A Simulation Study of the Effect of the 2014 New National Allocation Policy for Deceased Donor Kidneys on Adult Recipients

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Introduction

Patients with end-stage renal disease often prefer kidney transplantation to dialysis in that the kidney recipients have a longer survival time [1], better quality of life and fewer expenses on treatment [2]. However, the vast demand for kidneys far outweighs the supply. Currently, 95,328 patients are still waiting for kidneys based on the Organ Procurement and Transplantation Network (OPTN) registration data as of January 25, 2018 [3]. Due to the limited number of kidneys from live donors, the organ supply has expanded to kidneys from deceased donors which now becomes the major source of kidneys. The increase in the number of the expanded criteria donor kidneys leads to more discarded donated organs [4], and among the kidneys transplanted there are more recipient complications and shorter allograft survival [5]. Therefore, it is necessary to develop the deceased kidneys allocation system.

In the end of 2014, a new deceased kidney allocation policy was implemented to narrow the gap between supply and demand that probably was broaden by the past 20 years policy which favored candidates with longest waiting time. The old system prioritized allocation for patients with longer waiting time, high sensitization and zero HLA antigen mismatches [6]. The initialization of waiting time began when a candidate was listed and had a glomerular filtration rate (GFR) or creatinine clearance less than 20 mL/min/1.73 m2, or started dialysis [6], which unfavored those who had limited access to the waiting list or delayed in listing [7]. Thus, implementation of the new system is essential to improve allocation process.

The new national policy applies the longevity matching that patients with top 20th Estimated Post-Transplant Survival(EPTS) could have priorities to receive transplant from deceased donors with a kidney donor profile index(KDPI) smaller 20% [6]. EPTS stratifies patients by their age, dialysis duration, prior solid organ transplant and presence or diabetes [6], while KDPI classifies donors by their age, height, weight, cause of death, ethnicity, serum creatinine, history of hypertension and diabetes hepatitis C status, and donation after circulatory death status [8,9]. Generally higher EPTS scores indicate shorter expected post-transplant survival, and lower KDPI are associated with better survival for the graft recipients [10]. This new matching approach aims to ensure that candidates with the longest expected survival time will receive the best kidneys.

Patients with lower EPTS would be ranked by a priority point system that favors those with zero HLA mismatches, prior living organ donors and high sensitization as shown in table 1. The start of waiting time is redefined as the earlier event of the time of dialysis initiation (even if prior to listing) or time of listing with an estimated GFR (eGFR) less than 20 mL/min/1.73 m2. Calculated panel-reactive antibodies (CPRA) measures level of sensitization and Table 2 shows its score system. Priority points are conferred for a CPRA >19%, and kidneys from donors with a KDPI>85% will be broadly shared for candidates with a CPRA$\geqslant$99% [11]. Payback system will be eliminated; blood type A2 and A2B kidneys to blood type B candidates will be gradually allocated [11].

Table 1: Priority point system for new kidney allocation [11]

Factor	Points Awarded
For qualified time spent waiting	1 per year (as 1/365 per day)
Degree of sensitization (CPRA)	0–202
Prior living organ donor	4
Pediatric candidate if donor KDPI<0.35	1
Pediatric candidate (age 0–10 yr at time of match) when offered a zero antigen mismatch	4
Pediatric candidate (age 11–17 yr at time of match) when offered a zero antigen mismatch	3
Share a single HLA-DR mismatch with donor	1
Share a zero HLA-DR mismatch with donor	2

Table 2: Priority points awarded based on CPRA > 19% [11]

CPRA (%)	Points
0–19	0
20–29	0.08
30–39	0.21
40–49	0.34
50–59	0.48
60–69	0.81
70–74	1.09
75–79	1.58
80–84	2.46
85–89	4.05
90–94	6.71
95	10.82
96	12.17
97	17.3
98	24.4
99	50.09
100	202.1

Thus, it is necessary to compare the two allocation systems and decide which system is better. I aim to simulate the new and old policies to see the effect of these allocation changes on the demographics of deceased donor transplant adult recipients.

Methods

Simulation model

I implemented a Markov model for each policy that embeds a decision tree for each week. The simulation cohort is the same as the waitlist in 2013. According to OPTN, there were 92582 patients at the start of 2013, 31532 joined the list during the year, 5099 patients underwent transplant from living donation, 3722 died before allocation, 6483 candidates left the waitlist for other reasons, and 11277 patients received kidneys from deceased donors. The model assumed that the weekly rate of mortality, living donor transplant, removal from the waitlist, and the number of new adding patients and available deceased donor kidneys are constant over the year. Thus, the corresponding probability is 0.038, 0.041 and 0.052, and around 606 new patients and 212 kidneys joined the list each week.

Table 3: Characteristics to sample distribution of candidates on waiting list in 2013

Characteristics	Category	Percent
Age [6]	18-34	9.3
	35-49	26.3
	50-64	43.5
	65+	20.8
Diabetes [6]		44.7
CPRA [6]	<1%	58.3
	1-<20%	9.5
	20-<80%	16
	80-<90%	6.4
	98-100%	9.8
Waiting time [6]	<1 year	28.6
	1-< 2 years	21.5
	2-< 3 years	16

	3-< 4 years	11.9
	4-< 5 years	7.9
	5+ years	14.1
Time on dialysis [12]	<1 year	20.73
	1-<2 years	11.69
	2-<3 years	11.93
	3-<4 years	11.03
	4-<6 years	15.48
	6-<11 years	16.04
	11+	13.09
Prior donor [13]		0.05
Prior Organ Transplant [12]		15.44

*All the data above are from 2012 or 2013 OPTN annual report.

The characteristics of each patient are sampled from the distribution of their characteristics from the national report as shown in table 3. Binary variables such as diabetes, prior donation experience, and prior organ transplant are drawn from the binomial distribution with the percentage as the probability. For continuous variables, age, CPRA, waiting time, and time on dialysis which are expressed as categories are first drawn from multinomial distribution and then drawn from the uniform distribution with the range of the category as two boundaries. EPTS would be calculated by the formula 1[3]. Then the EPTS is mapped with the 2017 threshold for top 20%, that EPTS larger than 2.707 [14].

Formula 1

$$\begin{aligned}\text{EPTS score} = {} & 0.0473\text{MAX}\,(\text{Age} - 25, 0) - 0.015 \times \text{Diabetes} \times \text{MAX}(\text{Age}-25,0) \\ & + 0.398 \times \text{Prior Organ Transplant} - 0.2373\text{Diabetes} \times \text{Prior Organ Transplant} \\ & + 0.315 \times \log(\text{Years on Dialysis} + 1) \\ & - 0.099 \times \text{Diabetes} \times \log(\text{Years on Dialysis} + 1) + 0.130 \times (\text{Years on Dialysis} = 0) \\ & - 0.348 \times \text{Diabetes} \times (\text{Years on Dialysis} = 0) + 1.262 \times \text{Diabetes}.\end{aligned}$$

Among the deceased donor kidneys, 84.2 % were donated after brain death(DBD), and 15.8 % were donated after circulatory death (DCD) [6]. Each DBD donor averagely contributed 1.57 kidneys, and DCD donated around 1.47 kidneys [11]. Thus, simple calculation derived that there should be 7255 deceased donors providing kidneys in 2013. Then the value KDPI of each donor was sampled from a multinomial distribution shown in table 4 [11] followed by a uniform distribution within the range, and one or two kidneys, from DBD, and DCD.

Table 4: KDPI distribution of deceased kidney donors from 2013 OPTN report [12].

	Category	Percentage
KDPI	KDPI ≤.20	22%
	KDPI 0.21-0.34	16%
	KDPI 0.35-0.85	53%
	KDPI >0.85	9%

Then, the allocation system was simulated every week for 52 times. Firstly, 606 new patients were added to the waitlist cohort, and those candidates who received kidneys from living donors, died before transplantation, left the waiting list for other reasons were removed. The remaining active patients with top 20% EPTS received kidneys from KDPI <= 20%. If the number of kidneys with KDPI <= 20% was

smaller than the patients with EPTS priority, the patients would randomly receive the kidneys and those patients would keep waiting. Else, all the EPTS priority patients received the kidneys, and remaining kidneys would be allocated to patients by their priority scores as calculated in Table 1. For the old allocation system, patients were ranked by their waiting time every week, and patients with high scores would receive the kidneys.

Overall, the model assumptions are: 1) Each variable is independent of each other; 2)There is no geographic variation of the behavior of the graft allocation, and I will treat the whole country as one transplant center; 3) The speed of new kidneys, new patients on the list, patients leaving the list is steady over the one-year course; 4) There is very little year difference in transplantation and donation cohort, so I can use 2012 data if I don't have accurate 2013 measurements; 5) The number of kidneys provided is approximately the same as the number of recipients.

Statistical Analysis

Characteristics of the simulated recipients of two allocation systems were reported as mean (SD) for continuous variables and frequency (percentage) for categorical variables. Chi-squared tests were used to compare categorical variables and t-test for continuous variables.

To compare the time to receive kidneys, I used Kaplan Meier method to estimate the empirical survival function and event was defined as the allocation of a kidney. The survival curve would be provided with 95% confidence interval. Because censoring events, such as death and removal from the waitlist, happened completely at random, I didn't take these observations into account. Log-rank test and Peto & Peto modification of the Gehan-Wilcoxon test was applied to compare the survival experience of different groups. Log-rank test evaluates the overall survival curve while Peto & Peto method applies greater weight to earlier events.

The simulation and survival curve were conducted in Python Jupiter Notebook, and statistical tests were performed in R studio.

Results

Overall, recipients of deceased kidneys under two simulation Model had quite similar attributes. Their age, prior organ transplant and diabetes used to calculate EPTS are quite similar as shown in Table 5. Thus, EPTS doesn't affect whether the candidate will receive a kidney. Recipients under new policy tend to significantly a higher level of sensitization and shorter waiting time which corresponds to the simulation of the allocation process.

Table 5: Comparison of the recipients under two policies.

		New Policy	Old Policy	p-value
Age	18-34	968(8.86%)	1008(9.23%)	0.076
	35-49	2956(27.07%)	2841(26.02%)	
	50-64	4790(43.86%)	4739(43.40%)	
	65+	2206(20.20%)	2332(21.36%)	
Diabetes	TRUE	4798(43.94%)	4930(45.15%)	0.075
	FALSE	6122(56.06%)	5990(54.85%)	
Prior Organ Transplant	TRUE	1580(14.47%)	1624(14.92%)	0.411

	FALSE	9340(85.53%)	9262(85.08%)	
CPRA		82.65(35.02)	24.68(36.40)	<0.001
Waiting Time(Week)		160.79(108.70)	387.20(27.68)	<0.001

* N(%) is reported for categorical variables, and mean(sd) for continuous variables

Kaplan-Meier estimate of the survival curves shows that there is no difference in time to kidney allocation between two policies as shown in Figure 1. For the new policy, top 20% EPTS candidates underwent shorter duration of waiting before they received the kidney.

Figure 1: Kaplan-Meier Estimate of time to kidney allocation by two policies

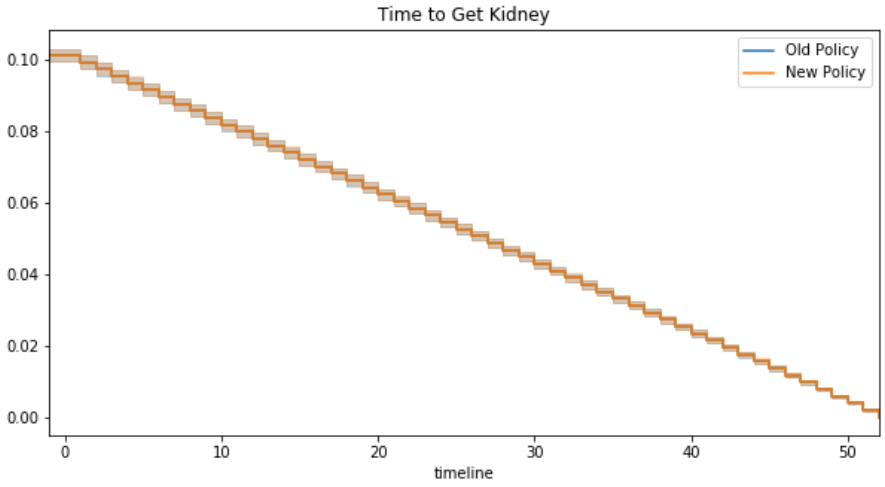

Figure 2: Kaplan-Meier Estimate of time to kidney allocation of the new policy by EPTS priority

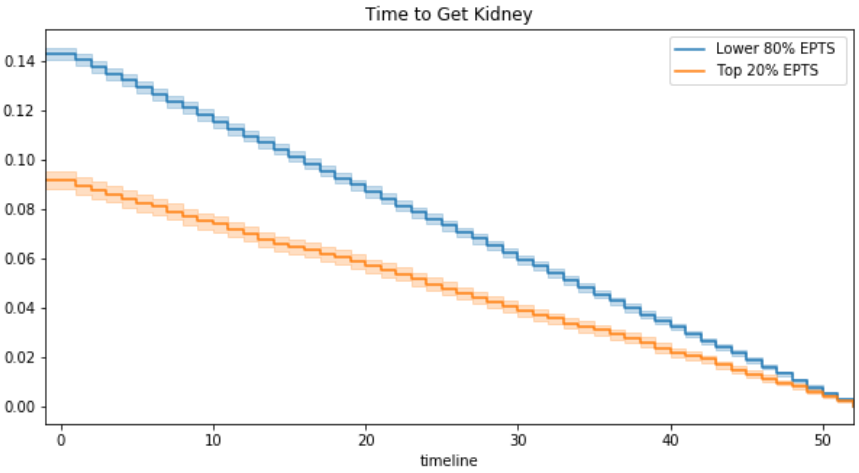

Figure 3 shows that, in earlier allocation stage, diabetic patients spent less time in waiting for kidneys, but the difference decreases after several weeks, corresponding to the results from the statistical tests as summarized in table 6. Peto & Peto tests show that the survival experiences were different between diabetic and non-diabetic recipients at the earlier phase, and there is an overall difference between different age groups. But all of these characteristics are not difference under the old policy.

Figure 3: Kaplan-Meier Estimate of time to kidney allocation of the new policy by diabetes

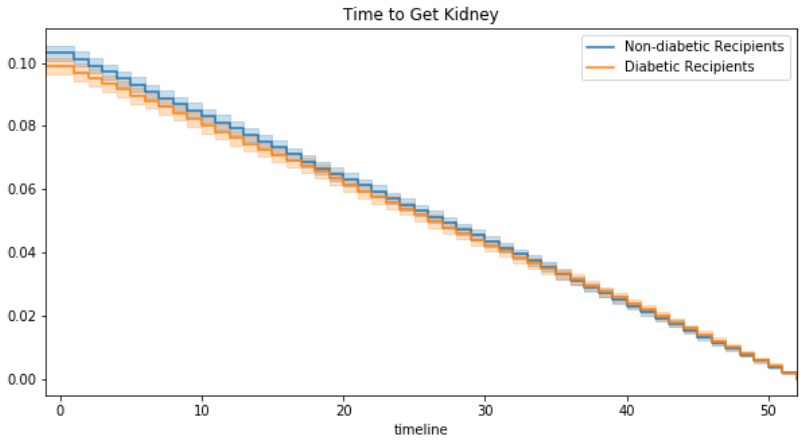

Table 6: Summary of p-value of log-rank test and Peto & Peto test of group difference on time to receive kidney

Characteristics	New Policy		Old Policy	
	Log-rank	Peto & Peto	Log-rank	Peto & Peto
Diabetes	0.784	0.034	0.783	0.415
Age	0.043	0.121	0.388	0.489
EPTS priority	<0.001	<0.001	0.768	0.992

Conclusion

The new allocation system that ranks recipients by EPTS and applies the point priority system enables candidates with a higher level of sensitization or diabetes to receive the kidneys earlier. EPTS doesn't decide whether a candidate receives a kidney, but it could decrease the waiting time in the earlier state. Also, it would be interesting to simulate the long-term effect of those recipients in further analysis, because evaluation of whether longevity matching actually fully utilizes the kidney is essential.

The results are credible because all the parameters were drawn from the national report, so there was no uncertainty. However, the model is not comprehensive in that several candidates and donors' properties and allocation procedure were simplified. Important factors such as blood type, HLA mismatch and regional priority were not considered. Also, the two policies have different definitions of waiting time, which was not distinguished in the simulation model due to lack of information.

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