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Predictors of Mid-Term Glomerular Filtration Rate after Deceased Donor Renal Transplantation: Kidney Donor Profile Index as a Predictor of Mid-Term GFR

Oya M. Andacoglu [1, 2], Jack Liu [3], Abigail L. Brooks [1], Amit Blumfield [3], Mehul Trivedi [3], Shoshana Lehman [4], Michael K. Parides [1], Enver Akalin [1], Jay A. Graham [1], Juan P. Rocca [1], Stuart M. Greenstein [1, 3, *]

1. Montefiore Medical Center, New York, USA; E-Mails: dr.oyaandacoglu@gmail.com; abigail.brooks57@gmail.com; mparides@montefiore.org; eakalin@montefiore.org; jgraham@montefiore.org; jrocca@montefiore.org; sgreenst@montefiore.org
2. Koc University, Organ Transplantation Center, Istanbul, Turkey
3. Albert Einstein College of Medicine, New York, USA; E-Mails: jaliu@montefiore.org; amitblumfield@gmail.com; mtrivedi248@gmail.com;
4. Yeshiva University - Stern College for Women, New York, USA; E-Mail: shoshanalehman@gmail.com

* **Correspondence:** Stuart M. Greenstein; E-Mail: sgreenst@montefiore.org

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Abstract

Glomerular filtration rate (GFR) is an excellent indicator of renal function; however, it is rarely evaluated as an endpoint. We investigated donor and recipient factors for associations that might be predictive of mid-term GFR after renal transplantation. We performed a retrospective review of 828 deceased donor renal transplantations performed at Montefiore Medical Center between the years 2009-2015. Donor characteristics included KDPI, [low

(<20%), medium (20-80%), high (>80%)], age, graft types [extended criteria (ECD), cardiac death (DCD), standard criteria (SCD)], CDC high risk, HCV status and cold ischemic time (CIT). Recipient factors included age at transplant, induction agent, BK status, CMV status, acute and chronic rejection, cPRA and DSA status. Primary outcome is 3-year GFR calculated via the MDRD equation. In univariate analysis, donor age, KDPI, ECD, and chronic rejection were significantly associated with changes in 3-year GFR ($p<0.001$). In the multivariable regression analysis, donor age, KDPI, and chronic rejection remained associated with changes in 3-year GFR ($p<0.001$). Acute rejection, DCD, HCV status, CIT, BK and CMV viremia, PRA, pretransplant or de novo DSA were not associated with changes in 3-year GFR ($p>0.05$). We conclude that donor age, KDPI, and chronic rejection are independently associated with 3-year GFR while acute rejection, DCD, HCV status, CIT, BK and CMV viremia, PRA, existing or de novo DSA were not. Based on these findings, current scoring systems may need refinement to address the prognosis of mid-term GFR.

Keywords
Donor renal transplantation; glomerular filtration rate; kidney transplant; recipient survival; risk prediction; risks score; donors and donation

1. Introduction

Glomerular filtration rate (GFR) is an excellent indicator of renal function; however, transplant outcomes have historically been based on patient and graft survival. Kidney donor profile index (KDPI) derived by calculating Kidney Donor Risk Index (KDRI) has been widely accepted and is validated to predict kidney graft performance in adult recipients; however, graft failure and patient survival underestimate the progression to chronic kidney disease, end stage renal disease and mid-term GFR [1]. Furthermore, there are limited data describing mid-term predictors of GFR after deceased donor renal transplantation. We investigated a) whether KDPI predicts mid- term GFR and b) whether other independent donor and recipient factors are predictive of mid-term GFR.

2. Materials and Methods

Adult deceased donor renal transplants performed at our institution between 2009-2015 were reviewed. We reviewed donor characteristics including: KDPI categorized as low (<20%) medium (20-80%) or high (>80%), donor age, graft type: extended criteria (ECD), cardiac death (DCD), standard criteria (SCD), CDC increased risk, HCV status and cold ischemic time (CIT). CDC increased risk is defined by the CDC Public Health Service as donors with risk factors for HIV, HBV, or HCV [2]. ECD graft is defined as one "who, at the time of death, is aged ≥60 or aged 50 to 59 yr and has any two the following three criteria: (1) Cause of death is cerebrovascular accident; (2) preexisting history of systemic hypertension; and (3) terminal serum creatinine >1.5 mg/dl" [3].

Recipient factors included: age at transplant, induction agent, BK and CMV status, acute and chronic rejection, cPRA, preoperative DSA and de novo DSA status. DSA was measured by One Lambda Luminex results. PRA was categorized as low immunogenic risk (0-20%), moderately sensitized (21-80%), and highly sensitized (81-100%). All biopsies were based upon classification

scores of the renal pathologists that used Banff criteria to diagnose acute and chronic rejection. According to the Banff Criteria, acute rejection was defined by tubulitis, interstitial inflammation, glomerulitis, peritubular capillaritis, and arteritis. Also in accordance with the Banff criteria, chronic rejection was defined by tubular atrophy, interstitial fibrosis, transplant glomerulopathy, multilayering of peritubular capillary (PTC) basement membranes, and transplant arteriopathy [4]. All biopsies were performed "for cause" as we currently do not perform protocol biopsies. Induction agent was chosen based on the sensitization status of the recipient. Non-sensitized patients with no pretransplant DSA were given basiliximab, whereas higher immunologic risk patients (PRA > 20 and presence of DSA) received anti-thymocyte globulin (ATG). Maintenance immunosuppression protocol included prednisone, mycophenolate mofetil and tacrolimus (standard triple immunosuppression therapy). Primary outcome was 3-year GFR calculated by MDRD equation. MDRD calculation is the default equation in the electronic medical record system of the institution therefore it was used as the primary method of GFR. Delayed graft function (DGF) data was not tracked given that we expected DGF in many of these kidneys as many were imported with long cold ischemic time and/or elevated terminal serum creatinine. BK and CMV viremia were performed "for cause" as we currently do not perform protocol viral tests. Demographic and clinical characteristics of donors and recipients are presented as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Linear regression was used to assess the change in 3-year GFR from baseline for the variables listed in Table 1. Three-year GFR was the dependent variable in these analysis of covariance models which included baseline GFR as a covariate. A multivariable regression model also used to jointly assess the relationship between factors found to be associated with the change in 3-year GFR in the univariate models. All statistical tests were conducted at two-sided 0.05 level. The analyses were conducted using the Statical Analysis Software System (SAS) version 9.4 (Cary, NC).

All study protocols were approved by the Montefiore Medical Center Institutional Review Board #2017-7715.

3. Results

3.1 Patient Demographics

We reviewed 828 patients. Donor and recipient characteristics are summarized in Table 1. Mean recipient age was 55.9 ±13.8 (range 21-85). Mean GFR at 1, 2, and 3 years was 49±14, 48±15, and 47±15. Mean donor KDPI was 60 ±27.2. We categorized KDPI as low (<20%) (n=67, 8%), medium (20-80%) (n=569, 69%) and high (>80%) (n=192, 23%). Graft loss at 3 years of follow-up was 6 (9%), 41 (7%) and 41 (21%) in low, medium and high KDPI groups, respectively (p=0.55). There were 4 (6%), 35 (6%), 28 (15%) deaths in low, medium and high KDPI categories at 3 years, respectively (p=0.04). Death censored graft loss was 3%, 1% and 8% in low, medium and high KDPI groups, respectively (p=0.57). Higher KDPI was significantly associated with lower 3-year GFRs both as a categorical and continuous variable (p<0.05).

Table 1 Donor and recipient characteristics. PRA: Panel reactive antibody, ATG: anti-thymocyte globulin, DSA: donor specific antibody, GFR: glomerular filtration rate, KDPI: kidney donor profile index, ECD: extended criteria donor, DCD: donation after cardiac death, HCV: hepatitis C virus.

Recipient characteristics	**N (%)**
Age (years)	55.86 ± 13.8
Male	488 (59%)
Ethnicity	
Caucasian	176 (21%)
African –American	279 (34%)
Hispanic	223 (27%)
Asian	17 (2%)
Other	37 (4%)
Declined to Report	96 (12%)
cPRA	
low risk (0-20%)	417 (50%)
moderately sensitized (21-80%)	212 (26%)
highly sensitized (81-100%)	199 (24%)
Induction	
ATG	478 (58%)
Basiliximab	346 (42%)
de novo DSA	111 (13%)
Preoperative DSA	105 (13%)
Acute rejection	68 (8%)
Chronic rejection	37 (4%)
Mean GFR at 1 year (mL/min)	49 ± 14
Mean GFR at 2 years (mL/min)	48 ± 15
Mean GFR at 3 years (mL/min)	47 ± 15
Donor characteristics	**N (%)**
Age (cutoff 70 years old)	43 ± 15

Mean KDPI	60 ±27.2
low (<20%)	67 (8%)
medium (20-80%)	569 (69%)
high (>80%)	192 (23%)
ECD	179 (22%)
DCD	84 (10%)
HCV positive	45 (5%)
Mean cold ischemic time	1277.9 ± 878 min

3.2 Associations Between GFR and the Variables

We had 179 ECD (22%), 84 DCD (10%), 45 HCV positive (5%), 143 CDC high-risk (17%) donors. Mean donor age was 43±15. Average recipient age for ECD graft was significantly higher than non-ECD recipients (60 vs. 37 years, p<0.0001). ECD grafts had mean GFR of 41.0 ±16.9 versus non-ECD grafts of 49.0 ±14.36 (p<0.0001). ECD grafts were also associated with higher mortality at 3 years (14.0% vs. 6.8%, p=0.002) and with graft failure (18.4% vs. 8.6%, p=0.0002). DCD grafts had similar GFR at 3 years compared to non-DCD grafts (46.0 ±15.8 vs. DCD 47.0 ±15.2 (p=0.57).

The mean donor age of HCV positive organs was similar to that of HCV negative organs (44.7 vs. 43.8 years, p=0.79). HCV-positive and -negative organ recipient age was also similar (59.0 ±6.3 vs. 53.3 ±13.5, p=0.05). When adjusted for donor and recipient age, HCV status was not associated with 3-year GFR (p=0.17). ECD rate in HCV positive organs was not significantly associated to the ECD rate in HCV negative organs (18.2% versus 24.7%, p=0.47).

Mean CIT was 1277.9 ±878.2 min. We grouped CIT as short (<24hrs) and long (> 24hrs). 40% had short CIT, whereas 60% had long CIT. CIT was not associated with 3-year GFR in univariate analysis (p=0.7).

BK and CMV viremia rates were 8.0% and 16.3% respectively. Mean preoperative cPRA was classified as 0-20% (low risk) (n=417, 50%), 21-80% (moderately sensitized) (n=212, 26%), and 81-100% (highly sensitized), (n=199, 24%). 13% of the patients had pretransplant DSA class I or class II. 13% developed de novo DSA class I or class II after the transplantation. None of these variables were associated with 3-year GFR (p>0.05).

Acute rejection occurred in 68 (8%) patients and they had no difference in GFR at 3 years compared to patients without acute rejection (41 ±20.3 vs. 43 ±15.3, p = 0.32). However, chronic rejection was associated with lower GFR at 3 years (34.0 ±18.7 vs. 44.0 ±15.6, p=0.0002).

Multivariable regression analysis is summarized in Table 2. Because donor age is a part of ECD determination, we did not include ECD status in our final model. In our multivariable regression analysis, donor age, and chronic rejection were associated with GFR at 3 years.

Table 2 Multivariable regression analysis**.** HCV = hepatitis C virus, DCD = donation after cardiac death.

Variable	Parameter Estimate	Standard Error	t-value	Pr > ltl
Intercept	84.54	2.98	27.42	< 0.05
Donor Age	-0.58	0.05	-8.78	< 0.05
Acute Rejection	-17.15	4.50	-3.78	p = 0.55
Chronic Rejection	-20.75	5.21	-5.23	< 0.05
Donor HCV	1.24	5.61	0.30	0.91
DCD	-3.41	2.93	-0.79	0.48
KDPI	-12.31	3.50	-2.68	< 0.05

4. Discussion

GFR is an excellent indicator of renal function. Determining predictors of GFR, has the potential to predict graft and patient survival. Prior studies assessed mainly donor variables to predict mid-term GFR. These variables often included: donor age, donor creatinine, donor cause of death, donor diabetes, and donor ethnicity [5-7]. The literature does not have a sufficient, reliable marker for predicting mid-term GFR function. We therefore attempted to analyze predictors of mid-term GFR and chose 3-year GFR as a primary endpoint (as it is widely accepted that 1-year GFR is a good marker for graft survival). However, both patients and transplant providers would agree that longer term graft survival should be the ultimate goal.

We analyzed a variety of predictors of mid-term GFR. The first predictor of mid-term GFR we looked at was the kidney donor profile index (KDPI). KDPI is derived by calculating Kidney Donor Risk Index (KDRI) and has been widely accepted to predict kidney graft performance in adult recipients. Rao et al. developed the kidney donor risk index (KDRI), leading to the widespread use of the KDPI as a marker of mid-term graft function. However, graft failure and patient survival underestimate the progression to chronic kidney disease, end stage renal disease and mid- term GFR [1].

In our study, we did find that higher KDPI was associated with lower patient survival and GFR at 3 years. In multivariable regression analysis KDPI remained significant. We also found that acute rejection, HCV status or DCD graft was not associated with 3-year GFR in contrast to the KDPI scoring system.

Surprisingly, we found that that DCD status was not associated with 3-year GFR even when adjusted for donor age may not necessarily merit an increased risk, as it does in the current scoring models.

In our results, when adjusted for donor and recipient age, HCV status was not associated with a decrease in 3-year GFR. We started using HCV NAT positive organs for naive recipients in 2018, after the initial reports regarding the use of HCV positive donors and reported suitable outcomes [8-11]. Of note, our results reflect the era before we started accepting HCV antibody and nucleic acid test

(NAT) positive organs for HCV negative recipients. In this study, HCV positive organs were used for only HCV positive recipients.

There are current studies that have attempted to correlate mid-term GFR with donor and recipient variables. For example, Elbadri et al. reported improved GFR at 5 years with younger donor age, the absence of CMV infection and the absence of rejection [12]. These findings support our results. However, their overall donor age was much younger than our cohort (mean 36, range 21-47) and, they did not include HCV positive donors in their review [13].

In our results, ECD grafts were associated with lower GFR and higher mortality at 3-years. Arnau et al. looked at 1-year GFR for ECD kidneys and marginal grafts defined by the Donor Risk Score (DRS) system reported by Schold et al. They did report worse GFR at 1 year for ECD donors (39.4±14.1 vs 53.8±19.1, $p<0.001$) [14]. We found strong associations between donor age and ECD status at 3-year GFR. Since donor age is a component of ECD determination, we did not include ECD status in our final multivariable model. In addition to GFR, ECD status was associated with 3-year mortality rate. This could be partly explained by increased age of ECD recipients compared to non-ECD recipients. Our findings are concurrent with most institutions 'practice to utilize ECD grafts for elder transplant candidates to expand the available donor pool, which could explain the higher mortality rate in this group.

We also found that the presence of chronic rejection was an independent predictor of lower GFR at 3-years. Schinstock et al. demonstrated an incidence of de novo DSA of 7.0% and they concluded it was a risk factor for reduced graft survival and could predict antibody mediated rejection at 1-year. They also found that GFR was affected by de novo DSA. Both class 1 and 2 DSA had a higher rate of decreasing GFR [15]. This is different from our results; 13% of our patients had pretransplant DSA and 13% developed de novo DSA, but neither was associated with 3-year GFR.

Our study has several major limitations. First, our study is a retrospective study with resultant selection bias due to transplant policy at the time and missing data. Secondly, we used the MDRD equation which is known to be less accurate than the CKD-EPI formula, mainly it is the default GFR calculation in our electronic medical record system. In addition, our patient population is skewed due to the large percentage of minority groups compared to other centers.

5. Conclusions

In conclusion, higher KDPI is predictive of lower GFR at 3-years as well as patient mortality. Donor age, and chronic rejection are independent predictors of 3-year GFR. Acute rejection, HCV status or DCD status are not associated with 3-year GFR even when adjusted for donor and recipient age. We believe the scoring systems should be refined and we recommend prospective studies to better determine the role of KDPI in predicting kidney function at mid-term.

Abbreviations

ATG Anti-thymocyte globulin
CDC Center for disease control
CIT cold ischemic time
DCD donation after cardiac death
DGF delayed graft function
DSA donor specific antibody

ECD Extended criteria donor
GFR Glomerular filtration rate
HVC Hepatitis V virus
KDPI Kidney donor risk profile
KDRI Kidney donor risk Index
PRA Panel reactive antibody
SCD Standard criteria donor

Author Contributions

All authors approve of the final version to be published and agree to be accountable for all aspects of the work in ensuring questions related to the accuracy or integrity of any part of the work. Contributions for each author are as follows: **OMA**: data analysis, data interpretation, drafting manuscript, revising manuscript; **JL**: data acquisition, data analysis, data interpretation, drafting manuscript, revising manuscript; **ALB**: data acquisition, data analysis, data interpretation, drafting manuscript, revising manuscript **AB**: data acquisition, data analysis, data interpretation, drafting manuscript, revising manuscript **MT**: data acquisition, data analysis, data interpretation, drafting manuscript, revising manuscript; **MP**: data acquisition, data analysis, data interpretation, drafting manuscript, revising manuscript; **SL:** data acquisition, data analysis, data interpretation, drafting manuscript, revising manuscript; **EA**: data acquisition, data analysis, data interpretation, drafting manuscript, revising manuscript; **JAG**: data acquisition, data analysis, data interpretation, drafting manuscript, revising manuscript; **JPR**: data acquisition, data analysis, data interpretation, drafting manuscript, revising manuscript; **SMG**: data acquisition, data interpretation, drafting manuscript, revising manuscript.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Hart A, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Robinson A, et al. OPTN/SRTR 2016 annual data report: Kidney. Am J Transplant. 2018; 18: 18-113.
2. Seem DL, Lee I, Umscheid CA, Kuehnert MJ. PHS guideline for reducing human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission through organ transplantation. Public Health Rep. 2013; 128: 247-343.
3. Rao PS, Ojo A. The alphabet soup of kidney transplantation: SCD, DCD, ECD--fundamentals for the practicing nephrologist. Clin J Am Soc Nephrol. 2009; 4: 1827-1831.
4. Jeong HJ. Diagnosis of renal transplant rejection: Banff classification and beyond. Kidney Res Clin Pract. 2020; 39: 17-31.
5. Nyberg SL, Matas AJ, Kremers WK, Thostenson JD, Larson TS, Prieto M, et al. Improved scoring system to assess adult donors for cadaver renal transplantation. Am J Transplant. 2003; 3: 715-721.
6. Schold JD, Kaplan B, Baliga RS, Meier-Kriesche HU. The broad spectrum of quality in deceased donor kidneys. Am J Transplant. 2005; 5: 757-765.

7. Moore J, Ramakrishna S, Tan K, Cockwell P, Eardley K, Little MA, et al. Identification of the optimal donor quality scoring system and measure of early renal function in kidney transplantation. Transplantation. 2009; 87: 578-586.
8. Rao PS, Schaubel DE, Guidinger MK, Andreoni KA, Wolfe RA, Merion RM, et al. A comprehensive risk quantification score for deceased donor kidneys: The kidney donor risk index. Transplantation. 2009; 88: 231-236.
9. de Vera ME, Volk ML, Ncube Z, Blais S, Robinson M, Allen N, et al. Transplantation of hepatitis C virus (HCV) antibody positive, nucleic acid test negative donor kidneys to HCV negative patients frequently results in seroconversion but not HCV viremia. Am J Transplant. 2018; 18: 2451-2456.
10. Sibulesky L, Kling CE, Blosser C, Johnson CK, Limaye AP, Bakthavatsalam R, et al. Are we underestimating the quality of aviremic hepatitis C-positive kidneys? Time to reconsider. Am J Transplant. 2018; 18: 2465-2472.
11. Kling CE, Perkins JD, Landis CS, Limaye AP, Sibulesky L. Utilization of organs from donors according to hepatitis C antibody and nucleic acid testing status: Time for change. Am J Transplant. 2017; 17: 2863-2868.
12. Kadatz M, Klarenbach S, Gill J, Gill JS. Cost-effectiveness of using kidneys from hepatitis C nucleic acid test-positive donors for transplantation in hepatitis C-negative recipients. Am J Transplant. 2018; 18: 2457-2464.
13. Elbadri A, Traynor C, Veitch JT, O'Kelly P, Magee C, Denton M, et al. Factors affecting eGFR 5-year post-deceased donor renal transplant: Analysis and predictive model. Ren Fail. 2015; 37: 417-423.
14. Arnau A, Rodrigo E, Miñambres E, Ruiz JC, Ballesteros MA, Piñera C, et al. Prediction of kidney transplant outcome by donor quality scoring systems: Expanded criteria donor and deceased donor score. Transplant Proc. 2012; 44: 2555-2557.
15. Schinstock CA, Cosio F, Cheungpasitporn W, Dadhania DM, Everly MJ, Samaniego-Picota MD, et al. The value of protocol biopsies to identify patients with de novo donor-specific antibody at high risk for allograft loss. Am J Transplant. 2017; 17: 1574-1584.