

Long-term follow-up after liver transplantation in Egyptians transplanted abroad

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ABSTRACT

Objectives: To study the long-term outcome after liver transplantation (LT) in Egyptian patients who underwent LT outside Egypt.

Methods: Between May 1993 and February 2004, over 150 Egyptians underwent LT outside Egypt. Data of 67 recipients were collected in Egypt through personal communications with the Overseas Liver Transplant Centers and through the records of the Egyptian Liver Transplant Association.

Results: Most patients underwent LT in Europe (73.1%), few in the United State of America (17.9%) and in Japan (9%). Sixty-one patients underwent cadaveric LT and the remaining 6 patients underwent living related liver transplantation (LDLT). The male to female ratio was 58:9. Median age was 45 (3-63 years). Hepatitis C virus (HCV) cirrhosis whether alone or mixed with schistosomiasis was the main indication for LT. Out of those 67 recipients, 52 (77.6%) survived after a median

follow-up period of 4.6 years (rang 1-10.5 years). Deaths were due to primary non-function in 3 patients, postoperative bleeding in one patient, recurrent hepatitis C virus (HCV) in 10 patients, and chronic rejection in one patient.

Conclusion: Egyptians underwent LT abroad showed a good long-term outcome. Due to the high prevalence of HCV, we expect a growing need for LT in Egypt. Although LDLT has been introduced recently in Egypt, cadaveric liver donation is still not legalized by the government. Efforts should be directed to expanding LDLT, legalizing cadaveric LT and also to the prevention and control of HCV infection in Egypt in order to avoid its devastating effect on the society as well as its enormous negative impact on Egypt's economy and future development.

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The evolution of liver transplantation (LT) in Egypt had passed through 3 distinctive phases. The first phase was before the 1990's where LT in Egypt was merely a theoretical therapeutic option and at that time the general impression was that LT is inevitably associated with graft failure and death whether during or shortly after the procedure. This off-putting impression was not only confined to the general population, but it was also the strong belief of many doctors in the medical field as well. This denial period was followed by the second phase which started in the early 1990's where a few

Egyptian patients underwent cadaveric liver transplantation (CLT) abroad and returned to Egypt in good health and were undisputable proofs of the good outcome following LT. It was only then when the appetite of the Egyptian surgeons was finally stimulated leading to the first living donor liver transplant (LDLT) being performed in 1991 at the National Liver Institute, Menoufiya University. At that time, a total of 3 LDLT procedures were performed and the longest survival was 11 months.¹ This breakthrough by the National Liver Institute encouraged the Egyptian surgeons to fight for a law

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to be passed allowing them to retrieve organs from brain-dead heart-beating cadaveric donors. In 1992, a decree was passed permitting cadaveric donations from prisoners, who were sentenced to death, and thereafter, at the National Cancer Institute in Cairo performed 2 CLT procedures; but unfortunately, both recipients died in the early postoperative period. Although we believe that this was a courageous step forward, the poor outcome following the procedures, as well as procuring organs from the executed, had a strong negative impact on the already fragile acceptance of the public to cadaveric donation. As a result, the law of cadaveric donation was indefinitely suspended, which was a major setback for LT in Egypt.

Throughout the 1990's, Egyptian patients continued to travel to Europe and USA seeking CLT, and a considerable number of them were lucky enough to receive transplants and return to Egypt in good health.^{2,3} These patients were a great asset to the cause of LT in Egypt. Their increasing numbers helped in changing the poor impression in the public's mind, doubting the success of the procedures. These patients were also highly motivated in helping their fellow Egyptian patients with whom they have shared enormous suffering linked to end stage liver disease and its complications. Their efforts led to the foundation of the Egyptian Liver Transplantation Association (ELTA) in 1998 and this has played a great role in promoting LT in Egypt. In the late 1990's and despite all sincere attempts to pass the law allowing cadaveric organ donation, all those efforts were sadly aborted in the Egyptian Parliament. Ironically this major setback led to the speedy launch of 2 successful LDLT programs in 2001, marking the beginning of the third phase of LT in Egypt. Almost all cases were performed by the help of overseas experienced teams and both those centers have performed over 120 LDLT procedures.⁴ Their remarkable success has encouraged other centers to follow and currently there are 3 major centers and 4 minor LDLT centers in Egypt and all those centers have performed over 140 LDLT procedures. Hereby we will study the results of those Egyptian recipients who underwent LT abroad and who have played a major role in the evolution of LT in Egypt.

Methods. Over 150 Egyptian patients underwent LT abroad between May 1993 and February 2004. We were able to collect complete data on only 67 patients out of those 150 recipients. The data were collected in Egypt through personal communications with the Overseas Liver Transplant Centers and through the records of the Egyptian Liver Transplant Association (ELTA). Forty-nine patients were transplanted in Europe (73.1%), 12 patients in USA (17.9%), and 6 patients in Japan (9%). Sixty-one patients (91%) underwent cadaveric

LT in Europe and USA, and only 6 patients (9%) underwent LDLT in Japan.

Results: The male to female ratio was 58:9; median age was 45 (range 3-63 years). Hepatitis C virus (HCV) induced end-stage liver cirrhosis was the main indication for LT in 55 patients (82.1%). Hepatitis C virus infection was either alone in 12 patients (17.9%) or mixed with other pathologies such as schistosomiasis in 25 patients (37.3%), hepatitis B virus (HBV) in 6 patients (9%), or hepatocellular carcinoma (HCC) in 12 patients (17.9%). Other indications for LT included pure schistosomiasis in one patient (1.5%), HBV in one patient (1.5%), biliary atresia in 6 children (9%), secondary biliary cirrhosis in 2 patients (3%), and primary sclerosing cholangitis in 2 patients (3%).

Out of 67 Egyptians underwent LT abroad, 52 (77.6%) survived after a median follow-up period of 4.6 years (rang 1-10.5 years); and the Kaplan-Meier Cumulative Survival at 6.4 years was 71.6% (**Figure 1**). Early deaths were due to graft primary non-function in 3 patients, and postoperative bleeding in one patient. Late deaths were due to recurrent HCV cirrhosis in 10 patients, and chronic rejection in one patient. All those 55 patients underwent LT for HCV cirrhosis developed HCV recurrence proved by HCV-polymerase chain reaction (PCR) and protocol liver biopsies. Out of those 55 recipients suffering from HCV recurrence, 34 recipients (61.8%) developed histologically proven HCV induced cirrhosis within 4 years following their transplant. Moreover, 15 patients (27%) progressed into end stage liver failure; out of these, 10 patients died from liver failure and the remaining 5 are seeking re-transplantation.

In HCV recipients, the overall survival after a median follow-up period of 4.6 years (rang 1-10.5 years) was 74.5% and the Kaplan-Meier Cumulative Survival at 6.4 years was 69.5% (**Figure 2**); 10 deaths were due to recurrent HCV cirrhosis and remaining 4 deaths were due to other causes (graft primary non-function in 3 patients, and postoperative bleeding in one patient).

Biliary complications were encountered in 12 patients (17.9%); this included simple bile leak in 3 patients, biliary obstruction in 8 patients, and biliary peritonitis in one patient. Seven patients were treated by endoscopic stenting and dilatation, while surgical reconstruction was needed in the remaining 5 patients. Vascular complications was encountered in 4 patients (5.9%); one had hepatic artery thrombosis and was successfully re-transplanted, 3 patients had venous outflow obstruction, 2 of them had a piggy-back cavo-caval anastomosis, this was successfully treated in all 3 patients by trans-jugular balloon dilatation. Postoperative bleeding was encountered in 5 (7.5%) patients, 2 of them required surgical exploration, and one patient died due to

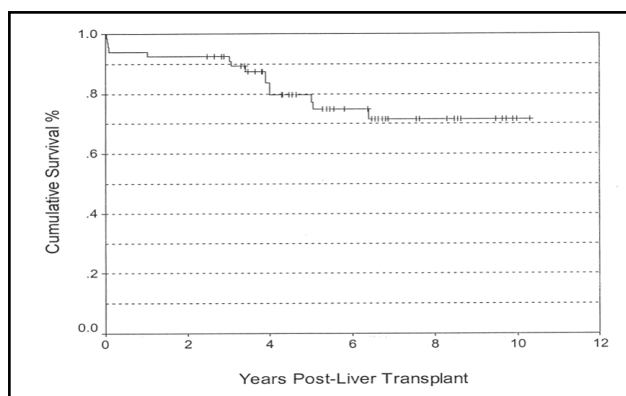


Figure 1 - Kaplan Meier cumulative survival curve in 67 Egyptians underwent liver transplant abroad.

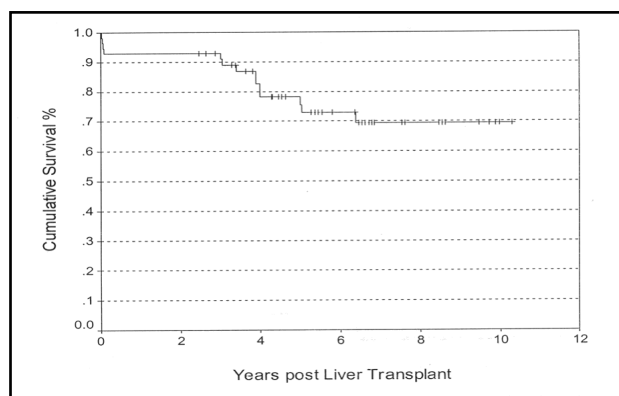


Figure 2 - Kaplan Meier cumulative survival curve survival after liver transplant for hepatitis C virus cirrhosis in 55 Egyptians underwent liver transplant abroad.

ruptured splenic artery aneurysm. Incisional hernia occurred in 3 patients (4.5%). Hepatocellular carcinoma was pre-operatively diagnosed in 8 patients, and incidentally discovered in 4 patients. All lesions were solitary, with no evidence of vascular invasion or extra-hepatic spread. The mean tumor size was 4 cm.²⁻⁹ Out of those 12 patients, only one patient developed recurrent tumor in the abdominal wall at the site of previous needle biopsy. This lesion was surgically excised and proven to be well differentiated recurrent HCC. No other lesions could be detected and he is doing well 6 years post LT.

The average costs of the LT procedure was \$130,000 (range \$70,000 to \$300,000), this included the costs of the medical care before and after the procedure as well as the immunosuppressive drugs for 3 months after the procedure; but did not include other expenses as traveling, accommodation, and so forth.

DISCUSSION. Egypt is a heavily populated country where the prevalence of chronic liver disease among persons representing the general population was found to be remarkably high. Hepatitis C virus infection was proven to be the main cause of severe chronic liver disease in Egypt, and it was highly associated with schistosomiasis.⁵ Unfortunately, the prevalence of HCV infection in Egypt is strikingly high approximately 26%.⁶⁻⁷ It is known that HCV genotype 4 is the principal genotype found in Egypt and that it shows a poor response to antiviral therapy compared with genotypes 2 and 3.⁸ It is also known that hepatitis HCV infection among Egyptians is linked to the development of hepatocellular carcinoma once they developed and established cirrhosis.⁹ In Egypt, it is only logical to predict that an increasing numbers of HCV patients will progress into end stage liver disease with the high potential of developing HCC; and for those patients LT is the only hope for cure.¹⁰

Since, using cadaveric donors is illegal and socially unacceptable, LT candidates had only one chance for cure; this is to travel abroad to Europe or North America to be listed for cadaveric LT where they have second priority after the local nationals. Few were lucky to get a cadaveric organ in a suitable time, but most of them missed the boat and sadly died in a foreign country. This was a frequent scenario until LDLT was recently introduced in Egypt; and although LDLT is known to offer excellent quality grafts which can be transplanted with optimal timing and under elective conditions and is associated with extremely high success rates;¹¹⁻¹² however, it generates many ethical debates;¹³⁻¹⁴ is it ethical to ask a person to donate part of his liver to save the life of others? Can the donor truly give informed consent under such circumstances? Would it not be considered as an "emotional blackmail"? Is it ethical to subject a healthy person to a major operation with a potential morbidity and mortality¹⁵ to save the life of others? Though donor mortality is very rare, but it has been reported in this study and other studies,¹⁶ and it is an unacceptable catastrophe. One other major concern that is strongly linked to live donation is the likelihood of organ trafficking which cannot be ignored especially in countries such as Egypt where there is a high poverty rate. For all the above moral dilemmas, we still believe that cadaveric liver donation is the logical way forward in Egypt even though it is fully understandable that there are many difficult hurdles to overcome. The religious aspect was thoroughly studied and since 1959 many Islamic Fatwas and sanctions were issued allowing organ and tissue transplantation; however, the most important of which is the historical decree issued in 1986 equating brain death with cadaveric and respiratory death.¹⁷⁻¹⁸ This decree paved the way for many cadaveric liver transplant programs to be launched in Saudi Arabia,¹⁹⁻²⁰ but surprisingly Egypt is still lagging behind! We believe that the real

hurdle in Egypt is not religious but it is rather the inherited socio-cultural believes; Egyptians throughout history have always felt very strongly on honoring the body after death which makes it extremely difficult for a family to accept taking organs from their beloved ones especially while the heart is still beating. This innate refusal becomes even stronger in the view of the noticeable disagreement between Egyptian physicians when it comes to accepting the concept of brain death. Moreover, the ever-increasing lack of trust in the health care system made it almost impossible to convince the public to donate their organ.

One other important argument against expanding LT in Egypt is that it will save only a few out of thousands and thousands of patients suffering from HCV and its complication; and we fully agree that efforts should be mainly directed to the prevention and control of HCV infection in Egypt in order to avoid its devastating effect on the society as well as its enormous negative impact on Egypt's economy and future development. Having said all that, we do not believe that it is appropriate to deprive someone from a certain modality of treatment just because you cannot provide it to others. Moreover, we believe that developing liver transplant programs in Egypt will not only save those few who were lucky to meet its need, but it will also benefit all those liver patients who are still at early stages of their disease. We believe that introducing liver transplant programs into an institute or a country will help in lifting up the standard of medical care for all liver patients by generating many highly specialized centers dedicated to meet the needs of all liver patients at different levels of the health care system. Costs are another legitimate concern in Egypt; it has been argued whether few patients should benefit from LT when there are many others who do not receive medication for common diseases? Who will absorb the high costs? Will it be offered to everyone or only to those who can afford it?

These are complex, interrelated questions that are easier to ask than to answer, and they require much thought and discussion by both individuals and society as a whole. However, we believe that launching LDLT programs was a significant step forward, until cadaveric donation is legalized in Egypt; and although almost all cases were carried out with the help and support of overseas experienced teams. We are hopeful that our local teams will be able to take over in the near future. We also trust that this remarkable success in live organ donation programs will not deter the ongoing efforts to legalize cadaveric organ donation, which is the ultimate goal in the future.

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