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Geographic Distribution of Cytomegalovirus Serology in Kidney and Pancreas Transplant Recipients in the United States

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Backgrounds. Cytomegalovirus (CMV) negatively affects transplant outcomes. The current geographic distribution of CMV risk within the US has not been described. **Methods.** CMV serostatus of donors and recipients in each US state were collected from the Scientific Registry of Transplant Recipients between April 1, 2015, and March 31, 2019. The objective was to describe rates of CMV recipient seropositivity (R+) and high-risk serostatus (D+/R-) across the US in kidney transplant recipient (KTR) and pancreas transplant recipient (PTR) and explore geographic disparities. **Results.** A total of 79276 KTRs and 4023 PTRs were included. The average KTR R+ rate across states was 59.5% (range 39%–76%); PTR R+ rate was 49.5% but with a broader range (0%–100%). The average KTR D+/R- rate across the US was 19% (range 8.7%–25%); PTR D+/R- rate was notably higher (26.9%, range 0%–50%). KTR seropositivity varied geographically with more R+ recipients in the southern states, Alaska, and Hawaii. D+/R- KTRs also varied by region, with higher rates in the Rocky Mountain Region as well as the Midwest and the northern-most states of the Northeast. Trends found in KTR persisted in PTR. **Conclusions.** The distribution of CMV serostatus in the US varies by state and allograft type. These data may be useful in further discussion of national CMV donor-matching strategies.

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INTRODUCTION

Cytomegalovirus (CMV) is one of the most common infections after solid organ transplant.¹ Response to CMV infection is highly dependent on cellular immunity.² Patients without previous exposure (seronegative, R-) who receive allografts from exposed donors (seropositive, D+) can develop the primary disease. Mismatched serostatus is a risk factor for severe infection and a plethora of negative infectious outcomes including recurrence, persistence, and antiviral resistance.³ Beyond the direct effects of infection, CMV has also been associated with negative graft outcomes thought to be related to inflammation and resultant alloreactivity.⁴ Despite the availability of potent antiviral agents and significant research dedicated to its prevention and treatment, CMV continues to negatively affect both short- and long-term graft and patient survival in the modern era.^{5,6} Improvement is needed in the prevention and treatment of CMV after solid organ transplant. Reduction in the overall incidence of high-risk CMV mismatch could result in decreased incidence of severe CMV infection and its negative sequelae. A novel kidney allocation strategy that weighs CMV serostatus in matching has been used in kidney transplant programs in Oregon since 2012.⁷ Preliminary data suggest reduced rates of CMV infection and disease after implementation without significant effects on wait-times, which has resulted in the national interest in this approach.⁸ Since 2015, the United

Network of Organ Sharing (UNOS) has required reporting of donor and recipient serologies at transplant. These data are available in the Scientific Registry of Transplant Recipients (SRTR). Although the national rates of serostatus at transplant have been reported, it is unknown if there is geographic variance in these rates that may affect the adaptability of CMV donor-matching strategies. Our study aimed to determine rates of seropositivity and CMV mismatch based on the state of transplant in a modern cohort of kidney transplant recipients (KTR) and pancreas transplant recipients (PTR) and compare these across geographic regions and allograft subtype.

MATERIALS AND METHODS

Study Design

We completed a retrospective cohort analysis of adult patients who received a kidney, simultaneous kidney-pancreas transplant, or pancreas transplant alone using data from the SRTR. Data found in the SRTR are provided by organ procurement organizations (OPOs) and transplantation centers that together comprise the Organ Procurement and Transplantation Network. The SRTR was queried for CMV serostatus in kidney and pancreas donors and recipients between April 1, 2015, and March 31, 2019, based on their US state of residence. These dates were selected as this represented when CMV donor/recipient status was consistently reported to UNOS. Patients were then divided into cohorts based on allograft type. All recipients of the pancreas were placed in the PTR group, and kidney-only recipients were placed in the KTR group. This study was approved by the local institutional review board.

Outcomes

The primary objective was to describe rates of CMV recipient seropositivity (R+) and high-risk serostatus (D+/R-) across the US in KTR and PTR. The secondary objective was to describe differences in rates of high-risk serostatus (D+/R-) between KTR and PTR and explore any geographic disparities.

Statistical Analysis

Patient characteristics were compared using the unpaired *t* test for continuous variables, and the chi-square or Fisher exact test for categorical variables, where appropriate. Incidence density maps were created using the ‘usmap’ package in R (version 3.6.0, R Core Team (2019). R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

There were 79 276 KTRs with evaluable serologies within the study period. The average seropositivity in KTR was 59.5%; however, this ranged from 39% to 76% (Figure 1). KTR seropositivity appeared to have geographic variation with more R+ recipients in the southern states, Alaska and Hawaii (Figure 2A). Of those KTRs with evaluable serologies 14 271 were D+/R-. The average rate of D+/R- across the US was 19.5% but ranged from 8.7% to 25%. High-risk serostatus also appeared to vary by region with higher rates of D+/R- in areas with lower rates of R+ including the Rocky Mountain Region as well as the Midwest and the northernmost states of the Northeast (Figure 3A).

We then performed a subgroup analysis specifically evaluating deceased donor transplants. There were

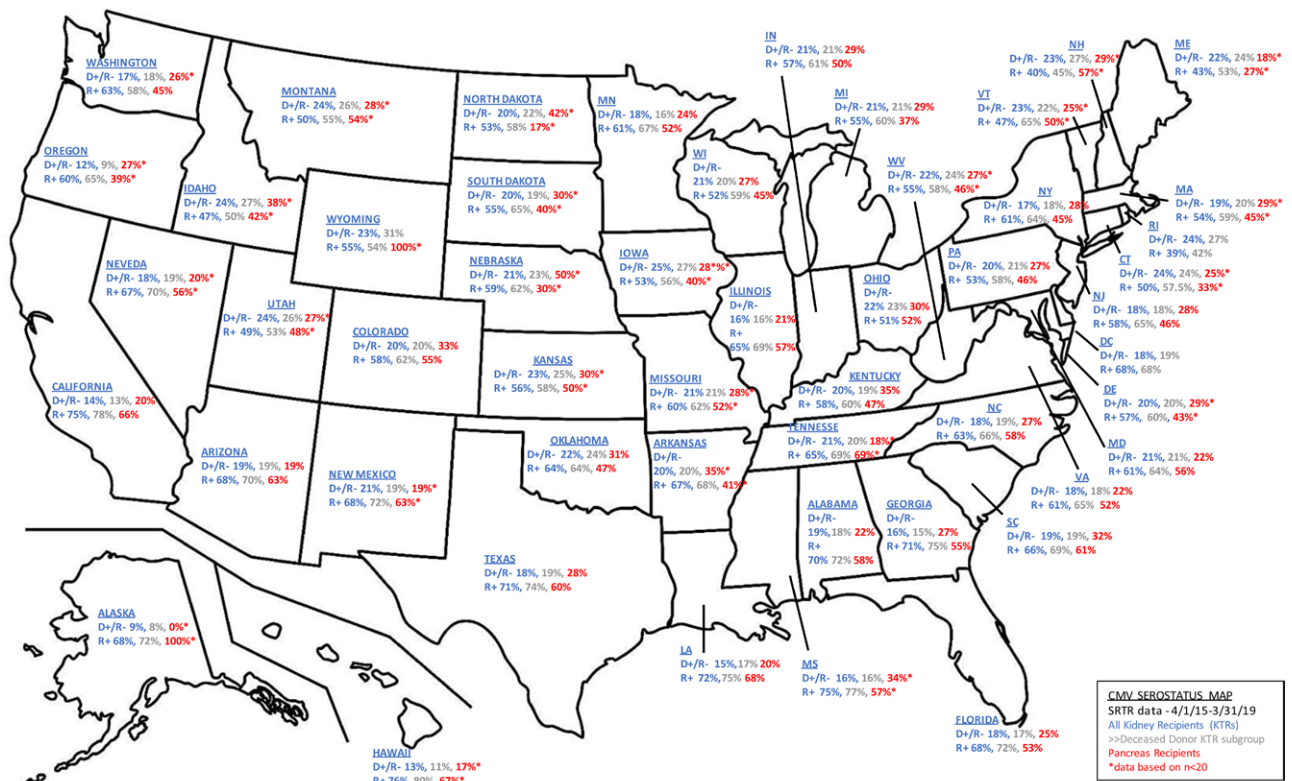


FIGURE 1. Cytomegalovirus composite serostatus map. CMV, cytomegalovirus; D+, CMV seropositive donor; KTR, kidney transplant recipient; SRTR, Scientific Registry of Transplant Recipients; R+, CMV seropositive recipient; R-, CMV seronegative recipient.

55 249 KTRs of deceased donor allografts with evaluable serologies. Average recipient seropositivity in these KTRs was 67.3% (n = 37 156) but ranged from 44% to 80% across the US (Figure 1). Seropositivity followed a

similar pattern of geographic variation to KTRs overall. (Figure 2B). Average rate of D+/R- in KTRs of deceased donors across the US was 18.3% (n = 10 123) but ranged from 8% to 31%. When looking only at deceased donor

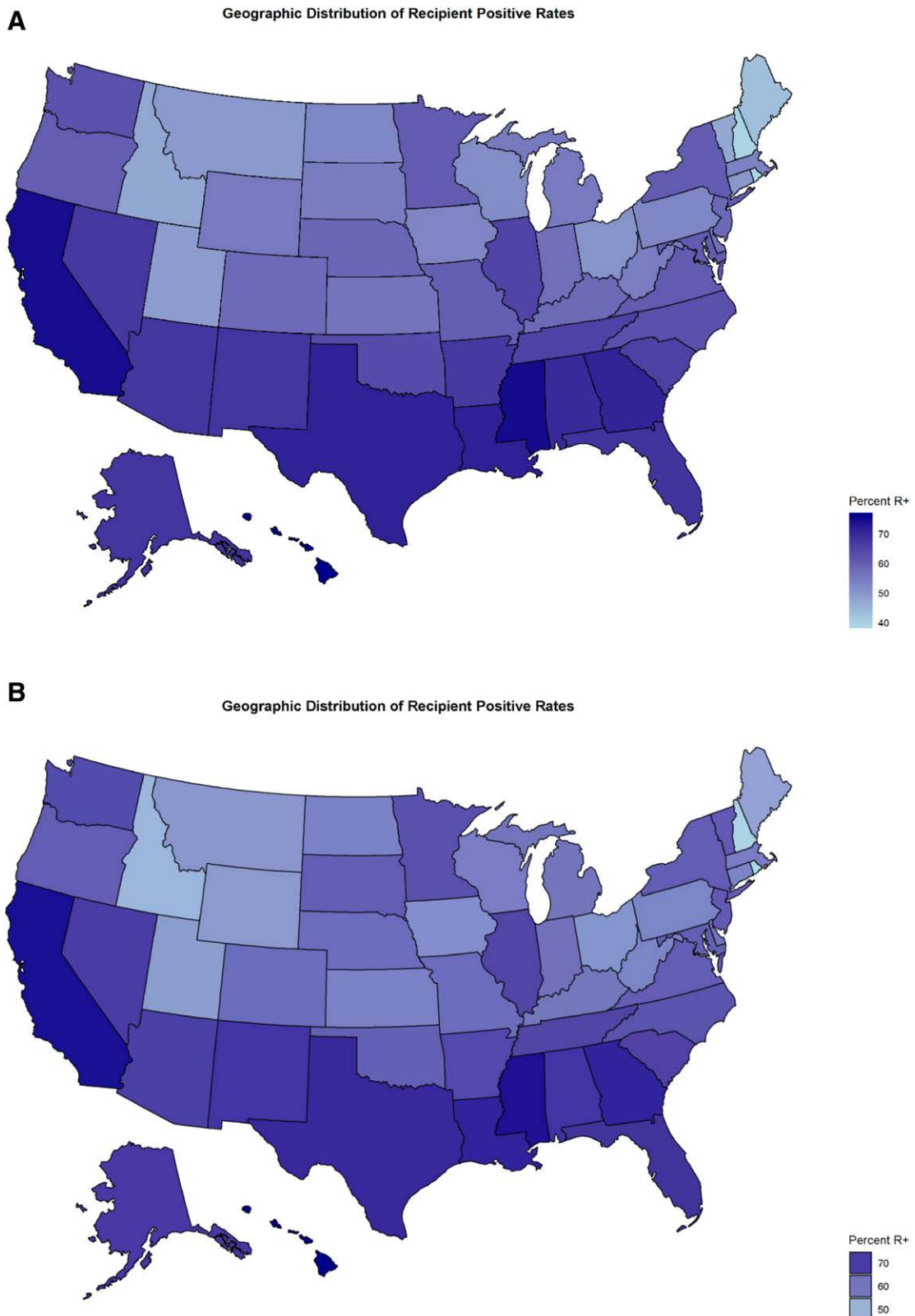


FIGURE 2. Geographic distribution of CMV recipient positive kidneys. A, Geographic distribution of R+ kidneys. B, Geographic distribution of R+ deceased donor kidneys. R+, cytomegalovirus seropositive recipient.

transplant, D+/R- variance was again similar to KTRs overall (Figure 3B).

There were 4023 PTR with evaluable serologies within the study period. The average seropositivity rate was lower

in PTRs than in KTRs at 49.5% (Figure 4). Rates of PTR seropositivity had a broader range than KTR from 0% to 100%, although the interpretation of this was complicated by low numbers of pancreas transplants in some states. Of those

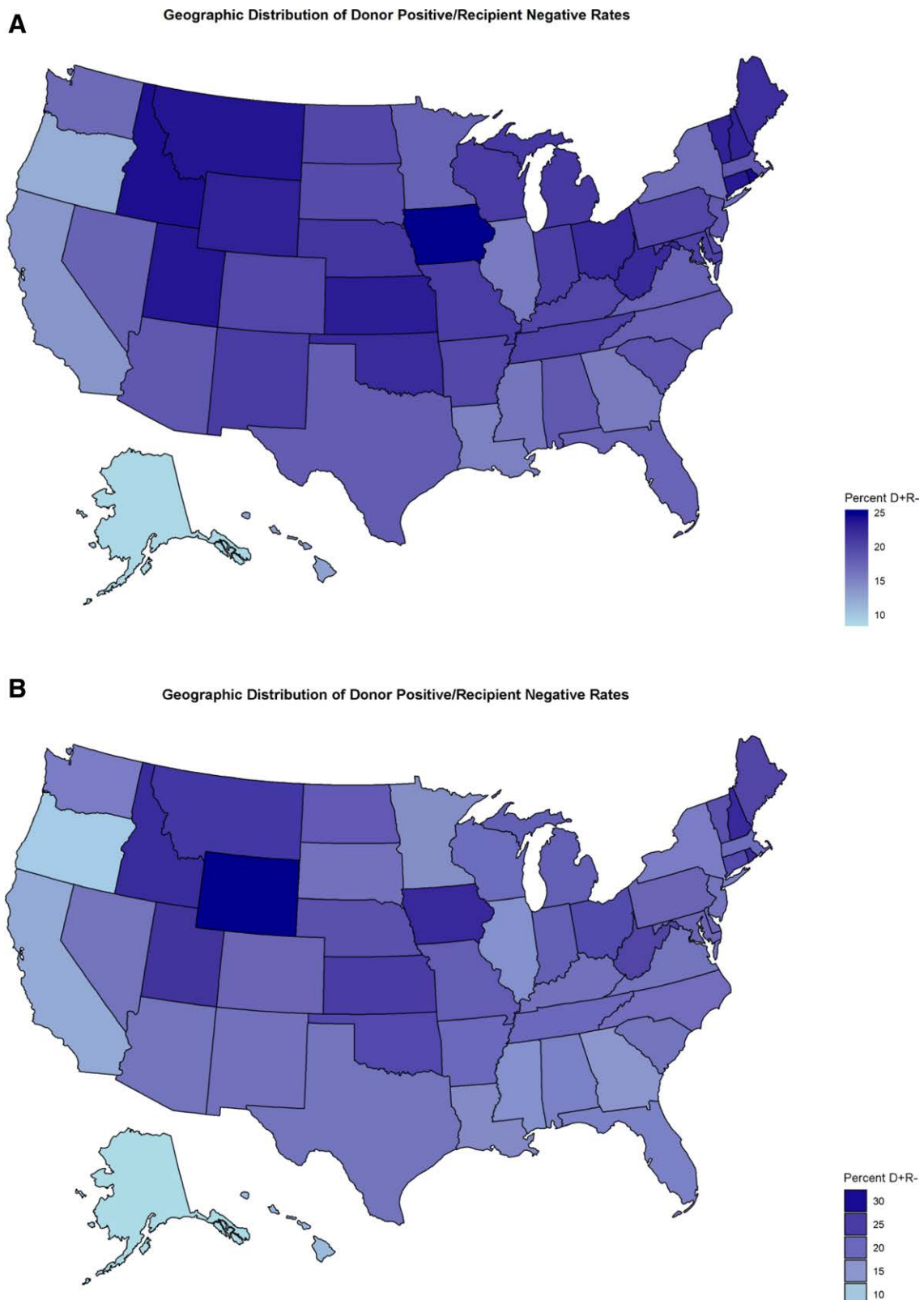


FIGURE 3. Geographic distribution of CMV donor positive/recipient negative kidneys. A, Geographic distribution of D+/R- kidneys. B, Geographic distribution of D+/R- deceased donor kidneys. D+, cytomegalovirus seropositive donor; R-, cytomegalovirus seronegative recipient.

Geographic Distribution of Recipient Positive Rates

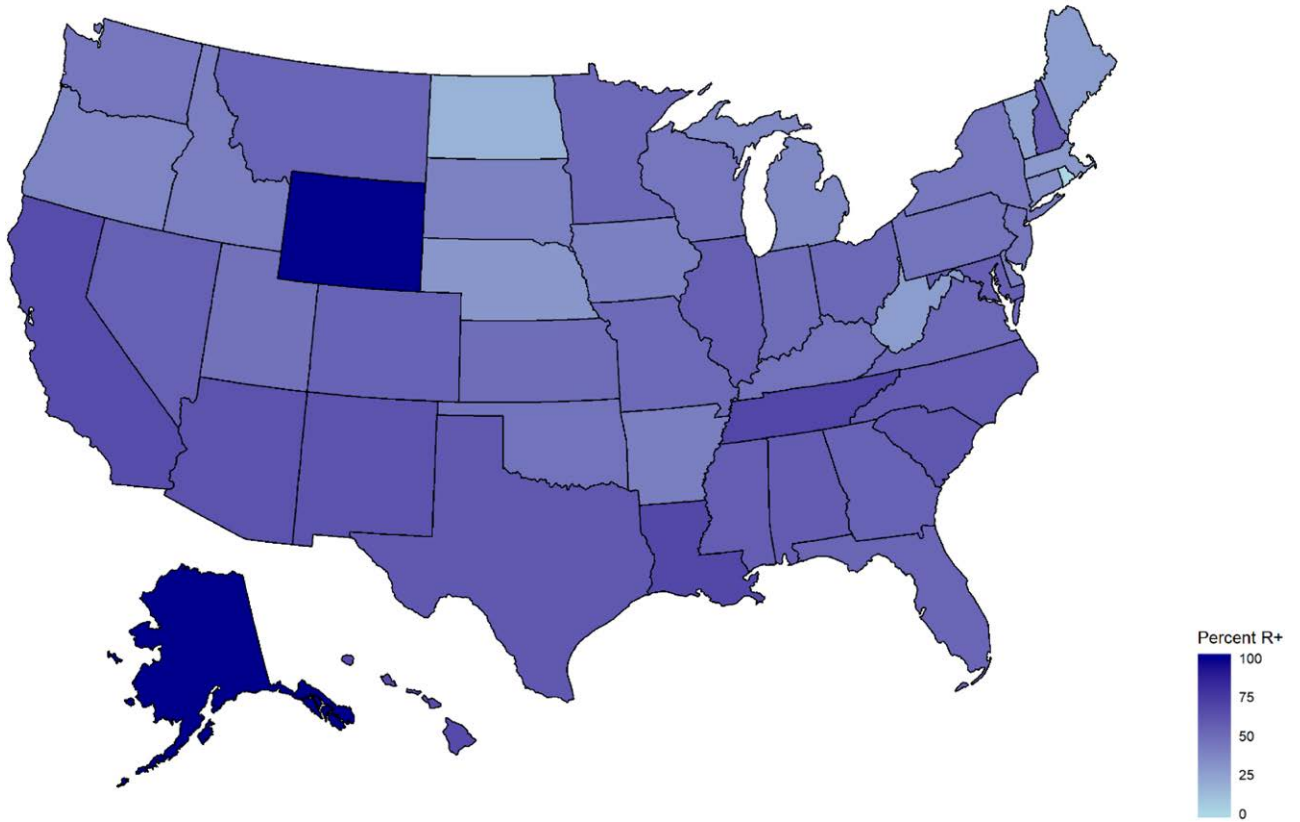


FIGURE 4. Geographic distribution of R+ pancreas. R+, cytomegalovirus seropositive recipient.

Geographic Distribution of Donor Positive/Recipient Negative Rates

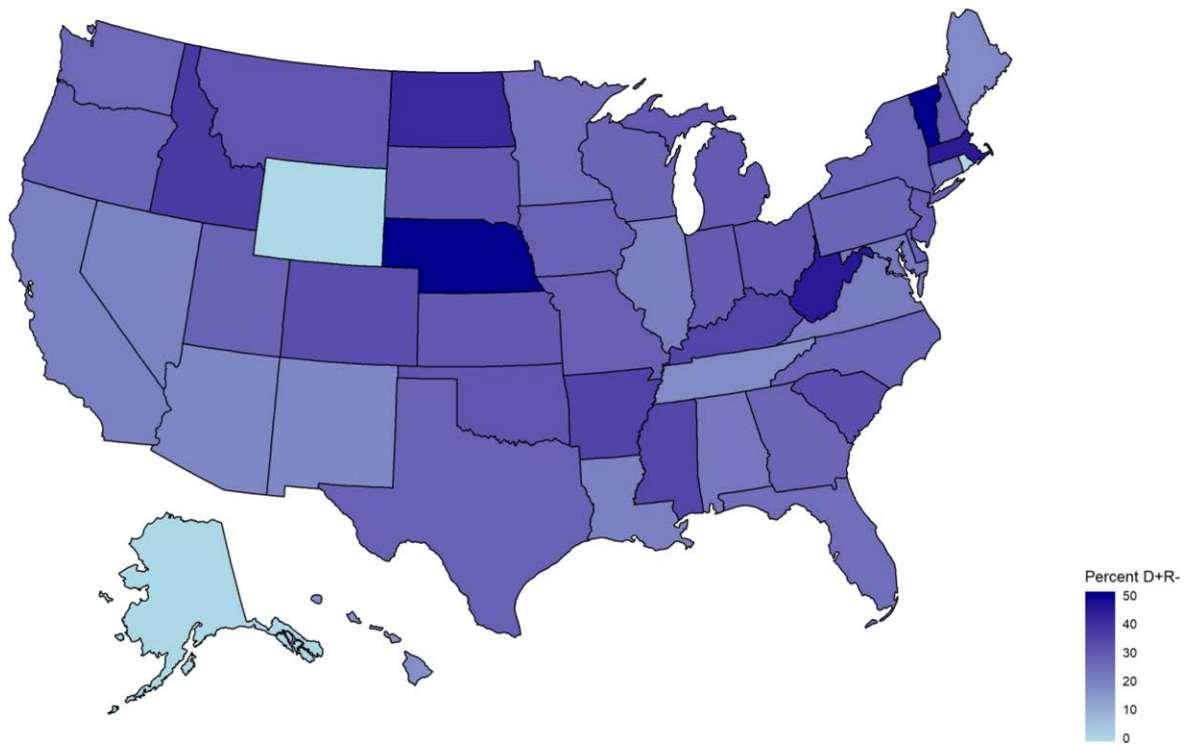


FIGURE 5. Geographic distribution of D+/R- pancreas. D+, cytomegalovirus seropositive donor; R-, cytomegalovirus seronegative recipient.

with evaluable serologies, 1009 were D+/R- with an average rate of 26.9% across the US (Figure 5). This also had a broad range from 0% to 50%.

To reduce variability in results due to low volume, the pancreas allograft analysis was then limited to only states that completed over 100 pancreas transplants in the study period (deemed “high-volume states” for this study). In this analysis, average rates of seropositivity were more comparable to KTR, with a narrower range (54.9%, range 45–68%, $n = 1605$, Table 1). The rate of D+/R- was also comparable to KTR, although notably higher at 24.7%, (range 19%–30%, $n = 713$, Table 1). Trends found in geographic variability in KTR persisted in PTR but overall with lower rates of R+ and higher rates of D+/R-. When looking only at the high-volume pancreas transplant states, the highest rates of D+/R- were in the Midwest and the Northeast with lower rates in the southern states, but the trend was not as consistent as in KTRs (Table 1 and Figure 6).

DISCUSSION

Our review of the national registry of solid organ transplant recipients and UNOS data suggest regional variance in the incidence of high-risk CMV serologic mismatch with increased representation in the Midwest and Northeast. As expected, this varies inversely with rates of recipient seropositivity, which was more prevalent in the southern states. When evaluating only deceased donors, to remove any interference related to living donors, these trends persisted. However, we noted variation between allograft subtypes, with a higher incidence of seronegativity in pancreas recipients, likely attributable to primary disease via either lack of exposure or lack of response due to functional immunosuppression in the setting of diabetes. Regional variation should be considered when evaluating any nation-wide application of allocation policy that employs CMV matching practices. In addition, the

variance should be taken into account when designing center-specific prophylaxis strategies and evaluating studies describing CMV prophylaxis and treatment in primary literature.

Primary CMV infection, as opposed to reactivation from latency, has been associated with more severe disease manifestations including high viral load, end-organ manifestations, recurrence, persistence, and antiviral resistance.^{3,9,10} Therefore, strategies to prevent CMV infection focus on patients with this high-risk CMV mismatch. Rather than a sole focus on preventing CMV after transplant, attention has turned to preventing CMV at allocation. Theoretically, a reduction in the incidence of CMV mismatch would decrease the risk of primary CMV and the negative associated sequelae. Indeed, there is evidence to suggest that serostatus may factor in allograft selection, but this had not been a formalized process.¹¹ This strategy has been successfully used in the Pacific Northwest within a single OPO to significantly reduce the incidence of D+/R- from the national average of 18.5%–2.9% ($P < 0.01$).⁷ Data regarding the incidence of CMV infection were not reported in this study; however, this strategy was associated with reduced rates of CMV infection in an unadjusted analysis presented in abstract form.¹² Although these results are encouraging and have resulted in significant attention, the ramifications of CMV matching nationwide are unclear. Indeed, the study authors caution that to avoid long wait times, matching must occur not only for CMV seronegative donors but also CMV seropositive donors. Indeed, rates of seropositive recipients of seropositive donors (D+/R+) increased significantly in tandem from 49.0% to 65.6% ($P < 0.1$) as a result of this strategy.⁷ This highlights several potential issues with national expansion. D+/R+ is also a risk factor for CMV infection. This is thought to be due to strain variation resulting in incomplete immune responses to donor strain reactivation and resultant superinfection.^{3,13} The use of potent induction at transplant is a risk factor for CMV infection in these patients.¹⁴ With increasing use of T-cell depletion strategies and maintenance regimens including the potent T-cell-specific agent tacrolimus,¹⁵ seropositive patients may be unable to mount CMV specific T-cell responses, making them functionally R-, and therein losing the proposed benefit of CMV matching.¹³ In addition, receiving a seropositive allograft has been associated with reduced graft survival regardless of recipient serostatus.¹⁶ This could be due to donor quality or may be attributed to CMV-related inflammation or alloreactivity and subsequent negative graft effects.^{4,17} Therefore, matching could potentially place seropositive patients at a disadvantage. CMV matching benefits seronegative recipients. These patients will get more timely transplant offers. Acknowledging geographic variance, could negatively impact southern states particularly if a national allocation process is implemented that would result in a greater number of allograft ship-outs to the Midwest and Northeast. These factors should be weighed in the discussion of CMV matching at a specific center and nationwide across the US.

Insight into serologic disparities between allograft subtypes may provide further insight to the conversation regarding allocation by CMV sero-matching. Literature suggests prophylaxis strategies should be not only sero-specific but also allograft-specific.^{18,19} Indeed, although extension of valganciclovir prophylaxis reduced late-onset CMV in kidney transplant recipients, extension has not been similarly successful in other allograft subtypes.^{20,21} This likely highlights degree of immunosuppression. In addition, type 1 diabetes mellitus has been associated

TABLE 1.
Serologic distribution of high-volume pancreas transplant states

High-volume states (>100 pancreas transplants during the study period)				
State	N = R+	% R+	N = D+/R-	% D+/R-
AZ	67	62.6	20	18.7
LA	78	68.4	23	20.2
CA	216	66.1	66	20.2
IL	156	56.9	57	20.8
VA	67	51.9	28	21.7
MD	86	56.2	34	22.2
MN	68	51.9	32	24.4
FL	154	53.3	71	24.6
GA	66	55.0	32	26.7
WI	69	45.1	41	26.8
PA	69	46.3	40	26.8
NC	84	58.3	39	27.1
TX	171	59.8	79	27.6
NY	95	44.8	59	27.8
IN	74	50.0	43	29.1
OH	85	51.8	49	29.9
Total	N = 1605	Mean 54.9%	N = 713	Mean 24.7%

D+, cytomegalovirus seropositive donor; R-, cytomegalovirus seronegative recipient.

Geographic Distribution of Donor Positive/Recipient Negative Rates

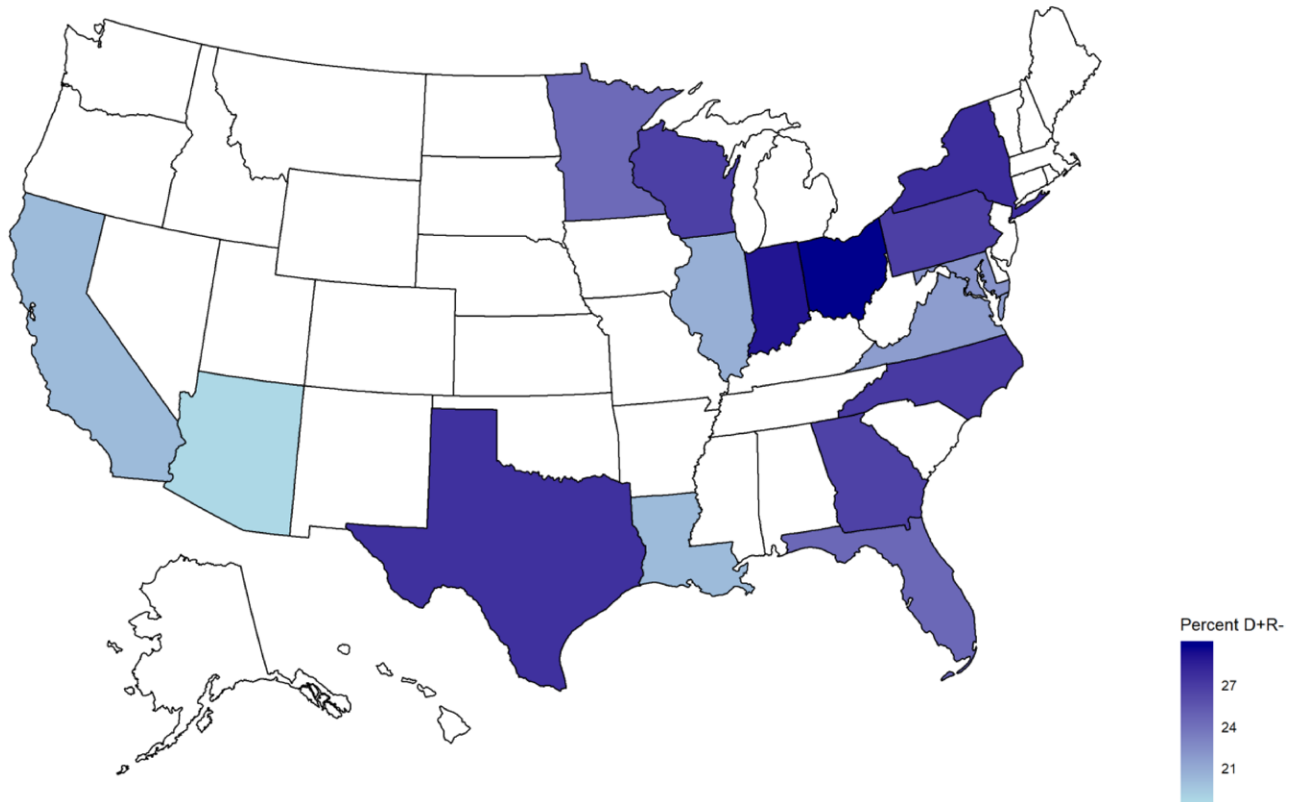


FIGURE 6. Distribution of D+/R- pancreas in high volume states. D+, cytomegalovirus-seropositive donor; R-, cytomegalovirus-seronegative recipient.

with reduced odds of CMV seropositivity.^{22,23} Therefore, when considering CMV matching as a prevention strategy, our data suggest that the initial focus should potentially be on pancreas allografts, where matching could be more crucial given the increased risk of seronegativity in this population.

Our study is not without limitations. Most importantly, our findings describe serology, as CMV infection is not a reportable measure required by UNOS. Serology is a risk factor but does not necessarily result in negative CMV outcomes. The negative sequelae are driven by multiple concomitant factors including serostatus at transplant but also induction and maintenance immunosuppression as well as the prophylaxis strategies employed and the patient substrate. In addition, serology data were evaluated by the state rather than at the level of each individual OPO. However, given the upcoming changes to allocation practices based on geography with a 250-nautical-mile radius rather than donor service area, this makes geographical presentation by US state more timely and useful than by OPO or region.²⁴ Although our study is descriptive in nature, it may provide valuable information for the discussion of nationwide implementation of CMV matching allocation strategies.

In conclusion, rates of CMV serostatus at transplant in both KTR and PTR appear to vary by state and region. PTR had lower rates of R+ and higher rates of D+/R- when compared to KTR but followed similar geographic variation across the US. However, when limiting the analysis to only high-volume pancreas transplant states the range of D+/R- variability was smaller and did not always follow the KTR trends, suggesting the possibility of surgeon serostatus

selectivity in pancreas donor acceptance. These data may be useful in further discussion of national CMV donor matching strategies. Furthermore, attention to the rates of seropositivity and high-risk serostatus in each allograft subtype, state, and region should be considered when selecting center-specific CMV prophylaxis modalities and when interpreting results of clinical CMV research from these areas.

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