First Kidney Allograft Mismatch and Survival in American Indians

Chelsea Joy Thomsen, MSPH, UACOMP; Harini Chakkera, MD, MPH, Mayo Clinic - Arizona; Robert C. Williams, PhD, NIH, NIDDK

Abstract

Over 90,000 individuals are awaiting renal allograft in the United States. This ongoing imbalance of supply and demand has made research aiming to improve renal allograft survival a necessity. Details of the collection, distribution, and outcomes of renal allografts found in the United Network for Organ Sharing (UNOS) database were used in a retrospective study to identify and evaluate differences in allograft survival between American Indians and other heritage groups. In particular, the study aimed to identify whether American Indians have a similar distribution of HLA mismatches between recipient and donor when compared to other populations; and whether this impacts overall kidney survival. Contingency table and Cox Regression analyses were applied and found that the Hazard Ratio was greater than 1 for all mismatches; and furthermore, an increase in mismatches was proportional to an increase in hazard ratio that was statistically significant. Recipients with 4, 5, or 6 mismatches showed an hazard ratio of 1.466 ($p<0.0564$). The HLA-DR allele has been known historically as the most important locus for transplants. Better matching, particularly at the DR locus, results in improved kidney survival time. Additionally, age, gender, and transplant era were used as major covariates in allograft survival using a proportional hazards model. Increasing age of recipient is associated with increased kidney survival time, and female gender is associated with decreased kidney survival time. Transplant era had a very high Chi-Square of 40.22 and an overall 5% increased survival with most recent transplants living longer than older era transplants. These results have implications for potential policy changes regarding organ allocation in addition to identifying an increased need in organ donation within specific heritage groups.

Introduction

- Continuing research and advances in understanding of the immune system have improved patient prognosis and survival rates.
- One important question is the role of kidney recipient heritage in the success or failure of the allograft. Identification of differences between populations and subsequent research of their cause is important for the continued advances in transplant medicine.
- Heritage groups studied were: American Indians, Whites, Blacks, Asians, and Hispanics.
- Identified the frequency of HLA mismatches in each heritage group, and compared allograft survival using age, sex, and transplant era as major covariates.
- Increasing understanding of transplant survival is important for organ allocation, increased survival for organ recipient, and for public health efforts aimed at increasing organ donation registration.

Methods

Data set provided by the United Network for Organ Sharing (UNOS)

- Identified all first kidney allograft recipients: 2264 American Indian, 129,820 White, 61,035 Black, 10,940 Asian, 30,379 Hispanic

Contingency Table Analysis

- Assessed HLA histocompatibility at the HLA A, B, and DR loci using a matching algorithm. Mismatch scores ranged from zero to six.
- Compared mismatch data between American Indians other heritage groups

Proportional Hazard Analysis

- Dependent variable: Kidney failure time (GTIME_KI)
- Censoring variable: kidney failure time (FAIL_KI)
- Covariates: age (years), gender (reference = male), transplant era, and locus mismatch (reference = 0 mismatch)
- HLAMIS, AMIS, BMIS, and DRMIS were individually evaluated as primary. A combined HLA 4-6 mismatch category was created and used in an additional regression (HLAMIS_MOD_7).

Contingency table analysis and COX regressions performed by standard methods using SAS software.

Results

Contingency Tables

- *American Indians versus Whites (Figure 1)*. American Indians have a lower frequency of mismatches in categories 1-3, and have higher frequency of mismatches in categories 4-6 ($p<0.001$)
- *American Indians versus Blacks (Figure 2)*. American Indians have higher frequency of mismatches in categories 1-3, and have lower frequency of mismatches in categories 4-6 ($p<0.001$)
- *American Indians versus Asians (Figure 3)*. American Indians have higher frequency of mismatches in categories 1-3, and have lower frequency of mismatches in categories 4-6 ($p<0.001$)
- *American Indians versus Hispanics (Figure 4)*. No significant difference between the mismatch scores 0-6 in these two heritage groups ($p = 0.434$) However, American Indians have a significant difference ($p < 0.0001$) for the HLA-DR locus, with very poor matching.

Cox Regressions

- American Indians vs. Whites: HR = 1.145 and $p = 0.0058$.
- American Indians vs. Blacks: HR = 0.647 and $p < 0.0001$
- American Indians vs. Asians: HR = 1.417 and $p < 0.0001$.
- American Indians vs. Hispanics: HR similar to 1.

Proportional Hazards Analysis

Age, gender, and transplant era were significantly related to kidney failure time:

- Age: HR < 1
- Transplant era: HR < 1
- Female Gender: HR > 1

Mismatches at HLA-A and HLA-B:

- not significantly related to kidney failure time.

Mismatches at HLA-DR:

- significantly related to kidney failure time.
  - HLA-DR, 1 mismatch: HR = 1.366 ($p = 0.0243$)
  - HLA-DR, 2 mismatches: HR = 1.414 ($p = 0.0177$)

Overall mismatches using variable HLAMIS (mismatch categories 1-6) was not significantly related to kidney failure time in American Indians. Combining mismatch categories 4-6 was marginally related to survival time, HR=1.466 ($p = 0.0564$). (*Table 1*)

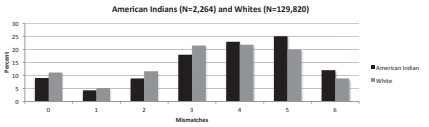

Figure 1 – HLA Mismatches in First Kidney Allografts. American Indians and Whites.

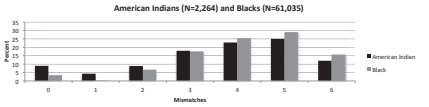

Figure 2 – HLA Mismatches in First Kidney Allografts. American Indians and Blacks.

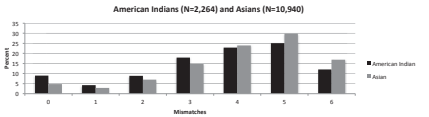

Figure 3 – HLA Mismatches in First Kidney Allografts. American Indians and Asians.

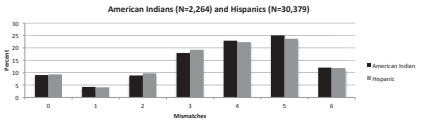

Figure 4 – HLA Mismatches in First Kidney Allografts. American Indians and Hispanics.

1. Primary: HLA-A mismatch

Parameter	DF	Chi-Square	Pr>ChiSq	HR
AGE	1	12.19	0.0005	0.989
GENDER	1	4.76	0.0292	1.236
TX_ERA	1	0.01	<0.0001	0.944
AMIS 1 (ref. 0)	1	0.01	0.9053	0.985
AMIS 2 (ref. 0)	1	0.09	0.3482	1.135

2. Primary: HLA-B mismatch

Parameter	DF	Chi-Square	Pr>ChiSq	HR
AGE	1	11.95	0.0005	0.989
GENDER	1	4.72	0.0299	1.234
TX_ERA	1	44.86	<0.0001	0.945
BMIS 1 (ref. 0)	1	0.37	0.5423	1.094
BMIS 2 (ref. 0)	1	1.24	0.2653	1.177

3. Primary: HLA-DR mismatch

Parameter	DF	Chi-Square	Pr>ChiSq	HR
AGE	1	11.23	0.0008	0.989
GENDER	1	4.87	0.0274	1.24
TX_ERA	1	39.84	<0.0001	0.948
DRMIS 1 (ref. 0)	1	5.07	0.0243	1.366
DRMIS 2 (ref. 0)	1	5.63	0.0177	1.414

4. Primary: Total HLA mismatch

Parameter	DF	Chi-Square	Pr>ChiSq	HR
AGE	1	10.71	0.0011	0.99
GENDER	1	5.02	0.025	1.245
TX_ERA	1	40.13	<0.0001	0.947
HLAMIS_MOD1 (ref. 0)	1	0.79	0.3756	1.307
HLAMIS_MOD2 (ref. 0)	1	1.15	0.2839	1.297
HLAMIS_MOD3 (ref. 0)	1	0.73	0.3935	1.207
HLAMIS_MOD7 (ref. 0)	1	3.64	0.0564	1.466

Table 1: Cox Regressions. DF, degrees of freedom; HR, hazard ratio.

Discussion and Conclusions

Cox Regressions

- HLA-DR allele has been known historically as the most important locus for transplants, and this was confirmed once more in our research
- Poorly-matched allografts, particularly at the DR loci, result in decreased kidney survival.
- American Indians have poorer kidney allograft survival compared to White and Asian heritage groups.
- American Indians have similar kidney allograft survival compared to Hispanics.
- American Indians have slightly superior kidney allograft survival compared to Blacks.

Proportional Hazards Analysis

- Increasing age of recipient is associated with increased kidney survival.
- Female gender is associated with decreased kidney survival time.
- Transplant era is associated with increased kidney survival (Chi-Square=40.22, overall 5% increased survival per year with most recent transplants living longer than older era transplants).

Future Directions

- Ongoing collection and evaluation of kidney allografts by UNOS would supplement this analysis by increasing the sample size of the populations studied and improve power.
- Allograft allocation practices and policies may be evaluated in the future to apply this data to reflect the importance of heritage in allograft survival.
- On a public health and community outreach level, increased education and awareness of the shortage of organ donation within the American Indian population in particular may foster an environment of increased donation within this group; and potentially increase overall allograft survival in these individuals.

Acknowledgements

I wish to thank my mentors Dr. Harini Chakkera and Dr. Robert C. Williams for their tremendous support and guidance. I would also like to thank the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) branch of the National Institutes of Health (NIH) in Phoenix, AZ for allowing me to pursue this project as a Special Volunteer at their facility.

This work was supported in part by Health Resources and Services Administration contract 234-2005-37011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.