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Review Article

Challenges and Infectious Complications in Living Donor Liver Transplantation in Egypt: A Comprehensive Review

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A B S T R A C T

Background: Living donor liver transplantation (LDLT) is a crucial therapeutic option for patients with end-stage liver disease in Egypt, where deceased donor grafts are scarce. This study aims to investigate the challenges and infectious complications associated with LDLT in Egypt.
Methods: A comprehensive review of relevant literature was conducted, focusing on factors affecting donor selection, the prevalence of infections in recipients, and the impact of healthcare providers' knowledge on organ donation. The study included data on complications affecting donors and recipients in the context of LDLT.
Results: The high prevalence of the hepatitis C virus and poverty in Egypt negatively impact the live donor pool. Lack of knowledge about liver donation, inadequate media coverage, and family pressure contribute to the low number of liver donors. Infectious complications play a significant role in the outcomes of LDLT, with bacterial infections being the most common. Donors also experience complications, with intraabdominal collections and pneumonia being the most frequent. Healthcare providers' knowledge and attitudes toward organ donation need improvement, and educational efforts should be tailored to the cultural and religious context.
Conclusion: Addressing the challenges in donor selection, raising public awareness about organ donation, and improving healthcare providers' knowledge are essential steps toward optimizing LDLT outcomes in Egypt. Moreover, it is crucial to monitor and manage infectious complications in both donors and recipients to ensure the success of the transplantation process.

1. Introduction

End-stage liver disease (ESLD) refers to patients with chronic liver failure who have irreversible damage and become decompensated with cirrhosis complicated with ascites, variceal hemorrhage, hepatic encephalopathy, or renal failure. ESLD is caused by various factors, including viral hepatitis, alcoholic hepatitis, metabolic disorders, and selected hepatic malignancies. In Egypt, HCV is the leading cause of chronic liver disease (24.3% prevalence) and is linked to schistosomiasis [1, 2]. Living donor liver transplant (LDLT) is an established treatment option for patients with ESLD. There are three types of liver transplant (LT): Deceased donor liver

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transplant (DDLT), transplants from living donors, and split transplants.
The prevalence of HCV in Egypt is the highest in the world, and LT is the only curative option for these patients. The first LDLT was performed in 1991 at the National Liver Institute in Egypt, and it is now a mainstay of therapy for patients suffering from ESLD [3, 4]. Due to cultural and logistical obstacles, the DDLT program has not yet been implemented in Egypt. Despite the ongoing reliance on LDLT in Egypt, systemic changes are emerging to support the introduction of deceased donor programs [5]. A large study found that age, pre-transplant diabetes, overweight status, and use of mTOR inhibitors significantly increase the risk of developing metabolic syndrome after LDLT in Egypt [5, 6]. This review aims to discuss the current status of Living Donor Liver Transplants in Egypt. It will also outline the challenges and complications associated with LT and the possible solutions.

2. Methods

A comprehensive literature search was done on relevant databases, including PubMed, Google Scholar, Scopus, Web of Science, and Cochrane. We used relevant keywords such as “Liver Cancers”,” “Portal System Infections,” “Living Donor Transplants”, “Transplants in Egypt”, “Liver Transplants History”, “Hepatitis C in Egypt”, “Donor Selection”, “COVID-19” and “Organ Donation Awareness” and combined them with their synonyms using appropriate Boolean operators (AND, OR).
Studies on living donor liver transplants in Egypt and those focusing on their infectious complication or history were included. Studies must be published in a peer-reviewed journal in English, and full-text articles must be available. The articles included were from inception to date and included systematic reviews, meta-analyses, original reviews, and narrative reviews. Case reports, case series, and articles unrelated to living donor transplants in Egypt disorders, infectious complications, or their associations were excluded. Unpublished articles or ones published in a language other than English were also excluded.

3. Discussion

3.1. History and current status

In 1963, Starzl et al. [7] described the first three trials of deceased donor liver transplantation (DDLT) that led to a 100% hospital mortality rate. Cyclosporine and advancements in graft preservation techniques have made DDLT a more reliable curative treatment [8]. Although DDLT has become a standard of care, the paucity of donors, technical difficulties, and cultural controversies have posed significant challenges to its use. As a result, LDLT emerged as an alternative to DDLT. In 1987, Strong et al. performed the first successful LDLT between a mother and her son [9]. Historically, Egypt has had the highest prevalence of the Hepatitis C virus (HCV) in the world, contributing to the high burden of end-stage liver disease. Based on a systematic review published in 2013, Egypt has a prevalence of 14.6% of HCV [10].

As brain death and cadaveric organ transplantation are not yet widely accepted in Egypt due to cultural and ethnic controversies, LDLT remains the only option for patients with ESLD. A surgical team from the National Liver Institute of Menofya University performed the first LDLT in Egypt in 1991 with suboptimal results, as the longest recipient survival was 11 months. As a result, Egypt began to develop centers for liver transplantation with the assistance and supervision of international experts, resulting in a more ambitious and prestigious process. The LDLT program at a private tertiary center was established in 2001. Egypt currently has thirteen comprehensive liver transplant centers [11].

A cross-sectional study in 2013 examined the current state of transplantation in the Arab world. According to the study, 3804 liver transplants were performed in 11 different Arab countries between 1990 and 2013, 2130 (56%) performed in Egypt, and most performed for HCV cirrhosis. Interestingly, all of them except two were LDLTs [12]. The collective data from 2014 to the present is limited. The field of liver transplantation in Egypt continues to improve, but reporting of these improvements is lacking.

3.2. Pediatric liver transplantation

Pediatric liver transplantation has its own set of indications and challenges. The most common indications for liver transplantation are chronic liver disease and its complications, genetic disorders, hepatic tumors, and re-transplantation [13]. The number of liver transplants for pediatric patients in Egypt is limited. According to estimates, only 160 LDLT procedures were performed by 2013[11]. A study reviewed the current status of pediatric liver transplantation and its limitations at a university hospital in Egypt. The study followed 41 pediatric patients who were referred for liver transplantation. Within the study period of six months, only four patients received LDLT, and eight patients, unfortunately, passed away while waiting for a transplant. There were several levels of limitations. For recipients, late presentations and existing co-morbidities were the most common limitations. On the donor side, refusal to donate was the most common limitation. Regarding the transplant program, it was not possible to perform surgery on patients who were less than one year of age or weighed less than eight kilograms. This limited the chances of nearly half of the participants. There was also a limitation in the lack of re-transplantation resources in the institution, which was necessary for one patient [14]. Re-transplant in Egypt: The data for the status of liver re-transplantation in Egypt is lacking. More studies are needed to explore this important aspect of liver transplantation.

3.3. Liver Transplantation in the COVID-19 Era

During the COVID-19 pandemic, liver transplantation was disrupted, as were many other healthcare services. Several steps were taken to minimize infection transmission between transplant patients and healthcare workers (HCWs), including small team groups and better distribution of workloads, periodic training, and audits by infection control teams, as well as appropriate personal protective equipment. For example, the LDLT program at El-Manial Specialized Hospital at Cairo University reopened on August 26, 2020, after a closure period when the national quarantine began in early March.

COVID-19 is considered a high-risk infection for patients who have undergone a liver transplant due to their immunosuppressive medications and concomitant morbidities in order to safeguard the well-being of patients before and following transplantation procedures, a multitude of protocols have been meticulously instituted. These encompass comprehensive screening assessments for donors and recipients in conjunction with rigorous infection prevention and control measures. Despite all precautions, one of the three liver transplant recipients mentioned in the study contracted COVID-19 on his eleventh post-transplant day and was re-admitted to the intensive care unit. Later on, his respiratory symptoms resolved, and he was discharged safely from the hospital [15].

A retrospective analysis of 41 living donor liver transplant recipients at a tertiary center assessed the outcomes of COVID-19 infection. Viral PCR and CT chest criteria were used to detect COVID-19 infection from April 2020 to April 2021. The patients were categorized into mild, moderate, severe, and critical, according to the National Health Commission of China. Approximately 30% of patients showed mild symptoms, 46.5% showed moderate symptoms, 14% were severe, and 9% were considered critical. Two patients died, resulting in a mortality rate of 5%. The severity of the disease was associated with female gender, obesity, and hypertension. The limited number of participants presented a challenge to the study [16].

Although the effectiveness of the COVID-19 vaccine in solid organ transplant recipients is lower than in the general population, a recent study conducted in Canada found a significant improvement in vaccination effectiveness against hospitalization and mortality after the third dose of the vaccine [17]. Therefore, national medical societies and authorities should strive to improve vaccine delivery, especially for vulnerable patients following liver transplantation. The World Health Organization (WHO) reported in December 2022 that less than 40% of the Egyptian population had been fully vaccinated. There are no details on the delivery of the booster vaccinations.

3.4. Quality of life after transplantation

Understanding and anticipating the quality of life after treatment are crucial components of an informed decision-making process, which is essential to patient autonomy. A significant operation, such as hepatic transplantation, necessitates implementing a predictive model that is, to some extent, anticipated and acknowledged by both the medical professionals and the patient involved. Additionally, it may predict survival for both patients and grafts. Researchers at a university hospital used the validated health-related quality of life (HRQOL) questionnaire in its Arabic version to assess the quality of life of 35 liver transplant recipients before and after

transplantation at one and six months. All dimensions of HRQOL improved significantly after transplantation. However, 17 highly educated patients who repeated the test one year after transplantation reported no improvement in mental health other than a limitation in their role[18].

Another study combined HRQOL with the liver disease quality of life 1.0 (LDQOL 1.0) to evaluate the quality of life in the pre-transplantation and post-transplantation phases for 103 patients and 50 patients on a waiting list. As a result of both questionnaire components, all recipients had significantly higher HRQOL scores than those on the waiting list [19].
Since LDLT has a significant effect on the donors as well as the recipients, a cohort study evaluated the quality of life of 30 normal volunteers and 30 donors between six months and four years after surgery using the short form 36 (SF-36 V2) at a private hospital. The quality of life after full recovery was not compromised. They resumed their regular activities within two to four months[20]. Another study used the Physical, Cognitive, Affective, Social, Economic, and Ego Functioning (PCASSE) quality of life questionnaire to measure 33 living liver donors' quality of life, which included emotional and physical aspects. At the second follow-up visit, three months after surgery, their scores were significantly lower than at baseline. Patients were able to return to their normal activities and occupations, which significantly affected the social domain of the questionnaire. Again, the overall quality of life was not reduced after complete resolution [21].

3.5. Challenges and opportunities

The transplantation of livers in Egypt is faced with many challenges. The shortage of organs in the face of increased demand for liver transplantation is one of the most pressing issues [12]. The lack of legislation in Egypt that permits deceased liver transplantation is one of the reasons for this shortage[22]. Although deceased liver transplants have been legalized in other Arab countries, their implementation remains limited due to cultural and logistical barriers [22].
The living donor liver transplant is the only one performed in Egypt and is associated with its challenges and risks [23]. In addition to these risks, the donor faces a risk of morbidity of 52.17% and mortality of 0.29% [23, 24]. After the donation, the donor's quality of life declines in the month following the donation but returns to its pre-donation level after three months [25].

Aside from the strict laws governing donation, LDLT is also hampered by the requirement that donors must be related to recipients, and if a donor cannot be found, the legal team must document the failure before finding a non-related donor who must be evaluated twice by an independent psychiatrist [26]. Additionally, the cost of the medical evaluation process that the donor must undergo ranges from 1050 to 1455 USD [27, 28]. Around 51.72% of patients awaiting liver transplantation are delisted due to the absence of a related donor [29].

Egypt's high HCV prevalence and poverty negatively impact the live donor pool [12]. About 56.6% of donors are rejected for donation [27], and about 96.2% of recipients are in contact with an excluded donor, with a median of three donors per recipient [30]. Anatomical variations are the most common cause of exclusion, followed by viral hepatitis [31]. Several factors contribute to the low number of liver donors in Egypt, including a lack of knowledge about liver donation, inadequate media coverage, and family pressure [22, 30]. According to a survey, 47% of Egyptians are willing to donate their organs after death. As soon as the participants were provided with information regarding the process, regulations concerning organ donation, and consenting options, this percentage increased to 78%. Furthermore, the participants did not understand the Egyptian transplant law articles. Many community-based interventions have successfully changed public behavior, especially in rural areas. Therefore, raising public awareness about organ donation through mass media campaigns and involving religious leaders and scholars is paramount [32].
One survey found that only 34% of healthcare providers would be willing to donate a liver. In Egypt, 53% of healthcare providers are unaware of the opinion of their religion regarding transplants, and 83% are dissatisfied with how the media covers organ donation [22]. A survey revealed that Egyptian medical students lacked an understanding of the legal aspects of organ donation (OD) and the OD process, negatively affecting their attitude towards OD. The undergraduate medical curriculum should be revised to emphasize the importance of organ transplantation and to define the concept of brain death to assist our prospective doctors in educating the public about this procedure and its advantages. Religious and cultural backgrounds should be taken into account in these approaches, as they play a significant role in influencing the decisions of Egyptians [33]. Continuing medical education for HCPs regarding liver transplantation and a better understanding of their religion's position on organ donation will enable them to recruit more donors [22].
A lack of suitable living donors and the lack of deceased donor grafts in Egypt has led to many Egyptian patients seeking transplants abroad in what is known as transplant tourism, where there are ample deceased donors [30, 34].

3.6. Complications associated with LDLT recipients

There is no doubt that infectious complications are among the most significant factors influencing the outcome of living donor transplantation for both the donor and the recipient. Infectious complications can be categorized into early or late complications.

3.7. An overview of early and late infections

A study of 128 liver transplant recipients found that bacterial infections were the most common early complications. The most prevalent pathogens among the study's survivors were Klebsiella and Pseudomonas. Acinetobacter dominated the non-survivors, followed by Methicillin-resistant Staphylococcus aureus (MRSA*).* In the same study, 29 patients experienced early mortality following LDLT, with sepsis accounting for 58% of the deaths. Within the initial year of the investigation, 23 participants experienced mortality, among whom five succumbed to sepsis, accounting for approximately 22% of the deaths. Four of them had CMV infection, one isolated from CMV, and three had concomitant bacterial infections (Pseudomonas, enterococci, and Acinetobacter), as well as disseminated candida in two of them. The fifth patient who died of sepsis without contracting CMV had a single Staphylococcus cohnii infection [35].

Infections that develop during the early, intermediate, or postoperative periods are more likely to result in death. A separate study revealed that out of 128 patients, 53.1% acquired infections during the early postoperative period and 27.3% during the intermediate postoperative period. The mean survival of recipients with early infections (approximately 30.7%) and intermediate infections (about 25.4%) was significantly lower than that of recipients without pretransplant infections. MSSA, MRSA, and Acinetobacter infections were associated with a higher mortality rate following transplantation. Similarly, recipients with CMV and Klebsiella infections were more likely to die during the intermediate period [36].
A multicenter study found that 416 infections occurred in 127 (52%) of the 246 patients who underwent LDLT and participated in the study. Gram-negative bacteria caused 310 infections (74%), while Gram-positive bacteria caused 87 infections (21%). Pseudomonas aeruginosa accounted for the majority of infections (110 episodes, or 26%), followed by Klebsiella species (79 episodes, or 19%), Escherichia coli (69 episodes, or 16%), Acinetobacter baumannii (33 episodes, or 8%), and MRSA (32 episodes, or 7.7%) [37].

3.8. Site of infection

Almost all patients, including a few with cholangitis, had an intra-abdominal bacterial infection. Other common infection sites include the lungs, urinary tract, and wounds [35]. In another study, 73.3% of the 45 patients had bacterial infections. Infections most frequently occur in the bile. Additionally, isolated Gram-negative bacteria were the most prevalent. Some individuals experienced only a single episode, while others experienced multiple episodes. Acinetobacter baumannii was the most frequently isolated organism in both single and repeated infection episodes (19% and 33.3%, respectively), followed by Escherichia coli for repeated infections (11.1%) and Pseudomonas aeruginosa for single infections (19%) [38]. The most frequent site in 246 individuals, the biliary tract, affected 169 patients (or 40.6%), followed by the abdominal area (129 patients, or 31.0%), pneumonia, 44 patients, or 10.6%, bloodstream patients, 39 patients, or 9.4%, and urinary tract infections, 35 patients, or 8.2% [38].

3.9. Hospital-associated infections

In a scholarly investigation involving 337 ESLD patients admitted to the intensive care unit (ICU), it was observed that approximately 36.5% (n=123) were suspected of having healthcare-associated infections (HAIs), with 57 of these cases subsequently receiving confirmation. The most reported hospital-associated infections were bloodstream infections (49.1%), urinary tract infections (31.6%), pneumonia (12.3%), and

spontaneous bacterial peritonitis (7%). Several Gram-positive bacteria were responsible for HAIs, with Staphylococcus aureus accounting for the majority (12/20, 60%). *Gram-negative bacteria most commonly found were Escherichia coli (12/57, 21.1%).* Gram-negative bacteria's prevalence is higher than Gram-positive bacteria's (43.9% versus 40.4%). Fungal infections were reported in 15.8% (9/57) of the patients. Candida species were the most prevalent (12.3%). Anaerobic infection was not detected. The discovery of *Sphingomonas paucimobilis* and *Achromobacter dentrificans* as pathogens for UTI and BSI, respectively, in the ICU was a first [39]. A study on Klebsiella pneumoniae isolates in liver transplant recipients found full resistance to several antibiotics, with Amikacin being the most effective (50% efficacy), highlighting the need for targeted antibiotic strategies [40].

3.10. Impact of pre-transplant infection

The results of a study involving 50 patients with chronic liver disease who underwent liver transplantation revealed that those with high scores on the Model for End-Stage Liver Disease were more prone to infection, both before and after surgery. Chest infection was the most prevalent infection (n=10), followed by nasal mucosal infection (n=8), UTI (n=6), SBP (n=4), and gastroenteritis (n=1). The mortality rate was elevated at 40%, compared to a 23.3% mortality rate observed in 30 patients who did not present with infections prior to transplantation. The impacted group's causes of death were primarily medical (infections and sepsis), approximately 75%, compared to 28.6% in the other group [41].

3.11. Hepatitis C virus (HCV)

Today, chronic HCV infection, predominantly genotype 4, is the leading cause of ESLD and the primary reason for liver transplantation, according to a study conducted at the Gastrointestinal Surgery Center at Mansoura University. A total of 453, or 90.6%, of the 500 participants were infected with HCV. A total of 450 individuals (about 90%) had HCV recurrences, which required administering antiviral medications following surgery [42]. While following 38 patients in different settings, recurrence was observed in 10 individuals (26.3%), with the smaller the graft, the higher the recurrence rate [43]. In the following study of 74 patients with HCV infection who were undergoing LDLT for end-stage cirrhosis or HCC, the latter finding was refuted. Among the 74 individuals, 23 (31.1%) had recurrences of HCV. Researchers found that despite the absence of serum hepatitis B virus deoxyribonucleic acid in recipients, pre-transplant positive antibody to hepatitis B core antigen (total) was significantly associated with the recurrence of HCV [44]. This high rate of HCV recurrence led to the conclusion that Sofosbuvir-based regimens were effective with high sustained virological response rates 12 and relatively safe in a difficult-to-treat population, recurrent HCV post-LDLT [45].

3.12. COVID-19

COVID-19 infection is more likely to occur in the context of LDLT due to the risk of chronic immunosuppression; however, the consequences in terms of morbidity and the need for hospitalization or intensive care are often matched to the population [16, 46].

3.13. Complications associated with the donor of LDLT

It is important to note that complications do not only affect the recipient but also the donor. Multiple studies have reported infectious complications that vary according to the setting. The most commonly observed complication in a handful of donors was intraabdominal collections (21.1% of 145 patients) [23]. Among the significant early infections, pneumonia has been reported in two patients out of fifty, as well as wound infections [24, 47].

The strength of this article lies in its comprehensive coverage of the infectious complications associated with living donor liver transplantation in Egypt, addressing both the donor and recipient perspectives. It also highlights the social, cultural, and legal factors that influence the availability of liver donors in the country. By providing an extensive analysis of the different types of infections, their prevalence, and their outcomes, this article offers valuable insights for healthcare professionals, policymakers, and researchers to understand better the challenges and opportunities in the field of liver transplantation in Egypt. The study complements recent localized data on post-transplant complications and educational interventions, though broader, multicentric studies are still needed [48].

However, the article has some limitations. Firstly, it relies heavily on existing studies, and given the dynamic nature of healthcare and the prevalence of infectious diseases, the data may become outdated over time. Secondly, the article does not directly compare the findings in Egypt to those from other countries or regions, which could have offered a better understanding of the global context.

4. Conclusions

Addressing the challenges and limitations in organ donation and transplantation can lead to better patient outcomes and a more robust healthcare system. This article presents a detailed overview of the infectious complications related to living donor liver transplantation in Egypt, emphasizing the need for improved awareness, education, and resources. Future research should focus on updating the findings presented in this article, comparing them to other regions, and exploring the potential for new strategies and interventions to improve the safety and success of living donor liver transplantation in Egypt.

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