Research Article

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Clinical and Laboratory Predictors for Acquiring COVID-19 Infections in Patients on Maintenance Hemodialysis in 5th Wave of Epidemic in Myanmar

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Abstract

Background: Patients on maintenance hemodialysis (MHD) are at high risk of contracting SARS-CoV-2 and developing severe COVID-19 infection because they have low innate immunity as well as poor antibody response to COVID-19 vaccine. This study aimed to assess the clinical and laboratory predictors for 5th wave of COVID-19 infections in patients on maintenance hemodialysis.

Methods: A hospital based, case control study was conducted in July 2022 to November 2022 among patients on MHD who had confirmed COVID-19 infection by nasopharyngeal swab PCR. Data were collected by using standardized forms and analysis was done.

Results: A total of 22 patients out of 61 patients on maintenance hemodialysis (MHD) developed COVID-19 infection in same public hemodialysis (HD) center in Yangon. The comparison of clinical and laboratory parameters (age, BMI, vaccination history, type of vaccine, duration from last vaccination , smoking status, vaccination time, comorbid status, duration of hemodialysis, hemoglobin level, serum albumin level and anti-Spike antibody level) was made between infected group and non-infected group. Patients in both groups had 4 doses of vaccine: Covaxin, Sinovax, Sinopharm and Covishield. Baseline clinical characteristics were not significantly different between infected cases and non-infected cases; mean age was 49.77 ± 11.58 years vs 51.92 ± 13.6 years; BMI was 19.75 ± 3.00 kg/m^2 vs 20.03 ± 2.76 kg/m^2 ; duration from last vaccination was 37.64 ± 2.22 days vs 38.77 ± 3.62 days; number of current smokers was 4 vs 8 ; and vaccination time in the morning was 14 vs 29 patients. The proportion of patients with past COVID-19 infection was the same; 63.6% (14/22) in infected group and 66.7 % (26/39) in non-infected group. Hemoglobin level was lower in infected groups (8.26 ± 2.07 gm% vs 8.33 ± 2.02 gm%); and serum albumin level was lower in infected group (42.47 ± 4.82 gm/dl vs 43.17 ± 4.10 gm/dl) too. The

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race, religion, comorbid status (diabetic nephropathy, coronary heart disease) and the duration of hemodialysis was not different between 2 groups. The proportion of patients with cerebrovascular accident was higher in infected group. Median (IQR) anti-Spike antibody level of infected cases was 4732 (5206) U/mL and it was 3195 (4883) U/mL in non-infected cases; it was not different significantly.

Conclusions: The baseline characteristics like age, race, religion, BMI, comorbid status (diabetic nephropathy, coronary heart disease), smoking status, duration of hemodialysis, past COVID-19 infection, anti-Spike antibody level, vaccination time and duration from last vaccination were non-predictors for 5th wave of COVID-19 infection among patients on MHD who had 4 doses of COVID-19 vaccine. The likely predictors were cerebrovascular accident, low hemoglobin and low serum albumin.

Keywords: COVID-19 infection, 5th wave, predictors, maintenance hemodialysis (MHD)

Background

COVID-19 infection has been threatening since 2019. Vaccination to SARS-CoV2 virus have tried with various doses (two doses, three doses and four doses) for prevention. On the other hand, SARS-CoV2 has been mutating since 2020 to overcome vaccination and anti-viral drugs; the wild type, the Alpha variant, the Delta variant and the Omicron variant have been causing effect on transmission, severity and mortality.

Patients on MHD were tendency to get severe form of COVID-19 infection and death because they had poor immunity and associated comorbidity (F. Wang et al., 2021) (Kooman et al., n.d.) (Khin Phyu Pyar et al., 2022) (Rincon-Arevalo et al., 2021) (Pyar, Kyaw, et al., 2022). Significant predictors of infection were living in a long-term care residence, black ethnicity and lower income quintiles in in-centre hemodialysis compared to home dialysis (Taji et al., 2021). In the study done in Iran described the patients on MHD as "the most sensitive and high-risk groups for COVID-19 because of advanced age, comorbidities disease, low-immune function and

frequent required visits, and patient overload in HD centers" (Kenarkoohi et al., 2022). Black race, male sex, nursing home status, and having comorbidities, such as diabetes and cardiac diseases, were associated with higher risk of COVID-19 infection as well as higher post–COVID-19 mortality (Salerno et al., 2021).

Clinical and laboratory predictors of COVID-19 infection may be related with antibody response to COVID-19 vaccination. Reported determinants of antibody response were multifactorial: age (Yen et al., 2021), previous infection (Aoun et al., 2022), immunosuppressive therapy (Yen et al., 2021), body mass index, iron deficiency anemia (Drakesmith et al., 2021) (Preston et al., 2021), serum albumin level (Aoun et al., 2022) (Yen et al., 2021), longer vintage of end-stage kidney disease (Anand et al., 2021), previous infection (Yen et al., 2021), the time of the day of vaccination (Nobis et al., 2019), vaccine type, sex, and days post-vaccination (L. Wang et al., 2019).

There were limited reports on clinical and laboratory predictors for COVID-19 infections in

patients on maintenance hemodialysis in Myanmar. Therefore, this study aimed to assess the clinical and laboratory predictors for 5th wave of COVID-19 infections in patients on maintenance hemodialysis.

Methods

Study design and population

A hospital based case control study was conducted in July 2022 to November 2022 among patients on MHD who had confirmed COVID-19 infection by nasopharyngeal swab PCR. Data were collected by using standardized forms and analysis was done. This study was approved by the Hospital Research and Ethics Committee of No.(1) Defence Services General Hospital (1000-Bedded) Mingaladon, Yangon.

Data collection and procedure

Demographic characteristics (sex, age, height, dry weight, smoking status, duration of MHD), comorbidity (cerebrovascular accident, coronary heart disease, diabetic nephropathy), nutritional status (hemoglobin, serum albumin), the name of each COVID-19 vaccine, date of each vaccination, timing of the day of vaccination of the last dose, timing of SARS-CoV-2 infection, and blood level of anti-Spike antibody were recorded. The data were checked by two medical officers and then, supervision, completeness, and consistency of collected data were performed by the principle investigator. Data were collected by using standardized forms and analysis was done.

Anti-Spike antibody was measured according to 'Double-antigen sandwich principle'. Total duration of assay was 18 minutes. For first incubation, 20 µL of sample, biotinylated SARS-CoV-2 S-RBD-specific recombinant antigen and SARS-CoV-2 S-RBD-specific recombinant antigen labeled with a ruthenium complex were done to form a sandwich complex. Then, second incubation was performed after addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture was aspirated into the measuring cell where the microparticles were magnetically captured onto the surface of the electrode. Next, unbound substances were removed with ProCell/ProCell M. Later, application of a voltage to the electrode to induce chemiluminescent emission was done; it was measured by a photomultiplier. Finally, the results were determined via a calibration curve, instrument specifically generated by 2-point calibration; and, a master curve was provided via the reagent barcode or e-barcode. These samples were measured by using Cobas E411 immunoassay analyzer.

Working Definition

Body mass index (BMI) was a person's weight in kilograms divided by the square of height in meters, an indicator of body fatness. BMI was categorized as underweight (< 18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2) and (≥ 30.0 kg/m^2) obese. Dry body weight was taken for calculation of BMI. Comorbidity was a presence of more or additional medical conditions or diseases in patients on MHD (cerebrovascular accident, coronary heart disease, diabetic nephropathy).

Smoking status was classified into smoker and non-smoker. Smoker was defined if patient was still smoking at the time of estimation of blood test irrespective of duration of smoking. Nonsmoker was defined if patient stopped smoking at the time of estimation of blood test irrespective of duration of quitting.

History of COVID-19 infection was defined if patient had signs and symptoms of COVID-19 infection with positive nasopharyngeal swab tests either with rapid test or PCR method.

Vaccination in the morning was defined if vaccination was done from 08:00 hour to 12:00 hour; vaccination in the afternoon was defined if vaccination was done from 12:00 hour to 18:00 hour.

Duration of maintenance hemodialysis was defined as total duration since first HD. Hemoglobin was normal if $\geq$ 11gm%; mild anemia was defined if hemoglobin was 8-10.9 gm%; moderate anemia was defined if hemoglobin was 6-7.9 gm%;and, severe anemia was defined if hemoglobin was < 6 gm%.

Serum albumin was normal if it was more than 30 mg% and was low if it was less than 30 mg%.

Statistical Analysis

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Statistical analysis was done by IBM® SPSS® version 26. All continuous data were done normality test by histogram as well as by Shapiro-Wilk test. If there was non-normal distribution in a variable in either group, comparison of that variable between the two groups was done by Mann Whitney U test and data were expressed as Median (IQR). If the variable was normal distribution in both groups, comparison was done by independent t test and data were expressed as mean ± SD. For the categorical variables, data were expressed as frequency (percentage) and compared by cross tabulation methods (either Pearson's Chi-square or Fisher's Exact test or Likelihood ratios, appropriately).

Results

A total of 22 patients on maintenance hemodialysis (MHD) developed COVID-19 infection during the study period. Their age, BMI, vaccination history, type of vaccine, duration from last vaccination, smoking status, time vaccination, comorbid status, duration of hemodialysis, hemoglobin level, total WBC count, absolute lymphocyte count, serum albumin level and anti-Spike antibody level were analyzed and compared with non-infected cases.

Table (1) Clinical and laboratory parameters in patients on MHD (n=61)

Variables	COVID infection	No COVID infection	Statistical test	p value
Frequency (%)	22 (36.1)	39 (63.9)		
Age (yr) Mean ± SD	49.77 ± 11.58	51.92 ± 13.6	t (59) = -0.624	0.535[*]
Sex Male Female	 8 (36.4) 14 (63.6)	 18 (46.2) 21 (53.8)	$X^2(1) = 0.551$	0.458[†]
BMI (kg/m²) Mean ± SD	19.75 ± 3.00	20.03 ± 2.76	t (59) = -0.372	0.711[*]
Diabetic nephropathy	2 (9.1)	8 (20.5)		0.305[‡]
Smoking (Yes)	4 (18.2)	8 (20.5)		1.000[‡]
Past Covid Infection	14 (63.6)	26 (66.7)	$X^2(1) = 0.557$	0.811[†]
HD duration < 6 months 6month – 1 year 1 – 2 years 2 – 3 years 3 – 4 years > 4 years	 8 (36.4) 4 (18.2) 3 (13.6) 3 (13.6) 4 (18.2) 0 (0)	 12 (30.8) 4 (10.3) 9 (23.1) 4 (10.3) 9 (23.1) 1 (2.6)	$X^2(5) = 2.647$	0.754[††]
Duration from last vaccination days Mean ± SD	37.64 ± 2.22	38.77 ± 3.62	t (59) = -1.332	0.188[*]
Vaccination Time Morning Afternoon	 14 (63.6) 8 (36.4)	 29 (74.4) 10 (25.6)	$X^2(1) = 0.777$	0.378[‡]
Hb (g %) Mean ± SD	8.26 ± 2.07	8.33 ± 2.02	t (59) = - 0.114	0.910[*]
Albumin (g/L) Mean ± SD	42.47 ± 4.82	43.17 ± 4.10	t (59) = - 0.604	0.548[*]
Antibody level Median (IQR)	4732 (5206)	3195 (4883)	Z = -0.827	0.408[**]

Table (1) reveals comparison of base line clinical characteristics in COVID-19 infected group and non-infected group among patients on MHD. They were not significantly different between

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infected cases and non-infected cases; mean age was 49.77 ± 11.58 years vs 51.92 ± 13.6 years; BMI was 19.75 ± 3.00 kg/m^2 vs 20.03 ± 2.76 kg/m^2; duration from last vaccination was 37.64 ± 2.22 days vs 38.77 ± 3.62 days; the number of current smokers was 4 vs 8; time vaccination in the morning was 14 vs 29 patients. Patients in both groups had 4 doses of vaccine: Covaxin, Sinopharm, Sinovax and Covishield.

The frequency of number of past COVID-19 infection was 64% in infected group and 68% in non-infected group. Hemoglobin level was lower in infected groups (8.26 ± 2.07 gm% vs 8.33 ± 2.02 gm%) and serum albumin level was lower in infected group (42.47 ± 4.82 gm/dl vs 43.17 ± 4.10 gm/dl) too. Comorbid status (cerebrovascular accident, coronary heart disease, diabetic nephropathy) of 2 groups was compared; 13.6% (3/22) of patients in infected group and 7.7%(3/39) of patients in non-infected group had cerebrovascular accident; 22.7% (5/22) of infected group and 25.6% (10/39) of non-infected group had coronary heart disease (CHD); and 10% (2/22) of infected group and 20% (8/39) of non-infected group had diabetic nephropathy. The duration of hemodialysis was not different between 2 groups. Anti-Spike antibody level of infected cases was 4732 (5206) U/mL and it was 3195 (4883) U/mL in non-infected cases; it was not different significantly.

Discussion

A hospital based case control study was conducted in July 2022 to November 2022 among patients on MHD who had confirmed COVID-19 infection by nasopharyngeal swab PCR. Patients in both groups had 4 doses of vaccine; Covaxin, Sinopharm, Sinovax and Covishield. In early 2022, different subtypes of the Omicron variant have been reported. The Omicron variant infection from Myanmar was reported in January 2022; the 4th wave of COVID-19 infection (Pyar, 2022) (Pyar K, 2022). In July 2022 to November 2022, 5th wave of epidemic in Myanmar was possibly due to the Omicron subvariant infection (Ministry of Health, 2022).

The earlier studies mentioned that old age, male sex, obesity, diabetes mellitus, chronic kidney disease, living in urban areas, being married and

having history of contact with the COVID-19 patients were significant risk factors for COVID-19 infection (Shahbazi et al., 2020). In addition, some study highlighted that socioeconomic factors and other factors controlling equity of health care system were related with COVID-19 infection: health disparities across age, race, ethnicity, language, income, and living conditions (Rozenfeld et al., 2020).

In this study, mean age in both infected and non-infected group was not statistically different; it was ten years younger than the risk age in Iran study. In age group over 60 years (n=17), 29.4% (5/17) got infected and 70.6%(12/17) did not acquire infection; old age was not the predictor of COVID-19 infection. In this study, female was more infected than male; not gave evidence for previous report (Shahbazi et al., 2020).

The proportion of ethnic groups in patients on MHD was Burmese 84%, Rakhine 3%, Karen 3%, Shan 3%, Danu 1%, Paoh 1%, Chin 1%, Kachin 1%, inlay 1%, Lesue 1% and Larhu 1%; it was in accordance with normal ethnic distribution in Myanmar. Regarding religion, the majority were Buddhist 95%; 4% were Christian; and 1% was Islam. It showed that neither race nor religion was the predictor for COVID-19 infection; this study overlooked previous report (Rozenfeld et al., 2020).

The patients on MHD were doing dialysis twice a week in public hospital; therefore, they exposed to other patients and health care personnel who were likely to have asymptomatic COVID-19 infection. Lin et al (2021) found that attending large gatherings and restaurant visits influenced the individual-level risk of contracting SARS-CoV-2 infection (Lin et al., 2021). Both COVID-19 infected cases and non-infected cases involved in this study had generally comparable/ similar background; they were gathering in same room with exposure to health care personnel; they were coming to public HD center twice a week; they had similar type of vaccine with same doses; and the poor immune condition generally.

Portugal study done in patients with autoimmune diseases showed that patients with connective tissue disorder taking TNFi and tocilizumab were found to be reduced the risk of infection by

SARS-CoV-2 and they had good prognosis. On the other hand, older age, patients with general comorbidities and rituximab were associated with increased risk for infection and worse prognosis (Cruz-Machado et al., n.d.). Another report revealed that the risk of COVID-19 infection was higher in older age, diabetic nephropathy, cerebrovascular accident and coronary heart disease (Can et al., 2022).

In this study, 13.6%(3/22) of patients in infected group and 7.7%(3/39) of patients in non-infected group had cerebrovascular accident; therefore, the risk was higher in patients on MHD with cerebrovascular accident. It gave another evidence to report by Can et al (Can et al., 2022). Nevertheless, 22.7%(5/22) of infected group and 25.6%(10/39) of non-infected group had coronary heart disease in this study; it neglected the report from US study(Can et al., 2022). Unlike the finding of US study, 10% of infected group and 20% of non-infected group had diabetic nephropathy in this study (Can et al., 2022). Therefore, diabetic nephropathy was not a risk factor for COVID-19 infection.

There were several controversial issues on relation between BMI and antibody response; obese individual had decrease antibody positivity (Ward et al., 2022) (Malavazos et al., 2021) and higher BMI was associated with lower titers of SARS-CoV-2 spike antibodies in men, but not in women (Yamamoto et al., 2022) (Kara et al., 2022). Following COVID-19 infection, those with high BMI had good antibody response (Zhai et al., 2022) (Pyar et al., 2022). BMI was 19.75 ± 3.00 kg/m^2 in infected group and 20.03 ± 2.76 kg/m^2 in non-infected group in this study; both groups were having normal BMI in this study.

The duration from last vaccination in infected group and non-infected group was 37.64 ± 2.22 days vs 38.77 ± 3.62 days in this study; not different. Generally, antibody begin to rise within the first few days following an infection with COVID-19 or after the vaccine. Later, the level steadily increase in concentration till 6 months; then, they decline gradually (Ortega et al., 2021).

The smoking status was 18.2% (4/22) in infected patients and 20.5%(8/39) in non-infected patients; it pay little attention to the previous report

"smokers were found to have low response to COVID-19 vaccine" (L. Wang et al., 2019).

Time vaccination in the morning was 63.6%(14/22) in infected group and 74.4% (29/39) in non-infected group in this study; it disregarded the finding "health care worker who received the SARS-CoV-2 vaccine in the afternoon had higher antibody response than those vaccinated in the morning" (L. Wang et al., 2019). In other words, the immune response of patients on MHD had not normal circadian rhythm.

The combination of a previous SARS-CoV-2 infection and vaccination, hybrid immunity, seemed to confer the greatest protection against SARS-CoV-2 infections (Pilz et al., 2022) (Goldberg et al., 2022). Regarding duration of protectivity, infection-acquired immunity boosted with vaccination lasted more than 1 year after infection (Hall et al., 2022) (Bates et al., 2022). The frequency of number of past COVID-19 infection was 64% in infected group and 68% in non-infected group; hybrid immunity was not different between 2 group in this study.

Hemoglobin level was lower in infected groups (8.26 ± 2.07 gm% vs 8.33 ± 2.02 gm%); it provided another evidence that anemia was a risk for COVID-19 infection (Drakesmith et al., 2021) (Preston et al., 2021). Serum albumin level was lower in infected group (42.47 ± 4.82 gm/dl vs 43.17 ± 4.10 gm/dl); it demonstrated the role of serum albumin in prevention of COVID-19 infection (Aoun et al., 2022) (Yen et al., 2021).

Risk of acquiring COVID-19 infection may be related with antibody response toward COVID-19 vaccination. Although the determinants of antibody response were multifactorial like age, previous infection, immunosuppressive therapy, body mass index, iron deficiency anemia, serum albumin level, longer vintage of end-stage kidney disease, previous infection, the time of the day of vaccination, vaccine type, sex, and days post-vaccination, anti-Spike antibody level of infected cases was 4732 (5206) U/mL and it was 3195 (4883) U/mL in non-infected cases; it was not different significantly.

Limitation of study

There are several limitations in this study: first, the sample size is not large as it was conducted in

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one HD center; secondly, it is better to analyze other predictors like serum iron, vitamin D level; thirdly, the viral load should be done at the time of diagnosis; finally, the variant and subtype of the Omicron variant should be performed to get better information.

Conclusions

The baseline characteristics like age, sex, ethnic group, religion, BMI, coronary heart disease, diabetic nephropathy, smoking status, duration of hemodialysis, past COVID-19 infection, time vaccination, duration from last vaccination and anti-Spike antibody level were non-predictors for 5ᵗʰ wave of COVID-19 infection among patients on MHD. The likely predictors were cerebrovascular accident, low hemoglobin and low serum albumin.

Recommendation

Patients on MHD attending public HD center are at high risk of acquiring COVID-19 infection, severe form of infection and high mortality owing to low immunity and anti-body response. Both booster vaccination and personnel protective measures to patients, their attendants and health care workers are essential. Surveillance is necessary particularly to those with cerebrovascular accident, low hemoglobin and low serum albumin.

Declaration of conflict of interest

The authors declared no potential conflicts of interests with respect to authorship and publication of this article.

Ethical approval

This study was approved by Hospital Research and Ethic Committee from Defence Services General Hospital (1000-Bedded) Mingaladon, Myanmar. Informed consent was also taken from each patients on MHD.

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