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Pre- versus Post-Kidney Allocation System Does Not Differentially Influence the Effect of HLA Mismatch on 3-Year Graft Survival

INTRODUCTION

- Kidney allocation has been challenging due to growing gap between the demand and supply of kidneys.
- The old allocation system was primarily based on waiting time and HLA matching (0-ABDR mismatches).
- On December 4, 2014, a new Kidney Allocation System (KAS) was implemented to improve the distribution of deceased donor kidneys. One of the critical changes in its allocation algorithm was reducing the priority of total HLA mismatch number.
- Since the KAS implementation, there is still a lack of knowledge on the impact of HLA mismatch on graft survival after the kidney allocation system. This information might provide insight into further improvement of kidney allocation algorithm.

Objective:
- This historical cohort study aimed to assess the effect of total number of HLA mismatch on 3-year graft and death-censored survival post kidney transplantation in the pre-KAS versus post-KAS allocation era.
- Total number of HLA mismatches = total number of HLA mismatches at the A-, B-, and DR- loci

METHOD

- Data source = UNOS (United Network for Organ Sharing) STAR files

- Inclusion criteria: Adult recipients of a solitary kidney only, deceased donor transplant between 2011-2017.
  - Adult (≥ 18 years old)
  - First time (Primary) kidney transplantation
  - Kidney from deceased donor
  - On dialysis at the time of transplant
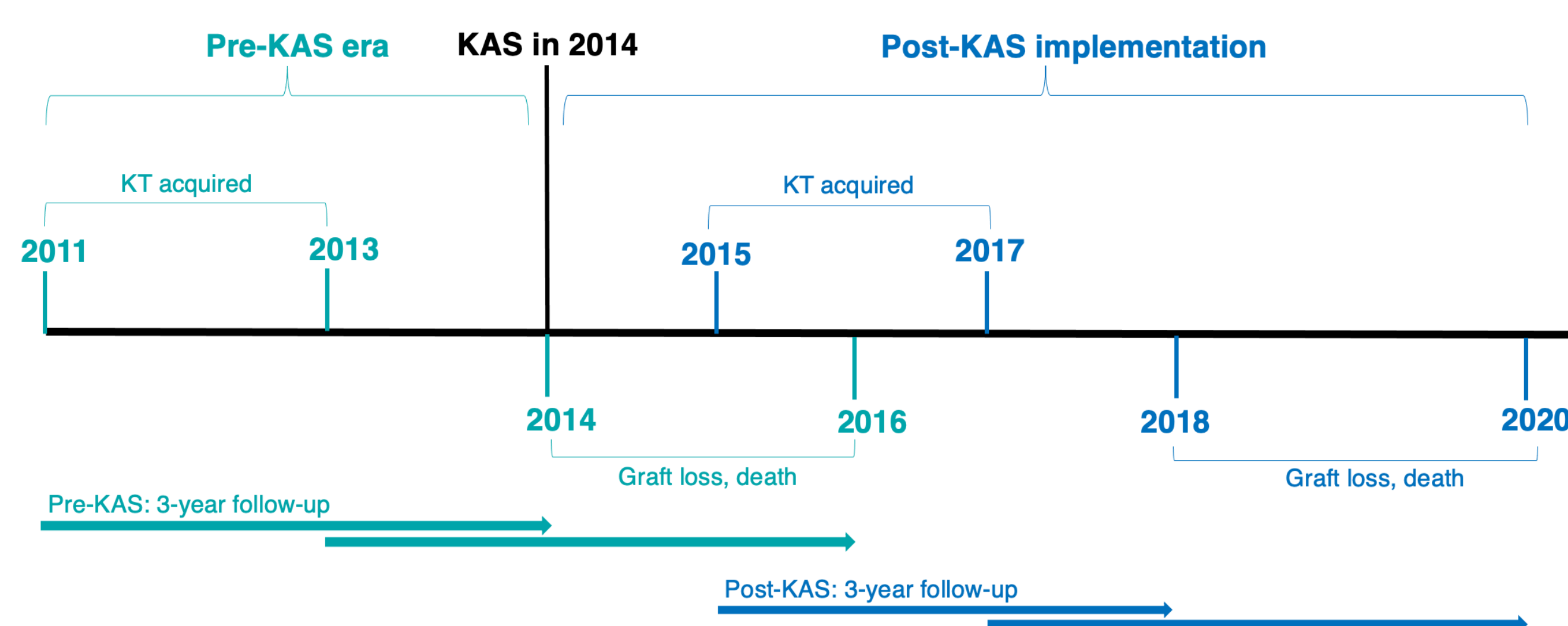
- Statistical analysis (SAS 9.4):
  - Kaplan-Meier (KM) method was used to calculate survival curves for both pre- and post-KAS, stratified on total number of HLA mismatches. Survival curves were compared by the log-rank test.
  - Cox proportional hazard (Cox P.H.) model was used to evaluate the effect of total HLA mismatches on graft and death-censored survival in the pre- vs. post-KAS allocation era. Hazard ratio (HR) and 95% confidence interval are provided as measures of strength of association and precision, respectively, adjusted for recipient and donor characteristics.

IMPLICATIONS:

- The implementation of KAS does not modify the effect of HLA mismatch on 3-year graft survival. This result may be due to relatively short-term follow-up. It is well known that HLA mismatch plays a cumulative role in graft loss. Thus, it may be worthwhile to further investigate this interaction with a 5-year or 10-year follow-up.
- The adjusted hazard of death-censored graft failure was notable for the effect of 6-ABDR HLA mismatch, increasing the risk by 41%. Such information may be helpful to consider in the kidney allocation process and can be further studied.

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RESULTS

Table 1: Summary of Donor Characteristics by Pre-/Post-KAS

Variable	Statistics or category	Pre-KAS	Post-KAS
KDPI	Mean (SD)	44.67 (26.73)	43.93 (25.74)
	Median (p25-p75)	44 (22-66)	43 (22-64)
ECD	No	16403 (82.99%)	22716 (85.66%)
	Yes	3362 (17.01%)	3803 (14.34%)

Table 2: Summary of Recipient Characteristics by Pre-/Post-KAS

| Variable	Statistics or category	Pre-KAS	Post-KAS
Age	Mean (SD)	53.58 (12.93)	52.66 (13.20)
	Median (p25-p75)	55 (45-63)	55 (43-63)
Gender	Female	7478 (37.83%)	10305 (38.86%)
	Male	12287 (62.17%)	16214 (61.14%)
Racial/Ethnic groups	White	7104 (35.94%)	8214 (30.97%)
	Black or African American	7239 (36.63%)	10177 (38.38%)
	Hispanic	3622 (18.33%)	5418 (20.43%)
	Asian	1401 (7.09%)	2017 (7.61%)
	AIAN	216 (1.09%)	333 (1.26%)
	NHPI	93 (0.47%)	144 (0.54%)
	Multiracial	90 (0.46%)	216 (0.81%)
Diabetes status	No	11669 (59.04%)	16313 (61.51%)
	Yes	8096 (40.96%)	10206 (38.49%)
cPRA	Mean (SD)	16.29 (29.90)	18.69 (32.44)
	Median (p25-p75)	0 (0-19)	0 (0-24)
cPRA	cPRA 0%	13271 (67.14%)	16797 (63.34%)
	cRPRA 1-79%	4533 (22.93%)	6748 (25.45%)
	cPRA 80-89%	933 (4.72%)	688 (2.59%)
	cRPRA 90-94%	463 (2.34%)	479 (1.81%)
	cPRA 95-98%	388 (1.96%)	538 (2.03%)
	cPRA 99-100%	177 (0.90%)	1269 (4.79%)
HLA mismatch level	0-ABDR mismatch	1218 (6.16%)	855 (3.22%)
	1-ABDR mismatch	187 (0.95%)	247 (0.93%)
	2-ABDR mismatch	742 (3.75%)	1077 (4.06%)
	3-ABDR mismatch	2472 (12.51%)	3538 (13.34%)
	4-ABDR mismatch	5354 (27.09%)	7529 (28.39%)
	5-ABDR mismatch	6633 (33.56%)	8896 (33.55%)
	6-ABDR mismatch	3159 (15.98%)	4377 (16.51%)
DR locus mismatch level	0-DR mismatch	3276 (16.57%)	3731 (14.07%)
	1-DR mismatch	9000 (45.54%)	12970 (48.91%)
	2-DR mismatch	7489 (37.89%)	9818 (37.02%)

AIAN - American Indian/Alaska Native
NHPI - Native Hawaiian/Other Pacific Islander

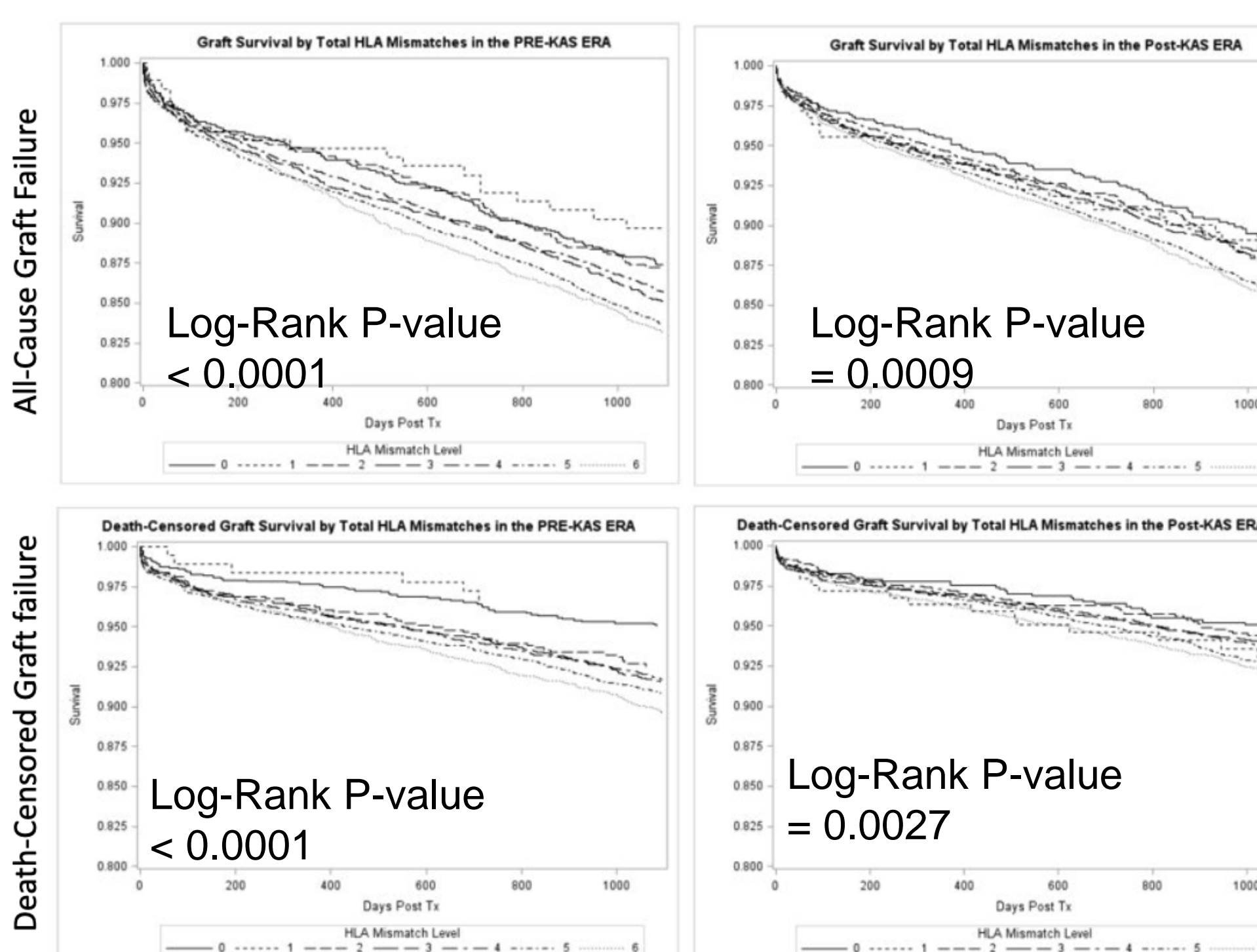**Table 3: Summary of Transplant Characteristics by Pre-/Post-KAS**

Variable	Statistics or category	Pre-KAS	Post-KAS
Waiting time (days)	Mean (SD)	981.12 (756.26)	923.61 (853.99)
	Median (p25-p75)	855 (387-1420)	712 (198-1434)
Cold ischemic time (hours)	Mean (SD)	17.44 (8.74)	17.69 (8.65)
	Median (p25-p75)	16.01 (11-22.01)	16.6 (11.36-22.50)
Delayed graft function	No	14095 (71.31%)	18265 (68.88%)
	Yes	5670 (28.69%)	8254 (31.12%)
Antibody induction	No	2786 (14.10%)	2390 (9.01%)
	Yes	16979 (85.90%)	24129 (90.99%)
Calcineurin inhibitor	No	1086 (5.49%)	1586 (5.98%)
	Yes	18679 (94.51%)	24933 (94.02%)
Mycophenolate	No	1244 (6.29%)	1075 (4.05%)
	Yes	18521 (93.71%)	25444 (95.95%)
Corticosteroids	No	6004 (30.38%)	8278 (31.22%)
	Yes	13761 (69.62%)	18241 (68.78%)

Table 1-3 (Characteristics): Comparison of all factors is statistically significant (p<0.05).
- Antibody induction has increased 5% after KAS implementation as well as the cPRA 95% above.

Figure 1: Comparison of Total HLA Mismatches Between Pre-KAS vs. Post-KAS
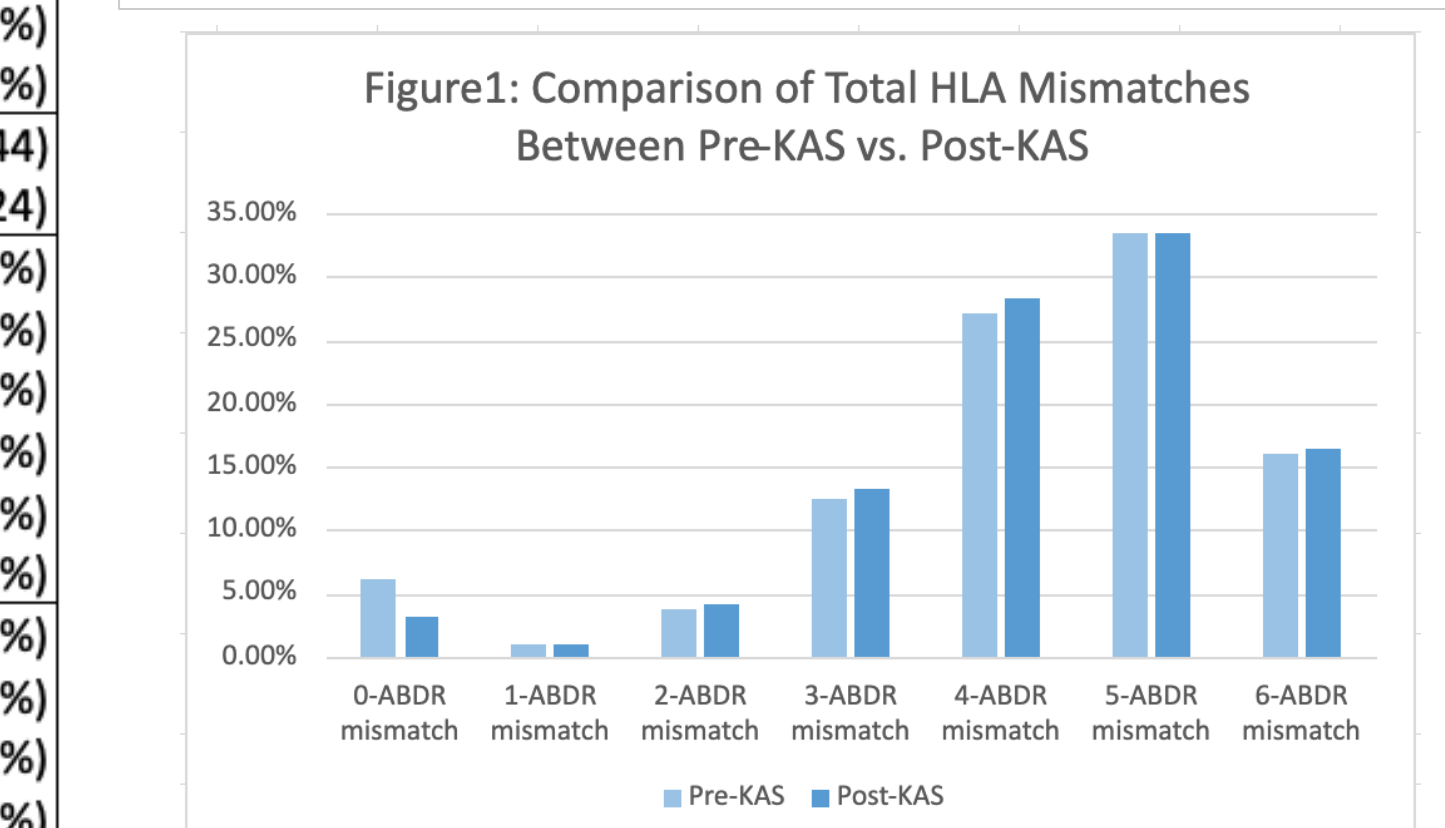
From figure 1: Distribution of total HLA mismatches between the pre- and post-KAS was statistically significant (p<0.0001). Post-KAS era had less 0-ABDR mismatches.

From figure 2 (KM curves):
- Irrespective of KAS era, survival curves are statistically significant between total number of HLA mismatches.
- However, the difference in survival curves among HLA mismatches is greater in pre-KAS era.

Table 4: Interaction Between HLA Mismatch and KAS Era

Outcome	Interaction	Pr > ChiSq
All-cause graft failure	HLA mismatch*KAS era	0.7844
Death-censored graft failure	HLA mismatch*KAS era	0.3306

Table 4 (Cox P.H.): The interaction terms for both endpoints are not statistically significant, therefore the effect of total number of HLA mismatches is not differentially affected by the KAS allocation system.

Table 5: Adjusted Hazard Ratio of 3-Year Graft Failure

Outcome	Variable	Effect	HR*	95% confidence interval	P-value
All-cause graft failure	KAS	Post-KAS	0.918	(0.873, 0.965)	0.0008
		Pre-KAS	-	-	
	HLA Mismatch	0	-	-	
		1	0.899	(0.657, 1.229)	0.5038
		2	1.034	(0.861, 1.242)	0.7195
		3	1.051	(0.908, 1.218)	0.505
		4	1.021	(0.888, 1.172)	0.7731
		5	1.134	(0.989, 1.301)	0.0718
		6	1.132	(0.980, 1.307)	0.0929
Death-censored graft failure	KAS	Post-KAS	0.838	(0.782, 0.898)	<.0001
		Pre-KAS	-	-	
	HLA Mismatch	0	-	-	
		1	1.031	(0.649, 1.639)	0.8965
		2	1.219	(0.928, 1.603)	0.1551
		3	1.276	(1.020, 1.598)	0.0331
		4	1.235	(0.997, 1.529)	0.0534
		5	1.334	(1.079, 1.650)	0.0078
		6	1.405	(1.128, 1.751)	0.0024

*Adjusted for KDPI, gender, delayed graft function, waiting time, cold ischemic time, cPRA, racial/ethnic groups, history of diabetes, age, antibody induction, CNI, MPA, MTORI, Steroids, and other immunosuppresants

Table 5 (Adjusted Hazard):
- For all-cause and death-censored graft failures, the KAS implementation has decreased the hazard of 3-year graft failure by 8% and 16%, respectively.
- 6-ABDR HLA mismatch was the only statistically significant effect (p=0.0024 <adjusted α = 0.0071**) for increasing the risk of 3-year death-censored graft failure by 41%.

**Bonferroni correction