Kidney Medicine

COVID-19 and Hospitalization Among Maintenance Dialysis Patients: A Retrospective Cohort Study Using Time-Dependent Modeling

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Rationale & Objective: The coronavirus disease 2019 (COVID-19) pandemic has had a profound impact on hospitalizations in general and on dialysis patients in particular. This study modeled the impact of COVID-19 on hospitalizations of dialysis patients in 2020.

Study Design: Retrospective cohort study.

Setting & Participants: Medicare patients on dialysis in calendar year 2020.

Predictors: COVID-19 status was divided into 4 stages: COVID1 (first 10 days after initial diagnosis), COVID2 (extends until the Post-COVID stage), Post-COVID (after 21 days with no COVID-19 diagnosis), and Late-COVID (begins after a hospitalization with a COVID-19 diagnosis); demographic and clinical characteristics; and dialysis facilities.

Outcome: The sequence of hospitalization events.

Analytical Approach: A proportional rate model with a nonparametric baseline rate function of calendar time on the study population.

Results: A total of 509,609 patients were included in the study, 63,521 were observed to have a SARS-CoV-2 infection, 34,375 became Post-COVID, and 1,900 became Late-COVID. Compared with No-COVID, all 4 stages had significantly greater adjusted risks of hospitalizations with relative rates of 18.50 (95% CI, 18.19-18.81) for COVID1, 2.03 (95% CI, 1.99-2.08) for COVID2, 1.37 (95% CI, 1.35-1.40) for Post-COVID, and 2.00 (95% CI, 1.89-2.11) for Late-COVID.

Limitations: For Medicare Advantage patients, we only had inpatient claim information. The analysis was based on data from the year 2020, and the effects may have changed due to vaccinations, new treatments, and new variants. The COVID-19 effects may be somewhat overestimated due to missing information on patients with few or no symptoms and possible delay in COVID-19 diagnosis.

Conclusions: We discovered a marked time dependence in the effect of COVID-19 on hospitalization of dialysis patients, beginning with an extremely high risk for a relatively short period, with more moderate but continuing elevated risks later, and never returning to the No-COVID level.

Visual Abstract included

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According to the Centers for Disease Control and Prevention, at the end of the year 2020, there were over 20 million reported cases of the coronavirus disease 2019 (COVID-19) with over 361,000 COVID-19 deaths in the United States; the numbers were almost tripled at the end of year 2021, with almost 55 million cases and over 824,000 COVID-19 deaths.[1] Studies have shown that the pandemic has had a profound impact on hospitalization, posthospitalization readmission, and death in the United States and across the world.[2-7] During the onset of the pandemic, although an increasing number of patients were hospitalized with COVID-19, overall hospitalizations fell precipitously in the United States, as hospitals curtailed noncritical medical services, patients deferred medical care to avoid exposure to the coronavirus, and health care centers reallocated resources to COVID-19 cases.[2,7-10] For Medicare dialysis patients, this decrease can be observed in Fig 1, which shows that the rate of hospitalizations from March to June of 2020 diverged from the historical rates of 2018 and 2019. Therefore, it is important to model the baseline hospitalization rate with a flexible function of calendar time.

Dialysis patients are particularly vulnerable to COVID-19 as they are typically older and have multiple comorbidities.[11,12] In addition, patients receiving in-center dialysis are at a greater risk of SARS-CoV-2 infection because they have to gather in and travel to and from dialysis facilities and interact with dialysis staff.[13-18] A year into the pandemic, the Preliminary Medicare COVID-19 Data Snapshot received by April 16, 2021 showed that dialysis patients had a greater rate of COVID-19 cases compared with the general Medicare population (20.61% compared with 6.53%) and a greater rate of COVID-19 hospitalizations (10.95% compared with 1.83%).[19] Salerno et al[16] observed a greater hazard of mortality for COVID-19 for patients on in-center hemodialysis than those on home hemodialysis or peritoneal dialysis. Ng et al[20] found that dialysis patients had a greater rate of in-hospital death among patients hospitalized with COVID-19. Similarly, Jager et al[5] found that COVID-19 resulted in greater risk of mortality in dialysis patients. The general effect of the pandemic indicates the importance of adjusting for COVID-19's effect when evaluating health care providers, especially dialysis facilities.

Due to the severity of the pandemic and the vulnerability of dialysis patients, it is important to study the impact of COVID-19 on this population. We began this investigation in response to a request from the Centers for Medicare and Medicaid Services (CMS) to consider

PLAIN-LANGUAGE SUMMARY

Dialysis patients are particularly vulnerable to coronavirus disease 2019 (COVID-19) as they are typically older and have multiple comorbidities. Thus, it is to be expected that infection would lead to increased morbidity and mortality compared with the general population. This analysis fits proportional rate models to estimate the effect of COVID-19 on hospitalizations and mortality. Although the pandemic initially reduced non-COVID-19 hospitalizations, this study found that dialysis patients with SARS-CoV-2 infections had a much greater rate of hospital admissions than patients without this diagnosis. The relative rate changed markedly over time, and we define stages of COVID1, COVID2, Post-COVID, and Late-COVID with separate estimated relative rates. This study provides a useful model for patients and physicians regarding hospitalization after SARS-CoV-2 infection.

appropriate changes to the Standardized Hospitalization Ratio (SHR) to accommodate the impact of the COVID-19 pandemic.[21] The calculations of SHR are directly related to the evaluations of dialysis facilities, so it is important to accurately adjust for COVID-19 effects. COVID-19 is now an important risk factor in many of the quality metrics that CMS uses to compare facilities. More generally, however, modeling the effects of COVID-19 with respect to hospitalization was an important investigation on its own. With both descriptive and statistical analysis, this study aims to assess the impact of the COVID-19 pandemic on hospitalizations of Medicare dialysis patients.

METHODS

Data Source

The study sample was the US population of Medicare patients on maintenance dialysis and associated with Medicare-certified dialysis facilities. Data were derived from the CMS claims, clinical, and administrative databases. The outcomes of interest were hospitalizations in calendar year 2020. A secondary model on data from April 1, 2020 to October 31, 2020 was fitted, and the model estimates were similar to using the whole year data. Patients were followed until the earliest of death, December 31, 2020, 3 days before transplant, or loss to follow-up. COVID-19 patients were identified from Medicare claims sources using codes U07.1 and B97.29. This work was exempted from formal approval from a research ethics committee and informed consent because the data used were derived from health records and had no identifier or group of identifiers.

Variables

We divided the period after a COVID-19 diagnosis into 4 stages. After the first diagnosis, the patient remained in a

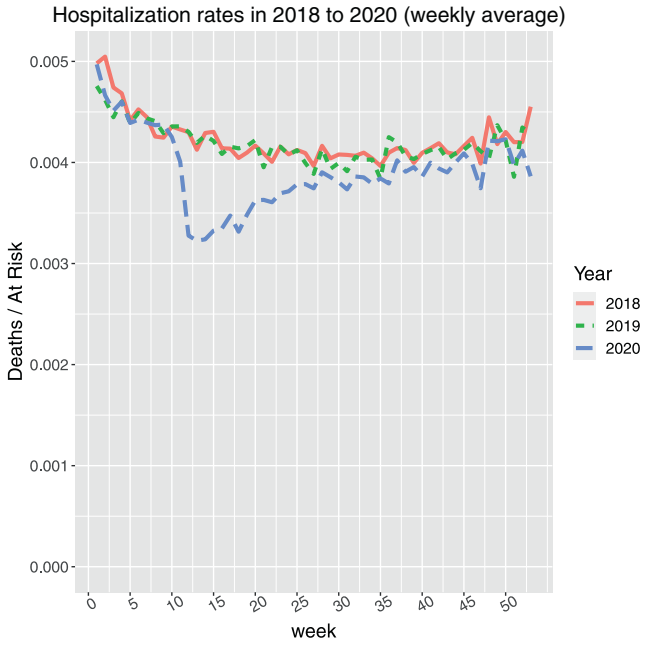

Figure 1. Unadjusted weekly hospitalization rates among Medicare dialysis patients at risk on January 1 of each year from 2018 to 2020. The decrease at the end of 2020 is potentially due to reporting delays.

"COVID" state until a consecutive 21-day period with no further reported COVID-19 diagnoses. After this 21-day period, the patient became "Post-COVID," and remained there until another hospitalization with a COVID-19 diagnosis, after which he/she became "Late-COVID." The "Late-COVID" group might include patients with reinfection, relapse, repositivity, or even no negative test result after the (first) infection, as negative test results were not available.[22] Overall, however, there was only a relatively small number (1,900) of them, so they were not further classified. The "COVID" state was divided into "COVID1," the first 10 days, and "COVID2," the remainder of the "COVID" state. We allowed for separate effects of COVID-19 in each of these 4 stages. A (time-dependent) indicator of whether a patient had a previous COVID-19 diagnosis, "Any-COVID," was used in this model to investigate possible interactions with other covariates. In this way, we assumed that the interactions of the COVID-19 effect with other covariates were the same in all 4 COVID-19 stages. All patients started in the "No-COVID" stage, but it is possible that some "No-COVID" patients had undiagnosed COVID-19 during the observation period as our ascertainment is incomplete. Figure 2 provides a description of these COVID-19 stage variables. In this analysis, a patient could go through the 4 COVID-19 stages only once and stay in the final stage, Post-COVID or Late-COVID, even if he/she might have recovered. The COVID-19 stages at a given time t are partially determined by previous hospitalization events, and such models are based on well-developed statistical methods, eg, Lin et al.[23]

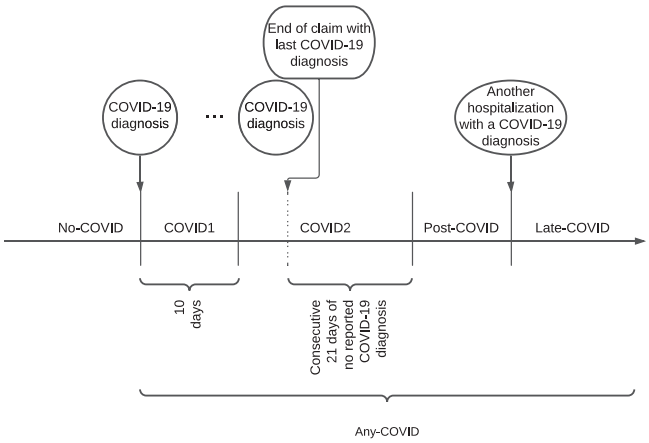

Figure 2. Description of the COVID-19 stages. The line indicates the time course of a dialysis patient who is in a no-COVID state at all times before diagnosis. Once diagnosis occurs, the individual proceeds through the COVID1 stage. No matter whether the patient had other COVID-19 diagnoses after the first one, the patient enters the COVID2 stage in 10 days. If there is a consecutive 21-day period without any COVID-19 diagnosis, the patient enters the post-COVID stage. The end of the last claim before the 21-day period could be either in the COVID1 stage or the COVID2 stage. If another hospitalization with a COVID-19 diagnosis happens during the post-COVID stage, the patient enters the late-COVID stage, where the patient stays until the end of his/her at-risk time. This progress could be censored by withdrawal, transplant, or death.

Along with the 4 COVID-19 stages, we included several patient demographic and clinical characteristics in the model, including age, sex, race, ethnicity, body mass index, time since kidney failure, proportion of time with Medicare Advantage coverage, and nursing home status. For patients with Medicare Advantage coverage, we only had data on inpatient hospital visits and therefore missed some health condition information that we had for non-Medicare Advantage patients. We included information on 13 incident comorbidities and 90 conditions for prevalent comorbidities. The incident comorbidities were those present when the patient first started dialysis, as reported in CMS Form 2728. The prevalent comorbidities were those identified through at least 6 months of Medicare inpatient claims within the previous calendar year, ie, 2019. In the model, we included an indicator for whether the patient had less than 6 months of Medicare coverage in 2019 and, for those patients, recorded no prevalent comorbidities. Some interaction terms and fixed effects for facilities were also included in the model. With some variations, the model in this analysis was used to compute the SHR based on 2017 to 2020 data in the Dialysis Facility Reports website, a CMS website used to communicate quality measures to dialysis facilities. Missingness was rare and was handled by mode imputation or included as a dummy variable.

Statistical Analysis

Descriptive statistics were calculated for all variables by COVID-19 stages, and simple summary statistics of observed hospitalizations were provided as an overall view of the dependence of the outcomes on the various COVID-19 stages. We also plotted the unadjusted hospitalization rate in 2020 compared with 2018 and 2019.

Further analysis was done using a proportional rate model. The primary outcome of interest was the sequence of hospitalization events. The Cox model used in survival analysis can be generalized to analyze recurrent event data of this sort.[23-25]

We assumed a nonparametric baseline rate function reflecting how the event rate varied over the calendar year. This is similar to the baseline hazard in the Cox model. The flexible baseline rate function captures the seasonal or other effects on hospitalizations and is especially useful for the year 2020 as the overall hospitalization rate changed dramatically over time due to the pandemic.

Covariates are modeled as acting multiplicatively on this baseline rate function and the multiplicative effect is termed a relative rate (RR). These are interpreted like hazard ratios in the ordinary Cox model. Facilities were also incorporated using indicator variables, so that each facility was assumed to have a baseline rate function proportional to the overall baseline rate function. This is the so-called "fixed effect" method. Compared with the random effect method, the fixed effect method has smaller bias and greater power in estimating the facility effects that are more extreme and so is suitable in detecting facilities that differ from the national norm.[26] They also are superior to random effects in estimating the effects of covariates, which can be confounded with the random effects.[26]

Model Checking

As in the SHR, we denoted the observed number of hospitalizations of a facility by O and let E denote the expected number of hospitalizations if the facility had outcomes that arose from the national norm. We plotted the weekly averaged O along with the weekly averaged E over the observation period to check whether the model-based E agreed with the pattern of O. In March to May, New York City was greatly impacted by the pandemic. Therefore, we plotted the O and E for New York City separately from the rest of New York State. The O and E plots for New York State and several other states and for COVID-19 patients provided an examination of the model's goodness of fit.

Patients who have frequent contact with the hospital system have a greater probability of COVID-19 diagnosis, and asymptomatic infections of SARS-CoV-2 would typically not be identified in our data set. Further, the true start of COVID-19 would typically be earlier than the reported date. These would lead to an overestimation of the COVID-19 impact on hospitalizations. To address a potential source of bias and also as a sensitivity analysis, we fitted

another model in which we modified the observed start of COVID-19 as follows: a first diagnosis at or within 7 days of hospitalization was taken to have occurred 7 days before the hospitalization; and a first diagnosis in the death report was taken to have occurred 14 days before.

Mortality

Many patients died during the observation period. Using a model similar to the hospitalization model, we also evaluated the effect of COVID-19 on mortality.

RESULTS

Descriptive Analysis

A total of 509,609 patients were included in the study, as described in the flow chart in Fig 3. Table 1 summarizes the baseline demographic and clinical characteristics of patients who never had a reported COVID-19 diagnosis (Never-COVID) compared with those who reached one of the 4 COVID-19 stages during 2020 (the COVID1 group in Table 1). Compared with Never-COVID, individuals of Hispanic ethnicity were overrepresented in the patients who had a reported COVID-19 diagnosis (22% vs 17%) as were those whose race category was Black (36% vs 33%). Patients with diabetes as the primary cause of kidney failure were overrepresented among the patients who had a reported COVID-19 diagnosis (53% vs 46%) as were those with diabetes as a prevalent comorbidity with complications (13% vs 9%) and without complications (38% vs 29%). Dementia was more commonly diagnosed in the patients who had a COVID-19 diagnosis (5% vs 3%). Comorbidities and other characteristics are summarized in Table S1. Summary statistics for the length of each COVID-19 stage are provided in Table 2.

Hospitalization outcomes by COVID-19 stages are summarized in Table 3. The 4 stages of COVID-19 resulted in very different rates of hospitalizations. The average number of events per person-year was 1.33 in the No-COVID group but 27.33 in the (10-day) COVID1 group. Note that Table 3 leads to rough, unadjusted estimates of RRs. The unadjusted RR of COVID1 versus No-COVID was $27.33/1.33 = 20.55$, and the unadjusted RRs for COVID2, Post-COVID, and Late-COVID were respectively 2.41, 1.59, and 2.80.

Statistical Analysis

To adjust for comorbidities and other covariates, we fitted a model with the 4 COVID-19 stages along with patient demographic and clinical characteristics as listed in the Methods.

COVID-19

The model fitting results are given in Table 4 and Table S2. The 4 stages of COVID-19 had quite different effects. COVID1 had an RR of 18.50 (95% CI, 18.19-18.81), indicating a hospitalization rate more than 18 times greater than that of patients in the No-COVID group; this was much greater than the RR of any other comorbidity.

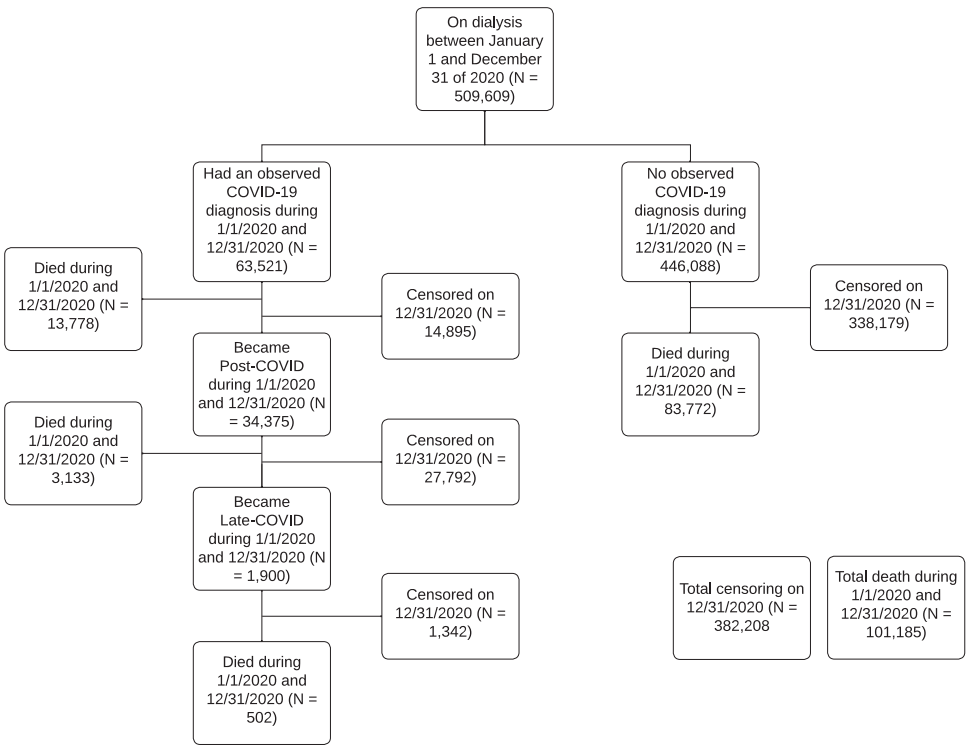

Figure 3. A flow chart of the number of patients at risk in each COVID-19 stage and the number of patients who died.

Table 1. Baseline Characteristics of Dialysis Patients by COVID-19 Stages

	Never-COVID N = 446,088	COVID1 N = 63,521	*P*[a]	COVID2 N = 52,550	Post-COVID N = 34,375	Late-COVID N = 1,900
Age, y, mean (SD)	64.7 (14)	64.6 (13.5)	0.60	64.3 (13.4)	62.9 (13.7)	63.6 (13.6)
Female	190,957 (42.8%)	28,398 (44.7%)	< 0.001	23,739 (45.2%)	15,770 (45.9%)	848 (44.6%)
Race	-	-	< 0.001	-	-	-
White	267,178 (59.9%)	36,369 (57.3%)	-	29,683 (56.5%)	18,554 (54%)	1,120 (58.9%)
Black	146,014 (32.7%)	22,909 (36.1%)	-	19,460 (37%)	13,712 (39.9%)	663 (34.9%)
Asian/Pacific Islander	26,438 (5.9%)	2,846 (4.5%)	-	2,233 (4.2%)	1,373 (4%)	77 (4.1%)
Native American	4,660 (1%)	1,131 (1.8%)	-	949 (1.8%)	582 (1.7%)	28 (1.5%)
Others	1,798 (0.4%)	266 (0.4%)	-	225 (0.4%)	154 (0.4%)	12 (0.6%)
Ethnicity	-	-	< 0.001	-	-	-
Non-Hispanic	369,551 (82.8%)	48,890 (77%)	-	40,456 (77%)	26,319 (76.6%)	1,369 (72.1%)
Hispanic	74,055 (16.6%)	14,260 (22.4%)	-	11,776 (22.4%)	7,834 (22.8%)	522 (27.5%)
Unknown	2,482 (0.6%)	371 (0.6%)	-	318 (0.6%)	222 (0.6%)	9 (0.5%)
Cause of kidney failure: diabetes	206,815 (46.4%)	33,838 (53.3%)	< 0.001	27,960 (53.2%)	17,617 (51.2%)	1,059 (55.7%)
Time since kidney failure	-	-	< 0.001	-	-	-
<90 d	64,062 (14.4%)	8,155 (12.8%)	-	6,951 (13.2%)	4,831 (14.1%)	257 (13.5%)
90 d-6 mo	18,935 (4.2%)	2,267 (3.6%)	-	1,870 (3.6%)	1,240 (3.6%)	84 (4.4%)
6 mo-1 y	36,162 (8.1%)	4,735 (7.5%)	-	3,891 (7.4%)	2,513 (7.3%)	126 (6.6%)
1-2 y	59,687 (13.4%)	8,289 (13%)	-	6,880 (13.1%)	4,459 (13%)	257 (13.5%)
2-3 y	54,863 (12.3%)	7,901 (12.4%)	-	6,563 (12.5%)	4,134 (12%)	230 (12.1%)
3-5 y	77,361 (17.3%)	11,608 (18.3%)	-	9,461 (18%)	6,122 (17.8%)	338 (17.8%)
>5 y	135,018 (30.3%)	20,566 (32.4%)	-	16,934 (32.2%)	11,076 (32.2%)	608 (32%)
BMI, kg/m^2	-	-	< 0.001	-	-	-
≤18.4	12,334 (2.8%)	1,491 (2.3%)	-	1,227 (2.3%)	838 (2.4%)	49 (2.6%)
18.5-24.9	112,522 (25.2%)	14,690 (23.1%)	-	12,198 (23.2%)	8,143 (23.7%)	479 (25.2%)
25-29.9	121,913 (27.3%)	16,916 (26.6%)	-	13,862 (26.4%)	8,956 (26.1%)	518 (27.3%)
≥30	199,319 (44.7%)	30,424 (47.9%)	-	25,263 (48.1%)	16,438 (47.8%)	854 (44.9%)

Note: Never-COVID were the patients who had no reported COVID-19 diagnosis during the observation period, and all other groups compared in this table were those who ever reached each stage during the observation period. Note that a patient who reached Late-COVID group also reached COVID1, COVID2, and Post-COVID stage.
Abbreviation: BMI, body mass index.
[a]*P*-value of a test for differences between the Never-COVID and COVID1 group.

COVID2 showed a more moderate but still quite large RR of 2.03 (95% CI, 1.99-2.08), which indicated a doubling of the rate of hospitalizations compared with a No-COVID patient. Similarly, the RR for Post-COVID and Late-COVID were 1.37 (95% CI, 1.35- 1.40) and 2.00 (95% CI, 1.89-2.11), respectively, indicating about a 37% and 100% increase in the rate of hospitalizations, respectively, as compared with a No-COVID patient.

The estimated baseline rate function, as shown in Fig 4 and Fig S1, illustrates the sharp decrease of non-COVID-19 hospitalizations at the beginning of the pandemic. This is as expected, as elective hospitalizations were deferred to avoid the spread of the coronavirus. The estimated baseline then gradually returned to normal in the summer of 2020, as the health care system recovered after the shock.

Secondary results

Age and sex, as well as their interactions with Any-COVID, had significant effects on hospitalizations. In general, COVID-19 had a larger impact on older patients and males. Compared with White patients, Black and Asian/Pacific Islander had lesser risks of hospitalizations in the No-COVID group but similar risks in the Any-COVID group. Hispanics had a lesser RR of hospitalization than non-Hispanics in the No-COVID group; this was reversed in the Any-COVID group. Most prevalent comorbidities led to greater risks of hospitalization. The proportion of days with Medicare Advantage coverage was related to a lesser risk of hospitalizations. More details can be found in Item S1.

Goodness of fit

For New York State, Fig 5 gives a plot of the weekly observed numbers of hospitalization admissions (O) along with the expected numbers (E) obtained from the fitted model, assuming all facilities had the same performance as the national average. Estimation results for other states were also explored. Plots for Michigan and Massachusetts

Table 2. Summary Statistics for the Length of Each COVID-19 Stage

	Minimum	First Quartile	Median	Mean	Standard Deviation	Third Quartile	Maximum
COVID1	0	10	10	9	2	10	10
COVID2	0	11	19	31	33	38	303
Post-COVID	0	37	107	109	76	170	293
Late-COVID	0	15	48	74	69	125	272

were typical and are provided in Fig 6. If the assumed model is true, then $(O-E)/\sqrt{E}$ approximately follows a standard normal distribution, so a fluctuation within ±2 can be accepted as due to randomness. Additional state plots are provided in Figures S2-S15. Overall, the model captured the temporal trends quite well.

To show the effect of having COVID-19 over time, an O and E plot for COVID1 stage patients can be seen in Fig 7. There was no systematic trend of O minus E, indicating the COVID-19 effect did not change significantly. Similar results are observed in Any-COVID patients, as shown in Figure S9.

Sensitivity analysis

In the model with modified date of diagnosis of COVID-19, the estimated RR for COVID1 versus No-COVID was 16.06, still very large, but less than 18.50 with the unaltered data. Other estimates in the risk adjustment changed only slightly. As an example, a similar O and E plot for New York City is shown in Fig S14. A figure similar to Fig 7 is also provided in Fig S15 for the data with modified COVID-19 start date. These results suggest that this change makes no difference of practical importance in the assessment of the COVID-19 effects.

Mortality

We fitted a Cox model to the mortality data using the same 4 COVID-19 stages defined for the hospitalization analysis. Most regression coefficients were similar to those in the hospitalization model, but there were some differences. The model estimates are shown in Table 4 and Table S3. Compared with the No-COVID group, COVID1 patients had the highest relative hazard, followed by COVID2, Late-COVID, and Post-COVID; compared with White patients, Black and Asian/Pacific Islander had lesser hazards in the No-COVID group; compared with non-Hispanics, Hispanics had a lesser relative hazard in the No-COVID group. Differences from the hospitalization model include that the COVID1 effect's estimate in the mortality model was much smaller than in the hospitalization model, while the COVID2 effect's estimate was much greater; women had a lesser relative hazard of mortality in the No-COVID group, compared with men, instead of greater. Other findings included a sudden increase in baseline mortality hazard in early spring (see Fig S10), in contrast to the sharp decrease in the baseline hospitalization rate. The baseline mortality hazard also increased in the summer and winter when the pandemic was more severe.[7]

DISCUSSION

Although others have examined the effect of COVID-19 in aggregate,[2,4,5,12,13,19] this analysis studied the impact over time after initial diagnosis of COVID-19. After exploring multiple ways of modeling the effect of COVID-19 (see Item S2), we modeled this as a series of stages from COVID to Post-COVID to Late-COVID, which provides a simple framework from which to view the time-varying effects. Having COVID-19 significantly raised the risk of hospitalizations for dialysis patients. The effect of COVID-19 was extremely high in a short period after the patient's first infection, decreased later, and increased again if the patient had another hospitalization with COVID-19. This is perhaps suggestive of the long COVID-19 effect and agrees with findings in the existing literature that COVID-19 patients had long-term and time-dependent symptoms and greater risk of hospitalization after discharge from a COVID-19–related hospitalization.[27-29]

In addition, from March to June, the presence of the virus substantially decreased hospitalization rates of dialysis patients without COVID-19. The nonparametric baseline rate (Fig 4) applies to the No-COVID group and is a function of calendar time. This captures the decrease in hospitalizations across the observational period and so accounts for effects of the virus on the No-COVID group.

To provide cost-effective health care, it is important to reduce hospital usage while maintaining the quality of

Table 3. Hospitalization Outcomes by COVID-19 Stages

	No-COVID	COVID1	COVID2	Post-COVID	Late-COVID
No. of hospitalizations	528,862	41,793	13,932	21,163	1,392
No. of days at risk	145,140,563	559,643	1,588,497	3,653,050	136,518
No. of events/year of exposure	1.33	27.33	3.21	2.12	3.73
Unadjusted RR versus No-COVID	1.00	20.55	2.41	1.59	2.80

Abbreviation: RR, relative rate.

Table 4. Model Fitting Results for the Main Characteristics

	Hospitalization			Mortality		
	Model Estimate	*P*	RR (95% CI)	Model Estimate	*P*	HR (95% CI)
COVID stage (reference: No-COVID)						
COVID1: first 10 days after COVID diagnosis	2.92	< 0.001	18.50 (18.19-18.81)	2.53	< 0.001	12.53 (12.04-13.05)
COVID2	0.71	< 0.001	2.03 (1.99-2.08)	1.84	< 0.001	6.30 (6.07-6.54)
Post-COVID	0.32	< 0.001	1.37 (1.35-1.40)	0.15	< 0.001	1.16 (1.10-1.21)
Late-COVID	0.69	< 0.001	2.00 (1.89-2.11)	1.42	< 0.001	4.13 (3.76-4.54)
Age in 2020[a]	-4.30E-5	0.50	1.00 (0.96-1.04)	3.45	< 0.001	31.62 (28.88-34.62)
Age square[a]	0.96	< 0.001	2.61 (2.25-3.04)	1.69	< 0.001	5.42 (3.41-8.64)
Age × Any-COVID[a]	0.45	< 0.001	1.57 (1.48-1.67)	0.14	0.02	1.15 (1.00-1.33)
Age square × Any-COVID[a]	0.55	< 0.001	1.74 (1.29-2.35)	-0.28	0.25	0.76 (0.34-1.70)
Female	0.06	< 0.001	1.06 (1.05-1.07)	-0.05	< 0.001	0.95 (0.93-0.97)
Race (reference: White)	-	-	-	-	-	-
Black	-0.08	< 0.001	0.92 (0.92-0.93)	-0.35	< 0.001	0.71 (0.69-0.72)
Asian/Pacific Islander	-0.26	< 0.001	0.77 (0.76-0.78)	-0.31	< 0.001	0.73 (0.71-0.76)
Native American	-0.01	0.30	0.99 (0.97-1.02)	-0.15	< 0.001	0.86 (0.81-0.93)
Others	-0.12	< 0.001	0.89 (0.85-0.93)	-0.34	< 0.001	0.71 (0.62-0.82)
Ethnicity (reference: non-Hispanic)	-	-	-	-	-	-
Hispanic	-0.12	< 0.001	0.88 (0.88-0.89)	-0.31	< 0.001	0.73 (0.71-0.75)
Unknown	-0.13	< 0.001	0.88 (0.83-0.93)	-3.71E-3	0.48	1.00 (0.87-1.14)
Cause of kidney failure: diabetes	0.01	0.02	1.01 (1.00-1.02)	0.15	< 0.001	1.16 (1.13-1.19)
Age × cause of kidney failure: diabetes[a]	-0.31	< 0.001	0.73 (0.70-0.76)	-0.87	< 0.001	0.42 (0.38-0.47)
Age × female[a]	-0.19	< 0.001	0.83 (0.79-0.86)	-0.37	< 0.001	0.69 (0.62-0.77)
Cause of kidney failure: diabetes × female	-0.01	0.12	0.99 (0.98-1.00)	-4.06E-4	0.49	1.00 (0.97-1.03)
Age square × cause of kidney failure: diabetes[a]	1.35	< 0.001	3.85 (3.13-4.73)	1.26	< 0.001	3.53 (1.94-6.43)
Age square × female[a]	0.65	< 0.001	1.92 (1.59-2.32)	0.25	0.20	1.28 (0.72-2.28)
Native American × Any-COVID	0.08	0.009	1.08 (1.01-1.15)	0.39	< 0.001	1.47 (1.29-1.68)
Asian/Pacific Islander × Any-COVID	0.35	< 0.001	1.42 (1.37-1.48)	0.59	< 0.001	1.81 (1.67-1.95)
Black × Any-COVID	0.10	< 0.001	1.10 (1.08-1.12)	0.17	< 0.001	1.19 (1.15-1.24)
Race: others × Any-COVID	0.14	0.01	1.15 (1.02-1.30)	0.09	0.26	1.10 (0.82-1.47)
Hispanic × Any-COVID	0.22	< 0.001	1.24 (1.22-1.27)	0.45	< 0.001	1.57 (1.50-1.65)
Ethnicity: Unknown × Any-COVID	-0.02	0.36	0.98 (0.88-1.09)	-0.30	0.008	0.74 (0.59-0.95)
Female × Any-COVID	-0.12	< 0.001	0.89 (0.88-0.90)	-0.10	< 0.001	0.91 (0.88-0.94)
Missing: Primary disease causing kidney failure	0.23	< 0.001	1.26 (1.19-1.34)	0.30	< 0.001	1.35 (1.18-1.55)
Proportion of days with Medicare Advantage coverage	-0.07	< 0.001	0.94 (0.93-0.94)	0.09	< 0.001	1.10 (1.08-1.12)
Time since kidney failure (reference: 6 mo-1 y)						
<90 d	0.30	< 0.001	1.34 (1.32-1.36)	0.18	< 0.001	1.20 (1.16-1.25)
90 d-6 mo[a]	0.04	< 0.001	1.04 (1.02-1.06)	0.16	< 0.001	1.17 (1.13-1.21)
1-2 y	0.07	< 0.001	1.07 (1.06-1.08)	0.08	< 0.001	1.09 (1.06-1.12)
2-3 y	0.11	< 0.001	1.11 (1.10-1.13)	0.22	< 0.001	1.25 (1.21-1.29)

(Continued)

Table 4 (Cont'd). Model Fitting Results for the Main Characteristics

	Hospitalization			Mortality		
	Model Estimate	*P*	RR (95% CI)	Model Estimate	*P*	HR (95% CI)
3-5 y	0.12	< 0.001	1.12 (1.11-1.13)	0.33	< 0.001	1.39 (1.35-1.42)
> 5 y	0.15	< 0.001	1.16 (1.15-1.17)	0.50	< 0.001	1.65 (1.61-1.69)
BMI, kg/m^2 (reference: ≥30)						
≤18.4	0.14	< 0.001	1.15 (1.14-1.17)	0.26	< 0.001	1.30 (1.25-1.35)
18.5-24.9	0.08	< 0.001	1.08 (1.07-1.09)	0.10	< 0.001	1.10 (1.09-1.12)
25-29.9	0.05	< 0.001	1.05 (1.04-1.05)	0.03	< 0.001	1.03 (1.02-1.05)

Abbreviations: BMI, body mass index; HR, hazard ratio; RR, relative rate.
[a]The variable "Age" is (age in years-65)/100

Figure 4. Estimated baseline rate function of hospitalizations, averaged by week.

care. The SHR, a risk-adjusted standardized measure, has been routinely used by the CMS to provide feedback to dialysis facilities and to assess their relative performance. The results of this analysis have shown a significant impact of the pandemic on hospitalizations of dialysis patients, indicating that adjustment for COVID-19 in the calculation of expected events in the SHR could be appropriate. As the pandemic progresses over time, COVID-19 effects should continue to be examined and adjusted for, as CMS is doing in the SHR and other quality metrics used to evaluate and compare facilities.

Our study has limitations. As mentioned previously, for patients with Medicare Advantage coverage, only inpatient claims were available, so fewer COVID-19 diagnoses were reported. Thus, it was more likely for a Medicare Advantage patient to reach Post-COVID stage than a non-Medicare Advantage patient. Also, the model considers the COVID-19 effects as constant over calendar time, but the true effects might have changed over time, as health professionals learned more about this disease and its treatment; the plots in Fig 7 and others, however, show that the model fits the data over time quite well. Additionally, the differences in COVID-19 trends in different geographic areas were not adjusted for. An additional adjuster based on area background might be helpful. Another limitation is potential overestimation of the COVID-19 effects due to missing information of patients with few or no symptoms and possible delay of reporting COVID-19 diagnosis. The raised baseline mortality hazard when the pandemic was high indicates, perhaps, that there were missed diagnoses, or alternatively, patients did not receive appropriate treatment for other conditions. However, the sensitivity analysis shows that the possibly

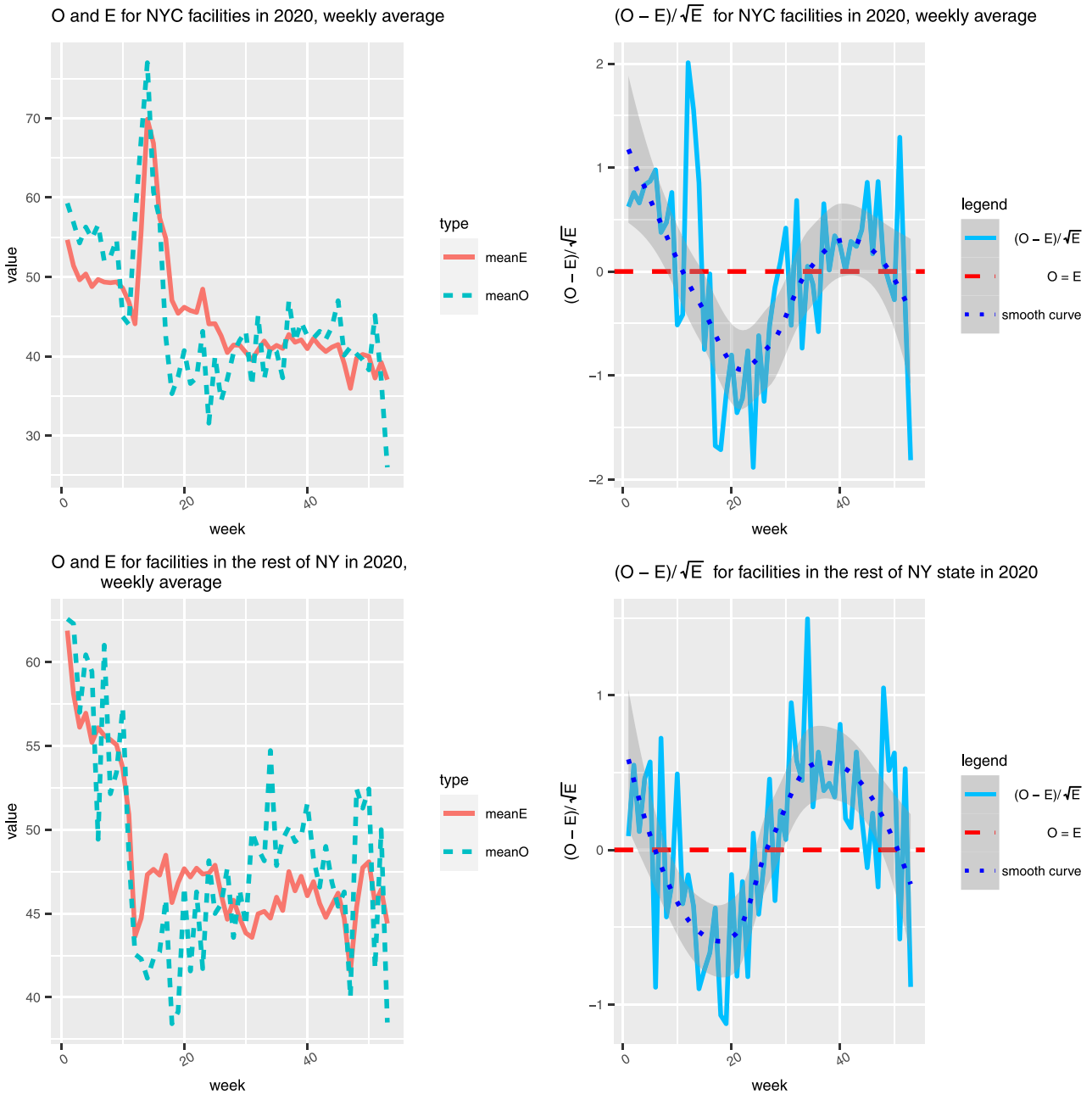

Figure 5. Weekly average number of hospitalizations observed (*O*) and the expected number (*E*) for New York City and the rest of New York. If the assumed model is true, then $(O-E)/\sqrt{E}$ approximately follows a standard normal distribution. Both New York City and the rest of New York State have this value within the normal ranges. The smoothed lines on the right panels are built by local regression (LOESS), and the gray area represents the pointwise 95% confidence intervals.

delayed report of COVID-19 diagnosis had a relatively small impact on the results. Finally, the cut-off of 10 days and 21 days was somewhat arbitrary and might reasonably have varied by a few days. However, as the results show, we needed cut-offs somewhere, and 10 and 21 days seem to serve the purpose well.

In this analysis, we have developed a model that studies the natural history of hospitalizations after SARS-CoV-2 infections of patients on dialysis based on national data. We accomplished this by introducing a series of 4 stages with a marked variation in the COVID-19 effect over time. This model was also adjusted for many variables to take into account a highly varied patient population and was used to create a revised quality measure, the SHR, for dialysis facilities.

This analysis shows that the COVID-19 significantly increased the risk of hospitalizations for dialysis patients, especially in the first few days after diagnosis. The

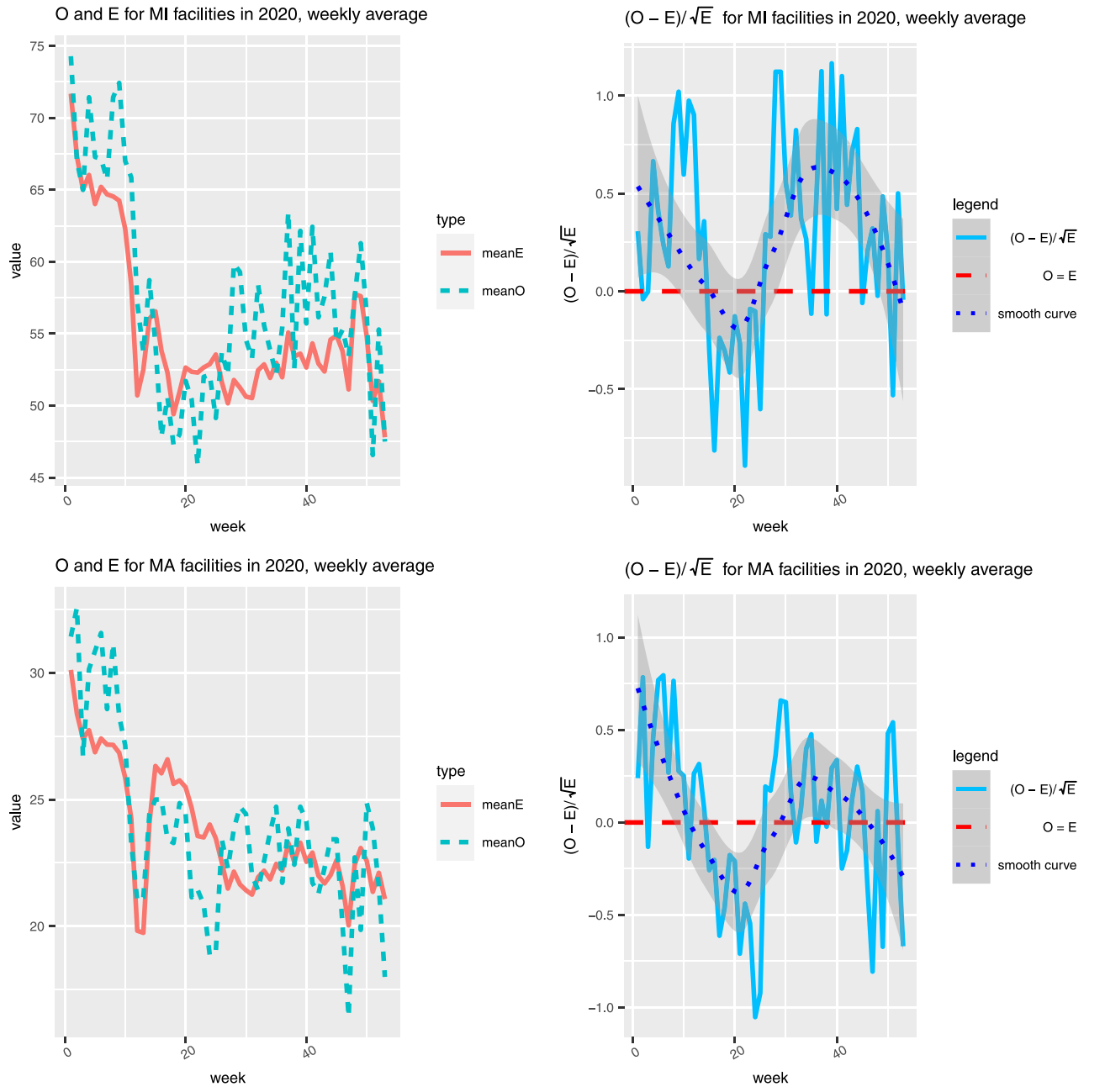

Figure 6. Observed (*O*) and Expected (*E*) plots for Michigan and Massachusetts. If the assumed model is true, then $(O-E)/\sqrt{E}$ approximately follows a standard normal distribution. Both Michigan and Massachusetts have this value within the normal ranges. The smoothed lines on the right panels are built by local regression (LOESS), and the gray area represents the pointwise 95% confidence intervals.

estimated effects, although they might be somewhat overestimated due to missing information of mild COVID-19 symptoms and the possible delays in reporting of COVID-19 diagnosis, are more highly significant than any other comorbidities included in this model. This study is based on dialysis patients, but the COVID-19 effect may have a similar pattern in other populations. However, the study was based on data from 2020, and the effect of COVID-19, especially after the appearance of different variants and vaccinations, has changed and is likely to continue to change in later years.

SUPPLEMENTARY MATERIAL

Figure S1: Estimated baseline rate function and age effect on hospitalization by group.

Figure S2: Observed (*O*) and expected (*E*) number of hospitalizations plots for all facilities over calendar time.

Figure 7. Observed (*O*) and expected (*E*) plots for COVID-19 patients in their first 10 days after COVID-19 diagnosis (COVID1 stage). If the assumed model is true, then $(O-E)/\sqrt{E}$ approximately follows a standard normal distribution. Except the first few weeks after the pandemic started and the end of the year, when there is potential underreporting of data, the rest of the variation is within the normal ranges. The smoothed lines on the right panels are built by local regression (LOESS), and the gray area represents the pointwise 95% confidence intervals.

Figure S3: Observed (*O*) and expected (*E*) number of hospitalizations plots for a combination of North Dakota, South Dakota, Montana, Wyoming, and Idaho, and Illinois over calendar time.

Figure S4: Observed (*O*) and expected (*E*) number of hospitalizations plots for Arizona and Washington over calendar time.

Figure S5: Observed (*O*) and expected (*E*) number of hospitalizations plots for Georgia and Indiana over calendar time.

Figure S6: Observed (*O*) and expected (*E*) number of hospitalizations plots for California and Oregon over calendar time.

Figure S7: Observed (*O*) and expected (*E*) number of hospitalizations plots for New Jersey and Florida over calendar time.

Figure S8: Observed (*O*) and expected (*E*) number of hospitalizations plots for Texas and Minnesota over calendar time.

Figure S9: Observed (*O*) and expected (*E*) number of hospitalizations for all COVID-19 patients over calendar time.

Figure S10: Unadjusted weekly mortality rates among Medicare dialysis patients at risk on January 1 of each year from 2018 to 2020.

Figure S11: Estimated baseline hazard function and age effect on mortality.

Figure S12: Observed (*O*) and expected (*E*) number of deaths plots for New York City and the rest of New York.

Figure S13: Observed (*O*) and expected (*E*) number of deaths plots for Michigan and Massachusetts.

Figure S14: Observed (*O*) and expected (*E*) number of hospitalizations plots for New York State over calendar time, using the model on the data with COVID-19 diagnosis dates modified by the 7/14-day rule.

Figure S15: Observed (*O*) and the expected number (*E*) for all COVID1 patients over calendar time, using the model on the data with COVID-19 diagnosis dates modified by the 7/14-day rule.

Item S1: Comments on secondary results.

Item S2: The analytical approach of how the four COVID-19 stages was arrived at and justified.

Table S1: Characteristics of patients by COVID-19 stages (complete Table 1).

Table S2: Effects of dialysis patients' characteristics on hospitalizations (complete Table 4 for hospitalization model).

Table S3: Effects of dialysis patients' characteristics on mortality (complete Table 4 for mortality model).

ARTICLE INFORMATION

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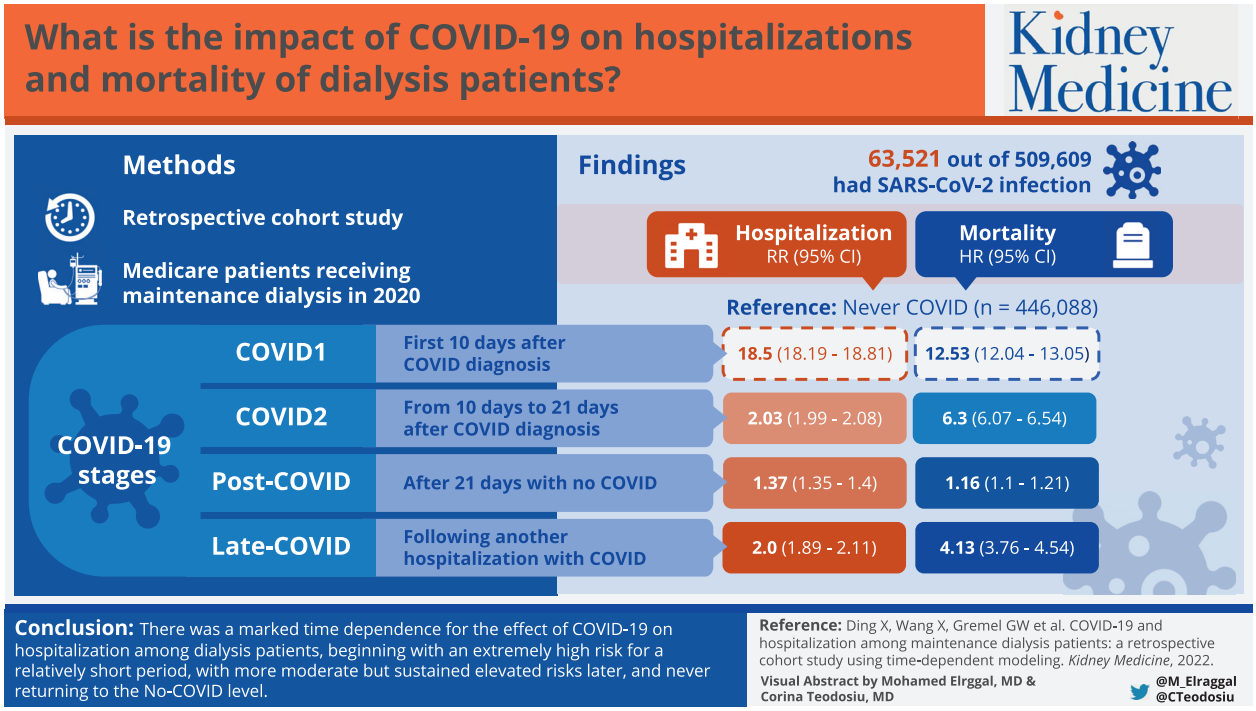
REFERENCES

1. Centers for Disease Control and Prevention. COVID data tracker. Trends in number of COVID-19 cases and deaths in the US reported to CDC, by state/territory. Accessed February 20, 2020. https://covid.cdc.gov/covid-data-tracker/#trends
2. Birkmeyer JD, Barnato A, Birkmeyer N, Bessler R, Skinner J. The impact of the COVID-19 pandemic on hospital admissions in the United States. *Health Aff (Millwood)*. 2020;39(11):2010-2017.
3. Cigna. Cigna study finds reduced rates of acute nonelective hospitalizations during the COVID-19 pandemic. Accessed September 2, 2022. https://newsroom.cigna.com/deferring-care-during-covid-19
4. Donnelly JP, Wang XQ, Iwashyna TJ, Prescott HC. Readmission and death after initial hospital discharge among patients with COVID-19 in a large multihospital system. *JAMA*. 2021;325(3):304-306.
5. Jager KJ, Kramer A, Chesnaye NC, et al. Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. *Kidney Int*. 2020;98(6):1540-1548.
6. Metzler B, Siostrzonek P, Binder RK, Bauer A, Reinstadler SJ. Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. *Eur Heart J*. 2020;41(19):1852-1853.
7. COVID-NET: COVID-19-Associated Hospital Surveillance Network, Centers for Disease Control and Prevention. Rates of COVID-19-associated hospitalization. Accessed May 23, 2021. https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html
8. Hartnett KP, Kite-Powell A, DeVies J, et al. Impact of the COVID-19 pandemic on emergency department visits - United States, January 1, 2019-May 30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(23):699-704.
9. Kendzerska T, Zhu DT, Gershon AS, et al. The effects of the health system response to the COVID-19 pandemic on chronic disease management: a narrative review. *Risk Manag Healthc Policy*. 2021;14:575-584.
10. The Council of State Governments. COVID-19 resources for state leaders. 2020-2021 executive orders. Accessed May 23, 2021. https://web.csg.org/covid19/executive-orders/
11. Hsu CM, Weiner DE, Aweh G, et al. COVID-19 among US dialysis patients: risk factors and outcomes from a national dialysis provider. *Am J Kidney Dis*. 2021;77(5):748-756.e1.
12. Weinhandl ED, Wetmore JB, Peng Y, Liu J, Gilbertson DT, Johansen KL. Initial effects of COVID-19 on patients with ESKD. *J Am Soc Nephrol*. 2021;32(6):1444-1453. doi:10.1681/ASN.2021010009
13. Hsu CM, Weiner DE. COVID-19 in dialysis patients: outlasting and outsmarting a pandemic. *Kidney Int*. 2020;98(6):1402-1404. doi:10.1016/j.kint.2020.10.005
14. Weiner DE, Watnick SG. Hemodialysis and COVID-19: an Achilles' heel in the pandemic health care response in the United States. *Kidney Med*. 2020;2(3):227-230.
15. Corbett RW, Blakey S, Nitsch D, et al. Epidemiology of COVID-19 in an urban dialysis center. *J Am Soc Nephrol*. 2020;31(8):1815-1823.
16. Salerno S, Messana JM, Gremel GW, et al. COVID-19 risk factors and mortality outcomes among Medicare patients receiving long-term dialysis. *JAMA Netw Open*. 2021;4(11):e2135379. doi:10.1001/jamanetworkopen.2021.35379
17. Couchoud C, Bayer F, Ayav C, et al. Low incidence of SARS-CoV-2, risk factors of mortality and the course of illness in the French national cohort of dialysis patients. *Kidney Int*. 2020;98(6):1519-1529.
18. Apata IW, Cobb J, Navarrete J, Burkart J, Plantinga L, Lea JP. COVID-19 infection control measures and outcomes in urban dialysis centers in predominantly African American communities. *BMC Nephrol*. 2021;22(1):81.
19. Centers for Medicare & Medicaid Services. Preliminary Medicare COVID-19 data snapshot. Accessed May 23, 2021. https://www.cms.gov/research-statistics-data-systems/preliminary-medicare-covid-19-data-snapshot
20. Ng JH, Hirsch JS, Wanchoo R, et al. Outcomes of patients with end-stage kidney disease hospitalized with COVID-19. *Kidney Int*. 2020;98(6):1530-1539.
21. The University of Michigan Kidney Epidemiology and Cost Center. Report for the Standardized Hospitalization Ratio. Accessed June 4, 2021. https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/ESRDQIP/Downloads/SHR-Methodology-Report_June2017.pdf
22. Yahav D, Yelin D, Eckerle I, et al. Definitions for coronavirus disease 2019 reinfection, relapse and PCR re-positivity. *Clin*

Microbiol Infect. 2021;27(3):315-318. doi:10.1016/j.cmi.2020.11.028
23. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J Royal Statistical Soc B*. 2000;62(4):711-730.
24. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. 2nd ed. John Wiley & Sons; 2002.
25. Lawless JF, Nadeau C. Some simple robust methods for the analysis of recurrent events. *Technometrics*. 1995;37(2):158-168.
26. Kalbfleisch JD, Wolfe RA. On monitoring outcomes of medical providers. *Stat Biosci*. 2013;5(2):286-302.
27. Maestre-Muñiz MM, Arias Á, Mata-Vázquez E, et al. Long-term outcomes of patients with coronavirus disease 2019 at one year after hospital discharge. *J Clin Med*. 2021;10(13):2945. doi:10.3390/jcm10132945
28. Goërtz YMJ, Van Herck M, Delbressine JM, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome?. *ERJ Open Res*. 2020;6(4):00542-2020. doi:10.1183/23120541.00542-2020
29. Ayoubkhani D, Khunti K, Nafilyan V, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. *BMJ*. 2021;372:n693. doi:10.1136/bmj.n693


What is the impact of COVID-19 on hospitalizations and mortality of dialysis patients?
Kidney Medicine
Methods
Retrospective cohort study
Medicare patients receiving maintenance dialysis in 2020
COVID-19 stages
COVID1
First 10 days after COVID diagnosis
COVID2
From 10 days to 21 days after COVID diagnosis
Post-COVID
After 21 days with no COVID
Late-COVID
Following another hospitalization with COVID
Findings
63,521 out of 509,609 had SARS-CoV-2 infection
Hospitalization RR (95% CI)
Mortality HR (95% CI)
Reference: Never COVID (n = 446,088)
18.5 (18.19 - 18.81)
12.53 (12.04 - 13.05)
2.03 (1.99 - 2.08)
6.3 (6.07 - 6.54)
1.37 (1.35 - 1.4)
1.16 (1.1 - 1.21)
2.0 (1.89 - 2.11)
4.13 (3.76 - 4.54)
Conclusion: There was a marked time dependence for the effect of COVID-19 on hospitalization among dialysis patients, beginning with an extremely high risk for a relatively short period, with more moderate but sustained elevated risks later, and never returning to the No-COVID level.
Reference: Ding X, Wang X, Gremel GW et al. COVID-19 and hospitalization among maintenance dialysis patients: a retrospective cohort study using time-dependent modeling. Kidney Medicine, 2022.
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