BRIEF COMMUNICATION

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Mortality among solid organ waitlist candidates during COVID-19 in the United States

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Funding information
Health Resources and Services Administration, Grant/Award Number: HHSH250201500009C

We examined the effects of COVID-19 on solid organ waiting list mortality in the United States and compared effects across patient demographics (e.g., race, age, and sex) and donation service areas. Three separate piecewise exponential survival models estimated for each solid organ the overall, demographic-specific, and donation service area-specific differences in the hazard of waitlist mortality before and after the national emergency declaration on March 13, 2020. Kidney waiting list mortality was higher after than before the national emergency (adjusted hazard ratio [aHR], 1.37; 95% CI, 1.23–1.52). The hazard of waitlist mortality was not significantly different before and after COVID-19 for liver (aHR, 0.94), pancreas (aHR, 1.01), lung (aHR, 1.00), and heart (aHR, 0.94). Kidney candidates had notable variability in differences across donation service areas (aHRs, New York City, 2.52; New Jersey, 1.84; and Michigan, 1.56). The only demographic group with increased waiting list mortality were Blacks versus Whites (aHR, 1.41; 95% CI, 1.07–1.86) for kidney candidates. The first 10 weeks after the declaration of a national emergency had a heterogeneous effect on waitlist mortality rate, varying by geography and ethnicity. This heterogeneity will complicate comparisons of transplant program performance during COVID-19.

KEYWORDS
health services and outcomes research, heart transplantation/cardiology, kidney transplantation/nephrology, kidney transplantation: living donor, liver transplantation/hepatology, lung transplantation: living donor, patient survival, waitlist management

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic continues to affect healthcare systems worldwide, including solid organ transplant systems. Recent studies have described substantial decreases in rates of transplant during the pandemic.[1] While the incidence of and mortality due to COVID-19 among solid organ transplant candidates and recipients has not yet been described in the United States, the cumulative incidence rate of COVID-19 among solid organ waitlist candidates in the United Kingdom was 3.8% through May 20, 2020, with an all-cause mortality rate of 10.2% among those who developed COVID-19.[2] This was substantially higher than overall population case-fatality rates, which have been estimated at 1%–6%,[3-5] emphasizing the importance of understanding the effect

of COVID-19 on the solid organ candidate population in the United States.

The Scientific Registry of Transplant Recipients (SRTR) reports on waiting list outcomes in our Program-Specific Reports (PSRs). Because COVID-19 may lead to worse outcomes for patients listed at transplant programs in regions with more severe outbreaks, reported waitlist mortality rate ratios for such programs may be worse in PSRs due to COVID-19 rather than differences in clinical care. That is, COVID-19 may confound waitlist mortality rate ratios and corresponding evaluations (e.g., the 5-tier rating system for waitlist mortality used by both insurers and patients). The geographic variability of differences before and after COVID-19 can measure the potential risk of confounding in the waitlist mortality rate ratio. If the relative waitlist mortality rates in parts of the United States are considerably higher after COVID-19 than before, the risk of confounding due to COVID-19 is high, especially if the areas experienced relatively severe outbreaks.

This study investigated early trends in waitlist mortality rates before and after the emergence of COVID-19 among organ transplant candidates in the United States. It aimed to answer three questions of interest to the transplant system:

1. Did the hazard of waitlist mortality differ before and after the COVID-19 national emergency declaration?
2. If so, did the difference in the hazard of waitlist mortality vary geographically across the United States? Donation service areas (DSAs) were the geographic areas because they were granular enough to separate major metropolitan areas. For example, state-level variability would obscure potential differences in California, while DSA-level variability would capture differences across, for example, San Francisco, Los Angeles, and San Diego.
3. Did the difference in the hazard of waitlist mortality vary across population subgroups?

This study was conducted as a part of a broad SRTR analysis of the impact of COVID-19 on solid organ transplantation in the United States (https://www.srtr.org/reports-tools/covid-19-evaluation/). The SRTR COVID-19 evaluation provides monthly updates of waitlist mortality, focusing on geographic and demographic differences, as the pandemic waxes and wanes across the United States.

2 | METHODS

2.1 | Population and data

This study used SRTR data, which includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight of the activities of the OPTN and SRTR contractors.

This analysis used SRTR Standard Analysis File (SAF) candidate datasets from August 2020, which represent all patients in the

United States who are, or have been, registered on the waiting list for a solid organ transplant since October 1, 1987. The SRTR SAFs have been described in great detail previously.[6,7] Because recording at least 95% of patient deaths on the waiting list can take 2 or more months due to a lag in reporting, candidates were included if they were prevalent on the organ transplant waiting list between March 13, 2019, and May 31, 2020. Therefore, this study presents early findings from the first 10 weeks after the declaration of the COVID-19 national emergency. Candidates with no reported listing date or age at listing or who were younger than 18 years at listing were excluded. Candidate follow-up was censored at transplant, recovery without a transplant, or transfer to another center. The analyses were performed separately for kidney, pancreas, liver, lung, and heart candidates. Waiting time and outcomes were included for patients regardless of whether they were listed as active or inactive.

2.2 | Measures

2.2.1 | Outcomes

The primary outcome was waitlist mortality, specifically the cause-specific hazard of waitlist mortality, which does not mathematically depend on the transplant rate.[8] Thus, any differences in the cause-specific hazard of waitlist mortality before and after COVID-19 are not inherently attributable to lower transplant rates after COVID-19.

2.2.2 | Predictors and covariates

The main predictor of interest was the COVID-19 pandemic, as defined by time before or after the declaration of a national emergency in the United States on March 13, 2020. These analyses track temporal trends in mortality before and after COVID-19, because individual-level incidence status and cause of death are not available in the SRTR SAF.

Covariates modeled for all solid organ types were age in years, sex, ethnicity, race, urban or rural residence, miles between candidate and program, blood type, body mass index (BMI), primary diagnosis, insurance type, previous transplants, and waiting time. In addition, these covariates were modeled for these types of transplants:

- Kidney: Calculated panel reactive antibodies (cPRA), dialysis duration, and whether the patient was also listed for pancreas transplant
- Pancreas: Listing for pancreas-only, pancreas-after-kidney, or simultaneous kidney–pancreas transplant
- Liver: End-stage liver disease (MELD) scores and hepatocellular carcinoma (HCC) status
- Heart and lung: Height at listing
- Lung: Lung allocation score (LAS)
- Heart candidates: Ventricular assist device (VAD) status at listing

2.2.3 | Time-varying covariates

Candidate characteristics with time-varying values were updated at the beginning of each month before and after March 13, 2020. For example, the LAS constantly changes as patients become more or less sick. Thus, a patient's LAS value at the beginning of each month was the value used for analyses for that entire month. The last available value was used for follow-up after removal from the waiting list.

2.3 | Statistical analysis

2.3.1 | Modeling framework

Given the interest in the time-varying effect of COVID-19 on waitlist outcomes, piecewise exponential models (PEMs) were used to estimate the rate of waitlist mortality after the COVID-19 declaration on March 13, 2020, versus before. PEMs are proportional hazards models with a constant baseline hazard in a priori defined intervals. The models included two intervals for the baseline hazard: before and after COVID-19. The time scale for these models was calendar time. To ensure sufficient precision, each analysis required a minimum number of events after March 13, 2020, detailed below in each subsection.

2.3.2 | Overall effect of COVID-19

The overall effect of COVID-19 was the difference between the intervals before and after March 13, 2020. For this analysis, the models assumed each covariate had the same effect before and after COVID-19. These models were estimated only when the cohort had more than 10 deaths both before and after COVID-19. A post hoc sensitivity analysis additionally adjusted the models for patient inactive status as a time-varying covariate.

To assess whether early trends in waitlist mortality rates attenuated in later months, a post hoc preliminary analysis using the December 2020 SAF modeled time trends in waitlist mortality hazard by month before and after COVID-19 using a PEM with a random effects for each month and adjusted for covariates.

2.3.3 | Geographic variability in the effect of COVID-19

Generalized linear mixed models (GLMMs) estimated the DSA-level variability in waitlist mortality rates before and after COVID-19. Specifically, the model included two DSA-level random effects: one for before March 13, 2020, and one for after. The empirical Bayes estimates of the individual DSAs estimated difference of each DSA from the national average before and after COVID-19. Therefore, the kidney model included, for example, 58 DSA-specific pre-COVID effects and 58 DSA specific post-COVID effects. The GLMMs allowed a correlation between the random effects. The difference between the pre- and post-COVID effects identified the relative difference in waitlist mortality rates after, compared with before, COVID-19. The GLMMs included an offset equal to the linear predictors from the PEMs for the overall effect of COVID-19, which accounted for candidate risk factors. These models were estimated only when the number of deaths in the post-COVID-19 period was more than twice the number of DSAs.

2.3.4 | Subgroup-specific effects for COVID-19

Separate models estimated the subgroup-specific effects of COVID-19. Specifically, the model included an interaction between each candidate risk factor and the overall effect of COVID-19, allowing the effect of COVID-19 to differ across, for example, candidate age groups. Models were only estimated for each of the covariates listed above when deaths in the post-COVID-19 period were at least 10 plus 2 times the number of variables in the model.

3 | RESULTS

3.1 | Adjusted effects of COVID

The hazard of mortality among kidney transplant candidates was 37% higher in the first 10 weeks after the COVID-19 national emergency than before (adjusted hazard ratio [aHR], 1.37; 95% CI, 1.23–1.52). The hazard of waitlist mortality for liver (aHR, 0.94; 95% CI, 0.78–1.15), pancreas (aHR, 1.01; 95% CI, 0.49–2.07), lung (aHR, 1.00; 95% CI, 0.59–1.70), and heart (aHR, 0.94; 95% CI, 0.57–1.54) candidates were similar before and after COVID-19 (Figure 1). Additionally adjusting for time-varying candidate inactive status did not meaningfully change the hazard ratios (Supplemental File 1).

Preliminary analysis of time trends using the December 2020 SAF showed that the hazard ratios for waitlist mortality among kidney candidates declined from the peak immediately following COVID-19 but remained high. The hazard ratios for other organs did not notably vary from month to month and did not increase after COVID-19 (Figure 2).

3.2 | Geographic variability

The hazard of waitlist mortality among kidney candidates in the New York City DSA was 2.52 times higher after the COVID-19 national emergency declaration than before, even after accounting for the higher hazard of waitlist mortality in the United States (Figure 3). Similarly, waitlist mortality was higher among kidney candidates after than before COVID-19 in New Jersey (aHR, 1.84) and Michigan (aHR, 1.56). Differences across DSAs in waitlist mortality for liver transplant candidates were notably smaller. The largest difference after, compared with before, COVID-19 occurred

Impact of COVID-19 on Mortality Hazard among Organ Waitlist Candidates
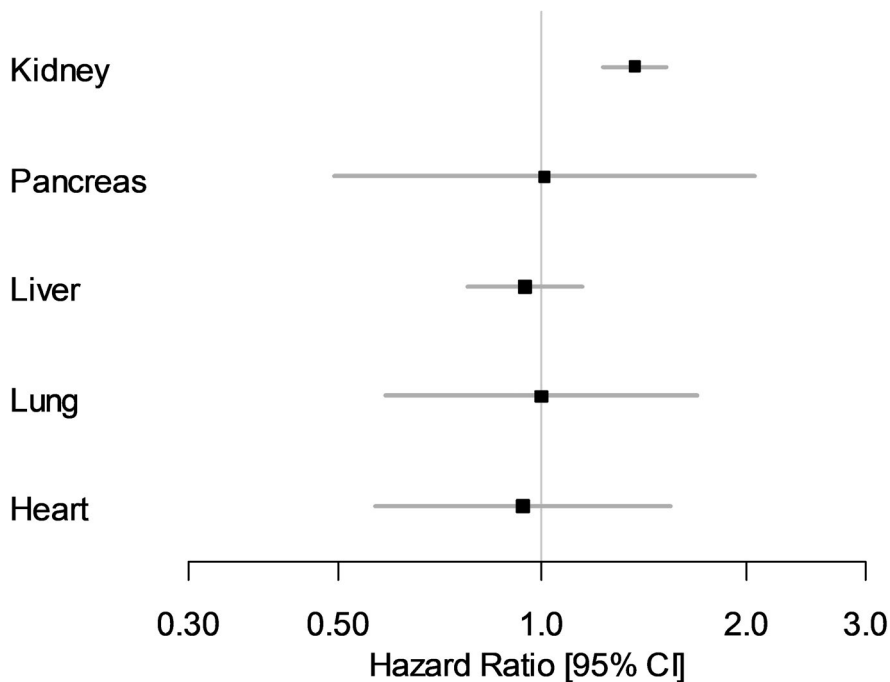
in DSAs serving primarily Milwaukee, Wisconsin (aHR, 1.11) and Hartford, Connecticut (aHR, 1.10). Models for lung, heart, and pancreas candidates were not estimated due to an insufficient number of deaths after March 13, 2020 (Supplemental File 2).

3.3 | Demographic variability

Only kidney and liver transplants had a sufficient number of deaths on the waiting list after COVID-19 to estimate differences in waitlist mortality across candidate subgroups. African American kidney waitlist candidates were the only subgroup with early signs of higher waitlist mortality rates after than before COVID-19 (aHR, 1.41; 95% CI, 1.07–1.86, compared with White candidates, Table 1). Liver candidates had dramatically higher waitlist mortality rates at higher MELD scores prior to COVID; this trend remained but was notably attenuated after the emergence of COVID-19 (Table 1). However, the confidence intervals for many subgroups, especially among liver transplant candidates, were notably wide, indicating relatively imprecise estimates.

4 | DISCUSSION

Waitlist mortality rates were notably higher at the outset of the COVID-19 national emergency among kidney waitlist candidates but not other solid organ transplant candidates. The differences in

kidney waitlist mortality rates varied geographically, with dramatically higher rates in the New York City DSA. The relative waitlist mortality rate for African Americans compared with White kidney candidates was higher after COVID-19 than before. The differences in waitlist mortality rates across categories of MELD attenuated in the months after the pandemic began, though the COVID-19 pandemic coincided with the beginning of the liver acuity circle allocation policy—an alternate possible explanation for changed in waitlist mortality rates at higher MELD scores.

Waitlist mortality rates have historically been lower for kidney candidates than for candidates for other solid organs.[9] However, the largest number of candidates are listed for kidney transplant, and kidney candidates have the longest waiting times.[9] Thus, a higher hazard of waitlist mortality among kidney candidates can represent a substantial number of additional deaths, especially if the higher waitlist mortality is sustained over a long period.

Among the many possible causes of the increased mortality rates among kidney waitlist candidates, a few warrant additional discussion. One hypothesis is that the mortality rate increased due to delayed transplants. We estimated the differences in the cause-specific hazard of waitlist mortality before and after COVID-19. The cause-specific hazard does not mathematically or inherently depend on changes in the transplant rate, although residual confounding could still cause a relationship between waitlist mortality and transplant rates. A second hypothesis is that the mortality rate increased due to deaths from COVID-19 directly or as the result of delayed medical care due to fear of infection. A limitation of the SRTR database
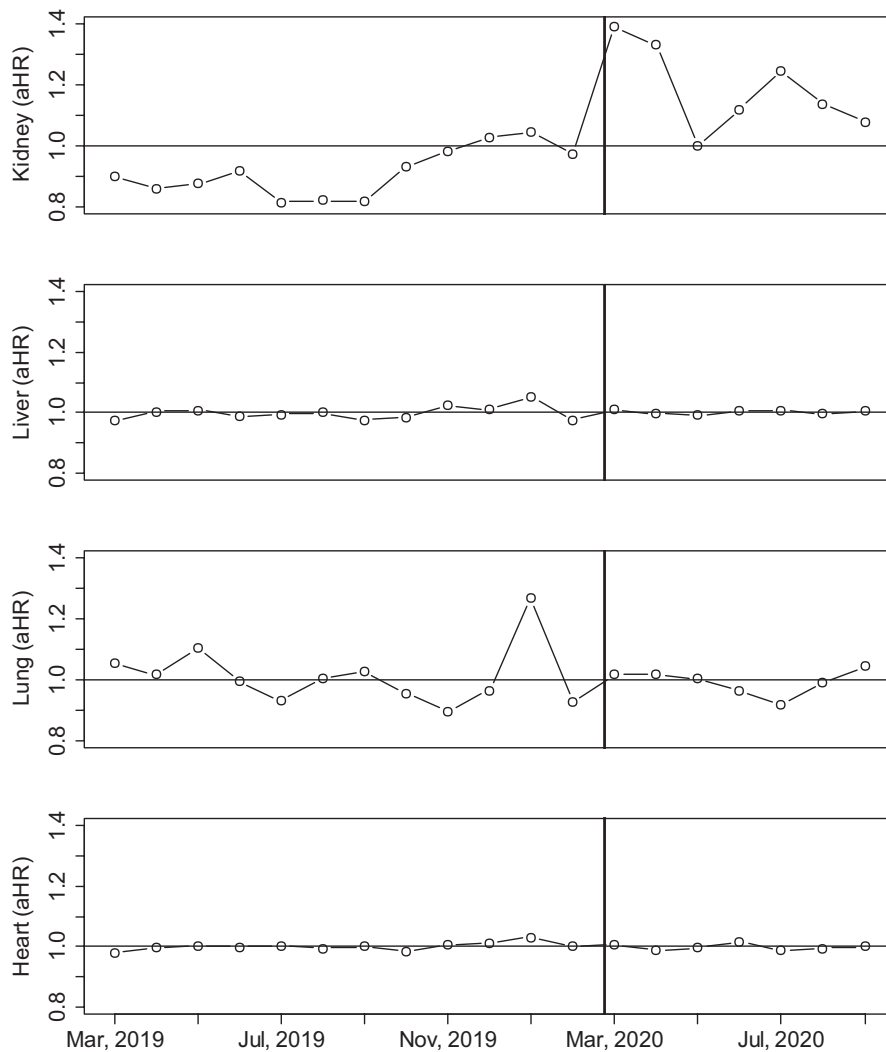
FIGURE 2 Time trends in waitlist mortality hazard among organ waitlist candidates
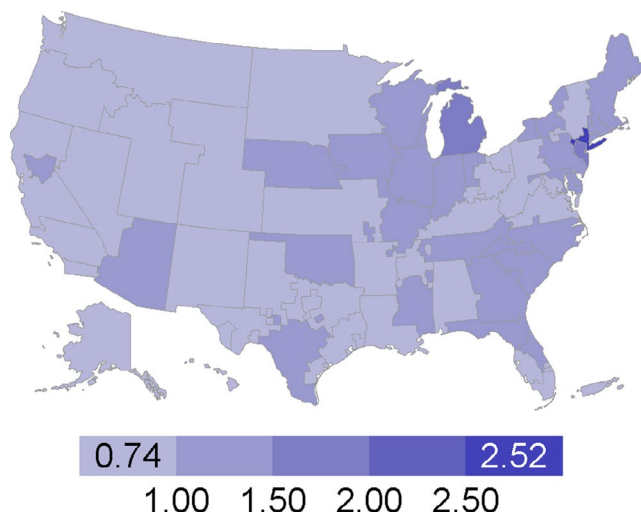

FIGURE 3 Geographic variation in waitlist mortality hazard for kidney transplant across the United States after COVID-19 compared to before [Color figure can be viewed at wileyonlinelibrary.com]

is that individual-level cause of death is significantly missing, preventing firm conclusions about which of these hypotheses is better supported. Inference about the impact of the pandemic on the

United States transplant system will be improved if individual level data about COVID incidence and mortality becomes available for transplant waiting list candidates. However, analysis by the US Renal Data System (USRDS) found that hospitalizations due to COVID-19 showed peaks in April and July—consistent with the peaks in waitlist mortality found in this study, and giving support to the hypothesis of direct increases in mortality due to COVID-19.[10] In the USRDS analysis, in-home peritoneal dialysis was protective against COVID-19 as compared to in-center hemodialysis. The USRDS also found that non-COVID hospitalizations were decreased compared to the same months in 2017–2019, giving support to the hypothesis of increases in mortality due to delayed medical care.[10] Additionally, evidence of increased overall mortality among kidney candidates in the United Kingdom[2] and the substantial increase in waitlist mortality in New York City, New Jersey, and Michigan—early COVID-19 hotspots in the United States—suggests that COVID-19 increased the waitlist mortality rate of kidney candidates, although, the relative contribution of the specific mechanisms (i.e., COVID-19 infection or delayed care) remains unknown.

Understanding the reasons for higher waitlist mortality among kidney candidates than candidates for other solid organs will require continued study. Analysis of the United Kingdom registry found that risk of developing COVID-19 was higher for kidney *candidates*

TABLE 1 Waitlist mortality changes by significant subgroups before COVID-19 to after

	Hazard ratio: Pre-Covid[a]	Hazard ratio: Post-COVID[b]	Hazard ratio: Change from pre to post COVID
Kidney candidates: Race			
White (REF)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)
Black	0.63 (0.55 to 0.72)	0.88 (0.69 to 1.12)	1.41 (1.07 to 1.86)
Asian	0.60 (0.48 to 0.74)	0.65 (0.44 to 0.95)	1.09 (0.70 to 1.69)
Other	0.65 (0.43 to 0.995)	1.04 (0.53 to 2.02)	1.58 (0.72 to 3.49)
Liver candidates: MELD score			
MELD less than 15	0.29 (0.23 to 0.38)	0.29 (0.18 to 0.47)	1 (0.58 to 1.69)
MELD 15–24 (REF)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)
MELD 25–34	5.78 (4.65 to 7.18)	3.84 (2.40 to 6.15)	0.67 (0.40 to 1.12)
MELD 35–39	18.09 (12.88 to 25.40)	6.96 (2.88 to 16.78)	0.38 (0.15 to 0.99)
MELD 40 or more	23.64 (16.99 to 32.90)	10.53 (5.00 to 22.18)	0.45 (0.20 to 1.01)

[a]Pre-COVID time period is March 13, 2019 to March 12, 2020.
[b]Post-COVID time period is March 13, 2020 to May 31, 2020.

than for kidney *recipients*.[2] Social distancing may have been more challenging for kidney transplant candidates undergoing in-center dialysis. Future studies of candidate health behaviors or candidate health care system interactions (e.g., dialysis for kidney candidates vs. pretransplant hospitalization for other solid organ candidates) may provide insight on why only kidney transplant candidates had a higher waitlist mortality rate.

Geographic differences in waitlist mortality were notable for kidney candidates, suggesting that PSRs should be modified in the short term to address changes in outcomes driven by the COVID-19 pandemic rather than by clinical care at transplant programs. As a temporary measure, PSRs released in January 2021 censored follow-up of transplant candidates on March 12, 2020, which should remove most of the risk of confounding due to COVID-19 in the early part of the pandemic from the waitlist mortality evaluations.

However, PSRs cannot indefinitely censor follow-up on March 12, 2020. As part of the COVID-19 evaluation, SRTR continues to investigate approaches to handling COVID-19 in PSRs. For example, the waitlist mortality models could adjust for the COVID-19 incidence in the transplant program's region. If this approach removes the DSA-level variability in waitlist mortality for kidney candidates, it is a viable approach for integrating candidate follow-up after the emergence of COVID-19. Alternatively, COVID-19 may become endemic throughout the United States and equally affect transplant programs. At this point, the DSA-level variability in waitlist mortality before and after COVID-19 would likely attenuate and normal follow-up could resume, possibly with the need to carve out data from March 13, 2020 to the date at which geographic variability is reduced.

The trend of higher waitlist mortality among African American kidney candidates after than before COVID-19 should be monitored. COVID-19 has already widened health disparities between African Americans and Whites.[11] Ongoing monitoring will be important in identifying widening health disparities in specific parts of the health system due to COVID-19 (e.g., waitlist mortality of kidney candidates). Differences in mortality by MELD scores deserve more

investigation, especially with respect to the nearly concurrent implementation of acuity circles. A limitation of this study was that there were currently too few mortality events to model subgroup differences for pancreas, lung and heart candidates. SRTR evaluation will continue to analyze possible subgroup differences during the course of the COVID-19 pandemic.

Preliminary time trends show that waitlist mortality among kidney candidates has remained high, and the SRTR continues to analyze whether the geographic variability in waitlist mortality remains high. Future analyses should continue to monitor waitlist mortality rates in solid organ transplant candidates and look for approaches to reduce geographic variation. This is critical for the return of the PSRs to normal reporting cohorts. While a limitation of the SRTR data is the lack of consistent cause-of-death data for transplant candidates and recipients, estimating geographic correlations of COVID-19 incidence with changes in waitlist mortality is being investigated as SRTR continues analyzing the impact of COVID-19.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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