carcinoma (HCC). No common waiting list exists across the country and transplant programs, and there is also no united sharing agreement, though the programs are moving in that direction. Each program has a donor service area for their primary listed patients. Allocation of livers to each program waiting list is primarily based on allocation for the patient in most need unless there is a logistically (donor/recipient combination) better matched for the offered for the liver. The recipients who were transplanted in this report had a mean MELD score of 21.6 ± 6.3 with a range of 6–40. Eight percent of patients were transplanted with an MELD of more than 30. About 5% of patients were in the intensive care unit and 5% on renal replacement therapy at the time of transplant at different centers.

Brain-dead donors are the main source of organ for transplant in all programs. Donation after cardiac death has not yet been approved as a potential donor pool. Due to the relative organ shortage and especially timely transplantation of pediatric patients, grafts from split livers and partial livers from living donors have been commonly used in this group of patients. In contrast to the diminishing practice of paid donation in kidney

transplantation in the country, all living liver donors are altruistic and not a single donor has been a paid one.

Discussion

Since the first successful liver transplant, the procedure has evolved rapidly. Despite the initial difficulties with low patient and graft survival, the procedure gained widespread acceptance for treatment of patients with end stage liver disease in the United States, Western Europe and subsequently the entire world mainly due to acceptance of the concept of brain death, better preservation solutions, improved technical aspects, more powerful immunosuppressive drugs, and subsequently, better patient and graft survivals.⁶ As a result of this progress, today, more than 25000 liver transplants are being performed each year around the world with a 1-year patient survival of approximately 90%.⁷ Due to the shortage in deceased donors, especially in Asian countries, transplantation of a segment of the liver from living donors became popular and has become the main source of LT in these countries.⁸

The first liver transplant in Iran was performed at the SOTC in 1993.⁹ Initially, growth of the program was slow especially due to challenges at that time regarding

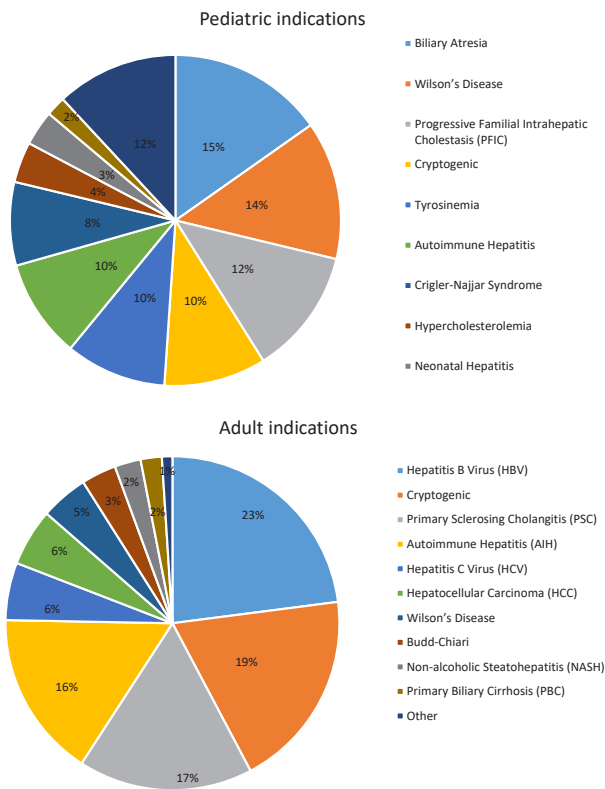


Figure 2. Top indications for Liver Transplant for Pediatric (a) and Adult (b) cases.

approval of the brain death concept. Previously in 1989, a fatwa (religious approval) from the Supreme Religious Leader had been obtained recognizing brain death; however, in the following decade, mostly renal transplants from living donors were performed, during which SOTC worked to strengthen its design and structure. Eventually, after passage of the Brain Death and Organ Transplantation Act by the parliament in the year 2000, SOTC expanded its activities on educating the public on organ donation. At the same time, mid-level medical staff and local physicians were trained on the diagnosis and management of brain dead patients and on ways to approach families of potential donors to get

permission for organ recovery.¹⁰

Initially, this was started in cities around Shiraz and then expanded throughout the Fars province and after demonstrating success, these efforts rapidly expanded to the rest of the country. By end of 2006, 18 brain death identification units and 13 organ recovery centers were actively involved in deceased donor organ recovery throughout Iran.¹¹ In the following years, this process continued to expand, leading to the recovery of organs from over 700 deceased donors per year in recent years, placing Iran at the highest deceased donor rate level in the Middle East. This increased availability of deceased donors not only caused a dramatic increase in the number of liver transplants, but also had a direct effect on greater use of deceased donor kidneys for patients with end stage renal disease in kidney transplant programs, which until recently were exclusively using kidneys from living donors.¹²

In addition to the efforts to expand the donor pool, one of the most important parameters in LT progress in Iran was financial support from the government for the procedure. In November of 2005, Iran Ministry of Health approved 100% coverage of the cost of inpatient LT care. This coverage, in addition to further support transplant programs, reduced social disparity in access and utilization of LT in the country and more patients in need of LT, in any socioeconomic class, were able to be evaluated, listed, and transplanted.¹³

As the largest and oldest transplant program in Iran, SOTC has also made advances in other types of solid organ transplantations. In 2011, aside from performing 345 LTs (291 deceased donors and 54 living donors), the program also performed 297 kidneys (all deceased donors), 29 pancreas, and 11 intestine and multi-visceral transplants. By 2013, SOTC performed 469 liver transplants from deceased and living donors with a large number of split-livers from the deceased donors supplying their pediatric LT demands. This progress in transplants has made this center one of the largest LT

Table 3. Numbers and Percentages^a of Different Age Groups in Transplanted Patients by Program

Transplant Programs	<12 years	12–18 years	19–25 years	26–35 years	36–45 years	46–55 years	56–65 years	>65 years	Total
Esfahan	0 (0)	0 (0)	5 (22.73)	5 (22.73)	6 (27.27)	5 (22.73)	1 (4.55)	0 (0)	22 (100%)
Kerman	1 (2.08)	2 (4.16)	5 (10.41)	11 (22.91)	16 (33.33)	7 (14.58)	6 (12.5)	0 (0)	48 (100%)
Mashhad	3 (2.4)	7 (5.6)	6 (4.8)	19 (15.2)	17 (13.6)	36 (28.8)	35 (28)	2 (1.6)	125 (100%)
Shiraz	617 (16.84)	284 (7.75)	402 (10.97)	635 (17.34)	622 (16.98)	647 (17.66)	403 (11)	53 (1.45)	3663 (100%)
Tehran 1	5 (0.8)	13 (2.07)	72 (11.48)	113 (18.02)	123 (19.62)	177 (28.23)	123 (19.62)	1 (0.16)	627 (100%)
Tehran 2	1 (1.00)	1 (1.00)	18 (18.0)	25 (25.0)	23 (23.00)	23 (23.00)	8 (8.0)	1 (1.00)	100 (100%)
Total	626 (13.95)	306 (6.82)	490 (10.92)	783 (17.45)	785 (17.5)	872 (19.44)	568 (12.66)	56 (1.25)	4487 (100%)

^a No. (%).

The values demonstrated in the table represent number of patients within that age group with the percentage of mentioned patients within that particular city.

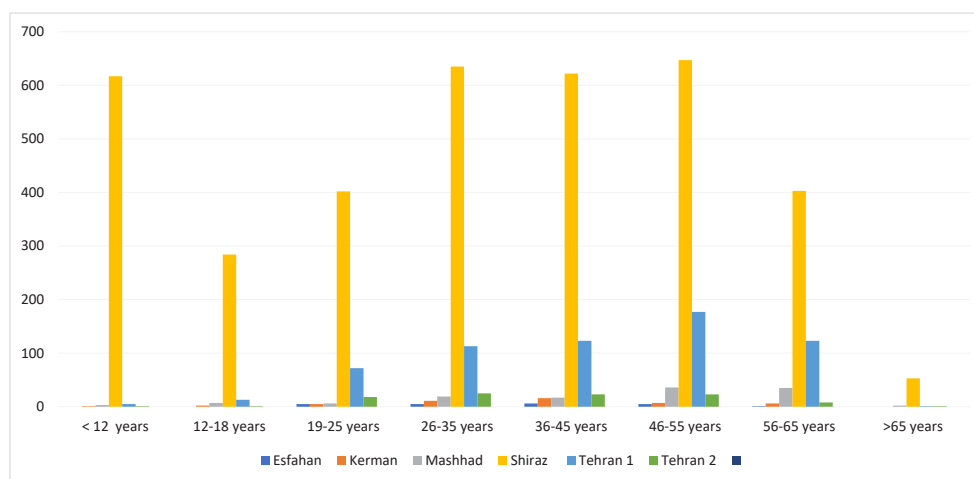


Figure 3. Numbers of Different Age Groups in Transplanted Patients by Program

programs in the world.

Advances in liver transplant techniques and especially the use of livers from living donors and split livers from deceased donors has helped transplantation in pediatric patients with end stage liver disease. SOTC has been the pioneer in pediatric LT as well and over the last 20 years, has performed over 900 liver transplants in this group of patients with overtime improvement in patient survival and excellent survival in the last 5 years.¹⁴⁻¹⁶ Expertise developed in split LT was followed by utilization of livers from living donors, again mainly for the pediatric patient population, and SOTC performed over 370 transplants from living donors over a period of 20 years. In contrast to the practice of paid donation in some living donor kidney transplantations in Iran, none of the livers utilized in LDLT have been from paid donors. In addition, utilization of deceased donor organs, which is based on altruistic donation, reduces pressure on use of paid living donors in kidney transplantation.

With the increased need for liver transplants, the second transplantation program started in Tehran in the year 2002. This program (at the IKHC, Tehran's first LT center) expanded to reach 100 LT per year over a period of 12 years, with excellent patient and graft survivals.¹⁷ Following the success of IKHC, four additional

university-based liver transplant programs in Kerman, Mashhad, Isfahan and a second center in Tehran (Taleghani hospital center) were also started to provide services in different parts of the country by transplant surgeons, hepatologists, anesthesiologists and mid-level personnel (all trained at SOTC). These programs are all at their beginning stages of productivity.

In response to the increased need for transplants, SOTC established a 3-year fellowship-training program in 2005 in order to train experts in the field of transplantation surgery. Fellows from Iran and other members of the Middle East Society of Transplantation (MESOT) filled the available training positions and since the year 2005, the program has trained 24 surgical fellows (16 for local programs and 8 for other Middle Eastern programs), 16 liver transplant anesthesiologists (12 for local and 4 for other countries) and has provided additional training for transplant hepatologists, pathologists, radiologists, and nurses from different hospitals and transplants centers in the country in shorter 3-6 month-long courses.

Interestingly, the data presented in this study demonstrates that the indications for LT in Iran are somewhat different from that of Western countries. Whether this is based on some selection bias or a real increased presence of certain liver diseases is not clear;

Table 4. Descriptive Demonstration of MELD and PELD Scores of LT Patients in Different Cities^a

Transplant Programs	MELD			PELD		
	N	Mean ± SD	Median (Q1-Q3)	N	Mean ± SD	Median (Q1-Q3)
Esfahan	15	19.8 ± 4.1	19 (17-23)	0	-	-
Kerman	47	18.51 ± 5.0	18 (15-21)	1	22 ± 0	22 (22-22)
Mashhad	122	18.96 ± 4.0	18 (17-21)	3	21.67 ± 5.5	22 (16-27)
Shiraz	2,805	21.84 ± 6.5	21 (18-25)	457	16.93 ± 9.7	16 (10-23)
Tehran 1	520	20.58 ± 5.6	19.5 (17-22)	3	19.33 ± 7.2	23 (11-24)
Tehran 2	99	25.56 ± 5.7	25 (21-29)	1	11 ± 0.0	11 (11-11)
Total	3,608	21.61 ± 6.3	20 (18-24)	465	16.97 ± 9.7	16 (10-23)

^a Total number of patients with MELD score available (415 patients had missing data).

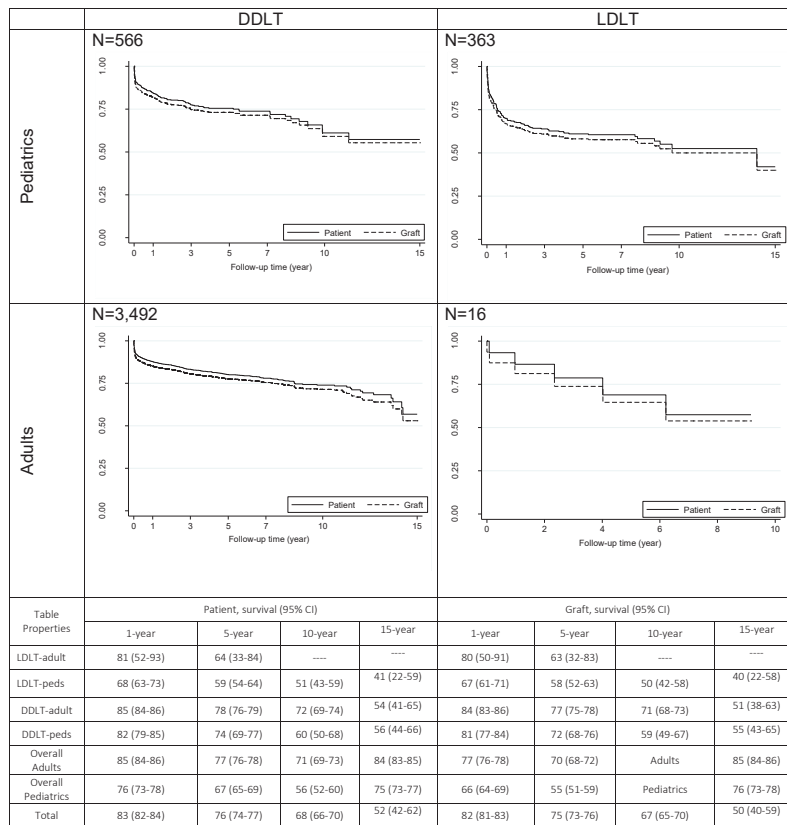


Figure 4. Survival in Pediatric and Adults Cases of Liver Transplant According to the Type of Donor.

however, there appears to be an increased number of patients with metabolic based diseases, autoimmune liver disease, hepatitis B, and primary sclerosing cholangitis (PSC). Liver diseases such as hepatitis C and HCC are less prevalent among transplanted patients than other indications since these disorders have low prevalence in the general hepatology practice of the country as well. There is a possibility that HCC patients either remain undiagnosed, or by the time they are diagnosed, their pathology is too far advanced to be considered for transplantation.

Currently, patients receiving LT for non-alcoholic steatohepatitis (NASH) make up only 2.5% of LTs performed in Iran; however, a large number of liver transplants under the diagnosis of “cryptogenic” could be due to end-stage NASH. Increases in the incidence of obesity and non-alcoholic fatty liver disease (NAFLD) in Iran could be a prelude that this may be a growing indication for LTs in the future as has been identified by prior studies.^{18,19}

The data shows a surprisingly low number of transplants performed due to acute liver failure (fulminant hepatitis). Looking more carefully into the potential reasons for this issue leads us to believe that most of these patients are either misdiagnosed, not transferable to the transplant centers (because of the logistics of their location in the country) and/or diagnosed too late to be considered for

transplantation. On the other hand, program reluctance and the potential to avoid these severe conditions for transplantation (because of the potential delays in finding an organ) cannot be overlooked. However, with increase in number of liver transplant programs in Iran, more critically ill patients and those in need for mechanical ventilation, intensive care unit, and renal replacement therapy have greater access to be managed and ultimately transplanted. In fact, an increasing trend for LT candidates with higher MELD scores or needing intensive care support is to be evaluated and managed with higher priority. In the recent years, more than 10% of patients transplanted had MELD scores greater than 30 and close to 5% with MELD scores greater than 35.

The new initiative by the Iranian ministry of health to eliminate viral hepatitis by expanding HBV vaccination for all people under age 40 along with a provision of almost free therapy for all HBV and HCV infected subjects in Iran is promising and will decrease the number of HBV and HCV related end-stage liver disease and patients who may need liver transplant in the future. Almost 95% of the Iranian population, which includes all rural farmers, industry workers and government employees, are covered by medical insurance and receive free medical care in public and university clinics and hospitals, with small out-of-pocket expense to the patients. More than 95% of the medications for liver diseases, including lamivudine,

tenofovir, the new interferon-free oral anti-HCV drugs, cyclosporine, tacrolimus, and azathioprine are widely available in Iran and are covered by insurance.¹³

In conclusion, LT has been a success story in Iran. Transplants are being performed from both deceased and living donors. An increase in the number of transplant programs has not only contributed to an increase in the number of transplants but has also allowed patients to receive care in local or regional centers without a need for long-distance travel for the actual transplantation and/or aftercare. Passage of the Brain Death Law has had the greatest impact on this success and has also contributed the expansion of efforts to increase the number of deceased donors. This, as a result, not only has increased organ availability for liver and kidney transplantation but has also facilitated development of successful pancreas, intestine, and multi-visceral transplant programs in the country. At this point, with increase in the number of transplant programs and further utilization of different organs for transplantation, there is yet to come to existence an organized system for registration and distribution of organs in the country. The need is there, and the first steps in this regard have been taken. In fact, the efforts that led into this analysis establish the foundation for creation of a national database similar to other registries such as the European Liver Transplant Registry (ELTR), the Scientific Registry of Transplant Recipients (SRTR) and the China Liver Transplant Registry (CLTR).

In the future, additional information on donor characteristics (for calculating a donor risk index) and more data surrounding the transplant index hospitalization with regards to patterns of practice, complications, and resource utilization will be collected. It seems that only with this degree of oversight can outcomes continue to improve.

Authors' Contribution

Shiraz Transplant program, Shiraz University of Medical sciences, Shiraz, Iran:

S.A. Malek-Hosseini; Concept, critical revision, final approval. S. Nikeghbalian; Critical revision, final approval. K. B. Lankarani; Acquisition of data, analysis of data, critical revision, final approval. H. Salahi, S.M. Dehghani, A. Eshraghian, K. Kazemi, A. Shamsaeefar, Mar. Moini, M.B. Khosravi, B. Geramizadeh, A. Taghavi, A. Bahador; Acquisition of data.

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Cleveland Clinic, Cleveland, Ohio, USA:

B. Eghtesad; Concept, design, analysis and interpretation of data, drafting article, critical revision, final approval.

Conflict of Interest Disclosures

The authors have no conflict of interest to report. There was no financial support for the conduct of this study.

Ethical Statement

The contribution of data by transplant programs was approved by their local Institutional Review Boards and Ethics Committees, and analysis of the data was done on identified information received from these institutions.


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