The Time to Negative Conversion among Adult COVID-19 Patients on Chronic Hemodialysis Admitted at the Philippine General Hospital — A Retrospective Cohort Study

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ABSTRACT

Objectives. In the Philippines, patients on chronic hemodialysis with COVID-19 remain admitted in hospitals despite clinical recovery because most free-standing dialysis units require proof of negative conversion via Reverse Transcriptase – Polymerase Chain Reaction (RT-PCR). This study aims to determine the time to negative conversion of COVID-19 RT-PCR testing among adult patients on chronic hemodialysis with COVID-19 admitted at the Philippine General Hospital (PGH) and bring insight in using the symptom or time-based procedure as recommended by local guideline, and ultimately, to ensure delivery of adequate hemodialysis despite being infected with COVID-19, shorten isolation period, and conserve resources especially in resource-limited settings.

Methods. This is a retrospective cohort study on all adult patients on chronic hemodialysis who were admitted in PGH after the diagnosis of COVID-19 by RT-PCR between March 2020 and February 2021. Descriptive statistics was used in summarizing the data.

Results. A total of 90 patients on chronic hemodialysis who tested positive for COVID-19 via RT-PCR admitted at PGH were included in the study. Most of these patients had moderate COVID-19 at 53.3%. The median number of days from onset of symptoms to clinical recovery was 14.5 days. The median time to first negative conversion was 18 days. Most of these patients had negative conversion at the second week. The correlation coefficient between time to clinical recovery and negative conversion was 0.214.

Conclusion. Among adult patients on chronic hemodialysis who were admitted in PGH after the diagnosis of COVID-19, the time to negative conversion was longer compared to the time to clinical recovery with a very weak correlation between the two.

Keywords: hemodialysis, COVID-19, RT-PCR

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INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has fast become widespread globally since its first emergence in Wuhan, China in December 2019.[1] As hospitals became overwhelmed with the great number of individuals testing positive for the disease, several admission and discharge guidelines were made to guide and unburden healthcare facilities. However, among high-risk patients, the test-based approach in discharging patients has been maintained in actual practice.[2]

In the Philippines, the shortage of dialysis centers that cater to End-Stage Kidney Disease (ESKD) individuals who

tested positive for COVID-19 uniquely presents a logistic challenge, as these patients remain admitted in COVID-19 hospitals with hemodialysis units despite the clinical resolution of their disease. Throughout the pandemic, surges have led our institution to limit the admission of patients on maintenance hemodialysis with COVID-19, forced us to shorten hemodialysis time, and reduce the frequency of hemodialysis of some patients. Majority of free-standing hemodialysis units require proof of negative conversion despite the joint recommendations of the Philippine Society of Nephrology (PSN), Philippine Society for Microbiology and Infectious Diseases (PSMID), and the Philippine Hospital Infection Control Society (PHICS) of accepting the symptom-based approach.[3] A retrospective cohort study observed the median from diagnosis to the first negative conversion via Reverse Transcriptase – Polymerase Chain Reaction (RT-PCR) assay to be 17 days for asymptomatic patients and 19.5 days for symptomatic patients (P = 0.07).[4] Among patients on hemodialysis, Qirjazi et al. found that approximately two weeks from the first positive COVID-19 PCR, 19 of 20 of their patients in their dialysis unit reached Ct values >28, the Ct value consistent with no infectivity or infectivity with no forward transmission potential.[5] Another study by Sinha et al. found the time to turn RT-PCR to negative was 14 days (3-40 days).[6] Our study uses the operational definition for time to negative conversion as the day 50% of the patients had first RT-PCR-negative result. Median time to clinical recovery is the day when 50% of the patients had no fever for at least three days without using fever-reducing medications and improvement or resolution of respiratory symptoms without any oxygen support. This definition for clinical recovery and the stratification of COVID-19 severity is lifted from the Interim Guidelines on COVID-19 management from PSMID.[7]

This study aims to determine the time to negative conversion of COVID-19 RT-PCR testing and compare the time to clinical recovery among adult patients on chronic hemodialysis admitted at the Philippine General Hospital (PGH), a tertiary government hospital assigned as one of the COVID-19 referral centers in the country. This knowledge will allow for a more systematic and evidence-based implementation of the test-based approach, or give insight whether such approach can be shifted to symptom or time-based procedure in order to ensure delivery of adequate hemodialysis despite being infected with COVID-19, shorten isolation period, and conserve resources especially in resource-limited settings.

METHODS

This is a retrospective cohort study on all adult patients on chronic hemodialysis who were admitted in PGH after the diagnosis of COVID-19 by RT-PCR for SARS –COV 2 between March 2020 and February 2021. Adults on hemodialysis but were asymptomatic for COVID-19, on hemodialysis for acute kidney injury (AKI), ESKD patients on hemodialysis for less than three months, those whose charts cannot be retrieved or whose COVID-19 RT-PCR results were missing, and those who died or got discharged without having a negative COVID-19 result were excluded.

Participants were identified using the COVID-19 census of the Division of Nephrology of PGH. In March 2020, some charts were still on paper while charts were being converted to electronic charts. PGH has a hospital-wide online database [Computerized Registry of Admissions and Discharges (RADish)] as electronic charts. RADish requires a unique passcode before each specific patient medical chart can be opened. Chart entries both on paper and electronic were reviewed. Demographic data including baseline characteristics, RT-PCR results per day, median duration in days to clinical recovery, and negative conversion were determined.

The testing process for COVID-19 uses the reverse-transcriptase polymerase (RT-PCR) test where the health workers use swabs to take nasopharyngeal and/or oropharyngeal samples from the patients. Samples are subjected to Viral RNA extraction, and then converted to DNA, since PCR test can only process DNA. The PCR test in UP-PGH uses the GenAmplify COVID-19 Detection Kit by Manila HealthTek. If a viral DNA is found, a chain reaction repeatedly copies the viral DNA to prove its presence in the sample.[8] Patients on chronic hemodialysis who are positive for COVID-19 are generally re-tested via RT-PCR on day 14 since symptom onset. If result is negative, isolation may be discontinued. If RT-PCR test is still positive, testing is repeated at least 24-hours apart until there is one documentation of at least one negative result.

Descriptive statistics was used in summarizing the data. The Kaplan-Meier curve was generated and the correlation coefficient was computed manually and verified using a free online statistical tool.[9] The correlation coefficient looks at the strength of a linear relationship between two variables, which in this study, is the relationship between the time to clinical recovery and the time to negative conversion. There are several formulas to obtain the correlation coefficient. One of the most commonly used and the one we used in this study is the Pearson's coefficient formula. The formula will return a value between -1 and 1, where 1 indicates a strong positive relationship, -1 indicates a strong negative relationship, and a result of zero indicates no relationship at all.[10] Using the online statistical tool, we input the number of days it took for each patient to achieve clinical recovery as the X values and the number of days to negative conversion as the Y values (or vice versa).

The protocol was approved by the University of the Philippines Manila- Research Ethics Board (UPM-REB). A waiver of informed consent was requested from the UPM-REB panel since the study involve review of anonymized medical records, and therefore will not have any direct alteration or changes to patient treatment. There are no direct benefits in the study. The authors of the study have no

conflict of interest to declare. We used the STROBE cohort checklist when writing our report.[11]

RESULTS

Data collection began in October 2021 and ended in January 2022. There were a total of 171 patients who underwent hemodialysis with COVID-19 admitted from March 2020 to February 2021 identified as potentially eligible for this study. Out of the 171 patients, 119 patients were diagnosed to have CKD 5D while the rest underwent hemodialysis for acute kidney injury or had been on maintenance hemodialysis for less than three months. Their charts were then reviewed and those who expired without any repeat COVID-19 RT-PCR result or never turned negative on RT-PCR were excluded. During the earlier months of the pandemic, RT-PCR testing was not yet available at PGH and samples were sent out to another institution. As such, some results cannot be found in the chart and were excluded in the study. A total of 90 patients on chronic hemodialysis and tested positive for COVID-19 via RT-PCR met our inclusion and exclusion criteria.

Table 1 shows the demographic data and clinical profile of the participants in this study. Out of the 90 patients, 54 (60%) were males, 36 (40%) were females. Most patients (32.22%) were 51-60 years old and the median age was 55 years old. The mean hemodialysis vintage was 2.95 years. Among the causes of ESKD, 43.33% was from hypertension, 28.89% was due to diabetes mellitus, 20% due to chronic glomerulonephritis, 2.22% was due to obstructive nephropathy and the remaining 4.44% of patients with ESKD were due to other causes such as analgesic nephropathy, gouty nephropathy, and Polycystic Kidney Disease. For patients grouped under chronic glomerulonephritis (CGN), this includes

Table 1. Demographic and Clinical Data of Adult COVID-19 Patients on Chronic Hemodialysis

Demographics	Number of Patients (N =90)
Sex	
Male	54 (60%)
Age	
19-30	8 (8.89%)
31-40	8 (8.89%)
41-50	16 (17.78%)
51-60	29 (32.22%)
61-70	21 (23.33%)
71-80	7 (7.78%)
81-90	1 (1.11%)
Cause of ESKD	
Diabetes Mellitus	26 (28.89%)
Hypertension	39 (43.33%)
Chronic Glomerulonephritis	18 (20%)
Obstructive Nephropathy	2 (2.22%)
Others	4 (4.44%)
Comorbidities	
Diabetes Mellitus	40 (44.44%)
Hypertension	81 (90%)
Cerebrovascular Disease	6 (6.67%)
Ischemic Heart Disease	17 (18.89%)
Heart Failure	19 (21.11%)
Malignancy	1 (1.11%)
Liver Cirrhosis	1 (1.11%)
Severity	
Mild COVID-19	15 (16.67 %)
Moderate COVID- 19	48 (53.33%)
Severe COVID-19	16 (17.78%)
Critical COVID-19	11 (12.22%)

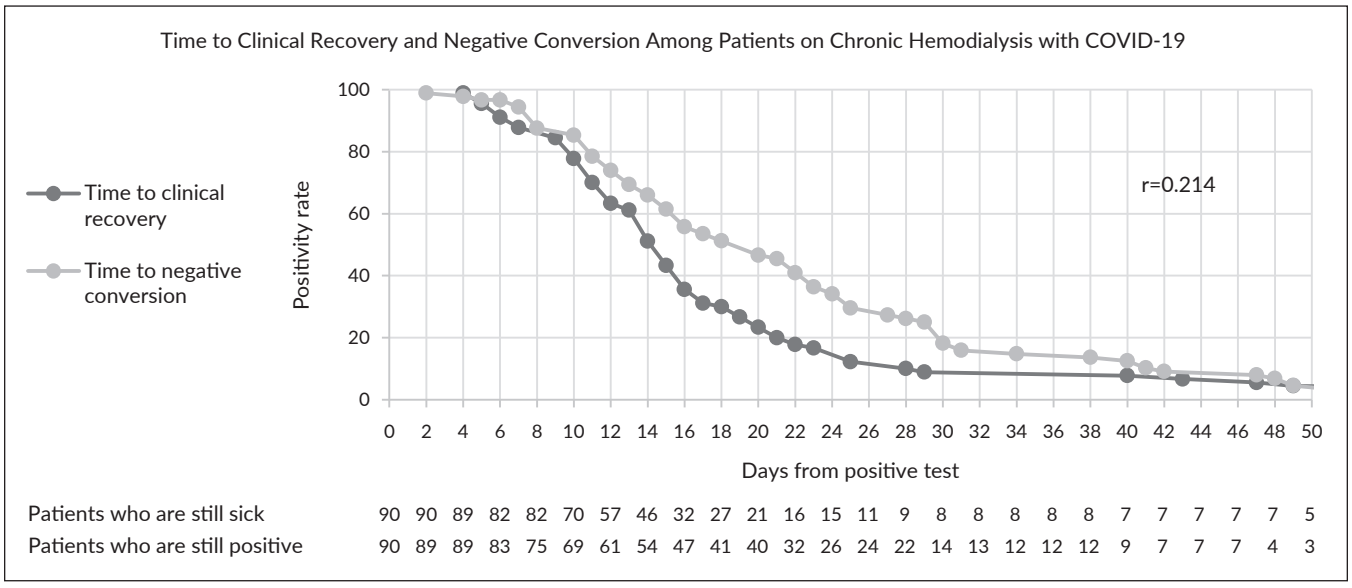

Figure 1. Patients with COVID-19 observed until clinically recovered and with negative conversion.

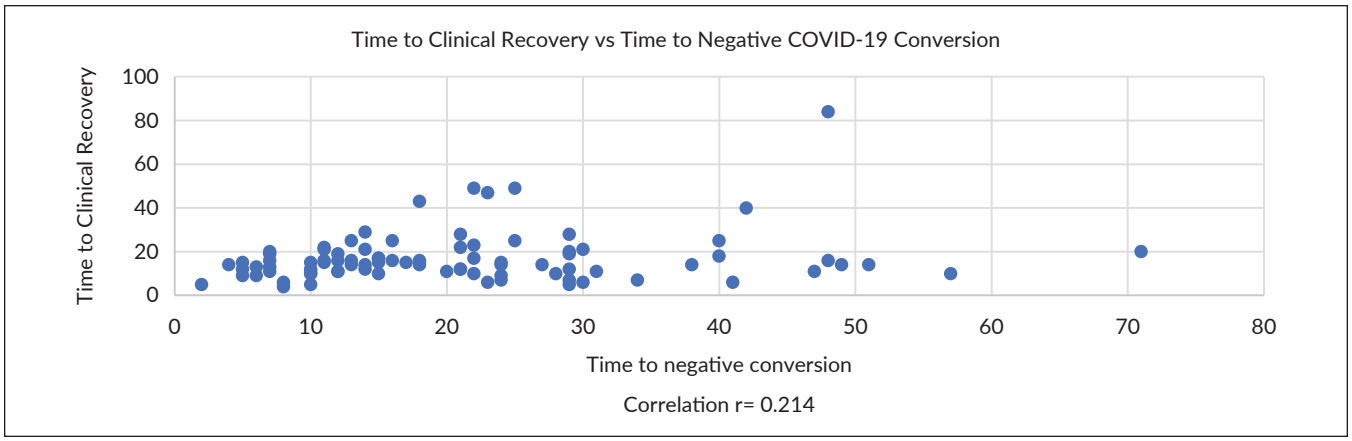

Figure 2. Scatter plot of patients and their time to negative conversion and clinical recovery.

those with acute glomerulonephritis whose conditions progressed to CGN as well as those with unknown etiologies but with epidemiologic characteristics, such as young age, which are consistent with CGN. Hypertension was the most common comorbidity at 90%, DM came in second at 44.44%, while heart failure was third at 21.11%. Most had moderate COVID-19 at 53.33% while 16.67% had mild, 17.78% had severe, and 12.22% had critical COVID-19.

Figure 1 shows the rate of negative conversion plotted with the rate of clinical recovery of all participants over time. The median time to first negative conversion was 18 days (IQR 11-28.5), with a mean of 20.88 days since the first positive swab. Most patients achieved their first negative conversion on the second week at 25.56% and 18.89% converted at the third week. By the 71st day (10th week), all the patients had negative conversion. The median number of days from onset of symptoms to clinical recovery was 14.5 days (11-19.5); the mean was 17.03 days. The earliest time a patient had clinical recovery was 4 days; the longest time a patient had clinical recovery was 84 days.

Table 2 compares the time to clinical recovery, time to negative conversion, and their respective correlation coefficients. Time to clinical recovery is seen to be longer as the severity of the disease worsens while the time to negative conversion shows a variable pattern. There is very weak correlation between the two variables across all strata of disease severity. In fact, the correlation coefficient among patients with moderate COVID-19, where majority of the patients in this cohort are stratified in, shows almost no correlation between the two.

Table 2. Time to Clinical Recovery and Time to Negative Conversion according COVID-19 Severity

COVID-19 Severity	Time in Days to Clinical Recovery	Time in Days to Negative Conversion	Coefficient Correlation (r value)
Mild	14.33	18	0.4867
Moderate	16.94	20	0.0829
Severe	18.07	15.5	0.2144
Critical	20.55	13	0.3663

Nine patients had their first negative conversion but had been positive again after re-testing. The most number of RT-PCR tests done in one patient was 16. This patient had persistent positive RT-PCR result despite having been clinically recovered at 18th day of illness and converted negative only after 45 days since his fist swab.

As seen in Figure 2, there is very weak positive correlation between the time to clinical recovery and time to negative conversion with an r value of 0.214. There were two patients who had negative RT-PCR results but did not clinically recover and hence were not included in the calculation of the correlation coefficient.

DISCUSSION

In summary, the results of this study showed that patients who are on chronic hemodialysis had moderate COVID-19. The median time to negative conversion was 18 days while the median time to clinical recovery was 14.5 days. There is very weak positive correlation between the two. Patients were further stratified according to disease severity and yielded a similar result, even showing almost no correlation for the majority of the patients in this cohort.

At the time this paper was completed, the joint recommendation of PSN, PHICS and PSMID then on dialytic patients who test positive on day 14 from symptom onset but were clinically improved was that they should continue isolation for another seven days (i.e., until day 21). They are then subjected to undergo any of the following tests: "RT-PCR, COVID-19 rapid antigen test or Enhanced "Chemiluminescence" Immunoassay (ECLIA) or enzyme-linked immunosorbent assay (ELISA) IgG Test, and if they test negative, may discontinue isolation and be admitted in their mother hemodialysis unit. If they still test positive at day 21 in any of these tests, they will be advised isolation

for another seven days (i.e., until day 28) and once they are cleared by IDS/attending nephrologist that patient has clinically recovered, they may be allowed to return to their mother dialysis unit.[3] However, our experience showed that all our patients were still required to have at least 1 negative RT-PCR result before being accepted back in the mother dialysis unit after hospital discharge. More recently, PSN has released an updated guideline last February 2022. The patients should be dialyzed in the mother dialysis unit using standard precautions according to COVID severity. If classified as mild to moderate COVID-19 who have clinically recovered, either symptom based or test based approach can be used. Both symptom and test- based approach recommends at least 14 days since symptoms first appeared or at least 24 hours have passed since recovery prior to returning to mother dialysis unit. An additional clause of a negative result to a Food and Drug Administration (FDA) Emergency Use Authorized COVID-19 molecular assay was also required if the test-based approach is to be followed. For severe to critical COVID-19 recovered cases, the approach is similar except that it requires 21 days since first symptoms appeared prior to giving clearance to return to mother dialysis unit.

In a dialysis center in Canada, 49 (36 on hemodialysis and 13 on peritoneal dialysis) of 1332 ESKD patients had COVID-19 between March 2020-December 2020. They used the cycle threshold (Ct) values of the COVID PCR test as surrogate to asses risk of infectious viral shedding. Their study showed that 19 out of the 20 who underwent serial Ct value monitoring reached Ct values >28 at approximately two weeks since the first PCR, the Ct value at which virus is considered unlikely to cause forward transmission. Ct values are inversely correlated with SARS-CoV-2 infectivity. In the general population, a consensus has emerged that no cultivatable virus can be recovered at 7-10 days after symptom onset at PCR CT value of 25-30.[5] Another prospective observational study by Sinha and colleagues have identified 131 adult patients on maintenance hemodialysis. 104 of these patients turned RT-PCR positive with median time to negative conversion of 14 (range 3-20) days from onset of symptoms. Their study included asymptomatic patients and had the day of detection as the day of onset of symptom.[6] In United Arab Emirates, outcomes of patients with ESKD on dialysis with COVID-19 was studied. One of the outcomes included was the time to negative conversion. They have subcategorized the patients among those who had positive IgG whose time to negative conversion was 19 days (IQR 11-28); among those not antibody tested was 15 days (IQR 7-26); those in whom IgG antibody was not detected had shorter time to negative conversion at median of three days (IQR 3-7).[12]

Limitations of this study include the following: at the start of the pandemic, 7-day intervals between RT-PCR tests have been implemented. At the later part of the year 2020, the infection control unit of the hospital have shortened the interval between tests to at least 24 hours so long as they are clinically recovered. This means that there might be patients who might have had shorter time to negative conversion but was just not tested. There were patients whose RT-PCR test have been delayed a few days after it had been actually ordered due to lack of laboratory personnel. Hence, the time to negative conversion may also have been affected by these logistical concerns. This study also does not reflect the time to negative conversion among those infected with the newer variants such as the lambda, delta, and omicron as these have emerged after the period of the study. It also does not reflect the impact of vaccination on the time to negative conversion as vaccine roll-out in the Philippines started only on March 2021.

CONCLUSION

Based on this review of COVID-19 positive chronic dialysis cohort, time to clinical recovery is shorter compared to the time to first negative conversion, with these two variables having very weak positive correlation. Those who have clinically recovered had prolonged hospital stay without any active medical management in anticipation of a negative COVID-19 RT-PCR result. This implies exposure to nosocomial infections and other complications of long hospital stay. This set of patients have been admitted longer than is needed by their medical condition. The findings of this study look promising to support the latest PSN recommendation to accept the symptom-based approach in discontinuing isolation among patients on chronic hemodialysis with COVID-19. However, the design and methodology of this study do not have the power to make this conclusion as we have not looked into the outcomes of patients who have clinically recovered but persistently tested positive for COVID-19; outcomes which have serious implications such as re-infection and transmission in this cohort and the health care workers exposed to them. The COVID-19 RT-PCR assay is highly sensitive that may remain positive weeks after the acute illness even among patients with high Ct values that reflect non-infectivity.[5] As our study looked into RT-PCR positivity only without the Ct values, this may explain the very weak correlation between the time to RT-PCR negative conversion and time to clinical recovery in our cohort.

The researchers recommend that a follow-up study be done to include patients on maintenance hemodialysis who have been vaccinated and the patients who had COVID-19 at the succeeding months after our study period to determine if vaccination and the newer variants have an effect on the negative conversion rate. It would be more informative to include the Ct values to determine if those who remain persistently positive on RT-PCR are still infective. Lastly, to determine whether transmission of COVID-19 would still occur among chronic hemodialysis patients clinically recovered but with persistent positive result on RT-PCR testing, we recommend further studies where these patients are dialyzed as a cohort in a designated hemodialysis unit

to observe for reinfection in the immediate period after they have been discharged.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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