Comparative Analysis of SARS-CoV-2 Reproduction Rates in the Dialysis and General Populations

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Chronic hemodialysis is a life-sustaining therapy, delivered mostly thrice weekly in dialysis clinics. For patients on dialysis who appear to have a heightened likelihood of severe infection or death from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), travel to these facilities and proximity to fellow patients and health care providers during hemodialysis may pose an increased risk for SARS-CoV-2 infection. To prevent contagion, dialysis providers have implemented several interventions. Our goal was to better understand the dynamics of SARS-CoV-2 spread among patients on hemodialysis compared with the general population in the United States.

We used aggregated daily counts of confirmed coronavirus disease 2019 (COVID-19) cases for the general population in the United States[1] and from Fresenius Medical Care North America, a large dialysis provider in the country, from March 1 to July 29, 2020. Following screenings in dialysis units, patients showing any relevant signs and symptoms or who had exposure to an infected person underwent nasopharyngeal or oropharyngeal swabs for RT-PCR testing for SARS-CoV-2. All patients included in the study were receiving in-center hemodialysis; patient characteristics are shown in Table 1. The time-varying reproduction number R_t, which represents the expected number of secondary cases arising from each new infectious individual at a particular time, was calculated using the method of Thompson *et al.*[2] R_t is estimated from daily cases and an uncertain serial interval with a mean of 4.7 days (SD of 2.9 days) and a 14-day moving average.

We fit cubic splines to the estimated R_t values and the logarithm ratio of general and dialysis populations using penalized inverse variance–weighted least squares with the smoothing parameter selected by the generalized maximum likelihood method.[3] We used the SSR function in the ASSIST R package[4] (R Foundation for Statistical Computing, Vienna, Austria). We tested the null hypothesis that the R_t of the general population and the R_t of the dialysis population are equal for the observation period; this is equivalent to testing that the logarithm ratio equals to zero. We constructed an F statistic and applied the bootstrap procedure to compute the P value.[5] Institutional review board review was not required because we used aggregated data without identifiable personal health information, per Common Rule 45 CFR §102(e).

We found that the SARS-CoV-2 R_t for the dialysis population and the R_t for the general population follow a similar trend; both of them reach the $R_t=1$ threshold within a few days of each other (Figure 1A). Similar trends are also seen in three of the largest states, California (Figure 1D), Florida (Figure 1E), and Texas (Figure 1F). Figure 1B shows the log ratio of the general population R_t and the dialysis population R_t over time. A value above zero corresponds to days when the general population R_t is larger. Over the entire observation period, the R_t for the general population and the R_t for the dialysis population are significantly different on the basis of an F test ($P<0.001$). The general population R_t was mostly larger than the dialysis population R_t, except between April 5 and April 24, 2020. Figure 1C shows the percentage change of the daily growth rate on the logarithmic scale; this metric declined below the 1% mark sooner in the dialysis population. By the end of July, the dialysis population's daily growth rates were below or at the 1% threshold, whereas the general population's daily growth rates were still fluctuating above the 1% mark. Although the trends in Figure 1 are similar for R_t and daily growth rates for both populations, for most days, R_t for the dialysis population is lower (Figure 1, Table 2). Table 2 shows that on July 29, the end of the observation period, the R_t

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Table 1. Demographics of patients on hemodialysis with confirmed COVID-19

Variable	Patient Characteristics			*P* Value[a]
	COVID-19–Positive Patients	COVID-19–Negative Patients	All Patients (%)	
Population, *n* (%)	10,558 (100)	201,364 (100)	211,922 (100)	
Age, yr, *n* (%)				
<18	3 (0)	52 (0)	55 (0)	>0.99
18–44	1121 (10.6)	21,139 (10.5)	22,260 (10.5)	0.71
45–54	1687 (16)	29,273 (14.5)	30,960 (14.6)	<0.001
55–64	2728 (25.8)	48,621 (24.1)	51,349 (24.2)	<0.001
65–74	2852 (27)	55,132 (27.4)	57,984 (27.4)	0.42
75+	2167 (20.5)	47,147 (23.4)	49,314 (23.3)	<0.001
Age, yr (SD)	62.6 (14)	63.5 (14.3)	63.5 (14.2)	<0.001
Dialysis vintage, mo (SD)	47.3 (49.8)	45.4 (50)	45.5 (50)	<0.001
Men, *n* (%)	5822 (55.1)	116,165 (57.7)	121,987 (57.6)	<0.001
Race, *n* (%)				
White	3981 (37.7)	81,995 (40.7)	85,976 (40.6)	<0.001
Black	3126 (29.6)	50,847 (25.3)	53,973 (25.5)	<0.001
Unknown	3155 (29.9)	60,808 (30.2)	63,963 (30.2)	0.50
Other	296 (2.8)	7714 (3.8)	8010 (3.8)	<0.001
Ethnicity, *n* (%)				
Non-Hispanic	5537 (52.4)	113,217 (56.2)	118,754 (56)	<0.001
Hispanic	1675 (15.9)	21,689 (10.8)	23,364 (11)	<0.001
Unknown	3346 (31.7)	66,458 (33)	69,804 (32.9)	0.005
Comorbid conditions, *n* (%)				
Diabetes	4891 (46.3)	82,739 (41.1)	87,630 (41.4)	<0.001
IHD	2101 (19.9)	41,898 (20.8)	43,999 (20.8)	0.03
PAD/PVD	967 (9.2)	17,918 (8.9)	18,885 (8.9)	0.37
CHF	2435 (23.1)	44,968 (22.3)	47,403 (22.4)	0.08
CVD	802 (7.6)	12,492 (6.2)	13,294 (6.3)	<0.001
COPD	973 (9.2)	20,185 (10)	21,158 (10)	0.007
Hypertension	7534 (71.4)	141,367 (70.2)	148,901 (70.3)	0.01

The patients received in-center hemodialysis in US Fresenius Medical Care North America dialysis facilities up to July 29, 2020. IHD, ischemic heart disease; PAD, peripheral arterial disease; PVD, peripheral vascular disease; CHF, congestive heart failure; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease.

[a]For continuous variables, *P* values result from the two-sided *t* test H_0: mean values for COVID-19–negative patients are equal to mean values for COVID-19–positive patients in the full population. For categorical variables, *P* values result from the chi-squared test H_0: proportion in COVID-19–negative patients is equal to the proportion in COVID-19–positive patients.

for the dialysis population was better (lower) for the United States in general and in some states (*e.g.*, Texas and California) and worse (higher) for other states (*e.g.*, Arizona and North Carolina). More than 60% of all COVID-19 cases among the dialysis population occur in the states shown in Table 2.

The R_t and daily growth rates indicate less SARS-CoV-2 spread among patients on chronic hemodialysis. We hypothesize that this finding is related to patients on hemodialysis having a more sedentary lifestyle and to such prevention measures as system-wide mandatory entrance screening for patients and staff, universal masking, testing of patients and staff with suspected SARS-CoV-2 infection, and dialysis shifts and clinics dedicated to patients with suspected or diagnosed COVID-19.[6] However, because patients on hemodialysis are part of the overall general population, the curves tend to follow similar trends of R_t and daily case growth factors.

The strength of our analysis is the large number of patients included. One potential limitation is the use of a backward estimator, in which the R_t computation is only on the basis of current and previous data points and does not account for future changes in the calculated R_t.[2] The consistency of our results for most states suggests that lifestyle of patients undergoing hemodialysis and interventions to prevent SARS-CoV-2 spread in this patient population were effective in reducing risk, as indicated by a SARS-CoV-2 reproduction number that was significantly lower than, but mirrored the background contagion of, the general population.

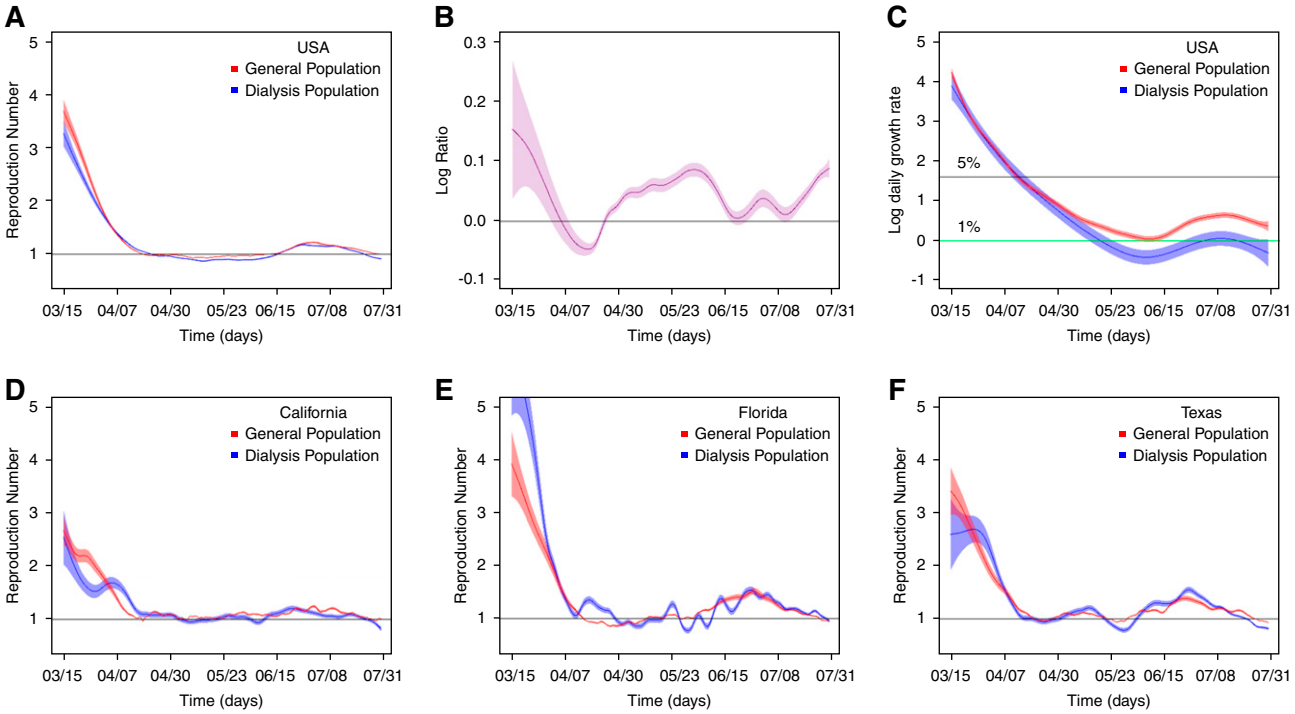

Figure 1. Comparison of key metrics describing the dynamics of COVID-19 spread. Reproduction and daily growth rates were significantly lower in the hemodialysis population but mirrored the background contagion of the general population. (A) Time-varying reproduction rate, R_t, for the United States general (red) and dialysis populations (blue). The general population R_t is below one between April 18th and June 10th, 2020, and at the threshold on June 29th, 2020. The dialysis population R_t is below one between April 22nd and June 15th, 2020, and from July 22nd, 2020 onward. (B) Logarithm ratio of general and dialysis population reproduction numbers. A value above the zero line indicates that the general population R_t is larger. (C) Daily case growth rates for the general and dialysis populations; at the 5% threshold, the daily case counts for both dialysis and general populations reach the first initial peaks. Prior to reaching the first peak, the daily growth rates for both populations were essentially the same. After reaching the initial peak (5% mark), the growth rates for the two populations started to diverge while maintaining similar trends. The dialysis population growth rates continued to decrease to be below the 1% threshold, whereas the general population decreased slowly and stayed above the 1% mark, which may be necessarily to mitigate and/or control the spread in the population. Time-varying reproduction rates for three of the largest states in the United States: (D) California, (E) Florida, and (F) Texas. These show similar trends as in the United States–wide trend but with substantial fluctuations at or near the R_t close to one mark. The shaded areas in (A–F) correspond to 95% confidence intervals.

Table 2. National and state-level R_t (SD) estimates on July 29, 2020

Geography	Dialysis Population	General Population	*P* Value[a]
Nationwide	0.9136 (0.0077)	0.9944 (0.0005)	<0.001
Pennsylvania	0.7400 (0.0648)	1.0501 (0.0030)	<0.001
California	0.8187 (0.0266)	1.0104 (0.0015)	<0.001
Texas	0.8221 (0.0175)	0.9246 (0.0045)	<0.001
Michigan	0.8497 (0.0924)	1.0287 (0.0095)	0.05
Alabama	0.9172 (0.0264)	0.9730 (0.0051)	0.04
New Jersey	0.9534 (0.0749)	1.1115 (0.0157)	0.04
Florida	0.9563 (0.0170)	0.9454 (0.0047)	0.54
Georgia	1.0208 (0.0320)	1.0122 (0.0052)	0.79
Arizona	1.0405 (0.0368)	0.9081 (0.0095)	<0.001
New York	1.0444 (0.0996)	0.9590 (0.0051)	0.39
North Carolina	1.0753 (0.0360)	0.9971 (0.0027)	0.03
Illinois	1.0795 (0.0497)	1.0964 (0.0097)	0.74
Ohio	1.1291 (0.0513)	1.0242 (0.0014)	0.04

The patients received in-center hemodialysis in US Fresenius Medical Care North America dialysis facilities up to July 29, 2020. States are ranked by their dialysis population R_t (SD) estimates.

[a]*P* values refer to the difference of R_t between dialysis and general populations.

DISCLOSURES

A. Cherif and P. Kotanko are employees of the Renal Research Institute, a wholly owned subsidiary of Fresenius Medical Care North America. P. Kotanko holds stock in Fresenius Medical Care; reports research funding from Fresenius Medical Care; reports honoraria from HSTalks and UpToDate; and reports scientific advisor or membership *via* editorial board of *Blood Purification* and editorial board of *Kidney and Blood Pressure Research*. L. Usvyat and J.L. Willetts are employees of Fresenius Medical Care North America. L. Usvyat has ownership interest in Fresenius Medical Care. The remaining author has nothing to disclose.

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P. Kotanko conceptualized the study; A. Cherif was responsible for modeling and simulations; A. Cherif and Y. Wang were responsible for analysis; A. Cherif, P. Kotanko, L. Usvyat, Y. Wang, and J.L. Willetts were responsible for interpretation of results and wrote the manuscript; and A. Cherif had full access to all of the data and codes used in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Dong E, Du H, Gardner L: An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 20: 533–534, 2020
2. Thompson RN, Stockwin JE, van Gaalen RD, Polonsky JA, Kamvar ZN, Demarsh PA, et al.: Improved inference of time-varying reproduction numbers during infectious disease outbreaks. *Epidemics* 29: 100356, 2019
3. Wang Y: *Smoothing Splines: Methods and Applications Monographs on Statistics and Applied Probability*, Boca Raton, FL, CRC Press, 2011
4. Wang Y, Ke C: ASSIST: A suite of R functions implementing spline smoothing techniques, 2013. Available at: http://CRAN.R-project.org/package=assist. Accessed September 1, 2020
5. Wang Y, Guo W, Brown MB: Spline smoothing for bivariate data with applications to association between hormones. *Stat Sin* 10: 377–397, 2000
6. Ikizler TA: COVID-19 and dialysis units: What do we know now and what should we do? *Am J Kidney Dis* 76: 1–3, 2020