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Cytomegalovirus Matching in Deceased Donor Kidney Allocation: Results From a U.S. National Simulation Model

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Background. Cytomegalovirus (CMV) infects >60% of adults and can pose an independent risk factor for allograft loss and mortality in solid organ transplant recipients. The purpose of this study is to evaluate the impact of a nationwide implementation of CMV seromatching (donor/recipient: D−/R− and D+/R+) in the U.S. deceased donor kidney allocation system (KAS). **Methods.** Adult candidates on the U.S. kidney-only transplant waiting list and deceased donor kidneys offered to the U.S. transplant centers were considered. A discrete-event simulation model, simulating the pre-COVID-19 period from January 1, 2015, to January 1, 2018, was used to compare the performances of currently employed KAS-250 policy (without CMV matching) to various simulated CMV matching policies parameterized by calculated panel reactive antibody exception threshold. Outcomes included CMV serodistribution, waiting time, access to transplantation among various groups, transplant rate, graft survival, kidney discard rate, and antigen-mismatch distribution, stratified by CMV serostatus. **Results.** CMV matching policy with a calculated panel reactive antibody exception threshold of 50% (namely, the $CMV_{\text{“>50\%”}}$ policy) strikes a better balance between benefits and drawbacks of CMV matching. Compared with KAS-250, $CMV_{\text{“>50\%”}}$ reduced CMV high-risk (D+/R−) transplants (6.1% versus 18.1%) and increased CMV low-risk (D−/R−) transplants (27.2% versus 13.1%); increased transplant rate for CMV R− patients (11.54 versus 12.57) but decreased for R+ patients (10.68 versus 10.48), yielding an increase in aggregate (11.09 versus 10.94); and reduced mean time to transplantation (by 6wk); and reduced kidney discard rate (25.7% versus 26.2%). **Conclusions.** Our findings underscore the feasibility and potential advantages of a nationwide CMV seromatching policy in kidney transplantation.

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Cytomegalovirus (CMV) is a ubiquitous β-herpesvirus infecting >60% of adults in the United States.[1,2] CMV seroprevalence is higher among women, non-White race, and populations of lower socioeconomic status and increases with age.[2,3] Once a host is infected with CMV, the virus persists throughout the host's lifetime. Although immunocompetent individuals can remain asymptomatic, immunocompromised individuals such as the recipients of solid organ transplant (SOT) are particularly vulnerable to its deleterious effects including increased risks of developing CMV infection and/or tissue invasive disease, superimposed bacterial and other opportunistic infections, cardiovascular and thrombotic complications, acute and chronic allograft rejection, graft loss, and mortality.[4-11]

CMV transmission, replication, and dissemination mainly depends on 3 factors in post-SOT: (1) CMV serostatus of the donor (D) and the recipient (R) (high-risk D+/R−, intermediate-risk D+/R+ and D−/R+, and low-risk D−/R−) (**Figure S1, SDC**, http://links.lww.com/TXD/A643)[6,8,12-18]; (2) the timely development of CMV-specific T-lymphocyte responses[19,20]; and (3) T-lymphocyte targeted immunosuppression (lympholytic induction agents such as rabbit anti-thymoglobulin[21] or alemtuzumab[22] and potent maintenance immunosuppressives, like tacrolimus, mycophenolic acid, and belatacept).[23,24]

Without a prevention strategy, CMV infection/disease occurs frequently after SOT (eg, 40%–100% of all kidney transplant recipients develop infection and up to 67% develop disease).[6,18,25,26] Two prevention strategies have been widely adopted in current practice: preemptive therapy and antiviral prophylaxis.[14,27-32] Although numerous studies identify antiviral prophylaxis to have greater efficacy compared with preemptive therapy,[8,14,26,29,33,34] the international consensus guidelines of the Transplantation Society do not unequivocally prefer one strategy over the other.[32]

Ganciclovir, Valganciclovir, and Letermovir have been approved by the U.S. Food and Drug Administration for prophylactic treatment in D+/R− transplants.[35,36] Over 80% of high- and intermediate-risk kidney transplant recipients in the United States use CMV prophylaxis (mainly Valganciclovir).[18] Despite the widespread use of CMV antiviral drugs, late-onset CMV infection/disease remains an important problem arising after prophylaxis cessation, particularly for D+/R− recipients, resulting in significantly worse survival than other CMV match groups (**Figure S2**, **SDC**, http://links.lww.com/TXD/A643).[7,35,37-40]

Numerous calls have been made[10,41,42] for actions to mitigate the impact of CMV on post-SOT. In addition to the aforementioned approaches, several prevention measures have been proposed.[15,16,32,40,43,44] This article focuses on one such proposal: CMV serological matching while allocating deceased donor organs.[10,16,17,45] CMV matching has been advocated and practiced as early as 1988 in the United States[46] and the United Kingdom,[47,48] despite some contradictory findings.[15,30,35,42,49] A recent U.S. pilot study[16] documented that successful CMV matching is possible without adversely affecting local transplant rates and waitlisted times. These encouraging results are based on the experiences of a small number of transplant centers or a single organ procurement organization. The impact of a nationwide CMV matching in deceased donor kidney allocation remains unclear.[17]

Given the high costs of experimenting with a nationwide implementation of CMV matching policy in practice, we utilized a detailed computer simulation model[50] to understand the impact of such a policy change. In particular, we compared the simulated allocation policy outcomes under the current Organ Procurement and Transplantation Network (OPTN) Kidney Allocation System (KAS) policy, which does not consider CMV matching, to various CMV matching policies that factor in calculated panel reactive antibody (cPRA) levels.

MATERIALS AND METHODS

Data Sources

This study used data from the United Network for Organ Sharing (UNOS) Standard Transplant Analysis Research files, which comprise data on all donors, waitlisted candidates, and transplant recipients in the United States submitted by OPTN members. The authors have abided by guidelines outlined in the declarations of Helsinki and Istanbul, and the University of Arizona Institutional Review Board approved the study.

Our computer model simulates the U.S. kidney transplant waiting list from January 1, 2015, to January 1, 2018. The data used in the model included all available candidate, donor, and waiting list history records for the simulated period sourced from OPTN files. Adult candidates (age ≥ 18) on the U.S. kidney-alone waiting list were included; identifying 185 621 individuals, which resulted in 210 572 waiting list registrations. Waiting list history data included 584 321 records containing updates to candidates' dynamic features, such as changes in a candidate's cPRA or switches between active/inactive waiting list status. Donor data included all transplanted deceased donor kidneys and those recovered for transplantation but not transplanted because "no recipient was located/list exhausted"; identifying 25 057 donors with a total of 44 936 potential kidneys for transplantation.

Handling Missing Data

Missingness in 2 variables are particularly relevant in our study: induction regimen used and CMV serostatus of the patient. To impute missing data in induction regimens for candidates who did not receive a transplant in UNOS records, but may receive one in the simulation, bootstrapping, stratified by transplanting center, was used.[51] If a center has not completed any transplant, its induction values were sampled from national induction usage distribution.

A 2-stage strategy was used to impute missing CMV status data for candidates and donors. First, a set of clinically relevant variables were identified (**Table S1**, **SDC**, http://links.lww.com/TXD/A643). Missing values in this set were imputed using median for numerical variables and bootstrapping for categorical variables based on the rest of the available data.[51] Given the completed set of variables from the first stage, a random forest-based imputation method called missForest is used in the second-stage to impute missing CMV status,[52,53] resulting in high validation accuracy (measured by the complement of proportion falsely classified): 96.4% for candidates and 94.5% for donors.

Simulation Model Overview and CMV Matching Protocol Evaluated

A previously validated simulation model developed by the leading authors and described in detail elsewhere[50] was used. This model resembles the Kidney-Pancreas Simulated Allocation Model[54] and was also utilized in another study[55] investigating the impact of a new policy proposal targeted towards reducing kidney discard rate. Although it is currently not publicly available, we have access to the source code of the Sandıkçı et al[50] model, allowing us to incorporate CMV matching into the U.S. KAS and evaluate its consequences.

Three major updates were introduced to the original version of the Sandıkçı et al[50] model: (1) The kidney allocation module was modified to comply with the most recent UNOS kidney allocation policy (the KAS-250 policy, effective as of March 2021) that eliminated donation service areas and UNOS regions. KAS-250 does not consider CMV matching in its allocations and forms the baseline for all comparisons. (2) The simulated allocation policy was expanded to also include an optional CMV matching protocol described in Lockridge et al.[16] When this option is activated, the offer list generated for a D− kidney excluded (where possible) R+ candidates, and that for a D+ kidney excluded (where possible) R− candidates, helping minimize the CMV mismatch among donors and recipients. Exception criteria in this protocol included: (a) zero-antigen mismatch transplants, helping control for HLA mismatch; (b) candidates with a cPRA above a given threshold (eg, >50%), allowing to keep cPRA prioritization points; and (c) lack of CMV-matched recipients. Candidates meeting the exception criteria were included in the offer list according to KAS-250 policy when a CMV-mismatched kidney arrived. (3) The posttransplant graft survival module, which replicated the Cox proportional hazards model of Kidney-Pancreas Simulated Allocation Model,[54] was updated by reestimating the Cox regression after adding CMV match status and induction immunosuppression status as new covariates to the original list of variables (**Table S2**, **SDC**, http://links.lww.com/TXD/A643).

Primary Outcomes and Sensitivity Analysis

Primary simulation outcomes included CMV serodistribution, equity-focused measures (transplant numbers and rates among ethnic minorities, blood types, gender, and highly sensitized patients [with cPRA > 85%]; waiting time, measured starting from earliest of the time of listing or time of regular dialysis administration, as defined by OPTN), and utility-focused measures (transplant rate, defined as the number transplanted per 100-patient years of active wait time; kidney discard rate, with discards defined as failing to accept an offered kidney after a maximum number of offers is made—this maximum number is determined as 210 after detailed calibration; HLA-mismatch level; and 1-y graft survival) under each simulated policy, stratified by CMV serostatus.

Sensitivity analysis was performed for the cPRA threshold defining the exception criteria in the CMV matching protocol. Thresholds >0%, >50%, >85%, >95%, >98%, >99%, and >100% (no cPRA exception) were tested. For simplicity, the CMV matching protocol with cPRA exception threshold x% is denoted $CMV_{\text{“}x\%\text{”}}$ when presenting results (eg, $CMV_{\text{“}>0\%\text{”}}$ denotes the CMV matching protocol with cPRA exception >0%).

Statistical Analysis

Point estimates along with 99% confidence intervals were obtained from 30 independent replications. Common random numbers[56] was used to reduce the variance in simulation estimates. Continuous variables were summarized with means and standard deviations, categorical variables with frequencies and percentages. Comparative analysis of continuous variables utilized the 2-sample Wilcoxon signed-rank test, while that of categorical variables utilized the 2-sided chi-squared test. Benjamini-Hochberg's multiple comparison adjustment was used in pairwise comparison of groups. Survival curves were estimated using the Kaplan-Meier method and the log-rank test was used to compare estimated survival among groups. Multivariate Cox analysis was performed to identify the predictors of graft failure. A $P < 0.05$ was considered significant for all statistical methods. The simulation code was developed using C/C++ and all statistical analyses were completed using R, Version 3.6.3.

RESULTS

Simulation Model Validation

Validation results for the simulation model was previously published in Sandıkçı et al.[50] Additional validation results, shown in Table S3 (**SDC**, http://links.lww.com/TXD/A643), confirm close parallels between actual and simulated data.

Candidate Characteristics

CMV− and CMV+ candidates exhibit significantly distinct listing attributes (**Table S4**, **SDC**, http://links.lww.com/TXD/A643). Compared with CMV− candidates, CMV+ candidates were more likely to be female (44.3% versus 28.7%), of non-White race (82.1% versus 18.8%), and repeat-transplant cases (15.1% versus 8.2%). At the time of listing, CMV+ candidates were older (51.1 versus 49.9 y), had a higher prevalence of diabetes (44.6% versus 36.8%), exhibited worse functional status (35.5% versus 28.7%), had slightly lower body mass index (28.1 versus 29.2), and experienced longer median waiting times (799.0 versus 445.6 d).

Impact of CMV Matching

Increasing the cPRA exception threshold employed in CMV matching restricts the exception set, causing larger deviations in the kidney offer sequence compared with that of the baseline policy and, therefore, yielding more pronounced differences in outcomes (Tables 1 and 2).

CMV Serodistribution

Compared with the baseline, CMV matching significantly decreased the proportion of high-risk (D+/R−) transplants (Tables 1 and 2): 18.1% (baseline) versus 8.6%, 6.1%, 5.1%, and 2.0% (CMV matching policies $CMV_{\text{“}>0\%\text{”}}$, $CMV_{\text{“}>50\%\text{”}}$, $CMV_{\text{“}>85\%\text{”}}$, and $CMV_{\text{“}>100\%\text{”}}$, respectively). Furthermore, the proportion of low-risk (D−/R−) transplants increased steadily with CMV matching, reaching its peak of 39.1% under the $CMV_{\text{“}>100\%\text{”}}$ policy versus 13.1% (baseline).

Distribution of Exception Statuses for CMV-mismatched Recipients

The proportion of CMV-mismatched recipients who received exceptions decreased from 25.5% under the $CMV_{\text{“}>0\%\text{”}}$ policy to 3.6% under the $CMV_{\text{“}>100\%\text{”}}$ policy (Table 3). The predominant cause of exceptions was cPRA, but the degree of this dominance depends on the cPRA threshold employed. As this threshold increases, zero-antigen mismatch becomes an increasingly important cause of exceptions.

Utility-focused Metrics

The overall number of deceased donor kidney transplants and the overall transplant rate increased steadily from the baseline (32 197 and 10.94, respectively) with higher cPRA thresholds in CMV matching, reaching their peak (32 755 and 11.25, respectively) under the $CMV_{\text{“}>100\%\text{”}}$ policy (Tables 1 and 2; Figure 1). These rises were driven by the increase in the CMV R− group, which more than offsets the decrease in the CMV R+ group.

Consequently, kidney discard rate decreased steadily with CMV matching: 26.23% (baseline) versus 24.96% (the $CMV_{\text{“}>100\%\text{”}}$ policy) (Figure 2). Although the discard rate remained stable for CMV D+ kidneys, it decreased for CMV D− kidneys.

The distribution of the number of HLA mismatch remained unchanged for the overall study cohort (Tables 1 and 2), whereas that for CMV R− (R+) recipients had a lower (higher, respectively) proportion of zero-antigen mismatch transplants (12% in baseline versus 11.1% in $CMV_{\text{“}>50\%\text{”}}$ for R− and 5.78% in baseline versus 6.08% in $CMV_{\text{“}>50\%\text{”}}$ for R+; data not tabulated).

Despite a minor increase in the average HLA mismatch level (from 3.89 to 3.96; data not tabulated) for CMV R− recipients after CMV matching, cumulative graft survival at 1-y improved up to 0.28 percentage points for CMV R− recipients, whereas it did not change for CMV R+ recipients (Figure 3).

TABLE 1.

Characteristics of DDKT recipients in the United States: KAS-250 policy (without CMV matching) versus CMV matching policies with various cPRA exception thresholds (based on simulated data from January 1, 2015, to January 1, 2018)

		CMV matching policy based on cPRA exception threshold					
Recipient characteristic	**KAS-250 policy (no CMV matching)**	**>0%**	**>50%**	**>85%**	**>95%**	**>99%**	**>100%[b]**
n[a]	32 197	32 346	32 452	32 499	32 576	32 693	32 755
Age[d], y, n (%)							
≤35	6231 (19.4)	6136 (19.0)	6102 (18.8)	6116 (18.8)	6110 (18.8)	6097 (18.6)	6109 (18.7)
35–50	9265 (28.8)	9348 (28.9)	9393 (28.9)	9401 (28.9)	9367 (28.8)	9346 (28.6)	9325 (28.5)
50–65	11 737 (36.5)	11 825 (36.6)	11 874 (36.6)	11 890 (36.6)	11 977 (36.8)	12 041 (36.8)	12 066 (36.8)
>65	4964 (15.4)	5038 (15.6)	5084 (15.7)	5092 (15.7)	5122 (15.7)	5208 (15.9)	5254 (16.0)
Gender, n (%)							
Female	13 997 (43.5)	14 222 (44.0)	14 141 (43.6)	13 893 (42.7)	13 597 (41.7)	13 378 (40.9)	13 228 (40.4)
Male	18 200 (56.5)	18 124 (56.0)	18 311 (56.4)	18 606 (57.3)	18 979 (58.3)	19 315 (59.1)	19 527 (59.6)
Race, n (%)							
White	10 958 (34.0)	11 180 (34.6)	11 569 (35.6)	11 991 (36.9)	12 291 (37.7)	12 546 (38.4)	12 810 (39.1)
Black	11 944 (37.1)	11 943 (36.9)	11 818 (36.4)	11 622 (35.8)	11 535 (35.4)	11 461 (35.1)	11 332 (34.6)
Hispanic	6480 (20.1)	6416 (19.8)	6340 (19.5)	6243 (19.2)	6156 (18.9)	6121 (18.7)	6068 (18.5)
Other	2815 (8.7)	2806 (8.7)	2725 (8.4)	2643 (8.1)	2593 (8.0)	2565 (7.8)	2545 (7.8)
Blood type, n (%)							
O	14 610 (45.4)	14 686 (45.4)	14 717 (45.4)	14 765 (45.4)	14 815 (45.5)	14 845 (45.4)	14 893 (45.5)
A	11 159 (34.7)	11 237 (34.7)	11 317 (34.9)	11 313 (34.8)	11 338 (34.8)	11 405 (34.9)	11 406 (34.8)
B	4696 (14.6)	4657 (14.4)	4635 (14.3)	4628 (14.2)	4635 (14.2)	4667 (14.3)	4684 (14.3)
AB	1731 (5.4)	1766 (5.5)	1783 (5.5)	1793 (5.5)	1788 (5.5)	1776 (5.4)	1771 (5.4)
UNOS region, n (%)							
1	880 (2.7)	881 (2.7)	888 (2.7)	902 (2.8)	909 (2.8)	931 (2.8)	932 (2.8)
2	3952 (12.3)	4052 (12.5)	4045 (12.5)	4070 (12.5)	4091 (12.6)	4120 (12.6)	4113 (12.6)
3	5039 (15.7)	5046 (15.6)	5055 (15.6)	5061 (15.6)	5076 (15.6)	5113 (15.6)	5108 (15.6)
4	3676 (11.4)	3712 (11.5)	3715 (11.4)	3716 (11.4)	3717 (11.4)	3736 (11.4)	3719 (11.4)
5	5248 (16.3)	5243 (16.2)	5275 (16.3)	5291 (16.3)	5284 (16.2)	5292 (16.2)	5291 (16.2)
6	1331 (4.1)	1300 (4.0)	1299 (4.0)	1298 (4.0)	1302 (4.0)	1285 (3.9)	1307 (4.0)
7	2943 (9.1)	2947 (9.1)	2965 (9.1)	2952 (9.1)	2943 (9.0)	2942 (9.0)	2946 (9.0)
8	1909 (5.9)	1912 (5.9)	1932 (6.0)	1933 (5.9)	1942 (6.0)	1944 (5.9)	1958 (6.0)
9	2064 (6.4)	2022 (6.3)	2033 (6.3)	2031 (6.2)	2035 (6.2)	2047 (6.3)	2072 (6.3)
10	2217 (6.9)	2254 (7.0)	2256 (7.0)	2272 (7.0)	2293 (7.0)	2302 (7.0)	2320 (7.1)
11	2938 (9.1)	2977 (9.2)	2991 (9.2)	2972 (9.1)	2984 (9.2)	2981 (9.1)	2990 (9.1)
Transplant type, n (%)							
Primary	26 235 (81.5)	26 311 (81.3)	26 403 (81.4)	26 542 (81.7)	26 843 (82.4)	27 273 (83.4)	27 623 (84.3)
Repeat	5961 (18.5)	6035 (18.7)	6049 (18.6)	5957 (18.3)	5733 (17.6)	5420 (16.6)	5132 (15.7)
HLA-A/B/DR mismatch, n (%)							
0	2481 (7.7)	2514 (7.8)	2521 (7.8)	2520 (7.8)	2502 (7.7)	2561 (7.8)	2609 (8.0)
1	129 (0.4)	119 (0.4)	119 (0.4)	118 (0.4)	128 (0.4)	132 (0.4)	134 (0.4)

(Continued)

TABLE 1.
Continued

Recipient characteristic	KAS-250 policy (no CMV matching)	CMV matching policy based on cPRA exception threshold					
		>0%	>50%	>85%	>95%	>99%	>100%[b]
2	930 (2.9)	899 (2.8)	893 (2.8)	901 (2.8)	927 (2.8)	963 (2.9)	987 (3.0)
3	3752 (11.7)	3664 (11.3)	3637 (11.2)	3651 (11.2)	3757 (11.5)	3817 (11.7)	3900 (11.9)
4	8668 (26.9)	8541 (26.4)	8568 (26.4)	8611 (26.5)	8640 (26.5)	8770 (26.8)	8781 (26.8)
5	10846 (33.7)	10994 (34.0)	11018 (34.0)	11018 (33.9)	11009 (33.8)	10961 (33.5)	10924 (33.4)
6	5391 (16.7)	5616 (17.4)	5697 (17.6)	5681 (17.5)	5612 (17.2)	5489 (16.8)	5419 (16.5)
cPRA (%)							
0	17048 (53.0)	15896 (49.1)	16776 (51.7)	17371 (53.5)	17926 (55.0)	18530 (56.7)	18935 (57.8)
1–50	4686 (14.6)	5564 (17.2)	4503 (13.9)	4655 (14.3)	4802 (14.7)	4959 (15.2)	5064 (15.5)
51–85	2536 (7.9)	2823 (8.7)	3070 (9.5)	2264 (7.0)	2341 (7.2)	2420 (7.4)	2468 (7.5)
86–95	2607 (8.1)	2704 (8.4)	2736 (8.4)	2843 (8.7)	2035 (6.2)	2132 (6.5)	2150 (6.6)
96–98	2072 (6.4)	2110 (6.5)	2106 (6.5)	2124 (6.5)	2188 (6.7)	1604 (4.9)	1613 (4.9)
99	971 (3.0)	987 (3.1)	1008 (3.1)	990 (3.0)	1016 (3.1)	715 (2.2)	724 (2.2)
100	2276 (7.1)	2262 (7.0)	2254 (6.9)	2251 (6.9)	2268 (7.0)	2333 (7.1)	1800 (5.5)
Diabetes[c], n (%)							
None	22802 (70.8)	22878 (70.7)	22974 (70.8)	23032 (70.9)	23042 (70.7)	23046 (70.5)	23077 (70.5)
Type I	874 (2.7)	883 (2.7)	889 (2.7)	902 (2.8)	909 (2.8)	909 (2.8)	903 (2.8)
Type II	8461 (26.3)	8527 (26.4)	8534 (26.3)	8508 (26.2)	8568 (26.3)	8683 (26.6)	8722 (26.6)
Unknown	59 (0.2)	58 (0.2)	56 (0.2)	57 (0.2)	57 (0.2)	54 (0.2)	53 (0.2)
BMI[c], n (%)							
≤25	11181 (34.7)	11125 (34.4)	11101 (34.2)	11018 (33.9)	10944 (33.6)	10864 (33.2)	10835 (33.1)
25–30	9672 (30.0)	9746 (30.1)	9770 (30.1)	9814 (30.2)	9800 (30.1)	9831 (30.1)	9836 (30.0)
30–35	7172 (22.3)	7254 (22.4)	7318 (22.6)	7370 (22.7)	7459 (22.9)	7555 (23.1)	7599 (23.2)
35–40	3421 (10.6)	3465 (10.7)	3504 (10.8)	3535 (10.9)	3591 (11.0)	3640 (11.1)	3671 (11.2)
>40	750 (2.3)	756 (2.3)	759 (2.3)	763 (2.3)	782 (2.4)	802 (2.5)	814 (2.5)
Functional status[c], n (%)							
Asymptomatic	19874 (61.7)	19986 (61.8)	20100 (61.9)	20169 (62.1)	20288 (62.3)	20386 (62.4)	20436 (62.4)
Disabled	11146 (34.6)	11193 (34.6)	11179 (34.4)	11146 (34.3)	11112 (34.1)	11128 (34.0)	11143 (34.0)
Severely disabled	36 (0.1)	34 (0.1)	33 (0.1)	32 (0.1)	33 (0.1)	32 (0.1)	33 (0.1)
Unknown	1141 (3.5)	1133 (3.5)	1140 (3.5)	1152 (3.5)	1143 (3.5)	1147 (3.5)	1143 (3.5)
Candidate CMV status, n (%)							
Negative	10034 (31.2)	10162 (31.4)	10816 (33.3)	11600 (35.7)	12345 (37.9)	12939 (39.6)	13435 (41.0)
Positive	22162 (68.8)	22184 (68.6)	21636 (66.7)	20899 (64.3)	20231 (62.1)	19754 (60.4)	19320 (59.0)
Donor CMV status, n (%)							
Negative	12851 (39.9)	12838 (39.7)	12957 (39.9)	13057 (40.2)	13129 (40.3)	13243 (40.5)	13326 (40.7)
Positive	19345 (60.1)	19509 (60.3)	19495 (60.1)	19442 (59.8)	19447 (59.7)	19450 (59.5)	19429 (59.3)

(Continued)

TABLE 1.
Continued

Recipient characteristic	KAS-250 policy (no CMV matching)	CMV matching policy based on cPRA exception threshold					
		>0%	>50%	>85%	>95%	>99%	>100%[b]
CMV match status, n (%)							
D−/R−	4204 (13.1)	7371 (22.8)	8840 (27.2)	9951 (30.6)	11 010 (33.8)	11 998 (36.7)	12 792 (39.1)
D−/R+	8647 (26.9)	5466 (16.9)	4117 (12.7)	3106 (9.6)	2119 (6.5)	1245 (3.8)	534 (1.6)
D+/R−	5830 (18.1)	2791 (8.6)	1976 (6.1)	1650 (5.1)	1335 (4.1)	941 (2.9)	643 (2.0)
D+/R+	13 515 (42.0)	16 718 (51.7)	17 519 (54.0)	17 793 (54.7)	18 112 (55.6)	18 508 (56.6)	18 787 (57.4)

[a] n: number of records in each group. Missing/unknown values in any particular variable are ignored when reporting summary statistics.
[b] No cPRA exception applies when this threshold is employed.
[c] At the time of listing.
[d] At the time of transplant.
BMI, body mass index; CMV, cytomegalovirus; cPRA, calculated panel reactive antibody; D−/R−, donor negative/recipient negative; D−/R+, donor negative/recipient positive; D+/R−, donor positive/recipient negative; D+/R+, donor positive/recipient positive; DDKT, deceased donor kidney transplant; KAS-250, current Organ Procurement and Transplantation Network Kidney Allocation System (effective as of March 2021); UNOS, United Network for Organ Sharing.

Equity-focused Metrics

Introducing CMV matching may reduce access to transplantation among female, non-White race, repeat, highly sensitized (cPRA > 85%), and CMV seropositive patients, but the degree of reduction depends on the cPRA exception threshold employed, with higher thresholds resulting in larger reductions (Tables 1 and 2). At the extreme, $CMV_{\text{“>100\%”}}$ resulted in 558 additional transplants (compared with baseline) whose recipients were more likely to be male, of White race, heavier, CMV seronegative, undergoing their first transplant, and having lower cPRA.

Mean time until transplantation among transplant recipients decreased by up to 55 d after CMV matching (Figure 4). Although both CMV R− and R+ groups gained faster access to transplantation when CMV matching is employed with cPRA exception thresholds up to 85%, only CMV R− group continued faster access for higher thresholds.

CMV matching did not change the overall blood type distribution of transplant recipients (Tables 1 and 2). However, using a cPRA threshold of 95% or higher, it increased the proportions of type O and type B recipients in the CMV R− group, and the proportion of type A recipients in the CMV R+ group (**Figure S4c**, **SDC**, http://links.lww.com/TXD/A643).

The geographic distribution of allograft utilization remained mostly unchanged with the introduction of CMV matching (Table 4), except when no cPRA exception was employed (ie, the $CMV_{\text{“>100\%”}}$ policy) for CMV D− kidneys. For D− kidneys, within region utilizations were 82%, 77%, 90%, and 77% for the U.S. Census regions South, Midwest, West, and Northeast, respectively, while the import rates were 22%, 14%, 9%, and 28%, respectively. Only with the $CMV_{\text{“>100\%”}}$ policy, within region utilization of D− kidneys increased by 1–3 percentage points and the import rates decreased accordingly. For D+ kidneys, within region utilizations were 84%, 76%, 90%, and 78% for the South, Midwest, West, and Northeast, respectively, while the import rates were 16%, 16%, 8%, and 34%, respectively.

Although CMV matching did not significantly alter the geographic distribution of transplanted organs, it resulted in higher overall number of transplants in all regions except the West, where it remained unchanged (**Figure S5**, **SDC**, http://links.lww.com/TXD/A643). Notably, $CMV_{\text{“>50\%”}}$ resulted in 28, 16, and 44 more transplants per year in the Midwest, Northeast, and South regions, respectively.

The mean Kidney Donor Profile Index increased from 40.68% to around 42% among CMV R− recipients, while that for CMV R+ recipients plateaued around 45.5% (**Figure S6**, **SDC**, http://links.lww.com/TXD/A643).

DISCUSSION

CMV seropositivity in the U.S. deceased donor kidneys increased from 60.1% in 2015 to 61.6% in 2022 ($P = 0.03$; **Figure S1**, **SDC**, http://links.lww.com/TXD/A643), while that in primary kidney-only adult recipients remained stable around 68% ($P = 0.24$). Consistent with previous studies,[15,35] we found that donor-recipient CMV serostatus match was a significant factor in posttransplant survival (**Figure S2**, **SDC**, http://links.lww.com/TXD/A643). Recipients of D+ kidneys had significantly worse survival than those of D− kidneys, regardless of recipients' CMV serostatus ($P < 0.01$), with D+/R− group displaying the worst survival ($P = 0.02$ or less for

TABLE 2.

Statistical comparison of DDKT recipient characteristics in the United States: KAS-250 policy (without CMV matching) versus CMV matching policies with various cPRA exception thresholds (based on simulated data from January 1, 2015, to January 1, 2018)

	P[a] comparing simulated KAS-250 policy (without CMV matching) vs CMV matching policy with cPRA exception threshold					
Recipient characteristic	**>0%**	**>50%**	**>85%**	**>95%**	**>99%**	**>100%**[d]
Age[c], y	0.65	0.42	0.42	0.42	0.15	0.15
Gender	0.25	0.80	0.10	<0.01**	<0.01**	<0.01**
Race	0.53	<0.01**	<0.01**	<0.01**	<0.01**	<0.01**
Blood type	0.89	0.89	0.89	0.89	0.89	0.89
UNOS region	1.00	1.00	1.00	1.00	1.00	1.00
Transplant type	0.69	0.69	0.69	0.01*	<0.01**	<0.01**
HLA-A/B/DR mismatch	0.42	0.30	0.33	0.88	0.99	0.88
cPRA (diabetes[b])	0.99	0.99	0.99	0.99	0.99	0.99
BMI[b]	0.93	0.82	0.36	0.04*	<0.01**	<0.01**
Functional status[b]	0.98	0.98	0.98	0.98	0.98	0.98
Candidate CMV status	0.50	<0.01**	<0.01**	<0.01**	<0.01**	<0.01**
Donor CMV status	0.67	0.98	0.67	0.64	0.38	0.28
CMV match status	<0.01**	<0.01**	<0.01**	<0.01**	<0.01**	<0.01**

Significance codes: 0 "**" 0.01 "*" 0.05 " " 1.

[a] From chi-squared test for categorical variables and Wilcoxon rank-sum test for numerical variables, both adjusted by BH method for multiple pairwise testing.

[b] At the time of listing.

[c] At the time of transplant.

[d] No cPRA exception applies when this threshold is employed.

BH, Benjamini-Hochberg; BMI, body mass index; CMV, cytomegalovirus; cPRA, calculated panel reactive antibody; DDKT, deceased donor kidney transplant; KAS-250, current Organ Procurement and Transplantation Network Kidney Allocation System (effective as of March 2021); UNOS, United Network for Organ Sharing.

TABLE 3.

Distribution of exceptions for CMV-mismatched DDKT recipients under various simulated CMV matching policies (based on simulated data from January 1, 2015, to January 1, 2018)

	Simulated CMV matching policy based on cPRA exception threshold					
Values	**>0%**	**>50%**	**>85%**	**>95%**	**>99%**	**>100%**[b]
n[a] (% of all recipients)	8257 (25.7)	6093 (18.9)	4756 (14.8)	3454 (10.7)	2187 (6.8)	1176 (3.7)
CMV exception, n (%)						
cPRA exception	7124 (86.3)	4945 (81.2)	3607 (75.8)	2321 (67.2)	1027 (47.0)	0 (0.0)
Zero-antigen exception	634 (7.7)	991 (16.3)	1123 (23.6)	1121 (32.5)	1153 (52.7)	1174 (99.8)
Both exceptions	500 (6.1)	155 (2.5)	24 (0.5)	10 (0.3)	4 (0.2)	0 (0.0)
No exception	0 (0.0)	1 (0.0)	2 (0.0)	2 (0.1)	2 (0.1)	2 (0.2)

[a] n: number of records in each group. Missing/unknown values in any particular variable are ignored when reporting summary statistics.

[b] No cPRA exception applies when this threshold is employed.

CMV, cytomegalovirus; cPRA, calculated panel reactive antibody; DDKT, deceased donor kidney transplant.

all pairwise comparisons). After adjusting for other confounders, D+/R− remained the only group with significantly worse graft survival ($P < 0.01$; **Table S2, SDC**, http://links.lww.com/TXD/A643).

Axelrod et al[57] used a Markov model to allocate CMV D− versus D+ kidneys to a hypothetical cohort of 100 000 CMV R− patients. They found that D−/R− transplants improve survival and reduce costs and that waiting for a CMV D− kidney remained the dominant strategy for up to 30 mo of additional waiting time.

Recent practice in the United States witnessed a significant increasing trend only in high-risk (D+/R−) transplants (from 17.3% in 2015 to 18.8% in 2022; $P < 0.01$; **Figure S1, SDC**, http://links.lww.com/TXD/A643), which may be due to overreliance on antiviral CMV prophylaxis. However, even in the contemporary antiviral era, worse survival in D+/R− recipients is well-documented,[14,15,31,35,42,58] which underscores the importance of some form of CMV matching during the allocation process. Once a host acquires CMV, the virus remains for life and viral reactivation or superinfection with a new CMV genotype may happen when exposed to immunosuppressive agents.

Lockridge et al[16] conducted a prospective CMV matching study in 1 donation service area in the U.S. Northwest region during 2012–2014 (pre-KAS-250 era). They reported that the $CMV_{\text{“>50\%”}}$ policy decreased D+/R− transplants from 18.5% to 2.9% and increased D−/R− transplants from 13.5% to 24.0%, without adversely affecting transplant rates and waitlisted days for CMV R− versus R+ patients. The impact of a nationwide expansion of CMV matching has been a topic of debate but had not been tested rigorously until our simulation-based study. Our results confirm the findings of Lockridge et al[16] at the national level, reemphasizing the importance and validity of employing national CMV

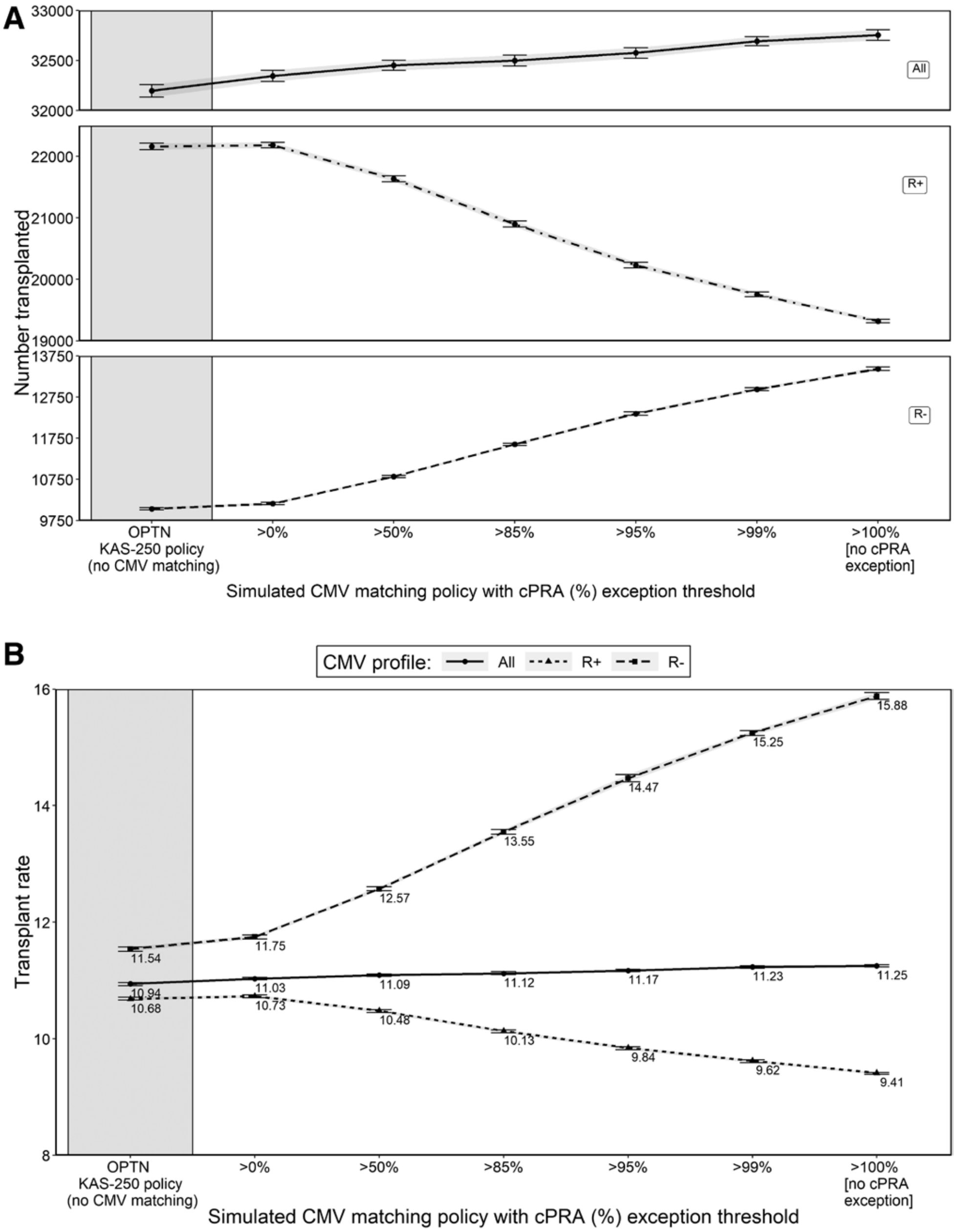

FIGURE 1. Transplant rate (ie, number transplanted per 100-patient years of active wait time) and total number of transplants for deceased donor kidney transplant (DDKT) from January 1, 2015, to January 1, 2018, collected under the OPTN KAS-250 policy (without CMV matching) vs simulated CMV matching policies with different cPRA exception thresholds, stratified by recipient CMV serostatus (based on simulated data). Numeric values indicate point estimates for the mean values of the policy outcomes while the error bars/shaded bands indicate 99% confidence intervals around the point estimates; nonoverlapping intervals indicate statistically significant difference between the simulated policy outcomes. CMV, cytomegalovirus; cPRA, calculated panel reactive antibody; KAS-250, current UNOS kidney allocation policy; OPTN, Organ Procurement and Transplantation Network; R−, CMV seronegative recipient; R+, CMV seropositive recipient.

matching in kidney allocation. We predict that significantly reducing, if not entirely eliminating, CMV mismatch as a prevention strategy is possible without perturbing equity- and utility-focused measures.

We tested CMV matching with various cPRA exception thresholds: $CMV_{\text{“>50\%”}}$ appears to strike a better balance between gains and losses than other CMV matching policies. Compared with current KAS-250 policy, $CMV_{\text{“>50\%”}}$ resulted in lower D+/R− transplants (6.1% versus 18.1%), higher D−/R− and D+/R+ transplants (27.2% versus 13.1% and 54.0% versus 42.0%, respectively), which imply reduced antiviral usage (3.15 versus 2.37 mo per recipient) assuming full adherence to the guidelines of the Transplantation Society[32] (ie, 6 mo of CMV antiviral prophylaxis for D+/R−, 3 mo for R+, and none for D−/R−), possibly leading to reductions in antiviral-related complications and healthcare costs. Increased number of D+/R+ transplants may raise concerns about viral reactivation or superinfection with a new CMV genotype.[59-61] Nonetheless, the risks associated with D+/R− likely outweighs those of D+/R+.[17] Different strategies may be required to monitor and initiate antiviral therapy as the number of D−/R− recipients at risk for primary CMV infection increases.[62]

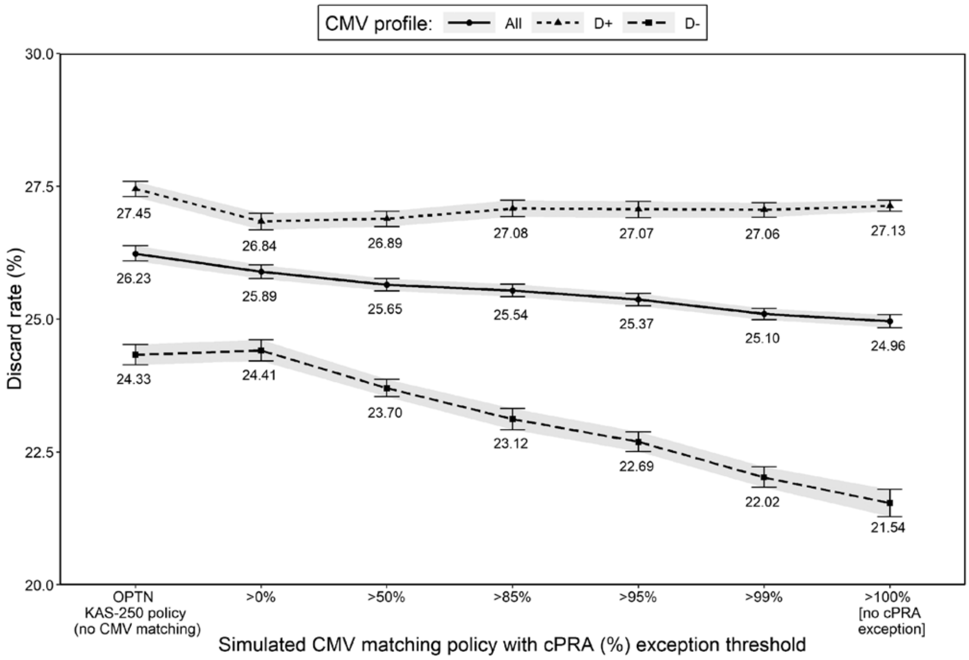

FIGURE 2. Proportion of deceased donor kidneys discarded under the OPTN KAS-250 policy (without CMV matching) vs simulated CMV matching policies with different cPRA exception thresholds, stratified by donor CMV serostatus (based on simulated data from January 1, 2015, to January 1, 2018). Numeric values indicate point estimates for the mean values of the policy outcomes while the error bars/shaded bands indicate 99% confidence intervals around the point estimates; nonoverlapping intervals indicate statistically significant difference between the simulated policy outcomes. CMV, cytomegalovirus; cPRA, calculated panel reactive antibody; D–, CMV seronegative donor; D+, CMV seropositive donor; KAS-250, current UNOS kidney allocation policy; OPTN, Organ Procurement and Transplantation Network.

Furthermore, $CMV_{\text{“>50\%”}}$ vis-à-vis KAS-250 resulted in more patients accessing transplantation (86 more patients per year, corresponding to 1.4% increase in transplant rate), faster access to transplantation (about 6 wk shorter on average), improved access for highly sensitized patients (24.6% versus 24.9%), and reduced donor kidney discard rate (26.2% versus 25.7%), but no significant change in any of the other outcomes measured.

The benefits of the $CMV_{\text{“>50\%”}}$ policy were not equally shared among different patient groups. The number of transplants increased for CMV R– patients (by 261 per year, or +7.8% from baseline), whereas it decreased for R+ patients (by 175 per year, or –2.4% from baseline). Contrary to popular belief,[17] however, median time to transplantation among transplant recipients decreased more for R+ group (by 8.4 wk, or –2.7% from baseline, for R+ versus by 5.9 wk, or –2.4% from baseline, for R–). To investigate the enduring effect on the time to transplantation of the CMV policy over time, we have stratified the waiting time calculations by listing year (**Tables S5** and **S6**, **SDC**, http://links.lww.com/TXD/A643). The observed reduction in the time to transplantation associated with the introduction of the $CMV_{\text{“>50\%”}}$ policy for the overall cohort continues to hold true for patients joining the simulated waiting list both before (ie, listing year ≤2014) and after (ie, listing years: 2015, 2016, and 2017) the simulation start date.

Furthermore, access to transplantation for non-White race was reduced (64.4% versus 66.0%), which is undesired but expected given the higher CMV seroprevalence in non-White race.[2,63] This disparity in access to transplantation becomes more pronounced as the cPRA exception threshold exceeds 50% (Table 1). Among higher cPRA values, non-White race has higher representation (**Figure S3**, **SDC**, http://links.lww.com/TXD/A643), which suggests that relatively less non-White patients would benefit from exceptions as the threshold is increased. This issue may be mitigated by designing matching protocols with additional exception criteria (such as race and Kidney Donor Profile Index) that override CMV sero-matching in allocation.

Jorgenson et al[17] raised a concern that nationwide CMV matching might negatively impact southern states by leading to more allografts being sent to the Midwest and Northeast. Although our implementation did not consider any CMV-related geographic information while allocating kidneys, we found that not only the overall geographical distribution of transplanted kidneys but also the import and export rates of CMV D– and D+ kidneys in each Census region remained stable, particularly under the $CMV_{\text{“>50\%”}}$ policy.

Another concern involves a possible increase in the number of HLA mismatches and associated decrease in graft survival.[59,64,65] Our findings refute this concern: not only the overall HLA mismatch distribution remained unchanged but also 1-y graft survival increased by a modest amount of 0.28 percentage points for CMV R– group ($P < 0.01$), with no reduction observed in CMV R+ groups.

CMV seromatching can be integrated into practice similar to ABO blood group matching, as we did in this study, or by introducing a point-based system similar to patient's sensitization level or proximity to donor hospital as in the current U.S. KAS. Future research should consider evaluating different approaches to incorporate CMV matching under various allocation policies including the currently debated continuous allocation.

The findings of this study do not diminish the value of CMV prophylactic treatment options. Posttransplant monitoring of CMV viral load and adherence to CMV prophylactic

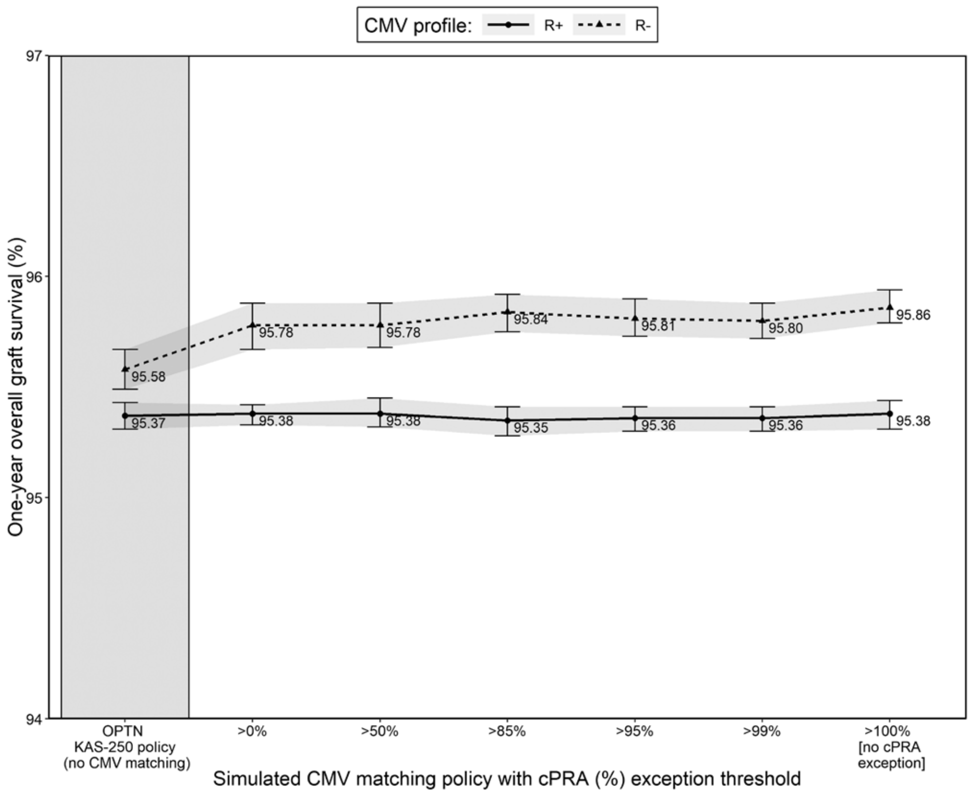

FIGURE 3. One-year overall graft survival of deceased donor kidney transplants from January 1, 2015, to January 1, 2018, collected under the OPTN KAS-250 policy (without CMV matching) vs simulated CMV matching policies with different cPRA exception thresholds, stratified by recipient CMV serostatus (based on simulated data). Numeric values indicate point estimates for the mean values of the policy outcomes while the error bars/shaded bands indicate 99% confidence intervals around the point estimates; nonoverlapping intervals indicate statistically significant difference between the simulated policy outcomes. CMV, cytomegalovirus; cPRA, calculated panel reactive antibody; KAS-250, current UNOS kidney allocation policy; OPTN, Organ Procurement and Transplantation Network; R–, CMV seronegative recipient; R+, CMV seropositive recipient.

treatment remain critically important even after any CMV matching in allocation.

This study is not without limitations. Using a retrospective database brings in issues such as reporting bias, possible errors, or missingness. Notably, UNOS registry data records CMV serostatus only for transplant recipients, but not for waiting candidates, which had to be imputed in our study. The accuracy of our imputation is very high, increasing credibility of the results, but misclassification errors cannot be entirely ruled out. Furthermore, the database and the simulation model focus on CMV serology, but not posttransplant CMV-related complications, which limits the understanding of posttransplant CMV outcomes.

We chose our study period as 2015–2018 specifically to represent the current era of transplant practices, including widespread use of CMV preventive strategies, and to avoid the disruptions caused by COVID-19. Although we believe this choice should not influence the main results of the study, we cannot exclude a possible selection bias. The simulated acceptance decisions are based on Scientific Registry of Transplant Recipients kidney offer acceptance model,[66,67] which does not consider donor/recipient CMV status. Revising the acceptance model to include CMV status can potentially affect simulated outcomes; however, it requires match-run data, which is not available to the authors at the time of the study. If introducing CMV matching to the national KAS drastically shifts the transplant centers' acceptance behavior, then our simulation results should be interpreted with appropriate prudence.

CONCLUSIONS

Our results serve as proof of concept for adaptability of a nationwide CMV seromatching policy. We identified an implementation with a cPRA exception threshold of 50% to provide highly desired changes in seromatching distribution while simultaneously improving or not significantly disrupting equity- and utility-focused metrics.

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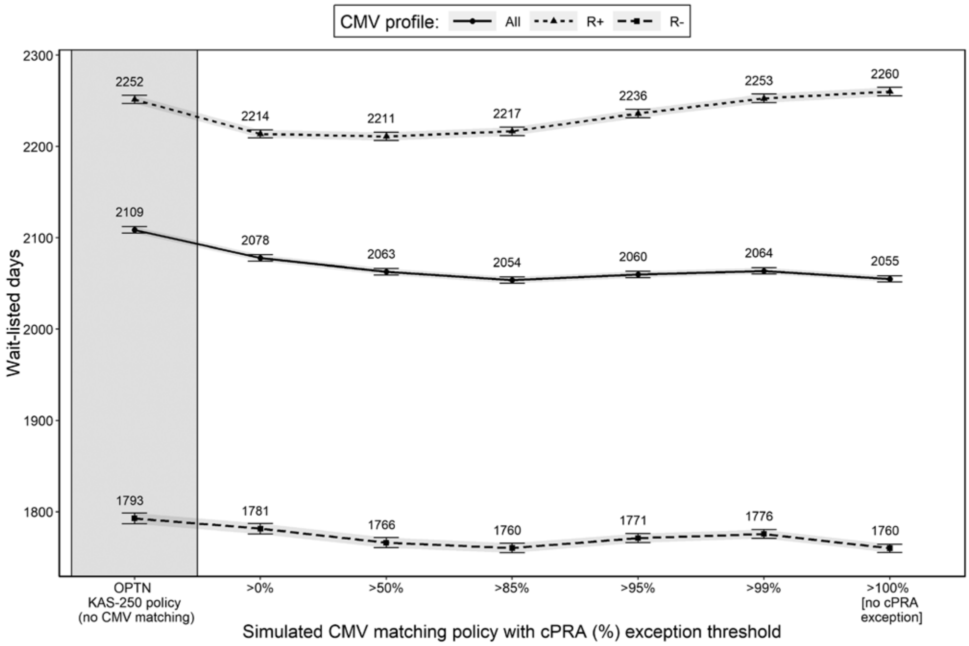

FIGURE 4. Waitlisted days for deceased donor kidney transplant recipients under the OPTN KAS-250 policy (without CMV matching) vs simulated CMV matching policies with different cPRA exception thresholds, stratified by recipient CMV serostatus (based on simulated data from January 1, 2015, to January 1, 2018). Numeric values indicate point estimates for the mean values of the policy outcomes while the error bars/shaded bands indicate 99% confidence intervals around the point estimates; nonoverlapping intervals indicate statistically significant difference between the simulated policy outcomes. CMV, cytomegalovirus; cPRA, calculated panel reactive antibody; KAS-250, current UNOS kidney allocation policy; OPTN, Organ Procurement and Transplantation Network; R−, CMV seronegative recipient; R+, CMV seropositive recipient.

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TABLE 4.

Geographic distribution of deceased donor kidneys transplanted[a] in the United States, stratified by allocation policy and CMV serostatus (based on simulated data from January 1, 2015, to January 1, 2018)

Donor organ region		KAS-250 policy	CMV matching policy based on cPRA exception threshold				P^c (KAS-250 vs CMV matching policies)			
From	To	(no CMV matching)	>0%	>50%	>85%	>100%[b]	>0%	>50%	>85%	>100%[b]
CMV seronegative donor organs, n (%)										
South	South	6802 (84.4)	6881 (84.4)	6893 (84.5)	6848 (84.3)	6851 (84.2)	1.00	1.00	1.00	1.00
	Midwest	352 (4.4)	354 (4.3)	352 (4.3)	352 (4.3)	349 (4.3)				
	West	116 (2.6)	117 (2.6)	122 (2.7)	125 (2.8)	80 (1.7)				
	Northeast	447 (10)	447 (10)	458 (10.2)	461 (10.2)	467 (10.1)				
Midwest	South	454 (13.6)	444 (13.3)	439 (13.1)	439 (13)	398 (11.6)	0.96	0.96	0.96	0.01*
	Midwest	2564 (76.7)	2559 (76.7)	2586 (76.9)	2604 (76.9)	2730 (79.3)				
	West	70 (2.1)	71 (2.1)	73 (2.2)	75 (2.2)	41 (1.2)				
	Northeast	253 (7.6)	263 (7.9)	265 (7.9)	268 (7.9)	274 (8)				
West	South	143 (5.6)	152 (6)	152 (5.9)	163 (6.3)	107 (4.1)	0.77	0.77	0.64	0.25
	Midwest	61 (2.4)	63 (2.5)	68 (2.7)	67 (2.6)	54 (2.1)				
	West	2276 (89.7)	2247 (88.8)	2272 (88.7)	2269 (88.2)	2387 (91.5)				
	Northeast	58 (2.3)	67 (2.6)	70 (2.7)	75 (2.9)	60 (2.3)				
Northeast	South	416 (16.5)	422 (16.8)	426 (16.8)	433 (16.8)	383 (14.5)	0.95	0.95	0.95	0.01*
	Midwest	116 (4.6)	123 (4.9)	124 (4.9)	127 (4.9)	111 (4.2)				
	West	43 (1.7)	45 (1.8)	47 (1.8)	48 (1.9)	22 (0.8)				
	Northeast	1945 (77.2)	1929 (76.6)	1936 (76.5)	1961 (76.4)	2128 (80.5)				
CMV seropositive donor organs, n (%)										
South	South	6802 (84.4)	6881 (84.4)	6893 (84.5)	6848 (84.3)	6851 (84.2)	1.00	1.00	1.00	1.00
	Midwest	352 (4.4)	354 (4.3)	352 (4.3)	352 (4.3)	349 (4.3)				
	West	245 (3)	246 (3)	246 (3)	248 (3)	264 (3.3)				
	Northeast	663 (8.2)	674 (8.3)	671 (8.2)	673 (8.3)	668 (8.2)				
Midwest	South	596 (15.3)	602 (15.4)	604 (15.4)	598 (15.4)	610 (15.7)	0.94	0.94	0.94	0.94
	Midwest	2942 (75.6)	2966 (75.7)	2964 (75.7)	2947 (75.7)	2932 (75.4)				
	West	88 (2.3)	92 (2.4)	92 (2.4)	92 (2.4)	100 (2.6)				
	Northeast	268 (6.9)	257 (6.6)	254 (6.5)	254 (6.5)	246 (6.3)				
West	South	277 (5.8)	289 (6)	295 (6.2)	293 (6.1)	312 (6.5)	0.90	0.90	0.90	0.90
	Midwest	103 (2.2)	108 (2.2)	109 (2.3)	109 (2.3)	109 (2.3)				
	West	4291 (89.8)	4272 (89.3)	4272 (89.1)	4279 (89.2)	4248 (88.7)				
	Northeast	109 (2.3)	115 (2.4)	118 (2.5)	114 (2.4)	122 (2.5)				
Northeast	South	412 (15.8)	420 (15.9)	410 (15.6)	419 (15.9)	434 (16.6)	1.00	1.00	1.00	1.00
	Midwest	102 (3.9)	107 (4.1)	103 (3.9)	108 (4.1)	108 (4.1)				
	West	52 (2)	52 (1.9)	52 (2)	52 (2)	59 (2.2)				
	Northeast	2042 (78.3)	2072 (78.2)	2060 (78.4)	2059 (78.1)	2018 (77)				

Significance codes: 0 "**" 0.01 "*" 0.05 " " 1.
[a] Summarized as "Count (%)"; missing/unknown values are ignored when reporting.
[b] No cPRA exception applies when this threshold is employed.
[c] From chi-squared test.
CMV, cytomegalovirus; cPRA, calculated panel reactive antibody; KAS-250, current Organ Procurement and Transplantation Network Kidney Allocation System (effective as of March 2021).

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