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REVIEW

Vaccinations in kidney transplant recipients: Clearing the muddy waters

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Abstract

Vaccine preventable diseases account for a significant proportion of morbidity and mortality in transplant recipients and cause adverse outcomes to the patient and allograft. Patients should be screened for vaccination history at the time of pre-transplant evaluation and vaccinated at least four weeks prior to transplantation. For non-immune patients, dead-vaccines can be administered starting at six months post-transplant. Live attenuated vaccines are contraindicated after transplant due to concern for infectious complications from the vaccine and every effort should be made to vaccinate prior to transplant. Since transplant recipients are on life-long immunosuppression, these patients may have lower rates of serological conversion, lower mean antibody titers and waning of protective immunity over shorter period as compared to general population. Recommendations regarding booster dose in kidney transplant recipients with sub-optimal serological response are lacking. Travel plans should be part of routine post-transplant assessment and pre-travel vaccines and counseling should be provided. More studies are needed on vaccination schedules, serological response, need for booster doses and safety of live attenuated vaccines in this special population.

Key words: Immunizations; Kidney transplant; Vaccines; Transplant outcomes; Serological response

Core tip: Vaccine-preventable disease can cause adverse patient and allograft outcomes

in kidney transplant recipients. Patients should be screened for vaccinations pre-transplant and catch up immunization should be provided at least four weeks prior to transplantation. For non-immune patients, catch-up immunization should start six months post-transplantation. Live attenuated vaccines are contra-indicated in transplant patients. There is limited data that suggests safety of live vaccines in selective population on low immunosuppression. Travel plans should be part of routine post-transplant assessment and pre-travel vaccines and counseling should be provided.

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BACKGROUND

With advancements in medicine and improved patient survival, there is a growing population of solid organ transplant (SOT) recipients[1]. Advanced immunosuppressive regimens have emerged and acute rejection rates have substantially declined[2]. Infection prophylaxis and rapid diagnosis of infectious complications have allowed patients to tolerate these more intense immunosuppressive regimens, yet vaccine preventable diseases still account for a significant proportion of morbidity and mortality in transplant recipients[2]. The Centers for Disease Control and Prevention (CDC) estimates that each year there are roughly 40000 cases and 4000 deaths attributable to invasive pneumococcal disease, which occurs in organ transplant recipients at a rate 25 times greater than in the general population[3]. It is estimated that the percentage of high-risk adults aged 18-64 vaccinated against pneumococcal disease to be only 21%[4]. Despite the burden of illness in this population, approved and recommended vaccinations remain underutilized[5,6].

The prevention of infection through vaccination is of paramount importance and of near equal importance is the timing of vaccination in relation to kidney transplantation (KT). Ideally, KT recipients (KTRs) should be vaccinated as early as possible as the response to vaccines is diminished in end-organ failure and in states of immunosuppression. In 2013, the guidelines of vaccination of adult solid organ transplant candidates and recipients were updated by the American Society of Transplantation (AST) and the Infectious Disease Society of America. They specify that vaccination is the responsibility of the primary care provider as well as the specialist or nephrologist. The vaccination status should be documented at the pre-transplant clinic and necessary immunizations must be administered as soon as possible thereafter[7,8]. When pre-transplant immunization is not possible, inactivated vaccines are generally considered safe after transplant. This review summarizes current evidence on the use of vaccination before and after KT, serological conversion rates in the setting of immunosuppression and the effect of vaccinations on kidney transplant outcomes.

PRE-TRANSPLANT VACCINATIONS

Patients with advanced chronic kidney disease (CKD) and dialysis dependent end stage renal disease (ESRD) on kidney transplant waitlist have high rates of infectious complications secondary to their already compromised immune systems. In this population, serological response to vaccinations may not be as optimal as in healthy individuals, but it is still better compared to post-transplant immunization. Hence, it is recommended to vaccinate patients with CKD, not requiring dialysis, so that they can mount an optimal immunological response. There is no consensus on the stage of CKD that would be ideal for administering vaccines. Too early-on administration might lead to "unnecessary" immunizations as many of these patients may never progress to ESRD. Dukes *et al*[9] conducted a prospective study in pre-dialysis patients (with serum creatinine > 2 mg/dL, mean serum creatinine 4.5 mg/dL) and found a favorable response to hepatitis B vaccine with subsequent booster dose as compared to dialysis patients historically[9]. Another prospective cohort study looked at rates of

seroconversion after hepatitis B immunization in CKD patients with mean serum creatinine of 3.4 +/- 1.5 mg/dL and mean estimated glomerular filtration rate (GFR) of 20 mL/min. They concluded that patient at higher GFR levels are more likely to respond to hepatitis B vaccination[10].

Some experts have recommended additional doses and/or boosters to improve serological response in CKD patients. García-Agudo *et al*[11] measured serological response in 155 CKD patients prospectively with two cycles of four double doses of conventional hepatitis B vaccine (at 0, 1, 2 and 6 mo), and additional four 20 mg dose of adjuvant vaccine in non-responders. Serological response was improved to 93.8% after the eighth dose compared to 75.9% after the fourth dose. Studies have shown that the humoral response to influenza vaccine is similarly better in hemodialysis patients compared to KTRs[12,13].

POST-TRANSPLANT VACCINATIONS

For those patients who are unable to obtain vaccinations pre-transplant, inactivated vaccines are considered safe when administered after kidney transplant. The optimal time for vaccination is not known but most transplant centers generally agree to wait at least 3-6 mo after transplantation or when patients are on stable maintenance levels of immunosuppressants. AST guidelines suggest avoiding all vaccinations, except influenza, within the first 6 mo post KT. Live-attenuated vaccinations (LAV) are contraindicated in KTRs due to risk of infection but family members of these patients can consider LAVs when appropriate to help provide herd immunity.

INFLUENZA VACCINE

Influenza is a common viral disease post-transplant and is associated with higher morbidity and mortality in immunosuppressed patients compared to a healthy host. Furthermore, influenza has been associated with increased risk of acute rejection after KT[14]. Although generally recommended to administer vaccination 3-6 mo after KT, the influenza vaccine may be given earlier than this time period if the transplantation occurs during the influenza season. Immunological response may be suboptimal with early vaccination; so patients may be revaccinated in the 3-6 mo period post KT if epidemiological risk for influenza exists based on the time of the year[7]. Thereafter, influenza vaccination should be offered yearly. Despite recommendations and safety profile of the influenza vaccine, this mode of protection against influenza is underutilized. Hurst *et al*[14] identified 51730 Medicare first-time KTRs from 2000 to 2006, of which 18.7% patients had influenza vaccination within the first year post-transplant and 43% of these patient received vaccines within the first 6 mo post-transplant. Multivariate analysis demonstrated that vaccination within the first year after transplant was associated with lower risk of allograft loss and death with adjusted hazard ratio of 0.77 ($P < 0.001$) and 0.82 ($P < 0.001$), respectively. Vaccination in the first 6 or 12 mo after transplant was not associated with increased risk for acute rejection[14].

Influenza vaccine preparations vary but both quadrivalent and trivalent vaccines can be used after KT. Only the LAV (FluMist) is contraindicated in transplant recipients and household members of transplant patients. One study investigated whether high-dose intradermal (ID) influenza vaccination would provide superior immunity to transplant patients compared to standard-dose intramuscular (IM) vaccine[15]. No significant difference was found in serological conversion rates between the high-dose ID and standard-dose IM vaccines. Similarly, there was no difference found in adverse effects between the two vaccines besides significantly higher rates of local adverse events including erythema, induration, tenderness, and pruritus with the ID vaccine[15].

Some studies have shown improved immunogenicity with higher doses of antigen in transplant recipients. Natori *et al*[16] showed significantly increased immunogenicity with high dose (60 mg) as compared to standard dose of influenza vaccine in SOT recipients. Since, high dose vaccine is not commercially available outside of North America, Mombelli *et al*[17] recently compared efficacy of double dose (30 mg) versus standard dose (15 mg) of inactivated trivalent influenza vaccine in SOT recipients and found a trend towards increased vaccine response and significantly higher rates of seroprotection with double dose, without any increase in vaccine-related serious adverse events. Another strategy that has been shown to be effective is to administer a booster dose five weeks after initial dose that led to significantly increased sero-conversion rates to all strains of influenza[18].

PNEUMOCOCCAL VACCINE

Infections from *Streptococcus pneumoniae* occur in SOT patients at an incidence rate of 146 infections per 100000 persons per year. Comparatively, the incidence rate of pneumococcal infections in the general population is 11.5 per 100000 persons per year[19]. There are two vaccines against *Pneumococcus*; the pneumococcal conjugate vaccine 13-valent vaccine (Prevnar 13® or PCV13) and the 23-valent polysaccharide vaccine (Pneumovax® or PPSV23). The CDC currently recommends administering PCV 13 followed by PPSV23 eight weeks later for immunocompromised patients including those with CKD, nephrotic syndrome, and SOT[20]. A booster dose of PPSV23 should be given at least five years after the first dose. If this booster dose is given before the age of 65, then a final dose of PPSV23 may be administered after 65 years of age, provided five years have elapsed since the previous dose. In the event, PPSV23 is administered prior to PCV 13; one should wait at least a year before giving PCV 13. Subsequent booster doses of PPSV23 may be administered as outlined earlier[21].

There have been no studies to date examining serological response or durability of response of PCV13 followed by PPSV23 in KTRs. However, some small randomized studies have explored the impact of the pneumococcal conjugate 7-valent (Prevnar-7 or PCV7) vaccine compared to PSSV23 in KTRs and did not find any improvement in duration of immune response[22,23]. Tobudic *et al*[24] found that immunogenicity was not improved when PPSV23 was boosted with PCV7. In this study, 62 patients were randomly assigned to PCV7 followed by PSSV23 after one year versus two doses of PSSV23 given one year apart. Immunogenicity of pneumococcal vaccination was not significantly different between the two strategies (87.5% for PCV7 *vs* 87.1% for PSSV23)[24].

DIPHTHERIA, TETANUS, PERTUSSIS VACCINE

Whooping cough, or pertussis, is a highly contagious infection caused by *Bordetella pertussis*. Recent outbreaks of pertussis are thought to be caused by waning pertussis immunity in adulthood. Therefore, a single dose of tetanus, diphtheria toxoid, and pertussis vaccine should be administered for all adults over the age of 18 to boost immunity to pertussis. Otherwise, tetanus and diphtheria is recommended every 10 years as an adult or when one sustains serious wounds including punctures, bites, scrapes, and burns[25].

HEPATITIS B VACCINE

Reactivation of hepatitis B after solid organ transplantation can rapidly cause severe hepatitis in the presence of potent immunosuppression[26]. Currently, the Advisory Committee on Immunization Practices (ACIP) recommends all hemodialysis (HD) patients be vaccinated for hepatitis B and to revaccinate this population when anti-HBs titers decrease to under 10 IU/mL[27]. Therefore, the majority of KTRs have been vaccinated to hepatitis B prior to transplant. The universal vaccination of HD patients has created an opportunity to expand the pool of possible deceased donor kidneys to include hepatitis B surface antigen (HBsAg) positive donors[28]. KTRs that are immune to hepatitis B either through vaccination or previous infection can be considered for HBsAg positive organs if the recipients' anti-HBs titers are above 10 IU/mL. There are several recent reports that showed patient and graft survival were similar to recipients with HBsAg-negative donors, with normal liver function and no evidence of HBV transmission[29,30]. Patients who receive living kidney transplants and pre-emptive transplants may require primary vaccination of hepatitis B after transplant[28,31-34].

HERPES ZOSTER VACCINE

Immunosuppression increases the incidence of herpes zoster infection approximately 7- fold compared to the immunocompetent host[35]. Until recently, the only vaccine available was a live-attenuated varicella zoster vaccine (Zostavax® or ZVL) which was contraindicated in KTRs. ZVL is FDA approved for prevention of herpes zoster in patients ≥ 50 years of age[36], however due to concerns about durability of the response, the ACIP recommends vaccination in ≥ 60 years of age. Comparatively, Shingrix® is a dead, recombinant zoster vaccine (RZV) which is approved to prevent

herpes zoster in patients ≥ 50 years[37]. RZV is a two dose vaccination given 2-6 mo apart and reduces the risk of shingles by more than 90%. Studies in healthy, non-transplant patients have demonstrated continued efficacy for three years post vaccination with 84.7% prevention of herpes zoster and reduced post-herpetic neuralgia in patients by 91.2%[38]. A Phase III randomized clinical trial found that humoral immunogenicity was significantly increased two months after vaccination in adult KTRs who received the RZV compared to placebo[39]. Further studies are required to determine the long term efficacy and safety of this vaccine in KTRs.

HPV VACCINE

Human papillomavirus (HPV) is a common sexually transmitted viral disease that is associated with cancers of the anus, penis, cervix, and vulva. Almost 14 million people are infected with HPV each year[40]. Three inactive HPV vaccines have been FDA approved for use in the United States. Both Gardasil® (4 valent vaccine) and Gardasil 9® (9-valent vaccine) are approved for use in females and males between 9 and 26 years of age[41,42]. Cervarix® is a bivalent HPV vaccine that is approved for use in females between the age of 9 and 25 years[43]. In the United States, only the 9-valent vaccine is currently available. The ACIP currently recommends that all patients with history of primary or secondary immunocompromising conditions, including SOT recipients, should receive a three dose series of HPV vaccine at months 0, 1-2, and 6 mo[40]. Serological and durability of immunological response post vaccination is unknown after kidney transplant.

MENINGOCOCCAL VACCINE

Menigococcal vaccine is indicated for KTRs who are travelling to highly endemic areas such as Sub-saharan Africa, Saudi Arabia or patients with history of splenectomy. It is also indicated for patients with atypical hemolytic uremic syndrome or antibody mediated rejection who are receiving eculizumab which is a complement inhibitor[44]. Effort should be made to administer meningococcal vaccine at least two weeks prior to the first dose of eculizumab. Patients should receive vaccination against meningococcal serogroups A, C, Y and W1235 by either Menactra or Menveo as well as vaccination against meningoccoal serogroup B with either Trumemba or Bexsero. Menactra or Menveo should be administered twice, at least 2 mo apart, with concurrent Trumemba or Bexsero vaccination. When Trumemba is given, three doses are required at 0, 1-2, and 6 mo while Bexsero is a two-dose series administered at least 1 mo apart. Vaccination should be repeated every 5 years for group A, C, Y, and W1235 with either Menactra or Menveo[21]. Immunogenic response to polysaccharide meningococcal vaccine is only 40% in SOT recepients with low titer antibodies developing only to menigococcus C. With conjugate vaccine, about half of the SOT recipients develop low antibody titers at least against one of the serogroups including A, C, Y and W-135. Two doses of conjugated quadrivalent menigococcal vaccine is recommended, followed by a booster every five years[45].

VACCINATION AGAINST CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is a double-stranded DNA virus that is ubiquitous with very high sero-prevalence. The virus can cause significant morbidity and mortality in immune-compromised organ transplant recipients. Anti-viral therapy currently used for CMV prophylaxis in SOT recipients is associated with adverse events including neutropenia. Hence, there is an unmet need for developing treatments with new mechanisms of action including effective vaccines. Earlier studies have shown variable impact on CMV immunogenicity with different vaccines administered pre transplant[46,47]. ASP0113 is a first-in-class bivalent DNA-based vaccine developed for preventing CMV infection in immuno-compromised transplant recipients. It contains equal quantities of the plasmids VCL-6365 and VCL-6368 encoding for glycoprotein B and phosphoprotein 65[48]. A phase I study demonstrated the immunogenicity and safety of ASP0113 in healthy adults[49]. In another randomized, double-blind placebo-controlled phase II study in allogeneic hematopoietic cell transplant (HCT) recipients, ASP0113 significantly reduced the occurrence and recurrence of CMV viremia with improved time to event and similar adverse events when compared to placebo[50]. A recently published phase-II placebo-controlled study randomized 149 CMV sero-negative recipients of kidneys from seropositive donors in a 1 : 1 manner to either 5

doses of ASP0113 or placebo on days 30, 60, 90, 120, 150 post-transplant. All patients received prophylactic valganciclovir/ganciclovir on days 10-100 after transplant. In this study, ASP0113 was not effective in preventing CMV viremia from day 100 through year one after first study vaccine injection but had a safety profile similar to placebo[51]. One possible reason for the lack of vaccine efficacy observed in this study could be related to the post-transplant administration of the vaccine when patients are heavily immunosuppressed resulting in a weak T-cell response. Future studies should follow a protocol that mandates pre-transplant use of ASP0113 when recipients likely have more robust T-cell response. Currently, an ongoing phase III study is evaluating the safety and efficacy of ASP0113 in CMV-seropositive allogeneic HCT recipients (NCT01877655).

LIVE ATTENUATED VACCINES

Despite several advantages of live-attenuated vaccines (LAV), it is not recommended to use these in immunocompromised host secondary to risk of vaccine-virus induced disease and uncontrolled replication of vaccine virus. There is scant data on safety of LAV in transplant recipients with stringent criteria such as need for minimal immunosuppression, with stable immunological parameters[52-54]. Live mumps, measles, rubella (MMR) vaccine is not recommended in KTRs. MMR serology should be checked prior to transplantation and non-immune patients should be vaccinated. If non-immune patients have exposure to measles, normal human immunoglobulin should be administered within six days of exposure[55,56]. When living KT is scheduled, pre-transplant non-immune patients should be vaccinated against Varicella Zoster using LAV with two doses at least 4-6 wk and 2-4 wk prior to transplant[57]. Generally, Herpes zoster vaccine Zostavax is contraindicated in KTRs secondary to risk of disseminated disease; however there is some data on the safety of Zostavax in pediatric patients with liver transplant[58,59]. In non-immune patients with risk exposure, administer Varicella zoster immunoglobulin within 96 h along with valacyclovir for 7 to 10 d[60].

While there are small studies suggesting no significant side effects with live attenuated yellow fever vaccines in transplant recipients traveling to sub-Saharan Africa and South America, it is still contraindicated post-transplantation secondary to risk of encephalitis[61-63]. In such patients, it is recommended to administer yellow fever vaccine pre-transplant in anticipation of travel to endemic areas. Other live vaccines to avoid in KTRs include oral typhoid vaccine, Bacille Calmette-Guerin vaccine and attenuated intra-nasal influenza vaccine[6,64-66].

INTERNATIONAL TRAVEL

A large number of immunocompromised patients including KTRs travel internationally to high risk destinations every year without adequate pre-travel advice and vaccinations[67-70]. These patients are at heightened risk of acquiring infections that could even lead to allograft rejection. Pre-travel vaccines could help in disease prevention or decrease the severity of disease in KTRs[64].

Preferably, patients should receive key vaccinations at least four weeks prior to undergoing transplantation but it may not be practical for area-specific travel vaccines for endemic diseases, especially, if travel plans are made post-transplantation. Some experts recommend restriction of travel within the first 12 mo post-transplantation[71]. During each physician encounter, specific questions should be asked about travel plans and referred to travel clinics ideally 12 wk prior to travel so that there is enough time for administration of required pre-travel vaccines, serological testing and additional boosters[45]. If travel is anticipated to endemic areas, then the recommended vaccinations are given in addition to routine vaccinations as listed in Table 1[45,64]. Since yearly influenza vaccine strains differ between different hemispheres and influenza seasons are in months of October-March in Northern hemisphere, April-September for southern hemisphere and all-year round in tropics, the ACIP recommends two vaccinations with hemisphere-specific trivalent influenza vaccines four weeks apart in immunocompromised patients crossing the hemispheres[72].

In endemic areas, mosquito-borne infections such as malaria and dengue may precipitate acute allograft rejections[73,74]. Traveler's diarrhea with organisms like *Escherichia coli*, *Campylobacter sp*, *Salmonella*, *Shigella*, *Giardia*, and *Entamoeba histolytica* are common especially in immunocompromised hosts. Patients should be advised to stay well hydrated as dehydration may also cause kidney dysfunction and calcineurin inhibitor toxicity. In addition to the pre-travel vaccines, KTRs should be counseled on

Table 1 Recommendations for various vaccines in kidney transplant recipients

Vaccine	Prior to transplant	After transplant	Prior to travel to endemic areas after transplant	Endemic areas	Antibody titers?
Hepatitis A	Yes	Yes	Yes		> 33 mIU/mL is protective
Hepatitis B	Yes	Yes	Yes		> 10 mIU/mL is protective
Pneumococcal	Yes	Yes	No		
Meningococcal	Yes	Yes	Yes	Sub-Saharan Africa, India, Philippines, Saudi Arabia	
Tdap	Yes	Yes	No		
Td	Yes	Yes	No		
MMR	Yes	No	No		
Varicella zoster	Yes	Only Shingrix may be given post-transplant	No		
Influenza	Yes	Yes - avoid live virus	No		
Rabies[1] only upon exposure	No	No	No		
Diphtheria	No	No	Yes[1]	SE Asia, Hajj travelers to Saudi Arabia	
Tick-borne encephalitis	No	No	No (live)		Can follow antibody titers
Japanese encephalitis	No	No	Yes, day 0 and 28	South, South East, and East Asia and part of Western Pacific	
Cholera	No	No	Yes, oral killed vaccine	South and South East Asia	
Yellow fever	No	No	No,	Sub-Saharan Africa, South America	
Typhoid	No	No	Yes, 2 wk prior to travel	South and South East Asia, Africa, Caribbean, Central and South America	

[1]Re-vaccination required if last vaccination was 10-15 years prior. MMR: Measles, mumps, rubella; TdaP: Tetanus toxoid, reduced diphtheria toxoid, acellular pertussis, Td: Tetanus diphtheria.

food and water hygiene measures, use of insect and mosquito repellants and safe sex practice. Chemoprophylaxis for malaria should be offered and anti-parasitic regimen(s) offered based on susceptibility pattern at destination site. Atovaquone-proguanil or doxycycline is commonly offered medications for malaria prophylaxis in areas with chloroquine resistance.

SEROLOGICAL RESPONSE IN KIDNEY TRANSPLANT RECIPIENTS

Since KTRs are on life-long immunosuppression, these patients may not mount comparable serological response to vaccinations with lower rates of seroconversion, lower mean antibody titers and waning of protective immunity over shorter period as compared to general population[64,75]. Moreover, serological response might vary depending on type of immunosuppressive medications. Calcineurin inhibitors and mammalian target of Rapamycin (mTOR) inhibitors impair interleukin-2 dependent T-cell proliferation while mycophenolate mofetil and azathioprine inhibit antigen dependent T-and B-cell interaction and proliferation and response to vaccines[15,76-79]. Further studies have shown that cyclosporine treated patients have poorer response post-influenza vaccination as compared to azathioprine treated patients, and patients on mTOR-inhibitors had lower immune response to H1N1 vaccination[80,81]. Patients had decreased response rates if they had received anti-CD20 monoclonal antibody as a part of immunosuppression protocol[82]. The issue becomes more complex with contemporary powerful immunosuppression including the depleting antibodies such

as Thymoglobulin and alemtuzumab.

At present, we have limited data on the timing, dosing and efficacy of vaccinations in organ transplant population. With the advent of new biologics as immunosuppressants and approval of newer vaccines, the waters have become muddier with respect to providing direction for vaccinations in KTRs. Beil *et al*[83] followed antibody titers in 94 pediatric KTRs who had vaccinations and found that titers were low in 31% with tetanus, 25% with diphtheria and 68% with hepatitis B virus immunization. Eckerle *et al*[82] systematically reviewed published data on the vaccination response in SOT recipients and found that they had 10%-16% less response rate as compared to general population. They found encouraging serological responder rates with tetanus, diphtheria, rabies, hepatitis A and polio vaccination, though antibody titers declined over time for diphtheria and hepatitis A vaccination. Efficacy of repeated hepatitis B vaccination is also reduced to 32%-36% as compared to 90%-95% in healthy controls[84-86]. Recommendations regarding booster dose in pediatric or adult KTRs with sub-optimal serological response are lacking. L'Huillier *et al*[87] published a strategy utilizing serology based immunization in pediatric liver transplant patients with some success.

HEALTHCARE WORKERS AND CLOSE CONTACTS OF TRANSPLANT RECIPIENTS

Since there is risk of transmission of infections in immunocompromised KTRs, it is of critical importance to fully immunize persons in close contact with KTRs. This helps in building herd immunity and protects KTRs from diseases. Annual influenza vaccination in all healthcare workers and all indicated age appropriate vaccinations including LAVs such as MMR, rotavirus vaccine and varicella vaccine should be administered to the children of transplant recipients[44,82]. Since there is virus shedding post-vaccination, patients and contacts should be counseled about strict hand washing at least for two weeks after administration of live vaccines[88-90]. Live oral polio vaccine is contra-indicated in close contacts; therefore, inactivated polio vaccine should be administered. Living-organ donors should avoid LAV at least 3-4 wk prior to transplantation[53,91].

EFFECTS OF VACCINATIONS ON TRANSPLANT OUTCOMES

There have been concerns about adverse effects of influenza vaccination on allograft function by upregulation of human leukocyte antigen (HLA) alloantibodies after vaccination. During Influenza A/ H1N1 pandemic in 2009, some studies had demonstrated anti-HLA antibodies post vaccination with AS03-adjuvanted monoclonal H1N1 vaccine but this did not translate in adverse clinical outcomes[92,93]. Many other clinical studies did not show increased risk of acute rejections or allograft dysfunction after influenza vaccination[94-97]. In fact, Hurst *et al*[14] had shown reduced risk of allograft loss if influenza vaccination is administered in the first post-transplant year. Influenza vaccination is deemed safe and should be recommended to all KTRs.

Lindemann *et al*[98] showed no increase in HLA antibodies after pneumococcal vaccination in KTRs. Mulley *et al*[99] recently published no effect on the development of de novo donor-specific antibodies and no increase in episodes of acute rejection or graft loss post-vaccination in SOT recipients based on a systematic review and meta-analysis of 90 studies involving 15645 vaccinated patients and 42924 controls. Further high-quality, controlled studies for assessing the post-vaccination outcomes in transplant recipients are needed.

CONCLUSION

KTRs are at increased risk of infectious complications in the setting of prolonged, chronic immunosuppression with increased morbidity and mortality. Awareness about vaccine-preventable diseases, administration of vaccines preferably prior to kidney transplantation and to close contacts could lower the burden of complications post-transplant. If the opportunity for pre-transplant primary vaccination is missed, patients should be offered immunization 6 mo post-transplantation. Patients should also be offered pre-travel endemic area specific vaccinations. LAVs are generally

contraindicated in KTRs. More studies are needed on vaccination schedules, serological response, need for booster doses and safety of LAVs in this special population. The emergence of newer data from such studies would enable transplant community to make more evidence based recommendations and further clear the muddy waters.

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MINIREVIEWS

Machine perfusion of the liver: Which is the best technique to mitigate ischaemia-reperfusion injury?

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Abstract

Longstanding research describes the mechanisms whereby the restoration of blood flow and reoxygenation (reperfusion) aggravates the ischaemic injury caused by a period of anoxia to a donor liver. This phenomenon, called ischaemia-reperfusion injury (IRI), leads to parenchymal cell death, microcirculatory failure, and inflammatory immune response. Clinically, IRI is the main factor responsible for the occurrence of posttransplant graft dysfunction and ischaemic-type biliary lesions. While extended criteria donor livers are more vulnerable to IRI, their utilisation is required to address the shortfall in donor organs. Thus, the mitigation of IRI should drive the setting of a new benchmark for marginal organ preservation. Herein, strategies incorporating different modalities of machine perfusion of the liver to alleviate IRI are discussed in conjunction with advantages and disadvantages of individual protocols. Techniques leading to reperfusion of the liver during machine perfusion (*in situ* normothermic regional perfusion and *ex situ* normothermic machine perfusion) may mitigate IRI by shortening the ischaemic period of the organs. This benefit potentially escalates from the minimum level, obtained following just partial alleviation of the ischaemic period, to the maximum level, which can be potentially achieved with ischaemia-free organ transplantation. Techniques that do not lead to reperfusion of the liver during machine perfusion (hypothermic, subnormothermic, and controlled-oxygenated rewarming) optimise mitochondrial oxidative function and replenish cellular energy stores, thereby lowering reactive oxygen species production as well as the activation of

downstream inflammatory pathways during reperfusion. Further mechanistic insights into IRI may guide the development of donor-specific protocols of machine perfusion on the basis of the limitations of individual categories of extended criteria donor organs.

Key words: Machine perfusion of the liver; Ischaemia-reperfusion injury; Liver transplantation; Organ preservation; Organ reconditioning

Core tip: Hepatic ischaemia-reperfusion injury (IRI) is the main culprit of post-transplantation graft dysfunction and ischaemic-type biliary lesions. Despite the increased demand, extended-criteria donor livers are more vulnerable to IRI, thereby presenting inferior postoperative outcomes. Hence, the mitigation of IRI should drive the setting of a new benchmark for extended-criteria donor organ preservation. Machine perfusion of the liver has the potential to mitigate IRI *via* a shortening of the ischaemic period of the livers or the reconditioning of their bioenergetic status. Interventions to further alleviate IRI, such as pharmacological or nonpharmacological metabolic modulation of donor organs, may amplify this effect.

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INTRODUCTION

Ischaemia-reperfusion injury (IRI) is the phenomenon whereby the hypoxic damage imposed on an organ is aggravated during the reestablishment of the blood flow along with reoxygenation[1]. This biphasic detrimental process affects donor livers during liver transplantation (LT) and is the main responsible factor for the occurrence of graft dysfunction (primary nonfunction and delayed graft function) after the procedure[2,3]. Additionally, IRI is associated with the occurrence of ischaemic-type biliary lesions (ITBL) posttransplantation, which, in turn, leads to high rates of graft loss and retransplantation[4,5]. During ischaemia, the absence of oxygen interrupts the shuttling of electrons through the mitochondria electron transport chain (ETC), as oxygen is the terminal electron acceptor during cellular respiration. The affected ETC interrupts the transfer of protons (H^+) across the inner mitochondrial membrane, thereby hampering the generation of the proton motive force required for oxidative phosphorylation and adenosine triphosphate (ATP) synthesis. The cellular ATP stores are then rapidly consumed and the process of anaerobic glycolysis is commenced in order to produce energy to the cells using the glycogen stores and the glucose available in the surrounding fluid. Activation of the former metabolic pathway results in lactate accumulation with local tissue acidosis as well as failure of the Na^+/K^+-ATPase pump with depolarisation of the cell membrane and influx of Ca^{2+}/Na^+ to the cytosol of the endothelial and Kupffer cells, leading to cell swelling. Additionally, the presence of vasoconstrictive substances such as endothelin and thromboxane-A2 not balanced by the vasodilatory nitric oxide (NO) can cause endothelial cell dysfunction with vasoconstriction and microcirculatory failure[2]. On reperfusion, when the blood flow is re-established, the damage caused by the ischaemic period is aggravated by the reoxygenation. This is initiated by the mitochondrial release of reactive oxygen species (ROS) due to an inhibited ETC causing the activation of Kupffer cells, which in turn will release proinflammatory cytokines, such as tumour necrosis factor-alpha/interleukin 1-beta, recruiting neutrophils and inducing the expression of adhesion molecules on sinusoidal endothelial cells. Activated neutrophils produce more ROS, perpetuating the inflammatory response that ultimately results in tissue damage and the initiation of cell death programs such as necrosis, apoptosis, or autophagy[2,3,6].

Donor organs with steatosis, organs that have been exposed to prolonged preservation times, organs from elderly donors, or organs from donation after

circulatory death (DCD) are all more vulnerable to IRI and therefore are referred to as marginal or extended criteria donor (ECD) organs[7]. The defining parameters of ECD organs can vary slightly amongst centres[8], although, consistently, ECD-LT is associated with high rates of graft dysfunction and lower patient and graft survival posttransplantation[9-11]. Despite inferior outcomes, the utilisation of ECD livers is required to tackle the shortfall of donor organs for transplantation. Whilst transplant surgeons do not have control over these donor features, they can consider alternatives to better preserve or even recondition ECD livers. The wider utilisation of ECD livers has exceeded the preservation capacities of traditional static cold storage (SCS), and machine perfusion (MP) of the liver is considered to be a possible alternative preservation method. The use of this technique may offer several advantages in comparison with SCS, including superior organ preservation, limiting ischaemia; the assessment of organ function prior to transplantation; and the possibility of improving or repairing highly vulnerable organs[12]. Nevertheless, benefits may vary between different modalities of MP (Table 1); therefore, those protocols are frequently seen as divergent or even competitive at this time. Herein, the advantages and limitations of each individual technique in relation to the possibility of IRI mitigation are briefly discussed in an attempt to identify which is the best technique of MP of the liver.

STUDY ANALYSIS

Machine perfusion of the liver and ischaemia-reperfusion injury

Considering its clinical significance, the mitigation of IRI should drive the setting of a new benchmark for ECD organ preservation. In accordance, the approach to this question might take into consideration how the different modalities of MP address IRI (Figure 1). For study purposes, these different modalities were categorised on the basis of either the occurrence of reperfusion of the liver during MP or not.

Techniques leading to reperfusion of the liver during machine perfusion

The common feature of this group of MP techniques is the abbreviation of the hypoxic period *via* reperfusion of the organ within physiological temperatures to support cellular metabolic function during preservation. This approach avoids further depletion of ATP stores and the accumulation of metabolic waste products, although experimental models have suggested that, even without the presence of leukocytes and platelets in the circuit, reperfusion during NMP induces oxidative tissue injury and the activation of the inflammatory immune response[13,14].

Ex situ normothermic MP (NMP) can be employed as a preservation method, fully replacing SCS; hence, it has the potential to limit the hypoxic injury to the minimum period required for organ preparation and the setting of the machine. Additionally, the presence of a constant flow of fluids in the vessels during organ preservation is advocated to improve the expression of vasoprotective endothelial genes alleviating the microcirculatory failure associated with IRI[15]. The benefits of this technique were recently shown in the largest clinical trial to date that compared this modality of NMP and SCS[16]. Nasralla *et al*[16] reported the results of transplantation of 121 donor livers following preservation NMP. The authors found a 50% decrease in the release of aspartate transaminase (AST) in the recipient within the first seven postoperative days in comparison with grafts that had SCS[16]. Nevertheless, the former study did not show superiority of NMP in terms of the occurrence of ITBL. This finding suggests that the limitation of hypoxic injury *per se* is not enough to prevent ITBL formation; thus, the etiopathogenesis of these lesions should rely also on the reperfusion injury, which is supported by an *in vitro* study[4]. The strongest evidence supporting the advantages of limiting IRI is the newly developed ischaemia-free organ transplantation (IFOT) technique[17], described by He *et al*[17], whereby complete elimination of hypoxia *via* continuous NMP was shown to prevent postreperfusion syndrome and vasoplegia after revascularisation of a severely steatotic donor liver. Moreover, NMP can also be performed after a period of SCS in an end-ischaemic approach. Whilst end-ischaemic NMP is logistically less challenging, it restrains the NMP's ability to shorten the time of hypoxic injury to the organs. Finally, NMP may take advantage of the nearly physiological environment to assess the function of the organ prior to transplantation and to offer therapeutic approaches, such as cytoprotective and/or metabolic-modulating agents, for the treatment of IRI during NMP. This option is still underexplored thus far, although experiments involving pharmacological modulation of the lipid metabolism during NMP exemplify the benefits of this approach[18].

In situ normothermic regional perfusion (NRP) re-establishes the delivery of

Table 1 Advantages and disadvantages of different modalities of machine perfusion of the liver

	Advantage	Disadvantage
Machine perfusion of the liver (All modalities)	Continuous circulation-improved preservation of the microcirculation; Nutrients and oxygen delivery for cellular metabolism; Removal of metabolic waste products; Delivery of cytoprotective agents and/or metabolic-modulating agents	Costly procedure; Requires specialised team
Techniques leading to reperfusion of the liver during machine perfusion (*In situ* normothermic regional perfusion; *Ex situ* normothermic machine perfusion)	Support organ full metabolism; Assessment of organ viability Assessment of hepatocellular injury; Potential to extend the period of organ storage; Possibility to shorten the ischaemic period of the livers	Persuade reperfusion on the machine; Risk of organ injury in case of organ failure or unrecognised problems with cannulation of the vessels; Require the use of an oxygen carrier in the perfusate
Techniques that do not lead to reperfusion of the liver during machine perfusion (Hypothermic oxygenated machine perfusion; dual-vessel hypothermic oxygenated perfusion; subnormothermic machine perfusion; controlled oxygenated rewarming)	Assessment of hepatocellular injury; Enhancement of mitochondrial function and replenishment of cellular energy stores; Lower rates of intra-hepatic biliary complications post-transplantation; Does not require oxygen carriers in the perfusate	Limited metabolic rate of the organs does not favour assessment of organ viability; Definition of the biomarkers to individualise perfusion times and assess responses to treatment in real-time is still pending
Ischaemia-free organ transplantation	Potential to abolish completely ischaemia-reperfusion injury	Limited application to donation after brainstem death thus far; Challenging procedure; Logistically challenging in a multivisceral retrieval setting; Just a single case reported

oxygen to the organs following asystole in DCD donors and, thus, limits the injury associated with a longer warm ischaemia period. Additionally, NRP may have a preconditioning effect, which could revert the detrimental mechanisms of warm injury[19,20]. While animal experiments involving dogs revealed that NRP is able to negate endothelial cell damage in livers harvested after 20 min of cardiac arrest[21], studies providing an in-depth analysis of the mechanistic effects of the procedure on the metabolism of human donor organs remain lacking.

Techniques that do not lead to reperfusion of the liver during machine perfusion

This category encompasses the hypothermic and subnormothermic techniques of MP as well as controlled oxygenated rewarming. All of them share as a common feature the absence of organ reperfusion, as perfusate temperatures do not exceed 20 °C. Within this category, the vast majority of mechanistic studies were performed so far on hypothermic oxygenated perfusion (HOPE) by the Zurich group. It has been proposed that the delivery of oxygen at hypothermic temperatures enhances the mitochondrial oxidative function, replenishing the cellular ATP stores prior to reperfusion[14]. This hypothesis is sustained by experimental studies that found a decrease in the expression of markers indicating oxidative tissue damage and the activation of Kupffer cells and leukocytes. In addition, these studies reported a lower release in the perfusate of markers of mitochondrial injury, damage-associated molecular patterns, and cytokines in livers after reperfusion following the HOPE procedure[13,14,22]. The Groningen group has been working on dual-vessel (hepatic artery and portal vein) hypothermic oxygenated perfusion (D-HOPE) and reported similar mechanistic findings to those obtained using HOPE[23,24].

Subnormothermic MP (SMP) is performed usually at around 20 °C with active oxygenation of the perfusion fluid. Transplant animal models suggest that SMP can positively impact mitochondrial function, increase organs' ATP stores, decrease the release of markers of tissue injury (*e.g.*, transaminases and cytokines), and improve graft function postoperatively[25,26]. Defenders of this technique advocate that the increase in the organ's metabolic rate that occurs as a result of the increase in temperature (from 10 °C to 20 °C) is sufficient for viability testing[25]. Minor *et al*[27] proposed a variant of the SMP technique called the controlled oxygenated rewarming (COR) method. In a reperfusion porcine model using *ex situ* NMP, as compared with hypothermic MP or SMP alone, COR was found to increase cellular ATP stores and decrease the release of lipid peroxides and markers of hepatocellular injury (AST and ALT) in the perfusate after reperfusion[27]. During NMP, organs that had undergone COR exhibited increased bile production, lower vascular resistance, and decreased expression of proinflammatory genes (*e.g.*, intercellular adhesion molecule 1, toll-like receptor 4, and tumour necrosis factor alpha)[27].

Which is the best technique of machine perfusion of the liver to mitigate ischaemia-reperfusion injury?

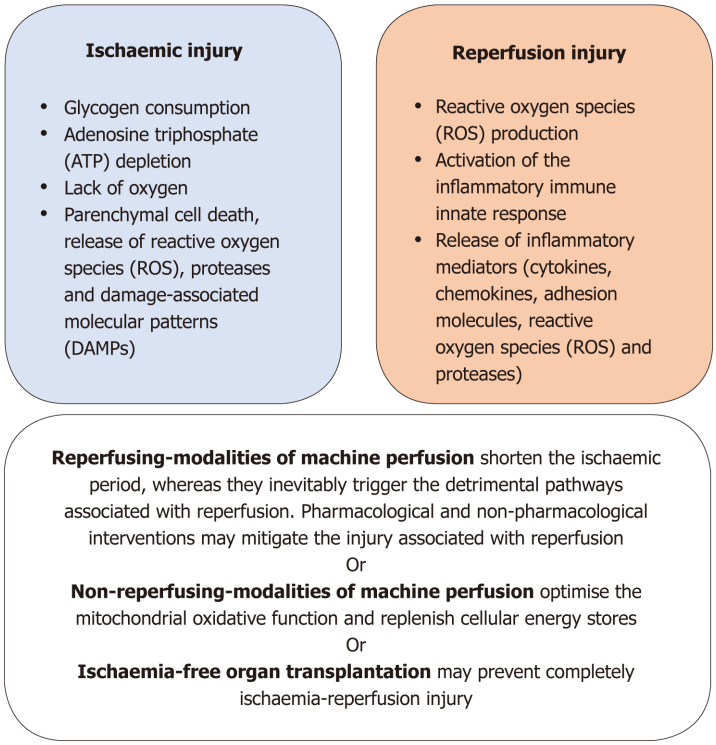

Figure 1 Mechanistic characteristic of the different periods of the ischaemia-reperfusion injury and the role of the diverse techniques of machine perfusion of the liver. Techniques leading to reperfusion of the liver during machine perfusion include *in situ* normothermic regional perfusion and *ex situ* normothermic machine perfusion; techniques that do not lead to reperfusion of the liver during machine perfusion include hypothermic machine perfusion, subnormothermic machine perfusion and controlled oxygenated rewarming.

Contemporary scientific evidence supports the concept that techniques of MP of the liver leading to organ reperfusion may mitigate IRI by shortening the ischaemic period. This benefit escalates from the minimum level, obtained following just partial alleviation of ischaemic injury during end-ischaemic NMP, to the maximum level, which can be potentially achieved with IFOT. However, these modalities of MP inevitably lead to ROS production, oxidative injury, and activation of the inflammatory immune response, with some degree of cell damage occurring during reperfusion[13]. Whilst this former detrimental phenomenon may not affect organs with enough metabolic reserve to overcome this injury, it can be a decisive factor when considering high-risk organs with limited metabolic reserve[28,29]. Consequently, most of the evidence accumulated thus far supports the advantages of NMP over SCS regarding organ preservation and viability assessment, although the resuscitative capacity of NMP *per se* is still unclear.

Mounting data suggest that techniques of MP of the liver that do not lead to organ reperfusion are able to mitigate IRI by way of optimisation of the mitochondrial oxidative function and replenishment of the cellular ATP stores during MP. The enhanced mitochondrial oxidative function decreases ROS production as well as the subsequent activation of downstream inflammatory pathways during reperfusion[30]. These mechanistic effects were shown to have a positive impact on the recovery of the metabolic function of discarded human donor livers submitted to NMP for viability assessment following the use of hypothermic oxygenated techniques of MP[29]. Conversely, the lower metabolic rate of the organs during hypothermic MP does not favour their functional assessment prior to transplantation. Arguably, strategies to evaluate mitochondrial metabolism and the energetic recovery of the organs, in real time, may warrant further promising studies be performed on this subject[22].

Despite the complex interaction between cells and signal molecules during IRI, future investigations determining the susceptibility of each individual cell population of the liver to the different periods of liver IRI (*i.e.*, warm ischaemia, cold ischaemia, and reperfusion) might help with driving the allocation of donor organs to specific MP techniques. Thus far, existing evidence associates warm ischaemia mainly with Kupffer-cell-mediated hepatocellular injury, whereas cold ischaemia damages primarily sinusoidal endothelial cells[2,31]. Cholangiocytes have been reported to be less vulnerable to anoxia than hepatocytes; however, during reperfusion, they produce higher amounts of ROS, leading to cell death[4]. If exposure of the organ to an

ischaemic period is unavoidable, the careful consideration of strategies to alleviate the local immune activation during reperfusion is desirable, such as employing preceding short periods of non-normothermic perfusions as a therapeutic approach or incorporating the delivery of pharmacological agents during NMP[29].

To conclude, whilst all techniques of MP of the liver have the potential to mitigate IRI, they offer different benefits and present diverse limitations. Therefore, there is no solid evidence yet to suggest the superiority of one technique over the others. A better mechanistic understanding of the intricate pathways of IRI may guide the development of personalised protocols of MP for groups of ECD organs, such as DCD livers, steatotic livers, or organs with prolonged cold ischaemia times.

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MINIREVIEWS

Immunometabolism: A target for the comprehension of immune response toward transplantation

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Abstract

Organ transplantation is a life-saving procedure, however predicting graft survival is still challenging. Understanding immune-cell pathobiology is critical to the development of effective therapies to prevent rejection. Over the recent years it has become progressively evident that the complex nature of immune cell behavioral dynamics is strongly dependent on cellular metabolism, which in turn, relies on competition for nutrients, oxygen and metabolites with other immune cells and microbiota. Furthermore, the influence of the inflammatory state can lead to substantial changes in conditions within the tissue micro-environment. Considering the context of immunity, alterations in metabolic pathways (glycolysis, the tricarboxylic acid cycle, the pentose phosphate pathway, the fatty acid oxidation and synthesis, and the amino acid metabolic pathways) will influence the production of different sets of cytokines and affect transplantation outcome. It is now known that naïve, resting and effector cells acquire different metabolic profiles and studies have shown that specifically targeting some of these metabolic routes can prevent differentiation of effector T cells in favor of Tregs. Ultimately, to develop effective therapies that will prevent graft loss and understanding how cell metabolism impacts the fate and function of immune cells is now a critical point of discussion. The distinct metabolic features and requirements observed in effector and suppressive cell subsets offer promising opportunities for selective regulation of the immune responses in transplantation and will be discussed in this review.

Key words: Transplantation; Metabolic processes; Immune tolerance; Metabolic activation; Inflammatory response

Core tip: In this review we summarize the most recent findings on metabolic pathways involved in the determination of immune cell fate and highlight the relevance of

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understanding how metabolic reprogramming is involved in the activation of dendritic cells and T cells, as well as development of strategies that target metabolic reprogramming to counteract effector cell activation in order to prevent graft failure.

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INTRODUCTION

Organ transplantation is a life-saving procedure, however predicting graft survival is still challenging. Sustaining transplantation tolerance is a key to overcome inflammatory challenges which lead to episodes of rejection or fibrosis and loss of graft function. Therefore, the goal of immunotherapies is to shape immune responses towards regulation to achieve long-term graft survival and eliminate the chronic use of immunosuppressants, which inflict severe side-effects.

Understanding immune-cell pathobiology is critical to develop new effective therapies that will prevent graft rejection. In allograft transplantation, the balance of immune responses towards alloantigen will depend on the coexistence of several mechanisms such as control in the frequency and function of alloreactive T cells *via* mechanisms of suppression such as expression of inhibitory molecules [*e.g.*, programmed death (PD)-1], and induction of T regulatory cells (Tregs)[1]. Recently, it has also come to light that metabolic reprogramming impacts the fate and function of immune cells and might be a key determinant of transplantation outcome. Unlike other cells in the body, immune cells are capable of responding to their external environment and modulate their cellular behavior accordingly, for instance, availability of energetic substrates can influence cellular metabolism and in turn strongly affect immune cell fate towards acquisition of effector functions, quiescence, proliferation, *etc*[2]. This cellular metabolic reprogramming can be triggered in response to energy requirements for synthesis or decomposition of cell components, production of soluble factors such as cytokines, differentiation and cell survival, and it will condition the effector or regulatory properties of the immune cells[3].

Undoubtedly, this new field of studies in immunometabolism will enable novel therapeutic approaches which increase chances of a successful transplantation outcome. The following sections will give some insight into general metabolic pathways and more specific metabolic signatures inherent to effector and suppressive cell subsets as well as some early work regarding immunometabolism in transplantation.

MAIN METABOLIC PATHWAYS INVOLVED IN IMMUNE CELL FATE

A very fine equilibrium of internal metabolites, such as reducing/oxidizing substrates, reactive oxygen species (ROS), as well as availability of growth factors and nutrients, weigh in to determine which metabolic pathway will be followed[2,3]. The concept of energy metabolism and nutrient sensing suggests that, after food breakdown, adenosine triphosphate (ATP) can be directly metabolized from nutrients or stored as alternative energy sources, such as proteins, glycogen or lipids[4]. Specifically considering immune cell function, changes in metabolic pathways have been associated to determination in proliferation, acquisition of effector function, specific cytokine signature and return to homeostasis. To simplify, in general six metabolic pathways are generally considered (Figure 1): (1) The glycolytic metabolic pathway; (2) The pentose phosphate pathway (PPP); (3) The tricarboxylic acid cycle (TCA); (4) Fatty acid oxidation (FAO); or (5) Synthesis; and(6) The amino acid metabolic pathway summarized from O´Neill *et al*[5].

The glycolytic pathway, also named glycolysis, initiates with the transport of glucose from extracellular space by specialized transporters (such as Glut1), to ultimately generate pyruvate and other products after a series of enzymatic reactions.

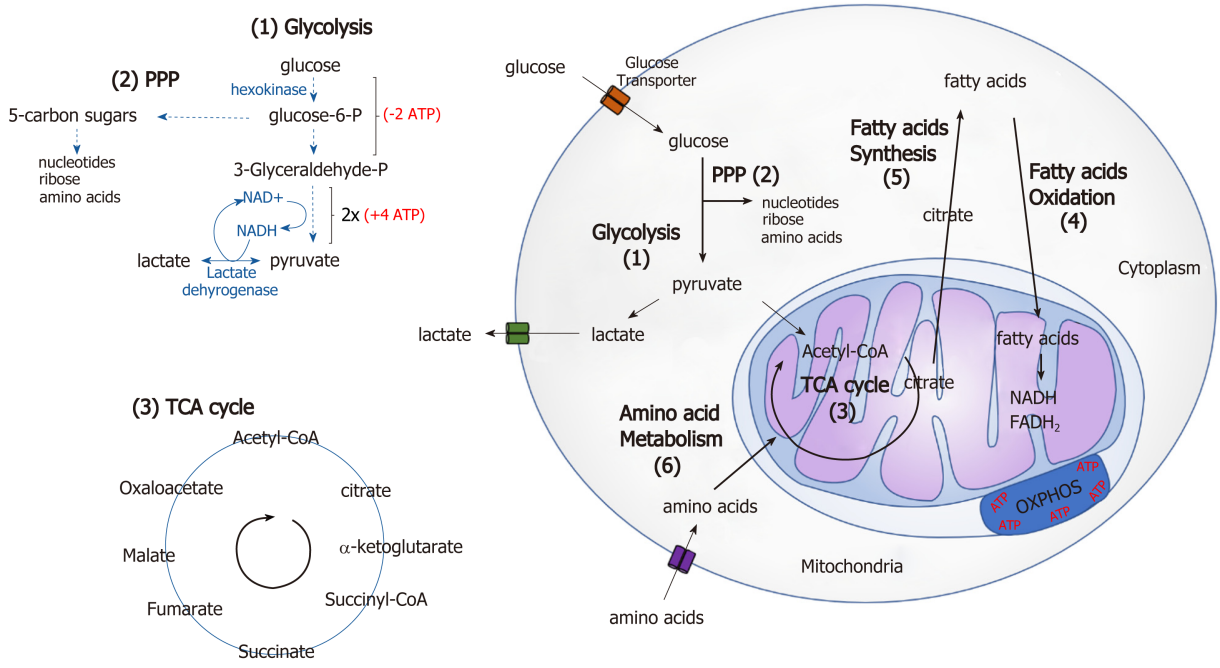

Figure 1 Six main metabolic pathways relevant for immune cell function. (1) Glycolysis is a process that occurs in the cytoplasm and involves conversion of glucose into pyruvate, (3) Which can either enter the tricarboxylic acid (TCA) cycle or be transformed into lactate and secreted. (2) The pentose phosphate pathway, is parallel to glycolysis and generates ribose for nucleotides, amino acids and nicotinamide adenine dinucleotide phosphate (NADPH), which is important for the synthesis of fatty acids and production of lipid ligands. (4) Fatty acid oxidation is a mitochondrial dependent aerobic process which consists on breaking down fatty acids into Acetyl-CoA units, generating NADH and FADH2, and driving ATP production from the E. (5) Fatty acid synthesis is a complex cytoplasmic process that is regulated by Acetyl-CoA, NADPH and fatty acid synthases to generate fatty acids. (6) Amino acid metabolism is very diverse, also important for cell growth and protein biosynthesis, as a consequence of the large number of different amino acids, which can feed different the carbon skeletons into pyruvate, acetyl CoA, and the citric acid cycle, which enter the TCA cycle. TCA: Tricarboxylic acid; PPP: Pentose phosphate pathway; OXPHOS: Oxidative phosphorylation.

After entering the cell, glucose is phosphorylated by ATP to form glucose-6-phosphate (G6P) in a reaction catalyzed by hexokinase. A series of enzymatic reactions degrade G6P to fructose-6-phosphate following by fructose-1,6-bisphosphate and finally to glyceraldehyde-3-phosphate, which, in turn, is converted to pyruvate in the cytosol[6]. In the mitochondria, pyruvate is imported and converted to Acetyl-CoA, then integrating the TCA cycle, which leads to production of NADH and FADH2, cofactors for oxidoreductase enzymes in the electron transport chain (ETC), important in the generation of ATP. Alternatively, in the cytosol, the lactate dehydrogenase enzyme can convert pyruvate into lactate, reoxidizing NADH to NAD+ which is necessary for glycolysis to continue[6]. In the absence of oxygen, glycolysis comes into action, catabolizing glucose into pyruvate, which is preferentially converted to lactate instead of Acetyl-CoA to enter the TCA cycle. Shift to glycolysis, even when oxygen is not a limitation is seen in some cases in a process known as aerobic glycolysis (fermentation) or Warburg effect, a process described by Otto Heinrich Warburg in which tumor cells tend to rely on glycolysis for ATP production rather than oxygen-dependent phosphorylation[7,8].

The PPP functions in parallel to glycolysis and is an important source for reducing molecules (*e.g.*, NADPH, required in anabolic reactions and critical to maintain redox balance under stress situations) and synthesis of pentoses (5-carbon sugars, important to maintain carbon homeostasis). The PPP reactions branches out into an oxidative and non-oxidative phase; the first oxidative phase converts G6P into NADPH, ribulose 5-phosphate and carbon dioxide, the second phase (non-oxidative) generates ribose 5-phosphate for the synthesis of nucleic acids and other sugar phosphate precursors used to build amino acids[9].

Mitochondrial FAO is a catabolic pathway that generates necessary products for the cell to produce energy, such as Acetyl-CoA, NADH+ and FADH2. The FAO is composed by two steps: the "activation" and the oxidation. The first step occurs in the cytosol and it is the formation of a fatty acid acyl-CoA with the consumption of ATP. The second step is called β-oxidation and generates quantities of Acetyl-CoA, NADH and FADH2. These products then enter the TCA cycle and the ETC, where they can be used for the generation of ATP[5]. On the other hand cells need lipids to produce cell membranes and other structures necessary for cell growth and proliferation so the

fatty acid synthesis (FAS) pathway converts intermediate products from glycolysis and TCA in acetyl-coA that is used to generate lipids[10]. In the mitochondria, citrate is synthesized from Acetyl-CoA and oxaloacetate, which is exported to the cytosol where it is cleaved to yield acetyl-CoA and oxaloacetate, then cytosolic Acetyl-CoA, is converted to Malonil-CoA and, by the effect of the fatty acid synthase, to Palmitate. Palmitate or palmitic acid is the most common saturated fatty acid in the human organism, and important for the composition of membrane phospholipids, substrate for the acylation of proteins, cholesterol synthesis and adipose triacylglycerols[6,11].

CROSSTALK BETWEEN CELL METABOLISM AND IMMUNE RESPONSES

The interplay between metabolic dysfunction and immune mechanisms involved in inflammation are being exposed by a growing number of studies and this knowledge is reshaping the understanding of what appeared to be independently functional systems of immunity and metabolism[12].

Dendritic cells (DCs) are a heterogeneous cell population key to immune homeostasis as they control activation and polarization of effector T cell responses and Treg differentiation. During DC maturation, the metabolic profile of precursors and differentiating DCs is eschewed, shifting from glycolysis to oxidative phosphorylation (OXPHOS), process that involves ROS, as well as an increase in expression of mitochondrial respiratory enzymes, ATP content and antioxidant capacity[13]. In activated DCs, glycolytic intermediates can also enter into the PPP, which support biosynthesis of nucleotides for increased protein output and the generation of NADPH, and the TCA cycle and support lipid membrane production and macromolecule biosynthesis[13,14]. Tolerogenic DCs (tolDCs), present a more active catabolic pathway, fatty acid metabolism, OXPHOS with increased respiratory capacity and highest mitochondrial oxidative activity as well as glycolytic capacity in comparison to mature DCs[14].

It is known that naive T cells have lower metabolic requirements, hence favor glycolysis and TCA cycle[15]. Once activated T cells undergo metabolic reprogramming which is believed necessary for cells to sustain the biosynthesis of lipids, proteins and nucleic acids required for cell proliferation and effector molecules, therefore, a change from OXPHOS in naïve or memory cells to increased glycolysis is observed in effector T cells[16] (Figure 2). Thus, increase in glycolysis, PPP, glutamine metabolism, combined with synthesis of cellular components characterizes early cell activation[7,15,17]. In general, *in vitro* studies have indicated that glycolysis is very important for effector cell development, evidenced also by data showing that GLUT1 deficiency impairs CD4+ effector function and proliferation while Tregs are enriched and functionally unaffected[18,19]. In a similar manner, glutamate metabolism is also involved in the differentiation of Th1 and Th17 effector T cells but does not seem to be critical for Tregs[18,20]. Effector T cells undergoing enhanced proliferation, including some subtypes of T helper cells, and CD8+ T cells, increase glycolysis and glutaminolysis as a mechanism to meet the increased metabolic demands of cell growth as well as optimize the production of proinflammatory cytokines, such as IL-2 and IFN-γ[21]. In Tregs glycolysis modulates the expression of FOXP3, as it was demonstrated that 2-DG (2-deoxy-d-glucose)-glycolysis inhibition in human T cells lead to decreased IL-2–IL-2R–STAT5 signaling, consequently limiting the generation of functionally suppressive Treg cells[22]. Furthermore, activation of the glycolytic-lipogenic metabolism seems to be involved in the Th17/Treg balance, for example, Acetyl-CoA carboxylase 1 (ACC1)-mediated de novo FAS affects Th17 cell differentiation but not Treg cells[23-25]. Potentially, drugs such as soraphen A (ACC-specific inhibitor) could be tested in preclinical animal models to verify improvement of graft survival.

In regards to lipids, they are essential components for the structure of cell membrane, which must be duplicated in preparation for each cell division, as well as important energy sources metabolized through beta-oxidation, not surprisingly, lipids are easily accessible to immune cells in adipose tissue which abundantly surrounds lymph nodes[26].

Lastly, fatty acid metabolism is involved in both CD4 and CD8 cell function. For instance, a study demonstrated that the suppression of FAS by inhibition of ACC1 restrained the generation of pro-inflammatory Th17 cells, whilst favoring the differentiation of FoxP3+ Tregs[23] while in case of memory CD8 T cells, activation favors neo-synthesis of fatty acids to support FAO[27].

In summary, differentiation, activation and effector function of immune cells seem to be directly or indirectly oriented by shifts in metabolic pathway. Thus, when

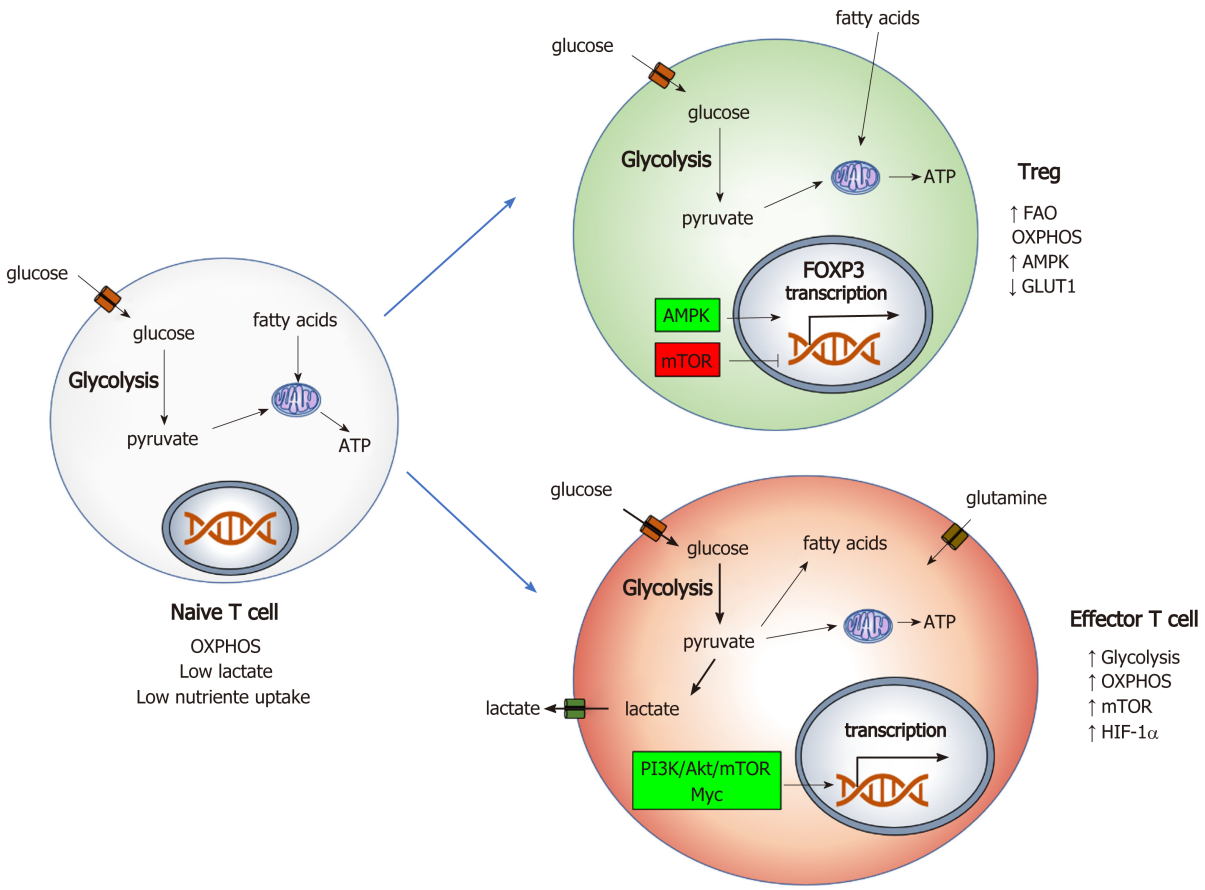

Figure 2 Main metabolic pathways in T cells – Naïve T cells are characterized by lower energy requirement, low glucose uptake and mainly use oxidative phosphorylation for energy generation. Once T cells are activated there is a switch in metabolic state which is accompanied by changes *via* the PI3K/Akt/mTOR axis and Myc. Increase in glycolysis and oxidative phosphorylation (OXPHOS) are characteristic in activated effector T cells, increase in glutamine uptake and fatty acid synthesis is also observed. In contrast, Tregs have metabolic features comparative to naïve T cells, producing energy by lipid oxidation and OXPHOS in mitochondria for the generation of adenosine triphosphate[7,42,43]. ATP: Adenosine triphosphate; AMPK: Adenosine monophosphate activated protein kinase; OXPHOS: Oxidative phosphorylation; FAO: Fatty acid oxidation.

considering metabolic parameters that affect immune cell fate, a variety factors will influence the tissue microenvironment such as: nutrient competition, oxygen consumption and metabolite production from tissue, immune cells and microbiota as well as the inflammatory state of the host[28,29].

TARGETING METABOLIC PATHWAYS IN TRANSPLANTATION

Solid organ transplantation is most-often the last resource for patients who suffer from end-stage organ disease, however, long-term acceptance and survival of transplanted tissues and organs is currently limited mainly due to immune-mediated mechanisms[30]. A great deal of effort has been dedicated to understanding the mechanisms underlying rejection by effector and emerging evidence does suggest a prominent role for nutritional and metabolic substrates on immune responses.

In transplantation, during which the tissue obligatorily goes through surgical trauma, lack of oxygenation or damage from reperfusion, the injury causes oxidative stress (OS) and release of Damage-associated molecular patterns and danger signals from necrotic cell death, which act as endogenous activators of innate immune mechanisms that promote inflammatory tissue damage and metabolic alterations in immune cells[31]. This signaling cascade will provoke the initial infiltration of cells into the allograft, followed by migration to lymph nodes, where T cells and DCs will initiate and allow propagation of allo-specific immune responses[28,29,32]. In the process of following antigenic activation, cells require a major shift in energy requirement as they change from a quiescent state to active-cytokine producing and proliferating immune cells, thus, this metabolic reprogramming includes balance between energy production and consumption based on availability of nutritional derived components,

mitochondrial or anaerobic respiration[16].

Regarding DC regulation, pharmacological intervention such as activation of AMPK signaling by peroxisome proliferator-activated receptor gamma coactivator (PGC) and Resveratrol to enhance PGC-1α activity has been demonstrated to generate tolDCs[33-35] , that have crucial role in inducing tolerance to the graft. DCs treated with Resveratrol showed reduced capacity to stimulate allogenic T cells and to induce CD4+ T cell migration[35]. Also, metabolic products like ATP may be recognized as a danger signal, whilst upon ATP degradation leads to decrease in pro-inflammatory signalling, regulating activation of antigen presenting cells or Treg cells[36,37].

Studies have shown that T cell activation and effector responses require metabolic reprogramming which relies glycolysis and glutaminolysis pathways[38-40], now researchers are investing whether intervening in this specific pathways can ameliorate graft survival. In a model of hematopoietic cell transplantation, Nguyen and colleagues demonstrated that alloantigen T cells demand on glycolysis for activation and GVHD (graft versus host disease) induction. In a pre-clinical murine GVHD model, blockage of glycolysis by use of rapamycin which inhibits mTORC1 or mTOR knockout mice, as well as use of 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3-PO), a specific inhibitor of pathway6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3, which also limits glycolysis, increased survival of mice[41].

Using murine models of skin and heart allograft transplantations, another study showed the effects of glycolysis and glutamine metabolism inhibition. Using a combination of 2-DG, 6-diazo-5-oxo-L-norleucine (glutamine metabolism inhibitor) and the anti-type II diabetes drug metformin, the group demonstrated an inhibition of allo-specific CD4+ and CD8+ T cell responses, preventing or delaying rejection in fully mismatched skin and heart allograft transplantation models[40].

In summary, these very fresh data seem to indicate that it is possible to hamper alloantigen-induced activation of effector responses by targeting some metabolic pathways.

CONCLUSION

Immunometabolism is a very new field to be explored, studies which have specifically targeted metabolic pathways in transplant models are only beginning to emerge. However, based on findings that it is possible to change metabolic reprogramming of DCs and T cells it may be possible to promote transplantation tolerance and avoid rejection. Most studies so far have focused in inhibition of glycolysis and the effects in T cells; this seems to improve graft survival in murine models, however long-term effects of this type of therapies and in the full components of the immune system have yet to be understood in order to declare metabolic intervention safe. It is important to continue research and find distinct metabolic signatures in different phases of DC and alloreactive T cell activation to specifically target immune alloreactive effector responses without deleterious side-effects.

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META-ANALYSIS

Proton pump inhibitors and adverse effects in kidney transplant recipients: A meta-analysis

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Abstract

BACKGROUND

The adverse renal effects of proton pump inhibitors (PPIs) are increasingly recognized in both the general population and patients with chronic kidney disease. Several pharmacokinetic studies have also raised concerns regarding the interaction between PPIs and immunosuppressive drugs in transplant patients. Whether the adverse effects of PPIs have a clinical significance in kidney transplant recipients remains unclear. We performed this meta-analysis to assess the risk of adverse effects in kidney transplant recipients on PPI compared with those without PPI exposure.

AIM

To investigate the risk of acute rejection, graft loss, hypomagnesemia, renal dysfunction, and overall mortality in kidney transplant recipients on PPI compared with those without PPI exposure.

METHODS

A systematic review was conducted in MEDLINE, EMBASE, and Cochrane databases from inception through October 2018 to identify studies that evaluated

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the adverse effects of PPIs in kidney transplant recipients, including biopsy-proven acute rejection, graft loss, hypomagnesemia, renal function, and overall mortality. Effect estimates from the individual studies were extracted and combined using random-effect, generic inverse variance method of DerSimonian and Laird. The protocol for this meta-analysis is registered with PROSPERO, No. CRD42018115676.

RESULTS

Fourteen observational studies with 6786 kidney transplant recipients were enrolled. No significant association was found between PPI exposure and the risk of biopsy-proven acute rejection at ≥ 1 year [pooled odds ratio (OR), 1.25; 95% confidence interval (CI), 0.82-1.91, I^2 = 55%], graft loss at 1 year (pooled OR = 1.30, 95%CI: 0.75-2.24, I^2 = 0%) or 1-year mortality (pooled OR = 1.53, 95%CI: 0.90-2.58, I^2 = 34%). However, PPI exposure was significantly associated with hypomagnesemia (pooled OR = 1.56, 95%CI: 1.19-2.05, I^2 = 27%). Funnel plots and Egger regression asymmetry test were performed and showed no publication bias.

CONCLUSION

PPI use was not associated with significant risks of higher acute rejection, graft loss, or 1-year mortality. However, the risk of hypomagnesemia was significantly increased with PPI use. Thus, future studies are needed to assess the impact of PPIs on long-term outcomes.

Key words: Proton pump inhibitors; Kidney; Renal transplantation; Meta-analysis hypomagnesemia; Systematic reviews

Core tip: Several pharmacokinetic studies have raised concerns regarding the interaction between proton pump inhibitors (PPIs) and immunosuppressive drugs in transplant patients. Whether the adverse effects of PPIs have a clinical significance in kidney transplant recipients remains unclear. We performed this meta-analysis to assess the risk of adverse effects in kidney transplant recipients on PPI compared with those without PPI exposure. We demonstrate that PPI use is not associated with significant risks of higher acute rejection, graft loss, or 1-year mortality. However, PPI use is associated with 1.56-fold increased risk of hypomagnesemia. Thus, future studies are needed to assess the impact of PPIs on long-term outcomes.

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INTRODUCTION

Proton pump inhibitors (PPIs) are commonly prescribed after transplantation for prophylaxis against peptic ulcer disease and for treatment of gastro-esophageal reflux disease or dyspepsia. Prolonged exposure to this class of medication has been shown to be associated with kidney dysfunction[1,2], as well as other non-renal adverse outcomes, including hypomagnesemia[3], fracture[4], or dementia[5] in the general population. The risk of kidney dysfunction associated with PPIs is particularly concerning to kidney transplant recipients who are already at risk for acute kidney injury.

Mycophenolate mofetil (MMF) is an antimetabolite that is commonly used as part of the maintenance immunosuppression in kidney transplant recipients[6]. MMF is a prodrug that is hepatically metabolized to the active compound mycophenolic acid (MPA) after oral administration. MPA exerts its immunosuppressive effects by reversibly inhibiting the de novo synthesis of purine nucleotides, leading to reduced proliferation of B- and T-cell lymphocytes, induction of activated T lymphocyte

apoptosis, and downregulation of adhesion molecule expression, resulting in lower leukocyte trafficking and recruitment[7]. Because gastrointestinal discomfort is a common side effect of MMF, PPIs are commonly prescribed to alleviate the symptoms. However, pharmacokinetic studies[8-12] have shown that PPIs reduce the absorption of MMF and lower the exposure to MPA presumably by its potent inhibition of gastric acidification compared with another class of acid suppressant, the H2-receptor antagonists[13,14]. Randomized controlled trials[15,16] and observational studies[17-19] have also shown that reduced exposure to MPA is associated with higher risk of acute rejection and overall worse allograft outcome in kidney transplant recipients. However, the clinical significance of this drug interaction in kidney transplant recipients is unknown. Several studies[20,21] have shown a possible increased risk of acute rejection with PPI exposure whereas others have not[22-24].

Some studies[25,26] have shown that concurrent PPI can increase tacrolimus drug concentration, leading to higher risk of toxicity through cytochrome or p-glycoprotein inhibition in patients with certain Cytochrome P450 2C19 (CYP2C19) and/or CYP3A5 genotypes. However, this is not expected to increase the risk of rejection, but calcineurin inhibitor toxicity may lead to renal dysfunction. Other commonly used immunosuppressive drugs are not known to have significant interaction with PPIs.

PPI may also interfere with magnesium absorption in the gastrointestinal tract, causing hypomagnesemia[3]. The mechanism of renal dysfunction related to PPIs is not clear although acute interstitial nephritis (AIN) associated with PPIs has been purposed[1,2].

Therefore, we conducted this systematic review and meta-analysis to investigate the adverse outcomes in kidney transplant recipients on PPI compared with those without PPI exposure. The outcomes of interest include biopsy-proven acute rejection, graft loss, kidney dysfunction, hypomagnesemia, and overall mortality.

MATERIALS AND METHODS

Search strategy

The protocol for this meta-analysis is registered with PROSPERO, No. CRD420-18115676. PRISMA statement guidelines were followed for conducting and reporting meta-analysis data[27]. A systematic review was conducted in MEDLINE, EMBASE, and Cochrane databases from inception to October 2018 to identify studies that evaluated adverse effects of PPIs in kidney transplant recipients by using the search terms "kidney transplant" and "proton pump inhibitor," as described in the online supplementary data without any language restriction. References of selected articles were also manually searched for additional studies.

Inclusion criteria

Studies were eligible for this meta-analysis if the following inclusion criteria were met: (1) Randomized controlled trial, cohort (either prospective or retrospective), case–control study or cross-sectional study published as an original study to evaluate the outcomes of kidney transplantation in patients on PPIs; (2) Odds ratios (ORs), relative risk (RR), hazard ratio (HR), and standardized incidence ratio (SIR) with 95% confidence intervals (CIs) or sufficient raw data to calculate these ratios were provided; and (3) Subjects not on PPIs were used as comparators in cohort and cross-sectional studies.

Study eligibility was independently evaluated by the investigators (BB and CT). Any disagreement was resolved by mutual consensus. The quality of each study was appraised using the Newcastle–Ottawa quality scale[28]. This scale assesses each study in three domains, including the: (1) Representativeness of the subjects; (2) Comparability between the study groups; and (3) Ascertainment of the exposure of interest for the case–control study and the outcome of interest for the cohort study. The modified version of the Newcastle–Ottawa scale as described by Herzog *et al*[29] was used for cross-sectional studies.

Review process and data extraction

The two study investigators independently reviewed the titles and abstracts of all retrieved articles. Articles that apparently did not fulfill the inclusion criteria were excluded. Only potentially relevant articles underwent full-text review to determine eligibility. A standardized data collection form was used to extract the following information from the included studies: First author's name, year of publication, year of study, country where the study was conducted, study design, source of population, number of subjects, baseline characteristics of the subjects, and effect estimates. This data extraction process was performed by both investigators to ensure accuracy.

Statistical analysis

All statistical analyses were performed using Comprehensive Meta-analysis version 3 software (Eaglewood, NJ, United States). The pooled RRs of acute rejection, graft loss, hypomagnesemia, and overall mortality in kidney transplant recipients on PPIs compared with subjects not on PPIs were calculated using the generic inverse method of DerSimonian and Laird[30]. The random-effects model was used, given the high likelihood of between-study variance due to the difference in underlying population and methodology. Cochran's Q-test, which was supplemented by I^2 statistics, was used to evaluate statistical heterogeneity. I^2 statistics quantify the proportion of the total variation across studies, that is, due to true heterogeneity rather than chance. An I^2 value of 0% to 25% represents insignificant heterogeneity, > 25% to ≤ 50% represents low heterogeneity, > 50% to ≤ 75% represents moderate heterogeneity, and > 75% represents high heterogeneity[31].

RESULTS

The initial search yielded 838 articles, all of which underwent title and abstract review (Figure 1). Most of the articles were excluded at this step because they were case reports, letters to the editor, review articles, or interventional studies, which clearly did not fulfill our inclusion criteria. Eighteen studies underwent full-length article review, and four were excluded because they did not include controls or did not report the outcome of interest. Therefore, 14 studies met our inclusion criteria[20-24,32-40] and were included in the meta-analysis. The baseline characteristics of the included studies are summarized in Table 1. These 14 observational studies consisted of 6786 kidney transplant recipients (> 1907 with PPI exposure and 2528 without PPI exposure).

Acute biopsy-proven rejection and graft loss

Table 2 summarizes the findings across the studies that reported allograft outcomes. Definitions of biopsy-proven acute rejection and presumed rejection across included studies are also shown in Supplementary Table S1. Pooled data for acute rejection at ≥ 1 year were available from six studies with 2427 kidney transplant recipients (980 with PPI exposure and 1447 without PPI exposure). No significant association was found between PPI exposure and the risk of biopsy-proven acute rejection at ≥ 1 year (pooled OR = 1.25, 95%CI: 0.82-1.91, I^2 = 55%, Figure 2). At 3 mo, acute rejection risk was also not significantly different between the two groups (pooled OR = 1.54, 95%CI: 0.64-3.82). Acute cellular rejection was more common than antibody-mediated rejection (AMR) and the rejection rates were similar between the two groups, except in studies by Courson *et al*[21] and Rouse *et al*[24] which demonstrated higher rates of AMR among the PPI group. The median time to rejection was reported to be similar between the two groups across four studies (approximately 3-4 mo post-transplant). Graft loss at 1 year was also not different between those with and without PPI exposure (pooled OR = 1.30, 95%CI: 0.75-2.24, I^2 = 0%, Figure 3).

Renal function

All but one study reported no significant short term (3 mo to 1 year) difference in renal function, as summarized in Table 3. Uludag *et al*[37], which had the most extended follow-up period of all included studies (median, 109 mo; interquartile range, 82-156 mo), however demonstrated that the serum creatinine level in the PPI group was higher than that in the non-PPI group (1.44 ± 0.99 *vs* 1.24 ± 0.46 mg/dL).

Hypomagnesemia

Table 4 summarizes data across eight studies. The risk of hypomagnesemia in the PPI group was significantly higher than in the non-PPI group (pooled OR = 1.56, 95%CI: 1.19-2.05, I^2 = 27%, Figure 4) based on three studies. Sezer *et al*[35], Van Ende *et al*[33], and Uludag *et al*[37] did not report a significant difference in the magnesium level between those with and without PPI exposure, whereas Alhosaini *et al*[34] reported a significant difference between the two groups (magnesium: 1.70 ± 0.12 *vs* 1.79 ± 0.17 for those with PPI and without PPI exposure; P = 0.006). Gomes-Neto *et al*[38] and Douwes *et al*[40] (who analyzed data from an overlapping set of patients) reported a significant inverse correlation between PPI use and plasma magnesium level. The proportion of hypomagnesemia also did not differ between the two groups, but a study by Shabaka *et al*[36] noted that those with PPI exposure seemed to develop significantly more severe hypomagnesemia (defined as magnesium level < 1.3 mg/dL) compared with those without PPI exposure (21% *vs* 5%).

Overall mortality

Table 1 Characteristics of included studies

Ref.	Country	Type	Total N	Race	Immuno-suppressive regimen	CNI use (% Cyclosporine)	PPI			No PPI			Quality Scale[3]
							N	Age	M/F	*N*	Age	M/F	
Patel *et al*[32] 2012	United States	Retrospective	561	NR	Tacrolimus, MMF, Prednisone	0%	155	52±13[1]	NR	406	48±14	NR	3-2-2
Knorr *et al*[20] 2014	United States	Retrospective	597	52% Black	rATG, MMF, Tacrolimus, Prednisone	<3%	213	55±12	122/91	384	55±13	210/174	4-2-3
van Boekel *et al*[22] 2014	The Netherlands	Retrospective	202	98.5% Caucasian	Tacrolimus, MMF. Prednisone	0%	125	47.7±12.8	61.6%/38.4%	77	46.7±13.3	66.2%/43.8%	4-2-3
Van Ende *et al*[33] 2014	Belgium	Cross-sectional	512	98% Caucasian	Varies	47% (tacrolimus 35 %)	101	53 ± 13	59%/41%	411	53 ± 13	59%/41%	4-2-3
Alhosaini *et al*[34] 2015	United States	Retrospective	83	59% Caucasian, 19% Black	CNI (Tacrolimus, Cyclosporine), MPA, Prednisone	5/83 (6%)	43	54 ± 15.1	25/18	40	49.7 ± 16.4	24/16	4-2-3
Sezer *et al*[35] 2015	Turkey	Retrospective	354	NR	NR	NR	164	38.6 ±10.7	NR	96	NR	38.6 ±10.7	3-2-2
Courson *et al*[21] 2016	United States	Retrospective	286	51% Caucasian, 17% Black, 10% Asian	Tacrolimus, MMF or MPS, early steroid withdrawal	0%	171	56±13	118/53	115	54±13	88/27	4-2-3
Patel *et al*[23] 2017	United States	Retrospective	522	24% Black	Tacrolimus, reduced-dose MMF, prednisone	11/522 (2%) converted to cyclosporine	183	54 (44-63)[2]	102/81	339	53 (43-60)	219/120	4-2-3
Shabaka *et al*[36] 2017	Spain	Cross-sectional	938	NR	CNI-based regimen	NR	NR	NR	NR	NR	NR	NR	3-2-2
Rouse *et al*[24] 2017	United States	Retrospective	211	55% Caucasian, 30% Black	Tacrolimus, MMF or MPS, Prednisone	0%	35	55±10.7	25/10	176	63±14	124/52	4-2-3
Uludag *et al*[37] 2017	Turkey	Retrospective	292	NR	NR	NR	223	36±10	129/104	69	33±11	42/27	3-2-2
Kipp *et al*[39] 2018	United States	Retrospective	819	NR	NR	NR	404	NR	NR	415	NR	NR	3-1-2
Douwes *et al*[40] 2018	The Netherlands	Cross-sectional	706	NR	NR	NR	NR	53 ± 13	57%/43%	NR	53 ± 13	57%/43%	3-1-2

Gomes-Neto *et al*[38] 2018	The Nether-lands	Cross-sectional	703	NR	NR	NR	NR	53 ± 13	57%/43%	NR	53 ± 13	57%/43%	3-1-2

[1]Data expressed as mean ± SD;
[2]Data expressed as Median (Range);
[3]According to the NOS (Newcastle-Ottawa Scale) classification. NR: Not reported; CNI: Calcineurin inhibitor; MMF: Mycophenolate mofetil; MPS: Mycophenolate sodium; MPA: Mycophenolate; rATG: Rabbit antithymocyte globulin; PPI: Proton pump inhibitors.

All-cause mortality data were available from five studies (Table 5), with three studies reporting 1-year survival and two reporting longer-term all-cause mortality. One-year mortality did not significantly differ between PPI and non-PPI use (pooled OR = 1.30, 95%CI: 0.51-3.29, I^2 = 41.4%; Figure 5). The two studies that reported long-term mortality outcomes (Douwes *et al*[40] and Gomes-Neto *et al*[38]) seemed to analyze data from a highly overlapping set of patients (n = 706 *vs* 703); hence, pooled HR was not calculated. With a median follow-up duration of 5.4 years (range, 4.8-6.1 years) in both studies, the adjusted HRs for all-cause mortality was significantly associated with PPI use (HR = 1.94, 95%CI: 1.32-2.88, and HR = 2.01, 95%CI: 1.43-2.83, respectively).

Evaluation for publication bias

The funnel plots (Supplementary Figure S1 to Figure S4) and Egger's regression asymmetry test were performed and showed no significant publication bias (P > 0.05 for all outcomes).

Sensitivity analysis

Sensitivity analysis was performed by excluding one study at a time to investigate the effect of each study on the pooled OR for each outcome assessed. The pooled effect estimate from this sensitivity analysis remained essentially unchanged.

DISCUSSION

This meta-analysis showed no significant association between exposure to PPIs and higher risk of acute biopsy-proven rejection, graft loss, or overall mortality, but a significantly higher risk of hypomagnesemia among those with PPI exposure was noted. No short-term difference in renal function was found between the two groups.

Despite several pharmacokinetic studies that have clearly showed significantly reduced MPA exposure following concomitant administration of PPIs and MMF in both healthy volunteers[12,41] and in immediate post-transplant kidney transplant recipients[10,11], there was no significant association between PPI use and increased risk of acute rejection in our study, suggesting that the effect may not be large enough to be clinically significant. Because none of the included studies reported MPA drug level or direct gastric pH measurement, it is difficult to ascertain whether a significant interaction between PPIs and MMF exists in the real-world setting. Three studies (van Boekel *et al*[22], Courson *et al*[21], and Patel *et al*[23]) reported the total cumulative MMF exposure or mean daily dose between the two groups. In all three studies, despite the PPI group receiving a slightly lower cumulative MMF dose compared to the non-PPI group (non-significant in the study by van Boekel *et al*[22] and Patel *et al*[23]; significant in the study by Courson *et al*[21]), no significant difference in acute rejection was found. Interestingly, in black patients, PPI was found to be significantly associated with a higher risk of acute rejection in one study[20].

Another potential reason for the lack of a significant association between PPI use and acute biopsy-proven rejection is that the majority of the kidney transplant recipients enrolled in the included studies were on tacrolimus, with none or only a small percentage of recipients on cyclosporine. The use of tacrolimus as the calcineurin inhibitor instead of cyclosporine may help lower the risk of reduced MPA exposure with PPI use. Cyclosporine, unlike tacrolimus, can reduce the enterohepatic recirculation of MPA in the gastrointestinal tract[42,43], thus further lowering total MPA exposure. The enteric-coated mycophenolate sodium does not appear to have a significant interaction with PPI[8,41,44], unlike MMF.

We did not demonstrate a significant difference in renal function as measured by estimated glomerular filtration rate or serum creatinine between the PPI and the non-PPI group in the short term (3 mo to 1 year). Extrapolating from observational studies in the general population, this is not unexpected as the risk of kidney dysfunction seems to be associated with more prolonged PPI use and may have a long latent

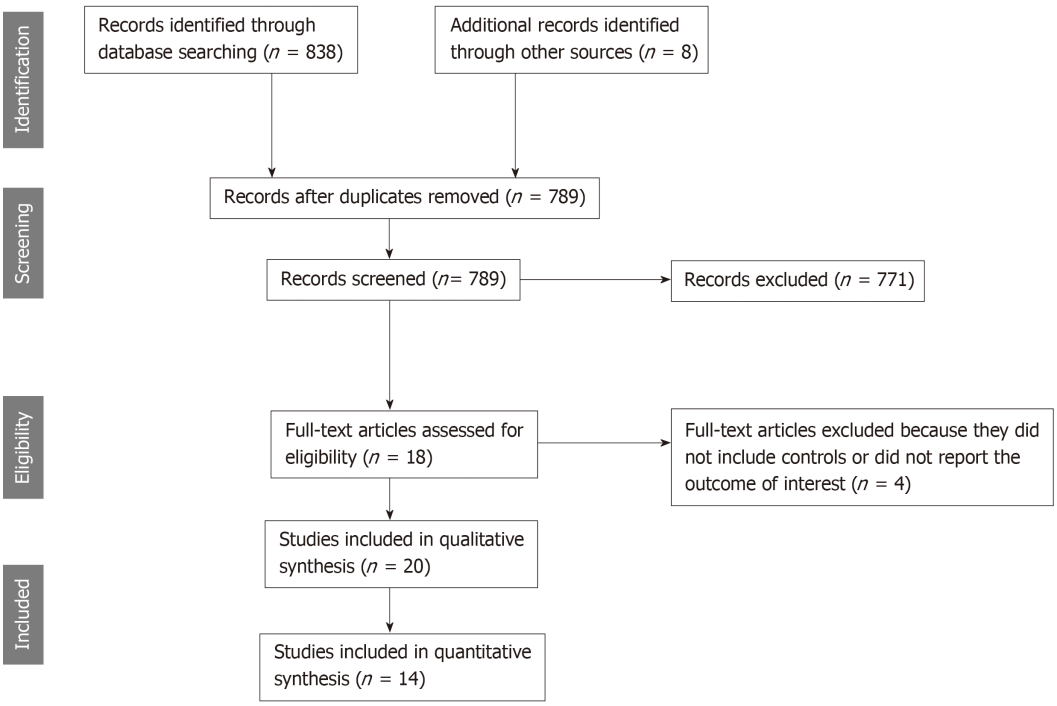

Figure 1 Study selection.

period[1,45]. Uludag *et al*[37] also confirmed this observation by noting a significantly higher serum creatinine level in PPI users compared with non-users at a longer median follow-up of 109 mo.

The risk of hypomagnesemia in the PPI group was significantly higher than that in the non-PPI group in our study. This is consistent with studies in the general population that report hypomagnesemia with prolonged PPI use[3]. The exact mechanism of PPI-induced hypomagnesemia is unknown. Urinary magnesium excretion has been shown to be low in patients with hypomagnesemia related to PPI use[46], suggesting that reduced absorption from the gastrointestinal tract is the main cause. It is hypothesized that the TRMP6 (transient receptor potential melastatin) pathway in gut epithelial cells, which mediates magnesium absorption, is inhibited by the high pH milieu caused by PPI use[47]. This inhibition is more pronounced in certain individuals with additional polymorphisms of the related cellular pathway proteins or other risk factors, which explains why the incidence and degree of hypomagnesemia vary among PPI users[47]. Some studies have also reported that high-dose oral magnesium supplementation can correct hypomagnesemia associated with PPI[48], suggesting that the paracellular passive absorption in the bowel remains intact.

In kidney transplant recipients, hypomagnesemia has been shown to be associated with various adverse consequences[49]. Low magnesium level has been associated with accelerated decline of allograft function and a higher rate of graft loss in patients with cyclosporine-induced nephropathy[50], consistent with animal studies showing a higher degree of renal tissue fibrosis associated with low magnesium[51] that appears to be partially correctable with magnesium supplementation[51,52]. Hypomagnesemia may also lead to a higher incidence of new-onset diabetes after transplant[53], which is a separate risk factor for allograft loss and overall mortality.

Our study did not show a significant difference in the 1-year overall mortality, as expected, because the risks of acute rejection, graft loss, and kidney dysfunction did not significantly differ between the PPI and non-PPI groups. Only hypomagnesemia was found to be significantly associated with PPI use; hence, this may not be clinically significant to drive a mortality difference at least in the short term. However, Douwes *et al*[40] and Gomes-Neto *et al*[38] reported a significant association between PPI use and long-term all-cause mortality despite adjustment for confounders. Furthermore, both studies also showed a significant interaction between PPI use and hypomagnesemia. As noted previously, Uludag *et al*[37] has also reported significantly worse kidney function in the PPI group with longer follow-up (median, 109 mo). Hypomagnesemia or renal dysfunction may be a late manifestation associated with prolonged exposure to PPIs, which may eventually be clinically significant enough to cause higher mortality. Further studies are needed to clarify this question.

Although we believe the literature review process was rigorous and the included

Table 2 Acute rejection and graft loss

Ref.	Biopsy-proven acute rejection at 1 yr (%)	Biopsy-proven or presumed rejection at 3 mo (%)	Median time to rejection	Antibody mediated rejection (%)	Graft loss (%)
Patel *et al*[32] 2012					
PPI	25 (16%)	NR	4.1 mo	3.3%	NR
No PPI	60 (15%)	NR	3.3 mo	3.1%	NR
P	0.69	-	NS	NS	-
Knorr *et al*[20] 2014					
PPI	32/213 (15%)	NR	110 ± 91 d	1/32 (3.1%)	9/213 (4.2%)
H2A	46/384 (12%)	NR	110 ± 112 d	2/46 (4.3%)	19/384 (4.9%)
P	0.15	-	1.0	NR	0.84
van Boekel *et al*[22] 2014					
PPI	NR	25/125 (20%) BPAR: 13/125 (10.4%)	NR	NR	NR
H2RA	NR	15/77 (19.5%) BPAR: 7/77 (9.1%)	NR	NR	NR
P	-	NS	-	-	-
Courson *et al*[21] 2014					
PPI	16/171 (9.4%)	NR	116±92 d[1]	5/16 (31%)	4/171 (2.3%)
H2RA	3/115 (2.6%)	NR	both	0	2/115 (1.7%)
P	0.029	-	NS	0.53	1
Patel *et al*[23] 2017					
PPI	11/183 (19%)	12/183 (4.9%)	106 (57-286) days[2]	1/11 (9.1%)	9/183 (4.9%)
H2RA	28/339 (14%)	9/339 (3.5%)	139 (96-339) days	2/28 (7.1%)	8/339 (2.4%)
P	0.35	0.44	0.28	NR	0.12
Rouse *et al*[24] 2017					
PPI	5/35 NR		NR	2/5 (40%)	NR
H2RA	26/176	NR	NR	3/26 (12%)	NR
P	1.0	-	-	0.03	-
Uludag *et al*[37] 2017					
PPI	36/233 (15.5%)	NR	NR	NR	11/233 (4.7%)
No PPI	5/69 (7.2%)	NR	NR	NR	2/69 (2.9%)
P	0.08	-	-	-	0.51

[1]Data expressed as mean ± SD;
[2]Data expressed as Median (Range). NR: Not reported; NS: Not significant; H2RA: H2-receptor antagonists; PPI: Proton pump inhibitors.

studies were of high quality, this meta-analysis has some limitations. Therefore, the interpretation of the results needs to be performed with caution. First, this meta-analysis is based solely on observational studies. Although this is appropriate for our clinical question, it may be inherently subject to selection bias and unadjusted confounders. Second, certain important baseline characteristics could not be obtained or compared across all studies. Of interest to transplant recipients, comparison of different immunosuppressive regimens, drug level, dosage, and adherence to both immunosuppressive drugs or acid suppressive therapy between the two groups was not possible in most included studies due to either their observational or retrospective design. Third, the definitions of various outcomes of interest varied across studies, such as the cut-off value for hypomagnesemia, definition of severe rejection, or the use of different criteria for the classification of AMR and cell-mediated rejection. Finally, most of the included studies only reported follow-up data for a relatively short-term period (approximately 1 year). Therefore, we cannot rule out the possibility that prolonged exposure of PPIs (longer than a year) may lead to adverse outcomes. Further study is needed to address whether long-term PPI exposure in kidney transplant recipients is associated with worse outcomes.

In conclusion, PPI use was not associated with significant risks of higher acute rejection, graft loss, or 1-year mortality. However, the risk of hypomagnesemia was significantly increased with PPI use.

Table 3 Renal function

Ref.	eGFR			Cr		
	PPI	No PPI	*P*	PPI	No PPI	*P*
Knorr *et al*[20]	53.1 ± 20.2[1]	55.1 ± 20.6	0.29	NR	NR	-
van Boekel *et al*[22]	49.5 ± 12.3	50.7 ± 12.5	NS	1.5 ± 0.4 at 3 mo	1.5 ± 0.4	NS
Patel *et al*[23]	49.0 (39.4–63.2)[2]	49.9 (39.3–60.8)	0.78	NR	NR	-
Uludag *et al*[37]	-	-	-	1.49 ± 0.99 mg/dL	1.24 ± 0.46 mg/dL	0.017
Alhosaini *et al*[34]	49.4 ± 14.9	52.8 ± 14.3	0.29	-	-	-
Kipp *et al*[39]	NR	NR	-	1.896 ± 1.53	1.812 ± 1.25	*P* = 0.4098

[1]Data expressed as mean ± SD;
[2]Data expressed as Median (Range). NR: Not reported; NS: Not significant; eGFR: Estimated glomerular filtration rate; PPI: Proton pump inhibitors.

Table 4 Hypomagnesemia

Ref.	Serum / Plasma magnesium level			Hypomagnesemia					
	PPI	No PPI	*P*	Definition of hypomagne-semia	PPI	No PPI	*P*	Correlation between PPI and hypomagne-semia	Magnesium supplemen-tation
Sezer *et al*[35]	1.5 ± 0.04 mg/dl	1.7 ± 0.02 mg/dl	*P* < 0.05	NR	NR	NR		NR	NR
Shabaka *et al*[36]	NR	NR		NR	OR 1.55, (95%CI 1.09-2.20)	1		NR	NR
Kipp *et al*[39]	NR	NR		NR	215 (53.1%)	185 (44.6%)	*P* < 0.013	NR	NR
Alhosaini *et al*[34]	1.70 ± 0.12	1.79 ± 0.17	0.006	Serum Mg < 1.8 mg/dL	33/43	24/40	*P* > 0.05	NR	Use of Mg supplement: PPI 47% *vs* Non-PPI 21% (*P* = 0.02)
				Serum Mg < 1.3 mg/dL	9/43 (21%)	2/40 (5%)	*P* = 0.03		
Uludag *et al[37]*	0.728 mmol/L	*vs* 0.755 mmol/L,	*P* = 0.061	NR	NR	NR		NR	NR
Van Ende *et al*[33]	NR	NR		Serum Mg < 1.7 mg/dL	β: −0.84 (0.26; 2.71), *P* = 0.78			β: −0.84 (0.26; 2.71), *P* = 0.78	NR
Douwes *et al*[40]	NR	NR		Serum Mg < 1.8 mg/dL (0.75 mmol/L)	HR 3.25 (1.26-8.39)	1		β: -0.08, *P* = 0.046	Mean Mg intake: 330 ± 85 mg/d, (*P* = 0.204)
Gomes-Neto *et al*[38]	NR	NR		NR	β: -0.05, *P* = 0.04	NR		β: -0.05, *P* = 0.04	NR

[1]Data expressed as mean ± SD; [2]Data expressed as Median (Range); NR: Not reported; NS: Not significant; PPI: Proton pump inhibitors; Mg: Magnesium.

Table 5 Mortality

Ref.	1-yr mortality			Mortality beyond 1 yr (PPI *vs* no PPI)
	PPI	No PPI	*P*	
Knorr *et al*[20]	9/213 (4.2%)	17/384 (4.4%)	1	
Courson *et al*[21]	3/171 (1.8%)	3/115 (2.6%)	0.687	
Patel *et al*[23]	6/183 (3.3%)	3/339 (0.9%)	0.007	
Douwes *et al*[40]	NR	NR		HR 1.94 (95%CI: 1.32-2.88)
Gomes-Neto *et al*[38]	NR	NR		HR 2.01 (95%CI: 1.43-2.83)

NR: Not reported; NS: Not significant; eGFR: Estimated glomerular filtration rate; PPI: Proton pump inhibitors.

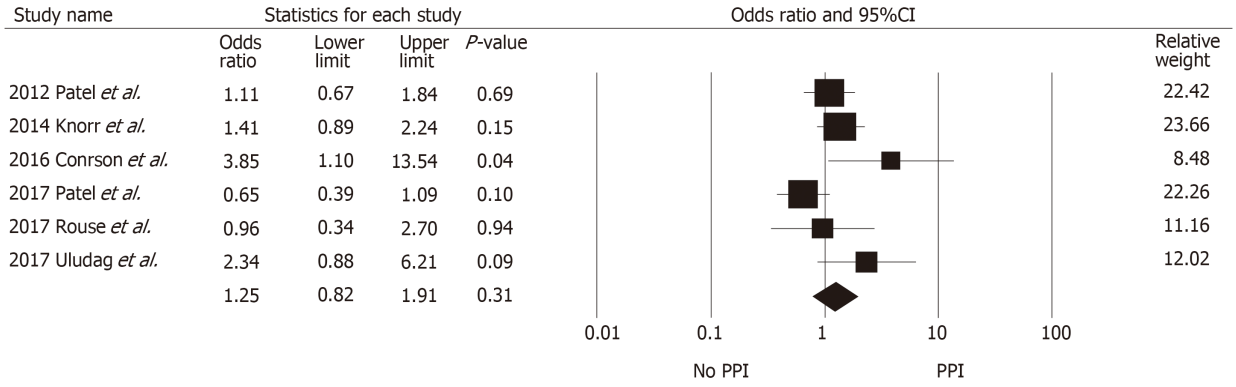

Figure 2 Forest plot of all included studies evaluating the risk of biopsy-proven rejection at one year or more in proton pump inhibitors users compared with non-users.

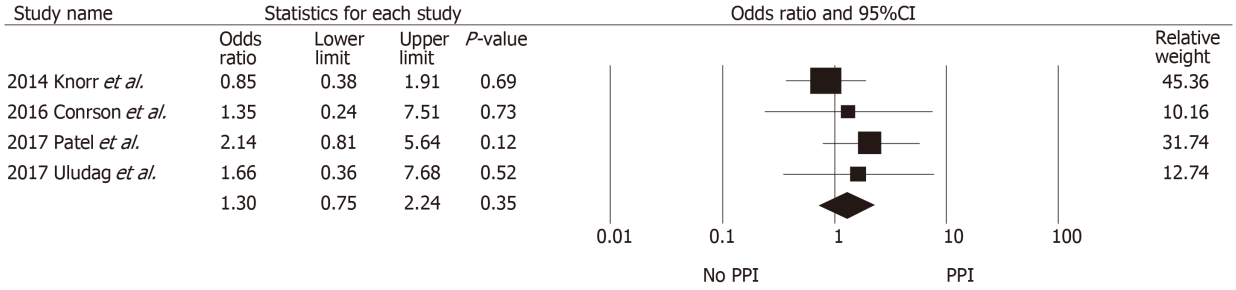

Figure 3 Forest plot of all included studies evaluating the risk of graft loss in proton pump inhibitors users compared with non-users.

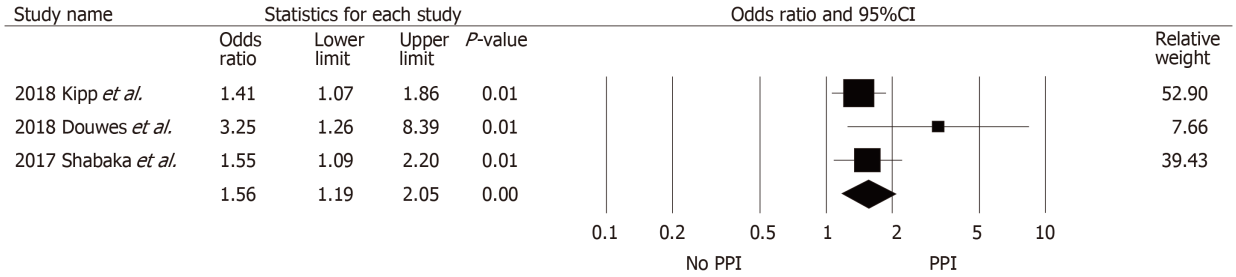

Figure 4 Forest plot of all included studies evaluating the risk of hypomagnesemia in PPI users compared with non-users.

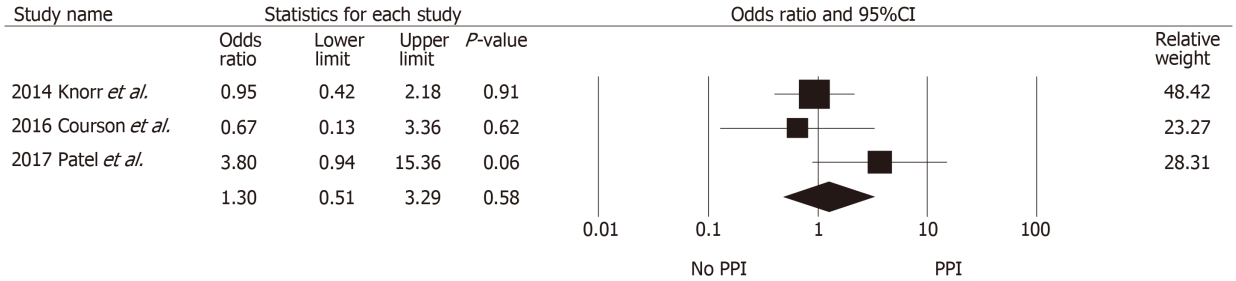

Figure 5 Forest plot of all included studies evaluating the risk of one-year mortality in PPI users compared with non-users.

ARTICLE HIGHLIGHTS

Research background

Adverse renal effects of PPIs are increasingly recognized in clinical practice. Pharmacokinetic studies have also raised concerns regarding the interaction between PPIs and immuno-

suppressive drugs in transplant patients. Whether the adverse effects of PPIs have a clinical significance in kidney transplant recipients remains unclear.

Research motivation
Proton pump inhibitors are commonly used after transplantation for prophylaxis against peptic ulcer disease and for treatment of gastro-esophageal reflux disease or dyspepsia. Prolonged exposure to this class of medication has been shown to be associated with kidney dysfunction, as well as other non-renal adverse outcomes, including hypomagnesemia, fracture, or dementia in the general population. The clinical significance of this drug interaction in kidney transplant recipients is unknown. Several studies have shown a possible increased risk of acute rejection with PPI exposure whereas others have not.

Research objectives
We performed this systematic review and meta-analysis to investigate the adverse outcomes in kidney transplant recipients on PPI compared with those without PPI exposure.

Research methods
A systematic review was conducted in MEDLINE, EMBASE, and Cochrane databases from inception to October 2018 to identify studies that evaluated adverse effects of PPIs in kidney transplant recipients. The outcomes of interest include biopsy-proven acute rejection, graft loss, kidney dysfunction, hypomagnesemia, and overall mortality. The protocol for this meta-analysis is registered with PROSPERO, No. CRD42018115676.

Research results
The authors found no significant association between exposure to PPIs and higher risk of acute biopsy-proven rejection, graft loss, or overall mortality, but a significantly 1.56-fold higher risk of hypomagnesemia among those with PPI exposure was noted. No short-term difference in renal function was found between the two groups.

Research conclusions
PPI use was not associated with significant risks of higher acute rejection, graft loss, or 1-year mortality. However, the risk of hypomagnesemia was significantly increased with PPI use. In the long-term, PPI use may also be associated with kidney dysfunction and increased overall mortality.

Research perspectives
This study demonstrated significant hypomagnesemia in kidney transplant recipients who received PPIs. Since hypomagnesemia is associated with new onset diabetes new-onset diabetes after transplantation, future large-scale clinical studies are needed to assess the impact of PPIs on long-term outcomes.

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MINIREVIEWS

Considerations for hematopoietic stem cell transplantation in primary immunodeficiency disorders

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Abstract

Primary immunodeficiency disorders (PIDs) result from inborn errors in immunity. Susceptibility to infections and oftentimes severe autoimmunity pose life-threatening risks to patients with these disorders. Hematopoietic cell transplant (HCT) remains the only curative option for many. Severe combined immunodeficiency disorders (SCID) most commonly present at the time of birth and typically require emergent HCT in the first few weeks of life. HCT poses an unusual challenge for PIDs. Donor source and conditioning regimen often impact the outcome of immune reconstitution after HCT in PIDs. The use of matched or unmatched, as well as related versus unrelated donor has resulted in variable outcomes for different subsets of PIDs. Additionally, there is significant variability in the success of engraftment even for a single patient's lymphocyte subpopulations. While certain cell lines do well without a conditioning regimen, others will not reconstitute unless conditioning is used. The decision to proceed with a conditioning regimen in an already immunocompromised host is further complicated by the fact that alkylating agents should be avoided in radiosensitive PIDs. This manuscript reviews some of the unique elements of HCT in PIDs and evidence-based approaches to transplant in patients with these rare and challenging disorders.

Key words: Primary immunodeficiency disorders; Hematopoietic stem cell transplant; Autoimmunity; Conditioning regimens; Engraftment

Core tip: Primary immunodeficiency disorders (PIDs) result from inborn errors in immunity and hematopoietic cell transplant (HCT) still remains the only curative option for many of these disorders. Severe combined immunodeficiency disorders are a medical emergency and require HCT within the first few weeks of life. Optimal donor selection, conditioning regimen and outcomes of immune reconstitution vary greatly among these disorders. This manuscript reviews some of the unique elements of HCT in PIDs and

evidence-based approaches to transplant in patients with these rare and complex disorders.

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INTRODUCTION

Primary immunodeficiency disorders (PIDs) result from inborn errors in immunity. Many PIDs present with severe life-threatening infections and immune dysregulation that can be fatal if not diagnosed and treated early in life. Hematopoietic cell transplant (HCT) is a curative option for many PIDs. Besides for donor selection, individual conditioning regimens must be taken into account when considering a successful outcome of HCT[1]. The unique immunologic defects involved in PIDs and clinical manifestations of these disorders pose unique challenges to the immunologist and transplant specialist.

SEVERE COMBINED IMMUNODEFICIENCY DISORDER

Severe combined immunodeficiency disorders (SCID) belong to a subgroup of genetic disorders characterized by impaired T-cell development, sometimes also accompanied by B cell and Natural Killer (NK) cell deficiency. The genetic pathophysiology responsible for a subtype of SCID determines the cellular phenotype of the specific disorder.

Reticular dysgenesis is an autosomal recessive variant of SCID that is a product of adenylate kinase 2 (AK2) deficiency and presents as T-B-NK- SCID. A defect in the ability to clear toxic products of purine metabolism due to adenosine deaminase (ADA) deficiency also results in a T-B-NK-phenotype whereas the presentation of the rarer purine nucleoside phosphorylase (PNP) deficiency is more variable with T cell function being most severely affected.

Cytokine signaling abnormalities common to T and NK cell pathways such as IL-2R common gamma chain and JAK3 result in T-B+NK- SCID, whereas a defect in the IL-7R alpha chain results in T-B+NK+ SCID. T-cell receptor abnormalities due to an absence of CD45, CD3 and CORO1A affect T cell development and therefore will still allow for B cell and NK cell production. Thymic hypoplasia, as seen in DiGeorge syndrome due to 22q11.2 deletion as well as FOXN1 deficiency, also results in T cell deficiency. Lymphocyte receptor chain (VDJ) recombination defects due to the absence of RAG1, RAG2 and ARTEMIS proteins result in T-B-NK+ SCID.

All SCID subtypes follow an autosomal recessive inheritance pattern with the exceptions of the IL-2R gamma chain, which is the only known X-linked SCID, as well as DiGeorge syndrome which can result from a de novo or autosomal dominant mutation[2]. Since the introduction of T cell receptor excision circle (TREC) assay to the newborn screening program in the United States and other countries, SCID has been diagnosed at a younger age thereby preventing many serious infectious complications.[2,3].

While ADA deficiency can be, at least temporarily, treated with enzyme replacement therapy[3] and gene therapy is investigated for x-linked SCID, HCT still remains the only curative option for other SCIDs and many PIDs. As with all HCT, donor selection is of critical importance. HLA-matched related donors (MRD) are preferred, but unrelated donor (URD) HCT still has excellent survival rates particularly in the first 3.5 mo of life or in older infants without prior infections. Both of these donor sources have the benefit of short engraftment time compared to others. A MRD HLA-identical sibling is a donor of choice for HCT in cases of SCID. Acceptable alternatives include matched URD, haploidentical parent or a mismatched unrelated donor (MMRD) or umbilical cord donor (UCB). A consideration to take into account with matched sibling donors (MSD) is that a family member may be a carrier for the disease. There are no uniform guidelines regarding the approach to conditioning when MMRDs are used. Infants with active infections and who do not have a MSD have fared best with haploidentical T-cell-depleted transplants in the

absence of any pretransplant conditioning. Generally, however, reduced-intensity or myeloablative pretransplant conditioning was associated with an increased likelihood of a CD3+ T cell recovery to more than 1000/mm^3[5]. Graft-*vs*-host disease (GVHD) occurs when mature T cells are not removed from the donor source, resulting in inflammation and rejection of the graft. Mature T cell removal from the graft minimizes the risk for GVHD. T-cell depleted haploidentical and UCB transplants, however, carry a higher risk for viral infections. UCB also results in a longer engraftment time[4].

SCID marked by an absence of host T cells implies potentially less resistance to the graft. Therefore, pre-transplant conditioning recommendations vary. Immunosuppression regimens include: fludarabine, cyclophosphamide, anti-thymocyte globulin, alemtuzumab, rituximab and other monoclonal antibodies. Myeloablative therapy includes cyclophosphamide, fludarabine, antithymocyte globulin (ATG) and alemtuzumab. T-cell negative SCID typically does not require myeloablative therapy. Partly myeloablative agents are busulfan, melphalan, treosulfan. Reduced intensity conditioning (RIC) is a myeloablative approach that is less toxic than the fully myeloablative chemotherapy regimens and agents include melphalan, anti-CD45 antibodies, total body irradiation, thiotepa, and/or busulfan. Partial defects in known SCID-causing genes, as is the case with Omenn syndrome, allow for limited T cell production. Such disorders are more prone to graft rejection and require some degree of myeloablative chemotherapy. B cell negative SCIDs have better rates of T cell engraftment after a myeloablative regimen.

Primary Immune Deficiency Treatment Consortium identified factors that impact outcome of immune reconstitution and survival of 100 SCID patients post-HCT. Active infection at the time of HCT negatively impacted survival with a rate of 80% for those over 3.5 mo of age and with an active infection at the time of HCT. CMV was one of the most common infections in these patients. MSD recipients had the best clinical outcomes for SCID and good survival was identified for all alternative donor recipients. However, the study reported that 6 of 11 UCB recipients died. There was no significant difference in the short-term survival of patients who received chemotherapy-based conditioning (RIC/MAC) compared with those transplanted without conditioning or with immunosuppression conditioning (IS) that included one of the following: fludarabine, cyclophosphamide, ATG, or alemtuzumab. However, 9 of 11 (82%) patients who died received IS, RIC, or MAC. The use of RIC or MAC was associated with a decreased need for a second HCT and an increased likelihood of independence from immunoglobulin replacement[5,6].

Among recipients of non-MSD HCT, multivariate analysis showed that the SCID genotype strongly influenced survival and immune reconstitution. Overall survival was similar for patients with *RAG*, *IL2RG*, or *JAK3* defects and was significantly better than for patients with *ADA* or *DCLRE1C* mutations who had the worst outcomes. Patients with *RAG* or *DCLRE1C* mutations had poorer immune reconstitution than other genotypes. Patients with RAG defects, however, had better survival than did those with *DCLRE1C* mutations despite both conferring a T-B-NK+ phenotype. Among the *DCLRE1C*-deficient patients, 64% of deaths were due to noninfectious causes compared with 9% in *RAG*-deficient patients, suggesting that the difference in survival may be related to increased sensitivity to alkylating chemotherapy in patients with *DCLRE1C* genotype, which is associated with a DNA-repair defect[6].

Younger age and freedom from infection at the time of HCT had a positive impact on survival. Infection status significantly affected survival of patients who underwent HCT at older than 3.5 mo of age but not those who underwent HCT at younger than 3.5 mo of age. Genotype was not associated with overall treatment failure. Although survival did not correlate with the type of conditioning regimen that was used, recipients of reduced-intensity or myeloablative conditioning had a lower incidence of treatment failure, better T- and B-cell reconstitution but a higher risk for GVHD compared with those who did not receive conditioning or who received only immunosuppression. Genotype and conditioning regimen had a strong impact on B- and T-cell reconstitution after non-MSD HCT. Genotypes associated with lack of B cells (*RAG*, *DCLRE1C*) or nonfunctional B cells (IL2RG/JAK3) were associated with a poorer B-cell reconstitution than genotypes associated with functional B cells (IL7R/CD3/CD45). The use of RIC/MAC was associated with improved T cell reconstitution. CD4+ and CD4+CD45RA+ cell counts at 6 and 12 mo post-HCT served as biomarkers predictive of overall survival and long-term T-cell reconstitution[6].

ADULT PATIENTS

Although early HCT for PIDs is preferred, atypical presentation and late diagnosis

results in the need to address HCT in an adult subgroup of patients, especially in non-SCID scenarios[7]. Fox *et al*[8] reported the outcome of HCT in 29 young adult patients with PIDs that included common variable immunodeficiency, GATA2 deficiency, X-linked lymphoproliferative disease and SCID among others. Reduced-intensity, T-cell–depleted HCT had an overall survival rate of 85.2% at 3 years. There was no significant difference in outcome between those undergoing MRD transplants and matched or 1 antigen MMUD transplants. Acute GVHD (aGVHD) incidence had a rate of 6.5% and 31% had chronic GVHD (cGVHD). With the exception of one patient, all with cGVHD were able to discontinue systemic immune suppression 3 mo after HCT[8].

DNA REPAIR-ASSOCIATED PID

Although data supports the use of conditioning with alkylating agents in order to increase the likelihood of full T and particularly B cell reconstitution, caution must be used in the use of alkylating agents and ionizing radiation in PIDs with defects in the DNA-repair pathway. While scattered reports exist, there is still limited data on survival, engraftment and long-term effects of using such agents in these patients. Slack *et al* collected HCT outcome data for DNA ligase 4 deficiency, Cernunnos-XLF deficiency, Nijmegen Breakage Syndrome and Ataxia-Telangiectasia (AT). MAC and RIC regimens were used. The authors reported that overall survival was significantly superior when RIC was used suggesting that an RIC regimen should be used in patients with radiation sensitivity. In patients with AT, overall survival was 25%. 67% of the 6 patients who died experienced GVHD grade 2-3. Death was due to multi-organ failure, viral activation or post-transplant lymphoproliferative disorder[9].

DONOR SOURCE

Compared to patients with MSD or familial-mismatched donor transplant, recipients of URD HCT showed an inferior survival rate (100% *vs* 58.8%, $P = 0.042$). The survival of patients who received a combination of CSA and methotrexate treatment for GVHD prophylaxis was significantly lower (47.5%) than that of patients administered other treatment (CSA only prophylaxis, CSA plus mycophenolate mofetil combination prophylaxis, or no prophylaxis)[10].

Dvorak *et al*[11] reported outcomes of HCT in SCID without chemotherapy conditioning in MSD and URD recipients. For those subjects who had a genetic diagnosis, defects includeIL2RG, JAK3, ADA (NK-SCID) and RAG, DCLRE1C, LIG4 mutations (NK+SCID). Authors admitted a selection bias of patients who were deemed unlikely to be able to tolerate chemotherapy. The majority of patients had one or more opportunistic infections. Majority of patients engrafted donor T cells (94%) and subsequently survived (5-year OS 71%). 92% of patients undergoing URD HCT achieved donor T-cell engraftment, compared to 97% for MSDs. However, estimated 5-year overall and event-free survival was worse for URD recipients (71% and 60%, respectively), compared to MSD recipients (92% and 89%, respectively). The use of ATG was associated with an improved overall survival in the URD recipients. Interestingly, the development of GVHD in URD was associated with donor myeloid or B cell chimerism. cGVHD was 5% in MSD patients compared to the 33% in URD recipients. Among the URD recipients, the use of serotherapy resulted in an estimated 5-year event-free survival (EFS) of 71% compared to 38% in the non-serotherapy group, although this did not reach statistical significance. However, as all re-transplanted patients survived, the use of serotherapy was associated with a higher estimated 5-year OS of 100% compared to the 51% of those patients that did not receive serotherapy. 63% of MSD recipients reached freedom from gamma globulin replacement compared to 8% of URD recipients. MSD recipients with NK− SCID were more likely to recover B cell function (85%; 35/41) compared to those with NK+ SCID (56%; 9/16). An effectively normal immune system was seen in significantly more MSD recipients (72%; 41/57) compared to URD recipients (26%; 6/23) who survived without a conditioned second HCT. Conditioned second HCTs were more common in NK+ SCID undergoing URD HCT (38%) *vs* NK- (4%)[11].

IMMUNE RECONSTITUTION

Conditioning generally improves the likelihood of T cell reconstitution and is usually needed for B cell reconstitution. However, certain SCID subtypes are more permissive

to T cell reconstitution even when conditioning is not used. SCID that does not involve B cell impairment usually results in T cell reconstitution from any type of donor. However, when using donors other than matched siblings, B cell function is not regained unless conditioning is used. SCID with an isolated T cell deficiency generally does not require conditioning if a MSD is available and immune reconstitution is expected in such cases. However, less data is available for matched URDs. SCID of T-B-NK+ phenotype rarely sees B cell recovery unless conditioning is used. In cases of T-B-NK- SCID B cell function is best recovered after MSD even without a conditioning regimen. B cell reconstitution is less predictable in unconditioned mismatched related donors and URDs[11,12].

T-cell reconstitution is necessary for appropriate B-cell function. B cell recovery therefore tends to lag behind T cell reconstitution. Although studying a small cohort, Scarselli *et al*[12] reported that good humoral function was usually associated with the presence of donor B-cell chimerism and promoted by myeloablative conditioning. The majority of patients were able to discontinue supplemental immune globulin. CD19+ CD27+ memory B cells were significantly below normal at 1 and 2 years and increased starting 3-5 years of follow up. Interestingly, switched memory B-cells (CD19+CD27+IgD-IgM-) were restored earlier and better than IgM-memory B-cells (CD19+CD27+IgD+IgM+), which remained significantly reduced in the long-term cohort. B-cell absolute counts and percentages did not differ between MSD and MMRD in long-term surviving patients, but the latter group had lower counts of memory B-cells[12].

IMMUNE POLYENDOCRINOPATHY, ENTEROPATHY X-LINKED

Immune polyendocrinopathy, enteropathy X-linked (IPEX) is a rare x-linked immune dysregulatory disorder. The classic presentation is early onset of enteropathy resulting in failure to thrive, autoimmune endocrinopathy and dermatitis in male infants. Management revolves around immunosuppressive treatment, but HCT remains the only curative option.

The underlying mechanism for the disorder is a mutation in the transcription factor FOXP3 which is responsible for regulatory T (Treg) cell development. Tregs are critical for maintaining immune homeostasis[13].

Barzaghi *et al*[14] reported findings of long-term follow-up of patients with IPEX, comparing outcomes between patients who received systemic immunosuppression versus HCT. IPEX patients had similar overall survival, regardless of the treatment option received. Disease-free survival, however, of HCT patients showed resolution of autoimmunity as compared to the disease progression seen in the non-transplanted patients. IPEX patients with severe organ impairment at HCT had the lowest chance of survival even after receiving a RIC regimen pre-HCT. Variables such as stem cell source, type of donor and chimerism did not correlate with outcome[14].

Kucuk *et al*[15] reported a single-center experience of HCT for 7 patients with IPEX. Median age at diagnosis was 4.5 years, and 6.7 years at HCT. Recipients showed full donor engraftment, but 6/7 had mixed chimerism. 5/8 received RIC while the remainder received a myeloablative regimen. All recipients initially demonstrated full donor engraftment but all except for one patient had mixed chimerism. One patient with mixed chimerism experienced cGVHD while the remainder developed autoimmune cytopenias. Older age at transplantation was associated with an increased risk of decreasing donor chimerism. Two of the 3 patients who did not survive received myeloablative conditioning. Nonmyeloablative conditioning regimens led to complete or mixed chimerism with reconstitution of donor FOXP3 cells.[15]

CHRONIC GRANULOMATOUS DISEASE

Chronic granulomatous disease (CGD) is a primary immunodeficiency disorder of the NADPH oxidase complex that results in a phagocytic functional defect secondary to the impairment of reactive oxygen species (ROS) production. The impairment of neutrophils and monocytes results in recurrent severe life-threatening infections. CGD is also marked by significant immune dysregulation, and the autoimmunity that accompanies this disorder carries its own significant risk of morbidity[16]. The overall incidence of CGD in the US is approximately 1/200,000 live births[17].

The NADPH oxidase complex is composed of the cell membrane-bound glycoprotein gp91^{phox} (*CYBB* gene) and non-glycosylated protein p22^{phox} (*CYBA*), as

well as p47^{phox} (*NCF1*), p67^{phox} (*NCF2*) and p40^{phox} (*NCF4*) which are cytosolic proteins. Mutations in any of these components result in defective ROS production and clinical CGD manifestations. A mutation in the X-linked *CYBB* is responsible for approximately 65% of CGD cases. *NCF1* mutations account for 20% of cases, *NCF2* and *CYBA* mutations are less common with a rate of 5% each, while *NCF4* is the rarest with only one reported case[16,18].

X-linked CGD patients generally have more severe disease due to the lower superoxide production than the autosomal recessive phenotypes. Most cases of CGD present in early childhood with severe invasive infections, however late diagnosis has also been reported. Catalase positive bacteria and fungi are the pathognomonic agents of these infections. *Aspergillus* is the most commonly isolated pathogen, while *Burkholderia* infection is associated with the greatest severity. S. aureus, *Nocardia* and *Serratia* are also among the common pathogens associated with CGD[19]. Bacille Calmette-Guerin (BCG) and Mycobacterium tuberculosis are pathogens identified in developing countries[16].

Allogeneic hematopoietic stem cell transplantation (HSCT) still remains the only curative option for CGD. Guidelines do not exist for the timing and conditioning regimen of HCT in CGD. Unlike with SCID which typically presents early in life, CGD may not be diagnosed until relatively later in life and the question then arises about the success of HCT in this adult group of patients. In a subgroup analysis of a Korean cohort, 11 CGD patients received HCT. Three of 11 CGD patients in the study received HCT when they were 19 years old or older. Two identical twins were diagnosed at 1 mo of age, while another received his diagnosis at 5 years of age. All three patients had successful engraftment[10].

As with all cases of HCT, prior infections can increase post-transplant complications and therefore adversely affect outcomes. Historically, the use of myeloablative therapy was not standard due to the concern for infections in these already immunocompromised patients[20]. However, reports of RIC for CGD patients reported a high rate of graft failure. Seger *et al*[20] reported a 27 CGD patient cohort and 23 of those patients received a myeloablative busulfan-based regimen with donors being HLA-identical siblings. The successful outcomes of this patient cohort suggested that myeloablative conditioning followed by transplant is a feasible option for these patients. Martinez and colleagues[21] reported the outcomes of eleven children after matched sibling (4/11) and URD (MUD, 7/11) transplantation with the mean age of 3.8 years. 70% of these patients had intractable infections or steroid-dependent CGD at the time of transplantation. The authors reported 100% survival of all patients and stable engraftment with full donor chimerism in 9 of 11 patients with a follow up range of 1-9 years. The MUD conditioning regimen used was busulfan, cyclophosphamide, fludarabine and alemtuzumab. Hoenig *et al*[22] reported a case of a hemizygous *CYBB* male patient who underwent a haploidentical HSCT after myeloablative conditioning with successful engraftment. Parta and colleagues[23] reported the first case of a successful haploidentical transplantation and stable neutrophil engraftment using post-transplant high dose cyclophosphamide in a male patient with a CYBB mutation who also had refractory infectious pericarditis.

Patients with CGD and intractable infections or severe autoimmunity, are a unique group in which myeloablative therapy carries the risk of increased mortality. Güngör *et al*[24] reported 56 patients with CGD. The conditioning regimen consisted of six doses of intravenous fludarabine, anti-thymocyte globulin. In HLA-matched unrelated-donor transplants, low-dose (defined as < 1 mg/kg) alemtuzumab was recommended. Busulfan was administered at days 5 to 3 and sometimes on day 2 prior to transplant. OS was 93% at a median follow up time of 21 mo and EFS was 89%. Graft failure occurred in 5% of patients. aGVHD of grade III–IV was 4% and cGVHD was 7%. 93% achieved ≥ 90% donor chimerism[24].

Yanir *et al*[25] reported a higher incidence of autoimmune disease after HCT for CGD. This was attributed to the preparative regimen of 4 doses of alemtuzumab on days 5 to 2 compared to a previously reported cohort of patients that received alemtuzumab in 3 doses on days 8 to 6 or ATG instead. This regimen was suggested to cause a greater depletion and subsequent slower reconstitution of regulatory T cells[25].

WISKOTT-ALDRICH SYNDROME

Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency disorder caused by a defect in the gene that encodes the Wiskott-Aldrich syndrome protein (WASp). WASp is a regulator of the actin cytoskeleton in hematopoietic cells. A pathogenic mutation in this gene not only predisposes to PID but also malignancy[26]. WAS

manifests as microthrombocytopenia, eczema and susceptibility to infections. HCT is curative for WAS. Ngwube *et al*[27] reported findings of a retrospective review of 12 patients who received HCT for WAS with a pre-transplant myeloablative regimen, most receiving anti-thymocyte globulin. Four patients received MRD, 5 received URD and 3 obtained a mismatched unrelated graft. 1 patient received UCB cells while bone marrow was the source for the remainder donor cells. OS was 92% at 5-year post-HCT follow up. Mixed donor chimerism was observed in 45% of patients. Immune reconstitution was not affected by chimerism status. Two patients received a second transplant with RIC. There was no statistically significant difference in outcome between MRD, MUD, and MMURD[27].

The use of UCB for WAS HCT has been reported in a larger cohort as well[28,29]. In a study of 90 recipients of UCB, most received myeloablative conditioning with anti-thymocyte globulin. OS at 5 years was 75%. Age less than 2 years was associated with improved event-free survival[29].

The use of pre-transplant RIC has been reported in HCT for patients with WAS[30,31]. Thakkar and colleagues[30] reported three patients with WAS who underwent RIC prior to receiving HCT. MUD, T-cell replete haploidentical as well as T-cell receptor αβ and CD19-depleted haploidentical HCT were performed. All patients reached donor chimerism. GVHD was limited to one patient who demonstrated grade 1 aGVHD and all patients became transfusion independent[30].

Identifying a suitably matched donor often poses a challenge. When matched donors are not available, alternate donor sources are considered[32]. A prospective study of 5 patients who received haploidentical stem cell transplant and post-transplantation cyclophosphamide showed an overall 100% survival and an average of 27.5 d to platelet counts over 50,000/mm^3. All recipients showed 100% donor chimerism, with an average follow-up time of 2 years[33].

DOCK-8 DEFICIENCY

Dedicator of cytokinesis 8 (DOCK8) deficiency is an autosomal recessive combined immunodeficiency that presents with recurrent severe and primarily viral, cutaneous and systemic infections as well as atopic disorders such as anaphylaxis, atopic dermatitis and asthma. Patients with DOCK8 deficiency are also at a higher risk for malignancy[34]. HCT is the only cure for this PID and successful haploidentical transplants have been reported. Shah *et al* reported outcomes in 7 patients (age range 7 to 25 years) with DOCK8 deficiency who underwent haploidentical related donor HCT. Conditioning included low-dose cyclophosphamide, fludarabine, busulfan and 200 cGy total body irradiation. Patients also received cyclophosphamide as post-transplantation GVHD prophylaxis. All patients attained over 90% donor engraftment by day 30 post-HCT. While 4/7 developed aGVHD, none developed cGVHD (follow up range of 9.5 to 31.7 mo). One patient died at day 165 post-HCT from possible pneumonia as well as worsening pulmonary fibrosis which was suggested to have been a complication of his frequent pulmonary infections [35].

A retrospective study of 81 patients with DOCK8 deficiency showed that RIC resulted in 97% survival compared to 78% with a fully myeloablative regimen. Matched related HCT showed better survival (89%) than unrelated HCT (81%). The study also reported that whereas 78% of patients older than 8yo survived, those younger than 8yo fared better at 96% survival. Overall, 89% of HCT recipients achieved over 90% donor T-cell chimerism[36].

CONCLUSION

PIDs pose unique diagnostic and treatment challenges. In addition to predisposing to life-threatening infections and serious complications arising from immune dysregulation, these disorders also require individualized approaches to HCT that are often dictated by the genetic defects involved. Combining currently available data with future larger studies that assess factors that impact survival and long-term outcomes of HCT in PIDs will lead the way in improving standardization of HCT in these patients.

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EDITORIAL

Blessing and a curse of outpatient management of delayed graft function

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Abstract

Delayed graft function (DGF) is a common complication occurring most often after deceased donor kidney transplant with several donor characteristics as well as immunologic factors that lead to its development post-transplant. These patients require dialysis and close kidney function monitoring until sufficient allograft function is achieved. This has resulted in limited options for DGF management, either prolonged hospitalization until graft function improves to the point where dialysis is no longer needed or discharge back to their home dialysis unit with periodic follow up in the transplant clinic. DGF is associated with a higher risk for acute rejection, premature graft failure, and 30-d readmission; therefore, these patients need close monitoring, immunosuppression management, and prompt allograft biopsy if prolonged DGF is observed. This may not occur if these patients are discharged back to their home dialysis unit. To address this issue, the University of Wisconsin-Madison created a clinic in 2011 specialized in outpatient DGF management. This clinic was able to successfully reduce hospital length of stay without an increase in 30-d readmission, graft loss, and patient death.

Key words: Delayed graft function; Kidney transplantation; Immunosuppression; Acute rejection; Kidney donor profile index; Kidney donor risk index; Dialysis

Core tip: Delayed graft function (DGF), traditionally defined as needing dialysis within seven days following kidney transplant, occurs most often after deceased donor kidney transplantation. Both donor characteristics, as well as immunologic factors, influence the development of DGF. Historically, outpatient management has been difficult, often leading to increased length of stay (LOS), however, the DGF clinic at University of Wisconsin - Madison which was established in 2011 has shown that it is possible to

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provide high-quality outpatient DGF management without increasing LOS, 30-d readmission, or acute rejection rates.

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APPROACH TO MANAGING DELAYED GRAFT FUNCTION

Delayed graft function (DGF) is most often defined as the need for dialysis within the first seven days following kidney transplantation. However, this definition is subject to center level variation[1]. It is more commonly seen after deceased donor kidney transplantation with an estimated incidence of 30%[1,2].

Certain factors are associated with the development of DGF including the cause of donor death, donor age, kidney donor profile index (KDPI), cold ischemia time (CIT), and higher serum creatinine at the time of death[3]. KDPI is a numerical measure of overall kidney quality in deceased donor (DD) kidneys. It is derived by first calculating kidney donor risk index (KDRI) which incorporates several donor characteristics including age, height, weight, cause of death, history of diabetes, history of hypertension, ethnicity, Hepatitis C status, serum creatinine, and donation after circulatory death (DCD) status. Lower KDRI and KDPI scores are associated with increased donor quality and expected longevity whereas higher scores (> 85%) are associated with increased risk for DGF as well as decreased graft survival and longevity[4,5]. Longer CIT, over 20 h, is also associated with a higher incidence of DGF[6]. There is a higher risk of developing DGF following DCD kidney transplantation due to the presence of warm ischemia and reduced perfusion during procurement[7].

DGF is a costly complication and often leads to prolonged hospitalization. DGF recovery is most often seen within 7 to 10 d[8], however, it can take up to three to four weeks for DGF to completely resolve to the point where dialysis is no longer needed. Managing DGF poses a unique challenge for health care providers who are tasked with reducing hospital stay while at the same time ensuring these patients are receiving close monitoring of kidney function. Traditionally DGF management has been limited to either prolonged length of stay (LOS) until allograft recovery has been achieved or discharge back to their home dialysis center with regular follow up in the clinic. These patients are often medically complex with fluctuating volume status, so care must be taken to prevent inappropriate dialysis during DGF recovery. They are at high risk for readmission within the first 30 d after transplantation[9]. Those with DGF are also at higher risk for acute rejection which can lead to premature graft failure and is associated with decreased 1, 3, and 5-year graft survival[3,10,11]. Therefore, not only is optimizing immunosuppression critical but prompt diagnosis with renal allograft biopsy, if prolonged DGF is observed, is also important. These opportunities may be missed if patients are not followed closely in the transplant clinic.

Because outpatient DGF management has been challenging due to the need for ongoing dialysis and close monitoring of kidney function, the transplant clinic is the ideal setting for DGF follow-up. However, this can be difficult for patients and family members who do not reside near the transplant center. In order to address this need for consistent outpatient DGF management, the University of Wisconsin Hospital created an outpatient clinic in July 2011 which specializes in DGF management. This multidisciplinary clinic consists of transplant nephrology physicians, experienced advanced practice providers (APPs) specialized in kidney transplantation, social workers, and pharmacists. DGF discharge planning frequently is initiated upon consultation to transplant nephrology when DGF is suspected. These patients are then either discharged home (if local) or to a nearby hotel with a support person along with a scheduled clinic visit within 1-3 d of discharge. Majority of these patients are required to follow up in the DGF clinic 3 d per week. Each clinic visit day begins with labs which are usually completed in the outpatient labs at the hospital. These include complete metabolic panel, complete blood count, should be urinalysis, urine protein-creatinine ratio, beta-2-microglobulin, tacrolimus drug level. Patients then proceed to the clinic where height, weight, and vital signs are obtained. They then undergo assessment and physical exam by either an APP or physician. If dialysis is deemed

necessary, an appointment is then scheduled for dialysis in the hospital inpatient dialysis unit that same day. Prior to leaving clinic, a follow-up appointment is scheduled and a new medication list is provided to the patient. DGF clinic follow up continues until adequate graft function is achieved. During dialysis, all patients go through the same standard isolation precaution of contact or airborne isolation or no isolation. If no improvement in graft function is noted within 7 to 14 d after transplantation, a kidney transplant biopsy is scheduled. Donor-specific antibodies (DSA) are monitored on all patients at the time of a kidney biopsy. Also, DSA are monitored on all patients, based on the immunological risk as described previously[12]. In the near future, we are also planning to monitor DGF and perform biopsy based on the new biomarkers, along with the banking of the tissue, serum and urine sample[13].

To assess the impact of this clinic on outpatient DGF management, Muth *et al*[14] conducted a retrospective review of 697 DD performed from July 2009 to July 2014. Patients were divided into three groups, no DGF, and DGF before and after implementation of the DGF clinic. Baseline characteristics of the three groups were similar. They compared LOS, 30-d readmission, acute rejection, and patient/graft survival. What they found was a significant decrease in LOS post-DGF clinic compared pre-DGF clinic[14]. DGF clinic patients were less likely to develop acute rejection, while 30-d readmission, graft loss and patient death did not differ significantly between pre and post-DGF clinic[14]. These findings suggest outpatient DGF management can successfully reduce LOS without increasing adverse outcomes or compromising patient care. To achieve this, we needed a dedicated multidiscplinary team as well as a motivated patient with their support person to navigate DGF, because often times, the patient is overwhelmed due to the frequent nature of clinic visits as well as being away from home. In summary, our experience with intensive multidisciplinary outpatient management of DGF has been effective in closely monitoring and supporting patients in their DGF recovery, and limiting adverse events. Based on our experience, we recommend a transplant center to weigh the cost-benefit of this complex patient. Centers with a high volume of DGF may benefit from establishing a DGF clinic.

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REVIEW

Histological and clinical evaluation of marginal donor kidneys before transplantation: Which is best?

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Abstract

Organ shortage represents one of the major limitations to the development of kidney transplantation. To increase the donor pool and to answer the ever increasing kidney request, physicians are recurring to marginal kidneys as kidneys from older donors, from hypertensive or diabetic donors and from non-heart beating donors. These kidneys are known to have frequently a worse outcome in the recipients. To date major problem is to evaluate such kidneys in order to use or to discard them before transplantation. The use of such kidneys create other relevant question as whether to use them as single or dual transplant and to allocate them fairly according transplant programs. The pre-transplant histological evaluation, the clinical evaluation of the donor or both the criteria joined has been used and according the time each criterion prevailed over the others. Aim of this review has been to examine the advantages and the drawbacks of any criterion and how they have changed with time. To date any criterion has several limitations and several authors have argued for the development of new guidelines in the field of the kidney evaluation for transplantation. Several authors argue that the use of omic technologies should improve the organ evaluation and studies are ongoing to evaluate these technologies either in the donor urine or in the biopsies taken before transplantation.

Key words: Kidney evaluation; Pre-transplant biopsies; Kidney donor evaluation; Kidney risk profile index; Omic technologies; Deceased donor score; Donor risk score

Core tip: With the extension of donor pool to high risk donors, the kidney pre-transplant

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evaluation became mandatory. Different criteria have been used, each of them with advantages and limitations. Probably the use of pre-transplant kidney biopsies in those kidneys coming from donors with the highest profile index seem to give the better results. These could be improved applying omic technologies either to donor urine or to pre-transplant biopsies. However the application of omic technologies is time consuming and not everywhere applicable. Several studies on these technologies are to date ongoing, but their results are yet not known.

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INTRODUCTION

To date, organ shortage represents one of the major limitations to the development of kidney transplantation.

To increase the donor pool many transplant programs accept kidneys from the so-called extended criteria donors (ECDs)[1,2]. Kidneys from the ECD pool are known to have worse outcomes in recipients with a higher rate of delayed graft function (DGF), primary non function (PNF), and reduced function of the allograft and reduced graft survival[3]. The main challenge is to evaluate such kidneys before transplantation either for a better and fair allocation or for discarding the kidney in the case of a very poor evaluation of the offered kidney.

Several factors related to the donors are known to influence the post-transplant outcomes. Figure 1 identifies which donor, procurement and graft characteristics principally influence the outcomes. They may be divided into clinical and histological factors and factors related to the donor and related to the offered kidney and to the procurement management.

Historically, the evaluation of the kidneys from ECDs has been made histologically by the so-called zero-time biopsy[4], by clinical evaluation of the donor by different kidney allocation scores or by a combination of histological and clinical parameters.

Additionally, it should be highlighted that the need of a clear evaluation of the "so called" marginal donors became a must with the increased use of such kidneys. With time the experience documented that several kidneys from ECD pool performed well, while other kidneys labeled as standard criteria donors (SCD) did not perform well. Hence, the opportunity of a safe evaluation also for SCD. De facto the recent kidney donor risk index (KDRI) automatically offers the evaluation for any kidney.

The aim of this review is to describe the aforementioned evaluation criteria of ECD kidneys and to describe how they have changed with time.

SELECTION CRITERIA OF THE ARTICLES INCLUDED IN THIS REVIEW AND THEIR DRAWBACKS

The criteria to evaluate the kidneys have been histological, clinical and mixed histological-clinical. We have searched for all the papers concerning these points. The main studies concerning the most important scoring systems are shown on Table 1. With the exception of the two single centre studies as Maryland Aggregate Pathology Index (MAPI) and the Irish nomogram, all the studies considered included a large number of patients with the limitation to be retrospective in the attempt to validate the original findings. Clearly, in this review are also included articles documenting the drawbacks of the different scoring systems and these articles may include a limited number of patients. Similarly, the studies evaluating the omics on the renal biopsies or on the donor urine have a limited number of patients.

HISTOLOGICAL EVALUATION OF DONOR KIDNEYS

By 1999, Karpinski *et al*[5] considering that kidneys from high risk donors had worse outcomes in the recipient after transplantation tried to establish which donor or

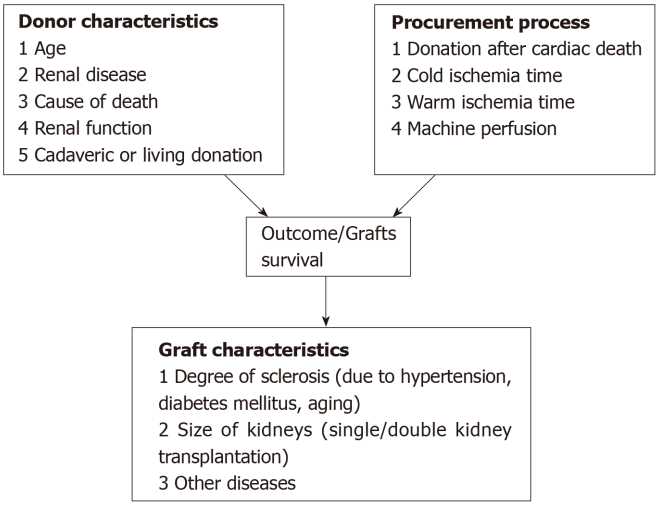

Figure 1 Main donor, procurement and graft related factors influencing the post-transplant outcomes.

kidney variables were most relevant to these poor outcomes. For high donor risk, they considered donation after cardiac death donors, donors over 55 years of age, donors with a history of hypertension or diabetes, and donors with abnormal kidney anatomy or abnormal renal function[6]. The study found that a low calculated creatinine clearance (CrCl) and donor kidney pathology were the main predictors of worse outcomes

In particular, the donor renal pathology was scored 0-3 in each of four distinct aspects: Glomerulosclerosis, interstitial fibrosis, tubular atrophy and vascular disease (Table 2). Previous studies have documented the relevance of pre-implantation histological findings on recipient outcomes[7-9]. None of these studies had been concordant, and the study of Karpinski *et al*[5]may be considered a pioneering study documenting the relevance of the pathology score over the transplant outcomes.

Since the study of Karpinski *et al*[5], several studies have documented the relevance of the pathology score of donor kidneys over the outcomes, while other studies did not find a similar usefulness of the pathology score.

One of the most important studies in favor of the pathology score has been the study of Remuzzi *et al*[10]. According to this study, the pathology score allows transplant kidneys with a score up to 3 to be used as single kidneys, while kidneys with a score from 4 to 6 are better allocated as dual transplants and kidneys with a score of 7 or higher should be discarded.

Additionally, the study documents the importance of the pre-transplant renal biopsy for donors over 60 years when comparing the renal outcomes with and without biopsy (Figure 2).

In a different study, Mancilla *et al*[11] suggested the utility of zero-time biopsy in the case of living donor kidneys, particularly for donors with borderline renal function or with a history of familial renal disorders[12,13]. In a study from Kayler *et al*[14] a correlation of histological findings on pre-implantation biopsy with kidney graft survival was also found but was restricted to vascular lesions, while glomerulosclerosis and low-grade interstitial fibrosis did not have statistical significance.

Based on 371 pre-transplant biopsies and correlating the findings with post-transplant outcomes, Munivenkatappa *et al*[15] developed the MAPI. In the study, glomerulosclerosis, glomerular size and periglomerular fibrosis in addition to vascular pathology and arteriolar hyalinosis were considered in developing the MAPI score (Table 3). The authors found that the five-year actuarial graft survival rate was related to the MAPI scoring (Figure 3) and that the MAPI score at the multivariate analysis correlated with the risk of graft failure better than any other clinical parameter (Table 4). This study suddenly received several comments, which brought up several unanswered questions about the relevance of pre-transplant biopsies in predicting post-transplant outcomes. Many of these questions were raised by Nickeleit[16].

One point that is not clarified is whether wedge specimens or needle biopsies should be used. This issue is well described in a further paper[17] that considers wedge biopsies to be safer and superior to core biopsies in finding significant findings.

Another point is whether frozen or paraffinized sections should be used, even if the original MAPI score found paraffinized sections to be more reliable.

Table 1 Descriptive table of selected clinical scoring system

Score	Authors	Variables included in risk score	Score grades	Outcome
Expanded criteria donor	Port *et al*[58], 2002	Donor age	SCD	Relative risk of graft failure compared to SCD
		Cerebrovascular accident as cause of death	ECD	RR>1.7
		Serum creatinine> 1.5mg/dL		
		History of hypertension		
Deceased donor score	Nyberg *et al*[65], 2003	Age		5-year graft survival
		History of hypertension	A (0-9 points)	Grade A 82%
		Creatinine clearance	B (10-19 points)	Grade B 79%
		HLA mismatch	C (20-29 points)	Grade C 72%
		Cause of death	D (30-39 points)	Grade D 65%
Donor risk score (DRS)	Schold *et al*[67], 2005	Donor risk factors		5-year graft survival
		Race	I	Grade I 76.7%
		Age	II	Grade II 73.6%
		History of hypertension	III	Grade III 66.3%
		History of diabetes	IV	Grade IV54.8%
		Cause of death	V	Grade V 47.6%
		History of hypertension		
		History of diabetes		
		Cause of death		
		HLA-Dr mismatch		
		CMV mismatch		
		Cold ischemia time		
DGF nomogram	Irish *et al*[70], 2003	Donor risk factors	Continuous point score	Delayed graft function
		Age		
		Serum creatinine		
		History of hypertension		
		Cause of death		
		Donor after cardiac death		
		Recipient risk factors		
		Peak PRA		
		Race		
		Gender		
		History of diabetes mellitus		
		Previous transplant		
		Pretransplant dialysis		
		Pretransplant transfusions		
		Combined transplantation		
		HLA mismatch		
		Cold ischemia time		
KDRI	Rao *et al*[71], 2009	Donor risk factors	KDRI quintile	5-year graft survival
		Age	0.45-0.79	82%
		Race	0.80-0.96	79%
		Height	0.97-1.15	NA
		Weight	1.16-1.45	NA
		History of hypertension	>1.45	63%
		History of diabetes		
		Cause of death		
		Serum creatinine		
		Hepatitis C		
		Donation after cardiac death		
		HLA-B mismatch		

		HLA-DR mismatch		
		Cold ischemia time		
		Double or *en bloc* transplant		
Donor-only KDRI	OPTN[72], 2014	Donor risk factors		5-year graft survival
		Age	<0.6	80%
		Race	0.61-0.79	78%
		Height	0.80-0.99	74%
		Weight	1.00-1.19	66%
		History of hypertension	1.20-1.59	59%
		History of diabetes	1.60-1.99	52%
		Cause of death	>1.99	44%
		Serum creatinine		
		Hepatitis C		
		Donation after cardiac death		

ECD: Expanded criteria donor; KDRI: Kidney donor risk index; OPTN: The Organ Procurement and Transplantation Network; SCD: Standard criteria donor.

Additionally, it should be better defined when zero-time biopsies should be taken: before or after reperfusion. Biopsy time is relevant in detecting the complement activation that is predictive of early antibody mediated rejection[18].

An important point, not well considered by the MAPI score is how the lesions should be scored and whether the Banff criterion is appropriate[19]. This point is relevant for comparing zero-time biopsies with subsequent post-transplant biopsies. Nickeleit[16]'s conclusions were that much remains to be determined about zero-time biopsies and that consensus guidelines remain to be defined.

Recommendations on these points have been given by two German workshops and described by Pisarski *et al*[20] in 2016. The German recommendations advocate a detailed assessment of the findings and do not agree with the recommendations of the Interpretation Biopsy Banff Working Group[21], whose approach is adopted for a general pathologist, without specific training in the field.

The issue of an expert pathologist was addressed in 2012 in a study of the pre-implantation biopsies in the Organ Procurement Organization (OPOS) that found a lack of concordance among OPOS pathologists[22]. The lack of a correlation between the findings of on-call pathologists and the lack of association between their findings and the transplant outcomes is highlighted by two papers[23,24] that advocate for specific training in renal pathology to optimize the histological evaluation of donor kidneys. It could also be argued that a renal pathologist "per se" could not be expert enough in evaluating such biopsies. Probably a specific training should be the best solution.

By 2011, Mueller *et al*[25], reviewing several studies on histopathology-based variables at zero-time biopsies, highlighted the limitations due to sampling errors, confounding clinical variables, and inter-observer variability[26,27] and advocated for a validated approach for the analysis of pathology findings. In particular, they advocate for the use of omic technologies such as proteomics, transcriptomics and metabolomics that could have the potential to improve the significance of the histological findings. Table 5 highlights the principal studies that were conducted until 2011[28,39].

A study from Krol *et al*[40], documented that the apoptosis of tubular epithelial cells in pre-implantation biopsies is related to DGF. Their findings were confirmed by another study [41]that found a relationship between high *BAX*/*BCL2* expression in pre-implantation biopsies and DGF, confirming that apoptosis-related gene expression levels are predictors of DGF.

A recent study[42] confirmed that zero-time biopsies in ECDs showed a significant increase in the transcripts of *MCP-1*, *RANTES*, *TGF beta* and *IL 10*, documenting a higher gene expression of inflammatory cytokines in ECDs that could predict the post-transplant outcome.

In recent years, several studies, often retrospective, and several reviews and meta-analyses did not confirm the utility of zero-time biopsy in allocating or discarding ECD kidneys. Wang *et al*[43] reviewed 47 studies published between 1994 and 2014, where each study included pre-transplant biopsies format least 50 donors and compared the histological findings with post-transplant outcomes. Overall, 15 scoring systems were proposed by the studies, but none were able to correlate with post-transplant outcomes.

Table 2 Histological score according Karpinski

Histological score	
Glomerular score	0 = no globally sclerosed glomeruli
	1 = < 20% global glomerulosclerosis
	2 = 20-50% global glomerulosclerosis
	3 = > 50% global glomerulosclerosis
Tubular score	0 = absent
	1 = < 20% of tubules affected
	2 = 20-50% of tubules affected
	3 = > 50% of tubules affected
Interstitial score	0 = absent
	1 = < 20% of cortical parenchyma replaced by fibrous connective tissue
	2 = 20-50% of cortical parenchyma replaced by fibrous connective tissue
	3 = > 50% of cortical parenchyma replaced by fibrous connective tissue
Vascular score	0 = absent
	1 = increased wall thickness but to a degree that is less than the diameter of the lumen
	2 = wall thickness that is equal or slightly greater than the diameter of the lumen
	3 = wall thickness that far exceeds the diameter of the lumen, with extreme narrowing

Naesens[44] reviewed the problems and the utility of zero-time biopsy and highlighted that the major problems were the wedge *vs* core needle biopsy[45,46]; frozen *vs* paraffin-embedded tissue[47,48]; pathologist's experience[23,24]; different composite histological scoring such as the Pirani score[49], Chronic Allograft Damage Index (CADI)[50], and Donor Score[23]; and the lack of utilizing hard clinical end-points in evaluating graft and recipient outcomes. The author concluded that zero-time biopsies are not useful for assigning or discarding kidneys or improving dual kidney transplantation programs. The author recognizes that the molecular phenotype in pre-transplant biopsies could be useful in donor selection and in peri-transplant management even if the time required could make such a procedure difficult[51-54].

Two recent Italian studies on the utility of pre-implantation biopsy in allocating ECD kidneys[4,55] concluded that histological evaluation was not superior to donor clinical evaluation in allocating ECD kidneys either as a single kidney or as a dual kidney transplant. The authors concluded that, according to their experience, the histological score poorly evaluates the donor kidney quality. Accordingly, the use of histological criteria to assign as single or dual kidneys does not seem to offer advantages over the evaluation made on clinical basis.

A Banff Pre-implantation Biopsy Working Group has been established to develop guidelines for the interpretation of pre-implantation renal biopsies[56]. The last working group meeting stated that to date, histological parameters are poorly correlated with post-transplant outcomes and that remain significant limitations in understanding the role of pre-implantation biopsies.

Recently, Carpenter *et al*[57] from Columbia University examined their experience and compared procurement biopsies with reperfusion paraffin-embedded biopsies and with post-transplant biopsies. All the findings were then correlated with allograft failures and patient deaths. No agreement has been found between frozen procurement biopsies and paraffin-embedded biopsies, and frozen procurement biopsies were poorly correlated with post-transplant biopsies and the hard end-point considered.

COMBINED CLINICAL AND HISTOLOGICAL EVALUATION OF DONOR KIDNEYS

A different approach to evaluating ECD kidneys has been to combine histological findings with clinical donor-related parameters. The latter have been identified since the publication of the study by Port *et al*[58]. In a study in 2001, Verran *et al*[59] found that the combination of abnormal biopsy findings with donor age and donor cardiovascular disease and hypertension was associated with poor outcomes.

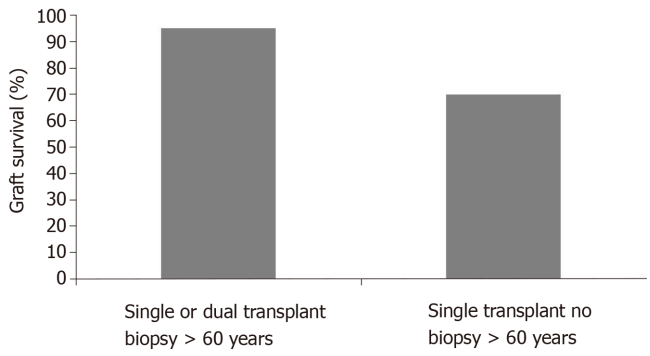

Figure 2 36 month graft survival for donors over 60 years according pre-transplant biopsy.

In an Italian study[60], donor kidneys were assigned with good results according to donor renal function [estimated glomerular filtration rate (eGFR) under or over 50 mL/min] and the previously mentioned Karpinski score.

The largest study that evaluated the predictive value of clinical and histological findings taken together was conducted by Anglicheau*et al*[61]. The authors, evaluating 313 kidney transplants from donors aged >50 years, developed the so-called Anglicheau score. The best predictive parameters were a history of hypertension in the donor, serum creatinine levels under or over 1.5 mg/dL and glomerulosclerosis less than or over 10%. These parameters in the multivariate analysis significantly correlated with renal function at 1 year post-transplantation.

A different study[62] recognizes the utility of zero-time biopsy, but, as none of the histological variables and scores provided a good prediction of post-transplant outcomes, the histological findings need to be integrated with all the known donor-related clinical parameters.

Finally, a very recent Spanish study[63] highlights the utility of evaluating the pre-transplant donor biopsies in the donor with the highest kidney donor profile index (KDPI) that is based on several deceased donor variables.

CLINICAL EVALUATION OF DONOR KIDNEYS

In an attempt to improve the evaluation of the donor kidneys, principally in the US, where the donor kidney evaluation is strictly connected with their discard or their allocation to different recipients according to national programs, several clinical donor quality scoring systems have been performed.

The first one was the characterization and a better definition of ECDs. According to the report of the Kidney Working Group[1], kidneys belonging to the ECD were kidneys with a relative risk of graft failure of 1.7 with respect to standard kidneys. These kidneys are characterized by a donor age older than 59 years with two of the following characteristics: cerebrovascular accident as cause of death, history of hypertension or creatinine over 1.5 mg/dL[2].

Nyberg *et al*[64] evaluated 241 consecutive cadaveric renal transplants and gave a score based on recognized clinical factors responsible for DGF. These factors were age, cause of death, history of hypertension, diabetes mellitus, creatinine clearance and presence in the donor of renal artery stenosis. A scoring system was developed from these seven donor variables, allowing stratification of cadaver kidneys into four classes (grades A, B, C, D). Univariate and multivariate analyses were performed, and a significant decline in early renal function was observed with an increase in the score. Additionally, the multivariate analysis had a better prognostic value with respect to each single variable considered in the univariate analysis.

Later, Nyberg *et al*[65], in an attempt to validate his scoring system, applied the analysis to a wider population, including 34324 transplant patients from the UNOS registry in the period between 1994 and 1999. This study allowed us to evaluate the feasibility of the score on a larger follow-up. The study allowed the recognition of five clinical variables as predictive of a poorer outcome [age, cause of death, history of hypertension, creatinine clearance and human leukocyte antigen (HLA) mismatch]. This score was called the Deceased Donor Score or Nyberg score and was able to predict renal function at 12 mo and graft survival at 6 years (Figure 4).

A further study by the same author[66] also confirmed these data for kidneys

Table 3 Maryland Aggregate Pathology Index scoring system for pre-transplant kidney biopsies

	HR (95%CI)	*P* value	MAPI points	
			Absent	Present
Arteriolar hyalinosis	3.93 (2.02-7.64)	<0.0001	0	4
PGF (any)	4.09 (1.65-10.14)	0.002	0	3
Scar (any)	2.58 (1.24-5.38)	0.01	0	3
GS > 15%	1.87 (1.17-2.99)	0.009	0	2
WLR interlobular arteries > 0.5	2.05 (1.21-3.47)	0.008	0	2

MAPI: Maryland Aggregate Pathology Index; WLR: Wall to lumen ratio; CI: Confidence interval.

receiving machine reperfusion.

To further improve clinical factors able to evaluate kidney status and to predict outcomes after transplantation, Schold *et al*[67] studied different clinical variables that were applied to transplants included in the National Scientific Transplant Registry from 1996 to 2002.

The variables were age, race, and history of hypertension, diabetes mellitus, and cause of death, cold ischemia time, HLA mismatch, and immunological status and CMV status. This was called the Donor Risk Score and allowed for the calculation of the multivariate estimates for graft loss by donor grade (Figure 5).

A further study[68] compared the different clinical risk scores and documented that the Donor Risk Score was better associated with subsequent allograft function.

ECD-KDRI-KDPI

As already mentioned, by 2002, in an attempt to improve the utilization of marginal deceased donor kidneys, the concept of ECD *vs* SCD was introduced[1,2]. With time this dichotomy (SCD/ECD) demonstrated several drawbacks. Indeed, the experience documented that several kidneys labeled as ECD performed well, while other kidneys labeled as SCD did not perform well[69]. To improve these limitations other different scoring systems have been attempted. The donor score of Nyberg and the donor risk score of Schold have been described. Additionally, Irish *et al*[70] applied a nomogram aimed at predicting the risk of DGF based on 16 donor and recipient risk factors. Moore *et al*[68] documented that Schold's donor risk score is the scoring system that best predicts graft outcomes, but the need still remains for a simple and validated system that applies to the entire donor population viewed as a continuum and not in a dichotomous fashion.

In 2009, Rao *et al*[71]analyzed 69440 deceased donor adult transplants registered in the Scientific Registry of Transplant Recipients (SRTR) and proposed a new continuous KDRI for deceased donor kidneys combining donor and transplant variables.

Rao's KDRI included 14 donor and transplant factors, each associated with shorter graft survival. Table 6 shows the mentioned risk factors.

The KDRI is a continuous spectrum for any kind of donor (ECD and SCD) and allows for dividing the donor population into quintiles based on their KDRI. By the end of 2014, the KDRI was implemented by the OPTN[72]. Indeed, as some transplant factors are not known at the time of transplant, the donor-only KDRI based on 10 donor factors has been implemented.

All the mentioned donor scoring systems are shown in Table 1[73]. Woodside *et al*[74] examined the SRTR data from 2002 to 2010, and applying the KDRI, they found that kidneys belonging to the same KDRI quintile had similar outcomes independently of their belonging to ECD or SCD. However, ECD kidneys had a higher discard rate.

The use of the KDRI was further validated by several studies. Jun *et al*[75] examined the use of the KDRI in donors with acute kidney injury (AKI) and found a good correlation between KDRI quintiles and graft outcomes.

A different study[76] documented that the KDRI was a good prognostic tool for graft outcomes in deceased donor kidney transplantation with a short cold ischemia time. In this study, the KDRI correlated with renal function at 1 year, and a high KDRI was associated with a high risk of graft failure.

Recently, a Spanish study validated the usefulness of the KDRI in a European population[77]. The study evaluated 144 renal transplants. All kidneys transplanted

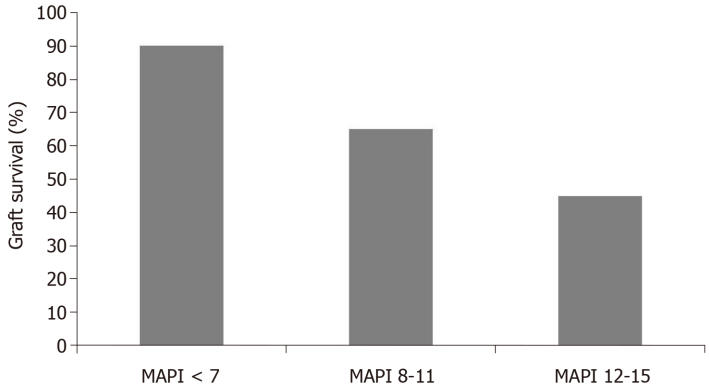

Figure 3 Five years graft survival for the study population according low, intermediate and high Maryland Aggregate Pathology Index score ranges. MAPI: Maryland Aggregate Pathology Index.

were evaluated by the KDRI and biopsied. The aims of the study were to verify the concordance between the KDRI and the histological findings and to validate the prognostic value of the KDRI for transplant outcomes. The study concluded that there was a poor concordance between the KDRI and histological score and that the KDRI had a good prognostic value.

Strictly connected with the KDRI is the KDPI. The KDPI represents the relative risk of graft failure in the case of a particular deceased donor compared to a reference donor. The KDPI was introduced in 2014 in the US[78] and is derived by ranking the KDRI on a scale of 0-100% with reference to a donor cohort in the OPTN. It is useful and is represented by a number that helps in deciding the allocation of a specific organ[79].The KDRI and KDPI are strictly related.

These scoring systems have advantages over the ECD system because they represent a continuum, are based on 10 donor factors and represent a measure of donor quality.

Limitations of the KDRI and KDPI are represented by the fact that they do not include all of the donors' factors that could impact the graft outcome. Additionally, the KDPI is a measure of the donor and is not specific for each kidney taken individually.

The KDPI is useful for introducing the concept of the so-called longevity matching. The concept consists of allocating kidneys with a higher KDPI to patients on dialysis with a lower life expectancy. A retrospective study[80] documented those patients older than 50 years or with a long waiting list time who were transplanted with kidneys with a high KDPI had a better survival than similar patients remaining on dialysis. This is particularly evident for patients older than 70 years[81]. Notwithstanding, a German study[82]reporting the experience of transplanting kidneys with a high KDPI observed that poor kidney quality, even when matching donors and recipients is the main factor responsible for poor outcomes. Several studies have evaluated the utility of the KDPI even outside of the US.

In a retrospective study, Lehner *et al*[83] evaluated the utility of the KDPI in almost 1000 European kidney transplants. The study found rather good outcomes in the case of donors with a very high KDPI. A Spanish study[84] evaluated the KDPI score on 389 transplants. The study documented that only the KDPI correlated with the risk of graft failure. This study also documented the utility of the KDPI measure in a cohort of European patients.

To further improve the KDPI, a retrospective study[85] was conducted in the US. The study evaluated the KDPI in adult transplant recipients in the OPTN/UNOS database from 2000 to 2015. This study, while validating the usefulness of the KDPI, found that terminal serum creatinine of the donor (one of the components of the KDPI) is not a useful variable.

Another European study[86] analyzed 1,305 kidney transplants. The study retrospectively applied the KDPI in 889 deceased donors and the living donor kidney profile index (LKDPI) in 416 living donors using the LKDPI realized by a US study for living donation[87].The European study was able to validate both the KDPI and LDKPI.

A major concern is what to do with donor kidneys with very a high KDPI (>80%).

In the US, the discard rate of these kidneys is approximately 50%. However, the allocation of kidneys with a KDPI higher than 80% in patients older than 60 years results in a lower patient mortality compared to patients who remain on the waiting list[88]. Indeed, several kidneys with a KDPI higher than 80% are viable. A recent

Table 4 Cox Multivariate analysis showing association of Maryland Aggregate Pathology Index score and clinical parameters to risk of graft failure

	HR (95%CI)	*P* value
MAPI	1.21 (1.05-1.40)	0.008
Donor age	1.03 (1.00-1.07)	0.096
Cold ischemia (h)	3.66 (0.77-17.40)	0.102
Donor history of hypertension	1.62 (0.67-3.97)	0.287
Donor terminal creatinine> 1.5 mg/dL	1.34 (0.43-4.18)	0.611
CVA as cause of donor death	0.98 (0.35-2.73)	0.973

CVA: Cerebrovascular accident; MAPI: Maryland Aggregate Pathology Index.

study[89] evaluated the 1-year eGFR and graft failure for kidneys transplanted with a KDPI higher than 80%. The discard of such kidneys had been decided with the help of a pre-Tx kidney biopsy, renal resistance and kidney injury biomarker levels. The 1-year eGFR was low but satisfying. The authors request the use of new biological tools for a proper evaluation of these kidneys.

An Italian multicenter study tried to reduce the discard rate of kidneys with a KDPI higher than 80% using pre-transplant kidney biopsy for these kidneys[90]. The discard rate was reduced from 50% to 15%-37% according to the KDPI. The 1-year eGFR was lower for these marginal kidneys, but the graft survival was similar to that of standard kidneys. The study highlighted the utility of pre-transplant biopsy for kidneys with a very high KDPI.

Finally, a recently raised relevant question is whether the KDPI may be universally applied in allocating marginal kidneys or whether it is UNOS specific. A recent study from Ruggenenti *et al*[91] documented the allocation and good graft survival of 37 renal transplants with donors with a KDPI between 96% and 100% after a pre-transplant biopsy. These kidneys should have been discarded according to the UNOS criteria[92]. Similar findings have come from a previous study by Ekser *et al*[93]. The 5-year graft survival was 91%, and the mean KDPI was 97%. More than 80% of these kidneys should have been discarded according to the UNOS[94].

The question of UNOS specificity of the KDPI is examined in a recent study by Ruggenenti *et al*[95]. According to the author, the difference in ethnicity may only partially explain the different results and the different discard rates of UNOS and several European studies[96]. The author highlights the usefulness of pre-transplant biopsy for kidneys of donors with a very high KDPI.

In conclusion, the KDRI/KDPI represents an easy scoring system that could facilitate the decision to discard organs or allocate them in the best way.

According to several studies, the KDPI may also be applicable to European patients, even though this point is to date debated.

Based on the KDPI, the UNOS is implementing new allocation systems such as "longevity matching". Each candidate willing to participate in the "longevity matching" will receive an "estimated post-transplant survival score" (EPTS) and will receive a graft according to the matching KDPI/EPTS.

The allocation of kidneys with the highest KDPI is debated. Often, these kidneys are discarded[97], but the use of pre-transplant biopsy may allow allocation of many of these kidneys, thus reducing the discard rate[98].

MACHINE PERFUSION AND PERFUSATE BIOMARKERS

Hypothermic machine perfusion is increasingly used in deceased donor kidney transplantation, but the question still remains on how efficient are MP in assessing the quality of an organ?

One study evaluating the reasons for discarding 12536 ECD kidneys found that 15% of perfused kidneys were discarded partly based on high renovascular resistance (RR)[99]. In a prospective study by Jochmans *et al*[100] RR values of 302 MP kidneys were evaluated. The study conclusions were that RR as a standalone quality assessment tool cannot be used to predict the graft outcomes.

More recently, Parikh *et al*[101]in a prospective observational cohort study examined the association between pump parameters and graft outcomes. They found an association between 1 h perfusate flow and DGF but with a border line value.

In conclusion, according the currently available data, there is a weak correlation

Table 5 Studies on molecular markers measured in 0-h biopsies (up to 2011)

Ref.	Pats	f/u	Findings/timing of biopsy-technology
Hoffmann *et al*[28], 2002	24	1 h	IRI injury ass w increased adhesion, chemotaxis, apoptosis, monocyte recruitment/activation transcripts.Post-reperfusion/RT-PCR
Hauser *et al*[29],2004	36	1	Increased Communication, apoptosis, inflammation
Kainz*et al*[30],2004	10	1	DD kidneys distinctly different transcripts in the TI but not in the G compartment compared to LD. End of CIT/microarrays
Avihingsanon *et al*[31],2005	75	6	15 selected genes associated with outcomes, included DGF, REJ and 6 mofunction. Post-reperfusion/RT-PCR
Kainz*et al*[32],2007	31	12	Increased immunity, signal transduction, oxidative stress response associated with lower 1-year function
Park *et al*[33],2007	15	12	Increased inflammation and immune response at 1-year in uncomplicated grafts
Mas *et al*[34],2008	33	3	Increased immunity, inflammation and apoptosis genes associated with DGF. End of CIT/microarrays
Mueller *et al*[35],2008	87	12	Increased acute phase, complement, chemochines and reduced metabolism, transporters in DD versus LD, transcriptome identifies risk for DGF better than clinical ± histological markers. Post-reperfusion/ microarrays
Perco *et al*[36], 2009	82	12	Increasedimmunity/defense, communication, apoptosis in damaged kidneys, CADI score + clinic explained 14%, 3 biomarkers 28% of 1-year creatinine variability. End of CIT/ microarrays
Naesens *et al*[37], 2009	28	36	Complement genes differ between LD and DD and are associated with early and late function. End of CIT and post-transplant/ microarrays
Bodonyi-Kovacs *et al*[38], 2010	75	48	Pre-selected genes associated with 2-year graft function. Post-reperfusion/ RT-PCR
Cravedi *et al*[39], 2010	49	12	LD*vs* DD differ by inflammation, donor age and ITGB2 prognostic for 1-year function. Post-reperfusion/RT-PCR

f/u:Follow up in months; IRI:Ischemia-reperfusion injury; DD:Deceased donor; LD:Living donor; IGF:Immediate graft function; DGF:Delayed graft function; REJ:Rejection; CIT: Cold ischemia time; TI:Tubulointerstitial; G:Glomerular.

between perfusion parameters and graft outcomes and additional studies are needed.

FUTURE PERSPECTIVES AND EMERGING TECHNOLOGIES

All the scoring systems, either histological or clinical, need to be improved with the help of new tools. Indeed, several cited studies advocate for newest approach in the evaluation of donor kidneys. Nickeleit[16] stated that new consensus guidelines remain to be defined on zero-time biopsies. Mueller *et al*[25] highlighting the confounding variables, advocate for the use of omic technologies in the evaluation of kidney biopsies. This point is also highlighted by the Banff Pre-Implantation Biopsy Working Group[56]. The usefulness of biomarkers in the evaluation of donor kidneys has also

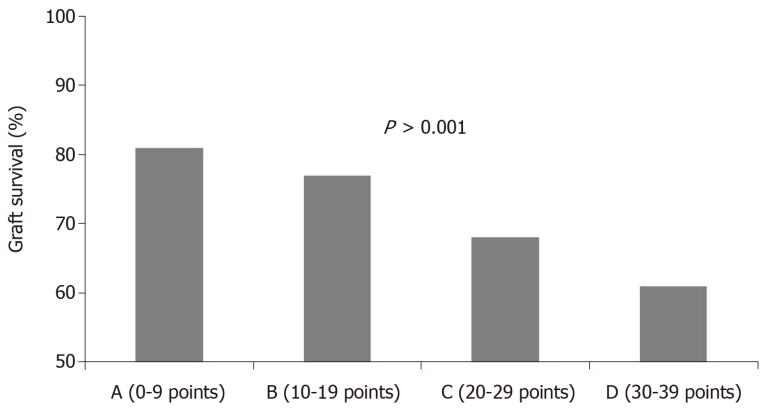

Figure 4 Grade of deceased donor kidney score significantly influenced graft survival at 6 years after transplantation.

been highlighted by another recent study[90].

There are a number of emerging technologies to examine an organ at molecular level ranging from proteomics to metabolomics to transcription studies.

The most important study on proteomics is the study of Reese *et al*[102] who examined the association between four different biomarkers and the post-transplant renal function. All the urine injury biomarkers strongly associated with donor AKI, but resulted of limited value in predicting DGF or early graft function

By using transcription analysis, Scian *et al*[103] validated a set of three genes (*CCL5*, *CXCR4* and *ITGB2*) that was up regulated in kidneys with a low eGFR post-transplantation.

Gustafson *et al*[104] still by transcription analysis found a set of 13 genes (Table 7) associated with allograft loss at two or three years after transplantation.

By metabolomics studies, Guy *et al*[105] found in the perfusate of the hypothermic machine significant lower levels of gluconate, glucose, inosine and leucine in kidneys with DGF.

Finally, a novel technique able to recondition the kidney and to restore normal function prior to transplantation is the *ex vivo* normothermic perfusion. Phase I studies in ECD documented its safety and feasibility in clinical practice[106].

Some studies are ongoing, but their results are to date unknown.

An important study aims to evaluate the relevance of molecular biomarkers of aging in the blood of donors. This study (Senesce Test) has been completed, but no results are available yet (NCT02335333)[107]. Another NIH study coordinated by Yale University is testing biomarkers characteristic of renal injury in the urine of the donor and in the perfusion media (NCT01848249)[108].

The PREDICTION study aims to evaluate the improvement in viability of marginal kidneys treated by pulsatile perfusion[109].

CONCLUSION

The increase in the demand of kidneys for transplantation may only be satisfied with the increase in the use of marginal donors as kidneys from aged donors or with the use of donation after cardiac death donors.

Such kidneys need to be carefully evaluated either to be discarded or for a fair allocation.

The histological evaluation met several drawbacks as the time of the biopsy (pre or post reperfusion, the type of biopsy (wedge versus core biopsy), the pathologist involved in the evaluation (pathologist on-call or trained pathologist in this field).

Additionally, the difficulty of obtaining adequate histological analysis from pre implantation biopsies and the risk/benefit considerations to prolong cold ischemia time waiting for chronic histological abnormalities that often show poor correlation with clinical outcomes represents the most relevant drawback. All these drawbacks led to give more importance to the clinical evaluation of the donor. The KDRI/KDPI is an easily applicable scoring system, but this system also has its drawbacks especially in the evaluation of donors with the highest KDPI.

In the US, the use of KDPI led to a very high discard rate of the marginal donor kidneys, while other studies documented that several of these kidneys might be

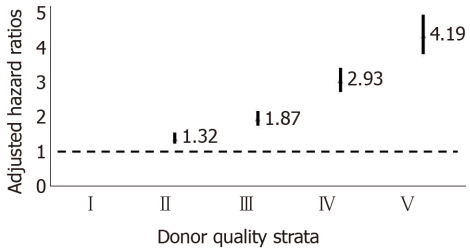

Figure 5 Multivariate estimates for graft loss by donor grade (Hazard ratio expressed as mean +/- confidence interval.

usefully transplanted.

Overall, is not easy to establish how many centers have taken part to the different scoring system as many of them are retrospective studies.

The elaboration of the Port scoring of standard criteria donors versus expanded criteria donors has been done comparing retrospectively 24756 SCD versus 4312 ECD from almost all the UNOS centers.

The MAPI has been done in a single center considering 371 transplants.

The Nyberg deceased donor score was made in three steps. In a first step 241 transplants were enrolled in two centers. Then in the attempt to give more strength to the scoring system, this was evaluated retrospectively on 34324 UNOS kidney transplants and in a third phase on 48952 UNOS kidney transplants.

The Donor risk score of Schold was evaluated retrospectively on 45850 data from SRTR.

The DGF nomogram of Irish was evaluated in a single center in UK on 217 prospective transplant patients.

Finally the KDRI of Rao was retrospectively evaluated on 69440 patients from SRTR. Subsequently the scoring was evaluated prospectively in different countries.

A hope for the future seems to come from the use of biomarkers. However, to date the use of urine biomarkers offers discordant results and does not provide sufficient power to be used in the kidney evaluation.

According recent studies, the use of pre-implantation biopsy has been shown to have its major utility in the evaluation of kidneys with a very high KDPI.

A very recent study from Moeckli *et al*[110] helps in clarifying what's new in the current and emerging techniques of kidney evaluation. In particular the study concerns the use of omics and states that the most promising is transcriptome profile, also according the already cited studies.

Waiting for the advent of omics it seems that the best strategy in evaluating kidneys for transplantation is the clinical one. In the case of a very high KDRI pretransplant biopsy may be useful in allocating or not the kidneys

Table 6 Donor and transplant factors and corresponding hazard ratios for graft failure

	Hazard ratio	95%CI	*P* value
Donor parameter			
Age	1.013	1.011-1.015	< 0.0001
Afro American race	1.20	1.13-1.27	< 0.0001
Serum creatinine	1.25	1.17-1.23	< 0.0001
Hypertensive	1.13	1.08-1.19	< 0.0001
Diabetic	1.14	1.04-1.24	0.0040
Cause of Death	1.09	1.04-1.14	0.0002
Height	0.96	0.94-0.97	< 0.0001
Weight	0.98	0.97-0.99	0.0003
Donation after cardiac death	1.14	1.02-1.28	0.0246
HCV positive	1.27	1.13-1.43	< 0.0001
Transplant parameter			
HLA-DR mismatch	0.88	0.84-0.92	< 0.0001
Cold ischemia time	1.005	1.003-1.008	< 0.0001
En bloc transplant	0.70	0.57-0.84	0.0002
Double kidney transplant	0.86	0.75-1.00	0.0494

HLA:Human leukocyte antigen; HCV:Hepatitis C virus.

Table 7 Genes included in the study

ID	Symbol	Gene description	CADI-12 correlation	*P* value
3954887	*CHCHD 10*	Coiled-coil-helix-coiled-coil-helix domain containing 10	0.404	2.85×10^{-5}
4019160	*KLHL 13*	Kelch-like family member 13 (Drosophila)	0.369	1.49×10^{-4}
3326826	*FJX1*	Four jointed box 1 (Drosophila)	0.367	1.60×10^{-4}
3120343	*MET*	Met proto-oncogene (hepatocyte growth factor receptor)	0.352	3.01×10^{-4}
2864449	*SERUNC5*	Seine incorporator 5	0.318	0.0012
2567583	*RNF149*	Ring finger protein 149	0.280	0.0046
2879105	*SPRY4*	Sprout homolog 4 (Drosophila)	0.270	0.0062
3776504	*TG1F1*	TGFB-induced factor homeobox 1	0.244	0.0140
2898441	*KAAG1*	Kidney associated antigen 1	0.240	0.0154
3361971	*ST5*	Suppression of tumorigenity 5	0.232	0.0197
2459352	*WNT9A*	Wingless-type MMTV integration site family member 9A	0.212	0.0332
3021696	*ASB15*	Ankrin repeat and SOCS box-containing 15	-0.263	0.0079
3193339	*RXRA*	Retinoid X receptor alpha	-0.300	0.0023

CADI-12: Chronic allograft damage index at 12 mo.

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MINIREVIEWS

Pancreatic transplantation: Brief review of the current evidence

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Abstract

Kidney transplantation is the treatment of choice for management of end-stage renal disease. However, in diabetic patients, the underlying metabolic disturbance will persist and even may get worse after isolated kidney transplantation. Pancreatic transplantation in humans was first introduced in 1966. The initial outcome was disappointing. However, this was changed after the improvement of surgical techniques together with better patient selection and the availability of potent and better-tolerated immune-suppression like cyclosporine and induction antibodies. Combined kidney and pancreas transplantation will not only solve the problem of organ failure, but it will also stabilise or even reverse the metabolic complications of diabetes. Combined kidney and pancreas transplantation have the best long term outcome in diabetic cases with renal failure. Nevertheless, at the cost of an initial increase in morbidity and risk of mortality. Other transplantation options include pancreas after kidney transplantation and islet cell transplantation. We aim by this work to explore various options which can be offered to a diabetic patient with advanced chronic kidney disease. Our work will provide a simplified, yet up-to-date information regarding the different management options for those diabetic chronic kidney failure patients.

Key words: Combined kidney pancrease transplantation; Renal transplantation; Diabetic kidney disease; Diabetes mellitus

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Core tip: Kidney transplantation is the treatment of choice for end-stage renal disease. Combined kidney-pancreas transplantation provides the patients with the highest long term survival. There are different surgical approaches for combined kidney-pancreas transplantation with recognised advantages and limitations of each technique. Islet cell transplantation is a minimally invasive treatment option but carries a risk of sensitisation to a wide range of human leukocyte antigen antigens.

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INTRODUCTION

Diabetes mellitus (DM) is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide[1]. Successful pancreas transplantation provides optimisation of glucose metabolism for diabetic patients[2]. The current management options for diabetic patients with advanced CKD are summarised in Figure 1.

Pancreas transplant alone (PTA) is another option for managing diabetic patients with normal renal function. Moreover, transplantation of the islets of Langerhans is a promising alternative to whole pancreas transplantation which can provide adequate glycemic control without exposing the recipient to major surgical interventions[2].

DIABETIC ELIGIBILITY CRITERIA FOR TRANSPLANTATION

Diabetes is classified into two main subtypes, type 1 and type 2, based on the American Diabetes Association classification system. The discrimination between the two types of DM may be difficult in many cases[3]. Table 1 summaries the main characteristics of type 1 and type 2 DM in children and adolescents[4].

Pancreas transplantation is offered primarily to type 1 diabetic CKD patients, an approach that was supported by the fact of absence of endogenous insulin and normal insulin sensitivity. However, some cases with insulin-dependent type 2 diabetes in the United States have been accepted on simultaneous pancreas-kidney (SPK) waiting list if their body mass index (BMI) is less than 30 kg/m^2, requiring insulin, but < 1.5 U/kg per day. About 6% only of SPK waiting list cases are type 2 DM[2]. The plan for transplan-tation modality is simplified in Figure 2.

MANAGEMENT OPTIONS FOR DIABETIC PATIENTS WITH ADVANCED CKD

In advanced CKD, Preemptive kidney transplantation from a living donor will offer the patient the highest patient survival rate at five years reaching up to 91% (compared to 84% for non-extended-criteria donor transplant, and 70% for extended-criteria donor transplants)[5]. Nevertheless, this management option will not usually solve diabetes-related medical condition (as DM control may be impaired if steroids were used post kidney transplantation either as maintenance therapy or for treatment of rejection episodes)[1,2].

In the United Kingdom, the national five-year patient survival is 88% for SPK recipients, and 78% for pancreas only transplant recipients. Pancreas allograft survival rate at five years is 75% for SPK recipients and 45% pancreas-only transplants[6].

A retrospective analysis of long-term survival of 18549 patients with type 1 DM in the United States has demonstrated that the patient survival at eight years for SPK recipients was similar to living-donor kidney recipients (about 72%) while the survival for cadaveric kidney recipients was only 55%[7]. SPK is associated with significantly elevated early mortality risk most probably secondary to the surgical procedure itself, and the related complications, which result in prolonged and recurrent hospitalisation is the first few months post-transplantation[1,7]. On the other

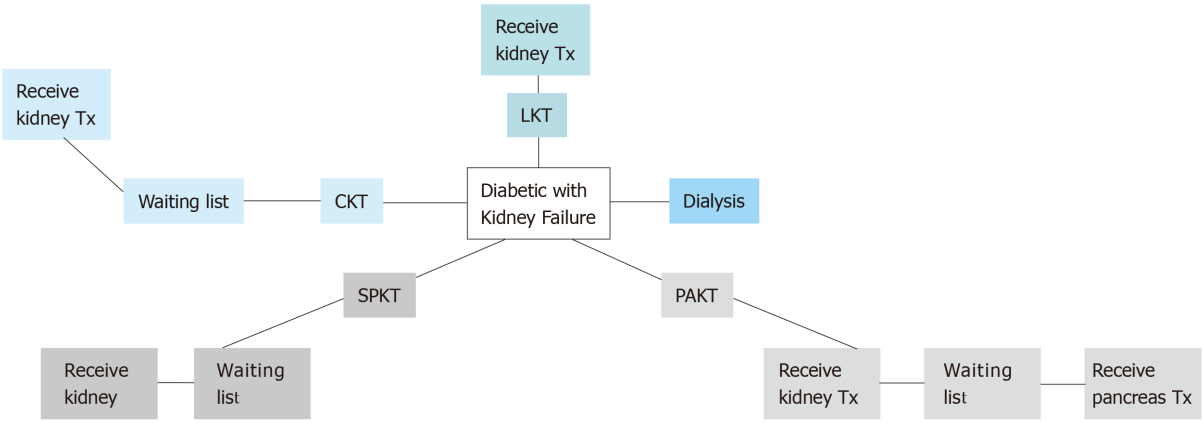


Figure 1 Options for diabetic patients with kidney failure. LKT: Living kidney transplantation. CKT: Deceased kidney transplantation; SPKT: Simultaneous pancreas and kidney transplantation; PAKT: Pancreas after kidney transplantation.

hand, the long-term outcome for SPK is better than any other transplantation option in diabetic patients[1,7]. Recent data regarding kidney allograft survival with various types of kidney pancreas transplantation are summarized in Table 2[8].

The kidney outcomes for pancreas after kidney (PAK) were from the time of pancreas transplant, which may explain the lower survival rates compared to those of SPK recipients[8]. The maintenance of a functioning pancreas allograft was associated with the favourable long-term outcome with SPK most probably secondary to stabilisation or even improvement of most of the DM associated systemic complications as illustrated in Table 3.

Data collected from 20,854 pancreas transplant recipients between 1996 and 2012 by the United Network for Organ Sharing (UNOS) was analysed for patient and graft survival[16]. The best graft survival outcome was observed in recipient ranged between 40-49 years old. Additionally, the study documented an inverse relationship between recipient age and patient survival, with reduced patient survival in those who are older than 50 years[16].

SURGICAL IMPLANTATION TECHNIQUES

In SPK operation, the kidney is usually transplanted into the left iliac fossa by the traditional approach using the iliac vessels for vascular anastomosis[2]. There are several options for pancreatic implantation reflecting the fact that there is no standard optimal technique, each surgical option has its advantages as well as disadvantages. One of the challenges is the exocrine and endocrine drainage of the pancreatic allograft[2]. The various pancreatic implantations techniques are simplified in Figure 3[2,3,17,18], while the possible complications of pancreatic transplantation were summerized in Table 4[19].

PRETRANSPLANT ASSESSMENT

The patient evaluation should follow the local protocol for transplant candidate. This includes detailed medical, surgical, and psychosocial history; a meticulous physical examination; and laboratory evaluation. However, the pretransplant workup should be very strict to identify any possible undiagnosed condition related to DM that will negatively affect the outcome. Particular attention should be given for assessing cardiovascular status and the presence of peripheral vascular disease[20].

Pancreatic transplantation is associated with an increased risk of mortality in the early post-operative period, and the most frequent cause of death is of cardiovascular event[20]. There is no universally standardised cardiovascular screening protocol for asymptomatic CKD patients[21]. Some of the internationally published protocols are illustrated in Figure 4[21].

The initial cardiac assessment could be suggested by myocardial perfusion imaging (MPI) together with exercise-based (+/- dobutamine) stress test, and results should be interpreted by an expert cardiologist[21]. Myocardial perfusion studies provide valuable information regarding functional capacity, the extent of myocardial viability, and the extent of stress-induced ischemia as well as the degree of stress defect

Table 1 Comparison of criteria of type 1 and type 2 diabetes mellitus[4]

	Type 1 diabetes	Type 2 diabetes
Prevalence	Common, increasing	Increasing
Age at presentation	Throughout childhood	Puberty
Onset	Typically, acute severe	Insidious to severe
Ketosis at onset	Common	5% to 10%[1]
Affected relative	5% to 10%	75% to 90%
Female: male	1:1	Approximately 2:1
Inheritance	Polygenic	Polygenic
HLA-DR3/4	Strong association	No association
Ethnicity	Most common in non- Hispanic white	All[2]
Insulin secretion	Decreased/absent	Variable
Insulin sensitivity	Normal when controlled	Decreased
Insulin dependence	Permanent	Variable
Obese or overweight	20% to 25% overweight[3]	> 80% obese
Acanthosis nigricans	12%[4]	50% to 90%[4]
Pancreatic antibodies	Yes[5]	No[6]

[1]Reported frequency of ketonuria or ketoacidosis at time of diagnosis of type 2 diabetes mellitus (T2DM) varies widely.
[2]In North America, T2DM predominates in native America, African-American, Hispanic, Canadian First Nation, Pacific Islander, and Asian-American youth.
[3]With increased prevalence of childhood overweight, 20% to 25% of newly diagnosed with type 1 diabetes mellitus (T1DM) are overweight, which is higher than the prevalence of overweight in a similar population without T1DM. However, the prevalence of obesity is not increased among children and adolescents with T1DM. Recent weigh loss is common at presentation of children with T1DM, including among those who are overweight or obsess.
[4]These frequencies of acanthosis nigricans are based on a registry study in the United States. Populations with lower rates of obesity or difference ethnic mixes may have different results.
[5]Autoantibodies to insulin (IAA), islet cell cytoplasm (ICA), glutamic acid decarboxylase (GAD), tyrosine phosphatase (insulinoma associated) antibody (IA-2 and IA-2β), or zine channel antibody (ZnT8) are present at diagnosis in 85% to 89% of patients with T1DM.
[6]One study reported that 9.8% of youth with phenotypic T2DM have pancreatic antibodies to IA-2 and/or GAD. HLA: Human leukocyte antigen.

reversibility[21]. Some studies demonstrated an increased risk of cardiovascular events among patients who fail to complete exercise stress test regardless of the presence of negative test results[21].

The decisions regarding coronary catheterisation and revascularisation should be considered based on cardiologist recommendations. Patients with significant coronary pathology that is not amenable to revascularisation are not candidates for pancreatic transplantation[20].

SUGGESTED POST-OPERATIVE FOLLOW UP PLAN

Following successful transplantation BTS recommends reviewing the recipients in clinic twice to three times per week for the first month, weekly visits for the next two months, monthly for another three months, then every 2-3 months later on[22]. The clinic visit should include a detailed history of any new symptoms, careful medical examination and appropriate laboratory investigations (including immune-suppressant drug levels if possible). The patient care should involve a multidisciplinary team including a pharmacist, social worker, dietician, and psychologist[22].

Meticulous pancreatic donor and recipient selection criteria together with the modern immune suppression protocols have steadily decreased the incidence of pancreatic rejection to range between 10% to 20% in the first year post-transplant[2]. The majority of the early complications of the transplantation can be attributed to surgical and technical failures rather than an immunological injury. Complications include anastomotic leak, vascular thrombosis of the graft, graft pancreatitis, and infection[2,23].

ACUTE REJECTION

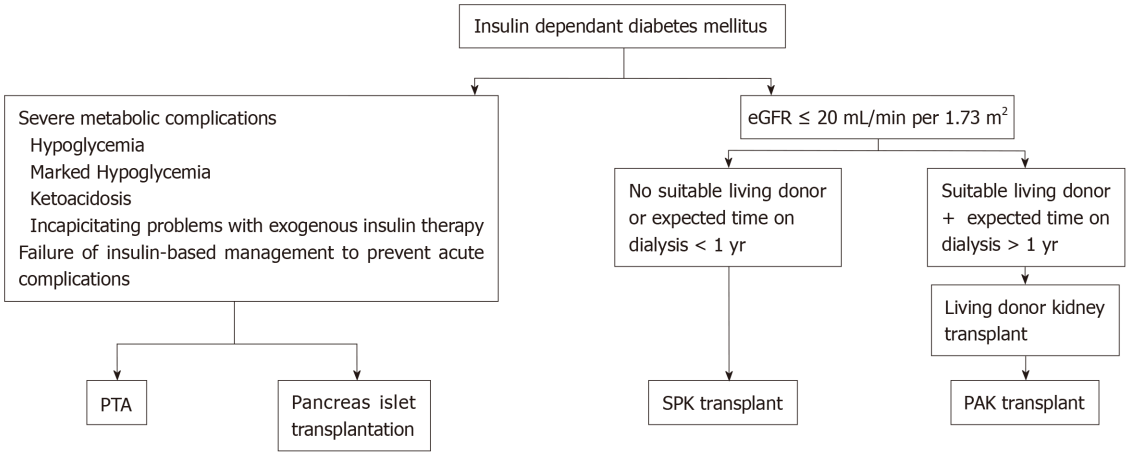


Figure 2 Algorithm for clinical decision making for diabetic patients. KTA: Kidney transplant alone; SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney; PTA: Pancreas transplant alone.

Most cases of pancreas allograft rejection are asymptomatic, so we should keep a high index of suspicion to detect allograft rejection early enough to allow early initiation of the proper therapy. The islet cells are spared in the initial phase of rejection, and hyperglycaemia is a late finding[2]. We should start our workup once allograft dysfunction is suspected (*e.g.*, elevated serum amylase and/or lipase)[2,24]. A recommended approach for evaluation of pancreatic allograft dysfunction is illustrated in Figure 5[24].

Maintenance immunosuppressive therapy for pancreatic transplantation is similar for that used for kidney transplantation. Most centres use a combination of a calcineurin inhibitor (predominantly tacrolimus), an antimetabolite (mycophenolate mofetil or mycophenolate sodium), and low-dose corticosteroids[2,20]. Induction therapy with lymphocyte-depleting agents (*e.g.*, antithymocyte globulin and alemtuzumab) allows early steroid withdrawal and steroid free regimens which are adopted by some centres[2].

ISLET CELL TRANSPLANTATION

Islet transplantation is an evolving and promising therapeutic option for management of type 1 DM. Successful isolation of islet cells from the whole pancreas is followed by infusion of the cells to the portal vein of the recipient via a percutaneous catheter as illustrated in Figure 6[25].

Keeping in mind that the major mass of the pancreas if formed of exocrine gland with only scattered clusters of endocrine cells, separation of islet cells from exocrine part will not only allow transplantation via minimally invasive technique (infusion of islets isolated from cadaveric pancreas via the portal vein), but it will also avoid vascular and allograft duodenal anastomoses, hence avoiding an essential source of surgical complications[2].

On the other hand, this therapeutic option is facing significant challenges that include: Achieving insulin independence necessitates transplantation of an adequate islet mass, which requires isolation from multiple donors (typically 2 to 4 donors), thus islet cell recipients are exposed to numerous human leukocyte antigen (HLA) mismatches which may jeopardize the possibility of future transplantation due to sensitization and formation of donor-specific antibodies[2,23]; The patient would require lifelong immune suppression even if received islet cell transplantation alone[2,23]; Despite the satisfactory short-term outcome of this technique (about 80% of the cases remained insulin independent after two years), the long-term outcome is still disappointing[2]; In the case of advanced CKD in addition to DM, Islet cell transplantation alone is not a valid option in the management of such medical condition.

CONCLUSION

There is no individual management plan for diabetic patients with advanced CKD; instead, we have different management options that depend on the patient comorbidities as well as personal preferences. Nevertheless, each option has its

Table 2 Kidney transplant graft failure rates associated with simultaneous pancreas-kidney and pancreas after kidney[8]

Type of the allograft	1 yr	5 yr	10 yr
SPK	3.1%	16.5%	37.7%
PAK (deceased donor)	3.3%	21.2%	51.2%
PAK (living donor)	3.0%	13.7%	37.0%

SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney.

limitations and possible complications. The best management plan for diabetic patient approaching ESRD is SPK which will offer the best long-term survival, in addition to the better quality of life and regression of most of DM complications. However, this approach is associated with early increased risk of morbidity and mortality. PTA and islet cell transplantation are possible options for managing diabetic patients. However, they are not suitable alone for patients with concomitant advanced CKD. The pretransplant workup for SPK is more stringent compared to kidney transplantation alone to minimise the risk of early postoperative morbidity and mortality and to achieve long-term patient and graft survival. Islet cell transplantation carries the risk of sensitisation against a group of HLA antigens, which makes the patients less likely to get a compatible kidney allograft in the future. PAK is not recommended above the age of 50 as it is negatively affecting the survival of patients older than 50 years. Additionally, it may result in loss of kidney allograft as a complication of this major intervention.

Table 3 Sample of studies evaluating the effect of pancreatic transplantation on the complications of diabetes mellitus

Ref.	Patient cohorts	Outcomes of interest	Time after transplant (yr)	Results
Cardiovascular disease				
Fiorina *et al*[9], 2000	SPK (n = 42) *vs* KTA (n = 26) *vs* type 1 diabetes (n = 20)	Left ventricular systolic and diastolic function assessed by radionuclideventriculograph y	4 yr	Left ventricular ejection fraction was higher in SPK recipients than in KTA recipients [75.7 (SD 1.8%) *vs* 65.3% (2.8%); P = 0.02] and type 1 diabetes controls (75.7 (1.8%) *vs* 61.2 (3.7%); P = 0.004).
Biesenbach *et al*[10], 2005	SPK (n = 12) *vs* KTA (n = 10)	Composite endpoint of myocardial infarction, stroke, and amputation	10 yr	Lower incidence of myocardial infarction (16% *vs* 50%), stroke (16% *vs* 40%), and amputations (16% *vs* 30%) in SPK *vs* KTA recipients (P < 0.05 for composite endpoint of all three events)
Diabetic nephropathy				
Fioretto *et al*[11], 1998	PTA: Pre-transplant *vs*post-transplant (n = 8)	Native kidney biopsy:structural morphology before and after transplant	10 yr	Improvement in glomerular basement membrane thickening, tubular basement membrane thickening, and mesangial expansion after transplantation compared with before
Boggi *et al*[12], 2011	PTA: Pre-transplant *vs* post-transplant (n = 71)	Proteinuria and estimatedGFR (eGFR)	Up to 4 yr	Overall, proteinuria decreased from 1.36 (SD 2.72) g/d pre-transplant to 0.29 (0.51) g/d post-transplant (P < 0.01) eGFR decreased by about 20% from 94 (39) mL/min per 1.73m2 to 75 (22) mL/min per 1.73 m^2 (P < 0.01)
Diabetic neuropathy				
Havrdova *et al*[13], 2016	SPK: Pre-transplant *vs*post-transplant (n = 12)	Epidermal nerve fiberdensity on skin biopsy, autonomic function tests, and nerve conduction studies	Up to 8 yr	No improvement in epidermal nerve fiber density or functional deficits on autonomic function tests
Boggi *et al*[12], 2011	PTA: Pre-transplant *vs*post-transplant (n = 71)	Clinical neurologicexamination (vibration threshold), nerve conduction studies, and autonomic function tests (lying-to-standing test)	Up to 4 yr	Significant improvement in mean vibration thresholds, nerve conduction studies, and autonomic function tests after PTA compared with before
Diabetic retinopathy				
Boggi *et al*[12], 2011	PTA: Pre-transplant *vs* post-transplant (n = 71)	Visual acuity scores andfundoscopic examination	Up to 4 yr	Before transplantation, 7.5% of patients had no retinopathy and remained lesion-free at 4 yr. Of the 29.5% with non-proliferative retinopathy, 75% improved and 25% remained unchanged. In the remainder with proliferative retinopathy, lesions remained stable in 82% and progressed in 18%

Giannarelli *et al*[14], 2006	PTA (n = 33) *vs* type 1 diabetes (n = 35)	Visual acuity scores, fundoscopic examination, and angiography in selected cases	Up to 30 mo	Before transplant, 9% of patients with PTA and 6% of those with type1 diabetes had no retinopathy, 24% and 29% had non-proliferative retinopathy, and 67% and 66% had proliferative retinopathy. Overall, the percentage of patients with improved or stabilized retinopathy was significantly higher in the PTA group (P < 0.01)
Koznarova *et al*[15], 2000	SPK (n = 43) **Vs** KTA (n = 45)	Visual acuity scores and fundoscopic examination	3 yr	In the SPK group, fundoscopic findings at the end of follow-up had improved, stabilized, or deteriorated in 21.3%, 61.7%, and 17.0%, respectively. In the KTA group these figures were 6.1 %, 48.8%, and 45.1% (P < 0.001)

KTA: Kidney transplant alone; SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney.

Table 4 Complications of pancreatic transplantation[19]

Complications	
Early complications	
Allograft parenchymal complications	Acute pancreatitis
	Necrotizing pancreatitis
	Fistulous tracts
Infection and abscesses	
Entric complications	Anastomosis leakage at duodeno-enterostomy
	Ileus Colonic infection.
Vascular complications	Venous or arterial graft thrombosis
	Acute bleeding
Late complications	
Allograft parenchymal complications	Rejection
	Pseudocyst formation
	Post-transplant lymphoproliferative disease
Enteric complications	Small bowel obstruction
	Colonic infection
Vascular complications	Arterial or venous pseudoaneurysms

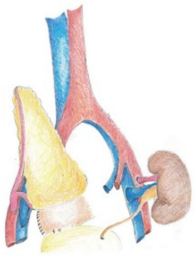
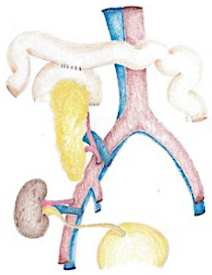
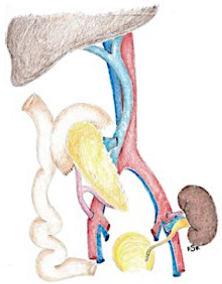
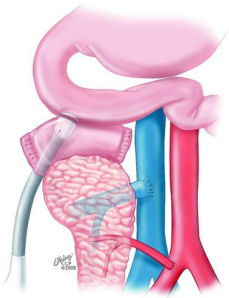
Procedure	Advantages	Disadvantages
Bladder exocrine drainage and systemic venous endocrine drainage[17] 	Pancreatic dysfunction can be detected early by changes of urinary amylase Easley accessible for biopsy Reduced rate of infection due to the relative sterility of the lower urinary tract Technical considerations (Bladder vasculature promote healing, bladder mobilisation permits tension-free, multi-layer anastomosis, Control of anastomotic leakage can be achieved by bladder catheter)	Fluid and electrolyte imbalance Metabolic acidosis Urologic complications (cystitis, haematuria, urethritis, balanitis and urethral stricture) Lower urinary tract infection and stone formation Reflux pancreatitis Enteric conversion if indicated will expose the patient to another major surgery
Enteric exocrine drainage and systemic venous endocrine drainage[17] 	More physiologic approach Avoid urologic complications Avoid the future risk of enteric conversion	Higher incidence of pancreatitis, leakage of pancreatic enzymes, and peripancreatic fluid collections More risk of anastomotic leakage, peritonitis, intra-abdominal collection and sepsis Inability to measure exocrine secretions for early detection of graft dysfunction Allograft biopsy is more challenging Occasional need for diverting Roux en y limb
Enteric exocrine drainage and portal venous endocrine drainage[17] 	Same advantages mentioned above in addition to: Avoid the risk of postprandial hypoglycaemia Better lipoprotein metabolism	Same points as mentioned above in addition to: Higher risk of vascular thrombosis
Duodenal exocrine drainage and systemic venous endocrine drainage[18] 	A modification of enteric exocrine drainage with systemic venous endocrine drainage with additional benefits in the form of: Improved accessibility for biopsy via endoscopy[3,16] It expands the options for exocrine drainage sites, especially in cases of pancreas retransplantation[16]	Same disadvantages mentioned above with enteric exocrine drainage and systemic venous endocrine drainage except for relatively easily accessible allograft

Figure 3 Various pancreatic implantation techniques.

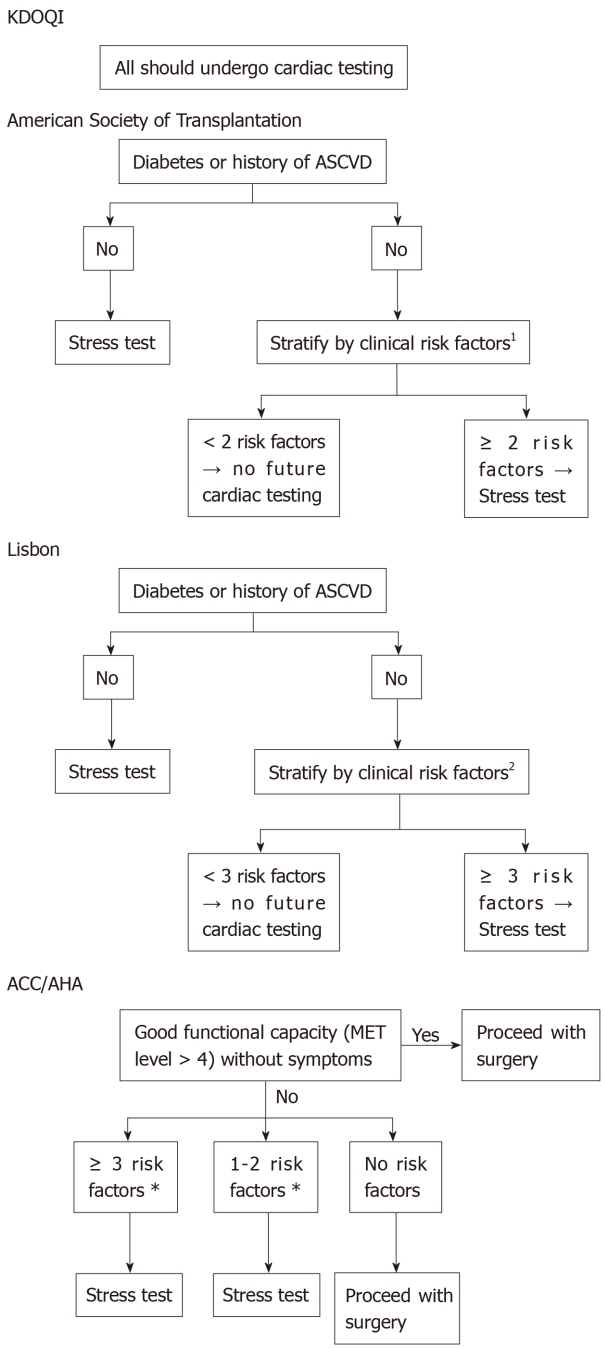


Figure 4 Outlines of preoperative cardiac risk assessment guidelines.[1]Hypertension, age (> 45 for men or > 55 for women), cigarette smoking, left ventricular hypertrophy, dyslipidemia, family history of coronary disease. [2]Hypertension, left ventricular hypertrophy, dyslipidemia, age > 60, > one year on dialysis. [3]Ischemic heart disease, cerebrovascular disease, renal insufficiency, diabetes. KDOQI: Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines; AST: American Society of Transplantation; Lisbon: Report of the Lisbon Conference on the Care of the Kidney Transplant Recipient; ACC/AHA: American College of Cardiology/American Heart Association.

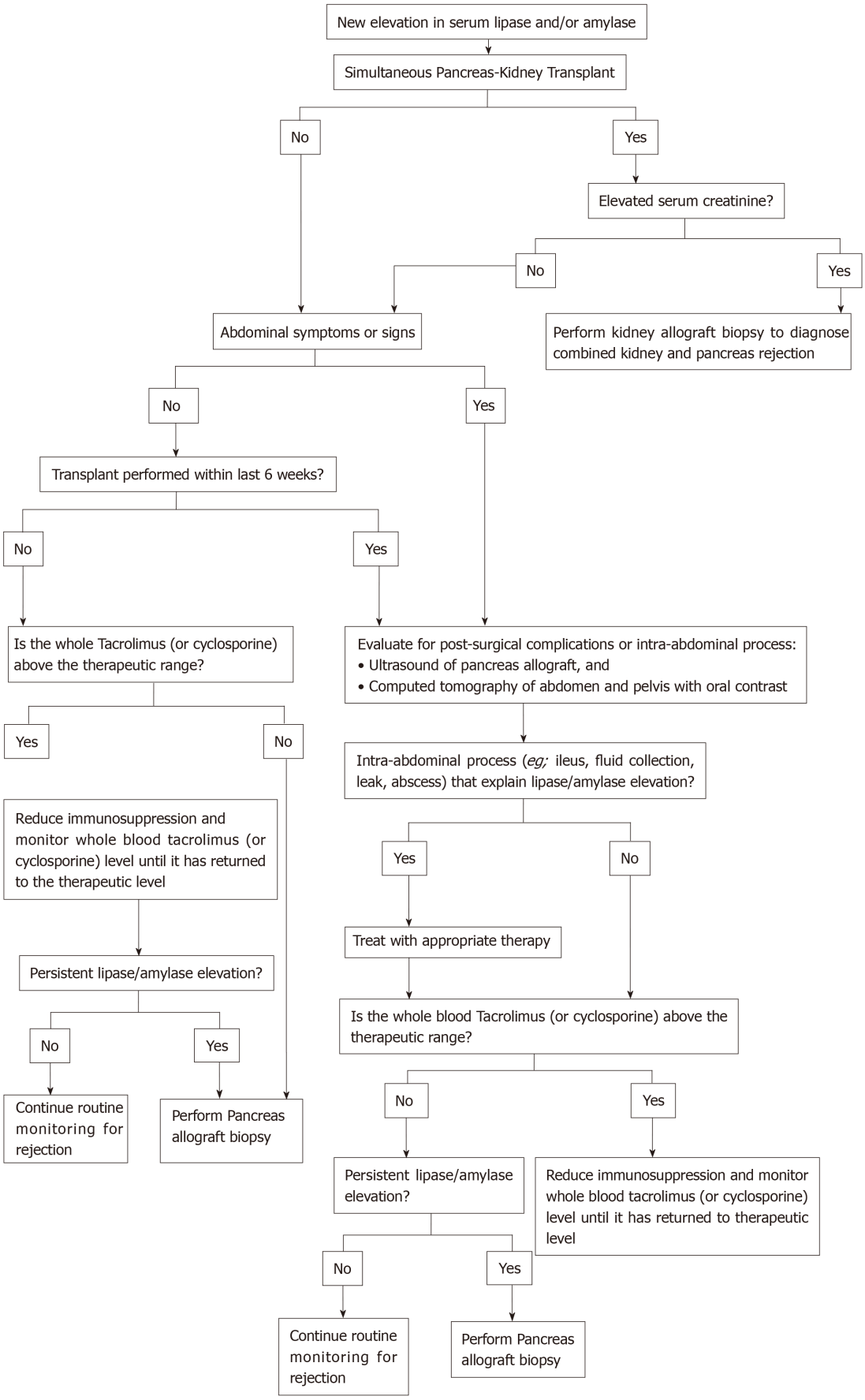


Figure 5 Algorithm for evaluation of pancreatic allograft dysfunction[24].

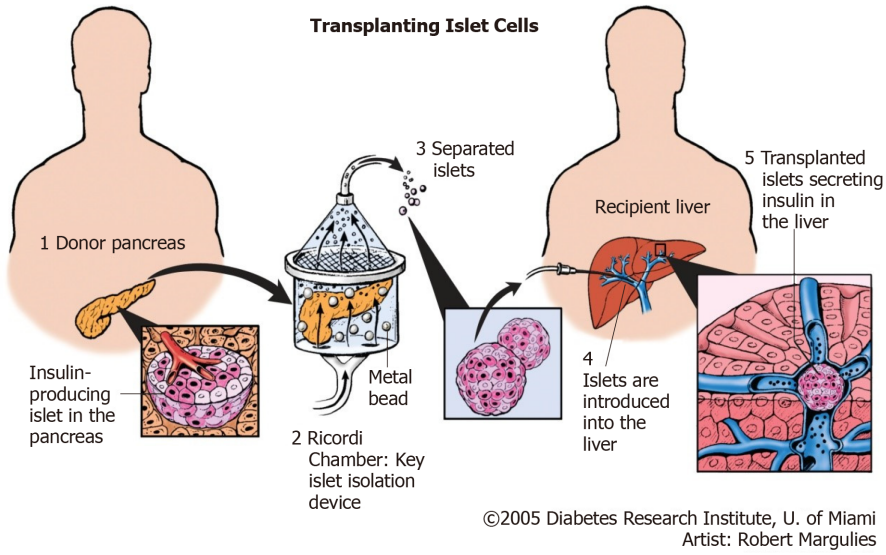


Figure 6 Principles of islet cell transplantation[25].

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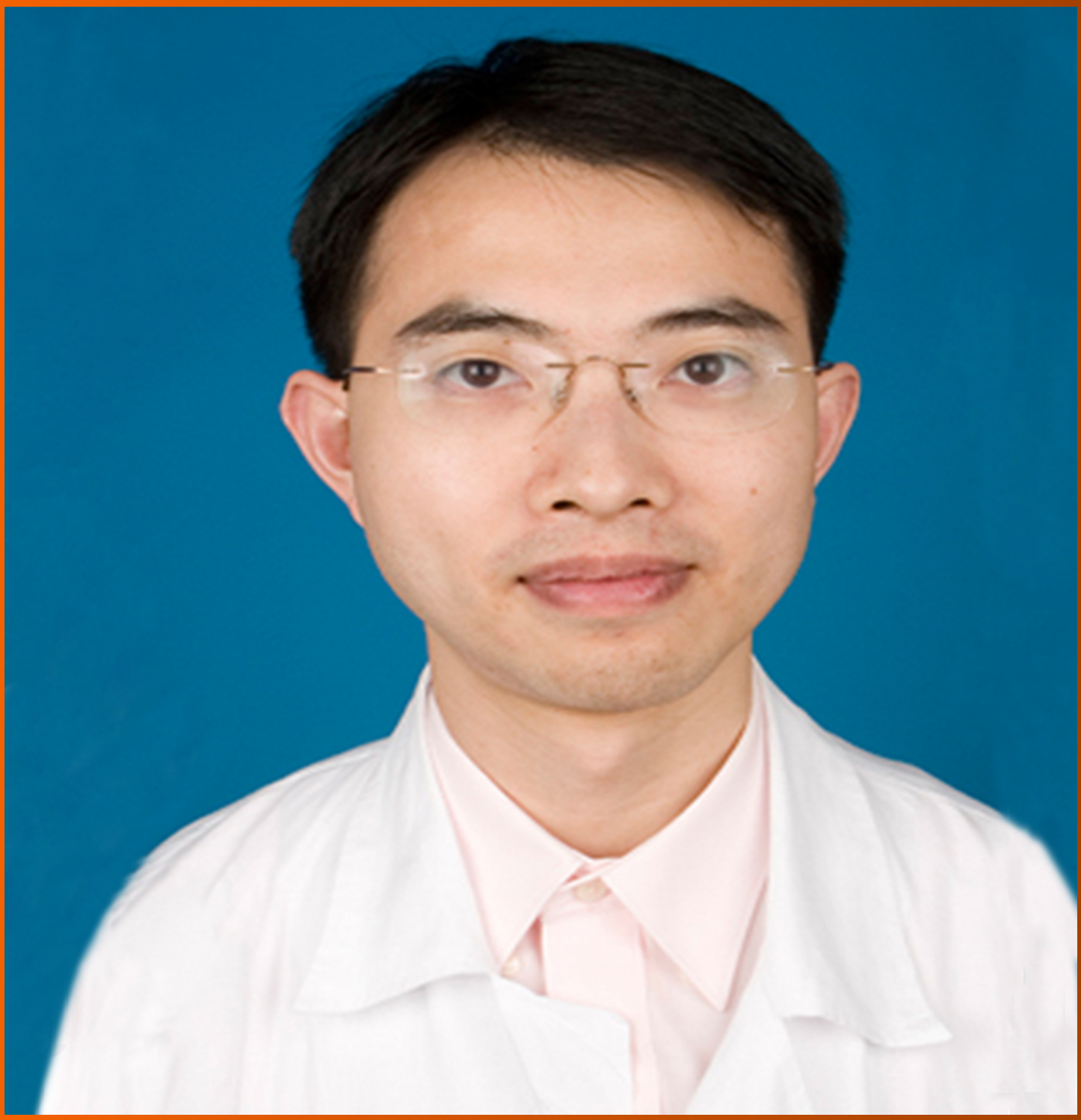

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WJT mainly publishes articles reporting research results obtained in the field of transplantation and covering a wide range of topics including bone marrow transplantation, bone transplantation, bone-patellar tendon-bone grafting, brain tissue transplantation, corneal transplantation, descemet stripping endothelial keratoplasty, fetal tissue transplantation, heart transplantation, kidney transplantation, liver transplantation, lung transplantation, pancreas transplantation, skin transplantation, transplantation immunology, and vascularized composite allotransplantation.

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REVIEW

Review of abdominal solid organ transplantation in Jehovah's Witness patients

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Abstract

Managing blood loss in Jehovah's Witness (JW) patients is a matter of controversy. These patients will not accept transfusions of red blood cells, white blood cells, platelets or plasma, even if that is required to save their lives. There are many discussions regarding safety of operating upon JW patients in general surgical procedures, but in solid organ transplantation there is a paucity of literature on this subject. We have reviewed individual case reports and small series documenting on experience with solid organ transplantation in JW patients and the strategies adopted to facilitate that. It is clear that such patients require the surgical team to dedicate more time to ensure their safe management. This begins with a thorough, detailed consent of exactly which products and interventions they will or will not accept. Planning must begin weeks before surgery if possible. Each case must be assessed individually, but provided they meet fitness requirements, there are no absolute contraindications to abdominal organ transplantation.

Key words: Anaemia; Blood transfusion; Informed consent; Jehovah's Witness; Transplantation

Core tip: There is a fairly limited global experience in solid organ transplantation in Jehovah's Witness patients. We have reviewed and consolidated the literature available in addition to reviewing blood products administration in Jehovah's Witness patients undergoing solid organ transplantation. We have also highlighted the complexity of the consent and pre-operative planning involved prior to solid organ transplantation in these patients.

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INTRODUCTION

Due to the doctrines of their faith, Jehovah's Witness (JW) patients will not accept transfusions of red blood cells, white blood cells, platelets or plasma, even if that is required to save their lives. This belief originates from a few biblical quotations, the most pertinent being, "You are to abstain from food sacrificed to idols, from blood, from the meat of strangled animals, and from sexual immorality"[1]. In addition to not accepting the four main constituents of blood, decisions on other fractions of blood are a matter of personal choice dependent on their conscience. Critical to their adherence to this is their belief in apocalypticism, whereby armageddon is imminent. Thus, according to the Watch Tower publication, blood transfusions "may result in the immediate and very temporary prolongation of life, but at the cost of eternal life for a dedicated Christian"[2].

The limitations on transfusion, understandably lead to apprehension in performing complex surgical procedures in JW patients, as it would inherently carry an increased risk. It is therefore essential that patients are adequately assessed pre-operatively, any strategies for optimisation of haemoglobin are adopted, and a thorough discussion is undertaken with the patient to determine exactly what blood products and blood conservation technologies they will accept (Table 1). There are individual case reports and small series published on experience with solid organ transplantation in JW patients and the strategies adopted to facilitate that.

PRE-OPERATIVE ASSESSMENT AND OPTIMISATION

JW patients, who undergo major abdominal surgery such as solid organ transplantation without a blood transfusion, are likely to suffer a period of transient anaemia, which could potentially be profound depending on surgical blood loss. A patient's fitness to withstand this should be assessed pre-operatively, in particular with regards to cardio-respiratory reserve. One option would be to perform cardiopulmonary exercise testing or a cardiac stress test. Provided they are assessed to be fit enough to withstand transient severe anaemia, one must also ensure that the patient's haemoglobin is at an adequate level pre-operatively. Certainly, operating on JW patients who are already anaemic should be avoided except in emergency situations.

Standard options utilised in other areas of medicine to increase haemoglobin concentration can be adopted pre-operatively, but will often take several weeks to have their full effect. These include recombinant human erythropoietin (RhEpo), iron, B12 and folic acid. The use of RhEpo is particularly useful although patients must be aware of the risks associated with infusion, including the risk of sudden death due to anaphylaxis[3]. Also, some formulations of RhEpo are suspended in human albumin, and therefore this should be specifically discussed with JW patients. Iron can be supplemented orally or intravenously (IV), although IV infusion is associated with relatively high rates of anaphylaxis and hypersensitivity reactions[4]. Vitamin B12 and folic acid supplementation provide a more subtle increase in haemoglobin, but are useful adjuncts.

PLASMA DERIVATIVES

Cryoprecipitate

Standard cryoprecipitate supplied by National Health Service Blood and Transplant contains Factor VIII: C, von Willebrand Factor, fibrinogen, Factor XIII and fibronectin and is produced by further processing of fresh frozen plasma (FFP)[5]. As such, it provides a multi-modal approach as a rescue therapy to minimise or control bleeding. The most common uses for cryoprecipitate are disseminated intravascular coagulation (DIC), liver disease or other causes of hypofibrinogenaemia. It has been used in JW patients undergoing cardiac surgery but not solely, making it difficult to appraise its

Table 1 Acceptability of different products by Jehovah's Witnesses

Generally not acceptable	May be acceptable	Generally acceptable
Red cells	Red cell substitutes	Crystalloids and colloids
	Haemoglobin (human, animal, or synthetic)	
White cells	White cell substitutes	Recombinant erythropoietin
	Interferons or interleukins	
Plasma	Plasma substitutes	Recombinant factor VIIa
	Albumin	
	Immunoglobulins	
	Cryoprecipitate	
	Clotting factors	
Platelets	Platelet substitutes	Artificial blood substitutes
	Platelet factor 4:	
	Acute hypervolaemic haemodilution	
	Intraoperative cell salvage[1]	
	Cardiopulmonary bypass or extracorporeal membrane oxygenation[1]	
	Renal dialysis[1]	
	Plasmapheresis	
	Epidural blood patch	
	Transplants	
	Topical biological haemostatic agents	

[1]Provided it is a closed circuit.

individual effect[6]. It is not appropriate to use cryoprecipitate in prophylaxis of bleeding if the patient is not depleted in coagulation factors.

Fibrinogen concentrate

Fibrinogen concentrate is produced from pooled human plasma. It is used primarily in cases of congenital hypofibrinogenaemia but is also used for treatment of bleeding when there is an acquired deficiency such us in liver failure or DIC. It has advantages over FFP and cryoprecipitate for replacement of fibrinogen in that it is stored as a powder, with a standard dose, at room temperature. This can quickly be reconstituted in small volumes and does not require ABO cross matching. Furthermore, during manufacture, viral inactivation steps are commonly carried out. These characteristics allow more accurate dose administration and reduce risk of fluid overload, transfusion related acute lung injury and risk of viral infection when compared to FFP and cryoprecipitate. An observational study found it to be as efficacious as cryoprecipitate in massive obstetric haemorrhage[7]. Additionally, it is also associated with a significant reduction in red cell loss, FFP and platelet administration[8]. Its highly refined manufacturing process may make it more acceptable to JW patients (it can be used to treat dilutional coagulopathy when high volumes of crystalloids/colloids are used to restore circulating volumes).

Coagulation factors

Coagulation factor replacement therapy may be in the form of single factor concentrates or prothrombin complex concentrates (PCC). PCC will be discussed below. Single factor concentrates may be either plasma derived or produced through recombinant DNA techniques. Factors VII, VII, IX and XIII are used most commonly to treat patients with haemophilia or other inherited coagulation factor deficiencies. Plasma derived factor concentrates are produced from pooled plasma by chromatography and undergo viral reduction. As they originate from human blood, they are not accepted by all JW patients, but this is left to personal decision. More recently, coagulation factors have been produced using recombinant DNA techniques, and these have been more widely accepted by JW patients.

Due to the reduction of coagulation factors through large volume blood loss, there is a role for their replacement in the bleeding patient. Factor XIII, for example, may be administered to improve clot stability. Prophylactic use of factor IX concentrate has been described for use in the JW patients undergoing complex cardiothoracic surgery in combination with other therapies such as acute normovolaemic haemodilution[9]. Use of recombinant factor VIIa has been reported in JW patients receiving liver

transplantation, and studies have shown it to be beneficial in controlling bleeding during surgery or trauma[9,10].

Prothrombin complex concentrates

PCC contain a mixture of vitamin K dependent proteins. They are produced through further refinement of cryoprecipitate following the removal of anti-thrombin and factor XI. PCC can be found in three factor (II, IX and X) and four factor (II, VII, IX and X) concentrates. Originally developed for treatment of haemophilia, it is now most commonly used to reverse warfarin. PCC may be used to treat dilutional coagulopathy resulting from use of crystalloids to maintain circulating volume following massive blood loss. Like fibrinogen concentrate, the refinement process of PCC may make it more acceptable to JW patients; it can be kept in the pharmacy rather than blood bank. It has shown to be effective along with cryoprecipitate in cardiac surgery[6] .

The main risks associated with the use of PCC are increased incidence of thrombotic events such as stroke, myocardial infarction and pulmonary embolism. These risks, however, are low and reduced further by the inclusion of therapeutically effective levels of protein S and C as well as the reduction in the use of activated coagulation factors. Unlike FFP, PCC is not associated with the risk of transfusion related acute lung injury as antibodies associated with this are removed during its production.

Intravenous immunoglobulins (Anti-D)

IV immunoglobulins (IVIg) are derived from plasma pools of thousands of screened donors and are highly refined through use of cold alcohol fractionation and ion exchange chromatography. They are used in the treatment of primary and secondary immune deficiencies as well as autoimmune inflammatory conditions. The use of anti-hepatitis B hyperimmunoglobulin became standard practice in the 1990s to reduce recurrence of hepatitis B in liver transplant patients[11]. Increasing numbers of studies have shown improved survival rates and reduced levels of graft dysfunction and rejection in patients receiving IVIg[12]. These benefits are thought to be due to more than simply the clearing of pathogenic antibodies. Although not completely understood, it is believed that IVIg provides a combination of immune-supporting and immuno-suppressive properties.

Amongst these immune-modulatory properties, IVIg has been seen to reduce circulating levels of pro-inflammatory cytokines, such as tumour necrosis factor, whilst upregulating anti-inflammatory cytokines, for example interleukin 11. It has also been found to interfere with the maturation and differentiation of dendritic cells, which are associated in the pathogenesis of allograft rejection[11,12]. IVIg have been included in protocols to desensitize patients prior to ABO incompatible transplants to be performed. Studies looking at this approach have been small, but evidence available indicates significant improvement in outcome with use of IVIg in ABO incompatible liver transplant[13].

DRUGS

Aprotinin

Aprotinin is an anti-fibrinolytic molecule that has been used to reduce bleeding in major surgery. Its usage was fairly widespread in liver and heart surgery prior to a study demonstrating increased mortality[13]. Following this, its distribution was temporarily suspended, but the European Medicines Agency recommended lifting this suspension in 2012[14]. Dosage described for use in JW patients for prevention of excessive blood loss is 2000000 KIU, followed by 500000 KIU/h[15].

Tranexamic acid

Tranexamic acid is a synthetic analogue of lysine and has anti-fibrinolytic actions. Some areas of medicine have adopted fairly widespread use of tranexamic acid, including trauma and obstetrics. There are case reports on the use of tranexamic acid specifically in JW patients in combination with other strategies[16-20].

Desmopressin

Desmopressin is a synthetic replacement for vasopressin. It has a variety of uses, but in the case of JW patients is useful as it stimulates the release of von Willebrand Factor, and has been used to facilitate major surgery in JW patients[21]. However, caution should be used to avoid significant systemic hypotension[22].

Red cell substitutes

No red-cell substitute is yet available for widespread clinical use, although some perfluorocarbons have been used in trials. Blood substitutes may be derived from human haemoglobin, in which case JW patients may not accept them.

TOPICAL BIOLOGICAL HAEMOSTATIC AGENTS

A variety of topical preparations are available on the market to stop or minimise bleeding intra-operatively. These often contain human plasma derivatives, which should be discussed with the patient.

Cellulose pads

Cellulose-based agents are formed into mesh, gauze or sponges. In the presence of blood, it forms a gelatinous mass similar to a synthetic clot, helpful for haemostasis. An example is Kaltostat (ConvaTec, Greensboro NC, United States), which also has antimicrobial properties.

Fibrin glues and sealants (Tisseel)

These are often available in pre-filled syringes or vials for mixing. They are effective either over a broad surface such as a cut liver or a specific bleeding point. Tisseel (Baxter Healthcare, Deerfield IL, United States) consists of two components – a sealer containing human fibrinogen and a synthetic anti-fibrinolytic (aprotinin) and a human thrombin solution.

Collagen

Sponge matrices embedded with human fibrinogen and/or thrombin, such as Vitagel (Stryker, Kalamazoo MI, United States) are also available. In addition to the active biological component, they promote platelet aggregation and provide a framework for thrombus formation. This is particularly effective if the patient is on antiplatelet therapy.

BLOOD CONSERVATION TECHNOLOGIES

Most JW patients feel that the external tubing of a cardiopulmonary bypass circuit, dialysis tubing or cell salvage equipment is an extension of their own circulation, as long as an unbroken circuit is maintained.

Cell salvage

Cell salvage is generally acceptable to JW patients, although again should be explicitly discussed pre-operatively. A small number of JW patients will only accept cell salvage if continuous auto-transfusion is performed and will not accept batched preparation for transfusion. However, most feel that so long as a continuous circuit is maintained, batched preparation is acceptable. A number of machines are available for cell salvage (*e.g.*, Haemonetics Cell Saver, Munich, Germany), although to our knowledge only the CATS machine by Fresenius AG (Bad Homburg, Germany) provides continuous auto-transfusion.

There are some limitations to the use of cell salvage, such as the presence of malignant or infective sources. If either of these are present, then auto-transfusion into the systemic circulation may well be detrimental to the patient. In small bowel or pancreas transplantation, cell salvage should be stopped at the time that the small bowel is opened. If liver transplantation is being performed for hepatocellular carcinoma, one could argue against its usage, but a balanced approach to the risks is required.

Acute normovolaemic haemodilution

This is a blood conservation strategy employed by anaesthetists at the time of surgery, whereby between one and three units of whole blood are drained from the patient in the anaesthetic room, and an equal volume of crystalloid or colloid is replaced into their circulation. These units of whole blood can then be transfused to the patient during or after surgery. However, most JW patients will only accept this if the bags of blood and tubing remain connected at all times (closed circuit)[23]. This is particularly useful in patients with a high pre-operative haemoglobin.

ALTERNATIVE STRATEGIES

Whole-body cooling has previously been performed to reduce oxygen consumption and thereby allow permissive anaemia. However, this is no longer recommended due to other detrimental effects, including coagulopathy, impaired wound healing and increased wound infection rates[24]. Hypotensive anaesthesia has been shown to reduce blood loss in major surgery[25]; however, its use remains controversial. Hyperbaric oxygen has been utilised on a few occasions as a rescue therapy in extreme anaemia to reverse tissue hypoxaemia[26,27]. However, there are obvious logistical limitations to this.

CONSENT

Although some doctrines are fixed within the JW faith, some beliefs relevant to blood products are more variable from person to person. It is therefore essential to take the time to have a detailed, frank discussion with the patient about their beliefs. Ideally, a specific standardised consent form should be utilised for JW patients undergoing surgery, in which they must declare whether they will accept or decline each of the blood products or interventions detailed above. This consent process should be performed in the presence of an independent witness, and the patient may wish to discuss the issues with the Elders of the Witness community or consult the JW Hospital Liaison Committee, who often provide a useful intermediary role. No assumptions should be made, and it is important to ask candidly whether they will truly wish to decline a blood transfusion even if it costs their life. Eventualities should be discussed, in the event that they later need further procedures or interventions and are not fit to consent (*e.g.*, renal dialysis whilst unconscious).

PUBLISHED EXPERIENCE

Liver transplantation

A number of case reports and series have been published demonstrating experience in liver transplantation in JW patients. The first published case of successful liver transplantation in a JW patient without the use of blood products was in 1996[28]. The added complication in liver transplantation is the fact that many patients requiring a transplant may be coagulopathic, have portal hypertension or thrombocytopaenia.

Jabbour *et al*[29] published the largest series of liver transplantation in JW patients, with 27 transplants over a 5-year period. Pre-operative management included RhEpo, iron and folic acid for blood augmentation. Intra-operatively, cell salvage was used in all patients, and all living donor recipients had also had acute normovolaemic haemodilution. They reported two deaths, one from primary non-function, and the second died from severe anaemia and coagulopathy[29]. Another series included nine patients in Liege, Belgium, where cell salvage and high-dose aprotinin were used. Two patients required transfusion, one with permission from the family, and the other (6-year-old child) against the family's wishes. There is also a published series of 4 patients in Brazil[30] and 2 in Australia[31].

Living related liver transplantation has also been performed where donor and recipient were both JW. In one such case, splenic embolisation, RhEpo, iron, cell salvage and aprotinin were used[32]. In another case, the recipient hepatectomy was performed in two stages due to a hypertrophied, enlarged left lobe of the liver, which was excised 2 wk after receiving the liver transplant[33]. Jabbour *et al*[34] also published a series of eight successful liver transplants in JW patients, all with RhEpo, cell salvage and acute normovolaemic haemodilution.

Splenic embolisation may also be utilised to control hypersplenism and portal blood flow in an effort to improve thrombocytopaenia and minimise operative blood loss[35]. Some centres have also reported that strategies to avoid blood transfusions in JW patients has had a positive impact by reducing overall blood use in non-JW patients undergoing liver transplantation as well[36].

Pancreas transplantation

Decisions to proceed to pancreas transplantation may be more complex than liver transplantation as the original condition will often be less imminently life threatening, therefore the surgical risks involved may not be outweighed by the benefit. There is also the option of islet transplantation, which may be performed by open rather than percutaneous approach to minimise the risk of bleeding.

There are two series published in the literature. Boggi *et al*[37] performed six

simultaneous pancreas and kidney transplants. All patients recovered, however, one was readmitted with unexplained anaemia and became haemodynamically unstable. This patient received a blood transfusion. A second series of five patients is also published with successful outcomes[38]. Both centres used pre-operative RhEpo, iron and B12 as well as cell salvage.

Kidney transplantation

Surgical blood loss tends to be less problematic in kidney transplantation compared with liver and pancreas, as such the operative risks to JW patients are likely to be less. Published experience in renal transplantation in JW patients dates back to the 1980s. Kaufman *et al*[39] published an early series demonstrating comparable outcomes in JW patients, although there were two deaths due to a combination of severe anaemia and early rejection episodes. More recently, a case of successful human leukocyte antigen-incompatible living donor kidney transplantation has been reported[40], where cryoprecipitate was required due to fibrinogen depletion following four sessions of pre-operative plasma exchange.

CONCLUSION

The global experience in abdominal solid organ transplantation in JW patients remains fairly limited, although some case series have been published for each organ. It is clear that such patients require the surgical team to dedicate more time to ensure their safe management. This begins with a thorough, detailed consent of exactly which products and interventions they will or will not accept. Based on this, planning must begin weeks before surgery if possible. Their cardiopulmonary fitness must be assessed in context of being able to withstand severe anaemia. Preconditioning the patient with RhEpo, iron, B12 and folic acid optimises their condition for the time of surgery. Interventions such as acute normovolaemic haemodilution and cell salvage should be utilised to minimise the effective surgical blood loss. Each case must be assessed individually, but provided they meet fitness requirements, there are no absolute contraindications to abdominal organ transplantation.

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REVIEW

Therapeutic apheresis in kidney transplantation: An updated review

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Abstract

Therapeutic apheresis is a cornerstone of therapy for several conditions in transplantation medicine and is available in different technical variants. In the setting of kidney transplantation, immunological barriers such as ABO blood group incompatibility and preformed donor-specific antibodies can complicate the outcome of deceased- or living- donor transplantation. Postoperatively, additional problems such as antibody-mediated rejection and a recurrence of primary focal segmental glomerulosclerosis can limit therapeutic success and decrease graft survival. Therapeutic apheresis techniques find application in these issues by separating and selectively removing exchanging or modifying pathogenic material from the patient by an extracorporeal aphaeresis system. The purpose of this review is to describe the available techniques of therapeutic aphaeresis with their specific advantages and disadvantages and examine the evidence supporting the application of therapeutic aphaeresis as an adjunctive therapeutic option to immunosuppressive agents in protocols before and after kidney transplantation.

Key words: Kidney transplantation; Therapeutic plasma exchange; Double-filtration plasmapheresis; Immunoadsorption; Extracorporeal photopheresis; Desensitization; Antibody-mediated rejection; Focal segmental glomerulosclerosis

Core tip: Kidney transplantation is the treatment of choice for patients with end-stage renal disease. However, pre-transplant immunological barriers and post-transplant clinical conditions still influence negatively graft and patient's survival. Therapeutic aphaeresis can be applied in many of these conditions using a variety of devices and procedural approaches. This topic review will present a critical evaluation of the available modalities and examine the evidence supporting the application of therapeutic

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aphaeresis in kidney transplantation as an adjunctive therapeutic option in protocols both for pre-operative procedures and during the post-transplant period.

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INTRODUCTION

Therapeutic apheresis (TA), from the Greek αφαιρώ, *i.e.*, remove, is a therapeutic method by which pathogenic blood components such as cells, harmful antibodies and inflammatory mediators causing morbidity, are separated and selectively removed, exchanged or modified by an extracorporeal apheresis system. The clinical applications of TA include renal diseases in native kidneys, metabolic diseases, autoimmune and rheumatic diseases, hematological diseases, neurological disorders, overdose and poisoning, and cover the field of solid organ transplantation[1].

TA techniques widely used in transplantation medicine, as an adjunctive therapeutic option include therapeutic plasma exchange (TPE) and selective TA techniques such as double-filtration plasmapheresis (DFPP), immunoadsorption (IA), and extracorporeal photopheresis (ECP)[1] (Table 1). In the specific field of kidney transplantation (KT), TA is principally employed as an adjunctive therapeutic option to immunosuppressive agents in protocols both for preoperative procedures and during the posttransplant period in the clinical conditions reported in Table 2.

The objectives of this review are the description of technical characteristics, mechanisms of action, advantages, disadvantages, and complications of the TA techniques used in KT, and the rationale examination and evidence supporting the application of TA in treating clinical conditions in KT through the presentation of the current therapeutic protocols.

THERAPEUTIC PLASMA EXCHANGE

Mechanisms of action

TPE, through the removal and replacement of plasma, removes high-molecular-mass pathological substances (> 15000 Da) such as pathogenic antibodies, immune complexes, paraproteins, cytokines and adhesion molecules, and exogenous poisons[2]. In some clinical conditions such as in thrombotic thrombocytopenic purpura (TTP), replacement with normal plasma is indicated to supply the deficient or missing plasma components[2].

However, evidence suggests that TPE also has immunomodulatory effects also. TPE has been associated with a variety of autoimmune diseases with a decline in B cells and natural killer (NK) cells, an increase in T cells, an increase in T suppressor cell function, and an increase in regulatory T cells (Tregs)[3-6]. The immunomodulatory effects of TPE determine an increased susceptibility of cell-mediated and humoral immunity to immunosuppressive agents, and numerous therapeutic protocols integrate the administration of these agents with TPE to enhance their immunosuppressive effects.

The influence of TPE on the Th1/Th2 cytokine-producing-cell balance is controversial. Some studies suggest that TPE induces a shift of the Th1/Th2 balance in favor of Th2 differentiation and the suppression of the Th1 cytokines (IFN-γ and IL-2)[7,8] which evoke cell-mediated immunity and phagocyte-dependent inflammation[9]. Conversely, other studies indicate that TPE is associated with a shift in cytokine-producing peripheral blood lymphocytes from a Th2 dominant pattern (IL-4, IL-6, IL-10), primarily involved in the humoral immune response, to a Th1 predominance[10,11]. Accordingly, further studies are required to elucidate whether TPE contributes to the shift of Th1/Th2 balance and in what way.

Techniques of plasma removal: Centrifugation- vs filtration-based devices

TPE can be achieved by employing centrifugation- or filtration-based devices. Centrifugal TPE (cTPE) is an automated system designed to separate plasma from whole blood utilizing centrifugal force as the basis of operation[2,12]. During treatment,

Table 1 Therapeutic apheresis techniques performed in the setting of kidney transplantation

TPE
cTPE
mTPE
Selective therapeutic apheresis techniques
DFPP
IA
IA using immobilized antibodies
IA using immobilized staphylococcal protein A
IA using immobilized antigens and synthetic epitopes
ECP

TPE: Therapeutic plasma exchange; cTPE: Centrifugal therapeutic plasma exchange; mTPE: Membrane therapeutic plasma exchange; DFPP: Double filtration plasmapheresis; IA: Immunoadsorption; ECP: Extracorporeal photopheresis.

blood is withdrawn from the patient and pumped through an extracorporeal circuit into a rapidly rotating centrifuge chamber, enabling a nonselective plasma separation and removal based on the density of the individual blood substances. The rest of the blood elements returns to the patient by intermittent or continuous flow mixed with a replacement fluid (RF), typically albumin or fresh frozen plasma (FFP), which is required to avoid hypotension[2,12].

Conventional membrane TPE (mTPE) uses highly permeable membranes, with pore sizes of 0.2-0.6 μm diameter, sufficient to separate plasma notselectively from the cellular blood components based on molecular size[13]. The choice of RF depends essentially on the indication for TPE and patient clinical parameters, and does not differ between cTPE and mTPE[13]. A head-to-head comparison of cTPE and mTPE provides a comparable treatment quality[14]. However, mTPE devices are less effective at removing higher-molecular-mass proteins such as IgM and immune complexes[15].

Plasma removal efficiency (PRE; the percentage of plasma removed *vs* plasma processed) is much higher with cTPE than with mTPE. For each 1-1.5 plasma volume exchanged or 2.5-4.0 L, during a session, almost 60%-70% of the original plasma components will be removed with a cTPE device[16]. When the procedure is extended beyond 1.5 plasma volumes, the amount of the removed plasma components decreases as large-molecular-mass substances are slowly equilibrated between their extra vascular and intravascular distribution[16]. In mTPE, to avoid filter clotting and to prevent hemolysis due to high transmembrane pressure (TMP), the PRE is limited to 30%-35%[13]. A consequence of this disparity in PRE is that mTPE devices need to process three or four times the patient's blood volume to obtain an equivalent reduction in the target molecule[17]. As a result, procedure times lead to be longer and/or require higher blood flow rates (BFRs) on mTPE devices.

Choice of vascular access: To achieve higher BFRs, mTPE devices are almost all in need of a central venous catheter (CVC) that is able to maintain BFRs typically in the 150-200 mL/min range, while the lower BFR needed for a cTPE device (50 mL/min) can often be achieved through 17 gauge peripheral vein needles[17,18]. Recently, an update of the World Apheresis Association (WAA) registry data showed more severe adverse events (AEs) in the procedures performed with a CVC[19]. Common severe AEs of CVCs include central-line-associated bloodstream infections (CLABSIs), deep vein thrombosis (DVT), and arterial or venous bleeding[13,19]. Nevertheless, mTPE with a CVC vascular access is the preferred technique in patients with renal failure who require hemodialysis and TPE as they can receive both treatments sequentially using the same dialysis machine.

Choice of anticoagulation: cTPE commonly uses regional citrate anticoagulation (RCA), which binds ionized calcium, a necessary cofactor in the coagulation cascade, to prevent clotting. Bleeding disorders are not common with RCA. However, citrate utilization is often complicated with systemic hypocalcemia (60%-70% of the overall complications during cTPE) resulting from intravascular citrate accumulation potentially leading to severe complications ranging from perioral and/or acral paresthesias to frank tetany and a QT prolongation of the electrocardiogram (ECG) with life-threatening arrhythmia requiring intravenous calcium replacement, often continuous infusion, with the return fluid[19-21]. Hypocalcemia can be further exacerbated if the replacement fluid is FFP, which contains up to 14% citrate by

Table 2 Clinical indications for therapeutic apheresis in kidney transplantation

Desensitization in ABO-i kidney transplantation
Desensitization in patients with preformed HLA-antibodies
Desensitization of deceased donor kidney transplant recipients
Desensitization of living donor kidney transplant recipients
AMR
Recurrence of primary FSGS
Prevention of recurrence and recurrence of complement-mediated aHUS
De novo TMA
Antiphospholipid syndrome and systemic lupus erythematosus
Recurrent and *de novo* anti-GBM disease
Recurrence of ANCA- AAVs

ABOi: ABO incompatible; HLA: Human leukocyte antigens; AMR: Antibody-mediated rejection; FSGS: Focal segmental glomerulosclerosis; aHUS: Atypical haemolytic uremic syndrome; TMA: Thrombotic microangiopathy; GBM: Glomerular basement membrane; ANCA: Antineutrophil cytoplasmic antibody; AAVs: ANCA associated vasculitis.

volume[12,13].

In mTPE, systemic anticoagulation with unfractionated heparin (UFH) is routinely used to maintain circuit patency, while citrate is not preferred because the higher BFRs, as well as the lower PRE, lead to a greater fraction of citrate being returned to the patient[13]. During TPE, antithrombin III (AT III) levels decrease significantly, and heparin itself is filtered with a sieving coefficient (SC) of 1. As a consequence, in comparison to hemodialysis, in mTPE, higher doses of heparin may be required to achieve a clot-free circuit that in association with the bulk removal of plasma, which also involves the nonselective removal of clotting factors, results in a higher risk for bleeding[13]. The risk of heparin-induced thrombocytopenia (HIT) type II is less frequent with low molecular weight heparin (LMWH) in comparison to UFH[18].

Additional differences between cTPE and mTPE are the increased risk of platelet (PLT) loss in centrifugal devices and the potential activation of complement and leukocytes on the artificial membrane described for mTPE[22,23].

SELECTIVE TA TECHNIQUES

Over time, selective TA techniques have been developed to avoid the removal of key plasma constituents that occur with conventional TPE by targeting a specific molecule, antibody, or cellular element[24]. Below, we focus on selective TA techniques that find application in transplantation medicine.

Double filtration plasmapheresis

Double-filtration plasmapheresis (DFPP), or cascade filtration plasmapheresis, is a variation of mTPE, introduced in Japan by Agishi *et al*[25] in the 1980s, for desensitization in ABO-i KT, and over time it has been used for other indications. The circuit contains two plasma filters with different pore sizes, a primary membrane plasma separator to isolate the plasma, and then the plasma fractionator (PF), which is a high molecular-mass filter that removes target macromolecules based on molecular size and mass, primarily immunoglobulins (Ig)[23-25]. The advantage of DFPP is that the PF allows smaller molecules, such as albumin, to pass through the membrane and return to the patient. This results to minimize, or potentially eliminate, the need for an RF and the associated complications, including allergic reaction and infection[23-25]. A disadvantage of DFPP is that the performance of the PF is not sufficient to remove small-molecular-mass IgG and substances smaller than albumin[23-25].

Immunoadsorption

Immunoadsorption (IA) is a TA technique that enables the selective removal of humoral factors from separated plasma through a secondary device with high-affinity absorbers. The adsorption columns contain a specific ligand for the substance to be removed, and the depleted plasma is then returned to the patient[24]. An advantage of IA is that RF is not required because the plasma volume remains the same and albumin is not adsorbed. Over time, different IA devices have been developed.

IA using immobilized antibodies: IA columns containing immobilized antibodies

selectively bind a circulating molecule and remove it from the plasma[24]. A Thera-Sorb™-Ig adsorber column, containing polyclonal sheep anti-human IgG antibodies immobilized on sepharose, has been shown to be effective in depleting all subclasses of IgG and has been used in ABO-i KT[26]. IA using bound antibodies can also be applied for the depletion of preformed or newly synthesized cytotoxic antibodies in the rejection of allogeneic organ transplants[24]. These columns are utilized in pairs, one working while the other is being regenerated with washing fluids, shifting periodically during the procedure. The online regeneration of the columns enables large volumes of plasma to be treated so that IgG extraction more efficient[24]. Usually, up to two plasma volumes are processed during an Ig apheresis treatment.

IA using immobilized staphylococcal protein A: IA columns containing immobilized staphylococcal protein A (SPA), which has a high avidity for the Fc portions of IgG1, IgG2, and IgG4, have been used to deplete IgG auto antibodies or circulating immune complexes that contain IgG[24]. Furthermore, SPA has been shown to be a B-cell super antigen[27]. The interaction of SPA with peripheral B cells, expressing B cell receptors (BCRs) with VH regions capable of binding SPA, induces B cell apoptosis through the dissipation of mitochondrial membrane potential, the induction of the caspase pathway, and DNA fragmentation[27]. Thus, the exposure of the patient's blood to SPA during IA may also trigger a beneficial immunosuppressive effect. The Immunosorba column, containing SPA bound to sepharose, has been used in acute AMR in KT and in highly sensitized patients waiting for KT[28-31]. During a treatment, two absorbers work alternately. While one is adsorbing, the other is regenerated through the elution of bound antibodies, and vice versa.

IA using immobilized antigens and synthetic epitopes: IA columns containing immobilized antigens and synthetic epitopes are the most specific way to remove Ig as these columns are developed to extract only the antibodies that are reactive with that specific antigen, leaving untouched all other plasma components[24].

The Globaffin column is a regenerative twin adsorber system that utilizes the synthetic peptide GAM which covalently binds to an insoluble sepharose carrier matrix. Peptide GAM has a strong binding affinity, especially to the constant (Fc) section of subclass 1, 2 and 4 IgG antibodies, and finds clinical application in different conditions, including acute AMR and perioperative Ig depletion, in sensitized renal transplant recipients[32].

The glycosorb ABO column contains synthetic terminal trisaccharide A/B blood group antigens covalently linked to a sepharose matrix and has been developed to remove A or anti-B antibodies in recipients of organ transplants from ABO-i donors[33]. However, in a minority of patients, antibody elimination has been demonstrated to be incomplete with the glycosorb ABO column[34]. The inadequate adsorption of core-chain-dependent A/B antibodies may explain this finding[35], but further studies are needed.

ECP

ECP is a cell therapy procedure that begins with the separation of peripheral white blood cells (WBCs) and nonnucleated cells from plasma by centrifugation. Then, the isolated suspension of WBCs undergoes extracorporeal treatment with 8-methoxypsoralen (8-MOP) followed by exposure to ultraviolet A (UVA) light prior to reinfusion in the patient[36]. The combination of 8-MOP and UVA results in the cross-linking of pyrimidine bases in DNA, leading to the apoptosis of lymphoid cells, largely T-cells and natural killer (NK) cells[37]. Upon reinfusion, the phagocytosis of apoptotic lymphoid cells is performed by immature dendritic antigen-presenting cells (iDCs), which subsequently undergo maturation and present self-antigens in a pro-tolerant signaling environment[38]. The activated T cells differentiate into several cell lineages, particularly Tregs, which mediate a specific immunological tolerance by inducing anergy or apoptosis in self-reactive lymphocytes[38].

ECP was initially used in patients with cutaneous T-cell lymphoma (CTCL)[39]. However, over the years, the indications for ECP have increased as it promotes anti-inflammatory and tolerogenic responses without causing global immuno-suppression[40]. In solid organ transplantation, ECP has been successfully used to treat acute heart allograft rejection and chronic allograft dysfunction after lung transplantation[41,42]. In addition, ECP was also used as a part of calcineurin inhibitor (CNI) sparing protocols to reduce drug side effects such as nephrotoxicity, and neurological or infectious complications[43].

In KT, there are only a few reports available on the use of ECP in recurrent or refractory acute rejection after the failure of standard immunosuppression and in antibody-mediated chronic rejection (AMCR), but they have encouraging preliminary results[44]. Finally, ECP was also employed as a preventive treatment in a small case

series with a favorable outcome: Rejection did not occur in any of the treated patients, and the authors described a notable increase in circulating Tregs[45].

INDICATIONS FOR TA IN KT

Desensitization in ABO-incompatible KT

ABO blood group incompatibility is the first and most significant immunological barrier to a successful transplantation and for a long time has been a contraindication to KT. Hyper acute rejection or AMR in nondesensitized ABO-incompatible (ABO-i) KTs occurs due to the presence of circulating preformed antibodies against the blood group antigens A and B (isohemagglutinins), which are strongly exposed on the surface of endothelial cells and kidney parenchymal cells[46]. However, ABO-i KT was first attempted in the 1970s using A2 donors for recipients of blood groups O and B with only regular immunosuppression[47]. This was possible because, compared to blood group A1 and blood group B individuals, the A2 antigen is less reactive with isohemagglutinins and is expressed in lower amounts on the surface of red blood cells and tissue cells[48]. As experience increased, it became clear that low initial anti-A2 antibody titers in the recipient (IgG ≤ 1:2) were a requirement for the transplantations to be successful from an ABO A2 donor, significantly restricting the number of possible candidates[48-51].

To overcome the ABO barrier in KT and to increase donor pools, specific desensitization protocols have been refined to achieve a depletion of preformed antiA and/or antiB antibodies and the modulation of Bcell immunity[52]. In this context, the use of TA techniques represents a cornerstone of current desensitization protocols.

In the early days of ABO-i KT, Alexandre *et al*[53] introduced an effective desensitization protocol based on plasmapheresis and splenectomy. Subsequently, splenectomy was progressively replaced by the anti-CD20 antibody rituximab (RTX) due to the surgical risk and increased risk of sepsis. Initially, RTX has been used in combination with DFPP and splenectomy in 2002[54], while the first report of the use of RTX instead splenectomy came from Karolinska University Hospital in 2003[55]. In this protocol, in combination with RTX and conventional immunosuppression (tacrolimus, mycophenolate mofetil, and prednisolone), antigen-specific IA with a Glycosorb ABO column on pretransplant days - 6, - 5, - 4, and - 1[55]. After transplantation, three more IA sessions were performed every third day. Moreover, if there was a significant increase in the antibody titers, more sessions were added[55].

In contrast to the Swedish protocol[55], Wilpert *et al*[56] adopted an on-demand strategy for postoperative IA. Instead of scheduling pre-emptive posttransplant IA, they submitted patients to IA if their antibody titers were higher than 1: 8 in the first postoperative week and higher than 1: 16 in the second postoperative week, without any additional risk for the patients[56].

Ishida *et al*[57], in a retrospective cohort of 191 ABO-i KT recipients without postoperative administration of any prophylactic treatment for rejection, found no correlation between levels of antibody rebound and the incidence of AMR, even with antibody titers higher than 1: 64. The authors concluded that no treatment is necessary for rebounded anti-A/B antibodies as there is an immunological accommodation for elevated titers[57]. In fact, immunological accommodation is established early (2 wk) after successful KT and could explain the resistance to AMR despite the rebound of anti-A/B antibodies in the recipient[58]. The exact mechanisms of accommodation remain to be elucidated, although several have been proposed[59]. Similar results have been reported by previous studies[34].

In contrast, a group from Johns Hopkins reported that the incidence of AMR was significantly higher in recipients with high postoperative titers (≥ 1:64), but the clinical significance was variable, as there was no consistent clinical correlation for AMR[60]. The authors hypothesized that postoperative TPE could be helpful in preventing the rebound of anti-A/B titers until tolerance or accommodation occurs[60].

Consequently, the utility of postoperative antibody monitoring and prophylactic apheresis appears unclear and controversial. The transplant community should conduct larger studies with sufficient statistical power and with uniform and validated antibody titer measurements to find appropriate answers to this delicate issue.

Currently, cTPE is the preferred antibody removal strategy in the United States; membrane separation use is widespread in Japan, while IA is frequently practiced in Europe because of its safety and efficacy[58].

In many protocols, the number of pretransplant apheresis sessions is scheduled according to baseline antiA/B antibody titers[61,62]. Typically, on the day of transplantation, the target for an antibody level is ≤ 1:8 regardless of the applied TA

because higher levels have been correlated with a higher incidence of AMR[63]. However, the choice of TA technique could also be scheduled according to baseline antibody titers. In fact, the Guy's Hospital ABO-i desensitization regimen introduced such a desensitization scheme tailored to initial antibody titers[64]. In patients with baseline titers of ≤ 1:8, apheresis treatment was omitted, while RTX was not applied in patients with titers < 1:16[64]. DFPP was used in those with titers between 1:16 and 1:64 and antigen-specific IA (glycosorb-ABO IA columns) was used in those with titers above 1:64[64]. The justification for the use of IA only for those patients with titers > 1:64 was that these patients were expected to require the highest number of sessions, and DFPP is notably correlated with a higher risk of bleeding[65]. Instead, DFPP was preferred in patients with titers between 1:16 and 1:64 because it is a less-expensive technique, and fewer cycles of antibody removal should not significantly alter coagulation parameters[64]. The exact number of apheresis sessions depended on the course of the titers[64]. In conclusion, tailoring the intensity of desensitization treatment according to individual immunological risk should be the recommended strategy.

Desensitization in patients with preformed HLA-antibodies

Preformed anti-HLA antibodies represent another major immunological barrier to a successful KT. Sensitization occurs when the transplant candidate develops immunological memory to the donor's antigens from prior transplants, blood transfusions, and pregnancies[66,67]. Approximately 30% of the KT candidates have detectable anti-HLA antibodies and approximately half of them are "highly" sensitized with HLA antibody reactivity to over 80% of potential donors (panel reactivity antibody ≥ 80%)[68].

KT with donor-specific anti-HLA antibodies (DSAs) at pretransplant is known as HLA-incompatible transplantation. After transplantation, DSAs in high amounts cause hyperacute rejection, while in small amounts they reduce the survival of the graft by causing acute AMR and/or chronic humoral rejection[69,70]. As such, highly sensitized candidates present difficulties in finding a cross-match-negative kidney, and waiting on the list for an acceptable match may be exhausted. According to Fuggle *et al*[71], sensitized candidates remain on the waiting list for a compatible donor kidney two to three times longer than nonsensitized KT candidates. The possibilities for the highly sensitized candidate that is waiting on the deceased-donor transplant list are higher after a desensitization protocol and even better in those with an available living donor. In this context, TA has a central role as an anti-humoral therapeutic strategy.

Desensitization of deceased donor kidney transplant recipients: Current desensitization protocols commonly use a combination of high-dose intravenous immunoglobulin (IVIG) and RTX to lower the titers of preformed HLA-antibodies in candidates on the waiting list and increase the chances of finding an acceptable deceased-donor[72]. Moreover, TA (TPE or IA), if performed while on the waiting list, has historically been shown to reduce the long waiting times in highly sensitized candidates[29,73,74]. Such strategies, however, are not always effective and may produce risks correlated with extended immunosuppression on dialysis.

Regarding the efficacy of HLA antibody reduction, in preventing hyperacute rejection, acute AMR and later transplant glomerulopathy, by peri-pretransplant TPE in deceased-donor KT (DDKT), the available data are limited[75-77]. Beimler *et al*[75] reported for the first time a successful DDKT in two cross-match-positive recipients with a single peri-pretransplant TPE session and RTX. Cold ischemic time (CIT) due to the therapeutic protocol was not prolonged because TPE was performed during the transport of the kidneys from the donor center to the transplant center. After desensitization, the cross match turned negative, and TPE sessions were extended during the posttransplant period until stable allograft function was achieved to avoid an early rebound of DSAs[75]. Both patients showed good graft outcomes two years after KT[75]. Using the same desensitization protocol, the same group reported excellent short- and medium-term outcomes in a larger cohort of 12 DDKTs with positive cross matches, which turned negative after desensitization[76]. Recently, a retrospective cohort study of DSA-positive recipients who received DDKT showed that a single peri-pretransplant TPE session, in combination with anti-human thymocyte globulin (ATG) as induction immunosuppression, did not result in a lower incidence of acute AMR within 6 mo in comparison with the DSA-positive recipients who did not receive a TPE session[77]. Posttransplant TPE was not performed because the protocol included 3 to 5 d of ATG induction[77].

Loupy *et al*[78], from the Paris group, reported the results of a combined posttransplant prophylactic IVIg/RTX/TPE treatment in DDKT with preformed DSAs but a negative cross match on the day of transplant. The patients received 9 TPE sessions on an alternate-day basis at posttransplant plus IVIg 2 g/kg at days 0, 2, 42,

and 63 and RTX on days 2 and 22. At 1-year posttransplant, patient and graft survival rates and the rate of acute AMR were comparable between the patients who received only IVIg and those who also received RTX and TPE. However, the estimated glomerular filtration rate (e-GFR) was significantly worse, and proteinuria was significantly higher in the IVIg group, as well as the rate of chronic AMR[78]. These differences in long-term function were characterized by a significant decrease in the DSA mean intensity of fluorescence (MFI), as detected with the Luminex solid phase immunoassay, in the group of patients receiving the more intensive post transplant prophylactic regimen in comparison with the IVIg group[78]. Recently, the Paris group reported the long-term results of a high immunological risk program including patients with high peak DSA levels (MFI > 3000) and a negative cross match at transplantation day who received a posttransplant desensitization protocol with high-dose IVIg, TPE and RTX. The results were compared to a control group including patients with a lower immunological risk (MFI between 500 and 3000) on transplantation day and in whom posttransplant desensitization was based on IVIg alone[79]. Patient survival was the same between the two groups. However, there were significantly more cases of acute T-cell rejection and AMR in the group with MFI > 3000, which clinically translated into significantly lower graft survival[79].

IA, aimed at preventing humoral graft injury, has also been used with mixed results. The Vienna transplantation center reported a favorable allograft outcome in a series of highly sensitized kidney transplant recipients after a peri-pretransplant IA session with a staphylococcal protein A column supplemented by repeat posttransplant treatment[80]. Subsequently, the same group described that a single peri-pretransplant IA, in addition to pre-emptive ATG, can turn a positive cross match into a negative cross match, enabling a successful DDKT supported by a favorable long-term graft survival at 3 years[81]. The authors confirmed these data by extending their initial experience in a later paper[82]. Repeated posttransplant IA sessions have been performed in this protocol to prevent a potentially harmful rebound of DSAs[81,82]. In line with the Vienna group, Higgins *et al*[83], in a previous study, reported a cohort with a successful cross-match conversion and prevention of hyper-acute rejection by peri-pretransplant IA treatment. However, in this case, a considerably high graft loss rate was observed during follow-up, with only 54% of transplants surviving after a median follow-up of 26 mo[83]. The difference in the outcome between these studies could be explained by the significant differences between the desensitization protocols. Unlike the Vienna group[81,82], Higgins *et al*[83] did not repeat post-transplant IA sessions. In addition, the Vienna group[81,82], to obviate an exaggerated increase of CIT, excluded transplantation for patients in whom a negative cross match could not be obtained by treatment with 6 L of plasma, while Higgins *et al*[83] in some patients prescribed more than 30 L plasma volume to convert a positive cross match, which resulted in significant increases in CIT (up to 62 h). However, the Vienna group recently reported that one-third of 101 DSA-positive recipients of DDKT underwent intense IA-based desensitization and experienced acute AMR and that DSA MFI levels were significantly associated with acute rejection (20 *vs* 71% AMR rates at < 5000 *vs* > 15000 peak DSA MFI)[84]. The 3-year graft-survival rate in DSA-positive recipients was significantly lower than that of the DSA-negative recipients (79% *vs* 88%; $P = 0.008$)[84].

These data highlight that MFI levels have significant prognostic value and suggest that the intensification of TA treatment in posttransplant desensitization protocols must be personalized according to MFI levels.

Desensitization of living-donor kidney transplant recipients: For sensitized candidates with an available but incompatible living donor, paired donor exchange (PDE) is the best alternative option. However, for most highly sensitized candidates, the chance of finding a match in the relatively small pools of donors in PDE programs is reduced, and desensitization alone or desensitization in combination with PDE present almost the only viable option for transplantation[85]. HLA-incompatible desensitized living-donor KT (LDKT) *vs* HLA-compatible LDKT has significantly lower graft survival[86]. Multicenter study results indicate, however, that it is worth desensitizing HLA-incompatible patients who have a potential living donor, as after KT these patients have significantly better long-term survival than highly sensitized candidates on a KT waiting list who did not receive a kidney from a deceased donor[87-89].

TA has a central role in current desensitization protocols. The most commonly used protocol is a combination of alternate-day TPE followed by low-dose IVIg (100-150 mg/kg) prior to transplantation[87-91]. Most transplant centers also initiate antirejection medications, tacrolimus, and mycophenolate mofetil (MMF), up to 2 wk prior to surgery[92]. Montgomery *et al*[87], in the largest series of HLA desensitization based on TPE plus low-dose IVIg, at the 5-year follow-up, showed a significantly greater

survival in patients who received LDKT (90.6%) than in those who remained on dialysis (51.5%) or in those placed on a DDKT wait list with or without KT (65.6%). On average, patients received 4 ± 4 TPE treatments before LDKT and 5 ± 4 TPE treatments after LDKT[87]. More recently, Orandi *et al*[88], in a larger multicenter (n = 22) United States study that involved 1025 patients, validated the results from the Baltimore group[87]. Gloor *et al*[93] , to overcome a positive cross match in 14 LDKT recipients added RTX and splenectomy to the protocol TPE/low-dose IVIg in an attempt to decrease the high AMR rate.

However, a 43% AMR rate was detected, while the patient and graft survival rates were 86% and 78%, respectively at 15 mo. Magee *et al*[94] reported their experience with TPE/low-dose IVIG plus RTX in 28 cross-match-positive patients. The AMR rate was high (39%), but within a mean follow-up of 22 mo, the mean serum creatinine level was good (1.5 mg/dL), and only 3 grafts were lost. Similar results, applying TPE/low-dose IVIg plus RTX, have been reported by the University of Illinois in 51 transplanted patients[95]. The acute rejection rate was 33%, with optimal graft survival at 2 years (93%).

Morath *et al*[96] examined the effect of adding one dose of RTX (375 mg/m^2) just prior to KT with IA performed before and after transplantation. After a median of 10 IA treatments, all ten patients were desensitized successfully and transplanted. The recipients also received a median of 7 posttransplant IA treatments. After a median follow-up of 19 mo, the reversible AMR rate was 30%, and the patient and allograft survival rates were 100% and 90%, respectively, with a mean serum creatinine level of 1.6 mg/dL[96]. Similar results with RTX plus IA have been reported recently by Kauke *et al*[97] on a small series of 8 LDKT recipients. Klein *et al*[98], on a series of 23 sensitized patients, performed pretransplant IA sessions plus tacrolimus, MMF, and steroids, with the goal of achieving an MFI < 1000 on transplantation day. On days 0 and 1, recipients also received one dose of RTX. The induction therapy was based on either ATG or basiliximab, and IA sessions were maintained posttransplantation until serum creatinine became < 2 mg/dL and MFI was stable at < 1000. This desensitization protocol showed excellent results at the 2-year follow-up, with a graft survival rate of 100% and a median serum creatinine level of 1.42 mg/dL[98]. To allow LDKT in 6 highly sensitized patients, Rostaing *et al*[99] performed an IA-based desensitization protocol plus IVIg, RTX, and ATG as induction therapy. This protocol effectively reduced or eliminated DSAs in 71% of recipients at the time of transplant. Three recipients manifested an AMR, but long-term renal function was good.

Woodle *et al*[100] in an alternative protocol incorporating TPE, the proteasome inhibitor bortezomib, and RTX, showed a significant decrease in DSAs in both LDKT and DDKT with successful transplantation in 19 of 44 highly sensitized patients and low acute rejection rates (18.8%) at 6 mo.

In a recent review, Malvezzi *et al*[101] proposed an algorithm based on MFI pretransplant levels for the use of the various TA techniques in desensitization protocols. In their experience, the authors suggest that the use of TPE should be restricted in cases where the highest pretransplant MFI is ≤ 9000. In such circumstances, TPE should be delivered on a daily basis until MFI becomes ≤ 3000. MFI must be assessed after every 5 sessions. If the MFI of the DSA is > 9000 but below 13000, DFPP can be implemented on a daily basis. When the target of MFI < 9000 is reached, DFPP can be converted to TPE. In the event that MFI is > 12000 before starting desensitization, IA has to be applied on a daily basis. When the MFI is reduced (*i.e.*, < 6000), IA can be replaced by DFPP or TPE to obtain an MFI threshold of about 3000. The authors conclude that in all of these scenarios, as soon as MFI is reduced to < 3000, KT can be performed as in this case DSA strength is low. In our opinion, based on current studies, the best strategy is to apply TA, preferably IA, plus RTX until MFI becomes < 3000. The addition of IVIG might also be relevant in this setting.

Antibody-mediated rejection

Antibody-mediated rejection (AMR) is a severe complication after KT with potentially deleterious effects on graft survival. Currently, AMR is widely recognized as a continuous process with varying degrees of activity and damage, clinically and histologically, expressed with multiple phenotypes, now identified as acute AMR, subclinical AMR, and chronic AMR[102,103].

Despite the use of desensitization protocols, up to one-third of highly sensitized recipients may develop AMR following transplantation[104,105]. Hence, the ability to successfully deliver incompatible transplants and optimize long-term results is contingent on the ability to successfully approach and manage an AMR. AMR is also of significant burden in non-sensitized individuals, as *de novo* DSA (dnDSA) can emerge early or late following KT[106].

Early acute AMR can be severe and result in graft loss, but it is also potentially

responsive to current treatments[103]. Instead, late acute AMR (more than 6 months posttransplant), can be a mixed cellular and humoral rejection, and it is often nonresponsive to current treatments, such as chronic AMR and, in some cases, subclinical AMR. Late acute and chronic AMR may result from dnDSA formation, the incomplete elimination of DSA following an earlier acute AMR episode, or the persistence of preformed DSA after desensitization[103]. TA, as an adjunctive therapeutic option, has a central role in the treatment of AMR.

TA and IVIG: When acute AMR occurs, TPE or IA plus IVIG and increased immunosuppression is considered the current standard of care (SOC) treatment, as it can be used to decrease antibody levels and arrest the rejection process in the majority of patients[103].

In a recent meta-analysis, Wan *et al*[107], regarding graft survival after antibody removal with TPE or IA, based on 5 RCTs, showed no benefit in the trials with a shorter follow-up (1-7 mo)[108,109], while those with a longer follow-up (2-5 years) showed a trend towards a benefit[28,110,111].

In a recent retrospective cohort study investigating TPE plus IVIG in late AMR, with approximately 50% of patients having chronic histology lesions, Lee *et al*[112] showed an improvement of graft survival in the intervention group compared to the control group who did not receive any therapy, in a mean follow-up of 7 years. In contrast, Einecke *et al*[113] observed no effect on graft survival after treatment with TPE plus IVIG in late AMR, with approximately 63% of patients having chronic histology lesions.

In conclusion, based on current data, the basis of establishing TPE plus IVIG as SOC treatment in AMR is lacking strong evidence, and a high-quality RCT with sufficient power to evaluate the efficacy of this treatment would provide reassurance on this delicate topic. However, it is extremely improbable that such a trial will be conducted due to the ethical perplexity of enrolling patients to a no-treatment group, which is historically related to high risks of graft failure.

Add-on treatments to TA and IVIG: Different add-on treatments in the current SOC treatment have been proposed over time per transplant center preference[103,107].

The use of RTX in acute AMR showed promising results in several small retrospective series[114,115]. In the first controlled trial using RTX plus TPE/IVIG *vs* IVIG alone, Lefaucheur *et al*[116] concluded that high-dose IVIG is inferior to combination therapy. However, in this trial, it was impracticable to determine which of RTX or TPE led to the improvement[116].

In addition, 2 retrospective cohort studies compared RTX plus TPE/IVIG to TPE/IVIG or IVIG alone, and both showed an improvement in graft survival in the RTX group[117,118]. The patients in the RTX group, however, received a higher dose of TPE and IVIG, limiting the ability to make a direct comparison between groups.

In a small multicenter double-blind RCT comparing RTX plus TPE/IVIG to placebo plus TPE/IVIG for the treatment of acute AMR, Sautenet *et al*[119] showed no additional benefit from RTX in graft survival after 1 year. However, the 1-year follow-up period may not have been long enough to identify a difference in graft survival. Recently, Oblak *et al*[120], with the limitations that a retrospective cohort study can provide, confirmed no evidence of any benefit in adding RTX to SOC treatment for AMR in a longer follow-up period (2 years).

Bortezomib, a proteasome inhibitor, in several nonrandomized retrospective studies and case reports, showed benefit to treat acute AMR in combination with TPE and IVIG[121,122] or TPE and RTX[123], while other studies have shown no improvement in e-GFR after bortezomib when used as add-on therapy with TPE and IVIG for late AMR[124].

The single RCT comparing the use of bortezomib, in patients with mixed AMR and acute cellular rejection, in conjunction with TPE and ATG *vs* TPE, RTX, and ATG or TPE and ATG alone, showed no difference in graft survival between the 3 groups[125].

The complement inhibitors eculizumab, a humanized monoclonal IgG antibody that binds to complement protein C5 and inhibits the formation of MAC, and C1-INH, a serine protease inhibitor that inactivates both C1r and C1s, inhibiting in this way the first step of the complement cascade, have also been evaluated in combination with TPE and IVIG in the treatment of AMR.

Locke *et al*[126] reported the first case report on the use of eculizumab in combination with TPE and IVIG to treat severe AMR, demonstrating a reversal of the AMR episode. In a study of 24 patients who developed severe oliguric AMR after HLA-incompatible LDKT, Orandi *et al*[127] showed that a combination of splenectomy plus eculizumab and RTX as an add-on therapy to TPE/IVIG resulted in an effective intervention for rescuing and preserving allograft function in comparison with splenectomy alone or eculizumab alone as an add-on therapy.

In an RCT in which 18 patients with acute AMR were assigned to C1-INH (Cinryze) plus TPE/IVIG or placebo plus TPE/IVIG, Montgomery *et al*[128] showed less transplant glomerulopathy at 6 months in the C1-INH group. A multicenter phase III RCT (NCT02547220) evaluating C1-INH as an add-on therapy to TPE/IVIG or IA/IVIG has just concluded, and we are waiting for the results to be published.

In conclusion, various add-on treatment options are employed for the current SOC treatment based on their targets in the steps of AMR pathogenesis with different results. Future RCTs should assess definitive endpoints, and until then, the regimen to be used should be considered on a case-by-case basis.

ECP: There are only a few reports available on the use of ECP in chronic AMR. Sunder-Plassman *et al*[129] employing intensive and long term ECP treatments (2 consecutive procedures every 2 wk for 17 cycles), showed a benefit in treating a single patient with chronic rejection. Dall'Amico *et al*[130] reported progressive improvement in renal function and consecutive biopsy specimens during the course of ECP in treating one patient with chronic rejection. In contrast, Horina *et al*[131] showed no response in treating two patients with two consecutive ECP procedures per month for 3 mo. Further experience on the usefulness of ECP in AMR is required.

Recurrence of primary focal segmental glomerulosclerosis

Approximately 30% of cases of primary focal segmental glomerulosclerosis (FSGS) recur after first KT and are associated with early graft loss in up to 50% of patients[132]. The prediction of recurrence is even higher than 75% in subsequent grafts when the first graft has been lost because of recurrence[133].

Primary FSGS seems to be induced by a circulating factor that targets podocytes. Several candidates have been suggested, although until now, the specific factor(s) involved remain unknown[134]. Recently, Delville *et al*[135] identified a panel of seven antibodies (CD40, PTPRO, CGB5, FAS, P2RY11, SNRPB2, and APOL2) that predict posttransplant FSGS recurrence with 92% accuracy. The pretransplant elevation of anti-CD40 antibody alone had the best correlation (78% accuracy) with recurrence of FSGS after transplantation[135]. In addition, anti-CD40 antibodies purified from patients with FSGS recurrence have been proven to be particularly pathogenic in human podocyte cultures[135].

TPE or IA with either a protein A or anti-IgG column have been used with benefit, alone or in combination with cyclophosphamide, with the scope to remove the putative circulating permeability factor[136-140]. Dantal *et al*[140] showed that the administration to rats of material eluted from protein A columns from patients with disease recurrence after KT increased the urinary albumin excretion.

In a literature review, Ponticelli[141] reported that approximately 70% of children and 63% of adults with recurrent FSGS receiving TPE or IA achieved complete or partial remission of proteinuria. Similar data have been reported in two recent meta-analyses[142,143].

The duration and frequency of TPE sessions are not yet unanimously agreed upon. A typical TPE regimen is 1.5 plasma volume exchanges for three consecutive days and then every other day for a total of two weeks[132].

TPE has also been used as an adjunctive treatment to other immunosuppressive agents. Canaud *et al*[144], in a series of 10 patients, reported good results by combining intravenous cyclosporine with high-dose steroids, mycophenolate, and frequent TPE sessions slowly tapered down for nine months.

In the last ten years, the use of RTX in recurrent FSGS has rapidly expanded with beneficial effects[145,146]. In addition to being a selective depleting agent of B-lymphocytes, RTX seems to have a direct protective effect on podocytes. RTX is able to protect sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) and acid sphingomyelinase (ASMase) by binding to SMPDL-3b, a protein exposed in podocyte lipid rafts that may be the target of the permeability factor of FSGS and that displays a sequence identified by RTX[147,148]. RTX, in combination with TPE, seems to have better efficacy, as suggested by case reports[149,150]. Other immunosuppressive agents, such as abatacept and antiTNFα agents, have shown prominent results in recurrent FSGS[151,152], but the experience of these agents in combination with TPE is inexistent.

Other indications of TA in KT

Complement-mediated atypical hemolytic uremic syndrome: Complement-mediated atypical hemolytic uremic syndrome (aHUS) is a rare disease that results from genetically determined complement deregulation with an alternative pathway of activity secondary to either loss-of-function mutations in regulators [factor H, factor I, and membrane cofactor protein (MCP)] or gain-of-function mutations in activators (C3 and factor B) of the alternative pathway[153]. In addition, complement-mediated aHUS may result from autoimmune mechanisms, including the development of auto

antibodies to complement proteins[153]. Mutations in factors H, factor I, factor B, and C3 have a high risk of recurrence (75%), and more than 90% of those with recurrence are strongly associated with graft failure, typically within the first year, because the altered proteins persist in the blood after KT[154]. In contrast, mutations of MCP are associated with a recurrence rate of only 20% and considerably more favorable graft survival rates because kidney transplants express normal proteins[155].

TPE can remove auto-antibodies against complement proteins or mutated circulating complement regulators while replacing absent or defective complement regulators and has been used in regimens for the prevention of recurrence, prior KT, and the recurrence of complement-mediated aHUS posttransplantation with relatively poor response to treatment[156]. The introduction of eculizumab, an anti-C5 monoclonal antibody, has favorably changed the outcomes and challenged the role of TPE in the treatment of aHUS.

The added therapeutic benefits ofTPE in a pre-emptive prophylactic protocol with eculizumab prior to KT, used by some centers[157], remain unclear and questionable. TPE remains an alternative therapeutic option only when eculizumab is not available in patients with anti-complement factor H antibodies and when thrombocytopenia is still present during the first days of eculizumab administration[158,159].

De novo* thrombotic microangiopathy:De novo* thrombotic microangiopathy (TMA) after KT may be due to any of the etiologies that induce TMA in the general population. However, the most common causes of TMA among kidney transplant recipients include drug-induced TMA due to calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors, ischemia reperfusion injury, AMR, and viral infections[160].

If switching to a different immunosuppressive regimen or if the treatment of underlying infection does not lead to a resolution of signs and symptoms of TMA and there is a clinical deterioration, TPE can be attempted to improve the course of the disease and subsequent graft damage[161], although the level of evidence is low. If available, eculizumab is the treatment of choice in these cases[162,163].

In AMR-associated TMA, improved outcomes have been reported with TPE and IVIG therapy[164]. Eculizumab is the recommended treatment in AMR-associated TMA if hemolysis persists despite maximal management with TPE and in those with TPE dependency[160].

Antiphospholipid syndrome and systemic lupus erythematosus: The antiphospholipid syndrome (APS) is a multisystem autoimmune disorder characterized clinically by thrombotic episodes in the arterial or venous circulation, and serologically by the persistent evidence of antiphospholipid antibodies (aPL). APS occurs either as a primary condition or secondary in the setting of an underlying systemic autoimmune disease, mainly systemic lupus erythematosus (SLE)[165]. The kidney is one of the organs that can be compromised by occlusion of a broad spectrum of renal blood vessels, ranging from glomerular capillaries to the main renal artery and vein[165].

Early graft arterial or venous thrombosis, or TMA, remains the most frequent cause of renal graft failure in patients with APS[166]. In addition, several studies have found that patients on maintenance hemodialysis, and consequently a substantial number of renal transplant recipients have a high prevalence of circulating aPL, which can damage the allograft[167,168]. Treatment of APS with long-term warfarin for arterial or venous thrombosis is recommended after renal transplantation and most transplant nephrologists prefer to inhibit the coagulation system in all patients with aPL and a history of coagulation events during the peritransplant period[169,170]. However, anticoagulation therapy increases the risk of bleeding complications, which may lead to early graft loss, and graft thrombosis takes place in 40% of the APS population despite anticoagulant therapy[171].

Prophylaxis with TPE for antibody removal, in addition to full anticoagulation therapy, before living-donor KT has been reported effective in one patient with primary APS[172] and in one patient with secondary APS in the setting of SLE[173]. However, in case of catastrophic APS (CAPS), which is characterized by diffuse TMA (vascular occlusions involving three or more organ systems)[174], prophylactic administration of eculizumab to prevent recurrence of CAPS after KT should be considered the preferred therapeutic option as have been used with success in one patient together with continuous systemic anticoagulation and standard immunosuppression[175].

Barbour *et al*[166] reported a case of acute recurrence of TMA after KT, in a patient with APS and lupus nephritis successfully treated with TPE albeit with some irreversible graft damage and renal impairment. These results suggest that further studies are warranted.

Recurrent and *de novo* anti-glomerular basement membrane disease: The histological recurrence of anti-glomerular basement membrane disease (GBM) may be as high as 50% in patients who receive a transplant while circulating anti-GBM antibodies persist[176,177]. However, there are only a limited number of documented cases of symptomatically recurrent anti-GBM disease, as most patients are asymptomatic[176].

De novo anti-GBM disease is seen in up to 15% of transplant recipients with Alport syndrome who develop anti-GBM antibodies to a collagen component [alpha5 (IV) NC1] carried by the transplanted kidney that is lacking in Alport patients[178]. The approach to the treatment is the same as in the native kidneys. TA should be used promptly to remove the causative antibody plus glucocorticoids and cyclophosphamide to inhibit further autoantibody production[177]. IA and TPE have comparable outcomes[179,180]

Recurrence of antineutrophil cytoplasmic antibody-associated vasculitis: The relapse of antineutrophil cytoplasmic antibody-associated vasculitis in KT patients is a rare event. In a recent review of 11 studies, including 441 patients, the relapse rate was 10%[181].

In the case of a recurrence, the treatment options for remission induction are similar to those of nontransplanted patients. Both cyclophosphamide- and RTX- based induction regimens have shown effectiveness in the treatment of posttransplant relapses[182].

TPE is recommended, in conjunction with glucocorticoids and either cyclophosphamide or RTX in the setting of relapse manifesting as alveolar hemorrhage, severe segmental necrotizing glomerulonephritis with serum creatinine above 4.0 mg/dL, and concurrent anti-GBM disease[182-184].

CONCLUSION

The application of TA in KT is currently a cornerstone of therapy for several clinical conditions, such as in desensitization protocols for ABO-i KT and in patients with preformed HLA-antibodies, in the treatment of AMR, and with the recurrence of different glomerulopathies after KT as in recurrent primary FSGS. However, strong evidence is scarce, and more clinical researches, with a high standard of quality RCTs, are demanded to establish the use of each TA method for the clinical problems that occur in KT.

In addition, in the era of new and emerging biological immunosuppressive therapies with an increasing number of specific actions and immune targets directed against cell-surface antigens or plasma-soluble molecules, the use of TA, and the optimal timing and dose, as an adjunctive therapeutic option becomes challenging in the study of future therapeutic protocols, which will best address open issues for better clinical outcomes.

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ORIGINAL ARTICLE

Retrospective Study

Histopathological characteristics and causes of kidney graft failure in the current era of immunosuppression

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Author contributions: Parajuli S and Djamali S had an original idea, designed the study, analyzed the data, prepared the manuscript; Aziz F, Garg N, Panzer SE, Joachim E, Muth B, Mohamed M, Blazel J, Zhong W, Astor BC, and Mandelbrot DA analyzed the data and edited the manuscript.

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Abstract

BACKGROUND

The histopathological findings on the failing kidney allograft in the modern era is not well studied. In this study, we present our experience working with kidney transplant recipients with graft failure within one year of the biopsy.

AIM

To report the histopathological characteristics of failed kidney allografts in the current era of immunosuppression based on the time after transplant, cause of the end-stage renal disease and induction immunosuppressive medications.

METHODS

In a single-center observational study, we characterized the histopathological findings of allograft biopsies in kidney transplant recipients with graft failure within one year after the biopsy.

RESULTS

We identified 329 patients with graft failure that met the selection criteria between January 1, 2006 and December 31, 2016. The three most common biopsy findings were interstitial fibrosis and tubular atrophy (IFTA, 53%), acute rejection

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(AR, 43%) and transplant glomerulopathy (TG, 33%). Similarly, the three most common causes of graft failure based on the primary diagnosis were AR (40%), TG (17%), and IFTA (13%). Most grafts failed within two years of post-transplant (36%). Subsequently, approximately 10%-15% of grafts failed every two years: > 2-4 years (16%), > 4-6 years (13%), > 6-8 years (11%), > 8-10 years (9%) and > 10 years (16%). AR was the most common cause of graft failure in the first six years (48%), whereas TG was the most prevalent cause of graft failure after 6 years (32%) of transplant.

CONCLUSION

In the current era of immunosuppression, AR is still the most common cause of early graft failure, while TG is the most prevalent cause of late graft failure.

Key words: Kidney biopsy; Acute rejection; Graft failure; Transplant glomerulopathy; Interstitial fibrosis and tubular atrophy

Core tip: There have been significant improvements in early graft survival. However, long-term graft survival has only had modest improvement. Causes of "true" late kidney allograft failure remain unclear. In this study, we explored the causes of graft failure based on the various factors, which may allow providers to determine interventions to prevent poor outcomes. We found, acute rejection, mainly antibody-mediated rejection, was the most common cause of early graft failure. And transplant glomerulopathy was a common cause of late graft failure, which occurred mainly after 6-7 years post-transplant even surpassed acute rejection.

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INTRODUCTION

Kidney transplantation is the best form of treatment for patients with end-stage renal disease (ESRD) of any cause. Kidney transplant recipients (KTRs) experience survival benefits in all age groups have a better health-related quality of life and transplant is cost-effective compared to dialysis[1-3]. There have been significant improvements in early graft survival due to advances in immunosuppression and the overall medical care of transplant recipients. However, long-term graft survival has only had a modest improvement[4-6]. Allograft failure among transplanted kidney recipients is now the fourth leading cause of ESRD in the United States[7]. Studies from nearly a decade ago suggest that antibody-mediated rejection (ABMR) and disease recurrence are the most common causes of graft failure[7,8]. However, the causes of "true" late kidney allograft failure remain unclear[9]. In this study, we explored the causes of graft failure based on time after transplant, causes of ESRD and induction immuno-suppressive medication in the current era, which may allow providers to determine interventions to prevent poor outcomes.

MATERIALS AND METHODS

Study population and design

We study KTRs who were transplanted at the University of Wisconsin, and who had graft failure between January 1, 2006 and December 31, 2016 and transplanted between January 1, 1994 to December 31, 2016. We chose 2006 as a current era because at that time most of our clinical practice including histopathological reporting were protocolized. Patients were included if they underwent a kidney biopsy within one

year prior to the graft failure. If they had multiple biopsies within one year prior to the graft failure, the biopsy closest to the graft failure was included in the analysis. Patients with primary graft dysfunction (defined as not having functional allograft and needing dialysis for at least 3 mo post-transplant or graft nephrectomy) or death with a functional graft were excluded from the study (Figure 1). This study was approved by the Health Sciences Institutional Review Board at the University of Wisconsin.

Data collection

We analyzed data on age, gender, race, re-transplant status, the cause of ESRD, type of transplant, induction immunosuppression, organ failure method before graft failure (re-transplant *vs* initiation of dialysis). In cases where a patient had multiple biopsy diagnoses, all diagnoses were also reported separately, although the primary diagnosis (first diagnosis) was used for the cause of graft failure. We divided the causes of graft failure based on the post-transplant interval divided into 2 years interval, based on the causes of ESRD and also the types of induction immunosuppressive medication.

Immunosuppression

Patients undergoing kidney transplant received induction immunosuppression with either a depleting (anti-thymocyte globulin, alemtuzumab or OKT3) or non-depleting (basiliximab or daclizumab) agent-based on immunological risk factors. Patients were typically maintained on a triple immunosuppressive regimen with a calcineurin inhibitor (CNI, usually tacrolimus), antiproliferative agent (usually mycophenolate mofetil or mycophenolic acid), and steroids. Some patients had early steroid withdrawal based on clinical judgment and the patient's request. Doses and drug levels were individually adjusted at physician discretion based on the patient's clinical condition, including infection, malignancy, and rejection. Patients were maintained on the same immunosuppressive medication until graft failure. However, if there was a feature of CNI toxicity on biopsy, then CNI trough goal was lowered or even discontinued based on physician discretion. Once the patient return on dialysis, immunosuppressive medication was tapered down and maintained only on low dose steroid. Switching to mTOR inhibitor among failing graft was not common practice.

Kidney allograft biopsy

The majority of the biopsies were performed for-cause, mainly for the unexplained rise in serum creatinine, concern for rejections, significant proteinuria, or the development of *de novo* donor-specific antibodies (DSA). Protocol biopsies were performed at months 3 and 12 for all patients with pre-transplant DSA, and 6-12 wk after treatment of rejection.

Rejection treatment

ABMR treatment protocols at our institution are based on both the severity of rejection and the time after transplant at which ABMR is diagnosed as described previously[10]. Briefly, for early rejection (within 3 mo post-transplant), treatment includes dexamethasone 100 mg bolus and taper, plasmapheresis (PP) 4-6 sessions, and intravenous immunoglobulin (IVIG) 100 mg/kg after each PP. Late rejection (> 3 mo post-transplant) is treated with dexamethasone 100 mg bolus and taper and IVIG 200 mg/kg every 2 wk × 3. Rituximab 375 mg/m^2 as a single dose is added based on clinical and laboratory characteristics. The treatment regimen for both smoldering and clinical rejection is the same at our institution.

Treatment of acute cellular rejection (ACR) is also based on Banff criteria and severity. Borderline and Banff stage I rejection is treated with steroid pulse. Banff II and III ACR are treated with steroid pulse and Thymoglobulin 6-10.5 mg/kg in 4 to 7 divided doses. In mixed rejection, steroid pulse, IVIG, Thymoglobulin 10.5 mg/kg ± rituximab are used.

Statistical analysis

Continuous data were compared using Student's *t*-test or the Wilcoxon rank-sum test, as appropriate, while categorical data were analyzed using Fisher's exact test or chi-square test. P values < 0.05 were considered statistically significant. All analyses were performed using the MedCalc Statistical Software version 16.4.3 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016).

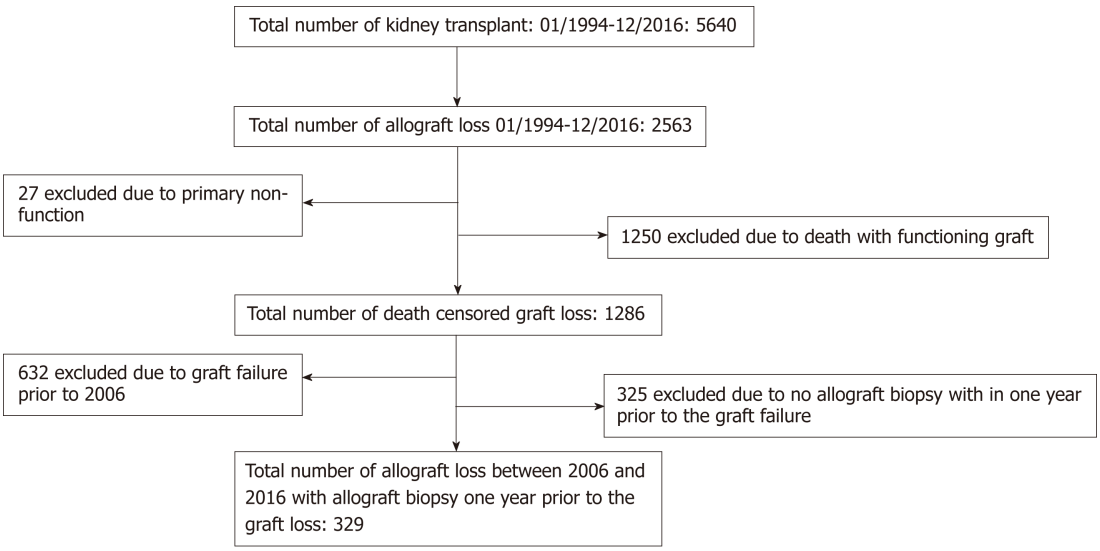

Figure 1 Study design: Death censored graft failure from 2006-2016 with allograft biopsy within one year prior to the graft failure.

RESULTS

Study population

A total of 654 patients had death-censored graft failure during the study period. Of these, 329 (50%) fulfilled our selection criteria and were included in the study.

Baseline characteristics

Out of the 329 KTRs included in the study, 127 (39%) were female and the majority were Caucasian (77%). Mean age at the time of transplant was 42.2 ± 13.7 years. Glomerulonephritis was the most common cause of ESRD and 33% were living KTRs. More than 50% had DSA around the time of graft failure. The mean interval from biopsy to graft failure was 106.5 ± 104.6 d (Table 1).

Biopsy findings

Interstitial fibrosis and tubular atrophy (IFTA) was the most common biopsy finding in 53% of all failed grafts, followed by acute rejection (AR) in 43% and transplant glomerulopathy (TG) in 33%. Less common findings were acute tubular necrosis, arteriosclerosis, recurrence of disease, donor vascular disease and BK nephropathy (BKVN) (Figure 2).

Common causes of graft failure based on the primary diagnosis

AR was the most common cause of graft failure and accounted for 40% (32% ABMR or mixed rejection and 8% ACR) of all graft failure. TG (17%), IFTA (13%), disease recurrence (7%) including the recurrence of diabetic nephropathy and glomerular disease, and BKVN (5%) were the following common causes of graft failure. Other less common causes of graft failure were donor vascular disease, prolonged acute tubular necrosis, CNI toxicity, and renal infarction (18% total graft failures). Among patients with AR as a cause of graft failure, 74 % had human leukocyte antigen (HLA) DSA at time of a biopsy, while 17% did not have HLA DSA and in 9% HLA DSA was not tested (Figure 3).

Common causes of graft failure based on the cause of ESRD

We further analyzed the cause of graft failure based on the three most common causes of ESRD: Glomerulonephritis, diabetes, and hypertension. AR was significantly higher in the glomerulonephritis and hypertension group compared to diabetes, and acute tubular necrosis was higher in the hypertension group (Table 2).

Common causes of graft failure based on the induction immunosuppressive medication

Patients were divided into two groups based on the induction immunosuppressive medication they received at time of transplant: Depleting agents (Anti-thymocyte globulin or alemtuzumab or OKT3) and non-depleting agents (basiliximab or daclizumab), which also included patients who received no or unknown induction. In the non-depleting group, TG was a significantly higher cause of graft failure

Table 1 Baseline characteristics, *n* (%)

Baseline characteristics	
Total number of graft failure	329 (100)
Female gender	127 (39)
Mean age at the time of transplant (yr)	42.2 ± 13.7
Caucasian	253 (77)
Causes of end stage renal disease:	
Glomerulonephritis	99 (30)
Diabetes	71 (22)
Hypertension	35 (11)
Polycystic kidney disease	34 (10)
Congenital disorder	9 (3)
Other	81 (25)
Mean number of transplants (Range 1-3)	1.29 ± 0.59
Living donor transplant	108 (33)
Induction Immunosuppression:	
Basiliximab	179 (54)
Thymoglobulin	52 (16)
Alemtuzumab	66 (20)
Other	32 (10)
Organ failure method:	
Resumption of dialysis	319 (97)
Re-transplantation (preemptive re-transplant)	10 (3)
DSA within a year prior to the graft failure:	
Present	184 (56)
Absent	89 (27)
Not tested	56 (17)
Mean graft survival (yr)	4.9 ± 4.4
Mean interval between biopsy and graft failure (d)	106.5 ± 104.6

DSA: Donor-specific antibodies.

compared to depleting agent group 48% *vs* 24% (Table 3).

Causes of graft failure according to time after transplant

AR, was the most common cause of graft failure in the early post-transplant period (within six years post-transplant) and accounted for 31% of total graft failures. (23% ABMR or mixed rejection and 8% ACR). There was a significant trend for graft failure due to rejection in the early post-transplant period (P = 0.001), while in the late post-transplant period, TG was the most common cause of graft failure ($P \leq 0.001$). The incidence of graft failure due to AR was higher up to 6 years post-transplant, with TG being the most common cause after 6 years (Figure 3). A total of 101 (48% of 212) graft failures within six years post-transplant were due to AR compared to 31 (26% of 117) after six years post-transplant (P = 0.01). TG was the primary cause of graft failure in 9% of patients within the first six years compared to 32% after six years ($P < 0.001$) (Figure 4). Rejection, TG, IFTA, and disease recurrence were evenly distributed as primary causes of graft failure after 10 years, each at approximately 20%-25%. Unsurprisingly, BKVN was more common in first 4 years post-transplant.

The most common time for graft failure was within two years post-transplant (n = 117, 36%). Subsequently, approximately 10%-15% of grafts failed every two years: > 2-4 years (n = 51, 16%), > 4-6 years (n = 44, 13%), > 6-8 years (n = 35, 11%), > 8-10 years (n = 31, 9%) and > 10 years (n = 51, 16%). Among 56 (17%) patients with the primary diagnosis of TG as a cause of graft failure, 25 (45%) had at least one episode of ABMR in the past. Similarly, around the time of last biopsy (± 3 mo), HLA-DSA was present in 30 (54%), DSA was not detected in 13 (23%) of the patients, and in 23% DSA was not checked around the time of biopsy (Figures 4 and 5).

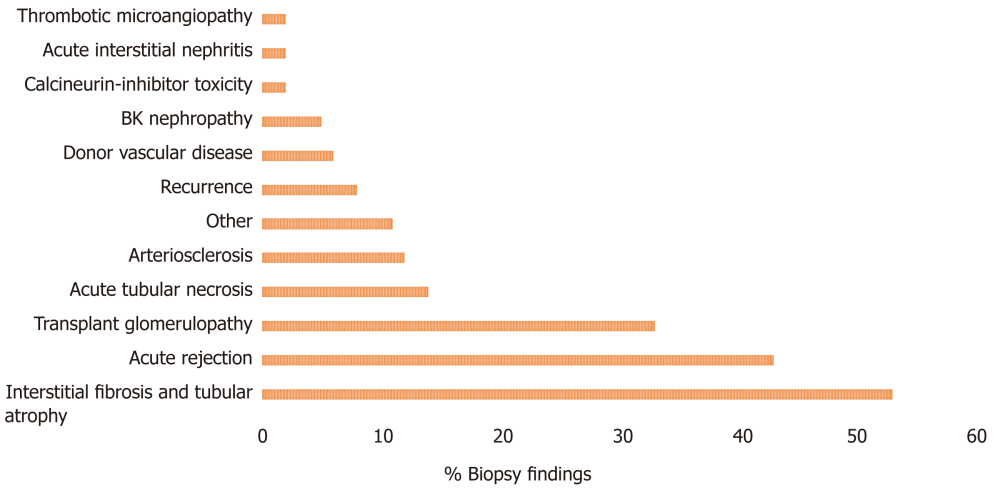

Figure 2 All histological findings on the biopsy. Interstitial fibrosis and tubular atrophy, acute rejection, and transplant glomerulopathy were the common histological findings in the failing graft.

DISCUSSION

In this study of the cause of graft failure among KTRs, we found that the primary cause of graft failure varies with time after transplantation. AR, mainly ABMR, was the most common cause of graft failure and accounted for 40% of graft failures, which peaked at 6 years post-transplant. After an AR, TG, one of the most specific histological findings of chronic ABMR[11], accounted for 17% of graft failure, which occurred mainly after 6-7 years post-transplant and was the most common cause of graft failure and even surpassed AR as a cause of graft failure. With careful adjustment of CNI dosing and with close monitoring of trough level, CNI toxicity was not a prevalent cause of graft failure in our cohort, which was considered one of the common cause of graft failure in the past.

There has been a dramatic improvement in the rate of AR. The half-life of a standard criteria deceased donor kidney in the United States has increased by almost 50%, from 10.6 years in 1989 to 15.5 years in 2005, and a similar pattern was seen with living donor transplantation[5]. This change was paralleled by a dramatic decline in graft failure within the first-year post-transplant period. Unfortunately, death-censored graft failure beyond the first year has remained unchanged since 1989[12]. During this time, our understanding of rejection and management have evolved, and graft failure due to hyperacute rejection is very rare. With newer protocols, ACR rates have decreased to less than 10% in the first year[5]. In the current era, our focus is on the prevention and treatment of ABMR. Certain newer therapeutics are considered for ABMR treatment based on their mechanism of action, such as anti-CD20 antibodies (*e.g.*, ofatumumab and ocrelizumab), anti-CD22 antibody (epratuzumab), agents targeting B cell activation (*e.g.*, atacicept and belimumab), and Anti-C5 antibody (eculizumab)[13-15], and others potentially in the investigational pipeline. Most of the work is being conducted in the fields of prevention and treatment of AR, and in time we may be able to effectively manage AR including acute ABMR. However, chronic changes and the lesser understood mechanisms of TG and IFTA may hinder our aim of prolonged graft survival.

TG has evolved as one of the histological features of chronic ABMR[16]. Overt TG is characterized histologically by glomerular basement membrane duplication in ≥ 1 of the capillary loops, mesangial expansion with or without mesangial hypercellularity, and mesangial cell interposition; glomerulitis can accompany these lesions[17]. The overall incidence of TG increases with time after transplant, occurring in approximately 20% by 5 years post-transplant[18,19]. TG is rarely diagnosed clinically within the first year of transplant, as TG lags behind the initial histologic stages of the disease[18]. In one study, subclinical TG (with stable renal function) was diagnosed in a protocol biopsy at a rate of 2.8% in the first year, which increased to 11.5% by 5 years post-transplant[18]. TG with significant proteinuria (> 2.5 g/day) is associated with worse graft survival outcomes compared with those with less proteinuria[20]. In the biopsy, TG is usually accompanied with the features of chronic damage to the allograft parenchyma mainly as fibrous intimal thickening of arteries, arteriolar hyalinosis and segmental and/or global glomerulosclerosis, IFTA and sometimes failure of peritubular capillaries[16]. Among patients with TG and active ABMR,

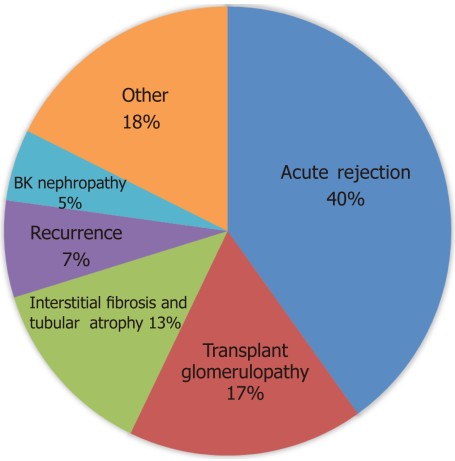

Figure 3 Overall causes of graft failure. Acute rejection is the most common cause of graft failure based on the primary biopsy diagnosis.

outcomes are even worse; in one large observational study, 76% of the recipients lost their graft with a median survival of 1.9 years after the diagnosis of chronic active ABMR[21]. Overall, TG is associated with poor long-term graft survival, as grafts with TG fail sooner than those without[22]. Much effort is being made to investigate therapeutic options for the treatment of TG. Cooper *et al*., studied the effects of high-dose IVIG in chronic ABMR and did not find any favorable outcomes. Nine of 20 treated patients in their study had a follow-up biopsy and only 4 had no histological progression[23]. Similarly, in a recent randomized double-blinded clinical trial, the addition of IVIG and rituximab was not useful in patients with TG[24].

IFTA is a final common pathway involving a number of independent and overlapping cellular and molecular pathways[25]. In a recent study, prior ACR was associated with inflammation within IFTA and presence of inflammation within IFTA was associated with accelerated IFTA, arterial hyperplasia and chronic glomerulopathy along with reduced renal function compared to those without inflammation[26]. There is no reliable way to differentiate the cause of IFTA based on the morphology alone, or immunohistochemistry and molecular techniques[27]. Tubular atrophy and interstitial fibrosis progress in parallel[28]. In one surveillance biopsy among 321 KTRs, interstitial fibrosis was present in 71% of the graft at two years[28]. To date, there is no consensus about the mechanism or treatment for IFTA but chronic immune rejection and inflammation is considered one of the mechanisms[29]. Also, immune cell-derived and locally active complement has been associated with the progression of chronic fibrosis[30]. These suggest that although not as strong association as with TG, IFTA could be related to an immune-derived mechanism leading to graft loss.

Calcineurin inhibitor toxicity, thrombotic microangiopathy, and other causes of graft loss each contributed to 5% or less to graft failure. Our observations have the limitations inherent in this type of study. As a single-center study, it may not be possible to generalize our results to other centers. We looked for the specific causes of graft failure based on the primary biopsy diagnosis, but the specific management based on the biopsy findings was beyond the scope of this study. Similarly, around 50% of our patient population were excluded due to no biopsy within one year prior to the graft failure and it was not possible to determine the histopathological characteristics of those patients. We also excluded the small number of patients with primary graft dysfunction to avoid any surgical and technical issues for graft failure.

In summary, AR is still the most common cause of early graft failure in the current era of immunosuppression. Most early graft failures within the first six years of transplant are related to AR and are in theory preventable. Similarly, more effective diagnostic, monitoring, and therapeutic strategies for TG and IFTA are needed to improve long-term graft survival.

Table 2 Histopathological characteristics of graft failure based on the cause of end stage renal disease, *n* (%)

	Glomerulonephritis (*n* = 99)	Diabetes (*n* = 71)	Hypertension (*n* = 35)
Acute rejection	49 (49)	21 (30)	19 (54)
Transplant glomerulopathy	14 (14)	14 (20)	4 (11)
Interstitial fibrosis and tubular atrophy	11 (11)	12 (17)	5 (14)
BK nephropathy	3 (3)	7 (10)	2 (6)
Acute tubular necrosis	1 (1)	5 (7)	3 (9)
Recurrence	6 (6)	6 (8)	1 (3)
Other	15 (15)	6 (8)	3 (9)

Table 3 Histopathological characteristics of graft failure based on the induction immunosuppressive agent, *n* (%)

	Depleting (127)	Non-depleting (*n* = 202)	*P* value
Acute rejection	46 (36)	86 (43)	0.25
Transplant glomerulopathy	31 (24)	96 (48)	0.003
Interstitial fibrosis and tubular atrophy	13 (10)	30 (15)	0.23
BK nephropathy	7 (6)	10 (5)	0.82
Acute tubular necrosis	6 (5)	10 (5)	0.92
Recurrence	6 (5)	8 (4)	0.74
Other	18 (14)	34 (17)	0.52

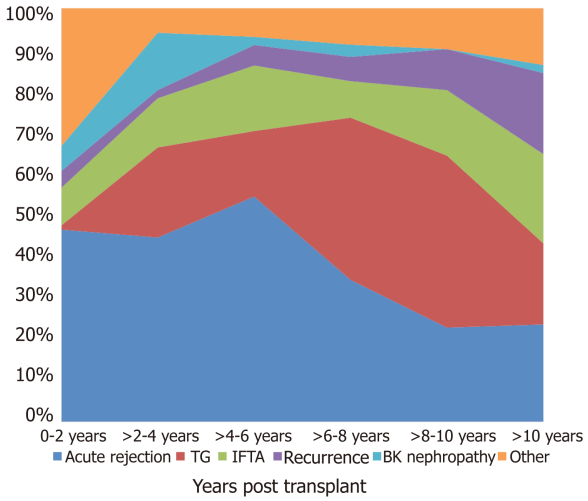

Figure 4 Causes of graft failure since time of transplant. IFTA: Interstitial fibrosis and tubular atrophy.

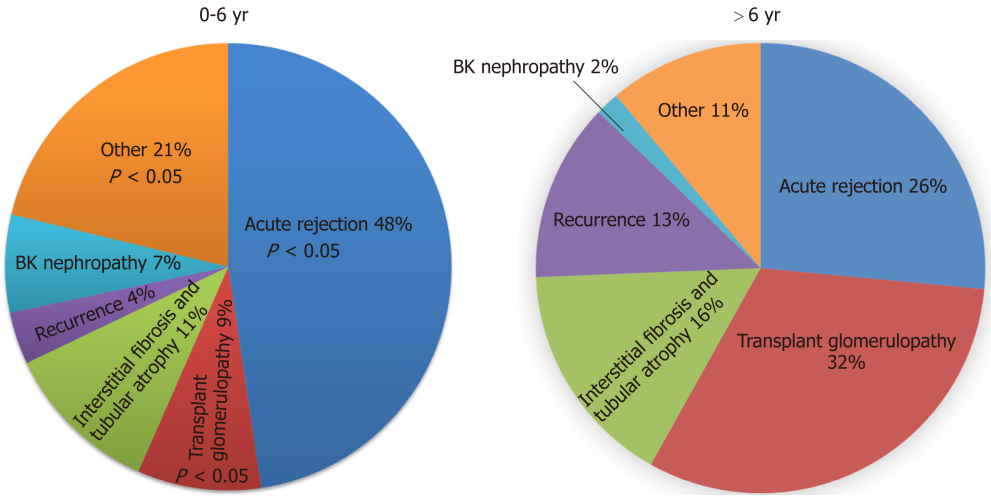

Figure 5 Transplant glomerulopathy is the predominant cause of graft failure after the 6th year. *P* < 0.05 compared to > 6 yr between acute rejection, transplant glomerulopathy and other.

ARTICLE HIGHLIGHTS

Research background

Although, there have been significant improvements in early graft survival due to advances in immunosuppression and the overall medical care of transplant recipients. However, long-term graft survival has only had modest improvement. The causes of "true" late kidney allograft failure remain unclear.

Research motivation

In this study, we explored the causes of graft failure based on various histopathological findings after transplant in the current era, which may allow providers to determine interventions to prevent poor outcomes.

Research objectives

The main objectives, of this study, was to identify the common causes of death censored graft failure among kidney transplant recipients. Knowing the causes may help provider to intervene on time and prevent for the graft loss.

Research methods

This was a single-center, retrospective study among kidney transplant recipients who were transplanted at the University of Wisconsin, and who had graft failure between January 1, 2006 and December 31, 2016 and transplanted between January 1, 1994 to December 31, 2016. Patients were included if they underwent a kidney biopsy within one year prior to the graft failure. We divided histopathological causes of graft failure based on the post-transplant interval divided into 2 years interval, based on the causes of ESRD and also the types of induction immunosuppressive medication. In cases where a patient had multiple biopsy diagnoses, all diagnoses were also reported separately, although the primary diagnosis (first diagnosis) was used for the cause of graft failure.

Research results

A total of 329 kidney transplant recipients fulfilled our selection criteria and were included in the study. The three most common biopsy findings were interstitial fibrosis and tubular atrophy (IFTA, 53%), acute rejection (AR, 43%) and transplant glomerulopathy (TG, 33%). Similarly, the three most common causes of graft failure based on the primary diagnosis were AR (40%), TG (17%), and IFTA (13%). Most grafts failed within two years of post-transplant (36%). Subsequently, approximately 10%-15% of grafts failed every two years: > 2-4 years (16%), > 4-6 years (13%), > 6-8 years (11%), > 8-10 years (9%) and > 10 years (16%). AR was the most common cause of graft failure in the first six years (48%), whereas TG was the most prevalent cause of graft failure after 6 years (32%) of transplant. Most early graft failures within the first six years of transplant are related to AR and are in theory preventable. Similarly, more effective diagnostic, monitoring, and therapeutic strategies for TG and IFTA are needed to improve long-term graft survival.

Research conclusions

In this study of the cause of graft failure among kidney transplant recipients, we found that the primary cause of graft failure varies with time after transplantation. AR, mainly antibody-mediated rejection (ABMR), was the most common cause of graft failure and accounted for 40% of graft failures, which peaked at 6 years post-transplant. After an AR, TG, one of the most specific histological findings of chronic ABMR, accounted for 17% of graft failure, which

occurred mainly after 6-7 years post-transplant and was the most common cause of graft failure and even surpassed AR as a cause of graft failure. Interestingly, calcineurin inhibitor toxicity was not a common cause of graft failure.

Research perspectives

Further studies in this field and specifically effective treatment of AR is needed to prolong the graft survival. Most of the work is being conducted in the fields of prevention and treatment of AR, and in time we may be able to effectively manage AR including acute ABMR. However, chronic changes and the lesser understood mechanisms of TG and IFTA may hinder our aim of prolonged graft survival and study should focus on the field of prevention or treatment of TG and IFTA.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy and safety of non-vitamin K antagonist oral anticoagulants post-kidney transplantation

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Institutional review board statement: The study protocol was reviewed and approved by the Hamilton Integrated Research Ethics Board (www.hireb.ca).

Informed consent statement: This was a retrospective study of anonymized/deidentified medical charts and health records. In consideration of the study design, the Hamilton Integrated Research Ethics Board waived request for informed consent from patients.

Conflict-of-interest statement: The authors deny any conflict of interest.

Data sharing statement: No additional data are available.

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Abstract

BACKGROUND

Novel oral anticoagulants (NOACs) were developed as alternatives to vitamin K antagonists, primarily warfarin, as they do not require routine monitoring and have limited drug-drug and drug-food interactions. However, the efficacy and safety of these agents in kidney transplantation are not well studied.

AIM

To assess the profile and safety of NOACs for patients who had kidney transplantation, and to provide recommendations and guidelines on therapeutic strategies in these patients.

METHODS

This was a retrospective study carried out among adult patients who were actively on the following NOACs (apixaban, rivaroxaban or dabigatran) in our renal transplantation program from December 2015 to December 2016. The patients were identified primarily through electronic medical record system (patient data linkage). Data on the clinical and laboratory profile of the patients were retrieved and analyzed with SPSS 22.0.

RESULTS

Complete data on 42 renal transplant patients were retrieved: 59.5% males, 90.5% were whites and 66.7% were older than 60 years old. The mean duration since renal transplantation of the patients was 8.8 ± 7.4 years. The most common risk

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factors for the development of end-stage renal disease in the subjects were hypertension (19.0%), polycystic kidney disease (19.0%), followed by diabetic nephropathy (16.7%) and chronic glomerulonephritis (16.7%). The main indications for NOACs use in the cohort were atrial fibrillation in 25 patients (59.5%) and venous thromboembolism in 10 patients (23.8%). Overall, 29 patients (69%) were treated with apixaban, 10 patients (23.8%) with rivaroxaban and 3 patients (7.14%) with dabigatran. No (0%) thromboembolic events were observed during the one-year period, but 3 (7.1%) bleeding events occurred in the cohort consisting of 1 patient treated with rivaroxaban 15 mg daily and 2 patients who received apixaban 2.5 mg twice daily. There were no significant changes in serum tacrolimus level three days after the initiation of NOACs among patients treated with tacrolimus (pre- and post-NOACs tacrolimus levels were 7.2516 and 7.8867 ng/mL, $P = 0.55$, respectively). Also, after one-year of treatment with NOACs there were no significant changes in the pre- and post-NOACs serum creatinine level ($P = 0.772$) and estimated glomerular filtration rates ($P = 0.232$).

CONCLUSION

No thromboembolic events or significant changes in renal profile were observed in our cohort of kidney transplant recipients who were treated with NOACs for at least a year. However, a few bleeding events were observed. This calls for further well-planned randomized controlled trials to assess the efficacy and safety of NOACs among renal transplant recipients.

Key words: Novel oral anticoagulants; Adult patients; Kidney transplantation; Renal outcomes; Efficacy

Core tip: No consensus is available in the literature about whether novel oral anticoagulants are effective and safe for renal transplant recipients. This is one of the first attempts to investigate the profile, safety and effectiveness of novel oral anticoagulants for adult renal transplant recipients. We investigated the role of novel oral anticoagulants in terms of its effect on thromboembolism, bleeding, creatinine clearance and immunosuppressive agents.

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INTRODUCTION

Non-Vitamin K antagonists also known as novel oral anticoagulants (NOACs) were developed as alternatives to vitamin K antagonists, primarily warfarin, as they do not require routine monitoring and have limited drug-drug and drug-food interactions[1]. NOACs are gaining popularity over the past few years as stroke-preventing agents for people with atrial fibrillation (AF)[1]. NOACs have also been recommended for the treatment of systemic embolic events in patients with nonvalvular AF and for the treatment of venous thromboembolism (VTE)[1-3]. They are recommended by the Canadian Cardiovascular Society guidelines for the management of AF with a class I recommendation[4]. Four NOACs, (dabigatran, rivaroxaban, apixaban, and edoxaban) have received approval from the United States Food and Drug Administration for the prevention of AF.

Kidney transplantation is considered the treatment of choice for patients with end-stage renal disease (ESRD) and has been shown to improve quality of life and survival rate for most patients compared to those maintained on dialysis[5,6]. AF occurs in over 7% of kidney transplant recipients in the first 3years after transplantation and is associated with reduced graft and patient survival[7]. NOACs represent a valuable anticoagulation therapy for kidney transplant recipients, which are at higher risk of

bleeding and thrombotic complications. However, NOACs use in renal transplant patients is not yet recommended as they are excreted via kidney and there are concerns it may interact with immunosuppressive therapy[5,7]. Indeed, as substrates of CYP3A4, apixaban and rivaroxaban, and p-glycoprotein, dabigatran; NOACs were suggested to interact with calcineurin inhibitors (CNIs) in a small retrospective study[8]. In heart and lung transplant recipients, a recent study showed that NOACs were effective and safe but associated with high rate of drug interactions that require dose reduction (by 45%)[9].

Given the fact that NOACs don't require frequent monitoring and due to their low interactions and lower risk of spontaneous bleeding, these agents carry a great advantage over warfarin[1]. However, the efficacy and safety of these agents in kidney transplantation are not well studied yet. In this study, we aimed to assess the safety of NOACs administration in patients after kidney transplantation, and to provide recommendations and guidelines on therapeutic strategies in these patients.

MATERIALS AND METHODS

This was a retrospective study carried out among adult patients who were actively on the following NOACs (apixaban, rivaroxaban or dabigatran) in our renal transplantation program from December 2015 to December 2016. The patients were identified primarily through the electronic medical record system (patient data linkage). We also included renal transplant recipients whose anticoagulation therapy with NOACs were stopped or changed but had at least one-year record of use of NOACs corresponding with our study period (*i.e.*, up to one year of use be December 1, 2016).

Only records of adult patients (age ≥ 18 years) were included. Data of pediatric renal transplant recipients, adult patients with medication adherence issues, and those who stopped NOACs >12 mo prior to the study, were excluded from the analysis. The electronic records of the patients were retrieved from the electronic medical record system (Patient link). The data of patients with incomplete information were available in the electronic medical record system were extracted from the patients' paper charts. Data on the clinical and laboratory profile of the patients were extracted.

Statistical analysis

The study was approved by Hamilton Integrated Research Ethics Board (HiREB). Also, because this was a retrospective study of anonymized/deidentified electronic records, HiREB waived request for informed consent from patients. Data were analyzed with SPSS 22.0 (IBM Corp., NY, United States). Continuous variables were expressed as means ± standard deviations and categorical variables were expressed as percentages. Chi-square tests were used for categorical variables and unpaired *t*-tests and one-way analyses of variance were used to compare continuous variables. P values < 0.05 were considered significant. The statistical methods of this study were reviewed by Dr. Mamta Gupta PhD (Public Health and Epidemiology/MPH Epidemiology and Biostatistics) from the Department of Epidemiology and Biostatistics, Alchemist Research and Data Analysis, Chandigarh, 160 036, India.

RESULTS

Our cohort included a total of 47 patients; only 42 patients were retained for further analysis after excluding 5 patients due to incomplete data. The clinical characteristics of patients are presented in Table 1. Most patients were males 25 (59.5%) and the vast majority 28 (66.7%) were older than 60 years old with 11 (26.2%) being ≥ 75 years old. The mean age in our cohort was 64.7 ± 13.88 years. The mean duration since renal transplantation of the patients was 8.8 ± 7.4 years (range 1 to 30 years). The average estimated glomerular filtration rate (eGFR) was 62.90 ± 18.98 mL/min/1.73 m^2. No significant difference in eGFR among age groups was noticed. A total of 38 patients were white (90.5%); only 2 were Asian, 1 Indian and 1 Hispanic. The Most common causes of ESRD in our cohort were hypertension and polycystic kidney disease, occurring in 8 patients (19.0%) each, followed by 7 patients with diabetic nephropathy and chronic glomerulonephritis (16.7%) (Table 2).

A total 29 patients (69%) were treated with apixaban, 10 patients (23.8%) with rivaroxaban and 3 patients (7.14%) with dabigatran (Table 2). Among those that were on apixaban, 58.6% were on low dose of 2.5 mg bid and 41.3% were on full dose of 5 mg bid. Similarly, of the 10 patients on rivaroxaban, 5 were on a full daily dose of 20 mg and 5 were on reduced daily dose of 15 mg. In our cohort, 25 patients (59.5%)

Table 1 Demographic characteristics of the patients

Age	No. patients	Age (yr, mean ± SD)	No. males	Weight	*n*	Estimated glomerular filtration rate
≤ 30	1	30	0	52	0	54
31-45	5	40.4 ± 5.86	2	96.20 ± 31.06	2	56.00 ± 18.67
46-60	8	56.4 ± 2.51	6	98.88 ± 29.79	3	65.13 ± 21.94
> 60	28	72.0 ± 6.71	17	78.25 ± 14.77	14	63.82 ± 18.88
Total	42	64.7 ± 13.88	25	83.69 ± 22.32	19	62.90 ± 18.98

Estimated glomerular filtration rate in (mL/min/1.73 m^2).

were on NOACs due to AF, 10 patients (23.8%) due to VTE and 5 patients (11.9%) due to both AF and VTE. Most patients were on tacrolimus-based anti-rejection (immunosuppressive) therapy (31; 76.8%) and 5 patients (11.9%) were on a cyclosporine-based regimen, and only 4 patients (9.6%) were on sirolimus-based regimen. In addition, all the 42 patients (100%) received oral prednisolone and mycophenolate mofetil. Table 3 shows the profile of the immunosuppressive agents received according the type of NOAC agent. NOACs were used without a concomitant antiplatelets therapy in 37 of the patients (88.1%).

Overall, we observed 3 bleeding events (7.1%) in our cohort consisting of 1 patient treated with rivaroxaban 15 mg daily and 2 patients who received apixaban 2.5 mg twice daily (Table 4). One of these was a major bleeding event which occurred while rivaroxaban was on hold for over a month in preparation for a cataract surgery. The patient had a background of severe retinopathy and had intraocular bleeding one day after the surgery. This bleeding event was assumed to be unrelated to the medication, and rivaroxaban was resumed a few months later. This patient didn't experience any further bleeding events after rivaroxaban resumption. The other two bleeding events were bleeding per-rectum events that occurred in two ladies on low-dose apixaban. There were no significant reduction in the patients creatinine, eGFR or CNI levels at the time of the events. The bleeding events in both cases were minor, didn't cause hemodynamic instability, and didn't require surgical intervention or complete cessation of NOACs.

On the other hand, no thromboembolic events (0%) were observed. In addition, no significant change in serum tacrolimus level was observed three days after the initiation of NOACs among patients treated with tacrolimus (pre- and post-NOACs serum tacrolimus level was 7.25 and 7.89 ng/mL, $P = 0.55$). Similarly, after one year of treatment with NOACs there was no significant change in the pre- and post-NOACs serum creatinine level with mean levels of 107.6 μmol/L and 113.11 μmol/L ($P = 0.772$) respectively, (median 107.5 *vs* 108.5 μmol/L, respectively). This is summarized in Figure 1. Besides, as shown in Figure 2, pre- and post-NOACs eGFR levels after one-year of treatment with NOACs did not significantly change with respective mean levels of 72.2 mL/min/1.73 m^2 and 65.9 mL/min/1.73 m^2 ($P = 0.232$; median: 68.2 *vs* 60.4 mL/min/1.73 m^2, respectively).

DISCUSSION

Dabigatran was the first NOAC agent released into the European market for VTE prophylaxis post joint replacement surgeries in 2008[1]. It was the first NOAC agent to get Food and Drug Administration approval for AF in 2010, and VTE in 2014. International recommendations suggested the need to change NOACs name from novel oral anticoagulation drugs to non-vitamin K antagonist agents keeping the same acronym; NOACs[10].

To our knowledge, this is the first study that addresses the efficacy and safety of NOACs in kidney transplantation recipients. Our results show that NOACs treatment has no effect on kidney function. Indeed, none of the NOACs used in our study induced changes in creatinine or eGFR levels after treatment. A previous study on lungs and heart transplantation suggested that NOACs can interact with CNIs[9]. Moreover, Wannhoff *et al*[11] suggested that cyclosporine has a higher rate of drug interaction with rivaroxaban in another liver transplantation study. On the other hand, Vanhove *et al*[12] reported similar, but clinically insignificant (< 20% change), interaction that didn't warrant CNI dose adjustments in transplant recipients.

In our study, we didn't report any thromboembolic event in any of the patients after CNI initiation. This might suggest NOACs are as effective in kidney trans-

Table 2 Clinical characteristics of the patient groups, *n* (%)

Variable	Age group (yr)		Total
	< 75	≥ 75	
Primary cause of ESRD			
Diabetic nephropathy	6 (19.4)	1 (9.1)	7 (16.7)
Hypertension	6 (19.4)	2 (18.2)	8 (19.0)
Glomerulonephritis	4 (12.9)	3 (27.3)	7 (16.7)
Polycystic kidney disease	6 (19.4)	2 (18.2)	8 (19.0)
Chronic Interstitial nephritis	3 (9.7)	1 (9.1)	4 (9.5)
Reflux/Congenital	3 (9.7)	2 (18.2)	3 (7.1)
Other	3 (9.7)	2 (18.2)	5 (11.9)
NOACs			
Dabigatran 150 mg bid	1 (3.2)	1 (3.2)	2 (4.8)
Dabigatran-Low Dose	1 (3.2)	0 (0.0)	1 (2.4)
Apixaban 5 mg bid	11 (35.5)	1 (9.1)	12 (28.6)
Apixaban-Low Dose	10 (32.3)	7 (63.6)	17 (40.5)
Rivaroxaban 20 mg/d	5 (16.1)	0 (0.0)	5 (11.9)
Rivaroxaban Low Dose	3 (9.7)	2 (18.2)	5 (11.9)
Cause of NOAC initiation			
VTE	8 (25.8)	2 (18.2)	10 (23.8)
AF	17 (54.8)	8 (72.7)	25 (59.5)
Other	2 (6.5)	0 (0)	2 (4.8)
VTE and AF	4 (12.9)	1 (9.1)	5 (11.9)
Calcineurin inhibitors			
Advagraf	22 (71.0)	5 (45.5)	27 (64.3)
Prograf	3 (9.7)	1 (9.1)	4 (9.5)
Cyclosporin	1 (3.2)	4 (36.4)	5 (11.9)
Sirolimus	3 (9.7)	1 (9.1)	4 (9.5)
None	2 (4.8)	0 (0)	2 (4.8)
Clopidogrel			
Yes	4 (12.9)	1 (9.1)	5 (11.9)
No	27 (87.1)	10 (90.9)	37 (88.1)

NOACs: Novel oral anticoagulants; VTE: Venous thromboembolism; AF: Atrial fibrillation; ESRD: End stage renal disease.

plantation population as the general population. Also, we had a few bleeding events with low doses (2.5 mg twice daily) of apixaban and a moderate dose (15 mg daily) of rivaroxaban, which may suggest a good safety profile. However, there is a need to further assess the mechanisms of bleeding in patients exposed to NOACs. Although our study indicates that NOACs may be safe and effective for the prevention and treatment of thromboembolic events in renal transplant recipients, there is a need to highlight some of its important advantages and disadvantages compared to other vitamin K antagonists. Its major advantages include absence of food interactions, few strong drug interactions, predictable pharmacokinetic and pharmacodynamic properties, a rapid onset and offset of action, a short half-life, and the absence of the need for laboratory monitoring[13].

However, pharmacokinetic and pharmacodynamic studies show that NOACs elimination is dependent on renal clearance to varying extents; but compared with vitamin K antagonists, the efficacy and safety of the NOACs is preserved in patients with moderate renal impairment[14,15]. There is a need to administer NOACs with caution in individuals with severe kidney or hepatic damage particularly the elderly. This is because up to 25%, 33% and 80% of apixaban, rivaroxaban and dabigatran, respectively are eliminated through the kidneys as an active drug[13-15]. In severe renal or hepatic damage, the elimination of the drug may be affected requiring adjustments in the dosing of the NOAC agent.

Our analysis only included renal transplant recipients with an eGFR of > 54 mL/min/1.73 m^2. Therefore, dosage adaptation of the NOACs should ideally not be

Table 3 Profile of the cases that developed bleeding

	Case 1	Case 2	Case 3
Age	77	73	87
Gender	Male	Female	Female
NOACs on use	Rivaroxaban	Apixaban	Apixaban
NOACs dose	15mg daily	2.5mg bid	2.5mg bid
Type of bleeding	Major	Non-major	Non-major
Site of bleeding	Intra-ocular	Bleeding per rectum	Bleeding per rectum
Time to bleed	> 1 yr post starting	> 1 yr post starting	> 1 yr post starting
Base line Cr/eGFR	93/72.6	67/79.5	122/38.44
Cr/eGFR at bleeding	144/38.6	58/93.9	147/31.0
CNI in use	Cyclosporin	Tacrolimus	Cyclosporin
CNI level at bleeding time	C0: 91	5.8 (within target)	C0: 116
Antiplatelet used	None	None	None
note	Rivaroxaban was on hold at the time of bleeding. Bled post cataract surgery.		

NOACs: Novel oral anticoagulants; CR: Creatinine; eGFR: Estimated glomerular filtration rate; CNI: Calcineurin inhibitors.

necessary. However, considering the very limited or no prior experience in the use of NOACs in kidney transplant recipients (with/without renal impairment), doses of NOACs were administered to the patients in this study using the Health Canada dosing algorithm for each of the NOACs according to renal function and clinical status of the patients[14,16]. Thus, the effectiveness of NOACs observed in our data can only be interpreted in the context of kidney transplant recipients with sufficiently preserved renal function. Several clinical trials such as the EINSTEIN, ARISTOTLE, and RE-LY trials have previously demonstrated the safety and efficacy of these NOACs in individuals with varying levels of renal impairment[17-19].

In the present study, 3 of the subjects received dabigatran with tacrolimus-based CNIs. Previous studies have called for caution in the use of NOACs and immunosuppressive agents due to the potential for drug-drug interactions[8,20,21]. A study suggested that dabigatran should not be administered to patients receiving CNIs because CNIs are known substrates of both CYP 450 3A4 and P-gp, and can lead to increased exposure to dabigatran[8,20]. Because of the limited evidence of NOACs usage with CNIs in the setting of solid organ transplantation, this clinical recommendation was made based on an underpowered analysis of nine heart transplant recipients immunosuppressed with CNIs and treated with dabigatran for AF, VTE, or atrial thrombus[8]. In the study, patients who received tacrolimus with dabigatran were more likely to require a decrease in tacrolimus dose during therapy and numerically had more major bleeding events[8]. However, observations from the RE-LY trial indicate that concomitant use of dabigatran with P-gp inhibitors (like amiodarone or verapamil) increased dabigatran exposure but was not associated with significant differences in the event rate or bleeding[22,23]. A recent review indicates that in patients receiving dabigatran etexilate for the treatment and prevention of VTE, there is no need for dose adjustments and no contraindication to its co-administration with P-gp inhibitors so long as the patients have a creatinine clearance greater than 50 mL/min[24]. All the patients in our study had creatinine clearance greater than 50 mL/min and none of those who received dabigatran had a bleeding event. Recent expert opinion conclude that provided adequate attention is given to renal function, the co-administration of NOACs and CNIs in solid organ transplantation is safe and effective[24].

This study has some limitations. First, this was a retrospective observational study, therefore any reported association does not imply causation. Second, all the patients in this study had sufficiently preserved renal function (creatinine clearance > 50 mL/min), therefore we cannot report on the safety or efficacy of the NOACs in kidney transplant recipients with substantial renal impairment. Third, more than half of the patients received low doses of the NOAC agent. Therefore, our finding may not reflect the outcomes in renal transplant recipients treated with higher doses of NOAC agent.

In conclusion, our study suggests that NOACs may be safe and effective for the prevention and treatment of thromboembolic events in renal transplant recipients with limited complications. Further studies need to be conducted to assess the

Table 4 Profile of the immunosuppressive agents received according the type of Novel oral anticoagulants agent

NOAC	Calcineurin inhibitor used, *n* (%)					Total
	Advograf	Pyograf	Cycosporin	Sirolimus	None	
Dabigatran 150 mg bid	2 (7.4)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4.8)
Dabigatran-low dose	1 (3.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.4)
Apixaban 5 mg bid	8 (29.6)	1 (25.0)	0 (0)	2 (50.0)	1 (50.0)	12 (28.6)
Apixaban-low dose	10 (37.0)	2 (50.0)	3 (60.0)	2 (50.0)	0 (0)	17 (40.5)
Rivaroxaban 20 mg/d	4 (14.8)	1 (25.0)	0 (0)	0 (0)	0 (0)	5 (11.9)
Rivaroxaban low dose	2 (7.4)	0 (0)	2 (40.0)	0 (0)	1 (50.0)	5 (11.9)

All patients also received prednisolone and mycophenolate mofetil. NOACs: Novel oral anticoagulants.

effectiveness and safety profile of NOACs compared to other vitamin K antagonists (*e.g.*, warfarin) in kidney transplant population.

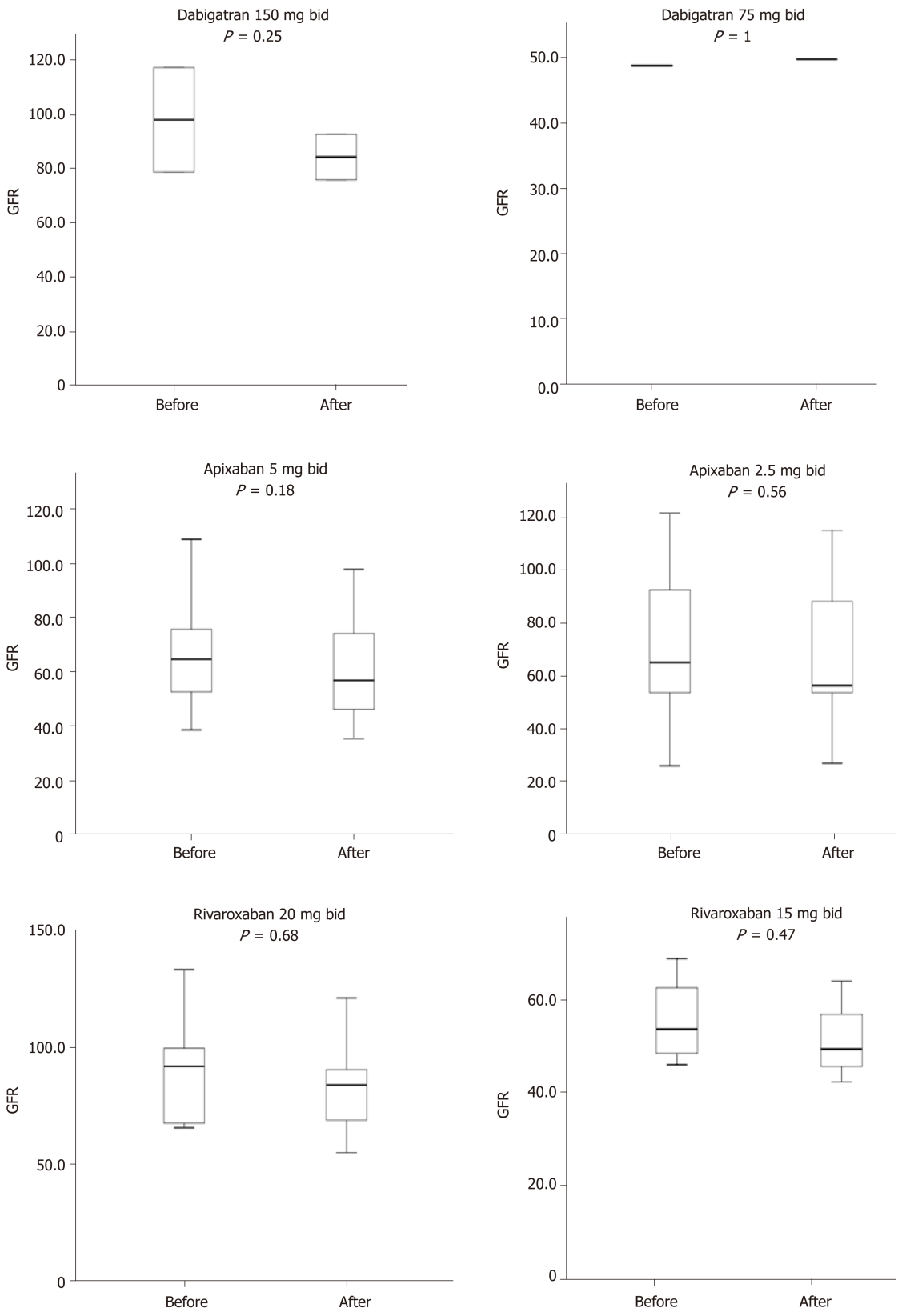

Figure 1 Creatinine levels before and after treatments with novel oral anticoagulants. Boxplots showing the distribution of creatinine levels (μM) before and after novel oral anticoagulants treatment. Points indicate individual patients, with colors representing age groups.

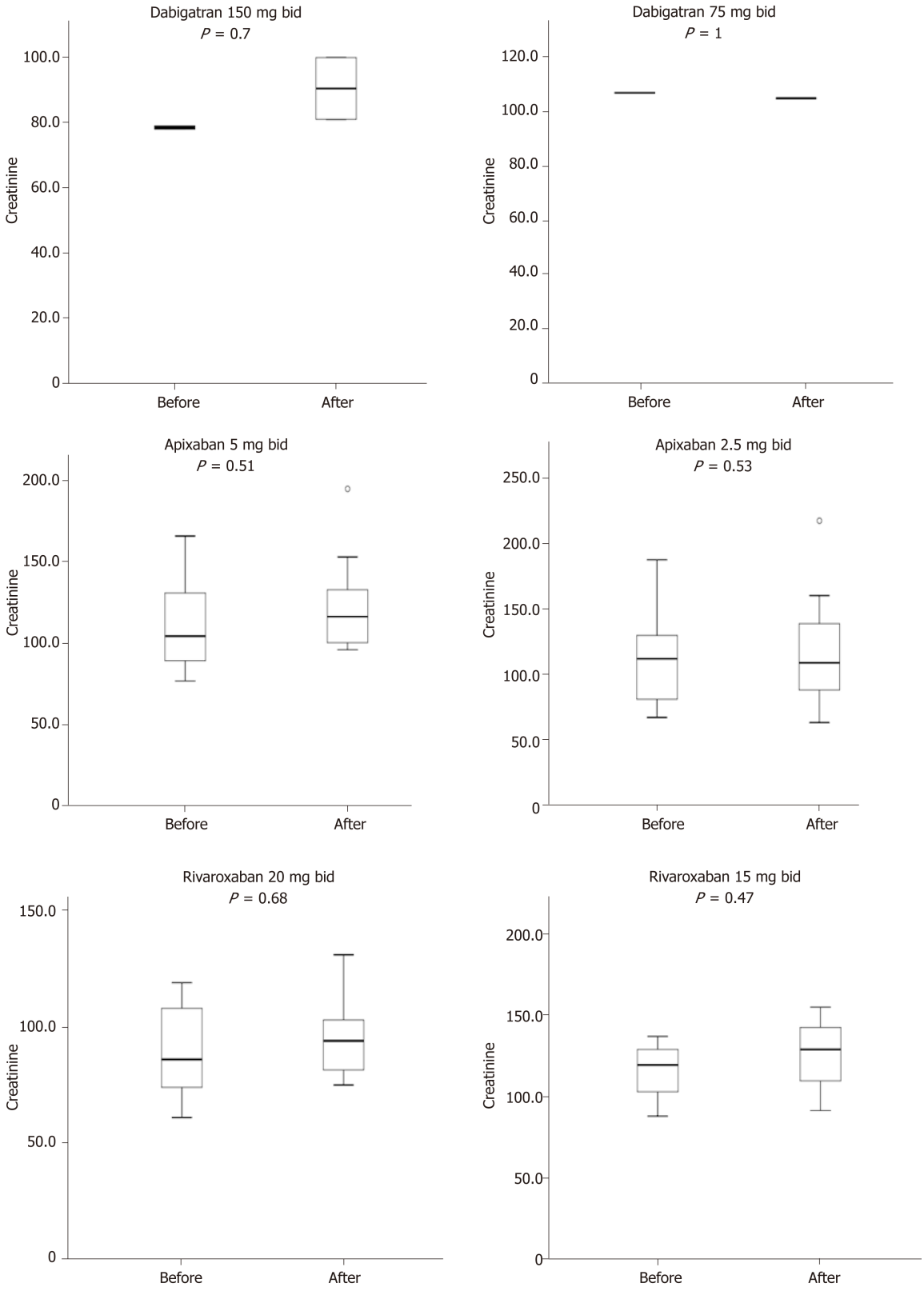

Figure 2 Estimated glomerular filtration rate before and after treatments with novel oral anticoagulants. Boxplots showing the distribution of estimated glomerular filtration rate levels (mL/min/1.73 m^2) before and after novel oral anticoagulants treatment. Points indicate individual patients, with colors representing age groups.

ARTICLE HIGHLIGHTS

Research background

Novel oral anticoagulants are increasingly being used in recent times for preventing stroke in individuals with atrial fibrillation and for the management of systemic embolic events and

venous thromboembolism. With the increased risk of atrial fibrillation and thrombotic events observed in kidney transplant recipients, whether novel oral anticoagulants have clinical significance in this group of patients remains unclear.

Research motivation

Novel oral anticoagulants are being used as an oral anticoagulation agent for the prevention of embolic events in individuals with atrial fibrillation and for the treatment of venous thromboembolism. They also have the advantage of not requiring frequent monitoring and having a lower adverse effects profile. There are concerns regarding the clinical use of novel oral anticoagulants in renal transplant recipients because of its renal excretion and the likelihood of its interaction with immunosuppressive agents. Although, novel oral anticoagulants have successfully been used for anticoagulation in heart-lung transplant recipients, its use for this role in kidney transplant recipients is unknown.

Research objectives

We performed this retrospective study to assess the efficacy and safety of novel oral anticoagulants administration in patients after kidney transplantation, and to provide recommendations and guidelines on therapeutic strategies in these patients.

Research methods

This was a retrospective study carried out among adult patients who were actively on the following novel oral anticoagulants (apixaban, rivaroxaban or dabigatran) in our renal transplantation program from December 2015 to December 2016. The outcomes of interest include the profile of the patients, thromboembolic and bleeding events, and kidney dysfunction.

Research results

The authors observed 3 (7.1%) bleeding events in the cohort. Also, no (0%) thromboembolic events were observed. In addition, no significant changes in pre- and post- novel oral anticoagulants tacrolimus level, creatinine level, and estimated glomerular filtration rates were observed.

Research conclusions

Novel oral anticoagulants appear to be as effective in the renal transplantation population as in the general population. Also, we had a few bleeding events and no changes in renal function after the initiation of novel oral anticoagulants which suggests a good safety profile.

Research perspectives

This study demonstrated that novel oral anticoagulants are safe and effective in renal transplant recipients. There is a need for further clinical studies to assess the mechanisms of bleeding in patients exposed to novel oral anticoagulants. Randomised controlled trials are needed to compare the effectiveness and safety of novel oral anticoagulants compared to other vitamin K antagonists (*e.g.*, warfarin) in kidney transplant population.

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AIMS AND SCOPE

The primary aim of *World Journal of Transplantation* (*WJT*, *World J Transplant*) is to provide scholars and readers from various fields of transplantation with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJT mainly publishes articles reporting research results obtained in the field of transplantation and covering a wide range of topics including bone marrow transplantation, bone transplantation, bone-patellar tendon-bone grafting, brain tissue transplantation, corneal transplantation, descemet stripping endothelial keratoplasty, fetal tissue transplantation, heart transplantation, kidney transplantation, liver transplantation, lung transplantation, pancreas transplantation, skin transplantation, transplantation immunology, and vascularized composite allotransplantation.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Impact of recipient functional status on 1-year liver transplant outcomes

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Institutional review board statement: This study was deemed exempt by the University of Massachusetts Medical School Institutional Review Board.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained from the Scientific Registry of Transplant Recipients (SRTR). The SRTR is contracted to UNOS by the United States Department of Health and Human Services to manage data collected via government-mandated reporting by all United States transplant centers.

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Abstract

BACKGROUND

The Karnofsky Performance Status (KPS) scale has been widely validated for clinical practice for over 60 years.

AIM

To examine the extent to which poor pre-transplant functional status, assessed using the KPS scale, is associated with increased risk of mortality and/or graft failure at 1-year post-transplantation.

METHODS

This study included 38278 United States adults who underwent first, non-urgent, liver-only transplantation from 2005 to 2014 (Scientific Registry of Transplant Recipients). Functional impairment/disability was categorized as severe, moderate, or none/normal. Analyses were conducted using multivariable-adjusted Cox survival regression models.

RESULTS

The median age was 56 years, 31% were women, median pre-transplant Model

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for End-Stage for Liver Disease score was 18. Functional impairment was present in 70%; one-quarter of the sample was severely disabled. After controlling for key recipient and donor factors, moderately and severely disabled patients had a 1-year mortality rate of 1.32 [confidence interval (CI): 1.21-1.44] and 1.73 (95%CI: 1.56-1.91) compared to patients with no impairment, respectively. Subjects with moderate and severe disability also had a multivariable-adjusted 1-year graft failure rate of 1.13 (CI: 1.02-1.24) and 1.16 (CI: 1.02-1.31), respectively.

CONCLUSION

Pre-transplant functional status is a useful prognostic indicator for 1-year post-transplant patient and graft survival.

Key words: Patient survival; Transplantation; Liver disease; Clinical decision-making; Graft survival; Risk assessment/risk stratification

Core tip: Poor functional status, as defined by The Karnofsky Performance Status scale, is a strong predictor of worse 1-year post-transplant outcomes (patient and graft survival) in a national United States liver transplant population.

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INTRODUCTION

Due to increasing organ shortages in the United States, patients on the liver transplant waiting list are older and sicker than ever before, while wait time continues to climb[1-3]. Among the 15000 patients with End-Stage Liver Disease on the transplant waiting list in 2013, 20% were over 65 years old, 20% had been waiting for at least 5 years already, 20% died while awaiting transplant; fewer than 6000 patients received an organ[2]. In 2002, in response to increasing shortages and waitlist mortality, the liver allocation system was reorganized to prioritize patients according to urgency[4]. "Urgency" was defined according to risk of 3-month mortality, calculated using 3 objective laboratory values (creatinine, bilirubin, international normalized ratio) to create individualized Model for End-Stage for Liver Disease (MELD) scores used to rank patients. Although this system successfully lowered population-level waitlist mortality rates, it is an insufficient summary measure for describing global health status[5,6], and has recently been shown to underestimate mortality risk among subgroups of "frail" patients[6-8].

Frailty is increasingly recognized as an important predictor of outcomes after major surgical procedures including liver transplantation[9-11]. Frailty syndrome is defined by a cluster of signs and symptoms that are hallmark sequelae of liver disease, malnutrition, sarcopenia, functional impairment/disability, which ultimately lead to increased vulnerability to stressors due to depleted physiologic reserve[12]. However, there is no gold standard measure of frailty[13].

Liver and lung transplant centers in the United States are mandated to submit Karnofsky Performance Status (KPS) functional status data on all patients, with other clinical data, to the Organ Procurement and Transplantation Network (OPTN) each quarter. This frailty measure has been widely used in clinical practice and research for over 60 years and has been extensively validated across a wide range of disease groups including transplant, liver disease, and End-Stage Renal Disease populations[14-27]. However, though several studies have used KPS as a predictor of liver transplant outcomes, the majority of studies were limited in generalizability as they were either single-center studies[28,29], conducted outside of the United States[11,30], limited to the early post-transplant period[11,30,31], and/or took place before MELD implementation, at which point the transplant recipient population shifted dramatically[28,32]. In 2013, the Liver and Intestinal Transplant Committee of OPTN

publicly asked for researchers to fill this gap in the literature regarding the utility of the KPS scale in a national liver transplant population[18].

To our knowledge, this will be the first study to evaluate a standardized, validated measure of functional status as a predictor of 1-year post-transplant outcomes in a national United States liver transplant population. Using data from the only comprehensive nationwide transplant database, the United Network for Organ Sharing (UNOS) Scientific Registry of Transplant Recipients (SRTR), we assessed the clinical utility of the KPS scale for the prediction of 1-year post-liver transplant patient and graft survival.

MATERIALS AND METHODS

Study design and sample

This retrospective cohort study used data from the SRTR. The SRTR is contracted to UNOS by the United States Department of Health and Human Services to manage data collected via government-mandated reporting by all United States transplant centers. This study was deemed exempt by the University of Massachusetts Medical School Institutional Review Board.

The study population included patients that underwent a first liver transplant between January 1, 2005 and October 1, 2014 (Figure 1). Exclusion criteria consisted of the following: (1) Pediatric transplant (< 18 years); (2) Multi-organ transplant; (3) UNOS Status 1 or acute liver failure; (4) ICU pre-transplant; or (5) Subjects with missing data in any of the key variables of interest (variables with ≥ 5% missing values were not used in this study). Pediatric and multi-organ transplants were excluded because the organ allocation systems for these patients are separate, and represent a distinct set of indications and disease courses, than the general United States liver transplant population. In addition, the risk of complications and graft loss are higher in these groups. We excluded urgent (Status 1 or acute hepatic necrosis) and ICU-admitted patients. This was done because these are often patients who rapidly decline due to an inciting event (*e.g.*, infection) and may, therefore, be categorized as being of poor functional status due to the event as opposed to being "frail", which is conceptualized as a chronic process leading to depletion of physiologic reserve.

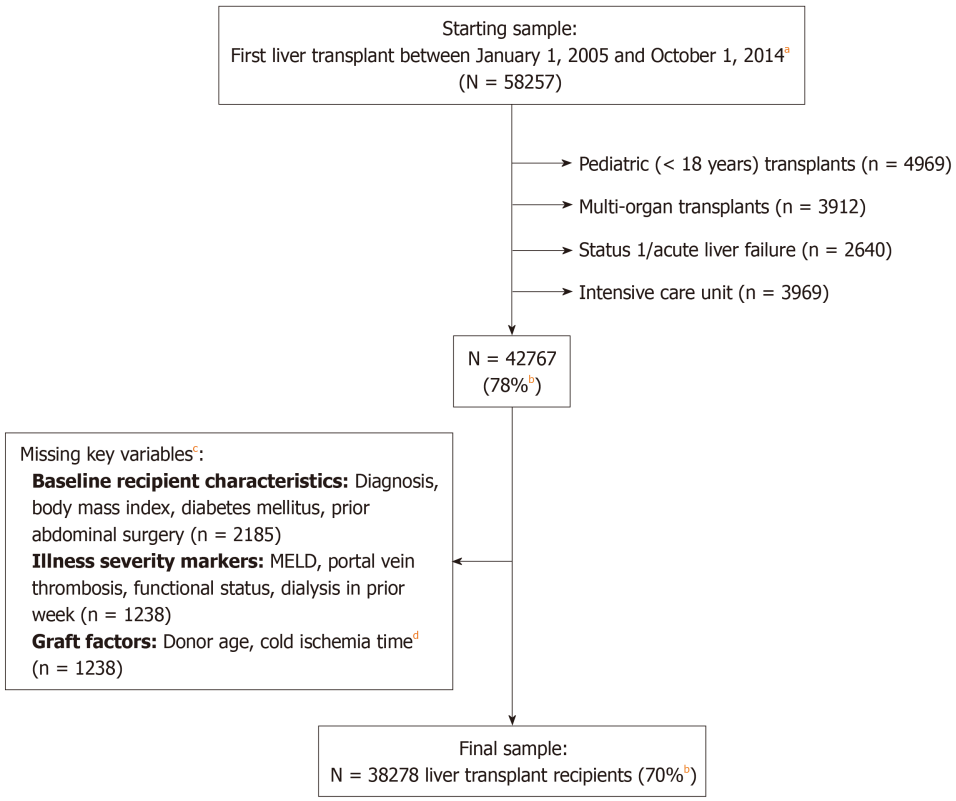
Data collection

Exposure variable: The primary exposure of interest was provider assessment of preoperative ("pre-transplant") functional status using the KPS scale (Table 1). The KPS defines functional status on an 11-point scale from 100% (normal, no complaints, no evidence of disease) to 0% (dead) in 10% increments, with 3 corresponding tiers. We used the 3-tiered version of the scale based on higher inter-rater reliability scores[33]. We assigned labels to the categories with respect to level of functional impairment/disability as follows: Subjects with minimal or no symptoms of disease (80%-100%) were labeled "(A) None/Normal [function]"; subjects needing varying levels of assistance in daily activities (50%-70%) were labeled "(B) Moderate [impairment in function]"; and subjects who were disabled and/or hospitalization indicated and/or moribund (10%-40%) were labeled "(C) Severe [functional impairment/disability]".

Study end points: The primary outcome of interest was 1-year all-cause mortality (Social Security Death Master File/Organ Procurement and Transplant Network data). As mortality after transplantation is highest in the early postoperative period and likely related to operative risks and complications that may become less relevant for long-term outcomes, the importance of functional status may change with time and context[34]. Therefore, we also examined death rates during the 1-month postoperative period (day 0-30) as compared to residual risk during the remaining 11 months of the year (day 31-365). The secondary outcome of interest was 1-year graft failure.

Lastly, among patients who did not experience either adverse outcome (death or graft failure), we describe the proportion that was able to return to "Normal" functional status during the first year post-transplant. Transplant centers must report follow-up data on transplant recipients at 6-month post-transplant, 1-year, and annually thereafter; follow-up records from day 0 to 395 (365 + 30 d) with functional status data available (< 5% of recipients were missing follow-up functional status) were analyzed (but counted once per patient).

Potential confounding variables: Potential confounders were identified from a priori clinical knowledge, literature review, and variables included in the SRTR risk-



[a]Re-transplants were not included in analyses
[b]Percent = $N_{remaining}$ / $N_{starting\ sample}$
[c]Only variables with < 5% missing values were considered
[d]Deceased donor cold ischemia time (living donor values corrected to median)

N: Number in study population; n: Number in group.

Figure 1 Study inclusion/exclusion criteria flow chart. Scientific Registry of Transplant Recipients.

adjustment models, available at srtr.org. Potential confounders included recipient sociodemographic and medical/surgical history factors (*i.e.*, information known at least 2 weeks before transplant, *e.g.*, primary liver diagnosis; Table 2), pre-transplant illness severity markers (*e.g.*, last-calculated laboratory MELD; Table 3), and all Donor Risk Index factors (*e.g.*, cause of death; Table 4)[34,35]. Every variable evaluated as a potential confounder was categorized and is described in Tables 2-4 (exceptions: Baseline functional status, time on the waitlist, and MELD component labs are listed for descriptive purposes only).

Statistical analysis

We explored bivariate relationships between the primary exposure (functional status) and potential confounders of interest using contingency table analyses [chi-squared tests for categorical variables, ANOVA for continuous variables, and Spearman's rho (r_s) for ordered-variable correlations, using expanded KPS, continuous MELD]. Relationships between variables and post-transplant time were explored graphically. One-year cumulative failure rates were estimated using the Kaplan Meier method.

To quantify the extent to which impaired functional status was associated with increased risk of 1-year all-cause mortality and 1-year graft failure, we developed separate Cox survival regression models for each outcome. We applied a manual forward approach, sequentially adding conceptually meaningful groups of variables to the model. With the exception of recipient age, sex, race/ethnicity, and MELD, variables (and variable interactions) with p-values of > 0.05 were excluded from the final model. Goodness-of-fit and proportionality of hazards were tested using the omnibus Gronnesby and Borgan test and martingale residuals and confirmed non-significant (no evidence of poor fit) for all models reported[36].

Results are reported as hazard ratios (HR) with 95% confidence interval (CI); *P*-values ≤ 0.05 were considered statistically significant. All analyses were conducted using Stata version 13 (StataCorp LP, College Station, TX, United States).

Table 1 Karnofsky Performance Status scale and variable handling

Condition[a]	%	Rating criteria
A ("None/Normal") Able to carry on normal activity and to work; no special care needed	100	Normal, no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
B ("Moderate") Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most of his personal needs
	50	Requires considerable assistance and frequent medical care
C ("Severe") Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospital admission is indicated although death not imminent
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

[a]Author-assigned variable labels in parentheses.

RESULTS

Sample characteristics

The final study sample included 38278 liver transplant recipients (Figure 1). The median [interquartile range (IQR)] age was 56 (51-61) years and MELD was 18 (12-25). Women represented 31% of the sample and the largest ethnic minority was Hispanic/Latino (12.7%). Median follow-up time was 3.3 (1.5-6.0) years after transplant.

At pre-transplant assessment, approximately 70% of the sample had some degree of functional impairment or disability. Approximately one-quarter (23.7%) had "Severe" functional impairment/disability (≤ 40% function), 45.8% were "Moderately" impaired, and the remaining 30.5% had no functional impairments (≥ 80% function). The median (IQR) pre-transplant functional performance status score was 60% (50%-80%) and the mean (standard deviation) was 61% (21%).

Baseline characteristics and changes over waitlist course

Table 2 describes baseline characteristics of the sample by category of pre-transplant functional status. Subjects who were of worse functional status pre-transplant were more likely to be female, of Hispanic/Latino race/ethnicity, and/or have Medicaid insurance. Primary diagnosis of hepatic malignancy was associated with better physical function. Baseline and pre-transplant functional status were moderately correlated (r_s = 0.42, P < 0.001). Sixty-percent of recipients maintained the same level of function over their waitlist course while 30% declined from a higher level of function at baseline.

Table 3 describes recipient clinical characteristics pre-transplant by category of pre-transplant functional status. Significant weight loss (≥ 5% of baseline weight) over the waitlist period was more common among transplant recipients who were impaired/disabled pre-transplant, and the weight loss occurred more rapidly. Poor functional status was moderately correlated with worse (higher) MELD scores (r_s = -0.49; P < 0.001). However, only 64% of subjects with MELD scores ≥ 30 were "Severely" impaired/disabled, and less than half (44%) of patients with MELD scores < 15 were of "Normal" functional status. Cirrhosis severity according to Child-Pugh class was associated with severity of functional status. Around 10% of severely impaired subjects were on dialysis pre-transplant, compared to < 1% of Normal functional status subjects.

Table 4 describes donor characteristics by categories of pre-transplant functional status. Donor characteristics were mostly comparable across functional status categories. Only 8.3% of living donor liver transplant recipients was Severely impaired/disabled (n = 729). Functionally impaired patients were slightly less likely to receive higher risk organs (*e.g.*, donor ≥ 70 years, nationally allocated or with

Table 2 Baseline characteristics[a] by pre-transplant functional status, Scientific Registry of Transplant Recipients 2005-2014 (*n* = 38278)

Characteristic[b]	Functional impairment/disability		
	A: None (*n* = 11674)	B: Moderate (*n* = 17530)	C: Severe (*n* = 9074)
Sociodemographics			
Age in years			
18-44	11.6	10.3	12.7
45-54	28.9	30.2	32.1
55-64	44.9	45.3	43.2
≥ 65	14.5	14.3	12.0
Women	26.8	32.1	33.4
Race/ethnicity			
White	73.1	74.3	70.4
Hispanic/Latino	10.6	12.5	15.9
Black	8.9	8.4	9.1
Health insurance			
Private	68.1	55.3	54.2
Medicare	18.5	26.5	24.6
Medicaid	8.8	14.0	17.0
Medical/Surgical History			
Functional impairment at registration			
None	74.6	33.4	22.4
Moderate	19.9	57.0	35.4
Severe	2.5	6.6	37.0
Primary cause of liver disease			
Non-Cholestatic	56.2	64.7	75.8
Cholestatic	9.5	8.1	7.8
Malignancy	30.1	23.0	12.5
Hepatitis C	44.4	45.5	42.1
Diabetes[c]	23.2	25.8	25.3
Previous Abdominal Surgery	46.2	51.6	50.3

[a]Characteristics known at least 2 weeks prior to transplant;
[b]Column percentage;
[c]Diabetes types 1, 2, or unspecified. All distributions varied significantly across categories of functional status ($P < 0.001$).

prolonged cold ischemia time).

All-cause mortality

Death within one year was observed in 3595 (9.4%) transplant recipients. The mortality rate was directly related to functional status. Among patients that were severely impaired/disabled, 12.8% died compared with 9.3% of those with moderate functional limitations and 6.9% of those with normal functional status at the time of transplant.

Table 5 describes the results of unadjusted and adjusted Cox regression models for 1-year mortality. Subjects with severe or moderate functional impairment pre-transplant were at significantly increased risk of dying within one year post-transplant. After multivariable adjustment, severely and moderately impaired patients had 1-year mortality rates that were 1.73 (CI: 1.56-1.91) and 1.32 (CI: 1.21-1.44) times greater than the hazard for subjects without any functional impairment, respectively.

Mortality risks were greatest in the immediate postoperative period (day 0-30) when 881 (2.3%) deaths were observed in a single month. The adjusted 30-d mortality risk for Severely impaired/disabled patients was more than double (HR: 2.10; CI: 1.71-2.59) that of patients of "Normal" functional status, after adjusting for all variables controlled for in the full 1-year survival model (Table 5). Approximately three-quarters (n = 2714) of all one-year deaths occurred during the remaining 11 mo of the postoperative year (day 31-365); HRs were comparable to estimates for overall one-year mortality (< 10% relative difference).

Table 3 Pre-transplant clinical characteristics by pre-transplant functional status, Scientific Registry of Transplant Recipients 2005-2014 (*n* = 38278)

Characteristic[a]	Functional impairment/disability		
	A: None (*n* = 11674)	B: Moderate (*n* = 17530)	C: Severe (*n* = 9074)
Waitlist time, mo	4.0 (1.3-10.2)	3.7 (1.1-10.3)	2.1 (0.4-8.4)
Weight loss ≥ 5%[b]	19.7	24.2	27.0
BMI, kg/m^2			
Underweight (< 18.5)	1.6	1.6	2.4
Normal (18.5-25)	28.3	27.5	27.1
Overweight (25-30)	37.0	36.0	34.0
Obese (≥ 30)	33.2	35.0	36.5
MELD			
< 15	49.9	34.9	14.3
15-29	45.9	56.5	45.9
≥ 30	4.2	8.6	39.8
Total bilirubin	2.3 (1.2-4.4)	3.0 (1.6-6.1)	6.6 (2.9-17.2)
International normalized ratio	1.4 (1.2-1.7)	1.5 (1.3-1.9)	2.0 (1.5-2.6)
Serum creatinine	0.9 (0.7-1.2)	1.0 (0.8-1.3)	1.4 (0.9-2.3)
Serum sodium	137 (134-140)	136 (133-139)	135 (132-139)
Child Pugh score			
A (Good)	23.8	11.8	4.1
B (Fair)	38.7	33.8	18.5
C (Poor)	37.5	54.4	77.4
Ascites[c]			
None	36.9	23.0	14.0
Mild/Moderate	48.4	52.4	43.5
Severe	14.8	24.6	42.6
Encephalopathy[d]			
None	52.7	36.6	26.0
Grade 1-2	44.4	57.5	61.4
Grade 3-4	2.9	5.9	12.6
Albumin			
> 3.5	26.7	19.3	22.8
2.8-3.5	41.7	41.2	39.0
< 2.8	31.6	39.6	38.2
Dialysis[e]	0.9	1.6	10.9
Portal Vein Thrombosis	6.5	9.7	12.4

[a]Column percentage or median (interquartile range);
[b]Relative to weight at time of waitlist registration;
[c]Mild/Moderate ascites: Diuretic-responsive; Severe ascites: Diuretic-refractory;
[d]Encephalopathy grade 1-2 (or precipitant-induced); Grade 3-4 (or chronic);
[e]Dialyzed at least twice in prior week. All distributions varied significantly across categories of functional status ($P < 0.001$). BMI: Body mass index; MELD: Model for End-Stage Liver Disease.

Graft failure

Graft failure was observed in 2214 of the study population within one year of transplant. The estimated failure rate on day 365 was 6.2% (cumulative failure or death rate on day 365: 12.7%). Approximately half (53.8%) received a second transplant within the first post-transplant year, of which 75.9% (n = 905) survived the year; 98.6% (n = 1008) of those who did not undergo retransplantation within the first postoperative year did not survive to 1-year post-transplant.

Table 6 describes the results of unadjusted and adjusted Cox regression models for 1-year graft failure. Subjects with severe and moderate impairment/disability had multivariable-adjusted 1-year graft failure rates that were 1.16 (CI: 1.02-1.31) and 1.13 (CI: 1.02-1.24) times higher than patients with normal function, respectively.

Table 4 Donor characteristics by pre-transplant functional status, Scientific Registry of Transplant Recipients 2005-2014 (*n* = 38278)

Characteristic[a]	Functional impairment/disability			*P* value
	A: None (*n* = 11674)	B: Moderate (*n* = 17530)	C: Severe (*n* = 9074)	
Transplant type: Living donor	5.5	5.0	2.3	< 0.001
Donor Risk Index[b]	1.6 (1.3-1.9)	1.6 (1.3-1.9)	1.5 (1.2-1.9)	< 0.001
Age in years				
18-39	37.3	37.1	39.9	
40-49	19.7	19.7	19.7	
50-59	19.8	20.4	20.7	
60-69	11.7	12.7	10.8	
≥ 70	5.5	4.9	3.9	< 0.001
Women	40.5	41.4	40.9	0.35
Race/ethnicity				
White	68.2	68.1	65.6	
Black	17.2	17.9	17.5	
Other	14.6	14.0	16.9	< 0.001
BMI, kg/m^2				
Underweight (< 18.5)	2.9	2.9	2.6	
Normal (18.5-25)	36.5	35.9	36.2	
Overweight (25-30)	33.5	34.2	33.4	
Obese (≥ 30)	27.1	27.0	27.9	0.43
Cause of death				
Trauma	34.3	34.1	34.1	
Anoxia	21.5	22.5	24	
Cardiovascular accident	41.4	40.9	39.4	< 0.01
Donation after cardiac death	12.6	13.2	12.1	0.04
Split/Partial liver	1.5	1.4	1.3	0.38
Allocation type				
Regional	17.8	19.9	23.3	
National	6.6	5.0	3.8	< 0.001
Cold ischemia time ≥ 8 h	30.9	28.9	27.9	< 0.001

[a]Column percentage or median (interquartile range);
[b]Donor risk index as described by Feng *et al*[35], 2006. BMI: Body mass index.

Functional status post-liver transplant

Among the 33764 (88.2%) transplant recipients who experienced neither outcome (death or graft failure within a year), 95% (*n* = 32004) had at least 1 follow-up functional status assessment within a year. The majority (86.3%) recovered from transplant and reached "Normal" functional status within 1 year. Of the 7258 recipients in this subsample that were severely impaired/disabled pre-transplant, 81% (*n* = 5861) recovered full physical function ("Normal" functional status) within 1 year of transplant.

DISCUSSION

Almost 1 in 4 patients included in this national study of 38278 United States adults that underwent non-urgent liver transplantation between 2005 and 2014 had severe functional impairment/disability at the time of transplant. This group of patients was found to have a markedly increased hazard of dying and/or having graft failure at 1 year compared to Normal functional status patients. This increased hazard was observed in both unadjusted and multivariable-adjusted regression analyses controlling for a variety of potentially confounding factors of prognostic importance. Approximately 86% of recipients who did not experience 1-year death or graft failure (and had follow-up data available) recovered from transplant and reached "Normal"

Table 5 Association between pre-transplant functional status and 1-year (all-cause) post-transplant mortality, Scientific Registry of Transplant Recipients 2005–2014 (*n* = 38278[a])

Functional impairment/disability	Hazard Ratio (95%CI)					
	1-Yr		Day 0-30[c]		Day 31-365[d]	
	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
Severe	1.94 (1.77-2.13)	1.73 (1.56-1.91)	2.40 (1.99-2.89)	2.10 (1.71-2.59)	1.82 (1.64-2.02)	1.62 (1.45-1.82)
Moderate	1.38 (1.27-1.51)	1.32 (1.21-1.44)	1.60 (1.34-1.92)	1.53 (1.27-1.83)	1.33 (1.20-1.46)	1.26 (1.15-1.40)
None	Referent		Referent		Referent	

[a]Adjusted model *n* = 380762 [missing albumin (*n* = 1) or donor body mass index (*n* = 200)];
[b]Adjusted for recipient age, sex, race, insurance, body mass index (BMI), diabetes, previous abdominal surgery, liver disease, MELD, albumin, portal vein thrombosis, dialysis; donor age, race, BMI, donor type (living or deceased) and cause of death, donation after cardiac death, allocation type, cold ischemia time ≥ 8 hours; interactions: recipient BMI and diabetes, recipient hepatitis C and portal vein thrombosis, recipient hepatitis C and donor age;

[c]Postoperative day 0−30: *n* = 38,278; 881 deaths;

[d]Postoperative day 31−365: *n* = 37352; 2714 deaths. BMI: Body mass index; CI: Confidence interval; MELD: Model for End-Stage Liver Disease.

functional status within 1-year.

We present data from the first national study illustrating the role of pre-transplant functional status as a predictor of one-year survival among liver transplant recipients. Our results are in agreement with the findings from earlier studies that evaluated Poor functional status as a predictor of adverse transplant outcomes[11,28-30]. Two such studies, each with approximately 4000 United Kingdom recipients of a liver transplant, reported a near 2-fold increased risk of post-transplant mortality at 90 d for the worst functioning group relative to the highest functioning group[11,30]. Studies have also shown that objective measures of physical function, such as walking distance or speed and grip strength, are also strong predictors of adverse liver transplant outcomes regardless of recipient age, size, or cause/severity of liver disease[29].

Implications

Insight into a transplant patient's global health status guides day-to-day clinical management, as well as transplant decisions, particularly in the face of contradictory laboratory or otherwise objective measures of pathological disease progression (*e.g.*, MELD score). Capturing such insight through the use of a quantitative physical health scale may help transplant teams to strategize and communicate complex medical and surgical management decisions with patients, families, and the many other members of multidisciplinary transplant teams that provide longitudinal care for liver transplant patients.

Knowledge of a patient's functional status before transplant may practically assist transplant teams to anticipate, communicate, and coordinate resources for postoperative critical care, rehabilitation after discharge, and potentially longer-term occupational therapy to help patients recover physical health and quality of life[37]. Many well-established risk factors for adverse outcomes among patients undergoing liver transplant may be unpredictable or sudden (spontaneous bacterial peritonitis), unavoidable (older age), and/or untreatable (portal vein thrombosis). Furthermore, many of the strongest predictors of adverse outcomes are present in a relatively small percentage of the liver transplant population. Many risk factors are unknown until very close to transplant time (*e.g.*, life support, cold ischemia time), whereas functional impairment can present very early and progress insidiously in end-stage liver disease patients over the course of waiting for an organ. All patients can also be assigned a value for functional status at baseline, which can be used as a reference point to assess change over time. While this scale is an all-encompassing global physical function measure and a patient can fall anywhere on the continuous scale, many risk factors considered in transplant decisions are individual dichotomous variables, which are usually assessed in combination with other risk factors that can take time to accumulate. Thus, as functional status is a harbinger of adverse outcomes and may present early, it may be a useful clinical tracking tool that can be used for strategic care management.

Promising interventional studies have also shown that "prehabilitation", physical therapy (*e.g.*, strength training) and nutritional support, designed to improve functional status (or slow decline) in anticipation of a physiologic stressor such as surgery[38,39], is effective at improving postoperative recovery and outcomes after

Table 6 Association between pre-transplant functional status and 1-year graft failure, Scientific Registry of Transplant Recipients 2005-2014 (*n* = 38278)

Functional impairment/disability	Events, *n*[a]	Hazard Ratio (95%CI)	
		Unadjusted	Adjusted[b]
Severe	527	1.10 (0.98-1.23)	1.16 (1.02-1.31)
Moderate	1051	1.12 (1.01-1.23)	1.13 (1.02-1.24)
None	636	Referent	Referent

[a]Number of graft failures within 1 year of liver transplantation;
[b]Adjusted for recipient age, sex, race, body mass index (BMI), primary diagnosis of liver disease, MELD, portal vein thrombosis; donor age, race, BMI, donor type (living or deceased) and cause of death, donation after cardiac death, cold ischemia time ≥ 8 h; interactions: recipient hepatitis C and portal vein thrombosis, recipient hepatitis C and donor age. BMI: Body mass index; CI: Confidence interval; MELD: Model for End-Stage Liver Disease.

major abdominal surgery[40-44]. Although none of these studies focused on liver transplant patients, several included cohorts that similarly have a high likelihood of becoming frail due malnutrition, inflammation, and sarcopenia (*e.g.*, cancer patients[41,42] and older populations[43,44]). Prehabilitation has the potential for providing clinicians with a way to not only recognize, but also slow or prevent decline to the point of "Severe" impairment/disability. However, more research on prehabilitation specific to a liver disease population is warranted. Frailty due to liver failure may not respond to the same interventions that have successfully slowed progression of frailty due to aging as there may be fundamental differences in etiology and pathogenesis between these populations that may limit their effectiveness[45].

Strengths and limitations

Strengths of this study include its use of the SRTR with complete capture of every solid organ transplant in the United States since 1987, including waitlist, donor, follow-up, and external data file linkages (*e.g.*, Social Security Death Master File). Mandated reporting of KPS providing more than a decade of nationally representative data on functional status is also a major strength of our investigation.

This study is limited by reliance on the less-than-ideal KPS scale as it is the only available measure of functional status in the SRTR. The KPS uses multiple domains in the assessment of function and concern may arise that it is less objective or standardized than direct measures of frailty such as grip strength or walking distance. However, the KPS has been extensively validated across a wide range of diseases over the last 60 years, and the simplest 3-tiered scale version used in this analysis has shown excellent inter-rater reliability regardless of provider type or setting[33]. The KPS has in fact been validated in transplant populations specifically, compared with the Short Form survey and other physical function scales for liver disease patients[46], and extensively validated in end-stage renal disease populations[14,19].

Several different measures of physical function and composite frailty scores have been used in the literature and were effective predictors of waitlist and transplant outcomes. However, such direct measures of frailty would demand more resources (time, training, materials) from transplant centers than the KPS alone. Furthermore, their advantages over the use of the KPS should be evaluated in terms of predictive value (area under the curve) before major investment in resource-intensive measures that may already capture similar predictive information.

In summary, we have demonstrated that there is substantial value in using a simple 3-point functional status scale for predicting one-year liver transplant outcomes. We highlight areas where future research may further the validity, and ultimately, the clinical utility of the Karnofsky Functional Performance scale in a liver transplant population. It is important to continue to develop objective measures for describing global health status and illness severity to help in the allocation of organs and waitlist management, patient health improvement, and accurate adjustment for transplant center case-mix for transplant reimbursement.

ARTICLE HIGHLIGHTS

Research background

Frailty is increasingly recognized as an important predictor of outcomes after major surgical procedures including liver transplantation. The Karnofsky Performance Status (KPS) scale has

been widely validated for clinical practice for over 60 years.

Research motivation
To investigate the impact of frailty on liver transplant outcomes.

Research objectives
We wanted to determine the extent to which poor pre-transplant functional status, assessed using the KPS scale, is associated with increased risk of mortality and/or graft failure at 1-year post-transplantation. This would give clinicians some objective assessment and help on the decision to allocate livers for high-risk recipients.

Research methods
This study included 38278 United States adults who underwent first, non-urgent, liver-only transplantation from 2005 to 2014 (Scientific Registry of Transplant Recipients). Functional impairment/disability was categorized as severe (10%-40% of optimal function), moderate (50%-70%), or none/normal (80%-100%). Analyses were conducted using multivariable-adjusted Cox survival regression models. We explored bivariate relationships between the primary exposure (functional status) and potential confounders of interest using contingency table analyses [chi-squared tests for categorical variables, ANOVA for continuous variables, and Spearman's rho (r_s) for ordered-variable correlations, using expanded KPS, continuous Model for End-Stage for Liver Disease (MELD)]. Relationships between variables and post-transplant time were explored graphically. One-year cumulative failure rates were estimated using the Kaplan Meier method.

Research results
The median age was 56 years, 31% were women, median pre-transplant MELD was 18. Functional impairment was present in 70%; one-quarter of the sample was severely disabled. After controlling for key recipient and donor factors, moderately and severely disabled patients had a 1-year mortality rate of 1.32 [confidence interval (CI): 1.21-1.44] and 1.73 (95%CI: 1.56-1.91) compared to patients with no impairment, respectively. Subjects with moderate and severe disability also had a multivariable-adjusted 1-year graft failure rate of 1.13 (CI: 1.02-1.24) and 1.16 (CI: 1.02-1.31), respectively.

Research conclusions
Pre-transplant functional status is a useful prognostic indicator for 1-year post-transplant patient and graft survival. It is important to continue to develop objective measures for describing global health status and illness severity to help in the allocation of organs and waitlist management, patient health improvement, and accurate adjustment for transplant center case-mix for transplant reimbursement. We present data from the first national study illustrating the role of pre-transplant functional status as a predictor of one-year survival among liver transplant recipients. Our results are in agreement with the findings from earlier studies that evaluated Poor functional status as a predictor of adverse transplant outcomes. We have not proposed any theory. The index of frailty - The KPS scale - can be used as a predictor of 1-year post-transplant outcomes (patient and graft survival) in a national United States liver transplant population. Poor functional status predicts 1-year post-liver transplant outcomes. No new methods were proposed. We used very well-established methods of outcome research. It will help to determine objective measures for describing frailty and overall clinical status to help in the allocation of organs and waitlist management, patient health improvement, transplant reimbursement, and policy changes.

Research perspectives
That patients' pre-transplant frailty plays a critical role in transplant outcomes and the transplant community need to study it with more detail. To perform prospective and randomized studies associating frailty index with other biomarkers and correlate them with transplant outcomes. Associating frailty indexes with other biomarkers and correlate them with transplant outcomes. To measure the impact of interventions to improve frailty pre-transplant and correlate it with outcomes.

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FIELD OF VISION

Challenges of pancreas transplantation in developing countries, exploring the Turkey example

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Abstract

Pancreas transplantation significantly improves the quality of life for people with type 1 diabetes, primarily by eliminating the need for insulin and frequent blood glucose measurements. Despite the growing numbers of solid organ transplantations worldwide, number of pancreas transplantations in the developing countries` remain significantly low. This difference of pancreas transplantation practices was striking among the participating countries at the 1st International Transplant Network Meeting which was held in Turkey on 2018. In this meeting more than 40 countries were represented. Most of these counties were developing countries located in Africa, Middle East or Asia. The aim of this article is to identify the challenges and limiting factors for pancreas transplantations in these developing countries, by exploring the Turkish example. The challenges faced by the developing countries are broadly classified in four categories; wait-listing, donor pool, team work and follow up. Under these categorical titles, issues are further discussed in detail, giving examples from Turkish practice of pancreas transplantation. Additionally, several solutions to these challenges have been proposed- some of which have already been undertaken by the Turkish Ministry of Health. With the insight and methods presented in this article, pancreas transplantation should be made possible for the potential recipients in the developing countries.

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Key words: Pancreas transplantation; Challenges; Transplantation; Quality of life; Developing country

Core tip: With the insight and methods presented in this article, pancreas transplantation should be made possible for the potential recipients in the developing countries. This short communication attempts to summarize the expert discussions on pancreas transplantation occurring during the 1st International Transplant Meeting involving more than 40 countries' representatives.

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INTRODUCTION

The outcome of pancreas transplantations has improved over the last few decades, with one-year graft survival rates currently at about eighty percent and three-year graft survival rates at sixty percent[1-3]. This has been made possible by improvements in immunosuppression, refinement of surgical technique, better recipient- and donor-selection criteria, and interdisciplinary post-transplant patient management[4,5]. Unlike other forms of transplantation, the main goal of pancreas transplant surgery is to achieve insulin independence, with resultant decreased morbidity and increased quality of life, rather than to save lives[6,7]. Pancreas transplantation can restore glucose control and is intended to prevent, pause, or reverse secondary complications from diabetes, rendering it the definitive treatment option for these patients[8,9].

Pancreas transplantation can be performed by three different routes. The first is pancreas transplantation alone, which accounts for approximately 8% of all pancreas transplantations worldwide[10]. The second and most commonly used route is simultaneous pancreas and kidney transplantation (SPKT), which provides the best outcome of the three and accounts for 80% of all pancreatic transplants worldwide[11]. The third route is pancreas after kidney transplantation which is an additional option for selected patients[12]. Islet cell transplantation is another important method for achieving insulin independence, but it is beyond the scope of this article.

Despite these positive developments in pancreas transplantation, in Turkey, as well as other developing countries, pancreas transplants have not flourished as much as kidney and liver transplants. In this article, we discuss ways to improve both the number and outcome of pancreas transplantations in developing countries, by exploring the example of Turkey.

COMMUNICATION IS THE KEY

There are many challenges regarding pancreas transplantation in developing countries and communication between specialists is the key to overcome these challenges. To explore these, we retrieved and analyzed the expert discussions by the pancreas transplant panel of the 1st International Transplant Meeting in 2019, where representatives of more than 40 countries presented their experience of different types of transplantations, with a focus on the specific challenges involved. A list of the participating counties can be found in the appendix[13].

ASSESSMENTS AND OPTIMIZATION STRATEGIES

The challenges found to be common in all developing countries were categorized into four main groups. Challenges and strategies for optimizing current practice are discussed in detail below using examples from Turkey's applications.

Wait-listing

Those on pancreas transplant wait-lists can be classified into two groups. The first consists of typical recipients, who are Type-1 diabetic patients with a low or normal body mass index (BMI). These patients are also prone to ketosis and unable to produce insulin because of autoimmune beta-cell destruction. Their C-peptide levels are extremely low or undetectable[14].

The second group can be classified as atypical recipients, who have Type-2 diabetes[15]. These recipients should be carefully selected, taking into account their BMI and insulin requirement, in order to avoid significant insulin resistance. Before listing for transplantation, their BMI should be less than 30 kg/m^2 and their insulin requirement less than 100 units per day. In this way, it can be ensured that the recipient can become euglycemic after pancreas transplantation.

In developing countries, lack of regular exercise, poor nutritional choices, and relatively higher smoking rates lead to higher body mass indices, which may increase the cardiovascular risk in potential recipients[16]. These types of patients are either not listed or are suspended from the list due to their high cardiovascular risk. Consequently, this keeps the SPKT transplant wait-list short and decreases the driving force and motivation of dedicated transplant teams and relevant organizations. Even though it is very difficult to achieve in some areas, more promotion and attention to good healthcare advice in diabetic patients is necessary. According to data from the Turkish Ministry of Health, in 2016, 11 patients were waiting for SPKT, out of a population of 79.8 million. The pancreas-only wait-list consisted of 274 patients, which although is considerably more than the SPKT list is also lower than the expected listing rate when compared to other countries[17].

In some countries, such as Turkey, the allocation system itself can be a reason for the lack of drive to perform such transplants. Under the Turkish system, all organ offers are coordinated by the National Coordination Center (NCC), a branch of the Ministry of Health. The NCC oversees nine regional coordination centers in Turkey[17]. The allocation of organs is performed in a hierarchical fashion, and the NCC is responsible for all assignment and strategic decisions.

With regard to pancreas allocation, the system in Turkey differs from others in Europe and in North America. For example, in the United Kingdom, when deceased-donor kidneys become available for transplantation, they are offered by the National Health Service Blood and Transplant organization through the National Kidney Allocation Scheme, which prioritizes patients listed for a pancreas transplant[18]. As a result of this practice, on each occasion where a pancreas from a deceased donor is available, a single kidney is offered with the pancreas for SPKT. This priority does not exist in the Turkish allocation system. Thus, it is possibly taking the survival benefit opportunity of adding a pancreas to the transplanted donor kidney away from the potential recipient.

Donor pool

For the pancreatic donor pool, there are three options of donation worldwide: Donation after brain death (DBD), donation after circulatory death (DCD), and segmental pancreas living donation[19,20]. There has been an increase in the number of European and American transplant programs that utilize the option of DCD donors for their recipients. All these donors are selected using strict criteria, including a BMI lower than 30, hemoglobin A1c levels within normal ranges, age below 55, and no fatty infiltration of the pancreas. With regard to living-donor segmental pancreas transplantation, the main experience comes from surgeons in Minnesota, where more than 160 such transplants have been performed since 1977, with very good results.

At present, only the DBD resource is utilized in developing countries, including Turkey. The criteria for DBD donation are slightly less strict than DCD and allow donation up to the age of 60 and mild steatosis. The overall rate of DBD donors in developing countries is relatively low, and donors complying with these criteria are even lower. As a result, in 2016, only six deceased-donor pancreas transplants were performed in Turkey from brain-dead donors complying with these criteria. Table 1 and Figure 1 show clearly the huge variability in pancreas transplantations between different countries in 2016.

In pancreas transplantation, prolonged cold ischemia time is one of the most important risk factors for early pancreatic graft failure[20]. Prolonged cold ischemia can be a difficult issue to manage in a large geographical area such as Turkey, where the peninsula is intercontinental, situated at the crossroads of the Balkans, Caucasus, Middle East, and Eastern Mediterranean. Keeping this geography in mind, existing modes of organ transportation should be used effectively to provide quick solutions for transplant centers.

Lastly, the lack of trained local procurement teams also contributes to the decreased donor pool, either through not being able to retrieve the pancreas in the first place or

Table 1 The number of pancreas transplants performed globally in 2016[27]

Country	Number of Pancreas Transplants performed in 2016
Kuwait	1
Romania	1
Peru	1
Kazakhstan	1
Uruguay	2
Estonia	2
Lithuania	2
Belarus	2
Thailand	2
Mexico	3
New Zealand	4
Chile	4
South Africa	4
Colombia	5
Slovenia	5
Russian Federation	6
Turkey	6
Hungary	6
Croatia	7
Denmark	7
Switzerland	11
Belgium	11
Saudi Arabia	11
Israel	12
Norway	20
Sweden	24
Netherlands	25
Portugal	25
Austria	26
Finland	27
Iran (Islamic Republic of)	30
Poland	38
Japan	38
Czech Republic	41
Argentina	48
Australia	51
Italy	67
Spain	73
France	90
Canada	95
Germany	97
Brazil	134
United Kingdom	206
United States	1013

Data of the WHO-ONT Global Observatory on Donation and Transplantation office (Source: Global Observatory on Donation and Transplantation Data).

by injuring the pancreatic vessels or parenchyma and rendering the organ untransplantable. According to Turkish Ministry of Health data, between 2002 and 2016, 121 DBD organs were unable to be used due to pathological or technical reasons[21].

Team-work

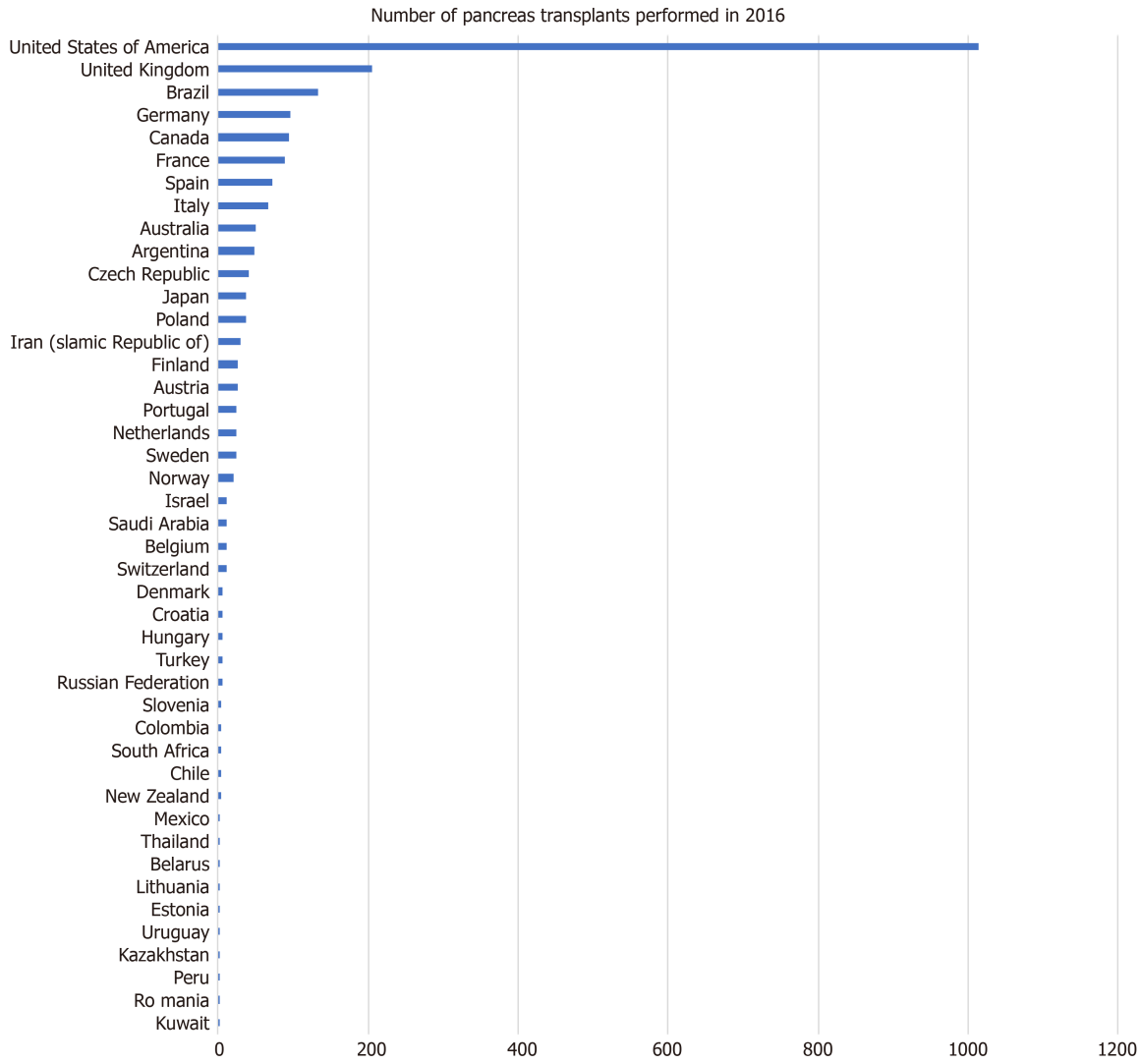

Figure 1 The number of pancreas transplants performed globally in 2016[27]**.** Data of the WHO-ONT Global Observatory on Donation and Transplantation office (Source: Global Observatory on Donation and Transplantation Data).

Another challenging aspect of pancreas transplantation is that it requires extensive team work, with an endocrinologist or diabetologist, nephrologist, transplant surgeon particularly trained in pancreas transplantation, intensivist, donor coordinator who can identify potential pancreas donors, and competent retrieval team[22]. Knowledge, clear communication, and trust are essential, and without them, as well as an overall low center volume, pancreas transplantation can result in significantly unfavorable outcomes. To establish clear communication within a team, hierarchical borders may need to be removed as some will come with a lower level of knowledge or contribution of opinion. In some cases, they may turn any discussion field into a monarchial arena.

In addition, the steep learning curve of pancreas transplantation is particularly difficult to accomplish in Turkey because the healthcare and transplantation services are provided by different sectors, such as the Ministry of Health, universities, and the private sector, leading to a lack of collaborative culture.

Follow-up

With potentially life-threatening complications seen in up to 25%-30% of recipients, post-transplant follow-up is critical. This is particularly important during the first 90 d[23], as technical failure is the most common cause of graft loss, accounting for more than seventy percent of all losses[24]. Technical failures can be the result of graft thrombosis, anastomotic leak, and pancreatitis, and management of these serious complications requires skill, expertise, experience, and a patient-centered approach. Therefore, the team of physicians dedicated to the care of the pancreas transplant recipient and the necessary protocols in managing all aspects of the patient care should be prepared in advance, following local consensus and international

guidelines, to avoid conflicting views and leave no room for error. Regular audits of patient and graft outcomes are paramount.

DISCUSSION

In order to increase transplantation rates from DBD donors, more effort should be directed towards increasing the assessment and therefore the diagnosis of brain death. Since most of these donors come from Intensive Care Units, the intensive care specialists should be particularly trained in detecting brain death, including complicated cases[25]. Annual nationwide courses are funded by the Ministry of Health in Turkey to train these intensive care specialists and donor coordinators, with the aim of providing a standardized communication platform for handling future difficult cases[2]. However, attendance on these courses is optional.

Training of medical professionals should go hand in hand with educating the public about brain death and organ donation[26]. There is an urgent need to increase public knowledge of the facts and benefits of organ donation and transplantation. Such efforts need to targ*et al*l socioeconomic levels of the population and start at school age, so that organ donation becomes a normal part of life, much like donating blood.

Also, medical teams should be well prepared to procure donor organs in a timely manner. Therefore, local organ-procurement teams are crucial in large geographical areas to ensure quick, efficient retrieval and optimal preservation of the pancreas. The Turkish Ministry of Health is developing a new program to train local procurement teams, which will be directly in contact with the nine regional coordination centers.

At the transplant centers, it is important to ensure the presence of skilled, experienced, and functioning teams. Because the healthcare and transplantation services in Turkey are provided by different sources, an independent or semi-dependent body should be established to monitor and measure the effectiveness of all three main suppliers; Ministry of Health hospitals, university hospitals, and the private sector. Since the populations served, as well as the service policies of these suppliers, differ from each other in important ways, such an overseeing body would pave the way for standardization of transplantation and donation activities throughout the country. In this way, good clinical practice can be shared for the benefit of patients.

In Turkey, the role of the private sector in healthcare is continuing to increase, and the topics of "equity" and "allocdtion of resources" are being increasingly debated. It is therefore necessary to review the different health policies to ensure an individual-centered approach is put into practice, which in turn should decrease the negative effects of unequal distribution of funds in transplantation, ensuring that everyone's needs are met in terms of equity and achieving similar donation rates from all sources of healthcare providers.

Last, but not least, the allocation system should be connected to local procurement teams to shorten cold ischemia times and changed to provide the SPKT option for more recipients by allocating the pancreas together with the kidney. Additionally, national data on donation and transplantation should be published annually by the Ministry of Health or an independent establishment, to provide further standardization and dissemination of information nationwide.

CONCLUSION

Successful pancreas transplantation has shown to be efficacious in significantly improving the quality of life of people with diabetes, primarily by eliminating the need for exogenous insulin and frequent daily blood glucose measurements. Therefore, pancreas transplantation should be made possible for potential recipients in developing countries through patient optimization, improving the allocation systems to favor pancreas donation and transplantation where necessary, the adoption of dedicated teams at all stages of the process, including training local procurement teams, and promoting education, audit, and the sharing of good clinical practice.

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