Declined Offers for Deceased Donor Kidneys Are Not an Independent Reflection of Organ Quality

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Key Points
- 13% of deceased donor kidneys are declined ≥100 times before transplantation, with 3% accumulating >1000 declined offers
- Hard-to-place kidneys have more frequent delayed graft function, but similar long-term adjusted graft and patient survival outcomes
- Frequently declined kidneys may represent missed opportunities for earlier successful transplant for the patients who are passed over

Abstract
Background Deceased donor kidney offers are frequently declined multiple times before acceptance for transplantation, despite significant organ shortage and long waiting times. Whether the number of times a kidney has been declined, reflecting cumulative judgments of clinicians, is associated with long-term transplant outcomes remains unclear.

Methods In this national, retrospective cohort study of deceased donor kidney transplants in the United States from 2008 to 2015 (n=78,940), we compared donor and recipient characteristics and short- and long-term graft and patient survival outcomes grouping by the sequence number at which the kidney was accepted for transplantation. We compared outcomes for kidneys accepted within the first seven offers in the match-run, after 8–100 offers, and for hard-to-place kidneys distinguishing those requiring >100 and >1000 offers before acceptance.

Results Harder-to-place kidneys had lower donor quality and higher rates of delayed graft function (46% among kidneys requiring >1000 offers before acceptance versus 23% among kidneys with ≤7 offers). In unadjusted models, later sequence groups had higher hazard of all-cause graft failure, death-censored graft failure, and patient mortality; however, these associations were attenuated after adjusting for Kidney Donor Risk Index (KDRI). After adjusting for donor factors already taken into consideration during allocation, and recipient factors associated with long-term outcomes, graft, and patient survival outcomes were not significantly different for the hardest-to-place kidneys compared with the easiest-to-place kidneys, with the exception of death-censored graft failure (adjusted hazard ratio, 1.16, 95% CI, 1.05 to 1.28).

Conclusion Late sequence offers may represent missed opportunities for earlier successful transplant for the higher-priority waitlisted candidates for whom the offers were declined.

Kidney transplantation is the ideal treatment for patients with ESKD, but access is limited by severe organ shortage in the United States. As a result, only 39% of patients receive a deceased donor kidney transplant within 5 years of being added to the waiting list, another 37% die or are removed from the waiting list by 5 years, and only 42% of all patients on hemodialysis survive >5 years (1). Despite the shortage, approximately 20% of deceased donor kidneys are discarded annually, and 86% of transplanted kidneys are declined at least once before acceptance in the United States (2–4). As a result, there has been increasing interest in identifying and addressing factors driving inefficient organ placement and ultimately organ discard (4–6).

The US allocation system, using a predefined algorithm, creates a patient priority list specific to each
kidney that is referred to as a “match-run”. Transplant centers and their patients can either accept or decline each organ offer. Most kidneys are declined multiple times before eventually being accepted for transplantation, underscoring the presence of subjective evaluations in an otherwise objective allocation system (7,8). The most commonly cited reasons for decline are donor-related factors, especially procurement biopsy results (2,7). Evidence describing poor reproducibility of biopsies and acceptable unilateral transplant outcomes has raised concerns about the weightage given to these factors when evaluating a deceased donor kidney offer (3,9–11). Declined organ offers are of particular concern, given certain patient groups are more likely to have offers declined on their behalf and declined offers are associated with the subsequent death or delisting of patients (4).

Deceased donor kidneys that are declined for >100 patients are deemed “hard-to-place” for reporting purposes in the United States. The fact that a given kidney has been declined by multiple other centers is often thought to reflect the quality of the organ, which in turn influences decisions by centers that receive offers after the kidney has been declined repeatedly. Given the evidence that factors unrelated to donor or recipient quality, such as day of the week, influence how easily an organ is successfully placed, or the likelihood that a deceased donor kidney will be discarded, it is important to understand whether the accumulation of many declined offers for a kidney provides insight into the subsequent allograft function (3,5–8). We attempt to ascertain the relationship between the number of times a deceased donor organ is declined before acceptance and graft and patient outcomes, hypothesizing that kidneys turned down many times result in successful transplant outcomes.

Methods
This study used data from the Organ Procurement and Transplantation Network (OPTN). The OPTN data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the OPTN. The Health Resources and Services Administration, US Department of Health and Human Services provides oversight to the activities of the OPTN contractor. This national registry study used deceased donor kidney offer data from the national United Network for Organ Sharing (UNOS) Potential Transplant Recipient file and recipient/donor data from the June 2019 Standard Transplant Analysis and Research files on the basis of the OPTN database as of June 7, 2019. Starting with offers for all deceased donor kidney transplants performed in the United States from 2008 to 2015, we excluded offers that were automatically bypassed (except for bypasses due to a center’s voluntary minimum acceptance criteria) and offers made to candidates after their transplant or death date. After these exclusions, we calculated new match-run sequence numbers. Given the median acceptance position of seven and the definition of “hard-to-place” at 100 offers, four “exposure” groups were categorized on the basis of the kidney’s acceptance position in the match-run: (1) 1–7, (2) 8–100, (3) 101–1000, and (4) >1000 (7). Next, recipient and donor information was merged with the offer data after excluding recipients of multiorgan transplants and pediatri (aged <18 years) recipients. Although transplants for multiorgan and pediatric recipients do not appear in the final analysis cohort, any declined offers made to these candidates were still counted when generating the match-run sequence number for transplanted kidneys. The final analysis cohort included all transplants where both merged recipient and donor match-run data were available (Figure 1).

For each group, descriptive statistics for transplant characteristics, recipient characteristics, and the short-term outcomes of primary nonfunction (PNF) and delayed graft function (DGF) were calculated and compared between groups using the chi-squared and Kruskal–Wallis tests. PNF was defined as a reported graft failure (GF) date matching the transplant date, and DGF was defined as requiring dialysis within the first week after transplant. Kaplan–Meier curves and log-rank tests compared unadjusted graft and patient survival among match-run groups. We estimated the probability of graft and patient survival at 1, 3, 5, and 10 years post-transplant by exposure groups from the survivor functions. Follow-up data on GF and patient death are collected and reported periodically by transplant centers and supplemented by the social security death master file in the UNOS registry, and for this study follow-up was censored at the patient’s latest recorded follow-up status date in the registry as of June 7, 2019.

We compared the hazards of all-cause (overall) GF, death-censored GF (DCGF), and patient death outcomes across match-run groups using unadjusted and multi-variable Cox Regression models. Donor characteristics were examined using Kidney Donor Risk Index (KDRI) Rao as a composite measure and each of its component variables individually in univariate models. Transplant characteristics included number of HLA mismatches and cold ischemia time (CIT), and recipient characteristics included age, sex, race/ethnicity, history of diabetes, dialysis time, prior organ transplant, high panel reactive antibodies (PRA) (end calculated panel reactive antibodies [cPRA] ≥98%), and cause of ESKD. Adjusted model one included only match-run group and donor quality using the composite KDRI measure. Adjusted model two included match-run group and all donor, transplant, and recipient factors examined in univariate models except for the individual KDRI components and cause of ESKD to avoid redundancy.

To identify potential differences by geographic region, we compared the distribution of kidneys transplanted in each match sequence group across OPTN regions using the chi-squared test. Kaplan–Meier survival curves comparing DCGF across the four match-run sequence groups within each region were constructed, both unadjusted and adjusted for KDRI. Regions 1, 6, 8, and 10 were combined for the regional survival curves because there were very few kidneys transplanted at match-run position >1000 in these regions. To explore potential differences in outcomes across transplant centers with different experiences, we identified “aggressive” centers using offer acceptance ratios (OARs) from the Scientific Registry of Transplant Recipients Program-Specific Report data from July 2017 (the
closest date available to our study cohort with OARs reported). We identified the 75th percentile threshold among 201 transplant centers in our study with OAR data available for high-risk (KDRI >1.75) kidneys, and classified centers with an OAR above that threshold as “aggressive” and all other centers as “nonaggressive.” We compared the match sequence group of all transplanted kidneys at aggressive versus nonaggressive centers using the chi-squared test. We plotted unadjusted Kaplan–Meier death-censored graft survival curves for hard-to-place (>100 offers) versus non-hard-to-place kidneys (1–100 offers) at aggressive and nonaggressive centers, and compared across the four groups using the log-rank test. We also considered death-censored graft survival curves adjusted for KDRI, at the median KDRI value.

Data on all characteristics were >99% complete with the exception of 1% missing CIT, and complete patient analysis was performed for survival models (adjusted model 1: \( n=78,539 \), adjusted model 2: \( n=77,035 \)). Statistical analyses were performed using Stata 15 (StataCorp, College Station, TX); \( \alpha=0.05 \) determined statistical significance. This study was approved by the Columbia University Irving Medical Center Institutional Review Board. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Because the Kidney Allocation System (KAS) changed on December 4, 2014 and our primary analyses included transplants through 2015, sensitivity analysis adding a binary KAS era variable to the adjusted survival models were performed to evaluate potential era effects. Because highly sensitized candidates were more likely to be overrepresented in the low match-run groups after KAS implementation, due to increases in allocation priority points, a second sensitivity analysis excluding high PRA candidates was
performed to assess whether changes in allocation prioritization affected observed relationships between match-run group and survival outcomes.

**Results**

**Donor and Transplant Characteristics**

From 2008 to 2015, 78,940 adults received deceased donor kidney-alone transplantation, with over half the patients (45,094, 57%) transplanted at a match-run sequence number of 1–7 (group 1). Another 23,886 (30%) patients received a kidney at sequence number 8–100 (group 2), 7293 (9%) between sequence numbers 101 and 1000 (group 3), and 2667 (3%) at a sequence number >1000 (group 4) (Table 1). Donors of kidneys accepted later in the match-run were older (median age 45 years in group 4 versus 39 in group 1), with higher terminal creatinine (1.2 versus 0.9 mg/dl), and more frequently hypertensive or diabetic (39% and 14%, respectively, in group 4 versus 25% and 6% in group 1) (Table 1). Although we noted a stepwise increase in the median KDRI from group 1 through 3 and no difference between groups 3 and 4, there was overlap in the Kidney Donor Profile Index (KDPI) score across all four groups, and

### Table 1. Donor, transplant, and recipient characteristics by match-run group

| Characteristics                                | Match-Run Position of Transplanted Kidney, Median (Interquartile Range) or n (%) |
|------------------------------------------------|----------------------------------------------------------------------------------|
| **Donor Characteristics**                      |                                                                                  |
| KDRI*                                          | 1.19 (0.96–1.49)                                                                |
| KDPI                                          | 45 (23–68)                                                                      |
| Age, yr                                       | 41 (25–52)                                                                      |
| Weight, kg                                    | 79 (66–94)                                                                      |
| Height, cm                                    | 170 (163–178)                                                                   |
| Black race                                    | 10,910 (14)                                                                     |
| History of hypertension                       | 22,331 (28)                                                                     |
| History of diabetes                           | 5999 (8)                                                                        |
| COD: CVA                                      | 25,621 (32)                                                                     |
| Terminal serum creatinine                     | 0.9 (0.7–1.3)                                                                   |
| HCV positive*                                 | 2018 (3)                                                                        |
| DCD                                           | 12,891 (16)                                                                     |
| **Transplant characteristics**                |                                                                                  |
| CIT, h^a                                       | 16.3 (11.2–22.3)                                                                |
| Number of HLA mm                              | 4 (3–5)                                                                         |
| Racial and ethnicity                          |                                                                                  |
| *White*                                        | 35 (43–62)                                                                      |
| *Black*                                        | 31,450 (40)                                                                     |
| *Hispanic*                                     | 12,327 (16)                                                                     |
| *Other/multiracial                            | 6817 (9)                                                                        |
| History of diabetes^a                          | 28,042 (36)                                                                     |
| Dialysis time, yr^a                            | 3.8 (1.9–6.0)                                                                   |
| Preemptive                                    | 6637 (8)                                                                        |
| <4 yr                                         | 35,265 (45)                                                                     |
| 4–8 yr                                        | 27,065 (34)                                                                     |
| Prior organ transplant                        | 11,402 (14)                                                                     |
| cPRA ≥98%                                      | 3721 (5)                                                                        |
| Cause of ESKD                                  |                                                                                  |
| *GN*                                           | 15,316 (19)                                                                     |
| Diabetes                                      | 21,840 (28)                                                                     |
| Hypertension                                  | 20,441 (26)                                                                     |
| Cystic kidney disease                         | 6318 (8)                                                                        |
| Other/unknown                                  | 15,025 (19)                                                                     |

Comparing across match-run groups: All P<0.001, except donor weight (P=0.07). KDRI, Kidney Donor Risk Index; KDPI, Kidney Donor Profile Index; COD, cause of death; CVA, cerebrovascular accident; HCV, Hepatitis C Virus; DCD, donation after circulatory death; CIT, cold ischemia time; F, female; cPRA, calculated panel reactive antibodies.

^a Missing values excluded: KDRI/KDPI, 401 (0.51%); weight, 57 (0.07%); height, 3 (0.00%); donor hypertension, 496 (0.63%); donor diabetes, 412 (0.52%); creatinine, 14 (0.02%); HCV, 10 (0.01%); CIT, 1,068 (1%); recipient diabetes, 418 (0.53%); dialysis time category, 49 (0.06%).
Kidneys from all KDPI deciles were accepted within each match-run group (Figure 2). CIT increased with later match-run groups from a median of 14 hours (interquartile range [IQR], 10–20) in group 1 to 32 hours (IQR, 26–38) for group 4 (Table 1).

Recipient Characteristics

Recipients of kidneys from the earlier match-run groups were younger, with median age of 53 and 55 years in groups 1 and 2, respectively, whereas recipients in the hard-to-place groups were a median of 59 years old at

| KDPI Decile | Median Number of Offers |
|-------------|------------------------|
| 0–10        | 14 (IQR, 10–20)        |
| 11–20       | 23 (IQR, 17–27)        |
| 21–30       | 30 (IQR, 25–35)        |
| 31–40       | 37 (IQR, 32–42)        |
| 41–50       | 44 (IQR, 39–52)        |
| 51–60       | 55 (IQR, 50–64)        |
| 61–70       | 65 (IQR, 60–74)        |
| 71–80       | 75 (IQR, 70–82)        |
| 81–90       | 85 (IQR, 80–90)        |
| 91–100      | 95 (IQR, 90–95)        |

Figure 2. Number of offers before deceased donor kidneys are accepted for transplantation, by Kidney Donor Profile Index (KDPI) decile, showing that a larger proportion of kidneys in the higher KDPI deciles are transplanted later in the match-run after more declined offers.

| Outcomes                        | Match-Run Position of Transplanted Kidney |
|--------------------------------|-------------------------------------------|
|                                | Full Cohort (n=78,940) | 1–7 (n=45,094) | 8–100 (n=23,886) | 101–1000 (n=7293) | >1000 (n=2667) |
| Primary nonfunction, n (%)     | 352 (0.45) | 168 (0.37) | 102 (0.43) | 52 (0.71) | 30 (1.12) |
| Delayed graft function, n (%)  | 20,707 (26) | 10,148 (23) | 6639 (28) | 2703 (37) | 1217 (46) |
| Overall graft survival probability, %, yr | 92.87 | 93.42 | 92.69 | 90.97 | 90.43 |
|                               | 84.91 | 85.79 | 84.45 | 82.30 | 81.30 |
|                               | 74.90 | 76.08 | 74.30 | 71.13 | 70.79 |
|                               | 47.63 | 49.10 | 47.33 | 41.58 | 41.60 |
| Death-censored graft survival probability, %, yr | 95.82 | 96.22 | 95.76 | 94.41 | 93.43 |
|                               | 91.53 | 92.06 | 91.40 | 89.69 | 88.75 |
|                               | 86.48 | 87.08 | 86.42 | 84.20 | 83.04 |
|                               | 72.03 | 72.78 | 72.25 | 68.14 | 67.49 |
| Patient survival probability, %, yr | 96.30 | 96.50 | 96.13 | 95.65 | 95.97 |
|                               | 91.21 | 91.74 | 90.74 | 89.94 | 89.97 |
|                               | 83.58 | 84.58 | 82.81 | 80.67 | 81.52 |
|                               | 59.69 | 61.03 | 59.42 | 53.76 | 54.34 |
| Number of events, n (%)        | 24,891 (32) | 13,399 (30) | 7904 (33) | 2641 (36) | 947 (36) |
| All-cause graft failure        | 11,979 (14) | 6510 (14) | 3703 (16) | 1278 (18) | 488 (18) |
| Death-censored graft failure   | 16,609 (21) | 8848 (20) | 5372 (22) | 1785 (24) | 604 (23) |

Comparing across match-run groups: All P<0.001.
transplant (Table 1). Females, prior transplant recipients, and highly sensitized candidates appeared more frequently in the earliest match-run group compared with the others. In the earliest match-run group, 7% of recipients had final cPRA =98% compared with only 1% in all other groups. A larger proportion of recipients in the earliest match-run group had ESKD attributed to GN, and this group had less diabetic- and hypertension-related ESKD compared with the later groups. Dialysis time at transplant was highest in group 2, with a median of 4.1 years of dialysis vintage compared with 3.8 years in group 1 and 3.1 years in groups 3 and 4. Preemptive recipients were more frequent in the later match-run groups (10% in groups 3 and 4) compared with the earlier match-run groups (9% and 7% in groups 1 and 2, respectively). White recipients comprised a larger proportion of the earliest match-run group (45%) than the later three groups (38%, 40%, and 34%).

Outcomes

A higher proportion of organs placed later in the match-run experienced primary allograft nonfunction (0.37%, 0.43%, 0.71% and 1% for groups 1–4, respectively), and DGF doubled from group 1 to group 4 (23%, 28%, 37%, and 46%) (Table 2). Long-term overall graft survival followed a similar trend, although differences between groups were less pronounced. Although kidneys allocated earliest in group 1 had 1- and 3-year overall graft survival probabilities of 93% and 86%, respectively, the extremely hard-to-place kidneys in group 4 had 90% and 81% graft survival at years 1 and 3, respectively (Table 2). Both death-censored graft survival (Figure 3B) and overall patient survival (Figure 3C) followed similar patterns across the four groups (Table 2). Median follow-up time in the cohort was 4.9 years (IQR, 3.0–7.0) for both overall and death-censored graft survival and 5.0 years (IQR, 3.1–7.0) for patient survival.

In unadjusted Cox models, recipients in groups 2–4 had significantly higher hazards of overall GF (Supplemental Table 1), DCGF (Table 3), and death (Table 4) compared with those transplanted in group 1. Transplants with hard-to-place kidneys requiring 101–1000 offers or >1000 offers before acceptance for transplantation had 1.26 (95% confidence interval [95% CI], 1.20 to 1.31) times and 1.29 (95% CI, 1.21 to 1.38) times the hazard of GF, respectively, compared with kidneys placed within the first seven matches (Supplemental Table 1). Donor, transplant, and recipient characteristics were significantly associated with survival outcomes and were included for adjustment in multivariable models. KDRI as a composite score of donor risk was significantly associated with higher GF (hazard ratio [HR], 1.09, 95% CI, 1.01 to 1.16, Supplemental Table 1) or DCGF (HR, 1.13, 95% CI, 1.03 to 1.24, Table 3) compared with the easiest-to-place kidneys, and there were no longer any significant associations between match-run group and patient survival (Table 5). In fully adjusted model 2 controlling for donor, transplant, and recipient characteristics, the associations between match-run group and overall graft and patient survival outcomes were further attenuated (Supplemental
There were no significant differences in patient mortality or GF between kidneys placed later in the match-run and those placed within the first seven offers after controlling for all donor, transplant, and recipient factors. When considering DCGF (Table 3), receiving a transplant at match position 8–100 was significantly protective compared with receiving a transplant at match position 1–7 (adjusted HR, 0.94, 95% CI, 0.90 to 0.98), and there was no significant difference between survival after transplant at match position 101–1000 versus 1–7 (P=0.15). Recipients of the hardest-to-place kidneys (match sequence >1000) still had increased DCGF (adjusted HR, 1.16, 95% CI, 1.05 to 1.28) in the fully adjusted model; however, this was lower than the estimate from the unadjusted model (unadjusted HR, 1.36, 95% CI, 1.24 to 1.49).

**Geographic and Center Variation**

There was significant variation across OPTN regions in the proportion of transplanted kidneys that were hard.
to place or extremely hard to place ($P<0.001$). In all regions except for 2 and 9, the majority of kidneys were transplanted from match sequence 1–7 (Table 5). Region 2 transplanted the most hard-to-place kidneys overall (2180 kidneys with >100 declines), and extremely-hard-to-place kidneys accounted for nearly four times as many transplants in Region 9 compared with the next highest region (19% in Region 9 versus 5% in Region 5).

Although unadjusted DCGF was significantly different across match sequence groups in most regions (Supplemental Figure 1), after adjusting for KDRI clear differences persisted only in Region 7, where the extremely-hard-to-place kidneys did worse, and in Region 9, where kidneys transplanted from match position 1–7 did better than other kidneys (Supplemental Figure 2).

Among 251 transplant centers included in our study, 51 transplant centers were defined as “aggressive” centers by

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**Table 4. Unadjusted and adjusted survival analyses examining associations between the sequence number at which the kidney was accepted for transplantation and patient mortality**

| Characteristics                        | Unadjusted Models |        |        |        | Adjusted Model 1 |        |        |        | Adjusted Model 2 |        |        |
|----------------------------------------|-------------------|--------|--------|--------|------------------|--------|--------|--------|------------------|--------|--------|
|                                        | Hazard Ratio      | 95% CI | P Value |        | Hazard Ratio      | 95% CI | P Value |        | Hazard Ratio      | 95% CI | P Value |
| **Transplant/Donor Characteristics**   |                   |        |        |        |                   |        |        |        |                   |        |        |
| Sequence #                             |                   |        |        |        |                   |        |        |        |                   |        |        |
| 0–7                                    | reference group   |        |        |        | 1.00             | 0.96, 1.03 | 0.84 |        |        | reference group   |        |        |
| 8–100                                  | 1.10              | 1.07, 1.14 | <0.001 |        | 1.00             | 0.94, 1.02 | 0.27 |        |        | 0.98             | 0.94, 1.02 | 0.27 |
| 101–1000                               | 1.27              | 1.21, 1.34 | <0.001 |        | 1.03             | 0.98, 1.08 | 0.31 |        |        | 0.97             | 0.92, 1.03 | 0.30 |
| >1000                                  | 1.25              | 1.15, 1.35 | <0.001 |        | 1.02             | 0.94, 1.11 | 0.67 |        |        | 0.94             | 0.86, 1.03 | 0.21 |
| KDRI                                   | 2.12              | 2.05, 2.19 | <0.001 |        | 2.11             | 2.04, 2.19 | <0.001 |        |        | 1.52             | 1.47, 1.58 | <0.001 |
| Age, yr                                | 1.02              | 1.02, 1.02 | <0.001 |        |                   |        |        |        |                   |        |        |
| Weight, kg                             | 1.00              | 1.00, 1.00 | <0.001 |        |                   |        |        |        |                   |        |        |
| Height, cm                             | 1.11              | 1.06, 1.16 | <0.001 |        |                   |        |        |        |                   |        |        |
| History of hypertension                | 1.56              | 1.51, 1.61 | <0.001 |        |                   |        |        |        |                   |        |        |
| History of diabetes                    | 1.53              | 1.45, 1.61 | <0.001 |        |                   |        |        |        |                   |        |        |
| COD: CVA                               | 1.44              | 1.39, 1.48 | <0.001 |        |                   |        |        |        |                   |        |        |
| Terminal serum creatinine              | 1.01              | 1.00, 1.03 | 0.08 |        |                   |        |        |        |                   |        |        |
| HCV positive                           | 1.51              | 1.39, 1.64 | <0.001 |        |                   |        |        |        |                   |        |        |
| DCD                                    | 0.95              | 0.91, 0.99 | 0.02 |        |                   |        |        |        |                   |        |        |
| CIT, h                                 | 1.01              | 1.01, 1.01 | <0.001 |        |                   |        |        |        | 1.00             | 1.00, 1.00 | <0.001 |
| Number of HLA mm                       | 1.04              | 1.03, 1.04 | <0.001 |        |                   |        |        |        | 1.01             | 1.00, 1.02 | 0.07 |
| **Recipient Characteristics**          |                   |        |        |        |                   |        |        |        |                   |        |        |
| Age, yr                                | 1.05              | 1.05, 1.05 | <0.001 |        |                   |        |        |        | 1.04             | 1.04, 1.05 | <0.001 |
| Sex, F (versus M)                      | 0.81              | 0.79, 0.84 | <0.001 |        |                   |        |        |        | 0.90             | 0.87, 0.93 | <0.001 |
| Racial and ethnicity                   |                   |        |        |        |                   |        |        |        |                   |        |        |
| White                                  | reference group   |        |        |        |                   |        |        |        |                   |        |        |
| Black                                  | 0.83              | 0.80, 0.86 | <0.001 |        |                   |        |        |        | 0.79             | 0.76, 0.82 | <0.001 |
| Hispanic                               | 0.68              | 0.64, 0.71 | <0.001 |        |                   |        |        |        | 0.62             | 0.59, 0.65 | <0.001 |
| Other/multiracial                      | 0.63              | 0.60, 0.68 | <0.001 |        |                   |        |        |        | 0.56             | 0.53, 0.60 | <0.001 |
| History of diabetes                    | 2.21              | 2.14, 2.27 | <0.001 |        |                   |        |        |        | 1.79             | 1.73, 1.84 | <0.001 |
| Dialysis time                          |                   |        |        |        |                   |        |        |        |                   |        |        |
| Preemptive                             | 0.69              | 0.64, 0.73 | <0.001 |        |                   |        |        |        | 0.67             | 0.63, 0.71 | <0.001 |
| <4 yr                                  | reference group   |        |        |        |                   |        |        |        |                   |        |        |
| 4–8 yr                                 | 1.13              | 1.09, 1.17 | <0.001 |        |                   |        |        |        | 1.33             | 1.28, 1.37 | <0.001 |
| >8 yr                                  | 1.17              | 1.12, 1.23 | <0.001 |        |                   |        |        |        | 1.77             | 1.68, 1.87 | <0.001 |
| Prior organ transplant                 | 0.92              | 0.88, 0.96 | <0.001 |        |                   |        |        |        | 1.23             | 1.17, 1.30 | <0.001 |
| cPRA ≥98%                              | 0.97              | 0.89, 1.06 | 0.52 |        |                   |        |        |        | 1.19             | 1.09, 1.31 | <0.001 |
| Cause of ESKD                          |                   |        |        |        |                   |        |        |        |                   |        |        |
| GN                                     | reference group   |        |        |        |                   |        |        |        |                   |        |        |
| Diabetes                               | 2.78              | 2.64, 2.92 | <0.001 |        |                   |        |        |        |                   |        |        |
| Hypertension                           | 1.64              | 1.56, 1.73 | <0.001 |        |                   |        |        |        |                   |        |        |
| Cystic kidney disease                  | 1.02              | 0.94, 1.10 | 0.653 |        |                   |        |        |        |                   |        |        |
| Other/unknown                          | 1.40              | 1.32, 1.49 | <0.001 |        |                   |        |        |        |                   |        |        |
| Post-KAS era (versus pre-KAS)           | 1.15              | 1.08, 1.22 | <0.001 |        |                   |        |        |        |                   |        |        |

KDRI, Kidney Donor Risk Index; COD, cause of death; CVA, cerebrovascular accident; HCV, Hepatitis C Virus; DCD, donation after circulatory death; CIT, cold ischemia time; F, female; M, male; cPRA, calculated panel reactive antibodies; KAS, Kidney Allocation System.
their high-risk kidney offer acceptance ratio. The distribution of match sequence group of the transplanted kidneys was significantly different between those transplanted at aggressive versus nonaggressive centers ($P<0.001$). At aggressive centers, 17% of the transplanted kidneys were hard to place, including 5% that required more than 1000 offers, compared with only 11% hard-to-place kidneys at nonaggressive centers (Supplemental Table 2). Although hard-to-place kidneys had significantly lower unadjusted death-censored graft survival compared with kidneys placed within 100 offers at both aggressive and nonaggressive centers, after adjustment for KDRI only hard-to-place kidneys at nonaggressive centers differed slightly from the rest (Supplemental Figure 3).

Sensitivity Analyses

After controlling for KAS era plus other characteristics from multivariable adjusted model 2, there was no difference in observed associations between match-run group and graft or patient survival outcomes (Supplemental Table 3). In the additional sensitivity analyses excluding recipients with end cPRA $\geq 98\%$ ($n=3721$), adjusted estimates of all graft and patient survival outcomes remained the same (Supplemental Table 3), suggesting allocation prioritization for highly sensitized candidates was not confounding observed outcome associations.

Discussion

Although the need for kidney transplantation continues to grow, the discard rate of deceased donor kidneys in the United States remains much higher than in other countries, reaching a new high of 4460 kidneys discarded in 2019 (12–16). An efficient allocation system with rapid early acceptance of organs by the centers at which they are initially offered would likely decrease discards, by avoiding the accrual of unacceptable cold ischemia, particularly for donors with less-than-ideal characteristics (2,5,6,17,18). The current system of receiving and evaluating deceased donor kidney offers is also potentially adversely affected by the awareness that the organ was repeatedly declined by multiple other centers.

The reference group in our study was selected to represent kidneys that were placed within the national median of seven offers (7), and the second group represents kidneys accepted beyond the median but before reaching “hard-to-place” designation (8–100 offers). We further stratified the hard-to-place kidneys into two groups to examine whether there were differences between the kidneys accepted at match positions $>100$ but within 1000 offers and the extremely hard-to-place kidneys, namely, those that were eventually accepted for a patient below the 1000th position on the match-run because the kidney was declined for $>1000$ different patients with higher allocation priority.

Not surprisingly, KDRI was higher for kidneys transplanted later in the match-run, and the differences in unadjusted outcomes observed between match-run groups in our study are likely also driven by the differences in KDRI because KDRI remained a significant predictor for all survival outcomes, even after adjusting for additional transplant and recipient factors. Although there is a stepwise worsening of outcomes as the sequence number increases, some of this is the result of the detrimental effect of CIT and associated preservation injury (19,20). Despite the small increase in PNF, the extremely low incidence makes it an unlikely primary driver of the reluctance to use later sequence organs. Although organs transplanted later in the match-run appear to have somewhat inferior longer-term graft survival for both DCGF and overall graft outcomes in unadjusted analyses, the clinical relevance of the small observed differences is debatable, especially if associated with shorter wait times. Notably these differences disappear completely or are dramatically attenuated after accounting for just the KDRI, further supporting the notion that the number of times an organ is declined is not independently and meaningfully informative of the eventual outcome. In fully adjusted models, the number of declined offers that a kidney accumulated remained associated with poor outcomes only for increased DCGF for the most

| Table 5. Distribution of match-run positions of deceased donor kidneys transplanted within each Organ Procurement and Transplantation Network region, 2008–2015 |
|---|---|---|---|---|
| OPTN Region | Match-Run Position of Transplanted Kidney, n (%) |  |  |  |
| | 1–7 | 8–100 | 101–1000 | >1000 |
| 1 | 1974 (69) | 727 (26) | 125 (4) | 15 (1) |
| 2 | 4851 (46) | 3503 (33) | 1701 (16) | 479 (5) |
| 3 | 7002 (63) | 3324 (30) | 726 (6) | 129 (1) |
| 4 | 4124 (61) | 2141 (31) | 485 (7) | 56 (1) |
| 5 | 6642 (52) | 4240 (33) | 1177 (9) | 670 (5) |
| 6 | 2084 (68) | 888 (29) | 74 (2) | 2 (0) |
| 7 | 3040 (54) | 2140 (38) | 389 (7) | 97 (2) |
| 8 | 3680 (68) | 1261 (23) | 469 (9) | 16 (0) |
| 9 | 1567 (30) | 1581 (30) | 1143 (22) | 1009 (19) |
| 10 | 4264 (66) | 1926 (30) | 266 (4) | 30 (0) |
| 11 | 5866 (66) | 2155 (24) | 738 (8) | 173 (2) |
| All | 45,094 (37) | 23,886 (30) | 7293 (9) | 2667 (3) |

OPTN, Organ Procurement and Transplant Network.
extreme instances, namely, the 3% of kidneys that were extremely hard to place.

The small observed differences in unadjusted outcomes at 5 years, although statistically significant, appear to be of limited clinical significance. For example, given the 5-year patient survival for even the hardest-to-place kidneys is nearly double that of remaining on dialysis, it is hard to justify not accepting a kidney, regardless of the sequence number at which it is being offered, when a better offer in the near future is not guaranteed (1,2,12). The fact that kidneys that are declined for >1000 patients result in a successful transplant in the overwhelming majority of instances raises questions about the validity or appropriateness of organ declines, the missed opportunities for the patients passed over, and the overall effect on objective allocation prioritization (4).

The risk/benefit calculations at various positions on the match-run are very different, although all patients are balancing the idea of the current offer with a future possibility of a better organ offer. Candidates at the top of the match-run are likely to receive additional offers within a reasonable time frame that may not necessarily be better, whereas candidates lower down have to wait much longer for the next offer, which again may not be better quality. When the time between offers increases, the incremental improvement in organ quality must be much larger to offset the detrimental effects of increased time on dialysis. Although the differences in PNF rates suggest that, perhaps in some instances, clinicians are accurately identifying organs that should be passed over, the very low incidence relative to the number of declined offers and the number of potentially transplantable discards raises concerns that these may instead be a consequence of the protracted allocation process, or the patients that centers are choosing for these organs. Our findings suggest the clinician gestalt that is reflected in multiple declines accumulated by most kidneys does not significantly add to the assessment of organ quality when other measured variables are taken into account.

Our analysis demonstrates significant overlap in organ quality across match sequence groups. More than 70% of the kidneys in the highest two KDPI deciles (lowest quality) were accepted within the first 100 offers, and even some of the best-quality kidneys became hard to place or extremely hard to place. We also show that although hard-to-place kidneys tend to be lower quality as measured by KDRI, they have good long-term graft and patient survival outcomes—not far from the easiest-to-place kidneys. After considering existing measures of donor quality (KDPI) and recipient post-transplant survival, the number of times that a kidney has been declined (i.e., the match sequence number) does not provide any additional insights with regard to longer-term allograft function.

Kidneys requiring >100 offers for acceptance tended to be transplanted into older recipients who were more likely to have diabetes, whereas those with high levels of sensitization and greater dialysis time were more likely to receive a kidney earlier in the match-run, reflecting known allocation prioritization. Our analysis also demonstrates that despite highly sensitized candidates being significantly more likely to appear in the earliest match-run group, this overrepresentation alone was not enough to explain the observed lack of association between match-run groups and adjusted survival outcomes. Large differences in the frequency of transplantation of hard-to-place and extremely-hard-to-place kidneys across regions and between centers that more or less frequently accept high-risk kidneys suggest different centers have very different levels of experience with hard-to-place kidneys. After accounting for KDRI, any differences in outcomes for hard-to-place kidneys between these different groups were minimized or disappeared completely.

One limitation of our study is that outcomes for discarded kidneys, which would have also accumulated a significant number of declines, are unknown; however, prior analyses have shown significant overlap in the quality of kidneys that are discarded and transplanted (2,3). Results may not be generalizable to populations outside the United States, with different systems for allocating and responding to offers for deceased donor kidneys. Given the variation in the number of candidates waitlisted at different centers, future work could examine outcomes by the number of transplant centers that have declined a given kidney in comparison with the candidate-level declines. Although the vast majority of offers in this dataset were declined due to organ or donor quality concerns (4), the extent to which declined offers are the result of recipient-related factors and reflect differences in waitlist management at different transplant centers is another potential area for investigation. The role of organ preservation methods and pump perfusion in outcomes for hard-to-place kidneys is another important area for potential future study.

In conclusion, after accounting for existing measures of donor quality and recipient factors, the number of times an organ has been declined for patients does not provide additional information on the organ quality. Instead, organs transplanted further down the match-run after many declined offers present patients with shorter wait times a somewhat premature opportunity for transplantation relative to higher-ranked candidates. In contrast, the declined offers for these hard-to-place kidneys likely represent a missed opportunity of improved survival and quality of life for the patients for which these organs were declined. Further studies are needed to understand the true causes for frequent organ offer declines to expand kidney transplantation and reduce discard of deceased donor kidneys.

Disclosures

D. Cohen reports having consultancy agreements with and a scientific advisor or member of Alexion and the International aHUS Registry Scientific Advisory Board; reports receiving research funding from CSL Behring and Natera; reports receiving honoraria from ITBMed Pharmaceuticals, Novartis, and Veloxis; and reports other interests/relationships as a member of the American Society of Transplantation, New York Society of Nephrology, and The Transplantation Society. L. Ratner reports having consultancy agreements with CareDx and Natera; reports having an ownership interest in Hansa BioPharma and Gilead; reports receiving research funding from Angion and CSL Behring; reports receiving honoraria from Case Western Reserve University, Emory University, Henry Ford Hospital, and University of California Irvine; and reports being a scientific advisor or member of the American Society of Transplant Surgeons. S. Husain reports receiving research funding from the National Center for Advancing Translational
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Author Contributions
S. Chaudhry, S. Husain, K. King, S. Mohan, and L. Ratner conceptualized the study; S. Mohan was responsible for the funding acquisition; S. Chaudhry, D. Cohen, S. Husain, K. King, S. Mohan, and L. Ratner were responsible for the investigation; S. Husain, K. King, and S. Mohan were responsible for the methodology; S. Mohan was responsible for the resources; D. Cohen, S. Husain, S. Mohan, and L. Ratner provided supervision; S. Chaudhry, D. Cohen, S. Husain, K. King, S. Mohan, and L. Ratner reviewed and edited the manuscript; K. King was responsible for the formal analysis and visualization; and S. Chaudhry wrote the original draft.

Supplemental Material
This article contains the following supplemental material online at http://kdnj360.asnjournals.org/lookup/suppl?doi=10.34067/KID.0004052021/-/DCSupplemental.

Supplemental Table 1. Unadjusted and adjusted survival analyses examining associations between the sequence number at which the kidney was accepted for transplantation and all-cause graft failure.

Supplemental Table 2. Distribution of match-run sequence category for kidneys transplanted at aggressive centers with the highest offer-acceptance ratios for high-risk kidneys versus other centers.

Supplemental Table 3. Comparing adjusted associations between sequence number and graft or patient survival upon sensitivity analyses accounting for KAS era or excluding high PRA recipients.

Supplemental Figure 1. Unadjusted death-censored graft survival curves across Organ Procurement and Transplantation Network regions, by match sequence group.

Supplemental Figure 2. Death-censored graft survival curves across match sequence groups, adjusted for Kidney Donor Risk Index (KDRI) and presented at the median KDRI, across Organ Procurement and Transplantation Network regions.

Supplemental Figure 3. Comparing death censored graft survival for hard-to-place and non-hard-to-place kidneys at aggressive and non-aggressive centers, in (A) an unadjusted model, and (B) a model adjusted for Kidney Donor Risk Index (KDRI), presented at the median KDRI.

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