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Association of Donor Inflammation– and Apoptosis-Related Genotypes and Delayed Allograft Function after Kidney Transplantation

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Abstract

Background—Delayed renal allograft survival (DGF) after a deceased donor kidney transplant is associated with an increased risk of allograft loss. Inflammatory response and apoptosis are associated with increased risk of DGF.

Study Design—Cross Sectional Study

Setting & Participants—We first recruited 616 recipients of kidneys from 512 deceased kidney donors and the donor DNA was genotyped. These recipients who were included in a prospective cohort study of 9 transplant centers in the Delaware Valley region, had their DGF outcome obtained through medical record abstraction. Then, we identified the recipient (n=349) of the contralateral deceased kidney donor, if not part of the cohort, through the USRDS registry. The final cohort consisted of 965 recipients of deceased donor kidneys from 512 donors.

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Descriptive Text for Online Delivery
Hyperlink: Supplementary Table S1 (PDF)
About: Adjusted association with 25% decline in eGFR for subjects in the Delaware Valley Cohort.
Hyperlink: Supplementary Table S2 (PDF)
About: Adjusted association with 50% decline in eGFR for subjects in the Delaware Valley Cohort.
Hyperlink: Supplementary Table S3 (PDF)
About : Adjusted association with allograft loss for subjects in the Delaware Valley Cohort.
Hyperlink: Supplementary Table S4 (PDF)
About: Adjusted association with acute rejection for subjects in the Delaware Valley Cohort.

Predictors—Donor single nucleotide polymorphisms (SNPs) in genes for tumor necrosis factor α (*TNF*), transforming growth factor β1 (*TGFB1*), interleukin 10 (*IL10*), p53 *(TP53)*, and heme oxygenase 1 (*HMOX1*).

Outcomes—DGF, defined as need for dialysis in the first week post-transplant. Secondary outcomes included acute rejection and eGFR.

Measurements—Information on DGF, acute rejection and eGFR for recipients in the Delaware Valley Cohort was obtained through medical record abstraction. For other recipients, information on DGF was obtained from UNOS forms and CMS claims in the USRDS registry.

Results—The *TGFB1*, *IL10*, *TP53* and *HMOX1* genes were not associated with DGF. The G allele of *TNF* polymorphism rs3093662 was associated with DGF in an adjusted analysis (OR= 1.85 compared to A allele, 95% C.I.=1.16–2.96, p=0.01). However this association does not achieve statistical significance after adjusting for multiple comparisons.

Limitations—Inadequate sample size for infrequent genotypes and multiple comparisons.

Conclusion—Due to the low frequency of donor SNPs of interest, a larger sample size and replication are necessary for conclusive evidence for the association of donor genotypes with DGF.

Keywords

Kidney Transplant; Deceased Donor Genotypes; Delayed Graft Function

Introduction

Delayed function of a deceased kidney allograft (DGF) defined by the need for dialysis within the first week post-transplant, portends a foreshortened allograft survival of 73% by the first year compared to 83 % for recipients who do not require dialysis. (1–10) In addition to reducing allograft survival, DGF prolongs the length of hospitalization and increases the costs of transplantation. (3) The reported incidence of DGF from various centers has previously ranged from 13.3 (8) to 52 %. (10) The increasing disparity between the number of persons on the deceased donor waiting list and the limited number of organs available for transplantation has stimulated the utilization of non-traditional donors of organs. The recent strategies to expand deceased donors who have characteristics that traditionally have precluded their use and to utilize non-heart beating persons as medically suitable donors is anticipated to increase the occurrence of DGF.

DGF on kidney allograft biopsies results from tubular epithelia damage, cellular necrosis and apoptosis, similar to that found in native kidneys with acute tubular necrosis.(11) Cytokines in the inflammatory response pathway also play an integral role in development of DGF in kidney allografts. Using inflammatory cytokines, the initial kidney injury stimulates activation of inflammatory leukocytes and this in turn, leads to formation of platelet-leukocyte plugs. These plugs along with erythrocytes, create a detrimental low-flow condition. (12–19) Production of inflammatory cytokines by the tubular cells and interstitium results in a concentration gradient that recruits inflammatory cells from the microvasculature to the matrix, and then through the injured tubular basement membrane, allowing interactions with tubular epithelial cells. The inflammatory cells and the tubular epithelial cells that have been sloughed also adhere to each other, leading to tubular obstruction and detrimentally increased intraluminal pressure. (20) Thus cytokines in the inflammatory response pathway, along with apoptosis, play an important role in occurrence of DGF.

Genes from the apoptosis and inflammatory response pathway were chosen on the basis of biological plausibility, frequency, potential role in the causal pathway of acute kidney injury

and presence of known functional SNPs, at the time of genotyping.(21) Factors such as the pro-apoptotic tumor protein p53 gene (*TP53*) and the anti-apoptotic, antioxidant heme oxygenase 1 gene (*HMOX1*) play an important role in modulating apoptosis in acute kidney injury. (22,23) Among others, the tumor necrosis factor α gene (*TNF*), transforming growth factor β1 gene (*TGFB1*), and interleukin 10 gene (*IL10*) play an important role in modulating inflammatory response in acute kidney injury. (22,23) Therefore we examined the association of SNPs in *TP53*, *HMOX1*, *TNF*, *TGFB1* and *IL10* with occurrence of DGF.

Methods

Patients

We recruited a cohort consisting of pairs of kidney transplant recipients of deceased kidney donors. We first recruited recipients of kidneys from deceased kidney donors included in a prospective cohort study enrolling recipients of kidney allografts from deceased donors transplanted between 1997 and 2003 at nine transplant centers in eastern Pennsylvania within the Gift of Life Donor Program. This Delaware Valley Cohort (DVC) which was studying the impact of DNA based HLA typing, consisted of nine transplant centers including Hospital of the University of Pennsylvania, Thomas Jefferson University Hospital, Hahneman University Hospital, Albert Einstein Medical Center, Lankenau Hospital, Hershey Medical Center, Geisinger Medical Center, Temple University and Lehigh Valley Hospital. All adult transplant recipients undergoing a deceased donor transplant were eligible. Patients were consented for participation at the time of or soon after transplantation. Starting in 2000, participants were also prospectively consented for genotyping for genes associated with kidney outcomes. Participants transplanted prior to 2000, were also consented for this study. Lymph node, spleen or blood samples of deceased donors were provided by Gift of Life Donor Program. We then identified the recipient of the contralateral deceased kidney donor, if not part of the DVC, through the United States Renal Data System registry (USRDS). Outcomes of the recipient of this contralateral deceased donor kidney were accessed through the USRDS. Approval for the USRDS data was obtained from the NIH, USRDS and Center for Medicare and Medicaid Services (CMS). USRDS provides CMS claims data as well as United Network of Organ Sharing (UNOS) form data. The Institutional Review Boards at the University of Pennsylvania and Hennepin County Medical Center approved this study.

Clinical Data for DVC Recipients

For recipients in the DVC, clinical data were collected prospectively from patient interviews and from inpatient and outpatient medical records at 6-month intervals until July 2004 for a maximum of 36 months post-transplantation. Referring community nephrologists were contacted to obtain data on kidney allograft function for those patients who did not return to their transplant center for routine visits. The main outcome of delayed graft function was defined as need for dialysis in the first week post-transplantation. For the recipient enrolled in the DVC, this use of dialysis was determined from the medical records. Renal function was measured using the 4-variable MDRD Study equation (24) to generate an eGFR. Baseline eGFR was established between 60–120 days post transplantation. Three other kidney function outcomes were also created: persistent 25% decline in eGFR, persistent 50% decline in eGFR, and kidney allograft loss. A persistent decline in eGFR was defined as two consecutive eGFR readings one month apart demonstrating the decline. Another secondary outcome, acute rejection, was defined as a clinical rejection event requiring use of intravenous steroid and/or antibody therapy during the first year post-transplant.

Clinical Data for Recipients of Contralateral Kidney, Identified through USRDS

In order to define the DGF outcome in the USRDS, we assessed the accuracy of the CMS claims and UNOS forms using the medical record as the gold standard among the DVC

recipients. Among all the 616 DVC recipients, only 263 of them have DGF outcome in CMS claims data. We utilized CMS claim data for dialysis treatment from the day after transplantation to day 7 post-transplantation. We could not utilize data from the day of transplant since the claim does not state whether the dialysis was conducted prior to or after the kidney transplant surgery. The false negative rate (FNR) and false positive rate (FPR) of claim-based DGF was 0.08 and 0.14, respectively. The FNR and FPR of UNOS form-based DGF was 0.44 and 0.05, respectively. Therefore, for the recipient of the contralateral deceased donor kidney, when not part of the DVC, dialysis use in the first week post-transplant was obtained from CMS claims and secondarily from the UNOS forms. A priori, we used simulations to compare the power using this definition of DGF outcome that enables us to include all recipients compared with an alternative strategy that eliminates recipients that only have UNOS form data. Despite the relative high false negative rate of the UNOS form-based DGF outcome, we found that using all the recipients always gave slightly better power in our simulations. Therefore, this composite is used in all of our association analysis. However, we always adjusted for the source of DGF outcome (medical record, CMS claims or UNOS form).

Genotyping

Either whole blood that remained from routine clinical testing, or lymph node or spleen specimens was used as a DNA source from donors. DNA was extracted from whole blood and tissue using Qiagen extraction kit and Puregene tissue extraction kit (both from Qiagen, Valencia, California), respectively. Given that the donor specimens used for DNA extraction were also used for clinical genotyping for HLA matching prior to transplantation, all samples provided DNA for genotyping. As a quality control measure, an A_{260}/A_{280} absorbance ratio was determined for all extracted DNA to ensure adequate DNA quality for genotyping. Based on the Seattle SNP database (http://pga.gs.washington.edu), we genotyped 8, 5, and 3 SNPs in *HMOX1*, *IL10*, and *TNF*, respectively. Genotyping was conducted for SNPs that had a minor allele frequency of greater than 10% based on our a priori power calculations. One SNP in *TNF* (rs1800629) gene is in the promoter region (http://snpper.chip.org) and one SNP in *IL10* (rs 3024498) is in the 3' untranslated region and is a putative splice site variant (www.genecards.org). We also genotyped a functional $(GT)_n$ repeat in the *HMOX1*gene utilizing a fragment analysis method from Applied Biosystems (ABI) with Genescan™ analysis software. The *IL10* SNP rs2222202 was genotyped using pyrosequencing (Biotage, Uppsala, Sweden). Due to the lack of tag SNP information for *TGFB1* and *TP53* in the HapMap and Seattle SNP database at the time of genotyping, we genotyped 2 functional SNPs in the *TGFB1* gene (rs1800472 and rs1982073) and tag SNPs in *TP53* found in the SNP500 database (http://snp500cancer.nci.nih.gov/home.cfm). We also genotyped a potentially functional SNP, rs 1042522, in *TP53* by utilizing a published protocol of Storey et al(25). Patients were genotyped for remaining SNPs utilizing an ABI Taqman assay (Applied Biosystems, California). As a quality control measure, five percent of the samples were genotyped as duplicates. Tests for Hardy-Weinberg Equilibrium (HWE) were done separately in African-American and non-African American donors (since 28 SNPs were genotyped, therefore the p-value cut-off for the HWE test was <0.002 which is 0.05/28 SNPs). (26)

Statistical Analysis of SNPs

Statistical analysis was conducted utilizing SAS v9.1 (The SAS Institute, http://www.sas.com), R (www.r-project.org) and STATA 9.0 (Stata Corporation, College Station, TX). Continuous variables were compared by t-tests and categorical variables by chi-square test and p-values were two-sided. Logistic regression with generalized estimation equations (GEE) was used to determine the association of single SNP genotypes with delayed graft function, due to two recipients being exposed to the same donor genotype. Recipients with the same donor were treated as a cluster. Some clusters have only one recipient if only a single kidney was transplanted. Exchangeable working correlation was assumed and empirical

variance estimates were used to adjust for the correlation. Multivariable models were fit by adjusting for confounders such as cold ischemia time, recipient race, extended criteria donor, donor cause of death, donor race, and source of DGF information (medical record or CMS claims or UNOS forms). (27)

For participants in the DVC, separate Cox proportional hazards models were used to investigate the association of single SNP genotype on time to 25% or 50% decline in kidney function, time to graft loss, and time to acute rejection. The proportional hazards assumption was tested by graphical analysis. (28) There was no evidence that the proportional hazards assumption was violated in the unadjusted model.

Results

Baseline characteristics and DGF outcomes

1,159 transplant recipients with deceased donors were enrolled in the DVC at 9 different centers (Figure 1). Of these, 975 recipients consented to genotyping. However the next of kin of only 512 unique donors consented to research, yielding 616 donor-recipient pairs available from the DVC. The outcomes of the remaining recipients of the contralateral deceased donor kidneys (n=349) were determined through the USRDS registry yielding a total of 965 recipients. The demographic and transplant related characteristics for the resulting 965 recipients of kidneys and their 512 deceased donors are listed in Table 1 and Table 2 respectively. Of these 965 recipients, 5 who were re-transplanted after their kidney transplant failed were included twice in our dataset. Thirty-five percent of all the recipients experienced delayed graft function (Table 3).

Concordance of DGF in the 2 recipients of a single donor's kidneys

Given that both kidneys of a deceased donor are usually utilized in two separate recipients, this study determined the concordance of DGF in the two recipients of the 512 donor kidneys in the study. The concordance rate was 57% for DGF; with 64, 194, and 195 paired recipients developing DGF, not developing DGF and being discordant on their DGF outcome. The level of concordance was statistically significantly higher than expected under chance (p=0.004) using a binomial exact test.(29)

Association of genotype with DGF

The genotypes were found to be in HWE. The frequencies of alleles were consistent with previously reported frequencies (SNP500 database and www.ensembl.org) (Table 4). Limited population frequency information was available for the *TNF* SNPs. The SNPs in the inflammation-related genes *TGFB1* and *IL10* and in the apoptosis-related genes *TP53* and *HMOX1* were not associated with delayed graft function (Table 4).

TNF and DGF—The G allele of *TNF* SNP rs3093662 was associated with DGF (OR= 1.85 compared to A allele, 95% C.I.=1.16–2.94, p=0.009) in the model (n=965) adjusted for cold ischemia time, recipient race, extended criteria donor, donor cause of death, donor race, donor age and source of DGF information (Table 4). However, the potential association of the *TNF* SNP rs3093662 with DGF does not retain statistical significance after adjusting for multiple comparisons. Similar direction of association was also seen in the subset of patients in the DVC only (n=616) and in DVC plus those with claims data (n=764) but with a wider confidence interval due to small sample size (DVC only: OR= 1.29 compared to A allele, 95% C.I.= 0.68 – 2.45, p=0.4; DVC plus claims data: OR=1.83, 95% C.I. =1.07–3.14, p=0.03).

Association of genotypes with secondary outcomes in the Delaware Valley Cohort

For recipients in the Delaware Valley Cohort with donor genotypes, during the median follow-up of 1010 days (range 1–1035 days) post-transplantation. The time to occurrence of 25% eGFR decline, 50% eGFR decline, kidney allograft loss, or acute rejection are shown in Figure 2. The SNPs in the inflammation-related genes *TNF*, *TGFB1*, and *IL10* and apoptosis-related genes *TP53* and *HMOX1* were not associated with acute rejection, kidney allograft loss, or eGFR decline (Tables S1–S4; provided as online supplementary material available with this article at www.ajkd.org).

Discussion

We showed that the *TNF* SNP rs3093662 in donors was associated with increased risk of DGF. The G allele was associated with 1.8 fold increased odds of DGF compared to the A allele in the study population (Table 4). However this association does not retain statistical significance after adjusting for multiple comparisons. The association of the donor *TNF* SNP with DGF has a similar direction of association among the subset of study participants enrolled in the Delaware Valley Transplant Cohort. The study did find a statistically significant concordance rate for DGF of 57% among the two recipients of a deceased donor kidney.

Our study is the first to study the association of DGF with the tag and functional SNPs in *IL10*, *TP53*, *TGFB1*, and *TNF* in deceased donors, in a multi-center cohort study of kidney transplant recipients (Table 4). This study also utilized a unique study design by utilizing both recipients of a deceased donor utilizing USRDS registry data.

The donor *TNF* SNP rs3093662 with a trend for association with DGF is located in the first intron of the *TNF*.(30,31) Prior studies have genotyped another *TNF* SNP, namely the promoter SNP rs1800629 in kidney transplant recipients, but not in donors, and found it to be associated with decreased kidney allograft survival.(32) The *TNF* SNP may contribute to DGF through several potential mechanisms. TNF-α, expressed in donor kidney tissue (33,34), is a proinflammatory cytokine which upregulates cell adhesion molecules.(35) TNF-α also contributes to kidney injury, since neutralizing antibodies to TNF-α decrease neutrophil infiltration and kidney injury in mice.(33,34) Higher levels of TNF-α expression occur in kidney allografts experiencing DGF than those without DGF. (36) Therefore it is biologically plausible that a donor polymorphism that increases TNF-α activity could make a recipient more susceptible to DGF.

Our study did not find associations with *TP53*, *HMOX1*, *TGFB1* and *IL10* donor gene polymorphisms and DGF. The literature supports the role of growth factors such as TGF-β1 expressed by tubular and interstitial cells in response to acute kidney injury.(37–39) The donor *TP53* and *HMOX1* gene products, probably expressed in the kidney tubules (40), play a role in tubular apoptosis seen in ischemia reperfusion injury in human kidney allografts.(41) Similarly, IL-10, expressed in donor kidney tissue, plays a role in ischemia-reperfusion injury. (34) Thus, SNPs in genes beyond the ones studied here that upregulate apoptosis and increase inflammatory response, may increase the risk of DGF. Other studies in kidney transplantation have not used the tag SNP approach used in our study. One study found association of *HMOX1* $(GT)_n$ repeat with kidney allograft survival but not with DGF.(42) It is possible that the association of SNPs in these genes was not seen in our study due to the small effect sizes of these SNPs and the limitation of our sample size. The limited sample size could possibly explain why the *TNF* SNP rs3093662, with a trend for association with DGF, was not associated with decreased kidney function and rejection in the subset of study patients in the DVC.

Our study has several limitations. First, DGF was defined as need for dialysis in the first week post-transplant. DGF was not determined by utilizing creatinine clearance to determine kidney

clearance. However, registry and patient-level studies usually define DGF as need for dialysis, as we did in our study. Also utilizing creatinine clearance is problematic in participants that are dialyzed. Second, not all recipient data was obtained from review of medical records. The study utilized USRDS data instead of medical record abstraction for the recipient of contrateral kidneys from donors providing organs to DVC participants. However, it was not practical to obtain consent from the recipient of the contralateral kidney to review medical records because this recipient could be in another part of the country given the national sharing system for kidneys. This study adjusted for the source of DGF data in the multivariate analysis (Table 4). The potential association of the *TNF* SNP rs3093662 with DGF was in the same direction in the subset of DVC patients with medical records data only. Third, a larger cohort of deceased donors with longer follow-up, is needed to determine the impact of the *TNF* polymorphism on DGF and long-term kidney allograft outcomes. The trend for association of the *TNF* SNP rs3093662 with DGF in this study, does not achieve statistical significance after adjusting for multiple comparisons. A larger cohort is also needed because the SNPs of interest had a low frequency thus require a larger sample size for proper assessment. Lastly, a larger cohort may allow for both donor and recipients SNPs to be studied together since both recipient and donor SNPs could play a role in DGF.

In conclusion, the donor *TNF* SNP rs3093662 needs to be further studied for its trend for association with DGF. This study highlights the need to study donor genotypes in determining the impact of donors on kidney allograft outcomes. If the association of *TNF* SNPs with DGF or kidney allograft outcomes is validated in independent studies, drugs that modulate *TNF* function can be studied to reduce the incidence of DGF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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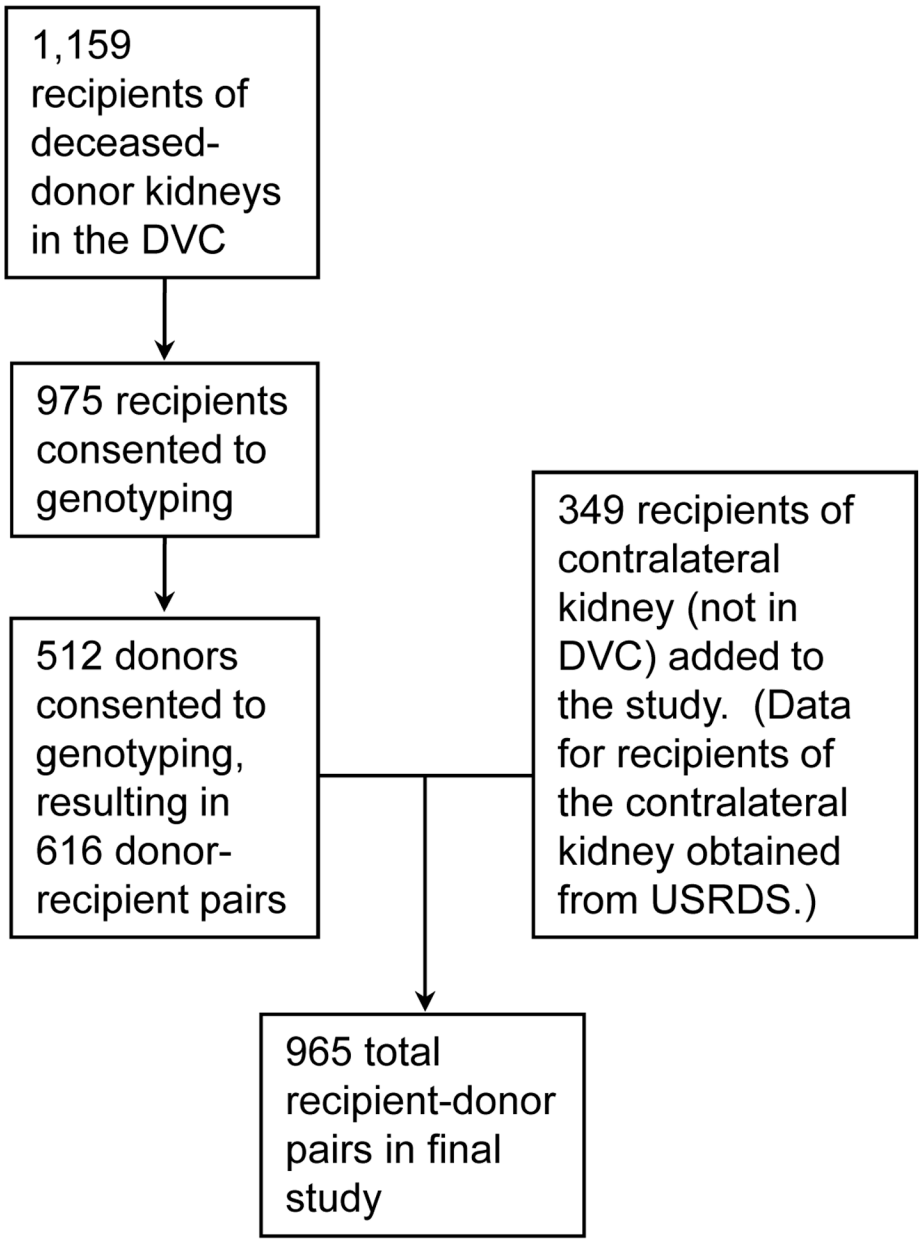

Figure 1.
Source of patients included in the study. Recipient-donor pairs were recruited from the Delaware Valley Cohort initially and then data for the recipient of the contra-lateral kidney of the donor was collected from the USRDS

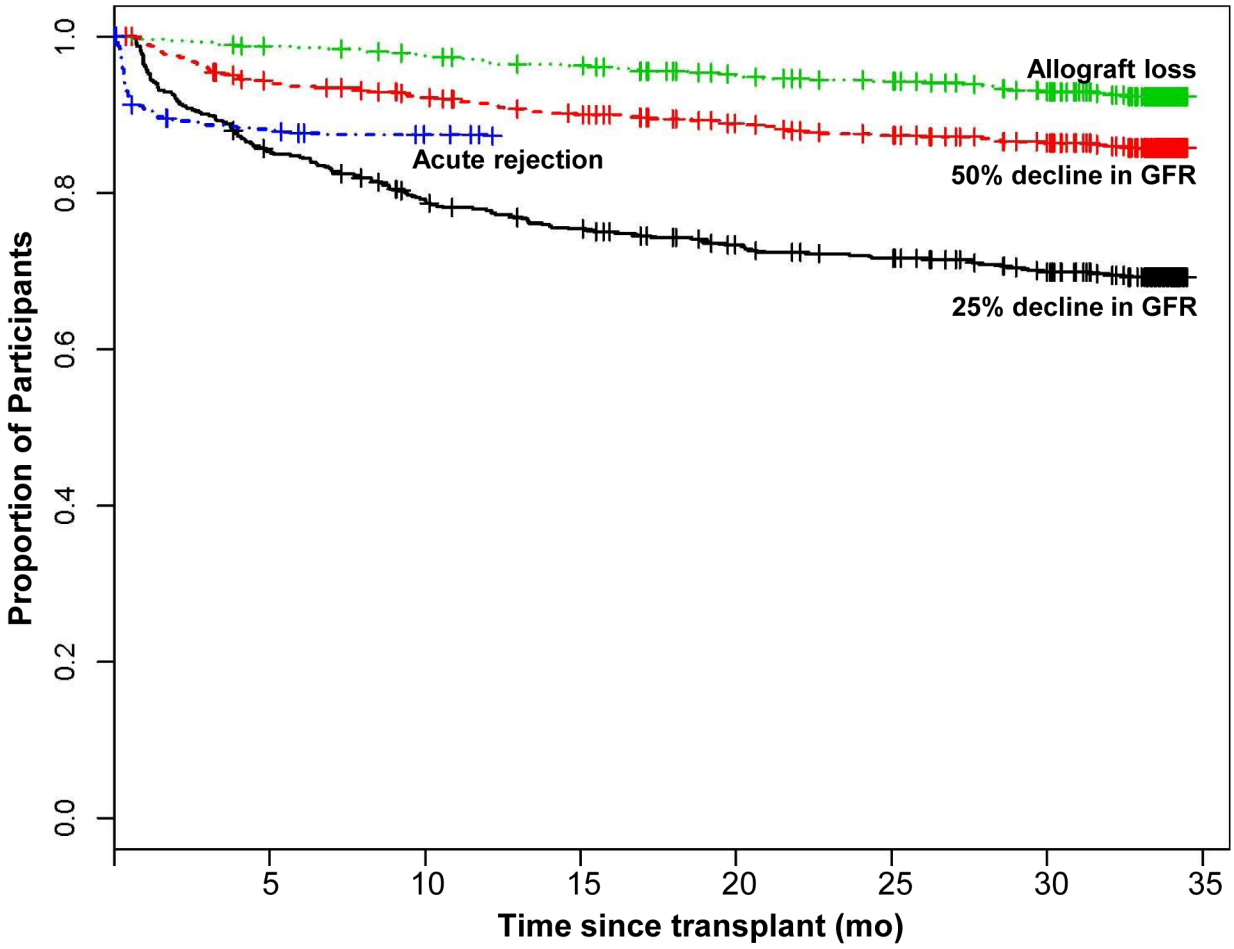

Figure 2.
Percentage of Recipients in the Delaware Valley Cohort experiencing 25% decline in eGFR, 50% decline in eGFR, acute rejection and graft loss.

Table 1

Demographic Characteristics stratified by Source of Recipient Data (Number in parenthesis is %, unless otherwise noted)

	DVC (n= 616)	USRDS (n= 349)
Recipient Ethnicity		
African American	188 (31 %)	106 (30 %)
White	412 (67 %)	229 (66 %)
Asian	14 (2 %)	14 (4 %)
Native American	2 (< 1%)	0
Recipient Sex		
Male	376 (61 %)	213 (61 %)
Female	240 (39 %)	136 (39 %)
Recipient Mean Age	48.6 years (±12.1)	45.5 (±15.3)
Dialysis Pre-transplant		
Yes	558 (92 %)	316 (91%)
No	47 (8 %)	33 (8 %)
Missing	11 (2 %)	-
Cause of ESRD		
Glomerulonephritis	125 (20 %)	92 (26 %)
Hypertension	126 (20 %)	64 (18 %)
Diabetes	200 (32 %)	85 (24 %)
Other kidney disease	165 (27 %)	108 (31 %)
Previous Transplant		
Yes	86 (14 %)	51 (15 %)
No	530 (84 %)	298 (85 %)
Recent Panel Reactive Antigen (PRA)		
>20 %	62 (11 %)	68 (11 %)
1–20 %	43 (8 %)	44 (13 %)
< 1 %	451 (81 %)	258 (76 %)
Missing	60 (10 %)	
Cold Ischemia Time		
>24 hours	79 (16 %)	62 (21 %)
12–24 hours	338 (68 %)	177 (60 %)
< 12 hours	83 (17 %)	56 (19 %)
Missing	116 (19 %)	54 (15 %)
Median (lowest – highest quartiles) distance organ traveled from procurement site to transplant center	43.63 miles (5.63 – 80.55)	53.96 miles (11.96 – 185.93)
Number of HLA mismatches		
0	52 (10 %)	48 (15 %)
1–2	94 (18 %)	45 (14 %)
3–4	239 (46 %)	113 (36 %)
5–6	134 (26 %)	112 (35 %)
Missing	97 (16 %)	31 (9 %)
Medicare primary payor	263 (43 %)	157 (45 %)

Table 2

Donor Characteristics (n=512)

Donor Mean Age in years	40.0 (±17)
Donor Sex	
Male	300 (59 %)
Donor Ethnicity	
African American	58 (11 %)
White	454 (89 %)
Donor Cause of Death	
Trauma	198 (39 %)
Other	314 (61%)
Extended Criteria Donor (ECD)[1]	
Yes	116 (23 %)
No	396 (77 %)

[1] ECD defined as donor age >60; or donor age >50 with any 2 of the following donor criteria: (1) terminal serum creatinine >1.5 mg/dl, (2) hypertension, or (3) death due to CVA.

Table 3

Outcomes post-transplantation By Source of Recipient Information

Source of Recipient Information	Medical Chart (n=605)	CMS Claims USRDS (n= 159)	UNOS Forms USRDS (n=201)	Total (n=965)
Dialysis in First Week Post-transplant				
Yes	228 (38 %)	65 (41 %)	49 (24 %)	342 (35 %)
No	377 (62 %)	94 (59 %)	152 (76 %)	623 (65 %)

Table 4

Adjusted and unadjusted association with DGF for inflammation and apoptosis related Polymorphisms [ND1]

Polymorphism	Gene	Minor Allele [ND2]	Participants With Minor Allele (%)		Unadjusted OR (95% C.I.)	Adjusted OR (95 % C.I.)
			With DGF	Without DGF		
rs3024498	*IL10*	C	107/281 (0.38)	203/511 (0.4)	0.93 (0.69 – 1.3)	0.89 (0.62 – 1.3)
rs3024494	*IL10*	T	3/282 (0.01)	5/521 (0.01)	1.1 (0.22 – 4.8)	0.22 (0.02 – 3.3)
rs1878672	*IL10*	C	157/253 (0.62)	312/470 (0.66)	0.83 (0.6 – 1.14)	0.82 (0.56 – 1.2)
rs3024493	*IL10*	A	56/262 (0.21)	108/478 (0.23)	0.93 (0.64 –1.3)	1.1 (0.70 – 1.7)
rs1554286	*IL10*	A	122/291 (0.42)	209/514 (0.41)	1.05 (0.79– 1.4)	0.99 (0.70 – 1.4)
rs3021094	*IL10*	G	48/260 (0.18)	104/494 (0.21)	0.85 (0.58– 1.2)	0.90 (0.57 – 1.4)
rs2222202	*IL10*	A	199/303 (0.66)	378/548 (0.69)	0.86 (0.64– 1.2)	0.85 (0.60 – 1.2)
rs2071746	*HMOX1*	T	216/294 (0.73)	402/561 (0.72)	1.1 (0.8– 1.5)	0.99 (0.68 – 1.4)
$(GT)_n$	*HMOX1*	L	205/326 (0.63)	388/606 (0.64)	0.95 (0.72– 1.3)	1.2 (0.87 – 1.7)
rs2071747	*HMOX1*	C	30/284 (0.11)	48/522 (0.09)	1.2 (0.71– 1.9)	0.92 (0.53 – 1.6)
rs2071748	*HMOX1*	A	191/293 (0.65)	352/545 (0.65)	1.0 (0.76– 1.4)	1.09 (0.77 – 1.6)
rs8140669	*HMOX1*	A	16/279 (0.06)	26/508 (0.05)	1.1 (0.58– 2.1)	0.42 (0.13 – 1.3)
rs6518952	*HMOX1*	T	20/297 (0.07)	30/550 (0.05)	1.3 (0.69– 2.2)	0.49 (0.18 – 1.4)
rs2071749	*HMOX1*	G	191/278 (0.69)	344/506 (0.68)	1.0 (0.76– 1.4)	1.1 (0.74 – 1.6)
rs5755720	*HMOX1*	G	146/295 (0.49)	268/532 (0.5)	0.97 (0.73– 1.3)	1.0 (0.72 – 1.4)
rs2285112	*HMOX1*	G	187/291 (0.64)	332/515 (0.64)	0.99 (0.73– 1.3)	1.0 (0.72 –1.5)
rs9894946	*TP53*	T	86/278 (0.31)	145/519 (0.28)	1.2 (0.84– 1.6)	1.1 (0.75 – 1.6)
rs1614984	*TP53*	A	187/277 (0.68)	321/512 (0.63)	1.24 (0.91– 1.69)	1.3 (0.90 – 1.8)
rs17884306	*TP53*	T	20/230 (0.09)	35/440 (0.08)	1.11 (0.61– 1.95)	1.2 (0.57 – 2.4)
rs4968187	*TP53*	T	4/290 (0.01)	9/544 (0.02)	0.85 (0.22– 2.68)	0.67 (0.13 – 3.3)
rs12951053	*TP53*	C	46/278 (0.17)	62/507 (0.12)	1.42 (0.94– 2.15)	1.5 (0.90 – 2.6)
rs1625895	*TP53*	A	78/278 (0.28)	118/504 (0.23)	1.28 (0.91– 1.78)	1.2 (0.81 – 1.8)
rs1042522	*TP53*	C	155/315 (0.49)	260/584 (0.45)	1.21 (0.92– 1.59)	1.3 (0.92 – 1.8)
rs1800472	*TGFB1*	A	10/292 (0.03)	17/542 (0.03)	1.1 (0.48– 2.42)	0.92 (0.32– 2.6)
rs1982073	*TGFB1*	C	163/256 (0.64)	295/464 (0.64)	1 (0.73– 1.38)	0.91 (0.62 – 1.3)
rs1800629	*TNF*	A	84/294 (0.29)	188/550 (0.34)	0.77 (0.56– 1.05)	0.84 (0.58 – 1.2)
rs3093662	*TNF*	G	53/303 (0.17)	64/566 (0.11)	1.66 (1.12– 2.47)*	1.9 (1.2 – 3.0)*
rs3091257†	*TNF*	A	43/229 (0.19)	84/439 (0.19)	0.98 (0.65– 1.47)	1.5 (0.91 – 2.5)

Adjusted for cold ischemia time, recipient race, extended criteria donor, donor cause of death, donor race, and source of DGF information (medical record or CMS claims or UNOS forms). The $(GT)_n$ SNP is categorized as short (S for ≤ 27 repeats) vs long repeats (L for >27 repeats

*denotes $p< 0.05$

†rs3091257 has been merged into rs1800628.[ND3]