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REVIEW

Lesson learnt from 60 years of liver transplantation: Advancements, challenges, and future directions

Eyad Gadour

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Abstract

Over the past six decades, liver transplantation (LT) has evolved from an experimental procedure into a standardized and life-saving intervention, reshaping the landscape of organ transplantation. Driven by pioneering breakthroughs, technological advancements, and a deepened understanding of immunology, LT has seen remarkable progress. Some of the most notable breakthroughs in the field include advances in immunosuppression, a revised model for end-stage liver disease, and artificial intelligence (AI)-integrated imaging modalities serving diagnostic and therapeutic roles in LT, paired with ever-evolving technological advances. Additionally, the refinement of transplantation procedures, resulting in the introduction of alternative transplantation methods, such as living donor LT, split LT, and the use of marginal grafts, has addressed the challenge of organ shortage. Moreover, precision medicine, guiding personalized immunosuppressive strategies, has significantly improved patient and graft survival rates while addressing emergent issues, such as short-term complications and early allograft dysfunction, leading to a more refined strategy and enhanced post-operative recovery. Looking ahead, ongoing research explores regenerative medicine, diagnostic tools, and AI to optimize organ allocation and post-transplantation car. In summary, the past six decades have marked a transformative journey in LT with a commitment to advancing science, medicine, and patient-centered care, offering hope and extending life to individuals worldwide.

Key Words: Liver transplantation; Model for end-stage liver disease; Liver grafts allocation; Immunology and organ rejection; Types of liver transplantation techniques

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Core Tip: Over the past 60 years, liver transplantation (LT) has become an effective and well-established curative intervention for patients presenting with acute and chronic liver failure. However, the cost, complexity, and shortage of donor organs for LT has greatly challenged this intervention. Nonetheless, modifications in patient selection criteria resulting in less stringent parameters for LT patient selection, the introduction of neoadjuvant therapies, and the rehabilitation of previously unsalvageable donors have had a significant impact in countering this challenge.

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INTRODUCTION

Overview of liver transplantation

Liver transplantation (LT) has proved to be an invaluable procedure, especially for patients diagnosed with hepatocellular and biliary malignancies and acute liver onditions characterized by life-threatening liver dysfunction, cirrhosis, and decompensated hepatic disorders[1]. According to Asrani *et al*[2], liver disorders are associated with an annual fatality rate of over two million persons globally. Therefore, liver disease and related failure accounts for one in every twenty-five deaths, with a male-to-female ratio of 3:1 across the globe[2]. This evidence places liver-related disorders as the eleventh leading cause of death globally.

Griffin *et al*[3], however, stressed that these liver-related deaths are grossly underestimated. Liver carcinomas and their associated malignancies account for the most significant proportion of liver-associated fatalities, with approximately 600000-900000 deaths. Based on the significant global burden associated with liver diseases and related comorbidities, LT has been associated with restoring normal body health, improving lifestyle, and extending a patient's lifespan by at least 15 years[4]. In 2021, global statistics accounted for 34694 liver transplants globally, whereas in 2022, reported 37436 liver transplants, which accounted for an approximately 8% increase[5,6].

Transplant oncology and organ allocation

Following the introduction of LT in 1963, this intervention has been heralded as the only solid organ transplantation protocol for the curative treatment of malignancies[7,8]. In the early stages of LT, malignancy recurrence in over 60% of the cases was associated with a diminished interest in investigating oncogenic indications[9]. Nonetheless, Starzl *et al*[10] and the Denver group cited the impact of tumor stage and type as useful risk factors for patient selection, from which favorable prognostic outcomes could be derived. Based on this hypothesis, investigations by Yamamoto *et al*[11] and Iwatsuki *et al*[8] comparing outcomes from hepatic resections and LT outcomes in hepatocellular carcinoma (HCC) showed that early- and intermediate-stage malignancies showed a more favorable prognosis, compared with advanced-stage HCC. Similar observations were reported on oncologic outcomes based on tumor characteristics by Muhlbacher[12].

Transplant oncology, a multidisciplinary field, has garnered increased recognition and renewed attention with the term coined in 2015 and the first international consensus meeting held in 2019[13-15]. As previously established, the LT field has been shrouded by significant organ supply and demand discrepancies. The "Milan Criteria (MC)" was proposed by Mazzaferro *et al*[16]. In 1996, a guideline on LT patient selection was offered based on the number and size of tumor lesions, and this has been the gold-standard selection criteria for patients with HCCs, with the MC incorporated into[17,18]. Despite LT patient allocation using the MC criteria being associated with significantly favorable outcomes, several critics have highlighted shortcomings related to the criteria, including its restrictiveness[19,20].

Over the past 60 years, a more broad-based, comprehensive, and thorough understanding of the usefulness of tumor biology has led to the development of more inclusive patient selection criteria, showing a change to more dynamic criteria and allowing further assessment of tumor characteristics over time[21,22]. Several oncologic indications in LT patients exist in the context of transplant oncology. These indications include HCCs, cholangiocarcinomas (perihilar and intrahepatic cholangiocarcinomas), hepatoblastomas, hepatic epithelioid hemangioendotheliomas, metastatic neuroendocrine tumors, and colorectal liver metastases.

In the case of HCCs, several diagnostic classifications depend on geographical location, including the Barcelona Clinic Liver Cancer algorithms and Hong Kong Liver Cancer classification[23,24]. LT offers complete local tumor management in cirrhotic patients presenting with HCC. While the MC are widely used for patient selection with HCC, the University of California-San Francisco criteria (2001)[25], the Up-to-7 criteria (2009)[26], Metroticket 2.0 criteria present significant evolutions in LT patient selection with HCC. The recent New York-California (NYCA) score, incorporating absolute alpha-fetoprotein levels over time, provides a dynamic assessment of tumor characteristics[22].

Liver graft allocation

Generally, the primary objectives of LT include prolonging survival rates and improving the overall quality of life of both donors and recipients. Liver grafts are a limited and invaluable resource, with several approaches to counter scarcity adopted in clinical settings[27]. Most of these approaches are centered on increasing donor rates, alternative treatment alternatives, and reducing the overall demand for liver grafts[27]. Several common ethical directives govern the allocation

process, serving the role of ethical balance in terms of justice, utility equity, and fairness in this complex process[27]. Several LT allocation policies have been developed to facilitate the best possible outcomes for LT patients on the donor waiting list, despite the limited resources at hand[27].

In the early days of center-based liver allocation, priority was typically assigned to prospective transplant candidates based on surrogate indicators of clinical urgency, such as the need for admission to the intensive care unit[28]. With advancements in outcomes and the establishment of LT as a recognized life-saving intervention, opaque and arbitrary decision-making and the wide geographical variations inherent in a center-based approach to organ allocation became unacceptable, ushering in the patient-focused organ allocation system era.

In the United States, waiting list priority was determined by the duration of waiting list time and clinical status before 1997[29]. However, evidence on this assertion concluded that the duration of transplant waiting list time did not correlate with waitlist mortality[27]. Thus, in establishing evidence-based systems, the criteria shifted from the duration of waiting list time to the prioritization of patients based on disease severity with the Child-Turcotte-Pugh classification system, the first attempt to objectify liver graft allocation[30]. The Child-Turcotte-Pugh tool criteria were primarily based on clinically assessed variables and laboratory-confirmed disease panels, such as ascites, encephalopathy, serum bilirubin levels, albumin levels, and prothrombin time[30]. The tool was also incorporated into the medical urgency-based organ allocation criteria in 1997, considering the patient's duration on the waiting list[31].

The United States Department of Health and Human Services 1998 publication, "Final rule," formalized the prioritization of medical urgency in organ allocation procedures over waiting time[32]. This organ allocation guidelines were devised to address several shortcomings of the objective Child-Turcotte-Pugh tool for organ allocation. These limitations were based on the tool's subjective clinical variables, such as ascites and encephalopathy, and its failure to consider renal function as a prognostic variable, necessitating a more accurate allocation score[33].

MODEL FOR END-STAGE LIVER DISEASE

In 2002, the model for end-stage liver disease (MELD), a score based on laboratory bilirubin, creatinine, and international normalized ratio (INR) measures, was validated in the United States for recipient ranking[31,34]. This score was initially developed as an objective 3-month measure of survival prognosis in patients undergoing transjugular intrahepatic portosystemic venous shunts[35]. As a testament to its precision, the MELD score accurately predicted 3-month mortality rates for many LT patients and was deemed superior to the Child-Turcotte-Pugh score[36-38]. Following this success, the MELD score was implemented in almost all countries participating in LT procedures. Consequently, this step significantly reduces organ waitlist mortality by prioritizing the sickest patients[39].

However, a few limitations were also brought to light following the implementation of the score, including an increase in the early post-transplant mortality rate and its failure to account for elevations in INR and creatine for other non-liver-associated complications[40-42]. Moreover, the MELD score has been associated with bias against women, attributed mainly to differences in height and the failure to reflect on the potential benefits of LT in patients diagnosed with hepatocellular malignancies[43,44]. Several modifications to the MELD score have been proposed to counter these challenges, such as the pediatric end-stage liver disease[45,46].

Owing to the valuable data presented, advances in the transplant oncology field of LT patient selection have been associated with a gradual move from a static, image-based approach to a more dynamic modality, as articulated in a review by Krendl *et al*[47]. Notably, modifications made from the MC over the years, resulting in the NYCA score, have been hailed as a critical stepping stone. Transplant oncology posits that testing tumor biology and its response to neoadjuvant treatment represents a critical tool in LT patient selection. For instance, the study by McMillan *et al*[48] revealed that patients diagnosed with intrahepatic cholangiocarcinoma who underwent neoadjuvant therapy before LT presented favorable outcomes.

Similarly, several studies reporting atezolizumab and bevacizumab in patients presenting with HCCs at various stages have demonstrated significant downstaging. Subsequently, they lowered the RETREAT tumor recurrence score and were thus eligible for LT[7,49-51].

ADVANCEMENTS IN SURGICAL TECHNIQUES IN LT

Since Dr. Starzl's first successful LT procedure back in 1963, the surgical techniques involved in the process have undergone a remarkable transition into complex, intricate, and highly efficient procedures[10]. For over half a century, research on surgical techniques and strategies for solid organ transplantation, especially LT, has unveiled several modalities involving donor and recipient surgical procedures. In Welch's 1955 experiment, a hepatic allograft was inserted into the right paravertebral gutter of a canine specimen with considerable care to not disturb the native liver[52]. It was not until a year later that Cannon proposed the concept of liver replacement (orthotopic transplantation). These breakthroughs were closely followed by the establishment of formal research programs on total hepatectomy and LT in *Canis familiaris* models from 1958 to 1960[53,54].

TYPES OF LT TECHNIQUES

Conventional LT technique

The said canine experiments entailed the total removal of the native liver, excision of the retrohepatic vena cava (RVC), and replacing it with a donor liver composed of a *de novo* RVC segment and its corresponding connecting hepatic veins. Subsequently, anastomosis of the RVC was performed above and below the liver. This procedure is closely followed by venous and arterial anastomoses of the connecting vascular tissues (portal vein, hepatic artery, and biliary tract) using conventional surgical procedures.

These procedures have remained the general model for LT, with Starzl *et al*[55] adopting the same anastomosis procedure in the first human trial in 1963. This procedure remained the gold-standard surgical procedure until the 1980s, based mainly on improved survival rates, which increased to approximately 60% in the early 1980s[56,57]. According to Polak *et al*[58], cross-clumping of the inferior vena cava (IVC) and portal vein is associated with significant hemodynamic consequences, such as the reduction of blood backflow to the heart, congested caval and splanchnic beds, and reduced renal function. This congestion is responsible for increased bleeding during hepatectomy and can be reduced using venous bypass, which was not introduced until the mid-1980s[59,60].

Piggyback technique

An alternative surgical technique to the conventional technique is the piggyback technique, which was described by Calne and Williams[61] in 1968 and popularized by Tzakis *et al*[62] in the late 1980s. Contrary to the traditional approach, the piggyback method entails preservation of the IVC, allowing it to stay *in situ* during hepatectomy. The "classical piggyback" procedure described by Tzakis *et al*[62] involved using a venous outflow reconstruction between the supra-hepatic end of the donor IVC and an orifice created of the hepatic veins present. This procedure has been associated with more favorable and feasible outcomes in several studies, with the highlights being shorter surgery times, reduced blood loss, and lower costs[63-70].

Currently, the piggyback surgical technique is most widely used in LT; however, the procedure is associated with several risks, including the elevated dangers of venous outflow obstruction, with reports of hepatic venous outflow blocks evident[71,72]. Several modifications of the piggyback technique are in place clinically, such as side-to-side anastomosis proposed by Belghiti *et al*[73] and end-to-end anastomosis by Cherqui *et al*[74].

Partial LT procedures

Despite significant recent advancements in LT, the treatment modality remains one of the most complex and critically challenging procedures in the medical field. This assertion is based on the significant challenges and difficulties encountered when treating patients with different indications of hepatic failure, where recovery is not a possibility without transplantation and where liver replacement devices are used as a bridge to transplant. However, the survival rates in these cases are significantly limited[75].

Nonetheless, over the years, most established LT centers have recently documented more than 90% survival rates following 1-year post-transplantation and 80% after a 3-year follow-up[76]. Unfortunately, despite these significant strides in the field, the demand for hepatic grafts has significantly exceeded the availability of these grafts. This limited availability has been associated with more extended liver transplant waiting lists based on the shortage of viable liver donors. These developments have motivated more profound research into the field, which has unraveled worthwhile potential alternative procedures, including split grafts, living-donor LT (LDLT), and extended criteria grafts (ECGs)[75].

Split-liver technique

This procedure was first performed in 1988 by Pichlmayr *et al*[77] in Hannover and Bismuth *et al*[78] in Paris. Since 1988, split-liver techniques have been carried out widely across the medical field, with some of the most notable contributions made by Emond *et al*[79] in 1989, following the splitting of nine whole livers, treating five adults and thirteen children in 10 months. The procedure was, however, characterized by biliary complications in the split grafts in 27% of the cases. In a more extensive trial by Vagefi *et al*[80] in 2011 involving 106 liver recipients over 7 years, the results revealed 93%, 77%, and 73% patient survival rates following 1-, 5-, and 10-years post-transplantation, with overall graft survival of 89%, 75%, and 65%, respectively, in adults. In the pediatric population, patient survival was expressed as 84%, 75%, and 69%, whereas graft survival was 77%, 63%, and 57%, respectively. Biliary and vascular complications were most evident in 29% and 11% of the population, respectively.

The split-liver technique involves the division of the donor's liver along segmented boundaries while maintaining vascular inflow and venous and biliary outflow for each division[81]. This technique employs conventional surgical methods to split the liver along the line of the falciform ligament, thus creating extended right and left grafts[82,83]. Alternatively, this split can be performed along the line at the middle of the hepatic vein, splitting the liver into full-left and full-right segments, potentially for two adult recipients[82,83].

Split-liver grafts are prepared using two generalized methods: The *in-situ* technique, which involves dissection and transection of the hilar and parenchyma before perfusion, and standard organ cooling during the procurement procedure [84]. The *ex-vivo* method involves the same process; however, in principle, this procedure is performed after procurement in the donor or recipient operating centers[85]. Recently, a systematic review by Lau *et al*[81] in 2021 concluded that the split-liver procedure increased the number of available livers, hence facilitating the transplantation of one donor liver to two recipients with technical advances in *in-situ* procedures shortening the cold ischemia time and, arguably, increasing graft quality.

LDLT

The concept of LDLT was presented at the same time as that of the split liver by Raia *et al*[86] between 1988 and 1989, describing the first LDLT attempt at a living donor graft in a child in Sao Paulo, Brazil. A year later, Strong *et al*[87] performed the first successful LDLT using a left lateral segment graft from a female donor in her 17-year-old son diagnosed with biliary atresia. The early 1990s witnessed an influx of LDLT procedures, with Hashikura *et al*[88] and Lo *et al*[89] performing successful procedures in adults using the left and right lobes, respectively, in Japan.

According to Polak *et al*[58], the LDLT procedure was initially designed as a measure to address the limitations in the number of liver donors and was exclusively considered for the pediatric population owing to the significantly high mortality rate of children on the liver transplant waiting list. Overall, LDLT was described as a significant success, with evidence suggesting comparable patient and graft survival across centers. Moreover, LDLT was associated with relative safety for the donor, with a 15%-20% complication rate and low mortality rate (0.1%-0.4%)[90-95].

Based on the positive results witnessed in the pediatric population (90% survival rate)[75] and the increasing queue of adults on the transplant list, LDLT grafts for adults were adopted, with the left lobes being initially used. However, the major challenge with this directive was the scarcity of left liver lobes for adults, with patients treated through this modality presenting small-for-size complications, resulting in unsatisfactory results[91,96]. Consequently, LDLT left liver lobes are still used as surgical interventions for more miniature adults and adolescents or in dual graft specifications[97-99]. However, this was not a total loss, with several centers reporting excellent patient and graft outcomes following careful patient and graft selection processes[89].

Therefore, the right-lobe LDLT graft became the most utilized LT technique in adults, with a long-term comparison close to that of whole LT. However, the rate of biliary complications and morbidity in living donors remains considerably high, especially when compared with living donors for pediatric recipients[100-104]. In terms of surgical techniques, the techniques adopted in LDLT are similar to those employed in deceased donor LT, with contrasts witnessed in complex vascular and biliary reconstructions due to multiple vessels and ducts. Moreover, excellent venous drainage in the anterior sector of the right liver lobe and an adequate graft size are critical in the post-operative function of the donated liver in LDLT, as articulated by Marcos *et al*[105]. These requirements render LDLT a challenging and technically complex procedure requiring specialized surgical training. LDLT, however, is very common in Japan and South Korea, where deceased donor LT was not allowed until recently based on cultural and legal barriers[106]. Moreover, LDLT procedures have recently become more prevalent in other parts of the globe, including India, Turkey, and the United States, with studies reporting excellent post-operative results[107-109].

ECGs

ECGs present another means of increasing the pool of available organs for transplantation. This modality involves the donation of liver grafts following cardiac death and low-quality grafts that were previously discarded based on their perceived low quality[75]. Current inventions in LT, primarily through hypodermic and normothermic machine perfusion, have significantly improved graft quality to the extent that organs can be incorporated into the LT process[110-113]. However, machine perfusion of renal grafts is not a novel practice in solid organ transplantation, having been around since the 1970s[114].

Moreover, studies have associated hypothermic perfusion with preserving cellular structures and rejuvenating mitochondrial functions, while producing superior outcomes in preserving ECGs, compared with outcomes realized from standard cold storage[115-117]. According to Butler *et al*[118], the significant merits associated with normothermic perfusion are in maintaining physiological conditions, thereby limiting the extent of endothelial damage, with similar results reported in several studies involving normothermic graft perfusion[111,113,118-120].

Domino LT

The Domino LT (DLT) concept was first described in Stockholm in 1993 during an international workshop on LT for familial amyloidosis polyneurotherapy. Subsequently, in 1995, Furtado[121] published the first successful DLT procedure in Portugal. This treatment protocol is mainly feasible in patients presenting with primarily inherited single-gene defects restricted to the liver, such as familial amyloidosis polyneurotherapy and maple syrup urine disease, with secondary debilitating extrahepatic presentation in other major body organs, such as the lungs, kidney, brain, or heart[122]. Therefore, complete liver replacement is recommended to mitigate the progression of the disease[123]. However, this liver is not entirely discarded and can be used for transplantation in another patient presenting with liver failure, as it takes one or two decades for the disease to become symptomatic in recipients[123-125]. This observation explains why DLT is primarily performed on elderly patients.

Until the end of 2019, the Familial Amyloidotic Poly-Neurotherapy World Transplant Register had recorded over a thousand (12,88) DLT procedures in over 21 countries[126]. DLT has been associated with positive outcomes, with Furtado[127] reporting overall patient survival rates of 70% and 60% in the first and third years, respectively, following the procedure. Significantly higher percentages were reported by Yamamoto *et al*[128], showing survival rates of 90% and 92% in the first and fifth year, respectively, following the procedure[127,128]. In a single-centered retrospective investigation by Karadagi *et al*[129], the overall patients' survival rate over 5 years was documented as 79%, similar to Ahmed *et al*'s findings of 83%, 76%, and 57% survival rates 3, 5, and 10 years post-treatment in 2022[130].

Significant modifications have been made to the DLT procedure compared with the early procedures, such as excluding the native IVC during organ harvesting, thus improving hemodynamic stability in already compromised patients[58]. In DLT, the procedure is only performed with the prospect that the transplanted allograft will not develop any clinical or subclinical symptoms of a genetic defect in the recipient. However, several studies have suggested that DLT allografts can transmit the primary disease post-transplantation[131-137].

IMPROVEMENTS IN ORGAN PRESERVATION

Effective organ preservation remains a critical feature of successful organ transplantation. The highlight of organ-preservation modalities was witnessed from the late 1960s to the late 1980s, with the development of several revolutionary organ-preservation solutions[138,139]. First to the scene was the Collins solution, developed in the late 1960s by Collins *et al*[140] for storing kidney grafts, which is the earliest described preservation method for organ transplantation. In 1980, the Euro Transplant Foundation made several modifications to the solution and labeled it the Euro-Collins solution, which was the standard preservation solution in Europe for the next 15 years[140,141].

The late 1970s saw the development of Marshall's solution, a hyperosmolar citrate solution which was associated with practical organ preservation for approximately 10 hours after harvesting[142,143]. This solution is still mainly applied in renal grafts. The University of Wisconsin also developed a University of Wisconsin solution (UWS) with a similar phosphate buffer system with high potassium and low sodium electrolyte makeup to the Collins solution[144]. The significant contrast between the two solutions was based on the replacement of glucose with raffinose and lactobionic acid, which acted as the metabolically inactive and osmotically active components of the UWS. The main reason for the inclusion of raffinose and lactobionic acid was their high molecular weight and ability to counteract transmembrane water shifts, thus preventing cellular edema, which is associated with an extended human liver graft preservation time of more than 15 hours[145].

The 1980s also saw the development of a low-potassium histidine-tryptophan ketoglutarate (HTK) solution used for the perfusion and flushing of organs and hypodermic storage during transport[146]. HTK solution is a highly used feature in general organ transplantation based on these and several other attributes, such as its closely similar composition to extracellular fluid. Recently, a mixture of the Institut Georges Lopez-1 solution and University of Wisconsin preservation solution has been broadly adopted in the LT field, with the Celsior preservation solution being a significant addition to the field[147].

For 60 years, the go-to standard of care for graft preservation has been static cold storage during solid organ transplantations[148]. However, high-risk allografts require dynamic preservation mechanisms; therefore, three active preservation methods are available for high-risk liver allografts, including normothermic machine perfusion, sub-normothermic machine perfusion, and hypothermic machine perfusion[149,150].

Normothermic machine perfusion has been associated with a 50% reduction in graft injury and organ discard in a meta-analysis comparing this modality with normal cold storage techniques[151]. Despite its high cost, normothermic machine perfusion has also been associated with significant improvements in laboratory perfusion parameters of marginal organs and can be performed *in situ* or *ex-situ*[150,152]. Meanwhile, sub-normothermic machine perfusion has primarily been applied to ECG procedures and performed at around 20 ℃ conditions[153]. This perfusion method has been associated with the mitigation of ischemia-reperfusion injury while maintaining liver metabolism and facilitating organ function assessment before LT. Hypothermic machine perfusion remains one of the most widely researched machine perfusion modalities to date, with promising outcomes reported from its application in cardiac death liver donors, revealing similar results to those of standard organ donation following brain death[154]. An investigation evaluating the outcomes of LT by Mergental *et al*[120] using discarded livers recovered using normothermic machine perfusion showed the survival of five livers with no complications reported during follow-up.

ADVANCEMENTS IN IMMUNOSUPPRESSIVE THERAPIES

Generally, organ transplantation would have been impossible; nonetheless, significant breakthroughs were made in the immunology field, with the most notable strides in this area documented between the 1940s and 1950s[155]. Medawar *et al*[156], a highly influential researcher in the field, made significant contributions after his investigations into skin grafting during World War II. He found that autografts and allografts healed successfully, but allografts were rejected in the subsequent weeks (precisely, two weeks)[75]. Drawing on Burnet's theory of immunological tolerance, Medawar *et al* [156] proposed that self- and non-self-graft recognition occurs during embryogenesis[155,156]. As explained by Song *et al* [157], graft rejections represent an immune-mediated disorder that can be mitigated through the sustained application of immunosuppression.

Numerous immunosuppression agents have been used in LT clinical practice for over 60 years. Furthermore, adequate immunosuppression has played a crucial role in alterations linked to graft rejection and the overall survival of LTs. Progress is noticeable in the markedly reduced mortality rates among LT patients attributable to graft rejection[158,159]. Nevertheless, as time progresses, long-term repercussions of immunosuppression have emerged as a significant concern for the morbidity of LT. In addition to susceptibility to opportunistic viral, bacterial, and fungal infections, the persistent application of immunosuppression could contribute to the development of degenerative and metabolic disorders and the onset of de novo malignancies[159].

The "secret cocktail BW22" composed of prednisone and azathioprine paired with locally synthesized anti-globulins, steroid-sparing agents, were among Denver's first immunosuppressive regimens used in solid organ transplantation [160]. However, this blend was associated with significantly low long-term survival rates, approximately 20%, cementing the need for more effective and robust immunosuppression. A retrospective analysis of findings from this procedure revealed the loss of 80% of all grafts owing to poor organ preservation methods, technical complications, cardiorespiratory complications, and immunologic complications in patients reaching tolerogenic states more than 20 years later, from this immunosuppressive regimen[161].

In the 1980s, the steroid-azathioprine blend was replaced with calcineurin inhibitor (CNI) immunosuppression, which was subsequently replaced by the mechanistic target of rapamycin (mTOR), co-stimulation inhibitors, and monoclonal antibodies (basiliximab) in the 2000s[62,162,163]. Based on their significant specificity through their selective action mechanisms, consequently leading to dosage minimization and tolerogenic suppression, CNI cyclosporine and tacrolimus are hailed as revolutionary highlights in solid organ transplantation, especially of the liver[164]. Consequently, the application of CNI cyclosporine and tacrolimus has been associated with significant increases in both graft and patient survival, leaping from 75% to 90% and 60% to 70% after 1 and 5 years post-intervention, respectively, as detailed by Starzl and Demetris[165].

In LT immunology, the initial insight was that rejection and tolerance represent different phases of a continuous spectrum. Therefore, eliminating early acute T-cell-mediated rejection at all costs may prove counterproductive to the extended survival of the graft in the long term[166,167]. This is mainly due to interruption of the route of graft acceptance, which involves an intricate interplay between specified clonal activation, deletion, and exhaustion[164]. Moreover, the extended acceptance of organ grafts under immunosuppression indicates a state of partial tolerance. The interaction between the immune systems of the donor and recipient has demonstrated positive outcomes in this context [168].

Current data on the advances made in immunosuppression for solid organ transplantation show that more than 500 multicenter trials on CNI and mTOR inhibitors have been performed globally to offer reduced cases of allograft rejection and optimize renal function[164]. Despite this progress, especially in minimizing immunosuppressive regimens, higher drug regimens (quadruple and triple) are still being applied in clinical settings[169]. Table 1 below highlights a list of the most commonly prescribed immunosuppressive drugs.

IMMUNE CHECKPOINT INHIBITORS

Immunosuppressive medications have transformed the field of clinical transplantation, enabling the prevention of immune system rejection of transplanted tissues. However, the administration of drugs like cyclosporine and tacrolimus has also introduced various side effects. Prompt recognition of drug-related neurotoxicity in transplant recipients, along with understanding its specific origins, is crucial[170]. The use of immune checkpoint inhibitors (ICIs), specifically nivolumab (a PD-1 inhibitor), pre-transplant in a patient presenting with HCC was first described by Nordness *et al*[171]. Unfortunately, the patient developed acute hepatic necrosis based on a profound immune reaction to the ICI and passed away. Nonetheless, contradicting results reported in a study by Tabrizian *et al*[172], following an analysis of nine patients, showed no severe rejection incidence or graft loss, with only one mild-acute rejection reported. Moreover, Chen *et al* [173], following pre-transplant treatment with toripalimab, an anti-PD-1-antibody similar to nivolumab, reported a case of acute hepatic necrosis.

Several studies have highlighted the significance of the programmed death ligand-1 and PD-1 pathways in graft acceptance[174]. However, graft rejection still remains a major concern following the peri-transplantation period of LT [174]. Based on these observations, literature has suggested shorter periods between ICI administration and LT, aimed at minimizing the risk of rejection[175]. Given the 27-day half-life of nivolumab and atezolizumab, a 3-month waiting period has been suggested[176]. However, results are still contentious and conflicting as most of these statistics are based on case reports and small case series[176]. Receptor occupancy and its effect on T-cell activity, in addition to time, have also been associated with significant impacts on graft acceptance, regardless of the ICI administered[177,178].

An investigation into post-LT use of ICIs has been associated with riskier side effects, compared with pre-transplant administration. This observation has been corroborated by studies by Cesario *et al*[178], in an investigation of 43 patients receiving ICIs pre-LT revealing eight severe graft rejections and four deaths. In the post-LT context, severe graft rejection was reported in 15 from a pool of 52 and 7 deaths due to liver failure[178]. Interestingly, acute graft rejection in the liver is very rare, thus, acute graft rejection post-LT in patients receiving ICIs calls for further investigation into this incidence. Montano-Loza *et al*[179] called for much close monitoring of patients administered ICIs in a decision table on the use of ICIs in LT recipients, based on individual risk and oncological usefulness.

Despite limited experience with ICIs, several studies have highlighted the absence of graft rejection incidence in 10 patients treated with atezolizumab, a PD-L1 antibody, regardless of the time of administration[50,51,178]. PD-L1 expression has been suggested as a potential biomarker based on its correlation with an increased risk of rejection[178].

COMMON MEDICAL AND SURGICAL COMPLICATIONS IN LT

In the early days of LT, survival rates the overall survival rate for the patients was about 30%, with most patients succumbing to rejection or infection[165]. Several studies put the overall survival rate of LT patients between 50% and 70%, depending on the type of indication[180,181]. Among these, indications with better survival outcomes in the long term are primary biliary cirrhosis and autoimmune cirrhosis. On the other hand, Hepatitis C and hepatocellular tumors have the worst outcomes, generally due to high recurrence rates[181].

Several factors are associated with overall LT survival rates, including donor and recipient characteristics, and perioperative and post-operative features[182]. Advanced age (> 50 years), high body mass index (BMI), prolonged hospitalization, use of vasopressors, and infection rates have been identified as indicators of poorer outcomes in donors. On the other hand, renal dysfunction, old age, urgent indication, poorer nutritional status, presence of infection or hepatitis, and requirement for mechanical ventilation are indications of poorer outcomes in recipients[182]. Perioperative conditions,

Table 1 A list of the most commonly prescribed immunosuppressive drugs in organ transplantation, adopted from Anghel *et al*[170]

Immunosuppression class	Drugs/therapies	Mechanism of action
Antimetabolites	Mycophenolate mofetil	Inhibition of de novo purine synthesis in lymphocytes
Biologic agents	Polyclonal antibodies (ATGAM, Thymoglobulin)	Lysis of lymphocytes
Calcineurin inhibitors	Cyclosporine A Tacrolimus	Inhibitors of an intracellular phosphate required for interleukin-2 production in the T lymphocytes
Corticosteroids	Methylprednisolone; Prednisone	Regulators of gene expression
Non-calcineurin inhibitors	Sirolimus; Everolimus	Inhibitors of mammalian target of target of rapamycin activation in lymphocytes, resulting in cycle cell arrest

such as cold and warm ischemia duration, requirements for blood transfusion, surgical challenges, and post-operative indications, including renal dysfunction, need for mechanical ventilation, extended intensive care unit stay, and primary dysfunction, are some of the factors associated with poor outcomes in LT[182].

Common medical complications in LT

Primary graft dysfunction: Primary non-function caused by early allograft dysfunction (EAD) represents one of the most dangerous complications of LT[183]. According to Agopian *et al*[184], EAD incidence is between 5% and 40% in all LT patients. The application of the model of early allograft function (MEAF) score[185] and liver graft assessment following transplantation (L-GrAFT) risk score facilitates the quantification of the levels of dysfunction[184]. The MEAF score evaluates parameters in terms of maximum alanine aminotransferase, INR, and bilirubin levels three days post-surgery, and has also been applied in the prognostic evaluation of LT patients within the first year following surgery[186]. Meanwhile, the L-GrAFT score is applied for the prognostic assessment of graft failure three-months post LT[184].

Cold and warm ischemia durations, in addition to indicative donor parameters such as elevated BMI, steatosis, and cause of death, are some of the most documented risk factors for early graft dysfunction[187]. However, a recent study has shown that an elevated serum sodium level in the donor can be linked to higher rates of EAD[188], although conflicting findings on this assertion exist in the literature[189]. Moreover, recent investigations on the duration of donor extraction, *i.e.*, the time taken from the aortic cross-clamp to the actual liver extraction, showed a correlation between this time and EAD rates[190].

Early graft dysfunction and primary graft non-function have a significantly higher incidence [up to 3.6-fold-after donation after circulatory death (DCD) compared with donation after brain death (DBD); yet survival rates are comparable with appropriate perioperative management[191-193]. Investigations conducted by Marcon *et al*[194] reported higher (though not statistically significant) rates of primary non-function, hepatic artery thrombosis (HAT), and ischemic cholangiopathy in recipients of previously discarded livers. The study also underscored the persistent disagreement among specialists, importance of expertise (including in the procurement phase), and necessity for proper donor/recipient matching to curb such outcomes[194].

Graft rejection: Graft rejection in LT is described in three general stages: Hyperacute (within hours following the transplantation procedure), acute (rejection occurring within 2-6 weeks after transplantation), and chronic rejection[195]. The hyperacute phase is characterized by manifestations similar to ischemic graft injuries[189]. ABO incompatibility between donor and recipient antibodies is the primary cause of this rejection. However, the prevalence rates of this type of rejection are meager, and urgent re-transplantation is recommended[189].

Secondly, the acute phase has been described as the most clinically frequent type of graft rejection, with an overall prevalence rate between 15% and 20% in all LT patients[189]. This type of rejection is mainly attributed to the T-lymphocyte response to the liver graft with old age, tacrolimus, and cirrhosis from alcohol abuse, identified as significant risk factors for this type of organ rejection[189]. The phase is also characterized by non-specific symptoms such as fever, pain, jaundice, malaise, and altered bile production. Steroids and increased immunosuppression regimens present the first-line treatments for this rejection phase[189].

Finally, the chronic graft rejection phase is primarily characterized by ductopenia and macrophages' total obstruction of the arterioles. This phase has been further associated with periportal edema, biliary dilatation, ascites, and hepatosplenomegaly following a year after transplantation[167,196]. Ramirez posited that this type of graft rejection is a consequence of cytomegalovirus infection, recurrent acute rejection, graft ischemia (related to artery stenosis), and antibody-mediated chronic rejection[189]. Steroids and graft retransplantation are the only feasible treatment interventions with studies showing the practical application of tacrolimus[197].

Post-transplant infections: Current organ transplantation guidelines emphasize the need for recipient screening for all acute or chronic infections (fungal, bacterial, or viral)[187]. Among the most documented infection contraindications for LT include HIV 1 and 2; hepatitis A, B, and C; CMV, tuberculosis, EBV, HHV, VZV; herpes simplex virus 1 and 2, among other venereal infections[187]. HIV 2, however, is not an absolute contraindication for liver transplant under current guidelines[187]. These guidelines stress the need for LT screens and precisely detailed reports of the local epidemiology of recipients, such as coccidioidomycosis and secondary prophylaxis screening[187]. Further details on disease-associated

contraindications, vaccination regimens, and prevention protocols for LT can be found in studies carried out by Fagiuoli *et al*[198] in 2014.

Surgical stress and immunosuppressive therapy have been associated with higher susceptibility to infection, with most LT patients being highly likely to suffer from some infections[187]. The most common infections within the first month post-transplant are bacterial and fungal infections at the incision sites, abdomen, bloodstream, urinary, and respiratory tracts[195]. Studies have shown that a higher graft loss rate is significantly associated with intra-abdominal infections [195]. These infections, however, can be mitigated by selective bowel decontamination using nonabsorbable oral antibiotics[199]. All *Clostridium difficile* infection risk factors must be mitigated[195].

In the first to the sixth months after surgery, opportunistic pathogens or activated latent-caused infections, such as HHV, CMV, and toxoplasma, among others, are common with prophylaxis and preemptive therapies applied to these infections[159]. Detailed intervention and infection management protocols have been described by Lucey *et al*[159], Esch *et al*[200], Gavaldà *et al*[199], Martin *et al*[201], and Muñoz *et al*[202]. Community-acquired infections, including respiratory, urinary, tract, and respiratory infections, are more common after 6 months of LT, with daily lifestyle changes, such as frequent hand-washing, use of gloves, smoking cessation, and avoiding decontaminated food and water, advised for these complications[199].

Other post-operative complications: Pulmonary complications associated with long surgery time, interoperative blood loss, liquid infusion, blood transfusion, sepsis, and changes in hemodynamic status are the most frequent complications after LT[187]. Moreover, pleural infusions in the right chest area, which can cause atelectasis and pneumonia (presenting in 5%-38% of LT patients), normally are self-healing, but in case of persistence, are treated using targeted antibiotic therapy and withdrawal of immunosuppression[189,203].

Moreover, the incidence of adult respiratory distress syndrome has been reported in about 4.5%-16% in all LT patients, with a mortality rate of about 80%[204]. Pulmonary edema caused by fluid overload, primarily due to renal failure, has been reported, although rarely[203]. Post-reperfusion syndrome (PRS) caused by severe ischemic or reperfusion liver injury has been recorded in over 55% of LT patients post-reperfusion[205]. Clinically, postreperfusion manifests as lowered cardiac output and reduced vascular resistance. PRS usually is an early indication of acute kidney injury (AKI), which affects close to 78% of LT patients. Significant risk factors for AKI include old donor age, high donor MELD score, high BMI, and an elevated need for intraoperative blood transfusion[191].

LT procedures have also been associated with an occurrence of neurologic complications occurring within the first month and up to a year following treatment. These complications have been described as multifactorial, and are inclusive of seizures, focal motor deficits, and encephalopathy[206]. Encephalopathy is the most common neurological complication, with a prevalence of between 1%-3% and an etiology primary from impaired graft function, the incidence of sepsis, and the use of CNI-immunosuppressants or steroids, among other causes[207,208]. Post-LT demyelinating inflammatory polyneuropathy is another complication, although rarely occurring[209].

Other complications

Cardiovascular complications: These complications account for about 25% of the mortality in LT patients 10 years following treatment[210,211]. Some of the most common risk factors, especially in LT patients, include hypertension (a common disorder in LT patients affecting between 36% and 77% of all patients), renal damage, diabetes mellitus, obesity, CNI immunosuppression, and steroid use. To curb these complications, studies have emphasized the need for lifestyle changes and pharmacological investigations including calcium channel blockers, beta-blockers, and angiotensin-converting enzyme inhibitors[189,212].

Metabolic syndrome and kidney diseases: Metabolic syndromes, such as hypertension, dyslipidemia, obesity, and insulin-resistant diabetes mellitus are associated with the development of post-LT non-alcoholic fatty liver disease and non-alcoholic steatohepatitis[213].

According to Gonwa *et al*[214], 5 years after LT, about 80% of LT patients develop chronic kidney disease, with 10% of this population needing dialysis or kidney transplantation within the next 10 years. Studies investigating the association between LT and kidney disease have articulated the application of CNI, leading to the occurrence of tubulointerstitial chronic fibrosis as a significant risk factor associated with kidney diseases in LT[215]. Moreover, post-transplant CMV infection, metabolic syndrome, and pre-transplant kidney dysfunction or impairment have been listed as significant risk factors[205].

Bone and dermatological non-oncologic complications: Bone complications resulting from cholestatic disease affectapproximately 65% of LT patients[216]. The etiology of this disease has been attributed to changes in hormonal levels induced by liver malfunction, resulting in the rearrangement of bone metabolism, in addition to IS and steroid use[216]. These conditions are treated with standard bone therapies such as osteoporosis.

Dermatological non-oncological complications encompass a significantly wide range of disorders, such as xerosis cutis, sebaceous hyperplasia, and steroid-induced acne, among others[187]. These complications occur within the first month following LT but subsequently improve. However, herpetic and fungal infection, and tinea of the nails and skin are more prevalent in LT[217].

Recurrent liver infection: Some of the most recurrent liver infections after LT include viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis (PSC). This recurrence is significantly associated with the application of immunosuppression, which facilitates faster disease development[218]. This recurrence has been reported in up to half of patients undergoing LT; however, this recurrence does not significantly affect the patient's prognosis.

De novo malignancies: These malignancies account for about 21%-25% of all functioning graft mortalities, with studies describing these malignancies in LT as highly aggressive[219,220]. De novo malignancies in LT are classified based on their causes, with the most recognized stratification being recipient factors and lifetime immunosuppressive therapies, as described by Watt *et al*[221]. This stratification articulates that recipient factors such as the presentation of PSC are associated with the development of non-skin cancer in about 22% of transplanted liver patients within ten years[221]. Moreover, in recipients diagnosed with HCC, 20% of these patients transplanted with livers have an increased probability of HCC recurrence between the 2nd and 25th years after transplantation[222]. Lifelong immunosuppression is associated with immune surveillance deficiencies that promote malignant cell survival and proliferation[187]. Moreover, immunosuppressive therapies are known to reactivate latent oncogenic viruses such as HHV.

In LT recipients, skin cancers are the most common type of malignancy, with a 20-fold higher risk, compared with other transplantation therapies[223,224]. In LT recipients, Kaposi's sarcoma, basal cell cancer, and squamous cell cancer are the most common de novo malignancies[225]. Secondly, post-transplant lymphoproliferative disorder, with a global incidence rate between 5% and 20%, is the second most common de novo malignancy, especially in the pediatric population, within the first 18 months following surgery[225].

Sarcopenia: Sarcopenia, described as a decrease in muscle mass and strength often related to old age, presents an exceptional risk factor among LT candidates due to chronic illness, malnutrition, hypermetabolic conditions, medication and treatment side effects, and a persistent inflammatory state[226,227]. A 2016 study by van Vugt *et al*[228] estimated that 22%-70% of patients diagnosed with end-stage liver disease present with sarcopenia. The incidence of sarcopenia in LT is a relevantly new area. A retrospective study of 142 patients in the University of Alberta liver transplant waitlist revealed that sarcopenia was associated with a 2.4-fold independent risk factor for mortality, especially in patients with MELD scores below 15[229]. A similar study conducted in patients in the LT waitlists showed a 15% increase in mortality susceptibility in patients presenting with sarcopenia[230]. Nonetheless, these assertions have been challenged by contradictory results from two studies by Yadav *et al*[231] and Wang *et al*[232]. A retrospective analysis of 396 patients presenting with end-stage liver disease has however, reinforced the association between sarcopenia and waitlist mortality, while also elucidating the significant costs associated with the disease in LT patients[233].

In the post-LT context, sarcopenia has been strongly associated with significantly poor post-LT outcomes in LT patients post transplantation, associated with a 4.8-time higher risk of mortality after a year, compared with non-sarcopenic patients[228,234,235]. several studies have listed sarcopenia as a significant risk factor in the incidence of adverse post-transplantation-related pulmonary events[236-238]. Several interventional therapies have been proposed in the management of sarcopenia including exercise programs, branched-chain Amino acid supplements, myostatin inhibition, and testosterone supplementation[227].

Biliary complications: These are quite common complications of LT, with incidence rates ranging from 2% to 19% globally, leading to post-operative morbidity and mortality rates[101,239,240]. Biliary leakage and biliary strictures are the most common types of biliary complications in LT, whereas intrahepatic strictures, papillary dysfunction, stone-caused, and cystic duct mucoceles are less frequent[240,241]. Bile leaks, with an 8.2% incidence, occur in the first to sixth months after the LT procedure[239]. Some of the most documented leakage sources of these complications include biliary anastomosis, cystic duct stump, liver surface or section injury, and technical mistakes[189]. Bile leaks manifest clinically as fever and abdominal pain with conservative management, such as biliary decompression[239].

Extrahepatic biliary strictures (EBS) present another most common form of biliary complication that affects at least one-third of the patients, normally occurring in the first years after LT[240]. Some of the most notable risk factors associated with EBS include edema, BL, HAT, or hepatic artery stenosis (HAS), biliary infections, and twists in the anastomotic stump. Ischemic-type biliary strictures/ischemic cholangiopathy or intrahepatic biliary strictures, presenting in 3%-16% of all LT patients, are worrisome biliary complications occurring within the first 6 months[241]. Over half of these patients will require re-transplantation and are a consequence of ischemic injuries leading to the development of fibrosis[241].

Surgical complications

Post-operative hemorrhage: This complication has been seen in approximately 5% of LT recipients, normally occurring within 48 hours post-surgery. Delayed graft function, thrombocytopenia, hypercalcemia, and dilution represent some of the most documented risk factors[189].

Vascular complications: These surgical complications have been documented in about 7% of all organ transplantation procedures and are significantly associated with elevated graft loss and mortality rates, with the poorest prognosis highlighted when these complications are diagnosed late[242]. One of the most common forms of vascular complications is HAT, with a 1.9%-9% incidence rate. HAT has been described as the leading cause of graft loss in organ transplantation, with the highest incidence rates observed in pediatric recipient population compared with adult recipients (42% *vs* 12%, respectively)[242,243]. Some of the most common risk factors associated with HAT include the need for blood transfusion, recipient hypercoagulability, prolonged cold ischemia time, damage to the endothelium, technical mistakes, and transplantation in low-volume institutions[243].

HAS represents another prevalent vascular complication in LT, with an incidence range of 0.8%-10%[242]. Technical injury, vessel injury, or twists/kinks in the vascular vessels have been attributed to HAS incidence, with patients remaining asymptomatic, whereas over 50% may experience subsequent HAT[189].

One of the rarer vascular complications in the hepatic artery pseudoaneurysm, with a 1%-3% incidence, develops in about 2-3 weeks after LT[244]. Studies have shown that fungal infection at anastomotic sites can result in a pseudoaneurysm in the extrahepatic tract[244]. This complication can be treated through arteriography, embolization, and urgent retransplantation. A similarly possible complication is arterial conduit occlusion, which has an incidence rate of about 8%

in instances where utilization of the native artery is not feasible. Older age (above 40 years) and the incidence of prior coronary artery bypass are significant risk factors.

Technical mistakes during surgery, such as twists or kinks in a redundant vessel and low flow through the vessel, are the principal causes of portal vein complications. Portal vein stenosis, with an approximately 5% incidence rate, presents the highest risk factor for split-liver, LDLT, and pediatric recipients[245]. Moreover, portal venous thrombosis, with an incidence of 2%-3% associated with a state of previous hypercoagulability and manifesting as sudden acute liver failure symptoms, portal hypertension symptoms, renal failure, and hemodynamic instability, is another known vascular complication of LT[189].

ETHICAL AND LEGAL CONSIDERATIONS IN LT

The rate of annual LT has significantly increased from the early days of LT. Despite these advances, liver grafts remain a scarce resource, with an estimated mortality rate of 15% among patients on waiting lists[246]. Several issues have emerged over the years regarding priority in terms of allocation, especially in instances where liver disorders are attributed to the patient's own choices, such as alcoholism and lifestyle choices. Thus, the scarcity of this life-saving resource warrants the incorporation of legal and ethical frameworks of equity, justice, utility, and benefits when prioritizing organ transplant recipients. According to Mellinger[247], the major bioethical guidelines and principles governing not only LT but also all aspects of organ transplantation include autonomy, non-maleficence, justice, and beneficence.

Following controversies surrounding liver allocation and prioritization frameworks witnessed in the early days of LT, a set of guiding principles was established to govern and assist in this accord carefully. In the 1960s, in the United States, the federal government became actively involved following the coalescing of local and regional organ-sharing programs, which came under the governance of the Public Health Service[247].

The establishment of the United Network for Organ Sharing (UNOS) in 1983 saw the transfer of these responsibilities from the Public Health System to the UNOS by Weimer[248]. 1983 also saw the declaration of LT as no longer an experimental treatment by a consensus conference of the National Institutes of Health in the United States by Weimer[248]. Subsequently, in 1984, following successful legislation of the National Organ Transplant Act, the Organ Procurement and Transplant Network (OPTN) was charged with ensuring ethical and legal organ donation, allocation, and transplantation. The OPTN is a private organization contracted by the Department of Health and Human Services to ensure the management of organ donation and allocation. A detailed copy of the OPTN guidelines, standards, and governance platform can be found at https://www.hrsa.gov/optn-modernization[249].

Moreover, the Uniform Anatomical Gift Act (UAGA), passed in 1968 and revised in 1987 and 2006, presents a set of legal standards in regard to organ donation with respect to altruism, autonomy, and maintaining public trust frameworks [250]. The Organ Procurement Organization (OPO) is charged with approaching families and eligible donors for donation while still assessing the feasibility of donated organs. OPOs are independent organizations and thus are located separately form organ transplantation centers, allowing them to reduce any conflicts of interest[247]. Under the UAGA protocol, physicians declaring donor deaths are prohibited from being involved in any aspect of organ donation and require hospitals to notify the OPO in incidences of imminent or actual death for registered organ donors for suitability assessments and family approaching[251].

In the United Kingdom, the Human Tissue Act of 2004 governs the process of organ donation with the process of organ donation to allocation under the management of the National Health Services' Blood and Transplant[247]. Organ donation frameworks are present in individual countries, which may be similar or different from the United States or United Kingdom frameworks. However, international organizations such as The European Union Directive on Organ Donation and Transplantation and the World Health Organization have set up their guidelines and legal frameworks governing organ allocation processes.

Autonomy

In organ transplantation, especially LT, the principle of autonomy, requiring respect for individual decisions and choices made on a patient's or donor's body and healthcare, is a critical legal and ethical requirement[247]. In the majority of countries, organ donation is viewed as "a gift". Per the United States laws under the UAGA, the primacy if the donor should be respected, *i.e.*, "where the deceased's wishes were known, next of kin does not have to give consent for donation and cannot override the deceased's stated wishes for donation"[247]. Several limits to autonomy exist, such as in instances in which the deceased patient's mental capacity is compromised, incapacitation to the extent that the patient cannot make sound medical decisions, or in the case of children.

Beneficence and non-maleficence

This framework is largely applied in cases of extended criteria donor requiring through assessment and evaluation of the risk of transplanting higher-risk organs associated with significantly poor prognostic and operational outcomes against the risk of death while recipients are on the waiting list[247].

Deceased from circulatory death donors and deceased from brain death donors

This legal and ethical framework employs the "donor death rule", which requires that all viable donors should be declared dead prior to any organ retrieval. Thus, the framework exempts physicians from declaring death from any process of organ donation, which consequently forms a critical tool for fostering public trust and preventing any conflicts

of interest[247]. Following a consensus in 2006 defining DCD and outlining ethical and medical guidance for organ donation following DCD, the criteria have been implemented widely, raising the number of available liver grafts[252]. This criterion is based on two principles: Firstly, DCD and DBD are declared in the event of total cessation of function, and secondly, this cessation is irreversible[247].

Utility

This framework demands that the best possible outcome be maximized. In LT, especially in DCD transplantation, biliary ischemia resulting in ischemic cholangiopathy and graft loss, which requires re-transplantation, is the most common risk factor, as documented by Feng *et al*[253] and Jay *et al*[254]. Thus, the framework emphasizes maximizing utility by minimizing the rates of poor outcomes, which entails proper selection of donors and recipients, minimization of cold and hot ischemia time, avoiding donors above 50 years and with a higher body mass, and preservation of DCD and DBD organs for patients with MELD scores higher than 20[255].

FUTURE DIRECTIONS AND CHALLENGES IN LT

Regenerative medicine and cell-based therapy

The liver represents one of the major body organs tasked with maintaining the homeostasis of nutrients and energy metabolism. Additionally, the liver serves as a detoxification, deoxidation, bile-producing, and secretory protein synthesis organ. Based on the complexity and high levels of toxicity attributed to these processes, the liver is exposed to a significant number of pathogens and other toxins. Thus, the liver is at greater risk of developing diseases such as hepatitis, cirrhosis, cancer, and other forms of liver disease (acute or chronic). The 21st century has been marked by tremendous efforts in the field of medicine, with further investigations in the field of organ transplantation, identifying cell-based and regenerative therapies as potential replacements for LTs[256].

Cell-based therapies or stem-cell-based therapies involve the stepwise modification of pluripotent stem cells into hepatocyte-like cells in *in vitro* settings and in the presence of growth factors[256]. The maturation of these hepatocyte cells can then be monitored based on their gene expression, functional protein presentation, secretion, and overall capacity for metabolism. This approach has been largely applied in mouse models, as expressed in investigations by Du *et al*[257]. Cell-based therapy has been associated with two critical roles, *i.e.*, control of disease progression through the stimulation of endogenous regeneration and inhibition of fibrosis[258].

Over the past 15 years, hepatocytes, macrophages, and stem cells have been transplanted as a bridges to surgery, supporting liver function. Firstly, hepatocyte therapy has been the go-to cell therapy for chronic liver disease as it has been associated with the induction of modest reductions in levels of ammonia and encephalopathy in both human and animal models[259]. However, this therapy has several drawbacks, including the significant difficulty encountered in isolating an adequate quantity of high-quality and metabolically active cells. These hepatocytes are harvested from non-feasible livers with variable levels of quantities and qualities[260]. Secondly, hepatocytes are known for their rapid deterioration when cultured *in vitro* and their subsequent sensitivity to freeze-thaw damage; thus, they are significantly affected by culture methods, materials, and cryopreservation methods[261].

Hepatic macrophages have been identified as key players in the dual-way process, reversible dynamic fibrogenesis-fibrosis resolution paradigm[262,263]. Based on investigations by Thomas *et al*[264] on the role of monocyte- or macrophage-based approaches in damping liver fibrosis in animal models of chronic liver injury, the administration of bone marrow-derived macrophages has been associated with improved liver fibrosis, regeneration, and an overall therapeutic benefit.

Liver tissue bioengineering

Tissue engineering, specifically three-dimensional cultures, has been associated with several advantages over two-dimensional cell cultures[228,230]. This three-dimensional approach has been instrumental *in vitro* models, especially in complex liver tissues, which are associated with interactions between hepatocytes, hepatic stellate cells, and the extracellular matrix (ECM)[200].

The quest for effective biocompatible scaffolds is directed towards the creation of organic or polymeric structures that emulate the liver's ECM and reproduce functional attributes like cell adhesion, viability, growth, and proliferation. Principal strategies revolve around biomaterials, including polymer-based three-dimensional (3D) constructs, decellularized ECM, and bioprinting of 3D structures. Another recent strategy involves the implementation of bioreactors to enhance various functions of hepatocytes within these constructs. Within bioreactors, a genuine 3Dmicroenvironment is established to enhance cell attachment, growth, and proliferation. This marked improvement in liver metabolism and function is achieved through optimization of the microenvironment niche.

Artificial intelligence in LT

Artificial intelligence (AI) is playing an increasingly important role in LT, enhancing various aspects of the process from pre-transplant evaluation to post-transplant care. One of the key areas where AI is making a significant impact is in the evaluation and selection of transplant candidates. Machine learning algorithms are being developed to predict outcomes, such as graft survival, patient survival, and the likelihood of complications[265-267]. These models analyze large datasets that include patient demographics, medical histories, and liver disease severity to help clinicians identify the most suitable candidates for transplantation[268]. AI's ability to integrate and process vast amounts of data allows for more

accurate risk stratification, enabling better prioritization of patients who are most in need of a transplant.

Additionally, AI has the potential to refine existing scoring systems like the MELD score by incorporating a wider range of variables, thereby improving the accuracy of predictions related to patient outcomes. AI is also being utilized to optimize organ matching and allocation processes[269,270]. Traditional methods for matching donors to recipients are being enhanced by AI algorithms that can analyze a more comprehensive set of factors, including genetic markers, liver anatomy, and immune profiles. This leads to better compatibility between donors and recipients, potentially improving graft survival and reducing the risk of rejection. Furthermore, AI can optimize the overall organ allocation process by taking into account medical urgency, geographical proximity, transportation logistics, and cold ischemia time. This holistic approach ensures that organs are allocated in a manner that maximizes patient outcomes, while also addressing logistical challenges[269,271].

During the surgical phase of LT, AI provides valuable support for both planning and execution. AI-powered image analysis tools assist surgeons by generating detailed 3D reconstructions of the liver and surrounding vasculature, which are particularly beneficial in complex cases involving anatomical variations or tumors. These advanced imaging techniques allow for more precise surgical planning and reducing the risk of complications during the operation. Moreover, AI systems are increasingly being integrated into robotic surgery platforms, offering real-time guidance by identifying anatomical structures and predicting potential bleeding points. This intraoperative support enhances a surgeon's ability to perform delicate procedures with greater accuracy, ultimately improving the overall success of the transplantation.

Post-transplantation AI continues to play a crucial role in monitoring patient health and managing potential complications. Predictive models are being developed to anticipate issues, such as graft rejection or infection, enabling earlier intervention and improving long-term outcomes. By continuously analyzing patient data, AI systems can identify subtle changes in biomarkers or clinical indicators that may suggest a developing problem, allowing for more proactive and personalized care. As AI technology continues to evolve, its integration into LT is likely to become even more sophisticated, offering the potential for further improvements in patient outcomes, resource allocation, and overall efficiency of the transplant process.

CONCLUSION

Over the past six decades, LT has evolved from a groundbreaking surgical intervention into a standardized and lifesaving procedure that has transformed the landscape of organ transplantation. The journey has been marked by a series of remarkable milestones, innovations, and paradigm shifts that have substantially improved patient outcomes and expanded the understanding of LT as a complex and dynamic field.

The initial breakthroughs in the 1960s and 1970s, culminating in the first successful human LT performed by Starzl *et al* [10] in 1967, set the stage for a new era in medical science. Subsequent decades witnessed advancements in surgical techniques, immunosuppressive therapies, and organ preservation methods, which have contributed to increased success rates and expanded access to LT. The introduction of cyclosporine in the 1980s revolutionized immunosuppression, significantly reducing the risk of graft rejection, and improving overall graft survival.

The late 20th century saw the refinement of organ allocation systems, addressing ethical concerns and ensuring a fair distribution of available organs. The MELD scoring system, implemented in the early 2000s, represents a landmark shift towards a more objective and transparent approach to organ prioritization based on the severity of illness. This contributed to a more equitable allocation of organs and optimized outcomes for patients awaiting transplantation.

Technological advancements have played a pivotal role in enhancing the field of LT. Imaging modalities such as computed tomography and magnetic resonance imaging have improved preoperative assessment and surgical planning. Additionally, the advent of machine perfusion techniques, both normothermic and hypothermic, has allowed better preservation and assessment of donor organs, expansion of the pool of viable grafts, and minimization of ischemia-reperfusion injury.

The past two decades have witnessed a surge in LDLT, offering a unique solution for the growing demand for donor organs. Advances in surgical techniques, donor safety, and post-operative care have made LDLT a viable option for selected patients. Simultaneously, split LT and utilization of marginal grafts have further broadened the donor pool, addressing the persistent challenge of organ shortage.

Immunological research has deepened our understanding of graft-host interactions, paving the way for personalized and targeted immunosuppressive strategies. The emergence of precision medicine in LT involves tailoring treatments based on individual patient characteristics, genetics, and immune responses, leading to improved graft survival and minimal adverse effects.

Clinical outcomes have witnessed significant improvements over the years, with overall patient and graft survival rates reaching commendable levels. Short-term complications, such as EAD, have been scrutinized, and strategies to mitigate these challenges have been implemented, resulting in enhanced post-operative recovery and long-term outcomes.

Looking forward, ongoing research endeavors focus on refining diagnostic tools, exploring regenerative medicine approaches, and leveraging AI to optimize organ allocation and post-transplant care. Continuous collaboration between clinicians, researchers, and policymakers will be pivotal in addressing emerging challenges, such as the impact of aging populations on donor organs and the evolving landscape of infectious diseases.

In conclusion, the past 60 years have witnessed a transformative journey in LT, marked by pioneering achievements, advancements in medical science, and a commitment to improving patient care. From experimental procedures to routine clinical practice, LT has become a cornerstone in the field of organ transplantation, offering hope and extended life to

countless individuals worldwide. As the trajectory of LT continues to ascend, it is essential to reflect on the progress made, acknowledge the challenges that lie ahead, and remain dedicated to advancing the frontiers of science, medicine, and patient-centered care in the years to come.

FOOTNOTES

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REFERENCES

1 **Meirelles Júnior RF**, Salvalaggio P, Rezende MB, Evangelista AS, Guardia BD, Matielo CE, Neves DB, Pandullo FL, Felga GE, Alves JA, Curvelo LA, Diaz LG, Rusi MB, Viveiros Mde M, Almeida MD, Pedroso PT, Rocco RA, Meira Filho SP. Liver transplantation: history, outcomes and perspectives. *Einstein (Sao Paulo)* 2015; **13**: 149-152 [PMID: 25993082 DOI: 10.1590/S1679-45082015RW3164]

2 **Asrani SK**, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. *J Hepatol* 2019; **70**: 151-171 [PMID: 30266282 DOI: 10.1016/j.jhep.2018.09.014]

3 **Griffin C**, Agbim U, Ramani A, Shankar N, Kanwal F, Asrani SK. Underestimation of Cirrhosis-Related Mortality in the Medicare Eligible Population, 1999-2018. *Clin Gastroenterol Hepatol* 2023; **21**: 223-225.e3 [PMID: 34728405 DOI: 10.1016/j.cgh.2021.10.036]

4 **Schnitzler MA**, Whiting JF, Brennan DC, Lentine KL, Desai NM, Chapman W, Abbott KC, Kalo Z. The life-years saved by a deceased organ donor. *Am J Transplant* 2005; **5**: 2289-2296 [PMID: 16095511 DOI: 10.1111/j.1600-6143.2005.01021.x]

5 **Terrault NA**, Francoz C, Berenguer M, Charlton M, Heimbach J. Liver Transplantation 2023: Status Report, Current and Future Challenges. *Clin Gastroenterol Hepatol* 2023; **21**: 2150-2166 [PMID: 37084928 DOI: 10.1016/j.cgh.2023.04.005]

6 **Elflein J**. Estimated number of worldwide kidney transplants in 2022, by region. 2022. Available from: https://www.statista.com/statistics/398657/kidney-transplants-by-world-region/

7 **Abdelrahim M**, Esmail A, Abudayyeh A, Murakami N, Saharia A, McMillan R, Victor D, Kodali S, Shetty A, Nolte Fong JV, Moore LW, Heyne K, Gaber AO, Ghobrial RM. Transplant Oncology: An Evolving Field in Cancer Care. *Cancers (Basel)* 2021; **13** [PMID: 34638395 DOI: 10.3390/cancers13194911]

8 **Iwatsuki S**, Starzl TE, Sheahan DG, Yokoyama I, Demetris AJ, Todo S, Tzakis AG, Van Thiel DH, Carr B, Selby R. Hepatic resection versus transplantation for hepatocellular carcinoma. *Ann Surg* 1991; **214**: 221-8; discussion 228 [PMID: 1656903 DOI: 10.1097/00000658-199109000-00005]

9 **Calne RY**, Williams R, Lindop M, Farman JV, Tolley ME, Rolles K, MacDougall B, Neuberger J, Wyke RJ, Raftery AT, Duffy TJ, Wight DG, White DJ. Improved survival after orthotopic liver grafting. *Br Med J (Clin Res Ed)* 1981; **283**: 115-118 [PMID: 6789932 DOI: 10.1136/bmj.283.6284.115]

10 **Starzl TE**, Iwatsuki S, Van Thiel DH, Gartner JC, Zitelli BJ, Malatack JJ, Schade RR, Shaw BW Jr, Hakala TR, Rosenthal JT, Porter KA. Evolution of liver transplantation. *Hepatology* 1982; **2**: 614-636 [PMID: 6749635 DOI: 10.1002/hep.1840020516]

11 **Yamamoto J**, Iwatsuki S, Kosuge T, Dvorchik I, Shimada K, Marsh JW, Yamasaki S, Starzl TE. Should hepatomas be treated with hepatic resection or transplantation? *Cancer* 1999; **86**: 1151-1158 [PMID: 10506698 DOI: 10.1002/(sici)1097-0142(19991001)86:7<1151::aid-cncr8>3.0.co;2-v]

12 **Mühlbacher F**, Huk I, Steininger R, Gnant M, Götzinger P, Wamser P, Banhegyi C, Piza F. Is orthotopic liver transplantation a feasible treatment for secondary cancer of the liver? *Transplant Proc* 1991; **23**: 1567-1568 [PMID: 1989293]

13 **Lai Q**, Levi Sandri GB, Lerut J. Selection tool alpha-fetoprotein for patients waiting for liver transplantation: How to easily manage a fractal algorithm. *World J Hepatol* 2015; **7**: 1899-1904 [PMID: 26244064 DOI: 10.4254/wjh.v7.i15.1899]

14 **Mehta SN**, Reinhold C, Barkun AN. Magnetic Resonance Cholangiopancreatography. Gastrointestinal Endoscopy Clinics of North America. 1997; 7: 247-270 [DOI: 10.1016/s1052-5157(18)30311-8]

15 **Hibi T**, Rela M, Eason JD, Line PD, Fung J, Sakamoto S, Selzner N, Man K, Ghobrial RM, Sapisochin G. Liver Transplantation for Colorectal and Neuroendocrine Liver Metastases and Hepatoblastoma. Working Group Report From the ILTS Transplant Oncology Consensus Conference. *Transplantation* 2020; **104**: 1131-1135 [PMID: 32217939 DOI: 10.1097/TP.0000000000003118]

16 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]

17 **Latt NL**, Niazi M, Pyrsopoulos NT. Liver transplant allocation policies and outcomes in United States: A comprehensive review. *World J Methodol* 2022; **12**: 32-42 [PMID: 35117980 DOI: 10.5662/wjm.v12.i1.32]

18 **De Carlis L**, Di Sandro S, Centonze L, Lauterio A, Buscemi V, De Carlis R, Ferla F, Sguinzi R, Okolicsanyi S, Belli L, Strazzabosco M. Liver-allocation policies for patients affected by HCC in Europe. *Curr Transplant Rep* 2016; **3**: 313-318 [PMID: 28473952 DOI: 10.1007/s40472-016-0117-6]

19 **Duffy JP**, Vardanian A, Benjamin E, Watson M, Farmer DG, Ghobrial RM, Lipshutz G, Yersiz H, Lu DS, Lassman C, Tong MJ, Hiatt JR, Busuttil RW. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. *Ann Surg* 2007; **246**: 502-9; discussion 509 [PMID: 17717454 DOI: 10.1097/SLA.0b013e318148c704]

20 **Lee Cheah Y**, K H Chow P. Liver transplantation for hepatocellular carcinoma: an appraisal of current controversies. *Liver Cancer* 2012; **1**: 183-189 [PMID: 24159583 DOI: 10.1159/000343832]

21 **Ilmer M**, Guba MO. Liver Transplant Oncology: Towards Dynamic Tumor-Biology-Oriented Patient Selection. *Cancers (Basel)* 2022; **14** [PMID: 35681642 DOI: 10.3390/cancers14112662]

22 **Halazun KJ**, Tabrizian P, Najjar M, Florman S, Schwartz M, Michelassi F, Samstein B, Brown RS Jr, Emond JC, Busuttil RW, Agopian VG. Is it Time to Abandon the Milan Criteria?: Results of a Bicoastal US Collaboration to Redefine Hepatocellular Carcinoma Liver Transplantation Selection Policies. *Ann Surg* 2018; **268**: 690-699 [PMID: 30048307 DOI: 10.1097/SLA.0000000000002964]

23 **Reig M**, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, Kelley RK, Galle PR, Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C, Bruix J. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol* 2022; **76**: 681-693 [PMID: 34801630 DOI: 10.1016/j.jhep.2021.11.018]

24 **Yau T**, Tang VY, Yao TJ, Fan ST, Lo CM, Poon RT. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. *Gastroenterology* 2014; **146**: 1691-700.e3 [PMID: 24583061 DOI: 10.1053/j.gastro.2014.02.032]

25 **Yao FY**, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; **33**: 1394-1403 [PMID: 11391528 DOI: 10.1053/jhep.2001.24563]

26 **Mazzaferro V**, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, Adam R, Neuhaus P, Salizzoni M, Bruix J, Forner A, De Carlis L, Cillo U, Burroughs AK, Troisi R, Rossi M, Gerunda GE, Lerut J, Belghiti J, Boin I, Gugenheim J, Rochling F, Van Hoek B, Majno P; Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; **10**: 35-43 [PMID: 19058754 DOI: 10.1016/S1470-2045(08)70284-5]

27 **Lee E**, Johnston CJC, Oniscu GC. The trials and tribulations of liver allocation. *Transpl Int* 2020; **33**: 1343-1352 [PMID: 32722866 DOI: 10.1111/tri.13710]

28 **Taniguchi M**. Liver transplantation in the MELD era--analysis of the OPTN/UNOS registry. *Clin Transpl* 2012; 41-65 [PMID: 23721009]

29 **Freeman RB Jr**, Edwards EB. Liver transplant waiting time does not correlate with waiting list mortality: implications for liver allocation policy. *Liver Transpl* 2000; **6**: 543-552 [PMID: 10980052 DOI: 10.1053/jlts.2000.9744]

30 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649 [PMID: 4541913 DOI: 10.1002/bjs.1800600817]

31 **Merion RM**, Sharma P, Mathur AK, Schaubel DE. Evidence-based development of liver allocation: a review. *Transpl Int* 2011; **24**: 965-972 [PMID: 21615548 DOI: 10.1111/j.1432-2277.2011.01274.x]

32 **Rule WK**. More on Educational Reform. *The Physics Teacher* 2003; 68-68 [DOI: 10.1119/1.1542033]

33 **Cholongitas E**, Germani G, Burroughs AK. Prioritization for liver transplantation. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 659-668 [PMID: 21045793 DOI: 10.1038/nrgastro.2010.169]

34 **Freeman RB**. A decade of model for end-stage liver disease: lessons learned and need for re-evaluation of allocation policies. *Curr Opin Organ Transplant* 2012; **17**: 211-215 [PMID: 22516923 DOI: 10.1097/MOT.0b013e3283534dde]

35 **Malinchoc M**, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31**: 864-871 [PMID: 10733541 DOI: 10.1053/he.2000.5852]

36 **Wiesner R**, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R; United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91-96 [PMID: 12512033 DOI: 10.1053/gast.2003.50016]

37 **Freeman RB Jr**, Wiesner RH, Harper A, McDiarmid SV, Lake J, Edwards E, Merion R, Wolfe R, Turcotte J, Teperman L; UNOS/OPTN Liver Disease Severity Score, UNOS/OPTN Liver and Intestine, and UNOS/OPTN Pediatric Transplantation Committees. The new liver allocation system: moving toward evidence-based transplantation policy. *Liver Transpl* 2002; **8**: 851-858 [PMID: 12200791 DOI: 10.1053/jlts.2002.35927]

38 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350 DOI: 10.1053/jhep.2001.22172]

39 **Freeman RB**, Wiesner RH, Edwards E, Harper A, Merion R, Wolfe R; United Network for Organ Sharing Organ Procurement and Transplantation Network Liver and Transplantation Committee. Results of the first year of the new liver allocation plan. *Liver Transpl* 2004; **10**: 7-15 [PMID: 14755772 DOI: 10.1002/lt.20024]

40 **Jurado-García J**, Muñoz García-Borruel M, Rodríguez-Perálvarez ML, Ruíz-Cuesta P, Poyato-González A, Barrera-Baena P, Fraga-Rivas E, Costán-Rodero G, Briceño-Delgado J, Montero-Álvarez JL, de la Mata-García M. Impact of MELD Allocation System on Waiting List and Early Post-Liver Transplant Mortality. *PLoS One* 2016; **11**: e0155822 [PMID: 27299728 DOI: 10.1371/journal.pone.0155822]

41 **Quante M**, Benckert C, Thelen A, Jonas S. Experience Since MELD Implementation: How Does the New System Deliver? *Int J Hepatol* 2012; **2012**: 264015 [PMID: 23091734 DOI: 10.1155/2012/264015]

42 **Lau T**, Ahmad J. Clinical applications of the Model for End-Stage Liver Disease (MELD) in hepatic medicine. *Hepat Med* 2013; **5**: 1-10 [PMID: 24696621 DOI: 10.2147/HMER.S9049]

43 **Lai JC**, Terrault NA, Vittinghoff E, Biggins SW. Height contributes to the gender difference in wait-list mortality under the MELD-based liver allocation system. *Am J Transplant* 2010; **10**: 2658-2664 [PMID: 21087414 DOI: 10.1111/j.1600-6143.2010.03326.x]

44 **Marvin MR**, Ferguson N, Cannon RM, Jones CM, Brock GN. MELDEQ : An alternative Model for End-Stage Liver Disease score for patients with hepatocellular carcinoma. *Liver Transpl* 2015; **21**: 612-622 [PMID: 25694099 DOI: 10.1002/lt.24098]

45 **Sarmast N**, Ogola GO, Kouznetsova M, Leise MD, Bahirwani R, Maiwall R, Tapper E, Trotter J, Bajaj JS, Thacker LR, Tandon P, Wong F, Reddy KR, O'Leary JG, Masica A, Modrykamien AM, Kamath PS, Asrani SK. Model for End-Stage Liver Disease-Lactate and Prediction of Inpatient Mortality in Patients With Chronic Liver Disease. *Hepatology* 2020; **72**: 1747-1757 [PMID: 32083761 DOI: 10.1002/hep.31199]

46 **Dutkowski P**, Linecker M, DeOliveira ML, Müllhaupt B, Clavien PA. Challenges to liver transplantation and strategies to improve outcomes. *Gastroenterology* 2015; **148**: 307-323 [PMID: 25224524 DOI: 10.1053/j.gastro.2014.08.045]

47 **Krendl FJ**, Bellotti R, Sapisochin G, Schaefer B, Tilg H, Scheidl S, Margreiter C, Schneeberger S, Oberhuber R, Maglione M. Transplant oncology - Current indications and strategies to advance the field. *JHEP Rep* 2024; **6**: 100965 [PMID: 38304238 DOI: 10.1016/j.jhepr.2023.100965]

48 **McMillan RR**, Javle M, Kodali S, Saharia A, Mobley C, Heyne K, Hobeika MJ, Lunsford KE, Victor DW 3rd, Shetty A, McFadden RS, Abdelrahim M, Kaseb A, Divatia M, Yu N, Nolte Fong J, Moore LW, Nguyen DT, Graviss EA, Gaber AO, Vauthey JN, Ghobrial RM. Survival following liver transplantation for locally advanced, unresectable intrahepatic cholangiocarcinoma. *Am J Transplant* 2022; **22**: 823-832 [PMID: 34856069 DOI: 10.1111/ajt.16906]

49 **Schmiderer A**, Zoller H, Niederreiter M, Effenberger M, Oberhuber G, Krendl FJ, Oberhuber R, Schneeberger S, Tilg H, Djanani A. Liver Transplantation after Successful Downstaging of a Locally Advanced Hepatocellular Carcinoma with Systemic Therapy. *Dig Dis* 2023; **41**: 641-644 [PMID: 36646054 DOI: 10.1159/000529023]

50 **Chouik Y**, Erard D, Demian H, Schulz T, Mazard T, Hartig-Lavie K, Antonini T, Mabrut JY, Mohkam K, Rode A, Merle P. Case Report: Successful liver transplantation after achieving complete clinical remission of advanced HCC with Atezolizumab plus Bevacizumab combination therapy. *Front Immunol* 2023; **14**: 1205997 [PMID: 37377975 DOI: 10.3389/fimmu.2023.1205997]

51 **Giudicelli H**, Roux C, Monsel A, Conti F, Scatton O, Allaire M. Successful advanced hepatocellular carcinoma downstaging with atezolizumab-Bevacizumab and radioembolization before liver transplantation. *Clin Res Hepatol Gastroenterol* 2023; **47**: 102167 [PMID: 37343767 DOI: 10.1016/j.clinre.2023.102167]

52 **Welch CS**. [Liver graft]. *Maroc Med* 1955; **34**: 514-515 [PMID: 13296493]

53 **Starzl TE**, Groth CG, Brettschneider L, Penn I, Fulginiti VA, Moon JB, Blanchard H, Martin AJ Jr, Porter KA. Orthotopic homotransplantation of the human liver. *Ann Surg* 1968; **168**: 392-415 [PMID: 4877589 DOI: 10.1097/00000658-196809000-00009]

54 **Moore FD**, Wheele HB, Demissianos HV, Smith LL, Balankura O, Abel K, Greenberg JB, Dammin GJ. Experimental whole-organ transplantation of the liver and of the spleen. *Ann Surg* 1960; **152**: 374-387 [PMID: 13772284 DOI: 10.1097/00000658-196009000-00003]

55 **Starzl TE**, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the Liver in Humans. *Surg Gynecol Obstet* 1963; **117**: 659-676 [PMID: 14100514]

56 **Starzl TE**, Klintmalm GB, Porter KA, Iwatsuki S, Schröter GP. Liver transplantation with use of cyclosporin a and prednisone. *N Engl J Med* 1981; **305**: 266-269 [PMID: 7017414 DOI: 10.1056/NEJM198107303050507]

57 **Krom RA**, Gips CH, Houthoff HJ, Newton D, van der Waaij D, Beelen J, Haagsma EB, Slooff MJ. Orthotopic liver transplantation in Groningen, The Netherlands (1979-1983). *Hepatology* 1984; **4**: 61S-65S [PMID: 6363260 DOI: 10.1002/hep.1840040717]

58 **Polak WG**, Peeters PM, Slooff MJ. The evolution of surgical techniques in clinical liver transplantation. A review. *Clin Transplant* 2009; **23**: 546-564 [PMID: 19486082 DOI: 10.1111/j.1399-0012.2009.00994.x]

59 **Griffith BP**, Shaw BW Jr, Hardesty RL, Iwatsuki S, Bahnson HT, Starzl TE. Veno-venous bypass without systemic anticoagulation for transplantation of the human liver. *Surg Gynecol Obstet* 1985; **160**: 270-272 [PMID: 3883552]

60 **Shaw BW Jr**, Martin DJ, Marquez JM, Kang YG, Bugbee AC Jr, Iwatsuki S, Griffith BP, Hardesty RL, Bahnson HT, Starzl TE. Venous bypass in clinical liver transplantation. *Ann Surg* 1984; **200**: 524-534 [PMID: 6385876 DOI: 10.1097/00000658-198410000-00013]

61 **Calne RY**, Williams R. Liver transplantation in man. I. Observations on technique and organization in five cases. *Br Med J* 1968; **4**: 535-540 [PMID: 4881063 DOI: 10.1136/bmj.4.5630.535]

62 **Tzakis A**, Todo S, Starzl TE. Orthotopic liver transplantation with preservation of the inferior vena cava. *Ann Surg* 1989; **210**: 649-652 [PMID: 2818033 DOI: 10.1097/00000658-198911000-00013]

63 **Fleitas MG**, Casanova D, Martino E, Maestre JM, Herrera L, Hernanz F, Rabanal JM, Pulgar S, Solares G. Could the piggyback operation in liver transplantation be routinely used? *Arch Surg* 1994; **129**: 842-845 [PMID: 8048855 DOI: 10.1001/archsurg.1994.01420320068013]

64 **Belghiti J**, Ettorre GM, Durand F, Sommacale D, Sauvanet A, Jerius JT, Farges O. Feasibility and limits of caval-flow preservation during liver transplantation. *Liver Transpl* 2001; **7**: 983-987 [PMID: 11699035 DOI: 10.1053/jlts.2001.28242]

65 **Lerut J**, Ciccarelli O, Roggen F, Laterre PF, Danse E, Goffette P, Aunac S, Carlier M, De Kock M, Van Obbergh L, Veyckemans F, Guerrieri C, Reding R, Otte JB. Cavocaval adult liver transplantation and retransplantation without venovenous bypass and without portocaval shunting: a prospective feasibility study in adult liver transplantation. *Transplantation* 2003; **75**: 1740-1745 [PMID: 12777866 DOI: 10.1097/01.TP.0000061613.66081.09]

66 **González FX**, García-Valdecasas JC, Grande L, Pacheco JL, Cugat E, Fuster J, Lacy AM, Taurá P, López-Boado MA, Rimola A, Visa J. Vena cava vascular reconstruction during orthotopic liver transplantation: a comparative study. *Liver Transpl Surg* 1998; **4**: 133-140 [PMID: 9516565 DOI: 10.1002/lt.500040206]

67 **Hosein Shokouh-Amiri M**, Osama Gaber A, Bagous WA, Grewal HP, Hathaway DK, Vera SR, Stratta RJ, Bagous TN, Kizilisik T. Choice of surgical technique influences perioperative outcomes in liver transplantation. *Ann Surg* 2000; **231**: 814-823 [PMID: 10816624 DOI: 10.1097/00000658-200006000-00005]

68 **Jovine E**, Mazziotti A, Grazi GL, Ercolani G, Masetti M, Morganti M, Pierangeli F, Begliomini B, Mazzetti PG, Rossi R, Paladini R, Cavallari A. Piggy-back versus conventional technique in liver transplantation: report of a randomized trial. *Transpl Int* 1997; **10**: 109-112 [PMID: 9089994 DOI: 10.1007/pl00003824]

69 **Lerut JP**, Molle G, Donataccio M, De Kock M, Ciccarelli O, Laterre PF, Van Leeuw V, Bourlier P, de Ville de Goyet J, Reding R, Gibbs P, Otte JB. Cavocaval liver transplantation without venovenous bypass and without temporary portocaval shunting: the ideal technique for adult liver grafting? *Transpl Int* 1997; **10**: 171-179 [PMID: 9163855 DOI: 10.1007/s001470050037]

70 **Miyamoto S**, Polak WG, Geuken E, Peeters PM, de Jong KP, Porte RJ, van den Berg AP, Hendriks HG, Slooff MJ. Liver transplantation with preservation of the inferior vena cava. A comparison of conventional and piggyback techniques in adults. *Clin Transplant* 2004; **18**: 686-693 [PMID: 15516245 DOI: 10.1111/j.1399-0012.2004.00278.x]

71 **Stieber AC**. One surgeon's experience with the piggyback versus the standard technique in orthotopic liver transplantation: is one better than

the other? *Hepatogastroenterology* 1995; **42**: 403-405 [PMID: 8586377]
72 **Brostoff JM**, Bhati CS, Syn WK. Late venous outflow obstruction after liver transplant: The 'piggy-back' syndrome. *Eur J Intern Med* 2008; **19**: 374-376 [PMID: 18549945 DOI: 10.1016/j.ejim.2007.10.013]
73 **Belghiti J**, Panis Y, Sauvanet A, Gayet B, Fékété F. A new technique of side to side caval anastomosis during orthotopic hepatic transplantation without inferior vena caval occlusion. *Surg Gynecol Obstet* 1992; **175**: 270-272 [PMID: 1514163]
74 **Cherqui D**, Lauzet JY, Rotman N, Duvoux C, Dhumeaux D, Julien M, Fagniez PL. Orthotopic liver transplantation with preservation of the caval and portal flows. Technique and results in 62 cases. *Transplantation* 1994; **58**: 793-796 [PMID: 7940712 DOI: 10.1097/00007890-199410150-00007]
75 **Sharma S**, Saner FH, Bezinover D. A brief history of liver transplantation and transplant anesthesia. *BMC Anesthesiol* 2022; **22**: 363 [PMID: 36435747 DOI: 10.1186/s12871-022-01904-1]
76 **Kim WR**, Lake JR, Smith JM, Schladt DP, Skeans MA, Harper AM, Wainright JL, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2016 Annual Data Report: Liver. *Am J Transplant* 2018; **18** Suppl 1: 172-253 [PMID: 29292603 DOI: 10.1111/ajt.14559]
77 **Pichlmayr R**, Ringe B, Gubernatis G, Hauss J, Bunzendahl H. [Transplantation of a donor liver to 2 recipients (splitting transplantation)--a new method in the further development of segmental liver transplantation]. *Langenbecks Arch Chir* 1988; **373**: 127-130 [PMID: 3287073 DOI: 10.1007/BF01262776]
78 **Bismuth H**, Morino M, Castaing D, Gillon MC, Descorps Declere A, Saliba F, Samuel D. Emergency orthotopic liver transplantation in two patients using one donor liver. *Br J Surg* 1989; **76**: 722-724 [PMID: 2670054 DOI: 10.1002/bjs.1800760723]
79 **Emond JC**, Whitington PF, Thistlethwaite JR, Cherqui D, Alonso EA, Woodle IS, Vogelbach P, Busse-Henry SM, Zucker AR, Broelsch CE. Transplantation of two patients with one liver. Analysis of a preliminary experience with 'split-liver' grafting. *Ann Surg* 1990; **212**: 14-22 [PMID: 2363599 DOI: 10.1097/00000658-199007000-00003]
80 **Vagefi PA**, Parekh J, Ascher NL, Roberts JP, Freise CE. Outcomes with split liver transplantation in 106 recipients: the University of California, San Francisco, experience from 1993 to 2010. *Arch Surg* 2011; **146**: 1052-1059 [PMID: 21931003 DOI: 10.1001/archsurg.2011.218]
81 **Lau NS**, Jacques A, McCaughan G, Crawford M, Liu K, Pulitano C. Addressing the challenges of split liver transplantation through technical advances. A systematic review. *Transplant Rev (Orlando)* 2021; **35**: 100627 [PMID: 34052472 DOI: 10.1016/j.trre.2021.100627]
82 **Rogiers X**. Split-Liver Transplantation. Springer Surgery Atlas Series. Heidelberg: Springer Berlin, 2019 [DOI: 10.1007/978-3-540-73796-4_15]
83 **Liu H**, Li R, Fu J, He Q, Li J. Technical Skills Required in Split Liver Transplantation. *Ann Transplant* 2016; **21**: 408-415 [PMID: 27363540 DOI: 10.12659/aot.896351]
84 **Emre S**, Umman V. Split liver transplantation: an overview. *Transplant Proc* 2011; **43**: 884-887 [PMID: 21486620 DOI: 10.1016/j.transproceed.2011.02.036]
85 **Battula NR**, Platto M, Anbarasan R, Perera MT, Ong E, Roll GR, Ferraz Neto BH, Mergental H, Isaac J, Muiesan P, Sharif K, Mirza DF. Intention to Split Policy: A Successful Strategy in a Combined Pediatric and Adult Liver Transplant Center. *Ann Surg* 2017; **265**: 1009-1015 [PMID: 27257738 DOI: 10.1097/SLA.0000000000001816]
86 **Raia S**, Nery JR, Mies S. Liver transplantation from live donors. *Lancet* 1989; **2**: 497 [PMID: 2570198 DOI: 10.1016/s0140-6736(89)92101-6]
87 **Strong RW**, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA. Successful liver transplantation from a living donor to her son. *N Engl J Med* 1990; **322**: 1505-1507 [PMID: 2336076 DOI: 10.1056/NEJM199005243222106]
88 **Hashikura Y**, Makuuchi M, Kawasaki S, Matsunami H, Ikegami T, Nakazawa Y, Kiyosawa K, Ichida T. Successful living-related partial liver transplantation to an adult patient. *Lancet* 1994; **343**: 1233-1234 [PMID: 7909905 DOI: 10.1016/s0140-6736(94)92450-3]
89 **Lo CM**, Fan ST, Liu CL, Lo RJ, Lau GK, Wei WI, Li JH, Ng IO, Wong J. Extending the limit on the size of adult recipient in living donor liver transplantation using extended right lobe graft. *Transplantation* 1997; **63**: 1524-1528 [PMID: 9175822 DOI: 10.1097/00007890-199705270-00027]
90 **Emond JC**, Heffron TG, Kortz EO, Gonzalez-Vallina R, Contis JC, Black DD, Whitington PF. Improved results of living-related liver transplantation with routine application in a pediatric program. *Transplantation* 1993; **55**: 835-840 [PMID: 7682738 DOI: 10.1097/00007890-199304000-00029]
91 **Miller CM**, Gondolesi GE, Florman S, Matsumoto C, Muñoz L, Yoshizumi T, Artis T, Fishbein TM, Sheiner PA, Kim-Schluger L, Schiano T, Shneider BL, Emre S, Schwartz ME. One hundred nine living donor liver transplants in adults and children: a single-center experience. *Ann Surg* 2001; **234**: 301-11; discussion 311 [PMID: 11524583 DOI: 10.1097/00000658-200109000-00004]
92 **Roberts JP**, Hulbert-Shearon TE, Merion RM, Wolfe RA, Port FK. Influence of graft type on outcomes after pediatric liver transplantation. *Am J Transplant* 2004; **4**: 373-377 [PMID: 14961989 DOI: 10.1111/j.1600-6143.2004.00359.x]
93 **Bourdeaux C**, Darwish A, Jamart J, Tri TT, Janssen M, Lerut J, Otte JB, Sokal E, de Ville de Goyet J, Reding R. Living-related versus deceased donor pediatric liver transplantation: a multivariate analysis of technical and immunological complications in 235 recipients. *Am J Transplant* 2007; **7**: 440-447 [PMID: 17173657 DOI: 10.1111/j.1600-6143.2006.01626.x]
94 **Grewal HP**, Thistlewaite JR Jr, Loss GE, Fisher JS, Cronin DC, Siegel CT, Newell KA, Bruce DS, Woodle ES, Brady L, Kelly S, Boone P, Oswald K, Millis JM. Complications in 100 living-liver donors. *Ann Surg* 1998; **228**: 214-219 [PMID: 9712567 DOI: 10.1097/00000658-199808000-00011]
95 **Fujita S**, Kim ID, Uryuhara K, Asonuma K, Egawa H, Kiuchi T, Hayashi M, Uemeto S, Inomata Y, Tanaka K. Hepatic grafts from live donors: donor morbidity for 470 cases of live donation. *Transpl Int* 2000; **13**: 333-339 [PMID: 11052268 DOI: 10.1007/s001470050710]
96 **Makuuchi M**, Kawasaki S, Noguchi T, Hashikura Y, Matsunami H, Hayashi K, Harada H, Kakazu T, Takayama T, Kawarasaki H. Donor hepatectomy for living related partial liver transplantation. *Surgery* 1993; **113**: 395-402 [PMID: 8456395]
97 **Hwang S**, Lee SG, Lee YJ, Sung KB, Park KM, Kim KH, Ahn CS, Moon DB, Hwang GS, Kim KM, Ha TY, Kim DS, Jung JP, Song GW. Lessons learned from 1,000 living donor liver transplantations in a single center: how to make living donations safe. *Liver Transpl* 2006; **12**: 920-927 [PMID: 16721780 DOI: 10.1002/lt.20734]
98 **Lee S**, Hwang S, Park K, Lee Y, Choi D, Ahn C, Nah Y, Koh K, Han S, Park S, Min P. An adult-to-adult living donor liver transplant using dual left lobe grafts. *Surgery* 2001; **129**: 647-650 [PMID: 11331460 DOI: 10.1067/msy.2001.114218]
99 **Kawasaki S**, Makuuchi M, Matsunami H, Hashikura Y, Ikegami T, Nakazawa Y, Chisuwa H, Terada M, Miyagawa S. Living related liver transplantation in adults. *Ann Surg* 1998; **227**: 269-274 [PMID: 9488526 DOI: 10.1097/00000658-199802000-00017]
100 **Lo CM**, Fan ST, Liu CL, Wei WI, Lo RJ, Lai CL, Chan JK, Ng IO, Fung A, Wong J. Adult-to-adult living donor liver transplantation using extended right lobe grafts. *Ann Surg* 1997; **226**: 261-9; discussion 269 [PMID: 9339932 DOI: 10.1097/00000658-199709000-00005]

101 **Thuluvath PJ**, Yoo HY. Graft and patient survival after adult live donor liver transplantation compared to a matched cohort who received a deceased donor transplantation. *Liver Transpl* 2004; **10**: 1263-1268 [PMID: 15376301 DOI: 10.1002/lt.20254]

102 **Olthoff KM**, Merion RM, Ghobrial RM, Abecassis MM, Fair JH, Fisher RA, Freise CE, Kam I, Pruett TL, Everhart JE, Hulbert-Shearon TE, Gillespie BW, Emond JC; A2ALL Study Group. Outcomes of 385 adult-to-adult living donor liver transplant recipients: a report from the A2ALL Consortium. *Ann Surg* 2005; **242**: 314-323, discussion 323 [PMID: 16135918 DOI: 10.1097/01.sla.0000179646.37145.ef]

103 **Morioka D**, Egawa H, Kasahara M, Ito T, Haga H, Takada Y, Shimada H, Tanaka K. Outcomes of adult-to-adult living donor liver transplantation: a single institution's experience with 335 consecutive cases. *Ann Surg* 2007; **245**: 315-325 [PMID: 17245187 DOI: 10.1097/01.sla.0000236600.24667.a4]

104 **Ito T**, Kiuchi T, Egawa H, Kaihara S, Oike F, Ogura Y, Fujimoto Y, Ogawa K, Tanaka K. Surgery-related morbidity in living donors of right-lobe liver graft: lessons from the first 200 cases. *Transplantation* 2003; **76**: 158-163 [PMID: 12865803 DOI: 10.1097/01.TP.0000072372.42396.47]

105 **Marcos A**, Orloff M, Mieles L, Olzinski AT, Renz JF, Sitzmann JV. Functional venous anatomy for right-lobe grafting and techniques to optimize outflow. *Liver Transpl* 2001; **7**: 845-852 [PMID: 11679981 DOI: 10.1053/jlts.2001.27966]

106 **Sugawara Y**, Makuuchi M. Advances in adult living donor liver transplantation: a review based on reports from the 10th anniversary of the adult-to-adult living donor liver transplantation meeting in Tokyo. *Liver Transpl* 2004; **10**: 715-720 [PMID: 15162463 DOI: 10.1002/lt.20179]

107 **Akarsu M**. Liver transplantation in Turkey: The importance of experience. *Turk J Gastroenterol* 2018; **29**: 629-630 [PMID: 30381270 DOI: 10.5152/tjg.2018.81018]

108 **Kim PT**, Testa G. Living donor liver transplantation in the USA. *Hepatobiliary Surg Nutr* 2016; **5**: 133-140 [PMID: 27115007 DOI: 10.3978/j.issn.2304-3881.2015.06.01]

109 **Narasimhan G**. Living donor liver transplantation in India. *Hepatobiliary Surg Nutr* 2016; **5**: 127-132 [PMID: 27115006 DOI: 10.3978/j.issn.2304-3881.2015.09.01]

110 **Dutkowski P**, de Rougemont O, Clavien PA. Machine perfusion for 'marginal' liver grafts. *Am J Transplant* 2008; **8**: 917-924 [PMID: 18416733 DOI: 10.1111/j.1600-6143.2008.02165.x]

111 **Fondevila C**, Hessheimer AJ, Ruiz A, Calatayud D, Ferrer J, Charco R, Fuster J, Navasa M, Rimola A, Taurá P, Ginés P, Manyalich M, Garcí a-Valdecasas JC. Liver transplant using donors after unexpected cardiac death: novel preservation protocol and acceptance criteria. *Am J Transplant* 2007; **7**: 1849-1855 [PMID: 17564639 DOI: 10.1111/j.1600-6143.2007.01846.x]

112 **Compagnon P**, Levesque E, Hentati H, Disabato M, Calderaro J, Feray C, Corlu A, Cohen JL, Ben Mosbah I, Azoulay D. An Oxygenated and Transportable Machine Perfusion System Fully Rescues Liver Grafts Exposed to Lethal Ischemic Damage in a Pig Model of DCD Liver Transplantation. *Transplantation* 2017; **101**: e205-e213 [PMID: 28403128 DOI: 10.1097/TP.0000000000001764]

113 **Mergental H**, Roll GR. Normothermic machine perfusion of the liver. *Clin Liver Dis (Hoboken)* 2017; **10**: 97-99 [PMID: 31186895 DOI: 10.1002/cld.661]

114 **Johnson RW**, Morley A, Swinney J, Taylor RM. The comparison of 24-hour preservation by hypothermic perfusion and cold storage on canine kidneys damaged by warm ischaemia. *Br J Surg* 1971; **58**: 299 [PMID: 4929356]

115 **Dutkowski P**, Krug A, Krysiak M, Dünschede F, Seifert JK, Junginger T. Detection of mitochondrial electron chain carrier redox status by transhepatic light intensity during rat liver reperfusion. *Cryobiology* 2003; **47**: 125-142 [PMID: 14580847 DOI: 10.1016/j.cryobiol.2003.08.004]

116 **Guarrera JV**, Henry SD, Samstein B, Reznik E, Musat C, Lukose TI, Ratner LE, Brown RS Jr, Kato T, Emond JC. Hypothermic machine preservation facilitates successful transplantation of "orphan" extended criteria donor livers. *Am J Transplant* 2015; **15**: 161-169 [PMID: 25521639 DOI: 10.1111/ajt.12958]

117 **van Rijn R**, Schurink IJ, de Vries Y, van den Berg AP, Cortes Cerisuelo M, Darwish Murad S, Erdmann JI, Gilbo N, de Haas RJ, Heaton N, van Hoek B, Huurman VAL, Jochmans I, van Leeuwen OB, de Meijer VE, Monbaliu D, Polak WG, Slangen JJG, Troisi RI, Vanlander A, de Jonge J, Porte RJ; DHOPE-DCD Trial Investigators. Hypothermic Machine Perfusion in Liver Transplantation - A Randomized Trial. *N Engl J Med* 2021; **384**: 1391-1401 [PMID: 33626248 DOI: 10.1056/NEJMoa2031532]

118 **Butler AJ**, Rees MA, Wight DG, Casey ND, Alexander G, White DJ, Friend PJ. Successful extracorporeal porcine liver perfusion for 72 hr. *Transplantation* 2002; **73**: 1212-1218 [PMID: 11981411 DOI: 10.1097/00007890-200204270-00005]

119 **Jayant K**, Reccia I, Virdis F, Shapiro AMJ. The Role of Normothermic Perfusion in Liver Transplantation (TRaNsIT Study): A Systematic Review of Preliminary Studies. *HPB Surg* 2018; **2018**: 6360423 [PMID: 29887782 DOI: 10.1155/2018/6360423]

120 **Mergental H**, Laing RW, Kirkham AJ, Perera MTPR, Boteon YL, Attard J, Barton D, Curbishley S, Wilkhu M, Neil DAH, Hübscher SG, Muiesan P, Isaac JR, Roberts KJ, Abradelo M, Schlegel A, Ferguson J, Cilliers H, Bion J, Adams DH, Morris C, Friend PJ, Yap C, Afford SC, Mirza DF. Transplantation of discarded livers following viability testing with normothermic machine perfusion. *Nat Commun* 2020; **11**: 2939 [PMID: 32546694 DOI: 10.1038/s41467-020-16251-3]

121 **Furtado A**, Tomé L, Oliveira FJ, Furtado E, Viana J, Perdigoto R. Sequential liver transplantation. *Transplant Proc* 1997; **29**: 467-468 [PMID: 9123085 DOI: 10.1016/s0041-1345(96)00206-0]

122 **Ericzon BG**, Larsson M, Herlenius G, Wilczek HE; Familial Amyloidotic Polyneuropathy World Transplant Registry. Report from the Familial Amyloidotic Polyneuropathy World Transplant Registry (FAPWTR) and the Domino Liver Transplant Registry (DLTR). *Amyloid* 2003; **10** Suppl 1: 67-76 [PMID: 14640044 DOI: 10.1080/13506129.2003.12088570]

123 **Celik N**, Squires JE, Soltys K, Vockley J, Shellmer DA, Chang W, Strauss K, McKiernan P, Ganoza A, Sindhi R, Bond G, Mazariegos G, Khanna A. Domino liver transplantation for select metabolic disorders: Expanding the living donor pool. *JIMD Rep* 2019; **48**: 83-89 [PMID: 31392117 DOI: 10.1002/jmd2.12053]

124 **Khanna A**, Hart M, Nyhan WL, Hassanein T, Panyard-Davis J, Barshop BA. Domino liver transplantation in maple syrup urine disease. *Liver Transpl* 2006; **12**: 876-882 [PMID: 16628687 DOI: 10.1002/lt.20744]

125 **Monteiro E**, Perdigoto R, Furtado AL. Liver transplantation for familial amyloid polyneuropathy. *Hepatogastroenterology* 1998; **45**: 1375-1380 [PMID: 9840068]

126 **FAPWTR**. Results from the Domino Liver Transplant Registry. Available from: http://www.fapwtr.org/ram_domino.htm

127 **Furtado AJ**. Domino liver transplantation using FAP grafts. HUC experience--hopes and realities. *Amyloid* 2003; **10** Suppl 1: 84-87 [PMID: 14640046 DOI: 10.1080/13506129.2003.12088572]

128 **Yamamoto S**, Wilczek HE, Nowak G, Larsson M, Oksanen A, Iwata T, Gjertsen H, Söderdahl G, Wikström L, Ando Y, Suhr OB, Ericzon BG. Liver transplantation for familial amyloidotic polyneuropathy (FAP): a single-center experience over 16 years. *Am J Transplant* 2007; **7**: 2597-2604 [PMID: 17868062 DOI: 10.1111/j.1600-6143.2007.01969.x]

129 **Karadagi A**, Romano A, Renneus Guthrie V, Kjaernet F, Ericzon BG, Nowak G. Effects of a Domino Liver Transplantation Program on Patient Survival and Waiting List Time: A Single-Center Retrospective Study. *Transplant Proc* 2021; **53**: 2983-2992 [PMID: 34749995 DOI: 10.1016/j.transproceed.2021.09.021]

130 **Ahmed O**, Vachharajani N, Chang SH, Park Y, Khan AS, Chapman WC, Doyle MBM. Domino liver transplants: where do we stand after a quarter-century? A US national analysis. *HPB (Oxford)* 2022; **24**: 1026-1034 [PMID: 34924293 DOI: 10.1016/j.hpb.2021.11.013]

131 **Stangou AJ**, Heaton ND, Hawkins PN. Transmission of systemic transthyretin amyloidosis by means of domino liver transplantation. *N Engl J Med* 2005; **352**: 2356 [PMID: 15930432 DOI: 10.1056/NEJM200506023522219]

132 **Schielke A**, Conti F, Goumard C, Perdigao F, Calmus Y, Scatton O. Liver transplantation using grafts with rare metabolic disorders. *Dig Liver Dis* 2015; **47**: 261-270 [PMID: 25498135 DOI: 10.1016/j.dld.2014.11.004]

133 **Popescu I**, Dima SO. Domino liver transplantation: how far can we push the paradigm? *Liver Transpl* 2012; **18**: 22-28 [PMID: 21987415 DOI: 10.1002/lt.22443]

134 **Franchello A**, Paraluppi G, Romagnoli R, Petrarulo M, Vitale C, Pacitti A, Amoroso A, Marangella M, Salizzoni M. Severe course of primary hyperoxaluria and renal failure after domino hepatic transplantation. *Am J Transplant* 2005; **5**: 2324-2327 [PMID: 16095518 DOI: 10.1111/j.1600-6143.2005.01014.x]

135 **Popescu I**, Habib N, Dima S, Hancu N, Gheorghe L, Iacob S, Mihaila M, Dorobantu B, Matei E, Botea F. Domino liver transplantation using a graft from a donor with familial hypercholesterolemia: seven-yr follow-up. *Clin Transplant* 2009; **23**: 565-570 [PMID: 19191809 DOI: 10.1111/j.1399-0012.2008.00935.x]

136 **Dowman JK**, Gunson BK, Bramhall S, Badminton MN, Newsome PN. Liver transplantation from donors with acute intermittent porphyria. *Ann Intern Med* 2011; **154**: 571-572 [PMID: 21502660 DOI: 10.7326/0003-4819-154-8-201104190-00015]

137 **Azoulay D**, Samuel D, Castaing D, Adam R, Adams D, Said G, Bismuth H. Domino liver transplants for metabolic disorders: experience with familial amyloidotic polyneuropathy. *J Am Coll Surg* 1999; **189**: 584-593 [PMID: 10589595 DOI: 10.1016/s1072-7515(99)00208-2]

138 **O'Callaghan JM**, Knight SR, Morgan RD, Morris PJ. Preservation solutions for static cold storage of kidney allografts: a systematic review and meta-analysis. *Am J Transplant* 2012; **12**: 896-906 [PMID: 22221739 DOI: 10.1111/j.1600-6143.2011.03908.x]

139 **Timsit MO**, Tullius SG. Hypothermic kidney preservation: a remembrance of the past in the future? *Curr Opin Organ Transplant* 2011; **16**: 162-168 [PMID: 21415818 DOI: 10.1097/MOT.0b013e3283446b07]

140 **Collins GM**, Bravo-Shugarman M, Terasaki PI. Kidney preservation for transportation. Initial perfusion and 30 hours' ice storage. *Lancet* 1969; **2**: 1219-1222 [PMID: 4187813 DOI: 10.1016/s0140-6736(69)90753-3]

141 **Dreikorn K**, Horsch R, Röhl L. 48- to 96-hour preservation of canine kidneys by initial perfusion and hypothermic storage using the Euro-Collins solution. *Eur Urol* 1980; **6**: 221-224 [PMID: 6993210 DOI: 10.1159/000473336]

142 **O'Callaghan JM**, Knight SR, Morgan RD, Morris PJ. A National Registry Analysis of Kidney Allografts Preserved With Marshall's Solution in the United Kingdom. *Transplantation* 2016; **100**: 2447-2452 [PMID: 26760566 DOI: 10.1097/TP.0000000000001033]

143 **Ross H**, Marshall VC, Escott ML. 72-hr canine kidney preservation without continuous perfusion. *Transplantation* 1976; **21**: 498-501 [PMID: 936278 DOI: 10.1097/00007890-197606000-00009]

144 **Wahlberg JA**, Southard JH, Belzer FO. Development of a cold storage solution for pancreas preservation. *Cryobiology* 1986; **23**: 477-482 [PMID: 3802886 DOI: 10.1016/0011-2240(86)90056-8]

145 **Yu WM**, Coddington D, Bitter-Suermann H. Rat liver preservation. I. The components of UW solution that are essential to its success. *Transplantation* 1990; **49**: 1060-1066 [PMID: 2360249 DOI: 10.1097/00007890-199006000-00007]

146 **Bretschneider HJ**. Myocardial protection. *Thorac Cardiovasc Surg* 1980; **28**: 295-302 [PMID: 6161427 DOI: 10.1055/s-2007-1022099]

147 **Adam R**, Delvart V, Karam V, Ducerf C, Navarro F, Letoublon C, Belghiti J, Pezet D, Castaing D, Le Treut YP, Gugenheim J, Bachellier P, Pirenne J, Muiesan P; ELTR contributing centres, the European Liver, Intestine Transplant Association (ELITA). Compared efficacy of preservation solutions in liver transplantation: a long-term graft outcome study from the European Liver Transplant Registry. *Am J Transplant* 2015; **15**: 395-406 [PMID: 25612492 DOI: 10.1111/ajt.13060]

148 **Chedid MF**, Pinto MA, Juchem JFG, Grezzana-Filho TJM, Kruel CRP. Liver preservation prior to transplantation: Past, present, and future. *World J Gastrointest Surg* 2019; **11**: 122-125 [PMID: 31057697 DOI: 10.4240/wjgs.v11.i3.122]

149 **Quillin RC 3rd**, Guarrera JV. Hypothermic machine perfusion in liver transplantation. *Liver Transpl* 2018; **24**: 276-281 [PMID: 29278454 DOI: 10.1002/lt.25004]

150 **Ravikumar R**, Jassem W, Mergental H, Heaton N, Mirza D, Perera MT, Quaglia A, Holroyd D, Vogel T, Coussios CC, Friend PJ. Liver Transplantation After Ex Vivo Normothermic Machine Preservation: A Phase 1 (First-in-Man) Clinical Trial. *Am J Transplant* 2016; **16**: 1779-1787 [PMID: 26752191 DOI: 10.1111/ajt.13708]

151 **Nasralla D**, Coussios CC, Mergental H, Akhtar MZ, Butler AJ, Ceresa CDL, Chiocchia V, Dutton SJ, García-Valdecasas JC, Heaton N, Imber C, Jassem W, Jochmans I, Karani J, Knight SR, Kocabayoglu P, Malagò M, Mirza D, Morris PJ, Pallan A, Paul A, Pavel M, Perera MTPR, Pirenne J, Ravikumar R, Russell L, Upponi S, Watson CJE, Weissenbacher A, Ploeg RJ, Friend PJ; Consortium for Organ Preservation in Europe. A randomized trial of normothermic preservation in liver transplantation. *Nature* 2018; **557**: 50-56 [PMID: 29670285 DOI: 10.1038/s41586-018-0047-9]

152 **Angelico R**, Perera MT, Ravikumar R, Holroyd D, Coussios C, Mergental H, Isaac JR, Iqbal A, Cilliers H, Muiesan P, Friend PJ, Mirza DF. Normothermic Machine Perfusion of Deceased Donor Liver Grafts Is Associated With Improved Postreperfusion Hemodynamics. *Transplant Direct* 2016; **2**: e97 [PMID: 27795989 DOI: 10.1097/TXD.0000000000000611]

153 **Schlegel A**, Muller X, Dutkowski P. Machine perfusion strategies in liver transplantation. *Hepatobiliary Surg Nutr* 2019; **8**: 490-501 [PMID: 31673538 DOI: 10.21037/hbsn.2019.04.04]

154 **Brüggenwirth IMA**, Lantinga VA, Lascaris B, Thorne AM, Meerdink M, de Kleine RH, Blokzijl H, van den Berg AP, Reyntjens KMEM, Lisman T, Porte RJ, de Meijer VE; DHOPE-PRO Trial Investigators. Prolonged hypothermic machine perfusion enables daytime liver transplantation - an IDEAL stage 2 prospective clinical trial. *EClinicalMedicine* 2024; **68**: 102411 [PMID: 38235423 DOI: 10.1016/j.eclinm.2023.102411]

155 **Burnet FM**. Theories of immunity. *Perspect Biol Med* 1960; **3**: 447-458 [PMID: 13806209 DOI: 10.1353/pbm.1960.0034]

156 **Medawar PB**. Immunological tolerance. *Science* 1961; **133**: 303-306 [PMID: 13768822 DOI: 10.1126/science.133.3449.303]

157 **Song AT**, Avelino-Silva VI, Pecora RA, Pugliese V, D'Albuquerque LA, Abdala E. Liver transplantation: fifty years of experience. *World J Gastroenterol* 2014; **20**: 5363-5374 [PMID: 24833866 DOI: 10.3748/wjg.v20.i18.5363]

158 **Dienstag JL**, Cosimi AB. Liver transplantation--a vision realized. *N Engl J Med* 2012; **367**: 1483-1485 [PMID: 22992048 DOI: 10.1056/NEJMp1210159]

159 **Lucey MR**, Terrault N, Ojo L, Hay JE, Neuberger J, Blumberg E, Teperman LW. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl* 2013; **19**: 3-26 [PMID: 23281277 DOI: 10.1002/lt.23566]

160 **Starzl TE**. The saga of liver replacement, with particular reference to the reciprocal influence of liver and kidney transplantation (1955-1967). *J Am Coll Surg* 2002; **195**: 587-610 [PMID: 12437245 DOI: 10.1016/s1072-7515(02)01498-9]

161 **Starzl TE**, Koep LJ, Halgrimson CG, Hood J, Schroter GP, Porter KA, Weil R 3rd. Fifteen years of clinical liver transplantation. *Gastroenterology* 1979; **77**: 375-388 [PMID: 376395 DOI: 10.1016/0016-5085(79)90294-4]

162 **Calne RY**, Rolles K, White DJ, Thiru S, Evans DB, McMaster P, Dunn DC, Craddock GN, Henderson RG, Aziz S, Lewis P. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. *Lancet* 1979; **2**: 1033-1036 [PMID: 91781 DOI: 10.1016/s0140-6736(79)92440-1]

163 **Starzl TE**, Todo S, Fung J, Demetris AJ, Venkataramman R, Jain A. FK 506 for liver, kidney, and pancreas transplantation. *Lancet* 1989; **2**: 1000-1004 [PMID: 2478846 DOI: 10.1016/s0140-6736(89)91014-3]

164 **Lerut J**, Iesari S. Immunosuppression and Liver Transplantation. *Eng* 2023; **21**: 175-187 [DOI: 10.1016/j.eng.2022.07.007]

165 **Starzl TE**, Demetris AJ. Liver transplantation: a 31-year perspective. Part I. *Curr Probl Surg* 1990; **27**: 49-116 [PMID: 2197064 DOI: 10.1016/0011-3840(90)90021-v]

166 **Neuberger J**, Adams DH. What is the significance of acute liver allograft rejection? *J Hepatol* 1998; **29**: 143-150 [PMID: 9696504 DOI: 10.1016/s0168-8278(98)80190-6]

167 **Wiesner RH**, Demetris AJ, Belle SH, Seaberg EC, Lake JR, Zetterman RK, Everhart J, Detre KM. Acute hepatic allograft rejection: incidence, risk factors, and impact on outcome. *Hepatology* 1998; **28**: 638-645 [PMID: 9731552 DOI: 10.1002/hep.510280306]

168 **Egawa H**, Umeshita K, Uemoto S. Optimal dosage regimen for rituximab in ABO-incompatible living donor liver transplantation. *J Hepatobiliary Pancreat Sci* 2017; **24**: 89-94 [PMID: 28002655 DOI: 10.1002/jhbp.419]

169 **Farkas SA**, Schnitzbauer AA, Kirchner G, Obed A, Banas B, Schlitt HJ. Calcineurin inhibitor minimization protocols in liver transplantation. *Transpl Int* 2009; **22**: 49-60 [PMID: 19121146 DOI: 10.1111/j.1432-2277.2008.00796.x]

170 **Anghel D**, Tanasescu R, Campeanu A, Lupescu I, Podda G, Bajenaru O. Neurotoxicity of immunosuppressive therapies in organ transplantation. *Maedica (Bucur)* 2013; **8**: 170-175 [PMID: 24371481]

171 **Nordness MF**, Hamel S, Godfrey CM, Shi C, Johnson DB, Goff LW, O'Dell H, Perri RE, Alexopoulos SP. Fatal hepatic necrosis after nivolumab as a bridge to liver transplant for HCC: Are checkpoint inhibitors safe for the pretransplant patient? *Am J Transplant* 2020; **20**: 879-883 [PMID: 31550417 DOI: 10.1111/ajt.15617]

172 **Tabrizian P**, Florman SS, Schwartz ME. PD-1 inhibitor as bridge therapy to liver transplantation? *Am J Transplant* 2021; **21**: 1979-1980 [PMID: 33316117 DOI: 10.1111/ajt.16448]

173 **Chen GH**, Wang GB, Huang F, Qin R, Yu XJ, Wu RL, Hou LJ, Ye ZH, Zhang XH, Zhao HC. Pretransplant use of toripalimab for hepatocellular carcinoma resulting in fatal acute hepatic necrosis in the immediate postoperative period. *Transpl Immunol* 2021; **66**: 101386 [PMID: 33744409 DOI: 10.1016/j.trim.2021.101386]

174 **Tanaka K**, Albin MJ, Yuan X, Yamaura K, Habicht A, Murayama T, Grimm M, Waaga AM, Ueno T, Padera RF, Yagita H, Azuma M, Shin T, Blazar BR, Rothstein DM, Sayegh MH, Najafian N. PDL1 is required for peripheral transplantation tolerance and protection from chronic allograft rejection. *J Immunol* 2007; **179**: 5204-5210 [PMID: 17911605 DOI: 10.4049/jimmunol.179.8.5204]

175 **Schwartzberg L**. Addressing the value of novel therapies in chemotherapy-induced nausea and vomiting. *Expert Rev Pharmacoecon Outcomes Res* 2014; **14**: 825-834 [PMID: 25227565 DOI: 10.1586/14737167.2014.957683]

176 **Woo SM**, Kimchy AV, Sequeira LM, Dorris CS, He AR, Rangnekar AS. Immunotherapy Use Prior to Liver Transplant in Patients with Hepatocellular Carcinoma. *Curr Oncol* 2022; **29**: 9813-9825 [PMID: 36547185 DOI: 10.3390/curroncol29120771]

177 **Gao Q**, Anwar IJ, Abraham N, Barbas AS. Liver Transplantation for Hepatocellular Carcinoma after Downstaging or Bridging Therapy with Immune Checkpoint Inhibitors. *Cancers (Basel)* 2021; **13** [PMID: 34944927 DOI: 10.3390/cancers13246307]

178 **Cesario S**, Genovesi V, Salani F, Vasile E, Fornaro L, Vivaldi C, Masi G. Evolving Landscape in Liver Transplantation for Hepatocellular Carcinoma: From Stage Migration to Immunotherapy Revolution. *Life (Basel)* 2023; **13** [PMID: 37511937 DOI: 10.3390/life13071562]

179 **Montano-Loza AJ**, Rodríguez-Perálvarez ML, Pageaux GP, Sanchez-Fueyo A, Feng S. Liver transplantation immunology: Immunosuppression, rejection, and immunomodulation. *J Hepatol* 2023; **78**: 1199-1215 [PMID: 37208106 DOI: 10.1016/j.jhep.2023.01.030]

180 **Tabrizian P**, Holzner ML, Mehta N, Halazun K, Agopian VG, Yao F, Busuttil RW, Roberts J, Emond JC, Samstein B, Brown RS Jr, Najjar M, Chapman WC, Doyle MM, Florman SS, Schwartz ME, Llovet JM. Ten-Year Outcomes of Liver Transplant and Downstaging for Hepatocellular Carcinoma. *JAMA Surg* 2022; **157**: 779-788 [PMID: 35857294 DOI: 10.1001/jamasurg.2022.2800]

181 **Åberg F**, Isoniemi H, Höckerstedt K. Long-term results of liver transplantation. *Scand J Surg* 2011; **100**: 14-21 [PMID: 21482501 DOI: 10.1177/145749691110000104]

182 **Saidi RF**. Current status of liver transplantation. *Arch Iran Med* 2012; **15**: 772-776 [PMID: 23199251]

183 **Chen XB**, Xu MQ. Primary graft dysfunction after liver transplantation. *Hepatobiliary Pancreat Dis Int* 2014; **13**: 125-137 [PMID: 24686540 DOI: 10.1016/s1499-3872(14)60023-0]

184 **Agopian VG**, Harlander-Locke MP, Markovic D, Dumronggittigule W, Xia V, Kaldas FM, Zarrinpar A, Yersiz H, Farmer DG, Hiatt JR, Busuttil RW. Evaluation of Early Allograft Function Using the Liver Graft Assessment Following Transplantation Risk Score Model. *JAMA Surg* 2018; **153**: 436-444 [PMID: 29261831 DOI: 10.1001/jamasurg.2017.5040]

185 **Pareja E**, Cortes M, Hervás D, Mir J, Valdivieso A, Castell JV, Lahoz A. A score model for the continuous grading of early allograft dysfunction severity. *Liver Transpl* 2015; **21**: 38-46 [PMID: 25204890 DOI: 10.1002/lt.23990]

186 **Jochmans I**, Fieuws S, Monbaliu D, Pirenne J. "Model for Early Allograft Function" Outperforms "Early Allograft Dysfunction" as a Predictor of Transplant Survival. *Transplantation* 2017; **101**: e258-e264 [PMID: 28557956 DOI: 10.1097/TP.0000000000001833]

187 **Agostini C**, Buccianti S, Risaliti M, Fortuna L, Tirloni L, Tucci R, Bartolini I, Grazi GL. Complications in Post-Liver Transplant Patients. *J Clin Med* 2023; **12** [PMID: 37834818 DOI: 10.3390/jcm12196173]

188 **Bastos-Neves D**, Salvalaggio PRO, Almeida MD. Risk factors, surgical complications and graft survival in liver transplant recipients with early allograft dysfunction. *Hepatobiliary Pancreat Dis Int* 2019; **18**: 423-429 [PMID: 30853253 DOI: 10.1016/j.hbpd.2019.02.005]

189 **Ramirez CGB**. Orthotopic Liver Transplantation: Complications. Contemporary Liver Transplantation. Springer Cham, 2016 [DOI: 10.1007/978-3-319-05543-5_41-2]

190 **Adelmann D**, Roll GR, Kothari R, Syed S, Burdine LJ, Tavakol M, Niemann CU. The Impact of Deceased Donor Liver Extraction Time on

Early Allograft Function in Adult Liver Transplant Recipients. *Transplantation* 2018; **102**: e466-e471 [PMID: 30048397 DOI: 10.1097/TP.0000000000002380]

191 **De Carlis R**, Di Sandro S, Lauterio A, Botta F, Ferla F, Andorno E, Bagnardi V, De Carlis L. Liver Grafts From Donors After Circulatory Death on Regional Perfusion With Extended Warm Ischemia Compared With Donors After Brain Death. *Liver Transpl* 2018; **24**: 1523-1535 [PMID: 30022597 DOI: 10.1002/lt.25312]

192 **Rodríguez-Sanjuán JC**, Ruiz N, Miñambres E, Toledo E, González-Noriega M, Fernández-Santiago R, Castillo F. Liver Transplant From Controlled Cardiac Death Donors Using Normothermic Regional Perfusion: Comparison With Liver Transplants From Brain Dead Donors. *Transplant Proc* 2019; **51**: 12-19 [PMID: 30655135 DOI: 10.1016/j.transproceed.2018.04.067]

193 **Coll E**, Miñambres E, Sánchez-Fructuoso A, Fondevila C, Campo-Cañaveral de la Cruz JL, Domínguez-Gil B. Uncontrolled Donation After Circulatory Death: A Unique Opportunity. *Transplantation* 2020; **104**: 1542-1552 [PMID: 32732830 DOI: 10.1097/TP.0000000000003139]

194 **Marcon F**, Schlegel A, Bartlett DC, Kalisvaart M, Bishop D, Mergental H, Roberts KJ, Mirza DF, Isaac J, Muiesan P, Perera MT. Utilization of Declined Liver Grafts Yields Comparable Transplant Outcomes and Previous Decline Should Not Be a Deterrent to Graft Use. *Transplantation* 2018; **102**: e211-e218 [PMID: 29702538 DOI: 10.1097/TP.0000000000002127]

195 **Bozkurt B**, Dayangac M, Tokat Y. Living donor liver transplantation. Chirurgia (Romania) 2017. Available from: https://avesis.medipol.edu.tr/yayin/3c126207-49cf-4542-920e-648f709ec0e1/living-donor-liver-transplantation

196 **Asmundo L**, Rizzetto F, Sgrazzutti C, Carbonaro LA, Mazzarelli C, Centonze L, Rutanni D, De Carlis L, Vanzulli A. Computed Tomography and Magnetic Resonance Imaging Signs of Chronic Liver Rejection: A Case-Control Study. *J Comput Assist Tomogr* 2024; **48**: 26-34 [PMID: 37422693 DOI: 10.1097/RCT.0000000000001511]

197 **van Hoek B**, Wiesner RH, Krom RA, Ludwig J, Moore SB. Severe ductopenic rejection following liver transplantation: incidence, time of onset, risk factors, treatment, and outcome. *Semin Liver Dis* 1992; **12**: 41-50 [PMID: 1570550 DOI: 10.1055/s-2007-1007375]

198 **Fagiuoli S**, Colli A, Bruno R, Craxì A, Gaeta GB, Grossi P, Mondelli MU, Puoti M, Sagnelli E, Stefani S, Toniutto P, Burra P; 2011 AISF Single Topic Group. Management of infections pre- and post-liver transplantation: report of an AISF consensus conference. *J Hepatol* 2014; **60**: 1075-1089 [PMID: 24384327 DOI: 10.1016/j.jhep.2013.12.021]

199 **Gavaldà J**, Vidal E, Lumbreras C. Infection prevention in solid organ transplantation. *Enferm Infecc Microbiol Clin* 2012; **30** Suppl 2: 27-33 [PMID: 22542032 DOI: 10.1016/S0213-005X(12)70079-4]

200 **Esch MB**, Prot JM, Wang YI, Miller P, Llamas-Vidales JR, Naughton BA, Applegate DR, Shuler ML. Multi-cellular 3D human primary liver cell culture elevates metabolic activity under fluidic flow. *Lab Chip* 2015; **15**: 2269-2277 [PMID: 25857666 DOI: 10.1039/c5lc00237k]

201 **Martin SI**, Fishman JA; AST Infectious Diseases Community of Practice. Pneumocystis pneumonia in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S227-S233 [PMID: 20070684 DOI: 10.1111/j.1600-6143.2009.02914.x]

202 **Muñoz P**, Rodríguez C, Bouza E. Mycobacterium tuberculosis infection in recipients of solid organ transplants. *Clin Infect Dis* 2005; **40**: 581-587 [PMID: 15712081 DOI: 10.1086/427692]

203 **Feltracco P**, Carollo C, Barbieri S, Pettenuzzo T, Ori C. Early respiratory complications after liver transplantation. *World J Gastroenterol* 2013; **19**: 9271-9281 [PMID: 24409054 DOI: 10.3748/wjg.v19.i48.9271]

204 **Meade MO**, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE; Lung Open Ventilation Study Investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008; **299**: 637-645 [PMID: 18270352 DOI: 10.1001/jama.299.6.637]

205 **Kalisvaart M**, de Haan JE, Hesselink DA, Polak WG, Hansen BE, IJzermans JNM, Gommers D, Metselaar HJ, de Jonge J. The postreperfusion syndrome is associated with acute kidney injury following donation after brain death liver transplantation. *Transpl Int* 2017; **30**: 660-669 [PMID: 27864895 DOI: 10.1111/tri.12891]

206 **Bronster DJ**, Emre S, Boccagni P, Sheiner PA, Schwartz ME, Miller CM. Central nervous system complications in liver transplant recipients--incidence, timing, and long-term follow-up. *Clin Transplant* 2000; **14**: 1-7 [PMID: 10693627 DOI: 10.1034/j.1399-0012.2000.140101.x]

207 **Lee EM**, Kang JK, Yun SC, Kim KH, Kim SJ, Hwang KS, Lee SG. Risk factors for central pontine and extrapontine myelinolysis following orthotopic liver transplantation. *Eur Neurol* 2009; **62**: 362-368 [PMID: 19797900 DOI: 10.1159/000242426]

208 **Lewis MB**, Howdle PD. Neurologic complications of liver transplantation in adults. *Neurology* 2003; **61**: 1174-1178 [PMID: 14610116 DOI: 10.1212/01.wnl.0000089487.42870.c6]

209 **Wilson JR**, Conwit RA, Eidelman BH, Starzl T, Abu-Elmagd K. Sensorimotor neuropathy resembling CIDP in patients receiving FK506. *Muscle Nerve* 1994; **17**: 528-532 [PMID: 7512691 DOI: 10.1002/mus.880170510]

210 **Mazuelos F**, Abril J, Zaragoza C, Rubio E, Moreno JM, Turrión VS, Cuervas-Mons V. Cardiovascular morbidity and obesity in adult liver transplant recipients. *Transplant Proc* 2003; **35**: 1909-1910 [PMID: 12962844 DOI: 10.1016/s0041-1345(03)00640-7]

211 **Ciccarelli O**, Kaczmarek B, Roggen F, DeReyck C, Goffette P, Danse E, Verbaandert C, Sempoux C, Wittebole X, Wallemacq P, Lerut J. Long-term medical complications and quality of life in adult recipients surviving 10 years or more after liver transplantation. *Acta Gastroenterol Belg* 2005; **68**: 323-330 [PMID: 16268419]

212 **Desai S**, Hong JC, Saab S. Cardiovascular risk factors following orthotopic liver transplantation: predisposing factors, incidence and management. *Liver Int* 2010; **30**: 948-957 [PMID: 20500807 DOI: 10.1111/j.1478-3231.2010.02274.x]

213 **Di Cola S**, Cusi G, Lapenna L, Gazda J, Fonte S, Mattana M, Mennini G, Pasqualetti P, Merli M. Diabetes and Metabolic Disorders: Their Impact on Cardiovascular Events in Liver Transplant Patients. *Can J Gastroenterol Hepatol* 2023; **2023**: 2199193 [PMID: 37396501 DOI: 10.1155/2023/2199193]

214 **Gonwa TA**, Mai ML, Melton LB, Hays SR, Goldstein RM, Levy MF, Klintmalm GB. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy: risk of development and treatment. *Transplantation* 2001; **72**: 1934-1939 [PMID: 11773892 DOI: 10.1097/00007890-200112270-00012]

215 **de Mattos AM**, Olyaei AJ, Bennett WM. Nephrotoxicity of immunosuppressive drugs: long-term consequences and challenges for the future. *Am J Kidney Dis* 2000; **35**: 333-346 [PMID: 10676738 DOI: 10.1016/s0272-6386(00)70348-9]

216 **Bjøro K**, Brandsæter B, Wiencke K, Bjøro T, Godang K, Bollerslev J, Schrumpf E. Secondary Osteoporosis in Liver Transplant Recipients: a Longitudinal Study in Patients With and Without Cholestatic Liver Disease. *Scand J Gastroenterol* 2003; **38**: 320-327 [PMID: 28248598 DOI: 10.1080/00365520310000681a]

217 **Sarac G**, Ozcan KN, Baskiran A, Cenk H, Sarac M, Sener S, Yilmaz S. Dermatological signs in liver transplant recipients. *J Cosmet Dermatol* 2021; **20**: 2969-2974 [PMID: 33480152 DOI: 10.1111/jocd.13944]

218 **Forman LM**, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002; **122**: 889-896 [PMID: 11910340 DOI: 10.1053/gast.2002.32418]

219 **Pruthi J**, Medkiff KA, Esrason KT, Donovan JA, Yoshida EM, Erb SR, Steinbrecher UP, Fong TL. Analysis of causes of death in liver transplant recipients who survived more than 3 years. *Liver Transpl* 2001; **7**: 811-815 [PMID: 11552217 DOI: 10.1053/jlts.2001.27084]

220 **Euvrard S**, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med* 2003; **348**: 1681-1691 [PMID: 12711744 DOI: 10.1056/NEJMra022137]

221 **Watt KD**, Pedersen RA, Kremers WK, Heimbach JK, Sanchez W, Gores GJ. Long-term probability of and mortality from de novo malignancy after liver transplantation. *Gastroenterology* 2009; **137**: 2010-2017 [PMID: 19766646 DOI: 10.1053/j.gastro.2009.08.070]

222 **Invernizzi F**, Maggi U, Mazza S, Baia M, Nosotti M, Mendogni P, Muiesan P, Cannata A, Iavarone M, Damarco F, Lampertico P, Donato MF, Rossi G. Focus on Very Late Hepatocellular Carcinoma Recurring After Liver Transplantation: A Case Report and Literature Review. *Transplant Proc* 2019; **51**: 2998-3000 [PMID: 31607618 DOI: 10.1016/j.transproceed.2019.04.095]

223 **Duncan FJ**, Wulff BC, Tober KL, Ferketich AK, Martin J, Thomas-Ahner JM, Allen SD, Kusewitt DF, Oberyszyn TM, Vanbuskirk AM. Clinically relevant immunosuppressants influence UVB-induced tumor size through effects on inflammation and angiogenesis. *Am J Transplant* 2007; **7**: 2693-2703 [PMID: 17941958 DOI: 10.1111/j.1600-6143.2007.02004.x]

224 **Herrero JI**, España A, Quiroga J, Sangro B, Pardo F, Alvárez-Cienfuegos J, Prieto J. Nonmelanoma skin cancer after liver transplantation. Study of risk factors. *Liver Transpl* 2005; **11**: 1100-1106 [PMID: 16123952 DOI: 10.1002/lt.20525]

225 **Manzia TM**, Angelico R, Gazia C, Lenci I, Milana M, Ademoyero OT, Pedini D, Toti L, Spada M, Tisone G, Baiocchi L. De novo malignancies after liver transplantation: The effect of immunosuppression-personal data and review of literature. *World J Gastroenterol* 2019; **25**: 5356-5375 [PMID: 31558879 DOI: 10.3748/wjg.v25.i35.5356]

226 **Cruz-Jentoft AJ**, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M; European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010; **39**: 412-423 [PMID: 20392703 DOI: 10.1093/ageing/afq034]

227 **Montgomery J**, Englesbe M. Sarcopenia in Liver Transplantation. *Curr Transplant Rep* 2019; **6**: 7-15 [PMID: 31595213 DOI: 10.1007/s40472-019-0223-3]

228 **van Vugt JL**, Levolger S, de Bruin RW, van Rosmalen J, Metselaar HJ, IJzermans JN. Systematic Review and Meta-Analysis of the Impact of Computed Tomography-Assessed Skeletal Muscle Mass on Outcome in Patients Awaiting or Undergoing Liver Transplantation. *Am J Transplant* 2016; **16**: 2277-2292 [PMID: 26813115 DOI: 10.1111/ajt.13732]

229 **Tandon P**, Ney M, Irwin I, Ma MM, Gramlich L, Bain VG, Esfandiari N, Baracos V, Montano-Loza AJ, Myers RP. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. *Liver Transpl* 2012; **18**: 1209-1216 [PMID: 22740290 DOI: 10.1002/lt.23495]

230 **Durand F**, Buyse S, Francoz C, Laouénan C, Bruno O, Belghiti J, Moreau R, Vilgrain V, Valla D. Prognostic value of muscle atrophy in cirrhosis using psoas muscle thickness on computed tomography. *J Hepatol* 2014; **60**: 1151-1157 [PMID: 24607622 DOI: 10.1016/j.jhep.2014.02.026]

231 **Yadav A**, Chang YH, Carpenter S, Silva AC, Rakela J, Aqel BA, Byrne TJ, Douglas DD, Vargas HE, Carey EJ. Relationship between sarcopenia, six-minute walk distance and health-related quality of life in liver transplant candidates. *Clin Transplant* 2015; **29**: 134-141 [PMID: 25430554 DOI: 10.1111/ctr.12493]

232 **Wang CW**, Feng S, Covinsky KE, Hayssen H, Zhou LQ, Yeh BM, Lai JC. A Comparison of Muscle Function, Mass, and Quality in Liver Transplant Candidates: Results From the Functional Assessment in Liver Transplantation Study. *Transplantation* 2016; **100**: 1692-1698 [PMID: 27314169 DOI: 10.1097/TP.0000000000001232]

233 **Carey EJ**, Lai JC, Wang CW, Dasarathy S, Lobach I, Montano-Loza AJ, Dunn MA; Fitness, Life Enhancement, and Exercise in Liver Transplantation Consortium. A multicenter study to define sarcopenia in patients with end-stage liver disease. *Liver Transpl* 2017; **23**: 625-633 [PMID: 28240805 DOI: 10.1002/lt.24750]

234 **Englesbe MJ**, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, Holcombe SA, Wang SC, Segev DL, Sonnenday CJ. Sarcopenia and mortality after liver transplantation. *J Am Coll Surg* 2010; **211**: 271-278 [PMID: 20670867 DOI: 10.1016/j.jamcollsurg.2010.03.039]

235 **Waits SA**, Kim EK, Terjimanian MN, Tishberg LM, Harbaugh CM, Sheetz KH, Sonnenday CJ, Sullivan J, Wang SC, Englesbe MJ. Morphometric age and mortality after liver transplant. *JAMA Surg* 2014; **149**: 335-340 [PMID: 24500820 DOI: 10.1001/jamasurg.2013.4823]

236 **Shirai H**, Kaido T, Hamaguchi Y, Yao S, Kobayashi A, Okumura S, Kamo N, Yagi S, Okajima H, Uemoto S. Preoperative low muscle mass has a strong negative effect on pulmonary function in patients undergoing living donor liver transplantation. *Nutrition* 2018; **45**: 1-10 [PMID: 29129228 DOI: 10.1016/j.nut.2017.06.027]

237 **Underwood PW**, Cron DC, Terjimanian MN, Wang SC, Englesbe MJ, Waits SA. Sarcopenia and failure to rescue following liver transplantation. *Clin Transplant* 2015; **29**: 1076-1080 [PMID: 26358578 DOI: 10.1111/ctr.12629]

238 **Wada Y**, Kamishima T, Shimamura T, Kawamura N, Yamashita K, Sutherland K, Takeda H. Pre-operative volume rather than area of skeletal muscle is a better predictor for post-operative risks for respiratory complications in living-donor liver transplantation. *Br J Radiol* 2017; **90**: 20160938 [PMID: 28181820 DOI: 10.1259/bjr.20160938]

239 **Raza A**, Omer A, Iqbal S, Gudsoorkar V, Koduru P, Krishnan K. Efficacy of Nasobiliary Tubes and Biliary Stents in Management of Patients with Bile Leak after Liver Transplantation: A Systematic Review. *Clin Endosc* 2019; **52**: 159-167 [PMID: 30959587 DOI: 10.5946/ce.2018.118]

240 **Akamatsu N**, Sugawara Y, Hashimoto D. Biliary reconstruction, its complications and management of biliary complications after adult liver transplantation: a systematic review of the incidence, risk factors and outcome. *Transpl Int* 2011; **24**: 379-392 [PMID: 21143651 DOI: 10.1111/j.1432-2277.2010.01202.x]

241 **de Vries Y**, von Meijenfeldt FA, Porte RJ. Post-transplant cholangiopathy: Classification, pathogenesis, and preventive strategies. *Biochim Biophys Acta Mol Basis Dis* 2018; **1864**: 1507-1515 [PMID: 28645651 DOI: 10.1016/j.bbadis.2017.06.013]

242 **Piardi T**, Lhuaire M, Bruno O, Memeo R, Pessaux P, Kianmanesh R, Sommacale D. Vascular complications following liver transplantation: A literature review of advances in 2015. *World J Hepatol* 2016; **8**: 36-57 [PMID: 26783420 DOI: 10.4254/wjh.v8.i1.36]

243 **Bekker J**, Ploem S, de Jong KP. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. *Am J Transplant* 2009; **9**: 746-757 [PMID: 19298450 DOI: 10.1111/j.1600-6143.2008.02541.x]

244 **Marshall MM**, Muiesan P, Srinivasan P, Kane PA, Rela M, Heaton ND, Karani JB, Sidhu PS. Hepatic artery pseudoaneurysms following liver transplantation: incidence, presenting features and management. *Clin Radiol* 2001; **56**: 579-587 [PMID: 11446757 DOI:

10.1053/crad.2001.0650]
245 **Kim WH**, Lee HJ, Yoon HC, Lee KH, Suh KS. Intraoperative Oxygen Delivery and Acute Kidney Injury after Liver Transplantation. *J Clin Med* 2020; **9** [PMID: 32092886 DOI: 10.3390/jcm9020564]
246 **McMaster P**. Transplantation for alcoholic liver disease in an era of organ shortage. *Lancet* 2000; **355**: 424-425 [PMID: 10841118 DOI: 10.1016/S0140-6736(00)82004-8]
247 **Mellinger J**. Ethical and Legal Aspects of Organ Donation. Liver Transplantation: Clinical Assessment and Management, Second Edition. 2021 [DOI: 10.1002/9781119634010.ch21]
248 **Weimer DL**. Medical Governance: Values, Expertise, and Interests in Organ Transplantation. American Governance and Public Policy series. Georgetown University Press, 2010. Available from: https://www.jstor.org/stable/j.ctt2tt6nh
249 Organ Procurement and Transplantation Network (OPTN) Modernization Initiative. HRSA. Available from: https://www.hrsa.gov/optn-modernization
250 **Sadler BL**, Sadler AM Jr. Organ Transplantation and the Uniform Anatomical Gift Act: A Fifty-Year Perspective. *Hastings Cent Rep* 2018; **48**: 14-18 [PMID: 29590516 DOI: 10.1002/hast.834]
251 **Verheijde JL**, Rady MY, McGregor JL. The United States Revised Uniform Anatomical Gift Act (2006): new challenges to balancing patient rights and physician responsibilities. *Philos Ethics Humanit Med* 2007; **2**: 19 [PMID: 17850664 DOI: 10.1186/1747-5341-2-19]
252 **Bernat JL**, D'Alessandro AM, Port FK, Bleck TP, Heard SO, Medina J, Rosenbaum SH, Devita MA, Gaston RS, Merion RM, Barr ML, Marks WH, Nathan H, O'connor K, Rudow DL, Leichtman AB, Schwab P, Ascher NL, Metzger RA, Mc Bride V, Graham W, Wagner D, Warren J, Delmonico FL. Report of a National Conference on Donation after cardiac death. *Am J Transplant* 2006; **6**: 281-291 [PMID: 16426312 DOI: 10.1111/j.1600-6143.2005.01194.x]
253 **Feng S**, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, Greenstein SM, Merion RM. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; **6**: 783-790 [PMID: 16539636 DOI: 10.1111/j.1600-6143.2006.01242.x]
254 **Jay CL**, Skaro AI, Ladner DP, Wang E, Lyuksemburg V, Chang Y, Xu H, Talakokkla S, Parikh N, Holl JL, Hazen GB, Abecassis MM. Comparative effectiveness of donation after cardiac death versus donation after brain death liver transplantation: Recognizing who can benefit. *Liver Transpl* 2012; **18**: 630-640 [PMID: 22645057 DOI: 10.1002/lt.23418]
255 **Vodkin I**, Kuo A. Extended Criteria Donors in Liver Transplantation. *Clin Liver Dis* 2017; **21**: 289-301 [PMID: 28364814 DOI: 10.1016/j.cld.2016.12.004]
256 **Zhang W**, Carpino G, Wangensteen KJ, Yan H, He Z. Editorial: Cell therapy, liver diseases, and regeneration. *Front Cell Dev Biol* 2022; **10**: 999305 [PMID: 36133918 DOI: 10.3389/fcell.2022.999305]
257 **Du Y**, Zhang W, Qiu H, Xiao C, Shi J, Reid LM, He Z. Mouse Models of Liver Parenchyma Injuries and Regeneration. *Front Cell Dev Biol* 2022; **10**: 903740 [PMID: 35721478 DOI: 10.3389/fcell.2022.903740]
258 **Bartlett DC**, Newsome PN. Hepatocyte cell therapy in liver disease. *Expert Rev Gastroenterol Hepatol* 2015; **9**: 1261-1272 [PMID: 26212798 DOI: 10.1586/17474124.2015.1073106]
259 **Fisher RA**, Strom SC. Human hepatocyte transplantation: worldwide results. *Transplantation* 2006; **82**: 441-449 [PMID: 16926585 DOI: 10.1097/01.tp.0000231689.44266.ac]
260 **Huebert RC**, Rakela J. Cellular therapy for liver disease. *Mayo Clin Proc* 2014; **89**: 414-424 [PMID: 24582199 DOI: 10.1016/j.mayocp.2013.10.023]
261 **Ferrer JR**, Chokechanachaisakul A, Wertheim JA. New Tools in Experimental Cellular Therapy for the Treatment of Liver Diseases. *Curr Transplant Rep* 2015; **2**: 202-210 [PMID: 26317066 DOI: 10.1007/s40472-015-0059-4]
262 **Duffield JS**, Forbes SJ, Constandinou CM, Clay S, Partolina M, Vuthoori S, Wu S, Lang R, Iredale JP. Selective depletion of macrophages reveals distinct, opposing roles during liver injury and repair. *J Clin Invest* 2005; **115**: 56-65 [PMID: 15630444 DOI: 10.1172/JCI22675]
263 **Fallowfield JA**, Mizuno M, Kendall TJ, Constandinou CM, Benyon RC, Duffield JS, Iredale JP. Scar-associated macrophages are a major source of hepatic matrix metalloproteinase-13 and facilitate the resolution of murine hepatic fibrosis. *J Immunol* 2007; **178**: 5288-5295 [PMID: 17404313 DOI: 10.4049/jimmunol.178.8.5288]
264 **Thomas JA**, Pope C, Wojtacha D, Robson AJ, Gordon-Walker TT, Hartland S, Ramachandran P, Van Deemter M, Hume DA, Iredale JP, Forbes SJ. Macrophage therapy for murine liver fibrosis recruits host effector cells improving fibrosis, regeneration, and function. *Hepatology* 2011; **53**: 2003-2015 [PMID: 21433043 DOI: 10.1002/hep.24315]
265 **Shafiee A**, Atala A. Tissue Engineering: Toward a New Era of Medicine. *Annu Rev Med* 2017; **68**: 29-40 [PMID: 27732788 DOI: 10.1146/annurev-med-102715-092331]
266 **Ehrbar M**, Sala A, Lienemann P, Ranga A, Mosiewicz K, Bittermann A, Rizzi SC, Weber FE, Lutolf MP. Elucidating the role of matrix stiffness in 3D cell migration and remodeling. *Biophys J* 2011; **100**: 284-293 [PMID: 21244824 DOI: 10.1016/j.bpj.2010.11.082]
267 **Bhat M**, Rabindranath M, Chara BS, Simonetto DA. Artificial intelligence, machine learning, and deep learning in liver transplantation. *J Hepatol* 2023; **78**: 1216-1233 [PMID: 37208107 DOI: 10.1016/j.jhep.2023.01.006]
268 **Lau L**, Kankanige Y, Rubinstein B, Jones R, Christophi C, Muralidharan V, Bailey J. Machine-Learning Algorithms Predict Graft Failure After Liver Transplantation. *Transplantation* 2017; **101**: e125-e132 [PMID: 27941428 DOI: 10.1097/TP.0000000000001600]
269 **Verma N**, Dhiman RK, Singh V, Duseja A, Taneja S, Choudhury A, Sharma MK, Eapen CE, Devarbhavi H, Al Mahtab M, Shukla A, Hamid SS, Jafri W, Butt AS, Ning Q, Chen T, Tan SS, Lesmana LA, Lesmana CRA, Sahu MK, Hu J, Lee GH, Sood A, Midha V, Goyal O, Ghazinian H, Kim DJ, Treeprasertsuk S, Mohan Prasad VG, Dokmeci AK, Sollano JD, Shah S, Payawal DA, Rao PN, Kulkarni A, Lau GK, Duan Z, Chen Y, Yokosuka O, Abbas Z, Karim F, Chowdhury D, Prasad AS, Sarin SK; APASL ACLF Working Party. Comparative accuracy of prognostic models for short-term mortality in acute-on-chronic liver failure patients: CAP-ACLF. *Hepatol Int* 2021; **15**: 753-765 [PMID: 34173167 DOI: 10.1007/s12072-021-10175-w]
270 **Tonon M**, Moreau R. Using machine learning for predicting outcomes in ACLF. *Liver Int* 2022; **42**: 2354-2355 [PMID: 36162084 DOI: 10.1111/liv.15399]
271 **Ge J**, Digitale JC, Fenton C, McCulloch CE, Lai JC, Pletcher MJ, Gennatas ED. Predicting post-liver transplant outcomes in patients with acute-on-chronic liver failure using Expert-Augmented Machine Learning. *Am J Transplant* 2023; **23**: 1908-1921 [PMID: 37652176 DOI: 10.1016/j.ajt.2023.08.022]

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REVIEW

Endothelial dysfunction in the kidney transplant population: Current evidence and management strategies

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Abstract

The endothelium modulates vascular homeostasis owing to a variety of vasoconstrictors and vasodilators. Endothelial dysfunction (ED), characterized by impaired vasodilation, inflammation, and thrombosis, triggers future cardiovascular (CV) diseases. Chronic kidney disease, a state of chronic inflammation caused by oxidative stress, metabolic abnormalities, infection, and uremic toxins damages the endothelium. ED is also associated with a decline in estimated glomerular filtration rate. After kidney transplantation, endothelial functions undergo immediate but partial restoration, promising graft longevity and enhanced CV health. However, the anticipated CV outcomes do not happen due to various transplant-related and unrelated risk factors for ED, culminating in poor CV health and graft survival. ED in kidney transplant recipients is an underrecognized and poorly studied entity. CV diseases are the leading cause of death among kidney transplant candidates with functioning grafts. ED contributes to the pathogenesis of many of the CV diseases. Various biomarkers and vasoreactivity tests are available to study endothelial functions. With an increasing number of transplants happening every year, and improved graft rejection rates due to the availability of effective immunosuppressants, the focus has now shifted to endothelial protection for the prevention, early recognition, and treatment of CV diseases.

Key Words: Endothelial dysfunction; Endothelium; Cardiovascular disease; Kidney transplantation; Chronic kidney disease; Nitric oxide; Flow-mediated dilatation; Nitro-glycerine-mediated dilatation; Biomarkers

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Core Tip: Endothelium promotes vascular homeostasis by regulating vascular permeability, leucocyte diapedesis, hemostatic response, and vascular tone. Endothelial dysfunction (ED) plays a key role in the genesis of cardiovascular (CV) and kidney outcomes seen in the chronic kidney disease and kidney transplant population. There is increased CV morbidity and mortality imparted due to ED in transplant recipients. Among various biomarkers and diagnostic tests available to detect endothelial function, flow-mediated dilation is a widely recognized and reproducible test available in clinical settings. Though overlooked in kidney transplant settings, promoting CV and graft health by monitoring endothelial functions and mitigating risk factors of ED can improve overall outcomes.

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INTRODUCTION

The endothelium, which forms the inner layer of the blood vessels, actively regulates vascular functions by sensing and responding to mechanical and biochemical signals. This vasoregulation happens through modulating vascular tone, mediating cellular adhesion, influencing the migration of inflammatory cells, and providing resistance to the action of pro-thrombotic and pro-inflammatory mediators. Under a homeostatic state, endothelial cells release nitric oxide (NO) under the influence of endothelial NO synthase (eNOS)[1]. NO is one of the major mediators of endothelial functions that prevents platelet aggregation and causes vasodilation by modulating the tone of vascular smooth muscle cells. In addition to NO, fibrinolytic and antithrombotic properties of the endothelium are also mediated through other mediators such as tissue plasminogen activator, antithrombin III, and prostacyclin[2]. Bone marrow-derived endothelial progenitor cells are responsible for the renewal of endothelial cells during repair.

Endothelial dysfunction (ED) is marked by a decrease in NO production/availability and an inflammatory endothelial cell phenotype (activated endothelial cells). There is poor expression of eNOS following damage to the endothelial glycocalyx, a gel-like layer of glycoproteins and extracellular matrix components involved in trans-endothelial transport at the blood-endothelial interface[3]. Additionally, there is eNOS uncoupling, leading to the generation of reactive oxygen species (ROS) instead of NO[4]. Thus, there is decreased NO availability and production. Activation of endothelial cells (novel immune cells) by various inflammatory signals results in the upregulation of cellular adhesion molecules, including e-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell-adhesion molecule-1 (VCAM-1), which promote inflammation. Subsequently there is leukocyte diapedesis in conjunction with increased endothelial permeability [2]. Activated endothelial cells behave like macrophages, secreting cytokines. The disturbed and inflamed endothelium favors permeation and trapping of lipoprotein particles beneath the endothelial cell layer, which can subsequently get oxidized[2]. The deposited lipoproteins are internalized by macrophages and smooth muscle cells, resulting in the formation of foam cells and the accumulation of fatty streaks. Altered efferocytosis (removal of apoptotic endothelial cells) leads to vascular stiffening[5]. Some endothelial cells may undergo endo-mesenchymal transition, facilitating deposition of the extracellular matrix, thereby further aggravating vascular stiffness[6]. Arterial constrictions due to lipid accumulation in conjunction with poor vasodilation increases regions of turbulent or oscillatory blood flow, which further exacerbates endothelial cell activation and denudation. Lipid-rich plaques with a thin fibrous cap in these areas are at high risk for rupture, causing thrombotic occlusions. This risk is exacerbated by the expression of pro-coagulant tissue factor, anti-fibrinolytic plasminogen activator inhibitor-1 (PAI-1), and von Willebrand factor (vWF)[2,7]. Thus, ED is a forerunner for atherosclerosis and thrombosis.

In this review, we examine cardiovascular (CV) diseases prevalent in chronic kidney disease (CKD) and transplant settings, focusing on their pathogenesis as it relates to ED. We emphasize the inadequacies in the prevention, diagnosis, and management of ED in real-world scenarios. By correlating the pathogenesis of ED with its diagnostic and therapeutic approaches, we aim to provide valuable insights for clinicians. We hope that this review will inspire researchers to undertake collaborative studies with clinicians, thereby advancing our understanding of ED in the context of kidney transplantation.

CV diseases due to ED in CKD

The decline in glomerular filtration rate in CKD leads to a fast-tracked CV aging trajectory. Patients with advanced CKD (stage 4 and 5) have the highest risk of dying from CV diseases. Almost 50% of all deaths in advanced CKD are due to CV diseases[8]. In addition to coronary artery diseases, heart failure (with both reduced and preserved ejection fraction),

arrhythmias, valvular abnormalities, peripheral arterial disease, and sudden cardiac death are also commonly observed in the CKD population[8]. ED contributes significantly to increased CV risk in patients with CKD. CKD is characterized by persistent low-grade inflammation due to oxidative stress, cardio-metabolic risk factors, infections, uremic toxins, acidosis, and mineral-bone alterations, all of which damage the endothelium[9,10]. Concrete evidence suggests the role of inflammation in causing CV diseases through the activation of endothelial cells in patients with CKD[11]. Levels of pro-inflammatory cytokines such as interleukins (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α), and high-sensitivity C-reactive protein (hs-CRP) positively correlate with increased CV risk in CKD[12]. Anti-inflammatory therapy with canakinumab (targets IL-1β) has shown an 18% reduction in the primary endpoint (non-fatal myocardial infarction, non-fatal stroke, or CV death) in patients with moderate CKD[13]. Oxidative stress and uremic toxins of CKD state induce pro-inflammatory signals and cause post-translational modification (oxidation and carbonylation) of both low-density lipoprotein (LDL) and high-density lipoprotein (HDL), which are CV risk factors[12]. Thus, alterations in lipoprotein particle profiles in CKD exacerbate the atherogenicity of LDL, and transform HDL from a protective to a potentially harmful entity. In addition to the above risk factors, metabolic acidosis, decreased levels of klotho (an anti-vascular aging protein), vascular calcification induced by phosphate alterations, and altered gut microbiome contribute to ED in CKD[12]. Dialysis modalities are also implicated in causing CV diseases like pulmonary hypertension through ED[14,15]. Hemodialysis (HD) patients have higher endothelial microparticles and pro-inflammatory monocytes [cluster of differentiation (CD) 14 + CD16 + monocytes] than patients on peritoneal dialysis (PD)[16].

In the clinical setting, a cohort study from India by Prasad *et al*[17] analyzing practice patterns in mild to moderate CKD, showed that renin-angiotensin-aldosterone system (RAAS) blockers were prescribed to 47.9% of CKD patients overall and 58.8% of those with proteinuria, while only 40.4% were on statins. Both the drug classes are protective to the endothelium. This highlights a missed opportunity in CKD to safeguard endothelial function due to non-compliance with guideline recommendations. Statins lower plasma cholesterol levels and decrease the endothelial trapping of modified lipoproteins. Statins also exhibit "pleiotropic" vascular benefits, including enhancing endothelial function by increasing NO bioavailability by upregulating eNOS, endothelial repair, reducing oxidative stress, and inhibiting inflammation. Statins also decrease the levels of endothelin-1, a potent vasoconstrictor[18]. In adults with dialysis-dependent CKD (unlike CKD patients not initiated on dialysis), the Kidney Disease: Improving Global Outcomes (KDIGO) recommend against starting statins or statin/ezetimibe combinations[19]. Although CV risk is elevated in this subgroup of CKD, the effectiveness of statins is uncertain due to significant competing mortality risks. RAAS activation promotes vascular stiffness by promoting pro-fibrotic and inflammatory pathways. RAAS activation causes smooth muscle cell proliferation, extracellular matrix deposition, and transforming growth factor β (TGF-β) secretion (pro-fibrotic)[20]. Despite the benefits, many patients with CKD are discontinued from RAAS inhibitors because of adverse events[21]. There is less inclusion of CKD patients in CV clinical trials despite calls for better representation[22]. Thus, in CKD, there is an unchecked and progressive endothelial damage. This culminates in increased CV risk as the patient prepares for a kidney transplant.

CV diseases after kidney transplant

Kidney transplant candidates have a notable prevalence of both pre-existing (risk factors acquired during CKD state) and *de novo* transplant-related CV risk factors, which contribute to adverse CV outcomes[23]. The traditional CV risk factors in the post-transplant period include hypertension (40%-90%), diabetes (24%-42%), dyslipidemia (50%), smoking (25%), and obesity. The non-traditional CV risk factors specific to kidney transplant settings include adverse effects of immunosuppressive medications, persistent secondary hyperparathyroidism after transplant, anemia, chronic inflammation, and graft dysfunction[23,24]. The spectrum of CV diseases in kidney transplant settings does not differ greatly compared to the CKD population, and include coronary artery disease, valvopathy, heart failure, stroke, cardiac arrhythmias, pulmonary artery hypertension, and peripheral arterial disease.

Despite comorbidities, patients with CKD after transplantation exhibit improved CV health compared to those who are waitlisted for transplant[25]. Kidney transplantation significantly improves maximal oxygen consumption (from 20.7 to 22.5 mL/kg/minute, $P < 0.001$) compared to those who remain on dialysis (declines from 18.9 to 17.7 mL/kg/minute, $P < 0.001$) at 1 year of follow-up[26]. Similarly, improvements were seen with ejection fraction in a kidney transplant group (improved from 60.1% to 63.2% $P = 0.02$) compared to a waitlisted group (61.4% to 59.3%)[26]. However, not all risk factors that are acquired in the pre-transplant period are mitigated. The leading cause of death with a functioning graft in the long-term remains due to CV causes[27]. There is a high incidence of myocardial infarction, heart failure, and stroke in the 1st year after kidney transplant [cumulative incidence in the 1st year is 2.6%, 95% confidence interval (CI): 1.9-3.2], and the risk continues to increase in the subsequent post-transplant years (cumulative incidence between the years 2-5 is 8.3; 95%CI: 7.1-9.5)[28].

There is a significant spillover of CV risk factors acquired from the pre-transplant period. Among 62706 kidney transplant recipients, 6.4% had atrial fibrillation before transplant. Over a mean follow-up of 4.9 years, those with atrial fibrillation experienced higher mortality (40.6% *vs* 24.9%), greater all-cause graft failure (46.8% *vs* 36.4%), and higher rates of ischemic stroke (2.8% *vs* 1.6%) after transplantation[29]. In a cohort of 1063 kidney transplant recipients, left ventricular hypertrophy [hazard ratio (HR) = 1.58; $P = 0.022$] and increased relative wall thickness (HR = 1.44; $P = 0.041$) before transplant independently predicted CV events after transplant. Persistent brachiocephalic fistula is also a risk factor for pulmonary arterial hypertension. In addition to the spillover of CV diseases, *de novo* CV diseases after transplantation do occur. The cumulative incidence of *de novo* congestive heart failure after kidney transplantation is 10.2% at 12 months and 18.3% at 36 months after transplant[30].

ED as a risk factor for increased CV risk

A recent review article by Cardinal *et al*[31] briefly addresses the immunopathogenesis of endothelial injury following kidney transplantation, with a primary focus on renal endothelium. ED extends beyond the kidneys and is a precursor to various CV diseases. Although direct evidence linking ED to different CV diseases in kidney transplant settings is sparse due to a limited number of studies, recent data suggest that a significant proportion of CV diseases in these settings may be attributable to ED. Also, as pointed out by Cardinal *et al*[31], ED damages the graft endothelium and causes graft failure.

The cumulative incidence of post-transplant myocardial infarction (PTMI) was 4.3% at 6 months, 5.6% at 12 months, and 11.1% at 36 months[32]. The role of ED in atherogenesis has already been explained. The high incidence of PTMI early post-transplant may be attributed to the high levels of inflammatory markers such as vWF, PAI-I, and homocysteine levels[33]. A hospital-based registry from the United States[34] showed notable increases in admissions among transplant recipients between 2005 and 2011 for congestive heart failure and cardiac arrhythmias (P = 0.01), which accounted for 16% to 17% of all hospital admissions. Coronary ED leads to heart failure with preserved ejection fraction[35]. Pre-emptive transplantation may reduce the risk of heart failure, and there is a lesser risk of coronary ED by avoiding HD [36]. The incidence of stroke after kidney transplantation varies from 1.1% to 8% and ischemic stroke is the most common variant. The risk of rupture of intracranial aneurysms may theoretically be increased in patients with autosomal dominant polycystic kidney disease (ADPKD). ADPKD is notably associated with RAAS activation and ED[37]. However, data show favorable CV outcomes in patients with ADPKD, including stroke[38]. In Cox regression analysis, modeling kidney transplant as a time-dependent covariate showed an adjusted HR (aHR) of 0.77 (95%CI: 0.67-0.89) for intracranial hemorrhage in ADPKD patients during the post-transplant period compared to the pre-transplant period[39]. The 3-year cumulative incidence of *de novo* peripheral arterial disease after kidney transplant is 20% among CKD patients with diabetes[40]. Ankle brachial index before transplant was an independent predictor of graft failure [odds ratio (OR) = 2.77; 95%CI: 1.68-4.58; P < 0.001] and secondary CV endpoints, namely myocardial infarction; cerebrovascular accident; and limb ischemia, gangrene, or amputation (HR = 1.39; 95%CI: 0.97-1.99; P = 0.076), and death (HR = 1.84; 95%CI: 1.26-2.68; P = 0.002)[41]. Important regulators of pulmonary circulation include endothelin-1 and NO, which are therapeutic targets in treating pulmonary hypertension[42]. One etiopathogenesis of pulmonary arterial hypertension is due to ED caused by arterio-venous fistula created for dialysis access[43]. Fistula ligation may be a reasonable option in patients with pulmonary hypertension after transplant.

RISK FACTORS FOR ED IN THE KIDNEY TRANSPLANT POPULATION AND CLINICAL IMPLICATIONS

Traditional risk factors

Obesity: The protective impact that obesity might have on patients undergoing dialysis disappears following a transplant. In obesity, ED is primarily driven by adipose tissue inflammation (increased IL-6, TNF-α), decreased expression of eNOS, insulin resistance, and oxidized LDL (oxLDL)[44]. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of eNOS, is elevated in obesity[44]. Weight gain happens in the 1st year after transplant, especially in children[45]. Steroid minimization is associated with lesser weight gain[46]. Obesity in transplant candidates is also a risk factor for diabetes mellitus[47], and sleeve gastrectomy in obese kidney transplant patients improved blood pressure and glucose control[48]. Pre-transplant obesity is a risk factor for delayed graft function[49]. Obstructive sleep apnea (OSA) associated with obesity may re-emerge long-term in transplant recipients, even if symptoms of OSA initially improved after the transplant[50]. OSA decreases NO production due to repeated episodes of hypoxia, and is a risk factor for pulmonary arterial hypertension[51,52].

Clinical vignette: The role of novel anti-obesity and anti-diabetic agents, particularly glucagon-like peptide-1 (GLP-1) analogs, in modulating the effects of ADMA represents a promising area of research.

Smoking: Smoking in kidney transplant candidates is associated with high rates of coronary artery disease[53], graft loss, and non-CV mortality[54]. Almost 50% of the kidney transplant population in a cohort study were current or former smokers. Smoking promotes ED by the generation of ROS, increased oxLDL, inactivation of eNOS, and increased expression of cell-adhesion molecules. Smoking cessation has been shown to improve endothelial functions. Among 1504 smokers, flow-mediated dilatation (FMD) (described in detail below) improved by 1% (P = 0.005) after 1 year in those who quit smoking, while remaining unchanged in those who continued (P = 0.643)[55].

Clinical vignette: Increased public awareness of the health risks associated with tobacco has driven many to use electronic cigarettes (e-cigarettes) as a potentially less harmful alternative to smoking. On the contrary, e-cigarettes also cause ED. E-cigarette users and smokers showed lower FMD compared to non-users[56]. They demonstrated higher concentrations of receptors for advanced glycation end products (RAGE) than smokers[56]. RAGE ligands amplify pro-inflammatory responses in the endothelial cells.

Dyslipidemia: In the initial year after kidney transplantation, dyslipidemia is seen in 60%-88% of both adult and pediatric patients, surpassing the prevalence seen in the general population[57]. Most of the commonly used immunosuppressives are associated with abnormal lipid metabolism, especially cyclosporine and mammalian target of rapamycin (mTOR) inhibitors[57]. Cyclosporine and corticosteroids have an additive effect on raising cholesterol, with partial improvement upon steroid withdrawal[58]. Conversely, mTOR inhibitors significantly increase both cholesterol and triglycerides in a dose-dependent manner[58]. Belatacept-based immunosuppression is associated with improved LDL levels[59]. The role of oxLDL and carbamylated LDL in atherogenesis has already been mentioned. OxLDL levels

correlated with increased proteinuria and graft fibrosis in a porcine renal transplantation model[60].

Statin use was linked to lower mortality in kidney transplant recipients (aHR = 0.95; 95%CI: 0.90-0.99)[61]. A trial showed that atorvastatin was more effective than switching from cyclosporine to tacrolimus in reducing total cholesterol and LDL, with additional LDL reduction when combined with tacrolimus[62]. Atorvastatin increased FMD from 4.0% to 6.5% ($P < 0.05$), while tacrolimus slightly improved FMD to 5.1% ($P < 0.05$), but adding atorvastatin to tacrolimus had no significant effect on FMD[62]. The role of statins (both LDL lowering and pleiotropic functions) in preventing ED has already been discussed. According to the KDIGO, kidney transplant recipients are advised to receive statin therapy irrespective of their LDL concentrations. The usage of statins in kidney transplant recipients is still 69.1% only as *per* the 2021 United States renal data system annual report[63].

Clinical vignette: The role of proprotein convertase subtilisin/kexin type 9 antibodies on lipid abnormalities and endothelial functions is still unexplored in the transplant recipients[64].

Hypertension: Hypertension is present in 50%-80% of kidney transplant recipients[65,66]. In the post hoc analysis of folic acid for vascular outcome reduction in transplantation trial, each 20-mmHg rise in baseline systolic blood pressure correlates with a 32% elevation in subsequent CV risk (HR = 1.32; 95%CI: 1.19-1.46) and a 13% increase in the risk of mortality (HR = 1.13; 95%CI: 1.01-1.27)[67]. The chances of graft failure in poorly controlled hypertensives are twice that of controlled hypertensives[68]. Inflammation is believed to play an important role in the pathogenesis of hypertension [69]. Chronic sympathetic nervous system activation, RAAS activation, obesity, high salt intake, immunosuppressive drugs, graft dysfunction, infections, and oxidative stress promote the release of pro-inflammatory cytokines causing endothelial damage leading to hypertension and further target organ damage[69]. Donor risk factors (age, hypertensive donors, graft renal artery stenosis, donor smoking, dyslipidemia, atherosclerosis) also play an important role[70]. Drugs such as calcineurin inhibitors (CNI), which includes both cyclosporine and tacrolimus, are hypothesized to enhance the expression of angiotensin II type 1 receptors and reduce NO production, leading to renal vasoconstriction[66]. Calcium channel blockers are theoretically beneficial in patients on CNI by facilitating calcium entry into vascular smooth muscles, leading to vasodilatation[66]. Posterior reversible encephalopathy syndrome in kidney transplant recipients associated with CNI usage is attributable to ED[71]. Spironolactone, a mineralocorticoid antagonist, has been shown to improve ED in experimental rat models[72]. However, a randomized controlled trial among kidney transplant recipients failed to show the effect of spironolactone in mitigating ED[73]. Despite increased plasma aldosterone levels with spironolactone treatment, there were no significant improvements in markers of ED such as nitrite, nitrate, cyclic guanosine monophosphate, arginine, citrulline, ornithine, ADMA, symmetric dimethylarginine, NG-monomethyl-L-arginine, vWF, tPA antigen, PAI-1 antigen and markers of inflammation-hs-CRP, ICAM, VCAM, and serum amyloid protein A compared to a placebo, except for a decrease in nitrite levels observed in patients with diabetes[73]. These findings suggest that mineralocorticoid receptor antagonism alone may not effectively mitigate ED or vascular inflammation prevalent in kidney transplant patients. This warrants further research to assess its potential benefits on vascular outcomes[24].

Higher salt intake (6%) in kidney transplant candidates often contributes to poor control of hypertension[74]. Higher salt is associated with post-prandial ED measured through FMD[75]. Hence, salt intake should be restricted for kidney transplant candidates. ED in hypertensive renal transplant recipients is linked to elevated ambulatory blood pressure and heightened BP variability (BPV), irrespective of mean blood pressure levels[76]. Notably, increased BPV in 24-hour systolic and diastolic readings is associated with ED measured through FMD[77]. Thus, ambulatory blood pressure monitoring in kidney transplant individuals has a significant diagnostic utility in preventing ED-related target organ damage[76].

Clinical vignette: Promising novel approaches for hypertension include cyclic guanosine monophosphate augmentation, RAAS inhibition using aldosterone synthase inhibitors and silencing RNA, and antisense therapies targeting angiotensinogen[78]. Theoretically, they all improve the production of NO and can have endothelial-protective effects; however, studies on transplant recipients are lacking.

Diabetes mellitus: Other than those who have pre-existing diabetes mellitus before transplantation, new-onset diabetes after kidney transplant (NODAT) develops in 10%-40% of kidney transplant recipients[79]. Though kidney transplantation improves microvascular outcomes in type I diabetic patients with simultaneous pancreas-kidney transplant recipients[80], most type II diabetes patients after kidney transplantation suffer from CV complications arising due to ED [81]. Hyperglycemia post-kidney transplant is significantly associated with an increased risk of major cardiac (HR = 1.113), vascular (HR = 1.168), and cerebrovascular events (HR = 1.156)[82]. Oxidative stress, mitochondrial fusion abnormalities, and inflammation play an important role in hyperglycemia-induced ED[83,84]. Some of the transplant-related immunomodulatory risk factors that cause both NODAT and ED include immunosuppressive drugs (corticosteroids, CNI, and mTOR inhibitors) and infections with hepatitis C virus and cytomegalovirus[79]. Sitagliptin, a dipeptidyl peptidase-4 inhibitor, showed no improved vasoreactivity as measured by laser doppler flowmetry or meaningful changes in the levels of inflammatory markers such as CRP, VCAM-1, adiponectin, and soluble TNF receptor-1[85]. However, metformin improves endothelial functions in non-transplanted subjects with type II diabetes[86]. A systematic review is underway to assess the effects of metformin on graft and patient survival in transplant recipients with type II diabetes mellitus[87].

Clinical vignette: Recommended measures to improve endothelial functions include reduced steroid/steroid-free immunosuppression in patients with low immunological risk, early post-operative basal insulin therapy for hyperglycemia for NODAT prevention, usage of newer anti-diabetic drugs with proven CV benefits like sodium glucose-2 inhibitors (SGLT-2 inhibitors), and GLP-1 analogs[88-91]. SGLT-2 inhibitors may improve endothelial functions by reducing oxidative stress, modulating adhesion molecules, and decreasing pro-inflammatory cytokines[92].

Non-traditional risk factors

Role of inflammation, toxins, infections, and oxidative stress: CKD is associated with retention of uremic solutes, inflammation, and oxidative stress. Factors causing inflammation in CKD include altered lipoprotein profiles, the gut microbiome, biomarkers of accelerated aging, oxidative stress, RAAS, and calcium-phosphate homeostasis. CKD and inflammation are interconnected in a bidirectional loop, where both exacerbate each other. The inflammatory state induces post-translational modifications of proteins in vascular biology, including the formation of glycated albumin, oxLDL, carbamylated sortilins, and AGEs[12,93]. They cause vascular calcification[94]. The inflammatory state leads to platelet activation, resulting in adherence to the endothelium and subsequent pathological thrombosis, which increases the risk of bleeding[95]. In CKD, dysbiosis of the gut microbiome results in the accumulation of bacterial-derived toxins such as endotoxins, indoxyl sulfate, p-cresyl sulfate, trimethylamine N-oxide, and phenylacetylglutamine[11]. These toxins can cause ED. A distinct population of monocytes, human leukocyte antigen (HLA)-DRhiIMs isolated from blood, produce higher amounts of TNF-α and IL-1β and is elevated in CKD[96].

Though kidney transplantation is associated with improved clinical outcomes, the inflammatory milieu of CKD continues to exist even after kidney transplant. Uremic toxins like ADMA (their role has been previously described) have been shown to persist in kidney transplant settings, and correlate with excess mortality and graft failure rates[97,98]. Hyperuricemia, hyperglycemia, hypertension, obesity, and dyslipidemia, which are common in the post-transplant state, cause ED[99]. Further, infections by immunomodulatory viruses such as cytomegalovirus, which are common in kidney transplant recipients, are known to cause expansion of pro-inflammatory and pro-thrombotic cell lines[100,101]. Coronavirus disease 2019 (COVID-19) is also known to cause similar immuno-thrombotic states in kidney transplant recipients[95]. Sepsis-induced acute kidney injury affects renal microvascular endothelial responses[102]. The gut microbiome in kidney transplant recipients is altered due to immunosuppressants and graft function[103].

Clinical vignette: Anti-inflammatory therapies like canakinumab and colchicine targeting atherosclerosis have never been tried in transplant settings. As transplantation is a risk factor for malignancy, the usage of immune checkpoint inhibitors for treating cancers can cause ED through the production of cytokines, and CV risk prevention is advised[104].

Uric acid: Purine metabolism through xanthine oxidase (XO) generates ROS, in addition to the production of uric acid [105]. ROS decreases NO availability through eNOS uncoupling. Uric acid, by itself, causes ED by entering the endothelial cells through uric acid transporters[105]. In transplant settings, hyperuricemia is one of the manifestations of CV toxicity[106]. In a study of 307 kidney transplant recipients, 47% had hyperuricemia at 6 months after transplant[107]. Over 4.3 years, hyperuricemia was associated with increased rates of new CV events and allograft dysfunction[107]. Serum uric acid levels negatively correlated with FMD in transplant settings[108]. Hyperuricemia was associated with higher anti-hypertensive medication use[109]. Allopurinol (an XO inhibitor) has been shown to improve FMD and reduce left ventricular mass in CKD patients, though no such studies have evaluated the same in kidney transplant recipients [110]. As mentioned earlier, colchicine (used in gout) has been recently added to the current standard of CV care[111].

Clinical vignette: The mechanism behind elevated blood pressure in hyperuricemic individuals involves both oxidative stress and intracellular urate activity, suggesting that anti-hyperuricemic drugs could be effective in controlling blood pressure[112].

Immunosuppressive drugs: Cyclosporine induces the release of endothelial microparticles, markers of endothelial activation[113]. Endothelial microparticles activate components of alternate complement pathways, leading to complement-mediated CV inflammation[114]. CNIs, both tacrolimus and cyclosporine, induce TGF-β production, which promotes endothelial-to-mesenchymal transition[115]. A small study of 31 renal transplant patients on cyclosporine and tacrolimus showed that the FMD in the cyclosporine group was significantly lower compared to healthy controls (6.3% *vs* 11.9%; $P = 0.024$). In contrast, no difference existed between the tacrolimus group and controls (8.8% *vs* 11.9%)[116]. CNI cause thrombotic microangiopathy (TMA) and chronic allograft nephropathy through ED.

Mycophenolate mofetil (MMF) has been shown to inhibit T-lymphocyte adhesion and penetration, indicating its potential as a therapeutic agent for mitigating ED in transplant recipients[117].

The "mTOR inhibitors" refer to medications that target the mTOR, a critical regulatory protein kinase involved in various cellular processes such as cell growth, proliferation, and metabolism. Sirolimus and everolimus are drugs used in both transplant settings and cardiology. mTOR inhibitors are associated with hyperuricemia, dyslipidemia, rejection, and proteinuria, which can cause ED[118]. In a prospective parallel-group study with a 7-month follow-up, sirolimus combined with MMF demonstrated superior FMD compared to MMF combined with cyclosporine[116].

Belatacept, a co-stimulation blocker of T cells used in CNI minimization strategy, has been associated with better metabolic and CV side effects than CNIs[119,120]. In the BENEFIT-EXT trial, which included elderly patients with comorbidities, the rate of serious CV events was 5.2 *per* 100 patient-years with cyclosporine and 4.1 *per* 100 patient-years with belatacept, representing a 21% relative risk reduction with belatacept[121].

Clinical vignette: Belatacept has been tried successfully as a rescue agent in *de novo* drug-induced TMA, which is caused due to endothelial activation[122].

Ischemia-reperfusion injury: Ischemia-reperfusion injury (IRI) is a complex process occurring when blood supply returns to tissues after a period of ischemia, leading to tissue damage and delayed graft function, especially in deceased donor kidney transplants. ED is a key component of IRI as reperfusion leads to endothelial cell death by releasing ROS [123]. There is consequent inflammation and thrombosis due to the activation of complement and coagulation pathways. Delayed graft function is associated with increased CV mortality and death-censored graft failure[124,125].

Clinical vignette: To prevent delayed graft function due to IRI strategies, include thymoglobulin administration, shorter cold ischemia time, hypothermic machine perfusion, and improving outcomes of higher kidney donor profile

index organs[125,126].

Allograft dysfunction and rejection: Allograft dysfunction caused by both chronic T-cell-mediated and antibody-mediated rejection is characterized by endothelial damage[127]. Usage of CNIs causes allograft vasculopathy due to ED. Also, graft dysfunction is associated with poorly controlled hypertension with resultant downstream adverse CV outcomes[128].

HLA antigens are expressed on the endothelial surfaces[129]. Both complement and non-complement binding HLA antibodies, responsible for antibody-mediated rejection damage the endothelium[130,131]. Non-HLA antibodies like anti-angiotensin-1 receptor antibodies can also damage the endothelium[132]. Accelerated arteriosclerosis in kidney allografts is 2.9 times more common when circulating antibodies are present[133].

The therapies available to treat antibody-mediated endothelial damage are limited. Mineralocorticoid antagonists and aldosterone synthase inhibitors were unable to prevent chronic allograft injury in clinical trials[134]. Therefore, the prevention and effective management of rejection may offer prospects for long-term improvement in endothelial function.

Clinical vignette: Donor-derived cell-free DNA generated from donor-cell damage or death is an emerging non-invasive biomarker employed to study endothelial injury in the allograft[135].

Risk factors implicated due to dialysis modality: Microcirculatory dysfunction is a well-described phenomenon with dialysis, more with HD than with PD. Circulatory stress during HD can cause acute, reversible segmental myocardial hypoperfusion and regional systolic contractile dysfunction (myocardial stunning). Repeated episodes result in cumulative injury, leading to heart failure[136]. Dialysis membranes and tubing have been shown to activate complement and the factor XII-driven contact system of coagulation[137]. This activation stimulates the intrinsic coagulation pathway and the kallikrein/kinin system, contributing to CV injury through pro-coagulant and pro-inflammatory effects[137]. Endothelial glycocalyx components, including hyaluronan, syndecan-1, and hyaluronidase activity are elevated in patients with HD[138]. HD is commonly associated with increased oxidative stress[139]. Compared to PD, HD arteries exhibit reduced contractility and endothelium-dependent relaxation[140]. ED has also been demonstrated with PD. Brachial FMD was significantly lower in PD patients (2.9%) compared to controls (6.2%; $P < 0.001$) in a prospective study [141].

Clinical vignette: Microcirculatory protection during HD includes maintenance of BPs within an optimal range, avoiding large-volume ultra-filtration rate, daily dialysis, dialysate cooling, ischemic pre-conditioning, and combining PD with HD[142]. Hemodiafiltration, which removes middle molecular proteins, caused improvement in FMD compared to HD[143].

Native kidney diseases: Patients with nephrotic syndrome demonstrate poor FMD when their disease is active[144]. Nephrotic syndrome broadly includes minimal change disease, focal segmental glomerulosclerosis (FSGS), and membranous nephropathy. The pathophysiological processes underlying the development of atherosclerotic lesions and FSGS appear to overlap, involving shared mechanisms such as endothelial cell injury, macrophage infiltration, dyslipidemia, and hypertension[145]. Soluble urokinase-type plasminogen activator receptor, a novel biomarker released from endothelial cells and leukocytes, is associated with FSGS recurrence and the development of coronary ED[146,147]. Other markers of endothelial activation such as vWF, VCAM, syndecan-1, and e-selectin are also elevated in nephrotic syndrome[148]. FSGS recurrence after kidney transplant is also associated with the production of angiotensin-receptor-1 antibodies, which are known to damage the renal endothelial cells[149]. FSGS recurrence is estimated to occur in 30%-50% of patients with transplantation. Hence, ED can be assumed to be significant in patients who had nephrotic syndrome before transplant and those who had recurrences in their allograft.

The disease process in ADPKD is primarily influenced by the RAAS and endothelial cell dysfunction associated with polycystin. Alongside these, the sympathetic nervous system activation, NO, endothelin-1, and ADMA are likely to exert pivotal deleterious effects on the endothelium[150,151].

TMA encompasses a clinical and pathological syndrome where endothelial damage precipitates manifestations such as thrombocytopenia, microangiopathic hemolytic anemia, and renal injury. Complement-mediated endothelial damage has been implicated as the primary pathogenesis of TMA[152]. Complement inhibitor therapies such as eculizumab have been shown to reduce the levels of markers of ED such as thrombomodulin, VCAM-1, and soluble tumor necrosis factor receptor 1[153].

Lupus nephritis patients after kidney transplant have been shown to have pre-mature CV events, which stem from ED [154]. ED in lupus nephritis is not localized to the kidney, but is systemic. The pathophysiology of ED in this condition is due to autoantibodies, inflammatory mediators, immune complex deposition in the vasculature, complement activation, oxidative stress, hypertension, and usage of immunosuppressive drugs such as corticosteroids and CNIs[155]. Newer biological agents and reduced steroid usage can improve endothelial functions in lupus nephritis patients[156].

ED has also been demonstrated in IgA nephropathy[157], anti-neutrophilic cytoplasmic antibody related vasculitis [158], and reflux nephropathy[158].

Clinical vignette: Statin therapy improves both dyslipidemia and FMD in patients with nephrotic syndrome[159].

Bone mineral disease: CKD-mineral and bone disorder (CKD-MBD) emerges due to disturbances in calcium and phosphorus regulation, accompanied by elevated parathyroid hormone and fibroblast growth factor 23 (FGF23) levels, and reduced levels of 1,25-dihydroxyvitamin D. These disruptions lead to aberrant bone restructuring and calcification beyond the skeletal system, contributing significantly to mortality rates among affected patients[160]. Phosphate retention due to low estimated glomerular filtration rate exacerbates vascular calcification and oxidative stress, leading to ED. Elevated phosphate levels disrupt vascular calcification regulation, inducing arterial wall thickening and stiffness, while

triggering the transformation of vascular smooth muscle cells into osteoblast-like cells[161]. Diabetic patients with CKD develop a typical MBD, namely, adynamic bone disease (low bone turnover state), known for accelerated vascular calcification[162]. However, the mechanisms of ED in a low turnover state are not clearly defined[161].

Kidney transplant recipients frequently encounter disruptions in phosphate homeostasis immediately following transplantation. This spectrum encompasses early-onset hypophosphatemia within the initial 3 months post-transplantation, progressing toward late-stage complications such as hyperphosphatemia, hyperparathyroidism, and increased FGF23 levels[163]. Vitamin D deficiency and elevated FGF23 levels are associated with ED[164]. Vitamin D deficiency is associated with elevated e-selectin levels[164]. Klotho, an anti-vascular aging and kidney protective protein, is implicated in MBD and CV diseases[165]. FGF23 decreases klotho levels, but klotho improves vitamin D levels. So, klotho by itself, and with vitamin D is protective for the endothelium. Vitamin D-FGF23-Klotho axis alterations are demonstrated in both kidney donors (after donation) and recipients[166]. RAAS inhibitors increase klotho levels[167].

Clinical vignette: Routine vitamin D supplementation to enhance endothelial function represents a promising area of research. The authors are part of a randomized controlled trial that looks at the change in FMD and endothelial biomarkers with vitamin D (cholecalciferol) supplementation in stable kidney transplant recipients.

Diet and nutrients: Diet is an important parameter that affects vascular aging[168]. A healthy diet is protective of the endothelium. The Mediterranean diet reduces oxidative stress and improves ED. A recent study showed that during a median follow-up of 5.4 years, higher adherence to the Mediterranean diet was associated with significantly lower risks of graft failure (HR = 0.68; 95%CI: 0.50-0.91), kidney function decline (HR = 0.68; 95%CI: 0.55-0.85), and graft loss (HR = 0.74; 95%CI: 0.63-0.88)[169]. The Mediterranean diet reduces the risk of developing NODAT[170]. In a randomized crossover trial of 22 stable kidney transplant recipients on RAAS blockade, a 6-week low-sodium diet (target: 50 mmol/24 h) significantly reduced systolic BP (from 140 to 129 mmHg) and diastolic BP (from 86 to 79 mmHg) compared to a regular-sodium diet (target: 150 mmol/24 h), without affecting urinary albumin excretion or estimated glomerular filtration rate[171]. Sodium restriction is thus effective for BP management in this population. The dietary approaches to stop hypertension (DASH) diet is characterized by a high intake of fruits, vegetables, legumes, nuts, and whole grains, along with low-fat dairy products. It emphasizes reduced consumption of sodium, red and processed meats, and sugar-sweetened beverages. In a prospective cohort study of 632 stable renal transplant recipients[172], a higher DASH score was associated with a reduced risk of renal function decline (HR = 0.57; 95%CI: 0.33-0.96; $P = 0.03$) and all-cause mortality (HR = 0.52; 95%CI: 0.32-0.83; $P = 0.006$) over a median follow-up of 5.3 years. Thus, both the Mediterranean and DASH diets may confer protective effects on endothelial function.

Isoflavone-containing soy products are protective of the endothelium. A small study of 20 patients with stable renal functions demonstrated improved FMD (3.2 ± 1.8% *vs* 6.3 ± 1.9%, respectively; $P < 0.001$) with 5 weeks of soy protein diet [173].

Clinical vignette: Intermittent fasting improves lipid profiles, decreases white adipose tissue, and enhances gut microbiome health. This leads to lower inflammation and a decreased risk of CV disease. Implementing intermittent fasting represents a compelling area of research in transplant settings for enhancing CV health.

Genomics: Personalized medicine for preventing CV events in kidney transplant recipients involves tailoring preventive and therapeutic strategies based on individual genetic, physiological, and clinical profiles. This approach integrates genetic risk assessments, such as the genetic risk score (GRS) derived from specific single nucleotide polymorphisms (SNPs), to identify patients at higher risk for CV complications. A composite GRS based on 27 SNPs, previously shown to predict CV events in the general population, demonstrated significant predictive value for major CV events in kidney transplant recipients (HR = 1.81; $P = 0.006$)[174]. This suggests that the GRS is applicable in renal transplant populations, with the potential for further refinement to enhance its predictive accuracy in this context. Polygenic risk scores from donors and recipients were able to predict the occurrence of NODAT[175]. The eNOS gene polymorphism identifies allograft outcomes related with atherosclerosis such as interstitial fibrosis and tubular atrophy[176].

Clinical vignette: Pharmacogenomics helps in precision prescribing and can avoid unnecessary CV side effects of immunosuppressants[177].

Figure 1 highlights the common pathways and risk factors leading to ED and major CV adverse events among post-kidney transplant recipients.

METHODS TO STUDY ENDOTHELIAL FUNCTIONS

Biomarkers

Biomarkers provide diagnostic information and insights into newer diagnostics, pathogenesis, and therapeutic targets. Biomarkers of endothelial activation and dysfunction are valuable for diagnosing vascular pathologies. These biomarkers often lack specificity and sensitivity in assessing CV disease in humans. Clinical utility is hindered by factors like small sample sizes, conflicting data, and poor understanding of some of the functions of biomarkers. Despite these challenges, biomarkers offer insights into disease mechanisms and are promising research tools for CV diseases. A massive surge in the endothelial biomarkers research occurred with the emergence of COVID-19 infection, where identifying these biomarkers helped us to study endothelial biology in inflammatory conditions and better risk stratify patients based on CV health[178,179]. The European Society of Cardiology is advocating for the integration of biomarkers alongside FMD for better prediction of CV events[180,181]. Detailed reviews of biomarkers have previously been published[182-184]. Table 1 lists a few important biomarkers belonging to various functional groups.

Table 1 Important biomarkers of endothelial dysfunction belonging to various functional groups

Functional group	Biomarkers
Oxidative stress	NADPH oxidase, ROS
Acute phase proteins	IL-1β, IL-6, TNF-α and its receptors, MCP-1, CRP, and SAA
Cell-adhesion molecules	ICAM-1, VCAM-1, e-selectin, p-selectin
Proteins modified by post-translational modification	OxLDL, OxHDL, carbamylated LDL, AGE, RAGE
Glycocalyx damage	Syndexan-1, endocan
Vascular tone	Endothelin-1, angiotensin II, resistin
Metabolizes catecholamines	Renalase
eNOS uncoupling	ADMA, SDMA
Thrombosis	PAI-1, angiopoietin-2, vWF, TF, soluble thrombomodulin, thromboxane A2, d-dimer, factor VIII, homocysteine
Marker of angiogenesis and hyperpermeability	VEGF-A, TGF-β1, PlGF
Marker of endothelial proliferation and apoptosis	Circulating endothelial cells
Membranous particles released from endothelial cells	Endothelial microvesicles
Endothelial-protective molecules	NO, klotho, sirtuins, Nrf2, PGI2
Others	miRNA, gut microbiota-derived metabolites, suPAR

ADMA: Asymmetric dimethylarginine; AGE: Advanced glycation end products; CRP: C-reactive protein; ICAM: Intercellular adhesion molecule; IL: Interleukin; MCP-1: Membrane cofactor protein-1; miRNA: Micro RNA; NADPH oxidase: Nicotinamide adenine dinucleotide oxidase; NO: Nitric oxide; Nrf2: Nuclear factor erythroid 2 related factor; OxLDL: Oxidized low-density lipoprotein; OxHDL: Oxidized high-density lipoprotein; PAI-1: Plasminogen activator inhibitor-1; PGI2: Prostaglandin I2; PlGF: Placental growth factor; RAGE: Receptors of advanced glycation end products; ROS: Reactive oxygen species; SAA: Serum amyloid A; SDMA: Symmetric dimethylarginine; suPAR: Soluble urokinase plasminogen activator receptor; TF: Tissue factor; TGF: Transforming growth factor; TNF: Tumor necrosis factor; VCAM: Vascular adhesion molecule; VEGF: Vascular endothelial growth factor; vWF: von Willebrand factor.

Vasomotor responses to determine endothelial functions

Arterial health is often assessed by examining the vessel's capacity for dilation in response to various stimuli. Physiologically, a key marker of arterial health is the ability of arteries to undergo endothelium-dependent vasodilation in reaction to reactive hyperemia. This phenomenon occurs due to increased shear stress resulting from elevated blood flow. In healthy arteries, this dilatory response is mediated by the endothelium through the release of vasodilatory factors such as NO, which counteracts the elevated shear stress by promoting vessel relaxation. Thus, impaired or blunted vasodilation in response to reactive hyperemia can serve as an indicator of ED. Additionally, arterial dilation is also elicited through the action of endothelium-dependent vasodilators, such as acetylcholine, bradykinin, and serotonin[185]. These mediators trigger the release of NO, which induces arterial vasodilation by stimulating guanylate cyclase, which increases cyclic guanosine monophosphate levels, leading to smooth muscle relaxation. Exogenous NO donors such as glyceryl-trinitrate and smooth muscle vasodilators such as adenosine are used to measure non-endothelial-induced vasodilation [185]. Consequently, the methodologies employed are designed to evaluate the vasodilatory capacity of arteries in response to diverse physiological stimuli, providing critical insights into their functional integrity. Blood flow, in addition to modulating vascular tone, influences a range of physiological processes, including the regulation of endothelial barrier permeability, angiogenesis, endothelial cell proliferation, apoptosis, differentiation, senescence, metabolic activities, inflammatory responses, morphological changes, and extracellular matrix remodeling[186]. Thus, blood flow measurement helps in understanding endothelial functions[187].

Coronary endothelial function measurement

Invasive methods: Coronary ED is characterized by the lack of expected vasodilation and the inadequate increase in blood flow within the epicardial coronary arteries following acetylcholine administration. These changes are commonly assessed using two main techniques: Quantitative coronary angiography and intravascular ultrasound[185]. While definitions of an abnormal angiographic response may vary across sources, a practical criterion is any degree of constriction of the epicardial arteries exceeding 0%, but not exceeding 90% following acetylcholine administration[188]. Agents other than acetylcholine that can be used include bradykinin, papaverine, and substance P[189]. Changes in coronary blood flow (CBF), a surrogate of coronary microvascular functions, are assessed through coronary flow reserve (CFR), calculated as maximal CBF during induced hyperemia divided by resting CBF. A CFR below 2.0 indicates an abnormality. Invasive methods like doppler flow velocity or thermodilution are used, albeit with technical challenges and reproducibility concerns[185].

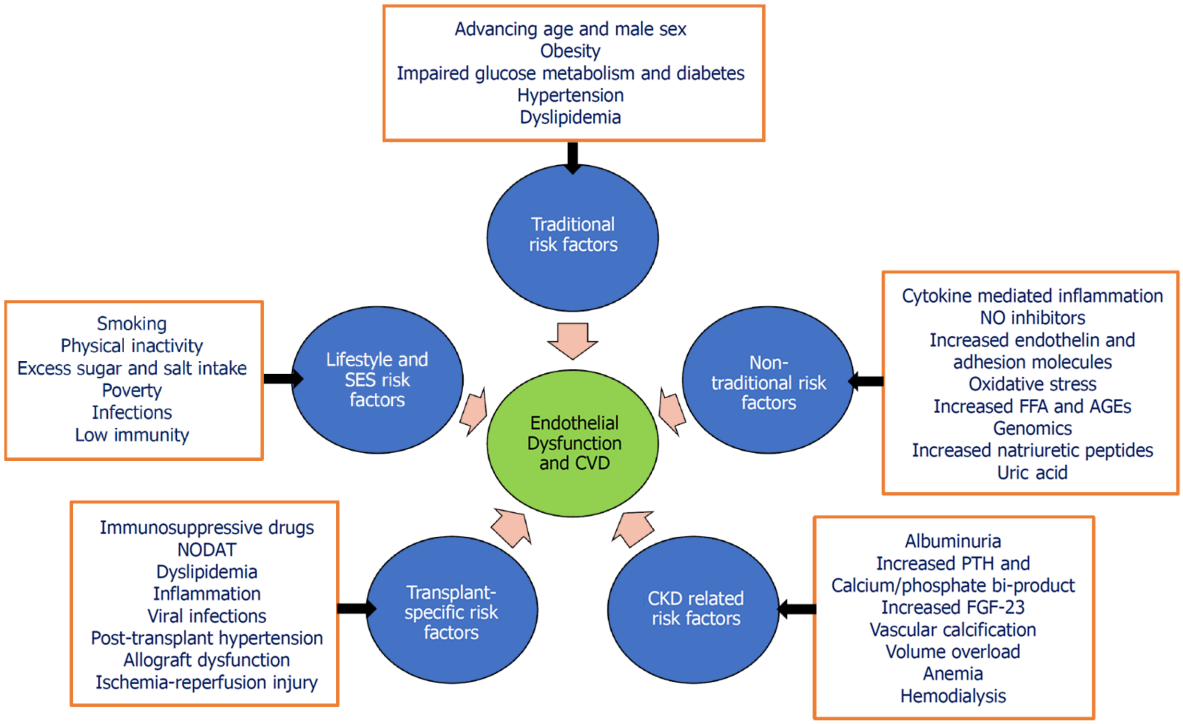


Figure 1 Common pathways and risk factors leading to endothelial dysfunction and major cardiovascular adverse events among post-kidney transplant recipients. AGEs: Advanced glycation end products; CKD: Chronic kidney disease; CVD: Cardiovascular diseases; FFA: Free fatty acids; FGF: Fibroblast growth factor; LVH: Left ventricular hypertrophy; NO: Nitric oxide; NODAT: New-onset diabetes after transplant; PTH: Parathyroid hormone; SES: Socioeconomic status.

Non-invasive methods to study coronary microvascular functions include the following[190]: (1) Contrast echocardiography; (2) Transthoracic doppler echocardiography; (3) Contrast tomography (CT); (4) Positron emission tomography (PET); (5) Single-photon emission computed tomography; and (6) Cardiac magnetic resonance imaging. Among these imaging modalities, PET offers precise global and regional myocardial perfusion (MP), blood flow, and function measurements, with advanced software enabling routine assessment of myocardial blood flow and viability using tracers like 18F-fluoro deoxy-glucose and 82-rubidium[191]. Enhanced PET/CT scanners facilitate accurate coronary microvascular dysfunction evaluation and disease detection, with promising applications in identifying vulnerable plaques through atherosclerotic plaque imaging[191].

Assessing peripheral arterial endothelial functions

For asymptomatic patients, invasive techniques, as mentioned before, may not be suitable. Therefore, non-invasive methods to detect endothelial functions have become increasingly popular[192]. Assessment by some of the techniques has been shown to replicate the endothelial functions in the coronary circulation[193-195].

FMD: Skeletal muscle arteries respond rapidly to reactive hyperemia of the supplying muscles[196]. FMD of conduit arteries like the brachial artery is a commonly used test to measure endothelial function[197]. Brachial artery FMD, a marker of endothelium-dependent vasodilation in response to vascular hyperemia (created by deflating an already inflated cuff at supra systolic blood pressure), mirrors NO production in the endothelium and aligns with coronary artery endothelial function[198]. It has good reproducibility. A small study[199] evaluated the reliability and reproducibility of FMD and peripheral arterial tonometry (PAT) for assessing endothelial function. Simultaneous FMD (brachial artery ultrasound) and PAT (EndoPAT 2000) assessments were performed twice with a 30-minute interval and repeated after 2 days. Within-day variability was lower for FMD (10%) compared to PAT (18%; $P < 0.05$), while between-day variability was similar (11%). A significant correlation between PAT and FMD was observed ($r = 0.57$, $P < 0.001$). FMD showed better reliability for both within- and between-day measurements compared to PAT. Systematic reviews demonstrate that even a modest increase of 1% in FMD value is linked to a significant 12% to 13% reduction in the risk of CV events, regardless of traditional CV risk factors[200,201]. This underscores the potential of FMD as a valuable vascular biomarker for stratifying CV risk. FMD is measured by real-time computer-based software, which will detect changes in the vessel wall diameters in response to hyperemia compared to baseline, *i.e.*, %FMD[202]. If not performed and analyzed consistently, FMD measurements can have high intra- and inter-observer variability. Standard reference ranges are available, which help identify and monitor at-risk individuals[198,203]. In 1579 healthy individuals, FMD was inversely correlated with age, body mass index, glucose, cholesterol, blood pressure, and brachial artery diameter. Receiver operating characteristic analysis indicated that FMD > 6.5% excludes coronary artery disease (95% sensitivity, 60% specificity), while FMD < 3.1% excludes 95% of healthy individuals[203]. A meta-analysis of 82 studies ($n = 3509$) found

an average FMD of 6.4% (95%CI: 6.2%-6.7%) with a significant age-related decline (-0.3%/decade)[203].

Nitroglycerin-mediated dilatation: Nitroglycerine-induced vasodilation (NMD), a marker of endothelium-independent vasodilation, is used as a control test for FMD to confirm that impaired FMD is not due to vascular smooth muscle dysfunction or structural alterations[204]. Instead, it confirms that the observed FMD impairment genuinely stems from ED. Combined FMD and NMD can better predict CV events than NMD alone[205]. NMD is usually performed by administering sublingual isosorbide dinitrite[144]. Again, the reference values for NMD are available for the general population[198].

Venous occlusion plethysmography: Forearm blood flow changes are measured *via* plethysmography in response to vasoactive substances introduced through a cannulated brachial artery, allowing quantification of both endothelial-dependent and independent vasodilation. Because of its semi-invasiveness, time-consuming, and impracticality for serial measurements, it has limited usage in the current era[206].

PAT: PAT is an innovative approach for evaluating endothelial function, utilizing finger plethysmography to measure pulse wave amplitude (PWA) at rest and during shear stress[207]. The reactive hyperemia-PAT index quantifies the ratio of PWA signal post-cuff release to baseline *via* computerized algorithms[208]. PAT offers advantages like using the subject's contralateral arm as an internal control and requiring minimal training. It correlates well with endothelial function across various populations and has predictive value for CV events[209,210].

Retinal artery diameters and reactivity: Evidence supports retinal microvascular analysis as a predictor of systemic CV risk and disease; however, this association is not yet strongly established[185]. Some studies highlight its clinical utility and predictive value for CV outcomes by assessing endothelial function, supporting its use in the primary and secondary prevention of chronic non-communicable diseases such as hypertension and diabetes mellitus[211,212]. Retinal vessel dimensions and flicker light-induced dilation are employed to detect endothelial functions[212]. Continuous retinal vessel diameter measurements during flicker light provocation reveal significant differences between those with CV disease and those with both CV disease + diabetes mellitus[212]. The distinct dilation and constriction patterns in diabetes mellitus ($P < 0.030$) could serve as a marker for monitoring CV disease progression[212]. The lack of randomized controlled studies and the non-availability of standard values hinder further progress in this field[185].

Studies on endothelial function testing in kidney transplant recipients: Kidney transplantation has been demonstrated to improve ED immediately after transplant, attributed to the reduction of uremia-related and traditional risk factors that cause endothelial damage[213-215]. The positive correlation measured in the above studies was seen until 90 days after the kidney transplant, as evidenced by improvement in FMD and biomarkers. However, their values were still significantly lower than in a healthy population[213]. In stable kidney transplant patients > 6 months after transplant, there was a significant decrease in FMD (-1.52% ± 2.74%; $P = 0.03$) at 3-6 months compared to baseline[216]. However, the decline in NMD was not significant. In a 6.5-year follow-up study of 152 kidney transplant recipients, significant post-transplant ED (defined as FMD ≤ 5.36%) was found to be associated with increased mortality (HR = 9.80; 95%CI: 1.29-74.62; $P = 0.03$) and higher risk of uncensored graft loss (HR = 7.80; 95%CI: 1.83-33.30; $P = 0.01$)[217]. Mortality risk increased with diminishing FMD levels until approximately 5% dilation, beyond which further reduction did not significantly affect the risk, suggesting a critical threshold for adverse outcomes in kidney transplant recipients[217]. Hence, a decline in FMD following an initial improvement is evident.

In a pilot study[218], MP reserve (MPR) was lower in kidney transplant patients (4.1 ± 1.1) compared to healthy controls (4.3 ± 1.6), but after adjusting for basal MP (1.3 ± 0.4 *vs* 1.0 ± 0.2 mL/minute/g) and cardiac workload, differences in MPR and stress MP (3.8 ± 1.0 *vs* 4.0 ± 0.9 mL/minute/g) were not significant. Increased resting MP in transplant patients is due to higher cardiac workload.

A study[219] analyzing endothelial biomarkers tried to delineate correlations between renalase and markers of inflammation and coagulation within a cohort of 62 kidney allograft recipients. Notably, renalase concentrations correlated with key endothelial markers such as vWF, thrombomodulin, ICAM-1, and VCAM-1[219]. Also, renalase was higher in hypertensive subjects compared to normotensive subjects[219]. ADMA (decreased eNOS) levels were associated with increased all-cause mortality (HR = 1.52; 95%CI: 1.26-1.83) in kidney transplant recipients[220].

CONCLUSION

ED in kidney transplant recipients is often under-recognized and inadequately treated, despite its significant CV implications. Increased CV mortality in this population is associated with ED. Many traditional and non-traditional risk factors for ED are modifiable, and optimal use of endothelial-protective medications is warranted. There is a critical need to include kidney transplant patients in CV clinical trials focusing on ED. Both FMD and biomarkers offer promise for early diagnosis of CV diseases compared to conventional diagnostic methods. As the number of kidney transplants continues to rise annually, emphasis should be placed on the prevention, early recognition, and treatment of ED to improve graft longevity and overall survival.

FOOTNOTES

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REFERENCES

1 **Bauer V**, Sotníková R. Nitric oxide--the endothelium-derived relaxing factor and its role in endothelial functions. *Gen Physiol Biophys* 2010; **29**: 319-340 [PMID: 21156995 DOI: 10.4149/gpb_2010_04_319]
2 **Mussbacher M**, Schossleitner K, Kral-Pointner JB, Salzmann M, Schrammel A, Schmid JA. More than Just a Monolayer: the Multifaceted Role of Endothelial Cells in the Pathophysiology of Atherosclerosis. *Curr Atheroscler Rep* 2022; **24**: 483-492 [PMID: 35404040 DOI: 10.1007/s11883-022-01023-9]
3 **Suzuki A**, Tomita H, Okada H. Form follows function: The endothelial glycocalyx. *Transl Res* 2022; **247**: 158-167 [PMID: 35421613 DOI: 10.1016/j.trsl.2022.03.014]
4 **Łuczak A**, Madej M, Kasprzyk A, Doroszko A. Role of the eNOS Uncoupling and the Nitric Oxide Metabolic Pathway in the Pathogenesis of Autoimmune Rheumatic Diseases. *Oxid Med Cell Longev* 2020; **2020**: 1417981 [PMID: 32351667 DOI: 10.1155/2020/1417981]
5 **Cabrera JTO**, Makino A. Efferocytosis of vascular cells in cardiovascular disease. *Pharmacol Ther* 2022; **229**: 107919 [PMID: 34171333 DOI: 10.1016/j.pharmthera.2021.107919]
6 **Huang Q**, Gan Y, Yu Z, Wu H, Zhong Z. Endothelial to Mesenchymal Transition: An Insight in Atherosclerosis. *Front Cardiovasc Med* 2021; **8**: 734550 [PMID: 34604359 DOI: 10.3389/fcvm.2021.734550]
7 **Shao Y**, Saredy J, Yang WY, Sun Y, Lu Y, Saaoud F, Drummer C 4th, Johnson C, Xu K, Jiang X, Wang H, Yang X. Vascular Endothelial Cells and Innate Immunity. *Arterioscler Thromb Vasc Biol* 2020; **40**: e138-e152 [PMID: 32459541 DOI: 10.1161/ATVBAHA.120.314330]
8 **Jankowski J**, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. *Circulation* 2021; **143**: 1157-1172 [PMID: 33720773 DOI: 10.1161/CIRCULATIONAHA.120.050686]
9 **Roumeliotis S**, Mallamaci F, Zoccali C. Endothelial Dysfunction in Chronic Kidney Disease, from Biology to Clinical Outcomes: A 2020 Update. *J Clin Med* 2020; **9** [PMID: 32718053 DOI: 10.3390/jcm9082359]
10 **Mihai S**, Codrici E, Popescu ID, Enciu AM, Albulescu L, Necula LG, Mambet C, Anton G, Tanase C. Inflammation-Related Mechanisms in Chronic Kidney Disease Prediction, Progression, and Outcome. *J Immunol Res* 2018; **2018**: 2180373 [PMID: 30271792 DOI: 10.1155/2018/2180373]
11 **Speer T**, Dimmeler S, Schunk SJ, Fliser D, Ridker PM. Targeting innate immunity-driven inflammation in CKD and cardiovascular disease. *Nat Rev Nephrol* 2022; **18**: 762-778 [PMID: 36064794 DOI: 10.1038/s41581-022-00621-9]
12 **Baaten CCFMJ**, Vondenhoff S, Noels H. Endothelial Cell Dysfunction and Increased Cardiovascular Risk in Patients With Chronic Kidney Disease. *Circ Res* 2023; **132**: 970-992 [PMID: 37053275 DOI: 10.1161/CIRCRESAHA.123.321752]
13 **Ridker PM**, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ; CANTOS Trial Group. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med* 2017; **377**: 1119-1131 [PMID: 28845751 DOI: 10.1056/NEJMoa1707914]
14 **Choi HY**, Lee JE, Han SH, Yoo TH, Kim BS, Park HC, Kang SW, Choi KH, Ha SK, Lee HY, Han DS. Association of inflammation and protein-energy wasting with endothelial dysfunction in peritoneal dialysis patients. *Nephrol Dial Transplant* 2010; **25**: 1266-1271 [PMID: 19926717 DOI: 10.1093/ndt/gfp598]
15 **Bolignano D**, Rastelli S, Agarwal R, Fliser D, Massy Z, Ortiz A, Wiecek A, Martinez-Castelao A, Covic A, Goldsmith D, Suleymanlar G, Lindholm B, Parati G, Sicari R, Gargani L, Mallamaci F, London G, Zoccali C. Pulmonary hypertension in CKD. *Am J Kidney Dis* 2013; **61**: 612-622 [PMID: 23164943 DOI: 10.1053/j.ajkd.2012.07.029]
16 **Merino A**, Portolés J, Selgas R, Ojeda R, Buendia P, Ocaña J, Bajo MA, del Peso G, Carracedo J, Ramírez R, Martín-Malo A, Aljama P. Effect of different dialysis modalities on microinflammatory status and endothelial damage. *Clin J Am Soc Nephrol* 2010; **5**: 227-234 [PMID: 20056757 DOI: 10.2215/CJN.03260509]
17 **Prasad N**, Yadav AK, Kundu M, Sethi J, Jaryal A, Sircar D, Modi GK, Kamboj K, Sahay M, Gopalakrishnan N, Kaur P, Vikrant S, Varughese S, Baid-Agrawal S, Singh S, Gang S, Parameswaran S, Kumar V, Ghosh A, Jha V. Prescription Practices in Patients With Mild to Moderate CKD in India. *Kidney Int Rep* 2021; **6**: 2455-2462 [PMID: 34514206 DOI: 10.1016/j.ekir.2021.06.011]

18 **Wolfrum S**, Jensen KS, Liao JK. Endothelium-dependent effects of statins. *Arterioscler Thromb Vasc Biol* 2003; **23**: 729-736 [PMID: 12615672 DOI: 10.1161/01.ATV.0000063385.12476.A7]

19 **Wanner C**, Tonelli M; Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int* 2014; **85**: 1303-1309 [PMID: 24552851 DOI: 10.1038/ki.2014.31]

20 **Whaley-Connell A**, Sowers JR. Obesity and kidney disease: from population to basic science and the search for new therapeutic targets. *Kidney Int* 2017; **92**: 313-323 [PMID: 28341271 DOI: 10.1016/j.kint.2016.12.034]

21 **Epstein M**. Hyperkalemia constitutes a constraint for implementing renin-angiotensin-aldosterone inhibition: the widening gap between mandated treatment guidelines and the real-world clinical arena. *Kidney Int Suppl (2011)* 2016; **6**: 20-28 [PMID: 30675416 DOI: 10.1016/j.kisu.2016.01.004]

22 **Colombijn JMT**, Idema DL, van Beem S, Blokland AM, van der Braak K, Handoko ML, In 't Veld LFH, Kaul T, Kolagasigil-Akdemir N, Kusters MPT, Meijvis SCA, Oosting IJ, Spijker R, Bots ML, Hooft L, Verhaar MC, Vernooij RWM. Representation of Patients With Chronic Kidney Disease in Clinical Trials of Cardiovascular Disease Medications: A Systematic Review. *JAMA Netw Open* 2024; **7**: e240427 [PMID: 38451526 DOI: 10.1001/jamanetworkopen.2024.0427]

23 **Rangaswami J**, Mathew RO, Parasuraman R, Tantisattamo E, Lubetzky M, Rao S, Yaqub MS, Birdwell KA, Bennett W, Dalal P, Kapoor R, Lerma EV, Lerman M, McCormick N, Bangalore S, McCullough PA, Dadhania DM. Cardiovascular disease in the kidney transplant recipient: epidemiology, diagnosis and management strategies. *Nephrol Dial Transplant* 2019; **34**: 760-773 [PMID: 30984976 DOI: 10.1093/ndt/gfz053]

24 **Birdwell KA**, Park M. Post-Transplant Cardiovascular Disease. *Clin J Am Soc Nephrol* 2021; **16**: 1878-1889 [PMID: 34556500 DOI: 10.2215/CJN.00520121]

25 **Pilmore H**, Dent H, Chang S, McDonald SP, Chadban SJ. Reduction in cardiovascular death after kidney transplantation. *Transplantation* 2010; **89**: 851-857 [PMID: 20048695 DOI: 10.1097/TP.0b013e3181caeead]

26 **Lim K**, Ting SMS, Hamborg T, McGregor G, Oxborough D, Tomkins C, Xu D, Thadhani R, Lewis G, Bland R, Banerjee P, Fletcher S, Krishnan NS, Higgins R, Zehnder D, Hiemstra TF. Cardiovascular Functional Reserve Before and After Kidney Transplant. *JAMA Cardiol* 2020; **5**: 420-429 [PMID: 32022839 DOI: 10.1001/jamacardio.2019.5738]

27 **Awan AA**, Niu J, Pan JS, Erickson KF, Mandayam S, Winkelmayer WC, Navaneethan SD, Ramanathan V. Trends in the Causes of Death among Kidney Transplant Recipients in the United States (1996-2014). *Am J Nephrol* 2018; **48**: 472-481 [PMID: 30472701 DOI: 10.1159/000495081]

28 **Andersson C**, Hansen D, Sørensen SS, McGrath M, McCausland FR, Torp-Pedersen C, Schou M, Køber L, Pfeffer MA. Long-term cardiovascular events, graft failure, and mortality in kidney transplant recipients. *Eur J Intern Med* 2024; **121**: 109-113 [PMID: 37903704 DOI: 10.1016/j.ejim.2023.10.026]

29 **Lenihan CR**, Montez-Rath ME, Scandling JD, Turakhia MP, Winkelmayer WC. Outcomes after kidney transplantation of patients previously diagnosed with atrial fibrillation. *Am J Transplant* 2013; **13**: 1566-1575 [PMID: 23721555 DOI: 10.1111/ajt.12197]

30 **Lentine KL**, Schnitzler MA, Abbott KC, Li L, Burroughs TE, Irish W, Brennan DC. De novo congestive heart failure after kidney transplantation: a common condition with poor prognostic implications. *Am J Kidney Dis* 2005; **46**: 720-733 [PMID: 16183428 DOI: 10.1053/j.ajkd.2005.06.019]

31 **Cardinal H**, Dieudé M, Hébert MJ. Endothelial Dysfunction in Kidney Transplantation. *Front Immunol* 2018; **9**: 1130 [PMID: 29875776 DOI: 10.3389/fimmu.2018.01130]

32 **Lentine KL**, Brennan DC, Schnitzler MA. Incidence and predictors of myocardial infarction after kidney transplantation. *J Am Soc Nephrol* 2005; **16**: 496-506 [PMID: 15615820 DOI: 10.1681/ASN.2004070580]

33 **Stewart G**, Jardine AG, Briggs JD. Ischaemic heart disease following renal transplantation. *Nephrol Dial Transplant* 2000; **15**: 269-277 [PMID: 10648681 DOI: 10.1093/ndt/15.2.269]

34 **Mathur AK**, Chang YH, Steidley DE, Heilman R, Khurmi N, Wasif N, Etzioni D, Moss AA. Patterns of Care and Outcomes in Cardiovascular Disease After Kidney Transplantation in the United States. *Transplant Direct* 2017; **3**: e126 [PMID: 28361110 DOI: 10.1097/TXD.0000000000000640]

35 **Wang Y**, Zhang J, Wang Z, Wang C, Ma D. Endothelial-cell-mediated mechanism of coronary microvascular dysfunction leading to heart failure with preserved ejection fraction. *Heart Fail Rev* 2023; **28**: 169-178 [PMID: 35266091 DOI: 10.1007/s10741-022-10224-y]

36 **Wali RK**, Wang GS, Gottlieb SS, Bellumkonda L, Hansalia R, Ramos E, Drachenberg C, Papadimitriou J, Brisco MA, Blahut S, Fink JC, Fisher ML, Bartlett ST, Weir MR. Effect of kidney transplantation on left ventricular systolic dysfunction and congestive heart failure in patients with end-stage renal disease. *J Am Coll Cardiol* 2005; **45**: 1051-1060 [PMID: 15808763 DOI: 10.1016/j.jacc.2004.11.061]

37 **Dennis MR**, Pires PW, Banek CT. Vascular Dysfunction in Polycystic Kidney Disease: A Mini-Review. *J Vasc Res* 2023; **60**: 125-136 [PMID: 37536302 DOI: 10.1159/000531647]

38 **Chedid M**, Kaidbay HD, Wigerinck S, Mkhaimer Y, Smith B, Zubidat D, Sekhon I, Prajwal R, Duriseti P, Issa N, Zoghby ZM, Hanna C, Senum SR, Harris PC, Hickson LJ, Torres VE, Nkomo VT, Chebib FT. Cardiovascular Outcomes in Kidney Transplant Recipients With ADPKD. *Kidney Int Rep* 2022; **7**: 1991-2005 [PMID: 36090485 DOI: 10.1016/j.ekir.2022.06.006]

39 **Yoo DJ**, Agodoa L, Yuan CM, Abbott KC, Nee R. Risk of intracranial hemorrhage associated with autosomal dominant polycystic kidney disease in patients with end stage renal disease. *BMC Nephrol* 2014; **15**: 39 [PMID: 24571546 DOI: 10.1186/1471-2369-15-39]

40 **Snyder JJ**, Kasiske BL, Maclean R. Peripheral arterial disease and renal transplantation. *J Am Soc Nephrol* 2006; **17**: 2056-2068 [PMID: 16775031 DOI: 10.1681/ASN.2006030201]

41 **Patel SI**, Chakkera HA, Wennberg PW, Liedl DA, Alrabadi F, Cha SS, Hooley DD, Amer H, Wadei HM, Shamoun FE. Peripheral arterial disease preoperatively may predict graft failure and mortality in kidney transplant recipients. *Vasc Med* 2017; **22**: 225-230 [PMID: 28466760 DOI: 10.1177/1358863X16689830]

42 **Galié N**, Manes A, Branzi A. The endothelin system in pulmonary arterial hypertension. *Cardiovasc Res* 2004; **61**: 227-237 [PMID: 14736539 DOI: 10.1016/j.cardiores.2003.11.026]

43 **Lentine KL**, Villines TC, Axelrod D, Kaviratne S, Weir MR, Costa SP. Evaluation and Management of Pulmonary Hypertension in Kidney Transplant Candidates and Recipients: Concepts and Controversies. *Transplantation* 2017; **101**: 166-181 [PMID: 26985742 DOI: 10.1097/TP.0000000000001043]

44 **Kwaifa IK**, Bahari H, Yong YK, Noor SM. Endothelial Dysfunction in Obesity-Induced Inflammation: Molecular Mechanisms and Clinical Implications. *Biomolecules* 2020; **10** [PMID: 32069832 DOI: 10.3390/biom10020291]

45 **Berkman ER**, Richardson KL, Clark JD, Dick AAS, Lewis-Newby M, Diekema DS, Wightman AG. An ethical analysis of obesity as a

contraindication of pediatric kidney transplant candidacy. *Pediatr Nephrol* 2023; **38**: 345-356 [PMID: 35488137 DOI: 10.1007/s00467-022-05572-8]

46 **Vincenti F**, Schena FP, Paraskevas S, Hauser IA, Walker RG, Grinyo J; FREEDOM Study Group. A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. *Am J Transplant* 2008; **8**: 307-316 [PMID: 18211506 DOI: 10.1111/j.1600-6143.2007.02057.x]

47 **Chang S**, Jiang J. Association of Body Mass Index and the Risk of New-Onset Diabetes After Kidney Transplantation: A Meta-analysis. *Transplant Proc* 2018; **50**: 1316-1325 [PMID: 29880352 DOI: 10.1016/j.transproceed.2018.02.075]

48 **Freeman CM**, Woodle ES, Shi J, Alexander JW, Leggett PL, Shah SA, Paterno F, Cuffy MC, Govil A, Mogilishetty G, Alloway RR, Hanseman D, Cardi M, Diwan TS. Addressing morbid obesity as a barrier to renal transplantation with laparoscopic sleeve gastrectomy. *Am J Transplant* 2015; **15**: 1360-1368 [PMID: 25708829 DOI: 10.1111/ajt.13116]

49 **Scheuermann U**, Babel J, Pietsch UC, Weimann A, Lyros O, Semmling K, Hau HM, Seehofer D, Rademacher S, Sucher R. Recipient obesity as a risk factor in kidney transplantation. *BMC Nephrol* 2022; **23**: 37 [PMID: 35042452 DOI: 10.1186/s12882-022-02668-z]

50 **Mallamaci F**, Leonardis D, Tripepi R, Parlongo G, Catalano C, Tripepi G, Castronovo V, Ferini-Strambi L, Zoccali C. Sleep disordered breathing in renal transplant patients. *Am J Transplant* 2009; **9**: 1373-1381 [PMID: 19459802 DOI: 10.1111/j.1600-6143.2009.02653.x]

51 **Kholdani C**, Fares WH, Mohsenin V. Pulmonary hypertension in obstructive sleep apnea: is it clinically significant? A critical analysis of the association and pathophysiology. *Pulm Circ* 2015; **5**: 220-227 [PMID: 26064448 DOI: 10.1086/679995]

52 **Ban K**, Noyan-Ashraf MH, Hoefer J, Bolz SS, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways. *Circulation* 2008; **117**: 2340-2350 [PMID: 18427132 DOI: 10.1161/CIRCULATIONAHA.107.739938]

53 **Kasiske BL**, Chakkera HA, Roel J. Explained and unexplained ischemic heart disease risk after renal transplantation. *J Am Soc Nephrol* 2000; **11**: 1735-1743 [PMID: 10966499 DOI: 10.1681/ASN.V1191735]

54 **Weinrauch LA**, Claggett B, Liu J, Finn PV, Weir MR, Weiner DE, D'Elia JA. Smoking and outcomes in kidney transplant recipients: a post hoc survival analysis of the FAVORIT trial. *Int J Nephrol Renovasc Dis* 2018; **11**: 155-164 [PMID: 29760559 DOI: 10.2147/IJNRD.S161001]

55 **Johnson HM**, Gossett LK, Piper ME, Aeschlimann SE, Korcarz CE, Baker TB, Fiore MC, Stein JH. Effects of smoking and smoking cessation on endothelial function: 1-year outcomes from a randomized clinical trial. *J Am Coll Cardiol* 2010; **55**: 1988-1995 [PMID: 20236788 DOI: 10.1016/j.jacc.2010.03.002]

56 **Mohammadi L**, Han DD, Xu F, Huang A, Derakhshandeh R, Rao P, Whitlatch A, Cheng J, Keith RJ, Hamburg NM, Ganz P, Hellman J, Schick SF, Springer ML. Chronic E-Cigarette Use Impairs Endothelial Function on the Physiological and Cellular Levels. *Arterioscler Thromb Vasc Biol* 2022; **42**: 1333-1350 [PMID: 36288290 DOI: 10.1161/ATVBAHA.121.317749]

57 **Skulratanasak P**, Larpparisuth N. Lipid management to mitigate poorer postkidney transplant outcomes. *Curr Opin Nephrol Hypertens* 2023; **32**: 27-34 [PMID: 36250471 DOI: 10.1097/MNH.0000000000000841]

58 **Riella LV**, Gabardi S, Chandraker A. Dyslipidemia and its therapeutic challenges in renal transplantation. *Am J Transplant* 2012; **12**: 1975-1982 [PMID: 22578270 DOI: 10.1111/j.1600-6143.2012.04084.x]

59 **Kumar J**, Reccia I, Virdis F, Podda M, Sharma AK, Halawa A. Belatacept in renal transplantation in comparison to tacrolimus and molecular understanding of resistance pattern: Meta-analysis and systematic review. *World J Transplant* 2021; **11**: 70-86 [PMID: 33816147 DOI: 10.5500/wjt.v11.i3.70]

60 **Chatauret N**, Favreau F, Giraud S, Thierry A, Rossard L, Le Pape S, Lerman LO, Hauet T. Diet-induced increase in plasma oxidized LDL promotes early fibrosis in a renal porcine auto-transplantation model. *J Transl Med* 2014; **12**: 76 [PMID: 24655356 DOI: 10.1186/1479-5876-12-76]

61 **Bae S**, Ahn JB, Joseph C, Whisler R, Schnitzler MA, Lentine KL, Kadosh BS, Segev DL, McAdams-DeMarco MA. Statins in Kidney Transplant Recipients: Usage, All-Cause Mortality, and Interactions with Maintenance Immunosuppressive Agents. *J Am Soc Nephrol* 2023; **34**: 1069-1077 [PMID: 36890643 DOI: 10.1681/ASN.0000000000000112]

62 **Wissing KM**, Unger P, Ghisdal L, Broeders N, Berkenboom G, Carpentier Y, Abramowicz D. Effect of atorvastatin therapy and conversion to tacrolimus on hypercholesterolemia and endothelial dysfunction after renal transplantation. *Transplantation* 2006; **82**: 771-778 [PMID: 17006324 DOI: 10.1097/01.tp.0000235446.50715.ef]

63 **USRDS**. Annual Data Report. [cited 23 October, 2024]. Available from: https://usrds-adr.niddk.nih.gov/2024

64 **Ueberdiek L**, Jehn U, Pavenstädt H, Gebauer K, Reuter S. Novel Therapeutic Strategies for Dyslipidemia: First Report of Inclisiran Therapy in a Kidney Transplanted Patient. *Transpl Int* 2023; **36**: 11104 [PMID: 36776901 DOI: 10.3389/ti.2023.11104]

65 **Weir MR**, Burgess ED, Cooper JE, Fenves AZ, Goldsmith D, McKay D, Mehrotra A, Mitsnefes MM, Sica DA, Taler SJ. Assessment and management of hypertension in transplant patients. *J Am Soc Nephrol* 2015; **26**: 1248-1260 [PMID: 25653099 DOI: 10.1681/ASN.2014080834]

66 **Tantisattamo E**, Molnar MZ, Ho BT, Reddy UG, Dafoe DC, Ichii H, Ferrey AJ, Hanna RM, Kalantar-Zadeh K, Amin A. Approach and Management of Hypertension After Kidney Transplantation. *Front Med (Lausanne)* 2020; **7**: 229 [PMID: 32613001 DOI: 10.3389/fmed.2020.00229]

67 **Carpenter MA**, John A, Weir MR, Smith SR, Hunsicker L, Kasiske BL, Kusek JW, Bostom A, Ivanova A, Levey AS, Solomon S, Pesavento T, Weiner DE. BP, cardiovascular disease, and death in the Folic Acid for Vascular Outcome Reduction in Transplantation trial. *J Am Soc Nephrol* 2014; **25**: 1554-1562 [PMID: 24627349 DOI: 10.1681/ASN.2013040435]

68 **Kim CS**, Oh TR, Suh SH, Choi HS, Bae EH, Ma SK, Jung JH, Kim B, Han KD, Kim SW. Uncontrolled hypertension is associated with increased risk of graft failure in kidney transplant recipients: a nationwide population-based study. *Front Cardiovasc Med* 2023; **10**: 1185001 [PMID: 37522087 DOI: 10.3389/fcvm.2023.1185001]

69 **Guzik TJ**, Nosalski R, Maffia P, Drummond GR. Immune and inflammatory mechanisms in hypertension. *Nat Rev Cardiol* 2024; **21**: 396-416 [PMID: 38172242 DOI: 10.1038/s41569-023-00964-1]

70 **Seeman T**, Myette RL, Feber J. Hypertension in pediatric kidney transplantation. *Pediatr Transplant* 2023; **27**: e14522 [PMID: 37118862 DOI: 10.1111/petr.14522]

71 **Jeelani H**, Sharma A, Halawa AM. Posterior Reversible Encephalopathy Syndrome in Organ Transplantation. *Exp Clin Transplant* 2022; **20**: 642-648 [PMID: 35924741 DOI: 10.6002/ect.2021.0268]

72 **Wang CC**, Lee AS, Liu SH, Chang KC, Shen MY, Chang CT. Spironolactone ameliorates endothelial dysfunction through inhibition of the AGE/RAGE axis in a chronic renal failure rat model. *BMC Nephrol* 2019; **20**: 351 [PMID: 31492107 DOI: 10.1186/s12882-019-1534-4]

73 **Mortensen LA**, Bistrup C, Stubbe J, Carlström M, Checa A, Wheelock CE, Palarasah Y, Bladbjerg EM, Thiesson HC, Jensen BL. Effect of

spironolactone for 1 yr on endothelial function and vascular inflammation biomarkers in renal transplant recipients. *Am J Physiol Renal Physiol* 2019; **317**: F529-F539 [PMID: 31166706 DOI: 10.1152/ajprenal.00025.2019]

74 **Hirano H**, Fujiwara Y, Maenosono R, Minami K, Uehara H, Okabe T, Nakamori K, Nomi H, Komura K, Inamoto T, Azuma H. Usefulness of Dietary Salt Restriction in Kidney Transplant Recipients: Analysis of Blood Pressure Levels Depending on the Differences in the Levels of Salt Intake. *Transplant Proc* 2023; **55**: 841-844 [PMID: 37169600 DOI: 10.1016/j.transproceed.2023.03.054]

75 **Dickinson KM**, Clifton PM, Keogh JB. Endothelial function is impaired after a high-salt meal in healthy subjects. *Am J Clin Nutr* 2011; **93**: 500-505 [PMID: 21228265 DOI: 10.3945/ajcn.110.006155]

76 **Pisano A**, Mallamaci F, D'Arrigo G, Bolignano D, Wuerzner G, Ortiz A, Burnier M, Kanaan N, Sarafidis P, Persu A, Ferro CJ, Loutradis C, Boletis IN, London G, Halimi JM, Sautenet B, Rossignol P, Vogt L, Zoccali C. Blood pressure monitoring in kidney transplantation: a systematic review on hypertension and target organ damage. *Nephrol Dial Transplant* 2021 [PMID: 33764450 DOI: 10.1093/ndt/gfab076]

77 **Ozkayar N**, Altun B, Yildirim T, Yilmaz R, Dede F, Arik G, Turkmen E, Hayran M, Aki FT, Arici M, Erdem Y. Blood pressure measurements, blood pressure variability and endothelial function in renal transplant recipients. *Clin Exp Hypertens* 2014; **36**: 392-397 [PMID: 24047335 DOI: 10.3109/10641963.2013.827706]

78 **Magavern EF**, Kapil V, Saxena M, Gupta A, Caulfield MJ. Use of Genomics to Develop Novel Therapeutics and Personalize Hypertension Therapy. *Arterioscler Thromb Vasc Biol* 2024; **44**: 784-793 [PMID: 38385287 DOI: 10.1161/ATVBAHA.123.319220]

79 **Jenssen T**, Hartmann A. Post-transplant diabetes mellitus in patients with solid organ transplants. *Nat Rev Endocrinol* 2019; **15**: 172-188 [PMID: 30622369 DOI: 10.1038/s41574-018-0137-7]

80 **Khairoun M**, de Koning EJ, van den Berg BM, Lievers E, de Boer HC, Schaapherder AF, Mallat MJ, Rotmans JI, van der Boog PJ, van Zonneveld AJ, de Fijter JW, Rabelink TJ, Reinders ME. Microvascular damage in type 1 diabetic patients is reversed in the first year after simultaneous pancreas-kidney transplantation. *Am J Transplant* 2013; **13**: 1272-1281 [PMID: 23433125 DOI: 10.1111/ajt.12182]

81 **Topitz D**, Schwaiger E, Frommlet F, Werzowa J, Hecking M. Cardiovascular events associate with diabetes status rather than with early basal insulin treatment for the prevention of post-transplantation diabetes mellitus. *Nephrol Dial Transplant* 2020; **35**: 544-546 [PMID: 31803915 DOI: 10.1093/ndt/gfz244]

82 **Wauters RP**, Cosio FG, Suarez Fernandez ML, Kudva Y, Shah P, Torres VE. Cardiovascular consequences of new-onset hyperglycemia after kidney transplantation. *Transplantation* 2012; **94**: 377-382 [PMID: 22820698 DOI: 10.1097/TP.0b013e3182584831]

83 **Gora IM**, Ciechanowska A, Ladyzynski P. NLRP3 Inflammasome at the Interface of Inflammation, Endothelial Dysfunction, and Type 2 Diabetes. *Cells* 2021; **10** [PMID: 33546399 DOI: 10.3390/cells10020314]

84 **Maruhashi T**, Higashi Y. Pathophysiological Association between Diabetes Mellitus and Endothelial Dysfunction. *Antioxidants (Basel)* 2021; **10** [PMID: 34439553 DOI: 10.3390/antiox10081306]

85 **Strøm Halden TA**, Åsberg A, Vik K, Hartmann A, Jenssen T. Short-term efficacy and safety of sitagliptin treatment in long-term stable renal recipients with new-onset diabetes after transplantation. *Nephrol Dial Transplant* 2014; **29**: 926-933 [PMID: 24452849 DOI: 10.1093/ndt/gft536]

86 **Nafisa A**, Gray SG, Cao Y, Wang T, Xu S, Wattoo FH, Barras M, Cohen N, Kamato D, Little PJ. Endothelial function and dysfunction: Impact of metformin. *Pharmacol Ther* 2018; **192**: 150-162 [PMID: 30056057 DOI: 10.1016/j.pharmthera.2018.07.007]

87 **Shamshad F**, Tungsanga S, Senior P, Shojai S, Ghimire A, Ye F, Kung JY, Hariramani VK, Abdulrahman A, Penney M, Sultana N, Muneer S, Okpechi I, Bello AK. Effect of metformin use on graft and patient survival in kidney transplant recipients with type 2 diabetes: a systematic review protocol. *BMJ Open* 2024; **14**: e078393 [PMID: 38760033 DOI: 10.1136/bmjopen-2023-078393]

88 **Darenskaya MA**, Kolesnikova LI, Kolesnikov SI. Oxidative Stress: Pathogenetic Role in Diabetes Mellitus and Its Complications and Therapeutic Approaches to Correction. *Bull Exp Biol Med* 2021; **171**: 179-189 [PMID: 34173093 DOI: 10.1007/s10517-021-05191-7]

89 **Schwaiger E**, Krenn S, Kurnikowski A, Bergfeld L, Pérez-Sáez MJ, Frey A, Topitz D, Bergmann M, Hödlmoser S, Bachmann F, Halleck F, Kron S, Hafner-Giessauf H, Eller K, Rosenkranz AR, Crespo M, Faura A, Tura A, Song PXK, Port FK, Pascual J, Budde K, Ristl R, Werzowa J, Hecking M. Early Postoperative Basal Insulin Therapy versus Standard of Care for the Prevention of Diabetes Mellitus after Kidney Transplantation: A Multicenter Randomized Trial. *J Am Soc Nephrol* 2021; **32**: 2083-2098 [PMID: 34330770 DOI: 10.1681/ASN.2021010127]

90 **Ikonomidis I**, Pavlidis G, Thymis J, Birba D, Kalogeris A, Kousathana F, Kountouri A, Balampanis K, Parissis J, Andreadou I, Katogiannis K, Dimitriadis G, Bamias A, Iliodromitis E, Lambadiari V. Effects of Glucagon-Like Peptide-1 Receptor Agonists, Sodium-Glucose Cotransporter-2 Inhibitors, and Their Combination on Endothelial Glycocalyx, Arterial Function, and Myocardial Work Index in Patients With Type 2 Diabetes Mellitus After 12-Month Treatment. *J Am Heart Assoc* 2020; **9**: e015716 [PMID: 32326806 DOI: 10.1161/JAHA.119.015716]

91 **Mone P**, Varzideh F, Jankauskas SS, Pansini A, Lombardi A, Frullone S, Santulli G. SGLT2 Inhibition *via* Empagliflozin Improves Endothelial Function and Reduces Mitochondrial Oxidative Stress: Insights From Frail Hypertensive and Diabetic Patients. *Hypertension* 2022; **79**: 1633-1643 [PMID: 35703100 DOI: 10.1161/HYPERTENSIONAHA.122.19586]

92 **Alshnbari AS**, Millar SA, O'Sullivan SE, Idris I. Effect of Sodium-Glucose Cotransporter-2 Inhibitors on Endothelial Function: A Systematic Review of Preclinical Studies. *Diabetes Ther* 2020; **11**: 1947-1963 [PMID: 32715425 DOI: 10.1007/s13300-020-00885-z]

93 **Jankowski V**, Saritas T, Kjolby M, Hermann J, Speer T, Himmelsbach A, Mahr K, Heuschkel MA, Schunk SJ, Thirup S, Winther S, Bottcher M, Nyegard M, Nykjaer A, Kramann R, Kaesler N, Jankowski J, Floege J, Marx N, Goettsch C. Carbamylated sortilin associates with cardiovascular calcification in patients with chronic kidney disease. *Kidney Int* 2022; **101**: 574-584 [PMID: 34767831 DOI: 10.1016/j.kint.2021.10.018]

94 **Gajjala PR**, Fliser D, Speer T, Jankowski V, Jankowski J. Emerging role of post-translational modifications in chronic kidney disease and cardiovascular disease. *Nephrol Dial Transplant* 2015; **30**: 1814-1824 [PMID: 25862763 DOI: 10.1093/ndt/gfv048]

95 **Stark K**, Massberg S. Interplay between inflammation and thrombosis in cardiovascular pathology. *Nat Rev Cardiol* 2021; **18**: 666-682 [PMID: 33958774 DOI: 10.1038/s41569-021-00552-1]

96 **Cormican S**, Negi N, Naicker SD, Islam MN, Fazekas B, Power R, Griffin TP, Dennedy MC, MacNeill B, Malone AF, Griffin MD. Chronic Kidney Disease Is Characterized by Expansion of a Distinct Proinflammatory Intermediate Monocyte Subtype and by Increased Monocyte Adhesion to Endothelial Cells. *J Am Soc Nephrol* 2023; **34**: 793-808 [PMID: 36799882 DOI: 10.1681/ASN.0000000000000083]

97 **Baskal S**, Post A, Kremer D, Bollenbach A, Bakker SJL, Tsikas D. Urinary excretion of amino acids and their advanced glycation end-products (AGEs) in adult kidney transplant recipients with emphasis on lysine: furosine excretion is associated with cardiovascular and all-cause mortality. *Amino Acids* 2021; **53**: 1679-1693 [PMID: 34693489 DOI: 10.1007/s00726-021-03091-8]

98 **Post A**, Bollenbach A, Bakker SJL, Tsikas D. Whole-body arginine dimethylation is associated with all-cause mortality in adult renal

transplant recipients. *Amino Acids* 2021; **53**: 541-554 [PMID: 33651245 DOI: 10.1007/s00726-021-02965-1]

99 **Ponticelli C**, Campise MR. The inflammatory state is a risk factor for cardiovascular disease and graft fibrosis in kidney transplantation. *Kidney Int* 2021; **100**: 536-545 [PMID: 33932457 DOI: 10.1016/j.kint.2021.04.016]

100 **Soleimanian S**, Yaghobi R, Karimi MH, Geramizadeh B, Roozbeh J. Altered Signatures of Plasma Inflammatory Proteins and Phonotypic Markers of NK Cells in Kidney Transplant Patients upon CMV Reactivation. *Curr Microbiol* 2022; **80**: 9 [PMID: 36445486 DOI: 10.1007/s00284-022-03116-9]

101 **Couzi L**, Pitard V, Moreau JF, Merville P, Déchanet-Merville J. Direct and Indirect Effects of Cytomegalovirus-Induced γδ T Cells after Kidney Transplantation. *Front Immunol* 2015; **6**: 3 [PMID: 25653652 DOI: 10.3389/fimmu.2015.00003]

102 **Molema G**, Zijlstra JG, van Meurs M, Kamps JAAM. Renal microvascular endothelial cell responses in sepsis-induced acute kidney injury. *Nat Rev Nephrol* 2022; **18**: 95-112 [PMID: 34667283 DOI: 10.1038/s41581-021-00489-1]

103 **Campbell PM**, Humphreys GJ, Summers AM, Konkel JE, Knight CG, Augustine T, McBain AJ. Does the Microbiome Affect the Outcome of Renal Transplantation? *Front Cell Infect Microbiol* 2020; **10**: 558644 [PMID: 33425774 DOI: 10.3389/fcimb.2020.558644]

104 **Efentakis P**, Choustoulaki A, Kwiatkowski G, Varela A, Kostopoulos IV, Tsekenis G, Ntanasis-Stathopoulos I, Georgoulis A, Vorgias CE, Gakiopoulou H, Briasoulis A, Davos CH, Kostomitsopoulos N, Tsitsilonis O, Dimopoulos MA, Terpos E, Chłopicki S, Gavriatopoulou M, Andreadou I. Early microvascular coronary endothelial dysfunction precedes pembrolizumab-induced cardiotoxicity. Preventive role of high dose of atorvastatin. *Basic Res Cardiol* 2024 [PMID: 38520533 DOI: 10.1007/s00395-024-01046-0]

105 **Maruhashi T**, Hisatome I, Kihara Y, Higashi Y. Hyperuricemia and endothelial function: From molecular background to clinical perspectives. *Atherosclerosis* 2018; **278**: 226-231 [PMID: 30326405 DOI: 10.1016/j.atherosclerosis.2018.10.007]

106 **Farouk SS**, Rein JL. The Many Faces of Calcineurin Inhibitor Toxicity-What the FK? *Adv Chronic Kidney Dis* 2020; **27**: 56-66 [PMID: 32147003 DOI: 10.1053/j.ackd.2019.08.006]

107 **Akalin E**, Ganeshan SV, Winston J, Muntner P. Hyperuricemia is associated with the development of the composite outcomes of new cardiovascular events and chronic allograft nephropathy. *Transplantation* 2008; **86**: 652-658 [PMID: 18791445 DOI: 10.1097/TP.0b013e3181814f5b]

108 **Dahle DO**, Jenssen T, Holdaas H, Asberg A, Soveri I, Holme I, Mjøen G, Eide IA, Pihlstrøm H, Dörje C, Halden TA, Hartmann A. Uric acid and clinical correlates of endothelial function in kidney transplant recipients. *Clin Transplant* 2014; **28**: 1167-1176 [PMID: 25124959 DOI: 10.1111/ctr.12435]

109 **Armstrong KA**, Johnson DW, Campbell SB, Isbel NM, Hawley CM. Does uric acid have a pathogenetic role in graft dysfunction and hypertension in renal transplant recipients? *Transplantation* 2005; **80**: 1565-1571 [PMID: 16371927 DOI: 10.1097/01.tp.0000183895.88572.13]

110 **Kao MP**, Ang DS, Gandy SJ, Nadir MA, Houston JG, Lang CC, Struthers AD. Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. *J Am Soc Nephrol* 2011; **22**: 1382-1389 [PMID: 21719783 DOI: 10.1681/ASN.2010111185]

111 **Deftereos SG**, Beerkens FJ, Shah B, Giannopoulos G, Vrachatis DA, Giotaki SG, Siasos G, Nicolas J, Arnott C, Patel S, Parsons M, Tardif JC, Kovacic JC, Dangas GD. Colchicine in Cardiovascular Disease: In-Depth Review. *Circulation* 2022; **145**: 61-78 [PMID: 34965168 DOI: 10.1161/CIRCULATIONAHA.121.056171]

112 **Borghi C**, Agnoletti D, Cicero AFG, Lurbe E, Virdis A. Uric Acid and Hypertension: a Review of Evidence and Future Perspectives for the Management of Cardiovascular Risk. *Hypertension* 2022; **79**: 1927-1936 [PMID: 35658505 DOI: 10.1161/HYPERTENSIONAHA.122.17956]

113 **Renner B**, Klawitter J, Goldberg R, McCullough JW, Ferreira VP, Cooper JE, Christians U, Thurman JM. Cyclosporine induces endothelial cell release of complement-activating microparticles. *J Am Soc Nephrol* 2013; **24**: 1849-1862 [PMID: 24092930 DOI: 10.1681/ASN.2012111064]

114 **Martin N**, Tu X, Egan AJ, Stover C. Complement Activation on Endothelial Cell-Derived Microparticles-A Key Determinant for Cardiovascular Risk in Patients with Systemic Lupus Erythematosus? *Medicina (Kaunas)* 2020; **56** [PMID: 33065972 DOI: 10.3390/medicina56100533]

115 **Woda CB**, Bruneau S, Mak AL, Haskova Z, Liu K, Ghosh CC, Briscoe DM. Calcineurin inhibitors augment endothelial-to-mesenchymal transition by enhancing proliferation in association with cytokine-mediated activation. *Biochem Biophys Res Commun* 2019; **519**: 667-673 [PMID: 31542230 DOI: 10.1016/j.bbrc.2019.09.043]

116 **Akoglu H**, Seringec N, Yildirim T, Yilmaz R, Okutucu S, Turkmen E, Evranos B, Kaya EB, Dikmenoglu N, Arici M, Erdem Y, Turgan C. Relationship between hemorheology and endothelial dysfunction in renal transplant patients receiving calcineurin inhibitors. *J Nephrol* 2013; **26**: 931-940 [PMID: 23147686 DOI: 10.5301/jn.5000237]

117 **Blaheta RA**, Leckel K, Wittig B, Zenker D, Oppermann E, Harder S, Scholz M, Weber S, Schuldes H, Encke A, Markus BH. Inhibition of endothelial receptor expression and of T-cell ligand activity by mycophenolate mofetil. *Transpl Immunol* 1998; **6**: 251-259 [PMID: 10342739 DOI: 10.1016/s0966-3274(98)80015-4]

118 **Ponticelli C**. The pros and the cons of mTOR inhibitors in kidney transplantation. *Expert Rev Clin Immunol* 2014; **10**: 295-305 [PMID: 24377908 DOI: 10.1586/1744666X.2014.872562]

119 **Bredewold OW**, van Oeveren-Rietdijk AM, Florijn B, Rotmans JI, de Fijter JW, van Kooten C, van Zonneveld AJ, de Boer HC. Conversion from calcineurin inhibitors to belatacept-based immunosuppressive therapy skews terminal proliferation of non-classical monocytes and lowers lymphocyte counts. *Transpl Immunol* 2024; **82**: 101976 [PMID: 38199271 DOI: 10.1016/j.trim.2023.101976]

120 **Yakubu I**, Moinuddin I, Gupta G. Use of belatacept in kidney transplantation: what's new? *Curr Opin Organ Transplant* 2023; **28**: 36-45 [PMID: 36326538 DOI: 10.1097/MOT.0000000000001033]

121 **Durrbach A**, Pestana JM, Florman S, Del Carmen Rial M, Rostaing L, Kuypers D, Matas A, Wekerle T, Polinsky M, Meier-Kriesche HU, Munier S, Grinyó JM. Long-Term Outcomes in Belatacept- Versus Cyclosporine-Treated Recipients of Extended Criteria Donor Kidneys: Final Results From BENEFIT-EXT, a Phase III Randomized Study. *Am J Transplant* 2016; **16**: 3192-3201 [PMID: 27130868 DOI: 10.1111/ajt.13830]

122 **Cicora F**, Paz M, Mos F, Roberti J. Use of belatacept as alternative immunosuppression in three renal transplant patients with de novo drug-induced thrombotic microangiopathy. *Case Rep Med* 2013; **2013**: 260254 [PMID: 24198835 DOI: 10.1155/2013/260254]

123 **Malinoski D**, Saunders C, Swain S, Groat T, Wood PR, Reese J, Nelson R, Prinz J, Kishish K, Van De Walker C, Geraghty PJ, Broglio K, Niemann CU. Hypothermia or Machine Perfusion in Kidney Donors. *N Engl J Med* 2023; **388**: 418-426 [PMID: 36724328 DOI: 10.1056/NEJMoa2118265]

124 **Phillips BL**, Ibrahim M, Greenhall GHB, Mumford L, Dorling A, Callaghan CJ. Effect of delayed graft function on longer-term outcomes after kidney transplantation from donation after circulatory death donors in the United Kingdom: A national cohort study. *Am J Transplant* 2021; **21**:

3346-3355 [PMID: 33756062 DOI: 10.1111/ajt.16574]
125 **Ponticelli C**, Reggiani F, Moroni G. Delayed Graft Function in Kidney Transplant: Risk Factors, Consequences and Prevention Strategies. *J Pers Med* 2022; **12** [PMID: 36294695 DOI: 10.3390/jpm12101557]
126 **Tingle SJ**, Figueiredo RS, Moir JA, Goodfellow M, Talbot D, Wilson CH. Machine perfusion preservation versus static cold storage for deceased donor kidney transplantation. *Cochrane Database Syst Rev* 2019; **3**: CD011671 [PMID: 30875082 DOI: 10.1002/14651858.CD011671.pub2]
127 **Langewisch E**, Mannon RB. Chronic Allograft Injury. *Clin J Am Soc Nephrol* 2021; **16**: 1723-1729 [PMID: 33820759 DOI: 10.2215/CJN.15590920]
128 **Lefaucheur C**, Viglietti D, Bouatou Y, Philippe A, Pievani D, Aubert O, Duong Van Huyen JP, Taupin JL, Glotz D, Legendre C, Loupy A, Halloran PF, Dragun D. Non-HLA agonistic anti-angiotensin II type 1 receptor antibodies induce a distinctive phenotype of antibody-mediated rejection in kidney transplant recipients. *Kidney Int* 2019; **96**: 189-201 [PMID: 31005275 DOI: 10.1016/j.kint.2019.01.030]
129 **Konvalinka A**, Tinckam K. Utility of HLA Antibody Testing in Kidney Transplantation. *J Am Soc Nephrol* 2015; **26**: 1489-1502 [PMID: 25804279 DOI: 10.1681/ASN.2014080837]
130 **Guidicelli G**, Guerville F, Lepreux S, Wiebe C, Thaunat O, Dubois V, Visentin J, Bachelet T, Morelon E, Nickerson P, Merville P, Taupin JL, Couzi L. Non-Complement-Binding De Novo Donor-Specific Anti-HLA Antibodies and Kidney Allograft Survival. *J Am Soc Nephrol* 2016; **27**: 615-625 [PMID: 26047793 DOI: 10.1681/ASN.2014040326]
131 **Loupy A**, Lefaucheur C, Vernerey D, Prugger C, Duong van Huyen JP, Mooney N, Suberbielle C, Frémeaux-Bacchi V, Méjean A, Desgrandchamps F, Anglicheau D, Nochy D, Charron D, Empana JP, Delahousse M, Legendre C, Glotz D, Hill GS, Zeevi A, Jouven X. Complement-binding anti-HLA antibodies and kidney-allograft survival. *N Engl J Med* 2013; **369**: 1215-1226 [PMID: 24066742 DOI: 10.1056/NEJMoa1302506]
132 **Delville M**, Lamarthée B, Pagie S, See SB, Rabant M, Burger C, Gatault P, Giral M, Thaunat O, Arzouk N, Hertig A, Hazzan M, Matignon M, Mariat C, Caillard S, Kamar N, Sayegh J, Westeel PF, Garrouste C, Ladrière M, Vuiblet V, Rivalan J, Merville P, Bertrand D, Le Moine A, Duong Van Huyen JP, Cesbron A, Cagnard N, Alibeu O, Satchell SC, Legendre C, Zorn E, Taupin JL, Charreau B, Anglicheau D. Early Acute Microvascular Kidney Transplant Rejection in the Absence of Anti-HLA Antibodies Is Associated with Preformed IgG Antibodies against Diverse Glomerular Endothelial Cell Antigens. *J Am Soc Nephrol* 2019; **30**: 692-709 [PMID: 30850439 DOI: 10.1681/ASN.2018080868]
133 **Loupy A**, Vernerey D, Viglietti D, Aubert O, Duong Van Huyen JP, Empana JP, Bruneval P, Glotz D, Legendre C, Jouven X, Lefaucheur C. Determinants and Outcomes of Accelerated Arteriosclerosis: Major Impact of Circulating Antibodies. *Circ Res* 2015; **117**: 470-482 [PMID: 26056252 DOI: 10.1161/CIRCRESAHA.117.306340]
134 **Lahmer T**, Hermans R, Schmaderer C, Chang J, Stock K, Lutz J, Heemann U, Baumann M. Mineralocorticoid receptor antagonism and aldosterone synthesis inhibition do not improve glomerulosclerosis and renal interstitial fibrosis in a model of chronic kidney allograft injury. *Kidney Blood Press Res* 2012; **35**: 561-567 [PMID: 22890233 DOI: 10.1159/000339649]
135 **Garg N**, Samaniego MD, Clark D, Djamali A. Defining the phenotype of antibody-mediated rejection in kidney transplantation: Advances in diagnosis of antibody injury. *Transplant Rev (Orlando)* 2017; **31**: 257-267 [PMID: 28882367 DOI: 10.1016/j.trre.2017.08.005]
136 **Selby NM**, McIntyre CW. The vicious cycle of dialysis-induced cardiac injury--are dynamic changes in diastolic function involved? *Am J Kidney Dis* 2013; **62**: 442-444 [PMID: 23972056 DOI: 10.1053/j.ajkd.2013.06.003]
137 **Skinner SC**, Derebail VK, Poulton CJ, Bunch DC, Roy-Chaudhury P, Key NS. Hemodialysis-Related Complement and Contact Pathway Activation and Cardiovascular Risk: A Narrative Review. *Kidney Med* 2021; **3**: 607-618 [PMID: 34401728 DOI: 10.1016/j.xkme.2021.04.006]
138 **Vlahu CA**, Lemkes BA, Struijk DG, Koopman MG, Krediet RT, Vink H. Damage of the endothelial glycocalyx in dialysis patients. *J Am Soc Nephrol* 2012; **23**: 1900-1908 [PMID: 23085635 DOI: 10.1681/ASN.2011121181]
139 **Liakopoulos V**, Roumeliotis S, Gorny X, Dounousi E, Mertens PR. Oxidative Stress in Hemodialysis Patients: A Review of the Literature. *Oxid Med Cell Longev* 2017; **2017**: 3081856 [PMID: 29138677 DOI: 10.1155/2017/3081856]
140 **Chung AW**, Yang HH, Kim JM, Sigrist MK, Brin G, Chum E, Gourlay WA, Levin A. Arterial stiffness and functional properties in chronic kidney disease patients on different dialysis modalities: an exploratory study. *Nephrol Dial Transplant* 2010; **25**: 4031-4041 [PMID: 20466676 DOI: 10.1093/ndt/gfq202]
141 **Lee MJ**, Han SH, Lee JE, Choi HY, Yoon CY, Kim EJ, Han JH, Han JS, Oh HJ, Park JT, Kang SW, Yoo TH. Endothelial dysfunction is associated with major adverse cardiovascular events in peritoneal dialysis patients. *Medicine (Baltimore)* 2014; **93**: e73 [PMID: 25192486 DOI: 10.1097/MD.0000000000000073]
142 **McIntyre CW**. Update on Hemodialysis-Induced Multiorgan Ischemia: Brains and Beyond. *J Am Soc Nephrol* 2024; **35**: 653-664 [PMID: 38273436 DOI: 10.1681/ASN.0000000000000299]
143 **Bellien J**, Fréguin-Bouilland C, Joannidès R, Hanoy M, Rémy-Jouet I, Monteil C, Iacob M, Martin L, Renet S, Vendeville C, Godin M, Thuillez C, Le Roy F. High-efficiency on-line haemodiafiltration improves conduit artery endothelial function compared with high-flux haemodialysis in end-stage renal disease patients. *Nephrol Dial Transplant* 2014; **29**: 414-422 [PMID: 24235073 DOI: 10.1093/ndt/gft448]
144 **Inamdar N**, Tomer S, Kalmath S, Bansal A, Yadav AK, Sharma V, Bahuguna P, Gorsi U, Arora S, Lal A, Kumar V, Rathi M, Kohli HS, Gupta KL, Ramachandran R. Reversal of endothelial dysfunction post-immunosuppressive therapy in adult-onset podocytopathy and primary membranous nephropathy. *Atherosclerosis* 2020; **295**: 38-44 [PMID: 32004823 DOI: 10.1016/j.atherosclerosis.2019.08.013]
145 **Diamond JR**, Karnovsky MJ. Focal and segmental glomerulosclerosis: analogies to atherosclerosis. *Kidney Int* 1988; **33**: 917-924 [PMID: 3292816 DOI: 10.1038/ki.1988.87]
146 **Shoji J**, Mii A, Terasaki M, Shimizu A. Update on Recurrent Focal Segmental Glomerulosclerosis in Kidney Transplantation. *Nephron* 2020; **144** Suppl 1: 65-70 [PMID: 33260184 DOI: 10.1159/000510748]
147 **Corban MT**, Prasad A, Nesbitt L, Loeffler D, Herrmann J, Lerman LO, Lerman A. Local Production of Soluble Urokinase Plasminogen Activator Receptor and Plasminogen Activator Inhibitor-1 in the Coronary Circulation Is Associated With Coronary Endothelial Dysfunction in Humans. *J Am Heart Assoc* 2018; **7**: e009881 [PMID: 30371230 DOI: 10.1161/JAHA.118.009881]
148 **Roca N**, Jatem E, Martín ML, Muñoz M, Molina M, Martínez C, Segarra A. Relationship between soluble urokinase-type plasminogen activator receptor and serum biomarkers of endothelial activation in patients with idiopathic nephrotic syndrome. *Clin Kidney J* 2021; **14**: 543-549 [PMID: 33623677 DOI: 10.1093/ckj/sfz173]
149 **Abuzeineh M**, Aala A, Alasfar S, Alachkar N. Angiotensin II receptor 1 antibodies associate with post-transplant focal segmental glomerulosclerosis and proteinuria. *BMC Nephrol* 2020; **21**: 253 [PMID: 32615995 DOI: 10.1186/s12882-020-01910-w]
150 **Pietrzak-Nowacka M**, Safranow K, Płońska-Gościniak E, Nowacki A, Późniak P, Gutowski P, Ciechanowski K. Cardiovascular Involvement

in Patients with Autosomal Dominant Polycystic Kidney Disease: A Review. *Kidney Blood Press Res* 2024; **49**: 9-19 [PMID: 38096797 DOI: 10.1159/000529119]

151 **Sagar PS**, Rangan GK. Cardiovascular Manifestations and Management in ADPKD. *Kidney Int Rep* 2023; **8**: 1924-1940 [PMID: 37850017 DOI: 10.1016/j.ekir.2023.07.017]

152 **Blasco M**, Guillén-Olmos E, Diaz-Ricart M, Palomo M. Complement Mediated Endothelial Damage in Thrombotic Microangiopathies. *Front Med (Lausanne)* 2022; **9**: 811504 [PMID: 35547236 DOI: 10.3389/fmed.2022.811504]

153 **Cofiell R**, Kukreja A, Bedard K, Yan Y, Mickle AP, Ogawa M, Bedrosian CL, Faas SJ. Eculizumab reduces complement activation, inflammation, endothelial damage, thrombosis, and renal injury markers in aHUS. *Blood* 2015; **125**: 3253-3262 [PMID: 25833956 DOI: 10.1182/blood-2014-09-600411]

154 **Norby GE**, Leivestad T, Mjøen G, Hartmann A, Midtvedt K, Gran JT, Holdaas H. Premature cardiovascular disease in patients with systemic lupus erythematosus influences survival after renal transplantation. *Arthritis Rheum* 2011; **63**: 733-737 [PMID: 21360503 DOI: 10.1002/art.30184]

155 **Mak A**, Chan JKY. Endothelial function and endothelial progenitor cells in systemic lupus erythematosus. *Nat Rev Rheumatol* 2022; **18**: 286-300 [PMID: 35393604 DOI: 10.1038/s41584-022-00770-y]

156 **Zhai Y**, Liu Y, Qi Y, Long X, Gao J, Yao X, Chen Y, Wang X, Lu S, Zhao Z. The soluble VEGF receptor sFlt-1 contributes to endothelial dysfunction in IgA nephropathy. *PLoS One* 2020; **15**: e0234492 [PMID: 32790760 DOI: 10.1371/journal.pone.0234492]

157 **Halbwachs L**, Lesavre P. Endothelium-neutrophil interactions in ANCA-associated diseases. *J Am Soc Nephrol* 2012; **23**: 1449-1461 [PMID: 22942199 DOI: 10.1681/ASN.2012020119]

158 **Kaneyama K**, Kobayashi H, Yamataka A, Lane GJ, Miyano T. Serum soluble vascular cell adhesion molecule-1 (VCAM-1) concentrations in children with reflux nephropathy. *Pediatr Surg Int* 2005; **21**: 39-42 [PMID: 15372288 DOI: 10.1007/s00383-004-1260-1]

159 **Dogra GK**, Watts GF, Herrmann S, Thomas MA, Irish AB. Statin therapy improves brachial artery endothelial function in nephrotic syndrome. *Kidney Int* 2002; **62**: 550-557 [PMID: 12110017 DOI: 10.1046/j.1523-1755.2002.00483.x]

160 **Isakova T**, Nickolas TL, Denburg M, Yarlagadda S, Weiner DE, Gutiérrez OM, Bansal V, Rosas SE, Nigwekar S, Yee J, Kramer H. KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Am J Kidney Dis* 2017; **70**: 737-751 [PMID: 28941764 DOI: 10.1053/j.ajkd.2017.07.019]

161 **Sprague SM**, Martin KJ, Coyne DW. Phosphate Balance and CKD-Mineral Bone Disease. *Kidney Int Rep* 2021; **6**: 2049-2058 [PMID: 34386654 DOI: 10.1016/j.ekir.2021.05.012]

162 **Haarhaus M**, Evenepoel P; European Renal Osteodystrophy (EUROD) workgroup; Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD) working group of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA). Differentiating the causes of adynamic bone in advanced chronic kidney disease informs osteoporosis treatment. *Kidney Int* 2021; **100**: 546-558 [PMID: 34102219 DOI: 10.1016/j.kint.2021.04.043]

163 **Baia LC**, Heilberg IP, Navis G, de Borst MH; NIGRAM investigators. Phosphate and FGF-23 homeostasis after kidney transplantation. *Nat Rev Nephrol* 2015; **11**: 656-666 [PMID: 26416497 DOI: 10.1038/nrneph.2015.153]

164 **Yadav AK**, Tiwana S, Steel M, Ramachandran R, Kaski JC, Jha V, Banerjee D. Vitamin D deficiency, endothelial function and bone biomarkers in post-kidney transplantation patients from North India. *Int Urol Nephrol* 2019; **51**: 181-186 [PMID: 30456544 DOI: 10.1007/s11255-018-2014-7]

165 **Zou D**, Wu W, He Y, Ma S, Gao J. The role of klotho in chronic kidney disease. *BMC Nephrol* 2018; 19: 285 [PMID: 30348110 DOI: 10.1186/s12882-018-1094-z]

166 **Thongprayoon C**, Neyra JA, Hansrivijit P, Medaura J, Leeaphorn N, Davis PW, Kaewput W, Bathini T, Salim SA, Chewcharat A, Aeddula NR, Vallabhajosyula S, Mao MA, Cheungpasitporn W. Serum Klotho in Living Kidney Donors and Kidney Transplant Recipients: A Meta-Analysis. *J Clin Med* 2020; 9 [PMID: 32545510 DOI: 10.3390/jcm9061834]

167 **de Borst MH**, Vervloet MG, ter Wee PM, Navis G. Cross talk between the renin-angiotensin-aldosterone system and vitamin D-FGF-23-klotho in chronic kidney disease. *J Am Soc Nephrol* 2011; **22**: 1603-1609 [PMID: 21852584 DOI: 10.1681/ASN.2010121251]

168 **Theodoridis X**, Chourdakis M, Papaemmanouil A, Chaloulakou S, Georgakou AV, Chatzis G, Triantafyllou A. The Effect of Diet on Vascular Aging: A Narrative Review of the Available Literature. *Life (Basel)* 2024; **14** [PMID: 38398776 DOI: 10.3390/life14020267]

169 **Gomes-Neto AW**, Osté MCJ, Sotomayor CG, van den Berg E, Geleijnse JM, Berger SP, Gans ROB, Bakker SJL, Navis GJ. Mediterranean Style Diet and Kidney Function Loss in Kidney Transplant Recipients. *Clin J Am Soc Nephrol* 2020; **15**: 238-246 [PMID: 31896540 DOI: 10.2215/CJN.06710619]

170 **Li J**, Chong A, Carey S. Dietary interventions on the prevention and management of diabetes in post-kidney transplantation - A systematic review. *Nephrology (Carlton)* 2022; **27**: 269-280 [PMID: 34610191 DOI: 10.1111/nep.13982]

171 **de Vries LV**, Dobrowolski LC, van den Bosch JJ, Riphagen IJ, Krediet CT, Bemelman FJ, Bakker SJ, Navis G. Effects of Dietary Sodium Restriction in Kidney Transplant Recipients Treated With Renin-Angiotensin-Aldosterone System Blockade: A Randomized Clinical Trial. *Am J Kidney Dis* 2016; **67**: 936-944 [PMID: 26803690 DOI: 10.1053/j.ajkd.2015.11.026]

172 **Osté MCJ**, Gomes-Neto AW, Corpeleijn E, Gans ROB, de Borst MH, van den Berg E, Soedamah-Muthu SS, Kromhout D, Navis GJ, Bakker SJL. Dietary Approach to Stop Hypertension (DASH) diet and risk of renal function decline and all-cause mortality in renal transplant recipients. *Am J Transplant* 2018; **18**: 2523-2533 [PMID: 29464830 DOI: 10.1111/ajt.14707]

173 **Cupisti A**, Ghiadoni L, D'Alessandro C, Kardasz I, Morelli E, Panichi V, Locati D, Morandi S, Saba A, Barsotti G, Taddei S, Arnoldi A, Salvetti A. Soy protein diet improves endothelial dysfunction in renal transplant patients. *Nephrol Dial Transplant* 2007; **22**: 229-234 [PMID: 16998212 DOI: 10.1093/ndt/gfl553]

174 **Pihlstrøm HK**, Mjøen G, Mucha S, Franke A, Jardine A, Fellström B, Dahle DO, Holdaas H, Melum E. Genetic markers associated with long-term cardiovascular outcome in kidney transplant recipients. *Am J Transplant* 2019; **19**: 1444-1451 [PMID: 30457209 DOI: 10.1111/ajt.15191]

175 **Shaked A**, Loza BL, Van Loon E, Olthoff KM, Guan W, Jacobson PA, Zhu A, Fishman CE, Gao H, Oetting WS, Israni AK, Testa G, Trotter J, Klintmalm G, Naesens M, Asrani SK, Keating BJ. Donor and recipient polygenic risk scores influence the risk of post-transplant diabetes. *Nat Med* 2022; **28**: 999-1005 [PMID: 35393535 DOI: 10.1038/s41591-022-01758-7]

176 **Uyar M**, Sezer S, Ozdemir FN, Kulah E, Arat Z, Atac FB, Haberal M. Endothelial nitric oxide synthase polymorphism influences renal allograft outcome. *Clin Transplant* 2014; **28**: 223-228 [PMID: 24372826 DOI: 10.1111/ctr.12302]

177 **Nobakht E**, Jagadeesan M, Paul R, Bromberg J, Dadgar S. Precision Medicine in Kidney Transplantation: Just Hype or a Realistic Hope? *Transplant Direct* 2021; **7**: e650 [PMID: 33437865 DOI: 10.1097/TXD.0000000000001102]

178 **Leite AR**, Borges-Canha M, Cardoso R, Neves JS, Castro-Ferreira R, Leite-Moreira A. Novel Biomarkers for Evaluation of Endothelial Dysfunction. *Angiology* 2020; **71**: 397-410 [PMID: 32077315 DOI: 10.1177/0003319720903586]

179 **Gorog DA**, Storey RF, Gurbel PA, Tantry US, Berger JS, Chan MY, Duerschmied D, Smyth SS, Parker WAE, Ajjan RA, Vilahur G, Badimon L, Berg JMT, Cate HT, Peyvandi F, Wang TT, Becker RC. Current and novel biomarkers of thrombotic risk in COVID-19: a Consensus Statement from the International COVID-19 Thrombosis Biomarkers Colloquium. *Nat Rev Cardiol* 2022; **19**: 475-495 [PMID: 35027697 DOI: 10.1038/s41569-021-00665-7]

180 **Evans PC**, Rainger GE, Mason JC, Guzik TJ, Osto E, Stamataki Z, Neil D, Hoefer IE, Fragiadaki M, Waltenberger J, Weber C, Bochaton-Piallat ML, Bäck M. Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. *Cardiovasc Res* 2020; **116**: 2177-2184 [PMID: 32750108 DOI: 10.1093/cvr/cvaa230]

181 **Gyöngyösi M**, Alcaide P, Asselbergs FW, Brundel BJJM, Camici GG, Martins PDC, Ferdinandy P, Fontana M, Girao H, Gnecchi M, Gollmann-Tepeköylü C, Kleinbongard P, Krieg T, Madonna R, Paillard M, Pantazis A, Perrino C, Pesce M, Schiattarella GG, Sluijter JPG, Steffens S, Tschöpe C, Van Linthout S, Davidson SM. Long COVID and the cardiovascular system-elucidating causes and cellular mechanisms in order to develop targeted diagnostic and therapeutic strategies: a joint Scientific Statement of the ESC Working Groups on Cellular Biology of the Heart and Myocardial and Pericardial Diseases. *Cardiovasc Res* 2023; **119**: 336-356 [PMID: 35875883 DOI: 10.1093/cvr/cvac115]

182 **Xu SW**, Ilyas I, Weng JP. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. *Acta Pharmacol Sin* 2023; **44**: 695-709 [PMID: 36253560 DOI: 10.1038/s41401-022-00998-0]

183 **Jaime Garcia D**, Chagnot A, Wardlaw JM, Montagne A. A Scoping Review on Biomarkers of Endothelial Dysfunction in Small Vessel Disease: Molecular Insights from Human Studies. *Int J Mol Sci* 2023; **24** [PMID: 37685924 DOI: 10.3390/ijms241713114]

184 **Chia PY**, Teo A, Yeo TW. Overview of the Assessment of Endothelial Function in Humans. *Front Med (Lausanne)* 2020; **7**: 542567 [PMID: 33117828 DOI: 10.3389/fmed.2020.542567]

185 **Alexander Y**, Osto E, Schmidt-Trucksäss A, Shechter M, Trifunovic D, Duncker DJ, Aboyans V, Bäck M, Badimon L, Cosentino F, De Carlo M, Dorobantu M, Harrison DG, Guzik TJ, Hoefer I, Morris PD, Norata GD, Suades R, Taddei S, Vilahur G, Waltenberger J, Weber C, Wilkinson F, Bochaton-Piallat ML, Evans PC. Endothelial function in cardiovascular medicine: a consensus paper of the European Society of Cardiology Working Groups on Atherosclerosis and Vascular Biology, Aorta and Peripheral Vascular Diseases, Coronary Pathophysiology and Microcirculation, and Thrombosis. *Cardiovasc Res* 2021; **117**: 29-42 [PMID: 32282914 DOI: 10.1093/cvr/cvaa085]

186 **Tamargo IA**, Baek KI, Kim Y, Park C, Jo H. Flow-induced reprogramming of endothelial cells in atherosclerosis. *Nat Rev Cardiol* 2023; **20**: 738-753 [PMID: 37225873 DOI: 10.1038/s41569-023-00883-1]

187 **Zhou HL**, Jiang XZ, Ventikos Y. Role of blood flow in endothelial functionality: a review. *Front Cell Dev Biol* 2023; **11**: 1259280 [PMID: 37905167 DOI: 10.3389/fcell.2023.1259280]

188 **Samuels BA**, Shah SM, Widmer RJ, Kobayashi Y, Miner SES, Taqueti VR, Jeremias A, Albadri A, Blair JA, Kearney KE, Wei J, Park K, Barseghian El-Farra A, Holoshitz N, Janaszek KB, Kesarwani M, Lerman A, Prasad M, Quesada O, Reynolds HR, Savage MP, Smilowitz NR, Sutton NR, Sweeny JM, Toleva O, Henry TD, Moses JW, Fearon WF, Tremmel JA; Microvascular Network (MVN). Comprehensive Management of ANOCA, Part 1-Definition, Patient Population, and Diagnosis: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2023; **82**: 1245-1263 [PMID: 37704315 DOI: 10.1016/j.jacc.2023.06.043]

189 **Rocco E**, Grimaldi MC, Maino A, Cappannoli L, Pedicino D, Liuzzo G, Biasucci LM. Advances and Challenges in Biomarkers Use for Coronary Microvascular Dysfunction: From Bench to Clinical Practice. *J Clin Med* 2022; **11** [PMID: 35407662 DOI: 10.3390/jcm11072055]

190 **Mathew RC**, Bourque JM, Salerno M, Kramer CM. Cardiovascular Imaging Techniques to Assess Microvascular Dysfunction. *JACC Cardiovasc Imaging* 2020; **13**: 1577-1590 [PMID: 31607665 DOI: 10.1016/j.jcmg.2019.09.006]

191 **Slomka P**, Berman DS, Alexanderson E, Germano G. The role of PET quantification in cardiovascular imaging. *Clin Transl Imaging* 2014; **2**: 343-358 [PMID: 26247005 DOI: 10.1007/s40336-014-0070-2]

192 **Hanssen H**, Streese L, Vilser W. Retinal vessel diameters and function in cardiovascular risk and disease. *Prog Retin Eye Res* 2022; **91**: 101095 [PMID: 35760749 DOI: 10.1016/j.preteyeres.2022.101095]

193 **Anderson TJ**, Uehata A, Gerhard MD, Meredith IT, Knab S, Delagrange D, Lieberman EH, Ganz P, Creager MA, Yeung AC. Close relation of endothelial function in the human coronary and peripheral circulations. *J Am Coll Cardiol* 1995; **26**: 1235-1241 [PMID: 7594037 DOI: 10.1016/0735-1097(95)00327-4]

194 **Bonetti PO**, Pumper GM, Higano ST, Holmes DR Jr, Kuvin JT, Lerman A. Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. *J Am Coll Cardiol* 2004; **44**: 2137-2141 [PMID: 15582310 DOI: 10.1016/j.jacc.2004.08.062]

195 **Rubinshtein R**, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, Pumper GM, Lerman LO, Lerman A. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur Heart J* 2010; **31**: 1142-1148 [PMID: 20181680 DOI: 10.1093/eurheartj/ehq010]

196 **Wenceslau CF**, McCarthy CG, Earley S, England SK, Filosa JA, Goulopoulou S, Gutterman DD, Isakson BE, Kanagy NL, Martinez-Lemus LA, Sonkusare SK, Thakore P, Trask AJ, Watts SW, Webb RC. Guidelines for the measurement of vascular function and structure in isolated arteries and veins. *Am J Physiol Heart Circ Physiol* 2021; **321**: H77-H111 [PMID: 33989082 DOI: 10.1152/ajpheart.01021.2020]

197 **Poredos P**, Jezovnik MK. Testing endothelial function and its clinical relevance. *J Atheroscler Thromb* 2013; **20**: 1-8 [PMID: 22972428 DOI: 10.5551/jat.14340]

198 **Maruhashi T**, Kajikawa M, Kishimoto S, Hashimoto H, Takaeko Y, Yamaji T, Harada T, Han Y, Aibara Y, Mohamad Yusoff F, Hidaka T, Kihara Y, Chayama K, Nakashima A, Goto C, Tomiyama H, Takase B, Kohro T, Suzuki T, Ishizu T, Ueda S, Yamazaki T, Furumoto T, Kario K, Inoue T, Koba S, Watanabe K, Takemoto Y, Hano T, Sata M, Ishibashi Y, Node K, Maemura K, Ohya Y, Furukawa T, Ito H, Ikeda H, Yamashina A, Higashi Y. Diagnostic Criteria of Flow-Mediated Vasodilation for Normal Endothelial Function and Nitroglycerin-Induced Vasodilation for Normal Vascular Smooth Muscle Function of the Brachial Artery. *J Am Heart Assoc* 2020; **9**: e013915 [PMID: 31910779 DOI: 10.1161/JAHA.119.013915]

199 **Onkelinx S**, Cornelissen V, Goetschalckx K, Thomaes T, Verhamme P, Vanhees L. Reproducibility of different methods to measure the endothelial function. *Vasc Med* 2012; **17**: 79-84 [PMID: 22402933 DOI: 10.1177/1358863X12436708]

200 **Matsuzawa Y**, Kwon TG, Lennon RJ, Lerman LO, Lerman A. Prognostic Value of Flow-Mediated Vasodilation in Brachial Artery and Fingertip Artery for Cardiovascular Events: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2015; **4** [PMID: 26567372 DOI: 10.1161/JAHA.115.002270]

201 **Inaba Y**, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. *Int J Cardiovasc Imaging* 2010; **26**: 631-640 [PMID: 20339920 DOI: 10.1007/s10554-010-9616-1]

202 **Faita F**, Masi S, Loukogeorgakis S, Gemignani V, Okorie M, Bianchini E, Charakida M, Demi M, Ghiadoni L, Deanfield JE. Comparison of two automatic methods for the assessment of brachial artery flow-mediated dilation. *J Hypertens* 2011; **29**: 85-90 [PMID: 20842049 DOI: 10.1097/HJH.0b013e32833fc938]

203 **Heiss C**, Rodriguez-Mateos A, Bapir M, Skene SS, Sies H, Kelm M. Flow-mediated dilation reference values for evaluation of endothelial function and cardiovascular health. *Cardiovasc Res* 2023; **119**: 283-293 [PMID: 35709326 DOI: 10.1093/cvr/cvac095]

204 **Akamatsu D**, Sato A, Goto H, Watanabe T, Hashimoto M, Shimizu T, Sugawara H, Sato H, Nakano Y, Miura T, Zukeran T, Serizawa F, Hamada Y, Tsuchida K, Tsuji I, Satomi S. Nitroglycerin-mediated vasodilatation of the brachial artery may predict long-term cardiovascular events irrespective of the presence of atherosclerotic disease. *J Atheroscler Thromb* 2010; **17**: 1266-1274 [PMID: 20972354 DOI: 10.5551/jat.5181]

205 **Kajikawa M**, Maruhashi T, Hida E, Iwamoto Y, Matsumoto T, Iwamoto A, Oda N, Kishimoto S, Matsui S, Hidaka T, Kihara Y, Chayama K, Goto C, Aibara Y, Nakashima A, Noma K, Higashi Y. Combination of Flow-Mediated Vasodilation and Nitroglycerine-Induced Vasodilation Is More Effective for Prediction of Cardiovascular Events. *Hypertension* 2016; **67**: 1045-1052 [PMID: 26975705 DOI: 10.1161/HYPERTENSIONAHA.115.06839]

206 **Theodorakopoulou MP**, Schoina M, Sarafidis P. Assessment of Endothelial and Microvascular Function in CKD: Older and Newer Techniques, Associated Risk Factors, and Relations with Outcomes. *Am J Nephrol* 2020; **51**: 931-949 [PMID: 33311014 DOI: 10.1159/000512263]

207 **Nohria A**, Gerhard-Herman M, Creager MA, Hurley S, Mitra D, Ganz P. Role of nitric oxide in the regulation of digital pulse volume amplitude in humans. *J Appl Physiol (1985)* 2006; **101**: 545-548 [PMID: 16614356 DOI: 10.1152/japplphysiol.01285.2005]

208 **Xu Y**, Arora RC, Hiebert BM, Lerner B, Szwajcer A, McDonald K, Rigatto C, Komenda P, Sood MM, Tangri N. Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging* 2014; **15**: 736-746 [PMID: 24399339 DOI: 10.1093/ehjci/jet256]

209 **Lekakis J**, Abraham P, Balbarini A, Blann A, Boulanger CM, Cockcroft J, Cosentino F, Deanfield J, Gallino A, Ikonomidis I, Kremastinos D, Landmesser U, Protogerou A, Stefanadis C, Tousoulis D, Vassalli G, Vink H, Werner N, Wilkinson I, Vlachopoulos C. Methods for evaluating endothelial function: a position statement from the European Society of Cardiology Working Group on Peripheral Circulation. *Eur J Cardiovasc Prev Rehabil* 2011; **18**: 775-789 [PMID: 21450600 DOI: 10.1177/1741826711398179]

210 **Schnall RP**, Sheffy JK, Penzel T. Peripheral arterial tonometry-PAT technology. *Sleep Med Rev* 2022; **61**: 101566 [PMID: 34920273 DOI: 10.1016/j.smrv.2021.101566]

211 **Ikram MK**, Witteman JC, Vingerling JR, Breteler MM, Hofman A, de Jong PT. Retinal vessel diameters and risk of hypertension: the Rotterdam Study. *Hypertension* 2006; **47**: 189-194 [PMID: 16380526 DOI: 10.1161/01.HYP.0000199104.61945.33]

212 **Heitmar R**, Lip GYH, Ryder RE, Blann AD. Retinal vessel diameters and reactivity in diabetes mellitus and/or cardiovascular disease. *Cardiovasc Diabetol* 2017; **16**: 56 [PMID: 28446234 DOI: 10.1186/s12933-017-0534-6]

213 **Caglar K**, Yilmaz MI, Saglam M, Cakir E, Kilic S, Eyileten T, Sonmez A, Oguz Y, Oner K, Ors F, Vural A, Yenicesu M. Endothelial dysfunction and fetuin A levels before and after kidney transplantation. *Transplantation* 2007; **83**: 392-397 [PMID: 17318070 DOI: 10.1097/01.tp.0000251647.72673.c7]

214 **Yilmaz MI**, Saglam M, Caglar K, Cakir E, Ozgurtas T, Sonmez A, Eyileten T, Yenicesu M, Acikel C, Oguz Y, Ozcan O, Bozlar U, Erbil K, Aslan I, Vural A. Endothelial functions improve with decrease in asymmetric dimethylarginine (ADMA) levels after renal transplantation. *Transplantation* 2005; **80**: 1660-1666 [PMID: 16378057 DOI: 10.1097/01.tp.0000183750.22675.be]

215 **Recio-Mayoral A**, Banerjee D, Streather C, Kaski JC. Endothelial dysfunction, inflammation and atherosclerosis in chronic kidney disease--a cross-sectional study of predialysis, dialysis and kidney-transplantation patients. *Atherosclerosis* 2011; **216**: 446-451 [PMID: 21414625 DOI: 10.1016/j.atherosclerosis.2011.02.017]

216 **Junarta J**, Hojs N, Ramphul R, Lowe-Jones R, Kaski JC, Banerjee D. Progression of endothelial dysfunction, atherosclerosis, and arterial stiffness in stable kidney transplant patients: a pilot study. *BMC Cardiovasc Disord* 2020; **20**: 6 [PMID: 31914943 DOI: 10.1186/s12872-019-01309-y]

217 **Langberg NE**, Jenssen TG, Haugen AJ, Mjøen G, Birkeland KI, Åsberg A, Hartmann A, Dahle DO. Endothelial Dysfunction and 6-Year Risk of Mortality in Kidney Transplant Recipients. *Transplant Direct* 2022; **8**: e1262 [PMID: 34912949 DOI: 10.1097/TXD.0000000000001262]

218 **Päivärinta J**, Metsärinne K, Löyttyniemi E, Teuho J, Tolvanen T, Knuuti J, Koivuviita N. Myocardial perfusion reserve of kidney transplant patients is well preserved. *EJNMMI Res* 2020; **10**: 9 [PMID: 32040792 DOI: 10.1186/s13550-020-0606-6]

219 **Zbroch E**, Małyszko J, Małyszko J, Koc-Żórawska E, Myśliwiec M. Renalase, kidney function, and markers of endothelial dysfunction in renal transplant recipients. *Pol Arch Med Wewn* 2012; **122**: 40-44 [PMID: 22237745 DOI: 10.20452/pamw.1132]

220 **Frenay AR**, van den Berg E, de Borst MH, Beckmann B, Tsikas D, Feelisch M, Navis G, Bakker SJ, van Goor H. Plasma ADMA associates with all-cause mortality in renal transplant recipients. *Amino Acids* 2015; **47**: 1941-1949 [PMID: 26077715 DOI: 10.1007/s00726-015-2023-0]

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Solonas Symeou, Eleni Avramidou, Vassilios Papalois, Georgios Tsoulfas

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Abstract

Although national transplant organizations share common visions and goals, the creation of a unified global organization remains impractical. Differences in ethnicity, culture, religion, and education shape local practices and infrastructure, making the establishment of a single global entity unfeasible. Even with these social disparities aside, logistical factors such as time and distance between organ procurement and transplantation sites pose significant challenges. While technological advancements have extended organ preservation times, they have yet to support the demands of transcontinental transplantations effectively. This review presents a comparative analysis of the structures, operational frameworks, policies, and legislation governing various transplant organizations around the world. Key differences pertain to the administration of these organizations, trends in organ donation, and organ allocation policies, which reflect the financial, cultural, and religious diversity across different regions. While a global transplant organization may be out of reach, agreeing on best practices for the benefit of patients is essential.

Key Words: Organ transplantation; National transplant organizations; Organ donation; Global transplantation; Transplant systems

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Core Tip: Organ transplantation activities are managed by specific organizations in various countries, each with unique structures, protocols, and practices. These include differences in listing criteria, prioritization on waiting lists, donor preferences (living *vs* deceased), and organ distribution frameworks. This review explores these variations, particularly focusing on kidney and liver transplants, and highlights the lessons learned from this diverse organizational landscape that can promote future improvements.

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INTRODUCTION

The concept of organ transplantation has long captivated human imagination. Early myths, artwork, and accounts of deities or healers performing transplants are found in ancient civilizations known for their contributions to modern medicine, such as the Greeks, Chinese, Indians, and Egyptians[1,2]. Given this history, it is unsurprising that technological advancements and globalization have played a key role in the rapid progress of organ transplantation in modern times[3,4].

Since the first successful kidney transplant in 1954, using an identical twin as the donor, Murray and his team turned a mythological aspiration into reality, forever changing the landscape of modern medicine[5,6]. Organ transplantation has since been established as a vital treatment that can significantly prolong survival and improve the quality of life for patients with end-stage organ failure. However, successful transplantation requires strict adherence to well-defined conditions, supported by structured programs providing administrative and legislative guidance[7,8].

Organ failure is a life-threatening condition characterized by the progressive or acute loss of an organ's function. This can lead to organ insufficiency, poor prognosis, and the need for life-saving interventions such as dialysis[9,10]. For many vital organs, transplantation-whether from a deceased or living donor-is the only viable solution to restore function and prevent premature death[11]. In 2022 alone, 157553 organ transplants were performed worldwide[12,13].

Table 1 lists the countries active in the field of organ transplantation. Despite the widespread use of transplantation procedures, significant differences remain in the number of transplants performed and donor types across regions. The Americas lead with 62153 organ transplants, followed by Europe and the Western Pacific with 40337 and 29014 transplants, respectively[12]. Africa lags significantly, with only 286 transplants recorded in 2022, highlighting its considerable challenges and underdevelopment in this field[12]. Of the organs transplanted globally, 108818 came from deceased donors, which is the preferred source in most countries[12,13]. Notably, Africa reported no deceased organ donations in 2022, except in South Africa, the only country in the region with policies allowing deceased donor transplants. Table 2 summarizes this data by continent, as reported by the Global Observatory on Donation and Transplantation (GODT).

These disparities are closely linked to variations in the availability of well-structured transplant programs, education on organ donation, religious beliefs, funding, and public trust in healthcare systems. Robust transplant programs are well established in North America and Europe, accounting for their higher transplant numbers. Meanwhile, Asia and especially Africa, are hindered by limited access to transplant services, insufficient funding, and scepticism toward healthcare[14,15].

Modern transplant programs rely on government or local support and involve regulatory frameworks, infrastructure, operational processes for organ allocation and distribution, research, and training opportunities[16]. While most National Transplant Organizations (NTOs) share common goals, differences in their operational frameworks stem from social, religious, and economic factors unique to each country, making the formation of a "Global Transplant Organization" infeasible.

This review highlights these differences and the lessons they offer. Although the focus is on specific countries (United States, United Kingdom, Spain, Croatia, Eurotransplant, Scandiatransplant, India, Iran, and China), the review also includes insights from other nations. While the creation of a global transplant organization may be unlikely, the continuous pursuit of growth and improvement will enable NTOs to maintain shared visions and advance future practices.

Relevant academic literature was sourced from PubMed/MEDLINE, Scopus, and Embase databases using the following keywords: "Transplant Programs", "Global Transplantation", "Allocation Policies", "Structure of Transplant Organizations", and "Organ Donation Practices". Policy documents, white papers, government reports, and data on transplant organizations and healthcare expenditures were retrieved from Google, National Transplant Organization (NTO) websites, government portals, Eurostat, the GODT, and the International Registry in Organ Donation and Transplantation.

Initial screening excluded papers with irrelevant titles, non-English language documents, and case reports. Authors then reviewed the abstracts and full texts to determine eligibility. Ultimately, only studies focused on national transplant programs, NTOs, organ allocation and donation policies, and national and international legal frameworks for transplantation were included.

Table 1 Countries performing organ transplants by continent

Region	Country	Ref.
North and Central America	United States, Canada, Mexico, Guatemala, Dominican Republic, Cuba, Honduras, Nicaragua, El Salvador, Costa Rica, Panama, Jamaica, Trinidad and Tobago, Barbados	[12, 13]
South America	Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Paraguay, Peru, and Uruguay	
Europe	The 27 member states of the European Union, United Kingdom, Ukraine, Belarus, Switzerland, Bosnia and Herzegovina, North Macedonia, Moldova, Albania, Norway, Iceland, and Turkey	
Asia	Armenia, Azerbaijan, Afghanistan, Bangladesh, China, Georgia, India, Indonesia, Iran, Iraq, Israel, Japan, Jordan, Kazakhstan, Kuwait, Lebanon, Malaysia, Mongolia, Oman, Pakistan, Philippines, Qatar, Saudi Arabia, Singapore, South Korea, Syria, Sri Lanka, Taiwan, Thailand, United Arab Emirates, and Vietnam	
Oceania	Australia and New Zealand	
Africa	South Africa, Sudan, Ivory Coast, Ghana, Kenya, Egypt, Ethiopia, Nigeria, Namibia, Tanzania, and Mauritius	

Table 2 Annual (2022) overview of transplantation activity by region

Region	Deceased donors	Living donors	Total number of organ transplants	Ref.
Americas	20946	10527	62180	[12]
Europe	11649	9816	40337	
Western Pacific	6702	8535	29014	
South-East Asia	1244	13824	17214	
Eastern Mediterranean	1251	5674	8490	
Africa	-	286	286	

NTOS: STRUCTURAL ELEMENTS AND PRINCIPLES

Organizational framework

Organ donation and transplantation are sensitive topics that require detailed organization, management, and oversight for success. Factors such as an aging population, increased demand for organs, controversies around the allocation process, and the need for public trust necessitated the formation of formal NTOs[17,18].

In the United States, these concerns were recognized early by Congress, leading to the enactment of the National Organ Transplant Act (NOTA) in 1984, which laid the foundation for modern transplantation[19,20]. NOTA mandated the creation of the Organ Procurement and Transplantation Network (OPTN) and the Scientific Registry of Transplant Recipients (SRTR). It also stipulated that non-profit private organizations must operate these networks under federal contracts with the Health Resources and Services Administration (HRSA), a branch of the United States Department of Health and Human Services[20,21]. The requirement for a private organization to manage OPTN and SRTR was based on the understanding that medical experts are better suited to legislate on these matters than politicians[21-23]. Alongside NOTA, the HRSA's "Final Rule" clarified the structure and framework of the OPTN, emphasizing the need for equity and transparency in organ distribution[23,24]. The United Network for Organ Sharing (UNOS) was appointed as the contractor for the OPTN and is responsible for maintaining the waiting list, reviewing policies and laws related to transplantation, and managing 56 procurement teams and over 250 transplant centers[25].

In the United Kingdom, the National Health Service Blood and Transplant (NHSBT) oversees all deceased organ donations and transplantations[26]. Serving approximately 66.6 million people, the NHSBT supervises 12 regional organ donation teams and works with eight advisory groups that facilitate dialogue between clinicians, scientists, patients, and NHSBT representatives[27]. For living donation (LD), the Human Tissue Authority ensures that legal and ethical standards are met to protect the interests of both donors and recipients[28,29]. The United Kingdom's significant success in organ transplantation can be attributed to the implementation of the 2008 Organ Donation Taskforce recommendations, which called for structural reforms, new policies on donation and allocation, and clearer leadership roles to support transplant centers[30]. This overhaul led to a near doubling of deceased donation (DD), from 13 per million people (PMP) to 24.2 PMP over a decade[31].

Each NTO operates within the framework of its respective healthcare system, which varies by country. For example, Croatia, with a population of only 3.86 million, has a unique transplant program overseen by the Ministry of Health and led by a National Transplant Coordinator[32]. This streamlined system has made Croatia a leader in transplantation, boasting the highest rate of DD after brain death (DBD) in Europe, at 40.24 PMP in 2018[33].

Spain is another world leader in organ donation, with 47 donors PMP (2022)[34,35]. The success of Spain's NTO, Organización Nacional de Trasplantes (ONT), is attributed to its three-tiered structure that operates at national, regional, and local levels[36]. ONT works closely with regional offices in each of Spain's 17 autonomous regions to create policies,

review guidelines, and set strategic plans[37,38]. Spain's world-leading DD rate of 46.03 PMP and its total transplantation rate of 115.31 PMP, second only to the United States's 130.65 PMP, highlight the efficiency of this system[12,13].

NTOs from smaller countries often collaborate with others to fill gaps in donation capacity. These partnerships include bilateral agreements and broader alliances like Eurotransplant and Scandiatransplant[39-41]. Eurotransplant serves eight countries-Austria, Belgium, Croatia, Germany, Hungary, the Netherlands, Luxembourg, and Slovenia-covering 136 million people[40]. Similarly, Scandiatransplant serves six countries, including Denmark, Finland, Iceland, Norway, Sweden, and Estonia, covering 28.9 million people[41]. Table 3 exhibits data on donation and transplantation for both Eurotransplant and Scandiatransplant. In 2023, 2079 organ donors were utilized within the Eurotransplant, of which all were deceased donors, leading to a total of 6771 and 44 transplanted organs within the borders of Eurotransplant and non-member European countries, respectively. Scandiatransplant, on the other hand, recorded 690 organ donors, of which 12 were living donors, and 2316 transplanted organs, of which 2305 were among member states.

Significant progress has also been made in Asia[42,43]. For instance, India's National Organ and Tissue Transplant Organization oversees organ donation activities in collaboration with regional and state programs[44]. However, India faces challenges such as illegal organ trafficking and a shortage of donors[45,46]. China, after years of relying on organs from deceased prisoners, has developed a robust transplantation system supervised by the National Organ Donation and Transplantation Committee[47,48]. Despite these improvements, cultural and religious beliefs continue to limit organ donation in many Asian countries[49].

Funding and expenditure

Funding and healthcare expenditure are critical factors affecting the progress of organ transplantation, both in terms of quantity and quality[50,51]. Higher hospital budgets, supported by government funding, are linked to increased numbers of both living and deceased donors[52-54]. Financial compensation and coverage are particularly important for living donors, as the costs associated with donation, such as pre-surgical evaluations, transportation, loss of income, and long-term health risks, can be prohibitively high[54]. In some cases, these expenses can reach up to $49192, discouraging potential donors[54].

The correlation between healthcare expenditure and transplantation rates is evident, with Western countries like the United States, the United Kingdom, and France, which spend 17.30%, 11.30%, and 12.30% of their gross domestic product on healthcare, respectively, reporting higher donor and transplantation rates. However, countries like Spain, Portugal, and Croatia demonstrate that financial constraints do not necessarily inhibit progress. Good governance and effective planning can increase public trust in healthcare and improve donation and transplantation rates[55-57].

For example, Japan, which spends more on healthcare than other Asian countries, still lags behind South Korea in transplantation rates despite higher overall healthcare expenditure. This suggests that other factors, such as cultural and religious beliefs, play a significant role in transplantation activities[58].

Supplementary Table 1 presents data regarding trends in organ donation, and transplantation and healthcare expenditures in 2022 for various countries worldwide, constituting a representative sample of the current transplantation landscape.

Lessons

A robust operational and legislative framework is essential for the sustainability and success of a national transplant program. Countries seeking to reform their transplant systems should look to Spain's ONT as a model. Its global success-demonstrated by high transplantation and DD rates, alongside favorable public trust and attitudes towards the system, which have remained consistently above the European average for over three decades-offers many valuable lessons.

One of the key components of Spain's success is its multilayered structure. Other countries that have adopted similar frameworks have also seen continuous improvements. A central authority, supervised by the government and responsible for overall management and data analysis, along with clearly defined strategic plans and goals, plays a pivotal role in establishing a solid organization capable of meeting a country's demands and expectations. This central authority must also work to build public trust by adopting transparent legislation, implementing sound financial policies, and collaborating with the media. Localized committees, representing smaller administrative offices in each region, serve as the link between the government and local transplant centers, providing essential coordination. At the local level, transplant centers and hospitals are responsible for organ procurement, transplantation procedures, and conducting audits and quality assessments to identify and address obstacles and challenges.

However, NTOs must adapt to the unique characteristics of the populations that they serve, promoting research and education on organ donation and transplantation that is tailored to local needs. While there is a wide gap in healthcare expenditure across different countries, Spain has shown that financial constraints are not an insurmountable obstacle. In contrast, Japan and South Korea illustrate that higher spending does not necessarily correlate with higher donation and transplantation rates.

Though the field of medicine may occasionally rely on extraordinary occurrences, establishing a strong transplant organization should be based on long-term planning and governmental commitment, rather than chance. Despite the differences in structural frameworks and funding, countries aspiring to improve in this area should not be deterred by the inability to create a single global transplant organization. Instead, they should draw inspiration from successful programs that have achieved notable results.

Table 3 Annual (2023) overview of Eurotransplant and Scandiatransplant

	Year	Number of member countries	Organ donors	Deceased donors	Living donors	Total Tx	Tx within the alliance	Organs exchanged	Ref.
Eurotransplant	2023	8	2079	2079	-	6815	6771	1471 within Eurotransplant and 44 to non-member, European countries	[40]
Scandiatransplant	2023	6	690	678	12	2316	2305	546 within Scandiatransplant and 11 to non-member, European countries	[41]

Tx: Transplantations.

RECIPIENTS AND ALLOCATION

Liver

Liver transplantation (LT) is one of the most significant medical advances of the 20th century, recognized as the definitive treatment for patients with end-stage liver disease (ESLD)[59]. Today, LT is the second most frequently performed solid organ transplantation, with a global rate of 6.25 PMP in 2022. This aligns with the high prevalence and mortality of ESLD, which accounts for 4% of global deaths[60].

Indications

Historically, the primary indications for LT were cirrhosis and hepatocellular carcinoma (HCC), often resulting from chronic viral hepatitis [hepatitis B virus (HBV) and hepatitis C virus (HCV)], followed by alcoholic liver disease (ALD). However, recent trends show a shift in the leading causes of LT[60-62]. With the advent of vaccines and direct-acting antivirals against HCV, ALD and non-alcoholic fatty liver disease have emerged as the top causes of cirrhosis-related LT, accounting for 60% and 32.4% of cases globally, respectively[63-66]. Nonetheless, HBV and HCV remain major contributors to cirrhosis and HCC in various regions, particularly in countries like China (87 million affected), Nigeria (20 million), and India (40 million)[60-64].

Prioritization and distribution

Medical and surgical advancements, including immunosuppressive drugs, minimally invasive procedures, and genetically modified organs, have expanded the range of conditions treatable by LT[67,68]. Despite over 27000 procedures performed globally each year, with 1-year survival rates reaching 84% and 10-year survival at 61%, the demand for liver transplants still far exceeds supply[66,69]. Consequently, the allocation of this scarce resource remains a significant challenge and subject of debate for NTOs.

Prior to 1997, liver graft allocation in the United States was determined based solely on hospitalization status and waiting time, a system vulnerable to manipulation. In response, the UNOS revised the policy, introducing a four-tier status system based on patient severity. Status 1 patients (those with acute liver failure) were given priority, followed by statuses 2A, 2B, and C. The Child-Turcott-Pugh (CTP) score, which evaluates factors such as hepatic encephalopathy, ascites, bilirubin levels, and prothrombin time, was employed to classify patients in the lower statuses[70,71].

The model for ESLD (MESLD) score, designed initially to predict survival in patients undergoing transjugular intrahepatic portosystemic shunt, has since proven to be a more accurate predictor of 3-month mortality in ESLD patients [72]. The MESLD score, based on international normalized ratio, serum bilirubin, and serum creatinine, objectively ranges from 6 to 40, prioritizing the sickest patients[73,74]. In 2002, UNOS adopted a MESLD-based prioritization system, a model that many countries have since followed[73]. Adjustments, such as the inclusion of sodium levels and exception points for HCC, have been made over time to further refine the system[75].

Other countries have developed their own allocation models. The United Kingdom employs the Total Benefit Score, which considers recipient and donor criteria, while France uses the Liver Score, focusing on indication for transplantation, waiting time, and MESLD score[76,77]. In Scandinavia, where transplantation volumes are lower, waiting time remains the primary criterion[78,79].

In Asia, transplant allocation models vary widely. Iran, for instance, lacks a national transplant registry, with local hospitals managing waiting lists and prioritization[79]. In contrast, Japan and China have implemented systems based on MESLD, CTP, and waiting time[77].

Kidneys

In 2022, 102149 kidney transplants were performed globally, making kidneys the most frequently transplanted organ, with donations from both deceased and living donors[12,13]. An estimated 4 million people worldwide undergo renal replacement therapy, with hemodialysis being the dominant treatment method, accounting for 69% of cases[80-82]. Although hemodialysis sustains life for patients with acute kidney injury and chronic end-stage kidney disease, kidney transplantation (KT) offers superior outcomes, including improved quality of life, reduced mortality, and better cost-effectiveness[83-87].

Indications

Kidney disease is a global health concern, affecting approximately 850 million people, which accounts for more than 10% of the global population[88,89]. Recent reports indicate that the highest prevalence is in Asia and the United States, with rates ranging from 7.0% to 34.3% in Asia and 14.9% in the United States, followed by Eastern Europe at 12.8%[90,91].

Current kidney disease: Improving Global Outcomes guidelines recommend that patients with a glomerular filtration rate (GFR) of less than 15 mL/min per 1.73 m² (G5) should be considered eligible for KT. Preemptive transplantation (PEKT) should also be considered for adults with a GFR of 15–20 mL/min per 1.73 m² or a risk of requiring kidney replacement therapy greater than 40% within two years. Studies show that PEKT leads to better patient outcomes, including lower mortality and morbidity, and improved graft survival compared to non-PEKT[92-94]. The leading causes of end-stage kidney disease are diabetes, hypertension, and glomerulonephritis[90].

Prioritization and distribution

The critical shortage of available kidneys necessitates an effective allocation policy to ensure fair access to transplantation and improved post-surgical outcomes. Outside Asia, most kidney transplants come from deceased donors, and therefore, allocation policies must ensure equal opportunities for recipients while maintaining transparency and cost-effectiveness [12].

In the United States, it took over two decades to reform the Kidney Allocation System (KAS)[95]. Previously, waiting time was the primary criterion, with less emphasis on factors such as immunization levels, human leukocyte antigen (HLA) match, and blood type[96]. This led to significant disparities, particularly for ethnic minorities who may not have been promptly listed[97]. The lack of assessment for graft survival also contributed to mismatched transplants, where less durable kidneys were allocated to patients with longer life expectancies, resulting in poor post-transplant outcomes[98]. To address these issues, the KAS was introduced in 2014.

KAS incorporates biological factors into the matching criteria and better accounts for waiting time[96]. It uses the Kidney Donor Profile Index, which is based on ten donor characteristics, including biological, demographic, and biochemical parameters, to estimate the longevity of the graft[96]. Similarly, the estimated post-transplant survival score prioritizes patients with the highest likelihood of long-term survival[99,100]. In 2021, KAS was further updated, replacing donor service area boundaries with a 250-nautical-mile radius to create a more equitable distribution system[101].

In the United Kingdom, a tier-based scheme introduced in 2006 aimed to increase fairness for ethnic minorities and highly sensitized patients by grouping recipients into five categories based on age and HLA match[102]. However, challenges persisted, including longer wait times for sensitized patients and a mismatch between graft durability and recipient longevity[103]. A two-tier system was introduced in 2019, categorizing hard-to-match patients or those waiting more than seven years into "Tier A", and incorporating a longevity-matching element[104].

In France, the Unified Allocation Score system adjusts matching criteria based on recipient age, aiming for minimal donor-recipient age differences and optimal HLA matches for younger patients[105]. Spain employs virtual cross-matching to increase the chances of highly sensitized patients receiving a graft. Eurotransplant considers urgency and expected outcomes during the allocation process, while ensuring a balance in organ exchanges among member states[40,106]. In Scandiatransplant, patients with rare HLA types and highly sensitized individuals (panel reactive activity > 80%) are prioritized to reduce waiting time and improve graft survival[41].

Asia, despite its technological advancements, faces significant challenges in KT. Mistrust in public healthcare, cultural and religious concerns, and a lack of education about the benefits of transplantation contribute to low rates of deceased kidney donation. For example, China has a donation rate of 10.44 PMP, Japan 14.53 PMP, and South Korea 39.96 PMP, compared to Spain's 77.68 PMP and the United States' 82.78 PMP[12,42,107].

Different countries in Asia adopt varying allocation systems based on their needs. India prioritizes former living donors and relatives of deceased donors in its scoring system, while Japan, with a heavy reliance on living donors, often resorts to ABO-incompatible transplantations to overcome its limited donor pool[108,109]. Iran's compensated living donor program remains a controversial topic, as it involves financial incentives for organ donors, raising ethical concerns about whether such practices represent altruism or organ trafficking[110-112].

Lessons

The establishment of international organ exchange organizations, such as Eurotransplant and Scandiatransplant, has proven beneficial, increasing donor pools and improving transplant outcomes. These alliances foster international collaboration and strengthen global strategies in organ transplantation. While differences in allocation policies and cultural attitudes pose challenges to creating a single global transplant system, countries can still learn from successful programs around the world.

A unified global approach to preventing organ failure could reduce the demand for transplants. NTOs and international committees should prioritize reducing alcohol consumption, promoting healthy diets, and educating the public about diseases such as diabetes and hypertension, which are major contributors to organ failure. Prevention campaigns aimed at addressing these risk factors can help reduce the overall demand for transplants.

Additionally, specialized teams could be created to identify patients eligible for preemptive KT, which would improve patient quality of life and reduce healthcare costs. Countries struggling to reform their transplant programs should be provided with financial and technical support through international collaborations.

ORGAN DONATION AND DONORS

Legislation is critical in ensuring ethical practices in organ transplantation, fair allocation of organs, and the safety of both donors and recipients. Key regulations include guidelines on donation types (living or deceased), criteria for determining brain or circulatory death (DCD), and systems for organ donation (opt-in *vs* opt-out). A robust legal framework helps build public trust, encourages donation, and improves patient outcomes[113].

Organ donation occurs in two primary forms: LD and DD[114]. LD involves a healthy person donating an organ (*e.g.*, a kidney or part of the liver) to a recipient. Donations can be directed to a specific individual or non-directed, where the organ is offered to an unknown recipient. In most countries, LD is viewed as a purely altruistic act, and the commercialization of organs is strictly prohibited by law and international consensus[115]. However, in Iran, the government supports compensated LD, which has led to significant controversy[111,116]. While this program has reduced waiting times for kidney transplants, critics argue that it contradicts the principles outlined in the Declaration of Istanbul, which condemns organ trafficking[115,116].

DD occurs after an individual is declared dead, either through DBD or DCD [117]. While DBD remains the primary source of organs for transplantation, advances in organ preservation have increased the use of DCD donors[118]. Cultural, religious, and educational factors significantly influence donation rates across different countries. For instance, some religious groups, such as Buddhists, Confucianists, and certain Jewish and Islamic communities, hold beliefs that discourage organ donation[119-122]. These views contribute to lower deceased donor rates in countries like China, Japan, India, and Pakistan[123-125].

In contrast, Western countries, where DD is more common, have well-established donation systems[126,127]. The use of DCD donors has grown in recent years due to improved preservation techniques, contributing significantly to the overall number of transplants in countries like the United States, Belgium, the Netherlands, and Spain[54,128,129]. However, some countries, such as Greece, Finland, and Germany, still have low rates of DCD donations[130-132].

In 2022, Spain had a DCD donation rate of 22.10 PMP, the United States 14.27 PMP, Belgium 13 PMP, and the Netherlands 10.10 PMP, while Finland, Greece, and Germany reported negligible rates[12,13].

Donation after death: Ethical considerations and policy implications

Donation after death, particularly donation after DCD, presents specific ethical considerations that must be clearly defined within the legal framework of each transplant program[133,134]. Ethical issues related to DCD donation include respect for the patient's autonomy, their right to refuse any potential life-sustaining treatment, and their decision on whether or not to become an organ donor. Additional ethical challenges encompass avoiding conflicts of interest between end-of-life care providers, physicians declaring death, and procurement teams. Other considerations include the extent to which recipients need to be informed about the donor's medical history and circumstances of death, as well as the appropriate timing for approaching families and initiating evaluations to determine organ donor eligibility[133,134]. Efforts to maximize both donation after DBD and DCD donations require complex, multidisciplinary collaborations among healthcare professionals, organ donation coordinators, and intensive care unit doctors[9].

Another classification of organ donation is based on the presumption of the donor's consent, categorized into two policies: Opt-in and opt-out. These policies apply solely to DD[135]. The opt-in system requires individuals to actively express their willingness to donate their organs after death and register in a national organ donor registry. In some countries, like South Korea, individuals must indicate their consent when obtaining their driver's license from local authorities[135,136]. In the United States, consent can be completed online[137].

Conversely, in an opt-out transplant program, all individuals are automatically considered potential organ donors unless they explicitly opt out. The effectiveness of donation policies is directly proportional to the capacity of a transplant program[37,138]. Spain, Portugal, and the United Kingdom have adopted an opt-out policy, which suggests that this legislation has contributed significantly to their success (Supplementary Table 1).

Lessons

Clear policies are essential for building public trust, ensuring equitable access, and maintaining safe practices in transplantation. Significant differences exist among countries regarding the expansion of the donor pool and the preference for deceased versus LD. These differences reflect regional backgrounds, social beliefs, and traditions. Cultural, educational, and religious factors often play a more substantial role in these disparities than financial parameters. Populations with inadequate education on organ donation and transplantation, or those from specific religious backgrounds, often exhibit lower donation and transplantation rates. Addressing these factors is crucial when exploring solutions to improve donation rates.

As the demand for organ transplantation continues to grow, decisive strategies are necessary. These include promoting transplant education and awareness, training young physicians, partnering with international transplant pioneers, seeking financial support from other countries for cooperation, and reevaluating current transplant legislation in collaboration with religious leaders.

DISCUSSION

Organ transplantation is a remarkable achievement of modern medicine practiced worldwide[3,4]. In 2022, a total of 108818 organs were transplanted globally, with the majority performed in the United States and Europe (62153 and 40337 organs, respectively) and the fewest in Africa (268 transplants) (Table 2). Despite the increasing demand for organ

transplants due to an aging population and rising non-communicable diseases, a unified global transplant organization remains an unrealized vision.

In many countries, while NTOs may share similar ethics and objectives, significant disparities persist. These differences are evident in the structural and legislative frameworks, funding, and operational principles of transplantation systems. Socioeconomic, religious, and cultural factors often drive these disparities. As no universal guidelines or consensus for establishing NTOs exist, each country adopts a model tailored to its specific context. For example, in the United States, the OPTN is managed by the private non-profit organization UNOS under a contract from the HRSA[23-25]. In contrast, other countries' NTOs are either directly or indirectly supervised by their governments[26,35-37]. Spain's three-tiered model is particularly noteworthy, demonstrating success with leading donation and transplantation rates of 47 and 115.31 PMP, respectively, despite lower spending compared to other countries (Supplementary Table 1).

Organ shortage remains a well-documented issue, with demand far exceeding donor supply[69,108]. Efforts to address this problem include revising death determination criteria, amending legislation on organ donation types and policies, and adjusting allocation policies for greater equity and transparency[77,113]. Providing a clear legal framework is vital for building public trust and confidence in organ donation[113]. This is especially important in diverse regions like Asia, where certain traditions and social and religious beliefs hinder organ donation, particularly DD[121]. Supplementary Table 1 highlights the lower rates of DD in Asian countries compared to other regions. In Europe, Central European and Scandinavian countries have addressed graft shortages by forming international alliances, such as Eurotransplant and Scandiatransplant[40,41]. These alliances facilitate the exchange of unmatched organs, policy reforms, and discussions on challenges and future prospects.

Limitations

This review offers a comprehensive overview of national transplant programs across various countries with diverse socioeconomic, religious, and cultural backgrounds. However, several limitations exist. Although many countries perform transplant procedures, this study focuses primarily on a select few, namely, the United States, United Kingdom, Spain, Croatia, Eurotransplant and Scandiatransplant member states, India, China, and Iran. Information on other countries, such as Portugal, France, Japan, and South Korea, is included but to a lesser extent due to length constraints. Publicly available and up-to-date data are scarce for many African states, and official transplant and donation websites are lacking in numerous countries, including those in South America. Additionally, only English-language literature was considered, potentially omitting valuable information from official sources and publications in other languages.

Future directions

The need for further advancements in transplantation is clear, as is the necessity for continued research. Recognizing the limitations of the current study, future work would benefit from interviews and direct discussions with transplant officials, representatives, and physicians from around the world, particularly from regions with limited available data. These discussions would allow experts to share key aspects of their programs, as well as their visions and challenges. Additionally, employing questionnaires and a more flexible study design that includes material in languages other than English could provide a more comprehensive understanding of the topic and improve the interpretation of valuable data.

CONCLUSION

Various factors, including education, finances, religion, and social influences, affect organ transplant practices and create gaps and disparities among countries. These factors reflect the organizational and legislative frameworks, ethics, and operational patterns of each national transplant organization, making the establishment of a unified global organization challenging. Nevertheless, widely applicable practices such as ongoing education, public awareness campaigns, regular evaluation of policies and guidelines, and international collaborations like Eurotransplant and Scandiatransplant should be seriously considered by all countries aiming to advance in the field.

FOOTNOTES

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REFERENCES

1 **Nordham KD**, Ninokawa S. The history of organ transplantation. *Proc (Bayl Univ Med Cent)* 2022; **35**: 124-128 [PMID: 34970061 DOI: 10.1080/08998280.2021.1985889]

2 **Shayan H**. Organ transplantation: from myth to reality. *J Invest Surg* 2001; **14**: 135-138 [PMID: 11453178 DOI: 10.1080/089419301300343282]

3 **Dangi A**, Yu S, Luo X. Emerging approaches and technologies in transplantation: the potential game changers. *Cell Mol Immunol* 2019; **16**: 334-342 [PMID: 30760918 DOI: 10.1038/s41423-019-0207-3]

4 **Martin DE**, Van Assche K, Domínguez-Gil B, López-Fraga M, García Gallont R, Muller E, Capron AM. Strengthening Global Efforts to Combat Organ Trafficking and Transplant Tourism: Implications of the 2018 Edition of the Declaration of Istanbul. *Transplant Direct* 2019; **5**: e433 [PMID: 30882038 DOI: 10.1097/TXD.0000000000000872]

5 **Barker CF**, Markmann JF. Historical overview of transplantation. *Cold Spring Harb Perspect Med* 2013; **3**: a014977 [PMID: 23545575 DOI: 10.1101/cshperspect.a014977]

6 **Tan SY**, Merchant J. Joseph Murray (1919-2012): First transplant surgeon. *Singapore Med J* 2019; **60**: 162-163 [PMID: 31069396 DOI: 10.11622/smedj.2019032]

7 **Mah J**, Johnston-Webber C, Prionas A, Romagnoli J, Streit S, Wharton G, Mossialos E, Papalois V. How to Structure a Successful Organ Donation and Transplantation System in Eight (Not So Easy) Steps: An Italian Case Study. *Transpl Int* 2023; **36**: 11010 [PMID: 37359826 DOI: 10.3389/ti.2023.11010]

8 **Black CK**, Termanini KM, Aguirre O, Hawksworth JS, Sosin M. Solid organ transplantation in the 21(st) century. *Ann Transl Med* 2018; **6**: 409 [PMID: 30498736 DOI: 10.21037/atm.2018.09.68]

9 **Pedersen PB**, Henriksen DP, Brabrand M, Lassen AT. Prevalence of organ failure and mortality among patients in the emergency department: a population-based cohort study. *BMJ Open* 2019; **9**: e032692 [PMID: 31666275 DOI: 10.1136/bmjopen-2019-032692]

10 **Husain-Syed F**, Ricci Z, Brodie D, Vincent JL, Ranieri VM, Slutsky AS, Taccone FS, Gattinoni L, Ronco C. Extracorporeal organ support (ECOS) in critical illness and acute kidney injury: from native to artificial organ crosstalk. *Intensive Care Med* 2018; **44**: 1447-1459 [PMID: 30043276 DOI: 10.1007/s00134-018-5329-z]

11 **Vanholder R**, Domínguez-Gil B, Busic M, Cortez-Pinto H, Craig JC, Jager KJ, Mahillo B, Stel VS, Valentin MO, Zoccali C, Oniscu GC. Organ donation and transplantation: a multi-stakeholder call to action. *Nat Rev Nephrol* 2021; **17**: 554-568 [PMID: 33953367 DOI: 10.1038/s41581-021-00425-3]

12 **Global Observatory on Donation and Transplantation (GODT)**. Data – Summary by country. Available from: https://www.transplant-observatory.org/

13 **International Registry In Organ Donation and Transplantation (IRODaT)**. Database. Available from: https://www.irodat.org/?p=database&c=IN#data

14 **Muller E**. Transplantation in Africa - an overview. *Clin Nephrol* 2016; **86**: 90-95 [PMID: 27879190 DOI: 10.5414/CNP86S125]

15 **Chan-On C**, Sarwal MM. A Comprehensive Analysis of the Current Status and Unmet Needs in Kidney Transplantation in Southeast Asia. *Front Med (Lausanne)* 2017; **4**: 84 [PMID: 28691007 DOI: 10.3389/fmed.2017.00084]

16 **Johnston-Webber C**, Mah J, Streit S, Prionas A, Wharton G, Mossialos E, Papalois V. A Conceptual Framework for Evaluating National Organ Donation and Transplantation Programs. *Transpl Int* 2023; **36**: 11006 [PMID: 37334013 DOI: 10.3389/ti.2023.11006]

17 **Alfano G**, Perrone R, Fontana F, Ligabue G, Giovanella S, Ferrari A, Gregorini M, Cappelli G, Magistroni R, Donati G. Rethinking Chronic Kidney Disease in the Aging Population. *Life (Basel)* 2022; **12**: 1724 [PMID: 36362879 DOI: 10.3390/life12111724]

18 **Nitta K**, Okada K, Yanai M, Takahashi S. Aging and chronic kidney disease. *Kidney Blood Press Res* 2013; **38**: 109-120 [PMID: 24642796 DOI: 10.1159/000355760]

19 **Abouna GM**. Ethical issues in organ transplantation. *Med Princ Pract* 2003; **12**: 54-69 [PMID: 12566971 DOI: 10.1159/000068158]

20 **McDiarmid SV**, Pruett TL, Graham WK. The oversight of solid organ transplantation in the United States. *Am J Transplant* 2008; **8**: 739-744 [PMID: 18318780 DOI: 10.1111/j.1600-6143.2007.02147.x]

21 **Brown RS Jr**, Higgins R, Pruett TL. The evolution and direction of OPTN oversight of live organ donation and transplantation in the United States. *Am J Transplant* 2009; **9**: 31-34 [PMID: 18853948 DOI: 10.1111/j.1600-6143.2008.02433.x]

22 **United Network for Organ Sharing (UNOS)**. History of UNOS. 2014. Available from: https://unos.org/about/history-of-unos/

23 **National Academies of Sciences**, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Board on Health Sciences Policy; Committee on A Fairer and More Equitable, Cost-Effective, and Transparent System of Donor Organ Procurement, Allocation, and Distribution. Realizing the Promise of Equity in the Organ Transplantation System. Hackmann M, English RA, Kizer KW, editors. Washington (DC): National Academies Press (US); 2022 [PMID: 35226429]

24 **Organ Procurement and Transplantation Network (OPTN)**. Final Rule. Available from: https://optn.transplant.hrsa.gov/about/final-rule/

25 **United Network for Organ Sharing (UNOS)**. How UNOS, OPOs and transplant programs work together to save lives. Available from: https://unos.org/about/national-organ-transplant-system/

26 **NHS Blood and Transplant (NHSBT)**. Home. 2019. Available from: https://www.nhsbt.nhs.uk/

27 **NHS Blood and Transplant (NHSBT)**. ODT Clinical – Advisory Groups. Available from: https://www.odt.nhs.uk/odt-structures-and-standards/clinical-leadership/advisory-groups/

28 **Living donation**. ODT Clinical - NHS Blood and Transplant (NHSBT). ODT Clinical–Living Donation. Available from: https://www.odt.nhs.uk/living-donation/#:~:text=The%20Human%20Tissue%20Authority%20

29 **Human Tissue Authority (HTA)**. About HTA. Available from: https://www.hta.gov.uk/about-the-HTA

30 **Department of Health**. Organs for Transplant: A Report from the Organ Donation Taskforce. 2008. Available from: https://xueshu.baidu.com/usercenter/paper/show?paperid=7f7b698f107efd36892669737b554c3e&site=xueshu_se&hitarticle=1

31 **Johnston-Webber C**, Mah J, Prionas A, Streit S, Wharton G, Forsythe J, Mossialos E, Papalois V. Solid Organ Donation and Transplantation

in the United Kingdom: Good Governance is Key to Success. *Transpl Int* 2023; **36**: 11012 [PMID: 37305339 DOI: 10.3389/ti.2023.11012]
32 **Živčić-Ćosić S**, Bušić M, Župan Ž, Pelčić G, Anušić Juričić M, Jurčić Ž, Ivanovski M, Rački S. Development of the Croatian model of organ donation and transplantation. *Croat Med J* 2013; **54**: 65-70 [PMID: 23444248 DOI: 10.3325/cmj.2013.54.65]
33 **Mah J**, Johnston-Webber C, Prionas A, Bušić M, Streit S, Wharton G, Mossialos E, Papalois V. Organ Donation in Croatia: The Importance of a National Champion, a Comprehensive Plan, and International Collaborations. *Transpl Int* 2023; **36**: 11011 [PMID: 37305341 DOI: 10.3389/ti.2023.11011]
34 **Rada AG**. Spain remains world leader in organ donation for 32 consecutive years. *BMJ* 2024; **384**: q175 [PMID: 38262671 DOI: 10.1136/bmj.q175]
35 **La Moncloa**. One in 4 EU donors comes from Spain. Available from: https://www.lamoncloa.gob.es/lang/en/gobierno/news/Paginas/2023/20230830_eudonors.aspx#:~:text=With%20a%20rate%20of%2047,44.5%20donors%20per%20million%20people
36 **Manyalich M**, Mestres CA, Ballesté C, Páez G, Valero R, Gómez MP. Organ procurement: Spanish transplant procurement management. *Asian Cardiovasc Thorac Ann* 2011; **19**: 268-278 [PMID: 21885556 DOI: 10.1177/0218492311411590]
37 **Streit S**, Johnston-Webber C, Mah J, Prionas A, Wharton G, Casanova D, Mossialos E, Papalois V. Ten Lessons From the Spanish Model of Organ Donation and Transplantation. *Transpl Int* 2023; **36**: 11009 [PMID: 37305337 DOI: 10.3389/ti.2023.11009]
38 **Matesanz R**, Domínguez-Gil. The Spanish Model of Organ Donation and Transplantation. Cham: Springer, 2016
39 **Peritore D**, Pretagostini R, Di Ciaccio P, Fiaschetti P, Gabbrielli F, Oliveti A, Stabile D, Ricci A, Vaia F, Nanni Costa A. Italy-Greece cooperation for transplantation of medically urgent Greek patients: is it an effective, efficient model? *Transplant Proc* 2012; **44**: 1843-1845 [PMID: 22974851 DOI: 10.1016/j.transproceed.2012.06.049]
40 **Eurotransplant**. Eurotransplant homepage. Available from: https://www.eurotransplant.org/
41 **Scandiatransplant**. Scandiatransplant homepage. Available from: https://www.scandiatransplant.org/
42 **Tan J**, Mabood Khalil MA, Kee T, Tiong HY, Khan TT, El-Madhoun I, Ishida H, Jasuja S, Ahmad G, Tang SCW, Vathsala A. Deceased donor kidney transplant policies in Asia - implications on practice and recommendations for the future. *Lancet Reg Health Southeast Asia* 2024; **21**: 100312 [PMID: 38361593 DOI: 10.1016/j.lansea.2023.100312]
43 **Bagheri A**. Organ transplantation laws in Asian countries: a comparative study. *Transplant Proc* 2005; **37**: 4159-4162 [PMID: 16387068 DOI: 10.1016/j.transproceed.2005.11.016]
44 **National Organ and Tissue Transplant Organization (NOTTA)**. Homepage. Available from: https://notta.mohfw.gov.in/
45 **The Lancet Regional Health-Southeast Asia**. Organ transplantation in India: needs a bigger push. *Lancet Reg Health Southeast Asia* 2024; **21**: 100366 [PMID: 38361597 DOI: 10.1016/j.lansea.2024.100366]
46 **Ambagtsheer F**, Bugter R. The organization of the human organ trade: a comparative crime script analysis. *Crime Law Soc Change* 2023; **80**: 1-32 [DOI: 10.1007/s10611-022-10068-5]
47 **Huang J**. The "Chinese Mode" of organ donation and transplantation. *Hepatobiliary Surg Nutr* 2017; **6**: 212-214 [PMID: 28848741 DOI: 10.21037/hbsn.2017.07.08]
48 **Shi BY**, Liu ZJ, Yu T. Development of the organ donation and transplantation system in China. *Chin Med J (Engl)* 2020; **133**: 760-765 [PMID: 32195670 DOI: 10.1097/CM9.0000000000000779]
49 **Wu Y**, Elliott R, Li L, Yang T, Bai Y, Ma W. Cadaveric organ donation in China: A crossroads for ethics and sociocultural factors. *Medicine (Baltimore)* 2018; **97**: e9951 [PMID: 29517702 DOI: 10.1097/MD.0000000000009951]
50 **Bendorf A**, Pussell BA, Kelly PJ, Kerridge IH. Socioeconomic, demographic and policy comparisons of living and deceased kidney transplantation rates across 53 countries. *Nephrology (Carlton)* 2013; **18**: 633-640 [PMID: 23692370 DOI: 10.1111/nep.12101]
51 **Raghupathi V**, Raghupathi W. Healthcare Expenditure and Economic Performance: Insights From the United States Data. *Front Public Health* 2020; **8**: 156 [PMID: 32478027 DOI: 10.3389/fpubh.2020.00156]
52 **Sultana S**, Hossain ME, Khan MA, Saha SM, Amin MR, Haque Prodhan MM. Effects of healthcare spending on public health status: An empirical investigation from Bangladesh. *Heliyon* 2024; **10**: e24268 [PMID: 38234878 DOI: 10.1016/j.heliyon.2024.e24268]
53 **Friele RD**, Coppen R, Marquet RL, Gevers JK. Explaining differences between hospitals in number of organ donors. *Am J Transplant* 2006; **6**: 539-543 [PMID: 16468963 DOI: 10.1111/j.1600-6143.2005.01200.x]
54 **Polireddy K**, Crepeau RL, Matar AJ. Eliminating financial disincentives to living kidney donation - a call to action. *Front Med (Lausanne)* 2023; **10**: 1061342 [PMID: 37457572 DOI: 10.3389/fmed.2023.1061342]
55 **World Bank Group**. Database. Available from: https://www.worldbank.org/en/who-we-are
56 **Eurostat**. Healthcare expenditure statistics – overview (2021). Available from: https://ec.europa.eu/eurostat/statisticsexplained/index.php?title=Healthcare_expenditure_statistics_-_overview&oldid=625409#Healthcare_expenditure
57 **Office for National Statistics (ONS)**. Healthcare Expenditure, UK Health Accounts provisional estimates–2022. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthcaresystem/bulletins/healthcareexpenditureukhealthaccountsprovisionalestimates/2022#total-current-healthcare-expenditure
58 **Czekajewska JM**, Jaworowicz-zimny A. Organ Transplant in Present-Day Japan: Reasons behind Low Numbers of Deceased Donors. *Diametros* 2021 [DOI: 10.33392/diam.1630]
59 **Dababneh Y**, Mousa OY. Liver Transplantation. 2023 Apr 7. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [PMID: 32644587]
60 **Devarbhavi H**, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. *J Hepatol* 2023; **79**: 516-537 [PMID: 36990226 DOI: 10.1016/j.jhep.2023.03.017]
61 **Fung J**, Lai CL, Seto WK, Yuen MF. Nucleoside/nucleotide analogues in the treatment of chronic hepatitis B. *J Antimicrob Chemother* 2011; **66**: 2715-2725 [PMID: 21965435 DOI: 10.1093/jac/dkr388]
62 **Ozturk NB**, Bartosek N, Toruner MD, Mumtaz A, Simsek C, Dao D, Saberi B, Gurakar A. Approach to Liver Transplantation: Is There a Difference between East and West? *J Clin Med* 2024; **13**: 1890 [PMID: 38610655 DOI: 10.3390/jcm13071890]
63 **Rindler GA**, Gries A, Freidl W. Associations between overweight, obesity, and mental health: a retrospective study among European adults aged 50. *Front Public Health* 2023; **11**: 1206283 [PMID: 37533526 DOI: 10.3389/fpubh.2023.1206283]
64 **Huang DQ**, Terrault NA, Tacke F, Gluud LL, Arrese M, Bugianesi E, Loomba R. Global epidemiology of cirrhosis - aetiology, trends and predictions. *Nat Rev Gastroenterol Hepatol* 2023; **20**: 388-398 [PMID: 36977794 DOI: 10.1038/s41575-023-00759-2]
65 **Scientific Registry of Transplant Recipients (SRTR)**. OPTN/SRTR 2022 Annual Data Report: Liver. Available from: https://srtr.transplant.hrsa.gov/annual_reports/2022/Liver.aspx

66 **European Liver Transplant Registry (ELTR)**. Results – Specific results by disease. Available from: https://www.eltr.org/spip.php?article162

67 **Soyama A**, Hara T, Matsushima H, Hamada T, Imamura H, Tanaka T, Adachi T, Hidaka M, Eguchi S. Minimally Invasive Approach to Recipient Surgery in Living Donor Liver Transplantation. *Liver Transpl* 2021; **27**: 1678-1679 [PMID: 34382735 DOI: 10.1002/lt.26262]

68 **Chase B**. World's First Genetically – Edited Pig Kidney Transplant into Living Recipient Performed at Massachusetts General Hospital. Boston: Massachusetts General Hospital, 2024. Available from: https://www.massgeneral.org/news/press-release/worlds-first-genetically-edited-pig-kidney-transplant-into-living-recipient

69 **Lewis A**, Koukoura A, Tsianos GI, Gargavanis AA, Nielsen AA, Vassiliadis E. Organ donation in the US and Europe: The supply vs demand imbalance. *Transplant Rev (Orlando)* 2021; **35**: 100585 [PMID: 33071161 DOI: 10.1016/j.trre.2020.100585]

70 **Polyak A**, Kuo A, Sundaram V. Evolution of liver transplant organ allocation policy: Current limitations and future directions. *World J Hepatol* 2021; **13**: 830-839 [PMID: 34552690 DOI: 10.4254/wjh.v13.i8.830]

71 **Tsoris A**, Marlar CA. Use Of The Child Pugh Score In Liver Disease. [Updated 2023 Mar 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.

72 **Papatheodoridis GV**, Cholongitas E, Dimitriadou E, Touloumi G, Sevastianos V, Archimandritis AJ. MELD vs Child-Pugh and creatinine-modified Child-Pugh score for predicting survival in patients with decompensated cirrhosis. *World J Gastroenterol* 2005; **11**: 3099-3104 [PMID: 15918197 DOI: 10.3748/wjg.v11.i20.3099]

73 **Singal AK**, Kamath PS. Model for End-stage Liver Disease. *J Clin Exp Hepatol* 2013; **3**: 50-60 [PMID: 25755471 DOI: 10.1016/j.jceh.2012.11.002]

74 **Trivedi HD**. The Evolution of the MELD Score and Its Implications in Liver Transplant Allocation: A Beginner's Guide for Trainees. *ACG Case Rep J* 2022; **9**: e00763 [PMID: 35919673 DOI: 10.14309/crj.0000000000000763]

75 **French Liver Allocation Policy Handbook**. Agence de La Biomédecine Web Site. Available from: https://www.agence-biomedecine.fr/IMG/pdf/french-liver-allocation-policy-handbook.pdf

76 **NHS Blood and Transplant (NHSBT)**. National Liver Offering Scheme. Available from: https://www.odt.nhs.uk/odt-structures-and-standards/odt-hub-programme/national-liver-offering-scheme/#:~:text=In%202018%20NHS%20Blood%20and

77 **Tschuor C**, Ferrarese A, Kuemmerli C, Dutkowski P, Burra P, Clavien PA; Liver Allocation Study Group. Allocation of liver grafts worldwide - Is there a best system? *J Hepatol* 2019; **71**: 707-718 [PMID: 31199941 DOI: 10.1016/j.jhep.2019.05.025]

78 **Fosby B**, Melum E, Bjøro K, Bennet W, Rasmussen A, Andersen IM, Castedal M, Olausson M, Wibeck C, Gotlieb M, Gjertsen H, Toivonen L, Foss S, Makisalo H, Nordin A, Sanengen T, Bergquist A, Larsson ME, Soderdahl G, Nowak G, Boberg KM, Isoniemi H, Keiding S, Foss A, Line PD, Friman S, Schrumpf E, Ericzon BG, Höckerstedt K, Karlsen TH. Liver transplantation in the Nordic countries - An intention to treat and post-transplant analysis from The Nordic Liver Transplant Registry 1982-2013. *Scand J Gastroenterol* 2015; **50**: 797-808 [PMID: 25959101 DOI: 10.3109/00365521.2015.1036359]

79 **Kiani M**, Abbasi M, Ahmadi M, Salehi B. Organ Transplantation in Iran; Current State and Challenges with a View on Ethical Consideration. *J Clin Med* 2018; **7**: 45 [PMID: 29510570 DOI: 10.3390/jcm7030045]

80 **Phadke G**, Khanna R. Renal replacement therapies. *Mo Med* 2011; **108**: 45-49 [PMID: 21462611]

81 **Bello AK**, Okpechi IG, Osman MA, Cho Y, Htay H, Jha V, Wainstein M, Johnson DW. Epidemiology of haemodialysis outcomes. *Nat Rev Nephrol* 2022; **18**: 378-395 [PMID: 35194215 DOI: 10.1038/s41581-022-00542-7]

82 **An JN**, Kim SG, Song YR. When and why to start continuous renal replacement therapy in critically ill patients with acute kidney injury. *Kidney Res Clin Pract* 2021; **40**: 566-577 [PMID: 34781642 DOI: 10.23876/j.krcp.21.043]

83 **Yang F**, Liao M, Wang P, Yang Z, Liu Y. The Cost-Effectiveness of Kidney Replacement Therapy Modalities: A Systematic Review of Full Economic Evaluations. *Appl Health Econ Health Policy* 2021; **19**: 163-180 [PMID: 33047212 DOI: 10.1007/s40258-020-00614-4]

84 **Niu SF**, Li IC. Quality of life of patients having renal replacement therapy. *J Adv Nurs* 2005; **51**: 15-21 [PMID: 15941456 DOI: 10.1111/j.1365-2648.2005.03455.x]

85 **Tonelli M**, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, Klarenbach S, Gill J. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant* 2011; **11**: 2093-2109 [PMID: 21883901 DOI: 10.1111/j.1600-6143.2011.03686.x]

86 **Shi B**, Ying T, Chadban SJ. Survival after kidney transplantation compared with ongoing dialysis for people over 70 years of age: A matched-pair analysis. *Am J Transplant* 2023; **23**: 1551-1560 [PMID: 37460010 DOI: 10.1016/j.ajt.2023.07.006]

87 **Francis A**, Harhay MN, Ong ACM, Tummalapalli SL, Ortiz A, Fogo AB, Fliser D, Roy-Chaudhury P, Fontana M, Nangaku M, Wanner C, Malik C, Hradsky A, Adu D, Bavanandan S, Cusumano A, Sola L, Ulasi I, Jha V; American Society of Nephrology; European Renal Association; International Society of Nephrology. Chronic kidney disease and the global public health agenda: an international consensus. *Nat Rev Nephrol* 2024; **20**: 473-485 [PMID: 38570631 DOI: 10.1038/s41581-024-00820-6]

88 **Jadoul M**, Aoun M, Masimango Imani M. The major global burden of chronic kidney disease. *Lancet Glob Health* 2024; **12**: e342-e343 [PMID: 38365398 DOI: 10.1016/S2214-109X(24)00050-0]

89 **Gupta R**, Woo K, Yi JA. Epidemiology of end-stage kidney disease. *Semin Vasc Surg* 2021; **34**: 71-78 [PMID: 33757639 DOI: 10.1053/j.semvascsurg.2021.02.010]

90 **Liyanage T**, Toyama T, Hockham C, Ninomiya T, Perkovic V, Woodward M, Fukagawa M, Matsushita K, Praditpornsilpa K, Hooi LS, Iseki K, Lin MY, Stirnadel-Farrant HA, Jha V, Jun M. Prevalence of chronic kidney disease in Asia: a systematic review and analysis. *BMJ Glob Health* 2022; **7**: e007525 [PMID: 35078812 DOI: 10.1136/bmjgh-2021-007525]

91 **Kidney Disease Improving Global Outcomes (KDIGO)**. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *KIDNEY INT* 2024; **105** S117-S314. Available from: https://www.kidney-international.org/

92 **Azegami T**, Kounoue N, Sofue T, Yazawa M, Tsujita M, Masutani K, Kataoka Y, Oguchi H. Efficacy of pre-emptive kidney transplantation for adults with end-stage kidney disease: a systematic review and meta-analysis. *Ren Fail* 2023; **45**: 2169618 [PMID: 36705051 DOI: 10.1080/0886022X.2023.2169618]

93 **Jung GO**, Moon JI, Kim JM, Choi GS, Kwon CH, Cho JW, Kim SJ. Can preemptive kidney transplantation guarantee longer graft survival in living-donor kidney transplantation? Single-center study. *Transplant Proc* 2010; **42**: 766-774 [PMID: 20430167 DOI: 10.1016/j.transproceed.2010.02.050]

94 **Smith JM**, Biggins SW, Haselby DG, Kim WR, Wedd J, Lamb K, Thompson B, Segev DL, Gustafson S, Kandaswamy R, Stock PG, Matas AJ, Samana CJ, Sleeman EF, Stewart D, Harper A, Edwards E, Snyder JJ, Kasiske BL, Israni AK. Kidney, pancreas and liver allocation and distribution in the United States. *Am J Transplant* 2012; **12**: 3191-3212 [PMID: 23157207 DOI: 10.1111/j.1600-6143.2012.04259.x]

95 **Organ Procurement and Transplantation Network (OPTN)**. Kidney Allocation System (KAS). Available from: https://optn.transplant.hrsa.gov/professionals/by-organ/kidney-pancreas/kidney-allocation-system/#:~:text=Instead%20of%20match%20sequencing%20relying,learn%20more%20about%20the%20policies.

96 **El-Khoury B**, Yang TC. Reviewing Racial Disparities in Living Donor Kidney Transplantation: a Socioecological Approach. *J Racial Ethn Health Disparities* 2024; **11**: 928-937 [PMID: 36991297 DOI: 10.1007/s40615-023-01573-x]

97 **Melanson TA**, Hockenberry JM, Plantinga L, Basu M, Pastan S, Mohan S, Howard DH, Patzer RE. New Kidney Allocation System Associated With Increased Rates Of Transplants Among Black And Hispanic Patients. *Health Aff (Millwood)* 2017; **36**: 1078-1085 [PMID: 28583967 DOI: 10.1377/hlthaff.2016.1625]

98 **Israni AK**, Salkowski N, Gustafson S, Snyder JJ, Friedewald JJ, Formica RN, Wang X, Shteyn E, Cherikh W, Stewart D, Samana CJ, Chung A, Hart A, Kasiske BL. New national allocation policy for deceased donor kidneys in the United States and possible effect on patient outcomes. *J Am Soc Nephrol* 2014; **25**: 1842-1848 [PMID: 24833128 DOI: 10.1681/ASN.2013070784]

99 **Adler JT**, Husain SA, King KL, Mohan S. Greater complexity and monitoring of the new Kidney Allocation System: Implications and unintended consequences of concentric circle kidney allocation on network complexity. *Am J Transplant* 2021; **21**: 2007-2013 [PMID: 33314637 DOI: 10.1111/ajt.16441]

100 **Cron DC**, Husain SA, Adler JT. The New Distance-Based Kidney Allocation System: Implications for Patients, Transplant Centers, and Organ Procurement Organizations. *Curr Transplant Rep* 2022; **9**: 302-307 [PMID: 36254174 DOI: 10.1007/s40472-022-00384-z]

101 **Rudge C**, Johnson RJ, Fuggle SV, Forsythe JL; Kidney and Pancreas Advisory Group, UK Transplant NHS BT. Renal transplantation in the United Kingdom for patients from ethnic minorities. *Transplantation* 2007; **83**: 1169-1173 [PMID: 17496531 DOI: 10.1097/01.tp.0000259934.06233.ba]

102 **Newstead C**. Allocation of kidney transplants in the UK. *Br J Hosp Med (Lond)* 2011; **72**: 698-701 [PMID: 22241228 DOI: 10.12968/hmed.2011.72.12.698]

103 **NHS Blood and Transplant (NHSBT)**. Policies and guidance. Available from: https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/policies-and-guidance/

104 **Audry B**, Savoye E, Pastural M, Bayer F, Legeai C, Macher MA, Kerbaul F, Jacquelinet C. The new French kidney allocation system for donations after brain death: Rationale, implementation, and evaluation. *Am J Transplant* 2022; **22**: 2855-2868 [PMID: 36000787 DOI: 10.1111/ajt.17180]

105 **Eurotransplant**. Allocation of organs-Eurotransplant. Available from: https://www.eurotransplant.org/allocation/allocation-of-organs/#:~:text=The%20donor%20organs%20are%20offered,in%20the%20patient's%20transplant%20center

106 **Vathsala A**. Improving cadaveric organ donation rates in kidney and liver transplantation in Asia. *Transplant Proc* 2004; **36**: 1873-1875 [PMID: 15518680 DOI: 10.1016/j.transproceed.2004.08.131]

107 **Yagisawa T**, Mieno M, Ichimaru N, Morita K, Nakamura M, Hotta K, Kenmochi T, Yuzawa K. Trends of kidney transplantation in Japan in 2018: data from the kidney transplant registry. *Ren Replace Ther* 2019; **5**: 3 [DOI: 10.1186/s41100-019-0199-6]

108 **Tanabe K**. Japanese experience of ABO-incompatible living kidney transplantation. *Transplantation* 2007; **84**: S4-S7 [PMID: 18162988 DOI: 10.1097/01.tp.0000296008.08452.4c]

109 **Gordon EJ**, Gill JS. Where there is smoke there is fire: the Iranian system of paid donation. *Am J Transplant* 2013; **13**: 3063-3064 [PMID: 24224692 DOI: 10.1111/ajt.12486]

110 **Bagheri A**. Compensated kidney donation: an ethical review of the Iranian model. *Kennedy Inst Ethics J* 2006; **16**: 269-282 [PMID: 17091561 DOI: 10.1353/ken.2006.0017]

111 **Major RW**. Paying kidney donors: time to follow Iran? *Mcgill J Med* 2008; **11**: 67-69 [PMID: 18523518]

112 **Martínez-López MV**, McLaughlin L, Molina-Pérez A, Pabisiak K, Primc N, Randhawa G, Rodríguez-Arias D, Suárez J, Wöhlke S, Delgado J. Mapping trust relationships in organ donation and transplantation: a conceptual model. *BMC Med Ethics* 2023; **24**: 93 [PMID: 37914997 DOI: 10.1186/s12910-023-00965-2]

113 **Taherkhani S**. Differences between living and deceased donation in human uterus transplantation: A narrative review. *Int J Reprod Biomed* 2023; **21**: 193-204 [PMID: 37122889 DOI: 10.18502/ijrm.v21i3.13195]

114 **Human Tissue Authority (HTA)**. Types of living organ donation. HTA Web Site. Available from: https://www.hta.gov.uk/guidance-public/body-organ-and-tissue-donation/living-organ-donation/types-living-organ-donation.

115 **International Summit on Transplant Tourism and Organ Trafficking**. The Declaration of Istanbul on Organ Trafficking and Transplant Tourism. *Clin J Am Soc Nephrol* 2008; **3**: 1227-1231 [PMID: 18701611 DOI: 10.2215/CJN.03320708]

116 **Budiani-Saberi DA**, Delmonico FL. Organ trafficking and transplant tourism: a commentary on the global realities. *Am J Transplant* 2008; **8**: 925-929 [PMID: 18416734 DOI: 10.1111/j.1600-6143.2008.02200.x]

117 **Elmer A**, Rohrer ML, Benden C, Krügel N, Beyeler F, Immer FF. Organ donation after circulatory death as compared with organ donation after brain death in Switzerland - an observational study. *Swiss Med Wkly* 2022; **152**: w30139 [PMID: 35201682 DOI: 10.4414/smw.2022.w30132]

118 **Staubli SM**, Ceresa CDL, Pollok JM. The Current Role and Future Applications of Machine Perfusion in Liver Transplantation. *Bioengineering (Basel)* 2023; **10**: 593 [PMID: 37237663 DOI: 10.3390/bioengineering10050593]

119 **Oliver M**, Woywodt A, Ahmed A, Saif I. Organ donation, transplantation and religion. *Nephrol Dial Transplant* 2011; **26**: 437-444 [PMID: 20961891 DOI: 10.1093/ndt/gfq628]

120 **Cantarovich F**. The role of education in increasing organ donation. *Ann Transplant* 2004; **9**: 39-42 [PMID: 15478888]

121 **Doerry K**, Oh J, Vincent D, Fischer L, Schulz-Jürgensen S. Religious and cultural aspects of organ donation: Narrowing the gap through understanding different religious beliefs. *Pediatr Transplant* 2022; **26**: e14339 [PMID: 35735257 DOI: 10.1111/petr.14339]

122 **Badanta B**, González-Cano-Caballero M, Suárez-Reina P, Lucchetti G, de Diego-Cordero R. How Does Confucianism Influence Health Behaviors, Health Outcomes and Medical Decisions? A Scoping Review. *J Relig Health* 2022; **61**: 2679-2725 [PMID: 35141796 DOI: 10.1007/s10943-022-01506-8]

123 **Murakami M**, Fukuma S, Ikezoe M, Izawa S, Watanabe H, Yamaguchi H, Kitazawa A, Takahashi K, Natsukawa S, Fukuhara S. Knowledge Does Not Correlate with Behavior toward Deceased Organ Donation: A Cross-Sectional Study in Japan. *Ann Transplant* 2020; **25**: e918936 [PMID: 31896742 DOI: 10.12659/AOT.918936]

124 **Robson NZ**, Razack AH, Dublin N. Review paper: Organ transplants: ethical, social, and religious issues in a multicultural society. *Asia Pac J Public Health* 2010; **22**: 271-278 [PMID: 20460294 DOI: 10.1177/1010539509357446]

125 **Cowie S**, Choy SH, Shah DM, Gomez MP, Yoong BK, Koong JK. Healthcare System Impact on Deceased Organ Donation and Transplantation: A Comparison Between the Top 10 Organ Donor Countries With 4 Countries in Southeast Asia. *Transpl Int* 2023; **36**: 11233 [PMID: 37711402 DOI: 10.3389/ti.2023.11233]

126 **Alamouti-Fard E**, Garg P, Wadiwala IJ, Yazji JH, Alomari M, Hussain MWA, Elawady MS, Jacob S. Normothermic Regional Perfusion is an Emerging Cost-Effective Alternative in Donation After Circulatory Death (DCD) in Heart Transplantation. *Cureus* 2022; **14**: e26437 [PMID: 35800191 DOI: 10.7759/cureus.26437]

127 **Joshi Y**, Villanueva J, Gao L, Hwang B, Zhao C, Doyle A, Wu J, Jansz P, Macdonald P. Donation After Circulatory Death: A New Frontier. *Curr Cardiol Rep* 2022; **24**: 1973-1981 [PMID: 36272050 DOI: 10.1007/s11886-022-01798-y]

128 **Domínguez-Gil B**, Haase-Kromwijk B, Van Leiden H, Neuberger J, Coene L, Morel P, Corinne A, Muehlbacher F, Brezovsky P, Costa AN, Rozental R, Matesanz R; European Committee (Partial Agreement) on Organ Transplantation. Council of Europe (CD-P-TO). Current situation of donation after circulatory death in European countries. *Transpl Int* 2011; **24**: 676-686 [PMID: 21504489 DOI: 10.1111/j.1432-2277.2011.01257.x]

129 **Sonnenberg EM**, Hsu JY, Reese PP, Goldberg DS, Abt PL. Wide Variation in the Percentage of Donation After Circulatory Death Donors Across Donor Service Areas: A Potential Target for Improvement. *Transplantation* 2020; **104**: 1668-1674 [PMID: 32732846 DOI: 10.1097/TP.0000000000003019]

130 **Johnston-Webber C**, Prionas A, Wharton G, Streit S, Mah J, Boletis I, Mossialos E, Papalois V. The National Organ Donation and Transplantation Program in Greece: Gap Analysis and Recommendations for Change. *Transpl Int* 2023; **36**: 11013 [PMID: 37305340 DOI: 10.3389/ti.2023.11013]

131 **Lomero M**, Gardiner D, Coll E, Haase-Kromwijk B, Procaccio F, Immer F, Gabbasova L, Antoine C, Jushinskis J, Lynch N, Foss S, Bolotinha C, Ashkenazi T, Colenbie L, Zuckermann A, Adamec M, Czerwiński J, Karčiauskaitė S, Ström H, López-Fraga M, Dominguez-Gil B; European Committee on Organ Transplantation of the Council of Europe (CD-P-TO). Donation after circulatory death today: an updated overview of the European landscape. *Transpl Int* 2020; **33**: 76-88 [PMID: 31482628 DOI: 10.1111/tri.13506]

132 **Eden J**, Sousa Da Silva R, Cortes-Cerisuelo M, Croome K, De Carlis R, Hessheimer AJ, Muller X, de Goeij F, Banz V, Magini G, Compagnon P, Elmer A, Lauterio A, Panconesi R, Widmer J, Dondossola D, Muiesan P, Monbaliu D, de Rosner van Rosmalen M, Detry O, Fondevila C, Jochmans I, Pirenne J, Immer F, Oniscu GC, de Jonge J, Lesurtel M, De Carlis LG, Taner CB, Heaton N, Schlegel A, Dutkowski P. Utilization of livers donated after circulatory death for transplantation - An international comparison. *J Hepatol* 2023; **78**: 1007-1016 [PMID: 36740047 DOI: 10.1016/j.jhep.2023.01.025]

133 **Jericho BG**. Organ Donation After Circulatory Death: Ethical Issues and International Practices. *Anesth Analg* 2019; **128**: 280-285 [PMID: 29787408 DOI: 10.1213/ANE.0000000000003448]

134 **Pérez Castro P**, Salas SP. Ethical issues of organ donation after circulatory death: Considerations for a successful implementation in Chile. *Dev World Bioeth* 2022; **22**: 259-266 [PMID: 34773430 DOI: 10.1111/dewb.12338]

135 **Etheredge HR**. Assessing Global Organ Donation Policies: Opt-In vs Opt-Out. *Risk Manag Healthc Policy* 2021; **14**: 1985-1998 [PMID: 34012308 DOI: 10.2147/RMHP.S270234]

136 **Cho IS**, Lee HY, Park UJ, Kim HT, Roh YN. The effect of a mandatory choice systemfor organ donation after brain death onethical legitimacy and potential efficacyin a mathematical model. *Korean J Transplant* 2020; **34**: 2-7 [PMID: 35770263 DOI: 10.4285/kjt.2020.34.1.2]

137 **Health Resources and Services Administration (HRSA)**. Sign up to be an organ donor. Available from: https://www.organdonor.gov/sign-up

138 **Rudge CJ**. Organ donation: opting in or opting out? *Br J Gen Pract* 2018; **68**: 62-63 [PMID: 29371294 DOI: 10.3399/bjgp18X694445]

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MINIREVIEWS

Expanding role of antibodies in kidney transplantation

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Abstract

The role of antibodies in kidney transplant (KT) has evolved significantly over the past few decades. This role of antibodies in KT is multifaceted, encompassing both the challenges they pose in terms of antibody-mediated rejection (AMR) and the opportunities for improving transplant outcomes through better detection, prevention, and treatment strategies. As our understanding of the immunological mechanisms continues to evolve, so too will the approaches to managing and harnessing the power of antibodies in KT, ultimately leading to improved patient and graft survival. This narrative review explores the multifaceted roles of antibodies in KT, including their involvement in rejection mechanisms, advancements in desensitization protocols, AMR treatments, and their potential role in monitoring and improving graft survival.

Key Words: Antibodies; Humoral theory; Kidney transplantation; Rejection

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Core Tip: Antibodies are of crucial importance in kidney transplantation (KT), posing challenges such as antibody-mediated rejection (AMR) but also offering opportunities for better transplant outcomes through advanced detection, prevention, and treatment strategies. This review explores the role of antibodies in rejection, progress in desensitization, AMR treatments, and their potential to enhance graft survival, reflecting evolving strategies to manage and leverage antibodies in KT.

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INTRODUCTION

Kidney transplant (KT) is the preferred form of treatment for patients with end-stage kidney failure[1,2]. Considerable advancements have been made in the field of KT since its inception in the 1950s[3]. The success rates of KT have significantly improved over the years, largely due to advances in surgical techniques, immunosuppressive therapy, and the understanding of the immune responses involved in transplant rejection[3,4]. Two competing theories, the cellular and humoral, became popular as researchers sought to understand the mechanisms behind graft rejection. Among these, antibodies play key roles in damaging the graft. However, their crucial role in alloimmune responses was not fully recognized, particularly during the early days of transplantation[5,6]. In the recent past, significant advances have been made in understanding and expanding the role of antibodies in both the success and challenges of KT. From the early days of graft rejection to the development of more sensitive assays such as Luminex flow bead assays to detect low-titer antibodies, high-resolution sequence-based human leukocyte antigens (HLA) typing, a better understanding of immune mechanisms involved in the rejection processes, and the development of newer immunosuppressive drugs, the history of antibodies in KT reflects the broader advances in immunology and transplant medicine[7-10].

This review aims to provide a comprehensive overview of antibodies' evolving and multifaceted roles in KT, highlighting their detrimental and beneficial effects on the grafts.

ANTIBODIES AND KIDNEY ALLOGRAFT REJECTION

Antibodies play a crucial role in the immune response against transplanted kidneys. Historically, donor-specific antibodies (DSAs) have been associated with hyperacute (HAR) and accelerated acute rejections. HAR, occurring minutes to hours post-transplantation, is primarily mediated by high titer pre-formed DSAs binding to donor antigens on the vascular endothelium, leading to immediate graft loss. Accelerated acute rejection, a less severe form of HAR, occurs within 2-3 days of transplantation. It is also caused by pre-formed DSAs albeit in low titer. Acute antibody-mediated rejection (AMR) occurs days to weeks post-transplantation and is a result of DSAs, that may either be pre-formed or develop *de-novo* after transplantation. Chronic AMR, which develops over months to years, is a major cause of late graft failure and involves progressive fibrosis and vascular changes[11-15]. Clinically, the manifestations of the latter form of AMR range from asymptomatic in the early stages to nephrotic range-proteinuria, hypertension, and allograft dysfunction in the advanced stages.

The long-term effects of chronic AMR on kidney grafts include slow but progressive graft dysfunction, chronic allograft injury [manifested as transplant glomerulopathy (TG), interstitial fibrosis and tubular atrophy (IF/TA), and basement membrane multi layering (BMML)], vascular damage, and increased risk of graft loss. Indeed, chronic AMR has emerged as one of the leading causes of kidney graft loss in the long term.

HISTORICAL BACKGROUND AND EVOLUTION

The humoral theory of rejection, rooted in early immunological studies, suggests that antibodies play a crucial role in the rejection of transplanted organs. Its discussion needs to encompass at least three aspects: The discovery of antigens, methods for detecting antibodies, and the clinical KT activity. Emerging in the mid-20th century, humoral theory was based on the discovery of blood group antigens by Landsteiner[16] in 1901 and the identification of HLA by Dausset[17] in 1958. Dausset's discovery earned him a Nobel Prize and provided a critical link between immune recognition and graft rejection[17].

The history of the role of antibodies in KT dates back to the earliest attempts at KT. On December 25, 1952, Oeconomos and Hamburger performed a relatively less publicized KT at Necker Hospital in Paris, France, where a mother donated her kidney to her son. This was the first kidney graft that was removed from a voluntary living donor. No immunosuppression was used. The graft functioned for 21 days and was eventually rejected. A retrospective review of the archived slides revealed mixed acute cellular and humoral rejection[18]. In 1954, the first successful human KT was performed between identical twins by Murray and Merrill, which naturally avoided the problem of immune rejection[19]. Joseph Murray won the Nobel Prize for this great achievement. These examples of KTs demonstrated that immune compatibility was crucial for the success of this procedure and that even genetic proximity was unable to prevent the rejection of a transplanted organ in the absence of immunosuppression. As a consequence, no allotransplantations were performed until 1959 when immunosuppression started to be developed[20]. Subsequently, when an increasing number of allotransplants were attempted, graft rejection emerged as a common and often insurmountable challenge.

In the early days of KT, the primary focus was on cellular mechanisms of rejection, predominantly T-cell mediated responses as these were readily visualized in biopsy tissues under the microscope[5,6]. However, early observations also noted that some patients experienced rapid graft rejection, which could not be fully explained by cellular responses alone. During the same time, researchers also observed that KTs often failed despite the absence of cellular rejection markers on allograft biopsies, suggesting a potential humoral component in the rejection process. In 1960, Kissmeyer-Nielsen *et al*[11] were the first to observe the deleterious impact of allo-antibodies in kidney grafts. Other researchers observed that recipients with pre-existing antibodies against donor HLAs experienced higher rejection rates. Building on these findings, Paul Terasaki, in 1964, developed the microcytotoxicity test, which allowed for the detection of anti-HLA antibodies in recipients, revealing the correlation between these antibodies and transplant outcomes[21]. In 1969, Terasaki and Cai[22] reported on the significance of a positive complement-dependent cytotoxicity (CDC) assay in 225 transplants. Immediate

graft failure occurred in up to 80% (24 out of 30) of grafts carried out in patients with positive cross-match results. This led to the understanding that antibodies, through complement activation and antibody-dependent cellular cytotoxicity (ADCC), can damage graft tissues. These years also saw further advancements in serological techniques, such as the CDC assay, which enabled the detection of DSAs in transplant recipients. These tools allowed researchers to correlate the presence of DSAs with graft outcomes, reinforcing the notion that antibodies played a critical role in rejection[23,24].

The 1980s marked a significant period in transplant immunology with increased recognition of the role of antibodies in graft rejection. Researchers began to understand that antibodies against donor HLA could lead to graft injury. By the 1990s, the clinical significance of antibody-mediated mechanisms in kidney allograft rejection became widely accepted. Pathological criteria for AMR were established, including the identification of peritubular capillaritis, C4d deposition in peritubular capillaries (PTCs), and the presence of DSAs in the circulation[25]. The Banff classification of kidney allograft pathology, first convened in 1991, provided a standardized framework for diagnosing and categorizing rejection processes, including AMR[26,27].

In the 2000s and beyond, research into the molecular and cellular pathways of AMR expanded. Studies revealed the complex interactions between antibodies, complement activation, and endothelial injury[28-30]. Advances in immunosuppressive therapies aimed at reducing antibody production and mitigating complement-mediated damage improved graft survival rates[31-34].

The theory has since evolved with advancements in immunology, leading to improved organ-matching techniques and the development of therapies targeting AMR. Overall, the humoral theory of rejection, spanning over a century of research, underscores the importance of antibodies in transplant immunology and has significantly influenced modern transplantation practices and patient management strategies (Table 1).

ADVANCES IN THE DETECTION OF DSAS

Significant advancements have been made in the field of DSA detection, leading to improved sensitivity, specificity, and clinical utility of these biomarkers. These advancements have significantly improved the management of organ transplantation and the understanding of allorecognition. The key developments include high-throughput screening techniques, improved assay sensitivity, solid-phase assays, and the use of next-generation sequencing (NGS) to identify DSAs at a molecular level, allowing for a more precise understanding of the antibody repertoire and its implications for graft rejection and survival. In addition, advanced bioinformatics tools are being developed to analyze DSA data more effectively, integrating it with other clinical and immunological parameters to predict transplant outcomes. Innovations in wearable technology and point-of-care testing are enabling real-time monitoring of DSAs, facilitating timely interventions in transplant recipients. Understanding the role of DSAs in transplant rejection has led to the development of personalized immunosuppression strategies, aiming to tailor treatment based on individual DSA profiles. Research continues into identifying new biomarkers associated with DSAs and transplant outcomes, improving the ability to predict rejection and graft survival. These advancements contribute to more effective monitoring and management of transplant recipients, leading to better graft survival rates and overall patient outcomes[35].

ADVANCES IN COMPATIBILITY TESTING

Advancements in tissue compatibility testing have significantly improved KT outcomes by reducing the risk of organ rejection and increasing the success and longevity of transplants. Improved HLA typing has become crucial for transplant success, with advances in molecular techniques such as polymerase chain reaction and NGS allowing for more precise HLA matching. This better matching of donor and recipient HLA types reduces rejection risks and improves long-term graft survival. Additionally, crossmatching improvements using flow cytometry and Luminex-based assays have enhanced the detection of pre-existing antibodies in the recipient, such as DSAs, helping predict acute rejection and determine whether a transplant can safely proceed. Virtual crossmatch, a computerized system that simulates donor and recipient tissue interaction, offers faster, more accurate predictions of rejection likelihood, reducing unnecessary transplants and wait times. The introduction of single-antigen bead assays has further helped detect specific anti-HLA antibodies before transplants, allowing the selection of more compatible donors and reducing the risk of AMR. Desensitization protocols, including plasmapheresis and intravenous immunoglobulin (IVIG), are used for patients with high anti-HLA antibody levels, lowering antibody levels and enabling transplantation from less compatible donors, which expands the donor pool and shortens waiting times. Advances in immunosuppressive therapy, tailored to the individual's immunological risk profile, also complement these compatibility tests, further reducing the risk of rejection. Together, these advancements have led to higher KT success rates, longer graft survival, and improved patient outcomes, transforming KT into a more reliable and accessible treatment for end-stage kidney disease[36].

NON-HLA ANTIBODIES

The presence of non-HLA antibodies has been associated with poorer graft survival and increased rejection episodes. Their detection and management are becoming increasingly important in the field of transplantation to improve long-term outcomes and graft longevity[37-40]. These antibodies can be categorized as alloantibodies, which target

Table 1 The main milestones in the history of role of antibodies in kidney transplantation

Period	Key discoveries	Researchers
Early 20th century	Discovery of blood group antigens	Karl Landsteiner
1950s	Identification of human leukocyte antigens (HLA)	Jean Dausset
1952	First kidney transplant between living donor (mother) and son	N. Oeconomas, J. Hamburger
1954	First successful kidney transplant between identical twins	J P Merrill, J Murray
1964	Development of microcytotoxicity assay for detecting anti-HLA antibodies	Paul Terasaki
1970s-1980s	Elucidation of antibody-mediated graft damage mechanisms	Fritz Bach, John D. Dingell
1983	Introduction of flow cytometry and solid-phase assays	Margaret R Garovoy
1990s	Use of C4d in kidney transplant biopsies	H E Feuchet
2005	Virtual cross-match in kidney transplantation	

polymorphic antigens that differ between the recipients and donors, or, more commonly, as autoantibodies which recognize cryptic self-antigens. These antibodies target various non-HLA antigens found in various cells and tissues such as endothelial cells and smooth muscle cells of blood vessels, immune cells, tubular epithelial cells, mesangial cells, and podocytes. As the endothelial layer of the blood vessels is the main structure interjected between the immune system of the recipient and the grafted kidney, most of the antigens that trigger non-HLA autoantibody formation are endothelial autoantigens. Some of the well-studied non-HLA antibodies include anti-endothelial cell antibodies, which target endothelial cells of the transplanted kidney, potentially causing vascular inflammation and injury. Anti-angiotensin II type 1 receptor antibodies (AT1R) were described for the first time by Dragun *et al*[40] in 2005, and has generated the most interest in the KT community for the last 20 years. AT1Rs bind to the angiotensin II receptors on kidney cells and can lead to increased blood pressure and contribute to chronic rejection. Antibodies targeting the major histocompatibility complex class I-related chain A (MICA) glycoproteins were the first non-HLA antibodies described in KTs. Anti-MICA antibodies target the MICA molecules on the surface of endothelial cells and can be associated with graft rejection. Zou *et al*[41] were among the earliest and most important group of researchers to study the role of anti-MICA antibodies in KTs. The possible mechanism of anti-MICA antibody-mediated graft injury involves NKG2D-mediated cytotoxicity and complement-mediated cytotoxicity. Anti-vimentin antibodies target vimentin expressed in vascular endothelial cells, smooth muscle cells, T cells, neutrophils, platelets, epithelial cells, and fibroblasts. These antibodies bind and trigger the complement cascade as evidenced by the positivity of C4d in PTCs in those with chronic AMR. Patients with failing grafts have an increased prevalence of anti-vimentin antibodies in the circulation. Anti-vimentin antibodies have been reported in the context of two major histomorphological lesions: Chronic AMR and IFTA[42]. Anti-perlecan antibodies target perlecan, a heparan sulfate proteoglycan in the kidney's basement membrane, potentially leading to tissue damage and fibrosis[43,44].

SOLID PHASE ASSAYS FOR HLA ANTIBODY DETECTION IN CLINICAL KT

The CDC assay has been used for over 50 years for detecting HLA antibodies in KT recipients. This method has been replaced recently by more sensitive solid phase assays such as ELISA and bead-based technology including the Luminex method. The introduction of these techniques into clinical practice has revealed previously undetected sensitization in some patients and allowed the accurate assignment of antibody specificities directed at HLA-DQ and HLA-DP, which was not previously possible. Luminex flow bead assays offer several advantages over traditional methods for detecting low-titer antibodies, especially in terms of sensitivity, multiplexing capabilities, and the ability to detect a broad range of antibody specificities in a single sample. By combining high sensitivity, multiplexing, and the ability to quantify results accurately, Luminex flow bead assays represent a significant advancement over older methods in detecting low-titer antibodies, particularly in research and clinical settings where precision is critical[45].

ROLE OF ALLOANTIBODIES *VS* AUTOANTIBODIES IN KT

Although most of the literature on the role of antibodies in KT is related to alloantibodies, more recently, many autoantibodies against non-HLA targets have been incriminated in renal allograft injury (Table 2). The list of autoantigens against which these antibodies are directed is growing steadily. In the context of KT, alloantibodies are produced by the recipient's immune cells against non-self antigens from the donor, specifically targeting the donor kidney cells. These antigens are often HLA or blood group antigens. These antibodies often lead to rejection of the allograft kidney because they recognize the donor's kidney as foreign and attack it. They play a significant role in HAR, as well as acute and chronic rejection. They typically form in response to prior sensitization events such as previous transplants, blood transfusions, or pregnancy[46].

Table 2 Common examples of *allo*- and autoantibodies in kidney transplantation

Alloantibodies	ABO blood group antibodies
	Human leukocyte antigen antibodies
	MICA
Autoantibodies	Anti-AT1R
	Anti-ETAR
	Anti-perlecan
	Anti-agrin
	Anti-collagen type IV, III, and I
	Anti-fibronectin
	Anti-vimentin
	Anti-H-Y
	Anti-ARHGDIB
	Anti-PECR
	Anti-PRKCZ
	Anti-Phospholipid antibodies
	Anti-Phospholipase A2 receptors

ATIR: Angiotensin II type 1 receptor; ETAR: Endothelin A receptor; MICA: Major histocompatibility complex class I-related chain antigens; ARHGDIB: Rho guanine nucleotide exchange factor 2; PECR: Peroxisomal trans-2-enoyl-CoA reductase; PRKCZ: Protein kinase C zeta type.

On the other hand, autoantibodies are directed against the recipient's own tissues and antigens (*i.e.*, self-antigens). They are usually involved in autoimmune diseases. In the context of a KT, autoantibodies may be relevant if the recipient has a pre-existing autoimmune condition like lupus nephritis that led to kidney failure. After transplantation, such conditions may reoccur and affect the transplanted kidney. While autoantibodies do not directly cause rejection of a transplanted kidney, they may play a synergistic or additive role with anti-HLA DSAs in causing allograft rejection. However, their role in isolation in the absence of HLA DSA in causing allograft damage remains unknown. These antibodies are formed as a result of a dysfunction of the immune system regulatory pathways or expression of cryptic self-antigens exposed as a result of allograft injury. The concept of kidney damage-mediated autoantibody production leading to augmented kidney injury is not new. In the 1970s, Halloran *et al*[47] reported that rabbits that had rejected mismatched kidney allografts developed antibody-mediated injury in their native kidneys. This early work showed that an alloimmune attack on a kidney graft can result in the development of autoantibodies, possibly through the release or increased immunogenicity of kidney-specific autoantigens.

MECHANISM OF ANTIBODY ACTION IN AMR

AMR is a complex immunological response where DSAs target and attack the graft causing graft dysfunction and ultimately failure. It is now established that immunologic reactions associated with AMR can be triggered by circulating antibodies against donor HLA, non-HLA, or ABO blood group antigens, *i.e.* DSAs. The major mechanism involved in AMR is the activation of the classical complement pathway by the binding of DSAs to HLAs and subsequent binding of the C1 complex, which ultimately leads to the formation of the membrane attack complex (C5b-C9), which destroys the membrane of vascular endothelial cells (Figure 1). Complement activation also generates anaphylatoxins (C3a, C5a) that promote the migration of inflammatory cells, natural killer cells (NK), monocytes, and neutrophils, through the innate immune responses and amplify the inflammatory response[12-17]. Antigen-antibody interaction on endothelial cells is also known to increase von Willebrand factor along with externalization of P-selectin molecules resulting in increased platelet activation and leukocyte trafficking. This activation of the coagulation cascade leads to widespread microvascular injury evident as peritubular capillaritis, glomerulitis, and microvascular thrombosis (Figure 2). Antibodies can also mediate injury *via* complement-independent mechanisms such as ADCC. This is mediated through cells of the innate immune system (NK cells and macrophages). NK cells bind IgG-coated cells through Fcγ RIII receptors (Figure 1). Cytokines released from NK cells like granulysin and granzymes A and B damage endothelial cells[48].

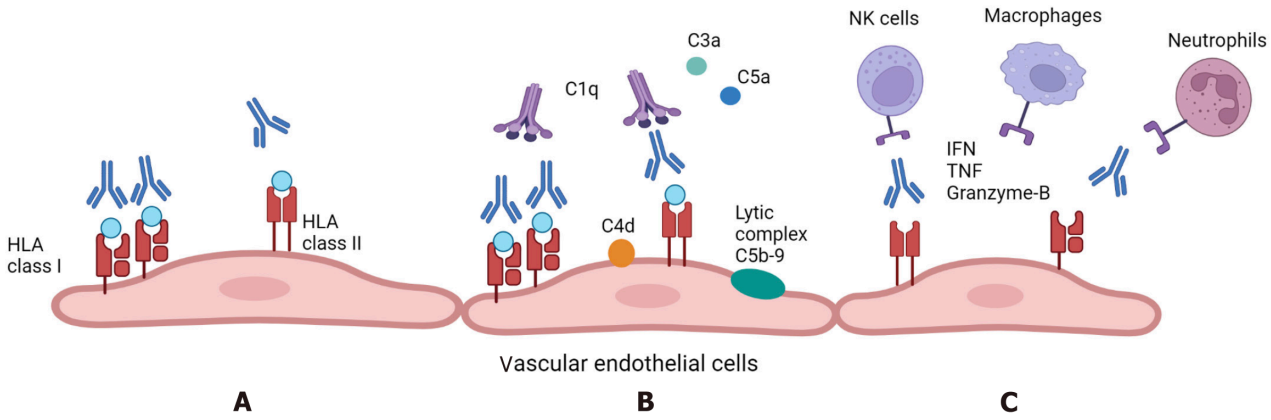


Figure 1 Mechanisms of antibody-mediated graft injury. The chief target of antibodies consists of vascular endothelial cells. A: Antibodies recognize class I and II human leucocyte antigens (HLA) as foreign and bind to them; B: This antibody binding to donor HLA antigens leads to complement-fixing and generation of anaphylatoxins and assembly of the membrane attack complex; C: Antibodies can also damage the graft tissue by antibody-dependent cellular cytotoxicity by engaging inflammatory cells. HLA: Human leucocyte antigen. This figure was created by BioRender.com (Supplementary material).

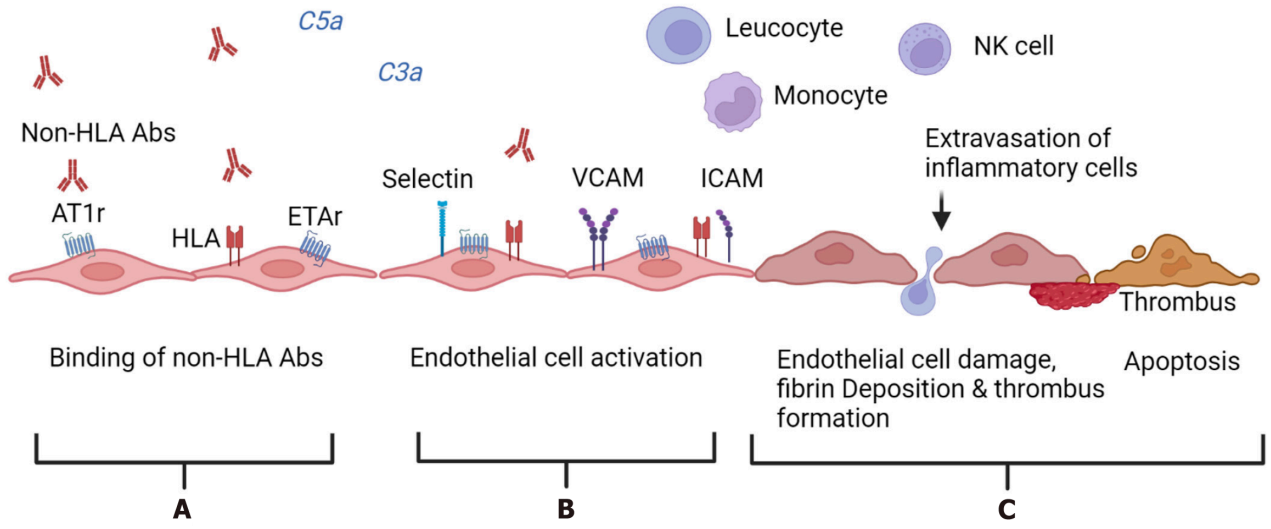


Figure 2 Mechanisms of action of non-human leucocyte antigen antibodies. A: The targets of these antibodies are non-human leucocyte antigens (HLA) molecules expressed on endothelial cells. Non-HLA antibodies recognize various antigens such as angiotensin type 1 receptor and endothelin A receptor on endothelial cells and bind to them; B: This antibody binding to donor non-HLA antigens leads to complement-fixation and generation of anaphylatoxins (C3a and C5a) and recruitment of inflammatory cells. These antibodies can also activate the endothelial cells resulting in increased expression of HLA, non-HLA, and adhesion molecules such as intercellular adhesion molecule and vascular cell adhesion molecule; C: This results in damage to the endothelial cells, initiation of thrombogenesis, and induction of apoptosis of these cells, ultimately resulting in microvascular injury, thrombosis, and inflammation. HLA: Human leucocyte antigen; ICAM: Intercellular adhesion molecule; VCAM: Vascular cell adhesion molecule. This figure was created by BioRender.com (Supplementary material).

ROLE OF NK CELLS IN AMR

The NK cells play a crucial role in mediating allograft injury by alloantibodies by recognizing IgG-coated target cells, inducing cell lysis through ADCC, secreting pro-inflammatory cytokines, and interacting with other immune cells. Their role is crucial in amplifying the immune response against the transplanted organ, leading to tissue injury and dysfunction. NK cells can directly damage endothelial cells in the transplanted organ, which is critical since these cells are often the primary targets in AMR. Damage to the endothelium can lead to thrombosis, inflammation, and graft dysfunction. Understanding the precise mechanisms of NK cell involvement in AMR can help in developing strategies to modulate their activity and improve transplant outcomes[49].

MECHANISM OF ACTION OF NON-HLA ANTIBODIES

Although the literature abounds on the mechanisms of HLA DSAs in inducing graft damage, data are scarce on the specific mechanisms or pathways of action of non-HLA antibodies in this context (Figure 2). Increasing evidence suggests

that these antibodies can act in both an alloimmune and autoimmune manner and may participate in allograft rejection. Several studies have shown that genetic mismatches of non-HLA molecules between the recipient and donor and the alloimmune responses against these molecules are significant predictors of kidney allograft outcome. Reindl-Schwaighofer *et al*[50] reported that genetic mismatches in the immune-accessible transmembrane non-HLA proteins can form DSAs and lead to graft damage. In addition, Steers *et al*[51] have shown that the genomic mismatches at the LIMS1 locus may result in allosensitization in hypoxia-induced conditions and kidney allograft rejection. These discoveries question the significance of non-HLA autoimmunity and suggest that the clinically pertinent non-HLA antibodies in KT may inflict allograft injury through alloimmune mechanisms. As the number of these antibodies is increasing, additional pathways are being explored for their pathogenicity. Non-HLA antibodies can activate the complement cascade, leading to the formation of the membrane attack complex and direct cell lysis. These antibodies can bind to target cells, such as endothelial cells in the graft, and recruit immune cells (*e.g.*, NK cells, macrophages) through their Fc receptors, leading to target cell destruction. In addition, non-HLA antibodies can directly activate endothelial cells, leading to the upregulation of adhesion molecules, pro-inflammatory cytokines, and chemokines, promoting inflammation and immune cell infiltration into the graft. Non-HLA antibodies also induce endothelial cell apoptosis, impairing the integrity of the blood vessels, causing capillary leakiness, and increasing the likelihood of graft thrombosis (Figure 2). It is important to note that the specific mechanisms of action of non-HLA antibodies can vary depending on the target antigen, antibody isotype, and individual patient factors.

PATHOLOGY OF AMR

The pathology of AMR, as for all types of rejection, is closely linked to the history and evolution of the Banff classification (Table 3). The Banff classification is a critical framework in the field of KT, specifically for assessing and categorizing KT pathology. Established during the Banff Conference on Allograft Pathology in 1991 and subsequently immensely updated and modified at consensus meetings held every two years, it provides a standardized system for diagnosing and grading the various forms of transplant-related kidney injuries, particularly acute rejection, and chronic allograft injury. Its key roles include standardization of diagnosis, classification of rejection types, guiding treatment decisions, serving as a benchmark for clinical trials and research, monitoring allograft health, and ultimately improving patient outcomes. Overall, the Banff classification plays a vital role in improving patient outcomes in KT by guiding diagnosis, treatment, and research in transplant pathology[52].

The Banff classification initially included alloantibodies but did not fully encompass their role in transplant injury for lack of evidence. Initially, it was believed that antibodies only affected the immediate post-transplant period[6]. However, over time, evidence showed that antibodies could cause various types of rejection over a longer period, leading to significant changes in the Banff classification (Table 3). Factors contributing to the increased focus on AMR included the identification of the C4d biomarker for AMR, improved detection techniques for anti-donor antibodies, more re-transplants, and higher rates of transplants across immunologic barriers due to organ shortages. AMR primarily targets the endothelial cells in blood vessels, with the severity and type of damage depending on the antibodies involved. The Banff classification's terminology and criteria for AMR have evolved significantly. Initially called HAR, the category was later renamed as AMR and subdivided based on clinical presentation in the Banff 1997 meeting. In 2001, the roles of antibodies beyond the immediate post-transplant period were recognized, and C4d staining and serology were included in diagnostics. For the first time, pathological criteria for diagnosing and classifying AMR were developed in this meeting (Figure 3). Since then, these have evolved and improved significantly over subsequent years to improve AMR's accuracy and clinical relevance. In 2005, criteria for chronic AMR, including specific pathological lesions, were established (Figure 4). In 2007, the category was renamed antibody-mediated changes to reflect the broader spectrum of antibody actions, and a subcategory for C4d deposition without evidence of active rejection was introduced. Further changes included the acceptance of focal C4d staining as a criterion for AMR in 2013, the inclusion of any degree of vascular inflammation ($v > 0$) in AMR diagnosis, and the incorporation of molecular diagnostics into the classification. In 2019, a subtype for chronic inactive AMR was added. Overall, the Banff classification has significantly advanced, particularly in the AMR category, incorporating molecular studies, removing the absolute requirement for C4d and DSAs for diagnosis, and eliminating the "suspicious for AMR" category[5,6,52]. The contemporary approach to diagnosing AMR now incorporates histology, immunohistochemistry (C4d), serology (DSAs), and molecular markers. Future directions include increasing emphasis on molecular diagnostics, the role of non-HLA antibodies, and ongoing refinement of criteria to incorporate new biomarkers and technologies, reflecting advancements in understanding the immunological mechanisms of rejection and the development of more sophisticated diagnostic tools to improve patient outcomes in KT[5,6,52].

SPECIFIC HISTOLOGICAL FEATURES OF CHRONIC AMR

Chronic AMR is characterized by specific histological features that differentiate it from other forms of rejection, particularly T cell-mediated rejection (TCMR) and acute AMR. One hallmark feature is TG, where there is duplication or splitting of the glomerular basement membrane, creating a double contour appearance, which reflects chronic endothelial damage. Another key feature is IF/TA, characterized by widespread fibrosis in the interstitial tissue and atrophy of renal tubules, often seen in chronic rejection but particularly prominent in chronic AMR when accompanied by other changes like TG and vascular involvement. The vascular changes in chronic AMR include peritubular capillary BMML and arterial intimal fibrosis, highlighting chronic antibody-mediated injury. Inflammation involving the PTC, is another

Table 3 Main updates in the nomenclature and classification of antibody-mediated rejection in the Banff classification (1991 to 2019)

Banff meetings, years	Category 2 Antibody-mediated rejection[1]	Basis of diagnosis and classification
Banff '93	Hyperacute rejection	Clinical criteria only
Banff '97	**Antibody-mediated rejection (AMR)**	
	Hyperacute	
	Accelerated acute	
Banff '97 update (2001)	Diagnostic criteria for **acute** antibody-mediated rejection were developed	Histological criteria
	Three types were described as: Types **I. ATN-like; II. Capillary; III. Arterial**	Immunohistopathological criteria
		Serological criteria
Banff '05	Diagnostic criteria for **chronic** antibody-mediated rejection were developed	
Banff '07	Antibody-mediated changes[2]	
	C4d deposition without rejection	
	Acute antibody-mediated rejection	
	Chronic active antibody-mediated rejection	
Banff '13	Antibody-mediated changes	
	Acute/active antibody-mediated rejection	Histological
	Chronic active antibody-mediated rejection	Immunohistopathological
	C4d-negative antibody-mediated rejection	Serological
Banff '15	Antibody-mediated changes	Molecular criteria
	Acute/active antibody-mediated rejection	
	Chronic active antibody-mediated rejection	
	C4d staining without evidence of rejection	
	Transplant arteriopathy may be seen in chronic	
	AMR	
Banff '17	Antibody-mediated changes	
	Active AMR	
	Chronic active AMR	
	C4d staining without evidence of rejection	
	3 criteria for AMR diagnosis remain but C4d	
	can substitute for DSA	
	DSA testing still advised	
	Suspicious for AMR eliminated	
Banff '19	Category 2: Antibody-mediated changes	Histological
	Active ABMR	Immunohistopathological
	Chronic active ABMR	Serological
	Chronic (inactive) ABMR	Molecular criteria
	C4d staining without evidence of rejection	Electron microscopy

[1]May coincide with categories 3, 4 and 5 and 6.
[2]With the identification of C4d positivity without rejection, the category name was changed from rejection to changes.
Changes in the nomenclature or criteria are in bold face.

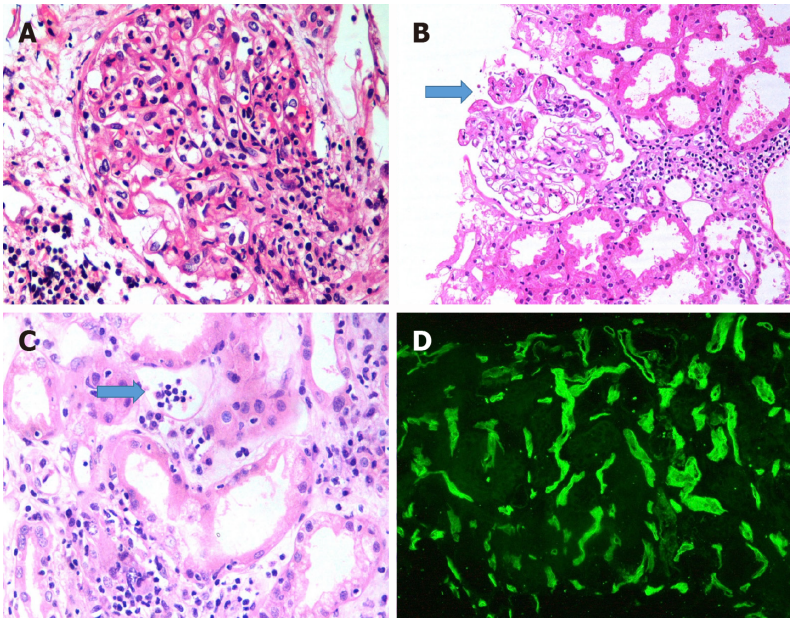


Figure 3 Pathology of acute antibody-mediated graft injury. The principal target of antibodies is the microcirculation and larger blood vessels. A: Severe glomerulitis. Many of the glomerular capillary lumens are obliterated by inflammatory cell infiltration (HE, × 400); B: A glomerulus showing fibrin thrombi obliterating some of the capillary lumens (arrow) (HE, × 200); C: A focus of moderate peritubular capillaritis (ptc2) (arrow) (HE, × 400); D: Diffuse C4d positivity (C4d) (C4d3) in peritubular capillaries (FITC, IF for C4d, × 200).

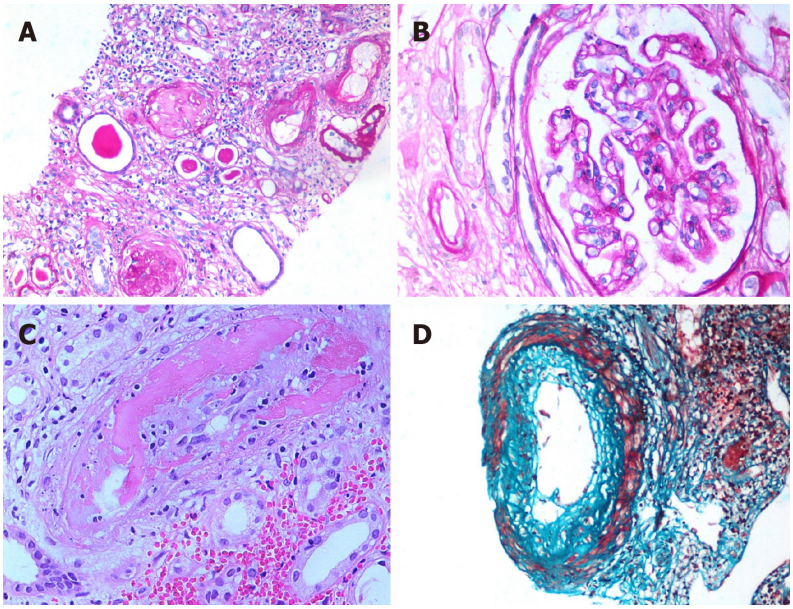


Figure 4 Pathology of acute and chronic antibody-mediated graft injury. The principal target of antibodies is the microcirculation and larger blood vessels. A: Severe interstitial fibrosis and tubular atrophy. This lesion is entirely non-specific and may result from a variety of immune and non-immune causes [Periodic acid-Schiff (PAS) stain, × 200]; B: A glomerulus showing double contouring of capillary walls and an occasional inflammatory cell infiltration obliterating the capillary lumen (arrow) (PAS, × 400); C: A small artery exhibiting fibrinoid necrosis of the wall (v3). This lesion is strongly suggestive of active antibody-mediated rejection (AMR) (HE, × 400); D: Moderate fibrointimal thickening of an interlobular size artery. This lesion may be seen in chronic AMR as well as chronic T cell-mediated rejection (Trichrome stain, × 400).

important feature, often presenting with mononuclear cell infiltration and suggesting ongoing endothelial damage. Additionally, C4d deposition along the PTCs, detected through immunohistochemical staining, is a distinctive marker of antibody-mediated complement activation, often persistent in chronic AMR and less commonly seen in TCMR. These histological features, particularly the presence of TG, vascular lesions, PTC, and C4d positivity, are critical in identifying chronic AMR and distinguishing it from other types of graft rejection[52].

USE OF ANTIBODIES IN THE TREATMENT OF AMR

The management of AMR has evolved with the understanding of its immunopathology and therapeutic options have expanded markedly. Traditional treatments included plasmapheresis, IVIG, and high-dose steroids. The addition of anti-CD20 monoclonal antibodies which deplete B cells, has improved outcomes in refractory cases. Eculizumab is a monoclonal antibody that targets complement protein C5. Eculizumab binding to this protein prevents activation of the terminal complement complex (C5b-C9). It has been used to prevent complement-mediated damage during AMR. Moreover, proteasome inhibitors targeting antibody-producing plasma cells are being investigated for their potential to treat AMR. An alternative approach to B cell or plasma-cell depletion is to target key cytokine/cytokine receptors that support the activation/proliferation of these antibody-producing cells. In this context, there is an emerging focus on the interleukin 6 (IL-6)/IL-6R pathway, which has several roles related to AMR. Personalized treatment strategies based on the specific immunologic profile of each patient are becoming more common, aiming to improve graft survival and function[53-57].

USE OF ANTIBODIES AND NOVEL BIOMARKERS AS DIAGNOSTIC AND MONITORING TOOLS

Advances in diagnostic techniques such as the solid phase Luminex assay have improved the detection and monitoring of DSAs. The development of non-invasive biomarkers, such as donor-derived cell-free DNA (dd-cfDNA) and gene expression profiling, provides early detection of rejection and monitoring of graft wellbeing. These tools enable timely intervention and personalized treatment adjustments, enhancing the optimal management of KT recipients[58].

dd-cfDNA is a promising non-invasive biomarker that has significantly improved monitoring in KT. Studies have shown that dd-cfDNA can detect rejection earlier than traditional methods, with high sensitivity and specificity. The reported sensitivity rates of dd-cfDNA for the detection of early rejection have varied from 80% to 90%, which is higher than serum creatinine or proteinuria, especially for acute rejection cases. Similarly, the specificity rates have ranged between 80%-95%, which reduces the chances of false positives when compared to other non-invasive markers.

dd-cfDNA improves graft rejection surveillance by detecting the rejection early with increased sensitivity and may prevent the need for invasive biopsies. Elevated dd-cfDNA can help distinguish between antibody-mediated and T-cell mediated rejections, guiding tailored immunosuppressive therapies. dd-cfDNA levels can be monitored to assess the effectiveness of immunosuppressive treatments, allowing for personalized adjustments. Studies suggest that dd-cfDNA monitoring can contribute to improved long-term graft survival rates. Early detection and intervention facilitated by dd-cfDNA monitoring can potentially reduce the need for costly interventions and hospitalizations[59].

ADVANCEMENTS IN DESENSITIZATION PROTOCOLS

Desensitization protocols emerged in the early 1990s to deal with the large numbers of HLA-incompatible patients waiting on maintenance hemodialysis[60]. Two largely accepted desensitization protocols include high-dose IVIG from Cedars-Sinai Medical Center and low-dose IVIG from John Hopkins Hospital, the latter in combination with plasmapheresis. These protocols typically involve combinations of plasmapheresis, IVIG, and rituximab, with the aims of reducing antibody levels and reducing the risk of AMR. Other protocols are modifications of these two protocols. Low-dose IVIG and plasmapheresis are used in ABO-incompatible and HLA-incompatible transplants, while high-dose IVIG is used to desensitize both living donor cross-match positive and highly sensitized deceased donation recipients on the waiting list. Recent advancements include the use of Imlifidase, a cysteine protease novel enzyme derived from the bacterium *Streptococcus pyogenes*, designed to cleave IgG in a quick initial reaction and subsequently 2 F(ab')2 fragments and a fully separated Fc fragment in a slower subsequent reaction. A single dose is given within 24 hours before transplantation to obtain a negative cross-match. Imlifidase application in KT, in desensitization protocols, represents a significant advancement for patients with high levels of DSA especially those who are resistant to conventional desensitization therapy. Overall, imlifidase represents a promising advancement in the field of KT, offering hope to many patients who previously had limited options due to high levels of DSAs. These therapies target various aspects of the immune response, offering new hope for highly sensitized patients[61-65].

BENEFICIAL ROLES OF ANTIBODIES

Not all antibodies are detrimental to the transplanted organ. Some antibodies may play a role in the accommodation/acceptance of the transplanted organs. In addition, antibodies are being explored for their potential therapeutic benefits. For instance, IVIG, initially used for desensitization and AMR treatment, has immunomodulatory properties that can enhance immune regulation and promote tolerance. Monoclonal antibodies targeting specific immune pathways, such as anti-CD40 and anti-IL-6, are being used for their ability to prevent rejection while minimizing immunosuppression-related complications[66-68]. Some antibodies could suppress the activity of certain immune cells (*e.g.*, T cells, NK cells) that would otherwise attack the graft. They might promote the production of molecules that protect the graft from immune damage. In some cases, the presence of certain antibodies might actually prevent the formation or effectiveness of other, more harmful antibodies. This could be through competition for binding sites, effectively neutralizing the

harmful ones or regulation of immune response. Emerging research suggests that even in the presence of DSAs, certain antibody profiles might be associated with better graft survival. This suggests a complex interplay between different antibody types and their overall effect on the graft. It is important to note that the concept of beneficial antibodies in transplantation is still under investigation. Identifying and characterizing these antibodies is crucial for developing strategies to promote transplant tolerance. This area of research holds great promise for improving long-term transplant outcomes by harnessing the power of the immune system itself[67,68].

TREATMENT OF AMR

The treatment strategies in AMR aim to reduce or eliminate DSAs and control the immune response to minimize graft damage and prolong graft survival. Treatments for AMR can be classified into traditional approaches and emerging therapies (Table 4). Traditional treatments like plasmapheresis, IVIG, and rituximab remain the backbone of AMR management, but emerging therapies such as eculizumab and imlifidase are showing promise in refractory cases. In clinical practice, AMR is often treated using a multi-modality approach. Combining plasmapheresis with IVIG and rituximab, for example, can help control antibody levels while suppressing B cell activity. Ongoing research into these treatments continues to refine AMR management strategies, particularly for patients who do not respond to conventional therapies[69].

Table 4 Examples of some traditional and emerging therapies in kidney transplantation

Traditional therapies	**Plasmapheresis**
	Immunoadsorption
	Intravenous immunoglobulin
	Anti-CD20 monoclonal antibody rituximab
	Complement inhibitors: Eculizumab, C1 INH
	Proteasome inhibitors: Bortezomib
Emerging therapies	Carfilzomib
	Tocilizumab
	Clazakizumab
	Daratumumab
	Belimumab
	Imlifidase
	Ofatumumab
	Obinutuzumab
	Inebilizumab

CURRENT STATUS OF ANTIBODIES IN KT

Today, the humoral theory of kidney allograft rejection is well-established and integral to transplant medicine. It underscores the importance of pre-transplant antibody screening, perioperative management, and post-transplant monitoring for the presence of DSAs[70]. Diagnostic techniques, such as solid-phase assays for DSA detection and molecular profiling of graft biopsies, have enhanced the precision of AMR diagnosis. Ongoing research focuses on novel therapeutic strategies to prevent and treat AMR, aiming to improve long-term outcomes for KT recipients[71-73].

In recent years, the role of antibodies in KT has continued to evolve with the advent of NGS and more sophisticated immunological assays. These technologies allow for even more precise matching and monitoring of donor-recipient pairs, reducing the risk of rejection and improving long-term outcomes[74-77].

Improvements in compatibility testing between donor and recipient may also decrease the risk of allograft rejection and increase survival of the transplant. The better matched the donor and the recipient are, the more tolerant the recipient's immune system will be to the transplanted organ or tissue. Additionally, a greater understanding of the disparity between the donor and recipient will better inform treatment strategies after transplantation and help avoid repeated episodes of AR[78-81]. Immunological research has resulted in huge advancements in transplant medicine. However, immune rejection still remains the most formidable barrier to successful transplantation.

FUTURE PERSPECTIVES

Ongoing research into the mechanisms of antibody-mediated injury and the development of targeted therapies will further improve outcomes for KT recipients. The future of antibody-based therapies in KT lies in precision medicine and the development of more effective immunomodulatory therapies and the potential for tolerance induction. Understanding the unique immunologic landscape of each patient will enable tailored desensitization protocols and rejection treatments. Additionally, the integration of novel diagnostic tools and biomarkers will facilitate real-time monitoring and early intervention. Research into gene therapy, cellular therapies, and other innovative approaches is also ongoing, and aims to achieve long-term graft acceptance without the need for lifelong immunosuppression. Continual research is needed to find ways to decrease the risk of rejection, improve diagnosis, and maintain long-term survival of the transplant; all of which would have a significant impact on long-term graft and patient survival[82-86].

CONCLUSION

In summary, the history of the role of antibodies in KT reflects a journey of discovery, innovation, and clinical application. The humoral theory of kidney allograft rejection highlights the crucial role of antibodies in transplant rejection, from initial observations of HAR to sophisticated modern diagnostic and therapeutic approaches. The history of the role of antibodies in KT is a testament to the advances in immunology and medical science. These advances have significantly influenced the management and success of KT.

FOOTNOTES

Author contributions: Abbas K and Mubarak M contributed equally to the conception and study design. All authors performed relevant research, participated in primary and final drafting, and read and approved the final manuscript.

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REFERENCES

1 **Galliford J**, Game DS. Modern renal transplantation: present challenges and future prospects. *Postgrad Med J* 2009; **85**: 91-101 [PMID: 19329704 DOI: 10.1136/pgmj.2008.070862]
2 **Tantisattamo E**, Maggiore U, Piccoli GB. History of kidney transplantation: a journey of progression and evolution for success. *J Nephrol* 2022; **35**: 1783-1786 [PMID: 36040564 DOI: 10.1007/s40620-022-01453-3]
3 **Nordham KD**, Ninokawa S. The history of organ transplantation. *Proc (Bayl Univ Med Cent)* 2022; **35**: 124-128 [PMID: 34970061 DOI: 10.1080/08998280.2021.1985889]
4 **Mccauley J**. A History of Kidney Transplantation. *Contemp Kidney Transplant* 2018 [DOI: 10.1007/978-3-319-14779-6_1-2]
5 **Loupy A**, Mengel M, Haas M. Thirty years of the International Banff Classification for Allograft Pathology: the past, present, and future of kidney transplant diagnostics. *Kidney Int* 2022; **101**: 678-691 [PMID: 34922989 DOI: 10.1016/j.kint.2021.11.028]
6 **Mubarak M**, Raza A, Rashid R, Shakeel S. Evolution of human kidney allograft pathology diagnostics through 30 years of the Banff classification process. *World J Transplant* 2023; **13**: 221-238 [PMID: 37746037 DOI: 10.5500/wjt.v13.i5.221]
7 **Terasaki PI**. Humoral theory of transplantation. *Am J Transplant* 2003; **3**: 665-673 [PMID: 12780557 DOI: 10.1034/j.1600-6143.2003.00135.x]
8 **Lefaucheur C**, Viglietti D, Mangiola M, Loupy A, Zeevi A. From Humoral Theory to Performant Risk Stratification in Kidney Transplantation. *J Immunol Res* 2017; **2017**: 5201098 [PMID: 28133619 DOI: 10.1155/2017/5201098]
9 **Terasaki PI**. A personal perspective: 100-year history of the humoral theory of transplantation. *Transplantation* 2012; **93**: 751-756 [PMID: 22453870 DOI: 10.1097/TP.0b013e3182483713]
10 **Filippone EJ**, Farber JL. The Humoral Theory of Transplantation: Epitope Analysis and the Pathogenicity of HLA Antibodies. *J Immunol Res* 2016; **2016**: 5197396 [PMID: 28070526 DOI: 10.1155/2016/5197396]
11 **Kissmeyer-Nielsen F**, Olsen S, Petersen VP, Fjeldborg O. Hyperacute rejection of kidney allografts, associated with pre-existing humoral

antibodies against donor cells. *Lancet* 1966; **2**: 662-665 [PMID: 4162350 DOI: 10.1016/s0140-6736(66)92829-7]
12 **Baldwin W 3rd**, Valujskikh A. Mechanisms Underlying Antibody-Mediated Rejection. *Circulation* 2020; **141**: 479-481 [PMID: 32078432 DOI: 10.1161/CIRCULATIONAHA.119.044541]
13 **Baldwin WM 3rd**, Valujskikh A, Fairchild RL. Mechanisms of antibody-mediated acute and chronic rejection of kidney allografts. *Curr Opin Organ Transplant* 2016; **21**: 7-14 [PMID: 26575854 DOI: 10.1097/MOT.0000000000000262]
14 **Wang S**, Zhang C, Wang J, Yang C, Xu M, Rong R, Zhu T, Zhu D. Endothelial Cells in Antibody-Mediated Rejection of Kidney Transplantation: Pathogenesis Mechanisms and Therapeutic Implications. *J Immunol Res* 2017; **2017**: 8746303 [PMID: 28255564 DOI: 10.1155/2017/8746303]
15 **Chong AS**. Mechanisms of organ transplant injury mediated by B cells and antibodies: Implications for antibody-mediated rejection. *Am J Transplant* 2020; **20** Suppl 4: 23-32 [PMID: 32538534 DOI: 10.1111/ajt.15844]
16 **Landsteiner K**. Ueber Agglutinationser-scheinungen normalen menschlichen Blutes. *Wien Clin Wschr* 1901; **14**: 1132-1134
17 **DAUSSET J**. [Iso-leuko-antibodies]. *Acta Haematol* 1958; **20**: 156-166 [PMID: 13582558 DOI: 10.1159/000205478]
18 **18 Callemeyn J**, Lamarthée B, Koenig A, Koshy P, Thaunat O, Naesens M. Allorecognition and the spectrum of kidney transplant rejection. *Kidney Int* 2022; **101**: 692-710 [PMID: 34915041 DOI: 10.1016/j.kint.2021.11.029]
19 **Kreis H**, Noël LH, Legendre C. The first transplant kidney biopsy ever performed. *Am J Transplant* 2013; **13**: 1367-1368 [PMID: 23621165 DOI: 10.1111/ajt.12214]
20 **Merrill JP**, Murray JE, Harrison JH, Guild WR. Successful homotransplantation of the human kidney between identical twins. *J Am Med Assoc* 1956; **160**: 277-282 [PMID: 13278189 DOI: 10.1001/jama.1956.02960390027008]
21 **Tilney NL**. Renal transplantation between identical twins: a review. *World J Surg* 1986; **10**: 381-388 [PMID: 3524026 DOI: 10.1007/BF01655297]
22 **Terasaki PI**, Cai J. Humoral theory of transplantation: further evidence. *Curr Opin Immunol* 2005; **17**: 541-545 [PMID: 16098722 DOI: 10.1016/j.coi.2005.07.018]
23 **Patel R**, Terasaki PI. Significance of the positive crossmatch test in kidney transplantation. *N Engl J Med* 1969; **280**: 735-739 [PMID: 4886455 DOI: 10.1056/NEJM196904032801401]
24 **Valenzuela NM**, McNamara JT, Reed EF. Antibody-mediated graft injury: complement-dependent and complement-independent mechanisms. *Curr Opin Organ Transplant* 2014; **19**: 33-40 [PMID: 24316758 DOI: 10.1097/MOT.0000000000000040]
25 **Colvin RB**. Antibody-mediated renal allograft rejection: diagnosis and pathogenesis. *J Am Soc Nephrol* 2007; **18**: 1046-1056 [PMID: 17360947 DOI: 10.1681/ASN.2007010073]
26 **Racusen LC**, Colvin RB, Solez K, Mihatsch MJ, Halloran PF, Campbell PM, Cecka MJ, Cosyns JP, Demetris AJ, Fishbein MC, Fogo A, Furness P, Gibson IW, Glotz D, Hayry P, Hunsickern L, Kashgarian M, Kerman R, Magil AJ, Montgomery R, Morozumi K, Nickeleit V, Randhawa P, Regele H, Seron D, Seshan S, Sund S, Trpkov K. Antibody-mediated rejection criteria - an addition to the Banff 97 classification of renal allograft rejection. *Am J Transplant* 2003; **3**: 708-714 [PMID: 12780562 DOI: 10.1034/j.1600-6143.2003.00072.x]
27 **Solez K**. History of the Banff classification of allograft pathology as it approaches its 20th year. *Curr Opin Organ Transplant* 2010; **15**: 49-51 [PMID: 19949334 DOI: 10.1097/MOT.0b013e328334fedb]
28 **Solez K**, Racusen LC. The Banff classification revisited. *Kidney Int* 2013; **83**: 201-206 [PMID: 23235566 DOI: 10.1038/ki.2012.395]
29 **Kenta I**, Takaaki K. Molecular Mechanisms of Antibody-Mediated Rejection and Accommodation in Organ Transplantation. *Nephron* 2020; **144** Suppl 1: 2-6 [PMID: 33238285 DOI: 10.1159/000510747]
30 **Halloran PF**, Madill-Thomsen KS, Pon S, Sikosana MLN, Böhmig GA, Bromberg J, Einecke G, Eskandary F, Gupta G, Hidalgo LG, Myslak M, Viklicky O, Perkowska-Ptasinska A; INTERCOMEX Investigators. Molecular diagnosis of ABMR with or without donor-specific antibody in kidney transplant biopsies: Differences in timing and intensity but similar mechanisms and outcomes. *Am J Transplant* 2022; **22**: 1976-1991 [PMID: 35575435 DOI: 10.1111/ajt.17092]
31 **Garg N**, Samaniego MD, Clark D, Djamali A. Defining the phenotype of antibody-mediated rejection in kidney transplantation: Advances in diagnosis of antibody injury. *Transplant Rev (Orlando)* 2017; **31**: 257-267 [PMID: 28882367 DOI: 10.1016/j.trre.2017.08.005]
32 **Gatault P**, Büchler M. Unraveling complexity of antibody-mediated rejections, the mandatory way towards an accurate diagnosis and a personalized treatment. *Presse Med* 2022; **51**: 104141 [PMID: 36209931 DOI: 10.1016/j.lpm.2022.104141]
33 **Lai X**, Zheng X, Mathew JM, Gallon L, Leventhal JR, Zhang ZJ. Tackling Chronic Kidney Transplant Rejection: Challenges and Promises. *Front Immunol* 2021; **12**: 661643 [PMID: 34093552 DOI: 10.3389/fimmu.2021.661643]
34 **Eller K**, Böhmig GA, Banas MC, Viklicky O. Editorial: Advances in the diagnosis and treatment in kidney transplantation. *Front Med (Lausanne)* 2022; **9**: 967749 [PMID: 35991631 DOI: 10.3389/fmed.2022.967749]
35 **Zhang R**. Donor-Specific Antibodies in Kidney Transplant Recipients. *Clin J Am Soc Nephrol* 2018; **13**: 182-192 [PMID: 28446536 DOI: 10.2215/CJN.00700117]
36 **Bhaskaran MC**, Heidt S, Muthukumar T. Principles of Virtual Crossmatch Testing for Kidney Transplantation. *Kidney Int Rep* 2022; **7**: 1179-1188 [PMID: 35685330 DOI: 10.1016/j.ekir.2022.03.006]
37 **Sorohan BM**, Baston C, Tacu D, Bucșa C, Țincu C, Vizireanu P, Sinescu I, Constantinescu I. Non-HLA Antibodies in Kidney Transplantation: Immunity and Genetic Insights. *Biomedicines* 2022; **10** [PMID: 35884811 DOI: 10.3390/biomedicines10071506]
38 **Dragun D**, Catar R, Philippe A. Non-HLA antibodies in solid organ transplantation: recent concepts and clinical relevance. *Curr Opin Organ Transplant* 2013; **18**: 430-435 [PMID: 23838648 DOI: 10.1097/MOT.0b013e3283636e55]
39 **Dragun D**, Hegner B. Non-HLA antibodies post-transplantation: clinical relevance and treatment in solid organ transplantation. *Contrib Nephrol* 2009; **162**: 129-139 [PMID: 19001820 DOI: 10.1159/000170845]
40 **Dragun D**, Müller DN, Bräsen JH, Fritsche L, Nieminen-Kelhä M, Dechend R, Kintscher U, Rudolph B, Hoebeke J, Eckert D, Mazak I, Plehm R, Schönemann C, Unger T, Budde K, Neumayer HH, Luft FC, Wallukat G. Angiotensin II type 1-receptor activating antibodies in renal-allograft rejection. *N Engl J Med* 2005; **352**: 558-569 [PMID: 15703421 DOI: 10.1056/NEJMoa035717]
41 **Zou Y**, Stastny P, Süsal C, Döhler B, Opelz G. Antibodies against MICA antigens and kidney-transplant rejection. *N Engl J Med* 2007; **357**: 1293-1300 [PMID: 17898098 DOI: 10.1056/NEJMoa067160]
42 **Carter V**, Shenton BK, Jaques B, Turner D, Talbot D, Gupta A, Chapman CE, Matthews CJ, Cavanagh G. Vimentin antibodies: a non-HLA antibody as a potential risk factor in renal transplantation. *Transplant Proc* 2005; **37**: 654-657 [PMID: 15848491 DOI: 10.1016/j.transproceed.2004.12.043]
43 **Dieudé M**, Cardinal H, Hébert MJ. Injury derived autoimmunity: Anti-perlecan/LG3 antibodies in transplantation. *Hum Immunol* 2019; **80**:

608-613 [PMID: 31029511 DOI: 10.1016/j.humimm.2019.04.009]
44 **Riesco L**, Irure J, Rodrigo E, Guiral S, Ruiz JC, Gómez J, López-Hoyos M, San Segundo D. Anti-perlecan antibodies and acute humoral rejection in hypersensitized patients without forbidden HLA specificities after kidney transplantation. *Transpl Immunol* 2019; **52**: 53-56 [PMID: 30458294 DOI: 10.1016/j.trim.2018.11.002]
45 **Halloran PF**, Einecke G, Sikosana MLN, Madill-Thomsen K. The Biology and Molecular Basis of Organ Transplant Rejection. *Handb Exp Pharmacol* 2022; **272**: 1-26 [PMID: 35091823 DOI: 10.1007/164_2021_557]
46 **Gosset C**, Lefaucheur C, Glotz D. New insights in antibody-mediated rejection. *Curr Opin Nephrol Hypertens* 2014; **23**: 597-604 [PMID: 25211610 DOI: 10.1097/MNH.0000000000000069]
47 **Halloran PF**, Famulski K, Reeve J. The molecular phenotypes of rejection in kidney transplant biopsies. *Curr Opin Organ Transplant* 2015; **20**: 359-367 [PMID: 25944235 DOI: 10.1097/MOT.0000000000000193]
48 **Chakravorty S**, Aryal S, Cochrane A, Nathan SD. Antibody-Mediated Rejection: Mechanisms, Pathology, and Therapeutics. *Curr Pulmonol Rep* 2024; **13**: 173-182 [DOI: 10.1007/s13665-024-00349-w]
49 **Metter C**, Torrealba JR. Pathology of the kidney allograft. *Semin Diagn Pathol* 2020; **37**: 148-153 [PMID: 32249077 DOI: 10.1053/j.semdp.2020.03.005]
50 **Reindl-Schwaighofer R**, Heinzel A, Kainz A, van Setten J, Jelencsics K, Hu K, Loza BL, Kammer M, Heinze G, Hruba P, Koňaříková A, Viklicky O, Boehmig GA, Eskandary F, Fischer G, Claas F, Tan JC, Albert TJ, Patel J, Keating B, Oberbauer R; iGeneTRAiN consortium. Contribution of non-HLA incompatibility between donor and recipient to kidney allograft survival: genome-wide analysis in a prospective cohort. *Lancet* 2019; **393**: 910-917 [PMID: 30773281 DOI: 10.1016/S0140-6736(18)32473-5]
51 **Steers NJ**, Li Y, Drace Z, D'Addario JA, Fischman C, Liu L, Xu K, Na YJ, Neugut YD, Zhang JY, Sterken R, Balderes O, Bradbury D, Ozturk N, Ozay F, Goswami S, Mehl K, Wold J, Jelloul FZ, Rohanizadegan M, Gillies CE, Vasilescu EM, Vlad G, Ko YA, Mohan S, Radhakrishnan J, Cohen DJ, Ratner LE, Scolari F, Susztak K, Sampson MG, Deaglio S, Caliskan Y, Barasch J, Courtney AE, Maxwell AP, McKnight AJ, Ionita-Laza I, Bakker SJL, Snieder H, de Borst MH, D'Agati V, Amoroso A, Gharavi AG, Kiryluk K. Genomic Mismatch at LIMS1 Locus and Kidney Allograft Rejection. *N Engl J Med* 2019; **380**: 1918-1928 [PMID: 31091373 DOI: 10.1056/NEJMoa1803731]
52 **52 Naesens M**, Roufosse C, Haas M, Lefaucheur C, Mannon RB, Adam BA, Aubert O, Böhmig GA, Callemeyn J, Clahsen-van Groningen M, Cornell LD, Demetris AJ, Drachenberg CB, Einecke G, Fogo AB, Gibson IW, Halloran P, Hidalgo LG, Horsfield C, Huang E, Kikić Ž, Kozakowski N, Nankivell B, Rabant M, Randhawa P, Riella LV, Sapir-Pichhadze R, Schinstock C, Solez K, Tambur AR, Thaunat O, Wiebe C, Zielinski D, Colvin R, Loupy A, Mengel M. The Banff 2022 Kidney Meeting Report: Reappraisal of microvascular inflammation and the role of biopsy-based transcript diagnostics. *Am J Transplant* 2024; **24**: 338-349 [PMID: 38032300 DOI: 10.1016/j.ajt.2023.10.016]
53 **Abbas K**, Aziz T, Musharaf W, Mubarak M, Zafar MN. Impact of pre-transplant donor specific antibodies detected by Luminex with negative microlymphocytotoxicity assay and flow crossmatch in live-related renal transplant recipients. *Clin Transplant* 2023; **37**: e14935 [PMID: 36799009 DOI: 10.1111/ctr.14935]
54 **Nickerson PW**. What have we learned about how to prevent and treat antibody-mediated rejection in kidney transplantation? *Am J Transplant* 2020; **20** Suppl 4: 12-22 [PMID: 32538535 DOI: 10.1111/ajt.15859]
55 **Abuazzam F**, Dubrawka C, Abdulhadi T, Amurao G, Alrata L, Yaseen Alsabbagh D, Alomar O, Alhamad T. Emerging Therapies for Antibody-Mediated Rejection in Kidney Transplantation. *J Clin Med* 2023; **12** [PMID: 37568318 DOI: 10.3390/jcm12154916]
56 **Park BH**, Kim YN, Shin HS. New treatment for antibody-mediated rejection: interleukin-6 inhibitors. *Clin Transplant Res* 2024; **38**: 1-6 [PMID: 38725179 DOI: 10.4285/ctr.23.0069]
57 **Ding Y**, Francis J, Gautam A, Pelletier L, Sanchorawala V, Quillen K. Durable renal response after combination of bortezomib, corticosteroids, rituximab, and plasmapheresis for late antibody-mediated renal transplant rejection. *Clin Nephrol* 2018; **89**: 252-259 [PMID: 29208204 DOI: 10.5414/CN109278]
58 **Halloran PF**, Reeve J, Madill-Thomsen KS, Demko Z, Prewett A, Gauthier P, Billings P, Lawrence C, Lowe D, Hidalgo LG; the Trifecta Investigators. Antibody-mediated Rejection Without Detectable Donor-specific Antibody Releases Donor-derived Cell-free DNA: Results From the Trifecta Study. *Transplantation* 2023; **107**: 709-719 [PMID: 36190186 DOI: 10.1097/TP.0000000000004324]
59 **Johnson AC**, Silva JAF, Kim SC, Larsen CP. Progress in kidney transplantation: The role for systems immunology. *Front Med (Lausanne)* 2022; **9**: 1070385 [PMID: 36590970 DOI: 10.3389/fmed.2022.1070385]
60 **Barbetta A**, Rocque B, Sarode D, Bartlett JA, Emamaullee J. Revisiting transplant immunology through the lens of single-cell technologies. *Semin Immunopathol* 2023; **45**: 91-109 [PMID: 35980400 DOI: 10.1007/s00281-022-00958-0]
61 **Jordan SC**, Choi J, Vo A. Kidney transplantation in highly sensitized patients. *Br Med Bull* 2015; **114**: 113-125 [PMID: 25935575 DOI: 10.1093/bmb/ldv013]
62 **Noble J**, Jouve T, Malvezzi P, Rostaing L. Desensitization in Crossmatch-positive Kidney Transplant Candidates. *Transplantation* 2023; **107**: 351-360 [PMID: 35939390 DOI: 10.1097/TP.0000000000004279]
63 **Thielke JJ**, West-Thielke PM, Herren HL, Bareato U, Ommert T, Vidanovic V, Campbell-Lee SA, Tzvetanov IG, Sankary HN, Kaplan B, Benedetti E, Oberholzer J. Living donor kidney transplantation across positive crossmatch: the University of Illinois at Chicago experience. *Transplantation* 2009; **87**: 268-273 [PMID: 19155983 DOI: 10.1097/TP.0b013e3181919a16]
64 **Mustian MN**, Locke JE. Positive Crossmatch Kidney Transplantation: State of the Art and Future Perspectives. *Curr Pharm Des* 2020; **26**: 3460-3467 [PMID: 32436820 DOI: 10.2174/1381612826666200521141749]
65 **Vo AA**, Lukovsky M, Toyoda M, Wang J, Reinsmoen NL, Lai CH, Peng A, Villicana R, Jordan SC. Rituximab and intravenous immune globulin for desensitization during renal transplantation. *N Engl J Med* 2008; **359**: 242-251 [PMID: 18635429 DOI: 10.1056/NEJMoa0707894]
66 **Marfo K**, Lu A, Ling M, Akalin E. Desensitization protocols and their outcome. *Clin J Am Soc Nephrol* 2011; **6**: 922-936 [PMID: 21441131 DOI: 10.2215/CJN.08140910]
67 **Mamode N**, Bestard O, Claas F, Furian L, Griffin S, Legendre C, Pengel L, Naesens M. European Guideline for the Management of Kidney Transplant Patients With HLA Antibodies: By the European Society for Organ Transplantation Working Group. *Transpl Int* 2022; **35**: 10511 [PMID: 36033645 DOI: 10.3389/ti.2022.10511]
68 **Platt JL**. Antibodies in transplantation. *Discov Med* 2010; **10**: 125-133 [PMID: 20807473]
69 **Butler CL**, Valenzuela NM, Thomas KA, Reed EF. Not All Antibodies Are Created Equal: Factors That Influence Antibody Mediated Rejection. *J Immunol Res* 2017; **2017**: 7903471 [PMID: 28373996 DOI: 10.1155/2017/7903471]
70 **Everly MJ**. Update on Alloantibodies in Solid Organ Transplantation. *Clin Transpl* 2014; 125-129 [PMID: 26281136]
71 **Morath C**, Opelz G, Zeier M, Süsal C. Clinical relevance of HLA antibody monitoring after kidney transplantation. *J Immunol Res* 2014;

2014: 845040 [PMID: 25374891 DOI: 10.1155/2014/845040]

72 **Seveso M**, Bosio E, Ancona E, Cozzi E. De novo anti-HLA antibody responses after renal transplantation: detection and clinical impact. *Contrib Nephrol* 2009; **162**: 87-98 [PMID: 19001816 DOI: 10.1159/000170841]

73 **Koktathong K**, Vejbaesya S, Bejrachandra S, Pattanapanyasat K. Flow cytometric crossmatch for kidney transplantation. *J Med Assoc Thai* 2005; **88**: 769-774 [PMID: 16083217]

74 **Chancharoenthana W**, Traitanon O, Leelahavanichkul A, Tasanarong A. Molecular immune monitoring in kidney transplant rejection: a state-of-the-art review. *Front Immunol* 2023; **14**: 1206929 [PMID: 37675106 DOI: 10.3389/fimmu.2023.1206929]

75 **Traitanon O**, Poggio ED, Fairchild RL. Molecular monitoring of alloimmune-mediated injury in kidney transplant patients. *Curr Opin Nephrol Hypertens* 2014; **23**: 625-630 [PMID: 25202838 DOI: 10.1097/MNH.0000000000000064]

76 **Llinàs-Mallol L**, Raïch-Regué D, Pascual J, Crespo M. Alloimmune risk assessment for antibody-mediated rejection in kidney transplantation: A practical proposal. *Transplant Rev (Orlando)* 2023; **37**: 100745 [PMID: 36572001 DOI: 10.1016/j.trre.2022.100745]

77 **Wiebe C**, Nickerson PW. More precise donor-recipient matching: the role of eplet matching. *Curr Opin Nephrol Hypertens* 2020; **29**: 630-635 [PMID: 32889983 DOI: 10.1097/MNH.0000000000000649]

78 **Wiebe C**, Nickerson PW. Human leukocyte antigen molecular mismatch to risk stratify kidney transplant recipients. *Curr Opin Organ Transplant* 2020; **25**: 8-14 [PMID: 31789952 DOI: 10.1097/MOT.0000000000000714]

79 **Renaldo A**, Roa-Bautista A, González-López E, López-Hoyos M, San Segundo D. Epitope-Level Matching—A Review of the Novel Concept of Eplets in Transplant Histocompatibility. *Transplantology* 2021; **2**: 336-347 [DOI: 10.3390/transplantology2030033]

80 **Meneghini M**, Crespo E, Niemann M, Torija A, Lloberas N, Pernin V, Fontova P, Melilli E, Favà A, Montero N, Manonelles A, Cruzado JM, Palou E, Martorell J, Grinyó JM, Bestard O. Donor/Recipient HLA Molecular Mismatch Scores Predict Primary Humoral and Cellular Alloimmunity in Kidney Transplantation. *Front Immunol* 2020; **11**: 623276 [PMID: 33776988 DOI: 10.3389/fimmu.2020.623276]

81 **Lachmann N**, Niemann M, Reinke P, Budde K, Schmidt D, Halleck F, Pruß A, Schönemann C, Spierings E, Staeck O. Donor-Recipient Matching Based on Predicted Indirectly Recognizable HLA Epitopes Independently Predicts the Incidence of De Novo Donor-Specific HLA Antibodies Following Renal Transplantation. *Am J Transplant* 2017; **17**: 3076-3086 [PMID: 28613392 DOI: 10.1111/ajt.14393]

82 **Geneugelijk K**, Spierings E. PIRCHE-II: an algorithm to predict indirectly recognizable HLA epitopes in solid organ transplantation. *Immunogenetics* 2020; **72**: 119-129 [PMID: 31741009 DOI: 10.1007/s00251-019-01140-x]

83 **Lemieux W**, Fleischer D, Yang AY, Niemann M, Oualkacha K, Klement W, Richard L, Polychronakos C, Liwski R, Claas F, Gebel HM, Keown PA, Lewin A, Sapir-Pichhadze R. Dissecting the impact of molecular T-cell HLA mismatches in kidney transplant failure: A retrospective cohort study. *Front Immunol* 2022; **13**: 1067075 [PMID: 36505483 DOI: 10.3389/fimmu.2022.1067075]

84 **Rodrigo E**, Chedid MF, Segundo DS, Millán JCRS, López-Hoyos M. Acute Rejection Following Kidney Transplantation: State-of-the-Art and Future Perspectives. *Curr Pharm Des* 2020; **26**: 3468-3496 [PMID: 32520680 DOI: 10.2174/1381612826666200610184433]

85 **Wen N**, Wu J, Li H, Liao J, Lan L, Yang X, Zhu G, Lei Z, Dong J, Sun X. Immune landscape in rejection of renal transplantation revealed by high-throughput single-cell RNA sequencing. *Front Cell Dev Biol* 2023; **11**: 1208566 [PMID: 37547477 DOI: 10.3389/fcell.2023.1208566]

86 **Suchanek O**, Clatworthy MR. Novel strategies to target the humoral alloimmune response. *HLA* 2020; **96**: 667-680 [PMID: 33022883 DOI: 10.1111/tan.14092]

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MINIREVIEWS

Large-for-size syndrome prophylaxis in infant liver recipients with low body mass

Konstantin Semash, Timur Dzhanbekov

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Abstract

Transplantation of the left lateral section (LLS) of the liver is now an established practice for treating advanced diffuse and unresectable focal liver diseases in children, with variants of the LLS primarily used in infants. However, the surgical challenge of matching the size of an adult donor's graft to the volume of a child's abdomen remains significant. This review explores historical developments, various approaches to measuring the required functional liver mass, and techniques to prevent complications associated with large-for-size grafts in infants.

Key Words: Pediatric liver transplantation; Large-for-size syndrome; Preoperative evaluation of donor and recipient; Liver volumetry; Monosegmental transplantation; Left lateral sector graft; Reduced size liver graft; Abdominal wall reconstruction; Liver transplantation; Liver resection

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Core Tip: Transplantation of the left lateral section is a well-established treatment for advanced liver diseases in children, particularly infants. This review highlights the ongoing challenge of matching adult donor grafts to the smaller abdominal capacity of pediatric recipients. It also discusses the evolution of surgical approaches, methods for accurately assessing required liver mass, and strategies for mitigating complications related to large-for-size grafts.

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INTRODUCTION

The world's first attempt for performing pediatric liver transplantation (LT) was made by T. Starzl [1] in 1963 to a 3-year-old boy with biliary atresia. Still, the patient died of bleeding before the end of the surgical intervention. The subsequent series of liver transplants were unsuccessful until, in 1967, Starzl *et al*[1] reported the first successful pediatric LT from a deceased donor[1].

In 1984, Broelsch *et al*[2] in the United States and Bismuth *et al*[4] in France independently performed the first reduced-size LTs, thereby expanding the boundaries of transplant surgery in pediatric practice[2-6].

In 1988, Pichlmayr *et al*[5] reported the first split transplantation, which consisted of dividing the liver into 2 grafts and giving a chance for life to two patients at once. The growing number of patients on the waiting list and the shortage of organs from deceased donors, especially for children, prompted the search for new resources, one of which was a transplantation of part of the liver from a living donor. Broelsch *et al*[2] and co-authors developed the technique of related transplantation of the left lateral segment of the liver, which was implemented for the first time in the world in 1989[2,7,8]. In the USSR, the first attempt at transplanting the left lobe of the liver was made in 1977 by Galperin[9-12].

With the accumulation of experience, the surgical community was faced with the problem of matching the size of the graft with the volume of the child's abdominal cavity. Low body weight in children suffering from chronic liver diseases leads to a discrepancy between the size of the recipient's abdominal cavity and the donor's liver fragment, which can cause the development of intra-abdominal hypertension when closing a postoperative wound. An increase in intra-abdominal pressure and, as a consequence, the development of abdominal compartment syndrome are formidable complications that require finding ways to solve them.

In anticipation of the story about the main problem, we should dwell on the most frequently encountered terms and concepts. Large-for-size syndrome usually occurs in pediatric LT due to the implantation of an excessively large liver graft into a small recipient cavity, resulting in increasing intra-abdominal pressure, and intra-abdominal hypertension which could lead to poor graft or recipient outcomes[13]. That is why the algorithm for preoperative preparation of patients must include accurate measurements: The volume of the liver graft, the size of the recipient's abdominal cavity, and the liver mass coefficient necessary to meet the body's needs.

According to the literature, today there is no clear consensus for measuring the volume of the intended graft, its mass, the required functional parenchyma, and methods for reconstructing the anterior abdominal wall during transplantation of the left lateral segment of the liver. We consider it necessary to dwell separately on the most common aspects of the above issues.

SURGERY PLANNING

Donor liver volumetry

LT is gradually advancing, including in developing countries[14]. Today, to accurately determine the size of the liver segments, two instrumental methods are used – ultrasound and computed tomography (CT) with 3D modeling. Since the density of the liver parenchyma is almost equal to the density of water, it is this property that is used in CT volumetry and allows one to measure its volume in cm^3. Many authors give preference to CT in the preoperative assessment of left lateral section (LLS) volume. Others have an alternative point of view. Thus, Hatsuno *et al*[15] in his work compared the data on the average calculated volume of the LLS of the liver of 101 patients using ultrasound and CT. According to ultrasound 261 ± 118 cm^3 and CT volumetry 274 ± 123 cm^3, the relationship between the results of the two imaging methods was linear and statistically significant. Based on this, the author concluded that ultrasound has acceptable levels of sensitivity and specificity for routine measurement of the volume of the LLS[15].

Another important parameter in measuring the future LLS graft, which must be taken into account in pediatric practice, is its anteroposterior size. Kasahara *et al*[16] introduced the concept of "ratio of thickness" (RT)-the ratio of the maximum thickness of the graft to the dorso-ventral size of the recipient's abdominal cavity[16].

Along with the calculation of the graft-to-recipient weight ratio (GRWR), the calculation of RT, according to Sakamoto *et al*[17], can be decisive in choosing surgical tactics. These indicators can be taken into account when deciding whether to reduce the LLS liver graft. He proposes the following algorithm for preoperative evaluation of graft type selection. As can be seen from the above diagram, when GRWR ≥ 4.0% or RT ≥ 1, there is a need to reduce the graft volume. Next, the RT indicator comes into force, which, if it exceeds one, dictates the need for transplantation of a single segment of the liver (segment II), or non-anatomical reduction of LLS when this coefficient is < 1. According to the algorithm proposed by the author, transplantation of the native LLS can only be performed with a combination of GRWR < 4% and RT < 1 (Figure 1)[17].

A rather simple and interesting classification of liver LLS grafts by thickness is proposed by Shirouzu *et al*[18]. It divides grafts into 2 types: Blowfish (short and thick) and Flatfish (flat and long)[18]. Based on the characteristics of the

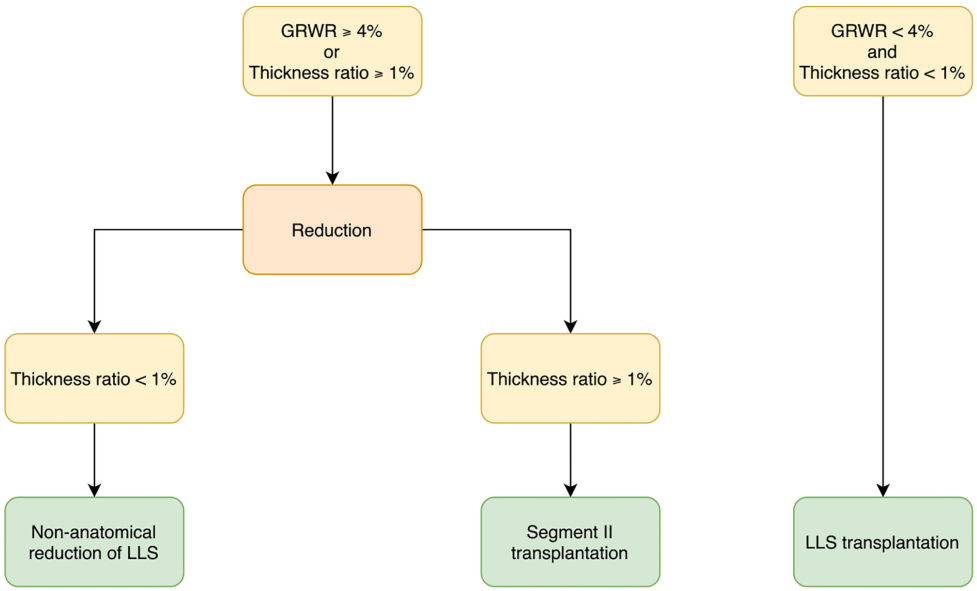


Figure 1 The preoperative algorithm for selecting the type of graft. LLS: Left lateral section; GRWR: Graft to recipient weight ratio.

graft obtained in the preoperative period, two surgical tactics are proposed. The Blowfish graft is hyperreducible. In turn, the Flatfish type LLS configuration does not require additional intervention and, according to surgeons, can be freely placed in the recipient's abdominal cavity.

Based on data from CT volumetry or ultrasound of the donor's liver, there is a need to accurately calculate the standard liver volume (SLV) for the recipient in order to avoid receiving a transplant that is too small or, on the contrary, too large. For this purpose, the formulas presented below in Table 1 were developed[19-27].

As can be seen from the many formulas given in the table, there is no consensus and formula for calculating the required graft mass. We will dwell in more detail on just some of them. The weight of the liver at birth is approximately 5% of the newborn's body weight. This value is not constant throughout life and by the age of 16 it reaches a certain plateau, amounting to about 2%. According to Shirouzu *et al*[18] age, weight, or height are not accurate criteria for calculating the required liver mass, especially in sick children, who are often retarded in physical development. They consider it appropriate to take the body surface area as an individual value in each specific case as a reference point[19]. Based on this, using the method of simple regression of CT data to calculate (96 patients were studied, including 65 children), Urata *et al*[19] developed a formula for calculating the SLV (Table 1).

Noda *et al*[21] conducted another study to calculate a SLV appropriate for age. The study included 54 patients aged from 10 days to 22 years. Based on CT data, it was possible to calculate the liver volume ratio for individuals of different ages (Table 2), and thereby, like K. Urata, confirm the correlation between age and changes in liver volume[21].

Based on the percentage of liver weight to recipient weight (GRWR), Kiuchi *et al*[28] propose to classify transplants into 5 groups: (1) Very small (extra-small-for-size)-XS; GRWR < 0.8%; (2) Small (small-for-size)-S; GRWR 0.8%-1.0%; (3) Medium (medium-for-size)-M; GRWR1-3.0%; (4) Large (large-for-size)-L; GRWR 3%-5.0%; and (5) Extra-large-for-size-XL; GRWR ≥ 5.0%.

After analyzing data from 276 related LTs, he concluded that the use of small grafts (less than 1% of the recipient's body weight) leads to a decrease in his survival. This probably occurs due to greater trauma to hepatocytes after reperfusion (the so-called "portal attack"). At the same time, large transplants, although they have some anatomical and immunological disadvantages, demonstrate higher survival[28].

Based on two- and three-dimensional CT volumetry data, Yoshizumi *et al*[20] analyzed data from 70 healthy Japanese adults (46 men, 24 women, aged 20 to 65 years) and applied all the formulas that existed at that time (2008) for comparative analysis of liver volume. He concluded that the F. DeLand and A. Heinemann formulas overestimate liver volume compared to CT data, while the K. Urata formula, on the contrary, underestimates it[20].

Analysis of the formulas of Noda *et al*[21] and Yoshizumi *et al*[20] did not show a significant difference, however, they tend to underestimate the volume of the liver if its volume exceeds 1600 cm^3. Such deviations are most likely associated with differences between the racial groups studied. This thesis is confirmed by the fact that DeLan *et al*[22] and Heinemann *et al*[27] calculated their formulas based on research data from a Western group of people, and Urata *et al*[19], Noda *et al*[21] and Yoshizumi *et al*[20] from an Eastern one. Concluding his analysis, Yoshizumi *et al*[20] indicates that it is impossible to recognize one or another formula as unsuitable, and each of them requires an individual approach[20,29]. The Herden *et al*[23] formula presented in Table 1 (called "Hamburg") also deserves special attention, since it is more focused on young children, who are of particular interest in our work. The development of a formula for calculating SLV for children was based on autopsy data from 388 white patients under the age of 16 years. This formula was then applied to retrospectively recalculate all pediatric transplants performed between January 2000 and December 2010 at a single center. Depending on the graft weight and the calculated standard liver weight, the children were divided into 4 groups: (1) Small-for-size grafts ≤ 0.5; (2) Adequate graft (Size-matched grafts) > 0.5 to ≤ 1.5; (3) Large-for-size grafts > 1.5 to ≤ 2; and (4) Extra-large-for-size grafts > 2.

Table 1 Formulas for calculating standard liver volume

Ref.	Formula	Used material (*n*)
DeLand *et al*[22], 1968	LV = 1020 × BSA -220	Autopsy (550)
Urata *et al*[19], 1995	LV = 706.2 × BSA +2.4	CT (96)
Noda *et al*[21], 1997	LV= 50.12 × BW 0.78	CT (54)
Heinemann *et al*[27], 1999	LV = 1072.8 × BSA - 345.7	Autopsy (1332)
Vauthey *et al* [26], 2002	LV = 18.51 × BW + 191.8	CT (292)
Yoshizumi *et al*[20], 2003	LV = 772 × BSA	Deceased donor grafts (1413)
Herden *et al* [23], 2013	Formula 1: For children from 0 month up to 1 year old: LV = -143.062973 + 4.274603051 × BH (cm) + 14.78817631 × BW (kg)	Autopsy (246)
	Formula 2: For children from year up to 16 years old: LV = -20.2472281 + 3.339056437: For BH (cm) + 13.11312561× BW (kg)	Autopsy (142)
Yang *et al*[24], 2018	LV = 331−4.1 × age + 41.6 × gender + 15.3 × BW; Gender: Male = 1, female = 0	CT (790)
Yang *et al*[25], 2021	BW ≤ 20 kg: LV = 707.12 × BSA 1.09; BW > 20 kg, males: LV = 691.90 × BSA 1.06; females: LV = 663.19 × BSA 1.04	CT (792)

LV: Liver Volume; BSA: Body Surface Area; BW: Body Weight; BH: Body High; CT: Computed tomography.

Table 2 Average liver volume and liver volume concerning body weight in each age group, mean ± SD

Groups	Quantity	Mean age	Liver volume (cm^3/kg)	Liver volume / body weight (cm^3/kg)
I	6	3.2 months	178.2 ± 81.9	34.09 ± 5.5
II	6	1 year 5.7 months	281.0 ± 51	28.56 ± 5.4
III	7	3 years 4.1 months	425.9 ± 94.9	31.83 ± 5.9
IV	10	7 years	596.5 ± 218.3	25.42 ± 4.5
V	8	13 years 9.4 months	1024.0 ± 210.3	23.77 ± 3.9
VI	17	18 years 10 months	1114.3 ± 192.9	20.17 ± 3.1

In addition, the GRWR was calculated for the patients included in the study, and the children were also divided into four groups: (1) Small-for-size grafts < 1%; (2) Size-matched grafts ≥ 1% to < 3%; (3) Large-for-size grafts ≥ 3% to < 4%; and (4) Extra-large-for-size grafts ≥ 4%.

When comparing the results of the Hamburg formula and GRWR, a significant difference was noted in groups "b" and "c", while no significant differences were found in groups "a" and "d". The next step was to compare graft survival in all four groups, where an increased risk of liver transplant rejection was found in children who received a small-sized liver fragment, while "large grafts" showed better survival rates[23].

It is important to note that there is no "ideal" formula for calculating SLV. Some formulas may overestimate or underestimate liver volume, which can be attributed to the fact that calculations may vary based on the results of CT volumetric analysis or GRWR indices depending on the index population. Consequently, data obtained in one region of the world may not always be directly applicable to another. For instance, it is well known that Asian adults tend to have smaller overall body sizes compared to European adults[20,29]. This variability is one of the reasons why there is no international consensus on the various published indices.

However, having knowledge of CT and/or ultrasound data-volumetry of the donor liver, as well as calculating the proper graft coefficient, the surgeon often intraoperatively has to deal with problems that a "large transplant" may entail. This mainly concerns the impossibility of primary closure of the wound due to the high tension of the tissues of the anterior abdominal wall. In order to prevent such complications and prevent the development of intra-abdominal hypertension, graft reduction methods, the use of monosegmental grafts and various options for plastic surgery of the anterior abdominal wall have been developed. It is advisable to dwell in more detail on each of the existing approaches

3D modeling

Currently, in the era of modern technology, methods for preventing large-for-size syndrome using 3-D printing have begun to be developed. Thus, a group of scientists from Korea, based on a CT scan of a patient, printed a 3D model of his abdominal cavity. Also, a graft printout was performed based on a CT scan of the donor's liver. After this, the graft was "fitted in". Thus, 16 patients, including children of the first year of life, were examined and prepared for LT. All the 16

cases with 3D printed abdominal cavity showed appropriate fitting of the donor's liver graft to both the 3D printed model and actual recipient's abdominal cavity with no large-for-size syndrome after LT[30].

SURGERY

Monosegmental transplantation

In the 1990s, Houssin *et al*[31] described a new graft reduction technique. It was proposed to use only one segment, resection of segment III of the LLS of the liver and use it as a graft. Since then, many different experiments have been carried out, but there is no single concept regarding monosegmental transplantation. According to Enne *et al*[32], with GRWR > 4, transplantation of the third segment is necessary, which seems technically simpler than transplantation of the second segment. The reduction method, from the author's point of view, does not pose a danger to the afferent vascular pedicle or the left hepatic vein. In addition, the advantage of this technique is that the vascular anastomoses are performed in the same way as in LLS transplantation, and are not isolated intraparenchymatously as in SII transplantation. This study is based on 13 segment III transplantations. Patients operated on were aged from 27 to 454 days (average age was 211 days and with body weight from 2.45 kg to 7.4 kg (average body weight-5.2 kg). In the postoperative period, surgical complications occurred in 29, 4% of cases. This includes pleural effusion, diaphragm paralysis, stricture of biliary anastomoses, and biliary fistula. Of these, vascular complications accounted for 7.4% (1 case of portal vein thrombosis and 1 case of hepatic artery thrombosis were encountered). In this series of observations, there was no need for liver retransplantation. Patient survival was 85% over a follow-up period of up to 21 months[32].

Speaking about monosegmental transplantations, one cannot fail to mention the Japanese School of Transplant Surgery, which has achieved great success in this area. For the first time, Makuuchi *et al*[33] mentioned resections of individual liver segments using intraoperative ultrasound in Japan[33]. Subsequently, this technique was improved by Mizuta *et al*[34], who successfully performed 3 transplantations of the 2nd segment of the liver in newborns weighing up to 3 kg. The second segment of the liver, in its anatomical configuration, is thinner than the third, which was the reason for the choice in its favor when planning transplantation for recipients weighing less than 5 kg. Mizuta *et al*[34] technique is as follows: For the most accurate anatomical resection, the portal vessels between segments II and III are ligated and intersected. Next, using the ultrasound contrast agent Sonazoid and ultrasound itself, the demarcation line between the second and third segments was determined intraoperatively, following which the parenchyma was divided[34]

In addition, in their study, Mizuta *et al*[34] substantiate the need to apply a temporary porto-caval shunt to children under 3 weeks of age. From his point of view, the imposition of an anastomosis between the recipient's portal vein and his umbilical vein, which at this age is not yet obliterated, prevents the development of intestinal edema in very young children without portal hypertension. In cases of transplantation to slightly older children, when the umbilical vein is already obliterated, a direct portacaval shunt is applied. Thus, having performed 3 successful liver transplants in children weighing up to 3 kg and up to 27 days of age, Mizuta *et al*[34] consider it advisable to use segment II as a graft, especially in cases of fulminant liver failure in newborns.

Another Japanese surgeon, Sakamoto *et al*[17], shares a similar opinion, considering transplantation of SII for children weighing less than 5 kg to be more justified and safer than transplantation of SIII or the entire LLS of the liver. In addition to calculating the GRWR coefficient, which should not exceed 4%, it also calculates the above-mentioned TR coefficient, which in turn should not exceed one. From the point of view of surgical technique, his resection method also consists in ligating the portal branches to the third segment, which leads to the appearance of a demarcation line along which the division of the hepatic parenchyma is carried out. In preoperative assessment of the type of graft and selection of the optimal volume of resection, Sakamoto *et al*[17] suggests using 3D computer modeling[17].

Reduced and hyper-reduced grafts of the LLS

As an alternative to monosegmental transplantation, many authors[2,17,35-43], including Attia *et al*[44], suggest to use of a two-segment reduced liver graft. From his point of view, this technique has several advantages. Firstly, vascular anastomoses are applied as during transplantation of the native LLS of the liver, without disturbing the vascular architecture. Second, preserving the medial half of the second segment prevents torsion of the left hepatic vein, which sometimes occurs in third segment liver transplants. Note that Attia *et al*[44] were the first to perform a hyperreduced split transplant using this technique. The LLS was reduced by two additional parenchymal transections. The first plane of parenchyma dissection was determined by the portal branch of the third segment into which the probe was inserted. The main portal inflow in the third segment was necessarily preserved. A second resection plane passed through the second segment to further reduce the graft mass (Figure 2).

In 2008, Attia *et al*[44] published the results of his work. Of the 4 children, one died 5 days after surgery from massive hemorrhage in the brain with normal graft function. The second child died 10 months later, also with a normally functioning graft, due to primary pulmonary hypertension. The author cites only one case of arterial thrombosis, which was successfully resolved by re-anastomosing the hepatic artery. Data for thrombosis of the portal and hepatic veins, as well as biliary complications are not provided in the work[44].

Around the same time, in February 2008, Japanese surgeon Kasahara *et al*[45] published his experience of using hyper reduced LLS liver grafts in three children weighing less than 7 kg. Unlike Attia *et al*[44], who performed reductions of grafts obtained from deceased donors, he describes reductions during related transplantation. Moreover, all manipulations with the graft were carried out in the donor's body under conditions of preserved blood circulation, which made it possible to avoid prolonged warm and cold ischemia. To select the optimal resection line, Kasahara *et al*[45] suggests using intraoperative ultrasound with Doppler ultrasound[45].

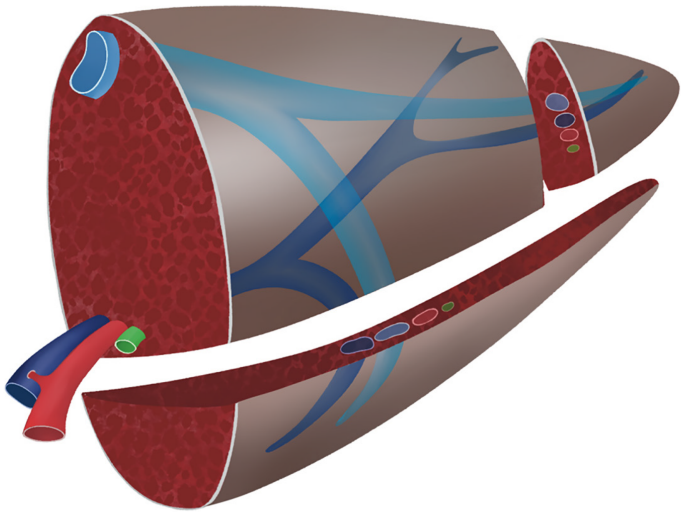


Figure 2 The scheme of hyper-reduction of the left lateral section graft, performed in both vertical and horizontal planes.

The technique for performing vascular anastomoses did not differ from that for transplanting the entire LLS. Biliary reconstruction was carried out with the jejunal loop switched off according to Roux. There were no complications in donors, nor vascular complications in recipients. In the above series of observations, 3-month survival after transplantation was 100%.

Another representative of the Japanese school of pediatric transplant surgeons, Shehata *et al*[46], when choosing the optimal transplant size, gives the leading importance to the calculation of GRWR and, in cases where this coefficient exceeds 4%, suggests hyperreduction of the LLS of the liver[46,47]. According to the author, from September 2000 to December 2009, 49 Liver transplants were performed on children whose average age was 7 months and weight 5.45 kg. Of these, 5 patients underwent partial resection of the liver, 26 patients underwent monosegmental transplantation, and 18 patients underwent hyperreduction of the liver monosegment. All graft reduction procedures were performed "in situ" during surgery at the donor. Postoperative complications were distributed as follows: Hepatic artery thrombosis occurred in two patients (4.1%), thrombosis and portal vein strictures in eight patients (16.3%). The average graft survival rate during the first year after surgery was 83.7%. Thus, M. Shehata believes that reducing the size of the LLS with GRWR > 4% should be a necessary procedure for LT in children weighing less than 5 kg[46].

Argentine colleagues Ardiles *et al*[48], in 2013, published their 14 years of experience in LT in pediatric practice. The surgical aspects of the liver graft reduction technique are similar to those presented above[48].

Balci *et al*[49] report about 4 infants who underwent living donor LT with heterotopically implanted reduced monosegmental or left lateral segment grafts. Reduced monosegment III grafts were used in 2 cases, and reduced left lateral segment grafts were used in the other 2 patients. All patients recovered from the LT operation and are doing well at a mean follow-up of 8 months[49].

Park *et al*[50] reported the Korean experience of the use of reduced and hyper-reduced LLS grafts. Thus, the average age and body weight of the patients were 4.0 ± 1.7 months and 5.3 ± 1.4 kg, respectively, for three cases of pediatric LT with HRLLS graft. The mean weight of the hyper-reduced LLS grafts was 191.7 ± 62.1 g and the GRWR was 3.75% ± 1.57%. All patients recovered from their respective LT operation and are actually in good health, more than 6 years after the LT. There was one case of pediatric deceased donor LT with in situ size reduction of recipient-graft size. Another case presented dextroplantation of a reduced LLS graft. A case of pediatric living donor LT using a monosegment graft procured by pure 3-dimensional laparoscopic LLS resection and in situ reduction was also reported. Authors concluded that making a hyper-reduced LLS or monosegment graft during living donor LT and split LT can be a useful option for treating pediatric patients[50].

It is important to mention that most authors who use liver graft reduction techniques perform it before implantation in situ at the donor stage of the operation, and in cases of using organs from a deceased donor–ex-situ at the "back table" stage. In situ, graft reduction is justified by the fact that the related donor is always a somatically healthy person who does not suffer from disorders of the hemostatic system, which significantly reduces the risk of blood loss when performing reduction compared to conditions of coagulopathy in the recipient. However, the literature also describes a case of partial reduction of the graft after implantation. Zenitani *et al*[51] described a clinical case that required reduction of the LLS liver graft after implantation. According to preoperative calculations, GRWR did not exceed 3.8%, but intraoperatively this coefficient was 4.3%. After the blood flow was started, zones of graft hypoperfusion appeared, and therefore a decision was made to perform partial resection. The author used a technique that was previously described for liver resections in adult patients, but this method was not used in children. A soft intestinal sponge was applied to the area of the graft that was to be reduced to flatten its surface, and then the liver parenchyma was cut off along the resulting line using a linear stapler. Emphasizing the positive aspects of this method of resection, the author notes the reduction in the duration of the operation and the minimization of surgical complications, such as bleeding or bile leakage[51].

It should be borne in mind that in patients with liver cirrhosis and ascites, the abdominal cavity is enlarged compared to that of healthy peers. Thanks to this circumstance, favorable conditions are created for the placement of a "large"

transplant in the abdominal cavity of the recipient - a child. In the absence of portal hypertension, ascites, or in the development of fulminant liver failure, when cirrhosis and its complications do not have time to form, the size of the recipient's abdominal cavity may not correspond to the size of the graft, not only in the total volume but also in the anteroposterior plane. Based on this, in addition to the term "graft-to-recipient weight ratio", the term "thickness ratio", which was mentioned earlier, was introduced into clinical practice. That is why, along with classical methods of graft reduction, new non-anatomical types of reduction are being introduced. For example, to overcome the discrepancy between the anterior-posterior size of the graft and the abdominal cavity of the recipient, Kasahara *et al*[16] have resorted to removing the anterior surface of the graft since 2013 to reduce its thickness by more than 40%. In turn, this resection method increases the wound surface of the graft and the duration of the operation but provides a great advantage for the primary closure of the postoperative wound[16].

In 2021, Gavriilidis and Hidalgo[52] published a systematic review on the outcomes of using large grafts in children and surgical techniques for preventing large-for-size syndrome[52]. The review included case reports and retrospective studies on neonatal transplants where either mono-segmental transplantation or reduction of the LLS graft was performed. The authors concluded that a GRWR > 4% is a significant risk factor for the development of large-for-size syndrome. Mono-segmental transplantation and LLS graft reduction help decrease graft volume and thickness, thus providing the smallest possible graft. Medial reduction, in particular, deserves special mention, as it involves a non-anatomical reduction of segment 3, altering both the volume and thickness of the graft and enabling primary abdominal wall closure. One of the key points noted by the authors is that donor graft volumetry is not the only factor influencing the development of large-for-size syndrome or the choice of surgical strategy for its prevention. They recommend considering the volume of the child's abdominal cavity, which can be affected by comorbid conditions such as liver size, ascites, sarcopenia, abdominal wall elasticity, and the thickness of the liver graft. The main causes of graft loss and patient mortality were infections (sepsis), thrombosis of the graft's afferent vessels, and graft rejection. Retransplantation was required in 10 patients, six of whom needed it in the early postoperative period following the initial surgery.

The experience of various centers with the use of reduced grafts and monosegmental transplantation is presented in Table 3. The largest cumulative experience among transplant centers involves the use of reduced grafts, with reductions performed both in situ and during the "back table" phase. Monosegmental transplantation is performed almost twice as rarely, likely due to the technical challenges associated with monosegmental resection. Nevertheless, the outcomes of these methods are comparable[52].

Anterior abdominal wall reconstruction

Some authors have a completely different point of view and in their works, they demonstrate that there is no need to use mono-segmental, reduced, or hyper-reduced liver grafts. Primary abdominal wall closure after pediatric LT is neither always possible nor advisable, given the graft-recipient size discrepancy and its potential large-for-size scenario. Some authors present delayed sequential abdominal wall closure. For example, Molino *et al*[53] demonstrate 27 cases of delayed sequential abdominal wall closure after pediatric LT due to large-for-size syndrome using a temporary silicone insert. All these patients had longer ICU and overall hospital stay but complete abdominal closure was achieved in 26 of 27 patients [53].

Zakaria *et al*[54] in their work present that temporary abdominal closure by silicon patch was done in 39 patients (52.7%) in the large-for-size group and 29 patients (11.3%) in the other group with a significant difference between both groups. Staged reduction in the size of the silicon patch until complete abdominal closure was done in 9 patients in the large-for-size group and the median time of abdominal re-closure was 5 days range 2–17 days[54].

In German surgeons Schulze *et al*[55] opinion, all mono- and reduced-size liver transplants increase surgical risks for the donor, increase the cold ischemia time, and for the recipient the incidence of biliary complications and impaired venous outflow from the graft increases. In addition, when transplanting the SIII monosegment, the main problem of pediatric transplantation is not solved-a reduction in the ventro-dorsal size of the liver, since the main thickness of the parenchyma falls on the third segment. To confirm his views, the author cites the experience of 41 successful liver transplants in children weighing less than 10 kg, where in all cases only LLS graft was used. When the GRWR was greater than 4% and the anterior abdominal wall could not be closed primarily, he used a temporary silicone insert. Overall patient and graft survival rates according to the authors data were 97% and 93%, respectively. The frequency of vascular complications was distributed as follows: Two arterial thromboses and one portal vein thrombosis in the early postoperative period. The author did not provide data on the presence of biliary complications. Thus, in approximately 50% of cases, the author was able to close the anterior abdominal wall primarily, subject to the following conditions: An intraoperative picture in which the edges of the surgical wound were brought together without tension; the second criterion was portal perfusion of the graft, measured by intraoperative duplex ultrasound. When the portal vein velocity decreased to 10 mL/min after wound closure, plastic surgery of the anterior abdominal wall was resorted to. The third condition was peak airway pressure. If it increased after suturing the surgical wound, a temporary silicone insert was used. Schulze *et al*[55] believe that ultimately, if these three criteria are taken into account, it is possible to avoid the need for reduction of the liver graft or plastic surgery of the anterior abdominal wall using artificial materials, and perform primary closure of the surgical wound[55].

There is no clear opinion regarding the use of various synthetic and biological materials for plastic surgery of postoperative wounds. Some authors believe that the lack of primary wound closure is a mandatory indication for the use of these materials. Others resort to all sorts of options for reducing the size of the graft, which were mentioned above. The latter's concerns are explained by the high risk of infectious complications when using inserts of a different nature, especially in children receiving immunosuppressive therapy.

Table 3 Left lateral section graft reduction techniques, performed in various transplant centers

Ref.	Number of patients	Recipient age, month, median	Recipient weight (kg), median (range)	Donor type	Graft type
Strong *et al*[67], 1982	1	5	4.7	DDLT	Mono-segment III
Mentha *et al*[41], 1986	1	11	6.9	DDLT	Mono-segment III
Srinivasan *et al* [68], 1999	6	7	3.45 (2.45–5.46)	DDLT	Reduced LLS graft (segment III reduction)
Noujaim *et al*[69], 2002	2	N/A	2.6	DDLT	Mono-segment III
Kasahara *et al* [70], 2003	14	7	5.95 (3.5–7.4)	LDLT	Hyper-reduced LLS graft (segment III, *n* = 13, Segment II, *n* = 1)
Attia *et al*[44], 2008	4	2.8	4.9 (2.9–7.8)	DDLT	Hyper-reduced LLS graft (segment III reduction)
Grabhorn *et al* [73], 2008	10	0.5	3.25 (2–4)	DDLT	Reduced LLS graft (*n* = 5); hyper-reduced LLS graft (*n* = 4)
Enne *et al*[32], 2004	12	12	6.2 (4.6–9.0)	LDLT	Mono-segment III
Thomas *et al* [71], 2010	9	10	7.5	DDLT (*n* = 9); LDLT (*n* = 1)	Hyper-reduced LLS graft
Shehata *et al*[46], 2012	44	7	5.45 (2.8–8.0)	LDLT	Mono-segment III (*n* = 26); reduced mono-segment III (*n* = 18)
Kanazawa *et al* [39], 2013	31	7	5.8 (2.8–8.5)	LDLT	Hyper-reduced LLS graft
Sakamoto *et al* [17], 2014	5	5	6.2 (4.0–9.4)	LDLT	Mono-segment II
Sanada *et al*[72], 2017	13	5	3.3 (2.6–7.1)	LDLT	Mono-segment II (*n* = 12); Mono-segment III (*n* = 1)
Raices *et al*[76], 2019	59	14	8.0 (7.0–8.9)	LDLT	Hyper-reduced LLS graft
Kitajima *et al*[74], 2018	89	7.3	5.9 (2.4–9.4)	LDLT	Hyper-reduced LLS graft (*n* = 47), Mono-segment II (*n* = 42)
Hirata *et al*[75], 2009	25	10	7.1 (6.4–8.0)	LDLT	Reduced LLS graft (Medial reduction)
Gautier *et al* [64], 2015	6	6	5.3 (3.5-6.0)	DDLT (*n* = 2); LDLT (*n* = 4)	Reduced LLS graft (*n* = 5), Hyper-reduced LLS graft (*n* = 1)
Balci *et al*[49], 2021	4	7.5	5.9 (4.6-7.8)	LDLT	Reduced LLS graft (*n* = 2), Reduced segment III graft (*n* = 2)
Park *et al*[50], 2022	6	4	5.3 (4.4-5.7)	LDLT (*n* = 5) DDLT (*n* = 1)	Reduced LLS graft (*n* = 3), Hyper-Reduced LLS graft (*n* = 3)

LLS: Left lateral section; DDLT: Deceased donor liver transplantation; LDLT: Living donor liver transplantation.

In addition, fluid loss through the wound increases, the length of stay of children in the intensive care unit increases, and the need for repeated surgical interventions arises. However, despite all the positive and negative aspects of plastic materials, the frequency of their use and the pace of development are growing every year. All materials used for plastic surgery of abdominal wall defects can be divided into 2 types: Synthetic and biological (obtained from tissues of various animals).

According to the opinions of some authors, the use of biomaterials significantly reduces the risk of developing infectious complications compared to synthetic ones[56-59]. Technically, performing plastic surgery of the anterior abdominal wall does not present any great difficulties. As a rule, the material is fixed to the peritoneum. In this case, the skin is separated from the underlying layers for 3-5 cm in advance to create greater elasticity, then it is sutured with separate sutures[60].

Caso *et al*[56] from Spain in 2014 used a biomaterial obtained from the dermal matrix of a pig. A retrospective analysis of 6 cases of its use proved the validity of this approach. Materials created based on collagen stimulate neoangiogenesis, and increase the migration of fibroblasts to the site of their application, thereby improving engraftment rates and reducing the risks of infectious complications. The observation period averaged 22 months and, according to the data

provided by the author, did not lead to wound infection in any case. In addition, the author is convinced that repeated intervention in the long-term postoperative period is not required and the abdominal wall is not subject to reconstruction [56].

The opposite opinion is shared by Australian surgeon Karpelowsky *et al*[59], who in their work cites the experience of using biomaterial made from the small intestine of a pig as a temporary patch for plastic surgery of the anterior abdominal wall. The study group included 10 children who underwent LT at the age of 5 to 15 months. The biomaterial was removed 3-6 days after transplantation. The author reported only one case of wound infection. In long-term follow-up, not a single case of wound infection or the appearance of a ventral hernia has been described[59].

Several published works are devoted to the plastic surgery of postoperative wounds using synthetic materials, often silicone or polytetrafluoroethylene. The previously mentioned some authors resort to the use of silicone inserts during LT and consider it necessary to remove them on the fifth postoperative day. By this time, the swelling of the graft and the anterior abdominal wall decreases, which makes final closure of the wound possible[46,53].

Another surgical option, described by Canadian researchers, is not to close the abdominal fascia. Thus, the surgical team determined the type of abdominal wall closure that would be performed based on the amount of tension required to reapproximate skin and/or fascia, and any evidence of respiratory compromise (increased airway pressures) by simulated abdominal wall closure. If the surgical team felt that fascial closure was not possible, closure of skin only was attempted. If skin closure was not safely possible, then a silastic mesh was cut to size and sutured circumferentially to the fascia with non-absorbable suture, and then vacuum system applied[61].

Belgian colleagues led by Lafosse *et al*[62] describe an interesting experience in the combined use of a patch of biological origin with an intradermal expander. A 2.5-year-old patient who underwent 3 Liver fragment transplantations required reconstructive surgery on the portal vein. The "old" postoperative scar formed after excision cast doubt on the possibility of primary closure of the wound after surgery. In this regard, expanders with 40 mL of 0.9% NaCl were introduced subcutaneously into the patient's upper abdominal cavity. Over 2 months, their volume was gradually increased by adding saline through the valves. After 10 weeks, when with the help of expanders, it was possible to increase the area of healthy skin, an operation was performed to apply a meso-Rex shunt. The aponeurotic layer was sutured using a biological mesh from porcine intestines, and thanks to preliminary preparation, skin sutures were applied without difficulty[62].

Goetz *et al*[63] reported about using biologic meshes for abdominal wall expansion in 6 cases of pediatric split LT[63]. Biologic mesh implantation for abdominal wall expansion was done in median 7 days (range: 3–11 days) after transplantation when signs of abdominal compartment syndrome with portal vein thrombosis in 3 and of the liver artery in 1 case occurred. In 2 cases, bovine acellular collagen matrix and 4 cases ovine reinforced tissue matrix was used. Median follow-up was 12.5 months (range: 4–28 months) and showed good liver perfusion by sonography and normal corporal development without signs of ventral hernia. One patient died because of fulminant graft rejection and emergency re-transplantation 11 months after the initial transplantation.

In the Russian transplant center named after academician V. I. Shumakov[64], sufficient experience in the use of "large" liver transplants in children with low body weight was accumulated. Despite numerous indications of the risk of developing compartment syndrome when using "large" LLS and descriptions of methods for preventing SIAH found in modern literature, the center has accumulated unique experience in the use of "large" LLS grafts in children with low body weight, which indicates the real possibility of closing the anterior abdominal wall when using "large" LLS, even with GRWR 4.0 or more. The report, that in all cases, native LLS graft was used[64,65]. They used a special technique for applying caval and portal anastomoses, as well as the original method of positioning the graft (in which the graft is placed in the position of the removed liver more to the right, with the resection surface of the graft towards the diaphragm), in the vast majority of cases they were able to close the surgical wound primarily and without tension. In the observed groups, there were no cases of the development of abdominal compartment syndrome, except in one case, during simultaneous transplantation of LLS of the liver and small intestine, where a xenopericardial flap was used for plastic surgery of the anterior abdominal wall. Also, they used silicone mesh sutured circumferentially to the fascia and applied vacuum-assisted closure dressing (Figure 3). The experience of various centers with the use of various surgical techniques for abdominal wall reconstruction is presented at Table 4.

Discussion of limitations of methods for preventing large-for-size syndrome

Currently, there is no consensus on the most preferable method for preventing large-for-size syndrome. The calculation of SLV is important, although, as mentioned earlier, there is no "ideal" formula for determining SLV. Some formulas may overestimate or underestimate liver volume, which can be attributed to the fact that calculations may differ based on the results of CT volumetric analysis or GRWR indices depending on the index population. Data obtained in one region of the world may not always be directly applicable to another. For example, it is known that Asian adults tend to have smaller overall body sizes compared to European adults. This variability is one of the reasons why no international consensus exists on these various published indices. This was partially confirmed in studies on SLV by various authors, where analysis of different population groups yielded varying SLVs[20,23,29]. However, there is limited data on this topic, and further research is needed. Nevertheless, CT volumetry of the donor liver plays a critical role in determining transplantation strategy, particularly when assessing the size compatibility of the potential graft with the recipient's abdominal cavity. For this reason, it is essential not only to evaluate GRWR but also to consider the thickness of the LLS graft and the volume of the recipient's abdominal cavity.

Transplantation of a mono-segment carries certain surgical risks for the patient. Transplantation of the liver's third segment is rarely practiced globally nowadays, although attempts to use it have been documented[33,41,52,58,67,68]. This is due to the fact that the resection of the third liver segment is technically more challenging. Some authors note, that in aspect of implantation, transplantation of segment III is more challenging, particularly in terms of vascular reconstruction

Table 4 Abdominal wall plastic surgery, performed in various transplant centers

Ref.	Number of patients	Surgery type	Material used for abdominal cavity protection
Molino *et al*[53], 2022	27	Partial abdominal wall closure	Silicone inserts
Zakaria *et al*[54], 2021	37	Partial abdominal wall closure	Silicone inserts
Schulze *et al*[55], 2011	11	Partial abdominal wall closure	Silicone inserts
Caso *et al*[56], 2014	6	Partial abdominal wall closure	Patches made from dermal matrix of a pig
Karpelowsky *et al*[59], 2009	10	Partial abdominal wall closure	Patches made from pig intestine
Goldaracena *et al*[61], 2020	18	Not to close abdominal fascia	N/A
Lafosse *et al*[62], 2012	1	Skin expander	N/A
Gautier *et al*[64], 2015	4	Partial abdominal wall closure	Xenopericardial flaps, vacuum aspiration abdominal wound dressings
Shehata *et al*[46], 2012	24	Partial abdominal wall closure, Skin-only closure	Polytetrafluoroethylene insert, silicone inserts
Goetz *et al*[63], 2023	6	Partial abdominal wall closure	Biologic meshes

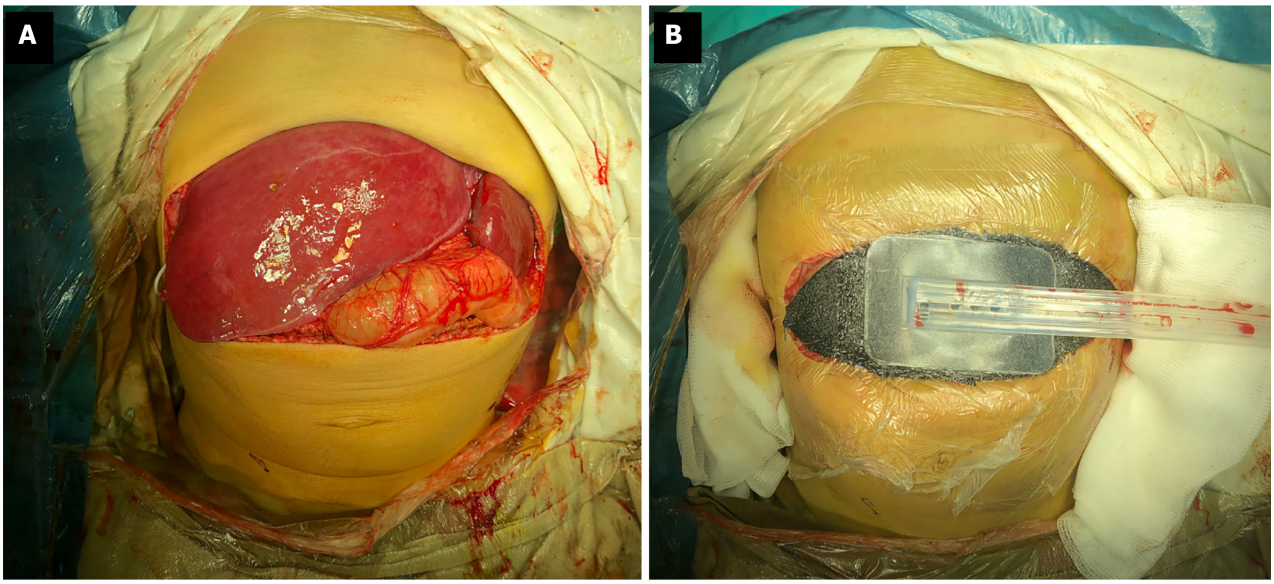


Figure 3 Partial abdominal closure technique using vacuum aspiration abdominal wound dressing. A: Overall appearance after the implantation of a large left lateral section graft. Primary closure of the abdominal cavity is not feasible; B: Appearance after the application of a vacuum-assisted closure system.

[64]. Additionally, some authors argue that transplanting the third segment does not address the issue of reducing the ventro-dorsal size of the graft, since the main thickness of the parenchyma falls on the third segment[55]. Consequently, transplantation of segment II is the preferred technique today. However, the resection of a mono-segment suitable for subsequent transplantation can be a technically complex procedure. In some clinics, the LLS of the liver is removed, followed by ex-situ resection of the third segment. This approach may increase the duration of cold ischemia and result in a more severe reperfusion syndrome[55,66], which could, in turn, affect the postoperative course for the recipient.

Reduction and hyper-reduction of the LLS graft are performed either ex-situ during the "back table" stage or after the graft has been implanted in the recipient's body[69]. One of the primary disadvantages of this method is the presence of a large number of wound surfaces on the graft, which could potentially lead to additional complications, such as bleeding or bile leakage[64,70,71]. Technically, reduction is simpler to perform than mono-segment resection, which can be considered one of the advantages of this procedure[72]. Also, reduced grafts were also utilized in emergency transplantations for children suffering from acute liver failure, where there is often insufficient time for detailed surgical planning [73]. Despite that, multivariate analysis revealed that fulminant liver failure, hepatofugal portal vein flow before LT, and non-anatomical reduction of LLS graft were associated with poor graft survival[74].

The use of silicone inserts, xenopericardial flaps or negative pressure wound therapy systems for temporary closure of the abdominal wall has shown promising results in cases where primary closure of the abdominal cavity is not possible

[55,61,64]. However, the primary drawback of this approach is the necessity for one or more additional surgical procedures to achieve definitive closure of the abdominal cavity. Although in most cases the abdominal cavity can be successfully closed in several stages, there have been reports of cases where closure was not possible, albeit these reports are rare[53]. This increases the duration of hospitalization and may lead to associated complications, such as wound infections, anesthesia-related issues, and surgical complications. These potential complications are also relevant when using subcutaneous expanders[62].

Despite these limitations, the use of techniques aimed at preventing the development of large-for-size syndrome is justified[75]. Such interventions expand the pool of available donor organs and provide the opportunity to save children who might otherwise not survive without these preventive measures, especially in children with low body mass[76].

Undoubtedly, all approaches aimed at ensuring the safety of transplantation in low-weight pediatric patients are crucial, including initial donor liver assessment, volumetry, and the evaluation of the child's abdominal cavity capacity. The further development of innovative technologies, such as 3D modeling, has the potential to enhance these approaches [30]; however, these technologies are not available in all clinics due to the lack of appropriate equipment and their high cost.

It is also important to note that donor selection criteria, surgical approaches, and the experience in performing such procedures can vary significantly across different centers. As a result, institutional, national, underpowered sample, selection, detection, and learning curve biases may have influenced the outcomes[52].

CONCLUSION

Upon reviewing contemporary literature regarding the use of LLS grafts in pediatric patients, it becomes evident that despite the array of global practices, the optimal technical approach for employing "large" LLS grafts remains undetermined. Factors such as the potential for intra-abdominal hypertension, stemming from discrepancies between pediatric abdominal cavity volume and donor graft size, alongside the diversity of diseases and their varying severity, necessitate the application of diverse preventive measures. Common strategies include non-anatomical reduction, partial or hyperreduction of the graft, monosegmental transplantation, and abdominal wall reconstruction. Nonetheless, the definitive course of action typically emerges intraoperatively. Surgeons should utilize all available preoperative data, particularly CT volumetry of the donor liver and the native size of the child's liver. This allows for a clear determination, even at the donor evaluation stage, of which surgical technique will be employed to prevent large-for-size syndrome. In cases where preoperative planning is not feasible (*e.g.*, urgent split LT), graft reduction and/or anterior abdominal wall reconstruction (delayed abdominal wall closure) should be considered. Additionally, it is important to take into account the resources available at the clinic, as not all facilities may have access to the necessary tools for abdominal wall reconstruction.

FOOTNOTES

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REFERENCES

1 **Starzl TE**, Groth CG, Brettschneider L, Penn I, Fulginiti VA, Moon JB, Blanchard H, Martin AJ Jr, Porter KA. Orthotopic homotransplantation of the human liver. *Ann Surg* 1968; **168**: 392-415 [PMID: 4877589 DOI: 10.1097/00000658-196809000-00009]

2 **Broelsch CE**, Emond JC, Thistlethwaite JR, Rouch DA, Whitington PF, Lichtor JL. Liver transplantation with reduced-size donor organs. *Transplantation* 1988; **45**: 519-524 [PMID: 3279573 DOI: 10.1097/00007890-198803000-00003]

3 **Buell JF**, Funaki B, Cronin DC, Yoshida A, Perlman MK, Lorenz J, Kelly S, Brady L, Leef JA, Millis JM. Long-term venous complications after full-size and segmental pediatric liver transplantation. *Ann Surg* 2002; **236**: 658-666 [PMID: 12409673 DOI:

10.1097/00000658-200211000-00017]
4 **Bismuth H**, Houssin D. Reduced-sized orthotopic liver graft in hepatic transplantation in children. *Surgery* 1984; **95**: 367-370 [PMID: 6367125]
5 **Pichlmayr R**, Ringe B, Gubernatis G, Hauss J, Bunzendahl H. [Transplantation einer Spenderleber auf zwei Empfnger (Splitting-Transplantation) - Eine neue Methode in der Weiterentwicklung der Lebersegmenttransplantation]. *Langenbecks Arch Chiv* 1988; **373**: 127-130 [DOI: 10.1007/bf01262776]
6 **Starzl TE**, Demetris AJ. Liver transplantation: a 31-year perspective. Part I. *Curr Probl Surg* 1990; **27**: 49-116 [PMID: 2197064 DOI: 10.1016/0011-3840(90)90021-v]
7 **Strong RW**, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA. Successful liver transplantation from a living donor to her son. *N Engl J Med* 1990; **322**: 1505-1507 [PMID: 2336076 DOI: 10.1056/NEJM199005243222106]
8 **Griffith BP**, Shaw BW Jr, Hardesty RL, Iwatsuki S, Bahnson HT, Starzl TE. Veno-venous bypass without systemic anticoagulation for transplantation of the human liver. *Surg Gynecol Obstet* 1985; **160**: 270-272 [PMID: 3883552]
9 **Galperin EI**, Karagiulian SR. Hepatic surgery in the USSR. *HPB Surg* 1991; **4**: 191-202 [PMID: 1931787 DOI: 10.1155/1991/72586]
10 **Shumakov VI**, Galperin EI. Transplantation of the left liver lobe. *Transplant Proc* 1979; **11**: 1489 [PMID: 382547]
11 **Gautier SV**, Latypov RA, Monakhov AR. Surgical Aspects of Split Liver Transplantation: a Review. *Russ J Gastroenterol, Hepatol, Coloproctol* 2019; **29**: 7-17 [DOI: 10.22416/1382-4376-2019-29-3-7-17]
12 **Lichterman B**. Valery Ivanovich Shumakov. *BMJ* 2008; **336**: 778-778 [DOI: 10.1136/bmj.39521.777083.be]
13 **Pu X**, He D, Liao A, Yang J, Lv T, Yan L, Yang J, Wu H, Jiang L. A Novel Strategy for Preventing Posttransplant Large-For-Size Syndrome in Adult Liver Transplant Recipients: A Pilot Study. *Transpl Int* 2021; **35**: 10177 [PMID: 35185367 DOI: 10.3389/ti.2021.10177]
14 **Semash K**, Dzhanbekov T, Akbarov M, Mirolimov M, Usmonov A, Razzokov N, Primov Z, Gaybullaev T, Yigitaliev S. Implementation of a living donor liver transplantation program in the Republic of Uzbekistan: a report of the first 40 cases. *Clin Transplant Res* 2024; **38**: 116-127 [PMID: 38895775 DOI: 10.4285/ctr.24.0013]
15 **Hatsuno T**, Kaneko T, Ito S, Nakao A. Sonographic measurement of the volume of the left lateral segment of the liver. *J Clin Ultrasound* 2002; **30**: 117-122 [PMID: 11948566 DOI: 10.1002/jcu.10050]
16 **Kasahara M**, Sakamoto S, Shigeta T, Uchida H, Hamano I, Kanazawa H, Kobayashi M, Kitajima T, Fukuda A, Rela M. Reducing the thickness of left lateral segment grafts in neonatal living donor liver transplantation. *Liver Transpl* 2013; **19**: 226-228 [PMID: 23172804 DOI: 10.1002/lt.23572]
17 **Sakamoto S**, Kanazawa H, Shigeta T, Uchida H, Sasaki K, Hamano I, Fukuda A, Nosaka S, Egawa H, Kasahara M. Technical considerations of living donor hepatectomy of segment 2 grafts for infants. *Surgery* 2014; **156**: 1232-1237 [PMID: 24909347 DOI: 10.1016/j.surg.2014.05.003]
18 **Shirouzu Y**, Ohya Y, Hayashida S, Yoshii T, Asonuma K, Inomata Y. Reduction of left-lateral segment from living donors for liver transplantation in infants weighing less than 7 kg: technical aspects and outcome. *Pediatr Transplant* 2010; **14**: 709-714 [PMID: 20477975 DOI: 10.1111/j.1399-3046.2010.01332.x]
19 **Urata K**, Kawasaki S, Matsunami H, Hashikura Y, Ikegami T, Ishizone S, Momose Y, Komiyama A, Makuuchi M. Calculation of child and adult standard liver volume for liver transplantation. *Hepatology* 1995; **21**: 1317-1321 [PMID: 7737637 DOI: 10.1002/hep.1840210515]
20 **Yoshizumi T**, Gondolesi GE, Bodian CA, Jeon H, Schwartz ME, Fishbein TM, Miller CM, Emre S. A simple new formula to assess liver weight. *Transplant Proc* 2003; **35**: 1415-1420 [PMID: 12826175 DOI: 10.1016/s0041-1345(03)00482-2]
21 **Noda T**, Todani T, Watanabe Y, Yamamoto S. Liver volume in children measured by computed tomography. *Pediatr Radiol* 1997; **27**: 250-252 [PMID: 9126583 DOI: 10.1007/s002470050114]
22 **DeLand FH**, North WA. Relationship between liver size and body size. *Radiology* 1968; **91**: 1195-1198 [PMID: 5699624 DOI: 10.1148/91.6.1195]
23 **Herden U**, Wischhusen F, Heinemann A, Ganschow R, Grabhorn E, Vettorazzi E, Nashan B, Fischer L. A formula to calculate the standard liver volume in children and its application in pediatric liver transplantation. *Transpl Int* 2013; **26**: 1217-1224 [PMID: 24118382 DOI: 10.1111/tri.12198]
24 **Yang X**, Wang H, Dong B, Hu B, Hao X, Chen X, Zhao J, Dong Q, Zhu C. Standard Liver Volume-Predicting Formulae Derived From Normal Liver Volume in Children Under 18 Years of Age. *Front Pediatr* 2021; **9**: 629645 [PMID: 33681103 DOI: 10.3389/fped.2021.629645]
25 **Yang X**, Yang JD, Lee S, Hwang HP, Ahn S, Yu HC, You H. Estimation of Standard Liver Volume Using CT Volume, Body Composition, and Abdominal Geometry Measurements. *Yonsei Med J* 2018; **59**: 546-553 [PMID: 29749138 DOI: 10.3349/ymj.2018.59.4.546]
26 **Vauthey JN**, Abdalla EK, Doherty DA, Gertsch P, Fenstermacher MJ, Loyer EM, Lerut J, Materne R, Wang X, Encarnacion A, Herron D, Mathey C, Ferrari G, Charnsangavej C, Do KA, Denys A. Body surface area and body weight predict total liver volume in Western adults. *Liver Transpl* 2002; **8**: 233-240 [PMID: 11910568 DOI: 10.1053/jlts.2002.31654]
27 **Heinemann A**, Wischhusen F, Püschel K, Rogiers X. Standard liver volume in the Caucasian population. *Liver Transpl Surg* 1999; **5**: 366-368 [PMID: 10477836 DOI: 10.1002/lt.500050516]
28 **Kiuchi T**, Kasahara M, Uryuhara K, Inomata Y, Uemoto S, Asonuma K, Egawa H, Fujita S, Hayashi M, Tanaka K. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. *Transplantation* 1999; **67**: 321-327 [PMID: 10075602 DOI: 10.1097/00007890-199901270-00024]
29 **Yoshizumi T**, Taketomi A, Kayashima H, Yonemura Y, Harada N, Ijichi H, Soejima Y, Nishizaki T, Maehara Y. Estimation of standard liver volume for Japanese adults. *Transplant Proc* 2008; **40**: 1456-1460 [PMID: 18589128 DOI: 10.1016/j.transproceed.2008.02.082]
30 **Park S**, Choi GS, Kim JM, Lee S, Joh JW, Rhu J. 3D Printing Model of Abdominal Cavity of Liver Transplantation Recipient to Prevent Large-for-Size Syndrome. *Int J Bioprint* 2022; **8**: 609 [PMID: 36404778 DOI: 10.18063/ijb.v8i4.609]
31 **Houssin D**, Soubrane O, Boillot O, Dousset B, Ozier Y, Devictor D, Bernard O, Chapuis Y. Orthotopic liver transplantation with a reduced-size graft: an ideal compromise in pediatrics? *Surgery* 1992; **111**: 532-542 [PMID: 1598673]
32 **Enne M**, Pacheco-Moreira LF, Cerqueira A, Balbi E, Halpern M, Luiz Pereira J, Santalucia G, Gracia J, De Souza E Oliveira FG, Paranhos GK, Miecznikowski R, De Faria LJ, Pereira Diaz André R, Caroli Bottino A, Manoel Martinho J. Liver transplantation with monosegment from a living donor. *Pediatr Transplant* 2004; **8**: 189-191 [PMID: 15049801 DOI: 10.1046/j.1399-3046.2003.00140.x]
33 **Makuuchi M**, Hasegawa H, Yamazaki S. Ultrasonically guided subsegmentectomy. *Surg Gynecol Obstet* 1985; **161**: 346-350 [PMID: 2996162]
34 **Mizuta K**, Yasuda Y, Egami S, Sanada Y, Wakiya T, Urahashi T, Umehara M, Hishikawa S, Hayashida M, Hyodo M, Sakuma Y, Fujiwara T, Ushijima K, Sakamoto K, Kawarasaki H. Living donor liver transplantation for neonates using segment 2 monosubsegment graft. *Am J*

Transplant 2010; **10**: 2547-2552 [PMID: 20977646 DOI: 10.1111/j.1600-6143.2010.03274.x]

35 **Azouz SM**, Diamond IR, Fecteau A. Graft type in pediatric liver transplantation. *Curr Opin Organ Transplant* 2011; **16**: 494-498 [PMID: 21836516 DOI: 10.1097/MOT.0b013e32834a8c9c]

36 **Cox K**, Nakazato P, Berquist W, Concepcion W, Tokunaga Y, Esquivel C. Liver transplantation in infants weighing less than 10 kilograms. *Transplant Proc* 1991; **23**: 1579-1580 [PMID: 1989298]

37 **Darwish AA**, Bourdeaux C, Kader HA, Janssen M, Sokal E, Lerut J, Ciccarelli O, Veyckemans F, Otte JB, de Goyet Jde V, Reding R. Pediatric liver transplantation using left hepatic segments from living related donors: surgical experience in 100 recipients at Saint-Luc University Clinics. *Pediatr Transplant* 2006; **10**: 345-353 [PMID: 16677359 DOI: 10.1111/j.1399-3046.2005.00477.x]

38 **Kasahara M**, Sakamoto S, Umeshita K, Uemoto S. Effect of graft size matching on pediatric living-donor liver transplantation in Japan. *Exp Clin Transplant* 2014; **12** Suppl 1: 1-4 [PMID: 24635782 DOI: 10.6002/ect.25liver.l5]

39 **Kanazawa H**, Sakamoto S, Fukuda A, Uchida H, Hamano I, Shigeta T, Kobayashi M, Karaki C, Tanaka H, Kasahara M. Living-donor liver transplantation with hyperreduced left lateral segment grafts: a single-center experience. *Transplantation* 2013; **95**: 750-754 [PMID: 23503505 DOI: 10.1097/TP.0b013e31827a93b4]

40 **Malagó M**, Rogiers X, Broelsch CE. Reduced-size hepatic allografts. *Annu Rev Med* 1995; **46**: 507-512 [PMID: 7598483 DOI: 10.1146/annurev.med.46.1.507]

41 **Mentha G**, Belli D, Berner M, Rouge JC, Bugmann P, Morel P, Le Coultre C. Monosegmental liver transplantation from an adult to an infant. *Transplantation* 1996; **62**: 1176-1178 [PMID: 8900322 DOI: 10.1097/00007890-199610270-00026]

42 **Ogawa K**, Kasahara M, Sakamoto S, Ito T, Taira K, Oike F, Ueda M, Egawa H, Takada Y, Uemoto S. Living donor liver transplantation with reduced monosegments for neonates and small infants. *Transplantation* 2007; **83**: 1337-1340 [PMID: 17519783 DOI: 10.1097/01.tp.0000263340.82489.18]

43 **Soubrane O**, Dousset B, Ozier Y, Garnier JF, Devictor D, Pariente D, Bernard O, Houssin D, Chapuis Y. The choice of the reduction technique for orthotopic liver transplantation (OLT) in children using a reduced-size graft. *Transplant Proc* 1990; **22**: 1487-1488 [PMID: 2389375]

44 **Attia MS**, Stringer MD, McClean P, Prasad KR. The reduced left lateral segment in pediatric liver transplantation: an alternative to the monosegment graft. *Pediatr Transplant* 2008; **12**: 696-700 [PMID: 18786070 DOI: 10.1111/j.1399-3046.2007.00882.x]

45 **Kasahara M**, Fukuda A, Yokoyama S, Sato S, Tanaka H, Kuroda T, Honna T. Living donor liver transplantation with hyperreduced left lateral segments. *J Pediatr Surg* 2008; **43**: 1575-1578 [PMID: 18675660 DOI: 10.1016/j.jpedsurg.2008.02.056]

46 **Shehata MR**, Yagi S, Okamura Y, Iida T, Hori T, Yoshizawa A, Hata K, Fujimoto Y, Ogawa K, Okamoto S, Ogura Y, Mori A, Teramukai S, Kaido T, Uemoto S. Pediatric liver transplantation using reduced and hyper-reduced left lateral segment grafts: a 10-year single-center experience. *Am J Transplant* 2012; **12**: 3406-3413 [PMID: 22994696 DOI: 10.1111/j.1600-6143.2012.04268.x]

47 **Tanaka H**. Advances in pediatric liver transplantation from the pediatric surgeon's perspective. *Pediatr Surg Int* 2023; **39**: 253 [PMID: 37624479 DOI: 10.1007/s00383-023-05533-8]

48 **Ardiles V**, Ciardullo MA, D'Agostino D, Pekolj J, Mattera FJ, Boldrini GH, Brandi C, Beskow AF, Molmenti EP, de Santibañes E. Transplantation with hyper-reduced liver grafts in children under 10 kg of weight. *Langenbecks Arch Surg* 2013; **398**: 79-85 [PMID: 23093088 DOI: 10.1007/s00423-012-1020-y]

49 **Balci D**, Bingol-Kologlu M, Kirimker EO, Ergun E, Kansu A, Kuloglu Z, Kirsaclioglu CT, Fitoz S, Can O, Kendirli T, Karayalcin K. 3D-reconstruction and heterotopic implantation of reduced size monosegment or left lateral segment grafts in small infants: A new technique in pediatric living donor liver transplantation to overcome large-for-size syndrome. *Surgery* 2021; **170**: 617-622 [PMID: 34052026 DOI: 10.1016/j.surg.2021.04.015]

50 **Park C**, Chung Y. Pediatric liver transplantation using hyper-reduced left lateral section and monosegment graft for infant patients: A collective review of Korean experience. *Ann Liver Transplant* 2022; **2**: 121-126 [DOI: 10.52604/alt.22.0022]

51 **Zenitani M**, Ueno T, Nara K, Nakahata K, Uehara S, Soh H, Oue T, Kondo H, Nagano H, Usui N. A case of pediatric live-donor liver transplantation with a left lateral segment reduction by a linear stapler after reperfusion. *Pediatr Transplant* 2014; **18**: E197-E199 [PMID: 24977299 DOI: 10.1111/petr.12307]

52 **Gavriilidis P**, Hidalgo E. Alternatives to left lateral sector in paediatric liver transplantation-a systematic review on monosegmental and reduced grafts. *Hepatobiliary Surg Nutr* 2022; **11**: 567-576 [PMID: 36016740 DOI: 10.21037/hbsn-20-792]

53 **Molino JA**, Hidalgo E, Quintero J, Coma A, Ortega J, Juamperez J, Mercadal-Hally M, Riera L, Riaza L, Bilbao I, Dopazo C, Caralt M, Pando E, Gómez-Gavara C, Charco R. Delayed sequential abdominal wall closure in pediatric liver transplantation to overcome "large for size" scenarios. *Pediatr Transplant* 2022; **26**: e14132 [PMID: 34472687 DOI: 10.1111/petr.14132]

54 **Zakaria HM**, Alobthani S, Elsarawy A, Saleh Y, Zidan A, Alabbad S, Elsheikh Y, Algoufi T, Shagrani M, Troisi RI, Broering D. Large for size in pediatrics liver transplant using left lateral segment grafts: A single center experience. *Pediatr Transplant* 2021; **25**: e14044 [PMID: 34076330 DOI: 10.1111/petr.14044]

55 **Schulze M**, Dresske B, Deinzer J, Braun F, Kohl M, Schulz-Jürgensen S, Borggrefe J, Burdelski M, Bröring DC. Implications for the usage of the left lateral liver graft for infants ≤10 kg, irrespective of a large-for-size situation--are monosegmental grafts redundant? *Transpl Int* 2011; **24**: 797-804 [PMID: 21649741 DOI: 10.1111/j.1432-2277.2011.01277.x]

56 **Caso Maestro O**, Abradelo de Usera M, Justo Alonso I, Calvo Pulido J, Manrique Municio A, Cambra Molero F, García Sesma A, Loinaz Segurola C, Moreno González E, Jiménez Romero C. Porcine acellular dermal matrix for delayed abdominal wall closure after pediatric liver transplantation. *Pediatr Transplant* 2014; **18**: 594-598 [PMID: 25039398 DOI: 10.1111/petr.12319]

57 **de Ville de Goyet J**, Struye de Swielande Y, Reding R, Sokal EM, Otte JB. Delayed primary closure of the abdominal wall after cadaveric and living related donor liver graft transplantation in children: a safe and useful technique. *Transpl Int* 1998; **11**: 117-122 [PMID: 9561677 DOI: 10.1007/s001470050114]

58 **Ghazi B**, Deigni O, Yezhelyev M, Losken A. Current options in the management of complex abdominal wall defects. *Ann Plast Surg* 2011; **66**: 488-492 [PMID: 21372667 DOI: 10.1097/SAP.0b013e31820d18db]

59 **Karpelowsky JS**, Thomas G, Shun A. Definitive abdominal wall closure using a porcine intestinal submucosa biodegradable membrane in pediatric transplantation. *Pediatr Transplant* 2009; **13**: 285-289 [PMID: 19032420 DOI: 10.1111/j.1399-3046.2008.01086.x]

60 **Kim J**, Lee JM, Yi NJ, Hong SK, Choi Y, Hong K, Han ES, Lee KW, Suh KS. Long-Term Outcomes of Abdominal Wall Reconstruction with Expanded Polytetrafluoroethylene Mesh in Pediatric Liver Transplantation. *J Clin Med* 2021; **10** [PMID: 33918151 DOI: 10.3390/jcm10071462]

61 **Goldaracena N**, Echeverri J, Kehar M, DeAngelis M, Jones N, Ling S, Kamath BM, Avitzur Y, Ng VL, Cattral MS, Grant DR, Ghanekar A.

Pediatric living donor liver transplantation with large-for-size left lateral segment grafts. *Am J Transplant* 2020; **20**: 504-512 [PMID: 31550068 DOI: 10.1111/ajt.15609]

62 **Lafosse A**, de Magnee C, Brunati A, Bayet B, Vanwijck R, Manzanares J, Reding R. Combination of tissue expansion and porcine mesh for secondary abdominal wall closure after pediatric liver transplantation. *Pediatr Transplant* 2012; **16**: E150-E152 [PMID: 21848529 DOI: 10.1111/j.1399-3046.2011.01488.x]

63 **Goetz M**, Jurczyk M, Grothues D, Knoppke B, Junger H, Melter M, Schlitt HJ, Brunner SM, Brennfleck FW. Biological abdominal wall expansion in pediatric liver recipients after transplantation with large-for-size organs. *Pediatr Transplant* 2023; **27**: e14405 [PMID: 36201376 DOI: 10.1111/petr.14405]

64 **Gautier SV**, Dzhanbekov TA, Akhaladze DG. Large-volume left lateral liver transplantation in infants. *Russ J Transplantology Artif Organs* 2016; **17**: 77-89 [DOI: 10.15825/1995-1191-2015-4-77-89]

65 **Semash KO**, Dzhanbekov TA, Akbarov MM. Vascular complications after liver transplantation: contemporary approaches to detection and treatment. A literature review. *Russ J Transplantology Artif Organs* 2023; **25**: 46-72 [DOI: 10.15825/1995-1191-2023-4-46-72]

66 **Semash K**, Salimov U, Dzhanbekov T, Sabirov D. Liver Graft Machine Perfusion: From History Perspective to Modern Approaches in Transplant Surgery. *Exp Clin Transplant* 2024; **22**: 497-508 [PMID: 39223808 DOI: 10.6002/ect.2024.0137]

67 **Strong R**, Lynch S, Yamanaka J, Kawamoto S, Pillay P, Ong TH. Monosegmental liver transplantation. *Surgery* 1995; **118**: 904-906 [PMID: 7482280 DOI: 10.1016/s0039-6060(05)80283-1]

68 **Srinivasan P**, Vilca-Melendez H, Muiesan P, Prachalias A, Heaton ND, Rela M. Liver transplantation with monosegments. *Surgery* 1999; **126**: 10-12 [PMID: 10418586 DOI: 10.1067/msy.1999.98686]

69 **Noujaim HM**, Mayer DA, Buckles JA, Beath SV, Kelly DA, McKiernan PJ, Mirza DF, de Ville De Goyet J. Techniques for and outcome of liver transplantation in neonates and infants weighing up to 5 kilograms. *J Pediatr Surg* 2002; **37**: 159-164 [PMID: 11819191 DOI: 10.1053/jpsu.2002.30242]

70 **Kasahara M**, Kaihara S, Oike F, Ito T, Fujimoto Y, Ogura Y, Ogawa K, Ueda M, Rela M, D Heaton N, Tanaka K. Living-donor liver transplantation with monosegments. *Transplantation* 2003; **76**: 694-696 [PMID: 12973111 DOI: 10.1097/01.TP.0000079446.94204.F9]

71 **Thomas N**, Thomas G, Verran D, Stormon M, O'Loughlin E, Shun A. Liver transplantation in children with hyper-reduced grafts - a single-center experience. *Pediatr Transplant* 2010; **14**: 426-430 [PMID: 20214746 DOI: 10.1111/j.1399-3046.2010.01294.x]

72 **Sanada Y**, Hishikawa S, Okada N, Yamada N, Katano T, Hirata Y, Ihara Y, Urahashi T, Mizuta K. Dorsal approach plus branch patch technique is the preferred method for liver transplanting small babies with monosegmental grafts. *Langenbecks Arch Surg* 2017; **402**: 123-133 [PMID: 27456678 DOI: 10.1007/s00423-016-1479-z]

73 **Grabhorn E**, Richter A, Fischer L, Ganschow R. Emergency liver transplantation in neonates with acute liver failure: long-term follow-up. *Transplantation* 2008; **86**: 932-936 [PMID: 18852658 DOI: 10.1097/TP.0b013e318186d64a]

74 **Kitajima T**, Sakamoto S, Sasaki K, Narumoto S, Kazemi K, Hirata Y, Fukuda A, Imai R, Miyazaki O, Irie R, Teramukai S, Uemoto S, Kasahara M. Impact of graft thickness reduction of left lateral segment on outcomes following pediatric living donor liver transplantation. *Am J Transplant* 2018; **18**: 2208-2219 [PMID: 29673096 DOI: 10.1111/ajt.14875]

75 **Hirata Y**, Agarwal S, Varma S, Balradja I, Verma S, Naganathan S, Gupta S. Impact of Medial Reduction of the Left Lateral Segment: A Novel Technique for Living Donor Liver Transplantation for Small Pediatric Recipients. *Liver Transpl* 2020; **26**: 1534-1538 [PMID: 32471006 DOI: 10.1002/lt.25808]

76 **Raices M**, Czerwonko ME, Ardiles V, Boldrini G, D'Agostino D, Marcó Del Pont J, Pekolj J, Mattera J, Brandi C, Ciardullo M, de Santibañes E, de Santibañes M. Short- and Long-Term Outcomes After Live-Donor Transplantation with Hyper-Reduced Liver Grafts in Low-Weight Pediatric Recipients. *J Gastrointest Surg* 2019; **23**: 2411-2420 [PMID: 30887299 DOI: 10.1007/s11605-019-04188-y]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Physiology and health assessment, risk balance, and model for end-stage liver disease scores: Postoperative outcome of liver transplantation

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Abstract

BACKGROUND

Liver transplantation aims to increase the survival of patients with end-stage liver diseases and improve their quality of life. The number of organs available for transplantation is lower than the demand. To provide fair organ distribution, predictive mortality scores have been developed.

AIM

To compare the Acute Physiology and Chronic Health Evaluation IV (APACHE IV), balance of risk (BAR), and model for end-stage liver disease (MELD) scores as predictors of mortality.

METHODS

Retrospective cohort study, which included 283 adult patients in the post-operative period of deceased donor liver transplantation from 2014 to 2018.

RESULTS

The transplant recipients were mainly male, with a mean age of 58.1 years. Donors were mostly male, with a mean age of 41.6 years. The median cold ische-

mia time was 3.1 hours, and the median intensive care unit stay was 5 days. For APACHE IV, a mean of 59.6 was found, BAR 10.7, and MELD 24.2. The 28-day mortality rate was 9.5%, and at 90 days, it was 3.5%. The 28-day mortality prediction for APACHE IV was very good [area under the curve (AUC): 0.85, $P < 0.001$, 95%CI: 0.76-0.94], $P < 0.001$, BAR (AUC: 0.70, $P < 0.001$, 95%CI: 0.58–0.81), and MELD (AUC: 0.66, $P < 0.006$, 95%CI: 0.55-0.78), $P < 0.008$. At 90 days, the data for APACHE IV were very good (AUC: 0.80, $P < 0.001$, 95%CI: 0.71–0.90) and moderate for BAR and MELD, respectively, (AUC: 0.66, $P < 0.004$, 95%CI: 0.55–0.77), (AUC: 0.62, $P < 0.026$, 95%CI: 0.51–0.72). All showed good discrimination between deaths and survivors. As for the best value for liver transplantation, it was significant only for APACHE IV ($P < 0.001$).

CONCLUSION

The APACHE IV assessment score was more accurate than BAR and MELD in predicting mortality in deceased donor liver transplant recipients.

Key Words: Liver transplantation; Acute physiology and chronic health evaluation IV; Balance of risk; Model for end-stage liver disease; Mortality; Intensive care unit

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Core Tip: The organ allocation policy has been improving in recent decades, with the utilization of models and scales that reduce mortality among patients on the waiting list and enable a better assessment of post-transplant prognosis with appropriate donor-recipient matching. This article aims to compare the Acute Physiology and Chronic Health Evaluation IV, balance of risk, and model for end-stage liver disease scores as predictors of mortality.

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INTRODUCTION

Brazil is one of the leading countries in transplantation in the world, ranking 2nd in absolute numbers of liver transplants among 35 countries, behind the United States, in the year 2019[1]. Nevertheless, the number of patients awaiting liver transplantation remains high, with 2688 adults on the waiting list in 2020, of whom 646 (24%), a significant number, died [1]. The organ allocation policy has been improving in recent decades, with the utilization of models and scales that reduce mortality among patients on the waiting list and enable a better assessment of post-transplant prognosis with appropriate donor-recipient matching. To distribute the organs offered fairly, considering the severity of the patient, scores have been developed to significantly predict mortality.

In 2006, Brazil adopted the model for end-stage liver disease (MELD) score as the scoring system for allocating candidates on the liver transplant waiting list, associating it with ABO system compatibility and the size of the organ to the recipient. Adopting the MELD score changed the priority criteria for allocation, which used to be based on the date of entry on the list, to considering the severity of the patient with objective criteria. The scale was developed in the United States and has been employed worldwide. The Score ranges from 6 to 40[2] in a scoring system that assesses the severity of cirrhosis and predicts survival in 90 days[3]. The Score is obtained through laboratory tests using a logarithmic formula, including international normalized ratio, total bilirubin, and creatinine[4]. The higher the MELD score, the worse the prognosis and the higher the risk of death. The MELD score underwent some modifications over time, such as the adaptation to MELD-Sodium (MELD-Na), where serum sodium is valued differently due to hyponatremia[3], used in the United States since 2016[5] and in Brazil since 2019[6]. Renal dysfunction is common in liver transplant candidates and significantly increases the risk of mortality, making careful management of renal function essential for optimizing transplant outcomes[7]. The search for improvements motivated researchers to develop other methods to predict mortality, some specific to liver transplantation in intensive care unit (ICU), such as the Acute Physiology and Chronic Health Evaluation (APACHE). The APACHE was developed by Knaus *et al*[8] through a study published in 1981 to assess mortality prediction in the ICU using data from the first 24 hours of admission. It has been updated over time, with the current version being IV, which considers 129 variables: Age, sex, admission, discharge or death dates, systolic and diastolic blood pressure, body temperature, heart rate, respiratory rate, blood glucose, urea, serum creatinine, hematocrit, white blood cells, albumin, and bilirubin levels, urinary output in the first 24 hours of ICU admission, pH, fraction of inspired oxygen, partial pressure of carbon dioxide, partial pressure of oxygen, bicarbonate, Glasgow Coma Scale, mechanical ventilation, diagnosis, admission information, and chronic patient condition[9].

Each item represents a value, and through a calculation, it results in an estimated percentage of mortality for the patient. Some studies demonstrate adequate correlation with prognosis and good calibration for predicting death[2,8,10-14]. The balance of risk (BAR) score was developed to find scores with good prognostic correlation and better calibration than MELD. The calculation is based on recipient data (MELD, retransplantation, life support, age, cold ischemia) and donor age. Each item is assigned a value from 0 to 27, where the higher value indicates a higher probability of death[15], calculated for one, three, and five years. A study published in Campinas/São Paulo (2015) evaluated the BAR score in a cohort, where the authors found moderate discrimination and adequate calibration in predicting mortality[16].

In an analysis conducted on the population of liver transplant recipients in the United States, using the United Network for Organ Sharing database by the University of Zurich, the superiority of the BAR system was demonstrated when compared to other predictive systems such as donor age MELD, donor risk index (DRI), and survival outcomes following liver transplantation (SOFT)[17]. The patient on the liver transplant waiting list is in a unique situation due to the certainty of the only available therapy for their survival, which is the allocation of a new organ[18] either from a deceased or living donor. The deceased donor must have brain death, meet legal criteria, and have family consent for donation[19]. The living donor must meet legal criteria, be a relative or have a court order, and the procedure should not (cannot) cause any harm to their health[19]. The liver has specificities in its transplantation, such as the cold ischemia time, which varies for deceased or living donors. Prolonged cold ischemia times are associated with a higher chance of liver injury[3,19]. The Score that classifies cirrhotic patients on the waiting list for transplantation can impact their prognosis and survival, which is why comparing the three studied methods can help predict the outcome and facilitate the choice of the best one.

Few studies address this topic, and the comparisons made in this work were not found in other research, which justifies the motivation and importance of this study and its conclusions.

MATERIALS AND METHODS

Study population

This is a retrospective cohort study involving 283 adult recipients (above 18 years old) who underwent deceased donor liver transplantation (DDLT) at a referral center located in southern Brazil from January 1, 2014 to June 30, 2018. Only the first admission to the ICU within the same hospitalization was considered. The exclusion criteria included patients transplanted for severe acute liver failure, liver-kidney combined transplantation, retransplantation, and those for whom the required data for analysis were not available.

After the surgical procedure, patients were allocated to the transplant-specialized ICU. The data obtained in the ICU routine were stored in a spreadsheet using Microsoft Excel® (2010), and the SPSS® software (Statistical Package for the Social Sciences) was used[20]. The APACHE IV data were analyzed using the Epimed Monitor program[21], the BAR was calculated online[15] using data from the electronic medical records of the institution where the transplants took place, and the MELD was calculated using its original formula[17], since the data were obtained from the time of selection and within the stipulated time frame. The MELD and APACHE IV scores were routinely calculated in the hospital, while the BAR score was calculated based on the patient's medical records.

Some indices were not analyzed, such as the DRI and SOFT, due to missing data, which would make it impossible to perform a proper analysis of the patients. This work is part of a more extensive ongoing study that evaluates administrative aspects of patients admitted to the ICU of the Irmandade Santa Casa de Misericórdia of Porto Alegre-Brazil. The Research Ethics Committee approved it under the Brazil Platform, CAAE number 19687113.8.2001.5335. The present study complies with ethical norms and guidelines, including Resolution of the National Health Council No. 466/12[22], which exempts the application of the Informed Consent Form, as there is no exposure of personal data.

Statistical analysis

For data description, measures of central tendency and variability, including mean, standard deviation, median, and interquartile range, were used according to the distribution of the variables. The non-parametric Mann-Whitney test was used to assess differences in distribution between medians. For data description, descriptive statistics were used to calculate the mean and standard deviation or median and interquartile range according to the distribution of the variables. For categorical variables, absolute and relative frequencies were used, and the t-student test was applied to compare means.

To evaluate calibration (95%CI) and the ability to classify survivors and non-survivors (discharge and death in the ICU/hospital), respectively, receiver operating characteristic (ROC) curves were plotted and the respective areas under the curve (AUC) were calculated for APACHE IV, BAR, and MELD scores. For data analysis and comparison purposes, calibration is considered excellent when the AUC result is 0.9-0.99, very good (0.8-0.89), good (0.7-0.79), moderate (0.6-0.69), and poor (< 0.6)[10].

The survival curve to assess the probabilities of death over the follow-up period was constructed using the Kaplan-Meier method, with the *P* value calculated by the log-rank test. The sensitivity, specificity, and optimal cutoff point values, according to the percentage of correct classification, will be calculated later. The Hosmer-Lemeshow test will assess the degree of calibration (agreement between predicted and observed probability of death).

RESULTS

Data of 283 consecutive adult patients who underwent DDLT were analyzed after establishing the inclusion and exclusion criteria in their immediate postoperative period in the ICU (Table 1). The mean age of the recipients was 58.1 ± 9.4 years, with the majority being male (66.8%). The donors had a mean age of 41.6 ± 16.7 years, with the majority being male (68.2%). The mean cold ischemia time was 3.1 hours (2.4-3.8), and the median length of stay in the ICU after liver transplantation was 5 days (range: 3-7).

The mean MELD score was 24.2 ± 5.3 points; the mean BAR score was 10.7 ± 3.2; for APACHE IV, the mean was 59.6, with a range of 23.4 points, and the median APACHE IV probability of death was 2.57 (1.51-4.78). There were 27 deaths within the first 28 days out of 283 patients (9.5%) and an additional 9 deaths out of 256 patients within 90 days (3.5%).

In Table 2, the survival rates up to the 5th year are demonstrated. The survival rates were 90.1% in the first month, 87.6% in the third month, and 82.5% in the first year. From there, the survival rate was stable up to the 5th year, with a value of 78.2%. Table 3 presents the AUC for 28 and 90 days after liver transplantation. Regarding 28 days, significant values for predicting death are demonstrated, with descending significance from APACHE IV (AUC: 0.85, $P < 0.001$, 95%CI: 0.76-0.94), to BAR (AUC: 0.70, $P = 0.001$, 95%CI: 0.58-0.81), and to MELD (AUC: 0.66, $P = 0.006$, 95%CI: 0.55-0.78).

Also, a significant descending value is demonstrated for prediction at 90 days for the APACHE IV scale (AUC: 0.80, $P < 0.001$, 95%CI: 0.71-0.90), BAR (AUC: 0.66, $P = 0.004$, 95%CI: 0.55-0.77), and MELD (AUC: 0.62, $P = 0.026$, 95%CI: 0.51-0.72). ROC curves were used to compare the APACHE IV, BAR, and MELD scales to predict survival at 28 and 90 days, and the AUC were calculated (Figure 1). APACHE IV provided the most adequate prediction, followed by BAR and MELD.

The comparison of deaths and survivors at 28 days, 90 days, and overall deaths, as shown in Table 4, with variables including recipient age, ICU length of stay, cold ischemia time, APACHE IV scores (points and probability of death), BAR, and MELD, showed statistical significance for APACHE IV, BAR, and MELD at 28 days and overall mortality, but not for 90 days. The APACHE IV score demonstrated the highest discriminatory power.

Analyzing which would be the best value for performing liver transplantation, as determined by the AUC for 90 days (Table 3), as it predicts death over a longer time frame, Figure 2A shows the difference in survival for each Score, considering APACHE 64.5 points. Through the log-rank test, $P < 0.001$ was found, indicating a significant difference in transplanting below 64.5, increasing the tendency towards survival. For BAR (Figure 2B), a score of 10.5 was used ($P = 0.483$), showing no significant difference in transplanting below this value. Finally, for MELD (Figure 2C), a value of 24 was used ($P = 0.073$), indicating a trend towards better survival when transplanting below 24, although not statistically significant.

DISCUSSION

The analysis of 283 Liver transplant patients regarding their demographic and clinical characteristics is shown in Table 1, with the mean age among them being 58.1 ± 9.4 years and the majority being male (66.8%), similar to the findings in other studies [2,16,23-26]. The mean age of the donors was 41.6 ± 16.7 years, with the majority being male (68.2%). This is similar to the findings reported by de Campos Junior *et al*[16] and Martínez *et al*[23], who also observed a mean age of 41.6 ± 13.2 years.

The mean cold ischemia time was 3.1 hours (2.4-3.8), which is shorter than the 6.9 hours reported by Victor Senna[24], 7.13 hours by Hu *et al*[2], and 7 hours by Martínez *et al*[23]. Possible explanations for the differences could be related to shorter distances traveled for organ procurement or the efficiency of the procurement team belonging to the same transplant center, which would streamline the procurement/transplant process[25]. The median length of stay in the ICU was 5 days (3-7), which agrees with the 5.6 days reported in the study by Lee *et al*[26] but is higher than the 3.71 days reported by Hu *et al*[2].

Regarding APACHE IV, the probability of death was 2.57%, with a mean score of 59.6 (± 23.4) for patients undergoing liver transplantation. As presented in Table 3, these values showed very good calibration for death at 28 and 90 days (AUC: 0.85, $P < 0.001$, 95%CI: 0.76-0.94) and (AUC: 0.80, $P < 0.001$, 95%CI: 0.71-0.90), respectively. The results of this study are consistent with other studies that also reported excellent calibrations for the outcome of death in patients undergoing liver transplantation[2,10,26]. According to the validation of using the APACHE IV score in patients undergoing liver transplantation by Rodrigues Filho EM, acceptable calibration was found to predict mortality in these patients[10,27].

The average score found for the BAR in our study was 10.7 ± 3.2 (Table 1), higher than the mean of 8 (4-14) reported by Martínez *et al*[23], considering the table available on the BAR scale website[15]. The score analysis establishes the perspective of one-year survival to be 90% for values between 5-8; for the 10.7 value found, it represents 86%, resulting in a difference of 4% between the two studies regarding the BAR score.

The mean MELD score was 24.2 ± 5.3 points (Table 1), similar to the study by Victor Senna[24], where the mean was 24.38. Other studies found lower mean MELD values, such as 16 for Volk *et al*[25], 18.09 for Hu *et al*[2], 20.16 for de Campos Junior *et al*[16], and 21 for Martínez *et al*[23]. When analyzing the MELD score concerning deaths at 28 days (Table 4), we found significant values of 28.3 ± 8.1 points for deaths and 23.7 ± 4.7 points for survivors ($P = 0.008$). At 90 days, there is also a statistical difference ($P = 0.016$).

When separately analyzing the MELD score for overall mortality (Table 4) between survivors and non-survivors, we found statistically significant differences, with 26.1 ± 6.7 for the deceased and 23.7 ± 4.8 for the survivors ($P = 0.013$). These results were similar to those of Lee *et al*[26] and Hu *et al*[2], who found a mean of 27 and 25.7 for non-survivors. As for survivors, they found a mean of 16 and 16.87, respectively. The differences among survivors may indicate that those in our study were more severe than those in the other studies.

Table 1 Demographic and clinical characteristics of liver transplant patients in the immediate postoperative period, *n* (%)/mean ± SD/ median (P25-P75)

Variables	*n* = 283
Recipient age (years)	58.1 ± 9.4
Recipient gender	
Female	94 (33.2)
Male	189 (66.8)
Donor age (years)	41.6 ± 16.7
Donor gender	
Female	90 (31.8)
Male	193 (68.2)
Cold ischemia time (hours)	3.1 (2.4-3.8)
ICU time (days)	5 (3-7)
Transplant day MELD	24.2 ± 5.3
APACHE IV	59.6 ± 23.4
APACHE IV probability of death	2.57 (1.51-4.78)
BAR score	10.7 ± 3.2
Death in 28 days	27 (9.5)
Death in 90 days	9/256 (3.5)

ICU: Intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation IV; BAR: Balance of risk; MELD: Model for end-stage liver.

Table 2 Probability of survival over time

	1 month	3 months	6 months	1 year	2 years	3 years	4 years	5 years
Survival rate (%)	90.1	87.6	85.9	82.5	79.6	78.2	78.2	78.2

Table 3 Areas under the curve for death at 28 and 90 days

Variables	Death in 28 days						Death in 90 days					
	AUC	95%CI	*P* value	Cutoff point	Sensitivity	Specificity	AUC	95%CI	*P* value	Cutoff point	Sensitivity	Specificity
APACHE IV	0.85	0.76-0.94	< 0.001	71.50	77.80%	83.20%	0.80	0.71-0.90	< 0.001	64.50	77.80%	72.10%
BAR score	0.70	0.58-0.81	0.001	10.50	66.70%	55.90%	0.66	0.55-0.77	0.004	10.50	61.10%	55.90%
MELD	0.66	0.55-0.78	0.006	24	77.80%	35.20%	0.62	0.51-0.72	0.026	24	75.00%	35.20%

APACHE: Acute Physiology and Chronic Health Evaluation IV; BAR: Balance of risk; MELD: Model for end-stage liver.

Significant differences were also observed in all analyses between deceased and survivors for death at 28, 90 days, and overall mortality for the BAR and APACHE IV scores, as shown in Table 4. The survival rates of our patients at 1, 3, and 5 years were 82.5%, 78.2%, and 78.2% (Table 2). Deaths in the first 28 days were 27 (9.5%), and from there until 90 days, an additional 9 (3.5%) occurred. The data found by Volk *et al*[25] were similar in years 1 and 3, and worse in year 5, respectively, 83%, 75%, and 68%. It is observed that the highest mortality rate occurs in the immediate and early post-transplant periods, stabilizing after the third year. The numerical differences in the fifth year can be speculated and related to the etiology, presence or absence of hepatocellular carcinoma, greater long-term follow-up facilities, recurrences of the underlying disease, and treatment adherence.

Table 4 Comparison between variables and deaths at 28 days, 90 days, and overall death, mean ± SD/ median (P25 – P75)

Variables	Death in 28 days			Death in 90 days			Death		
	Yes	No	*P* value	Yes	No	*P* value	Yes	No	*P* value
Recipient's age	59.2 ± 12.1	58.0 ± 9.1	0.604	62.4 ± 7.0	57.8 ± 9.2	0.135	59.3 ± 9.3	57.8 ± 9.5	0.275
ICU stay time	5 (3-8)	5 (3-7)	0.603	5 (4.5-18)	5 (3-7)	0.114	5 (3-10)	5 (3-7)	0.130
Cold ischemia time	3.3 (2.4-4.2)	3.1 (2.4-3.8)	0.634	2.9 (1.6-3.4)	3.1 (2.4-3.8)	0.208	3.3 (2.5-3.8)	3.1 (2.4-3.8)	0.571
APACHE IV points	92.0 ± 32.1	56.1 ± 19.4	< 0.001	86.1 ± 32.5	55.7 ± 18.9	< 0.001	76.5 ± 30.4	55.2 ± 19.0	< 0.001
APACHE IV prob death	13.4 (4.6-26.9)	2.4 (1.4-4.1)	< 0.001	11.6 (3.6-25.3)	2.3 (1.4-3.9)	< 0.001	4.9 (2.2-18.7)	2.3 (1.4-3.9)	< 0.001
BAR	13.2 ± 4.1	10.5 ± 2.9	0.002	12.7 ± 4.1	10.5 ± 2.9	0.003	11.8 ± 3.8	10.5 ± 2.9	0.016
MELD	28.3 ± 8.1	23.7 ± 4.7	0.008	27.1 ± 7.7	23.7 ± 4.7	0.016	26.1 ± 6.7	23.7 ± 4.8	0.013

ICU: Intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation IV; BAR: Balance of risk; MELD: Model for end-stage liver.

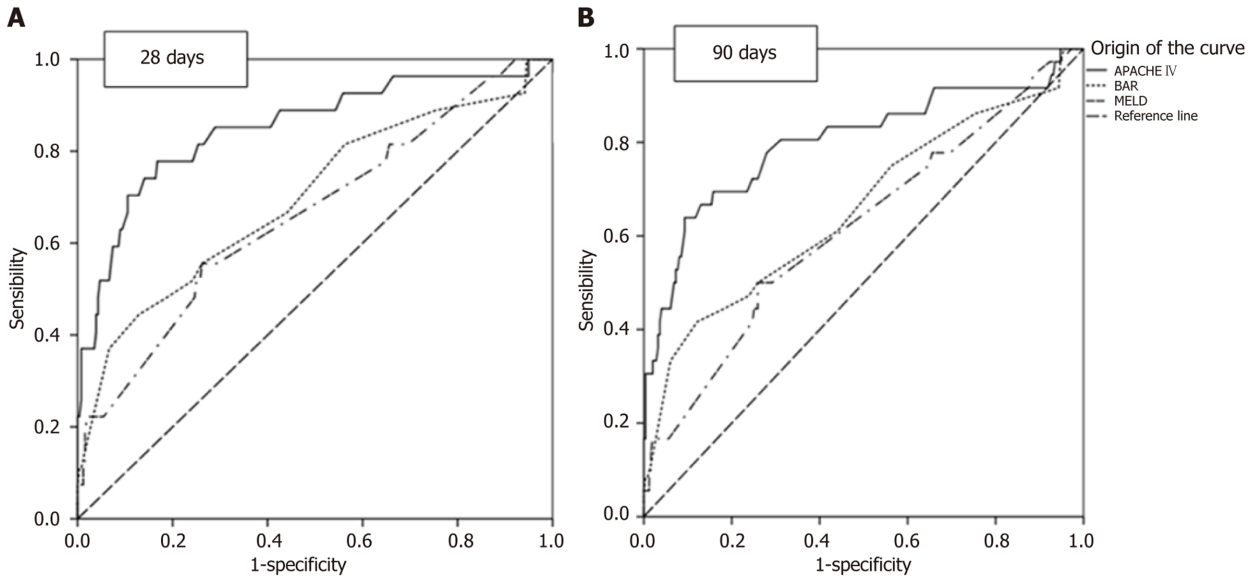


Figure 1 Areas under the curve for Acute Physiology and Chronic Health Evaluation IV, balance of risk, and model for end-stage liver disease scores considering 28 days and 90 days mortality as the outcome. A: 28 days; B: 90 days. APACHE IV: Acute Physiology and Chronic Health Evaluation IV; BAR: Balance of risk; MELD: Model for end-stage liver disease.

To understand which of the three scores better predicts mortality, differences were observed in the prediction for 28 days, 90 days, and overall mortality. Other studies were similar[2,26,27], but there are no standardized criteria regarding the time frame for data evaluation, as in the study by Zakareya *et al*[28], which assessed the outcome at 3 months, 1 year, and 5 years. Others have relied solely on overall mortality[2,26].

A study conducted in Seoul by Lee *et al*[26] compared various mortality prediction scores (APACHE IV, Simplified Acute Physiology Score, APACHE II, MELD-Na, MELD, and Child-Turcotte-Pugh) post-liver transplantation and found 0.91 (95%CI: 0.86-0.96) for APACHE IV, which was the best Score for predicting mortality during in-hospital stay, which averaged 40 days for non-survivors. Another study conducted in China by Hu *et al*[2] found better calibration for APACHE IV 0.937 (95%CI: 0.892-0.981) compared to MELD 0.694 (95%CI: 0.51-0.817) during hospital stay. This study showed an APACHE IV of 0.85 ($P < 0.001$, 95%CI: 0.76-0.94) for death at 28 days, with very good calibration, similar to the results of the two studies, consistent with the outcome presented in Table 3, and a better mortality predictor when compared to BAR and MELD.

Regarding the 90-day period, Lee *et al*[26] found that APACHE IV had an AUC of 0.87 (95%CI: 0.79-0.95), indicating very good calibration, similar to what we found (Table 3), with an AUC of 0.80 ($P < 0.001$, 95%CI: 0.71-0.90). These findings for APACHE IV in both studies are better than those for the other scores.

The study conducted by Martínez *et al*[23], regarding BAR, found a mortality prediction of 0.755 (95%CI: 0.689-0.812), indicating good calibration in predicting mortality at 90 days. This study demonstrated an AUC of 0.66 ($P = 0.004$, 95%CI: 0.55-0.77) for the same time period, indicating moderate calibration despite showing statistical significance in distinguishing between those who died and those who did not.

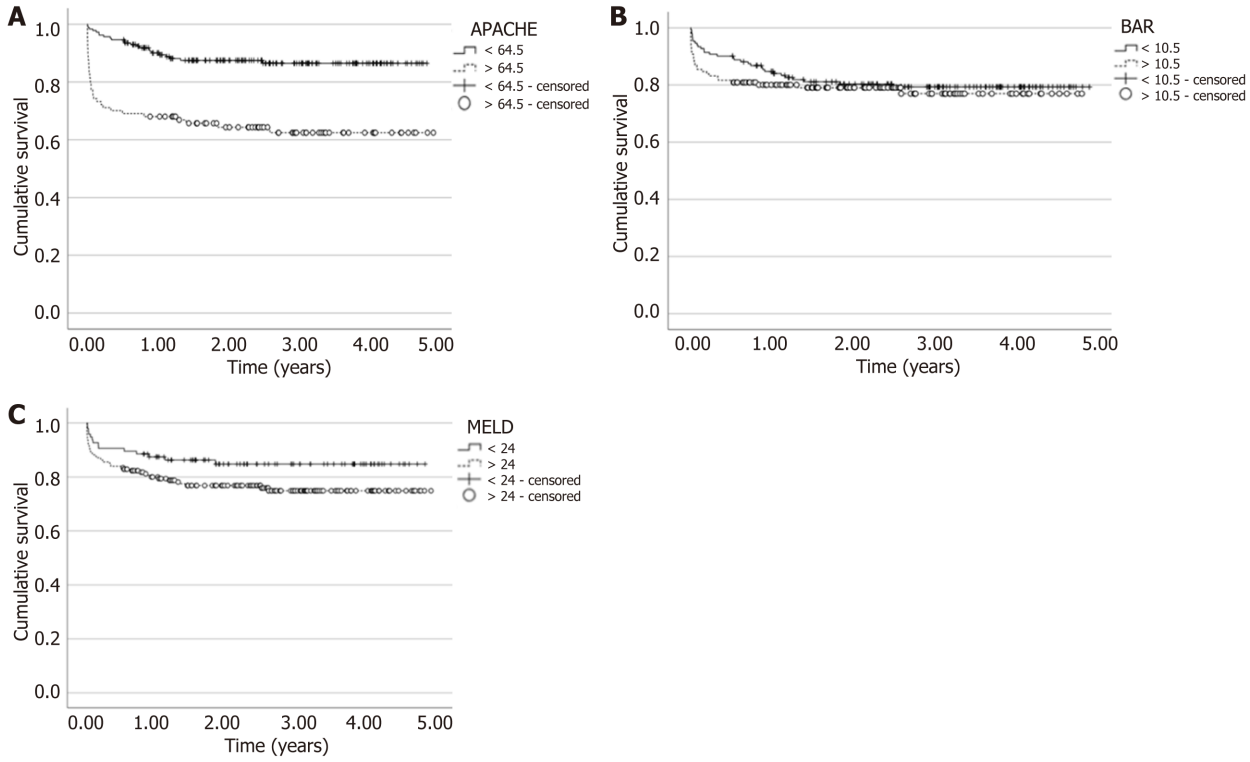


Figure 2 Cumulative survival. A: Survival calculated for Acute Physiology and Chronic Health Evaluation IV (areas under the curve 64.5); B: Survival calculated for balance of risk (areas under the curve 10.5); C: Survival calculated for model for end-stage liver disease (areas under the curve 24). APACHE IV: Acute Physiology and Chronic Health Evaluation IV; BAR: balance of risk; MELD: Model for end-stage liver disease.

According to Brandão *et al*[29], MELD showed an AUC of 0.60 (95%CI: 0.51-0.69) with moderate calibration at three months, similar to our study, where MELD had an AUC of 0.62 (P = 0.026, 95%CI: 0.51-0.72), also demonstrating moderate calibration but with statistical significance. In an integrative review conducted in 2015, it was concluded that the MELD system reduced mortality while waiting for an organ, but on its own, it does not appear to be a good predictor of mortality post-liver transplantation[30]. As for the APACHE IV, good calibration for predicting mortality was found. The comparison of APACHE IV, MELD, and BAR scores for predicting deaths at 28 days, 90 days, and overall mortality showed statistical significance concerning APACHE IV, BAR, and MELD at 28 days, 90 days, and overall mortality. The APACHE IV score demonstrated the highest discriminatory power.

Regarding the survival assessment, the calibration found (APACHE IV 64.5) was used for transplantation, with this being the only Score to show statistical significance (P < 0.001) by the log-rank test. In the study by de Campos Junior *et al* [16] for BAR, a calibration of 11 (P = 0.01) was found, unlike our study where, for a calibration of 10.5, the P value was equal to 0.483. Another study[31] found a calibration of 14 for BAR, obtaining a log-rank test with P = 0.42; whereas for Martínez *et al*[23], a value of 15 was verified with P < 0.01 for survival at three months, but their study includes both living and deceased donors. For APACHE IV and MELD, no studies with log-rank probability tests were found for adult transplanted patients. No current studies comparing APACHE IV, MELD, and BAR were found; therefore, there are no means to establish comparative analyses with results from other research[15].

CONCLUSION

In the present study, the APACHE IV score proved to be a better predictor of mortality than the BAR and MELD scores, accurately predicting mortality at 28 and 90 days and overall mortality. The performance of the APACHE IV score was very good at 28 days and good at 90 days. The performance of the BAR score was good at 28 days and poor at 90 days. And the performance of the MELD score was moderate at 28 days and poor at 90 days. However, for the data to be applied more broadly, further studies would be necessary, including analyses conducted at different transplant centers and with longer follow-up periods. This highlights a limitation of the study, as it is a retrospective research where some information was not filled out, and the surgical technique used, along with changes in renal function prior to transplantation, were not directly analyzed, which could influence the results. Further studies are still needed to confirm such superiority in order to evaluate whether the change in scoring to classify patients on the waiting list for liver transplantation is more effective.

FOOTNOTES

Author contributions: Hohenreuther R contributed to the methodological development and material support, collected data, interpreted results, conducted data analysis, wrote and revised the manuscript; Silveira AT collected data and interpreted the results; Lacerda BG contributed to the methodological development and material support; Filho EMR and Garcez A conducted data analysis and interpreted the results; Fernandes SA contributed to the conception and critical review of the manuscript; Marroni CA designed the research project, collaborated in writing, and critically reviewed the manuscript. All authors have read and approved the final manuscript.

Institutional review board statement: The Research Ethics Committee approved it under the Brazil Platform, CAAE number 19687113.8.2001.5335.

Informed consent statement: The present study complies with ethical norms and guidelines, including Resolution of the National Health Council No. 466/12, which exempts the application of the Informed Consent Form, as there is no exposure of personal data.

Conflict-of-interest statement: There is no conflict of interest for any of the researchers.

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REFERENCES

1 Anual ABTO. Available from: https://site.abto.org.br/publicacao/xxvi-no-4-anual/
2 **Hu Y**, Zhang X, Liu Y, Yan J, Li T, Hu A. APACHE IV is superior to MELD scoring system in predicting prognosis in patients after orthotopic liver transplantation. *Clin Dev Immunol* 2013; **2013**: 809847 [PMID: 24348682 DOI: 10.1155/2013/809847]
3 **Bittencourt PL**, Zollinger CC, Lopes EP de A. Manual de cuidados intensivos em hepatologia. Barueri - SP. Available from: https://www.manole.com.br/
4 **Ministério da Saúde**. BRASIL. Available from: https://bvsms.saude.gov.br/bvs/saudelegis/gm/2009/prt2600_21_10_2009.html
5 Mudanças na política de sódio sérico do MELD - OPTN. Available from: https://optn.transplant.hrsa.gov/news/meld-serum-sodium-policy-changes/
6 Brasil. Portaria 2049. Available from: https://bvsms.saude.gov.br/bvs/saudelegis/gm/2019/prt2049_12_08_2019.html
7 **O'leary J**, Levitsky J, Wong F, Nadim M, Charlton M, Kim W. Protecting the Kidney in Liver Transplant Candidates: Practice-Based Recommendations From the American Society of Transplantation Liver and Intestine Community of Practice. *Am J Transplant* 2016; **16**: 2516-2531 [DOI: 10.1111/ajt.13790]
8 **Knaus WA**, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. *Crit Care Med* 1981; **9**: 591-597 [PMID: 7261642 DOI: 10.1097/00003246-198108000-00008]
9 Apache IV Score. Available from: https://intensivecarenetwork.com/Calculators/Files/Apache4.html
10 **Rodrigues Filho EM**, Garcez A, Nedel WL. [Validation of APACHE IV score in postoperative liver transplantation in southern Brazil: a cohort study]. *Braz J Anesthesiol* 2019; **69**: 279-283 [PMID: 31072607 DOI: 10.1016/j.bjan.2018.11.010]
11 **Dahhan T**, Jamil M, Al-tarifi A, Abouchala N, Kherallah M. Validation of the APACHE IV scoring system in patients with severe sepsis and comparison with the APACHE II system. *Crit Care* 2009; **13**: P511 [DOI: 10.1186/cc7675]
12 **Zimmerman JE**, Kramer AA, Mcnair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. *Crit Care Med* 2006; **34**: 1297-1310 [DOI: 10.1097/01.ccm.0000215112.84523.f0]
13 **Choi JW**, Park YS, Lee YS, Park YH, Chung C, Park DI, Kwon IS, Lee JS, Min NE, Park JE, Yoo SH, Chon GR, Sul YH, Moon JY. The Ability of the Acute Physiology and Chronic Health Evaluation (APACHE) IV Score to Predict Mortality in a Single Tertiary Hospital. *Korean J Crit Care Med* 2017; **32**: 275-283 [DOI: 10.4266/kjccm.2016.00990]
14 **Rodrigues-Filho EM**, Garcez A. APACHE IV score in postoperative kidney transplantation. *Rev Bras Ter Intensiva* 2018; **30**: 181-186 [PMID: 29995083 DOI: 10.5935/0103-507X.20180032]
15 Online BAR Score Calculation. Available from: https://www.assessurgery.com/bar-score/bar-score-calculator/
16 **de Campos Junior ID**, Stucchi RS, Udo EY, Boin Ide F. Application of the BAR score as a predictor of short- and long-term survival in liver

transplantation patients. *Hepatol Int* 2015; **9**: 113-119 [PMID: 25788385 DOI: 10.1007/s12072-014-9563-3]

17 **Dutkowski P**, Oberkofler CE, Slankamenac K, Puhan MA, Schadde E, Müllhaupt B, Geier A, Clavien PA. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. *Ann Surg* 2011; **254**: 745-53; discussion 753 [PMID: 22042468 DOI: 10.1097/SLA.0b013e3182365081]

18 **Ahmed A**, Keeffe EB. Current indications and contraindications for liver transplantation. *Clin Liver Dis* 2007; **11**: 227-247 [PMID: 17606204 DOI: 10.1016/j.cld.2007.04.008]

19 Organ Donation: Transplants, Waiting Lists, and How to Become a Donor. Available from: https://antigo.saude.gov.br/saude-de-a-z/doacao-de-orgaos

20 SPSS. Available from: https://bvsms.saude.gov.br/bvs/areas_tematicas/faq_transplantes.php

21 **Zampieri FG**, Soares M, Borges LP, Salluh JIF, Ranzani OT. The Epimed Monitor ICU Database®: a cloud-based national registry for adult intensive care unit patients in Brazil. *Rev Bras Ter Intensiva* 2017; **29**: 418-426 [PMID: 29211187 DOI: 10.5935/0103-507X.20170062]

22 Conselho Nacional de Saúde. Available from: https://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf

23 **Martínez JA**, Pacheco S, Bachler JP, Jarufe N, Briceño E, Guerra JF, Benítez C, Wolff R, Barrera F, Arrese M. Accuracy of the BAR score in the prediction of survival after liver transplantation. *Ann Hepatol* 2019; **18**: 386-392 [PMID: 31036493 DOI: 10.1016/j.aohep.2019.01.002]

24 **Victor Senna D**. Transplante de fígado no estado do Rio de Janeiro: análise retrospectiva do período 2013-2017. *Αγαη* 2019; 8

25 **Volk ML**, Hernandez JC, Lok AS, Marrero JA. Modified Charlson comorbidity index for predicting survival after liver transplantation. *Liver Transpl* 2007; **13**: 1515-1520 [PMID: 17969207 DOI: 10.1002/lt.21172]

26 **Lee H**, Yoon S, Oh SY, Shin J, Kim J, Jung CW, Ryu HG. Comparison of APACHE IV with APACHE II, SAPS 3, MELD, MELD-Na, and CTP scores in predicting mortality after liver transplantation. *Sci Rep* 2017; **7**: 10884 [PMID: 28883401 DOI: 10.1038/s41598-017-07797-2]

27 **Ko M**, Shim M, Lee SM, Kim Y, Yoon S. Performance of APACHE IV in Medical Intensive Care Unit Patients: Comparisons with APACHE II, SAPS 3, and MPM(0) III. *Acute Crit Care* 2018; **33**: 216-221 [PMID: 31723888 DOI: 10.4266/acc.2018.00178]

28 **Zakareya T**, Taha M, Elzohry H, Darwiesh E, Aglan R, Elhelbawy M, Zakaria H, Deif M, Abbasy M. BAR Score Performance in Predicting Survival after Living Donor Liver Transplantation: A Single-Center Retrospective Study. *Can J Gastroenterol Hepatol* 2022; **2022**: 2877859 [PMID: 35223683 DOI: 10.1155/2022/2877859]

29 **Brandão A**, Fuchs SC, Gleisner AL, Marroni C, Zanotelli ML, Cantisani G; Liver Transplantation Group. MELD and other predictors of survival after liver transplantation. *Clin Transplant* 2009; **23**: 220-227 [PMID: 19210688 DOI: 10.1111/J.1399-0012.2008.00943.X]

30 **Moraes ACO**, Oliveira PC, Fonseca-Neto OCLD. The impact of the Meld score on allocation and outcome of liver transplantation: an review. *Arq Bras Cir Dig* 2017; **30**: 65-68 [PMID: 28489174 DOI: 10.1590/0102-6720201700010018]

31 **Boecker J**, Czigany Z, Bednarsch J, Amygdalos I, Meister F, Santana DAM, Liu WJ, Strnad P, Neumann UP, Lurje G. Potential value and limitations of different clinical scoring systems in the assessment of short- and long-term outcome following orthotopic liver transplantation. *PLoS One* 2019; **14**: e0214221 [PMID: 30897167 DOI: 10.1371/journal.pone.0214221]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Patients admitted in the intensive care unit after solid organ or bone marrow transplantation: Retrospective cohort study

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Abstract

BACKGROUND

Solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT) revolutionized the survival and quality of life of patients with malignant diseases, various immunologic, and metabolic disorders or those associated with a significant impairment in a patient's quality of life.

AIM

To investigate admission causes and treatment outcomes of patients after SOT or HSCT treated in a medical intensive care unit (ICU).

METHODS

We conducted a single-center, retrospective epidemiological study in the medical ICU at the University Hospital Centre Zagreb, Croatia covering the period from January 1, 2018 to December 31, 2023.

RESULTS

The study included 91 patients with either SOT [28 patients (30.8%)] or HSCT [63 patients (69.2%)]. The median age was 56 (43.2-64.7) years, and 60.4% of the patients were male. Patients with SOT had more comorbidities than patients after HSCT [χ^2 (5, n = 141) = 18.513, P < 0.001]. Sepsis and septic shock were the most frequent reasons for admission, followed by acute respiratory insufficiency in patients following HSCT. Survival rate significantly differed between SOT and HSCT [χ^2 (1, n = 91) = 21.767, P < 0.001]. ICU survival was 57% in the SOT and

12.7 % in the HSCT group. The need for mechanical ventilation [χ^2 (1, n = 91) = 17.081, P < 0.001] and vasopressor therapy [χ^2 (1, n = 91) = 36.803, P < 0.001] was associated with survival. The necessity for acute renal replacement therapy did not influence patients' survival [χ^2 (1, n = 91) = 0.376, P = 0.54]. In the subgroup of patients with infection, 90% had septic shock, and the majority had positive microbiological samples, mostly Gram-negative bacteria. The ICU survival of patients with sepsis/septic shock cumulatively was 15%. The survival of SOT patients with sepsis/shock was 45%.

CONCLUSION

Patients with SOT or HSCT are frequently admitted to the ICU due to sepsis and septic shock. Despite advancements in critical care, the mortality rate of patients with refractory septic shock and multiorgan failure in this patient population is extremely high. Early recognition and timely ICU admittance might improve the outcome of patients, especially after HSCT.

Key Words: Liver transplantation; Kidney transplantation; Hematopoietic stem cell transplantation; Critical care; Sepsis; Septic shock; Mortality

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Core Tip: Solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT) have significantly improved the survival and quality of life of numerous patients. We conducted a comprehensive study of 91 post-transplantation patients in a tertiary intensive care unit (ICU) and identified sepsis and septic shock as the main admission diagnoses. The necessity for mechanical ventilation and vasopressor therapy significantly impacted survival. The ICU survival rate was 57% in the SOT group and 12.7% in the HSCT group. Early recognition and prompt ICU admittance of post-transplant patients are crucial for improving outcomes, particularly following HSCT.

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INTRODUCTION

Solid organ transplantation (SOT) has revolutionized the survival and quality of life of patients with end-organ dysfunction. It provides either effective treatment for terminal diseases or those associated with a significant impairment in a patient's quality of life.

Hematopoietic stem cell transplantation (HSCT) today enables the effective treatment of several diseases. For instance, autologous HSCT is used to treat lymphoma, multiple myeloma and various solid tumors, while allogeneic HSCT is used for hematologic, immunologic, and metabolic disorders[1]. The development and progress of immunosuppression protocols enabled longer graft and patient survival after SOT, and have also improved the success of HSCT[2]. In addition to the immense usefulness of immunosuppression, there also exist disadvantages, such as side effects, drug-drug interactions, and increased host susceptibility to infections. Even though there have been positive experiences of solid organ and hematopoietic stem cell co-transplantation (for example in the treatment of multiple myeloma and end-stage chronic kidney disease) which would enable a shorter duration of immunosuppressive therapy[3], such an approach is currently not a part of routine clinical practice.

The risk of developing an infection depends on various factors, including the level of immunosuppression, the time since transplantation, the type of transplanted organ, acute or chronic rejection of the graft, previous host or donor infections, *etc*[3]. Patients after SOT or HSCT can develop bacterial, viral, or fungal infections. The initial manifestation of the infection may differ from those seen in the general population. For example, fever is often absent due to chronic corticosteroid therapy, which is often an integral component of immunosuppression protocols. If the infection is not recognized in time and adequate treatment is not initiated, it can progress to sepsis and septic shock[4].

Sepsis is highly prevalent. According to Rudd *et al*[5] in 2017 there were 48.9 million sepsis cases and 11 million sepsis-related deaths worldwide, accounting for 20% of all global deaths[5]. Moreover, sepsis and septic shock are considered to be the leading causes of critical care-related mortality worldwide[6]. Sepsis mortality varies globally, ranging from 20% to 60%[6-9] with lower mortality rates in developed countries. Infection with Gram-negative bacteria and the use of mechanical ventilation or renal replacement therapy during hospitalization in the intensive care unit (ICU) are considered risk factors for in-hospital death in patients with sepsis[10]. Patients with septic shock have higher mortality rates than patients with sepsis, ranging from 26 to 45% in Europe and North America[9,11], and up to 70% reported in Turkey[8]. Paradoxically, studies suggest that SOT patients with sepsis may experience better outcomes compared with those

without SOT[12]. The study conducted by Ackerman *et al*. is considered the first sepsis-SOT study to examine high-risk ICU patients, analyzing 439 patients with SOT and sepsis. The reported mortality of sepsis-SOT patients was quite low, at 16.1%.

The patient population with SOT and HSCT is growing and comprises an increasing number of patients hospitalized in ICUs worldwide[13-16]. Studies on critically ill patients with either diagnosis are scarce.

The primary endpoint of our research was to investigate the causes of admission and outcome (survival) of hospitalization in the medical ICU of patients after SOT or HSCT. Secondary endpoints were to investigate the necessity for organ support, including mechanical ventilation, acute renal replacement therapy and vasopressor administration.

MATERIALS AND METHODS

Data sources and recruitment

We conducted a single-center epidemiological retrospective cohort study in the medical ICU at the University Hospital Centre Zagreb, Croatia. Critically ill adult patients (≥ 18 years old) hospitalized in the period from January 1, 2018 to December 31, 2023 were considered for inclusion in the study. Patients who underwent either solid organ (liver, kidney) or hematopoietic stem cell (autologous, allogeneic) transplantation and were hospitalized in the ICU for more than 24 hours were included in the study.

Data collection

Data on patient demographics (age, sex), comorbidities (cardiovascular (hypertension, coronary artery disease, peripheral artery disease, history of stroke or transient ischemic attack), respiratory (chronic obstructive pulmonary disease, asthma, pulmonary hypertension, interstitial lung disease), chronic kidney disease, chronic hemodialysis, diabetes and malignant disease), laboratory, clinical and microbiology data were collected from electronic medical records.

Outcome measures

Primary outcome measures were indications for admission to the ICU and ICU survival. Secondary outcomes were the necessity for organ support (mechanical ventilation, acute renal replacement therapy, vasopressor administration), ICU length of stay, and hospital length of stay.

Definitions of medical terms

Malignant disease is defined according to Brown *et al*[17] as a disease of uncontrolled proliferation by transformed cells subject to evolution by natural selection[17]. Sepsis and septic shock were defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[18]. Acute kidney injury was defined according to the KDIGO 2012 criteria[19].

The Acute Physiology And Chronic Health Evaluation II (APACHE II)[20] and Sequential Organ Failure Assessment (SOFA)[21] scores were used to assess organ dysfunction and/or predict mortality.

Statistical analyses

IBM SPSS Statistics 29.0.1.0. software was used for statistical analysis. Normality analysis was performed using the Shapiro-Wilk test. Numerical variables with normal distribution were expressed as means and SD, and numerical variables that were not normally distributed as median with interquartile range. Categorical variables were presented through frequency distributions. Numerical variables were compared using the student t-test or Mann-Whiney *U*-test. Categorical data comparison was carried out using the χ^2 test or Fisher's exact test. A P value < 0.05 was considered statistically significant. The statistical methods of this study were reviewed by Luka Bielen for University of Zagreb, School of medicine.

RESULTS

In the reporting period, 3249 patients were hospitalized in the medical ICU, out of which 116 had either solid organ or HSCT. Twenty-five patients were hospitalized in the ICU for less than 24 hours and were therefore excluded from the study. In total, 91 (2.1%) with either SOT (28 patients (30.8%); 23 kidney, 4 liver, 1 patient kidney and liver transplant) or HSCT (63 patients (69.2%); 15 autologous, 45 allogeneic, 3 both autologous and allogeneic) were included in the study.

Descriptive data

The median age was 56 (43.2-64.7) years with 60.4% male patients (Table 1). Patients with SOT had more comorbidities than patients after HSCT, χ^2 (5, n = 141) = 18.513, P < 0.001. Cardiovascular comorbidities, chronic kidney disease, and chronic hemodialysis were more frequent in the group of solid organ recipients. There was no difference in respiratory nor vasopressor support at the ICU admission between the two groups of patients. The APACHE II score was higher in patients with HSCT compared to patients with SOT (Table 1).

Table 1 Patients' characteristics at intensive care unit admission, *n* (%)/median (25th-75th percentiles)

	Total population (*n* = 91)	SOT (*n* = 28)	HSCT (*n* = 63)	χ^2	*P* value
Age at admission (years)	56 (43.2-64.7)	61 (51.5-68)	54 (40.5-61)	NA	< 0.01
Age at transplantation (years)	50 (36.2-59)	50 (36.7-58.2)	51 (35-60)	NA	0.86
Male gender	55 (60.4)	17 (60.7)	38 (60.3)	0.001	0.97
Comorbidities					
Cardiovascular	56 (61.5)	26 (92.9)	30 (47.6)	16.76	< 0.01
Respiratory	13 (14.3)	3 (10.7)	10 (15.9)	NA	0.51
Chronic kidney disease	34 (37.4)	26 (92.9)	8 (12.7)	53.22	< 0.01
Chronic hemodialysis	11 (12.1)	9 (32.1)	2 (3.2)	NA	< 0.01
Diabetes	16 (17.6)	7 (25)	9 (14.3)	1.53	0.21
Malignant disease	11 (12.1)	4 (14.3)	7 (11.1)	NA	0.70
Disease severity					
SOFA	9 (6-11)	7.5 (5-11)	9 (7-10)	NA	0.37
APACHE II	22 (17.5-27)	19 (14-22)	23 (19-27)	NA	0.01
Respiratory support	48 (52.7)	12 (42.9)	36 (57.1)	1.58	0.20
Vasoactive medication support	32 (35.2)	9 (32.1)	23 (36.5)	0.16	0.68

APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; SOT: Solid organ transplantation; HSCT: Hematopoietic stem cell transplantation; NA: Not applicable.

Outcome data

Sepsis and septic shock were the most frequent reasons for admission for the entire population, followed by acute respiratory insufficiency in patients following HSCT (Figure 1). The need for organ support increased in both patient groups during the ICU stay. Patients treated due to hematological disease more frequently required mechanical ventilation and vasoactive medications in comparison with patients after SOT who more frequently needed acute renal replacement therapy (Table 2).

Survival rate significantly differed between recipients of solid organ transplants and HSCT, χ^2 (1, n = 91) = 21.767, P < 0.001. ICU survival was 57% in solid organ recipients and 12.7 % in the second group. Patients who underwent allogeneic HSCT had different survival rates in comparison to patients who underwent autologous HSCT, χ^2 (1, n = 63) = 3.927, P = 0.048.

The need for mechanical ventilation [χ^2 (1, n = 91) = 17.081, P < 0.001] and vasopressor therapy [χ^2 (1, n = 91) = 36.803, P < 0.001] was associated with survival. On the other hand, the necessity for acute renal replacement therapy did not influence patients' survival, χ^2 (1, n = 91) = 0.376, P = 0.54.

Patients with and without sepsis

As sepsis/septic shock was the most frequent cause for admission to the ICU we compared data among the two groups; patients with sepsis/septic shock (53 patients; 16 patients with SOT and 37 HSCT) and patients admitted with no signs of infection (38 patients) (Table 3).

Patients' demographic data and comorbidities were similar between groups, with chronic kidney disease being the only significant difference. Patients with sepsis/septic shock had higher APACHE II and SOFA scores at admission compared to patients without infection. Moreover, the necessity for organ support including mechanical ventilation, vasopressor application, and acute renal replacement therapy, were all more prevalent in the group of patients with sepsis/septic shock.

In the group of patients with sepsis vasopressor administration was needed in 10/16 (62.5%) SOT patients and 37/37 (100%) HSCT patients, mechanical ventilation in 11/16 (69%) SOT and 36/37 (97%) HSCT, acute renal replacement therapy in 13/16 (81%) SOT and 21/37 (57%) HSCT patients. Cumulatively, 90% of patients had septic shock. All patients with HSCT were neutropenic, 26 (70%) were receiving immunosuppressive therapy, 8 had acute graft-versus-host disease (GVHD) and 5 had chronic GVHD. The median time from hospital to ICU admission in SOT patients was 2 days and in HSCT patients 16 days.

Thirteen patients (81%) with SOT had positive microbiological samples, in which Gram-negative bacteria predominated (11 patients, 84%). All patients in the HSCT group had positive microbiological samples, two patients had a fungal infection, 12 Gram-negative, and others had a polymicrobial infection. Gram-negative bacteria included *P. aeruginosa*, *A. baumannii*, *K. pneumoniae* and *E. coli*.

Table 2 Organ support during intensive care unit stay and outcome, *n* (%)/median (25th-75th percentiles)

	Total population (*n* = 91)	SOT (*n* = 28)	HSCT (*n* = 63)
Mechanical ventilation	73 (80.2)	18 (64.3)	55 (87.3)[a]
Vasoactive medication support	65 (71.4)	13 (46.4)	52 (82.5)[a]
Acute renal replacement therapy	51 (56)	21 (75)	30 (47.6)[a]
ICU survival	24 (26.4)	16 (57.1)	8 (12.7)[a]
7 days survival	49 (53.8)	22 (78.6)	27 (42.9)[a]
28 days survival	36 (39.6)	21 (75)	15 (23.8)[a]
60 days survival	27 (29.7)	18 (64)	9 (14.3)[a]
ICU LOS	7 (3-17)	9.5 (3-26)	7 (3.2-16)
Hospital LOS	28 (12-48.7)	35.5 (17.2-48.7)	22 (11.2-48.7)

[a]$P < 0.05$.

SOT: Solid organ transplantation; HSCT: Hematopoietic stem cell transplantation; LOS: Length of stay; ICU: Intensive care unit.

The overall ICU survival differed between patients with sepsis/septic shock and other diagnoses [χ^2 (1, n = 91) = 6.93, P = 0.008] reaching 15% in patients with sepsis/septic shock and 42% in patients without infection. In patients with sepsis in the SOT group 7 (44%) patients survived.

DISCUSSION

We presented data on 91 patients who had undergone solid organ (kidney or liver) or HSCT (autologous and/or allogeneic) admitted to the medical ICU of a tertiary clinical center. These patients represented a minority of patients admitted to the ICU accounting for approximately 2%. The most common reason for admission was sepsis (53 patients, 58%). The need for organ support was significant. The overall ICU survival was rather low (26.4%) and differed between the SOT (57.1%) and HSCT (12.7%) groups of patients.

Approximately one-third of patients were admitted after SOT, with a predominance of kidney recipients. The variation in admissions might be explained by the fact that UHC Zagreb carries out most kidney transplantations in Croatia, while liver transplantation has only recently become more frequent at our institution. Notably, patients who had undergone heart or lung transplants were mostly treated in other specialized units and were not part of this study. UHC Zagreb is renowned for its expertise in treating patients with hematopoietic stem cells and is currently the only center performing allogeneic HSCT in Croatia, which partially accounts for the majority of hematological patients in our study.

We observed certain discrepancies in demographic data and comorbidities between SOT and HSCT patients. SOT patients tended to be older and had more comorbidities, particularly cardiovascular diseases, chronic kidney disease, and chronic hemodialysis, compared to HSCT patients. This could be attributed to the high number of kidney transplant recipients, in whom cardiovascular diseases and chronic kidney disease with ongoing hemodialysis are common indications for transplantation[22].

Sepsis and septic shock (58%) were the most common causes of ICU admission regardless of the type of transplant. Interestingly, at the ICU admission half of the patients required respiratory support and one-third vasopressor application. The need for organ support increased during the ICU stay, specifically in the HSCT group, indicating failure of conventional sepsis/septic shock treatment. 97% of HSCT patients required mechanical ventilation, 100% vasopressor and 57% acute renal replacement therapy pointing toward the development of multiorgan failure. Given the percentage of vasopressor necessity, we can claim that 90% of patients with infection had septic shock. However, due to the study's retrospective design, the exact dosage of vasopressors used was unknown, making it challenging to accurately estimate the prevalence of refractory septic shock[23]. In refractory septic shock, patients do not respond to conventional therapy and develop progressive multiorgan failure. This subset of patients has very high mortality, reaching 80-90% regardless of age, comorbidities, and country's economic standards[24-26]. The dose and timing of vasopressors significantly affect patient survival in the ICU. Patients whose vasopressor dosage can be rapidly reduced have lower mortality, while those requiring increasing doses have higher mortality[26,27]. Besides the substantial need for organ support in the described population, the presence of positive microbiological samples is also interesting. 80 % of SOT patients and all HSCT patients had positive microbiology samples with the predominance of Gram-negative bacteria. Previous research found that Gram-negative sepsis is associated with higher mortality[28]. Given the large percentage of multiorgan failure and Gram-negative infection in the described population high mortality is expected. However, the ICU survival of patients with sepsis/septic shock of only 15% is extremely low. Patients with SOT had better survival than HSCT, approximately 45 %, which is in accordance with the mortality of patients with septic shock. Ackerman *et al*[12] reported rather low mortality of SOT patients with sepsis[12]. However, in that population, 90% of patients with sepsis had a median SOFA of 7, 10% of patients had septic shock, 40 % had positive microbiology results of any source, and 15% had positive blood

Table 3 Comparison of patients with and without sepsis, *n* (%)/median (25th-75th percentiles)

	Sepsis/ septic shock (*n* = 53)	Other diagnoses (*n* = 38)
Age at admission	55 (43.5-63.2)	57 (46-65)
Age at transplantation	50 (36.7-58.2)	54 (41-59)
Male gender	30 (56.6)	25 (65.8)
Comorbidites		
Cardiovascular	32 (60.4)	24 (63.2)
Respiratory	5 (9.4)	8 (21.1)
Chronic kidney disease	18 (34.0)	16 (42.1)[a]
Chronic hemodialysis	4 (7.5)	7 (18.4)
Diabetes	10 (18.9)	6 (15.8)
Malignant disease	7 (13.2)	4 (10.5)
Respiratory support at admission	27 (50.9)	21 (55.3)
Vasoactive medication support at admission	26 (49.1)	6 (15.8)[a]
APACHE II	24.5 (19-28)	19.5 (15.5-23)[a]
SOFA	9 (7-12.5)	8 (5-9)[a]
Acute renal replacement therapy	35 (66.0)	16 (42.1)[a]
Mechanical ventilation	47 (88.7)	26 (68.4)[a]
Vasoactive medication support	47 (88.7)	18 (47.4)[a]
ICU LOS	8 (4-17)	5 (2-16)
Hospital LOS	30 (14.5-52.5)	19 (11-45)
ICU survival	8 (15.1)	16 (42.1)[a]
7 days survival	22 (41.5)	27 (71.1)[a]
28 days survival	15 (28.3)	21 (55.3)[a]
60 days survival	10 (18.9)	17 (44.7)[a]

[a]$P < 0.05$.

APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; SOT: Solid organ transplantation; LOS: Length of stay; ICU: Intensive care unit.

cultures with fewer Gram-negative microorganisms. In contrast, septic shock was present in 62% of our SOT population, 69% received mechanical ventilation, 80% had positive microbiology samples and the SOFA score was higher. Considering the above, even though the number of included patients in our research is rather low, patients were severely ill, and the survival rate might be considered acceptable.

On the contrary, all patients after HSCT died during the ICU stay. Infection and GVHD remain common causes of nonrelapse transplant-related mortality[29,30]. In critical illness, neutropenia is recognized as an independent risk factor for increased mortality[31,32]. Previous research found an extremely low probability of ICU survival (< 10%) in patients with leukemia[33], as well as after allogeneic HSCT[34]. Factors associated with decreased survival of hematological patients are previous allogeneic stem cell transplantation, the time between hospital and ICU admission, time spent in the ICU, need for mechanical ventilation, acute renal replacement therapy or vasopressor therapy, *etc*[34,35]. Another possible explanation for the extremely high mortality rate of HSCT patients might be that most patients with HSCT, particularly allogeneic bone marrow transplantation in our institution are treated in a hematological high-dependency unit during the HSCT procedure, or if admitted due to complications such as acute GVHD. These patients are transferred to the ICU only in cases of severe hemodynamic instability or acute respiratory failure requiring mechanical ventilation. Hemodynamic instability unresponsive to volume resuscitation or even low doses of noradrenaline, or failure to achieve optimal oxygenation despite maximal oxygen flow through an oronasal mask, are the most common indications for the presentation of these patients to the intensivist. Therefore, the high incidence of mechanical ventilation and vasopressors in this group is expected. The long period between hospital and ICU admission (16 days) supports this observation, although due to the retrospective study design, we could not reconstruct precisely the time between the onset of organ injury and ICU admission. Nevertheless, our results could imply the need to revise the hospital policy of delayed ICU admission. The more intensive hemodynamic monitoring and earlier or more precise circulatory stabilization could impact the survival rate. It has been shown previously that allogeneic HSCT recipients admitted to the ICU as soon as

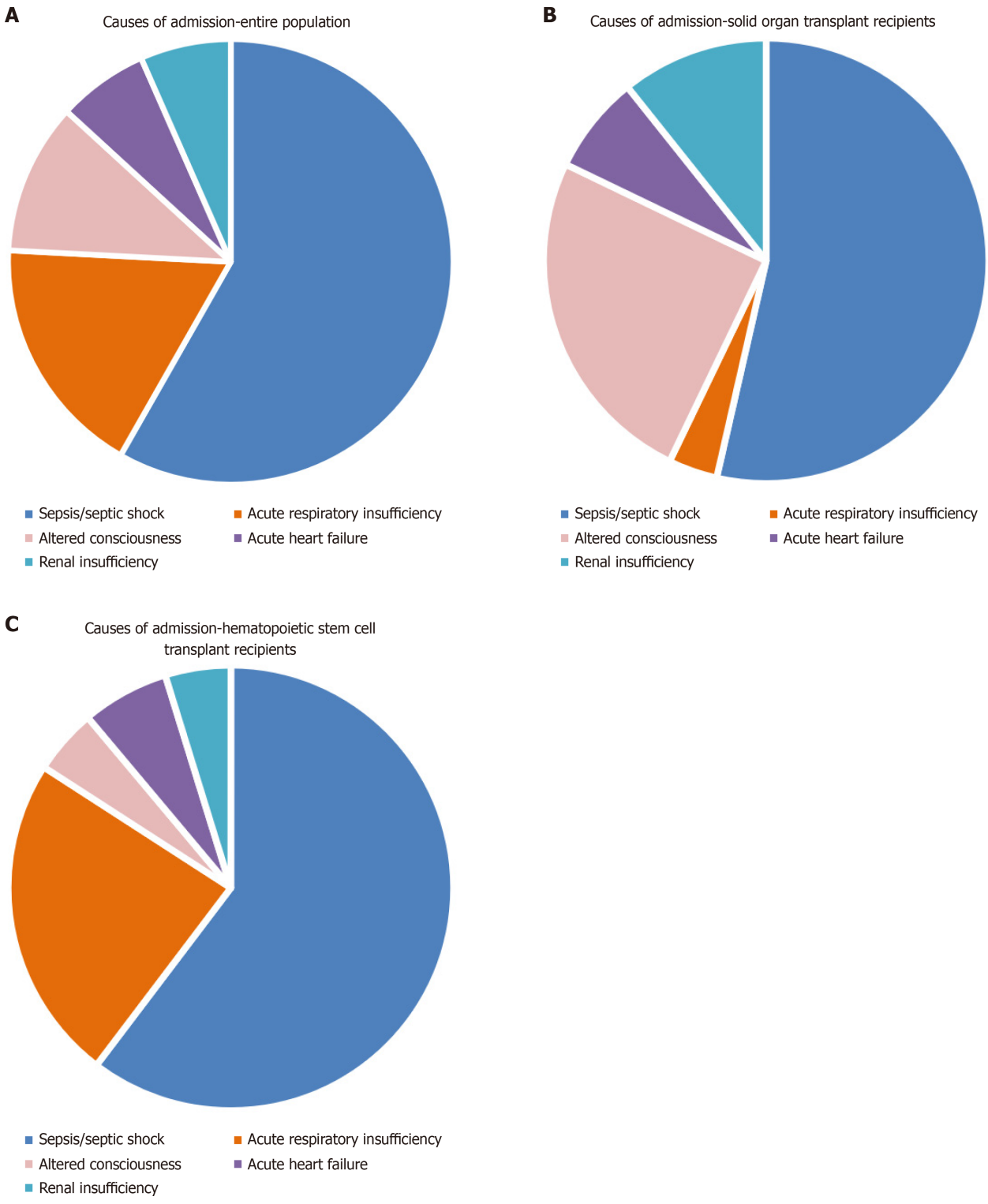


Figure 1 Causes of admission to the intensive care unit. A: Entire population; B: Solid organ transplant recipients; C: Hematopoietic stem cell transplant recipients.

they show signs of organ injury had a better outcome. Patients who were admitted later on following the first organ injury (> 1 day) or with more organ injuries (> 2 organ injuries) had the worst outcome[36]. A significant proportion of our HSCT patients had severe acute GVHD or chronic GVHD, which preceded the episode of sepsis/septic shock and the patient's deterioration. Acute GVHD has been described as an unfavorable prognostic factor in the ICU[37-40]. In several earlier cohort studies, nearly all severe GVHD patients who required mechanical ventilation died[41-43]. The question of whether these patients should be admitted to the ICU, particularly if requiring mechanical ventilation, remains to some extent controversial[44]. In critically ill patients with chronic GVHD, liver GVHD was associated with poor outcomes, as well as the need for mechanical ventilation or hemodialysis[45].

The most significant limitation of our study is its retrospective design due to which some patients might have been excluded from the study and some clinical data were missing, specifically regarding the vasopressor dose (noradrenaline equivalent dose). Moreover, the sample size is rather low and uneven between the SOT and HSCT groups.

Another limitation of the current research might be the different duration and level of immunosuppression among groups. Patients who undergo SOT receive induction immunosuppression during surgery and continue lifelong maintenance therapy to prevent allograft rejection. The level of immunosuppression varies between liver and kidney recipients, usually being lower in the liver recipients[22]. HSCT is performed by first conditioning the recipient with chemotherapy and/or total body irradiation followed by the infusion of donor HSCs. Patients after allogeneic HSCT receive immunosuppression to prevent and treat acute GVHD[1]. Based on the above we could conclude that patients who are treated with allogeneic HSCT are the most immunocompromised subgroup of patients presented in this study and probably had the highest risk of developing sepsis.

CONCLUSION

This paper provides an overview of the SOT and HSCT patients treated in the medical ICU of a high-volume transplant center. The gathered data sheds light on the frequency and causes of admission, disease severity, and treatment outcomes, and provides an opportunity to analyze the strengths and areas for improvement in critical care for this patient population. We can conclude that patients undergoing SOT and HSCT are often admitted due to infection, requiring extensive organ support, and despite advancements in critical care, the mortality rate remains high. Our results emphasize the importance of early recognition of this patient population in our emergency rooms and general wards and raise awareness of their increased risk of a lethal outcome. This paper also raises several important questions. Should patients with SOT and HSCT be admitted to the ICU at an earlier stage? Should protocols for admitting post-HSCT patients be enhanced or modified? Should the establishment of specialized ICU for post-transplant patients be considered? Lastly, should the education of intensivists in the field of transplantation medicine be expanded in high-volume transplant centers to improve patient outcomes post-transplantation?

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REFERENCES

1 **Michniacki TF**, Choi SW, Peltier DC. Immune Suppression in Allogeneic Hematopoietic Stem Cell Transplantation. *Handb Exp Pharmacol* 2022; **272**: 209-243 [PMID: 34628553 DOI: 10.1007/164_2021_544]
2 **Black CK**, Termanini KM, Aguirre O, Hawksworth JS, Sosin M. Solid organ transplantation in the 21(st) century. *Ann Transl Med* 2018; **6**: 409 [PMID: 30498736 DOI: 10.21037/atm.2018.09.68]
3 **Spitzer TR**, Tolkoff-Rubin N, Cosimi AB, McAfee S, Dey BR, Chen YB, Delmonico F, Sykes M, Sachs DH, Kawai T. Twenty-year Follow-up of Histocompatibility Leukocyte Antigen-matched Kidney and Bone Marrow Cotransplantation for Multiple Myeloma With End-stage Renal Disease: Lessons Learned. *Transplantation* 2019; **103**: 2366-2372 [PMID: 30801529 DOI: 10.1097/TP.0000000000002669]
4 **Mella A**, Mariano F, Dolla C, Gallo E, Manzione AM, Di Vico MC, Cavallo R, De Rosa FG, Costa C, Biancone L. Bacterial and Viral Infection and Sepsis in Kidney Transplanted Patients. *Biomedicines* 2022; **10** [PMID: 35327510 DOI: 10.3390/biomedicines10030701]
5 **Rudd KE**, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C, Machado FR, Reinhart KK, Rowan K, Seymour CW, Watson RS, West TE, Marinho F, Hay SI, Lozano R, Lopez AD, Angus DC, Murray CJL, Naghavi M. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet* 2020; **395**: 200-211 [PMID: 31954465 DOI: 10.1016/S0140-6736(19)32989-7]
6 **Kari KA**, Wan Muhd Shukeri WF, Yaacob NM, Li AY, Zaini RH, Mazlan MZ. Prevalence and Outcome of Sepsis: Mortality and Prolonged Intensive Care Unit Stay among Sepsis Patients Admitted to a Tertiary Centre in Malaysia. *Malays J Med Sci* 2023; **30**: 120-132 [PMID: 38239259 DOI: 10.21315/mjms2023.30.6.12]
7 **Rhee C**, Jones TM, Hamad Y, Pande A, Varon J, O'Brien C, Anderson DJ, Warren DK, Dantes RB, Epstein L, Klompas M; Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program. Prevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality in US Acute Care Hospitals. *JAMA Netw Open* 2019; **2**: e187571 [PMID: 30768188 DOI: 10.1001/jamanetworkopen.2018.7571]
8 **Baykara N**, Akalın H, Arslantaş MK, Hancı V, Çağlayan Ç, Kahveci F, Demirağ K, Baydemir C, Ünal N; Sepsis Study Group. Epidemiology of sepsis in intensive care units in Turkey: a multicenter, point-prevalence study. *Crit Care* 2018; **22**: 93 [PMID: 29656714 DOI: 10.1186/s13054-018-2013-1]
9 **Bauer M**, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019- results from a systematic review and meta-analysis. *Crit Care* 2020; **24**: 239 [PMID: 32430052 DOI: 10.1186/s13054-020-02950-2]
10 **Sakr Y**, Jaschinski U, Wittebole X, Szakmany T, Lipman J, Ñamendys-Silva SA, Martin-Loeches I, Leone M, Lupu MN, Vincent JL; ICON Investigators. Sepsis in Intensive Care Unit Patients: Worldwide Data From the Intensive Care over Nations Audit. *Open Forum Infect Dis* 2018; **5**: ofy313 [PMID: 30555852 DOI: 10.1093/ofid/ofy313]
11 **Daviaud F**, Grimaldi D, Dechartres A, Charpentier J, Geri G, Marin N, Chiche JD, Cariou A, Mira JP, Pène F. Timing and causes of death in septic shock. *Ann Intensive Care* 2015; **5**: 16 [PMID: 26092499 DOI: 10.1186/s13613-015-0058-8]
12 **Ackerman KS**, Hoffman KL, Díaz I, Simmons W, Ballman KV, Kodiyanplakkal RP, Schenck EJ. Effect of Sepsis on Death as Modified by Solid Organ Transplantation. *Open Forum Infect Dis* 2023; **10**: ofad148 [PMID: 37056981 DOI: 10.1093/ofid/ofad148]
13 **Terrault NA**, Francoz C, Berenguer M, Charlton M, Heimbach J. Liver Transplantation 2023: Status Report, Current and Future Challenges. *Clin Gastroenterol Hepatol* 2023; **21**: 2150-2166 [PMID: 37084928 DOI: 10.1016/j.cgh.2023.04.005]
14 **Wang JH**, Hart A. Global Perspective on Kidney Transplantation: United States. *Kidney360* 2021; **2**: 1836-1839 [PMID: 35373000 DOI: 10.34067/KID.0002472021]
15 **Kosuta I**, Ostojic A, Vujaklija Brajkovic A, Babel J, Simunov B, Sremac M, Mrzljak A. Shifting perspectives in liver diseases after kidney transplantation. *World J Hepatol* 2023; **15**: 883-896 [PMID: 37547033 DOI: 10.4254/wjh.v15.i7.883]
16 **D'Souza A**, Fretham C, Lee SJ, Arora M, Brunner J, Chhabra S, Devine S, Eapen M, Hamadani M, Hari P, Pasquini MC, Perez W, Phelan RA, Riches ML, Rizzo JD, Saber W, Shaw BE, Spellman SR, Steinert P, Weisdorf DJ, Horowitz MM. Current Use of and Trends in Hematopoietic Cell Transplantation in the United States. *Biol Blood Marrow Transplant* 2020; **26**: e177-e182 [PMID: 32438042 DOI: 10.1016/j.bbmt.2020.04.013]
17 **Brown JS**, Amend SR, Austin RH, Gatenby RA, Hammarlund EU, Pienta KJ. Updating the Definition of Cancer. *Mol Cancer Res* 2023; **21**: 1142-1147 [PMID: 37409952 DOI: 10.1158/1541-7786.MCR-23-0411]
18 **Singer M**, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 801-810 [PMID: 26903338 DOI: 10.1001/jama.2016.0287]
19 **Khwaja A**. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012; **120**: c179-c184 [PMID: 22890468 DOI: 10.1159/000339789]
20 **Knaus WA**, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818-829 [PMID: 3928249]
21 **Vincent JL**, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998; **26**: 1793-1800 [PMID: 9824069 DOI: 10.1097/00003246-199811000-00016]
22 **van den Hoogen MWF**, Seghers L, Manintveld OC, Roest S, Bekkers JA, den Hoed CM, Minnee RC, de Geus HRH, van Thiel RJ, Hesselink DA. Care for the organ transplant recipient on the intensive care unit. *J Crit Care* 2021; **64**: 37-44 [PMID: 33784577 DOI: 10.1016/j.jcrc.2021.03.003]
23 **Nandhabalan P**, Ioannou N, Meadows C, Wyncoll D. Refractory septic shock: our pragmatic approach. *Crit Care* 2018; **22**: 215 [PMID: 30231909 DOI: 10.1186/s13054-018-2144-4]

24 **Brown SM**, Lanspa MJ, Jones JP, Kuttler KG, Li Y, Carlson R, Miller RR 3rd, Hirshberg EL, Grissom CK, Morris AH. Survival after shock requiring high-dose vasopressor therapy. *Chest* 2013; **143**: 664-671 [PMID: 22911566 DOI: 10.1378/chest.12-1106]

25 **Brand DA**, Patrick PA, Berger JT, Ibrahim M, Matela A, Upadhyay S, Spiegler P. Intensity of Vasopressor Therapy for Septic Shock and the Risk of In-Hospital Death. *J Pain Symptom Manage* 2017; **53**: 938-943 [PMID: 28062334 DOI: 10.1016/j.jpainsymman.2016.12.333]

26 **Chotalia M**, Matthews T, Arunkumar S, Bangash MN, Parekh D, Patel JM. A time-sensitive analysis of the prognostic utility of vasopressor dose in septic shock. *Anaesthesia* 2021; **76**: 1358-1366 [PMID: 33687732 DOI: 10.1111/anae.15453]

27 **Roberts RJ**, Miano TA, Hammond DA, Patel GP, Chen JT, Phillips KM, Lopez N, Kashani K, Qadir N, Cairns CB, Mathews K, Park P, Khan A, Gilmore JF, Brown ART, Tsuei B, Handzel M, Chang AL, Duggal A, Lanspa M, Herbert JT, Martinez A, Tonna J, Ammar MA, Nazer LH, Heavner M, Pender E, Chambers L, Kenes MT, Kaufman D, Downey A, Brown B, Chaykosky D, Wolff A, Smith M, Nault K, Gong MN, Sevransky JE, Lat I; Observation of VariatiOn in fLUids adMinistEred in shock-CHaracterizAtion of vaSoprEssor Requirements in Shock (VOLUME-CHASERS) Study Group and SCCM Discovery Network. Evaluation of Vasopressor Exposure and Mortality in Patients With Septic Shock. *Crit Care Med* 2020; **48**: 1445-1453 [PMID: 32706559 DOI: 10.1097/CCM.0000000000004476]

28 **Tsachouridou O**, Pilalas D, Nanoudis S, Antoniou A, Bakaimi I, Chrysanthidis T, Markakis K, Kassomenaki A, Mantzana P, Protonotariou E, Skoura L, Metallidis S. Mortality due to Multidrug-Resistant Gram-Negative Bacteremia in an Endemic Region: No Better than a Toss of a Coin. *Microorganisms* 2023; **11** [PMID: 37512883 DOI: 10.3390/microorganisms11071711]

29 **Carreira AS**, Salas MQ, Remberger M, Basso IN, Law AD, Lam W, Pasic I, Kim D, Michelis FV, Viswabandya A, Gerbitz A, Lipton JH, Husain S, Kumar R, Mattsson J. Bloodstream Infections and Outcomes Following Allogeneic Hematopoietic Cell Transplantation: A Single-Center Study. *Transplant Cell Ther* 2022; **28**: 50.e1-50.e8 [PMID: 34656808 DOI: 10.1016/j.jtct.2021.10.008]

30 **Fuji S**, Kapp M, Einsele H. Possible implication of bacterial infection in acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Front Oncol* 2014; **4**: 89 [PMID: 24795865 DOI: 10.3389/fonc.2014.00089]

31 **Bouteloup M**, Perinel S, Bourmaud A, Azoulay E, Mokart D, Darmon M; pour le Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie (GRRR-OH). Outcomes in adult critically ill cancer patients with and without neutropenia: a systematic review and meta-analysis of the Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie (GRRR-OH). *Oncotarget* 2017; **8**: 1860-1870 [PMID: 27661125 DOI: 10.18632/oncotarget.12165]

32 **Georges Q**, Azoulay E, Mokart D, Soares M, Jeon K, Oeyen S, Rhee CK, Gruber P, Ostermann M, Hill QA, Depuydt P, Ferra C, Toffart AC, Schellongowski P, Müller A, Lemiale V, Tinquaut F, Bourmaud A, Darmon M. Influence of neutropenia on mortality of critically ill cancer patients: results of a meta-analysis on individual data. *Crit Care* 2018; **22**: 326 [PMID: 30514339 DOI: 10.1186/s13054-018-2076-z]

33 **Schellongowski P**, Staudinger T, Kundi M, Laczika K, Locker GJ, Bojic A, Robak O, Fuhrmann V, Jäger U, Valent P, Sperr WR. Prognostic factors for intensive care unit admission, intensive care outcome, and post-intensive care survival in patients with de novo acute myeloid leukemia: a single center experience. *Haematologica* 2011; **96**: 231-237 [PMID: 21071501 DOI: 10.3324/haematol.2010.031583]

34 **Garcia Borrega J**, Heger JM, Koehler P, Holtick U, Hallek M, Scheid C, Böll B, Shimabukuro-Vornhagen A, Kochanek M, Eichenauer DA. Allogeneic stem cell transplant recipients admitted to the intensive care unit during the peri-transplant period have unfavorable outcomes-results of a retrospective analysis from a German university hospital. *Ann Hematol* 2022; **101**: 389-395 [PMID: 34668981 DOI: 10.1007/s00277-021-04698-3]

35 **Pohlen M**, Thoennissen NH, Braess J, Thudium J, Schmid C, Kochanek M, Kreuzer KA, Lebiedz P, Görlich D, Gerth HU, Rohde C, Kessler T, Müller-Tidow C, Stelljes M, Hullermann C, Büchner T, Schlimok G, Hallek M, Waltenberger J, Hiddemann W, Berdel WE, Heilmeier B, Krug U. Patients with Acute Myeloid Leukemia Admitted to Intensive Care Units: Outcome Analysis and Risk Prediction. *PLoS One* 2016; **11**: e0160871 [PMID: 27575819 DOI: 10.1371/journal.pone.0160871]

36 **Orvain C**, Beloncle F, Hamel JF, Del Galy AS, Thépot S, Mercier M, Kouatchet A, Farhi J, Francois S, Ifrah N, Mercat A, Asfar P, Hunault-Berger M, Tanguy-Schmidt A. Allogeneic stem cell transplantation recipients requiring intensive care: time is of the essence. *Ann Hematol* 2018; **97**: 1601-1609 [PMID: 29717367 DOI: 10.1007/s00277-018-3320-y]

37 **Holtan SG**, Pasquini M, Weisdorf DJ. Acute graft-versus-host disease: a bench-to-bedside update. *Blood* 2014; **124**: 363-373 [PMID: 24914140 DOI: 10.1182/blood-2014-01-514786]

38 **Mokart D**, Granata A, Crocchiolo R, Sannini A, Chow-Chine L, Brun JP, Bisbal M, Faucher M, Faucher C, Blache JL, Castagna L, Fürst S, Blaise D. Allogeneic hematopoietic stem cell transplantation after reduced intensity conditioning regimen: Outcomes of patients admitted to intensive care unit. *J Crit Care* 2015; **30**: 1107-1113 [PMID: 26193780 DOI: 10.1016/j.jcrc.2015.06.020]

39 **Orvain C**, Beloncle F, Hamel JF, Thépot S, Mercier M, Kouatchet A, Farhi J, Francois S, Guardiola P, Asfar P, Hunault-Berger M, Mercat A, Ifrah N, Tanguy-Schmidt A. Different Impact of the Number of Organ Failures and Graft-Versus-Host Disease on the Outcome of Allogeneic Stem Cell Transplantation Recipients Requiring Intensive Care. *Transplantation* 2017; **101**: 437-444 [PMID: 26950729 DOI: 10.1097/TP.0000000000001143]

40 **Platon L**, Amigues L, Ceballos P, Fegueux N, Daubin D, Besnard N, Larcher R, Landreau L, Agostini C, Machado S, Jonquet O, Klouche K. A reappraisal of ICU and long-term outcome of allogeneic hematopoietic stem cell transplantation patients and reassessment of prognosis factors: results of a 5-year cohort study (2009-2013). *Bone Marrow Transplant* 2016; **51**: 256-261 [PMID: 26569092 DOI: 10.1038/bmt.2015.269]

41 **Benz R**, Schanz U, Maggiorini M, Seebach JD, Stussi G. Risk factors for ICU admission and ICU survival after allogeneic hematopoietic SCT. *Bone Marrow Transplant* 2014; **49**: 62-65 [PMID: 24056739 DOI: 10.1038/bmt.2013.141]

42 **Depuydt P**, Kerre T, Noens L, Nollet J, Offner F, Decruyenaere J, Benoit D. Outcome in critically ill patients with allogeneic BM or peripheral haematopoietic SCT: a single-centre experience. *Bone Marrow Transplant* 2011; **46**: 1186-1191 [PMID: 21042315 DOI: 10.1038/bmt.2010.255]

43 **Gilli K**, Remberger M, Hjelmqvist H, Ringden O, Mattsson J. Sequential Organ Failure Assessment predicts the outcome of SCT recipients admitted to intensive care unit. *Bone Marrow Transplant* 2010; **45**: 682-688 [PMID: 19718056 DOI: 10.1038/bmt.2009.220]

44 **Lengliné E**, Chevret S, Moreau AS, Pène F, Blot F, Bourhis JH, Buzyn A, Schlemmer B, Socié G, Azoulay E. Changes in intensive care for allogeneic hematopoietic stem cell transplant recipients. *Bone Marrow Transplant* 2015; **50**: 840-845 [PMID: 25798675 DOI: 10.1038/bmt.2015.55]

45 **Lueck C**, Tzalavras A, Wohlfarth P, Meedt E, Kiehl M, Turki AT, Hoeper MM, Eder M, Cserna J, Buchtele N, Wolff D, Schellongowski P, Beutel G, Liebregts T. Impact of chronic graft-versus-host-disease on intensive care outcome in allogeneic hematopoietic stem cell recipients. *Bone Marrow Transplant* 2023; **58**: 303-310 [PMID: 36496524 DOI: 10.1038/s41409-022-01875-4]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Hepatocellular carcinoma recurrence after liver transplant: An Australian single-centre study

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide. Liver transplantation (LT) offers the most effective treatment. HCC recurrence is the strongest risk factor that decreases post-LT survival in patients transplanted for HCC. The rate of HCC recurrence is generally reported as 8%-20% in the literature. Many predictors of HCC have already been researched, however, to our knowledge there are no published studies on this topic using Australian data.

AIM

To determine the rate and identify predictors of HCC recurrence in a contemporary Western Australian LT cohort.

METHODS

We performed a retrospective cohort study of all liver transplants in patients with HCC at Sir Charles Gairdner Hospital between 2006 and 2021. Data was collected from various health record databases and included recipient demographics, serum biochemistry, radiology, operation notes, explant histopathology and details of recurrence. Overall survival of HCC patients post-LT, stratified for recurrence, was calculated by Kaplan Meier analysis. Univariate and multivariate Cox regression was used to determine predictors of HCC recurrence post-LT.

RESULTS
Between 1/1/2006 and 12/31/2021, 119 patients were transplanted with HCC. 8.4% of subjects developed recurrent HCC after LT with median follow-up time of 5.4 years. The median time to recurrence was 2.9 years ± 0.75 years. When comparing baseline characteristics, a greater proportion of subjects with recurrence had common characteristics on explant histopathology, including > 3 viable nodules (P = 0.001), vascular invasion (P = 0.003) and poorly differentiated HCC (P = 0.03). Unadjusted survival curves showed lower 1-year, 3-year, 5-year and 10-year survival rates in subjects with HCC recurrence compared to those without HCC recurrence (90% *vs* 92%, 70% *vs* 88%, 42% *vs* 80%, 14% *vs* 76%, respectively; log rank P < 0.001).

CONCLUSION
HCC recurrence was low at 8.4% in this contemporary Australian cohort, however it significantly impacted post-LT survival. Further studies are required to confirm predictors of recurrence and improve recipient outcomes.

Key Words: Liver cancer; Recurrence; Liver transplantation; Hepatocellular carcinoma; Predictors; Post-transplant survival; Australian data

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Core Tip: This is the first study looking at hepatocellular carcinoma (HCC) recurrence using Australian data. It is well established that HCC recurrence significantly reduces survival post liver transplantation (LT). Optimal selection of candidates to minimize post-LT HCC recurrence remains controversial. The rate of HCC recurrence post-LT in Western Australia is 8.4%. A higher proportion of the patients with HCC recurrence had common baseline characteristics on explant; > 3 tumours, vascular invasion, and poorly differentiated disease. A larger multicentre study is required to investigate the predictive effects of these variables on post-LT HCC recurrence.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer deaths worldwide[1,2] and the 7th in Australia[3]. In carefully selected patients with nonresectable HCC, liver transplantation (LT) has been validated as the most effective treatment due to complete removal of the HCC and replacement of the diseased liver[2,4]. Historically, LT led to high rates of HCC recurrence, however, since the implementation of selective criteria, such as the Milan criteria, post-LT recurrence has significantly reduced[5]. In 2007, Australia and New Zealand moved to the University of California and San Francisco (UCSF) expanded criteria, and most recently, in 2020, the Metroticket 2.0 (MT2) model has been adopted.

HCC recurrence is the strongest predictor of worse survival in patients with HCC post-LT[6]. Whilst selection criteria have been refined and improved, HCC recurrence remains an issue with reported rates between 8% and 20%[7]. Recurrence mainly occurs within 2 years[8] of the transplant and is postulated to be due to the progression of occult metastases following transplantation[7]. An extensive literature search identified the most important factors shown to influence likelihood of recurrence to be tumour burden, alpha-fetoprotein (AFP) levels, histopathological characteristics of the tumour, and neutrophil-lymphocyte ratio (NLR)[9]. In recent years, scoring systems aimed at predicting HCC recurrence post-LT have been proposed and validated using these variables, such as the model of recurrence after liver transplant score[10] and the risk estimation of tumor recurrence after transplant score[11].

Given the numerous potential predictive factors for HCC recurrence and changes in transplant eligibility for patients with HCC over time, there is no clear understanding regarding the significance and interaction each factor has. It is important to identify any regional variations or novel trends in listing characteristics, management, and outcomes. To the best of our knowledge, no publications on this topic include Australian data. In this study we aim to calculate the rate of HCC recurrence in an Australia LT cohort. We additionally intend to analyse pre-transplant predictive factors of HCC recurrence, identify any new variables of significance and document the survival of these patient's post-transplant.

MATERIALS AND METHODS

Study design and setting

We performed a single-centre, retrospective, cohort study of all liver transplants for HCC (including those in which HCC was found incidentally on explant analysis) undertaken at Sir Charles Gairdner Hospital (SCGH) between 2006 and 2021. Only liver transplants from deceased donors were performed. This study does not include any partial liver transplants or living-donor liver transplants. A minimum of 1 year follow-up time was required for all participants. Ethics approval was granted by the Sir Charles Gairdner Osborne Park Health Care Group Human Research Ethics Committee, approval No. 47721.

Study population

A total of 343 liver transplants were performed at SCGH during the study time. For inclusion to the study, patients were required to be adults (> 18 years of age), undergo a deceased-donor liver transplant for any cause with either: (1) A known diagnosis of HCC at the time of transplant (n = 100); or (2) Have a new diagnosis of HCC made on explant histology (n = 19). Patients who underwent multiple liver transplants (n = 4) were included in the study, provided that they only underwent a single liver transplant associated with HCC. Study participants were excluded if their transplant was not associated with HCC, if they were under the age of 18 years, or if they underwent multiple transplants associated with HCC. As per local management guidelines, patients underwent locoregional bridging therapy when indicated prior to their transplant. The protocol for downstaging at our centre was used when a patient did not meet the appropriate contemporary selection criteria for transplantation, for the majority of participants in this study that was the Milan criteria (defined below). The most appropriate modality of downstaging was selected based on availability of equipment and tumour characteristics. Following successful downstaging, patients were monitored for a minimum of 3 months to ensure they remained within transplant criteria, then they were activated on the liver transplant waiting list. Downstaging treatment modalities at our centre included radiofrequency ablation, microwave ablation, transarterial chemoembolization, selective internal radiation therapy and stereotactic body radiotherapy.

Data collection

All data was collected from electronic medical records and clinical databases including the Western Australia liver transplant database. Data was deidentified and compiled onto a new database for the purpose of this study. The collected variables include: (1) Age at transplant; (2) Sex; (3) Body mass index (BMI) at transplant; (4) Aetiology of liver disease; (5) Child Pugh score; (6) Model for end-stage liver disease score; (7) Number of nodules identified on the most recent radiological imaging prior to transplant; (8) Serum AFP levels (immediately pre-transplant and highest level documented); (9) NLR at the time of transplant; (10) Presence of pre-transplant biopsy; (11) HCC treatment pre-transplant; (12) Waiting time; (13) Cold ischemia time; (14) Explant histopathology analysis including number of nodules, vascular invasion, viable HCC, histological grade; and (15) Details of recurrence including time to recurrence, location, AFP levels at recurrence, treatment of recurrence. Overweight was defined as per the World Health Organisation, as a BMI ≥ 25, and obesity was defined as a BMI ≥ 30. Data on other pre-transplant comorbidities, donor characteristics, symptoms and quality of life were not collected or analysed.

Selection criteria definitions

The collected variables include an assessment of selection criteria eligibility. The criteria were defined as: (1) Milan criteria (single lesion ≤ 5 cm or up to three lesions all ≤ 3 cm, without vascular involvement or extrahepatic spread); (2) UCSF criteria (single lesion ≤ 6.5 cm or 2-3 Lesions ≤ 4.5 cm and total tumour diameter ≤ 8 cm); (3) MT2 criteria (group 1: Sum of number and size of lesions < 7 and AFP < 200 ng/mL; group 2: Sum of number and size of lesions < 6 and AFP 200-400 ng/mL; and group 3: Sum of number and size of lesions < 5 and AFP 400-1000 ng/mL).

Objectives

The primary objective of our study was to calculate the rate of HCC recurrence post-LT in Western Australia, within our selected period. Secondary objectives included validating the established pre-transplant predictive factors of HCC recurrence post-LT, identifying any new variables of significance within our results, and comparing survival between those that did develop HCC recurrence and those that did not.

Statistical analysis

Baseline characteristics were summarized in percentages for categorical variables. Mean and standard deviation were calculated for continuous variables. Categorical variables were compared using χ^2 test. Continuous variables were compared using the t test for normally distributed variables and the nonparametric Wilcoxon rank-sum test for measures not normally distributed. Kaplan Meier analysis was used to calculate the overall survival curve of all patients post-LT and the overall survival stratified for recurrence. Univariate and multivariate Cox regression was used to determine predictors of HCC recurrence post-LT. Statistical analysis was based on STATA software, release 17.0, College Station, Texas: Stata Corp LP.

RESULTS

Study cohort

A total of 343 LT s for any indication took place at the SCGH liver transplant centre between January 1, 2006–December 31, 2021; 119 (34.7%) of those transplants were associated with HCC, yielding a sample size of 119 transplants (Figure 1). Of these transplants, 100 (84.0%) occurred following a known diagnosis of HCC, the remaining 19 (16.0%) transplants resulted in an incidental finding of HCC in explant histopathological analysis. Recurrent HCC post-LT was documented in 10 (8.4%) cases, with a median follow-up time of 5 years (1-15.9 years). The follow-up duration was consistent among both groups.

Risk factors for HCC recurrence

When comparing baseline characteristics to those without recurrence, a greater proportion of subjects with recurrence were female (20% *vs* 14%, $P = 0.05$), had underlying chronic hepatitis B virus infection (30% *vs* 4%, $P = 0.001$), had higher AFP levels at time of transplant (41 ng/mL ± 50 ng/mL *vs* 13.7 ng/mL ± 30 ng/mL, $P = 0.01$), and had common characteristics on explant histopathology, including > 3 viable nodules (40% *vs* 15%, $P = 0.001$), the presence of vascular invasion (40% *vs* 23%, $P = 0.003$) and poorly differentiated HCC (10% *vs* 3%, $P = 0.03$). All patients with underlying chronic hepatitis B at time of transplant were on antiviral treatment with an undetectable viral load. A full comparison of baseline characteristics of patients with and without recurrence after LT is represented in Table 1. The presence of macrovascular invasion in the explant was the only value to reach statistical significance on both univariate and multivariate analysis [hazard ratio (HR) = 12.2, 95%CI: 1.47-102, $P = 0.02$ and HR = 18.6, 95%CI: 1.98-174, $P = 0.01$, respectively] (Table 2).

Survival

Overall survival of all patients who underwent a LT in association with HCC demonstrated a 1-year, 3-year, 5-year, 10-year and 15-year survival rate of 90.8%, 83.3%, 78.5%, 67.1%, and 52.3% respectively (Figure 2). Unadjusted survival curves showed lower 1-year, 3-year, 5-year and 10-year survival rates in subjects with HCC recurrence compared to those without HCC recurrence (90% *vs* 92%, 70% *vs* 88%, 42% *vs* 80%, 14% *vs* 76%, respectively; log rank $P < 0.001$) (Figure 3). The median time to recurrence was 2.9 years ± 0.75 years. Late recurrence (> 2 years) was more common than early recurrence (60% *vs* 40%) with the majority of recurrences (90%) being extrahepatic in location (Table 3). As of December 31, 2022, 32 of the patients included in the study had died. Seven of the deaths occurred in patients from the recurrence group, and all of those deaths were directly related to HCC recurrence. The median time to death following a diagnosis of HCC recurrence post-LT was 11 months. The remaining 25 deaths occurred in the non-recurrence group; 4 deaths were liver-related, 21 deaths were due to other causes.

DISCUSSION

In this single centre cohort study, using novel Australian data, we found the rate of HCC recurrence post-LT to be 8.4%. The median time to recurrence was 2.9 years with 60% of the recurrence cases being diagnosed > 2 years post-transplant. The rate of HCC recurrence post-LT differs between centres, however, when collated, the generally accepted figure is between 8%-20%[2]. A recent 2022 study investigating a new composite tool in the prediction of HCC recurrence documented a 5-year recurrence rate of 19.6% in their European cohort and 16.9% in their Latin American cohort[12]. A separate American 2022 study analysing the relationship of downstaging and HCC reported a recurrence rate of 12.5% [13]. Our study yields a recurrence rate at the lower end of what has become the accepted norm.

It has been consistently reported that HCC recurrence is the strongest risk factor impeding long-term post-LT survival [9,12], which is reflected in our data (Figure 2). The further from the transplant, the greater the disparity in survival. We did not find any additional factors, such as waitlist time or cold ischemia time to have a significant impact on survival. A 2021 study by El-domiaty *et al*[8] reported a similar set of results with 3-year, 5-year and 10-year survival rates of 53% *vs* 88.7%, 31% *vs* 86%, 12.4% *vs* 72.8%, respectively; log rank $P < 0.001$. This study reported 61.3% (46/75) of patients to experience an early recurrence (< 2 years post-transplant). A similar finding was reported in 2019 by Chagas *et al*[7] with the majority of their patients being diagnosed with recurrent HCC within 12 months (85%, 73/86). They support the recommendation for high intensity HCC surveillance within the first 2 years post-LT. We documented the median time to recurrence to be 2.9 years, therefore, support the notion to continue intense HCC surveillance beyond the 2-year mark. We additionally found the majority of recurrences were extrahepatic in location, in keeping with other centres[7,8]. The implication we draw is that HCC surveillance must include imaging beyond the liver alone, such as computerised tomography (CT) chest/abdomen/pelvis. This recommendation is shared by a 2017 study by Fernandez-Sevilla *et al*[14]. However, they reported 70% of their cases of recurrence being diagnosed within 2 years, hence advocating for a high intensity 2-year surveillance program only.

Due to the relatively small sample size of our study, we were unable to prove any associations between pre-transplant variables and their predictive effect on HCC recurrence, however, a significant difference was that the HCC recurrence group had higher pre-transplant AFP levels compared to the group without recurrence (41 ng/mL ± 50 ng/mL *vs* 13.7 ng/mL ± 30 ng/mL, $P = 0.01$). Additionally, the AFP levels were measured at the time of diagnosis of recurrence and found to be highly variable (4700 ng/mL ± 9394 ng/mL). These findings are in keeping with a large multicentre study by Chagas *et al*[7] which found that AFP levels > 1000 ng/mL at the time of recurrence were associated with a poorer prognosis of survival. We conclude from these results that while AFP levels are important in the surveillance and diagnosis of HCC, they should not solely be relied upon.

Table 1 Baseline characteristics of patients with hepatocellular carcinoma with and without recurrence after liver transplantation, *n* (%)

Variable	Without recurrence (*n* = 109)	With recurrence (*n* = 10)	*P* value
Age at transplant (years)	56.8	55.8	0.68
Female	15 (14)	2 (20)	0.05
Male	94 (86)	8 (80)	0.58
Aetiology of liver disease			
HCV	45 (41)	5 (50)	0.46
Alcohol	21 (19)	1 (10)	0.87
Alcohol +HCV	20 (18)	0 (0)	0.005
Non-alcoholic fatty liver disease	13 (12)	1 (10)	0.63
Hepatitis B virus	4 (4)	3 (30)	0.001
Primary sclerosing cholangitis	2(2)	0 (0)	0.74
Other	4 (4)	0 (0)	0.52
Child Pugh			
A	32 (30)	1 (10)	0.78
B	40 (37)	6 (60)	0.25
C	37 (34)	3 (30)	0.94
Model for End-stage liver disease	15 ± 7.0	16 ± 7.4	0.64
Within Milan Criteria	102 (94)	9 (90)	0.81
Within University of California and San Francisco	105 (96)	10 (100)	0.82
Within Metroticket 2.0			
Pre-transplant	101 (92)	9 (90)	0.55
Post-transplant	75 (68)	6 (60)	0.57
Comorbidities			
Obesity	35 (32)	2 (20)	0.34
Overweight	43 (40)	6 (60)	0.17
Overweight or obese	78 (71)	8 (80)	0.60
Morphology at time of transplant			
Number of nodules			
1	85 (78)	7 (70)	0.74
2-3	22 (20)	3 (30)	0.21
> 3	2 (2)	0 (0)	0.78
Serum markers pre-transplant			
AFP at time of transplant (ng/mL)	13.7 ± 30	41 ± 50	0.01
Highest pre-op AFP (ng/mL)	30.3 ± 64	41 ± 47	0.59
neutrophil-lymphocyte ratio at time of transplant	4.8 ± 13	2.9 ± 1.3	0.64
Biopsy pre-transplant performed	37 (34)	5 (50)	0.32
HCC treatment pre-transplant			
Transarterial chemoembolization	25 (23)	3 (30)	0.56
Ablative techniques	19 (17)	3 (30)	0.78
Surgery	0	0 (0)	0.25
Radiology (selective internal radiation therapy/choline kinase)	9 (8)	0 (0)	0.65

Combined	24 (22)	4 (40)	0.10
Waiting time (days)	166 ± 180	194 ± 153	0.63
Explant histopathology findings			
Number of viable nodules			
0	8 (8)	1 (10)	0.14
1	45 (43)	3 (30)	0.24
2-3	37 (35)	2 (20)	0.46
> 3	16 (15)	4 (40)	0.001
Vascular invasion	25 (23)	4 (40)	0.003
Type of vascular invasion			
Microvascular	25 (23)	3 (30)	0.001
Macrovascular	0 (0)	1 (10)	0.001
Viable HCC on explant	101 (92)	9 (90)	0.55
Histology grading			
Well differentiated	44 (40)	1 (10)	0.001
Moderately differentiated	48 (44)	6 (60)	0.46
Poor differentiated	3 (3)	1 (10)	0.03

Quantitative data were expressed as mean ± SD. *P* values for the comparison between groups. Maximum diameter of viable tumour in mm. AFP: Alpha-fetoprotein; HCV: hepatitis C virus; HCC: Hepatocellular carcinoma.

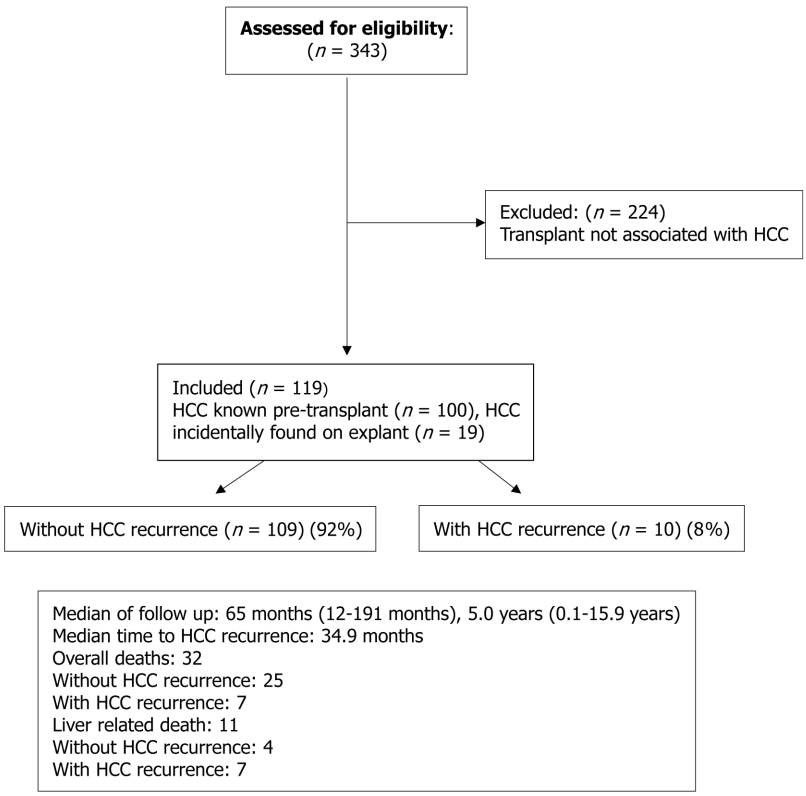


Figure 1 Study flow diagram. HCC: Hepatocellular carcinoma.

Table 2 Predictors of post-transplant hepatocellular carcinoma recurrence

Variable	Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (years)	0.98 (0.91-1.05)	0.62		
Male	1.55 (0.32-7.32)	0.57		
Female	0.64 (0.13-3.03)	0.58		
Obesity	0.56 (0.11-2.65)	0.46		
Overweight	2.07 (0.58-7.35)	0.25		
Histology pre-transplant performed	2.10 (0.60-7.31)	0.24		
Explant tumour characteristics				
Viable HCC on explant	0.72 (0.09-5.7)	0.76		
Number of viable lesions				
1	0.55 (0.05-5.3)	0.60		
2-3	0.44 (0.04-4.8)	0.50		
> 3	2.0 (0.22-17.9)	0.53		
Max diameter of viable tumour (mm)	1.02 (0.98-1.06)	0.19		
Sum of diameters (mm)	1.01 (0.96-1.0)	0.64		
Macrovascular invasion	12.2 (1.47-102)	0.02	18.6 (1.98-174)	0.01
Microvascular invasion	1.75 (0.43-7.04)	0.42		
Tumour differentiation				
Well	1.52 (0.17-13.1)	0.58		
Moderate	0.96 (0.10-8.6)	0.47		
Poor	1.87 (1.63-80.5)	0.12		
Serum markers				
Highest Pre-op alpha-fetoprotein	1.00 (0.64-1.00)	0.64		
neutrophil-lymphocyte ratio	0.90 (0.66-1.22)	0.51		
Waiting time (days)	1.00 (0.99-1.00)	0.55		
Cold Ischemia time (minutes)	1.00 (0.97-1.03)	0.70		
Wait time from HCC diagnosis to liver transplantation				
< 6 months	0.60 (0.17-2.15)	0.44		
> 6 months	1.64 (0.46-5.85)	0.43		

Results based on univariate and multivariate risk regression models. HCC: Hepatocellular carcinoma; HR: Hazard ratio.

Explant histopathological analysis provides the most reliable information regarding tumour characteristics; therefore, it can be used to predict recurrence. The presence of macrovascular invasion on explant was the only variable in our study to reach statistical significance on univariate and multivariate analysis, therefore, can be considered a predictor of recurrence. Macrovascular invasion is one of the most well-known independent risk factors of recurrence and is in fact an exclusion criterion for liver transplant under all selection criteria[15]. A single patient within our cohort was found to have macrovascular invasion on explant histology. There was no evidence of this on pre-transplant imaging. When comparing baseline characteristics in our study, a higher proportion of the recurrence group demonstrated > 3 viable nodules, the presence of microvascular invasion, macrovascular invasion, and poorly differentiated HCC. Additionally, a higher proportion of the non-recurrence group were documented to have well differentiated tumours. All of these findings are consistent with data reported at other centres. A recent publication by Tabrizian *et al*[13] reported variables independently associated with recurrence to be poor tumour differentiation [odds ratio (OR) = 3.37; 95%CI: 1.02-11.15, *P* = 0.05] and vascular invasion on explant pathologic findings (OR = 1.91; 95%CI: 1.03-3.50, *P* = 0.04).

To the best of our knowledge, this is the first published Australian series of HCC recurrence post-LT. A single liver transplant centre in Western Australia performs approximately 10% of all liver transplants in Australia per year. An Australia wide, multicentre study, collating data from all major transplant centres across Australia is currently being

Table 3 Characteristics of hepatocellular carcinoma recurrence after liver transplantation, *n* (%)

Variable	Overall (*n* = 10)
Time to recurrence (years)	2.9 ± 0.75
< 2	4 (40)
> 2	6 (60)
Location	
Hepatic	1 (10)
Extrahepatic	9 (90)
Alpha-fetoprotein at time of recurrence (ng/mL)	4700 ± 9394
Treatment of recurrence	
Yes	6 (60)
No	4 (40)
Type of treatment	
Systemic therapy	1 (10)
Surgery	0 (0)
Radiotherapy	1 (10)
Combined	2 (20)
Other	2 (20)

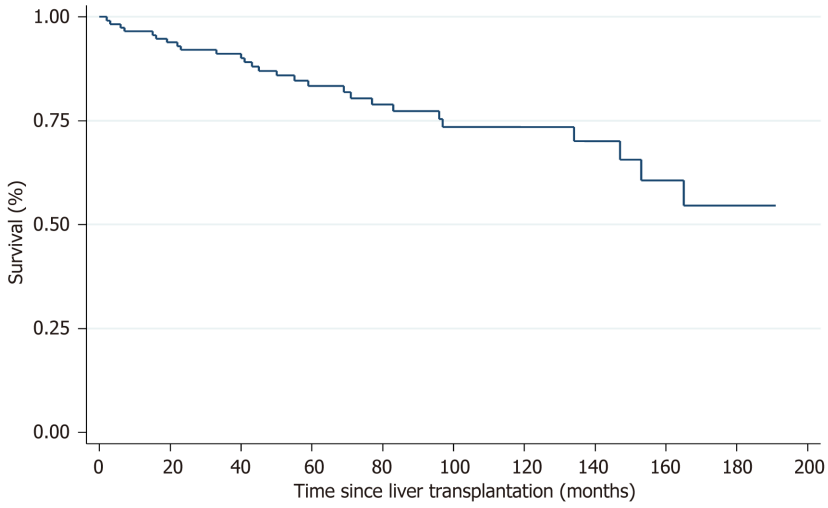


Figure 2 Overall survival of hepatocellular carcinoma patients who underwent liver transplantation.

planned. Regional variation in data may reflect differences in screening and treatment of HCC and HCC recurrence, allowing for identification of novel predictors of recurrence.

The major limitation of this study is the small sample size and limited number of endpoints (post-transplant HCC recurrences). A second limitation is that our data is of a single centre, thus limiting our external validity. Thirdly, the minimum follow-up is 1 year, thus the only survival rate that includes the entire cohort is the 1-year survival rate.

CONCLUSION

In summary, the rate of HCC recurrence in Western Australia is 8.4%. Common baseline characteristics were observed among the patients who developed recurrent HCC, notably relating to the explant histopathological analysis. Our findings support the idea to continue intense HCC surveillance beyond the first 2 years post-LT. We propose 6 monthly chest/abdomen/pelvis CT scans for 2 years, then annually until 5 years post-transplant. A larger, nation-wide study is required to further investigate the predictors of HCC recurrence post-transplant.

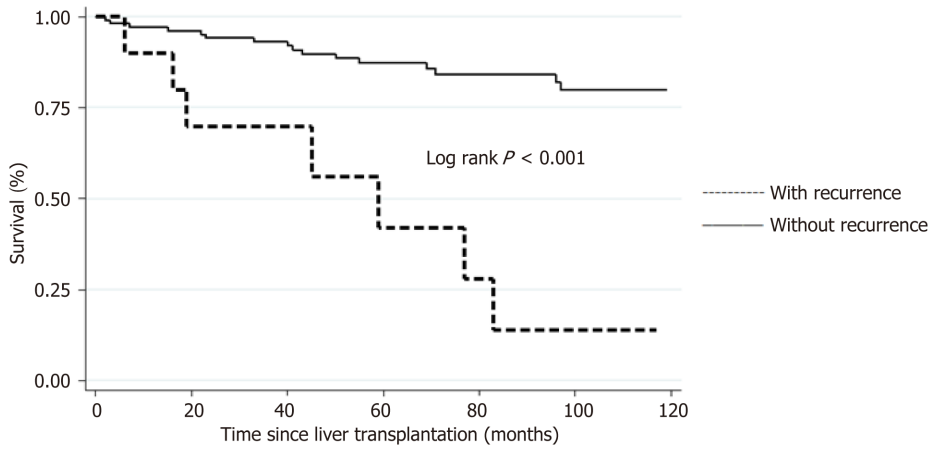


Figure 3 Survival of hepatocellular carcinoma patients stratified according to hepatocellular carcinoma recurrence.

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FOOTNOTES

Author contributions: Garas MG conceptualised and designed the study, coordinated and completed the data collection, carried out the data analysis, drafted the initial manuscript, and critically reviewed and revised the manuscript; Calzadilla-Bertot L conceptualised and designed the study, carried out a formal data analysis, critically reviewed and revised the manuscript; Smith BW, Delriviere L, Jaques B, Mou L, Adams LA, MacQuillan GC, Garas G, and Jeffrey GP conceptualised and designed the study and critically reviewed and revised the manuscript; Wallace MC conceptualised and designed the study, supervised the data collection and analysis, critically reviewed and revised the manuscript; all of the authors read and approved the final version of the manuscript to be published.

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STROBE statement: The authors have read the STROBE statement–checklist of items, and the manuscript was prepared and revised according to the STROBE statement–checklist of items.

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REFERENCES

1 **World Health Organisation**. Cancer. 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer

2 **Bzeizi KI**, Abdullah M, Vidyasagar K, Alqahthani SA, Broering D. Hepatocellular Carcinoma Recurrence and Mortality Rate Post Liver Transplantation: Meta-Analysis and Systematic Review of Real-World Evidence. *Cancers (Basel)* 2022; **14**: 5114 [PMID: 36291898 DOI: 10.3390/cancers14205114]

3 **Australia Government Cancer Australia**. Cancer Statistics. Cancer in Australia Statistics. 2022. Available from: https://www.canceraustralia.gov.au/impacted-cancer/what-cancer/cancer-australia-statistics

4 **Gabutti A**, Bhoori S, Cascella T, Bongini M. Hepatocellular Carcinoma Recurrence After Liver Transplantation. *Oncology (Williston Park)* 2020; **34**: 692516 [PMID: 32212134]

5 **Shin WY**, Suh KS, Lee HW, Kim J, Kim T, Yi NJ, Lee KU. Prognostic factors affecting survival after recurrence in adult living donor liver transplantation for hepatocellular carcinoma. *Liver Transpl* 2010; **16**: 678-684 [PMID: 20440777 DOI: 10.1002/lt.22047]

6 **Agarwal PD**, Lucey MR. Management of hepatocellular carcinoma recurrence after liver transplantation. *Ann Hepatol* 2022; **27**: 100654 [PMID: 34929349 DOI: 10.1016/j.aohep.2021.100654]

7 **Chagas AL**, Felga GEG, Diniz MA, Silva RF, Mattos AA, Silva RCMA, Boin IFSF, Garcia JHP, Lima AS, Coelho JCU, Bittencourt PL, Alves VAF, D'Albuquerque LAC, Carrilho FJ; Brazilian HCC Study Group. Hepatocellular carcinoma recurrence after liver transplantation in a Brazilian multicenter study: clinical profile and prognostic factors of survival. *Eur J Gastroenterol Hepatol* 2019; **31**: 1148-1156 [PMID: 31247632 DOI: 10.1097/MEG.0000000000001448]

8 **El-Domiaty N**, Saliba F, Vibert E, Karam V, Sobesky R, Ibrahim W, Pittau G, Ciacio O, Salloum C, Amer K, Saeed MA, Shawky JA, Sa Cunha A, Rosmorduc O, Cherqui D, Adam R, Samuel D. Early Versus Late Hepatocellular Carcinoma Recurrence After Transplantation: Predictive Factors, Patterns, and Long-term Outcome. *Transplantation* 2021; **105**: 1778-1790 [PMID: 32890134 DOI: 10.1097/TP.0000000000003434]

9 **Filgueira N**. Hepatocellular carcinoma recurrence after liver transplantation: Risk factors, screening and clinical presentation. *World J Hepatol* 2019; **11**: 261-272 [PMID: 30967904 DOI: 10.4254/wjh.v11.i3.261]

10 **Halazun KJ**, Najjar M, Abdelmessih RM, Samstein B, Griesemer AD, Guarrera JV, Kato T, Verna EC, Emond JC, Brown RS Jr. Recurrence After Liver Transplantation for Hepatocellular Carcinoma: A New MORAL to the Story. *Ann Surg* 2017; **265**: 557-564 [PMID: 27611615 DOI: 10.1097/SLA.0000000000001966]

11 **Mehta N**, Heimbach J, Harnois DM, Sapisochin G, Dodge JL, Lee D, Burns JM, Sanchez W, Greig PD, Grant DR, Roberts JP, Yao FY. Validation of a Risk Estimation of Tumor Recurrence After Transplant (RETREAT) Score for Hepatocellular Carcinoma Recurrence After Liver Transplant. *JAMA Oncol* 2017; **3**: 493-500 [PMID: 27838698 DOI: 10.1001/jamaoncol.2016.5116]

12 **Costentin C**, Piñero F, Degroote H, Notarpaolo A, Boin IF, Boudjema K, Baccaro C, Podestá LG, Bachellier P, Ettorre GM, Poniachik J, Muscari F, Dibenedetto F, Duque SH, Salame E, Cillo U, Marciano S, Vanlemmens C, Fagiuoli S, Burra P, Van Vlierberghe H, Cherqui D, Lai Q, Silva M, Rubinstein F, Duvoux C; French-Italian-Belgium and Latin American collaborative group for HCC and liver transplantation. R3-AFP score is a new composite tool to refine prediction of hepatocellular carcinoma recurrence after liver transplantation. *JHEP Rep* 2022; **4**: 100445 [PMID: 35360522 DOI: 10.1016/j.jhepr.2022.100445]

13 **Tabrizian P**, Holzner ML, Mehta N, Halazun K, Agopian VG, Yao F, Busuttil RW, Roberts J, Emond JC, Samstein B, Brown RS Jr, Najjar M, Chapman WC, Doyle MM, Florman SS, Schwartz ME, Llovet JM. Ten-Year Outcomes of Liver Transplant and Downstaging for Hepatocellular Carcinoma. *JAMA Surg* 2022; **157**: 779-788 [PMID: 35857294 DOI: 10.1001/jamasurg.2022.2800]

14 **Fernandez-Sevilla E**, Allard MA, Selten J, Golse N, Vibert E, Sa Cunha A, Cherqui D, Castaing D, Adam R. Recurrence of hepatocellular carcinoma after liver transplantation: Is there a place for resection? *Liver Transpl* 2017; **23**: 440-447 [PMID: 28187493 DOI: 10.1002/lt.24742]

15 **Mazzaferro V**, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R, Mariani L. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. *Liver Transpl* 2011; **17** Suppl 2: S44-S57 [PMID: 21695773 DOI: 10.1002/lt.22365]

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ORIGINAL ARTICLE

Retrospective Study

Comparative study of living donor kidney transplants: Right *vs* left

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Abstract

BACKGROUND

Transplant teams often hesitate to use the right kidney (RK) in living donor (LD) transplants due to the complexities of anastomosing the short, thin-walled right renal veins, which can potentially lead to graft loss or graft dysfunction. Nevertheless, circumstances may arise where selecting the RK over the left kidney (LK) is unavoidable. Consequently, it is crucial to thoroughly examine the implications of such a choice on the overall transplant outcome.

AIM

To compare transplant outcomes between recipients of RK and LK while examining the factors that influence these outcomes.

METHODS

We retrospectively analyzed data from adult patients who received LD kidney transplants involving meticulous patient selection and surgical techniques at our center from January 2020 to December 2023. We included all kidney donors who were over 18, fit to donate, and had undergone diethylenetriamine pentaacetic acid split function and/or computed tomography based volumetry. The variables examined comprised donor and recipient demographics, and outcome measures included technical graft loss (TGL), delayed or slow graft function (SGF), and post-transplant serum creatinine (SC) trends. We used a logistic regression model to assess the likelihood of adverse outcomes considering the donor kidney side.

RESULTS

Of the 250 transplants performed during the period, 56 (22%) were RKs. The recipient demographics and transplant factors were comparable for the right and LKs, except that the donor warm and cold ischemia time were shorter for RKs. TGL and SGF each occurred in 2% (n = 1) of RKs and 0.5% (n = 1) of LKs, the difference being insignificant. These complications, however, were not related to

the venous anastomosis. One RK (2%) developed delayed graft function after 48 hours, which was attributable to postoperative hypoxia rather than the surgical technique. The post-transplant SC trend and mean SC at the last follow-up were similar across both kidney sides.

CONCLUSION
The donor kidney side has little impact on post-transplant adverse events and graft function in LD transplants, provided that careful patient selection and precise surgical techniques are employed.

Key Words: Living donor; Right kidney; Right renal vein; Venous anastomosis; Technical graft loss; Early graft function

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Core Tip: Donor right kidneys (RKs) are associated with technical difficulty, and have a higher incidence of delayed graft function and peri-operative graft loss. Short length and thin wall of the renal vein makes the venous anastomosis challenging. We focus on the selection criteria for RKs and how to manage short veins during bench work, analyze our experience with RKs, and compare outcomes with left kidneys in living donor transplantation.

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INTRODUCTION

Kidney transplantation is widely regarded as the best treatment option for end-stage renal disease due to its positive impact on patient survival and quality of life[1]. However, the procedure's success depends on multiple factors, the most important being the vascular anastomoses between the donor kidney and the recipient vessels.

Anastomosing short and thin-walled veins of right kidneys (RKs) to the recipient's veins presents more challenges than left kidneys (LKs), which typically have more favorable characteristics; consequently, RKs are more prone to complications[2-5]. Such a risk is increased if the kidney recovery is laparoscopic, where the application of clips and staples shortens the vein, and the option of acquiring a caval cuff to make up for the loss in length is not available[4,6,7]. Grafts with renal veins shorter than 2.5 cm are particularly vulnerable—more so in obese recipients or if the donor kidney is large. The complexities associated with RKs have led to the preference for LKs and their preponderance in living donor (LD) transplants[6]. We analyzed the short-term outcomes of RK and LK transplants in our LD transplant series, which involved meticulous patient selection and surgical technique. We omitted long-term results because complications related to technical issues manifest in the early post-transplant period.

MATERIALS AND METHODS

Study design

We gathered data from hospital records of LD transplants performed at the Kidney Transplant Unit of Rehman Medical Institute in Peshawar, Pakistan, between January 2020 and December 2023. The data were divided into two groups based on the donor kidney side to determine its impact on transplant outcomes. It included donor and recipient demographics with information about the donor kidney's side, split function, number of arteries, donor nephrectomy types, open [open donor nephrectomy (ODN)] or laparoscopic [laparoscopic donor nephrectomy (LDN)], ischemia times, and immunosuppressant protocols. Outcome measures included rates of immediate graft function (IGF), slow graft function (SGF), delayed graft function (DGF), technical graft loss (TGL), and for graft function, we recorded number of hours it took for the pre-transplant serum creatinine (SC) to decrease by 50% (SC50), SC on day 7 after surgery (SCD7), days taken to normalize SC, and SC at last follow-up (LSC).

We included all kidney donors who were over 18, fit to donate, and had undergone diethylenetriamine pentaacetic acid (DTPA) split function and/or computed tomography (CT) based volumetry. Our sample size was 250, sampling was convenience type, and multiple colleagues were involved in data collection after being trained on the forms and coding used for various variables before data collection. All the information collected were rechecked to minimize errors and avoid bias.

Our choice of donor kidney depended on its vascular anatomy, DTPA-based split function, and CT-based volumetry; we opted for kidneys with a lower function and smaller volume (difference > 15 cc); however, if the right renal vein (RRV) was less than 2.5 cm, we opted for LKs. When both kidneys were approximately the same size, we preferred the RK if the LK had multiple arteries, provided the RRV had the minimum threshold length. In thin females, we even

accepted a 2 cm length because their iliac veins are more superficial, and valuable length could be gained by careful circumferential dissection of the RRV in the renal hilum (Figure 1). The right renal artery, generally longer than the vein, was shortened to match the length of the vein, as described elsewhere[2,6].

We used the following operational definitions. Donor warm ischemia (DWI) was defined as time from clamping the renal artery to cold flushing of the graft. Cold ischemia time (CIT) was defined as duration that the graft was stored in a cold solution. Recipient warm ischemia was defined as time from starting vascular anastomosis to graft reperfusion. TGL was defined as graft removal within 7 days of transplantation. DGF was defined as the need for dialysis in the 1st week after transplant. SGF was defined as SC > 3 mg/dL on day 5 after transplant.

All information gathered from the patient file reviews and electronic medical records was entered into a proforma and then transferred to an excel sheet. All recorded variables were compared between left or right-side nephrectomy to observe the differences in outcomes.

Surgical technique

All grafts were placed in the retroperitoneum with end-to-side anastomosis between the graft vessels and the recipient external iliac vessels or to more proximal vessels. Ice-filled swabs and cold saline irrigation kept the graft cool during the entire implantation procedure. Multiple arteries were implanted individually or placed on a common ostium. The vesico-ureteric anastomosis was extravesical, and fashioned over a stent.

Statistical analysis

Data collection and analysis utilized Microsoft Excel 2013 and Statistical Package for the Social Sciences version 25 (IBM Corp., Armonk, NY, United States). Qualitative data are described as frequencies and percentages, while quantitative data are expressed as mean with standard deviation. The independent sample *t*-test was employed to assess the statistical significance of differences between groups. Additionally, a linear regression model was utilized to evaluate the influence of confounding variables on outcomes. A post hoc subgroup analysis was performed based on the donor nephrectomy technique, (open or laparoscopic), donor relation (related or unrelated), and immunosuppression protocol (steroid based or steroid sparing). Missing data were addressed through exclusion, and patients lost to follow-up or who died were censored as graft loss. All *P* values were based on two-sided tests and significance was set at a *P* value < 0.05.

RESULTS

A total of 250 LD kidney recipients and donors who satisfied the eligibility criteria were included in the study. Table 1 provides details about donor and recipient demographics and Table 2 shows transplant-related ischemia times. Among donors, 126 (50.4%) were male and 124 (49.6%) were female. The mean age of RK donors was 35.1 ± 10.5 years and 33.6 ± 10.1 years for LKs. Two hundred and thirteen (85.2%) recipients were male and thirty-seven (14.7%) were female, with seven females who received RKs (13%) and 30 (16%) who received LKs. The mean age of recipients who received RKs was 37 ± 11.6 years and 38.7 ± 11.3 years for LKs.

The total number of transplants was 250, comprising 194 recipients (78%) who received LKs and 56 who received (22%) RKs. One hundred and eighty-two (73%) of the kidneys were recovered by ODN and sixty-eight (27%) by LDN. Of the latter, 65 (95%) were LKs and 3 (5%) were RKs. Compared to LKs, RKs had significantly smaller mean volumes (47 ± 2 *vs* 50 ± 2). Six (11%) RKs and thirty (15%) LKs had multiple arteries. Mean donor age, sex, weight, and artery multiplicity, along with mean human leukocyte antigen mismatches with recipients were not statistically different between the two groups. The RK DWI and CIT were significantly shorter than those of LKs (2.1 ± 0.9 *vs* 2.7 ± 1.7 and 40.1 ± 16.6 *vs* 48.6 ± 23.6, respectively), primarily because RKs were recovered by ODN, which also require less bench work. Significantly shorter DWI and CIT were recorded for ODN compared to LDN (1.81 ± 0.9 *vs* 4.7 ± 1.2 and 41.5 ± 18.2 *vs* 60.4 ± 26.8, respectively). The difference in rewarming ischemia (RWI) between right and LKs, or in ODN and LDN was not significant (Table 2).

As shown in Table 2, 96% of recipients of RKs and 99% of LKs had IGF; 1.7% of RKs and none of the LKs had SGF, while 1.7% of RKs and 0.5% of LKs had DGF; the difference was not statistically significant in either case. For both kidneys, SC50, SCD7, and LSC were comparable (Table 3).

There were two TGLs, one LK and one RK, both caused by arterial bleeding; one was an anastomotic blowout in an LK because of an infected graft recovered by LDN, and the other was a cautery burn away from the anastomosis in an RK.

DISCUSSION

This study is the first such report from Pakistan that addresses the impact of right *vs* left donor kidney on TGL, delayed and SGF, and post-transplant SC trends. There is substantial evidence that RK recipients may have worse outcomes than LK recipients in LD transplantation[2,4,8-10]. The main reason is the variable length of the RRV, which is usually short with thin, fragile walls (Figure 2), making venous anastomosis difficult, especially in obese recipients with limited exposure. Lifting the graft to access the anastomotic site risks tearing a stretched, fragile vein, and attempts at repair may further extend the tear. Dealing with this can prolong warm ischemia and risks DGF, but rushing the anastomosis to save time may result in partial or complete venous occlusion and thrombosis. If bleeding ensues because the anastomosis is not perfect, the perfused, swollen graft hampers access and control of bleeding becomes challenging. A clear preference

Table 1 Donor and recipient demographics and transplant factors

Parameters	Living donor kidneys (*n* = 250)		
	Right kidney	Left kidney	*P* value
Donor age in years	35.1 ± 10.5	33.6 ± 10.1	0.36
Donor sex	Males = 28 (50), females = 28 (50)	Males = 98 (51), females = 96 (49)	0.9
Mean donor weight in kg	65.9 ± 8.8	66.2 ± 11	0.9
Mean recipient age in years	37 ± 11.6	38.7 ± 11.3	0.32
Recipient sex	Males = 49 (87), females = 7 (13)	Males = 164 (84), females = 30 (16)	0.6
Mean recipient body mass index	23.6 ± 3.5	24.4 ± 3.8	0.1
Mean human leukocyte antigen mismatches, *n* ± SD	5 ± 2.9	5.5 ± 2.9	*0.32*
Donor kidney split function	47 ± 2	50 ± 2	0.000
Donor arteries multiplicity	Single = 51 (91), multiple = 5 (9)	Single = 161 (84), multiple = 31 (16)	0.17
Donor type	LRD = 42 (75), LURD = 14 (25)	LRD = 155 (80), LURD = 39 (20)	0.43
Donor nephrectomy type	ODN = 53 (95), LDN = 3 (5)	ODN = 182 (73), LDN = 68 (27)	0.000
Immunosuppressant, steroid sparing	6 (10.7)	20 (10.3)	0.9
Mean cold ischemia time in minutes	40.1 ± 16.6	48.6 ± 23.6	0.01
Mean donor warm ischemia in minutes	2.1 ± 0.9	2.7 ± 1.7	0.008
Mean recipient warm ischemia in minutes	44.2 ± 5.2	45.3 ± 8.3	0.36
Mean donor warm ischemia of cohort in minutes	ODN = 1.8 ± 0.9, LDN = 4.7 ± 1.2		0.000
Mean cold ischemia time of cohort in minutes	ODN = 41.5 ± 18.3, LDN = 60.4 ± 26.8		0.00

Data are *n* (%) or mean ± standard deviation (SD), unless otherwise indicated. LDN: Laparoscopic donor nephrectomy; LRD: Living related donor; LURD: Living unrelated donor; ODN: Open donor nephrectomy.

Table 2 Transplant outcomes and post-transplant serum creatinine trends

Parameter	Right kidney	Left kidney	*P* value
Immediate graft function	53 (96)	192 (99)	0.15
Slow graft function	1 (1.7)	1 (0.5)	
Delayed graft function	1 (1.7)	0	
Technical graft loss	1 (1.7)	1 (0.5)	
Mean pre-transplant SC in mg/dL	5.90 ± 2.05	5.78 ± 1.57	0.7
Mean time in hours to 50% fall in pre-transplant SC	17.36 ± 7.38	17.82 ± 10.15	0.8
Mean SC on post-transplant day 7 in mg/dL	1.107 ± 0.61	1.073 ± 0.42	0.6
Mean post-transplant time in days to normal SC	4.13 ± 2.848	4.11 ± 2.774	0.9
Mean SC on last follow-up in mg/dL	1.033 ± 0.217	1.038 ± 0.443	0.9

Data are *n* (%). SC: Serum creatinine.

among transplant teams for LKs is thus quite understandable[2,6], and the surge in LDN, more suitable for LKs than RKs, has further boosted this preference.

Nevertheless, under certain circumstances, RKs are a better choice for transplantation. This is commonly the case when the LK vascular anatomy is unfavorable or when there are concerns about compromising the donor residual renal function by removing a larger LK. Thus, it is prudent for transplant surgeons to be aware of the complexities of RK transplantation and the strategies to cope with them. The choice of RKs for transplantation must be a deliberate and a calculated one, based on the verifiable length of the RRV on CT imaging. A tip is to note the angle at which the RRV joins the inferior vena cava (IVC): A horizontal entry makes the length shorter than when it enters at an obtuse angle (Figure 3). We advocate a minimum vein length of 2.5 cm to perform a safe venous anastomosis; severe technical

Table 3 Cohort post-transplant serum creatinine trend

Parameter	Frequency		SC to decrease by 50% in hours	*P* value	Normalize SC	*P* value	SC at last follow-up	*P* value	SC on day 7 after surgery in days	*P* value
Open donor nephrectomy	RK	53 (95)	17.9 ± 10.2	0.6	4 ± 2.7	0.4	0.9 ± 0.2	0.02	1 ± 0.5	0.9
	LK	129 (67)								
	Total	182 (73)								
Laparoscopic donor nephrectomy	RK	3 (5)	17.2 ± 7.5		4.4 ± 2.8		1.1 ± 0.6		1 ± 0.3	
	LK	65 (33)								
	Total	68 (27)								
Living related donor	RK	42 (75)	17.3 ± 10	0.2	4 ± 2.7	0.2	0.99	0.000	1.0 ± 0.4	0.005
	LK	155 (80)								
	Total	197 (79)								
Living unrelated donor	RK	14 (25)	19.1 ± 7		4.6 ± 2.9		1.2		1.2 ± 0.8	
	LK	39 (20)								
	Total	53 (21)								
Steroid sparing immunosuppression	RK	6 (11)	15 ± 0.7	0.13	3.5 ± 2.4	0.23	0.97 ± 0.2	0.36	0.9 ± 0.4	0.07
	LK	20 (10)								
	Total	26 (10)								
Steroid based immunosuppression	RK	50 (89)	18 ± 0.9		4.2 ± 2.8		1 ± 0.4		1.1 ± 0.5	
	LK	174 (90)								
	Total	224 (90)								

Data are *n* (%).LK: Left kidney; RK: Right kidney; SC: Serum creatinine.

problems can arise with a shorter length, which cannot be mitigated with renal vein augmentation from the adjacent IVC in LDs[11]. A caval cuff can be taken in LDs, but only during ODN, because claims of acquiring a caval cuff in LDN with an Endo-TA stapler remain unsubstantiated[12]. A useful technique to gain a valuable centimeter of length during bench work is to mobilize the renal vein circumferentially and separate it from the artery by ligating and dividing all tributaries and lymphatic tissue between the two (Figure 1). In cases with short donor RRVs, fully mobilizing the recipient external iliac vein helps to lift the vein up, making anastomosis easier as it decreases the distance between the two venotomies and reduces tension on the anastomosis. Another critical point about RRV is identifying a thin oval area in its ventral wall that looks like a structural defect (Figure 4). Suturing through it requires the surgeon and the assistant to be cautious and gentle; any inadvertent tear here is exceedingly difficult to repair and could end up with narrowing, thrombosis, and graft loss[6]. The Achilles heel of an RK is its vein and not the artery, which can be shortened to match vein length even when disproportionately longer. Other considerations in selecting RKs for transplantation include the recipient's body mass index and the donor kidney size. In obese patients, the challenge of anastomosing a short donor RRV is exacerbated by the deep-seated iliac veins, whereas a large kidney restricts access to the anastomosis site following reperfusion.

In our series, we conducted a comprehensive preoperative assessment of the donor RRV to be sure of its length, and if short, we adopted the techniques described above: First, to increase the vein length during bench work; and second, to fully mobilize the recipient external iliac vein. We used a fine Prolene 6/0 suture with a C-1 needle for the anastomosis, paired with a lightweight Castroviejo needle holder. This choice results in smaller needle holes, reduces venous wall consumption, and ensures precise and smooth suturing. In contrast, a conventional needle holder is bulkier and prone to

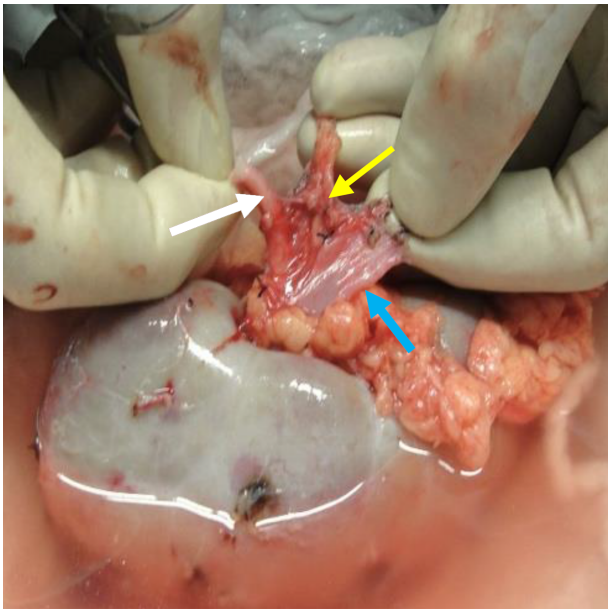


Figure 1 Right renal vein circumferential mobilization. Lymphatic tissue (yellow arrow) between the artery (white arrow) and the vein (blue arrow), needs to be excised to mobilize the vein.

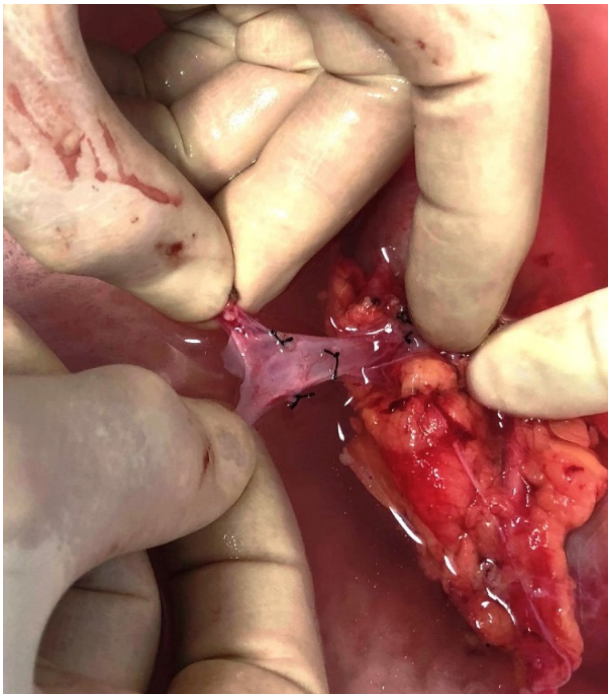


Figure 2 Thin-walled, fragile right renal vein on full stretch.

uncontrolled movements during unlocking, with the potential to tear the vein along the needle tract, and troublesome bleeding after clamp removal. Attention to detail explains why the venous anastomoses in our series were uneventful, as evidenced by there being no differences in RWI between the RKs and LKs. It also accounted for the low incidence of adverse post-transplant events and similar trends in post-transplant SC in both kidneys. DWI and CIT were shorter for RKs than LKs, as the former was mostly recovered by ODN (96% *vs* 50%), which is a faster method than LDN, and kidneys thus recovered require less bench preparation. Due to the limited cases for analysis, we could not confirm whether these factors influenced the transplant results.

Studies comparing outcomes of right and LK transplants have shown varying results. Analyses of the Organ Procurement and Transplant Network and Australian and New Zealand Dialysis and Transplantation data also supported the association between RK transplants and increased risks of DGF and graft loss[3,5]. Another large registry-based study found that recipients of RKs had a higher risk of DGF and graft loss than those receiving LKs; 36% of transplants with RKs experienced primary non-function, compared to only 9% with LKs[10]. On the contrary, two meta-

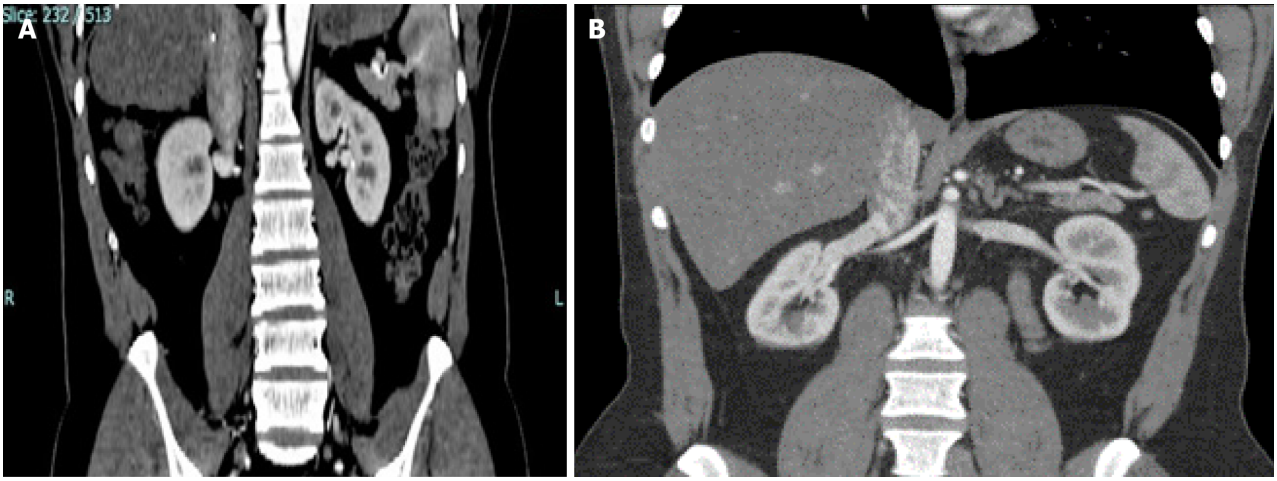


Figure 3 Computed tomography images showing right renal vein entry into the inferior vena cava. A: Short vein in horizontal entry because perpendicular is the shortest distance; B: Long vein in obtuse angle entry.

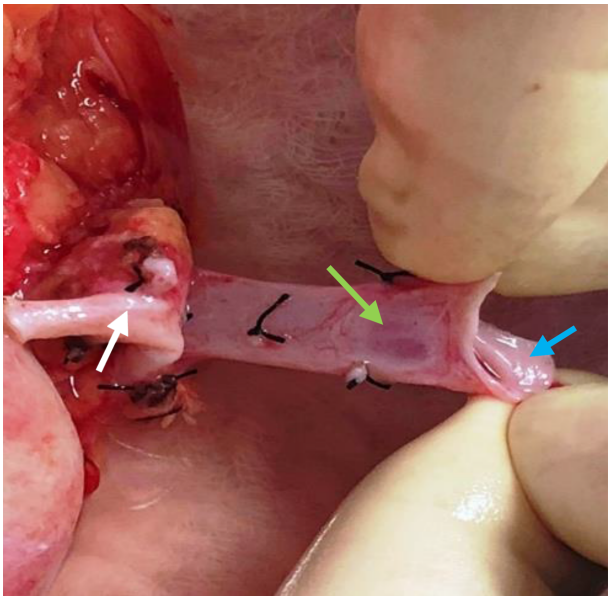


Figure 4 Lengthened right renal vein. The weak oval area is clearly visible (green arrow) and silk ligatures on tissue around the vein and artery (white arrow) are the result of circumferential dissection to mobilize the vein. The caval cuff (blue arrow) was used for suturing to avoid weak area.

analyses failed to identify a significant association between the incidence of DGF and graft loss in RK grafts, despite the exclusive use of LDN in the studies analyzed[13,14]. This was unexpected and difficult to explain, because application of staples in laparoscopic recovery consumes length, and makes the anastomosis difficult. The contradictory findings of the reported studies and the findings in our series suggest that there may be other factors beyond vein length that play a role in determining graft outcome in RK transplantation. Identifying these factors would necessitate a more extensive and inclusive study involving a comprehensive dataset encompassing all relevant variables.

The studies that showed RKs resulted in more technical losses and poorer early graft function than LKs did not differ in longer-term results[3,6,8,10]. This is because technical complications manifest in the early postoperative period, and after grafts exhibit immediate function, the side of the kidney does not have a role in longer-term function. Our study further substantiates this observation by demonstrating that the right and LKs perform comparably despite the former having a lesser volume. It demonstrates that the differences in right and LKs are not in their nephron characteristics but in their vascular anatomy. In other words, the longer-term outcome depends on factors other than laterality, such as graft quality, rejection episodes, drug toxicity, drug compliance and disease recurrence. However, early setbacks always have consequences, and grafts that recover from DGF have poorer outcomes than grafts with immediate function, irrespective of whether they are right or left[2,15].

We imagine that the observed inferior outcomes associated with RK transplants may stem from inaccuracies in preoperative donor assessment of RRV length, limited surgical proficiency, and unfamiliarity with the techniques required to manage challenging operative situations. When faced with the dilemma of choosing between an RK with borderline vein length and an LK with multiple arteries, opting for LK may be safer and less risky for a surgeon not well-

versed in dealing with fragile, short veins; studies suggest that transplants involving multiple arteries yield better outcomes than those involving kidneys with borderline-length veins[16]. Last, SCs in our recipients who received kidneys recovered by LDN were higher than those receiving kidneys recovered by ODN, suggesting that because RKs were recovered predominantly by ODN, this may have contributed positively to our results.

The main strength of our study is that it represents the largest cohort of LD transplants from Pakistan and is the first to report the impact of selecting right donor kidneys on graft outcomes and provide an insight for transplant surgeons when selecting RKs for transplantation. However, it is also important to recognize limitations of our study: It is retrospective in nature and carried out at a single center. A larger prospective multi-centric study would better identify factors other than donor vein length for disparity in outcomes between groups.

CONCLUSION

Contrary to common perception, our study shows that the donor kidney side has little impact on post-transplant adverse events and graft function in LD transplantation, provided careful patient selection and precise surgical techniques are employed.

FOOTNOTES

Author contributions: Khan T and Ahmad N designed the study and concept, and wrote the manuscript; Khan T, Ahmad N, and Asnath L analyzed the data; Ahmad N performed the statistical analysis; Iqbal Q, Hassan M, Khan N, and Shakeel S collected the data; Iqbal Q, Hassan M, and Asnath L contributed to reviewing and editing of the manuscript; All of the authors read and approved the final version of the manuscript to be published.

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REFERENCES

1 **Woodroffe R**, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, Taylor RS. Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study. *Health Technol Assess* 2005; **9**: 1-179 [PMID: 15899149 DOI: 10.3310/hta9210]

2 **Özdemir-van Brunschot DM**, van Laarhoven CJ, van der Jagt MF, Hoitsma AJ, Warlé MC. Is the Reluctance for the Implantation of Right Donor Kidneys Justified? *World J Surg* 2016; **40**: 471-478 [PMID: 26319261 DOI: 10.1007/s00268-015-3232-0]

3 **Mogulla MR**, Bhattacharjya S, Clayton PA. Risk factors for and outcomes of delayed graft function in live donor kidney transplantation - a retrospective study. *Transpl Int* 2019; **32**: 1151-1160 [PMID: 31209943 DOI: 10.1111/tri.13472]

4 **Tsoulfas G**, Agorastou P, Ko D, Hertl M, Elias N, Cosimi AB, Kawai T. Laparoscopic living donor nephrectomy: is there a difference between using a left or a right kidney? *Transplant Proc* 2012; **44**: 2706-2708 [PMID: 23146499 DOI: 10.1016/j.transproceed.2012.09.019]

5 **Khalil A**, Mujtaba MA, Taber TE, Yaqub MS, Goggins W, Powelson J, Sundaram C, Sharfuddin AA. Trends and outcomes in right vs. left living donor nephrectomy: an analysis of the OPTN/UNOS database of donor and recipient outcomes--should we be doing more right-sided nephrectomies? *Clin Transplant* 2016; **30**: 145-153 [PMID: 26589133 DOI: 10.1111/ctr.12668]

6 **Khan TT**, Ahmad N, Siddique K, Fourtounas K. Implantation of Right Kidneys: Is the Risk of Technical Graft Loss Real? *World J Surg* 2018; **42**: 1536-1541 [PMID: 29063227 DOI: 10.1007/s00268-017-4314-y]

7 **Liu KL**, Chiang YJ, Wang HH, Chu SH. Techniques of vascular control in laparoscopic donor nephrectomy. *Transplant Proc* 2008; **40**: 2342-2344 [PMID: 18790230 DOI: 10.1016/j.transproceed.2008.06.016]

8 **Adler JT**, Markmann JF, Yeh H. Renal allograft thrombosis after living donor transplantation: risk factors and obstacles to retransplantation. *Clin Transplant* 2016; **30**: 864-871 [PMID: 27101358 DOI: 10.1111/ctr.12750]

9 **Carolan C**, Tingle SJ, Thompson ER, Sen G, Wilson CH. Comparing outcomes in right versus left kidney transplantation: A systematic review and meta-analysis. *Clin Transplant* 2021; **35**: e14475 [PMID: 34496090 DOI: 10.1111/ctr.14475]

10 **Dobrijevic ELK**, Au EHK, Rogers NM, Clayton PA, Wong G, Allen RDM. Association Between Side of Living Kidney Donation and Post-Transplant Outcomes. *Transpl Int* 2022; **35**: 10117 [PMID: 35444489 DOI: 10.3389/ti.2022.10117]

11 **Khan TFT**, Baig MA, Zahid R, Mousa D. Right Renal Vein Augmentation in Deceased Donor Kidney Transplantation: Importance of the Contiguous Inferior Vena Cava. *UIJ* 2010; **3** [DOI: 10.3834/uij.1944-5784.2010.12.08]

12 **Modi P**, Kadam G, Devra A. Obtaining cuff of inferior vena cava by use of the Endo-TA stapler in retroperitoneoscopic right-side donor nephrectomy. *Urology* 2007; **69**: 832-834 [PMID: 17482916 DOI: 10.1016/j.urology.2007.01.031]

13 **Wang K**, Zhang P, Xu X, Fan M. Right Versus Left Laparoscopic Living-Donor Nephrectomy: A Meta-Analysis. *Exp Clin Transplant* 2015; **13**: 214-226 [PMID: 26086831]

14 **Liu N**, Wazir R, Wang J, Wang KJ. Maximizing the donor pool: left versus right laparoscopic live donor nephrectomy--systematic review and meta-analysis. *Int Urol Nephrol* 2014; **46**: 1511-1519 [PMID: 24595603 DOI: 10.1007/s11255-014-0671-8]

15 **Nogueira JM**, Haririan A, Jacobs SC, Weir MR, Hurley HA, Al-Qudah HS, Phelan M, Drachenberg CB, Bartlett ST, Cooper M. The detrimental effect of poor early graft function after laparoscopic live donor nephrectomy on graft outcomes. *Am J Transplant* 2009; **9**: 337-347 [PMID: 19067659 DOI: 10.1111/j.1600-6143.2008.02477.x]

16 **Moreno-Alarcón C**, Server-Pastor G, López-González PÁ, López-Cubillana P, Ruiz-Morcillo JC, Doñate-Iñíguez G, Olarte-Barragán EH, Gó mez-Gómez GA. Must we still be worried about multiple arteries in kidney transplantation? *Nephrourol Mon* 2013; **5**: 692-696 [PMID: 23577333 DOI: 10.5812/numonthly.4928]

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ORIGINAL ARTICLE

Observational Study

King's College criteria and the Clichy-Villejuif criteria require adjustments for assessing acute liver failure due to yellow fever

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Abstract

BACKGROUND

Acute liver failure (ALF) is a severe condition characterized by rapid deterioration of liver function in individuals without preexisting liver disease. Liver transplantation (LT) is the most impactful treatment. Yellow fever (YF) is an infectious disease that primarily affects the liver and has a high mortality rate. However, LT can be a viable option for treating rare cases with extensive liver involvement. However, the criteria for assessing the severity of ALF and determining the indications for transplantation have not been specifically validated for cases caused by YF.

AIM

To present necessary adjustments to established scoring systems for ALF secondary to YF.

METHODS
This was an observational, retrospective, single-center study. Fourteen consecutive patients with confirmed ALF due to YF were monitored in the intensive care unit by a specialized liver transplant team during a three-month epidemic outbreak in Brazil. During hospitalization, general supportive therapeutic measures were implemented, and the patients were regularly assessed using the King's College criteria and the Clichy-Villejuif criteria to determine the severity of liver failure. LT is considered a viable measure for patients with signs of end-stage liver failure.

RESULTS
Eight of 14 (57%) patients developed severe neurological alterations within the first 96 hours after hospital admission. Four patients underwent emergency LT, and despite a moderate viral infection of the graft after transplantation, the 5-year survival rate was 50%. Although the King's College criteria and the Clichy-Villejuif criteria are the main scoring systems for ALF, they are insufficient for predicting the risk of mortality in this context, primarily because of low serum bilirubin levels in the final stage of the disease and significant disparities between coagulation abnormalities and patient severity.

CONCLUSION
To ensure good applicability in cases of YF-induced ALF, the authors suggest adaptations to the King's College and Clichy-Villejuif criteria.

Key Words: Yellow fever; Acute liver failure; Liver transplantation; King's College criteria; Clichy–Villejuif criteria

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Core Tip: This study describes the application of current liver transplantation (LT) scoring systems, the King's College criteria and the Clichy-Villejuif criteria, for predicting outcomes in patients with acute liver failure (ALF) due to yellow fever (YF). We focused on 14 patients with confirmed ALF due to YF who were monitored by a liver transplant team during an epidemic in Brazil. Four patients underwent emergency LT following adaptations to the aforementioned scoring systems. The 5-year survival rate was 50%. These findings highlight the need to revise the criteria for transplantation for YF-associated ALF and demonstrate that LT can be a viable, life-saving option in specific cases.

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INTRODUCTION

Acute liver failure (ALF) is a serious condition characterized by rapid deterioration of liver function in individuals without preexisting liver disease, and liver transplantation (LT) has been the most impactful treatment in recent decades. Ongoing assessment of key clinical features in prognostic scoring systems is crucial in determining the outcome of ALF and guiding clinical decisions, including the need for LT.

Despite the inclusion of multiple clinical features in various scoring systems, hepatic encephalopathy, coagulopathy, and serum bilirubin levels remain the most critical because of their direct reflection of liver function and their strong correlation with patient outcomes. For example, hepatic encephalopathy provides a window into the extent of neurotoxicity caused by the inability of the liver to clear ammonia and other toxins, with higher grades of encephalopathy linked to a poor prognosis[1]. Coagulopathy, commonly assessed in terms of the international normalized ratio (INR), is a sensitive marker of synthetic liver failure, as the liver is responsible for producing clotting factors, and an increasing INR is a clear indicator of deteriorating liver function. Serum bilirubin levels, on the other hand, offer insight into the ability of the liver to excrete bile, and elevated levels reflect impaired bile metabolism, which is correlated with the severity of liver damage. These three features are prioritized in scoring systems because they provide a comprehensive view of both the synthetic capacity of the liver and its broader metabolic role, confirming their importance in determining the severity of ALF and guiding clinical decisions regarding the urgency of transplantation[2]. Despite the recognition of their clinical validity, their use in predicting the prognosis of FHF is challenging because of the rapid progression of the disease, the complexity of distinguishing useful markers at different stages and in cases with different etiologies, and differences in clinical response.

The King's College criteria and the Clichy-Villejuif criteria are the gold standard for determining the need for LT in patients with ALF[3] (Table 1). The performance of these criteria can be improved by considering the underlying cause of the disease and utilizing sequential assessments instead of single time-point estimates, particularly in cases of hyperacute

Table 1 Liver transplant indication criteria: King's College and Clinic-Villejuif

King's College criteria		Clichy-Villejuif criteria
Paracetamol induced liver failure (Acetaminophen)	**Non-paracetamol induced liver failure**	
Arterial potential of hydrogen < 7.3 (irrespective of the grade of encephalopathy)	PT > 100 seconds (INR > 6.5)	Age: Patients over the age of 30 years are at higher risk and are more likely to need a transplant
All three of the following	Any three of the following	Factor V levels
PT > 100 seconds (INR > 6.5)	Age < 10 years or > 40 years	Factor V level < 20% of normal for patients over 30 years old
Serum creatinine > 3.4 mg/dL (300 μmol/L)	Etiology: Non-A hepatitis, non-B hepatitis, and idiosyncratic drug reactions	Factor V level < 30% of normal for patients under 30 years old
Grade III or IV encephalopathy	Duration of jaundice before encephalopathy > 7 days. Prothrombin time > 50 seconds (INR > 3.5). Serum bilirubin > 17.5 mg/dL (300 μmol/L)	
		Grade of encephalopathy
		Presence of grade III or IV encephalopathy indicates a severe case

INR: International normalized ratio; PT: Prothrombin time.

etiologies[4].

Yellow fever (YF) is a mosquito-borne viral illness caused by an arbovirus of the *family Flaviviridae*, *genus Flavivirus*, encompassing positive-sense single-stranded RNA viruses. YF is an infectious disease endemic to forest areas in Africa and America and has a high mortality rate[5].

YF is typically described as a biphasic disease (Figure 1). After an incubation period of 3–6 days, the first phase, called the "viremic phase", begins. Symptom onset is typically abrupt, with fever, chills, asthenia, headache, back pain, generalized myalgia, nausea, and dizziness. Symptom onset may be followed by a "period of remission", during which the fever and symptoms disappear for approximately 24 hours. The second phase, called the "toxemic phase", affects 15%–25% of infected individuals and is characterized by the resurgence of high fever associated with vomiting, epigastric pain, jaundice, renal dysfunction, and hemorrhagic diathesis. YF is a disease characterized by multisystem involvement, but the liver is the most affected organ, making ALF a common cause of death[5]. Despite a comprehensive understanding of YF virus transmission and preventive measures, this infection remains a source of concern for public health, and its pathogenesis is still not fully understood. Recent clinical reports of YF-related liver failure highlight key aspects, such as extensive hepatocellular necrosis, microvesicular steatosis, and rapid onsets of coagulopathy, encephalopathy, and acute kidney injury[6-8].

YF was epidemic in Brazil between June YF and June 2018[9]. In this context, patients who developed ALF were evaluated for LT. In a pioneering effort worldwide, the first LTs for ALF caused by YF were performed[6].

The objective of this study was to describe and discuss the application of these criteria for assessing the severity of ALF caused by YF in a series of 14 cases from a single center.

MATERIALS AND METHODS

Study population and data collection

This was an observational, retrospective, single-center study conducted at the Liver Transplant Unit of Felicio Rocho Hospital. The study population comprised 14 patients who were admitted to the intensive care unit with confirmed ALF due to YF contracted during an epidemic in Brazil between January and February 2018. All patients were monitored by the LT team and were followed for 6 years by the medical team. Clinical, laboratory, and radiological data were evaluated both prospectively and retrospectively during this period.

All participants signed an informed consent form after being thoroughly informed about the study, and the study protocol was approved by the Ethics Committee of the Felicio Rocho Hospital, No. 2.851.504.

Clinical approach

The basic care protocol aligned with the guidelines of the local health authority. All patients with suspected YF were admitted and underwent imaging (abdominal ultrasound) and laboratory tests, including a complete blood count, INR, liver function tests, factor V tests, renal function tests, amylase, lipase, blood glucose, serological tests for hepatitis B virus [hepatitis B surface, hepatitis B surface antibody, hepatitis B core antigen immunoglobulin (Ig) G and IgM], hepatitis C (anti-hepatitis C virus), hepatitis A (anti-hepatitis A virus IgG and IgM), serology for YF and dengue, and RNA detection

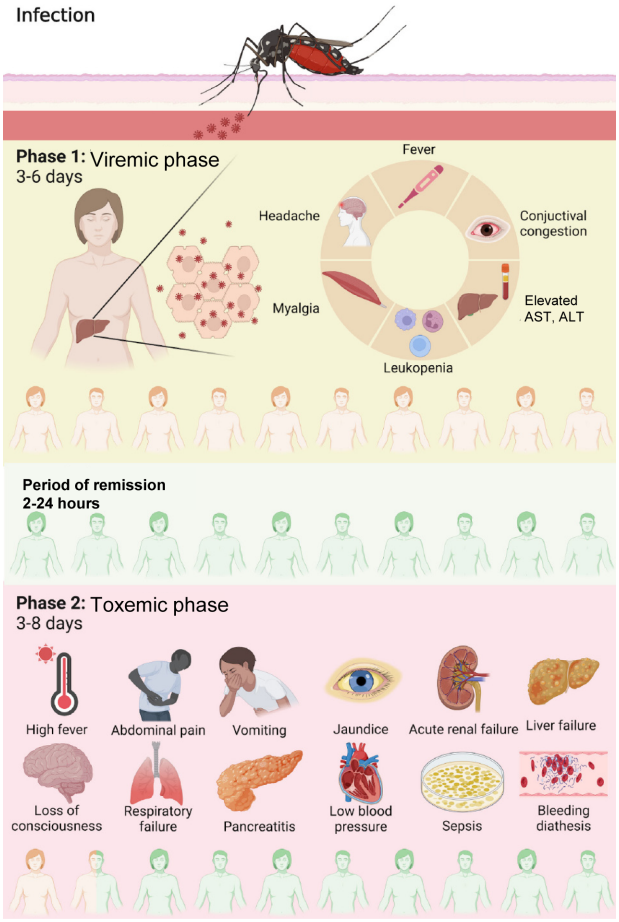


Figure 1 Yellow fever is typically described as a biphasic disease. The initial phase is the viremia phase, which is characterized by the presence of the virus in the bloodstream and associated symptoms. Following this phase, there is a remission phase which is characterized by temporary symptom improvement. Only approximately 15% of patients progress to the toxic phase, which is characterized by severe symptoms and potential complications. The transitions between these phases reflect the progression and severity of the disease. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

of the YF virus in serum *via* PCR. Blood samples were collected every 12 hours after patient admission, immediately before discharge, and at each follow-up visit (weekly during the first month, monthly until the 6th month, and semiannually thereafter).

During the toxemic phase of the disease, patients with laboratory-confirmed liver function impairment underwent regular clinical and laboratory evaluations. The King's College criteria and Clichy-Villejuif criteria were used to assess the severity of ALF and determine potential indications for emergency LT. All patients underwent neurological evaluation and cranial computed tomography when they presented with an altered mental status. In cases of severe acute renal failure, continuous hemodialysis was performed. Antibiotics were not routinely administered; they were used only in cases of suspected bacterial infection or as prophylaxis for patients undergoing LT. Plasmapheresis has been utilized in some of the more severe cases.

LT

The cases of patients who developed ALF with neurological alterations were discussed exhaustively in clinical meetings on a daily basis.

The liver transplant team, in consensus with a national committee of experts, recommended LT for patients showing signs of severe liver involvement and no expected survival even with the best supportive treatment. In these cases, the patients were listed for LT from deceased donors, provided on an emergency basis by the National Transplant System.

In cases where it was feasible, orthotopic LT was performed using the classic piggy-back technique. The immunosuppression protocol included induction with 125 mg of methylprednisolone during the anhepatic phase, followed by an additional 125 mg dose at the end of surgery, which was repeated at 24 hours and 48 hours after surgery. On the third postoperative day (POD), 20 mg of oral prednisone was introduced daily, while tacrolimus at a dose of 0.1 mg/kg was administered twice daily (every 12 hours) starting on the second POD. The explanted organs were subjected to histopathological and microbiological analyses.

RESULTS

Basic characteristics of the patients

All patients had lived in rural areas in the ten days preceding the onset of symptoms. The clinical and demographic characteristics of the patients are shown in Table 2.

Critical laboratory results

Clinical, laboratory, and histopathological data were obtained through a review of medical records. The laboratory test results are summarized in Table 3, and the evolution of the INR and factor V are detailed in Table 4. In addition to neurological changes, the INR was ≥ 3.5 (a minor criterion) in 4 patients and greater than 6.5 (a major criterion). Thus, an INR greater than 3.5 is indicative of severe disease and therefore correlated with an unfavorable outcome. However, 4 other patients did not have an INR above 3.5 but still had unfavorable outcomes. The King's College criteria could not be used to predict disease severity in these patients, who therefore could not be listed for transplantation (Figure 2).

The factor V level was particularly useful in some cases, as negative outcomes could not be predicted using the King's College criteria for some patients because their INR was less than 3.5. All the factor V levels in these patients were below 20%. Two of these patients underwent LT and had favorable post-transplantation outcomes. Transplantation was indicated for these patients according to the modified Clichy criteria.

In all patients, the total bilirubin (TB) levels progressively increased, peaking on the 14th day after symptom onset. The critical period for discussing the indications for LT was between days 4 and 10 after symptom onset, when neurological symptoms suggesting ALF presented. In all cases, TB levels were below 7 mg/dL, which was significantly lower than the cutoff value of 17.5 mg/dL in the King's College criteria. Importantly, in all 8 patients who either died or underwent LT, clinical jaundice was noted between days 3 and 4 of progression. Considering that neurological symptoms appeared between days 5 and 10, we can affirm that all patients in this group had both jaundice and encephalopathy for 7 days or less.

Among the 14 patients, 10 presented with neurological symptoms. Table 4 illustrates the relationship between the development of neurological symptoms and patient outcomes. Changes in mental status were progressive and associated with a poor prognosis, as 8 out of 10 patients progressed to liver failure or death. All patients presented developed neurological symptoms between days 4 and 10 after clinical presentation. This period corresponds chronologically to the toxemic phase, characterized by peak viremia and the most severe clinical manifestations. Patients experienced sensory depression, necessitating orotracheal intubation for airway protection on average 13 hours after the onset of neurological symptoms, indicating very rapid progression to severe disease. Only two patients who developed neurological symptoms did not progress to liver failure or death, and there was subsequent laboratory confirmation of bacterial sepsis.

All the final outcomes are listed in Figure 3. Patients were divided into two groups according to their progression. The first group included 6 patients whose prognosis was favorable, as defined by clinical improvement (CI) without any intervention. The second group included 8 patients whose prognosis was unfavorable, as defined by liver loss and the need for LT, or death. All the patients in the second group who did not undergo LT died; among the patients who underwent LT, 2 showed signs of CI after LT, and 2 died.

The explants of the four patients who underwent LT were subjected to anatomopathological evaluation. The weight of the explants ranged from 1007 g to 1263 g. There were no signs of arterial or venous thrombus or focal lesions in the explants. Microscopic analysis (Figure 4) revealed hepatocyte necrosis associated with inflammatory infiltration of discrete mononuclear cells (especially in zone 2) as well as frequent acidophilic degeneration of hepatocytes, namely, Councilman–Rocha–Lima bodies; macrovesicular and microvesicular steatosis; and areas of hemorrhage. There was a clear dissociation between the severity of hepatocyte cell injury and the inflammatory infiltrate, which was mild, located mainly in the portal tracts, and composed mainly of lymphocytes, macrophages in some cases, and neutrophils in rare cases. None of the patients had arteritis, bile duct injury, or interstitial collagen deposition.

Among the patients who underwent LT, two required surgical intervention due to hemorrhage at the surgical site on the second POD. At this time, graft samples were obtained. Two aspects stood out in the histological evaluation of these samples: (1) The presence of changes suggestive of YF; and (2) The difference in findings between the two patients, such as a more extensive and severe injury in cases that later resulted in death. The biopsied liver grafts were subjected to immunohistochemical analysis using an antibody against flavivirus envelope protein 4G2, which confirmed the presence of viral particles in the cytoplasm of hepatocytes. There was notable difference between the samples from the two patients. The first patient with histological findings indicating severe disease presented a large quantity of viral particles distributed throughout the section. The second patient presented only a small quantity of viral particles in zone 2. The liver graft from another patient who underwent LT was subjected postmortem biopsy. The findings were consistent with a severe case of YF, as described in other cases, and here, immunohistochemistry confirmed viral reinfection in the graft. However, the liver graft from one patient who underwent transplantation was not biopsied.

All 6 patients who experienced favorable outcomes in this study were followed for at least 6 months after discharge and did not exhibit any complications related to atrial fibrillation. None of them developed late or chronic liver failure.

Both patients who underwent LT and survived (patients 8 and 14) were followed for more than 5 years after LT. These patients had good graft function and a good quality of life without physical or neurological sequelae. One of the patients (patient 8) experienced episodes of acute cellular rejection requiring corticosteroid pulse therapy 3 years after LT; this patient had chronic renal dysfunction related to the use of calcineurin inhibitors, which were subsequently replaced by everolimus. Patient 14 has not presented any late complications to date and is on a low dose of tacrolimus.

Table 2 Demographic characteristics of patients with acute liver disease due to yellow fever at Felicio Rocho Hospital between January 20 and February 20, 2018 (*n* = 14), *n* (%)

Characteristics	Patients
Age (years); median (minimum-maximum)	53 (23-69)
Male sex	13 (92.8)
Vaccination for yellow fever more than 10 days ago	3 (21.4)
Comorbidities	
Smoking	3 (21.4)
Hypertension	2 (21.4)
Immunosuppressed (previous renal transplant)	1 (7.1)
Diabetes	0
Time from symptoms onset to admission (days), mean (minimum-maximum)	4-7 (1-8)
Signs and symptoms at hospital admission	
Myalgia	12 (85.7)
Fever	11 (78.6)
Jaundice	11 (78.6)
Vomiting	7 (50)
Headache	6 (42.9)
Abdominal pain	4 (28.6)
Diarrhea	2 (14.3)
Distance between exposure location and hospital (km), mean (minimum-maximum)	1487 (30-291)
Rural workers	6 (42.6)

DISCUSSION

Determining which patients with ALF who will likely survive with optimal supportive care and those who will likely die without LT remains challenging. Prognostic scoring systems can be used to identify patients who will not survive without LT and prevent surgeons from performing procedures on patients who are unlikely to benefit from an otherwise life-saving measure. While no model is flawless, the prognosis of ALF is determined on the basis of its etiology, severity according to laboratory and clinical indicators, and rate of progression.

In this study, we evaluated the use of the King's College criteria and the Clichy-Villejuif criteria in assessing the severity of ALF and the need for LT in patients with YF-induced ALF. Our findings revealed that these criteria, which have been proven useful in the assessment of other causes of ALF, cannot be used to accurately predict the risk of mortality in the context of YF-induced ALF. Moreover, the reliance of the King's College criteria on serum bilirubin levels and coagulation abnormalities did not align with the clinical severity observed in our patients.

The primary challenge encountered in this study was the discrepancy between laboratory markers and clinical presentation. Notably, even though our patients had severe clinical manifestations, their serum bilirubin levels were low during the critical period when decisions to perform LT were made. Additionally, coagulation abnormalities, as indicated by the INR, do not consistently correlate with patient outcomes. For example, some patients with INRs below the threshold for transplantation still experienced poor outcomes, whereas others with elevated INRs survived with only supportive care.

The inclusion of factor V levels in our evaluation provided additional insight into the severity of liver failure in these patients. Factor V levels below 20% were associated with worse outcomes, suggesting that this marker may be a valuable addition to existing criteria for assessing YF-induced ALF.

The 50% survival rate after LT in our cohort underscores the potential for LT to be a life-saving intervention for selected patients with YF-induced ALF. The presence of viral particles in liver grafts after transplantation highlights the complexity of managing YF in transplant recipients, emphasizing the need for tailored immunosuppressive protocols and vigilant monitoring.

Global warming has a profound effect on the dissemination of arboviruses, which are diseases transmitted by mosquitoes that were once predominantly confined to tropical regions. With 215 countries/territories potentially suitable for the most well-known vectors of arboviral diseases and an increasing number of cases reported in more than half of these countries/territories, arboviral diseases are indeed a source of concern for public health worldwide[10]. As temperatures continue to increase worldwide, vectors such as *Aedes aegypti* are expanding into temperate climates. Current research suggests that the incidence of mosquito-borne diseases could increase dramatically in response to climate change

Table 3 Clinical data of patients hospitalized at Felicio Rocho Hospital in 2018 yellow fever outbreak

Patients	Age (years)	Gender	Platelets (mL)	Aspartate aminotransferase (IU/L)	Alanine aminotransferase (IU/L)	Bilirubin (mg/dL)	International normalized ratio	Creatinine (mg/dL)	Lactate (IU/L)	Encephalopathy	Transplantation	Outcome
1	53	M	29000	9693	2282	17.2	2.9	12.4	133	4	No	Dead
2	64	M	26000	7900	4648	3.54	2.3	6.48	61	2	Yes	Alive
3	37	M	58000	8151	7206	8.16	> 10	7.1	164	3	Yes	Dead
4	49	M	89000	5160	2463	5.12	1.81	8.74	40	No	No	Alive
5	39	M	58000	8707	4509	6.81	2.9	8.81	125	4	No	Dead
6	58	M	12000	12590	7446	21.9	1.65	1.17	42	No	No	Alive
7	69	M	35000	8572	3987	5.9	> 10	8.11	135	3	Yes	Dead
8	57	M	29000	8451	3854	10.1	4.4	7.49	184	4	No	Dead
9	57	F	46000	28266	9680	4.47	> 10	5.06	115	4	No	Dead
10	63	M	56000	3650	2215	5.41	1.12	0.77	20	No	No	Alive
11	23	M	14000	9471	3926	13.47	1.7	0.92	20	No	No	Alive
12	46	M	79000	2791	2126	01.02	1.1	1.2	8	No	No	Alive
13	47	M	38000	12207	2992	8.15	2.9	1.46	41	3	Yes	Alive
14	40	M	49000	157	288	0.49	1.1	0.82	15	No	No	Alive

M: Male; F: Female.

[11]. Increased intercontinental travel facilitates the spread of these viruses, as infected individuals can transport pathogens across borders, resulting in outbreaks in new areas. The expansion of mosquito habitats and extensive global travel underscores the urgency of a coordinated international response to mitigate the impact of arboviruses in a warming world. In recent years, cases of YF have been reported in unvaccinated travelers returning from endemic regions to countries such as Belgium[12], China[13] and the Netherlands World Health Organization[14]. The influence of global warming on the transmission of arboviral diseases is further increased by extensive intercontinental travel, a hallmark of globalization. Increased intercontinental travel facilitates the spread of these viruses, as infected individuals can transport pathogens across borders, resulting in outbreaks in new areas. This interconnectedness means that local authorities in temperate countries, which have been historically spared from such diseases, must now be vigilant and proactive in their public health strategies. The expansion of mosquito habitats and increased global travel underscores the urgency of a coordinated international response to mitigate the impact of arboviruses in a warming world.

This study has several limitations that should be considered. First, the sample size was relatively small, comprising only 14 patients, which may limit the generalizability of the results. Selection bias is likely owing to the retrospective, single-center nature of the study, and the applicability of the study findings to other settings is limited. Additionally,

Table 4 Correlations between international normalized ratio, factor V, onset day of neurological symptoms, neurological symptoms, and outcomes in patients with acute liver disease due to yellow fever at Felicio Rocho Hospital between January 20 and February 20, 2018 (*n* = 14)

Cases	Concentrated fresh plasma	International normalized ratio									Factor V (%)									Day of onset of neurological symptoms	Neurological symptoms	Outcome
		D4	D5	D6	D7	D8	D9	D10	D12	D14	D4	D5	D6	D7	D8	D9	D10	D12	D14			
Case 1	Yes	-	-	-	-	1.7	-	1.2	-	2.9	-	-	-	-	-	-	-	-	-	D10	Initial slowing with rapid progression to stupor and coma	Death
Case 9	Yes	> 7	5.5	-	-	-	-	-	-	-	-	8.8	-	-	-	-	-	-	-	D5	Drowsiness and flapping with rapid progression to coma	Death
Case 12	Yes	-	-	4.4	2.3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	D5	Drowsiness, disorientation, progression to stupor and coma	Death
Case 13	Yes	2	2.2	3	2.7	-	-	-	-	-	16.6	22.4	-	-	-	-	-	-	-	D5	Recurrent seizures	Death
Case 4	Yes	4.1	6.6	7.9	> 9	-	-	-	-	-	-	-	15.6	-	-	-	-	-	-	D6	Agitation was intubated due to respiratory failure	Transplant
Case 8	No	-	2.3	2	-	-	-	-	-	-	15.8	21.5	-	-	-	-	-	-	-	D5	Slowing and mild disorientation	Transplant
Case 11	Yes	-	> 9	> 10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	D4	Drowsiness and flapping with rapid progression to coma	Transplant
Case 14	Yes	-	2.6	2.7	2	2.4	2.9	2.1	-	-	-	-	21	21.7	21.5	12.8	-	-	-	D9	Slowing, flapping, progression to stupor and coma	Transplant
Case 2	No	1.1	1.1	1	1	1	-	-	-	-	-	-	-	-	161	-	-	-	-	-		Clinical improvement
Case 3	No	1	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		Clinical improvement
Case 5	No	1.6	1.8	1.7	1.6	1.4	1.3	1.3	-	1.2	-	-	-	-	-	-	-	158	-	D10		Clinical improvement
Case 6	No	-	-	1.7	1.7	1.5	-	-	-	1.1	81.6	-	-	-	-	-	-	-	-	-		Clinical improvement
Case 7	No	1.4	1.5	1.6	1.7	1.6	1.4	1.4	-	1.2	44.4	-	-	-	-	-	-	-	-	D9	Mental confusion and disorientation, complete recovery. Bacterial sepsis	Clinical improvement
Case 10	No	1.2	1.1	1	1	1	1.1	1.1	-	-	-	-	-	-	-	-	-	-	-	-		Clinical improvement

D4: Day 4; D5: Day 5; D6: Day 6; D7: Day 7; D8: Day 8; D9: Day 9; D10: Day 10; D12: Day 12; D14: Day 14.

because of its uniqueness, the YF epidemic in Brazil may not reflect typical clinical scenarios elsewhere. Prospective, multicenter, large-sample studies are needed to validate our findings and to refine the proposed modifications to the King's College criteria and Clichy-Villejuif criteria for YF-induced ALF.

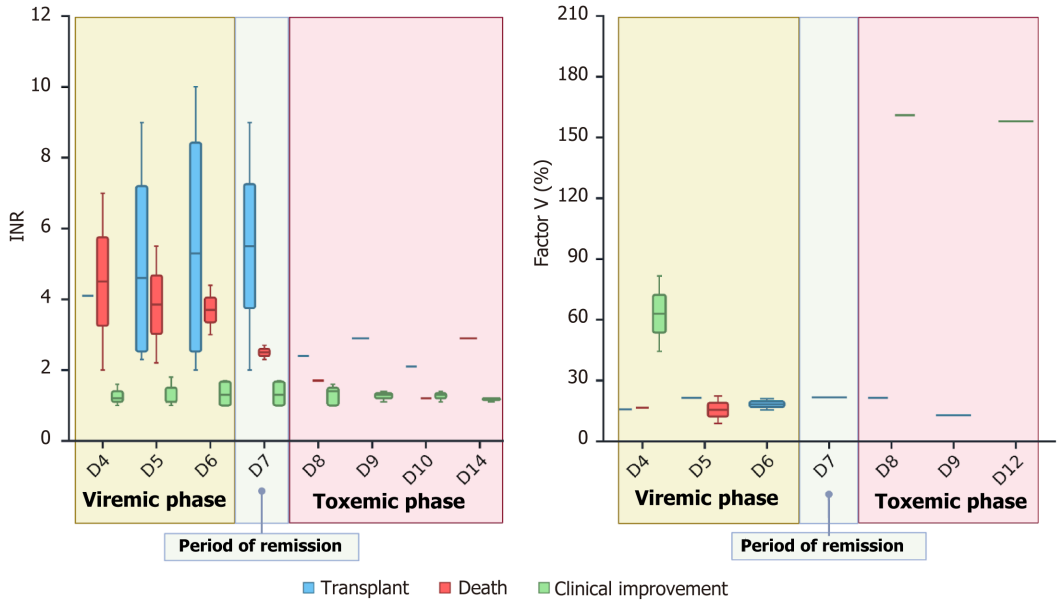


Figure 2 Analysis of international normalized ratio and factor V levels and clinical outcomes over time. This figure presents a comparative analysis of the international normalized ratio (INR) and factor V levels of patients, categorized by clinical outcomes and day of illness, categorized by the phases of yellow fever (viremia, remission, and toxicity). The figure includes two graphs: (1) One displaying INRs; and (2) The other showing factor V levels. Each data point represents the mean value for the specified day and outcome, with error bars indicating the standard deviation. The panels illustrate how INR and factor V levels vary across different clinical outcomes (transplantation, death, and clinical improvement) and days of illness. Trends reveal associations between elevated or decreased INRs and factor V levels with different clinical results, providing insights into their role in patient outcomes over time. INR: International normalized ratio. D4: Day 4; D5: Day 5; D6: Day 6; D7: Day 7; D8: Day 8; D9: Day 9; D10: Day 10; D12: Day 12; D14: Day 14.

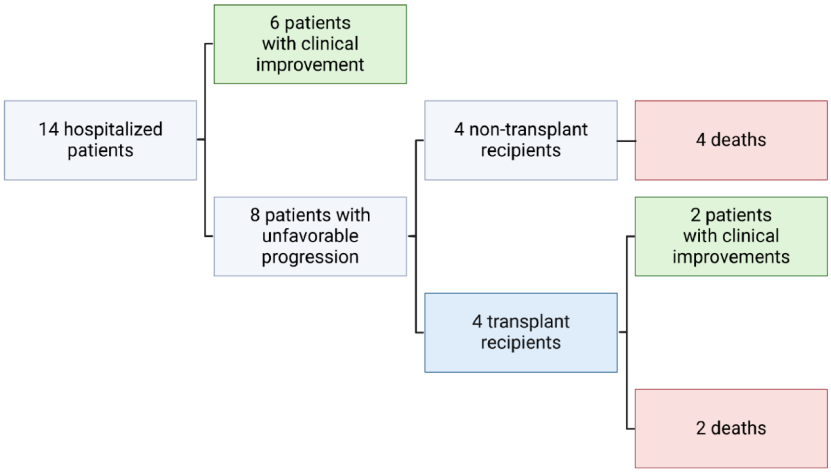


Figure 3 Patient outcomes flowchart. This flowchart depicts the clinical outcomes of the 14 patients studied. Among these patients, 6 experienced clinical improvement. Among the 8 patients who experienced clinical deterioration, 4 did not receive a liver transplant and subsequently died. The remaining 4 patients who received a transplant were further divided into two groups: (1) 2 patients experienced clinical improvement; and (2) While the other 2 patients died despite the transplant.

Our findings indicate that modifications to the King's College criteria and Clichy-Villejuif criteria are essential to enhance their accuracy in predicting ALF caused by YF. First, incorporating factor V levels as an additional marker is recommended, as levels below 20% are linked to negative outcomes and have been shown to be more useful than the INR is in some instances. Moreover, the reliance of the King's College criteria on serum bilirubin levels should be reconsidered, as our patients presented with severe clinical symptoms but had low bilirubin levels during the crucial period when transplant decisions were made. Finally, the interval between the onset of jaundice and encephalopathy should be considered more relevant for prognosis than solely conventional laboratory levels alone, as the rapid progression of neurological symptoms was a consistent indicator of severity in our patients. These adaptations aim to improve the prognostic accuracy of the criteria and support more informed clinical decisions in the specific context of YF-induced ALF.

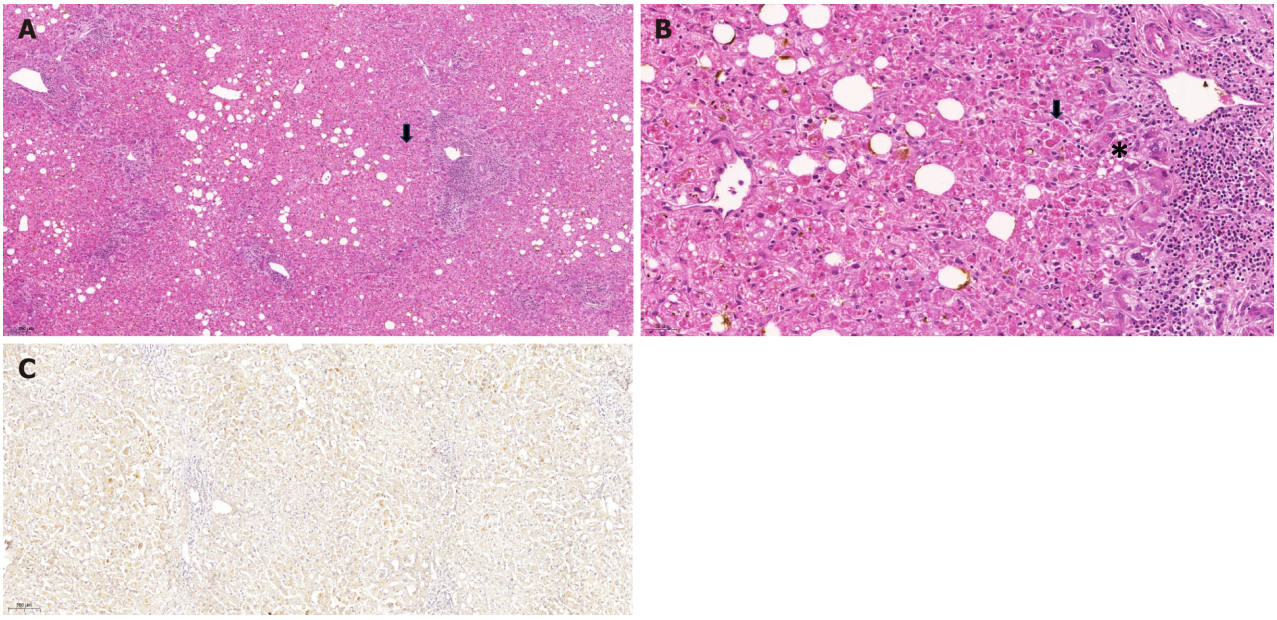


Figure 4 Liver histopathological analysis. Histopathological features of explanted livers from Yellow fever (YF) patients who underwent transplantation. A and B: Microscopic examination showing a midzonal lesion (arrows) with acidophilic bodies, steatotic hepatocytes (asterisk), hyperplasia and hypertrophy of Kupffer cells, and mild inflammation, mainly in the portal tracts. Note the periportal preservation of hepatocytes; C: YF virus antigen positivity in midzonal hepatocytes with acidophilic degeneration or steatosis and in Kupffer cells.

CONCLUSION

This study highlights the limitations of current scoring systems for LT in predicting outcomes for patients with ALF due to YF. The King's College criteria and Clichy-Villejuif criteria, while valuable for other etiologies of ALF, require adjustments to improve their applicability in the context of YF. Our findings suggest that incorporating additional markers, such as factor V levels, and considering the unique pathophysiology of YF can enhance prognostic accuracy and guide clinical decision-making.

LT can be a viable, life-saving option for patients with YF-induced ALF, as demonstrated by the survival of patients who undergo this procedure. The need for revised transplantation criteria tailored to the specific challenges of YF is evident. Future research should focus on validating these adjusted criteria in larger cohorts and exploring the underlying mechanisms of YF to develop more effective treatment strategies.

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FOOTNOTES

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REFERENCES

1 **Borkakoty A**, Kumar P, Taneja S. Hepatic Encephalopathy. *N Engl J Med* 2017; **376**: 186 [PMID: 28079344 DOI: 10.1056/NEJMc1614962]
2 **O'Grady JG**, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; **97**: 439-445 [PMID: 2490426 DOI: 10.1016/0016-5085(89)90081-4]
3 **Bernal W**, Auzinger G, Dhawan A, Wendon J. Acute liver failure. *Lancet* 2010; **376**: 190-201 [PMID: 20638564 DOI: 10.1016/S0140-6736(10)60274-7]
4 **Ichai P**, Legeai C, Francoz C, Boudjema K, Boillot O, Ducerf C, Mathurin P, Pruvot FR, Suc B, Wolf P, Soubrane O, Le Treut YP, Cherqui D, Hannoun L, Pageaux GP, Gugenheim J, Letoublon C, Saric J, Di Martino V, Abergel A, Chiche L, Antonini TM, Jacquelinet C, Castaing D, Samuel D; French Liver Transplant Teams. Patients with acute liver failure listed for superurgent liver transplantation in France: reevaluation of the Clichy-Villejuif criteria. *Liver Transpl* 2015; **21**: 512-523 [PMID: 25675946 DOI: 10.1002/lt.24092]
5 **Monath TP**, Vasconcelos PF. Yellow fever. *J Clin Virol* 2015; **64**: 160-173 [PMID: 25453327 DOI: 10.1016/j.jcv.2014.08.030]
6 **Song ATW**, Abdala E, de Martino RB, Malbouisson LMS, Tanigawa RY, Andrade GM, Ducatti L, Doi AM, Pinho JRR, Gomes-Gouvêa MS, Malta FM, Arantes RM Jr, Tonacio AC, Figueira Pinto L, Haddad LBP, Santos VR, Pinheiro RSN, Nacif LS, Galvão FHF, Alves VAF, Andraus W, Carneiro D'Albuquerque LA. Liver Transplantation for Fulminant Hepatitis Attributed to Yellow Fever. *Hepatology* 2019; **69**: 1349-1352 [PMID: 30218577 DOI: 10.1002/hep.30273]
7 **Duarte-neto AN**, Cunha MDP, Marcilio I, Song ATW, de Martino RB, Ho Y, Pour SZ, Dolhnikoff M, Saldiva PHN, Duarte MIS, Takakura CF, Lima FR, Tanigawa RY, Iglezias SD, Kanamura CT, dos Santos ABG, Perondi B, Zanotto PMDA, D'albuquerque LAC, Alves VAF. Yellow fever and orthotopic liver transplantation: new insights from the autopsy room for an old but re-emerging disease. *Histopathology* 2019; **75**: 638-648 [DOI: 10.1111/his.13904]
8 **Kallas EG**, D'Elia Zanella LGFAB, Moreira CHV, Buccheri R, Diniz GBF, Castiñeiras ACP, Costa PR, Dias JZC, Marmorato MP, Song ATW, Maestri A, Borges IC, Joelsons D, Cerqueira NB, Santiago E Souza NC, Morales Claro I, Sabino EC, Levi JE, Avelino-Silva VI, Ho YL. Predictors of mortality in patients with yellow fever: an observational cohort study. *Lancet Infect Dis* 2019; **19**: 750-758 [PMID: 31104909 DOI: 10.1016/S1473-3099(19)30125-2]
9 **da Rocha MM**, Codeço CT, da Silva CMFP. Spatiotemporal Evolution of the Yellow Fever Epidemic in Southeast Brazil from 2016 to 2019. *Vector Borne Zoonotic Dis* 2024 [PMID: 38813663 DOI: 10.1089/vbz.2024.0004]
10 **Leta S**, Beyene TJ, De Clercq EM, Amenu K, Kraemer MUG, Revie CW. Global risk mapping for major diseases transmitted by Aedes aegypti and Aedes albopictus. *Int J Infect Dis* 2018; **67**: 25-35 [PMID: 29196275 DOI: 10.1016/j.ijid.2017.11.026]
11 **Ryan SJ**, Carlson CJ, Mordecai EA, Johnson LR. Global expansion and redistribution of Aedes-borne virus transmission risk with climate change. *PLoS Negl Trop Dis* 2019; **13**: e0007213 [PMID: 30921321 DOI: 10.1371/journal.pntd.0007213]
12 **Bae HG**, Drosten C, Emmerich P, Colebunders R, Hantson P, Pest S, Parent M, Schmitz H, Warnat MA, Niedrig M. Analysis of two imported cases of yellow fever infection from Ivory Coast and The Gambia to Germany and Belgium. *J Clin Virol* 2005; **33**: 274-280 [PMID: 16036176 DOI: 10.1016/j.jcv.2004.12.001]
13 **Song R**, Guan S, Lee SS, Chen Z, Chen C, Han L, Xu Y, Li A, Zeng H, Ye H, Zhang F. Late or Lack of Vaccination Linked to Importation of Yellow Fever from Angola to China. *Emerg Infect Dis* 2018; **24**: 1383-1386 [PMID: 29723485 DOI: 10.3201/eid2407.171868]
14 **World Health Organization**. Imported case of yellow fever in the Netherlands. 2000. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2000_02_25-en

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SYSTEMATIC REVIEWS

Future of non-invasive graft evaluation: A systematic review of proteomics in kidney transplantation

Eleni Avramidou, Konstantina Psatha, Kallisti St John, Georgios Tsoulfas, Michalis Aivaliotis

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Abstract

BACKGROUND

Despite the developments in the field of kidney transplantation, the already existing diagnostic techniques for patient monitoring are considered insufficient. Protein biomarkers that can be derived from modern approaches of proteomic analysis of liquid biopsies (serum, urine) represent a promising innovation in the monitoring of kidney transplant recipients.

AIM

To investigate the diagnostic utility of protein biomarkers derived from proteomics approaches in renal allograft assessment.

METHODS

A systematic review was conducted in accordance with PRISMA guidelines, based on research results from the PubMed and Scopus databases. The primary focus was on evaluating the role of biomarkers in the non-invasive diagnosis of transplant-related com-plications. Eligibility criteria included protein biomarkers and urine and blood samples, while exclusion criteria were language other than

English and the use of low resolution and sensitivity methods. The selected research articles, were categorized based on the biological sample, condition and methodology and the significantly and reproducibly differentiated proteins were manually selected and extracted. Functional and network analysis of the selected proteins was performed.

RESULTS

In 17 included studies, 58 proteins were studied, with the cytokine CXCL10 being the most investigated. Biological pathways related to immune response and fibrosis have shown to be enriched. Applications of biomarkers for the assessment of renal damage as well as the prediction of short-term and long-term function of the graft were reported. Overall, all studies have shown satisfactory diagnostic accuracy of proteins alone or in combination with conventional methods, as far as renal graft assessment is concerned.

CONCLUSION

Our review suggests that protein biomarkers, evaluated in specific biological fluids, can make a significant contribution to the timely, valid and non-invasive assessment of kidney graft.

Key Words: Proteomics; Kidney transplantation; Graft evaluation; Non-invasive diagnosis; Kidney graft function

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Core Tip: In recent years, the role of diagnostic biomarkers in kidney transplantation has been emerged, particularly with proteomics being considered a powerful investigative tool. In this review, we critically analyze the spectrum of proteins exhibiting diagnostic accuracy in early, non-invasive evaluation of kidney grafts as well as the potent biological correlations between the variation of proteins detected in recipients experiencing some type of graft dysfunction or complication.

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INTRODUCTION

Over the past decade, the number of solid organ transplantation operations performed worldwide has increased[1]. Kidney transplantation (KT) is the most common solid organ transplantation, with more than 25000 KT performed each year. Kidney grafts can be derived either from living donations or from donations after death[2]. Particularly in the latter category, grafts can derive from donors with brain or circulatory death (DCD), including extended criteria donors (ECD).

Despite the increasing number of KT performed annually, the long-term survival of the recipient and the graft have plateaued over the past decade[3]. The lack of a non-invasive sensitive diagnostic method routinely used in clinical practice limits the early non-invasive detection of possible graft damage. Moreover, kidney ECD and DCD allografts, typically derived from suboptimal donors, demonstrate an elevated propensity for graft loss, delayed graft function and kidney graft injury, thus requiring higher level of monitoring and evaluation[4]. Current clinical chemistry and biochemistry diagnostics in transplantation rely on a limited set of biomarkers alongside conventional methods. The last few years, the role of diagnostic biomarkers in KT has gained prominence with the inclusion of biomarkers evaluation in Banff classification for rejection, particularly in the diagnosis of antibody-mediated rejection, highlighting their potential importance in the future of KT[5]. Despite the recent breakthroughs, there is no single biomarker able to diagnose the complexity of transplant pathology, leaving a gap in transplantation diagnostics and highlighting the need for further exploration of the possible role of proteomics.

Proteomics are considered a powerful tool within the omics field, enabling the simultaneous comprehensive analysis of thousands of proteins expressed within cells, tissues, or organisms[6-8]. This approach allows for real-time evaluation of an individual's state, distinguishing between health *vs* disease, and potentially predicting the susceptibility to specific complications. Proteomics analysis is a multi-analyte strategy, using cutting-edge technologies capable of assessing the complete set of proteins (proteome). While this approach is relatively new, the existing literature demonstrates promising results regarding sensitivity and specificity in the field of transplantation[8,9]. Proteomics in KT can be applied in kidney graft biopsies or in biological fluids, like serum and urine, providing a non-invasive multiplex, high throughput and amazingly sensitive diagnostic approach[10]. Furthermore, proteomics can also be applied to fluid from machine perfusion commonly used for the preservation of grafts, deriving from post mortem donation and particularly usually from DCD and ECD donors, facilitating early non-invasive diagnosis of transplant pathologies and preexisting graft damage[11]. Various proteomic approaches have been applied in clinical trials for diagnosing KT pathologies like rejection or BKV nephropathy, as well as for the detection of possible graft damage and the prediction of long- and short-term graft function[9]. Proteomics strategies provide a wide range of information, including identification of proteins in a

sample at a given space, at a given moment, relative abundance levels of proteins or quantitative proteomics and analysis of post-translational modifications of those proteins mapping their specifically modified sites and their interactions. The increasing use of proteomics in everyday clinical practice is directly linked to recent technological advances in quantitation methods. Complex clinical samples may be evaluated more accurately, comprehensively, and promptly through recent technological breakthroughs, particularly in mass spectrometry (MS), sample preparation techniques, and computer data processing ability with bioinformatics and artificial intelligence or platforms, such as MaxQuant, Perseus, ProteoSign, UniReD, STRING and other[12-17].

The aim of our systematic review is to evaluate potential protein biomarkers, detected in biological fluids, for the evaluation of possible subclinical injury and fibrosis of the graft, as well as prediction of its short- and long- term function.

MATERIALS AND METHODS

The primary aim of this review was to identify the most recent advances in proteomic diagnostic applications regarding kidney graft evaluation by means of a systematic review, and to investigate possible correlations between the different proteins identified.

Eligibility criteria, information sources and search strategy

Following the PRISMA statement, we executed a systematic review of the literature for relevant studies using PubMed and Scopus databases by two independent reviewers. The search was conducted in all fields using the following keywords "kidney transplantation" or "renal transplantation" and "proteomics" or "protein biomarkers" until March 2024. The PubMed and Scopus databases were last accessed on 14 April 2024. To be eligible for screening, the studies had to meet the following criteria: (1) Identification of KT proteomic biomarkers in graft injury and function evaluation as the main objective; (2) Research performed in human urine or blood samples; (3) Application of specific methodologies for the quantitative and qualitative analysis of the samples; and (4) English language journal publication.

Study selection

We performed a systematic review of scientific publications that analyzed the protein profiles of kidney transplant samples or that detected specific proteins. All relevant studies were retrieved from the PubMed and Scopus databases without any restrictions on the date of publication. Studies were evaluated for inclusion by following a 2-phase selection process, as illustrated in Figure 1. All obtained studies were independently screened by title and abstract, by two independent reviewers. Articles that passed by mutual agreement were subsequently evaluated completely by the same authors to assess eligibility for inclusion, based on the inclusion and exclusion criteria. A study was included if its main purpose was to investigate the possible role of proteomics in the evaluation of kidney graft and function. We included cohort studies, clinical trials and original articles. Abstracts and studies with an unsuitable study design, such as narrative reviews, systematic reviews, meta-analysis, letters to the editor, book chapters, articles not published in English and articles where the full-text was not available, were excluded.

Data extraction and protein selection

Study characteristics, laboratory, and diagnostic specificity and sensitivity were extracted from the selected studies. Extracted study characteristics consisted of author, year of publication, study design, sample size, type of proteomic, population description and specific diagnosis or situation evaluated. Regarding proteins extracted from the articles, a table was created with annotations based on UniProt Database[18].

Categorization of biomarkers based on gene ontology annotations

We aimed to provide a comprehensive overview of all the proteomic biomarkers associated with graft evaluation and prediction of function in KT. Firstly, biomarkers were classified into two categories based on the biological sample from which they were measured: "blood-based", "urine-based", with the "blood-based" proteomics subdivided into "serum-based" and "plasma-based".

The top-ranked proteins in the STRING database were used for gene set enrichment and annotation analyses (GSEA) based on gene ontology (GO), which is divided in the biological processes (BP), molecular functions (MF), and cellular components (CC), as well as functional and signaling pathways[14]. STRING facilitates GSEA by providing an enrichment analysis tool as part of its interface, using data from GO, KEGG, and other databases. The top ten categories on BP analysis were selected based on a combination of factors, including the pathophysiology mechanism correlated with KT, the protein count, and the false discovery rate. The top ten categories on MF and CC analysis where chosen based on protein count. Signaling pathways related to kidney dysfunction and kidney injury-associated key genes were retrieved from two different, freely available databases, REACTOME and WikiPathways[17-19]. Moreover, correlations based on disease-gene association and tissue expression were also used. The statistically significant GO terms and the significant pathways for hub-proteins were defined by the adjusted P values < 0.05.

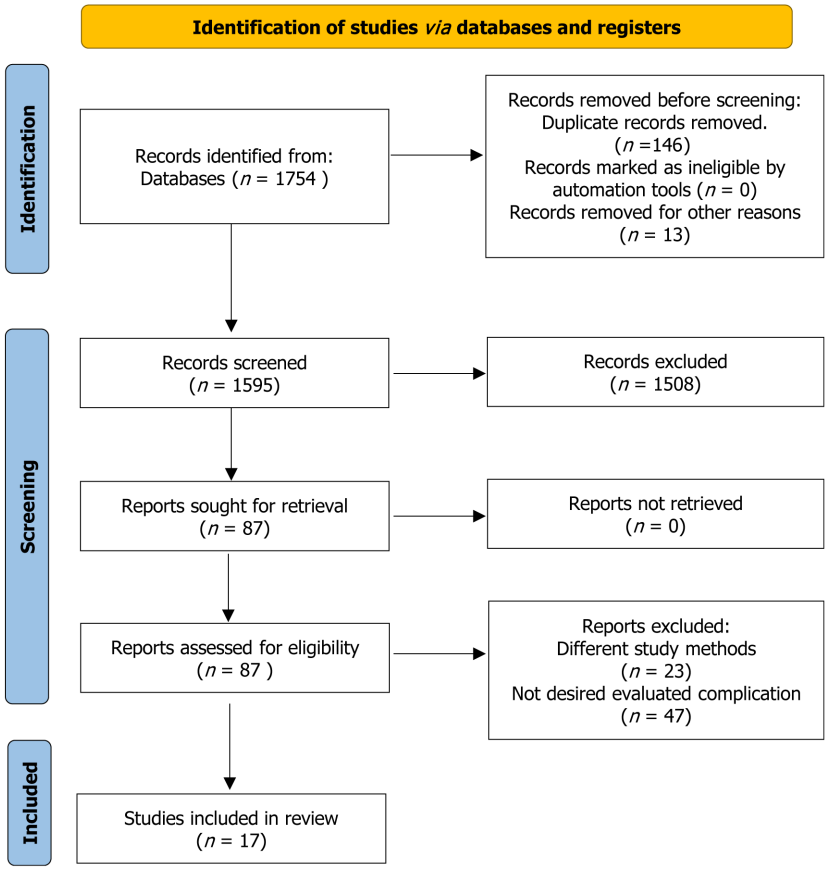


Figure 1 Prisma flow chart.

RESULTS

Study selection and characteristics of included studies

The search strategy followed for selecting the eligible studies included in our systematic review is summarized in the flow chart shown in Figure 1, following PRISMA 2020. A total of 1754 potentially relevant manuscripts were identified through search of the PubMed and Scopus database searches. Of 159 manuscripts were removed before the abstract screening. Following the title and abstract screen, 87 manuscripts met the eligibility criteria and were subsequently assessed for inclusion. Of these, 23 didn't use appropriate quantitation techniques and 47 didn't investigate the role of proteomics in the desired complications. In total, 17 studies met all the eligibility criteria and were included in this systematic review.

All manuscripts included in this review were published from 2013 onward, with most of them being published after 2018. The main characteristics of the eligible studies are presented in Table 1.

Sample and population characteristics

The median number of samples was 59 (interquartile range 117), whereas 12 (70.58%) studies had under 100 samples. Out of 17 proteomics studies, 13 used samples derived from urine and four used blood-based samples. Three of the blood-based samples were plasma and one study employed serum samples. Figure 2 shows quantitative data on biological sample selection in all included samples.

Evaluation techniques

The most commonly used methodology in the 16 articles reviewed was liquid chromatography - tandem MS (LC-MS/MS), targeted multiple reaction monitoring (MRM) or untargeted (discovery). This combines two techniques consecutively: Liquid chromatography and tandem MS, to create a powerful identification and quantitation tool for biomolecules with both high sensitivity and specificity. However, it is essential to consider the potential differences in detection sensitivity between the targeted MRM approach and the unbiased, system-wide, untargeted discovery approach in LC-MS/MS. MRM is optimized for specific analytes, which can result in higher sensitivity and precision, allowing for more accurate quantitation of (especially) low-abundance proteins or peptides. On the other hand, untargeted LC-MS/MS methods aim to detect a wide range of analytes in a single run, which can sometimes be at the expense of sensitivity for singular analytes. These differences can potentially lead to inconsistencies when comparing results between targeted and untargeted approaches. A few papers used both MRM and discovery LC-MS/MS, proving an effective way to mitigate and complement such sensitivity differences and validate results.

Table 1 Characteristics of the included studies

Ref.	Year of publication	Biomarker name	Type of fluid	Method of quantification	No. of samples	Condition evaluated	Data availability
Buscher *et al*[35]	2023	HGF, IGFB, P6, CD40, CX3CL1, SPARCL1	Plasma	Mass cytometry, PEA	39	Allograft function and rejection status	Yes
Başak Oktay *et al*[20]	2022	CXCL10	Urine	LC-MS/MS, ELISA	18	Chronic allograft dysfunction	No
Jeon *et al*[26]	2022	RBP4	Urine	LC-MS/MS, ELISA	49	Evaluation of renal graft function	On request
Carreras-Planella *et al*[24]	2021	Vitronectin	Urine	LC-MS/MS, ELISA	59	Assessment of fibrosis in kidney graft	No
Navarrete *et al*[22]	2020	Proteinase 3	Urine	Serine hydrolase ABPP with Nano-RP LC–MS/MS	32	Subclinical rejection	
Braun *et al*[36]	2020	PCK2	Urine	(Western blot, SDS-PAGE, IHC validation), nano-LC-MS/MS - both untargeted and targeted using PRM	22	Prediction of long-term graft outcome	Yes
Thorne *et al*[33]	2020	S-troponin and S-myoglobin	Plasma	LC-MS/MS, ELISA	225	Subclinical effects of remote ischemic recondi-tioning	On request
Bank *et al*[31]	2019	TIMP2	Urine	sandwich ELISA	83	Prediction of the occurrence and duration of functionally defined delayed graft function	Yes
Al-Nedawi *et al*[25]	2019	TFIID subunit 1, 3-hydroxy-3-methylglutaryl coenzyme A reductase, FN1 protein, Spectrin beta chain, Protein AMBP, Alpha-1-acid glycoprotein 2, Dynein heavy chain 3, axonemal, Insulin receptor substrate 1, Prothrombin, Alpha-1-acid glycoprotein 1, Melanotransferrin, Catalase, DIS3-like exonuclease 1, Kinetochore-associated protein 1, Keratin, type II cuticular Hb6, Neuroblast differentiation-associated protein AHNAK, Apolipoprotein E, Angiotensinogen, Vitamin D-binding protein, EGF-containing fibulin-like extracellular matrix protein 1, Keratin, type II cytoskeletal 3, DNA repair protein RAD50, Receptor-type tyrosine-protein phosphatase, Apolipoprotein A-II, Transthyretin, Hemoglobin subunit beta	Plasma	(SDS-PAGE), MS/MS	30	eGFR correlation and graft function evaluation	No
Mockler *et al*[29]	2018	CXCL10	Urine	LC-MS/MS (to measure creatinine), sandwich ELISA (to measure CXCL10 and CCL2)	59	Correlation with eGFR and long term renal graft outcome	No
Williams *et al*[32]	2017	C4BPA, alpha, guanylin, immunoglob- ulin superfamily member 8, and serum amyloid P-component.	Urine	TUPA (scheduled LC-MRM this is a type of MS), sandwich ELISA	52	Diagnosis of Delayed graft function	Yes
Hirt-Minkowski *et al*[27]	2016	CCL2, CXCL10	Urine	ELISA	185	Prediction of long-term renal graft outcome	Yes
Hirt-	2015	CXCL10	Urine	sandwich ELISA	154	Long-term renal	Yes

Minkowski *et al*[28]						allograft outcome evaluation	
Ho *et al*[23]	2016	MMP7	Urine	LC-MS/MS, ELISA	17	Subclinical graft injury and inflammation	Yes
Sigdel *et al* [21]	2013	ACAN, CLEC14A, GLB1, LGALS9B, LMAN2, MRC2 SEL, CD27, DPEP1, and F2	Urine	iTRAQ labeling, LC-MS/MS, ELISA	142	Evaluation of chronic allograft injury	Yes
Welberry Smith *et al* [30]	2013	Aminoacylase-1	Serum	LC-MS/MS, sandwich ELISA	194	Prediction of long-term outcome in patients with delayed graft function	Yes
Schmidt *et al*[34]	2013	Chitinase-3-like protein 1	Urine	MS	78	Evaluation of delayed graft injury and prediction of long-term renal graft outcome	Yes

LC-MS/MS: Liquid chromatography - tandem mass spectrometry; MRM: Targeted; ELISA: Enzyme-linked immunosorbent assay; HGF: Hepatocyte growth factor; CX3CL1: Fractalkine; IGFBP6: Insulin growth factor binding protein 6; CXCL10: C-X-C motif chemokine 10; SPARCL1: SPARC-like protein 1; RBP4: Retinol-binding protein 4; PCK2: Phosphoenolpyruvate carboxykinase 2; TIMP2: Tissue inhibitor of metalloproteinases-2; TFIID: Transcription initiation factor; C4BPA: C4b-binding protein alpha chain; CCL2: Chemokine ligand 2 ; MMP7: Matrix Metalloproteinase-7.

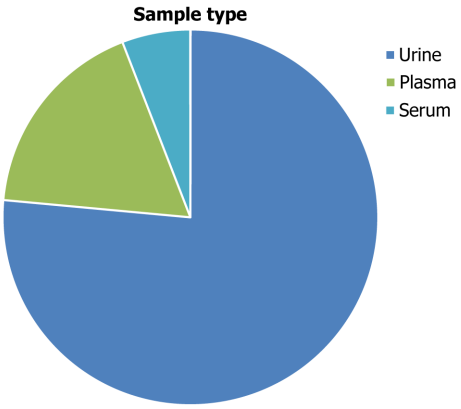


Figure 2 Quantitative data about the biological sample selection in all the included samples.

This method was most commonly paired with a direct or sandwich enzyme-linked immunosorbent assay (ELISA) for validation. ELISA uses a single antibody directly linked to an enzyme to detect and quantify a target protein in a given sample, while sandwich ELISA uses both a capture and a detection antibody for added sensitivity and specificity. Other methods used include targeted urine proteome assay, which is a type of multiple reaction monitoring (MRM), isobaric tags for relative and absolute quantitation labeling, as well as serine hydrolase activity-based protein profiling and proximity extension assay.

Biological samples proteome

In the total of 17 studies, 58 proteomic biomarkers were evaluated (Table 2). Of these, one protein (CXCL10) overlapped between different studies, as seen on the heatmap in Figure 3. Among 58 proteins identified, 23 were detected in urine samples, 33 were detected in plasma samples and two were detected in serum samples, with CXCL10 being detected both in urine and serum samples. Out of 58 proteomic biomarkers, 39 were found to be elevated compared to control/healthy samples, 12 were found to be down-regulated, six were related to better prognosis, one was detected only in samples from injured kidney grafts, and one appeared with increased activity in samples derived from complicated KT.

Protein categorization and enrichment analysis based on GO terms

All proteins deriving from healthy and pathological samples were subjected to GO enrichment analysis, including BP, CC and MF terms. A separate analysis of proteins found upregulated in samples from healthy and complicated KT was also performed. A total of 58 proteins were identified using their UniProt accession number. Figure 4 summarizes the top ten significant and enriched GO terms of BP, CC, and MF based on increased proteins in samples from complicated KT recipient cases, with the false discovery rate, a measure that describes how significant the enrichment is by showing p-

Table 2 The table contains the protein's name, UniProt number, cellular location, and code gene

Name	UniProt code	Cellular location	Sample type	Status	Code gene
Hepatocyte growth factor	P14210	Membrane, extracellular space	Plasma	Elevated	*HGF*
Insulin growth factor binding protein 6	P24592	Secreted	Plasma	Elevated	*IGFBP6*
CD40	P25942	Cell membrane and secreted	Plasma	Elevated	*CD40*
Fractalkine	P78423	Cell membrane	Plasma	Elevated	*CX3CL1*
SPARC-like protein 1	Q14515	Secreted, extracellular space and extracellular matrix	Plasma	Elevated	*SPARCL1*
C-X-C motif chemokine 10	P02778	Secreted, plasma membrane	Urine	Elevated	*CXCL10*
Retinol-binding protein 4	P02766	Cell wall, organelle, Secreted	Urine	Elevated	*RBP4*
Phosphoenolpyruvate carboxykinase 2	Q16822	Mitochondrion, ribosome	Urine	Elevated	*PCK2*
S troponin	P19429	Cytosol and sarcomere	Serum	Elevated	*TNNI3*
S myoglobin	P02144	Cytoplams and sarcoplasm	Serum	Elevated	*MB*
TIMP2	P16035	cytoplasmic vesicle, organelle, Secreted	Urine	Elevated	*TIMP2*
CCL2	P13500	Secreted	Urine	Elevated	*CCL2*
MMP7	P09237	Secreted, extracellular space, extracellular matrix	Urine	Elevated	*MMP7*
Aminoacylase-1	Q03154	Cytoplasm	Serum	Elevated	*ACY1*
Chitinase-3-like protein 1	P36222	Cytoplasm, endoplasmic reticulum, secreted	Urine	Elevated	*CHI3 L1*
Protein AMBP	P02760	Extracellular region, secreted	Plasma	Elevated	*AMBP*
Alpha-1-acid glycoprotein 2	P19652	Extracellular region, secreted	Plasma	Elevated	*ORM2*
Dynein heavy chain 3	Q8TD57	Cytoskeleton, cilium axoneme	Plasma	Elevated	*DNAH3*
Insulin receptor substrate 1	P06213	Cytosol, nucleus, plasma membrane, caveola	Plasma	Elevated	*INSR*
Catalase	P04040	Peroxisome	Plasma	Elevated	*CAT*
DIS3-like exonuclease 1	Q8TF46	Cytoplasm	Plasma	Elevated	*DIS3 L*
Kinetochore-associated protein 1	P50748	Cytoskeleton, spindle, nucleus, cytoplasm	Plasma	Elevated	*KNTC1*
Apolipoprotein E	P02649	Extracellular region, secreted	Plasma	Elevated	*APOE*
Angiotensinogen	P01019	Extracellular region, secreted	Plasma	Elevated	*AGT*
Vitamin D-binding protein	P02774	Extracellular region, secreted	Plasma	Elevated	*GC*
EGF-containing fibulin-like extracellular matrix protein 1	Q580Q6	Extracellular region, secreted	Plasma	Elevated	*EFEMP1*
C4b-binding protein alpha chain	P04003	Secreted	Urine	Elevated	*C4BPA*
Serum amyloid P-component	P02743	Secreted	Urine	Elevated	*APCS*
Aggrecan core protein	P16112	Secreted, extracellular space, extracellular matrix	Urine	Elevated	*ACAN*
C-type lectin domain family 14 member A	Q86T13	Membrane	Urine	Elevated	*CLEC14A*
Beta-galactosidase	P54803	Cytoplasm, lysosome	Urine	Elevated	*GLB1*
Galectin-9B	Q3B8N2	Cytosol, nucleus	Urine	Elevated	*LGALS9B*
Vesicular integral-membrane protein VIP36	Q12907	Endoplasmic reticulum, golgi apparatus, membrane	Urine	Elevated	*LMAN2*
C-type mannose receptor 2	Q9UBG0	Membrane	Urine	Elevated	*MRC2*

Protein sel-1 homolog 1	Q9UBV2	Endoplasmic reticulum membrane	Urine	Elevated	*SEL1 L*
CD27 antigen	P26842	Membrane	Urine	Elevated	*CD27*
Dipeptidase 1	Q9H4A9	Cell projection, microvillus membrane, cell membrane	Urine	Elevated	*DPEP1*
Transcription factor E2F2	Q14209	Nucleus	Urine	Elevated	*E2F2*
Keratin, type II cytoskeletal 3	P12035	Intermediate filament, keratin filament cytosol, exosome	Plasma	Decreased immediately, elevated 1 month after	*KRT3*
DNA repair protein RAD50	Q92878	Nucleus	Plasma	Decreased immediately, elevated 1 month after	*RAD50*
Receptor-type tyrosine-protein phosphatase	P23469	Integral component of membrane	Plasma	Decreased immediately po, elevated 1 month after	*PTPRE*
Vitronectin	P04004	Endoplasmic reticulum, golgi apparatus, organelles, secreted	Urine	Detected only in fibrotic grafts	*VTN*
proteinase 3	P24158	Lysosome, cytosol, plasma membrane, cytoplasmic vesicle, organelle, secreted	Urine	Increased activity	*PRTN3*
Transcription initiation factor TFIID subunit 1	P21675	Nucleus	Plasma	Decreased	*TAF1*
3-hydroxy-3-methylglutaryl coenzyme A reductase	P04035	Endoplasmic reticulum, ER membrane	Plasma	Decreased	*HMGCR*
Fibronectin	P02751	Extracellular region, secreted	Plasma	Decreased	*FN1*
Spectrin beta chain, non-erythrocytic 1	Q01082	Cytoskeleton	Plasma	Decreased	*SPTBN1*
Apolipoprotein A-II	V9GYM3	Extracellular region, secreted	Plasma	Decreased	*APOA2*
Transthyretin	E9KL36	Extracellular region, secreted	Plasma	Decreased	*HEL111*
Hemoglobin subunit beta	P68871	Cytosol, extracellular or secreted: Blood microparticle, exosome	Plasma	Decreased	*HBB*
Guanylin	Q02747	Secreted	Urine	Decreased	*GUCA2A*
Immunoglobulin superfamily member 8	Q969P0	Cell membrane	Urine	Decreased	*IGSF8*
Prothrombin	P00734	Extracellular region, secreted	Plasma	Elevated in good prognosis recipients	*F2*
Alpha-1-acid glycoprotein 1	P02763	Secreted	Plasma	Elevated in good prognosis recipients	*ORM1*
Melanotransferrin Isoform 1	P08582	Plasma membrane, GPI-anchor	Plasma	Elevated in good prognosis recipients	*MELTF*
Apolipoprotein A-I	P02647	Extracellular region, secreted	Plasma	Elevated in good prognosis recipients	*APOA1*
Keratin, type II cuticular Hb6	O43790	Cytoskeleton, keratin filament, cytosol extracellular region or secreted, exosome	Plasma	Elevated in good prognosis recipients	*KRT86*
Neuroblast differentiation-associated protein AHNAK	Q09666	Cytoskeleton, centrosome	Plasma	Elevated in good prognosis recipients	*AHNAK*

HGF: Hepatocyte growth factor; CX3CL1: fractalkine; IGFBP6: Insulin growth factor binding protein 6; CXCL10: C-X-C motif chemokine 10; SPARCL1: SPARC-like protein 1; RBP4: Retinol-binding protein 4; PCK2: Phosphoenolpyruvate carboxykinase 2; TIMP2: Tissue inhibitor of metalloproteinases-2; C4BPA: C4b-binding protein alpha chain; CCL2: Chemokine ligand 2; MMP7: Matrix Metalloproteinase-7.

values corrected for multiple testing within each category, using the Benjamini–Hochberg procedure, mentioned in the parenthesis. In the BP analysis performed based on increased proteins found in samples of KT recipients with some type of graft injury or complication, the majority of related proteins were involved in catalytic activity, immune response and stress defense. In terms of CC analysis, most proteins were located in the extracellular space, extracellular exosome and extracellular matrix, while a significant percentage of proteins were secreted from the cells. Of the MF terms, signaling receptor binding and molecular function regulator activity were the most important functions. In the analysis of elevated protein abundance levels correlated with good outcome, due to the limited protein number, only CC analysis was performed, and the results showed that all six proteins were located in the extracellular space, with three of them being particularly blood microparticles.

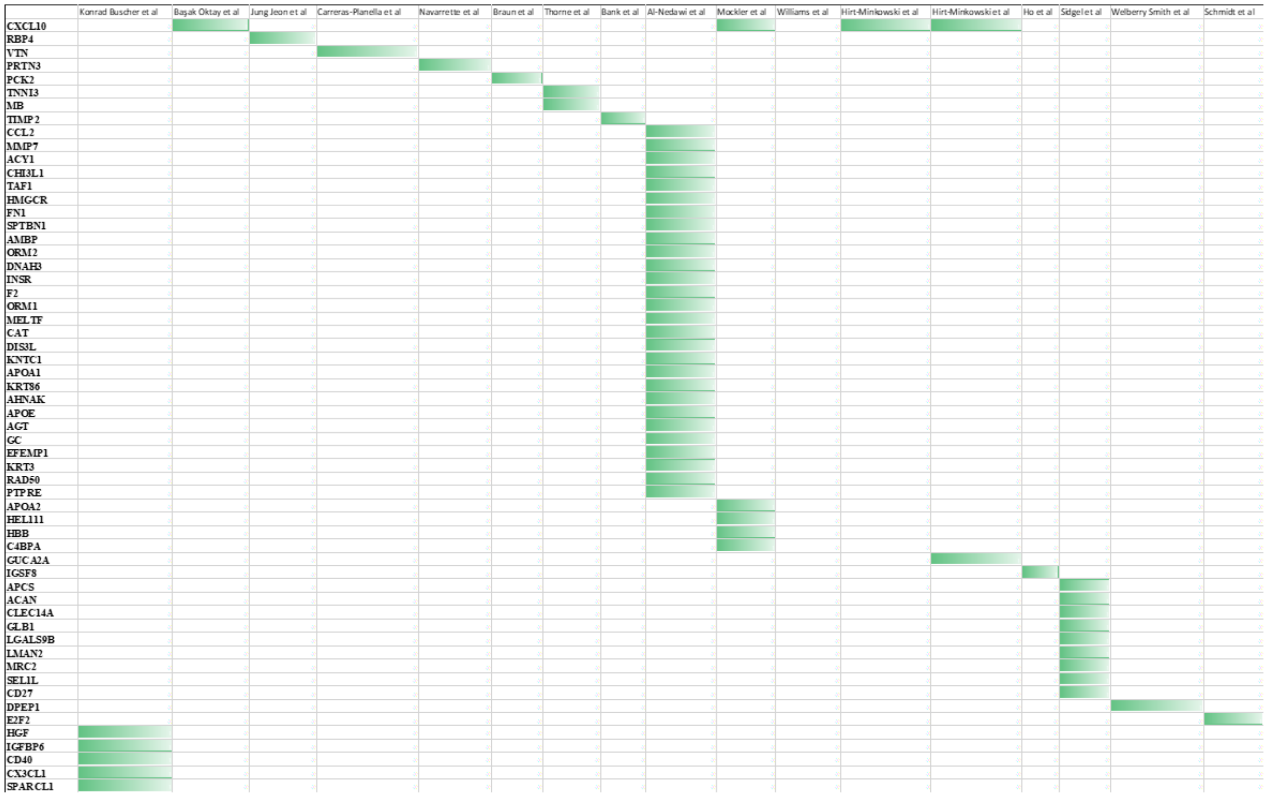


Figure 3 Heatmap representation of proteins detected across various studies related to kidney transplantation. Each column represents a different study or dataset, and each row represents a specific protein. Green color indicates the protein detection within each study.

Application of proteomics in kidney graft evaluation

The previously discussed proteomics findings exhibit both diagnostic and predictive value. Their diagnostic value relies on the correlation between the increase or decrease of specific proteins detected in biological fluids of KT recipients and the histological alterations observed in conventional biopsies, often accompanied by other functional biomarkers, such as creatinine. Among the 17 studies included in this systematic review, five studies investigated the potential connection between protein biomarker non-invasive assessment and conventional kidney biopsy results[20-36]. Out of those five studies, Başak Oktay *et al*[20] and Sigdel *et al*[21] focused on diagnosing chronic allograft dysfunction through proteomic assessment, while Navarrete *et al*[22], and Ho *et al*[23] investigated subclinical rejection and injury, and Carreras-Planella *et al*[24] explored possible correlation between specific protein biomarkers with fibrosis levels observed in kidney graft biopsies.

Evaluation and prediction of function of the kidney graft can be achieved by the evaluation of protein biomarkers in correlation with conventional methods, such as estimated glomerular filtration rate (eGFR) and creatinine levels assessment. Specifically, 12 studies correlated proteomic biomarkers with conventional laboratory kidney function evaluation techniques, in order to assess or predict its function[25-36]. Al-Nedawi *et al*[25] and Jeon *et al*[26] investigated potential links between bad outcome kidney transplant cases, based on the eGFR of the recipients, and proteomic assessment. For predicting long-term graft function, Hirt-Minkowski *et al*[27,28], Mockler *et al*[29], and Braun *et al*[36] emphasized the importance of measuring proteins at specific time points. Similarly, Welberry Smith *et al*[30] highlighted that measurement of specific protein biomarkers on days 1 and 2 post transplantation can be predictive of this complication. Bank *et al*[31] also correlated specific proteomic panels with eGFR and function of the kidney graft, particularly focusing their study on short-term graft function evaluation on days 1 and 10 after transplantation. Furthermore, Williams *et al*[32] also evaluated the same complication by correlating eGFR with specific biomarkers assessed 12-18 hours after transplantation. An additional important investigation was conducted by Thorne *et al*[33] where ischemic reconditioning, a situation that is part of KT process, was studied from the proteomics perspective. Moreover, long-term graft function prediction can also have significant clinical importance according to a study performed by Schmidt *et al*[34]. Lastly, Buscher *et al*[35] correlated specific plasma proteomic panels with allograft function based on creatinine levels, underscoring the diagnostic superiority of a proteomic panel in contrast to specific proteins in graft function evaluation.

DISCUSSION

Renal transplantation is the most common transplant operation and the only effective treatment for end-stage kidney

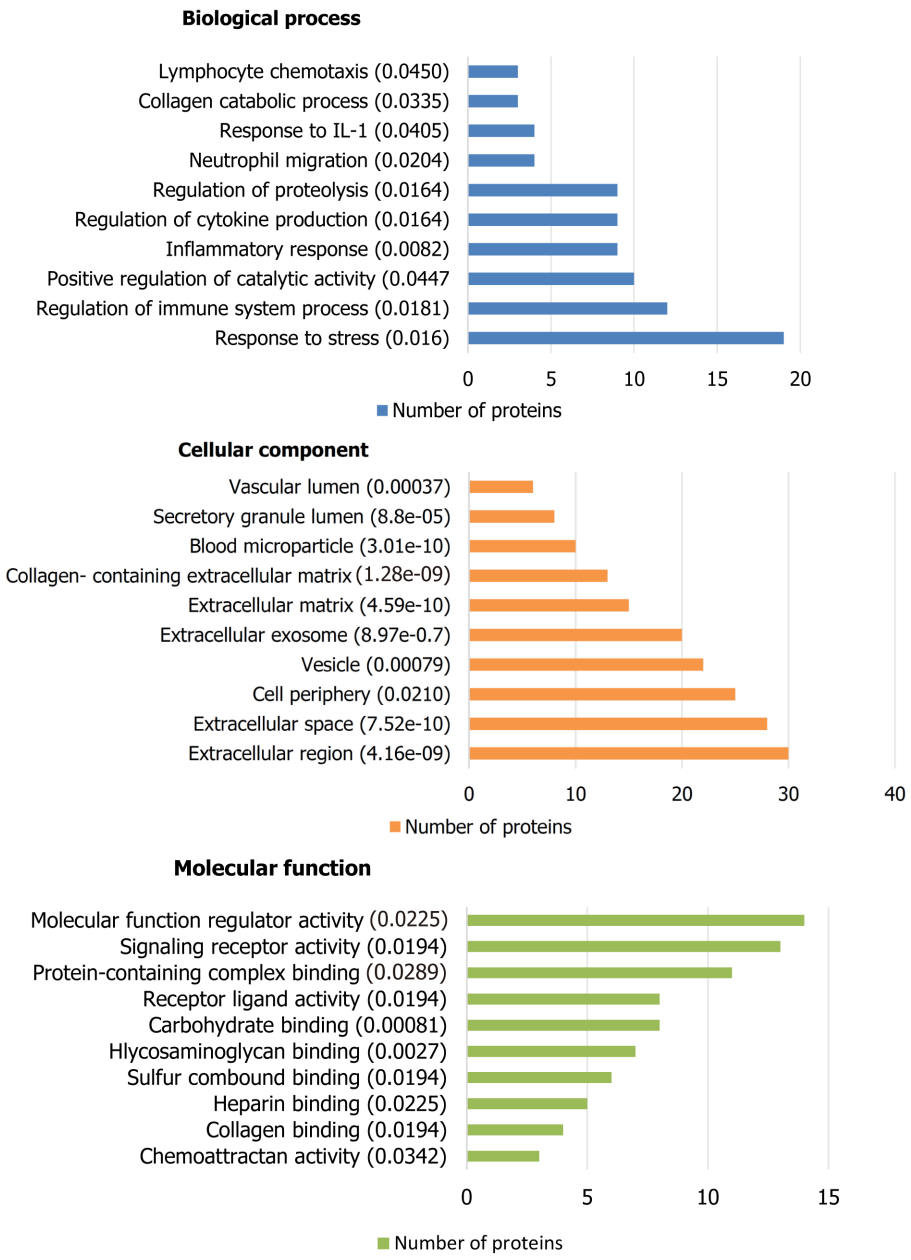


Figure 4 Gene ontology analysis of upregulated proteins detected on samples of kidney transplant recipients with graft injury or dysfunction. False discovery rate is mentioned in the parenthesis.

disease, offering recipients a significantly improved quality of life compared to dialysis. Despite the first successful kidney transplant operation being performed more than 70 years ago, graft-related complications still exist due to various causes. Current clinical practice for monitoring KT recipients relies on conventional markers such as serum creatinine, urine volume, proteinuria, and other laboratory tests. Although these biomarkers can indicate some form of kidney injury, they typically signal allograft damage only after it has occurred. Biopsies remain the primary tool for diagnosis, offering high sensitivity and specificity, but they are invasive procedures associated with major complications and potential graft loss[37]. Proteomic approaches offer exciting groundbreaking discoveries connecting basic translational research with transplant everyday clinical practice, enabling early assessment and prediction of various possible complications in a non- or minimal invasive way.

Proteomic data analysis, consisting of identification, relative quantitation and functional enrichment and signaling pathways analysis, represents a powerful strategy for deciphering intricate molecular activities and functional pathways associated with a particular group of proteins. Notably, in this systematic review among the GO terms, those correlated with immunological activity were significantly enriched, as seen in Figure 4. Specifically, the terms of regulation of immune system process, inflammatory response, regulation of cytokine production, response to IL-1, neutrophil migration and lymphocyte chemotaxis were enriched in total by 16 proteins in the GO BP analysis of upregulated proteins found in samples of KT recipients with complications, as shown on the bitmap on Figure 5. Analysis based on Reactome and WikiPathways databases has also underscored the association with immune response, notably IL-1. Given the strong relationship between KT and the immune system, both short- and long-term complications are often attributed to

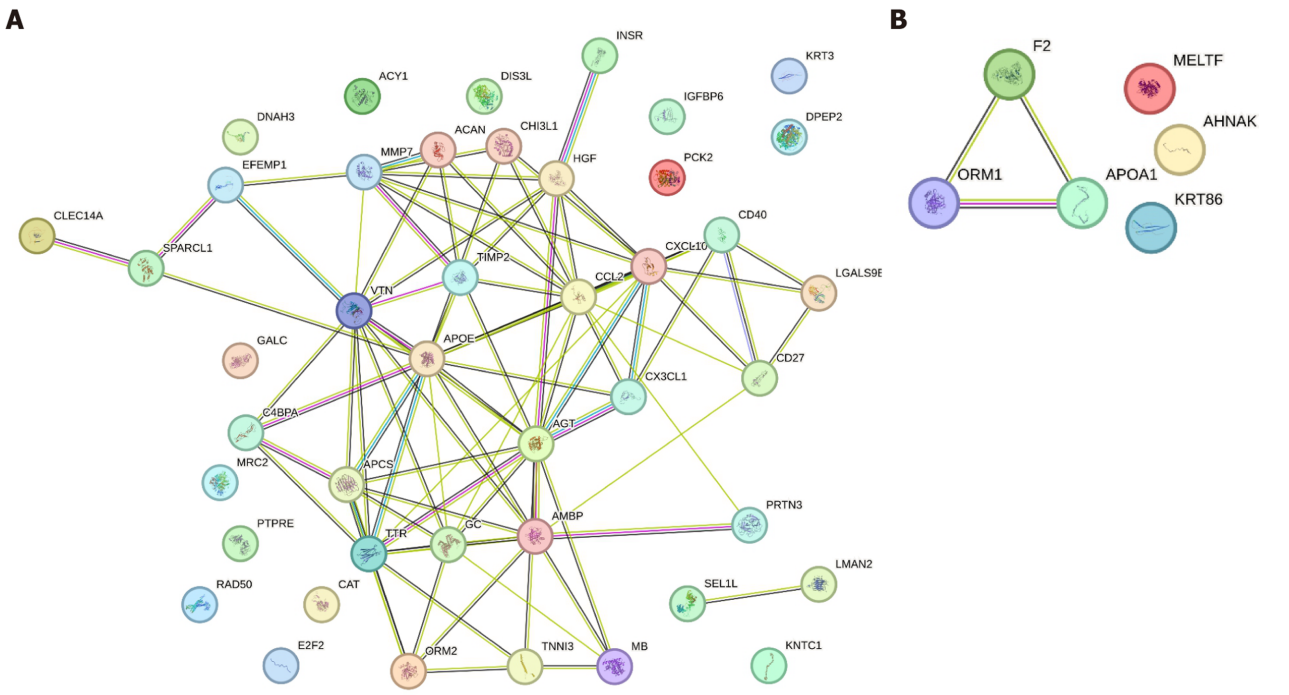


Figure 5 Protein interaction network analysis. A: A protein interaction network of upregulated proteins detected in biological fluids of recipients with complicated transplantations. The proteins related to immune biological pathways are highlighted; B: A protein interaction network of proteins related to normal kidney function.

abnormal immune responses[38,39]. Despite the latest major advancements in immunosuppression, even subclinical graft injury can jeopardize the function of the graft[40,41]. Particularly, the significantly enriched IL-1 highlights its importance as a cytokine target for potential immunosuppressive therapies[42-44]. The development of IL-1 target agents began in 1993 with the introduction of anakinra, a recombinant form of the naturally occurring IL-1 receptor antagonist, with major clinical applications due to its excellent therapeutics being related to its safety, short half-life and multiple routes of administration[45].

Another notable finding derived from the Reactome and WikiPathways analyses of proteins originating from pathological samples is the association with elastic fibers and wound healing pathways. These pathways are correlated with graft fibrosis, a form of subclinical graft injury resulting in long term dysfunction of the graft[46-49]. This correlation is also supported by the diseases-gene association, as well as highlighted by Carreras-Planella *et al*[24] in their study[24]. Specifically, Metalloproteinase-9 and Metalloproteinase inhibitor 2, two proteins found to be enriched in pathways related to fibrosis, have been reported to be correlated with kidney graft injury, and they have been also proved to have predictive value for the long-term graft function[50,51]. Moreover, Fibronectin, which is another protein omic related to fibrosis, has been correlated with a rare inherited kidney disorder, named Fibronectin glomerulopathy, which results in impaired stress fiber formation, even after successful transplantation[52].

One intriguing correlation in the disease-gene association was one associating four proteins of our analysis with amyloidosis. Amyloidosis is a rare condition caused by abnormal folding of proteins, which results in complications related to many organs, including the kidneys[53]. Regarding KT, amyloidosis can be caused, either as a result of recurrence of the preexisting condition, or as a newly developed complication leading to graft loss[54,55].

Another significant association found was with blood coagulation proteins. In particular, 10 upregulated proteins in complicated cases of KT demonstrated commonality with cardiovascular diseases, among these being Apolipoprotein E. Apolipoprotein E is a multifunctional protein central to lipid metabolism, contributing to atherosclerosis and consequent damage of the arteries[56]. The role of Apolipoprotein E in chronic kidney disease has been well documented, where lipid and non-lipid pathways are implicated in the disease onset and progression[57]. Subclinical graft injury of the graft and subsequent dysfunction are directly linked with damage of the vessels of the kidney graft. Particularly, specific gene polymorphisms, such as E4 allele have been related to poor long-term transplant outcome[58,59].

End-stage kidney failure is recognized as the primary reason for KT[60]. Myoglobin, Activation peptide fragment 1 and Angiotensin are proteins associated with kidney failure, and they were found to be enriched in the disease-gene association STRING analysis. Angiotensin is a well-studied biomarker related to kidney graft injury with the mechanism of the intrarenal RAS activation *via* inflammation and oxidative stress[61]. Myoglobin is linked to rhabdomyolysis, a pathological situation, resulting to serious graft damage[62].

In addition to the increased protein abundance levels found in complicated cases of KT, it is noteworthy to emphasize the possible protective or predictive role of proteins found to be elevated abundance levels in good prognosis KT recipients. Notably, Prothrombin, Alpha-1-acid glycoprotein 1, Melanotransferrin Isoform 1, Apolipoprotein A-I and Keratin type II cuticular Hb6 were reported to be increased in good prognosis patients by Al-Nedawi *et al*[25]. Prothrombin, Alpha-1-acid glycoprotein 1 and Apolipoprotein A-I also all interact, as indicated in Figure 5, due to their

co-expression in events related to blood cascade. In the context of KT and kidney disease, Alpha-1-Acid Glycoprotein has protective role to kidney injury, while apolipoprotein A has been related to lower prevalence of CKD, thus related to good kidney function[63,64].

Out of the 58 protein biomarkers evaluated in the total of 17 studies, CXCL10 is the only one mentioned in more than one study. Particularly, the role of this protein biomarker in KT evaluation is studied by Başak Oktay *et al*[20], Mockler *et al*[29] and Hirt-Minkowski *et al*[27,28]. CXCL10 has been reported to be elevated in pathological urine or serum samples of KT recipients. This protein is a cytokine that belongs to the CXC chemokine family and it is secreted by activated B cells, monocytes/macrophages, endothelial cells, and fibroblasts in response to interferon gamma (IFN-γ). CXCL10 plays a pivotal role in inflammation, due to its chemoattractive effects for monocytes/macrophages, T cells, natural killer (NK) cells, and dendritic cells *via* cell surface chemokine receptor CXCR3[65]. Involvement of CXCL10 in renal diseases is well-documented, with the biomarker having a pivotal role in Mesangial Proliferative Glomerulonephritis, acute kidney injury and lupus nephritis[66]. Its significant role in renal disease pathophysiology is supported by the observation that renal resident mesangial cells, renal tubular epithelial cells, podocytes, endothelial cells, and infiltrating inflammatory cells express CXCL10 under inflammatory conditions[66].

Lastly, it is important to highlight the choice of quantitation methods in different proteomics studies. As mentioned in the results section, the most used methodology is LC-MS/MS, targeted on untargeted. Using an untargeted MS-based approach with a targeted follow-up, as was done in LC-MS/MS followed by ELISA, has an added benefit of eliminating bias in protein selection, further validating the results, while ensuring that increased quantitation of specific proteins was accurately measured and recorded[67]. On the other hand, using a targeted approach allows research bias to play a part in the experiment, so only previously recognized proteins with potential for biomarker status can be used. Using non-MS based methods guarantees this targeted approach, however it does increase specificity, as well as ease the load for data analysis and management.

Our study has some specific limitations. The primary limitation was the heterogeneity among enrolled studies, with big heterogeneity of sample, population, time of sample collection and researched pathology being reported, which limited the possible statistical analysis possibility. Moreover, the study used a comprehensive seed proteomic dataset from a systematic literature review, including databases of PubMed and Scopus. Additionally, during the proteomic data collection, only association with graft injury and function were considered while information regarding the source of the graft (living or cadaveric donation, brain or circulatory death donation) were not taken into consideration in the separate analysis. Lastly, the variation recorded in studies in detection sensitivity between LC-MS/MS and MRM methods used can pose substantial challenges. LC-MS/MS provides wide detection but has variable quantitation, while MRM delivers very sensitive and accurate tailored quantitation. These differences may cause discrepancies in comparative analyses, adding bias, hindering data standardization and integration. Advanced statistical models and thorough standardization are required to harmonize data and produce accurate, dependable outcomes across research.

CONCLUSION

This systematic review showed that very few proteomic-level studies have been conducted to identify the key proteins associated with KT complications, and particularly with subclinical injury and prediction of graft function. Nevertheless, to the best of our knowledge, we were unable to locate any gene expression data regarding KT and non-invasive graft evaluation. We highlight the importance of new research studies to be held in order to identify the best possible panel of proteins for the early non/minimal invasive detection of different complications, as well as the best possible method of evaluation.

FOOTNOTES

Author contributions: Avramidou E and Aivaliotis M conceptualized and designed the research; Avramidou E and St John K performed the research through the databases; Avramidou E and St John K analysed the data; Avramidou E, St John K and Psatha K wrote the paper; Tsoulfas G and Aivaliotis M critically reviewed the paper. All the authors have read and approved the final manuscript. Avramidou E proposed the research idea and searched the databases. Aivaliotis M provided the analysis sources. The collaboration between Avramidou E and Aivaliotis M is crucial for the publication of this manuscript and other manuscripts still in preparation.

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REFERENCES

1 **Thongprayoon C**, Kaewput W, Pattharanitima P, Cheungpasitporn W. Progress and Recent Advances in Solid Organ Transplantation. *J Clin Med* 2022; **11** [PMID: 35456205 DOI: 10.3390/jcm11082112]
2 Current Strategies for Living Donor Kidney Transplantation [Internet]. Hergiswil (CH): European Dialysis and Transplant Nurses Association/ European Renal Care Association (EDTNA/ERCA); 2021– [PMID: 35816595]
3 **Alimi R**, Hami M, Afzalaghaee M, Nazemian F, Mahmoodi M, Yaseri M, Zeraati H. Factors Affecting the Long-Term Survival of Kidney Transplantation in Northeastern of Iran between 2000 and 2015. *Iran J Public Health* 2021; **50**: 2076-2084 [PMID: 35223575 DOI: 10.18502/ijph.v50i10.7508]
4 **Warmuzińska N**, Łuczykowski K, Bojko B. A Review of Current and Emerging Trends in Donor Graft-Quality Assessment Techniques. *J Clin Med* 2022; **11**: 487 [PMID: 35159939 DOI: 10.3390/jcm11030487]
5 **Huang E**, Mengel M, Clahsen-van Groningen MC, Jackson AM. Diagnostic Potential of Minimally Invasive Biomarkers: A Biopsy-centered Viewpoint From the Banff Minimally Invasive Diagnostics Working Group. *Transplantation* 2023; **107**: 45-52 [PMID: 36508645 DOI: 10.1097/TP.0000000000004339]
6 **Psatha K**, Kollipara L, Drakos E, Deligianni E, Brintakis K, Patsouris E, Sickmann A, Rassidakis GZ, Aivaliotis M. Interruption of p53-MDM2 Interaction by Nutlin-3a in Human Lymphoma Cell Models Initiates a Cell-Dependent Global Effect on Transcriptome and Proteome Level. *Cancers (Basel)* 2023; **15**: 3903 [PMID: 37568720 DOI: 10.3390/cancers15153903]
7 **Mischak H**, Kolch W, Aivaliotis M, Bouyssié D, Court M, Dihazi H, Dihazi GH, Franke J, Garin J, Gonzalez de Peredo A, Iphöfer A, Jänsch L, Lacroix C, Makridakis M, Masselon C, Metzger J, Monsarrat B, Mrug M, Norling M, Novak J, Pich A, Pitt A, Bongcam-Rudloff E, Siwy J, Suzuki H, Thongboonkerd V, Wang LS, Zoidakis J, Zürbig P, Schanstra JP, Vlahou A. Comprehensive human urine standards for comparability and standardization in clinical proteome analysis. *Proteomics Clin Appl* 2010; **4**: 464-478 [PMID: 21137064 DOI: 10.1002/prca.200900189]
8 **Ramalhete LM**, Araújo R, Ferreira A, Calado CRC. Proteomics for Biomarker Discovery for Diagnosis and Prognosis of Kidney Transplantation Rejection. *Proteomes* 2022; **10** [PMID: 35893765 DOI: 10.3390/proteomes10030024]
9 **Sirolli V**, Piscitani L, Bonomini M. Biomarker-Development Proteomics in Kidney Transplantation: An Updated Review. *Int J Mol Sci* 2023; **24** [PMID: 36982359 DOI: 10.3390/ijms24065287]
10 **van Leeuwen LL**, Spraakman NA, Brat A, Huang H, Thorne AM, Bonham S, van Balkom BWM, Ploeg RJ, Kessler BM, Leuvenink HGD. Proteomic analysis of machine perfusion solution from brain dead donor kidneys reveals that elevated complement, cytoskeleton and lipid metabolism proteins are associated with 1-year outcome. *Transpl Int* 2021; **34**: 1618-1629 [PMID: 34448265 DOI: 10.1111/tri.13984]
11 **Cox J**, Mann M. MaxQuant enables high peptide identification rates, individualized p.p.b.-range mass accuracies and proteome-wide protein quantification. *Nat Biotechnol* 2008; **26**: 1367-1372 [PMID: 19029910 DOI: 10.1038/nbt.1511]
12 **Tyanova S**, Temu T, Sinitcyn P, Carlson A, Hein MY, Geiger T, Mann M, Cox J. The Perseus computational platform for comprehensive analysis of (prote)omics data. *Nat Methods* 2016; **13**: 731-740 [PMID: 27348712 DOI: 10.1038/nmeth.3901]
13 **Baltsavia I**, Theodosiou T, Papanikolaou N, Pavlopoulos GA, Amoutzias GD, Panagopoulou M, Chatzaki E, Andreakos E, Iliopoulos I. Prediction and Ranking of Biomarkers Using multiple UniReD. *Int J Mol Sci* 2022; **23**: 11112 [PMID: 36232413 DOI: 10.3390/ijms231911112]
14 **Szklarczyk D**, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, Gable AL, Fang T, Doncheva NT, Pyysalo S, Bork P, Jensen LJ, von Mering C. The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. *Nucleic Acids Res* 2023; **51**: D638-D646 [PMID: 36370105 DOI: 10.1093/nar/gkac1000]
15 **Efstathiou G**, Antonakis AN, Pavlopoulos GA, Theodosiou T, Divanach P, Trudgian DC, Thomas B, Papanikolaou N, Aivaliotis M, Acuto O, Iliopoulos I. ProteoSign: an end-user online differential proteomics statistical analysis platform. *Nucleic Acids Res* 2017; **45**: W300-W306 [PMID: 28520987 DOI: 10.1093/nar/gkx444]
16 **UniProt Consortium**. The universal protein resource (UniProt). *Nucleic Acids Res* 2008; **36**: D190-D195 [PMID: 18045787 DOI: 10.1093/nar/gkm895]
17 **Vastrik I**, D'Eustachio P, Schmidt E, Gopinath G, Croft D, de Bono B, Gillespie M, Jassal B, Lewis S, Matthews L, Wu G, Birney E, Stein L. Reactome: a knowledge base of biologic pathways and processes. *Genome Biol* 2007; **8**: R39 [PMID: 17367534 DOI: 10.1186/gb-2007-8-3-r39]
18 **Slenter DN**, Kutmon M, Hanspers K, Riutta A, Windsor J, Nunes N, Mélius J, Cirillo E, Coort SL, Digles D, Ehrhart F, Giesbertz P, Kalafati M, Martens M, Miller R, Nishida K, Rieswijk L, Waagmeester A, Eijssen LMT, Evelo CT, Pico AR, Willighagen EL. WikiPathways: a multifaceted pathway database bridging metabolomics to other omics research. *Nucleic Acids Res* 2018; **46**: D661-D667 [PMID: 29136241 DOI: 10.1093/nar/gkx1064]
19 **Bruschi M**, Granata S, Candiano G, Petretto A, Bartolucci M, Ghiggeri GM, Stallone G, Zaza G. Proteomic analysis of urinary extracellular vesicles of kidney transplant recipients with BKV viruria and viremia: A pilot study. *Front Med (Lausanne)* 2022; **9**: 1028085 [PMID: 36465937 DOI: 10.3389/fmed.2022.1028085]
20 **Başak Oktay S**, Akbaş SH, Yilmaz VT, Özen Küçükçetin İ, Toru HS, Yücel SG. Association Between Graft Function and Urine CXCL10 and Acylcarnitines Levels in Kidney Transplant Recipients. *Lab Med* 2022; **53**: 78-84 [PMID: 34388247 DOI: 10.1093/labmed/lmab049]
21 **Sigdel TK**, Salomonis N, Nicora CD, Ryu S, He J, Dinh V, Orton DJ, Moore RJ, Hsieh SC, Dai H, Thien-Vu M, Xiao W, Smith RD, Qian WJ, Camp DG 2nd, Sarwal MM. The identification of novel potential injury mechanisms and candidate biomarkers in renal allograft rejection by quantitative proteomics. *Mol Cell Proteomics* 2014; **13**: 621-631 [PMID: 24335474 DOI: 10.1074/mcp.M113.030577]
22 **Navarrete M**, Korkmaz B, Guarino C, Lesner A, Lao Y, Ho J, Nickerson P, Wilkins JA. Activity-based protein profiling guided identification of urine proteinase 3 activity in subclinical rejection after renal transplantation. *Clin Proteomics* 2020; **17**: 23 [PMID: 32549867 DOI: 10.1186/s12014-020-09284-9]

23 **Ho J**, Rush DN, Krokhin O, Antonovici M, Gao A, Bestland J, Wiebe C, Hiebert B, Rigatto C, Gibson IW, Wilkins JA, Nickerson PW. Elevated Urinary Matrix Metalloproteinase-7 Detects Underlying Renal Allograft Inflammation and Injury. *Transplantation* 2016; **100**: 648-654 [PMID: 26906940 DOI: 10.1097/TP.0000000000000867]

24 **Carreras-Planella L**, Cucchiari D, Cañas L, Juega J, Franquesa M, Bonet J, Revuelta I, Diekmann F, Taco O, Lauzurica R, Borràs FE. Urinary vitronectin identifies patients with high levels of fibrosis in kidney grafts. *J Nephrol* 2021; **34**: 861-874 [PMID: 33275196 DOI: 10.1007/s40620-020-00886-y]

25 **Al-Nedawi K**, Haas-Neill S, Gangji A, Ribic CM, Kapoor A, Margetts P. Circulating microvesicle protein is associated with renal transplant outcome. *Transpl Immunol* 2019; **55**: 101210 [PMID: 31226423 DOI: 10.1016/j.trim.2019.06.002]

26 **Jeon HJ**, Shin DH, Oh J, Kee YK, Park JY, Ko K, Lee S. Urinary Retinol-Binding Protein 4 is Associated With Renal Function and Rapid Renal Function Decline in Kidney Transplant Recipients. *Transplant Proc* 2022; **54**: 362-366 [PMID: 35094884 DOI: 10.1016/j.transproceed.2021.10.028]

27 **Hirt-Minkowski P**, Rush DN, Gao A, Hopfer H, Wiebe C, Nickerson PW, Schaub S, Ho J. Six-Month Urinary CCL2 and CXCL10 Levels Predict Long-term Renal Allograft Outcome. *Transplantation* 2016; **100**: 1988-1996 [PMID: 27548845 DOI: 10.1097/TP.0000000000001304]

28 **Hirt-Minkowski P**, Ho J, Gao A, Amico P, Koller MT, Hopfer H, Rush DN, Nickerson PW, Schaub S. Prediction of Long-term Renal Allograft Outcome By Early Urinary CXCL10 Chemokine Levels. *Transplant Direct* 2015; **1**: e31 [PMID: 27500231 DOI: 10.1097/TXD.0000000000000537]

29 **Mockler C**, Sharma A, Gibson IW, Gao A, Wong A, Ho J, Blydt-Hansen TD. The prognostic value of urinary chemokines at 6 months after pediatric kidney transplantation. *Pediatr Transplant* 2018; **22**: e13205 [PMID: 29733487 DOI: 10.1111/petr.13205]

30 **Welberry Smith MP**, Zougman A, Cairns DA, Wilson M, Wind T, Wood SL, Thompson D, Messenger MP, Mooney A, Selby PJ, Lewington AJ, Banks RE. Serum aminoacylase-1 is a novel biomarker with potential prognostic utility for long-term outcome in patients with delayed graft function following renal transplantation. *Kidney Int* 2013; **84**: 1214-1225 [PMID: 23739232 DOI: 10.1038/ki.2013.200]

31 **Bank JR**, Ruhaak R, Soonawala D, Mayboroda O, Romijn FP, van Kooten C, Cobbaert CM, de Fijter JW. Urinary TIMP-2 Predicts the Presence and Duration of Delayed Graft Function in Donation After Circulatory Death Kidney Transplant Recipients. *Transplantation* 2019; **103**: 1014-1023 [PMID: 30300282 DOI: 10.1097/TP.0000000000002472]

32 **Williams KR**, Colangelo CM, Hou L, Chung L, Belcher JM, Abbott T, Hall IE, Zhao H, Cantley LG, Parikh CR. Use of a Targeted Urine Proteome Assay (TUPA) to identify protein biomarkers of delayed recovery after kidney transplant. *Proteomics Clin Appl* 2017; **11**: 10.1002/prca.201600132 [PMID: 28261998 DOI: 10.1002/prca.201600132]

33 **Thorne AM**, Huang H, O'Brien DP, Eijken M, Krogstrup NV, Norregaard R, Møller B, Ploeg RJ, Jespersen B, Kessler BM. Subclinical effects of remote ischaemic conditioning in human kidney transplants revealed by quantitative proteomics. *Clin Proteomics* 2020; **17**: 39 [PMID: 33292164 DOI: 10.1186/s12014-020-09301-x]

34 **Schmidt IM**, Hall IE, Kale S, Lee S, He CH, Lee Y, Chupp GL, Moeckel GW, Lee CG, Elias JA, Parikh CR, Cantley LG. Chitinase-like protein Brp-39/YKL-40 modulates the renal response to ischemic injury and predicts delayed allograft function. *J Am Soc Nephrol* 2013; **24**: 309-319 [PMID: 23291472 DOI: 10.1681/ASN.2012060579]

35 **Buscher K**, Rixen R, Schütz P, Hüchtmann B, Van Marck V, Heitplatz B, Jehn U, Braun DA, Gabriëls G, Pavenstädt H, Reuter S. Plasma protein signatures reflect systemic immunity and allograft function in kidney transplantation. *Transl Res* 2023; **262**: 35-43 [PMID: 37507006 DOI: 10.1016/j.trsl.2023.07.007]

36 **Braun F**, Rinschen M, Buchner D, Bohl K, Plagmann I, Bachurski D, Richard Späth M, Antczak P, Göbel H, Klein C, Lackmann JW, Kretz O, Puelles VG, Wahba R, Hallek M, Schermer B, Benzing T, Huber TB, Beyer A, Stippel D, Kurschat CE, Müller RU. The proteomic landscape of small urinary extracellular vesicles during kidney transplantation. *J Extracell Vesicles* 2020; **10**: e12026 [PMID: 33304478 DOI: 10.1002/jev2.12026]

37 **Kajawo S**, Ekrikpo U, Moloi MW, Noubiap JJ, Osman MA, Okpechi-Samuel US, Kengne AP, Bello AK, Okpechi IG. A Systematic Review of Complications Associated With Percutaneous Native Kidney Biopsies in Adults in Low- and Middle-Income Countries. *Kidney Int Rep* 2021; **6**: 78-90 [PMID: 33426387 DOI: 10.1016/j.ekir.2020.10.019]

38 **Etxebarria A**, Díez-martín E, Astigarraga E, Barreda-gómez G. Role of the Immune System in Renal Transplantation, Types of Response, Technical Approaches and Current Challenges. *Immuno* 2022; **2**: 548-570 [DOI: 10.3390/immuno2040035]

39 **Li Q**, Lan P. Activation of immune signals during organ transplantation. *Signal Transduct Target Ther* 2023; **8**: 110 [PMID: 36906586 DOI: 10.1038/s41392-023-01377-9]

40 **Seifert ME**, Agarwal G, Bernard M, Kasik E, Raza SS, Fatima H, Gaston RS, Hauptfeld-Dolejsek V, Julian BA, Kew CE, Kumar V, Mehta S, Ong S, Rosenblum F, Towns G, Mannon RB. Impact of Subclinical Borderline Inflammation on Kidney Transplant Outcomes. *Transplant Direct* 2021; **7**: e663 [PMID: 33511268 DOI: 10.1097/TXD.0000000000001119]

41 **Szumilas K**, Wilk A, Wiśniewski P, Gimpel A, Dziedziejko V, Kipp M, Pawlik A. Current Status Regarding Immunosuppressive Treatment in Patients after Renal Transplantation. *Int J Mol Sci* 2023; **24**: 10301 [PMID: 37373448 DOI: 10.3390/ijms241210301]

42 **Salvadori M**, Tsalouchos A. Innovative immunosuppression in kidney transplantation: A challenge for unmet needs. *World J Transplant* 2022; **12**: 27-41 [PMID: 35433332 DOI: 10.5500/wjt.v12.i3.27]

43 **Granata S**, La Russa D, Stallone G, Perri A, Zaza G. Inflammasome pathway in kidney transplantation. *Front Med (Lausanne)* 2023; **10**: 1303110 [PMID: 38020086 DOI: 10.3389/fmed.2023.1303110]

44 **Cavalli G**, Colafrancesco S, Emmi G, Imazio M, Lopalco G, Maggio MC, Sota J, Dinarello CA. Interleukin 1α: a comprehensive review on the role of IL-1α in the pathogenesis and treatment of autoimmune and inflammatory diseases. *Autoimmun Rev* 2021; **20**: 102763 [PMID: 33482337 DOI: 10.1016/j.autrev.2021.102763]

45 **Bachove I**, Chang C. Anakinra and related drugs targeting interleukin-1 in the treatment of cryopyrin-associated periodic syndromes. *Open Access Rheumatol* 2014; **6**: 15-25 [PMID: 27790031 DOI: 10.2147/OARRR.S46017]

46 **Vanhove T**, Goldschmeding R, Kuypers D. Kidney Fibrosis: Origins and Interventions. *Transplantation* 2017; **101**: 713-726 [PMID: 27941433 DOI: 10.1097/TP.0000000000001608]

47 **Cheng O**, Thuillier R, Sampson E, Schultz G, Ruiz P, Zhang X, Yuen PS, Mannon RB. Connective tissue growth factor is a biomarker and mediator of kidney allograft fibrosis. *Am J Transplant* 2006; **6**: 2292-2306 [PMID: 16889607 DOI: 10.1111/j.1600-6143.2006.01493.x]

48 **Saritas T**, Kramann R. Kidney Allograft Fibrosis: Diagnostic and Therapeutic Strategies. *Transplantation* 2021; **105**: e114-e130 [PMID: 33982910 DOI: 10.1097/TP.0000000000003678]

49 **Wekerle T**, Segev D, Lechler R, Oberbauer R. Strategies for long-term preservation of kidney graft function. *Lancet* 2017; **389**: 2152-2162 [PMID: 28561006 DOI: 10.1016/S0140-6736(17)31283-7]

50 **Kwiatkowska E**, Domanski L, Bober J, Safranow K, Romanowski M, Pawlik A, Kwiatkowski S, Ciechanowski K. Urinary Metalloproteinases-9 and -2 and Their Inhibitors TIMP-1 and TIMP-2 are Markers of Early and Long-Term Graft Function After Renal Transplantation. *Kidney Blood Press Res* 2016; **41**: 288-297 [PMID: 27160811 DOI: 10.1159/000443431]

51 **Akad Dincer S**, Sahin FI, Terzi YK, Gulleroglu K, Baskin E, Haberal M. Impact of Matrix Metalloproteinases 2 and 9 and Tissue Inhibitor of Metalloproteinase 2 Gene Polymorphisms on Allograft Rejection in Pediatric Renal Transplant Recipients. *Exp Clin Transplant* 2023; **21**: 333-337 [PMID: 32799785 DOI: 10.6002/ect.2020.0036]

52 **Ishimoto I**, Sohara E, Ito E, Okado T, Rai T, Uchida S. Fibronectin glomerulopathy. *Clin Kidney J* 2013; **6**: 513-515 [PMID: 26064516 DOI: 10.1093/ckj/sft097]

53 **Gurung R**, Li T. Renal Amyloidosis: Presentation, Diagnosis, and Management. *Am J Med* 2022; **135** Suppl 1: S38-S43 [PMID: 35085515 DOI: 10.1016/j.amjmed.2022.01.003]

54 **Sarihan I**, Caliskan Y, Mirioglu S, Ozluk Y, Senates B, Seyahi N, Basturk T, Yildiz A, Kilicaslan I, Sever MS. Amyloid A Amyloidosis After Renal Transplantation: An Important Cause of Mortality. *Transplantation* 2020; **104**: 1703-1711 [PMID: 32732850 DOI: 10.1097/TP.0000000000003043]

55 **Anand SK**, Sanchorawala V, Verma A. Systemic Amyloidosis and Kidney Transplantation: An Update. *Semin Nephrol* 2024; **44**: 151496 [PMID: 38490903 DOI: 10.1016/j.semnephrol.2024.151496]

56 **Huang Y**, Mahley RW. Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. *Neurobiol Dis* 2014; **72** Pt A: 3-12 [PMID: 25173806 DOI: 10.1016/j.nbd.2014.08.025]

57 **Hsu CC**, Kao WH, Coresh J, Pankow JS, Marsh-Manzi J, Boerwinkle E, Bray MS. Apolipoprotein E and progression of chronic kidney disease. *JAMA* 2005; **293**: 2892-2899 [PMID: 15956634 DOI: 10.1001/jama.293.23.2892]

58 **Cofán F**, Cofan M, Rosich E, Campos B, Casals E, Zambon D, Ros E, Oppenheimer F, Campistol JM. Effect of apolipoprotein E polymorphism on renal transplantation. *Transplant Proc* 2007; **39**: 2217-2218 [PMID: 17889142 DOI: 10.1016/j.transproceed.2007.06.011]

59 **Hernández D**, Salido E, Linares J, Cobo MA, Barrios Y, Rufino M, García S, Marín B, Lorenzo V, González-Posada JM, González-Rinne A, Torres A. Role of apolipoprotein E epsilon 4 allele on chronic allograft nephropathy after renal transplantation. *Transplant Proc* 2004; **36**: 2982-2984 [PMID: 15686675 DOI: 10.1016/j.transproceed.2004.10.038]

60 **Abecassis M**, Bartlett ST, Collins AJ, Davis CL, Delmonico FL, Friedewald JJ, Hays R, Howard A, Jones E, Leichtman AB, Merion RM, Metzger RA, Pradel F, Schweitzer EJ, Velez RL, Gaston RS. Kidney transplantation as primary therapy for end-stage renal disease: a National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQITM) conference. *Clin J Am Soc Nephrol* 2008; **3**: 471-480 [PMID: 18256371 DOI: 10.2215/CJN.05021107]

61 **Granata S**, Benedetti C, Gambaro G, Zaza G. Kidney allograft fibrosis: what we learned from latest translational research studies. *J Nephrol* 2020; **33**: 1201-1211 [PMID: 32193834 DOI: 10.1007/s40620-020-00726-z]

62 **Oliveira da Fonseca E**, Jittirat A, Birdwell KA, Fogo AB. Myoglobin cast nephropathy in a kidney transplant patient with normal creatine kinase. *Am J Kidney Dis* 2015; **65**: 628-631 [PMID: 25441432 DOI: 10.1053/j.ajkd.2014.07.029]

63 **Watanabe H**, Fujimura R, Hiramoto Y, Murata R, Nishida K, Bi J, Imafuku T, Komori H, Maeda H, Mukunoki A, Takeo T, Nakagata N, Tanaka M, Matsushita K, Fukagawa M, Maruyama T. An acute phase protein α(1)-acid glycoprotein mitigates AKI and its progression to CKD through its anti-inflammatory action. *Sci Rep* 2021; **11**: 7953 [PMID: 33846468 DOI: 10.1038/s41598-021-87217-8]

64 **Goek ON**, Köttgen A, Hoogeveen RC, Ballantyne CM, Coresh J, Astor BC. Association of apolipoprotein A1 and B with kidney function and chronic kidney disease in two multiethnic population samples. *Nephrol Dial Transplant* 2012; **27**: 2839-2847 [PMID: 22287661 DOI: 10.1093/ndt/gfr795]

65 **Lee EY**, Lee ZH, Song YW. CXCL10 and autoimmune diseases. *Autoimmun Rev* 2009; **8**: 379-383 [PMID: 19105984 DOI: 10.1016/j.autrev.2008.12.002]

66 **Gao J**, Wu L, Wang S, Chen X. Role of Chemokine (C-X-C Motif) Ligand 10 (CXCL10) in Renal Diseases. *Mediators Inflamm* 2020; **2020**: 6194864 [PMID: 32089645 DOI: 10.1155/2020/6194864]

67 **Wenk D**, Zuo C, Kislinger T, Sepiashvili L. Recent developments in mass-spectrometry-based targeted proteomics of clinical cancer biomarkers. *Clin Proteomics* 2024; **21**: 6 [PMID: 38287260 DOI: 10.1186/s12014-024-09452-1]

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SYSTEMATIC REVIEWS

Literature study on traditional Chinese medicine syndromes after renal transplantation

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Abstract

BACKGROUND

Kidney transplantation is the most effective means to treat patients with renal failure, but its postoperative problems such as rejection reactions, immunosuppressant poisoning, chronic transplant kidney nephropathy, *etc.* still have not been effectively solved. This study searched for literature on traditional Chinese medicine (TCM) syndromes after kidney transplantation in China, conducted statistical analysis of the results, and sought to identify the underlying patterns.

AIM

To understand the TCM syndromes after renal transplantation and associated rules and provide a theoretical basis for further clinical research.

METHODS

The literature pertaining to TCM syndromes in renal transplantation, published in the China National Knowledge Infrastructure, Wanfang database, and WIP database from 1970 to 2021, was meticulously searched and comprehensively and statistically analyzed.

RESULTS

Following the established inclusion and exclusion criteria, 13 studies were selected for analysis. Post-renal transplantation, no significant discrepancy was noted among the groups based on the location of TCM viscera. However, when categorized according to TCM pathogenic factors, the groups with spleen and kidney yang deficiency, as well as liver and kidney yin deficiency, exhibited a statistically significant difference in the frequency.

CONCLUSION

Currently, the research on TCM syndromes pertaining to renal transplantation is

in its nascent phase. It is imperative to conduct a multicentric, large-scale survey of TCM syndromes subsequent to renal transplantation in the ensuing years.

Key Words: Kidney transplantation; Syndrome; Literature analysis; Traditional Chinese medicine; Systematic review

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Core Tip: At present, there are no reports on clinical research on the traditional Chinese medicine (TCM) syndromes and constitution of kidney transplant patients with multicenter and diverse approaches. This study searched for literature on TCM syndromes after kidney transplantation in China, conducted statistical analysis of the results, and sought to identify the underlying patterns.

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INTRODUCTION

Although kidney transplantation remains the most efficacious modality for the management of renal failure; several challenges, such as graft rejection, immunosuppressant toxicity, and chronic allograft nephropathy, persist as unresolved postoperative issues. Concurrently, amidst ongoing enhancements in the pertinent post-transplantation renal technologies, several medical professionals within China have started investigating the applications of traditional Chinese medicine (TCM) in the post-transplantation renal context. This involves the assessment of TCM symptomatology and constitutional types, which are fundamental to the therapeutic management of diseases. Currently, clinical research reports on TCM syndromes and constitutions of patients undergoing kidney transplantation, involving multicenter collaboration and employing a variety of methodologies, are scarce. In the present study, we comprehensively reviewed the literature on TCM syndromes post-kidney transplantation within China, followed by a statistical analysis of the findings, with the objective of elucidating the intrinsic patterns.

MATERIALS AND METHODS

Inclusion criteria

Relevant reports on TCM syndromes post-kidney transplantation were retrieved from esteemed databases such as the China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform, and Wipu Information. Next, we meticulously analyzed the statistical findings. This rigorous screening procedure was designed to identify and select the literature aligning with the specific research criteria pertaining to TCM syndrome categorization, clinical syndrome differentiation, and therapeutic modalities subsequent to kidney transplantation.

Exclusion criteria

(1) The basic content of the article is repetitive; (2) Articles with identical or partially identical data from the same author organization; (3) Articles published from different perspectives by the authors applying the same data; (4) Articles with serious data bias; (5) Articles not in line with the actual clinical situation; and (6) Articles without specific evidence of phenotyping.

Consultation strategy

In the initial phase, a fuzzy search algorithm was applied to comprehensively search the CNKI, Wanfang Data Knowledge Service Platform, and Wipu Information using the term "kidney transplantation". The literature spanning from 1970 to 2021 was meticulously examined, yielding 109 articles through an "OR" Boolean search, including full texts containing the keywords "identification", "evidence", or "evidence type" for a subsequent secondary search. Following this, we thoroughly analyzed whether the retrieved literature complied to the inclusion criteria. Subsequently, the inclusion and exclusion criteria were applied to comprehensively review the entire text. The literature and findings were meticulously examined, and expert consultations were sought, resulting in the identification of 13 articles that conformed to the specified criteria.

Statistical analysis

All enrolled documents were systematically categorized according to their TCM syndrome diagnosis and subsequently

entered into an Excel spreadsheet for data compilation. The resulting data were meticulously analyzed utilizing *t*-tests and one-way analysis of variance (ANOVA) *via* Statistical Package for the Social Sciences 21.0 software, yielding statistically significant differences where *P*-values were found to be less than 0.05.

RESULTS

Our statistical data indicated that, out of a cohort of 2681 patients who underwent renal transplantation, in conformity with the prevalence of TCM symptomatology, the four predominant symptom categories, arranged in decreasing order of frequency, were spleen and kidney yang deficiency (constituting 27.27%), liver and kidney yin deficiency (comprising 20.32%), qi and yin deficiency (accounting for 18.87%), and spleen and kidney qi deficiency (representing 18.37%). These four categories were the most frequently observed, together constituting 84.83% of all recorded symptoms. The least common symptom was that of kidney-yin deficiency (Tables 1, 2, 3, 4 and 5).

DISCUSSION

In the 1970s, Chinese researchers initiated the integration of TCM into the realm of kidney transplantation. Numerous commendable advancements have been achieved in the clinical deployment of TCM subsequent to kidney transplantation procedures[1]. Nevertheless, at present, all investigations are being conducted within a solitary medical center, characterized by divergent criteria for syndrome differentiation and therapeutic efficacy assessment across several departments, compounded by a significant degree of subjectivity amongst the medical practitioners, consequently exerting a constrained impact on the outcomes of the research. We primarily investigated the symptoms of TCM following kidney transplantation to enhance the precision of diagnostic differentiation and therapeutic interventions *via* comprehensive summarization, thereby augmenting clinical efficacy. "Treatment predicated on syndrome differentiation" constitutes the core and quintessence of TCM[2,3]. It is crucial to select an optimal statistical methodology to mitigate subjective biases inherent in the statistical data processing. This is essential for deriving clinically pertinent TCM evidence from patient data and literature sources[4]. Diverse pathologies following renal transplantation lack specific nomenclature within the domain of TCM, necessitating their categorization based on the individual constitutional states of patients. Uremia, inherently, represents a deficiency of the viscerals, whereas the surgical intervention further traumatically affects the venous and collateral circulation, compromising the qi and blood, thereby adding complexity to the classification[5]. Subsequent to renal transplantation, several complications including graft rejection, immunosuppressive medication toxicity, and chronic allographic nephropathy, among others, present with congruent clinical manifestations. The therapeutic approach of TCMs, characterized by dialectical treatment, obviates the need for invasive methodologies such as renal biopsy involved in conventional Western medicine[6-8]. Consequently, the profound importance of investigating TCM syndromes post-kidney transplantation cannot be overstated, and it is imperative to collate and analyze the literature to facilitate taxonomic inquiry.

After a renal allograft transplantation, the graft initiates its functional activity, thereby augmenting urinary excretion, facilitating the elimination of metabolic by-products, rectifying acid–base discrepancies, and restoring homeostasis of electrolytes, and normalizing the renal function. However, these functions can only eliminate the evil qi and cannot support the righteousness. Damage to the righteousness directly affects the spleen and kidney function of transportation, causing spleen and kidney yang deficiency and reduced transportation[9].

This is also consistent with the results of our statistics. The defense of the recipient's "positive qi" against the donor's "allogeneic kidney" after kidney transplantation is a manifestation of the confrontation between good and evil[10]. An equilibrium between the yin and yang energies within the internal organs is crucial. An analysis of our statistical findings revealed that the post-kidney transplantation categorization of TCM's organ elements did not yield statistically significant differences when subjected to one-way ANOVA, irrespective of the patient cohort. Consequently, the negligible discrepancy between the categorization based on internal organ elements and disease locations, as well as the non-substantial differentiation amongst patient groups, could be attributed to the limited data available for such grouping criteria. Moreover, an analysis of the aggregation of pathogenic elements within the framework of TCM revealed a statistically significant disparity, with the liver and kidney yin deficiency cohort demonstrating a markedly higher prevalence of patients compared to the kidney yin deficiency cohort alone. Similarly, the spleen and kidney yang deficiency cohort exhibited a considerable increase in patient numbers in relation to the kidney yang deficiency cohort. This connotes that yin insufficiency is the primary etiology of liver-kidney yin insufficiency post-kidney transplantation, whereas yang insufficiency is the predominant cause of spleen–kidney yang insufficiency. Consequently, a therapeutic approach focusing on consolidating the constitutional integrity and eradicating exogenous pathogens subsequent to kidney transplantation is warranted. In the context of a unidirectional ANOVA, the statistical analysis revealed no significant disparities among the three groups. Although deficiency syndrome is the primary type after kidney transplantation, no difference existed in different subtypes.

The differential characteristics between Western medicine and TCM are marked by the latter's non-reliance on instrumental measurement outcomes, and its nature is not one of absolute dichotomy. Within the domain of complexity science, the human body is perceived as a self-organizing, self-regulating, self-stabilizing, and self-adaptive open system embodying complexity[11,12]. It is imperative to acknowledge the multifaceted nature of outcomes to categorize the evidence in TCM. Within the realm of contemporary scientific inquiry, it is common to encounter intricate amalgamations of different constituent elements, mirroring the inherent complexity and variability inherent in the onset, progression,

Table 1 Statistical table of traditional Chinese medicine syndrome classification

Group	Spleen and kidney qi deficiency	Spleen qi deficiency	Spleen kidney yang deficiency	Kidney qi deficiency	kidney yin deficiency	Qi-yin deficiency	kidney yang deficiency	Yin yang imbalance	Liver-kidney yin deficiency	Qi stagnation and blood stasis	Combined with dampness and heat
1	13	9	8	6	7	5	3	10	170	6	8
2	2	5	4	3	2	1	1	1	17	17	8
3	99	33	97	63	6	82	63	1	103	10	9
4	35	4	285	14		102			170		
5	27	11	83	21		7			12		
6	61	33	97	26		117			21		
7	99		28			82			6		
8	18		26			27			21		
9	20		28			2			12		
10	60		25			14					
11	4		50			27					
12	18					21					
13	14					3					
Mean	34.35	15.83	66.45	22.16	5	35.28	22.33	4	59.11	11	8.33
SD	32.80	13.54	79.87	21.81	2.64	41.42	35.23	5.19	69.33	5.56	0.57
Frequency	481	95	731	133	15	494	67	12	532	33	25

Table 2 Grouping according to the elements of traditional Chinese medicine visceral disease location

Group	Kidney	Spleen and kidney	Other
1	Kidney qi deficiency	Spleen and kidney qi deficiency	Deficiency of both qi and yin
2	Kidney yin deficiency	Spleen-kidney yang deficiency	Qi stagnation and blood stasis
3	Kidney yang deficiency		Combined with dampness and heat
F value/*t* value	1.5 (*F*)	-1.236 (*t*)	0.8 (*F*)
P value	0.269	0.243	0.466

Table 3 Grouping by traditional Chinese medicine pathogenic factors

Group	Yin deficiency	Yang deficiency	Deficiency of vital energy
1	Kidney yin deficiency	Spleen-kidney yang deficiency	Spleen-kidney qi deficiency
2	Liver-kidney yin deficiency	kidney-yang deficiency	Spleen qi deficiency
3			Kidney qi deficiency
4			stagnation of qi and blood
F value/*t* value	-2.541 (*t*)	-2.323 (*t*)	0.799 (*F*)
P value	0.031	0.045	0.507

and transformation of diseases. Similarly, prospective investigations into the evidence base of Chinese medicine post-renal transplantation must be attuned to this level of sophistication.

Table 4 Single factor analysis of variance based on the location of traditional Chinese medicine visceral diseases

Group	Square sum	DOF	MS	*F* value	Statistical significance
Interblock	16473.599	4	4118.400	1.790	0.141
Intragroup	154109.679	67	2300.144		
Sum	170583.278	71			

Table 5 A single factor analysis of variance based on the pathogenic factors of traditional Chinese medicine

Group	Square sum	DOF	MS	*F* value	Statistical significance
Interblock	10291.829	3	3430.610	1.413	0.247
Intragroup	157860.808	65	2428.628		
Sum	168152.638	68			

CONCLUSION

We conducted a literature review of TCM syndromes after renal transplantation. The results obtained outlined their syndromic characteristics; however, due to the limitations of the sample size and the level of research, the research criteria of the selected literature varied, and the conclusions of the study are debatable. There exists a lack of dynamic observation and analysis indexes within a fixed time, making it difficult to meet the reality of Chinese medicine clinical diagnosis and treatment. The diagnostic and inclusion criteria of Chinese medicine symptoms after renal transplantation cannot be completely unified, and the gold standard of postoperative pathological typing has not been combined. Therefore, it is not possible to describe the Chinese medicine symptom typing following renal transplantation in an all-round manner. Large samples and multi-center clinical data are required to meet the clinical needs of Chinese medicine and to provide objective basis and reference value for the clinical diagnosis and treatment of Chinese medicine in renal transplantation.

FOOTNOTES

Author contributions: Guo YP was responsible for drafting of manuscript; Bao LX and Wen Q were responsible for data acquisition; Wang YY and Hang G were responsible for data analysis; Chen B was responsible for study concept, design and critical revision of the manuscript; all authors have read and approved the final manuscript.

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REFERENCES

1 **Liu D**, Tang S, Gan L, Cui W. Renal-Protective Effects and Potential Mechanisms of Traditional Chinese Medicine after Ischemia-Reperfusion Injury. *Evid Based Complement Alternat Med* 2021; **2021**: 5579327 [PMID: 33680054 DOI: 10.1155/2021/5579327]

2 **Wang X**, Pang F, Du XG. Analysis of Traditional Chinese Medicine Symptoms in Children with Spastic Cerebral Palsy, a Protocol for Data Mining. *J Multidiscip Healthc* 2023; **16**: 3143-3149 [PMID: 37905184 DOI: 10.2147/JMDH.S426969]

3 **Lu A**, Jiang M, Zhang C, Chan K. An integrative approach of linking traditional Chinese medicine pattern classification and biomedicine diagnosis. *J Ethnopharmacol* 2012; **141**: 549-556 [PMID: 21896324 DOI: 10.1016/j.jep.2011.08.045]

4 **Liu ML**, Zhang XY, Ding L, Pan SM, Wu DY, Li XY. [Application and progress of data mining in study of compatibility law of traditional Chinese medicine]. *Zhongguo Zhongyao Zazhi* 2021; **46**: 5233-5239 [PMID: 34738424 DOI: 10.19540/j.cnki.cjcmm.20210303.501]

5 **Sun YY**, Li ZJ, Wang JD. [Clinical observation on treatment of 18 patients with pulmonary infection after renal transplantation by integrative traditional Chinese and Western medicine]. *Zhongguo Zhongxiyi Jiehe Zazhi* 2005; **25**: 797-800 [PMID: 16248241]

6 **Wang X**, Zhang X, Li J, Hu B, Zhang J, Zhang W, Weng W, Li Q. Analysis of prescription medication rules of traditional Chinese medicine for bradyarrhythmia treatment based on data mining. *Medicine (Baltimore)* 2022; **101**: e31436 [PMID: 36343087 DOI: 10.1097/MD.0000000000031436]

7 **Morozumi K**, Takeda A, Otsuka Y, Horike K, Gotoh N, Narumi S, Watarai Y, Kobayashi T. Reviewing the pathogenesis of antibody-mediated rejection and renal graft pathology after kidney transplantation. *Nephrology (Carlton)* 2016; **21** Suppl 1: 4-8 [PMID: 26971899 DOI: 10.1111/nep.12777]

8 **Xin Z**, Wu L, Zhou J, Zhuang J, Peng W, Song T, Lin T, Lu X, Ying B. Analysis of Factors Influencing Kidney Function of Recipients After Renal Transplantation in Southwestern China: A Retrospective Study. *Front Med (Lausanne)* 2020; **7**: 519582 [PMID: 33282882 DOI: 10.3389/fmed.2020.519582]

9 **Jin ZD**, Chen JH. [Progress on the research of prevention and treatment of renal transplantation rejection by integrative Chinese and Western medicine]. *Zhongguo Zhongxiyi Jiehe Zazhi* 2004; **24**: 764-766 [PMID: 15366610]

10 **Parviainen T**, Lyyra P, Nokia MS. Cardiorespiratory rhythms, brain oscillatory activity and cognition: review of evidence and proposal for significance. *Neurosci Biobehav Rev* 2022; **142**: 104908 [PMID: 36220367 DOI: 10.1016/j.neubiorev.2022.104908]

11 **Kuang DY**. [A discussion of the methodological approaches to research in traditional Chinese medicine--multi-branch of science, multi-approach, multi-parameter, synchronic examination and correlation analysis]. *Zhongguo Zhongxiyi Jiehe Zazhi* 1982; **2**: 115-117 [PMID: 6222817]

12 **Li Z**, Xu C. The fundamental theory of traditional Chinese medicine and the consideration in its research strategy. *Front Med* 2011; **5**: 208-211 [PMID: 21695627 DOI: 10.1007/s11684-011-0126-x]

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SYSTEMATIC REVIEWS

Efficacy of antimicrobials in preventing resistance in solid organ transplant recipients: A systematic review of clinical trials

Carlos M Ardila, Pradeep K Yadalam, Jaime Ramírez-Arbelaez

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Abstract

BACKGROUND

In the absence of effective antimicrobials, transplant surgery is not viable, and antirejection immunosuppressants cannot be administered, as resistant infections compromise the life-saving goal of organ transplantation.

AIM

To evaluate the efficacy of antimicrobials in preventing resistance in solid organ transplant recipients.

METHODS

A systematic review was conducted using a search methodology consistent with the preferred reporting items for systematic reviews and meta-analyses. This review included randomized clinical trials that evaluated the efficacy of antimicrobial agents (prophylactic or therapeutic) aimed at preventing antimicrobial resistance. The search strategy involved analyzing multiple databases, including PubMed/MEDLINE, Web of Science, Embase, Scopus, and SciELO, as well as examining gray literature sources on Google Scholar. A comprehensive electronic database search was conducted from the databases' inception until May 2024, with no language restrictions.

RESULTS

After the final phase of the eligibility assessment, this systematic review ultimate-ly included 7 articles. A total of 2318 patients were studied. The most studied microorganisms were cytomegalovirus, although vancomycin-resistant enterococci, *Clostridioides difficile*, and multidrug-resistant *Enterobacterales* were also analyzed. The antimicrobials used in the interventions were mainly maribavir, valganciclovir, gancic-lovir, and colistin-neomycin. Of concern, all clinical trials showed significant proportions of resistant microorga-nisms after the interventions, with no statistically significant differences between the groups (mean resistance 13.47% *vs* 14.39%), except for two studies that demonstrated greater efficacy of maribavir and valganciclovir (mean resistance 22.2% *vs* 41.1% in the control group; $P < 0.05$). The total reported deaths in three clinical trials were 75, and there were 24 graft rejections in two studies.

CONCLUSION

All clinical trials reported significant proportions of antimicrobial-resistant microorganisms following interventions. More high-quality randomized clinical trials are needed to corroborate these results.

Key Words: Antimicrobial resistance; Antimicrobials; Antivirals; Solid organ transplant recipients; Infections; Microorganisms; Cytomegalovirus

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Core Tip: This systematic review evaluates the efficacy of antimicrobial agents in preventing resistance among solid organ transplant recipients. Despite varying results across studies, maribavir and valganciclovir showed promise in reducing resistance rates compared to controls. However, overall, significant proportions of antimicrobial-resistant microorganisms were observed post-intervention, highlighting the urgent need for further high-quality randomized clinical trials to validate these findings and improve outcomes in organ transplantation.

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INTRODUCTION

Antimicrobial resistance is a worldwide health issue that requires urgent, collaborative efforts across multiple sectors, countries, and disciplines[1,2]. Antimicrobial resistance disproportionately affects the most at-risk groups, including immunocompromised individuals and solid organ transplant recipients (SOTR)[2]. Even with improvements in surgical procedures, infection control, and preventive measures, microbial infections persist as the primary cause of infections following solid organ transplantation[3]. In the absence of effective antimicrobials, transplant surgery is not viable, and antirejection immunosuppressants cannot be administered, as resistant infections compromise the life-saving goal of organ transplantation[1-3]. Additionally, the incidence of bacterial infections caused by vancomycin-resistant enterococci, as well as multidrug-resistant and extensively drug-resistant *Enterobacteriaceae* and non-fermenting gram-negative bacteria, has steadily risen over the past several decades[3,4]. Antibiotic abuse is also responsible for the rising incidence of *Clostridioides difficile* (*C. difficile*) infection in SOTR, contributing to more frequent recurrences, graft loss, and mortality [3,5]. The increasing occurrence of *Candida* species intolerant to fluconazole and *Aspergillus fumigatus* resistant to azoles is worrisome[6]. Additionally, the emergence of ganciclovir-resistant cytomegalovirus (CMV) following solid organ transplantation is a growing concern[3,7].

To mitigate infection risks following solid organ transplantation, appropriate prophylactic medications should be administered both immediately before and after the surgery[3]. Moreover, measures such as strict hand hygiene, contact isolation, and selective bowel decontamination are essential to limit the transmission of multidrug-resistant and extensively drug-resistant bacterial strains. Likewise, implementing a comprehensive antimicrobial stewardship policy is crucial[2,3]. This policy should optimize the selection of antimicrobials, their timing, dosage, duration, and route of administration to effectively reduce the occurrence of resistant and extensively drug-resistant bacterial strains and minimize adverse antimicrobial effects[3,8,9].

Evaluating clinical trials dedicated to the management of antimicrobials in preventing resistance among SOTR is of paramount importance. These trials provide critical insights into the efficacy of various antimicrobial regimens and strategies in real-world settings, helping to identify the most effective practices for reducing the incidence of resistant infections. By rigorously assessing different antimicrobial protocols, clinical trials contribute to the optimization of treatment guidelines, ensuring that SOTR receive the best possible care. Furthermore, these trials can uncover potential adverse effects and resistance patterns associated with specific antimicrobials, guiding clinicians in making informed decisions that balance efficacy and safety.

The relevance of a systematic review in this context cannot be overstated. This systematic review, being the first of its kind in this area, will synthesize and critically appraise the existing evidence from clinical trials, offering a comprehensive overview of the current knowledge on antimicrobial efficacy in preventing resistance among SOTR. Such a review will not only highlight gaps in the current research but also provide a robust evidence base for future studies and policy-making. By collating and analyzing data from multiple sources, this systematic review aims to establish a clear understanding of effective antimicrobial practices, ultimately contributing to improved clinical outcomes and reduced antimicrobial resistance in the transplant population.

MATERIALS AND METHODS

Protocol and registration

A systematic review was conducted using a search methodology consistent with the preferred reporting items for systematic reviews and meta-analyses criteria[10]. The review methodology was officially registered with PROSPERO.

Eligibility criteria

The systematic review was structured around a question developed using the population, intervention, comparison, and outcomes framework:

In SOTR (population), how effective are antimicrobial agents (intervention) compared to placebo, no intervention, or alternative regimens (comparison) in preventing antimicrobial resistance (outcomes)?

The primary outcome assessed was the incidence of antimicrobial resistance. Secondary outcomes included rates of infection, graft survival, patient mortality, and adverse effects associated with antimicrobial usage.

This review included randomized clinical trials that evaluated the efficacy of antimicrobial agents (prophylactic or therapeutic) aimed at preventing antimicrobial resistance. The review focused on studies involving SOTR and those comparing antimicrobial agents with placebo, no intervention, or other antimicrobial regimens. Exclusion criteria included observational studies, case reports, case series, editorials, reviews, commentaries, non-human studies, and clinical trials involving transplant types other than solid organ transplants.

Information sources

The search strategy involved analyzing multiple databases, including: PubMed/MEDLINE, Web of Science, Embase, Scopus, and SciELO, as well as examining gray literature sources on Google Scholar. A comprehensive electronic database search was conducted from the databases' inception until May 2024, with no language restrictions. Additionally, further records were identified by reviewing the reference lists and citations of all selected full-text articles for potential inclusion in the study.

Search strategy

The search contained the following terms: "Solid Organ Transplant" OR "Kidney Transplant" OR "Liver Transplant" OR "Heart Transplant" OR "Lung Transplant" OR "Pancreas Transplant" AND "Antimicrobial Agents" OR "Antibiotics" OR "Antifungal Agents" OR "Antiviral Agents" OR "Antimicrobial Prophylaxis" AND "Antimicrobial Resistance" OR "Bacterial Resistance" OR "Multidrug Resistance" OR "Fungal Resistance" OR "Viral Resistance" AND "Infections" OR "Bacterial Infections" OR "Fungal Infections" OR "Viral Infections".

These search techniques utilize syntax and operators specific to each database to retrieve articles pertinent to defined queries. Modifications may be necessary to tailor the exploration functionality and syntax rules of each individual database.

Table 1 presents the search strategies employed for each respective database utilizing the designated terms.

Study selection

Two researchers independently assessed the relevance of titles and abstracts, followed by a comprehensive evaluation of full-text articles. An unbiased assessment of full texts was conducted to ascertain eligibility. Discrepancies were resolved through discussion; in cases of persistent disagreement, a third expert was consulted. The Kappa test was employed to measure interobserver agreement, with a score exceeding 80 indicating high consistency.

Data collection

Two researchers independently collected data using customized extraction methods. A comparative analysis was conducted to ensure uniformity in the gathered data. Information regarding patients, interventions, controls, microorganisms studied, incidence of new infections, and adverse events was compiled from the reviewed articles. Additionally, systematic documentation of details such as authorship, publication year, and country of origin was conducted.

Assessment of bias risk and study quality in individual studies

Two researchers assessed the risk of bias and the quality of the included clinical trials using the Jadad scale[11]. The Jadad scale is a five-point system that evaluates three key criteria: Randomization, blinding, and withdrawals/dropouts. Scores range from 0 to 5, with higher scores indicating better quality; a score of 0-2 points indicates low quality, while a score of 3-5 points indicates high quality. For randomization, the trial receives 1 point if it is described as randomized, an additional point if the randomization method is described and appropriate and loses 1 point if the randomization method is

Table 1 Search strategies implemented across selected databases

Database	Search strategy
PubMed/MEDLINE	["Organ Transplantation" (MeSH) OR "Kidney Transplantation" (MeSH) OR "Liver Transplantation" (MeSH) OR "Heart Transplantation" (MeSH) OR "Lung Transplantation" (MeSH) OR "Pancreas Transplantation" (MeSH)] AND ["Anti-Bacterial Agents" (MeSH) OR "Antibiotics" (MeSH) OR "Antifungal Agents" (MeSH) OR "Antiviral Agents" (MeSH) OR "Antimicrobial Prophylaxis" (MeSH)] AND ["Drug Resistance, Microbial" (MeSH) OR "Drug Resistance, Bacterial" (MeSH) OR "Drug Resistance, Multiple, Bacterial" (MeSH) OR "Drug Resistance, Fungal" (MeSH) OR "Drug Resistance, Viral" (MeSH)] AND ["Infections" (MeSH) OR "Bacterial Infections" (MeSH) OR "Fungal Infections" (MeSH) OR "Viral Infections" (MeSH)]
Scopus	TITLE-ABS-KEY ("Organ Transplantation" OR "Kidney Transplantation" OR "Liver Transplantation" OR "Heart Transplantation" OR "Lung Transplantation" OR "Pancreas Transplantation") AND ("Anti-Bacterial Agents" OR "Antibiotics" OR "Antifungal Agents" OR "Antiviral Agents" OR "Antimicrobial Prophylaxis") AND ("Drug Resistance, Microbial" OR "Drug Resistance, Bacterial" OR "Drug Resistance, Multiple, Bacterial" OR "Drug Resistance, Fungal" OR "Drug Resistance, Viral") AND ("Infections" OR "Bacterial Infections" OR "Fungal Infections" OR "Viral Infections")
SciELO	[("Organ Transplantation" OR "Kidney Transplantation" OR "Liver Transplantation" OR "Heart Transplantation" OR "Lung Transplantation" OR "Pancreas Transplantation") AND ("Anti-Bacterial Agents" OR "Antibiotics" OR "Antifungal Agents" OR "Antiviral Agents" OR "Antimicrobial Prophylaxis") AND ("Drug Resistance, Microbial" OR "Drug Resistance, Bacterial" OR "Drug Resistance, Multiple, Bacterial" OR "Drug Resistance, Fungal" OR "Drug Resistance, Viral") AND ("Infections" OR "Bacterial Infections" OR "Fungal Infections" OR "Viral Infections")]
Embase	('Organ Transplantation'/exp OR 'Kidney Transplantation'/exp OR 'Liver Transplantation'/exp OR 'Heart Transplantation'/exp OR 'Lung Transplantation'/exp OR 'Pancreas Transplantation'/exp) AND ('Anti-Bacterial Agents'/exp OR 'Antibiotics'/exp OR 'Antifungal Agents'/exp OR 'Antiviral Agents'/exp OR 'Antimicrobial Prophylaxis'/exp) AND ('Drug Resistance, Microbial'/exp OR 'Drug Resistance, Bacterial'/exp OR 'Drug Resistance, Multiple, Bacterial'/exp OR 'Drug Resistance, Fungal'/exp OR 'Drug Resistance, Viral'/exp) AND ('Infections'/exp OR 'Bacterial Infections'/exp OR 'Fungal Infections'/exp OR 'Viral Infections'/exp)
Web of Science	TS = ("Organ Transplantation" OR "Kidney Transplantation" OR "Liver Transplantation" OR "Heart Transplantation" OR "Lung Transplantation" OR "Pancreas Transplantation") AND TS = ("Anti-Bacterial Agents" OR "Antibiotics" OR "Antifungal Agents" OR "Antiviral Agents" OR "Antimicrobial Prophylaxis") AND TS = ("Drug Resistance, Microbial" OR "Drug Resistance, Bacterial" OR "Drug Resistance, Multiple, Bacterial" OR "Drug Resistance, Fungal" OR "Drug Resistance, Viral") AND TS = ("Infections" OR "Bacterial Infections" OR "Fungal Infections" OR "Viral Infections")
Google Scholar	"Organ Transplantation" OR "Kidney Transplantation" OR "Liver Transplantation" OR "Heart Transplantation" OR "Lung Transplantation" OR "Pancreas Transplantation" AND "Anti-Bacterial Agents" OR "Antibiotics" OR "Antifungal Agents" OR "Antiviral Agents" OR "Antimicrobial Prophylaxis" AND "Drug Resistance, Microbial" OR "Drug Resistance, Bacterial" OR "Drug Resistance, Multiple, Bacterial" OR "Drug Resistance, Fungal" OR "Drug Resistance, Viral" AND "Infections" OR "Bacterial Infections" OR "Fungal Infections" OR "Viral Infections"

inappropriate or not well described. For blinding, the trial gets 1 point if it is described as double-blind, an additional point if the blinding method is described and appropriate and loses 1 point if the blinding method is inappropriate or not well described. For withdrawals and dropouts, the trial receives 1 point if it provides a detailed description, including the numbers and reasons for the withdrawals and dropouts.

Summary measurements

Information from the trials was collected utilizing descriptive statistics, encompassing mean variances, standard deviation values, and ranges, particularly focusing on continuous outcomes. If the studies exhibited notable homogeneity, the potential for conducting a meta-analysis was assessed.

RESULTS

Study selection

Following the search protocol, 319 studies were identified in electronic databases. After removing duplicates and applying eligibility criteria, 13 documents underwent a comprehensive full-text review. The studies were excluded primarily because they were not randomized clinical trials or because they did not investigate microorganisms with previously reported resistance. After the final phase of the eligibility assessment, this study ultimately included 7 articles. Figure 1 provides a detailed depiction of the examination flowchart.

Features of the investigations

Table 2 summarizes the main characteristics of the seven randomized clinical trials included in this review[12-18]. The review encompasses trials published between 2004[18] and 2022[12,13] examining data from a total of 2318 patients. Most of these studies were conducted in North America. This table also indicates the microorganisms studied, with a particular focus on CMV. Consequently, the most frequently used medications were maribavir, valganciclovir, and ganciclovir.

Of concern, all clinical trials showed significant proportions of resistant microorganisms after the interventions, with no statistically significant differences between the groups (mean resistance: 13.47% *vs* 14.39% in the control group), except for two studies that demonstrated greater efficacy of maribavir[13] and valganciclovir[18] (mean resistance: 22.2% *vs* 41.1% in the control group; $P < 0.05$). On the other hand, Ultraviolet-C light cleaning[12] and the combination of colistin-neomycin did not show significant differences in the incidence of resistance in the studied microorganisms[14].

Table 2 Summary of the main characteristics of the studies

Ref.	Patients	Intervention/control	Microorganisms studied	Incidence of antimicrobial resistance	Adverse events
Rock *et al*[12]	1085	Routine and discharge patient room cleaning using ultraviolet-C light *vs* routine and discharge patient room cleaning	Vancomycin-resistant enterococci and *Clostridioides difficile*	6.52 *vs* 6.68 *per* 1000 patient-days in vancomycin-resistant enterococci ($P > 0.05$) and 3.78 *vs* 2.64 *per* 1000 patient-days in *Clostridioides difficile* infections ($P > 0.05$)	Not reported
Avery *et al*[13]	352	Maribavir 400 mg twice daily versus valganciclovir/ganciclovir, foscarnet, or cidofovir	Cytomegalovirus	44.4% *vs* 76.1% ($P < 0.05$)	40 deaths, dysgeusia, nausea, diarrhea
Fariñas *et al*[14]	105	Colistin-neomycin *vs* no treatment	Multidrug-resistant (*Enterobacterales*)	9.4% *vs* 13.5% ($P > 0.05$)	Diarrhea
Papanicolaou *et al*[15]	120	Maribavir 400, 800, or 1200 mg at a ratio of 1:1:1	Cytomegalovirus	30%, 37.5%, 27.5% ($P > 0.05$)	32 deaths, dysgeusia, nausea
Boivin *et al*[16]	275	Ganciclovir *vs* valganciclovir	Cytomegalovirus	2.3% *vs* 3.6% ($P > 0.05$)	2 deaths, gastrointestinal problem
Boivin *et al*[17]	80	Valganciclovir *vs* ganciclovir	Cytomegalovirus	2.5% *vs* 2.5% ($P > 0.05$)	1 death, 23 grafts rejected, abdominal pain, diarrhea
Boivin *et al*[18]	301	Valganciclovir *vs* ganciclovir	Cytomegalovirus	0% *vs* 6.1% ($P < 0.05$)	1 graft rejected

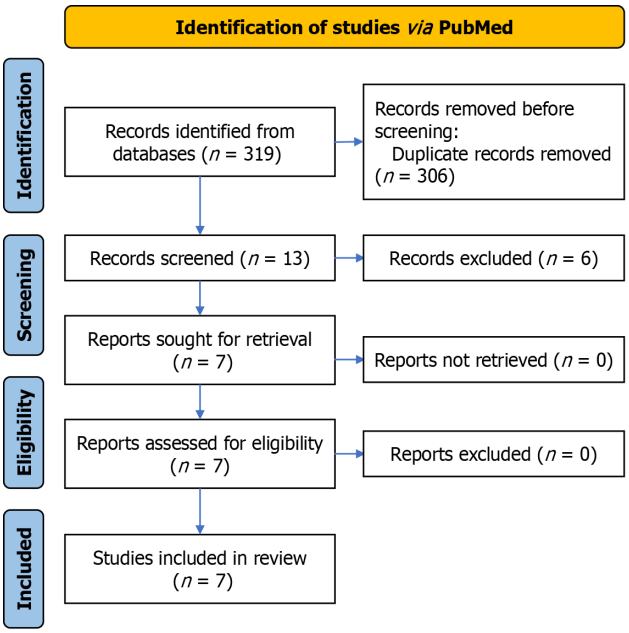


Figure 1 Detailed depiction of the examination flowchart.

The total reported deaths in three clinical trials were 75[13,15-17] and there were 24 graft rejections in two studies[17,18]. Moreover, dysgeusia, nausea, and diarrhea were also among the most reported adverse events.

Assessment of bias risk

Most of the included studies demonstrate a high risk of bias due to poor blinding and lack of proper randomization methods, except for Papanicolaou *et al*[15], which meets all the Jadad criteria for high methodological quality. Studies by Avery *et al*[13] and Fariñas *et al*[14] both scored 3, showing good methodological quality with some risks of bias. These results suggest that the overall quality of evidence from these trials might be compromised, affecting the reliability of the conclusions drawn from the systematic review (Table 3).

Table 3 Risk of bias and quality of the selected randomized clinical trials[11]

RCT	Randomization	Double blinding	Withdraw	Proper randomization	Proper double blinding	Score
Rock *et al*[12]	1	0	0	0	0	1
Avery *et al*[13]	1	0	1	1	0	3
Fariñas *et al*[14]	1	0	1	1	0	3
Papanicolaou *et al*[15]	1	1	1	1	1	5
Boivin *et al*[16]	1	0	0	0	0	1
Boivin *et al*[17]	1	0	0	0	0	1
Boivin *et al*[18]	1	1	0	0	0	2

RCT: Randomized controlled trial.

DISCUSSION

This systematic review underscores the ongoing challenge of antimicrobial resistance in SOTR, despite the use of prophylactic and therapeutic antimicrobial agents. While some interventions showed promise, a significant proportion of resistant microorganisms persisted across studies, highlighting a critical gap in current antimicrobial strategies. The lack of statistically significant differences between most intervention groups suggests that current protocols may be inadequate in addressing the complexity of resistance in this vulnerable population. These findings call for high-quality randomized clinical trials to explore innovative therapies and optimize existing regimens for better long-term outcomes.

Addressing resistance to anti-CMV medications is particularly challenging. Current drugs, like valganciclovir and ganciclovir, target the CMV DNA polymerase (UL54) and rely on activation by the viral UL97 protein kinase. Mutations in CMV genes coding for UL54 or UL97 can lead to resistance[19]. Maribavir, however, has a distinct mechanism of action that does not require activation by UL97[20] and binds to a different site on UL97 compared to valganciclovir and ganciclovir[13], making it effective against strains resistant to these drugs due to UL54 or UL97 mutations[21,22]. This positions maribavir as a promising option for treating resistant CMV infections, though it cannot be used alongside valganciclovir or ganciclovir, as it inhibits the UL97 protein kinase[13].

Two clinical trials in SOTR with resistant CMV demonstrated the efficacy of maribavir. Avery *et al*[13] found that maribavir was more effective than ganciclovir, valganciclovir, foscarnet, or cidofovir in clearing CMV viremia by week 8, with fewer cases of neutropenia and acute renal injury. Maribavir also cleared viremia more rapidly, an important factor as persistent viremia can signal clinical deterioration. The CMV consensus forum confirmed that treating viremia prevents disease, with viral load serving as a surrogate endpoint in CMV clinical studies[23]. These results highlight maribavir's potential to transform CMV treatment by effectively targeting drug-resistant strains while maintaining an improved safety profile[13]. Similarly, Papanicolaou *et al*[15] found that maribavir at doses of 400-1200 mg BID cleared CMV viremia in two-thirds of transplant recipients with resistant infections within six weeks, with no additional adverse effects, confirming its safety and viability as a long-term treatment option for this high-risk group.

Two clinical trials demonstrated that resistance rates to ganciclovir were comparable whether treated with oral valganciclovir or intravenous ganciclovir[16,17]. Although drug resistance mutations significantly impact viral load reduction and early kinetics, they do not consistently correlate with adverse clinical outcomes[16]. The incidence of ganciclovir resistance in SOTR varies based on the specific group studied, immunosuppressive drugs used, antiviral approach, and resistance detection techniques[24]. Reported rates of ganciclovir-resistant CMV mutations range from 0% in seropositive kidney transplant patients to 27% in lung transplant recipients[24,25], consistent with the findings of this review.

In another trial, the effectiveness of oral colistin-neomycin in preventing multidrug-resistant *Enterobacterales* infections in SOTR was examined. Resistance to colistin was detected in 5.6% of the experimental group and 1.9% of the control group, suggesting that this intervention did not reduce infection rates and may contribute to antimicrobial resistance[14,26-28]. Additionally, Rock *et al*[12] found that supplementing routine cleaning with Ultraviolet (UV)-C disinfection did not significantly reduce new infections of vancomycin-resistant enterococci or *C. difficile* in SOTR. While UV-C light can eliminate pathogens from surfaces[29-31], its clinical impact on reducing multidrug-resistant organisms and *C. difficile* infections remains inconclusive, likely due to the evolving nature of UV-C disinfection practices[28,29].

Overall, this review underscores the persistent challenge of antimicrobial resistance in SOTR. The substantial rates of resistance, graft rejection, and mortality reported across trials emphasize the need for optimizing treatment strategies. Adverse events like dysgeusia, nausea, and diarrhea further highlight the delicate balance between therapeutic efficacy and tolerability. While some interventions showed promise, the widespread prevalence of resistant microorganisms indicates an urgent need for more rigorous studies to assess long-term outcomes and safety profiles of these treatments.

Future research should prioritize longitudinal, multicenter trials with larger sample sizes to assess the long-term efficacy of antimicrobial interventions in preventing resistance in SOTR. These studies should explore combination therapies with different mechanisms of action and include robust surveillance programs to monitor resistance patterns. Additionally, focusing on patient-centered outcomes, such as quality of life and functional status, alongside comprehensive profiling of adverse events, is crucial. Cost-effectiveness analyses should also be integrated to evaluate the

economic impact of these interventions. Addressing these aspects will offer a deeper understanding of optimal antimicrobial strategies and their implications for both patient care and healthcare resource management.

This review identified significant risks of bias in most included studies, primarily due to inadequate blinding and randomization. Notably, Papanicolaou *et al*[15] adhered to the Jadad *et al*[11] criteria, demonstrating high methodological quality. Avery *et al*[13] and Fariñas *et al*[14] showed moderate quality with some biases. These limitations in study quality may affect the reliability of conclusions regarding the efficacy of antimicrobial interventions in preventing resistance among transplant recipients. Similar issues were observed in other systematic reviews assessing clinical trials[32,33]. To improve future research, rigorous study design should be prioritized, including strict blinding, appropriate allocation concealment, and robust randomization methods.

Several limitations of this systematic review warrant consideration. Significant heterogeneity in study designs, interventions, and outcome measures across trials complicates direct comparison and synthesis of results. The focus on specific antimicrobial agents or pathogens also limits the generalizability of findings to broader transplant populations and different healthcare settings. Additionally, publication bias may skew results, with positive outcomes more likely to be published. Short follow-up periods in some trials may not capture long-term outcomes, such as late-onset infections or resistance development. Incomplete reporting of adverse events and variations in microbiological testing methods further complicate interpretation of the evidence. Future research should address these limitations to enhance the robustness and applicability of findings for clinical practice and policy in transplant medicine.

CONCLUSION

This systematic review highlights the significant challenges in managing infections among SOTR, particularly due to high rates of antimicrobial resistance observed across a variety of pathogens post-intervention. While certain agents, such as maribavir and valganciclovir, demonstrate efficacy against CMV infections, antimicrobial effectiveness varies broadly depending on the pathogen and clinical context. These findings underscore the need for individualized treatment strategies that account for pathogen profiles and patient-specific factors. Methodological limitations, including biases from inadequate blinding and randomization, may affect the reliability of findings across the reviewed studies. The clinical impact of antimicrobial resistance is considerable, with high incidences of mortality and graft rejection reported in transplant populations. To advance the field, there is an urgent need for well-designed, multicenter trials to validate results, standardize treatment protocols, and explore novel therapeutic options for a broader spectrum of infections, ultimately aiming to optimize antimicrobial strategies and improve transplant outcomes.

FOOTNOTES

Author contributions: Ardila CM performed the conceptualization, data curation, data analysis, manuscript writing, and revision of the manuscript; Yadalam PK performed the data curation, data analysis, and revision of the manuscript; Ramírez-Arbeláez J performed the data curation, data analysis, and revision of the manuscript.

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REFERENCES

1 **Guardabassi L**, Butaye P, Dockrell DH, Fitzgerald JR, Kuijper EJ; ESCMID Study Group for Veterinary Microbiology (ESGVM). One Health: a multifaceted concept combining diverse approaches to prevent and control antimicrobial resistance. *Clin Microbiol Infect* 2020; **26**: 1604-1605 [PMID: 32702500 DOI: 10.1016/j.cmi.2020.07.012]

2 **So M**, Walti L. Challenges of Antimicrobial Resistance and Stewardship in Solid Organ Transplant Patients. *Curr Infect Dis Rep* 2022; **24**: 63-

75 [PMID: 35535263 DOI: 10.1007/s11908-022-00778-1]
3 **Silva JT**, Aguado JM. Current state of antimicrobial stewardship and organ transplantation in Spain. *Transpl Infect Dis* 2022; **24**: e13851 [PMID: 35579889 DOI: 10.1111/tid.13851]
4 **Oriol I**, Sabé N, Simonetti AF, Lladó L, Manonelles A, González J, Tubau F, Carratalà J. Changing trends in the aetiology, treatment and outcomes of bloodstream infection occurring in the first year after solid organ transplantation: a single-centre prospective cohort study. *Transpl Int* 2017; **30**: 903-913 [PMID: 28500792 DOI: 10.1111/tri.12984]
5 **Hosseini-Moghaddam SM**, Luo B, Bota SE, Husain S, Silverman MS, Daneman N, Brown KA, Paterson JM. Incidence and Outcomes Associated With Clostridioides difficile Infection in Solid Organ Transplant Recipients. *JAMA Netw Open* 2021; **4**: e2141089 [PMID: 34964852 DOI: 10.1001/jamanetworkopen.2021.41089]
6 **Fernández-Ruiz M**, Cardozo C, Salavert M, Aguilar-Guisado M, Escolà-Vergé L, Muñoz P, Gioia F, Montejo M, Merino P, Cuervo G, Garcí a-Vidal C, Aguado JM; CANDIPOP Project, the CANDI-Bundle Group; GEIRAS-GEMICOMED (SEIMC)REIPI. Candidemia in solid organ transplant recipients in Spain: Epidemiological trends and determinants of outcome. *Transpl Infect Dis* 2019; **21**: e13195 [PMID: 31610077 DOI: 10.1111/tid.13195]
7 **Escribano P**, Rodríguez-Sánchez B, Díaz-García J, Martín-Gómez MT, Ibáñez-Martínez E, Rodríguez-Mayo M, Peláez T, García-Gómez de la Pedrosa E, Tejero-García R, Marimón JM, Reigadas E, Rezusta A, Labayru-Echeverría C, Pérez-Ayala A, Ayats J, Cobo F, Pazos C, López-Soria L, Alastruey-Izquierdo A, Muñoz P, Guinea J; ASPEIN study group. Azole resistance survey on clinical Aspergillus fumigatus isolates in Spain. *Clin Microbiol Infect* 2021; **27**: 1170.e1-1170.e7 [PMID: 33010446 DOI: 10.1016/j.cmi.2020.09.042]
8 **Ramírez-Arbeláez JA**, Arroyave-Zuluaga RL, Barrera-Lozano LM, Hurtado V, González-Arroyave D, Ardila CM. Relationship between Intraoperative Bile Culture Outcomes and Subsequent Postoperative Infectious Complications: A Retrospective Cohort Study. *Biomed Res Int* 2024; **2024**: 3930130 [PMID: 38803514 DOI: 10.1155/2024/3930130]
9 **Ardila CM**, Bedoya-García JA. Antimicrobial resistance in dentistry. *Oral Dis* 2024; **30**: 805-806 [PMID: 35836349 DOI: 10.1111/odi.14316]
10 **Page MJ**, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Int J Surg* 2021; **88**: 105906 [PMID: 33789826 DOI: 10.1016/j.ijsu.2021.105906]
11 **Jadad AR**, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1-12 [PMID: 8721797 DOI: 10.1016/0197-2456(95)00134-4]
12 **Rock C**, Hsu YJ, Curless MS, Carroll KC, Ross Howard T, Carson KA, Cummings S, Anderson M, Milstone AM, Maragakis LL. Ultraviolet-C Light Evaluation as Adjunct Disinfection to Remove Multidrug-Resistant Organisms. *Clin Infect Dis* 2022; **75**: 35-40 [PMID: 34636853 DOI: 10.1093/cid/ciab896]
13 **Avery RK**, Alain S, Alexander BD, Blumberg EA, Chemaly RF, Cordonnier C, Duarte RF, Florescu DF, Kamar N, Kumar D, Maertens J, Marty FM, Papanicolaou GA, Silveira FP, Witzke O, Wu J, Sundberg AK, Fournier M; SOLSTICE Trial Investigators. Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomized Clinical Trial. *Clin Infect Dis* 2022; **75**: 690-701 [PMID: 34864943 DOI: 10.1093/cid/ciab988]
14 **Fariñas MC**, González-Rico C, Fernández-Martínez M, Fortún J, Escudero-Sanchez R, Moreno A, Bodro M, Muñoz P, Valerio M, Montejo M, Nieto J, Ruiz-San Millan JC, Casafont-Morencos F, Martinez-Martínez L, Fariñas-Álvarez C; ENTHERE Study Group, the Group for Study of Infection in Transplantation of the Spanish Society of Infectious Diseases and Clinical Microbiology (GESITRA-SEIMC) and the Spanish Network for Research in Infectious Diseases (REIPI). Oral decontamination with colistin plus neomycin in solid organ transplant recipients colonized by multidrug-resistant Enterobacterales: a multicentre, randomized, controlled, open-label, parallel-group clinical trial. *Clin Microbiol Infect* 2021; **27**: 856-863 [PMID: 33359562 DOI: 10.1016/j.cmi.2020.12.016]
15 **Papanicolaou GA**, Silveira FP, Langston AA, Pereira MR, Avery RK, Uknis M, Wijatyk A, Wu J, Boeckh M, Marty FM, Villano S. Maribavir for Refractory or Resistant Cytomegalovirus Infections in Hematopoietic-cell or Solid-organ Transplant Recipients: A Randomized, Dose-ranging, Double-blind, Phase 2 Study. *Clin Infect Dis* 2019; **68**: 1255-1264 [PMID: 30329038 DOI: 10.1093/cid/ciy706]
16 **Boivin G**, Goyette N, Rollag H, Jardine AG, Pescovitz MD, Asberg A, Ives J, Hartmann A, Humar A. Cytomegalovirus resistance in solid organ transplant recipients treated with intravenous ganciclovir or oral valganciclovir. *Antivir Ther* 2009; **14**: 697-704 [PMID: 19704173]
17 **Boivin G**, Goyette N, Gilbert C, Humar A, Covington E. Clinical impact of ganciclovir-resistant cytomegalovirus infections in solid organ transplant patients. *Transpl Infect Dis* 2005; **7**: 166-170 [PMID: 16390409 DOI: 10.1111/j.1399-3062.2005.00112.x]
18 **Boivin G**, Goyette N, Gilbert C, Roberts N, Macey K, Paya C, Pescovitz MD, Humar A, Dominguez E, Washburn K, Blumberg E, Alexander B, Freeman R, Heaton N, Covington E. Absence of cytomegalovirus-resistance mutations after valganciclovir prophylaxis, in a prospective multicenter study of solid-organ transplant recipients. *J Infect Dis* 2004; **189**: 1615-1618 [PMID: 15116297 DOI: 10.1086/382753]
19 **El Chaer F**, Shah DP, Chemaly RF. How I treat resistant cytomegalovirus infection in hematopoietic cell transplantation recipients. *Blood* 2016; **128**: 2624-2636 [PMID: 27760756 DOI: 10.1182/blood-2016-06-688432]
20 **Chou S**, Marousek GI. Accelerated evolution of maribavir resistance in a cytomegalovirus exonuclease domain II mutant. *J Virol* 2008; **82**: 246-253 [PMID: 17942550 DOI: 10.1128/JVI.01787-07]
21 **Biron KK**, Harvey RJ, Chamberlain SC, Good SS, Smith AA 3rd, Davis MG, Talarico CL, Miller WH, Ferris R, Dornsife RE, Stanat SC, Drach JC, Townsend LB, Koszalka GW. Potent and selective inhibition of human cytomegalovirus replication by 1263W94, a benzimidazole L-riboside with a unique mode of action. *Antimicrob Agents Chemother* 2002; **46**: 2365-2372 [PMID: 12121906 DOI: 10.1128/AAC.46.8.2365-2372.2002]
22 **Chou S**, Wu J, Song K, Bo T. Novel UL97 drug resistance mutations identified at baseline in a clinical trial of maribavir for resistant or refractory cytomegalovirus infection. *Antiviral Res* 2019; **172**: 104616 [PMID: 31568799 DOI: 10.1016/j.antiviral.2019.104616]
23 **Natori Y**, Alghamdi A, Tazari M, Miller V, Husain S, Komatsu T, Griffiths P, Ljungman P, Orchanian-Cheff A, Kumar D, Humar A; CMV Consensus Forum. Use of Viral Load as a Surrogate Marker in Clinical Studies of Cytomegalovirus in Solid Organ Transplantation: A Systematic Review and Meta-analysis. *Clin Infect Dis* 2018; **66**: 617-631 [PMID: 29020339 DOI: 10.1093/cid/cix793]
24 **Gilbert C**, Boivin G. Human cytomegalovirus resistance to antiviral drugs. *Antimicrob Agents Chemother* 2005; **49**: 873-883 [PMID: 15728878 DOI: 10.1128/AAC.49.3.873-883.2005]
25 **Limaye AP**. Ganciclovir-resistant cytomegalovirus in organ transplant recipients. *Clin Infect Dis* 2002; **35**: 866-872 [PMID: 12228824 DOI: 10.1086/342385]
26 **Errico G**, Gagliotti C, Monaco M, Masiero L, Gaibani P, Ambretti S, Landini MP, D'Arezzo S, Di Caro A, Parisi SG, Palù G, Vespasiano F,

Morsillo F, Moro ML, Procaccio F, Ricci A, Grossi PA, Pantosti A, Nanni Costa A; SInT Collaborative Study Group. Colonization and infection due to carbapenemase-producing Enterobacteriaceae in liver and lung transplant recipients and donor-derived transmission: a prospective cohort study conducted in Italy. *Clin Microbiol Infect* 2019; **25**: 203-209 [PMID: 29800674 DOI: 10.1016/j.cmi.2018.05.003]

27 **Tacconelli E**, Mazzaferri F, de Smet AM, Bragantini D, Eggimann P, Huttner BD, Kuijper EJ, Lucet JC, Mutters NT, Sanguinetti M, Schwaber MJ, Souli M, Torre-Cisneros J, Price JR, Rodríguez-Baño J. ESCMID-EUCIC clinical guidelines on decolonization of multidrug-resistant Gram-negative bacteria carriers. *Clin Microbiol Infect* 2019; **25**: 807-817 [PMID: 30708122 DOI: 10.1016/j.cmi.2019.01.005]

28 **Carling PC**. The need for clinically relevant studies of non-touch disinfecting systems. *J Hosp Infect* 2013; **84**: 340 [PMID: 23838149 DOI: 10.1016/j.jhin.2013.01.016]

29 **Health Quality Ontario**. Portable Ultraviolet Light Surface-Disinfecting Devices for Prevention of Hospital-Acquired Infections: A Health Technology Assessment. *Ont Health Technol Assess Ser* 2018; **18**: 1-73 [PMID: 29487629]

30 **Otter JA**, Yezli S, Salkeld JA, French GL. Evidence that contaminated surfaces contribute to the transmission of hospital pathogens and an overview of strategies to address contaminated surfaces in hospital settings. *Am J Infect Control* 2013; **41**: S6-11 [PMID: 23622751 DOI: 10.1016/j.ajic.2012.12.004]

31 **Rock C**, Curless MS, Nowakowski E, Ross T, Carson KA, Trexler P, Carroll K, Maragakis LL. UV-C Light Disinfection of Carbapenem-Resistant Enterobacteriaceae from High-Touch Surfaces in a Patient Room and Bathroom. *Infect Control Hosp Epidemiol* 2016; **37**: 996-997 [PMID: 27174660 DOI: 10.1017/ice.2016.111]

32 **Ardila CM**, Bedoya-García JA, Arrubla-Escobar DE. Antibiotic resistance in periodontitis patients: A systematic scoping review of randomized clinical trials. *Oral Dis* 2023; **29**: 2501-2511 [PMID: 35735133 DOI: 10.1111/odi.14288]

33 **Ardila CM**, Bedoya-García JA. Microbial resistance to oral antiseptics used in hospitalized patients: A systematic scoping review of randomized clinical trials. *Spec Care Dentist* 2023; **43**: 443-451 [PMID: 36181674 DOI: 10.1111/scd.12781]

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SCIENTOMETRICS

Machine learning in solid organ transplantation: Charting the evolving landscape

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Abstract

BACKGROUND

Machine learning (ML), a major branch of artificial intelligence, has not only demonstrated the potential to significantly improve numerous sectors of healthcare but has also made significant contributions to the field of solid organ transplantation. ML provides revolutionary opportunities in areas such as donor-recipient matching, post-transplant monitoring, and patient care by automatically analyzing large amounts of data, identifying patterns, and forecasting outcomes.

AIM

To conduct a comprehensive bibliometric analysis of publications on the use of ML in transplantation to understand current research trends and their implications.

METHODS

On July 18, a thorough search strategy was used with the Web of Science database. ML and transplantation-related keywords were utilized. With the aid of the VOS viewer application, the identified articles were subjected to bibliometric variable analysis in order to determine publication counts, citation counts, contributing countries, and institutions, among other factors.

RESULTS

Of the 529 articles that were first identified, 427 were deemed relevant for bibliometric analysis. A surge in publications was observed over the last four years, especially after 2018, signifying growing interest in this area. With 209 publications, the United States emerged as the top contributor. Notably, the "*Journal of*

Heart and Lung Transplantation" and the "*American Journal of Transplantation*" emerged as the leading journals, publishing the highest number of relevant articles. Frequent keyword searches revealed that patient survival, mortality, outcomes, allocation, and risk assessment were significant themes of focus.

CONCLUSION

The growing body of pertinent publications highlights ML's growing presence in the field of solid organ transplantation. This bibliometric analysis highlights the growing importance of ML in transplant research and highlights its exciting potential to change medical practices and enhance patient outcomes. Encouraging collaboration between significant contributors can potentially fast-track advancements in this interdisciplinary domain.

Key Words: Machine learning; Artificial Intelligence; Solid organ transplantation; Bibliometric analysis

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Core Tip: Machine learning (ML) is transforming solid organ transplantation by improving donor-recipient matching, post-transplant monitoring, and patient care *via* advanced data analysis and outcome forecasting. This bibliometric analysis of 427 relevant publications shows a significant increase in interest and research, especially since 2018, with the United States leading the way. Key themes include patient survival, mortality, outcomes, allocation, and risk assessment, demonstrating ML's promising ability to transform medical practices and improve patient outcomes in transplantation. Collaboration among key contributors is critical for accelerating progress in this interdisciplinary field.

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INTRODUCTION

Machine learning (ML) is a subfield of artificial intelligence (AI) that concentrates on the creation of algorithms that are capable of learning and generating predictions or decisions without explicit programming[1,2]. It enables computers to analyze large volumes of data, identify patterns, and learn from examples to improve performance on certain tasks[3].

ML has found numerous applications in the field of medicine, revolutionizing healthcare practices[1,3]. Medical diagnostics has made use of ML algorithms for the analysis of medical imaging, such as computed tomography and X-ray scans. Diseases have been better identified and categorized as a result of this[4]. ML algorithms have been utilized to predict patient outcomes too[5], such as mortality rates[6], response to the treatment[7], and progression of the diseases [8], based on clinical information and patient data. Additionally, ML has facilitated the development of personalized medicine, enabling tailored treatment plans by considering individual patient variables[9].

In the field of solid organ transplantation, ML has emerged as a valuable tool for improving outcomes of the patients and optimizing allocation of the organs[10]. ML algorithms were utilized to develop models that assess the suitability of potential organ-recipient matching, taking into account various factors such as donor-recipient compatibility, organ quality, and recipient medical characteristics[11-13]. These models help transplant programs make more informed decisions and maximize the chances of successful transplantations[10]. Furthermore, ML has been applied to predict post-transplant complications and outcomes[14,15], such as rejection episodes and graft survival[16].

In this study, we conducted a comprehensive bibliometric analysis of all published articles in the field of the use of ML in solid organ transplantation. By systematically analyzing the vast body of literature, we aimed to gain a deeper understanding of the research trends, key contributors, and the overall impact of ML in this critical area of medicine. Further, by mapping interrelationships and showcasing key works of leading contributors in the field of ML applied to transplantation, we aim to illuminate these connections, paving the way for enhanced collaboration and collective advancements in transplantation research.

MATERIALS AND METHODS

Search strategy

On July 18, a systematic search was done using the Web of Science database, a comprehensive database that include high-quality articles. To identify ML articles, topics for the keyword “machine learning” were searched in all fields. Then we used the keywords "kidney transplant*", "liver transplant*", "lung transplant*", "heart transplant" and "pancreas transplant*" with appropriate ‘*’ use to compensate for relevant keywords. The final query was "machine learning" (all fields) and "kidney transplant*" or "liver transplant*" or "lung transplant*" or "heart transplant" or "pancreas transplant*"

(all fields).

Importantly, this research focused solely on bibliometric analysis, it did not involve the extraction of patient data and was deemed exempt from obtaining approval from the institutional review board.

Variables and analysis

We analyzed a variety of bibliometric variables, such as the citations of searched articles, annual publications, top-contributed countries, top-published institutions and authors, journals, keywords, and top-cited articles, after extracting and exporting the data in accordance with the search strategy. We employed VOS viewer software (version 1.6.19) and Microsoft Excel 2016 to generate tables and figures. VOS viewer is a software that has been developed in the Java programming language by Van Eck and Waltman from Leiden University[17]. VOS viewer can calculate how strongly an author, an affiliation, or a country is connected to others *via* citation references using an indicator called "total link strength". This measure aids in assessing the strength of connections between variables within the network.

VOS viewer network visualization interpretation

In VOS viewer network visualizations, terms are shown as circles/squares, and their sizes are determined by their respective weights, with larger circles indicating higher occurrences. Different clusters of terms are assigned specific colors, facilitating the identification of related groups. Lines connecting the circles represent co-citation relationships, and thicker lines indicate stronger connections between the terms. The distance between the circles roughly signifies the level of relatedness based on co-citation; closer circles suggest a stronger relationship between the terms. The visualization offers a clear representation of the relationships, significance and weight (size), and associations (proximity and links) among the terms in the network map.

RESULTS

The preliminary inquiry yielded a total of 529 articles. Following a meticulous manual review process to eliminate irrelevant articles, a subset of 427 articles deemed pertinent were selected for inclusion in the bibliometric analysis. These selected articles collectively garnered 3979 citations, averaging approximately 9.32 citations per article.

Annual publications

The number of publications discussing ML in transplantation has shown a remarkable trend over the last four years. From 2007 to 2016, the annual publication count was limited to 1 to 7 publications. However, in 2017, there was a notable increase with 15 publications, and this trend continued to grow each year. By 2022, the number of publications reached a peak with 134 publications, indicating the growing interest and potential impact of ML in transplantation research and patient care (Figure 1).

Top contributing countries

The United States emerged as the leading contributor with 209 publications, 2288 citations (57.5%), and a high total link strength (n = 137). Followed by Canada with 59 publications and 828 citations (20.81%), and China with 43 publications and 336 citations (8.44%) (Figure 2 and Table 1).

Top contributed institutions

The top-contributed institutions in the field of ML in transplantation were identified based on their publication and citation count. University of Toronto in Canada emerged as the leading institution according to the number of publications with 39 publications (9.13%) and 301 citations. Followed by University of California System in the United States with 34 publications (7.96%) and 263 citations and Mayo Clinic in the United States with 23 publications (5.39%) and 457 citations. Other prominent institutions included Johns Hopkins University in the United States with 19 publications (4.45%), and 458 citations, UDICE French Research Universities in France with 18 publications (4.22%) and 472 citations and University of Texas System in the United States with 18 publications (4.22%) and 638 citations. In terms of the number of citations, University of Texas System in the United States and University of Alberta in Canada, had the highest citations count with 638 and 585 citations, respectively (Table 2).

Top contributed Journals

The leading journal in terms of publications was found to be the "*Journal of Heart and Lung Transplantation*", accounting for 47 publications, representing approximately 11% of the total research output. The "*American Journal of Transplantation*" followed closely with 33 publications (7.7%). Other prominent journals included "*Transplantation*" with 17 publications (3.9%) and "*Transplant International*" with 12 publications (2.8%) (Table 3).

Top contributed authors

The analysis of author contributions in the field of ML in transplantation revealed the top authors who have made significant research contributions. Cheungpasitporn, Wisit and Thongprayoon, Charat had the highest number of publications in the field of ML in transplantation (n = 13). Followed closely by Leeaphorn, Napat (n = 12), Cooper, Matthew (n = 11), Erdman, Lauren (n = 11), Jadlowiec, Caroline C (n = 11), and Pattharanitima, Pattharawin (n = 11) (Table 4).

Table 1 Top countries based on the number of publications and citations

Country	Publications (*n* = 427)	Citations	Percentage from total citations (*n* = 3979) (%)	Total link strength
United States	209	2288	57.5	137
Canada	59	828	20.81	89
China	43	336	8.44	7
Spain	34	516	12.97	46
England	27	737	18.52	38
France	25	538	13.52	49
Germany	25	649	16.31	37
Italy	20	202	5.08	31
Belgium	16	436	10.96	37
South Korea	15	163	4.1	3
Australia	13	538	13.52	33
Austria	13	607	15.26	47
Thailand	12	21	0.53	12
Brazil	11	50	1.26	7
Netherlands	10	322	8.09	29
India	9	77	1.94	9
Switzerland	9	130	3.27	12
Sweden	8	16	0.4	17
Portugal	6	4	0.1	4
Saudi Arabia	6	42	1.06	8

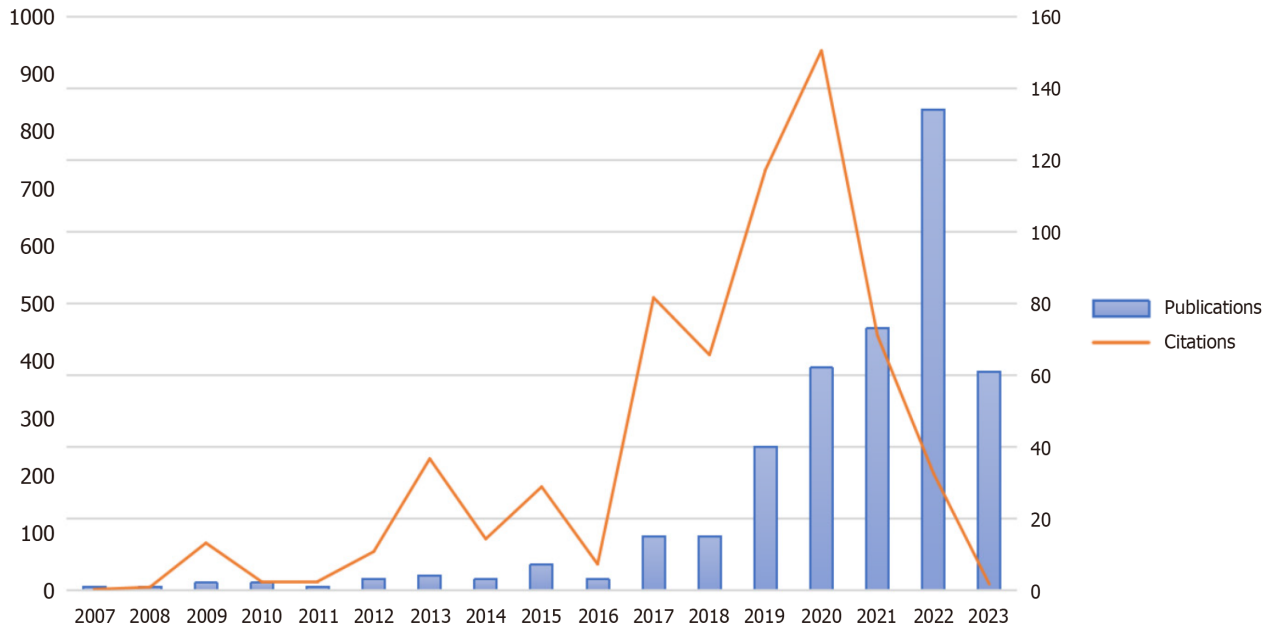


Figure 1 Annual publications and citations of machine learning articles in the field of solid organ transplantation (2007-2023).

Figure 3 shows the network visualization of the top contributed authors and their interconnections.

Keywords

The most frequently encountered keywords were "Survival" (*n* = 58), "Kidney transplantation" (*n* = 43), "Mortality" (*n* = 40), Model (*n* = 36), Classification (*n* = 31), Risk (*n* = 31) and Liver transplantation (*n* = 30).

Table 2 Top contributed institutions

Institution	Country	Number of publications	Percentage (%)	Total citations
University of Toronto	Canada	39	9.13	301
University of California System	United States	34	7.96	263
Mayo Clinic	United States	23	5.39	457
Johns Hopkins University	United States	19	4.45	458
UDICE French Research Universities	France	18	4.22	472
University of Texas System	United States	18	4.22	638
Harvard University	United States	17	3.98	359
Pennsylvania Commonwealth System of Higher Education	United States	15	3.51	396
University of Alberta	Canada	14	3.28	585
University of Pittsburgh	United States	14	3.28	395
Assistance Publique Hopitaux Paris	France	13	3.04	458
Inserm, the French National Institute of Health and Medical Research	France	13	3.04	465
Paris Cité University	France	13	3.04	293
Stanford University	United States	12	2.81	17
Thammasat University	Thailand	12	2.81	23
University of Pennsylvania	United States	12	2.81	79
Medical University of Vienna	Austria	11	2.58	576
University of Mississippi	United States	11	2.58	15
Columbia University	United States	10	2.34	48
Duke University	United States	10	2.34	122

Table 3 Top journals based on the number of publications, *n* (%)

Journal	Publications (*n* = 427)
Journal of Heart and Lung Transplantation	47 (11)
American Journal of Transplantation	33 (7.7)
Transplantation	17 (3.9)
Transplant International	12 (2.8)
PLOS One	11 (2.6)
Scientific Reports	11 (2.6)
Hepatology	10 (2.3)
Journal of Clinical Medicine	9 (2.1)
Frontiers in Immunology	7 (1.6)
Lecture Notes in Computer Science	7 (1.6)
Liver Transplantation	7 (1.6)

Figure 4 presents a network visualization of the top occurring keywords grouped into four clusters. Clusters' primary focus were kidney transplantation, liver transplantation, survival and mortality outcomes. Cluster number one included kidney transplantation as the dominating keyword with other keywords such as: Rejection, acute rejection, immunosuppression, risk prediction and deep learning. Cluster number two included liver transplantation as the dominating keyword with other keywords such as: Survival analysis and allocation. The third and fourth clusters included survival and mortality related keywords as the dominating keywords with other keywords such as: Hepatocellular carcinoma, heart transplantation, lung transplantation, outcomes and prognosis.

Table 4 Top contributed authors

Author	Publications	Percentage (%)
Wisit Cheungpasitporn	13	3.04
Charat Thongprayoon	13	3.04
Napat Leeaphorn	12	2.81
Matthew Cooper	11	2.58
Lauren Erdman	11	2.58
Caroline C Jadlowiec	11	2.58
Pattharawin Pattharanitima	11	2.58
Michael A Mao	10	2.34
Shennen A Mao	10	2.34
Gonzalo Sapisochin	10	2.34
Pradeep Vaitla	10	2.34
Wisit Kaewput	9	2.11
Anna Goldenberg	8	1.87
Philip F Halloran	8	1.87
César Hervas-Martinez	8	1.87
Lawrence Lau	8	1.87
Alexandre Loupy	8	1.87
Maarten Naesens	8	1.87
Mamatha Bhat	7	1.64
Javier Briceno	7	1.64
Shaf Keshavjee	7	1.64
Tommy Ivanics	6	1.41
Pajaree Krisanapan	6	1.41
Carmen Lefaucheur	6	1.41
Pitchaphon Nissaisorakarn	6	1.41

Top ten cited articles

Among the 427 studies that discussed ML and solid organ transplantation, "Decision tree and random forest models for outcome prediction in antibody incompatible kidney transplantation" published in *Biomedical Signal Processing and Control Journal*, stand out as the most cited (n = 162 citations). Followed by "Machine Learning Algorithms Outperform Conventional Regression Models in Predicting Development of Hepatocellular Carcinoma" published in the *American Journal of Gastroenterology* (n = 152 citations), and "Prediction of Acute Kidney Injury after Liver Transplantation: Machine Learning Approaches vs. Logistic Regression Model" published in *Journal of Clinical Medicine* (n = 96 citations) (Table 5).

DISCUSSION

ML, a groundbreaking technology with the potential to revolutionize various medical fields, has emerged as a powerful tool in transplantation, particularly for predicting post-transplant outcomes and providing invaluable insights into patient prognosis[2,3,18,19]. By analyzing historical patient data, including pre-transplant risk factors and post-transplant complications, ML models offer predictive insights that help clinicians identify patients at higher risk of complications or graft failure[20]. These predictive capabilities enable proactive interventions and personalized treatment plans, leading to improved patient management and long-term transplant survival[10,15,16]. The application of ML in this context involves two main approaches: Algorithm models to determine post-transplant survival time and techniques to assess whether matching pairs surpass specific post-transplant endpoints based on the latest follow-up of the recipient[2,10,14,15].

Unlike traditional statistical methods and regression analyses, ML offers the ability to handle complex datasets by incorporating multiple variables to analyze various end-points in medicine, including both favorable and unfavorable

Table 5 Top ten cited articles in the field of machine learning in solid organ transplantation

Title	First author	Journal	Publication year	Total citations
Decision tree and random forest models for outcome prediction in antibody incompatible kidney transplantation	Torgyn Shaikhina	*Biomedical Signal Processing and Control*	2019	162
Machine learning algorithms outperform conventional regression models in predicting development of hepatocellular carcinoma	Amit Singal	*American Journal of Gastroenterology*	2013	152
Prediction of acute kidney injury after liver transplantation: Machine learning approaches vs. logistic regression model	Hyung-Chul Lee	*Journal of Clinical Medicine*	2018	96
Assessing rejection-related disease in kidney transplant biopsies based on archetypal analysis of molecular phenotypes	Jeff Reeve	*JCI Insight*	2017	90
Application of machine-learning models to predict tacrolimus stable dose in renal transplant recipients	Jie Tang	*Scientific Reports*	2017	83
Predicting the graft survival for heart-lung transplantation patients: An integrated data mining methodology	Asil Oztekin	*International Journal of Medical Informatics*	2009	79
Machine-learning algorithms predict graft failure after liver transplantation	Lawrence Lau	*Transplantation*	2017	76
Applying machine learning in liver disease and transplantation: A comprehensive review	Ashley Spann	*Hepatology*	2020	66
Predicting graft survival among kidney transplant recipients: A Bayesian decision support model	Kazim Topuz	*Decision Support Systems*	2018	64
Transcriptional trajectories of human kidney injury progression	Pietro Cippa	*JCI Insight*	2018	58

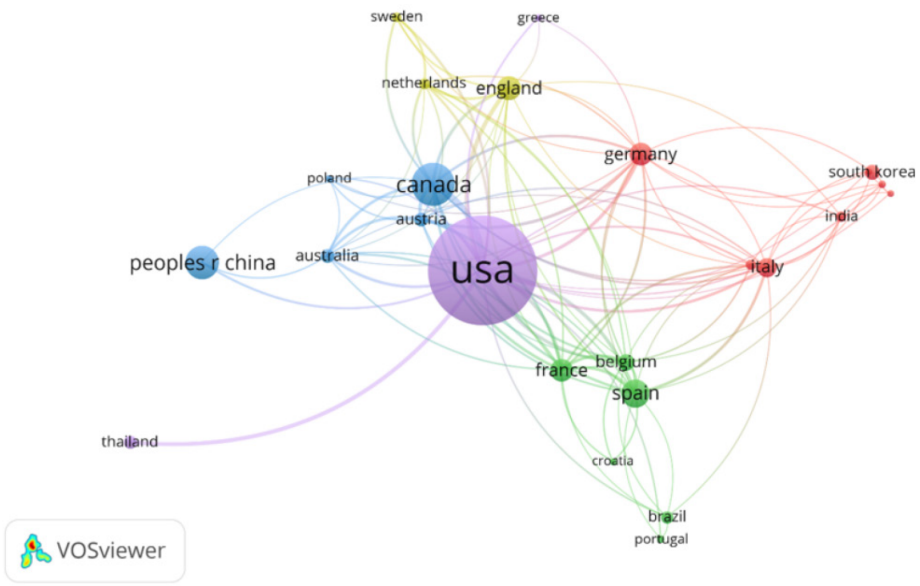


Figure 2 The network visualization of the top contributing countries and their interconnections. Each circle represents a country, and the size of the circles indicates the frequency of occurrence. Larger circles indicate that the country publishes more frequently. Countries included in the same cluster, which occurred frequently together, are displayed in the same color. The distance and line thickness between two circles represent the degree of the relationship between countries.

outcomes[21]. This is particularly pertinent in transplantation, where statistical methods may misestimate outcomes like graft loss[22]. ML provides computational tools that can enhance the decision-making process in medicine, particularly in the context of organ transplantation. Despite their complexity, these computational tools hold promise in improving the understanding of complex medical scenarios and facilitating more informed and precise decision-making in transplantation and other medical disciplines[10,23].

Our study contributes to the field by employing a bibliometric analysis to comprehensively assess the research output in the domain of ML usage in solid organ transplantation. By systematically reviewing a wide range of publications over time, this type of analysis is able to shed light on the prevailing research trends in this rapidly evolving field[24-27]. This bibliometric analysis offers valuable insights into the progress and advancements made in the application of ML to transplantation research. Additionally, our study provides a comprehensive overview of the key areas of interest and the

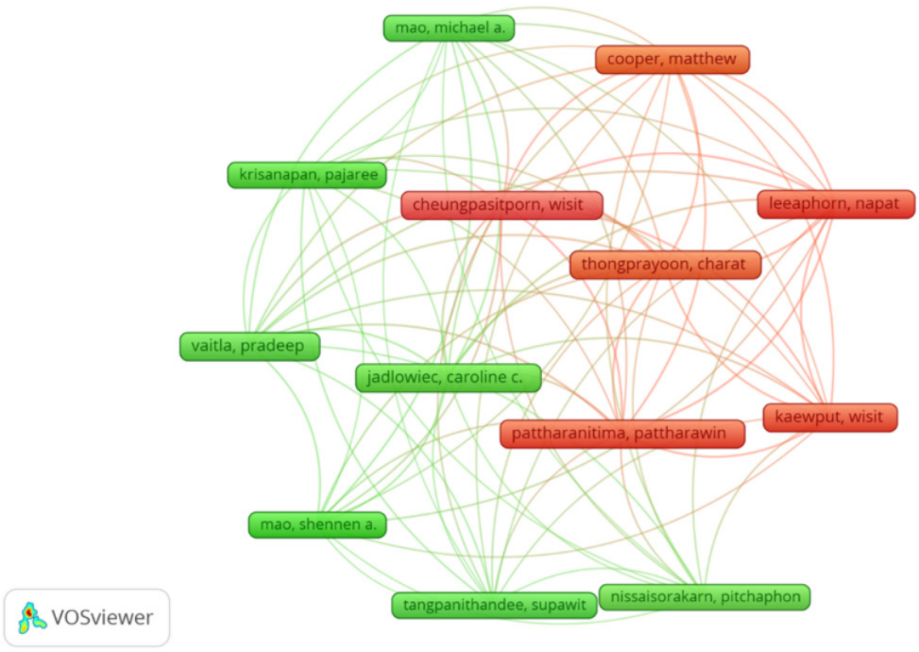


Figure 3 The network visualization of the top contributed authors in the field of machine learning and solid organ transplantation and their interconnections. Each square represents an author, and the size of the square represents the frequency of occurrence. Larger squares indicate that the author appears more frequently. Authors included in the same cluster, who occurred frequently together, are displayed in the same color. The distance and line thickness between the two squares show the degree of the relationship.

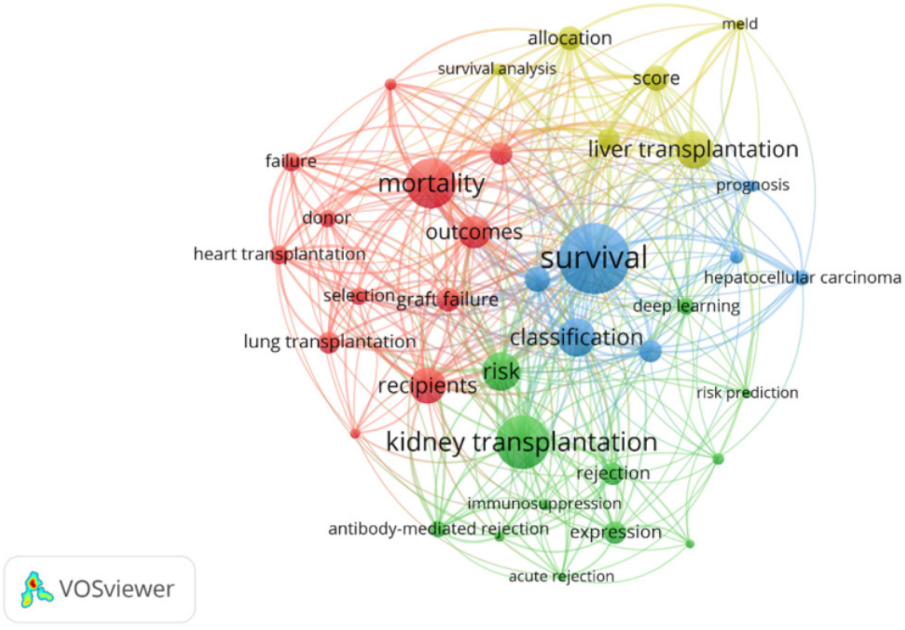


Figure 4 Cluster visualization of the most frequently occurring keywords and their interconnections. Each circle represents a keyword with a label, and the size of the circles indicates the frequency of occurrence. Larger circles indicate that the keyword appears more frequently. Keywords included in the same cluster, which occur frequently together, are displayed in the same color. The distance and line thickness between the two circles show the degree of the relationship.

major contributors to the field. The findings from our bibliometric analysis serve as a foundation for future researchers and clinicians to further explore and deepen our understanding of ML's role in optimizing transplant procedures and improving patient outcomes; furthermore, it may be a way to communicate and collaborate between centers that contribute most to this field.

Our analysis revealed that specialized transplantation journals have shown significant interest in the field of ML usage in solid organ transplantation. The majority of publications were found in esteemed journals like the Journal of Heart and Lung Transplantation, American Journal of Transplantation, Transplantation, and Transplant International. This emphasis on ML by transplant journals underscores its growing importance in transplant medicine and its potential to

enhance patient care and transplant outcomes.

The analysis of the most frequent keywords highlights the current hot topics in the field of ML usage in solid organ transplantation: Patient survival, mortality, outcomes, prediction classification, and risk assessment. The recurrence of these keywords highlights the critical significance of harnessing ML to create predictive algorithms, enabling the identification of high-risk patients, optimizing donor-recipient matching, and personalizing treatment plans (Figure 4).

ML algorithms

ML algorithms analyze historical data and find patterns in massive, unstructured, and complex datasets using statistical, probabilistic, and optimization methods. According to their learning methodologies, ML algorithms can be categorized into three primary categories: Supervised learning, unsupervised learning, and reinforcement learning[3].

In supervised learning, the input features and their matching target outputs are supplied in labeled data, from which the algorithm learns. The objective is to acquire an understanding of the relationship between inputs and outputs so that the algorithm can predict new, unseen data with accuracy. Support Vector Machines (SVM), Decision Trees, Random Forests (RF), Naïve Bayes, and Neural Networks are examples of common algorithms in this category. Supervised learning is frequently employed in tasks such as regression, in which the algorithm predicts a continuous value, and classification, in which the algorithm gives a label to input data[28].

Unsupervised learning algorithms operate on unlabeled data, which means that they are not trained with the desired outputs. Without explicit direction, the algorithm explores structures or patterns in the data. Typical tasks in unsupervised learning include clustering and dimensionality reduction. Unsupervised learning algorithms include Principal Component Analysis, K-Means, Hierarchical Clustering, and Autoencoders[29].

In contrast to supervised and unsupervised learning, reinforcement learning does not explicitly correct suboptimal actions and does not require labeled input/output pairs for training. Rather, it emphasizes finding a middle ground between exploring new possibilities and making use of already-existing knowledge. It does this by having an agent learn from interactions with its surroundings in order to accomplish particular objectives. To maximize the cumulative reward, the agent acts, responds to feedback from the environment in the form of incentives or penalties, and modifies its behavior. When the best course of action is unknown ahead of time, reinforcement learning is frequently employed. Popular reinforcement learning algorithms include Q-Learning, Deep Q Networks, and Policy Gradient Methods[30].

The characteristics of the problem and the available data determine which algorithm is best. Every type of ML algorithm has specific advantages and disadvantages. Rather than employing unsupervised ML algorithms, the majority of ML applications have been developed using supervised ones. In the supervised version, the model is created by learning a dataset with known labels, allowing predictions to be made about the outcomes of examples without labels[2, 3].

ML applications

Recent years have seen significant advances in solid organ transplantation using ML applications. Various studies have explored the use of different ML algorithms to predict graft survival and other critical outcomes in kidney, liver, heart and lung and pediatric transplantation[13]. Specifically, Shadabi *et al*[31] employed an ensemble of artificial neural networks (ANN) to predict post kidney transplantation graft survival. Additionally, Ravikumar *et al*[19] utilized the SVM technique to improve donor and recipient pair matching, increasing the likelihood of graft and recipient survival. These studies illustrate the ways in which ML enhances the outcome of kidney transplantation.

In liver transplantation, the success of the procedure significantly hinges on the compatibility and efficacy of the donor-recipient match. In recognition of this critical aspect, Briceño *et al*[32] proposed a novel donor-recipient matching model that employs two ANN models. The initial ANN was intended to enhance the probability of graft survival, whereas the second ANN was optimized to reduce the likelihood of graft loss. Their groundbreaking work sought to improve liver transplantation outcomes by developing a powerful decision-making system that maximized the concepts of equity, efficiency, and fairness. In keeping with this line of inquiry, a number of additional investigations have employed ML algorithms to predict diverse facets of organ transplantation, encompassing waitlist mortality and post-transplant consequences[13].

Two ANN models were proposed for matching donors and recipients. The first ANN was designed to enhance the probability of graft survival, whereas the second ANN was designed to reduce the likelihood of graft loss. They aimed to develop an efficient system that enhances the equity, thereby improving the outcome of liver transplantation, by using a dataset with over 1000 donor-recipient pairs and 64 donor, recipient, and transplantation variables.

Several ML algorithms have been used in more recent research to predict liver transplantation outcomes. Nagai *et al*[33] created an ANN algorithm for predicting 90-day waitlist mortality, with an area under the curve of 0.936. They divided 105140 patients from the Organ Procurement and Transplantation Network/United Network for Organ Sharing registry listed for transplant between 2002 and 2021 into training and validation datasets. In terms of predicting mortality, the ANN 90-day mortality model performed superior to MELD-based models in every subset. In a similar vein, Bertsimas *et al*[34] proposed an "optimized prediction of mortality" (OPOM) model for 90-day waitlist mortality that makes use of optimal classification trees. The MELD-Na model had an areas under receiver operating characteristic curves (AUROCs) of 0.841, while the OPOM model had 0.859 and could reduce waitlist mortality. In addition to the 90-day prediction timeline, ML models have been tested for cirrhosis patient 1-year mortality. Kanwal *et al*[35] designed three ML models using extreme gradient descent boosting, logistic regression (LR) with LASSO regularization, and a limited LR model. With 107939 cirrhosis patients included, they were able to predict 1-year mortality with an AUROC of 0.78. Deep neural networks (DNNs), RF, and LR models were compared by Guo *et al*[36] and their DNN and RF models outperformed the LR model (AUROC = 0.69) for 1-year mortality prediction, with AUROCs of 0.85-0.86. lastly, Kwong *et al*[37] created an RF model to predict waitlist dropout in patients with hepatocellular carcinoma who were listed for transplant. Using 12

predictive features, they were able to achieve a concordance statistic of 0.74 for waitlist dropout prediction at the 3-, 6-, and 12-month marks. These studies demonstrate the expanding role of ML algorithms in enhancing liver transplant outcome prediction, providing insightful information and possible advantages for liver transplant patient care.

Studies have utilized ML techniques to improve decision-making and predict crucial outcomes in the realm of thoracic organ transplantation. Delen *et al*[18] relied on the UNOS thoracic transplantation database to employ support vector regression, multilayer perceptron, and regression trees to predict the time frame from transplant to death or last follow-up, yielding positive findings. Oztekin *et al*[38] predicted post-lung transplant QoL using genetic algorithms for feature selection and ML algorithms. These studies show that ML can improve thoracic organ transplantation outcomes and provide valuable insights.

In the context of pediatric transplantation, ML techniques have also been investigated. For example, a study[39] used RF and conditional inference trees to determine the influence of specific donor variables. factors on pediatric liver transplantation. At the same time, Miller *et al*[40] assessed a variety of ML algorithms, such as ANN, decision tree, and RF, to predict mortality in the years following pediatric heart transplants. These studies emphasize the potential of ML to enhance outcomes in a variety of transplantation scenarios and its capacity to enhance the field of organ transplantation medicine. Despite the presence of certain obstacles, including small data sizes and insufficient data, the field's ongoing research has the potential to transform transplantation practices and improve patient care.

Overall, use of ML in organ transplantation research has the potential to improve the accuracy of predictions and decision-making processes, thereby optimizing transplantation outcomes and providing medical practitioners with valuable tools. Nevertheless, in order to fully leverage the potential of these techniques and confront the distinctive obstacles that arise in each transplantation scenario, additional research and the standardization of methodologies are imperative.

Emerging frontiers: The intersection between ML and solid organ transplantation is highly promising. As the technology matures and datasets become even more comprehensive, the promise of ML-driven insights in transplantation becomes an exciting frontier, ripe for exploration and innovation.

Predictive analytics: The advanced predictive algorithms of ML show immense promise. It is anticipated that, in the imminent future, these algorithms will serve to markedly refine the process of organ allocation[13]. This requires a system capable of determining recipient compatibility with particular organ donors with an unprecedented degree of accuracy. Utilizing a comprehensive set of variables and analyzing their complex interactions, this evolving methodology has the potential to surpass the current conventional allocation paradigms. Moreover, as we delve deeper into post-transplant scenarios, ML models are being honed to predict individualized patient outcomes following a transplant. Whether it's the potential of organ rejection, susceptibility to infections, or the overall patient survival trajectory, these models leverage extensive datasets to provide these insights.

Advanced imaging and personalized medicine: ML makes advances in analyzing medical images across multiple specialties[4], transplantation is on the cusp of similar advancements. In the near future, transplantation could gain deeper, more nuanced insights into the viability and quality of donor organs, based on the success of ML-powered image analytics in other medical disciplines. These innovations would revolutionize the selection process, enabling medical professionals to make informed decisions regarding organ matches and allocations.

Similarly, as personalized medicine gains traction in other medical fields, transplantation may soon stand to gain. In a future governed by the integration of ML and advanced biomedicine, healthcare practitioners may have the ability to design immunosuppression regimens that are meticulously tailored to the unique biological and physiological profiles of individual recipients. This has the potential to not only mitigate adverse reactions but also significantly decrease the likelihood of organ rejection. Coupled with ML's anticipated predictive capabilities, we may soon be able to predict with unmatched precision how patients will respond to various post-transplant treatments.

Challenges: Although ML has the potential to improve organ transplantation, it also faces a number of challenges[13,23]. Three main areas of concern are the consistency, model security, and quality of the data used in modeling[41-44]. Moreover, a model's generalizability may be restricted and potential biases may be introduced by small sample sizes, variability amongst transplant centers, and inconsistent data collection[13,41-44]. Several models lack external validation and perspective, emphasizing the need for post-implementation monitoring and rigorous external validation in different datasets or data models[13].

Additionally, it is imperative to incorporate both clinical and non-clinical characteristics into research to guarantee equitable transplantation outcomes. Factors such as resource availability, donor-recipient physical compatibility, and geographic disparity can have a significant impact on the results. Depending on how the ML model is developed, certain important population segments may not be well represented, potentially leading to biased predictions[13]. The focus should be placed on procedures that guarantee objectivity in model evaluations. Moreover, If trained on biased or incomplete data, ML can result in inaccurate predictions for donor-recipient matching or post-transplant care, which can lead to misinformation[43,45]. The risk of suboptimal clinical outcomes is heightened by the challenge of comprehending the rationale behind the decisions made by complex ML models ("black-box" models)[45].

Converting ML results into practical clinical insights presents challenges outside of the data itself. Although ML can spot trends, the clinical or physiological justification for them may be elusive, thus results must be both accurate and interpretable[13]. The need for real-time predictions in some transplant scenarios increases this demand. Furthermore, the performance of a model can vary depending on the patient population to which it is applied. As a result, a model developed for one population may not be suitable for another, highlighting the necessity of thorough validation on separate datasets[23,41,42]. Additionally, the steep learning curve that healthcare professionals have is one of the possible

bottlenecks brought about by applying ML. However, with recent advances, many ML libraries are developing user-friendly functions to improve interpretability[43].

CONCLUSION

This bibliometric analysis underscores the growing significance of ML in solid organ transplantation, especially in donor-recipient matching, post-transplant monitoring, and patient management. The increase in publications, driven by contributions from the United States and prominent journals, indicates a heightened interest in the field. The potential of ML to enhance patient outcomes is clear; however, ongoing research and collaboration are crucial to overcome existing challenges and optimize its influence on transplantation practices.

FOOTNOTES

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REFERENCES

1 **Deo RC**. Machine Learning in Medicine. *Circulation* 2015; **132**: 1920-1930 [PMID: 26572668 DOI: 10.1161/CIRCULATIONAHA.115.001593]
2 **Haug CJ**, Drazen JM. Artificial Intelligence and Machine Learning in Clinical Medicine, 2023. *N Engl J Med* 2023; **388**: 1201-1208 [PMID: 36988595 DOI: 10.1056/NEJMra2302038]
3 **Choi RY**, Coyner AS, Kalpathy-Cramer J, Chiang MF, Campbell JP. Introduction to Machine Learning, Neural Networks, and Deep Learning. *Transl Vis Sci Technol* 2020; **9**: 14 [PMID: 32704420 DOI: 10.1167/tvst.9.2.14]
4 **Currie G**, Hawk KE, Rohren E, Vial A, Klein R. Machine Learning and Deep Learning in Medical Imaging: Intelligent Imaging. *J Med Imaging Radiat Sci* 2019; **50**: 477-487 [PMID: 31601480 DOI: 10.1016/j.jmir.2019.09.005]
5 **Heo J**, Yoon JG, Park H, Kim YD, Nam HS, Heo JH. Machine Learning-Based Model for Prediction of Outcomes in Acute Stroke. *Stroke* 2019; **50**: 1263-1265 [PMID: 30890116 DOI: 10.1161/STROKEAHA.118.024293]
6 **Moll M**, Qiao D, Regan EA, Hunninghake GM, Make BJ, Tal-Singer R, McGeachie MJ, Castaldi PJ, San Jose Estepar R, Washko GR, Wells JM, LaFon D, Strand M, Bowler RP, Han MK, Vestbo J, Celli B, Calverley P, Crapo J, Silverman EK, Hobbs BD, Cho MH. Machine Learning and Prediction of All-Cause Mortality in COPD. *Chest* 2020; **158**: 952-964 [PMID: 32353417 DOI: 10.1016/j.chest.2020.02.079]
7 **Sammut SJ**, Crispin-Ortuzar M, Chin SF, Provenzano E, Bardwell HA, Ma W, Cope W, Dariush A, Dawson SJ, Abraham JE, Dunn J, Hiller L, Thomas J, Cameron DA, Bartlett JMS, Hayward L, Pharoah PD, Markowetz F, Rueda OM, Earl HM, Caldas C. Multi-omic machine learning predictor of breast cancer therapy response. *Nature* 2022; **601**: 623-629 [PMID: 34875674 DOI: 10.1038/s41586-021-04278-5]
8 **Grueso S**, Viejo-Sobera R. Machine learning methods for predicting progression from mild cognitive impairment to Alzheimer's disease dementia: a systematic review. *Alzheimers Res Ther* 2021; **13**: 162 [PMID: 34583745 DOI: 10.1186/s13195-021-00900-w]
9 **Cammarota G**, Ianiro G, Ahern A, Carbone C, Temko A, Claesson MJ, Gasbarrini A, Tortora G. Gut microbiome, big data and machine learning to promote precision medicine for cancer. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 635-648 [PMID: 32647386 DOI: 10.1038/s41575-020-0327-3]
10 **Balch JA**, Delitto D, Tighe PJ, Zarrinpar A, Efron PA, Rashidi P, Upchurch GR Jr, Bihorac A, Loftus TJ. Machine Learning Applications in Solid Organ Transplantation and Related Complications. *Front Immunol* 2021; **12**: 739728 [PMID: 34603324 DOI: 10.3389/fimmu.2021.739728]
11 **Vagefi PA**, Bertsimas D, Hirose R, Trichakis N. The rise and fall of the model for end-stage liver disease score and the need for an optimized machine learning approach for liver allocation. *Curr Opin Organ Transplant* 2020; **25**: 122-125 [PMID: 32073494 DOI:

10.1097/MOT.0000000000000734]
12 **Bishara AM**, Lituiev DS, Adelmann D, Kothari RP, Malinoski DJ, Nudel JD, Sally MB, Hirose R, Hadley DD, Niemann CU. Machine Learning Prediction of Liver Allograft Utilization From Deceased Organ Donors Using the National Donor Management Goals Registry. *Transplant Direct* 2021; **7**: e771 [PMID: 34604507 DOI: 10.1097/TXD.0000000000001212]
13 **Gotlieb N**, Azhie A, Sharma D, Spann A, Suo NJ, Tran J, Orchanian-Cheff A, Wang B, Goldenberg A, Chassé M, Cardinal H, Cohen JP, Lodi A, Dieude M, Bhat M. The promise of machine learning applications in solid organ transplantation. *NPJ Digit Med* 2022; **5**: 89 [PMID: 35817953 DOI: 10.1038/s41746-022-00637-2]
14 **Bhat M**, Rabindranath M, Chara BS, Simonetto DA. Artificial intelligence, machine learning, and deep learning in liver transplantation. *J Hepatol* 2023; **78**: 1216-1233 [PMID: 37208107 DOI: 10.1016/j.jhep.2023.01.006]
15 **Chen C**, Chen B, Yang J, Li X, Peng X, Feng Y, Guo R, Zou F, Zhou S, Hei Z. Development and validation of a practical machine learning model to predict sepsis after liver transplantation. *Ann Med* 2023; **55**: 624-633 [PMID: 36790357 DOI: 10.1080/07853890.2023.2179104]
16 **Fusfeld L**, Menon S, Gupta G, Lawrence C, Masud SF, Goss TF. US payer budget impact of a microarray assay with machine learning to evaluate kidney transplant rejection in for-cause biopsies. *J Med Econ* 2022; **25**: 515-523 [PMID: 35345966 DOI: 10.1080/13696998.2022.2059221]
17 **van Eck NJ**, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics* 2010; **84**: 523-538 [PMID: 20585380 DOI: 10.1007/s11192-009-0146-3]
18 **Delen D**, Oztekin A, Kong ZJ. A machine learning-based approach to prognostic analysis of thoracic transplantations. *Artif Intell Med* 2010; **49**: 33-42 [PMID: 20153956 DOI: 10.1016/j.artmed.2010.01.002]
19 **Ravikumar A**, Saritha R, Chandra V. Support vector machine based prognostic analysis of renal transplantations. *2013 Fourth Int Conf Computi, Commun Netw Technol (ICCCNT)* 2013; **9**: 1-6 [DOI: 10.1109/icccnt.2013.6726819]
20 **Lau L**, Kankanige Y, Rubinstein B, Jones R, Christophi C, Muralidharan V, Bailey J. Machine-Learning Algorithms Predict Graft Failure After Liver Transplantation. *Transplantation* 2017; **101**: e125-e132 [PMID: 27941428 DOI: 10.1097/TP.0000000000001600]
21 **Briceño J**, Calleja R, Hervás C. Artificial intelligence and liver transplantation: Looking for the best donor-recipient pairing. *Hepatobiliary Pancreat Dis Int* 2022; **21**: 347-353 [PMID: 35321836 DOI: 10.1016/j.hbpd.2022.03.001]
22 **Kampaktsis PN**, Tzani A, Doulamis IP, Moustakidis S, Drosou A, Diakos N, Drakos SG, Briasoulis A. State-of-the-art machine learning algorithms for the prediction of outcomes after contemporary heart transplantation: Results from the UNOS database. *Clin Transplant* 2021; **35**: e14388 [PMID: 34155697 DOI: 10.1111/ctr.14388]
23 **Guijo-Rubio D**, Gutiérrez PA, Hervás-Martínez C. Machine learning methods in organ transplantation. *Curr Opin Organ Transplant* 2020; **25**: 399-405 [PMID: 32618714 DOI: 10.1097/MOT.0000000000000774]
24 **Rawashdeh B**, AlRyalat SA, Abuassi M, Prasad R, Cooper M. Unveiling transplantation research productivity of United States: A bibliometric analysis. *World J Transplant* 2023; **13**: 391-402 [PMID: 38174148 DOI: 10.5500/wjt.v13.i6.391]
25 **Rawashdeh B**, AlRyalat SA, Abuassi M, Syaj S, Jeyyab MA, Pearson T, Kim J. Impact of COVID-19 on abdominal organ transplantation: A bibliometric analysis. *Transpl Infect Dis* 2023; **25**: e14027 [PMID: 36762493 DOI: 10.1111/tid.14027]
26 **Rawashdeh B**, Arpali E, Al Abdallat H, Cooper M, Dunn T. Four Decades of Research Productivity and Hot Spots in Pancreas Transplantation. *Prog Transplant* 2024; **34**: 119-129 [PMID: 39196572 DOI: 10.1177/15269248241268719]
27 **Rawashdeh B**, Kim J, Prasad R, Cooper M. A Global Overview on the Evolution, Debate, and Research Output on Liver Transplant Perfusion Machines. *Exp Clin Transplant* 2024; **22**: 35-42 [PMID: 38284373 DOI: 10.6002/ect.2023.0180]
28 **Uddin S**, Khan A, Hossain ME, Moni MA. Comparing different supervised machine learning algorithms for disease prediction. *BMC Med Inform Decis Mak* 2019; **19**: 281 [PMID: 31864346 DOI: 10.1186/s12911-019-1004-8]
29 **Iqbal T**, Elahi A, Wijns W, Shahzad A. Exploring Unsupervised Machine Learning Classification Methods for Physiological Stress Detection. *Front Med Technol* 2022; **4**: 782756 [PMID: 35359827 DOI: 10.3389/fmedt.2022.782756]
30 **Liu E**, He R, Chen X, Yu C. Deep Reinforcement Learning Based Optical and Acoustic Dual Channel Multiple Access in Heterogeneous Underwater Sensor Networks. *Sensors (Basel)* 2022; **22** [PMID: 35214530 DOI: 10.3390/s22041628]
31 **Shadabi F**, Cox RJ, Sharma D, Petrovsky N. A Hybrid Decision Tree – Artificial Neural Networks Ensemble Approach for Kidney Transplantation Outcomes Prediction. *Lecture Notes in Computer Science* 2005 [DOI: 10.1007/11552451_16]
32 **Briceño J**, Cruz-Ramírez M, Prieto M, Navasa M, Ortiz de Urbina J, Orti R, Gómez-Bravo MÁ, Otero A, Varo E, Tomé S, Clemente G, Bañares R, Bárcena R, Cuervas-Mons V, Solórzano G, Vinaixa C, Rubín A, Colmenero J, Valdivieso A, Ciria R, Hervás-Martínez C, de la Mata M. Use of artificial intelligence as an innovative donor-recipient matching model for liver transplantation: results from a multicenter Spanish study. *J Hepatol* 2014; **61**: 1020-1028 [PMID: 24905493 DOI: 10.1016/j.jhep.2014.05.039]
33 **Nagai S**, Nallabasannagari AR, Moonka D, Reddiboina M, Yeddula S, Kitajima T, Francis I, Abouljoud M. Use of neural network models to predict liver transplantation waitlist mortality. *Liver Transpl* 2022; **28**: 1133-1143 [PMID: 35224855 DOI: 10.1002/lt.26442]
34 **Bertsimas D**, Kung J, Trichakis N, Wang Y, Hirose R, Vagefi PA. Development and validation of an optimized prediction of mortality for candidates awaiting liver transplantation. *Am J Transplant* 2019; **19**: 1109-1118 [PMID: 30411495 DOI: 10.1111/ajt.15172]
35 **Kanwal F**, Taylor TJ, Kramer JR, Cao Y, Smith D, Gifford AL, El-Serag HB, Naik AD, Asch SM. Development, Validation, and Evaluation of a Simple Machine Learning Model to Predict Cirrhosis Mortality. *JAMA Netw Open* 2020; **3**: e2023780 [PMID: 33141161 DOI: 10.1001/jamanetworkopen.2020.23780]
36 **Guo A**, Mazumder NR, Ladner DP, Foraker RE. Predicting mortality among patients with liver cirrhosis in electronic health records with machine learning. *PLoS One* 2021; **16**: e0256428 [PMID: 34464403 DOI: 10.1371/journal.pone.0256428]
37 **Kwong A**, Hameed B, Syed S, Ho R, Mard H, Arshad S, Ho I, Suleman T, Yao F, Mehta N. Machine learning to predict waitlist dropout among liver transplant candidates with hepatocellular carcinoma. *Cancer Med* 2022; **11**: 1535-1541 [PMID: 35029055 DOI: 10.1002/cam4.4538]
38 **Oztekin A**, Al-ebbini L, Sevkli Z, Delen D. A decision analytic approach to predicting quality of life for lung transplant recipients: A hybrid genetic algorithms-based methodology. *Eur J Oper Res* 2018; **266**: 639-651 [DOI: 10.1016/j.ejor.2017.09.034]
39 **Wadhwani SI**, Hsu EK, Shaffer ML, Anand R, Ng VL, Bucuvalas JC. Predicting ideal outcome after pediatric liver transplantation: An exploratory study using machine learning analyses to leverage Studies of Pediatric Liver Transplantation Data. *Pediatr Transplant* 2019; **23**: e13554 [PMID: 31328849 DOI: 10.1111/petr.13554]
40 **Miller R**, Tumin D, Cooper J, Hayes D Jr, Tobias JD. Prediction of mortality following pediatric heart transplant using machine learning algorithms. *Pediatr Transplant* 2019; **23**: e13360 [PMID: 30697906 DOI: 10.1111/petr.13360]

41 **Dou B**, Zhu Z, Merkurjev E, Ke L, Chen L, Jiang J, Zhu Y, Liu J, Zhang B, Wei GW. Machine Learning Methods for Small Data Challenges in Molecular Science. *Chem Rev* 2023; **123**: 8736-8780 [PMID: 37384816 DOI: 10.1021/acs.chemrev.3c00189]

42 **Alafif T**, Tehame AM, Bajaba S, Barnawi A, Zia S. Machine and Deep Learning towards COVID-19 Diagnosis and Treatment: Survey, Challenges, and Future Directions. *Int J Environ Res Public Health* 2021; **18** [PMID: 33513984 DOI: 10.3390/ijerph18031117]

43 **Tran J**, Sharma D, Gotlieb N, Xu W, Bhat M. Application of machine learning in liver transplantation: a review. *Hepatol Int* 2022; **16**: 495-508 [PMID: 35020154 DOI: 10.1007/s12072-021-10291-7]

44 **Dinsdale NK**, Bluemke E, Sundaresan V, Jenkinson M, Smith SM, Namburete AIL. Challenges for machine learning in clinical translation of big data imaging studies. *Neuron* 2022; **110**: 3866-3881 [PMID: 36220099 DOI: 10.1016/j.neuron.2022.09.012]

45 **Obermeyer Z**, Emanuel EJ. Predicting the Future - Big Data, Machine Learning, and Clinical Medicine. *N Engl J Med* 2016; **375**: 1216-1219 [PMID: 27682033 DOI: 10.1056/NEJMp1606181]

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CASE REPORT

Success of intravenous immunoglobulin and steroids in managing severe COVID-19 following lung transplantation: A case report

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) pneumonia with severe septic shock and acute respiratory distress syndrome (ARDS) are critical illnesses for patients following transplant. Intravenous immunoglobulin (IVIG) plays a role in both immune support and inflammation control, especially in immunocompromised patients. This case report describes the first successful experience using IVIG and pulse steroids to manage this critical condition following lung transplantation.

CASE SUMMARY

A 65-year-old male patient reported a history of chronic obstructive pulmonary disease and poor lung function and received bilateral sequential lung transplantations. Postoperatively, he developed COVID-19 pneumonia, severe septic shock, and ARDS. He recovered from this critical condition after empirical antibiotics administration and veno-venous extracorporeal membrane oxygenation, in addition to IVIG and pulse steroids.

CONCLUSION

IVIG is a valuable adjunct in managing severe sepsis in lung transplant recipients after COVID-19 infection. We aim, for the first time, to report the success of such a management approach for COVID-19 ARDS and sepsis in the post-lung transplant setting. With further investigations, this is a starting point for wider analysis of such an approach in this setting and consequently helps guide clinical practice for such a challenging patient population moving forward.

Key Words: COVID-19; Septic shock; Intravenous immunoglobulin; Lung transplantation; Post-transplant complications; Case report

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Core Tip: The first successful experience indicated intravenous immunoglobulin as a valuable adjunct in managing severe coronavirus disease 2019 infection complicated with severe acute respiratory distress syndrome and septic shock in a lung transplant recipient.

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INTRODUCTION

Patients with transplanted organs, who experience chronic immunosuppression, may demonstrate a heightened susceptibility to coronavirus disease 2019 (COVID-19) pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) compared with the general population[1]. Managing this condition, particularly in patients with exacerbation post-cytokine storm, with or without concurrent allograft deterioration, poses a significant challenge in the clinical setting, primarily because of the lack of targeted antiviral agents[2]. Intravenous immunoglobulin (IVIG) and corticosteroids have been explored for treating severe COVID-19, with varying results based on timing, dosing, and patient conditions[3-5]. This report emphasizes the efficacy of a combined therapeutic regimen that involved high-dose IVIG and corticosteroid pulses administered in a critical case of COVID-19 pneumonia with severe acute respiratory distress syndrome (ARDS) and septic shock in a patient who had undergone bilateral lung transplantation. The patient, requiring mechanical ventilation and extracorporeal membrane oxygenation (ECMO) support due to COVID-19 pneumonia, exhibited marked clinical improvement and progressive recovery of allograft function after IVIG and methylprednisolone therapy. This resulted in the patient's discharge 114 days after treatment initiation. The synergistic immunomodulatory action of IVIG and the anti-inflammatory and immunosuppressive capabilities of corticosteroids may provide a viable therapeutic approach for managing severe COVID-19 pneumonia, particularly in patients with transplanted lung grafts experiencing an uncontrolled inflammatory response.

CASE PRESENTATION

Chief complaints

A 65-year-old man was admitted to our chest surgery ward for preparation for lung transplantation due to the end-stage lung disease caused by chronic obstructive pulmonary disease (COPD) since 2015.

History of present illness

The patient suffered from COPD since 2015. He had episodes of acute COPD exacerbations with hospitalization. Recently, he demonstrated forced expiratory volume in 1 second of 14% of predicted values and severely limited 6-minute walking distance (154 m; 23.5% of predicted values). He received long-term oxygen support since 2017. Currently, he requires oxygen supplementation with oxygen of 2 L/minute for 24 hours a day to meet oxygen demand. He was listed as a recipient of lung transplantation in April 2023 because of progressive disease. The pretransplant chest plain film revealed hyperinflation and increased opacification of both lung fields except for the right lower lung field which demonstrated hypertranslucency (Figure 1A). The pretransplant chest computed tomography (CT) revealed a diffuse emphysematous change of bilateral lungs, with marked right lung destruction (Figure 2). He underwent sequential double lung transplantation on September 29, 2023. The donor was a 39-year-old male patient with diffuse subarachnoid hematoma without cardiopulmonary resuscitation. The donor's arterial blood gas analysis indicated an arterial oxygen partial pressure and fractional inspired oxygen (PaO_2/FiO_2) ratio of 591, and the chest plain film detected a bilateral clear lung field (Figure 1B). The donor's and recipient's human leukocyte antigen panel reactive antibody were both 0%. They were both 175 and 165 cm in height, respectively.

The sequential double lung transplantation took approximately 10 hours. The right-side lung transplantation was first conducted, followed by left-side lung graft implantation. Pleural adhesion lysis was performed after entering the bilateral pleural cavity. A thoracic surgeon performed an end-to-end anastomosis of the bronchus. The membranous portions of the donor and recipient bronchi were approximated and anastomosed with a running suture, whereas the cartilaginous layers were anastomosed with interrupted sutures. A cardiovascular surgeon performed the end-to-end anastomosis of pulmonary arteries and veins. The patient exhibited an unstable hemodynamic status during the left-side lung transplantation, which may be caused by the cardiac traction and compression. Venoarterial (V-A) ECMO with cannulation at the left femoral vein to the right femoral artery was implanted.

Postoperatively, the patient was transferred to the surgical intensive care unit. Primary graft dysfunction manifested itself as hypoxemia and alveolar infiltration on the chest radiograph (Figure 1C). Additionally, the COVID-19 rapid screen test was positive on postoperative day (POD) 1. Daily intravenous remdesivir of 100 mg was intravenously administered to reduce the viral load. V-A ECMO was shifted to veno-venous (V-V) ECMO with cannulation at the right

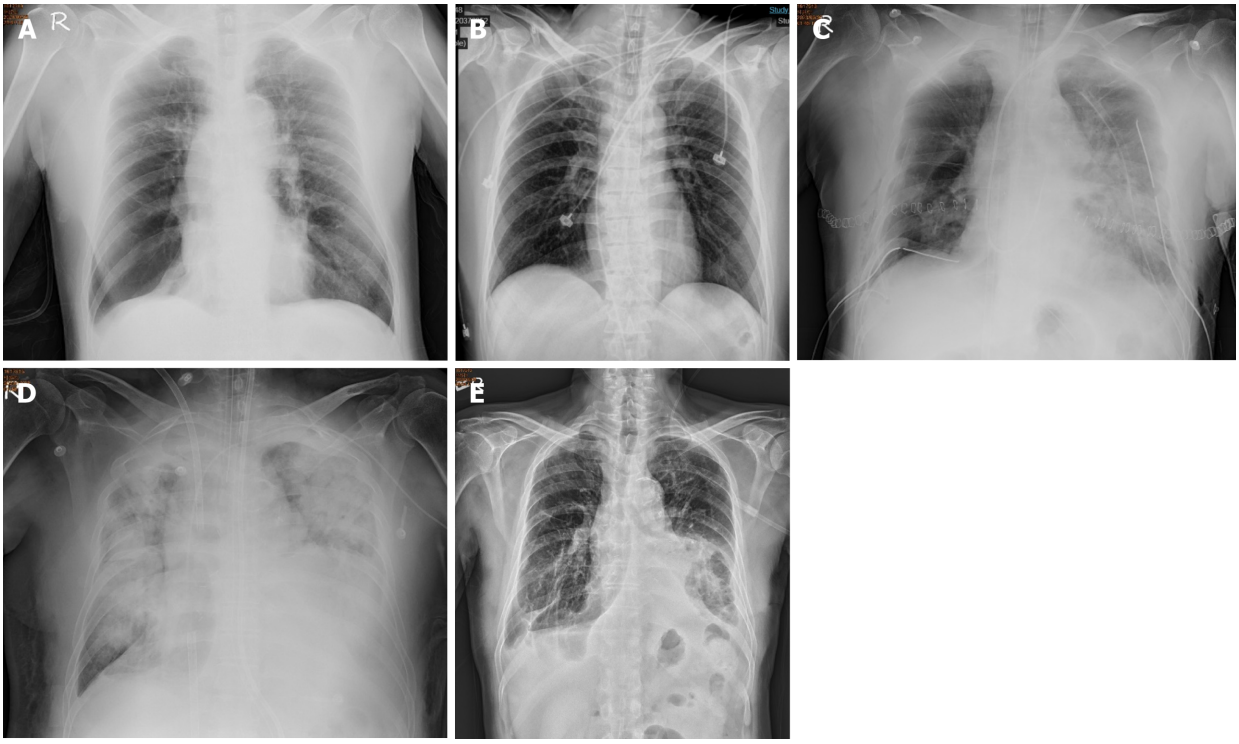


Figure 1 Chest plain film. A: The pretransplant chest plain film showed hyperinflation and increased opacification of both lung fields except for the right lower lung field which showed hypertranslucency; B: Donor chest plain film showing clear bilateral lung fields without opacity; C: Postoperative chest plain film showing increased infiltration in the left lung, with bilateral chest tube retention in the pleural cavities and surgical stitches over the chest wall; D: Chest plain film on postoperative day 8 showing diffuse patchy opacities over both lungs with veno-venous extracorporeal membrane oxygenation support; E: Chest plain film on postoperative day 121 showing a stable condition after the removal of the tracheostomy tube with full expansion of both lungs.

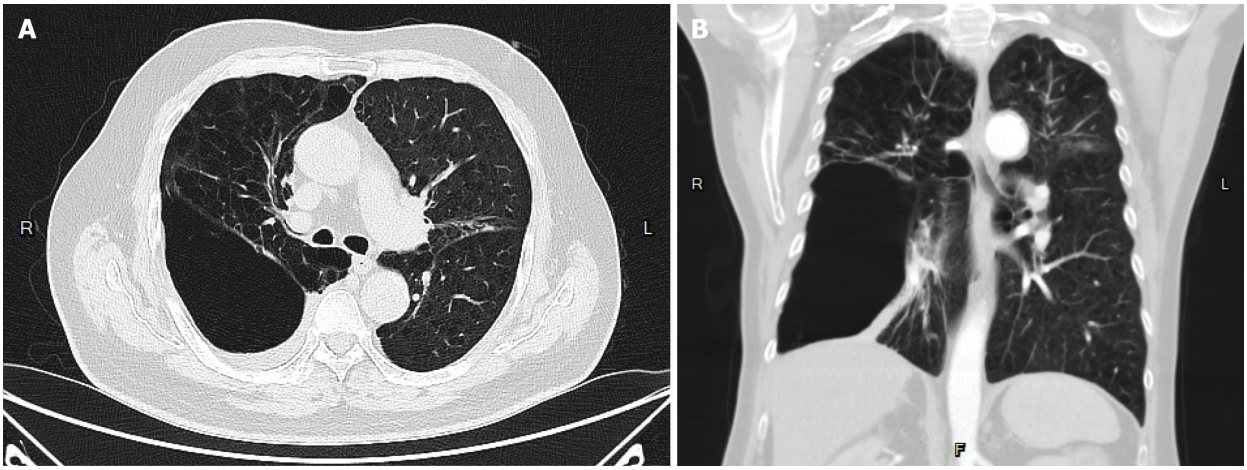


Figure 2 Recipient's pretransplant chest computed tomography. A: Axial view; B: Coronal view. Pretransplant chest computed tomography showed diffuse emphysematous change of bilateral lungs, with marked destruction of the right lung.

internal jugular vein and right femoral vein on POD 7 under stable hemodynamic status to reduce the incidence of V-A ECMO complications. However, severe ARDS and septic shock subsequently occurred on POD 8 (Figure 1D). The patient's oxygenation and hemodynamic status rapidly deteriorated, ultimately requiring the high ventilator settings and ECMO and vasopressor support within 5 days of IgG-enriched IVIG therapy plus steroids (intravenous Privigen of 5000 mg daily plus Medason of 125 mg every 12 hours), and the patient recovered gradually. The serum C-reactive protein level decreased from 16.09 mg/dL at the start of IVIG therapy to 4.11 mg/dL 5 days thereafter. Flexible bronchoscopy was performed at 3-day intervals for airway secretion clearance to assess the condition of the bronchial anastomosis (Figure 3). A bronchial complication was not observed. The V-V ECMO was removed on POD 35. A tracheostomy was conducted on POD 43. The patient was weaned off the ventilator on POD 50. The tracheostomy tube was removed on POD 110. The patient was discharged on POD 121 after the multidisciplinary team care and pulmonary rehabilitation. The follow-up chest plain film demonstrated the remission of pneumonia patches and a stable condition (Figure 1E).

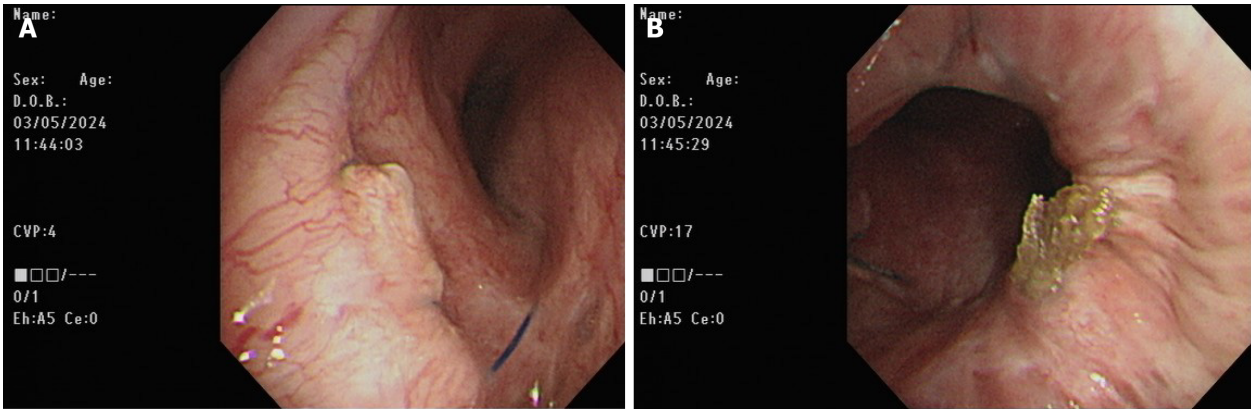


Figure 3 Post-operative flexible bronchoscopy. A: Right bronchial anastomosis; B: Left bronchial anastomosis. Bilateral bronchial anastomoses showing no dehiscence or stricture under flexible bronchoscopy.

The timeline of the events we mentioned was summarized as Table 1.

History of past illness

The patient was diagnosed with COPD in 2015. He had frequent episodes of secondary pneumothorax and COPD with acute exacerbations from 2015 to 2023.

Personal and family history

The patient, an ex-smoker, denied any family cancer history.

Physical examination

The physical examination showed a barrel-shaped chest and decreased bilateral chest sounds.

Laboratory examinations

The respiratory panel for virus screening was positive for COVID-19 on POD 1. Laboratory data on POD 8 (the day before the administration of IVIG and steroids) were as follows:

The results of the arterial blood gas analysis were as follows: PH, 7.471-7.488; PaCO, 39.7-35.4 mmHg; PaO_2, 73-77.8 mmHg; HCO^{3-}, 29.2-27.1 mmol/L; SO_2, 95.4%-96.4%; PiO_2/FiO_2, 112.3-119.7 mmHg, under V-V ECMO (pump speed, 2490 RPM; blood flow, 2.46 L/minute; gas flow, 2.5; FiO_2, 100%) and APRV MODE with T high, 4 seconds; T low, 0.4 seconds; P high, 26; P low, 0; P mean, 24; TVi, 290-285 mL; RR, 13-14 BPM; MV, 4.9-3.8 L/minute; SpO2, 88%-94%.

The patient's blood examination revealed an elevated leukocyte count of 18020/L, with 92.5% neutrophils, a low hemoglobin level at 8.8 g/dL, and a high procalcitonin level at 6.06 ng/mL.

The first positive sputum culture was reported on POD 10, which indicated the growth of *Stenotrophomonas maltophilia* and *Acinetobacter nosocomialis,* which were sensitive to tigecycline and minocycline.

Imaging examinations

The postoperative chest CT film revealed infiltration over the left lower lung field, which indicated primary graft dysfunction of the left lung. Chest plain film on POD 3 revealed patch opacities of bilateral lungs, indicating COVID-19 with pulmonary involvement.

MULTIDISCIPLINARY EXPERT CONSULTATION

An infection disease specialist and a rheumatologist recommended standard antibiotic and antiviral therapy in combination with IVIG, an immune-modulating agent to manage severe ARDS and septic shock.

FINAL DIAGNOSIS

The final diagnosis was post-lung transplantation COVID-19 complicated with ARDS and septic shock.

TREATMENT

IVIG infusion plus steroid administration, empiric antibiotic administration, and V-V ECMO support.

Table 1 Timeline of events

Timeline of events	
2023/9/28	Admission
2023/9/29	Sequential double lung transplantation; VA ECMO; inhale NO support
2023/9/30	COVID-19 (+) > remdisivir
2023/10/3	Turn off the inotropic agent
2023/10/7	ARDS and severe septic shock
2023/10/7-2023/10/12	IVIG plus steroids
2023/10/10	Turn off the inotropic agent
2023/10/27	Bedside rehabilitation
2023/11/5	Remove ECMO
2023/11/13	Tracheostomy
2023/12/5	Transfer to ordinary ward
2024/2/5	Discharge

ECMO: Extracorporeal membrane oxygenation; COVID-19: Coronavirus disease 2019; ARDS: Acute respiratory distress syndrome; IVIG: Intravenous immunoglobulin.

OUTCOME AND FOLLOW-UP

After IVIG infusion, empiric antibiotic administration, and V-V ECMO support, the patient recovered from ARDS and septic shock. Finally, the patient was weaned off the ventilator and was discharged POD 121. The patient remained stable during the outpatient follow-up.

DISCUSSION

Individuals who have undergone lung transplantation are at high risk for severe COVID-19, primarily because of a weakened immune system. The virus triggers an excessive immune reaction, also known as a cytokine storm, which is a severe hyperinflammatory state in such patients. This condition may cause septic shock, which is marked by severe circulation, cellular function, and metabolism disruptions, thereby substantially increasing the risk for mortality[6].

Messika *et al*[7] investigated 35 lung transplant recipients across 11 French transplant centers who contracted COVID-19 during the study period. The diagnosis was confirmed through positive reverse-transcription polymerase chain reaction tests for SARS-CoV-2 in 30 (85.7%) patients, with a strong suspicion in the remaining 5 (14.3%). Of the 13 patients with critical illness, 7 (53.9%) underwent invasive mechanical ventilation. The overall survival rate was 85.7%, following a median follow-up of 50 (range, 41.0-56.5) days. Among the non-survivors, four experienced bronchial complications or an increase in immunosuppression before contracting the virus. Lung transplant recipients with COVID-19 are at greater risk of critical conditions, such as septic shock, and are more likely to require intensive care unit admission and mechanical ventilation, causing higher mortality rates compared with the general population.

Septic shock incidence among lung transplant recipients with COVID-19 significantly varies across different studies, a variation that likely reflects differences in patient demographics, transplant-specific factors, and COVID-19 timing following transplant. Managing COVID-19 in these patients requires a nuanced approach that balances antiviral treatments, supportive care, and adjustments to immunosuppressive therapies. Early intervention is crucial, as is vigilant monitoring for sepsis signs and robust supportive care. The therapeutic regimen, including steroids, antiviral agents, such as remdesivir, and immunomodulatory drug administration, must be carefully customized to each patient's unique circumstances to reduce the risk of progression to septic shock[8].

IVIG is selected for its comprehensive range of antibodies, which neutralize a diverse array of pathogens. It provides passive immunity to recipients, improving the immune system's capacity to combat infections. Additionally, IVIG possesses anti-inflammatory properties, which play a crucial role in managing the systemic inflammatory response syndrome frequently associated with sepsis. This makes IVIG a valuable tool in both immune support and inflammation control.

IVIG administration is indicated for several purposes in organ transplantation and severe sepsis as follows:

Prophylaxis

IVIG is administered to prevent infections during high-risk periods, particularly just after an organ transplant, to improve patient outcomes by boosting immune defenses.

Treatment of established infections

IVIG serves as an adjunct to standard antimicrobial therapy. It is valuable when dealing with infections related to multidrug-resistant organisms or suspected polymicrobial infections, thereby improving treatment regimen efficacy.

Immune response modulation

IVIG helps in reducing the severity of the sepsis-associated inflammatory response. This immune system modulation decreases the risk of advancing to septic shock, thereby improving patient management and survival[9].

Few studies have discussed issues on IVIG and lung transplantations. IVIG was used for the desensitization protocol for recipients after lung transplantations.

The non-IVIG group demonstrated a higher incidence of donor-specific antibody development (58.8% *vs* 33.3%), with an odds ratio of 2.80 (95% confidence interval: 0.77-10.79, $P = 0.13$), compared with the IVIG group. The median time to antibody development was 9 (Q1, Q3: 7, 19) and 28 (Q1, Q3: 7, 58) days for the non-IVIG and IVIG groups, respectively. No significant differences were observed between the groups in terms of primary graft dysfunction 72 hours following transplant or the incidence of acute cellular rejection, antibody-mediated rejection, and chronic lung allograft dysfunction at 12 months[10].

A systematic review and meta-analysis demonstrated sufficient evidence to support that IVIG reduces sepsis mortality. However, fewer articles have revealed the role of IVIG in controlling sepsis in solid-organ transplantation, particularly in recipients after lung transplantation.

The limitation of the present study includes unavailable data on serum immunoglobulin levels that could represent the inflammation status.

To the best of our knowledge, this report is the first to address the successful experience and potential therapeutic value of IVIG in treating severe COVID-19 following lung transplantation[11].

CONCLUSION

IVIG represents a valuable adjunct in treating severe sepsis in lung transplant recipients after COVID-19. Its use, both prophylactically and therapeutically, supports the immune system's capacity to combat infections, thereby improving patient outcomes. This warrants investigation moving forward to determine the ideal management for such a patient population. This would consequently pave the way for establishing guidelines for managing such complex patients in the post-lung transplant setting.

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FOOTNOTES

Author contributions: Kuo YS wrote the manuscript; Kuo YS, Lin KH, Chen YY, Tsai YM, and Wu TH attended the postoperative care; Kuo YS and Huang HK performed the donor-lung graft harvest surgery; Kuo YS and Huang TW performed the sequential double lung transplantation in this case; All authors have read and approved the final manuscript.

Informed consent statement: After obtaining approval from the Institutional Review Board (IRB) at Tri-Service General Hospital, the study (IRB number: C202415028) was conducted in accordance with the approved protocol. The IRB approval process ensures that the study adheres to ethical guidelines and protects the rights and welfare of human subjects. The study participant provided informed consent before enrollment, and all data collected were kept confidential and handled in accordance with data protection regulations.

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REFERENCES

1 **Azzi Y**, Bartash R, Scalea J, Loarte-Campos P, Akalin E. COVID-19 and Solid Organ Transplantation: A Review Article. *Transplantation* 2021; **105**: 37-55 [PMID: 33148977 DOI: 10.1097/TP.0000000000003523]
2 **Castelli V**, Cimini A, Ferri C. Cytokine Storm in COVID-19: "When You Come Out of the Storm, You Won't Be the Same Person Who Walked in". *Front Immunol* 2020; **11**: 2132 [PMID: 32983172 DOI: 10.3389/fimmu.2020.02132]
3 **Kwapisz D**, Bogusławska J. Intravenous immunoglobulins (IVIG) in severe/critical COVID-19 adult patients. *Biomed Pharmacother* 2023; **163**: 114851 [PMID: 37167723 DOI: 10.1016/j.biopha.2023.114851]
4 **Ali HS**, Elshafei MS, Saad MO, Mitwally HA, Al Wraidat M, Aroos A, Shaikh N, Ananthegowda DC, Abdelaty MA, George S, Nashwan AJ, Mohamed AS, Khatib MY. Clinical outcomes of intravenous immunoglobulin therapy in COVID-19 related acute respiratory distress syndrome: a retrospective cohort study. *BMC Pulm Med* 2021; **21**: 354 [PMID: 34743710 DOI: 10.1186/s12890-021-01717-x]
5 **Liu X**, Cao W, Li T. High-Dose Intravenous Immunoglobulins in the Treatment of Severe Acute Viral Pneumonia: The Known Mechanisms and Clinical Effects. *Front Immunol* 2020; **11**: 1660 [PMID: 32760407 DOI: 10.3389/fimmu.2020.01660]
6 **Gusev E**, Sarapultsev A, Solomatina L, Chereshnev V. SARS-CoV-2-Specific Immune Response and the Pathogenesis of COVID-19. *Int J Mol Sci* 2022; **23** [PMID: 35163638 DOI: 10.3390/ijms23031716]
7 **Messika J**, Eloy P, Roux A, Hirschi S, Nieves A, Le Pavec J, Sénéchal A, Saint Raymond C, Carlier N, Demant X, Le Borgne A, Tissot A, Debray MP, Beaumont L, Renaud-Picard B, Reynaud-Gaubert M, Mornex JF, Falque L, Boussaud V, Jougon J, Mussot S, Mal H; French Group of Lung Transplantation. COVID-19 in Lung Transplant Recipients. *Transplantation* 2021; **105**: 177-186 [PMID: 33141808 DOI: 10.1097/TP.0000000000003508]
8 **Zimmermann J**, Glueck OM, Fertmann JM, Sienel WG, Yavuz G, Damirov F, Kovács JR, Tufman A, Irlbeck M, Kneidinger N, Michel S, Kauke T, Hatz RA, Schneider CP. COVID-19 in Recent Lung Transplant Recipients: Clinical Outcomes and Management Strategies. *Transplant Proc* 2022; **54**: 1504-1516 [PMID: 35120764 DOI: 10.1016/j.transproceed.2021.12.014]
9 **Perez EE**, Orange JS, Bonilla F, Chinen J, Chinn IK, Dorsey M, El-Gamal Y, Harville TO, Hossny E, Mazer B, Nelson R, Secord E, Jordan SC, Stiehm ER, Vo AA, Ballow M. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol* 2017; **139**: S1-S46 [PMID: 28041678 DOI: 10.1016/j.jaci.2016.09.023]
10 **Goldsby J**, Beermann K, Frankel C, Parish A, Stauffer N, Schandert A, Erkanli A, Reynolds JM. Preemptive immune globulin therapy in sensitized lung transplant recipients. *Transpl Immunol* 2023; **80**: 101904 [PMID: 37499884 DOI: 10.1016/j.trim.2023.101904]
11 **Pan B**, Sun P, Pei R, Lin F, Cao H. Efficacy of IVIG therapy for patients with sepsis: a systematic review and meta-analysis. *J Transl Med* 2023; **21**: 765 [PMID: 37898763 DOI: 10.1186/s12967-023-04592-8]



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