Clinical Practice Guidelines for Liver Transplantation in Saudi Arabia

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ABSTRACT

ارتبط الطلب على زراعة الكبد في المملكة العربية السعودية بارتفاع عبء أمراض الكبد في المملكة. تغيرت اتجاهات وبائيات مؤشرات زراعة الكبد بين المتلقين في المملكة العربية السعودية على مدى 20 عامًا. طغى التهاب الكبد الدهني غير الكحولي على فيروس التهاب الكبد الوبائي سي في المملكة بسبب استراتيجيات العلاج الفعالة لفيروس التهاب الكبد الفيروسي. أصبحت عوامل خطر الإصابة بـ NASH، مثل داء السكري من النوع 2 والسمنة وفرط شحميات الدم، مصدر قلق كبير ومؤشرًا رئيسيًا لزراعة الكبد في المملكة العربية السعودية. هناك أيضًا زيادة ملحوظة في انتشار وحدوث أمراض الكبد الوراثية لدى البالغين في المملكة العربية السعودية. أدت العوامل الجديدة المثبطة للمناعة وحلول الحفظ، وتطور القدرات الجراحية، والتعرف المبكر على الأمراض وعلاجها إلى زيادة معدل نجاح نتائج زراعة الكبد، لكن المخاوف بشأن الآثار الجانبية للعلاج المثبط للمناعة يمكن أن تعرض نتائج البقاء على قيد الحياة على المدى الطويل للخطر. على الرغم من ذلك، تستمر مؤشرات زراعة الكبد في الزيادة، مما يؤدي إلى تحديات مستمرة لزيادة عدد المتبرعين المحتملين وتقليل معدل وفيات المرضى مع توقع إجراء عملية الزرع. يعد المركز السعودي لزراعة الأعضاء مركز وطني معترف للتبرع بالأعضاء من أجل الزرع، ويقدم دعمًا مهمًا لتوفير الأعضاء وتخصيصها. يستعرض المستند توجيهات لمساعدة مقدمي الرعاية الصحية في علاج المرضى في بيئة زراعة الكبد.

The demand for liver transplantation in the Kingdom of Saudi Arabia (KSA) is associated with the country's high burden of liver disease. Trends in the epidemiology of liver transplantation indications among recipients in KSA have changed over 20 years. Non-alcoholic steatohepatitis has eclipsed the hepatitis C virus in the country due to the effective treatment strategies for HCV. Risk factors for NASH, like type 2 diabetes mellitus, obesity, and hyperlipidemia, are becoming a major concern and a leading indication for liver transplantation in the KSA. There is also a significantly increased prevalence and incidence of genetic adult familial liver diseases in KSA. New immunosuppressive agents and preservation solutions, improved surgical capabilities, and early disease recognition and management have increased the success rate of liver transplant outcome but concerns about the side effects of immunosuppressive therapy can jeopardise long-term survival outcomes. Despite this, indications for liver transplantation continue to increase, resulting in ongoing challenges to maximize the number of potential donors and reduce patient mortality rate while expecting to get transplanted. The Saudi Center of Organ Transplant is the recognized National Organ Donation Agency for transplantation, which renders important support for procurement and allocation of organs. This guidance document aims to help healthcare providers in managing patients in the liver transplant setting.

Keywords: liver transplantation, Saudi Arabia, guidelines, living donor, deceased donor

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The need for Saudi Practice Guidelines.

The first human liver transplantation (LT) in the Kingdom of Saudi Arabia (KSA) was performed in 1990, but the first LT program was commenced in 1994.[1] Until 1997, all LTs in KSA were from deceased donors.[1,2] The living donor LT (LDLT) program for children started in 1997, and the LDLT program for adults was initiated in 2001.[3] Thus, as of 2017, there were 2,233 LTs conducted: 1,133 livers from living-related donors, 95 from living-unrelated donors, and

1,005 from deceased donors.[4-7] However, these numbers are disproportional to the actual need for organ transplant, and drastic strategies and programs need to be refined and developed to meet the high demands for organ donations.

The demand for LT in the KSA is associated with the country's high burden of hepatic disease. The hepatitis B (HBV) epidemic in the early 1980s resulted in a high prevalence rate and a significant proportion of patients needing LT for end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC). However, the HBV vaccination program introduced in 1989 caused a substantial prevalence reduction, decreasing the requirement for HBV-related LT[8] but led to a changing trend in LT indications.[9] Although hepatitis C virus (HCV) is still the primary indication for LTs in KSA,[10] the indications for LT are changing from viral-induced hepatic disease to non-alcoholic fatty liver-related cirrhosis.[9] Risk factors that are common in KSA, like type 2 diabetes mellitus (T2DM), obesity, and hyperlipidemia, are becoming a significant concern and a leading indication for LT in the KSA due to non-alcoholic steatohepatitis (NASH)-related liver disease.[3] There is also a significantly increased prevalence and incidence of genetic adult familial liver diseases in KSA.[11]

The advent of new immunosuppressants and preservation solutions, improved surgical procedures, and the early disease recognition and management of manifestations have increased the success rate of LT outcome, but concerns about the side effects of immunosuppressive therapy can jeopardise long-term survival outcomes.[12-14] Despite this, indications for LT continue to increase, resulting in ongoing challenges to increase the number of potential donors and curtail waiting-list mortality.

Presently, KSA has 4 LT centers: 3 in the country capital, Riyadh, and one in the Eastern Province (Dammam).[3,4] Over 50% of the total LT in 2017 was conducted at the King Faisal Specialist Hospital and Research Centre (KFSHRC) in Riyadh, with results comparable with international standards.[3] In fact, the 2017 annual report of the Saudi Center for Organ Transplantation (SCOT) states that a total of 147 LDLT were performed, of which 131 (89%) LTs were from living-related donors and 16 (11%) from living-unrelated liver donors. Out of these 147 LDLTs, 110 (69%) were performed at KFSHRC.[4]

The SCOT is the national agency for organ donation and transplantation. The center carries many roles, from rendering necessary support for organ procurement allocation and transplantation in KSA to authorizing all programs for LT[5] and providing the required criteria for establishing LT Centers in KSA.[6] The most recent data on LT has been extracted from the International Registry in Organ Donation and Transplantation (IRODaT)[7] (Table 1).

These Clinical Practice Guidelines (CPG) aim to help physicians and other healthcare providers evaluate candidates for LT and correctly manage LT patients in KSA. It generates evidence and recommendations according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system.[15] The principles of the GRADE system reflect the quality of underlying data. There are 2 grades of recommendations: strong and weak. If the evidence quality is higher, a strong recommendation is necessary; if the inconsistency in values or ambiguity is more, then a weaker recommendation is granted. Table 2 shows the grading used in this CPG.

Table 2 - Grading of Recommendations Assessment Development and Evaluation (GRADE) system used in the Clinical Practice Guidelines for Liver Transplantation in Saudi Arabia.

GRADE evidence	
I	Randomized, controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology

Table 1 - Registered liver transplantation in the Kingdom of Saudi Arabia between 2018 and 2019.

Country	LDLT 2018	DDLT 2018	LDLT 2019	DDLT 2019	Split 2018	Split 2019
Saudi Arabia	207	62	241	78	0	4

DDLT: deceased donor liver transplant, LDLT: living donor liver transplant
Note: Data was extracted from the IRODaT

1. Organ Donation

Introduction. Currently, the KSA represents one of the leading countries in the Middle Eastern region in the field of LT,[19] but the supply of organ donation is still far from the requirements for LT. Indeed, the KSA possesses a wide supply-demand gap in transplants, assessed to be 2 to 4 per million population (pmp).[17] This creates a major shortage crisis in organs and a worsening waiting list of critically ill patients registered for transplantation.[20]

In the KSA, both deceased donor LT (DDLT) and LDLT are encouraged. However, donation after brain function loss and death is currently the only option available for DDLT in KSA, and for years, religious and ethical concerns have constrained the LT program from progressing. These concerns were mainly due to initial Islamic scholar opinions (Fatwa) advising against donation from brain dead individuals, which have negatively affected the perception of the local community. As a result, a study reported that from 162 patients diagnosed with brain death between 2001-2005, only 17% of patients consented to organ donation, and a majority of these were non-Saudis.[20] Since expatriate workers form the largest pool of deceased donors in KSA, ethical apprehensions arise on the financial compensation by the government, through SCOT, to the donor's next of kin. However, SCOT clarified that such monetary compensation is nothing but showing deep gratitude to the donor's family, as they are responsible for making the donation decision.[20]

Organ shortage crisis. The main challenge continues to be organ shortage. Although the lack of transplantable organs is a worldwide phenomenon, it is particularly evident in countries like KSA due to significant barriers, such as public awareness based on social, religious, and organizational values.[20]

Constraints related to understanding the concept of brain death and inadequate public awareness of the importance of donating organs for transplantation in many countries of the region have a negative impact on deceased organ donation.[25] The results of a survey conducted in 2018 of 500 respondents in KSA demonstrated that less than half of the respondents (44%) agreed with the statement that upon their death, they would allow their organs to be removed to help others in need, 26% neither agreed nor disagreed, and 30% disagreed.[26]

Another concern is that organ allocation in KSA for livers is center-dependant, that is, a center gets an organ irrespective of the need of patients. This situation creates disparities that impact organ donation. This procedure has been followed since early 1990s, leading to the unbalanced organ dispersal among patients within the KSA.[16] An equitable allocation system needs to be enforced to improve the LT program in the KSA.

Despite all efforts, there is an excessive discarding of livers. About half of the donated livers are rejected because of low standards of managing donors. Besides, the brain death protocol is finished in approximately 60% of patients.[3] There were 629 donors in 2016; however, surprisingly, only 399 (63%) correctly finalized the required protocol-based documentation procedures. Only 101 were consenting donors (25%), while 64 were DDLTs; thus, the liver donor conversion rate was merely 10%.[3] This severe organ shortage crisis has led to investments in LDLT in the 4 LT centers in the KSA.[3]

Reporting and documentation. The current reporting system for organ donation in KSA mandates all hospitals to comply with the Ministry of Health (MoH) regulation to report all cases of confirmed brain death donors to SCOT. Laws of enforcement, however, are not in place yet. It is suspected that only a quarter of the brain death cases is being reported to SCOT.[37] Appropriate policies are being introduced to enable procedures to confirm brain death and initiate the required process to manage deceased donor candidates. Saudi Centre for Organ Transplantation publicly provides the necessary documentation for declaring brain death.[38] Specific laws and regulations have been recently enforced including individual declaration of willingness to donate upon death for all Saudi citizens and foreigners living in Saudi Arabia. Declaration will be mandatory through the Ministry of Interior's electronic web services. This will hopefully result in limiting the loss of potential deceased organs. Recently, SCOT has implemented policies that include close monitoring and reporting of survival outcomes from all centers. Feedback will then be discussed in the National Liver Transplant Committee governed by SCOT.

Donation cascade. The Spanish organ donation system is one of the most efficient, with the highest number of donors pmp. Approximately 5.4% of all the LTs are performed in Spain, with a rate of 22.9 pmp.[34]

The National Transplant Organization of Spain has published good practice guidelines in the process of organ donation, which entails a series of recommendations to improve the effectiveness of their LT program.[35] The Spanish system is an organized and aggressive approach that optimizes the donation process component within

their healthcare system, yet to be fully replicated in other countries.

In KSA, it is feasible to adjust some of the Spanish model components for our healthcare system. In fact, the SCOT has already adopted the sequence of procedures for organ donation after death, which is publicly available.[36]

Deceased organ donation. With the steep rise in the requirement of transplantation came the realization that living-related donation was not an answer to the problem. Therefore, by the late 1980s, the need for an active DDLT program within the KSA became obvious.[21] In 1985, the setup for an active deceased organ donation and transplantation initiative was started. The National Kidney Foundation was first formed as the KSA organ donor referral center, to which all institutes were required to report any suitable donors.[21,22] This center was renamed as SCOT in 1993.[23] Media campaigns were used to educate the population and increase public and medical personnel awareness about the concept of brain death and the importance of transplantation program for various organs; addressing religious, social, and medical aspects of the program.[22]

In 1990, the first DDLT was performed, and nowadays, the KSA is one of the leading countries in the Middle Eastern region in the field of DDLT.[19] Despite the various social, religious, and organizational challenges, LT in KSA has increased substantially in the last 30 years with comparable outcomes to other well-recognized international centers.[3] Still today, many factors can affect the availability of deceased organ donors, such as the potential of clinically appropriate donors, governmental regulations, health care investment, public awareness and perceptions, tradition, and faith.[12]

In 2017, 79 deceased livers were transplanted in KSA. Of these, 69 (87%) livers were transplanted to adult recipients and 10 (13%) to pediatric recipients. These cases were distributed between the 3 LT centers.[4]

Not only is there a limited supply of organs for LTs, but the quality of available organs is also not uniform. An association between organ quality and quality of life after LT has been reported.[30,31]

In 2017, the MoH introduced a 3-year joint program with the Donation Transplantation Institute and SCOT. This project aimed to improve the donation and transplantation rates as well as communication with donor hospitals, by introducing a quality management system developed with inputs from popular prototypes in organ donation that amalgamate evidence-supported practices from Europe and USA, including the Organ Donation European Quality System.[32] Saudi Centre for Organ Transplantation has more comprehensive geographical coverage in KSA regions, by setting up an electronic alert system-based organ donation coordination through intensive care units (ICUs) of donating hospitals.[2] The ultimate goal of this project was to increase the donation rate up to 10 pmp.[33] According to data from the IRODaT, in 2019, the actual LT from deceased donors for KSA was 2.33 pmp, while the LT from living donors was 7.22 pmp.[7]

Donor maintenance. The donors are primarily heart-functional, brain-dead, and deceased. Many have major physiologic deficiencies, that are exaggerated post brain death. Prompt rectification of such defects is crucial to maintain proper post-transplant organ functioning. Hence, appropriate donor maintenance is vital to achieving good functioning of the graft for a long duration.[39]

Per the American Association of Neurology, brain death involves 3 cardinal signs, i) termination of brain functions, including the brainstem, ii) coma or unresponsiveness, and iii) breath cessation.[40] Improvement in the quality of donated graft can be achieved by providing appropriate attention to the parameters that help assess the blood flow in donor and pulmonary-protective ventilator tactics. Use of thyroxine, antidiuretic hormone, corticosteroid, and insulin as a supplementary hormone therapy has been reported to provide improved outcomes post-surgery.[41]

As an essential component of the donation process, the care of the donors should be standardized.[42]

Currently, the maintenance of brain death donors is mainly performed by intensivists in the referring hospital who communicate directly with the coordinators and doctors in SCOT. On-site care of donors by SCOT personnel is occasionally done. However, the donation system in KSA lacks well-trained coordinators who can optimize donor care.[20]

The transplant center determines the suitability of the donor or liver for harvesting or transplantation. The decision is based on the donor and organ status.[4]

Extended criteria donors (ECDs). The increasing need for LT is expected to surge even more in the years to come, necessitating exploration of ways to strengthen donor pool.

Organ shortage requires increasing number of potential donors and increased use of ECDs, also called marginal donors.[12] These represent a wide range of donors with adverse characteristics. Extended criteria donors liver grafts represent a higher primary graft

failure than standard-criteria donor grafts.[43] However, with an ECD, the waiting time may become shorter. Although ECD livers are not considered to be ideal and highly challenging for the transplant team, they can significantly shorten the waiting time to transplantation.[44]

Per the Eurotransplant definition, concerning the various classes of graft dysfunction, these criteria are used for ECDs:[12,45]

- Donor above 65 years of age
- Hospitalization in the ICU under ventilation support for more than 7 days
- Body mass index (BMI) >30 kg/m^2
- Serum sodium level more than 165 mmol/L
- Serum bilirubin level above 3 mg/dl
- Aspartate aminotransferase above 90 U/L
- Alanine aminotransferase level above 105 U/L

Graft failure in extended criteria donors. *Anticipated risks.* In the past 2 decades, many quality models for donor, recipient, or combining both have been developed. To estimate post-LT outcomes, the survival outcomes following LT,[46] Delta model of end-stage liver disease (D-MELD),[47] and balance of risk (BAR) scores[48] established. Such models integrate features of donor and recipient, along with LT characteristics; the donor risk index (DRI)[49] includes only donor and LT features to assess the quality of donor and organ.

Donor risk index. The overall survival after LT has steadily improved over the last 20 years.[50] Nevertheless, the increasing demand for organ availability causes augmented use of high-risk or ECD organs. During procurement and LT, donor-recipient matching occurs, and an extensive process is involved in choosing and finalizing an organ for LT.[51,52] Thus, identifying the donor-related factors that may derive from poor post-LT outcomes is extremely important. Furthermore, different regions have different donor characteristics and differences in medical management across organ procurement institutions, which have the potential to affect the post-LT results.[52]

Organ-specific DRI are introduced to estimate graft survival among different donor and recipient features. The use of livers with high DRI associates with amplified healthcare expenses that are risk-independent to patients.[52]

Graft failure risk can be substantially increased due to:

- recipient's age (more than 40 years)
- racial group (African versus White)
- death reason (cardiovascular [CV] injuries)
- type of graft (partial or split LDLT)
- height (by means of 10 cm reduction)

Besides, cold ischemia time and locality where the donor resides are regarded with respect to where the recipient is living.[12] Liver steatosis is not taken into account in DRI, which is a crucial limitation.[12]

BAR score. The BAR score recognizes a few significant predictors of recipient survival after transplantation and a study confirmed the superiority of the BAR score as compared to the other scoring systems.[48] Partial LTs (split and living donor LT), donation after circulatory death (DCD), and combined LTs are not considered. These predictors are: MELD score and age of recipient, age of donor, cold ischemia time, earlier transplantation, and pre-transplant life assistance dependency.

Rise in BAR scores implies reduced patient survival. Balance of risk score has a threshold, after which the mortality increases exponentially at BAR,[18] while it stays stable below 16.[12] The BAR score is suitable to explain the threshold when there is increased LT risk. This is especially advantageous when allocating ECD livers to sick patients, which is a common occurrence in KSA.

Disorders in liver donors. ***Liver steatosis.*** The frequency of steatosis in donors for LT is increasing over time. The prevalence of this condition in the Saudi population is predicted to be 25%.[54] Still, the SCOT statistics show that steatosis is the primary cause of unrecovered extinct livers of qualified donors agreed for donating between 1994 and 2017 (45.6%).[4] The rise in demand to increase the donor liver graft availability results in the possible inclusion of steatotic livers as donors. Although related to poor post-LT outcomes, the inclusion of steatotic livers has conflicting results in the literature, and further investigation is needed.[57]

In spite of poor outcomes than that of nonsteatotic donor livers, steatotic are the most common marginal donor livers presented in the recent 2 decades because of the scarcity of donor organs. Liver steatosis is not against cadaveric LT all the times.[58] Mild steatotic donor livers in LT could not substantially raise the risk for unfortunate outcomes after LT.[59] Metabolic syndrome especially obesity and diabetes negatively affected the number of living donors.[60] Increasing the donor pool needs proper introduction of novel approaches, including the use of living non-related liver donors under strict policies.

The classification of steatosis can range from mild (10-30%), moderate (30 to 60%), and severe (>60%), based on the proportion of hepatocytes that contain cytoplasmic fat droplets.[55,56] Moderate and severe steatotic donor livers can be considered for recipients in comparatively better clinical status but having an

desperate requirement for LT. Moderately and severely steatotic donor livers used for LT were reported to cause higher occurrence of primary non-function and a drift to rise 1-month recipient death rate. Still, the outcomes over on a more extended period were comparatively similar. This outcome led to the suggestion that recipients with good health might endure weak graft function in the beginning or severe post-LT difficulties and further supports the use of moderate and severe steatotic donors for LT.[59] Furthermore, it has been shown that microvesicular steatosis of donor livers has no adverse effect on the postoperative outcome after LT.[61]

The results from a study that combined the 2 major LT databases (United States and Europe) into one complete model to foresee outcome after LT, which focused on the effect of the existence of graft steatosis, showed that hepatic steatosis can be included in modern liver allocation models. Using the BAR score, microsteatosis or less than 30% of macrosteatotic grafts are safer to use until BAR score <18, while grafts with >30% macrosteatosis need to be used for BAR score of 9 or inferior.[62] These results are helpful, considering the current high prevalence of steatosis in LT donors in KSA.

Use of anti-HBc positive donors. Hepatic grafts from donors positive for anti-HBc antibody are frequently associated with HBV infection transmission to recipients, even in the absence of serological markers of active infection.[63] De novo HBV infection is mainly caused by transplanting anti-HBc positive grafts, and care must be taken by the LT centers when using these organs.

Studies have shown that use of hepatitis B immunoglobulin (HBIg) during the surgery along with the use of nucleos(t)ide analogs (NUCs) therapy for longer duration, like lamivudine, can prevent HBV infection in those who received hepatic allografts from those having anti-HBc positivity.[63,64]

De novo HBV infection developed in 19% of recipients with hepatitis B surface antigen (HBsAg)-positivity is not common in anti-HBc/hepatitis B surface antibody (anti-HBs) positive recipients (15%) than HBV naïve non-prophylactic patients (48%). Anti-HBV prophylaxis decreased the rates of such infections in anti-HBc/anti-HBs positive and HBV naïve recipients (3% and 12%). Liver grafts from that donors having anti-HBc positivity are safer to use, especially in recipients with HBsAg or anti-HBc/anti-HBs positivity. Recipients with HBsAg negativity must get lamivudine prophylaxis, similar to recipients with anti-HBc and anti-HBs positivity.[65]

In an international, European, multicenter retrospective analysis to measure the rates of HBV recurrence in LT recipients with HBV, it was shown that fewer recurrence incidents were reported when patients received HBIg and NUC as prophylaxis (4.3%) in the long-term of 7 years. The HBV-HCC recurrence rate was 9.5%.[66] However, lifelong HBIg use is both burdensome and costly, whereas sustained use of lamivudine for a longer time induces resistance formation. Lately, to bring in HBIg-free therapy regimens, highly efficacious NUCs, such as entecavir or tenofovir, were investigated either as a single-drug regimen or together with HBIg in a lower dosage with better outcomes.[67] The use of HbsAg donors is increasingly done in clinical practice and could help in expanding our local donor pool.[68]

Hepatitis C virus positive donors. These donors have varying (mild to severe) forms of infection. However, choosing viremic donors and those with seropositivity are crucial to LT for an uninfected recipient. A viremic donor may pose a 100% transmission risk through LT. Nevertheless, an aviremic but seropositive-only donor possesses lesser threat in terms of HCV transmission (up to 16% risk).[69]

Direct-acting antiviral therapy has proven to be highly effective in treating HCV infection. Its almost 100% cure rates suggest that organs with HCV positivity are safer to waitlisted patients who do not have HCV infection.[70]

Excellent outcomes of antiviral agents against viral hepatitis have rendered the LT fraternity with the advent to utilize organs from donors with viral hepatitis that require simple treatment post-LT.[69] However, ethical concerns should be considered and require a rigorous process of obtaining informed consent from potential recipients.[70]

Grafts from donors with viral hepatitis. During transplantation, stored fresh tissue grafts from donors, who are infected with HBV and HCV, are utilized for vascular reconstruction. This is how the recipients get infected and pose a risk of disease transmission.[71] To avoid these constraints, it is not advisable to store these arterial and venous tissues for use in patients other than relevant organ.[12]

Present/past cancer in donors. Malignancy transferring from donor to recipient due to LT is often a severe complication in patients with less immunity and is challenging for both transplant experts and recipients.[12]

The tumor transmission risk to the recipient of DDLT from donors affected by central nervous system (CNS) cancer is less common. Because cancers of the

CNS less frequently spread and affect outside the brain, marginal grafts can be used to increase the potential organ availability for LT. A recent study has shown that median survival of 40 months was attained in patients who received grafts from donors having a CNS cancer, and no donor-related cancer transformation has been found.[72]

However, the available literature remains incomplete. Further investigation is needed to understand the actual tumor transmission risk, possible risk factors, and readiness to treat recipients in case of a transmission. For donors with various primary brain tumor groups, the considerations are as follows:[73]

- Group I: organ donation is not contraindicated.
- Group II: organ donation can be considered when there are no risk factors present.
- Group III: organ donation is contraindicated, unless in cases of life-challenging emergency LT, in which the waiting-list death risk is higher compared to the risk of transmitting after the surgery.

The ultimate decision regarding LT from donors with primary brain tumor is with the specialists and other team members involved in the transplanting process, who should ponder the tumor transmission risk with the death risk during the waiting list period.[73]

Careful risk and benefit assessments of using organs from those having a present or past history of cancer require cautious evaluation before performing LT.[74] Individuals with glioblastoma multiforme, colorectal carcinoma (>T3), melanoma, choriocarcinoma, breast cancer (>T1c), and lung carcinoma are not suitable as LT donors.[12]

Use of organs from infected donors. The risk of microbial infections can occur following LT. The European Association for the Study of the Liver (EASL) Guidelines used a risk classification to assess the safety and suitability of donors based on infection type[12] and considers as absolute contraindications or unacceptable risk: positive donors for HIV-1 and HIV-2, multidrug-resistant (MDR) infections caused by bacteria, or West Nile virus (WNV), encephalitis, tuberculosis (TB), or others; for such patients, a concrete treatment strategy is unavailable.

In contrast to the US Centers for Disease Control and Prevention policy principle of "zero" risk donor to recipient transmission, the European guidelines take a more practical and pragmatic approach in which the clinical context is considered.[12] This seems to be more suitable for the KSA population (Table 3).

Table 3 - Risk stratification of microbial transmission from donor to recipient in liver transplantation (LT).

Risk classification	Description
Unacceptable risk	Diseases with no definitive treatment, such as HIV, MDR bacterial infections, and some viral CNS infections. Encephalitis without proven cause falls in this category, as well as active tuberculosis
Increased but acceptable risk	Justified by the severity of the recipient condition and risk of death. Examples are HCV and HBV in the donor.
Calculated risk	When recipients have the same disease as the donor or in cases where the infection can be mitigated by antibiotics, such as septicemia and bacterial meningitis.
Non-assessable risk	When the risk cannot be estimated based on donor data, such as organs from donors with highly resistant bacteria or fungal infection. The use of these organs should be avoided.
Standard risk	Donors whose evaluation did not reveal transmissible disease.

HIV: human immunodeficiency virus, MDR: multi drug-resistant, HCV: hepatitis C virus

Consent and ethical issues. The ideal organ donation model requires a significant capability to attain all available organs while upholding ethical morals. The ethical underpinning of the Western model is a combination of quality and deontology, concentrating on individual independence and advantage. The moral premise of this model is a "gift metaphor."

The donation system in KSA is incentive-based, which is not altruistic nor forcible since it preserves the individual autonomy and privacy with respect to accepting or rejecting incentives when attempting to increase usage, that practically builds a win-win state for the transplant recipients and the familial members of the deceased donor, as a minimum from a financial viewpoint. This model is not in contradiction with Saudi society values, which are based on non-secular religious underpinning.[5]

The incentives of this model are state-regulated. Although ideally, they are not mentioned when soliciting consent, the family members of the deceased are mostly aware, especially those of expatriates. The consent is usually obtained by an administrative coordinator from SCOT and occasionally by an in-house intensivist. A religious committee in each hospital is available to support the administrative coordinator.

Many challenges have been associated with society and the medical community regarding organ donation.

Social and moral values, death taboo, ignorance, and procrastination may influence the organ donation system.[75]

The ethical rules that underlie live donation are different from those that concern deceased donors. However, the more careful consideration of organ donation by ethicists, religious scholars, and healthcare fraternity is common to both donors. Organ donations within the circle of a family are very welcomed and respected. Altruistic donations are also acceptable. However, an organ donation carried out with a financial motive is strictly unethical.[76]

Since the 1990s, one of the main issues in the KSA relates to not properly using organs from the available cadaveric donors. Strategies have been placed to raise awareness about organ donation and raise positive consents.

In the KSA, the current system used to get consent for cadaveric donation is an "opting-in" system.[77] This procedure requires explicit donor consent before he/she dies or endorsement by a suitable family member during the donor's death.

This system contrasts with an "opting-out" model. Donatable organs are taken out from brain dead cadavers, albeit no clear consent is given except when the deceased has earlier expressed any wish against donating.[77]

Allocation and waiting-list death. Despite the widespread usage of living donors in the transplant centers in KSA, death on the waiting list has been substantial. Approximately one-third of the patients die before receiving a deceased organ. More alarming is the fact that two-thirds of the patients who need an emergency re-transplant die while waiting for an organ, and as mentioned, allocation favors centers rather than those patients in urgent need.[6]

Globally, the patient-oriented allocation (based on MELD score) has been favored over center-based allocation. Though in some European countries, notably Spain, the allocation is center-based. It is agreeable by all world centers, including KSA, that priority is given for 2 conditions: fulminant hepatic failure and re-transplant within 7 days of the first transplant. The center-based allocation in KSA has been built around zonal distribution with the core idea of supporting the transplant center receiving the donation in the respective zone. This, however, has not resulted in a major success, except for the period between 2006 and 2012, when a Mobile Donor Action Team (MDAT) operated in the Riyadh region supported by one of the transplant centers and yielded a triple number of donors immediately after its implementation by addressing logistical obstacles.[5] A major review of the allocation system needs to be urgently pursued to make the best use of all potential organs.

The proposal for a new organ distribution scheme should be based on the following assumptions:

- The transplant community (mainly SCOT and the four transplant centers) is responsible for stewarding donor organs and must avoid futility at all costs - loss of one graft translates into death on the waiting list.
- Each program is assumed to have transparent, reasonable, responsible approaches to list, care, and educate patients, including listing and allocation policy criteria.
- Programs should not have low survival rates based on listing practices, such as listing patients who have a poor chance of survival.
- Though a 5 or even 10-year survival is a better estimate of program performance, a shorter year survival may be chosen at the beginning of implementing new policies.
- All centers will observe and provide wait-list deaths and drop-outs (by following Scientific Registry of Transplant Recipients [SRTR] explanations) and coordinated by SCOT.

Emphasis must be put on the outcome rather than numbers.

Utility concerns. The decision to prioritize high-risk patients results in lower post-LT survival (as the patient already has a high death risk), better resource utilization, and uneven transplantation rates for various indications.

Comprehensive data collection is important. The following data needs to be collected by centers and reported regularly:

- Referral data, including number and pattern of patients
- Rate of LT (per month)
- Survival and death rates at different times, such as 3 months
- Drop-out rates (withdrawal from the waitlist for different reasons)
- Delisting due to health status improvement
- Deaths and drop-outs are calculated based on the number, percentage, rate, and time to events
- Events reporting should be standardized using the SRTR definitions.

Summary of organ donation. The SCOT oversees multifaceted logistics-related activities during the entire organ donation procedure, such as identifying the suitable donor, reporting, diagnosing, managing, documenting, and getting the required donor consent.[19,24] They firmly believe that continuous efforts are needed to increase public and medical community awareness on the importance of donation and transplantation of organs, to rise the count of transplantations.[27] Clear guidelines are needed to inform the population and health care professionals. Guidelines regarding the diagnosis of brain death and subsequently to the removal of life support in such donors are required. Additionally, guidelines related to organ donation and increased public awareness about brain death are a priority and should be considered as a medical condition.[28] Also, the knowledge and attitude of health care providers towards organ donation are concerning, and educational programs, especially for nursing and medical students, have been implemented.[29] National legislative, governing, and monitoring bodies, in order to ensure quality, health equity, and transparency in LT are needed nationwide to support SCOTs efforts.

2. Evaluation of an adult for liver transplant

Indications for liver transplantation. Liver transplantation is indicated for patients with ESLD who would benefit from the procedure to extend life expectancy and/or improve quality of life. End-stage liver disease can have many etiologies and includes decompensated cirrhosis, HCC, and acute liver failure.

Hepatitis B virus-related hepatic disease. Even though decompensated HBV cirrhosis is lessening globally because of extensive vaccination campaigns and the introduction of direct-acting antivirals, it is still considered a major cause of ESLD in KSA, with HCC being the third leading indication for LT.[9] The HBV status of the recipient needs to be assessed. If HBV DNA is detectable, regardless of the level, antiviral treatment with NUCs should be started because interferon (IFN) is not to be used in those having decompensated cirrhosis. Entecavir or tenofovir are the drugs of choice (Grade II-2),[78] and they act by improving liver function and decreasing the risk of HBV recurrence after LT. They are efficacious and safe in patients with advanced liver disease.[79-81] The dose of NUCs should be modified in those with poor creatinine clearance.[12]

It is essential to note that a significant proportion of decompensated patients who initiate NUCs therapy show improved hepatic function, that may, at times, result in delisting from LT waitlist (Grade II-2).[82,83] A recent study from KSA revealed HBV/HDV coinfection rate of 24%; however, this did not negatively impact LT outcomes.[9] On the other hand, one-third of patients may die within half a year due to hepatic function loss, irrespective of giving effective antiviral treatment,[12] and a precise prognosis is not available to predict patients who will not require LT for recovering and those who will succumb with no LT.

Hepatitis C virus-related hepatic disease. Hepatitis C virus infection is the leading LT indication. Hepatitis C virus genotype 4 (HCV-G4) is the most prevalent genotype in the Middle Eastern region.[84,85] In KSA, HCV forms approximately 29% of LT indications; of them, approximately 60% are related to HCV-G4.[86]

Liver transplantation candidates need pre-LT antiviral agents to lessen the post-LT HCV recurrence (Grade I). Interferon-based regimens are not recommended due to issues with safety and tolerability.[87,88] Treatment with IFN-free antiviral drugs has shown improved liver function, with some patients being delisted (Grade II).[89,90]

Treatment with sofosbuvir and ribavirin (RBV) for a few weeks before LT in patients with HCV genotype-1 (HCV-G1) or HCV-G4, compensated cirrhosis, and HCC prevented graft infection in the most patients[91] (Grade II). Sofosbuvir/ledipasvir given along with RBV for 12 or 24 weeks was evaluated in patients with HCV-G1 or HCV-G4 and compensated or decompensated cirrhosis. The rates of sustained viral response (SVR) at 12 weeks (SVR12) were above 95% and 85% in individuals with compensated and decompensated cirrhosis, respectively (Grade II).[89] The same study showed improvement in MELD scores by 1-8 points in about 66% of patients with decompensated cirrhosis. Sustained viral response at 12 weeks rates of ~95% was obtained with the use of the combined drugs of ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir with RBV in compensated cirrhotic cases with HCV-G1 infection.[92] Efficacy in those with compensated cirrhosis of all genotypes is obtained using the combined use of sofosbuvir, daclatasvir, and RBV (Grade II).[93] A report on patients infected with HCV-G4 concluded that the combination of ledipasvir and sofosbuvir, without RBV, is potent and safe in treating these patients, either in a pre- or post-LT setting.[94]

Alcoholic liver disease (ALD). It is most frequent in Western countries, where it is a common LT indication,[12] and LT for alcoholic cirrhosis has a favorable outcome.[95] A period of 6-month alcohol abstinence before LT is recommended (Grade II-3). This recommendation can

result in improved liver function and delisting of the patient and is a good predictor of patient compliance.

Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Due to epidemic levels of obesity and T2DM, NAFLD and NASH prevalence are emerging as serious health concerns in KSA.[54] Patients with NAFLD/NASH may progress to ESLD and require LT. The presence of metabolic syndrome is linked to many comorbidities, which increases the risk of complications related to surgery[96] and needs to be carefully evaluated. Conditions, such as obesity, hypertension, T2DM, and dyslipidemia require rigorous workup in the screening phase, and they may exacerbate in the post-LT phase (Grade III).[97]

Primary biliary cholangitis. Survival of primary biliary cholangitis (PBC) patients hugely increased well with the extensive use of ursodeoxycholic acid. Nevertheless, approximately 33% of patients show treatment failure and continue to develop cirrhosis, necessitating LT as the final option.[98] Indications for LT in individuals with PBC do not differ from those in patients with other liver diseases; those with decompensated hepatic disease, portal hypertension of advanced, complex stage, and non-controllable and non-tolerable pruritus are indicated for LT[12] (Grade II-3). The optimal timing for LT in PBC is when the total serum bilirubin reaches around 10 mg/dL.[99]

Primary sclerosing cholangitis (PSC). In PSC cases, decompensated hepatic disease, complicated portal hypertension, and recurring occurrences of cholangitis must be indicated for LT (Grade II-3).[12] The cholangiocarcinoma risk rises approximately 10-15% post a 10-year PSC course,[100] and this bile duct cancer should be left out using pre-LT radiological and biological markers (Grade III). Colon cancer should be monitored by annual colonoscopy in patients with PSC and ulcerative colitis (Grade II-3).

Autoimmune hepatitis (AIH). Autoimmune hepatitis affects more females than males, with the percentage of female patients in the KSA ranging from 60.8% in the central region to 75.7% in the Western region.[101] The prevalence of AIH among LT patients from KSA is estimated to be approximately 14.3%, based on a single-center report.[102] Liver transplantation is indicated for AIH in those with ESLD, or with acute hepatic failure during ineffective immunosuppressant therapy (Grade II-3).[103] The outcomes of LT for AIH patients are extremely good, with 1- (90%) and 5- year (80%) survival rates.[104]

Wilson's disease (WD). Wilson's disease is a rare autosomal recessive disease affecting copper metabolism. Only a few studies on WD patients of a small sample size have been conducted in KSA, mainly in regions where consanguineous marriages exceed 50%.[105] Wilson's disease can manifest as acute, subacute, or even chronic hepatic failure, leading to ESLD. Acute stage (Grade III) or ESLD development may require LT, and candidates with neuropsychiatric symptoms need neuropsychiatric examination.[12]

Hereditary hemochromatosis (HH). Hereditary hemochromatosis is an autosomal recessive disorder featured by iron overload. It is caused by a mutation in the HFE gene, the most common being *p.C282Y* and *p.H63D*. In the Saudi population, the frequency of *p.C282Y* is extremely low (<0.001), but the *p.H63D* mutation is relatively common.[106] Few HH patients (1%) transplant due to ESLD,[12] but they pose a higher risk of HCC than those affected by other cirrhosis causes.[107] Therapeutic phlebotomy is the generally recommended therapy for HH.[108] Iron overload mainly poses hepatic implications; nevertheless, it has the potential to develop multiple organ damage. The post-LT outcome for HH is favorable, with 1- (80.7%) and 5- year (74%) survival rates (Grade III).[109]

Primary hyperoxaluria type 1 (PHT1). This disease develops due to shortage of alanine:glyoxylate aminotransferase. It results in the accumulation of insoluble calcium oxalate salts in the kidney and other organs.[110] Hemodialysis is inadequate for oxalate clearance, requiring LT and kidney transplantation (KT) to rectify the metabolic irregularity.[111] Isolated KT reinstates oxalate excretion but is linked to increased recurrence. Pre-emptive LT before end-stage kidney disease is thus a recommended strategy, as LT improves the metabolic defect and averts renal failure[12] (Grade III).

Hepatocellular carcinoma. Hepatocellular carcinoma is the most frequent hepatic cancer. In the KSA, HCC comprises 87.6% of all hepatic malignancies, and the median ages at cancer recognition are 65 and 60 years for males and females, respectively.[112] This HCC incidence in KSA is a consequence of the increased occurrences of 2 major risk factors, namely HBV and HCV infection. Indications for LT in HCC patients are liver cirrhosis, Milan criteria (one lesion <5 cm or <3 lesions <3 cm each), no proof of portal vein (PV) invasion or extrahepatic spread, and no contraindications for LT[112] (Grade I). When these criteria are applied, 5-year survival rate exceeding 70% can be predictable.[113] To avert the patient from falling out of these criteria when on waiting list, local ablative treatment or chemoembolization can be given to resist cancer growth.

University of California San Francisco (UCSF) criteria have shown that the patients with the following measures possess a recurrence-less survival not substantially varied from those within the Milan principles: one nodule of <6.5 cm or many nodules with the hugest being <4.5 cm and the sum being <8 cm.[82] Nonetheless, the Milan criteria serve as the yardstick for choosing HCC patients to undergo LT and the source for appraising new suggested criteria. A 5-year survival is to be attained after downstaging post-LT as similar as the HCC patients who fit the norms for LT with no need of downstaging.[85] Another criteria includes the alpha-fetoprotein (AFP) levels above 500 ng/ml or a hike of 15 ng/ml per month which are poor prognosis criteria.[83] Like the AFP model, other measures have been used, that consider the nodule counts and sizes along with the AFP level.[84]

Cancer progression, downstaging, and bridging therapy make all patients estimated to wait for LT more than 6 months.[86,87]

Non-cirrhotic patients with non-resectable HCC, who have a resection and an intrahepatic HCC recurrence, are regarded as suitable LT candidates when the non-existence of macrovascular invasion and extrahepatic spread has been confirmed.[88]

Cholangiocarcinoma. It is the second most common hepatic neoplasia. A study on cancer incidence using data from the KFSHRC Tumor Registry program showed that 11% of cancer malignancies were due to cholangiocarcinoma.[114] Cholangiocarcinoma often features a poor prognosis and is separated into intrahepatic, hilar, and distal. Liver transplantation in such cases is contentious as the disease may recur.[115] For unresectable hilar cholangiocarcinoma, neoadjuvant

Recommendations for indication of liver transplantation:

- Entecavir or tenofovir is the recommended antiviral treatment for hepatitis B virus (HBV)-related liver disease prior to liver transplant (Grade II-2) as they improve hepatic function and reduce post-liver transplantation (LT) HBV recurrence risk.
- Antiviral drugs should be given if possible before LT (Grade I) to lessen post-LT hepatitis C virus (HCV) recurrence. Treatment with interferon (IFN)-free antiviral drugs can improve liver function, with some patients being delisted (Grade II).
- Treatment with sofosbuvir and ribavirin is recommended for a few weeks before LT in patients with HCV-G1 or HCV-G4, compensated cirrhosis, and hepatocellular carcinoma (HCC) to prevent graft infection in the majority of patients (Grade II). The combination of sofosbuvir, daclatasvir, and RBV is also useful in patients with compensated cirrhosis and with all genotypes (Grade II).
- A period of 6-month alcohol abstinence before LT is recommended (Grade II-3)
- In the setting of cirrhosis, conditions such as obesity, hypertension, type 2 diabetes mellitus (T2DM), and dyslipidemia should go through rigorous workup in the pre-transplant screening phase, to prevent exacerbation in the post-LT phase (Grade III).
- Patients with primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC) should be considered for LT if they present with decompensated hepatic disease, portal hypertension of difficult complex stage, recurrent cholangitis, and non-controllable and non-tolerable pruritus (Grade II-3).
- Cholangiocarcinoma, the bile duct cancer, needs to be left out by radiological and biological indicators using pre-LT in PSC patients (Grade III). Colon cancer should be monitored by annual colonoscopy in patients with PSC and ulcerative colitis (Grade II-3).
- LT is indicated for autoimmune hepatitis (AIH) patients with end-stage liver disease (ESLD), or acute hepatic failure during ineffective immunosuppressant therapy (Grade II-3).
- Wilson's disease can manifest as acute, subacute, or chronic hepatic failure, leading to ESLD. Acute stage (Grade III) or ESLD development may require LT.
- Pre-emptive LT before end-stage kidney disease is a recommended strategy, as LT improves the metabolic defect and averts renal failure (Grade III).
- Patients with HCC and present with liver cirrhosis, Milan criteria (a single lesion less than 5 cm or less than 3 lesions smaller than 3 cm each), no evidence of portal vein invasion or extrahepatic spread, and no contraindications for LT should be considered for LT (Grade I).
- For unresectable hilar cholangiocarcinoma, neoadjuvant chemoradiation and LT are considered therapy strategies (Grade II-3).
- LT can help other hepatic malignancies that do not feature extrahepatic metastatic spread, including fibrolamellar carcinoma and epithelioid hemangioendothelioma (Grade II-3).

chemoradiation and LT are considered a therapy strategy[116] (Grade II-3), assisting in achieving lesser recurrences and more remarkable long-term survival than other available therapy strategies.[116] Surgical removal is regarded as a suitable therapeutical option for extrahepatic cholangiocarcinoma.

Other hepatic malignancies. Liver transplantation can help treat other hepatic malignancies that do not feature extrahepatic metastatic spread, including fibrolamellar cancer and epithelioid hemangioendothelioma. Remarkable disease-free survival rates: 90% (one year), 82% (5 years), and 64% (10 years) (Grade II-3).[117]

Workup process. Management of pre-LT patients should aim at not only eliminating surgery risks but also managing contraindications of long-term immunosuppression following LT. Assessing a LT candidate needs the collaboration of a multidisciplinary team (MDT) of specialists to check for all related comorbidities[118] (Grade III).

Management of medical comorbidities

Obesity. Overweight and obese patients have significantly increased morbidity in terms of infections after LT and, consequently, more prolonged hospitalizations.[119] In obese patients (BMI >35), MDT discussion involving a diet specialist, psychology expert, hepatologist, anesthetic expert, and surgeon is needed. On the other hand, malnutrition is another major concern in cirrhotic patients; therefore, nutritional assessment and management of malnutrition are mandatory in the pretransplant setting.[120]

Older age. Though LT does not have any specific age requirement, patients above 65 years need a MDT discussion to evaluate comorbidities (Grade III). Elderly patients (>70 years) having several comorbid conditions are regarded as relatively contraindicated LT by all 4 LT centers in KSA.[3] However, 5-year death rate and graft loss in recipients above 70 years are similar to those in younger patients, signifying that patients need not be excluded based only on age, but these recipients develop a higher CV complications risk.[121] The impact of old donor age is more pronounced in younger recipients, and age-matching between the donor and the recipient should be incorporated into allocation policies with a multistep approach.[122]

Cardiovascular disease. Checking of CV function is essential in the assessment process. Traditional CV risk factors are associated with coronary artery disease (CAD) in candidates with hepatic disease, which are to be considered as indicators for cautious pre-LT assessment of coronary risk.[123] Electrocardiogram and transthoracic echocardiography need to be conducted in LT candidates to differentiate the pre-existing cardiac disease. To uncover asymptomatic ischemic heart disease, a cardiopulmonary exercise test is required if the candidate has several CV risk factors and is above 50 years (Grade II-3). In candidates with increased CV risk, a cardiology consultation is required for executing a coronary angiography when CAD is suspected. If the candidates received effective pre-LT CAD treatment, post-LT survival is not expressively varied between those having and not having obstructive CAD.[124]

Respiratory diseases. All LT candidates may require pulmonary function tests and chest X-ray (Grade II-3). Hepatopulmonary syndrome (HPS) is found in up to 17% of cirrhotic patients resulting from intrapulmonary vascular dilatations and hypoxemia and is recognized by measuring the alveolar-arterial oxygen gradient and conducting contrast echocardiography.[125] Hepatopulmonary syndrome can be treated only by LT (Grade II-2/3). Severe HPS patients with <50 mmHg oxygen partial pressure without 100% reversibility pose a hazard of permanent pulmonary failure post-LT and high-risk perioperative death.[126] Hepatopulmonary syndrome betterment and reversibility may take months after surgery.[127]

Portopulmonary hypertension (PPHTN) happens in 2% to 8% of cirrhotic patients. A disparity between vasodilators and vasoconstrictors may cause erroneous angiogenesis and pulmonary hypertension.[128] Portopulmonary hypertension is doubted when systolic pulmonary artery pressure is >30 mmHg on echocardiography, which needs to be established by right heart catheterization. Moderate (mean pulmonary artery pressure [MPAP] less than 35 mmHg) and severe PPHTN (less than 45 mmHg) are related to high post-LT death rates.[129] Managing PPHTN patients before surgery needs early disease detection and treatment using respiratory vasodilators epoprostenol (prostacycline) or endothelin receptor antagonist, or phosphodiesterase inhibitor type 5 (sildenafil), could support maintaining respiratory hemodynamics and had shown satisfactory results; though, long-term outcomes are yet to be known.[130] Hence, LT could be the treatment option in moderate PPHTN patients who show good response to clinical therapy and respiratory vasodilators and with moderate MPAP less than 35 mmHg (Grade II-2/3) under anesthetic consultation.[131]

Renal disease. Assessing kidney physiology is crucial for a LT candidate. Cirrhotic patients who suffer kidney

impairment pose a 7-fold high mortality risk post-LT, with half of them dying within a month.[132]

The hepatorenal syndrome, a reversible cause of kidney impairment, is defined as an acute decline in renal physiology manifested by increased serum creatinine (>0.3 mg/dl) to a percentage rise of 50% (1.5- fold) from baseline, caused due to pre-LT reasons other than those of acute kidney injury (AKI), including sepsis, decrease in blood volume, and parenchymal kidney disease.

Chronic kidney disease (CKD) is defined as a projected glomerular filtration rate (GFR) of less than 60 ml/min for more than 3 months.[133] Patients with ESLD having 1) GFR <30 ml/min, 2) hepatorenal syndrome wanting kidney replacement treatment over 8 to 12 weeks, and 3) kidney biopsy exposing >30% fibrosis and glomerulosclerosis, would be advantageous from getting both liver and renal grafts.[134] However, the requirement of combined LT-KT in those with creatinine clearance of 30-60 ml/min. The risk of deterioration of kidney function post LT alone needs to be balanced as a significance of LT and medication side effects, and the scarcity of renal grafts (Grade II-2).

Infection screening. Cirrhotic patients are immunosuppressed and at risk of severe infections.[135] All patients waiting for LT need to be assessed for any latent infections to avoid an exacerbation of infections after LT, especially with the use of immunosuppressive therapy[136] (Grade III).

Screening of infections in LT recipients needs to be progressed in various stages, such as:

A) Level 1: for all LT candidates.

B) Level 2: only in proposed LT recipient at the time of listing.

C) Level 3: in high-risk patients or those from high-risk endemic infection localities.

Level 1 includes tests for HIV 1 and 2 antibodies, HBV serology, HCV antibodies, hepatitis A virus (HAV) antibodies, cytomegalovirus (CMV), and chest X-ray. Level 2 comprises tests for *Mycobacterium tuberculosis* (history + purified protein derivative [PPD]-Mantoux + IFN-gamma release assays), Epstein-Barr virus (EBV), human herpesvirus 8, varicella-zoster virus, herpes simplex virus (HSV)-1, HSV-2, urine culture, parasitological exam and stool culture (*Strongyloidiasis stercoralis* serology, *Toxoplasma gondii* IgG, *Treponema pallidum* serology), with venereal disease research laboratory test, *Staphylococcus aureus* nasal/axillary swab, and dental review. Level 3 of screening needs to be carried out in subgroup of patients based on medical history, comorbidities, endemic diseases, and local epidemiologic conditions. The candidates should have been vaccinated to counter HAV and HBV, varicella, *Pneumococcus*, influenza, and tetanus.[136] Infected patients need to be monitored, similarly to dust exposure for aspergillosis, and those residing in WNV endemic localities for WNV serology and PCR. A chest radiograph is necessary to check for any lung infection, predominantly active or old TB. Purified protein derivative and TB quantiferon testing is also recommended, especially in older populations, as many KSA patients live in endemic areas for TB. Those testing positive with evidence of an active infection require prophylactic treatment with isoniazid under the care of an infectious disease specialist.

Both Gram-positive (*Staphylococcus aureus, Streptococci*) and Gram-negative bacteria (*Klebsiella spp.*) cause soft tissue infections, which comprise 11% of the infections. This increased risk is secondary to chronic edema of soft tissue and bacterial translocation. Cellulitis, the most common skin infection in those with cirrhosis, possesses 20% recurrence possibility.[137,138] Bacteremia can develop spontaneously or due to skin, respiratory, or urinary tract infections. Despite transitory bacteremia, associated with invasive treatment measures, including transarterial chemoembolization (TACE) is comparatively feasible, the threat of a pertinent medical influence does not deserve prophylaxis using antibiotics.[139,140] A prerequisite dental evaluation is recommended for potential liver transplant candidates. Untreated dental disease may pose a risk for infection and sepsis following liver transplantation.[140]

Pneumonia, the third foremost source of infections in cirrhotic patients, has a higher bacteremia risk than healthy people. Community-acquired infection is usually due to *Streptococcus pneumonia* and *H. influenza*. Immunization using pneumococcal vaccination is suggested in cirrhotic patients.[141,142]

Human immunodeficiency virus infection was regarded as not suitable for LT before the availability of antiretroviral treatment options. The reason being the low spontaneous HIV prognosis. The arrival of highly vigorous antiretroviral agents has been a beneficial revolution, resulted in improved prognosis.[143] The development of chronic hepatitis (HBV and HCV) appears quicker in patients with HIV coinfection, and many patients will form more dangerous hepatic cirrhosis. Patients with a controlled HIV disease, without any relevant event, and CD4 >100 to 150/mm^3 can be considered for LT.[144]

Candidemia characterizes a familiar infection in chronic hepatic disease patients and those with PSC

recognized in over 40% of bile samples, more specifically in those having dominant strictures.[145] Infection of invasive fungus aspergillosis is contraindicated to LT, and the treatment needs to be continued until the infection is clear radiographically, clinically, and microbiologically.[146]

Screening for neoplastic lesions. Treated cancers should not be the reason for the removal of LT candidates (Grade III). The long-term survival and recurrence at 1, 5, and 10 years under an immunosuppressant therapy need to be calculated, individually, with a consultation by cancer specialist. Generally, <10% recurrence risk is regarded as the cut-off for LT consideration. Recurrence-free period of about 5 years is often required (Grade III), which usually differs with cancer type.[147] Different risk factors, such as age, gender, alcohol drinking, and smoking habit of the candidate should be assessed cautiously.

In terms of the type of malignancy, for individuals aged over 50 years, checking for colorectal cancer is obligatory. A colonoscopy would be the preferred screening method; however, CT colonography can be an alternative.[118] The screening for lung neoplasia, otorhinolaryngology examination, esophageal and bladder cancers should be carried out, particularly in smokers and alcoholics[118] (Grade II-3). Upper gastrointestinal endoscopy is a general procedure carried out in all candidates, for both malignancy screening and to check esophageal and gastric varices, if present.[118]

All the female candidates should have a regular gynecological examination, comprising Pap smear and mammogram when required. Checking for prostate cancer needs to be carried out in all males over 40 years.[118] Besides, skin evaluation is imperative, as non-melanotic skin malignancies contraindicate LT.

Then, another dedicated screening for liver cancer, based on preoperative standard metastatic examination, comprising a bone scan and chest CT, is required. A positron emission tomography scan may be used to diagnose otherwise undetected neoplastic lesions.[148]

Anatomical evaluation. The assessment of arterial, venous, and biliary systems is crucial for LT (Grade II-3). In the past, patients were not regarded as eligible for LT if they had PV thrombosis (PVT). Still, with clinical, surgical, and radiological advancements, PVT by itself can denote a LT indication[149] (Grade II-3).

Several studies have shown that surgical thrombectomy, thromboendovenectomy with venous reconstruction, interposition of vein graft, portocaval hemitransposition, and radiological endovascular interventions may help remove venous obstruction in LT patients. Notably, 1- and 5-years survival after LT are same in PVT patients. Isolated PVT does not stop a surgery; anticoagulant does avert thrombus extension; nevertheless, in certain patients, entire portal system thrombosis (such as PV, superior mesenteric vein, splenic vein) may not favor a LT.

Recommendations

- Assessing a liver transplantation (LT) candidate needs the collaboration of a multidisciplinary team (MDT) of specialists to check for all related comorbidities (Grade III).
- Though LT does not have any specific age requirement, patients above 65 years need a MDT discussion to evaluate comorbidities (Grade III).
- To uncover asymptomatic ischemic heart disease, a cardiopulmonary exercise test is required if the candidate has several cardiovascular (CV) risk factors and is above 50 years (Grade II-3).
- All LT candidates may require pulmonary function tests and chest x-ray (Grade II-3).
- Hepatopulmonary syndrome (HPS) can be treated only by LT (Grade II-2/3).
- Liver transplantation could be the treatment option in moderate portopulmonary hypertension (PPHTN) patients who show good response to clinical treatment with respiratory vasodilators and with mean pulmonary artery pressure (MPAP) less than 35 mmHg (Grade II-2/3) under anesthetic consultation.
- The requirement of combined LT-KT in those with creatinine clearance of 30-60 ml/min. The risk of kidney function deterioration post LT alone needs to be balanced as a result of LT and medication side effects, and the scarcity of renal grafts (Grade II-2).
- All LT candidates needs to be assessed for any latent infections (Grade III)
- Treated cancers should not be the reason for removal of LT candidates (Grade III).
- The hunt for respiratory neoplasia; cancers in the ear, nose, and throat; esophageal and bladder malignancies should be done, especially in smokers and alcoholics (Grade II-3).
- The assessment of arterial, venous, and biliary systems is crucial for LT (Grade II-3).
- As a result of clinical, surgical, and radiological advancements, portal vein thrombosis (PVT) by itself can denote a LT indication (Grade II-3).
- The social situation, psychiatric condition, and addiction history of recipients should be assessed in order to evaluate the appropriateness of the candidate for transplantation (Grade III).

Biliary tree anatomy assessment is crucial in LDLT recipients, and non-invasive procedures including MRI, magnetic resonance cholangiography (MRCP), or endoscopic retrograde cholangiopancreatography (ERCP) are helpful in achieving it.

Social condition, psychiatric status and addiction. It is essential to evaluate the social situation, psychiatric condition, and habit-forming history of LT recipients to evaluate the appropriateness of the candidate for transplantation[150] (Grade III).

In patients with hepatic encephalopathy (HE), neuropsychological testing, CT brain scan or electroencephalography (EEG) are considered useful in identifying the reversibility of neuropsychiatric status. Active substance addiction or alcohol dependence is not favorable to LT due to the risk of recidivism, non-compliance, and graft injury.[151] All patients with previous alcohol-intake should follow an addiction rehabilitation program, with a careful assessment to ensure a low risk of recidivism before being listed for transplantation.[152] Liver transplantation in patients with active drug abuse may result in 27% recidivism, although this may not influence post-LT survival.[153]

3. Scoring system used to list patients for liver transplantation and managing patient complications while on the waitlist

Adoption of Child-Turcotte-Pugh (CTP) Scoring System. In 1997, OPTN/UNOS, for the first time in solid organ transplantation, the CTP score was adopted as a medical scoring system to evaluate severity of illness. Per UNOS classification, LT candidates were grouped into 4 classes for organ allocation: Status 1, 2A, 2B, and 3 (in descending order of LT importance).[154-156] Unfortunately, from the first year of implementation, the CTP score new policy got a lot of criticism because it did not lead to equitable allocation and proper prioritization, namely, waiting time was still more important than the rule that sicker patients should go first, and also it did not address the geographic difference in time to LT. Between 1998 and 1999, application of the Final Rule to prioritize organ allocation based on necessity, irrespective of geography, and lessening the waiting time to get LT.[157]

Replacement of CTP Scoring System by MELD Score System. On Feb 27, 2002, OPTN/UNOS altered the organ allocation system for LT for the second time to bring about the Final Rule recommendation. The MELD score substituted the CTP- based organ-sharing system. Delta model of end-stage liver disease scores ranging between 6 and 40 replaced waiting lists time favoring the rule of "the sickest first."

Following this system, dramatic changes occurred since its first year of implementation in 2003, namely a 12% decrease in the new LT candidate registration pool in the UNOS database, primarily with MELD score <10, a 10.2% rise in the rate of cadaveric LT, a reduction by >200 days of the time to LT and almost a 3.5% decline of waiting list death rates, compared to the pre-MELD era.[158]

Adding "Share Policy 15" then 35 to address geographic disparity of organ distribution. The MELD allocation system enhanced the liver graft allocation rate to the much-required patients, but there were still disparities in DDLT by location. For this reason, in 2005, the "Share 15" policy was adopted. Under this initiative, regional DDLT candidates with MELD scores ≥15 were allocated liver grafts before local DDLT candidates with MELD scores below 15. Then, in 2013 "Share 15" policy was changed to "Share 35," which prioritized local and regional DDLT candidates with MELD scores ≥35 before local DDLT candidates with MELD scores <35.

One year after adaptation and use of the "Share 35" policy, candidates with MELD scores ≥35 were found more likely to undergo DDLT. Regional sharing of liver grafts raised from 18.9% to 30.4%. There was a significant decrease in waitlist mortality for DDLT candidates with MELD scores >30, reduced discarding of liver grafts and increased overall DDLT volume.[159]

Addition of sodium into the MELD score calculation. Over time, several research reports have shown that low serum sodium associates with the intensity of portal hypertension, and it is correlated with ascites and hepatorenal syndrome (HRS).[160] Serum sodium (Na+) <126 during listing is related to poor outcomes, with significant hazard ratios of 7.8 and 6.3, respectively, and independent of MELD.[161]

In January 2016, OPTN/UNOS permitted the inclusion of Na into the MELD score estimation, with the help of a revised version of the MELD-Na formula for any patient with an initial MELD >11. This formula increases the MELD score for patients with serum sodium <137 mEq/dL; however, patients with sodium <125 mEq/dL do not get any additional MELD increase.[162]

MELD exceptions. The MELD system is based on equity and the idea that LT should be performed faster

for the sickest patients with high short-term mortality. However, the MELD score does not have a 100% sensitivity: it does not address those with low MELD scores but has high mortality without transplantation, such as patients with HCC. For this reason, 2 types of MELD exceptions were adopted: standardized exceptions, which are conditions with sufficient data, such as HCC, HPS, or amyloid neuropathy; and non-standardized MELD exceptions, which are conditions associated with a poor quality of life, such as recurrent encephalopathy or refractory pruritus, or rare diseases with a high risk of mortality.[163]

Hepatocellular carcinoma. Initially, in 2002, a MELD exception was given based on Milan criteria, which included either one lesion <5 cm in maximum diameter or up to 3 lesions with a maximum diameter of any lesion of 3 cm. Stage I tumors (<2 cm size) and stage II lesions were granted a MELD score of 24 and 29, respectively, with an increase in MELD every 3 months, provided the tumor remains within Milan criteria for LT.[113]

Due to an inequitable increase in DDLT for HCC candidates compared to non-HCC patients, along with discrepancies in diagnosis and new drop-out rate data, several modifications to the original MELD score exception assigned to HCC patients were issued to reduce this advantage.

In 2003, OPTN/UNOS reduced the initial MELD scores except 20 for stage I HCC, and 24 for stage II HCC.[164] In 2004, the MELD exception priority for stage I lesions was eliminated.[165] Then, in 2005, the initial MELD exception score for stage II HCC was reduced from 24 to 22. Patients continued to receive a 10% increase in exception points every 3 months, provided they remained within Milan criteria.[166] In 2015 ("Delay and Cap HCC" policy), a patient listed with an actual MELD score like without HCC in the first 6 months was then given a MELD score of 28. Every 3 months, extensions are applied to increase the MELD score to 30, 32, and 34 as the maximum.[167] In 2017, it was allowed standard exception points to be granted to patients who were down-staged as per criteria set by the UCSF (up to 5 tumors with the largest being 4.5 cm and

Table 4 - Management of infectious complications in liver transplantation (LT) listed patients.

Infectious Complication	Evidence	Recommendations
UTI	• Almost 90% of nosocomial UTIs are mainly Foley catheter-related and can precipitate to AKI	• Insertion of Foley catheters in patients should only be used when absolutely indicated
SBP	• SBP is a common precipitant of AKI and encephalopathy and often complicates gastrointestinal hemorrhage. • Nosocomial SBP is more often MDR, more frequently caused by gram-positive organisms, and has up to 50% mortality.	• All hospitalized patients with cirrhosis and ascites should undergo diagnostic paracentesis to rule out SBP at admission or if clinical deterioration occurs. • Primary prophylaxis in patients: with ascitic fluid total protein, <1.5 g/dL; CTP score 9 and serum bilirubin, 3 mg/dL or renal impairment (sCr, 1.2 mg/dL; serum blood urea nitrogen, 25; or serum Na, 130) • Secondary SBP prophylaxis is always indicated. • The drug of choice for the prophylaxis is norfloxacin or, if not available, daily ciprofloxacin or trimethoprim/sulfamethoxazole would be the preferred substitution. • Piperacillin/tazobactam or meropenem is recommended during SBP infection, and patients should receive intravenous albumin to prevent HRS
Clostridium difficile colitis	• Incidence and severity is increasing in hospitalized patients, directly related to liver disease as well as other modifiable risk factors namely, SBP antibiotic prophylaxis, other antibiotic use, and PPI use	• Low-risk patients can safely receive metronidazole, but patients with severe diseases require the use of either oral vancomycin or fidaxomicin
Pneumonia	• Usually precipitated by multiple risk factors: • Hepatic encephalopathy and gastrointestinal bleeding both increase the risk of aspiration • Use of PPIs increases gastrointestinal flora growth • Ascites increase intra-abdominal pressure that can result in atelectasis	• Pneumonia must always be distinguished from volume overload and atelectasis

UTI: urinary tract infection, AKI: acute kidney injury, SBP: spontaneous bacterial peritonitis, MDR: multi drug-resistant, PPI: proton pump inhibitor, CTP: Child-Turcotte-Pugh, sCR: serum creatinine, HRS: hepatorenal syndrome

Table 5 - Management of non- infectious complications in LT listed patients.

Non-infectious complication	Clinical outcome	Recommendations
Variceal bleeding	• 20% initial risk of death • Primary and secondary variceal hemorrhage prophylaxis is the standard of care for prevention. • Primary prophylaxis depends on the MELD score	• Carvedilol leads to a greater hemodynamic response than NSBB because of its alpha-adrenergic blockade, but this can worsen fluid accumulation • Hyponatremia should be avoided in high MELD patients. • NSBB will be a better option, but it should be avoided in patients with refractory ascites after SBP development, and those who require variceal band ligation • Secondary prophylaxis with endoscopic banding to obliteration and NSBB/ carvedilol, both modalities, if tolerated, are standard of care
Renal failure	• Renal dysfunction typically implies a substantially increased risk of mortality, commonly precipitated by a bacterial infection, then hypovolemia. • Other etiologies include HRS and parenchymal nephropathy.	• Identify and treat infection with antibiotic therapy. • Appropriate prophylactic antibiotic therapy should be used in variceal hemorrhage or SBP prophylaxis. • Antibiotic therapy administration should be used when an infection is suspected, and hypovolemia is treated. • Avoid overdosing lactulose, intravenous albumin administration when SBP occurs. • Withdraw diuretics and nephrotoxic drugs. • Vasoconstrictor medications are used to correct peripheral vasodilatation if HRS is suspected. • Midodrine, in combination with octreotide or terlipressin, is suggested, which does not require ICU monitoring
Refractory ascites and HH	• Ascites is the most common complication of cirrhosis that leads to hospital admission. • 50% of patients with compensated cirrhosis develop ascites over ten years, and 15% and 44% of patients will die in one and five years, respectively. • HH is a complication seen in approximately 5-16% of patients with cirrhosis, usually with ascites.	• Initial management, both with diuretics and sodium restriction, should be effective in 10-20% of cases. • Predictors of response are mild or moderate ascites/HH, especially with urine Na^+ excretion >78 mEq/day. • Spironolactone-based diuretics can be used and then add lop diuretics e.g. furosemide (1:4 ratio to preserve potassium). • In an intractable/recurrent ascites/HH, paracentesis and thoracentesis are often needed to optimize ventilator management and to help treat or prevent pneumonia during hospitalization. • TIPS is a good option in low MELD patients, but contraindicated in high MELD patients
Hepatic encephalopathy	• Precipitated by infection, dehydration, gastrointestinal bleeding, worsening hepatic function, TIPS placement, hypokalemia, hyponatremia, and numerous medications	• HE is prevented by avoiding dehydration and electrolyte optimization, specifically potassium repletion to avoid increased renal ammonia-genesis in the presence of hypokalemia, and avoidance of starvation. • Treatment options include: lactulose, rifaximin, sodium benzoate and polyethylene glycol • Replacement of benzodiazepine-derived sleep-aids with diphenhydramine, melatonin, or trazodone can also work. • Patients with TIPS who continue to experience refractory encephalopathy may need their TIPS downsized.
Hyponatremia	• Low serum Na levels reflect the intensity of portal hypertension, and is associated with ascites and HRS. Serum Na^+ <126 mEq/L at the time of listing is associated with poor outcomes. • The need for intervention in dilutional hyponatremia is dictated by the absolute serum Na level, the rapidity of decrease, and the presence or absence of symptoms.	• In asymptomatic patients, fluid restriction and limiting diuretic use are considered first-line interventions. • In symptomatic patients, serum Na should be corrected slowly; a correction of <10 mEq/L to 12 mEq/L in 24 hours and <18 mEq/L in 48 hours is recommended. • Vasopressin receptor antagonists (tolvaptan) remain an effective means of hyponatremia treatment when other therapeutic measures fail, and the risks have been considered

MELD: Model of End-stage Liver Disease, HRS: hepatorenal syndrome, HH: hereditary hemochromatosis, TIPS: Transjugular Intrahepatic Portosystemic Shunt, NSBB: Non selective Beta Blocker, SBP: Spontaneous Bacterial Peritonitis

the sum of tumors being <8 cm), within Milan criteria, and restriction on standardized exception points for HCC patients with AFP levels >1000 ng/mL that do not decrease to <500 ng/mL with treatment.[168,169]

Pulmonary complication of cirrhosis. Both HPS and portopulmonary hypertension (POPH), granted MELD score of 22 with an increase in MELD points equivalent to a 10% increase in mortality every 3 months, provided PaO_2 remains less than 60 mmHg, for patients with HPS and MPAP remains less than 35 mm Hg and pulmonary vascular resistance less than 400 dyn/s/cm for patients with POPH.[170]

Management and follow-up of liver transplant listed patients. Although the current allocation system allows timely access to donor organs for the sickest patients, a substantial percentage of patients are still removed from the transplant list for death or clinical deterioration due to infection-related removal or death related to ESLD complications.[171] The most common complications are either infectious or non-infectious complications,[172-181] many of which are described and recommendations for treatment in Tables 4 & 5.

4. Pediatric liver transplantation

Pediatric LT has been a major success and is now an established therapeutic entity.[182] The use of innovative surgical techniques has allowed for the application of LT even to very young infants with excellent results.[183] However, a gap between the number of patients suitable for LT and the number of donated human livers remains, and related LDLT has emerged as an alternative to DDLT.[184] The innovative techniques of reduced size and split LT relieved this shortage to some extent, allowing children greater access to transplants. Raia et al[185] and Broelsch et al[186] extended these techniques to resect left lateral segments from living adults for transplantation into children.

Pediatric LDLT with left lateral segment grafts (segments 2 and 3) has nearly eliminated waiting list deaths among children and improved graft and patient survival rates (Grade III).[187,188] The success of LT to treat advanced liver disorders has also opened it up to new indications, such as liver tumors and metabolic disorders,[190] with excellent short- and long-term patient and graft survival and significant improvements in the quality of life.[191] The most common diagnoses driving pediatric LT in KSA are genetic familial liver diseases, metabolic disorders, and biliary atresia (Grade II-3).[189]

Indications for Pediatric LT. Advanced cholestatic liver disease is a leading referral to pediatric liver transplant centers in the KSA.[189]

Recent advances in the genetic classification of this group of disorders promise highly personalized management, although genetic heterogeneity also poses a diagnostic challenge. Children-specific LT indications are summarized in Table 6.

Progressive familial intrahepatic cholestasis (PFIC). Progressive familial intrahepatic cholestasis is a group of autosomal recessive cholestatic disorders that presents intrahepatic cholestasis in children or early adulthood and often requires LT early in life. Our pediatric community in KSA is a leading referral for LT in children (Grade II-3).[189] Progressive familial intrahepatic cholestasis includes 3 major diseases characterized by failed secretion of bile acids (BAs) or phospholipids into the bile canaliculus to complete micelle formation.[192] Three types of PFIC have been identified, PFIC1, PFIC2, and PFIC3, with an estimated incidence of 1/50,000 - 100,000.[193]

Progressive familial intrahepatic cholestasis 1 and PFIC2 are caused by impaired secretion of bile salt

Table 6 - Indications for pediatric liver transplantation (LT).

Indications	Disease
Chronic liver disease	Progressive familial intrahepatic cholestasis (all types) Biliary atresia Autoimmune hepatitis Sclerosing cholangitis Caroli syndrome Wilson's disease Cystic fibrosis Alagille syndrome Glycogen storage diseases type 1a, 3 and 4 Tight Junction Protein Type 2 (TJP2) Bile acid coenzyme A: amino acid N-acyltransferase (BAAT) Tyrosinemia type 1 Alpha-1-antitrypsin deficiency
Acute liver failure	-
Liver tumors	-
Unresectable hepatoblastoma (without active extrahepatic disease)	-
Metabolic liver disease with life-threatening extrahepatic complications	Crigler Najjar Syndrome Urea cycle defects Hypercholesterolemia Organic acidemias Primary hyperoxaluria

or conjugated primary BAs into the canaliculi due, respectively, to defects in *ATP8B1* gene encoding the *FIC1* protein, and in *ABCB11* gene encoding the bile salt export pump protein (BSEP). They are characterized by infantile presentation with jaundice, pruritus, and failure to thrive but low or normal gamma-glutamyl transferase (GGT) activity.

ABCB4 gene encodes MDR3 protein, a phospholipid transporter involved in biliary phospholipid excretion. Reduced phospholipid level causes inefficient inactivation of detergent bile salts and epithelial injury of cholangiocytes resulting in high GGT cholestasis, the classical features of PFIC3. In addition to causing PFIC3 (symptoms ranging from neonatal cholestasis to biliary cirrhosis in adult), *ABCB4* mutations can also cause intrahepatic cholestasis of pregnancy and low phospholipid-associated cholelithiasis syndrome, and predispose an individual to medicine-induced cholestasis.[194]

Indication for LT in PFIC includes liver decompensation, failure to thrive, portal hypertension, or intractable itching not responding to medical therapy.[195]

Tight Junction Protein 2 (TJP2) & BA coenzyme A: amino acid N-acyltransferase (BAAT). Tight Junction Protein 2 & BAAT mutation-positive cases present with normal GGT cholestasis, high serum BA, and progressive cholestasis to ESLD. The primary role of TJP2 is to avert the back diffusion of bile salts from the canaliculi to the blood circulation at the paracellular level, explaining the reason behind presence of normal GGT, high serum BA, and fat malabsorption in children. However, it is still unclear why they also have progressive cholestasis with high liver enzymes and bilirubin progressing to ESLD.[196] Indications for LT include liver failure and severe failure to thrive.

Bile acid synthesis defects (BASD). Inborn errors of primary BA synthesis are rare inherited autosomal recessive disorders. The most frequent defects are the 3β-Δ5-hydroxy-C27-steroid oxidoreductase (3β-HSD) deficiency (OMIM 607765), which is due to mutations in HSD3B7; and to a lesser extent, the Δ4–3-oxosteroid-5β-reductase (Δ4–3-oxo-R) deficiency, due to mutations in AKR1D1.[197] These defects in enzymes catalyzing key reactions in the formation of the primary BAs, namely cholic acid (CA) and chenodeoxycholic acid in humans, lead to an inadequate synthesis of primary BAs that are critical for bile formation and to the production and the accumulation of atypical and hepatotoxic BA intermediates. These deficiencies commonly manifest in neonates or infants as cholestasis and can progress to early cirrhosis and liver failure unless treated early with CA.[198]

Alagille syndrome (ALGS). Alagille syndrome, a multiorgan disorder, having a variety of changes in clinical complications, observed even between patients of a single family. Most common characteristics include bile duct paucity on liver biopsy, cholestasis, congenital cardiac imperfections (chiefly concerning pulmonary arteries), butterfly vertebrae, ophthalmologic irregularities (mainly posterior embryotoxon), and characteristic facial features. Abnormalities in kidney function, growth failure, developmental delays, splenomegaly, and vascular anomalies are also reported. Disease diagnosis is recognized in a proband who fulfills the required criteria and/or possesses a heterozygous pathogenic variant in JAG1 or NOTCH2 as diagnosed by molecular genetic testing. The primary indication for LT in ALGS is ESLD secondary to progressive cholestasis, followed by growth failure as the next indication. Some other primary indications are intractable pruritus, portal hypertension, and fractures (Grade III).[199]

High disease burden of autosomal recessive cholestatic liver disease in KSA. Comparable with the local experience with other autosomal recessive disorders, most mutations were private young mutations that were rendered homozygous through the consanguinity loop (68%).[200]

However, the rest (32%) were founders based on their detection in apparently unrelated individuals, and the cumulative carrier frequency was 0.0115 (1 in 87). This translates into a minimum disease burden of cholestatic liver disease in KSA of 1:7246, a really high estimate even compared with countries with a high burden in children, such as Japan.[201]

Biliary atresia. Biliary atresia is a fibroinflammatory disease of the intrahepatic and extrahepatic biliary tree. Surgical hepatic portoenterostomy may restore bile drainage, but the intrahepatic disease progression results in complications of portal hypertension and advanced cirrhosis in most children,[202] becoming one among the most common LT indications in children. Although improvements in biliary atresia surgical treatments, a majority of children require LT (Grade II-3).[203] Indications for LT in biliary atresia include failed Kasai portoenterostomy, significant and recalcitrant malnutrition, recurrent cholangitis, and the progressive manifestations of portal hypertension. Extrahepatic complications of this disease, such as HPS and PPHTN, are also indications for LT.[204]

Urea cycle disorders (UCDs). These are a cluster of monogenic inborn faults of liver metabolism that cause life-threatening hyperammonemia. Flaws in the urea cycle pathway cause a propensity for hyperammonemia

Recommendations

- Pediatric LDLT with left lateral segment grafts (segments 2 and 3) is a recommended procedure that can reduce waiting list deaths among children and improve graft and patient survival rates (Grade III).
- In KSA, genetic familial liver diseases, metabolic disorders, and biliary atresia (Grade II-3) are the most common pediatric diagnoses and LT should be considered.
- The primary indication for LT in ALGS patients should be ESLD secondary to progressive cholestasis, followed by growth failure, then intractable pruritus, portal hypertension, and fractures (Grade-III).

and resultant neurological injury. Ornithine transcarbamylase (OTC) insufficiency is utmost familiar among the UCDs; others include argininosuccinate lyase insufficiency (argininosuccinic aciduria) and argininosuccinate synthetase deficiency (citrullinemia). All UCDs, except OTC deficiency, are autosomal recessive in inheritance. Quick and intrusive therapy is needed for survival. However, the prognosis is not strong relating to survival and neurological outcomes correlated with the number, severity, and duration of hyperammonemic episodes. The only known "cure" for UCDs is LT, which carries some significant morbidity and mortality (Grade III).[205]

Glycogen storage disorders (GSDs). GSDs are inherited disorders in which the concentration and/or structure of glycogen in body tissues is abnormal. Essentially, all known enzymes involved in the synthesis or degradation of glycogen and glucose have been discovered to cause some type of GSD.[206] Glycogen storage disorders types I, III, and IV can be associated with severe liver disease. The indications for LT in GSD I are either multiple liver adenomas bearing the risk of malignant transformation and/or poor metabolic controls.[207] In GSD III, the LT indication is liver failure and HCC. In GSD IV LT, the indication is progressive liver cirrhosis with portal hypertension.[208]

Tyrosinemia type 1. Tyrosinemia type I (hepatorenal tyrosinemia, HT-1) is an autosomal recessive condition resulting in hepatic failure with comorbidities involving the renal and neurologic systems and long-term risks for HCC.[209] The indications of LT in early life is liver failure that is not responded to medical therapy of NTBC [2-(2-nitro-4-trifluoromethylbenzoil)-1,3 cyclohxanedione]. After the age of 2 years, the indications are HCC and progressive liver disease with portal hypertension.

5. Liver transplantation - Surgical aspects in adults and pediatrics

Exceptional results have been achieved in LT through the standardization of surgical procedures, surgical innovations, such as LDLT and split LT (SLT),[186] improvements in pre-, intra-, and postoperative management with the adoption of an MDT approach to patient care, as well as improvements in immunosuppressive medications. Despite improved results, many challenges remain, emphasizing the importance of expertise and specialization. Some unique differences between adult and pediatric LT from a surgical perspective are highlighted.

In the Western world, the most common type of LT is the so-called "conventional" or "standard," where a whole liver is grafted.[210,211] However, in the KSA, due to the severe shortage of organs, LDLT is common and to a lesser extent SLT.[3]

Timing of liver transplantation. Performing LT in a timely fashion is key to achieve successful outcomes. The decision on transplant timing is a dynamic balance between avoiding early unnecessary morbidity and mortality of the transplant versus late with the poor outcome due to disease progression. In patients with acute liver failure, urgent evaluation and emergency transplantation are indicated. In children, the timing of LT in metabolic liver diseases differs as synthetic liver functions are normal. Nevertheless, some of these patients are at risk of serious neurologic complications. The decision and timing to proceed with LT are aided by consultation with the pediatric genetic specialist.[212,213]

Donor/recipient matching. Currently, due to the extreme shortage of deceased donor organ availability in KSA, the main source of organs is living donors. Matching recipient body size and donor liver size are

key factors for LT success in adults and more so in children, especially in low-weight recipients.[215]

In adults LDLT, a graft/recipient weight ratio (GRWR) of 1% is ideal, while in children, a ratio of up to 4% can bring about a successful outcome.[216] Cases of LT with GRWR >4 can present significant early graft dysfunction,[217] which is less likely in adults. Furthermore, primary closure of the abdomen would be impossible and may result in vascular complications and graft failure.[218] Various techniques have been described to reduce graft size, including mono-segmental, reduced, and hyper-reduced grafts.[183,219] Despite best efforts, closure of the abdomen occasionally needs to be staged with temporary closure with a mesh sheet to avoid compression of the graft.

Different types of liver transplantation.

Conventional or standard liver transplantation. Whole-liver grafts are used and implanted in the position where the unhealthy liver in the right upper quadrant is located earlier. In many European nations, the piggy-back procedure is considered, preserving the patient's inferior vena cava (IVC). The donor's suprahepatic IVC is anastomosed to the recipient's 3 hepatic veins (HVs), and the PV, hepatic artery (HA), and biliary tree are reconstructed by duct-to-duct anastomosis between the chief biliary tracts of donor and recipient[12] (Grade II-3). If the recipient's IVC cannot be preserved or in some cases of malignancy, the surgery involves vascular reconstruction with end-to-end anastomoses between the donor's IVC and the recipient's infra- and suprahepatic IVC. Standard LT is classified depending on the donor type (brain dead or cardiac death), but in KSA, only brain dead donations are available.

Domino liver transplantation. The most common domino LT indication is familial amyloidotic polyneuropathy (FAP) (Grade II-3). The patient with FAP gives liver to another while getting a deceased organ.[220] The FAP liver recipient should be above 55 years to reduce the risk of emerging FAP.[12] A graft with 3 distinct suprahepatic veins involving bench surgery for reconstruction is required in FAP patient to preserve IVC. The entire hepatectomy in the FAP donor is conducted because the blood circulation is preserved; however, complications are less if there is no portal hypertension.[221]

Partial graft transplantation. It is performed when there is a requirement for partial support to manage a specific or complete metabolic insufficiency. The graft volume should be enough to withstand the post-LT life of the patient. The ratio of patient's weight to the graft must be a minimum of 0.8%, indicating that an 80-kg patient may require a 640g graft at least.[12] This might cause an issue in adult living donors, and it is usually addressed using the right lobe for LT.[222]

Auxiliary liver transplantation. It can be performed orthotopically or heterotopically and is used in 2 types of situations: 1) patients with acute hepatic failure with the partial graft supporting the unhealthy liver while recovering, the graft is removed, and immunosuppression is reserved,[223] and 2) patients with functional congenital or metabolic disorders disturbing the otherwise healthy liver (Grade II-3). Curing metabolic disorder to evade a full LT may require implanting a partial liver graft while maintaining the function of native liver.[224] Decent outcomes are observed in young patients with acute hepatic failure (mostly viral or autoimmune),[225] but inferior results are seen with Budd-Chiari syndrome and WD.[226] Acute HBV infection remains a debatable indication due to the danger of graft reinfection.[227]

Split liver transplantation. Split liver transplantation involves splitting the liver into 2 parts, and how this division is made depends on who the recipients will be. If the liver is intended for one adult and one pediatric patient, it will be separated into a right lobe that also contains segment IV and a partial left lobe that comprises segments II and III[228,229] (Grade II-2). If the liver is intended for 2 adult patients, it will be separated into the right lobe (segments V-VIII) and left lobe (segments I-IV). Usually, the left lobe has a size of around 450g, which only allows it to be implanted in low-weight (50-55 kg) patients[230,231] (Grade II-2). Split liver transplantation is technically demanding and may increase perioperative complications; therefore, critical evaluation of donor livers suitable for splitting and careful screening of recipients is extremely important.[232]

Living donor liver transplantation. Living donor liver transplantation was first introduced to address the scarcity of pediatric sized cadaver donor livers, which bring about an inadmissibly increased rate of pediatric deaths on the waitlist. Pediatric LDLT became an alternative in these cases, where the living adult donor's segments II and III are relocated into a child.[233]

In Asia, including the KSA, because of the lack of deceased donors, the usage of LDLT slowly extended, terminating with the technique of adult recipients getting entire right lobe grafts (segments V-VIII) from living donors.[3,234] Right hepatectomy is considered safe for the donor[235] and needs careful dissection in which the right HA, right PV, right bile duct, and right suprahepatic vein are separated.[12] Graft/recipient weight ratio must be of at least 0.8% to ensure viability[222]

(Grade III). The recipient process is perplexing because of the anastomoses' size. Nevertheless, the outcomes are good and identical to patients who received whole grafts from deceased donors.[236] However, the main challenge is the significant morbidity in 38% of donors and causing death in 0.18%.[236] One-third of donors experience complications; most have type I or II on the Clavien-Dindo classification system.[237] The most common complications are biliary fistulas, which are generally treated conservatively; however, a few require hospitalization and surgery again.[238,239] Complication in the right lobe donors is more than that of donors of the opposite lobe, with the latter also showing more rapid normalization of serum bilirubin levels and prothrombin time.[240]

Surgical complications. *Vascular complications*

Arterial complications. The incidence of hepatic artery thrombosis (HAT) is approximately 3% in adults and as high as 8% in children;[241] graft dysfunction is the most common feature.[12] This can dramatically alter the graft survival time lowering up to 27.4% at 5 years, in contrast with 76.4% for non-HAT patients.[242] Re-intervention and revascularization can be the treatment option for 50% of HAT patients, whereas the other half requires re-LT[243] (Grade III). The most severe long-term complication is the incidence of ischemic biliary lesions or ischemic cholangiopathy (IC), which can require re-LT.[244]

Early identification is crucial, particularly in the pediatric population. This can be achieved with serial surveillance with Doppler ultrasound, which has a sensitivity of >90%.[245] Permissive hemodilution (hematocrit 20-25%), anticoagulation, and antiplatelets are non-standardized preventive measures practiced variably by transplant centers for the pediatric population.[246] Hepatic artery stenosis (HAS) can be a precursor to HAT, with an incidence in children of 2.8%.[247] It is diagnosed by Doppler ultrasound imaging, and the gold standard is angiography and is best managed by angioplasty and endovascular interventions.[248]

Venous complications. Stenosis or occlusion of the IVC is an uncommon but serious problem, with 1-6% incidence and, mostly, concerning intimal hyperplasia or fibrosis at the place of anastomosis.[249] The piggy-back technique (preservation of the IVC) may reduce the rate of complications arising due to anastomotic stenosis,[249] and endovascular techniques are the therapy of choice[250] (Grade II-3).

The use of the piggy-back technique, with the resultant requirement for anastomosis of the 3 HVs result in outflow problems affecting 30% of recipients.[12] This complication is now very rare due to the performance of anastomosis between the combination of the 3 HVs of the recipient and the IVC of the donor.[251] Patients receiving LDLT/SLT grafts are at particular risk, and graft positioning at the time of the transplantation is critical to minimize the incidence. HV obstruction clinically bears similarity to Budd-Chiari syndrome. Hepatic veins outflow obstruction is common terminology used to reflect HV obstruction instigated by compression or twisting of the anastomosis due to graft regeneration or intimal hyperplasia and fibrosis at the sites of anastomosis. Management by interventional radiology dilation with or without stenting resolves the obstruction.[252] Clinical problems, such as ascites, renal failure, lower limb edema, and splenomegaly, can resolve after endovascular interventions.

Portal vein thrombosis has an incidence of 2.1-26% in patients undergoing LT,[253] mainly due to complications such as smaller PV diameter, technical, size mismatch between the donor's and recipient's PV, and atretic or hypoplastic recipient PV in biliary atresia.[254] In patients with previous PVT, LT is associated with higher surgical complexity, and surgical alternatives include portocaval transposition, renoportal anastomosis, mesentericoportal anastomosis, and multi-visceral transplantation.[12] These, however, are associated with higher morbidity and mortality, with the rate of re-thrombosis reaching 13%, and short-term anticoagulation is therefore recommended.[253] Early PVT presents with graft dysfunction, bleeding, and ascites, and it is managed by thrombectomy, while late PVT showing symptoms of portal hypertension and can be managed by Meso-Rex or selective portosystemic shunts. Alternatively, it can be managed with interventional radiology. Symptomatic PV stenosis is best managed by interventional radiology. In up to half of the PV, stenosis requires more than one dilatation.[254]

Biliary tract complications. Biliary complications remain the Achilles heel of LT, with a reported incidence of up to 30% and include biliary leaks and biliary strictures. Biliary leaks can be anastomotic or, in cases of LDLT/SLT, from the cut edge of the liver. Leaks occur as an early postoperative complication and increase morbidity and mortality after LT. Presentation can be with peritonitis, irritability, vomiting, fever, bilious output from drains, and elevated liver enzymes. The cause can be technical or secondary to HA complications and timely surgical or radiologic intervention is advised to prevent septic complications.

The incidence of biliary leakage is approximately 5%.[255] Depending on its cause, it may have a

comparatively convenient option that includes ERCP procedure and sphincterotomy, temporarily placing a prosthesis, and many more solutions[12] (Grade II-3). For partial graft, the leak is occasionally located on the superficial split liver and is produced by tubules with a gradually decreasing flow. Very infrequently, tubular embolization or re-surgery is needed.[256]

Ischemic bile duct injuries. These may have various etiologies, such as ABO incompatibility, artery thrombosis, ischemia/reperfusion injury, among others,[12] and are among the most common complications (15-37%) in patients who received livers from DCD donors.[257] Additional cause is the reappearance of PSC (20-30%).[258,259] These injuries are presented by intrahepatic strictures chiefly disturbing their confluence, making a beaded appearance, with stenosis and dilatation of the entire biliary tract; cholestasis with intractable pruritus and recurrent cholangitis of liver abscesses are the chief manifestations.[12] Re-LT is suggested in these patients (Grade II-3).[260]

Anastomotic stenosis. Anastomotic stenosis occurs[261] in few adults (4-9%), while in children, it can be as high as 25%.[262,263] The pre-existing reasons for anastomotic strictures are related to suboptimal operation procedures or biliary leak, and their majority presents in the post-LT year, albeit it rises gradually later.[264] Late biliary strictures generally appear as a result of graft ischemia; a radiological examination differentiates HAT. Ischemic biliary strictures usually occur more than one time and upset the entire biliary tree. However, solitary biliary strictures are generally related to surgical anastomosis. The earliest indications are 5 to 10 times increased alkaline phosphatase and GGT levels.[265] Biliary dilatation is often absent in ultrasound, but diagnosis can be made by MRCP, with a sensitivity and specificity nearing 90%,[266] but the treatment ability is not sufficient. The regular treatment strategy involves endoscopic procedure with balloon dilatation and applying a stent, showing a better success rate (70-100%).[261,267] Percutaneous transhepatic cholangiogram is kept for patients who did not benefit from endoscopic therapy or those with complicated hepatico-jejunostomies and possesses a lesser success rate (50-75%).[268] When patients do not respond to either therapy, a hepatico-jejunostomy needs to be conducted (Grade II-3).[12]

Complications associated with partial grafts. The most common complication associated with partial grafts is anastomotic stenosis. An important related factor is the presence of bile leak,[269] and even though the underlying process is unknown, it may be associated with the local bile inflammatory effect or with weak local vascularity.[12] Some research reports relate duct-to-duct anastomosis size with the presence of stenosis.[270] The incidence of anastomotic stenosis can affect half of partial liver graft recipients, and although it may not disturb long-term survival, the quality of life may be impacted.[261] The success rate of endoscopic treatment (60-75%) is lesser compared to anastomotic stenosis after whole-LT.[271] Interventional radiology serves as a good therapy option through dilatation or stent insertion.[12] Around half of the cases need re-surgery, and the duct-to-duct anastomosis becomes a hepatico-jejunostomy (Grade III).[256]

Bowel perforation. Bowel perforation is a potentially devastating complication after LT in the pediatric population. Post-Kasai procedure recipients are particularly at risk, while other risk factors include high-dose steroid therapy, CMV infection, prolonged procedure, and re-operation for postoperative bleeding.

Recommendations

- Domino LT procedure is the preferred option for familial amyloidotic polyneuropathy (Grade II-3)
- Auxiliary LT should be used in two types of situations: 1) patients with acute hepatic failure with the partial graft supporting the unhealthy liver while recovering, and 2) patients with functional congenital or metabolic disorders disturbing the otherwise healthy liver (Grade II-3).
- In split LT (SLT), if the liver is intended for one adult and one pediatric patient, it should be separated into a right lobe that also contains segment IV and a partial left lobe that comprises segments II and III (Grade II-2). If the liver is intended for two adults, it should be split into the right lobe (segments V-VIII) and left lobe (segments I-IV). Usually, the left lobe has a size of around 450g, which only allows it to be implanted in low-weight (50-55 kg) patients (Grade II-2).
- Graft/recipient weight ratio needs to be minimum 0.8% to ensure viability (Grade III).
- Re-intervention and revascularization can be the treatment option for 50% of hepatic artery thrombosis, whereas the other half requires re-LT (Grade III).
- Monitoring for biliary leakage is recommended as its incidence is around 5%. Depending on its cause, it may have a comparatively convenient option, that included an endoscopic retrograde cholangiopancreatography (ERCP) procedure and sphincterotomy, temporarily placing a prosthesis, and many more solutions (Grade II-3).
- Re-LT is the recommended treatment for ischemic bile duct injuries (Grade II-3).
- Hepatico-jejunostomy should be performed for anastomotic stenosis in cases of no response to other therapies (Grade II-3).
- About 7% to -10% of adult patients loose liver graft post-LT, and re-LT is the ideal treatment (Grade II-2).

The diagnosis can be challenging in this age group, with abdominal distention being the only symptom presenting. The incidence is reported to be 10-20%.[272,273] Emergency laparotomy, washout, and repair are indicated.

Re-liver transplantation. Approximately 7-10% of adult patients lose transplanted grafts,[274] and re-LT is the only suitable therapy for these patients (Grade II-2).[275] The main causes of graft loss can be divided into early (HAT or main graft not functioning) and late-onset (IC, chronic rejection, or reappearance of the primary liver disease).[12] The re-LT rate in KSA is 3.7%, lower than worldwide rates, which vary between 5-22%,[276] and this can be attributed to the severe shortage of deceased donor grafts. Small-for-size syndrome is the leading indication for re-LT in KSA, followed by HAT, recurrence of the original disease, chronic rejection, and late vascular complications.[276] The timing of re-LT is a crucial time for patient and graft survival. Those with a re-LT time of fewer than 30 days have lower survival times than those with later re-LT,[276,277] and re-LT has higher morbidity and mortality compared with LT.[274] Currently, there is no consensus for defining specific survival outcomes in which re-LT should be avoided, and only the MELD score provides an objective stratification for re-LT candidates.[12] Re-LT recipients having MELD score >25 showed a reduced short-term survival (<60%), while those with MELD score >30 had a 20-40% survival rate.[278] The key parameter in establishing treatment success of re-LT is allograft quality, with aged donors and lengthy cold ischemia time are regarded as crucial aspects.[12]

Hepatitis C virus was regarded as an independent risk factor for re-LT. However, several studies show that re-LT can give an optimal survival time, with no significant differences in survival time between HCV positive, cryptogenic, cholestatic, or ALD patients when attuned to MELD scores and age (Grade II-3).[279-281]

The selection of recipients for re-LT needs to be integrated with disease severity, time since first LT, and graft quality, which are imperative than the cause of re-LT.[12]

6. Post-transplant care

Survival after LT has improved over time with fine-tuned immunosuppression protocols, postoperative care, and prevention and treatment of infections.[282] There are several causes of death post-LT. A year after surgery, infections and operation-related complications may form the reason for the deaths or graft losses in 60% of cases. After this period, cancers, renal failure, and cardiovascular manifestations are the most important causes of mortality.[12,283]

Immunosuppression. Post-LT patients require lifelong immunosuppression, which is key for graft survival. The sustained immunosuppressant usage may induce unavoidable consequences, like high infection risk, metabolic complications such as hypertension, T2DM); hyperlipidemia, obesity, and gout; and de novo cancers (including post-LT lymphoproliferative disorder [PTLD]).[283] The specific immunosuppression regimen should consider minimizing these side effects that may affect patient survival. Immunosuppression medication is maximized gradually during the first week of postoperative care, aiming to reduce the risk of acute cellular rejection.[12] Most LT centers in the KSA use 3 agents to prevent rejection in the immediate postoperative period. These include a glucocorticoid, such as prednisone, a calcineurin inhibitor (CNI), such as tacrolimus or cyclosporine, and a third agent, such as mycophenolate mofetil (MMF). After 6 months, with the stability of the graft function, most patients require only a single immunosuppressive agent, which is the main drug for long-term immunosuppression, typically a CNI.

Immunosuppressive drugs

Calcineurin inhibitor. Tacrolimus is the medicine of choice and main CNI in post-LT patients. A meta-analysis comparing tacrolimus with cyclosporin has shown that tacrolimus is better than cyclosporin in terms of improving survival and avoiding graft loss or rejection. However, no difference in renal function has been found.[284,285] The main side effects of CNI therapy are renal impairment, infections, gout, hypertension, hypercholesterolemia, glucose intolerance, hypomagnesemia, hyperkalemia, and tremor.[285]

Calcineurin inhibitor neurotoxicity post-LT is a rare but serious event, especially associated with posterior reversible encephalopathy syndrome (PRES) due to endothelial dysfunction secondary to CNIs. In a retrospective cohort of 1923 adult LT recipients, PRES was diagnosed radiologically in 19 patients (1%), with most cases occurring early post-LT.[286] A sustained-release formulation of tacrolimus was introduced, which offers a once-daily dosing option, but showing efficacy and safety identical to the twice-daily dosing regimen.[287,288] Such a formulation may help achieve patient medication adherence.[289]

Azathioprine (AZA) and mycophenolate mofetil. In LT, both the antimetabolites, AZA and MMF, are widely used. These drugs reduce purine synthesis,

impacting T and B lymphocyte proliferation, and they are used in combination with a CNI for preventing graft rejection. The use of these drugs has increased in the last 2 decades as they serve the purpose of decreasing the CNI's dose, especially in patients with kidney impairment, minimizing the effect of CNI nephrotoxicity. Mycophenolate mofetil has increasingly become the highly utilized antimetabolite drug, albeit no differences were observed with AZA regarding patient and graft survival.[147,290,291] Major side effects of MMF include diarrhea, leucopenia and bone marrow suppression. The enteric-coated formulation of mycophenolate sodium (EC-MPS) reduces the gastrointestinal side effects, but the LT data is limited.[292,293] A small size single-arm study in LT showed that the conversion from MMF to EC-MPS was related to substantial progress in gastrointestinal symptoms,[291] but no high-level evidence is existing as such.

Sirolimus (SRL) and everolimus (EVR). Sirolimus and EVR inhibit the mammalian target of rapamycin (mTORi), blocking interleukin (IL)-2 and IL-15 induced proliferation of T and B lymphocytes. The main side effects of mTORi are thrombocytopenia, leucopenia, impaired wound healing, hyperlipidemia, proteinuria, possible increased risk of HAT.[294] The use of EVR in combination with reduced tacrolimus dose prevents renal impairment post-LT.[295] It reduces the HCC recurrence rate in one year, as shown in a randomized multicenter study of LDLT.[296]

Basiliximab. Basiliximab is an induction agent, IL-2 receptor (CD25) monoclonal antibody used to decrease the side effects of immunosuppressants by diminishing or delaying the use of CNIs. This agent is used especially when the recipient has renal impairment prior to transplant, although studies have not found differences in patient and graft survival. A meta-analysis of 18 studies showed that LT patients receiving IL-2R antagonists had lesser acute rejection, steroid-resistant acute rejection, and no functioning of kidneys when related to decreased or late CNI use.[297]

Corticosteroids. Corticosteroids are part of the standard immunosuppression regimen with CNI and antimetabolite agents, starting with the induction in the immediate operative phase and then continuing with taper protocols. Steroids may be tapered by 2 months in patients at low risk for rejection, uncontrolled diabetes, severe osteoporosis, sepsis, or delayed wound healing. However, low-dose steroids should continue in autoimmune disease to try to prevent disease recurrence. Steroids have many side effects, including infections, hypertension, T2DM, and osteoporosis. Therefore, minimizing the corticosteroids regimen with time is prudent.[298] **Table 6** summarizes the side effects of immunosuppressive drugs.

The choice of immunosuppressive drugs varies between individuals and depends on many factors that include time after transplant, indication for transplant, rejection episodes, risk of cancer, renal impairment, risk of infections, and comorbid diseases.[283,299] In addition, drug-drug interactions must be considered during the use of immunosuppressive agents (**Table 7**).

Medical complications. Before and after LT, medication adherence is imperative in avoiding complications that may affect graft function; otherwise, it may increase costs after the surgery or even patient death.[118]

Early post-liver transplantation and long-term follow-up. Most deaths happen in the initial days after LT, and the causes differ based on the time after LT. Almost 60% of deaths are related to infections and intra- and perioperative surgical complications. Graft losses in the initial year post-LT and de novo cancers and cardiovascular manifestations are key mortality causes after this period.[12] Increased, adequate, and safer use of immuno suppressive agents may prevent

Recommendations

- Calcineurin inhibitors (CNI)-based regimen has shown better long-term graft and patient survival in liver transplantation (LT) recipients and can thus be considered as the primary immunosuppressive treatment; tacrolimus has better performance than cyclosporin A, even in hepatitis C virus (HCV) patients (Grade I).
- Treatment of mycophenolate mofetil (MMF) alone may induce acute cellular rejection and has not to be considered (Grade I). However, MMF along with MMF reduced CNI (minimum 50%) results in better advancement kidney function and possesses a lesser risk of acute rejection (Grade I).
- Safer conversion to Sirolimus (SRL) may offer adequate immunosuppression with no rise in rejection, graft loss, or infection in LT recipients (Grade I).
- Post-LT renal function can be improved using early EVR-based CNI-free immunosuppressive agents; however, care must be taken as it may increases the chance of acute rejection (Grade I)

Table 7 - Major drug-drug interactions involving immunosuppressive agents.

Antimicrobials	Calcineurin inhibitors	Mammalian target of rapamycin inhibitors	Mycophenolate
Fluoroquinolones (primarily ofloxacin > ciprofloxacin)	Increased levels	-	-
Macrolides (erythromycin > clarithromycin > azithromycin)	Markedly increased levels	Markedly increased levels	-
Rifamycins (rifampin > rifabutin)	Markedly decreased levels	Markedly decreased levels	-
Linezolid		Increased myelosuppression	Increased myelosuppression and platelet decrease
Triazoles (ketoconazole / voriconazole / posaconazole > itraconazole / fluconazole)	Increased levels	Increased levels (voriconazole contraindicated)	-
Ganciclovir / valganciclovir		Increased myelosuppression	Increased myelosuppression

acute rejections or graft loss, while chronic ductopenic rejection poses a lesser prognosis without re-LT.[300]

The increasing prevalence of NAFLD and aged LT recipients, de novo diabetes and metabolic bone disease, are diagnosed after LT. De novo malignancy and PTLD, although less common, are associated with significant mortality in NAFLD recipients. Earlier diagnosis, immunosuppression treatment modification, and rarely re-LT in the context of irreversible graft rejection and KT in end-stage renal disease (ESRD) are important for patient outcomes.[118,300]

Recurrence of disease

Hepatitis C virus recurrence: management and treatment post-liver transplantation. It is expected that HCV may recur post-LT in approximately 33% of LT patients who are HCV-infected, increasing the risk of clinical decompensation and graft loss.[301,302] Early antiviral treatment is suggested in these patients. Sustained viral response is related to better patient outcomes.[12,306] (Grade II-1). For genotype 1- and 4- infected LT recipients, such as patients with compensated cirrhosis, an initial treatment regimen with a sofosbuvir-based therapy or a combination of glecaprevir/pibrentasvir for 12 weeks is recommended with high SVR rates. While for decompensated cirrhosis, the treatment will be sofosbuvir-based therapy with RBV for 12 -24 weeks, as per the HCV guidelines: (https://www.hcvguidelines.org).

Preventing and treating hepatitis B virus recurrence. The recurrence of post-LT HBV causes allograft dysfunction, allograft cirrhosis, and graft failure.[309] Hepatitis B virus-related cirrhotic patients pose increased graft infection risk (~70%), hepatitis D virus-related cirrhotic patients have moderate (~40%) risk, and those with acute hepatic failure has comparatively lower (<20%) risk. The key cause of HBV recurrence is increased HBV DNA levels during the LT procedure.[12,310] Liver transplantation for HBV-related cirrhosis currently has exceptional long-term outcomes, with 5-year SVR ≥80%.[84,311,312]

The use of antivirals for patients waiting for LT subdues allograft HBV replication and recurrence. Thus, HBV patients with decompensated cirrhosis must require entecavir or tenofovir prior to LT.[309] Currently, >90% of patients with recurrent HBV infections require antiviral agents.[309]

Hepatitis B virus recurrence can be prevented by a combination of HBIg and antiviral drugs in high-risk patients. However, low dose HBIg, HBIg-free protocols, and monoprophylaxis with high-efficacy antiviral drugs can also be used in low-risk cases.[309] Because of the increased expenses related to HBIg therapy, many research projects have evaluated the efficacy of HBIg in reduced doses or even withdrawal in chosen patients. These approaches, along with NUCs, have successfully prohibited HBV recurrence and seem to be a possible strategy for HBeAg-negative in LT candidates with non-detectable HBV DNA traces. Besides, these regimens dramatically reduce costs when compared to high-dose intravenous HBIg regimens.[12] Five years after receiving intramuscular injections of HBIg (400 IU to 800 IU per month) along with lamivudine, the recurrence was merely 4%.[313] A randomized study has shown that a small dosage regimen of HBIg along with lamivudine, trailed by lamivudine monotherapy, has yielded good results in patients with undetectable HBV DNA levels during LT.[314]

Although recent studies have questioned the need for HBIg since NUCs have become more efficient, data is not consistent concerning HBV graft infection and HBV recurrence.[315]

Patients who got liver transplantation from anti-hepatitis C virus positive donors. The impact of anti-HBc positive liver grafts on survival and de novo HBV infection risk post-LT continue to be debatable.[316] Liver transplantation patients who received transplant from an anti-HBc positive donor must receive antiviral therapy soon after LT (Grade II-2).[317]

In terms of cost-effective treatment, lamivudine monotherapy is the best option. A recent study comparing lamivudine and entecavir monotherapy prophylaxis in HBsAg negative recipients that received anti-HBc positive grafts showed that de novo HBV was exceptionally infrequent, particularly with entecavir prophylaxis.[316] Hepatitis B immune globulin must not be given in HBsAg negative patients who received LT from an anti-HBc positive donor (Grade II-2).[12]

Managing patients transplanted for alcoholic liver disease. Liver transplantation candidates with ALD have a similar survival rate compared to those without ALD, but the post-LT death rate is high in patients with comorbid ALD.[283] Post-LT alcohol relapse in ALD patients varies a lot (10%-90%), and patients with an earlier disease detection of ALD must be advised to avoid alcohol at all (Grade II-2) and undergo psychiatric treatment or consultation if they start back alcohol consumption in the post-LT period (Grade II-3).[12,283]

Advice on smoking cessation must be considered. The risk of cardiovascular disease and associated manifestations or new-onset malignancies of the airway, pulmonary tract, or upper digestive tract, particularly in cigarette smokers, requires caution.[318]

Recurrence of NAFLD. Both NAFLD and NASH, recurrent and de novo, are common after LT.[9] Pre- and post-LT BMI, T2DM, arterial hypertension, and hyperlipidemia are the major risk factors for post-LT NAFLD/NASH.[12,318,319] Liver biopsy is required to confirm recurrent or de novo NAFLD/NASH, recognize fibrosis, and exclude alternate causes of altered liver chemistry tests (Grade III). Avoiding extreme weight gains and keeping hypertension, dyslipidemia, and T2DM in control are recommended (Grade III).[12,318]

Recurrence of cholestatic hepatic disease. Autoimmune hepatitis, PBC, and PSC recurrence differ from 10% to 50% and must be confirmed by liver biopsy and/or cholangiography (PSC) (Grade II-3).[12] Primary sclerosing cholangitis recurrence is common and leads to graft failure after LT for PSC. Keeping an inactive inflammatory bowel disease status may guard against PSC recurrence.[320] There is no convincing data to support the ursodeoxycholic acid prophylaxis in patients who underwent LT for PBC and PSC (Grade III).[12]

Managing hepatocellular carcinoma recurrence. The risk of HCC recurrence following LT affects between 15% and 20% of the cases. It is generally observed during a couple of years initially after LT, with a median survival lesser than a year.[321,322] The recurrence risk depends on numerous factors related to the tumor, patient, and treatment.[323]

Factors such as the histopathological characteristics of the tumor, AFP levels, and waiting time are well established. However, other biological factors related to tumor behavior and treatment must be identified since they can be used to refine selection criteria of transplant candidates to reduce recurrence.[323]

In patients who developed hepatic cirrhosis due to HCC recurrence, de novo HCC may progress, similar treatment protocol used for immunocompetent patients needs to be adhered, that may include hepatic resection, radiofrequency ablation or TACE (when possible) and, when indicated, re-LT.[12] Surveillance for de novo HCC needs to be carried out with radiological investigation of the abdomen every 6 months to one year.[318]

Currently, there is no supporting data suggesting that long-term (>5 years) recurrence-free survival is achieved using SRL (Grade I); however, it seems to be effective in 3-5 years, time in HCC patients within Milan criteria (Grade I). Therefore, an immunosuppressant treatment plan that comprises SRL starting many weeks post-LT must be used for patients who are affected due to HCC.[12,283]

Table 8 - Prevalence of cardiovascular risk factors and CKD in LT recipients beyond the first post-transplant year.

Risk factors	Prevalence rate %
Cardiovascular risk factor	
Metabolic syndrome*	50 - 60
Systemic hypertension	40 - 85
Diabetes mellitus	10 - 64
Obesity	24 - 64
Dyslipidemia	40 - 66
Cigarette smoking	10 - 40
CKD (stage 3-4)†	30-80
End-stage kidney disease	5-8

*Any 3 of the following: hypertension, obesity, dyslipidemia, and diabetes mellitus. †Estimated glomerular filtration rate = 15 to <60 mL/minute/1.73 m^2.

Several studies have attempted to demonstrate that sorafenib, a multikinase inhibitor, might be associated with benefits in survival and safety profiles; however, based on the current data, a recommendation for its use cannot be established.[12,324-326] Thus, it is recommended that therapy for HCC recurrence post-LT be personalized, and there is no evidence to utilize sorafenib in patients with disseminated recurrence (Grade III).[12]

Managing kidney dysfunction. Most LT recipients, who survive the initial 6 months, develop CKD.[327] The causes of CKD in LT patients (**Table 8**) depend on many factors that include long-time use of CNIs: hypertension, T2DM, obesity, atherosclerosis, hyperlipidemia, chronic HCV infection, pretransplant renal dysfunction, and perioperative AKI.[318]

Immediately after LT, incessant observing of kidney function is mandatory for detecting and managing CKD, including treating possible risk factors (Grade II-2).[12] Quantifying urinary protein by means of protein to creatinine concentration ratio is required a minimum once a year post-LT.[318] Reducing or completely withdrawing CNI-associated immunosuppression or using CNI-free treatment regimens is an appropriate regimen in LT recipients with abnormal kidney function (Grade I).[12,318] Kidney transplantation is helpful in improving survival and can be regarded as the ideal therapeutic option for LT patients with ESRD (Grade II-3).[12,318]

Preventing and treating infections. Infections are a serious concern following LT, as around two-thirds of the LT patients get them postoperatively. Therefore, preventing infections and using aggressive disease recognizing approaches are essential depending on the time after LT[12] (**Table 8**).

Infections may highly occur during 2-6 months post-LT with opportunistic agents, such as herpesviruses (especially CMV, herpes zoster and simplex, and EBV), fungi (*Aspergillus* and *Cryptococcus*), and more not-common bacterial infections (*Nocardia, Listeria,* and Mycobacteria). Therefore, assessing infections following LT should consider implementing prophylactic antimicrobials, avoid high-risk exposures, and minimize immunosuppression therapy.[318]

Following the 3 months after LT, with the reduction of immunosuppression regimens, the risk of infection becomes lower. After this period, infections in intra-abdominal, lower respiratory tract, or by community-acquired pathogens, such as enteric Gram-negative infections, *S. pneumonia*, and respiratory viruses, are quite common.[318] Bacterial pathogens cause most infections post-LT, particularly Gram-negative bacteria, including *Escherichia coli* and *Enterobacter, Pseudomonas*.[12] Surgical site, abdominal cavity, urinary tract, and bloodstream are the common locations. Intra-abdominal infections are related to graft loss and increased mortality.[328]

Cytomegalovirus, infection is the most common opportunistic infection in LT recipients. Although satisfactory prophylaxis has been shown to expressively lessen its incidence, it still involves pertinent illness. The most common syndromes are viremia, bone marrow suppression, colitis, and hepatitis.[329] For at least 3 months post-LT, CMV prophylaxis should be given to patients who have high CMV infection risk (Grade II-2).

Postulate lymphoproliferative disorder must be doubted in LT patients, particularly in patients who show seropositivity to EBV before LT or are treated with anti-lymphocyte globulin, an aggressive immunosuppressive agent, as they are at an increased risk of progressing PTLD (Grade III).[330] Treatment for PTLD needs reducing immunosuppressants. Further treatments include rituximab, chemotherapy, radiation, and surgery if no response is received by immunosuppressant reduction.[12]

Fungal infections have been reported over the last 2 decades, with a substantial reduction in invasive candidiasis and an insignificant rise in invasive aspergillosis in LT recipients.[331] Risk factors associated with invasive fungal infections are decreased length of LT surgery, transfusion needs during LT, cold ischemic time, usage of roux-en-Y biliary anastomosis, PVT, biopsy-proven rejection episodes, re-LT, and kidney replacement treatment.[331-333] Therapy protocol consists of reducing immunosuppressive therapy and using antifungal agents. Oral prophylaxis to counter *Candida species* is recommended in the initial months, as it lessens death rates resulting from fungal infection (Grade II-3). Prophylaxis for countering aspergillus is only endorsed in high-risk scenarios (Grade II-3).[12]

Pneumocystis jirovecci, the agent that causes pneumocystis pneumonia, is infrequent during trimethoprim-sulphamethoxazole (TMP-SMX) prophylaxis. However, TMP-SMX might cause kidney toxicity, and corticosteroids are helpful as an adjunctive treatment to decrease respiratory inflammation and fibrosis occurring after infection (Grade II-3).[12,334] Prophylaxis to counter *Pneumocystis jirovecci* with TMP-SMX is required in LT patients for 6 months to one year (Grade II-2).[12]

Liver transplantation patients may experience active TB (0.47-2.3%), particularly in the first year after surgery.[335,336] This infection has a high mortality rate, and treatment for latent TB is relevant. Isoniazid

Recommendations

- In most LT HBV-infected patients, a combination of HBIg and NUCs should be used as an effective strategy to prevent HBV recurrence (Grade I)
- Patients with undetectable HBV DNA during LT, without any prior resistance to NUCs can be benefited from HBIg in a lower dose or for a shorter duration up to 3 months, supported later by NUC monotherapy (Grade I)
- Entecavir or tenofovir monotherapy is efficient in controlling the recurrence of infection, but is not be adequate to evade HBV graft infection (Grade II-2)
- HBV recurrence needs to be treated with entecavir or tenofovir, with prompt initiation (Grade II-3)
- LT recipients who get from an anti-HBc positive donor must be given effective antiviral drugs soon after LT (Grade II-2)
- In HBsAg-negative LT recipients transplanted from an anti-HBc-positive donor, HBIg must not be used (Grade II-2)
- Patients with a prior ALD diagnosis must be advised to avoid alcohol at all (Grade II-2) and undergo psychiatric treatment or consultation if they start back alcohol consumption in the post-LT period (Grade II-3)
- Liver biopsy is required to confirm recurrent or de novo NAFLD/NASH, recognition of fibrosis, and exclusion of alternate causes of altered liver chemistry tests (Grade III). Avoid extreme weight gains and keeping hypertension, dyslipidemia, and T2DM in control are recommended (Grade III)
- AIH, PBC, and PSC recurrence differ from 10% to 50% and must be confirmed by liver biopsy and/or cholangiography (PSC) (Grade II-3)
- There is no convincing data to support the prophylactic use of ursodeoxycholic acid in patients who underwent LT for PBC and PSC (Grade III)
- Currently, there is no data suggesting that long-term (over 5 years) recurrence-free survival is achieved using SRL (Grade I); however, it seems to be effective in 3-5 years, time in HCC patients within Milan criteria (Grade I).
- It is recommended that therapy for HCC recurrence post-LT needs to be personalized, and there is no evidence to utilize sorafenib in patients with disseminated recurrence (Grade III).
- Immediately after LT, incessant observing of kidney function is mandatory for detecting and managing CKD, including treating possible risk factors (Grade II-2)
- Reducting or completely withdrawing CNI-associated immunosuppression or using CNI-free treatment regimens is an appropriate regimen in LT recipients with abnormal kidney function (Grade I)
- Kidney transplantation is helpful in improving survival and can be regarded as the ideal therapy for LT patients with ESRD (Grade II-3)
- For at least 3 months, CMV prophylaxis must be used in those at an increased risk of developing CMV infection (Grade II-2).
- PTLD must be doubted in LT patients, particularly those patients that show seropositivity to EBV before LT or that are treated with anti-lymphocyte globulin, an aggressive immunosuppressive agent, as they are at increased risk of progressing PTLD (Grade III)
- Oral prophylaxis to counter Candida species is recommended in the initial months, as it lessens death rates resulting from fungal infection (Grade II-3). Prophylaxis for countering aspergillus is only endorsed in high-risk scenarios (Grade II-3)
- TMP-SMX might cause kidney toxicity, and corticosteroids are helpful as adjunctive treatment to decrease respiratory inflammation and fibrosis occurring after infection (Grade II-3)
- Prophylaxis to counter *P. jirovecii* with TMP-SMX is required in LT patients for a period of half to one year (Grade II-2)
- Patients on anti-tuberculosis should be observed for possible side effects relevant to liver and acute rejection (Grade II-3).

Table 9 - Timeline of infectious complications following LT.

First month after LT	2-6 months after LT	> 6 months after LT
Nosocomial infections related to surgery and postoperative care	Opportunistic infections Reactivation of latent infections	Community-acquired infections

regimen for 9 months (along with vitamin B6) is the typical treatment option. It needs to be indicated in the following scenarios: PPD positive skin test, history of untreated TB, or chest radiography findings suggesting TB.[12] Treating active TB in LT recipients is complicated due to drug interactions between anti-TB and immunosuppressants, plus the liver toxicity related to the first-line TB treatment. Patients on anti-TB therapy should be observed for possible side effects relevant to liver and acute rejection (Grade II-3). Treatment of non-severe TB must include isoniazid and ethambutol, and no rifamycins. Levofloxacin can be chosen instead of isoniazid. Severe form of TB must consist of treatment with rifamycin in the earlier and maintenance stages.[12] Table 9 outlines the prophylactic strategies underlying the common microorganisms that affect LT recipients.

Managing metabolic syndrome. One year following LT, complications associated with cardiovascular risks and metabolic syndrome become increasingly relevant.[299] The number of LT recipients with underlying metabolic syndrome rises as the population's median BMI grows.[337] The clinical characteristics of metabolic syndrome, namely insulin-resistant (type 2) diabetes mellitus, obesity, dyslipidemia, and arterial hypertension, aid in delayed morbidity and mortality. It is estimated that the occurrence of metabolic syndrome in the LT population is between 50-60%.[12,338]

Liver transplantation recipients have a higher risk of cardiovascular disease, representing almost one-fourth of mortality in the post-LT, long-term follow-up.[339,340] Data has shown that the immunosuppressant treatment protocols exacerbate underlying systemic and metabolic disorders and de novo arterial hypertension after surgery, hyperlipidemia, T2DM, and obesity.[339] Hence, adequate therapy for modifiable risk factors by means of lifestyle and behavioral modifications, drug treatments, and changes to the immunosuppressive drugs are essential to prevent serious cardiovascular manifestations (Grade III).[12] Drug treatments in parallel with a balanced diet and routine physical exercise need to be implemented earlier to control arterial hypertension, hyperlipidemia, T2DM, and obesity (Grade II-3). Balanced diet and physical exercise initiatives can effectively help (Grade III).[12]

Bone disease. Bone loss increases in the first 6 months following LT and is related to higher fracture risk inducing obvious morbidity and poor quality of life.[341] Following the initial 6-12 months post-LT, bone loss reverses, and bone density increases. Annual examination of bone mineral density is advisable for patients with underlying osteoporosis and osteopenia. Similar examination is suggested every 2-3 years in those with normal values. After that, checking relies on how bone mineral density and associated risk factors change over time (Grade II-3).[12]

When the diagnosis of osteopenic bone disease is established or atraumatic fractures surge, associated risk factors for bone disease need to be evaluated. Particularly, calcium intake and 25-hydroxy-vitamin D need to be assessed. Gonadal and thyroid function evaluation, along with thoracolumbar radiography, need to be carried out. Besides, a complete medication history needs to be checked.[318]

For the osteopenic LT recipient, regular weight-bearing exercises in combination with calcium and vitamin D supplements should be performed (Grade II-3). Bisphosphonate must be used in LT recipients with osteoporosis or recent fractures (Grade II-2).[12,318]

De novo malignancies. The incidence of de novo cancers is higher in the LT population than a control population (age- and sex-matched non-LT) (**Table 10**). The incidence of de novo cancer following LT may increase up to 34% at 15 years after LT.[340,342,343]

The increased incidence of de novo malignancies is because of the loss of immunovigilance induced by immunosuppressants and other associated risk factors, such as viral infections with oncogenic capability (namely, EBV, human papillomavirus), PSC, cigarette smoking, and alcohol consumption.[12] Post-LT malignancy screening protocols are required, especially in patients at high risk to notice de novo malignancies at an initial and possibly curative phase (Grade II-2). Several risk factors associated with de novo cancers cannot be altered, such as age or pre-existing hepatic disease. Thus, routine oncology surveillance initiatives have been suggested, although the optimal surveillance protocol still needs to be defined.[12] The most common de novo malignancy in LT patients is skin malignancy. The most frequent are non-melanoma cancers, such as squamous and basal cell carcinoma.[344] Besides having a higher frequency, they tend to be more aggressive and metastasize more frequently in LT recipients than in a control population.[345] Many risk factors aid in the progression of non-melanoma skin malignancies post-LT and include advanced age, prolonged sun exposure, sunburn, fair skin, and skin malignancy history.[345] After surgery, LT recipients must attain dermatology consultation to evaluate cutaneous lesions with yearly assessments after five years or more post-LT (Grade I-1).

Malignancy in the upper gastrointestinal oropharyngeal-laryngeal and pulmonary cancers are particularly increasing in patients with alcoholic cirrhosis. These recipients should be subjected to a comprehensive surveillance strategy for identifying these malignancies (Grade II-3).[340] Pre- and post-LT history of smoking additionally raises the risk of head/neck and pulmonary de novo malignancies, stressing the significance of quitting smoking by LT patients.[346] Post-LT lymphoproliferative disorder is frequent in LT recipients and should be suspected when patients present with fever, weight loss, and night sweats, even without lymphadenopathy.[12] Epstein-Barr virus-associated PTLD was observed to be the most frequently encountered de novo malignancy after LT in a KSA transplant center during 2001-2010. Chemotherapy, along with reduced immunosuppression, serve as the treatment option.[347]

Patients who underwent LT for PSC with related bowel disease must take colonoscopy with biopsies every year to check and detect colorectal cancer (Grade II-3).[12,283] If dysplasia is diagnosed in a colonic biopsy, colectomy, including continence-preserving pouch procedures, must be tried.[283]

Table 10 - Prophylactic strategies for common microorganisms that affect LT recipients.

Organism	Drug/Dosage	Duration	Comments
CMV			
Donor-positive/recipient-negative	Valganciclovir (900 mg/day) or intravenous ganciclovir (5 mg/kg/day)	3-6 months	Valganciclovir is not FDA-approved for LT. Prolonged-duration regimens are effective in kidney transplantation.
Recipient-positive	Valganciclovir (900 mg/day), intravenous ganciclovir, or weekly CMV viral load monitoring and antiviral initiation when viremia is identified	3 months	Valganciclovir is not FDA-approved for LT.
Fungi	Fluconazole (100-400 mg daily), itraconazole (200 mg twice daily), caspofungin (50 mg daily), or liposomal amphotericin (1 mg/kg/day)	4-6 weeks (adjust duration)	Reserve for high-risk individuals (pretransplant fungal colonization, renal replacement therapy, massive transfusion, choledochojejunostomy, re-operation, re-transplantation, or hepatic iron overload).
P. jirovecii (P. carinii)	Trimethoprim sulfamethoxazole (single strength daily or double strength 3 times per week), dapsone (100 mg daily), or atovaquone (1500 mg daily)	6-12 months (adjust duration)	A longer duration of therapy should be considered for patients on augmented immunosuppression. Lifelong therapy should be considered for HIV-infected recipients.
TB (latent infection)	Isoniazid (300 mg daily)	9 months	Monitor for hepatotoxicity

Recommendations

- Adequate therapy for modifiable risk factors by means of lifestyle and behavioral modifications, drug treatments, and changes to the immunosuppressive drugs are essential to prevent serious cardiovascular manifestations post-LT (Grade III). Drug treatments in parallel with a balanced diet and routine physical exercise need to be implemented early to control arterial hypertension, hyperlipidemia, T2DM, and obesity (Grade II-3). Balanced diet and physical exercise initiatives can effectively help (Grade III)
- Annual examination of bone mineral density screening is advisable for patients with underlying osteoporosis and osteopenia. Similar examination is suggested every 2-3 years in those with normal values. After that, checking relies on how bone mineral density and associated risk factors change over time (Grade II-3)
- For the osteopenic LT recipient, regular weight-bearing exercises in combination with calcium and vitamin D supplements should be performed (Grade II-3). Bisphosphonate must be used in LT recipients with osteoporosis or recent fractures (Grade II-2)
- Post-LT malignancy screening protocols are required, especially in patients at high risk to notice de novo malignancies at an initial and possibly curative phase (Grade II-2).
- LT recipients must attain dermatology consultation after surgery to evaluate cutaneous lesions with yearly assessments after five years or more post-LT (Grade I-1).
- Malignancy in the upper gastrointestinal oropharyngeal-laryngeal, and pulmonary cancers, are particularly increasing in patients with alcoholic cirrhosis, and these recipients should be subjected to a comprehensive surveillance strategy for identifying these malignancies (Grade II-3)
- Patients who underwent LT for PSC with related bowel disease require colonoscopy every year, with biopsies for colorectal cancer checking and detection (Grade II-3)

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