Meeting Your Match: Assessing the Risk Factors of Donors and Recipients of Kidney Transplants

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Introduction

Approximately 2 in 1,000 individuals are living with end-stage kidney disease – kidney failure that can only be treated by a timely and costly kidney transplant or dialysis [1]. Kidney dialysis replaces part of the patient's kidney function but does not replace the jobs that healthy kidneys do. Conversely, kidney transplantation places a healthy donor kidney in the patient's body which filters waste better than dialysis. For this reason, kidney transplantation is preferred over dialysis.

Unfortunately, the number of people needing kidney transplant far exceeds the number of donors, and there are many risks associated with transplantation. Deceased donors must be considered brain dead and have had no prior cancer, diabetes, kidney or heart disease. As of April 14, 2022, there are 90,018 patients waiting for a kidney transplant [2]. The United Network for Organ Sharing (UNOS) matches donors and recipients by creating a match run ranking of donor and candidate information – including blood type, tissue type, percent reactive antibody, serum crossmatch, and location of hospital. Patients with higher rankings are those who are most likely to survive after the transplant and those in most urgent need of a transplant [3]. The median time for this matching process is currently 4 years and 1 month [3]. Once a transplant is done, patients can face post-surgical issues such as graft failure or death.

It is important to understand the risk factors associated with post-kidney transplant failure in order to optimize the matching process for successful kidney transplants. Dr. Augustine of Cleveland Clinic noted in a lecture that "patients aged 65 or older have a 50% chance of dying before they receive a transplant during a 5-year wait" [4]. A higher BMI has also been shown to reduce the success rate of a kidney transplant [5] [6]. Additionally, the diabetes status of the donor and recipient negatively impacts the graft success. On the other hand, social demographic variables such as both the donors and recipients being the same gender or race have been associated with a higher graft success rate [7]. Based on these literature review findings, this study aims to identify the risk factors associated with graft failure or death in our study population.

Table 1: Donor & Recipient Characteristics

Characteristic	N = 2,436[1]
Donor Age	39 (0,77)
Recipient Age at Transplant	52 (18,84)
Recipient Diabetes Status and Type	
None	1,566 (64%)
Type I	61 (2.5%)
Type II	246 (10%)
Type Other/Unknown	559 (23%)
Unknown	4
Recipient BMI	27.3 (10.6,53.8)
Donor History of Hypertension	
N	1,700 (70%)
Y	736 (30%)
Donor History of Diabetes	
N	2,287 (94%)
Y	149 (6.1%)
Donor Race	
Asian	58 (2.4%)
Black	315 (13%)
Other	381 (16%)
White	1,682 (69%)
Recipient Race	
Asian	173 (7.1%)
Black	763 (31%)
Other	24 (1.0%)
White	1,476 (61%)
Event	
1	1,686 (69%)
2	303 (12%)
3	447 (18%)

[1] Mean (Minimum,Maximum); n (%)

Data

The data for this analysis came from the United States Renal Data System (US-RDS) – a national database that collects information on End Stage Renal Disease. The cohort (N = 2,436) was restricted to recipients 18 years or older who received a deceased donor kidney between January 1, 2005 and December 31, 2005. The dataset includes seven social and health characteristics for both donors and recipients, along with the center number where the transplant took place and the event outcome. The outcome of interest is defined as graft failure or death 5 years post-transplant. From our particular dataset, 18.3% of patients are reported having a graft failure and 12.4% are reported dead after 5 years of the transplant. A summary of our variables of interest are listed in Table 1. The full summary of variables are listed in Tables 1A-B in Appendix A.

Methods

Initial Logistic Regression Model and Variable Selection

In order to determine which variables in our dataset to assess in our final multinomial model, we fitted two logistic regression models and determined which variables and interactions may be potential risk factors for death. Our binary outcome was living and organ failure. A patient was categorized as living if the variable *event* was coded as a 1 (living) and as organ failure if *event* was coded as 2 (death) or 3 (graft failure). To make our model intercept more interpretable we revised the model by centering Recipient BMI around its mean. Previous research shows that age has often been categorized as under 18, 18-39, 40-65, 65+ [8][9]. Therefore we coded *Donor Age* and *Recipient Age at Transplant* as categorical variables. Since *Donor History of Diabetes* is a binary variable, we also re-coded *Recipient Diabetes* from different types and statuses to a binary variable with one group as none and the other as yes. We also created a new indicator variable *Same Race* to identify whether the donor and recipient are the same race. In the first logistic regression model we included 14 variables choosing to exclude the variable categorizing the center from

which the patient came. We fitted a second logistic regression model with the same variables adding in several interaction terms of interest: *Donor hypertension*Donor History of Diabetes* and *Recipient Diabetes*Recipient BMI*. We determined that *Donor Age*, *Recipient Age*, *Recipient Diabetes, Recipient BMI*, *Donor Hypertension*, *Donor Diabetes*, *Donor Hypertension*Donor Diabetes, Recipient Diabetes*Recipient BMI*, and *Same Race* were all risk factors of organ failure.

Multinomial Regression

After selecting model covariates based on our literature review and logistic regression models, we fit a multinomial logistic regression model with nominal outcomes of *Living*, *Death*, and *Graft Failure*. We fitted a full multinomial regression model. Since both recipient and donor age seemed to be significant risk factors in our logistic models, we also added the interaction between *Recipient Age* and *Donor Age*.

$$log(\pi_j/\pi_0) = \beta_{0j} + \beta_{1j}I(\text{don\_age\_18-39}) + \beta_{2j}I(\text{don\_age\_40-65}) + \beta_{3j}I(\text{don\_age\_65+}) + \beta_{4j}I(\text{rec\_age\_tx\_40-65}) + \beta_{5j}I(\text{rec\_age\_tx\_65+}) + \beta_{6j}I(\text{rec\_diab}) + \beta_{7j}\text{rec\_BMI\_centered} + \beta_{8j}I(\text{don\_htn}) + \beta_{9j}I(\text{don\_hist\_diab}) + \beta_{10j}I(\text{same\_race}) + \beta_{11j}I(\text{don\_htn} * \text{don\_hist\_diab}) + \beta_{12j}I(\text{rec\_diab}) * \text{rec\_BMI\_centered} + \beta_{13j}I(\text{don\_age\_18-39} * \text{rec\_age\_tx\_40-65}) + \beta_{14j}I(\text{don\_age\_40-65} * \text{rec\_age\_tx\_40-65}) + \beta_{15j}I(\text{don\_age\_65+} * \text{rec\_age\_tx\_40-65}) + \beta_{16j}I(\text{don\_age\_18-39} * \text{rec\_age\_tx\_65+}) + \beta_{17j}I(\text{don\_age\_40-65} * \text{rec\_age\_tx\_65+}) + \beta_{18j}I(\text{don\_age\_65+} * \text{rec\_age\_tx\_65+})$$

We used a Hosmer-Lemeshow test to assess the goodness of fit of this multinomial model testing the null hypothesis "the model fits the data well" against the alternative hypothesis "the model does not fit the data well." And we used a Wald test to determine if the interaction between recipient age and donor age was significant.

We then fit a reduced multinomial regression model without the recipient age*donor age interaction term:

$$log(\pi_j/\pi_0) = \beta_{0j} + \beta_{1j}I(\text{don\_age\_18-39}) + \beta_{2j}I(\text{don\_age\_40-65}) + \beta_{3j}I(\text{don\_age\_65+}) + \beta_{4j}I(\text{rec\_age\_tx\_40-65}) + \beta_{5j}I(\text{rec\_age\_tx\_65+}) + \beta_{6j}I(\text{rec\_diab}) + \beta_{7j}\text{rec\_BMI\_centered} + \beta_{8j}I(\text{don\_htn}) + \beta_{9j}I(\text{don\_hist\_diab}) + \beta_{10j}I(\text{same\_race}) + \beta_{11j}I(\text{don\_htn} * \text{don\_hist\_diab}) + \beta_{12j}I(\text{rec\_diab} * \text{rec\_BMI\_centered})$$

We used another Hosmer-Lemeshow test to assess the goodness of fit of our reduced model. The reference group for both models is a transplant recipient who is living, aged 18-39, with no diabetes, of average BMI, with a donor who is under 18 years old, with no hypertension, and no diabetes. Additionally the donor and the recipient are not the same race.

Finally, we compared the two multinomial models using Akaike Information Criterion (AIC) values. A lower AIC indicates a better model fit and a $\Delta AIC = AIC_i - AIC_{min}$ between 4 and 7 indicate lack of support for good model fit [10].

Results

Multinomial Regression Model

After selecting our covariates from our logistic regression models, we determined our final reduced multinomial regression model from the Hosmer-Lemeshow tests (discussed below). The model summary of the full multinomial model can be found in Appendix B. We fitted this multinomial regression model to our data to determine which risk factors in our model are significant and we found out that when comparing death and living, the significant risk factors were *Donor Age under 18*, *Donor Age above 65*, *Recipient Age between 40 to 65*, *Recipient Age between 18 to 39*, *Recipient Age above 65*, *Recipient BMI, Donor Diabetes*, *Donor Hypertension*Donor Diabetes*, and *Recipient Diabetes*Recipient BMI* (Table 2). When comparing graft failure and living, the significant risk factors were *Donor Age under 18, Donor Age between 40 to 65*, *Donor Age between above 65*, *Recipient Age between 18 to 39*, *Recipient Age between 40 to 65*, *Recipient Age above 65, Donor Diabetes, Same Race*, and *Recipient Diabetes*Recipient BMI* (Table 2).

Model Diagnostics Comparison

As noted in our Methods section, we performed a Hosmer-Lemeshow test on both our full multinomial regression model and reduced multinomial regression model to check goodness of fit and Wald test on the interaction between recipient age and donor age to see if this interaction is significant. The Hosmer-Lemeshow test on our full model indicated that we do not have sufficient evidence to accept the null hypothesis that the model fits the data well (p-value = 0.047). We also noted that each interaction between *Donor Age* and *Recipient Age* categories showed insignificant

Table 2: Multinomial Regression Output

Variable	Estimate (95% CI)	P-Value
Intercept: 1	-3.786 (-4.521, -3.051)	5.76e-24*
Intercept: 2	-1.247 (-1.643, -0.851)	6.74e-10*
Donor Age (18-39]: 1	0.439 (-0.011, 0.889)	0.0557
Donor Age (18-39]: 2	0.284 (-0.124, 0.692)	0.172
Donor Age (39-65]: 1	0.328 (-0.128, 0.784)	0.158
Donor Age (39-65]: 2	0.82 (0.414, 1.226)	7.61e-05*
Donor Age (65-80]: 1	0.849 (0.172, 1.526)	0.014*
Donor Age (65-80]: 2	1.461 (0.834, 2.088)	4.89e-06*
Recipient Age (39-65]: 1	1.653 (0.998, 2.307)	7.51e-07*
Recipient Age (39-65]: 2	-0.769 (-1.038, -0.501)	1.93e-08*
Recipient Age (65-84]: 1	2.282 (1.589, 2.975)	1.08e-10*
Recipient Age (65-84]: 2	-0.897 (-1.286, -0.507)	6.33e-06*
Recipient Diabetes: 1	0.538 (0.275, 0.802)	6.14e-05*
Recipient Diabetes: 2	0.169 (-0.068, 0.406)	0.162
Recipent BMI Centered: 1	-0.043 (-0.079, -0.007)	0.0192*
Recipient BMI Centered: 2	-0.001 (-0.027, 0.026)	0.965
Donor Hypertension: 1	-0.241 (-0.568, 0.085)	0.148
Donor Hypertension: 2	0.132 (-0.133, 0.397)	0.33
Donor History Diabetes: 1	1.097 (0.369, 1.824)	0.00313*
Donor Hisotry of Diabetes: 2	1.018 (0.339, 1.698)	0.00331*
Same Race: 1	-0.253 (-0.507, 0)	0.0501
Same Race: 2	-0.515 (-0.735, -0.295)	4.46e-06*
Donor Hypertension*Donor History of Diabetes: 1	-1.312 (-2.34, -0.283)	0.0124*
Donor Hypertension*Donor History of Diabetes: 2	-0.699 (-1.548, 0.149)	0.106
Recipient Diabetes*Recipient BMI Centered: 1	0.069 (0.019, 0.119)	0.00637*
Recipient Diabetes*Recipient BMI Centered:2	0.045 (0.004, 0.086)	0.0318*

* Significance Level of 0.05

associations with outcomes (p-value > 0.05). To investigate further, we performed a Wald test on the interaction between *Recipient Age* and *Donor Age* which showed that the interaction is not a significant risk factor (p-value = 0.33). The Hosmer-Lemeshow test of our final reduced model indicated that we fail to reject the null hypothesis and we accept that our final model fits the data well (p-value = 0.25).

Finally, to choose the better of our two multinomial models, we compared the AIC values of each of the models. Our full model had an AIC of 3810.384 and the reduced model had an AIC of 3800.59. Our reduced model has a lower AIC value indicating that is the better of the two models. The ΔAIC of the full model 9.794 > 7 indicates that there is little support for the goodness of fit of our full model. We conclude that our reduced model is the better model.

Discussion

From our logistic and multinomial regression modeling procedure we identified risk factors of mortality in patients receiving kidney transplants. In particular, we note the difference in associated risk factors for patient death vs graft failure. For donors and recipients of the same race, holding all other variables constant we did not find enough evidence of a difference in odds of death vs. living compared to donors and recipients of different races. However, for donors and recipients of the same race, holding all other variables constant, the estimated odds ratio of graft failure vs. living is $e^{-0.52}$ = 0.59 compared to donors and recipients of different races (p-value = 4.5e-06). This result of decreased risk of graft failure for patients whose donor's race was the same as their own supports previous literature stating that transplants between donors and recipients of the same race are more likely to have successful grafts. Both donor age and recipient age across categories had significant impacts on both graft failure and death. We note for donors aged 40-65, holding all other covariates constant, we did not find enough evidence of a difference in odds of graft failure vs. living of the kidney recipient compared to donors under 18. However, for donors aged 40-65, holding all other covariates constant, there is a $e^{0.82}$ = 2.27 estimated odds ratio of graft failure vs. living is in kidney recipients compared to donors under 18 (p-value = 7.6e-05). We also found that recipients aged 40-65 and 65+, holding all other covariates constant, had higher estimated odds of death vs living but had lower estimated odds of graft failure vs living compared to recipients aged 18-39 (Table 2).

Based on our model, the interaction between recipient diabetes status is also a risk factor for both death and graft failure. For recipients with diabetes, holding all other variables constant, the estimated odds ratio of death vs. living is $e^{-0.04+0.069}$ = 1.03 for a one unit increase in BMI. For recipients without diabetes, holding all other variables constant, the estimated odds ratio of death vs living is $e^{-0.04}$ = 0.96 for a one unit increase in BMI. For recipients with diabetes, holding all other variables constant, the expected odds ratio of graft failure vs living is 1.05 for a one unit increase in BMI. Finally, for recipients without diabetes, holding all other variables constant, the estimated odds ratio of graft failure vs living is 0.99 for a one unit increase in BMI.

Our models show that risk factors for both death and graft failure for a patient receiving a kidney transplant come from attributes of both the donor and the patient. In our model, our variable indicating whether or not a patient and donor were of the same race was associated with decreased odds of graft failure may indicate that more biological and genetic attributes of patients and donors should be considered. In future analysis, we would like to look into obtaining and integrating genetic data as other potential risk factors for death and graft failure. Lastly, since risk factors that stem from recipients are also likely to influence ranking in kidney transplant candidacy, future research may look at more recipient background factors influencing transplant success.

Contribution from each individual team member
Isabel Gomez: Introduction and data summary statistics
Yichu Wang: Methods, multinomial regression and diagnostics
Maya Watanabe: Methods, logistic regression; Discussion
Zhehan Zhang: Results

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Appendix

A. Summary statistics of all dataset variables

Table 1A: Summary Statistics Donors

	Overall (N=2436)
Donor BMI	
Mean (SD)	26.6 (6.81)
Median [Min, Max]	25.6 [10.5, 75.3]
Donor Race	
Asian	58 (2.4%)
Black	315 (12.9%)
Other	381 (15.6%)
White	1682 (69.0%)
Donor Gender	
F	1054 (43.3%)
M	1382 (56.7%)
Donor Age	
Mean (SD)	39.3 (17.0)
Median [Min, Max]	42.0 [0, 77.0]
Categorical Donor Age	
(0,18]	317 (13.0%)
(18,39]	782 (32.1%)
(39,65]	1233 (50.6%)
(65,80]	99 (4.1%)
Missing	5 (0.2%)
Donor History of Diabetes	
N	2287 (93.9%)
Y	149 (6.1%)
Donor History of Hypertension	
N	1700 (69.8%)
Y	736 (30.2%)
Meets expanded donor criteria for kidney	
N	1928 (79.1%)
Y	508 (20.9%)

Table 1B: Summary Statistics Recipients

	Overall (N=2436)
Recipient BMI	
Mean (SD)	27.3 (5.26)
Median [Min, Max]	27.2 [10.6, 53.8]
Recipient Race	
Asian	173 (7.1%)
Black	763 (31.3%)
Other	24 (1.0%)
White	1476 (60.6%)
Recipient Gender	
F	949 (39.0%)
M	1487 (61.0%)
Recipient Age at Transplant	
Mean (SD)	52.3 (13.2)
Median [Min, Max]	54.0 [18.0, 84.0]
Categorical Recipient Age at Transplant	
(18,39]	432 (17.7%)
(39,65]	1603 (65.8%)
(65,84]	391 (16.1%)
Missing	10 (0.4%)
Recipient Diabetes Status and Type	
None	1566 (64.3%)
Type I	61 (2.5%)
Type II	246 (10.1%)
Type Other/Unknown	559 (22.9%)
Missing	4 (0.2%)
Recipient Years on Dialysis	
Mean (SD)	3.18 (3.10)
Median [Min, Max]	2.62 [-0.129, 24.4]
Recipient Diabetes	
0	1566 (64.3%)
1	866 (35.6%)
Missing	4 (0.2%)
Recipient Cold Ischemia Time >20 h	
N	1575 (64.7%)
Y	861 (35.3%)
Recipient and Donor of Same Race	
0	1226 (50.3%)
1	1210 (49.7%)
Number of Patients	
Mean (SD)	134 (31.1)
Median [Min, Max]	121 [101, 198]
Center	
1	121 (5.0%)
2	114 (4.7%)
3	150 (6.2%)
4	107 (4.4%)
5	153 (6.3%)
6	101 (4.1%)
7	149 (6.1%)
8	118 (4.8%)
9	105 (4.3%)
10	120 (4.9%)
11	198 (8.1%)
12	141 (5.8%)
13	102 (4.2%)
14	115 (4.7%)
15	103 (4.2%)
16	133 (5.5%)
17	108 (4.4%)
18	107 (4.4%)
19	191 (7.8%)
Event Outcome	
1	1686 (69.2%)
2	303 (12.4%)
3	447 (18.3%)
Recipient and Donor of Same Race	
0	1226 (50.3%)
1	1210 (49.7%)

B. Full multinomial model output

Table 2A: Multinomial Full Regression Output

Variable	Estimate (95% CI)	P-Value
Intercept: 1	-3.596 (-5.012, -2.181)	6.38e-07*
Intercept: 2	-1.087 (-1.612, -0.561)	5.09e-05*
Donor Age (18-39]: 1	-0.274 (-2.09, 1.541)	0.767
Donor Age (18-39]: 2	0.226 (-0.383, 0.834)	0.467
Donor Age (39-65]: 1	0.626 (-1.05, 2.303)	0.464
Donor Age (39-65]: 2	0.427 (-0.21, 1.065)	0.189
Donor Age (65-80]: 1	-10.948 (-1071.677, 1049.781)	0.984
Donor Age (65-80]: 2	1.904 (0.176, 3.632)	0.0308*
Recipient Age (39-65]: 1	1.291 (-0.197, 2.779)	0.089
Recipient Age (39-65]: 2	-1.172 (-1.912, -0.431)	0.00193*
Recipient Age (65-84]: 1	2.642 (1.002, 4.282)	0.00159*
Recipient Age (65-84]: 2	-0.516 (-1.848, 0.815)	0.447
Recipient Diabetes: 1	0.539 (0.276, 0.803)	6.15e-05*
Recipient Diabetes: 2	0.18 (-0.058, 0.418)	0.139
Recipent BMI Centered: 1	-0.043 (-0.079, -0.007)	0.0197*
Recipient BMI Centered: 2	0 (-0.026, 0.027)	0.973
Donor Hypertension: 1	-0.253 (-0.579, 0.074)	0.13
Donor Hypertension: 2	0.13 (-0.136, 0.395)	0.338
Donor History Diabetes: 1	1.104 (0.376, 1.832)	0.00295*
Donor Hisotry of Diabetes: 2	1.041 (0.36, 1.721)	0.00272*
Same Race: 1	-0.262 (-0.516, -0.007)	0.0437*
Same Race: 2	-0.501 (-0.722, -0.28)	8.79e-06*
Donor Hypertension*Donor History of Diabetes: 1	-1.284 (-2.312, -0.255)	0.0145*
Donor Hypertension*Donor History of Diabetes: 2	-0.744 (-1.594, 0.107)	0.0868
Recipient Diabetes*Recipient BMI Centered: 1	0.069 (0.019, 0.119)	0.00664*
Recipient Diabetes*Recipient BMI Centered:2	0.043 (0.002, 0.084)	0.0395*

* Significance Level of 0.05