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Game Changing Academic Papers
Year in Review

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Objectives

Heart Transplantation

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ORIGINAL ARTICLE

AJT

Study rationale, design, and pretransplantation alloantibody status: A first report of Clinical Trials in Organ Transplantation in Children-04 (CTOTC-04) in pediatric heart transplantation

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Anti-HLA donor-specific antibodies are associated with worse outcomes after organ transplantation. Among sensitized pediatric heart candidates, requirement for negative donor-specific cytotoxicity crossmatch increases wait times and mortality. However, transplantation with positive crossmatch may increase posttransplantation morbidity and mortality. We address this clinical challenge in a prospective, multicenter, observational cohort study of children listed for heart transplantation (Clinical Trials in Organ Transplantation in Children-04 [CTOTC-04]). Outcomes were compared among sensitized recipients who underwent transplantation with positive

Abbreviations: CDC-XM, complement-dependent cytotoxicity crossmatch; CHD, congenital heart disease; CTOTC, Clinical Trials in Organ Transplantation in Children; DSA, donor-specific antibody; ECMO, extracorporeal membrane oxygenation; EMB, endomyocardial biopsy; ICU, intensive care unit; IQR, interquartile range; ISHLT, International Society for Heart and Lung Transplantation; IVIG, intravenous immunoglobulin; LSA, Luminex LABScreen® single-antigen; LSM12, Luminex LABScreen® Mixed; MCS, mechanical circulatory support; MFI, median fluorescence intensity; MICA, major histocompatibility complex class I–related chain A; NIAID, National Institute of Allergy and Infectious Diseases of the National Institutes of Health; UNOS, United Network for Organ Sharing; VAD, ventricular assist device; VXM, virtual crossmatch.

Article Summary

- Prospective, multicenter study to assess the impact of pre-tx sensitization on pre-tx and post-tx outcomes in pediatric heart candidates, focusing on safety and efficacy of tx across +CDC-XM and impact of DSA on post-transplant outcomes
- HLA-antibodies associated with high waitlist mortality (historic requirement for –CDC-XM, as +CDC-XM associated with increased rejection, graft vasculopathy and dysfunction and failure)
- Identified higher frequency of sensitization than previously reported
  - Historic: 14-23%
  - Study: >50% and of those sensitized ~33% had peak MFI≥8000
- Risk factors:
  - CHD with prior cardiac surgery
  - Male sex; Weight at transplantation
  - VAD use

Lung Transplantation

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Mechanical Ventilation and Extracorporeal Membrane Oxygenation as a Bridging Strategy to Lung Transplantation: Significant Gains in Survival

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Mechanical ventilation (MV) and extracorporeal membrane oxygenation (ECMO) are increasingly used to bridge patients to lung transplantation. We investigated the impact of using MV, with or without ECMO, before lung transplantation on survival after transplantation by performing a retrospective analysis of 826 patients who underwent transplantation at our high-volume center. Recipient characteristics and posttransplant outcomes were analyzed. Most lung transplant recipients (729 patients) did not require bridging; 194 of these patients were propensity matched with patients who were bridged using MV alone (48 patients) or MV and ECMO (49 patients). There was no difference in overall survival between the MV and MV+ECMO groups ($p = 0.07$). The MV+ECMO group had significantly higher survival conditioned on surviving to 1 year (median 1,811 days ([MV] vs. not reached ([MV+ECMO], $p = 0.01$). Recipients in the MV+ECMO group, however, were more likely to require ECMO after lung transplantation (16.7% MV vs. 57.1% MV+ECMO, $p < 0.001$). There were no differences in duration of postoperative MV, hospital stay, graft survival, or the incidence of acute rejection, renal failure, bleeding requiring reoperation, or airway complications. In this contemporary series, the combination of MV and ECMO was a viable bridging strategy to lung transplantation that led to acceptable patient outcomes.

Abbreviations: BMI, body mass index; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization; LAS, lung allocation score; LVEF, left ventricular ejection fraction; MV, mechanical ventilation; PFTs, pulmonary function tests; SRTR, Scientific Registry of Transplant Recipients; UNOS, United Network for Organ Sharing; VIF, variance inflation factors

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Introduction

Lung transplantation is the most effective therapy for end-stage lung disease, but the scope of its application is limited by the paucity of suitable donors (1). The lung allocation score (LAS) was adopted in May 2005 to prioritize transplant recipients based on medical urgency rather the than length of time spent on the wait-list (2). This was a deliberate bid to decrease wait-list mortality, but it has also led to an increase in the clinical acuity among lung transplant recipients because those with higher LAS preferentially draw organ offers. Thus, there has been a corresponding increase in demand for ventilator and mechanical support to bridge these critically ill patients to transplantation.

As recently as 2010, mechanical ventilation (MV) was considered a relative contraindication for lung transplantation, and so the emphasis the LAS placed on transplanting the sickest patients created somewhat of a controversy. The morbidity, mortality, and increased incidence of nosocomial respiratory infection associated with MV were considered factors leading to long-term immobility and consequent respiratory and physical deconditioning among ventilated recipients (3). Indeed, many centers still cautiously approach MV as a bridge to lung transplantation and decline to list candidates (or delist candidates) once the recipient requires prolonged ventilator support. In

Article Summary

- Compared post-lung transplant survival among patients:
  - Mechanical ventilation alone
  - MV + ECMO
  - Each group propensity matched non-bridge patients
- MV+ECMO more likely to survive to 1-year than MV alone but more likely to need ECMO post-transplant
- No difference in duration of post-op MV, LOS, graft survival, acute rejection, airway complications

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ORIGINAL ARTICLE

AJT

Identification of risk epitope mismatches associated with de novo donor-specific HLA antibody development in cardiothoracic transplantation

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The development of de novo donor-specific HLA antibodies (dnDSA) after transplantation is associated with graft failure, mortality, and cost. There is no effective therapeutic intervention to prevent dnDSA or ameliorate associated injury. The aims of this study were to identify specific HLA factors associated with dnDSA development and to propose primary prevention strategies that could reduce the incidence of dnDSA without prohibitively limiting access to transplant. The investigation cohort included heart transplant recipients from 2008 to 2015 (n = 265). HLA typing was performed and HLA antibody testing was undertaken before and after transplantation. HLAMatchmaker analysis was performed for persistent dnDSA to identify potentially more immunogenic eplet differences. Validation was performed in recipients of lung transplants from 2008 to 2013 (n = 433). The majority of recipients with dnDSA had antibodies to identical eplet positions on DQ2 and DQ7. A high-risk epitope mismatch (found in DQA1*05 + DQB1*02/DQB1*03:01(7)) was associated with a 4.2- and 4.9-fold increased risk of dnDSA in heart and lung recipients respectively. HLA electrostatic potential modeling provided a plausible explanation for this observed immunogenicity. A theoretical allocation algorithm avoiding high-risk epitope mismatches was generated and predicted to reduce dnDSA by up to 72% without additional testing, eplet analysis, or cost.

KEYWORDS
alloantibody, alloantigen, clinical research/practice, heart transplantation/cardiology, histocompatibility, immunogenetics, lung transplantation/pulmonology

1 | INTRODUCTION

Donor-specific HLA antibodies (DSA) are a recognized risk factor for antibody-mediated rejection in all organ transplants and their presence is associated with graft loss, recipient mortality, and increased cost to the healthcare system.[1-3] DSA may be preexisting or de novo (dnDSA), when DSA are identified in recipient serum for the first time after transplantation. Recently published evidence suggests that dnDSA may result in a greater degree of allograft injury than preexisting DSA[4] and in cardiac transplantation, persistent dnDSA are reported to be particularly detrimental to allograft outcomes.[5] There is no consistently effective treatment for dnDSA and the associated allograft injury.[6] The risk associated with preexisting DSA may be circumvented by avoiding donor HLA mismatches during allocation to which recipient HLA antibodies are identified or managed with desensitization strategies.[7,8] However, reducing the even greater risk associated with the development of dnDSA, and particularly persistent dnDSA,[5] remains an unresolved challenge.

Abbreviations: dnDSA, de novo donor-specific HLA antibodies; DSA, donor-specific HLA antibodies; REM, risk epitope mismatch.

Article Summary

- Investigative cohort 265 heart transplant recipients and validation cohort 433 lung transplant recipients
- Majority of recipients with dnDSA had antibodies to identical eplet positions on DQ2 and DQ7
  - High risk epitope mismatch was associated with a 4.2 to 4.9 fold increased risk of dnDSA in heart and lung recipients, respectively
- Allocation algorithm avoiding high risk epitope mismatches could reduce dnDSA by up to 72%

Liver Transplantation

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ORIGINAL ARTICLE AJT

Physical frailty after liver transplantation

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Frailty is prevalent in liver transplant candidates, but little is known of what happens to frailty *after* liver transplantation. We analyzed data for 214 adult liver transplant recipients who had ≥1 frailty assessment using the Liver Frailty Index (LFI) at 3- (n = 178), 6- (n = 139), or 12- (n = 107) months posttransplant (higher values=more frail). "Frail" and "robust" were defined as LFI ≥4.5 and <3.2. Median pre–liver transplant LFI was 3.7, and was worse at 3 months (3.9; $P = .02$), similar at 6 months (3.7; $P = .07$), and improved at 12 months (3.4; $P < .001$). The percentage who were robust pre- and 3-, 6-, and 12-months posttransplant were 25%, 14%, 28%, and 37%; the percentage frail were 21%, 21%, 10%, and 7%. In univariable analysis, each 0.1 pre-transplant LFI point more frail was associated with a *decreased* odds of being robust at 3- (odds ratio [OR] 0.75), 6- (OR 0.77), and 12-months (OR 0.90) posttransplant ($P \leq .001$), which did not change substantially with multivariable adjustment. In conclusion, frailty worsens 3 months posttransplant and improves modestly by 12 months, but fewer than 2 of 5 patients achieve robustness. Pretransplant LFI was a potent predictor of posttransplant robustness. Aggressive interventions aimed at *preventing* frailty pretransplant are urgently needed to maximize physical health after liver transplantation.

KEYWORDS
clinical research/practice, comorbidities, geriatrics, liver transplantation/hepatology, nutrition, patient characteristics, quality of life (QOL), rehabilitation

1 | INTRODUCTION

Patients with cirrhosis are vulnerable to developing physical frailty that results from muscle wasting and undernutrition—2 conditions that are nearly inseparable from the state of cirrhosis itself.[1,2] In theory, liver transplantation should reverse these conditions and therefore, reverse physical frailty. However, no objective data exist on the extent to which—or how rapidly—physical frailty improves after liver transplantation. Such information is crucial to informing discussions with patients and caregivers about what to expect after liver transplantation and guiding prognosis regarding quality of life.

One of the major barriers to investigating recovery from physical frailty after liver transplantation has been the frailty measurement tools themselves.[3] While several studies have investigated frailty[1,4] or aspects of frailty (eg, cardiopulmonary fitness,[5,6] disability,[7,8]) in the pre–liver transplant setting, these tools have characteristics that have hampered efforts to fully understand if, how, and when frailty reverses after liver transplantation. For example, tools such as the Fried Frailty Index or Activities of Daily Living scale are subjective and scored on a noncontinuous scale, making them insensitive to

Abbreviations: FrAILT, Functional Assessment in Liver Transplantation; HCC, hepatocellular carcinoma; ICU, intensive care unit; IQR, interquartile range; LFI, Liver Frailty Index; MELD, Model for End-Stage Liver Disease.

Article Summary

- Assessed frailty using the Liver Frailty Index (LFI) pre-transplant and 3m, 6m, and 12m post-transplant
- Frailty worsened 3m post-transplant and improved only modestly at 12m
- Only 40% achieved robustness post-transplant
- Prehabilitation to prevent frailty is urgently needed

Living Kidney Donation

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ORIGINAL ARTICLE

AJT

GFR ≤25 years postdonation in living kidney donors with (vs. without) a first-degree relative with ESRD

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An increased risk of ESRD has been reported for living kidney donors, and appears to be higher for those donating to a relative. The reasons for this are not clear. One possibility is that ESRD is due to the nephrectomy-related reduction in GFR, followed by an age-related decline that may be more rapid in related donors. Between 1/1/1990 and 12/31/2014, we did 2002 living donor nephrectomies. We compared long-term postdonation eGFR trajectory for donors with (n = 1245) vs. without (n = 757) a first-degree relative with ESRD. Linear mixed-effects models were used to model the longitudinal trajectory of eGFR. With all other variables held constant, we noted a steady average increase in eGFR until donors reached age 70: 1.12 (95% CI: 0.92-1.32) mL/min/1.73m²/yr between 6 weeks and 5 years postdonation; 0.24 (0.00-0.49) mL/min/1.73m²/yr between 5 and 10 years; and 0.07 (−0.10 to +0.25) mL/min/1.73m²/yr between 10 and 20 years for donors with attained age less than 70. After age 70, eGFR declined. After we adjusted for predonation factors, the difference in eGFR slopes between related and unrelated donors was 0.20 mL/min/1.753 m²/year (0.07-0.33). Our data suggests that postdonation, kidney donor eGFR increases each year for a number of years and that eGFR trajectory does not explain any increase in ESRD after donation.

KEYWORDS
clinical research/practice, donors and donation, glomerular filtration rate (GFR), health services and outcomes research, kidney transplantation/nephrology, organ transplantation

1 | INTRODUCTION

A living kidney donor loses about 50% of kidney function with unilateral nephrectomy. The remaining kidney undergoes compensatory hypertrophy, and within 6 weeks of donor nephrectomy, glomerular filtration rate (GFR) returns to approximately 70% of preoperative values. It has been thought that, in the short term, there may be an additional small GFR improvement, followed by stabilization. However, during middle age, some individuals experience a slow, but steady, decline in GFR. If kidney function is normal at the beginning of this decline, it rarely leads to development of end-stage renal disease (ESRD). It was long believed, based on long-term clinical observations comparing donors to the general population, that living kidney donors had sufficient renal function to withstand this decline in GFR and to live a normal life without increased risk of ESRD.[1-4] However, two recent studies comparing donors with matched *healthy* controls, have suggested that donors have a slightly increased lifetime risk of ESRD.[5,6] In those two studies, the majority of ESRD was seen in those donating to a relative. Confounding this observation is that, in the absence of donation, relatives of those with ESRD are at increased risk of developing ESRD.[7-13] Additionally, in the first few decades of clinical transplantation, most donors were related to their recipient, so that, in general, related donors have longer follow-up than unrelated donors.[14]

An understanding of the pathogenesis of, and risk factors for, ESRD in donors is important for donor selection and counseling. For some, nephrectomy might not leave sufficient reserve for the "normal" age-related decline in GFR. It is also possible that donors might experience a more rapid decline in kidney function than observed in nondonors. A

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease.

Article Summary

- Compared long-term post-donation eGFR trajectory for donors with (n=1245) vs. without (n=757) a first-degree relative with ESRD
- Noted increases in eGFR every year post-donation until age 70
- eGFR slopes differed between related and unrelated donors by 0.20 mL/min/1.753m^2/year (0.07-0.33)
- Normal age-related decline in eGFR was not sufficient to explain increased risk of ESRD post-donation

Kidney Transplantation

SPECIAL ARTICLE AJT

Antibody-mediated rejection: New approaches in prevention and management

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Despite the success of desensitization protocols, antibody-mediated rejection (AMR) remains a significant contributor to renal allograft failure in patients with donor-specific antibodies. Plasmapheresis and high-dose intravenous immunoglobulin have proved to be effective treatments to prevent and treat AMR, but irreversible injury in the form of transplant glomerulopathy can commonly manifest months to years later. There is an unmet need to improve the outcomes for patients at risk for AMR. Updated Banff criteria now take into account the increasing understanding of the complex and heterogeneous nature of AMR phenotypes, including the timing of rejection, subclinical and chronic AMR, C4d-negative AMR, and antibody-mediated vascular rejection. Treatment for AMR is not standardized, and there is little in the way of evidence-based treatment guidelines. Refining more precisely the mechanisms of injury responsible for different AMR phenotypes and establishing relevant surrogate endpoints to facilitate more informative studies will likely allow for more accurate determination of prognosis and efficacious intervention using new therapeutic approaches. In addition to plasma exchange and intravenous immunoglobulin, a number of other add-on therapies have been tried in small studies without consistent benefit, including anti-CD20, proteasome inhibitors, complement inhibitors, anti-interleukin-6 receptor blockers, and immunoglobulin G-degrading enzyme of *Streptococcus pyogenes* (called IdeS).

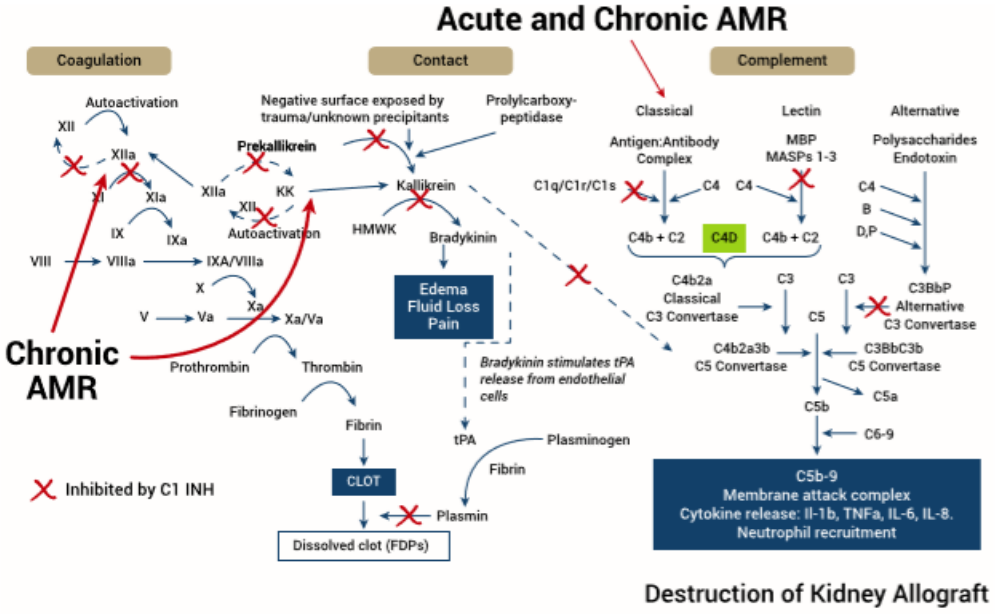
KEYWORDS
antibody-mediated (ABMR), autoantibody, basic (laboratory) research/science, clinical research/practice, kidney transplantation/nephrology, liver transplantation/hepatology, organ procurement and allocation, rejection:

1 | INTRODUCTION

Antibody-mediated rejection (AMR) is a significant complication following kidney transplantation that contributes toward both short- and long-term injury in approximately 1% to 10% of kidney transplant recipients.[1] The presence of antibodies that recognize donor human leukocyte antigens (HLAs), as well as incompatible ABO blood group antigens and other endothelial or xenogeneic antigens, has been associated with AMR and subsequent graft loss for some time, and the presence of donor-specific antibodies (DSAs) was once considered a contraindication to transplantation.[2] Despite use of desensitization protocols, up to one-third of highly sensitized recipients may develop acute AMR following transplantation.[1] DSAs present in the serum of sensitized patients are produced from long-lived plasma cells (LLPCs)

Abbreviations: aHUS, atypical hemolytic uremic syndrome; AMR, antibody-mediated rejection; AMVR, antibody-mediated vascular rejection; C1-INH, C1 esterase inhibitor; cg [score], chronic glomerulopathy; CI, confidence interval; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; ENDAT, endothelial-associated transcript; FDA, Food and Drug Administration; g [score], glomerulitis; HLA, human leukocyte antigen; HR, hazard ratio; IdeS, immunoglobulin G-degrading enzyme of *streptococcus pyogenes*; IF/TA, interstitial fibrosis and tubular atrophy; IgG, immunoglobulin G; IL-6R, interleukin-6 receptor; IVIg, intravenous immunoglobulin; LLPC, long-lived plasma cell; MFI, mean fluorescence intensity; ptc, peritubular capillary; SOC, standard of care; TCMR, T cell–mediated rejection.

Article Summary



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ORIGINAL ARTICLE

AJT

Turn down for what? Patient outcomes associated with declining increased infectious risk kidneys

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Transplant candidates who accept a kidney labeled increased risk for disease transmission (IRD) accept a low risk of window period infection, yet those who decline must wait for another offer that might harbor other risks or never even come. To characterize survival benefit of accepting IRD kidneys, we used 2010-2014 Scientific Registry of Transplant Recipients data to identify 104 998 adult transplant candidates who were offered IRD kidneys that were eventually accepted by someone; the median (interquartile range) Kidney Donor Profile Index (KDPI) of these kidneys was 30 (16-49). We followed patients from the offer decision until death or end-of-study. After 5 years, only 31.0% of candidates who declined IRDs later received non-IRD deceased donor kidney transplants; the median KDPI of these non-IRD kidneys was 52, compared to 21 of the IRDs they had declined. After a brief risk period in the first 30 days following IRD acceptance (adjusted hazard ratio [aHR] accept vs decline: ${}_{1.22}2.06_{3.49}$, $P = .008$) (absolute mortality 0.8% vs. 0.4%), those who accepted IRDs were at 33% lower risk of death 1-6 months postdecision (aHR ${}_{0.50}0.67_{0.90}$, $P = .006$), and at 48% lower risk of death beyond 6 months postdecision (aHR ${}_{0.46}0.52_{0.59}$, $P < .001$). Accepting an IRD kidney was associated with substantial long-term survival benefit; providers should consider this benefit when counseling patients on IRD offer acceptance.

KEYWORDS
clinical research/practice, infection and infectious agents, infectious disease, kidney transplantation/nephrology, organ acceptance, patient survival, Scientific Registry for Transplant Recipients (SRTR)

1 | INTRODUCTION

The percent of donors labeled increased risk for disease transmission (IRD) has increased from 10% in 2010 to 19.5% in 2015.[1] By definition, organs recovered from IRD donors maintain a low, but non-zero[2-4] risk of disease transmission ranging from <1 in 1000 for hepatitis C to <1 in 10 000 for HIV,[5,6] yet they are more likely to be recovered from younger and healthier donors.[1] While IRD kidneys can engender administrative burden through consent documentation,[7] medico-legal worries, patient concerns,[8,9] and recipient tracking and retesting, the pool of donors labeled IRD continues to grow as the national drug overdose epidemic persists and infiltrates deceased donor transplantation.[10] Understanding the risks and benefits associated

Abbreviations: aHR, adjusted hazard ratio; cPRA, calculated panel reactive antibody; DDKT, deceased donor kidney transplant; IQR, interquartile range; IRD, increased risk for disease transmission; KDPI, Kidney Donor Profile Index; OPTN, Organ Procurement and Transplantation Network; PHS, Public Health Service; SCD, standard criteria donor; SRTR, Scientific Registry of Transplant Recipients.

Article Summary

- Aim: To characterize the survival benefit of accepting IRD kidneys
- Utilized data from the SRTR (2010-2014) and studied 104,998 adult transplant candidates who were offered IRD kidneys that were eventually accepted by someone
- After 5-years, only 31% of candidates who declined IRDs later received non-IRDs
  - IRD KDPI: 21
  - Non-IRD KDPI: 53
- Those who accepted IRDs were at 33% lower risk of death 6m post-transplant and 48% lower risk >6m post-transplant

Kidney Transplantation

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ORIGINAL ARTICLE AJT

An economic assessment of contemporary kidney transplant practice

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Kidney transplantation is the optimal therapy for end-stage renal disease, prolonging survival and reducing spending. Prior economic analyses of kidney transplantation, using Markov models, have generally assumed compatible, low-risk donors. The economic implications of transplantation with high Kidney Donor Profile Index (KDPI) deceased donors, ABO incompatible living donors, and HLA incompatible living donors have not been assessed. The costs of transplantation and dialysis were compared with the use of discrete event simulation over a 10-year period, with data from the United States Renal Data System, University HealthSystem Consortium, and literature review. Graft failure rates and expenditures were adjusted for donor characteristics. All transplantation options were associated with improved survival compared with dialysis (transplantation: 5.20-6.34 quality-adjusted life-years [QALYs] vs dialysis: 4.03 QALYs). Living donor and low-KDPI deceased donor transplantations were cost-saving compared with dialysis, while transplantations using high-KDPI deceased donor, ABO-incompatible or HLA-incompatible living donors were cost-effective (<$100 000 per QALY). Predicted costs per QALY range from $39 939 for HLA-compatible living donor transplantation to $80 486 for HLA-incompatible donors compared with $72 476 for dialysis. In conclusion, kidney transplantation is cost-effective across all donor types despite higher costs for marginal organs and innovative living donor practices.

KEYWORDS
business/management, cost-effectiveness, economics, health services and outcomes research, kidney transplantation/nephrology, kidney transplantation/living donor, organ transplantation, simulation

1 | INTRODUCTION

The survival benefit of kidney transplantation in the management of patients with end-stage renal disease (ESRD) has been well established during the past 50 years. Wolfe and colleagues demonstrated superior patient survival after renal transplantation compared with long-term dialysis, particularly for patients with diabetes.[1,2] Subsequently, Whiting and associates demonstrated that deceased donor renal transplantation was cost-saving, with a breakeven cost occurring at 3 to 14 years depending on organ quality.[3] Living donor

Abbreviations: ABOi, ABO-incompatible; DDKT, deceased donor kidney transplantation; DES, discrete event simulation; DRG, diagnosis-related group; ESRD, end-stage renal disease; ICER, incremental cost-effectiveness ratio; ILDKT, incompatible living donor kidney transplantation; KDPI, Kidney Donor Profile Index; LDKT, living donor kidney transplantation; PHS, US Public Health Service; QALY, quality-adjusted life-year; SRTR, Scientific Registry of Transplant Recipients; USRDS, United States Renal Data System.

Institution at which work was performed: East Carolina University, Greenville, NC.

Article Summary

- All transplant options were associated with improved survival compared with dialysis
- Living donor and low-KDPI deceased donor transplant were associated with cost-savings compared to dialysis
- High-KDPI, ABOi and HLAi were cost-effective compared to dialysis
- Cost in US dollars:
  - LDKT compatible $39,939
  - LDKT incompatible $80,486
  - Dialysis $72,476

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