ORIGINAL ARTICLE

A Malaysian study on COVID-19 (SARS-CoV-2) vaccination immune response in haemodialysis patients: A prospective, multicentre, cohort study

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ABSTRACT

Introduction: Patients with end-stage renal disease (ESRD) have compromised immune systems, possibly reducing their vaccine-induced antibody responses compared to the general population. COVID-19 remains a persistent threat, with the virus continuing to mutate into new variants. Similar to influenza, there is a possibility that COVID-19 could resurge significantly, underscoring the importance of understanding vaccine-induced immunity in vulnerable populations. This study aims to determine the immunogenicity of this group to the COVID-19 vaccine.

Materials and Methods: Haemodialysis patients receiving the Pfizer-BioNTech mRNA vaccine were followed for at least 13 months. Blood samples were collected prior to every vaccine dose and at multiple intervals thereafter. Neutralising antibodies (nAb) against SARS-CoV-2 were measured. Patients voluntarily reported any COVID-19 infection.

Results: Between April 2021 and January 2023, 271 patients received at least one dose of the vaccine; 212 of these had at least one blood sample tested for nAb. Booster doses were given 26.2 weeks after the second dose. nAbs were detected in 16.8% of patients before vaccination. The nAb levels were higher than the non-convalescent patients after the first dose, but it was not statistically significant. Breakthrough infections were self-reported in 29.3% of patients. A significant association between breakthrough infections and history of COVID-19 infection cannot be established (p=0.188). There were 34 deaths (16.0%); 2 related to COVID-19. Younger age was associated with higher nAb reactivity post-first dose, but this difference diminished after the second dose.

Conclusion: Almost complete seropositivity (98.4%) was achieved after two doses of vaccine. Sustained antibody levels after the third dose suggest the value of a booster dose in protecting this vulnerable population. However, the occurrence of breakthrough infections highlights the need for continued monitoring, preventive measures, and further research to optimise vaccination strategies in haemodialysis patients.

KEYWORDS:
COVID-19 vaccine, haemodialysis, end-stage renal disease (ESRD)

INTRODUCTION

As of 2024, the WHO has reported over 700 million COVID-19 cases globally. In Malaysia, there have been more than 5 million cases, resulting in over 30,000 deaths.[1] The rise in hospitalisations and mortality has added a significant burden to the healthcare system. In the latest report, more than 50,000 individuals with end-stage renal disease (ESRD) in Malaysia were on dialysis in 2022.[2] The COVID-19 pandemic has significantly impacted this population, who are at a higher risk of infection compared to healthy individuals due to their compromised immune systems. COVID-19 remains a persistent threat, with the virus continuing to mutate into new variants. Similar to influenza, there is a possibility that COVID-19 could resurge significantly, underscoring the importance of understanding vaccine-induced immunity in vulnerable populations.

The lack of vitamin D and erythropoietin and accumulation of uremic toxins in ESRD patients affect the immune function of these patients. On top of that, the main receptor of SARS-CoV-2, the angiotensin converting enzyme 2 (ACE 2), is highly expressed in the kidney. All these conditions can induce cytokine storms, inflammation and oxidative stress, and in return, further damaging the kidney and worsening the severity of the infection.[3] The overall estimated case fatality rate of COVID-19 in ESRD patients undergoing renal replacement therapy was 18.06%, significantly higher than the global average of 4.98%.[4]

Vaccine development began in 2020 with the goal of preventing and reducing the morbidity and mortality caused by COVID-19. In December 2020, the FDA granted the first Emergency Use Authorisation (EUA) for a vaccine designed to

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prevent COVID-19.[5] Currently, there are two mRNA vaccines that encode the SARS-CoV-2 spike protein-Pfizer-BioNTech and Moderna. In Malaysia, haemodialysis patients received the Pfizer-BioNTech vaccine. Research indicates that two doses of the Pfizer-BioNTech vaccine are 94-95% effective in preventing confirmed COVID-19 cases and 75% effective in preventing severe COVID-19 in the general population.[6,7]

However, the effectiveness of the vaccine can differ based on various factors such as age, comorbidities, and immune status. In ESRD patients, the efficacy of the vaccine further depends on factors such as lack of vitamin D and erythropoietin, uremic conditions and use of immunosuppressants.[3] Seroconversion rates and antibody titres have been found to be significantly lower in ESRD patients, whether on dialysis or not, compared with healthy individuals.[8-11] Nevertheless, in haemodialysis patients, one dose of vaccine can reduce the risk of infection and serious outcomes by 41% and 46%, respectively, while two doses can bring these numbers to 69% and 83%.[3]

The Centers for Disease Control and Prevention (CDC) recommends that individuals who are severely or moderately immunocompromised should receive two or three doses of the same brand of COVID-19 vaccine.[12] They may also be eligible for additional doses. The use of additional doses is to enhance immunity, extend the duration of protection, and improve their ability to produce sufficient immune responses. No specific COVID-19 vaccine is preferred over another.

This study was carried out after the COVID-19 vaccine became available in Malaysia in early 2021, with the aim to gather local data examining the immune response of mRNA COVID-19 vaccine in haemodialysis patients and hence, to guide our national COVID-19 vaccination plan for this specific population. We find that there is still a lack of evidence on the immunogenicity and breakthrough infections representing the Malaysian population. This study provides real-world data on the effectiveness of the Pfizer-BioNTech (BNT162b2) COVID-19 vaccine in haemodialysis patients from this region.

MATERIALS AND METHODS

This study was conducted in eight dialysis units across four states in Peninsula Malaysia. Patients on haemodialysis who participated in COVID-19 vaccination program were eligible to be enrolled in this study and were prospectively followed up for at least 13 months. All subjects received the Pfizer-BioNTech (BNT162b2) mRNA vaccine. Full COVID-19 vaccination was defined as two doses of the vaccine administered 3 weeks apart. Booster dose was optional and was administered at least six months after the second dose.

All blood samples (3 to 5 ml) were taken by trained healthcare personnel at each centre. Baseline blood sample was taken on the day before the first vaccination dose. Subsequent blood samples were taken again before the second dose and one, six and 12 months thereafter (Figure 1). Additional sampling points were drawn for those who took three doses of the vaccine. These blood samples were then sent to the laboratory to be spun at 1000 x G for 15 minutes in a refrigerated centrifuge at 20˚C and the sera aliquoted into cryotubes. The cryotubes were then stored in a -80˚C freezer before being sent to the Institute of Medical Research to be analysed.

All samples were tested for IgG antibody against SARS-CoV-2 spike protein (S1) receptor-binding domain (RBD) by trained personnel, using the ADVIA Centaur SARS-CoV-2 spike IgG assay, sCOVG (Siemens Healthcare Diagnostic, NY, USA). The sCOVG assay is a fully automated two-step sandwich immunoassay using indirect chemiluminescent technology for qualitative and quantitative detection of IgG, including neutralising antibodies (nAb). The assay outputs an sCOVG index value was standardised to the WHO International Standard for anti-SARS-CoV-2 Immunoglobulin unit BAU/ml using a conversion factor of 21.8.[13] The positive threshold was 21.8 BAU/ml.

COVID-19 status was voluntarily reported by the patients. Breakthrough infection was defined as a SARS-CoV-2 virus infection that occurred at least 14 days after the last COVID-19 vaccine dose.

Statistical analysis

Continuous variables were summarised as means and standard deviations while categorical variables were expressed as frequencies and percentages. Chi-squared test or Fisher's exact test was used to compare between groups. Analysis was performed using STATA 11. A p-value of <0.05 was considered statistically significant.

RESULTS

Between April 2021 and March 2022, 271 patients (52.0% males) with a mean (SD) age of 61.1 (14.4) years received at least two doses of the Pfizer-BioNTech (BNT162b2) mRNA vaccine.

Of these, 212 patients who had at least one blood sample tested for neutralising antibodies were included in the study. Characteristics of these patients are shown in Table I. Booster dose was administered on average 26.2 weeks after the second dose. Median interval time between the second and booster doses was 25.4 weeks. There were 19 deaths (9.0%), of which 2 (10.5%) were related to COVID-19.

Breakthrough infections occurred in 62 (29.3%) patients; 21 (33.9%) and 41 (66.1%) occurred after the second and third doses, respectively, with a median time of 14.3 weeks after the second dose and 16.6 weeks after the third. Overall, a median (IQR) time of 15.5 (13.7, 18.1) weeks elapsed between the last vaccination dose and breakthrough infection. Seven (11.3%) of these patients were convalescent patients. There was no association between history of COVID-19 infection and breakthrough infection (p=0.188).

Neutralising antibody response

At some timepoints, the number of samples may be less than the total number of patients as some samples were compromised, volume was too little, or sample was not taken. The number of samples analysed are stated in the denominator.

Table I: Characteristics of subjects, n = 212

Characteristics	
Mean age, years (SD)	59.7 (14.7)
Gender	
Male, n (%)	112 (52.8)
Female, n (%)	100 (47.2)
Ethnicity	
Malay, n (%)	99 (46.7)
Chinese, n (%)	90 (42.5)
Indian, n (%)	15 (7.1)
Others, n (%)	8 (3.8)
Total doses of COVID-19 vaccine received	
2 doses, n (%)	25 (11.8)
2 doses + booster, n (%)	187 (88.2)

Table II: Neutralising antibody reactivity after doses 1 and 2

	Prior COVID-19 infection		p-value2
	No	Yes	
3 weeks post Dose 1			
Non-reactive	70 (39.8%)	10 (29.4%)	0.255
Reactive[1]	106 (60.2%)	24 (70.6%)	
1 month post Dose 2			
Non-reactive	1 (0.7%)	2 (6.1%)	0.08
Reactive[1]	154 (99.4%)	31 (93.9%)	

[1]Reactive (or positive) is determined according to the neutralising antibody index value of ≥ 1.00 U/ml (21.8 BAU/ml)
[2]Chi-squared test or Fisher's Exact test

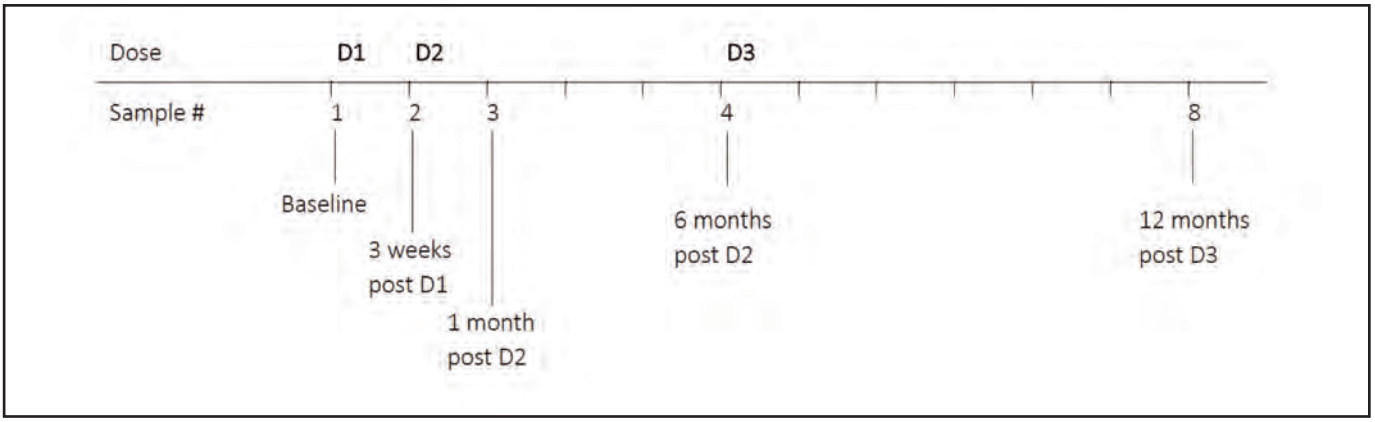

Fig. 1: Vaccination and blood sampling timeline

Neutralising antibodies against SARS-CoV-2 were detected in 16.8% (n=35/209) ESRD patients at baseline before their first vaccination dose, likely an indication of a recent or prior COVID-19 infection. The median (IQR) nAb titre among these convalescent individuals at baseline were 32.7 BAU/ml (24.6, 72.4) and ranged between 16.1 and 2180 BAU/ml, which was the upper limit of detection.

Neutralising antibodies were detected in 61.9% (n=130/210, median: 95.8 BAU/ml) and 98.4% (n=185/188, median: 2180 BAU/ml) patients after the first and second doses, respectively. The median nAb titres were higher three weeks after the first dose in patients previously exposed to COVID-19 infection (71.6 vs 35.1 BAU/ml) (Figure 3). However, it was not statistically significant (p=0.09). There were also no statistically significant differences in the neutralising antibody reactivity post-first and second doses between convalescent and non-convalescent individuals (Table II). A post hoc power calculation was performed based on the observed effect size and sample size, which indicated that the study had 99.8% power to detect the observed differences at a significance level of 0.05.

After adjusting for confounders, there were still no significant differences in reactivity between convalescent and non-convalescent individuals. Nevertheless, we found age to be significantly associated with nAb reactivity at 3 weeks post-first dose (adjusted OR 0.96, 95% CI 0.92, 0.97, p<0.001). The differences were no longer significant after the second dose.

Median nAb titres reached its peak detectable limit for all vaccinated patients 1 month (mean 4.4 weeks) after the

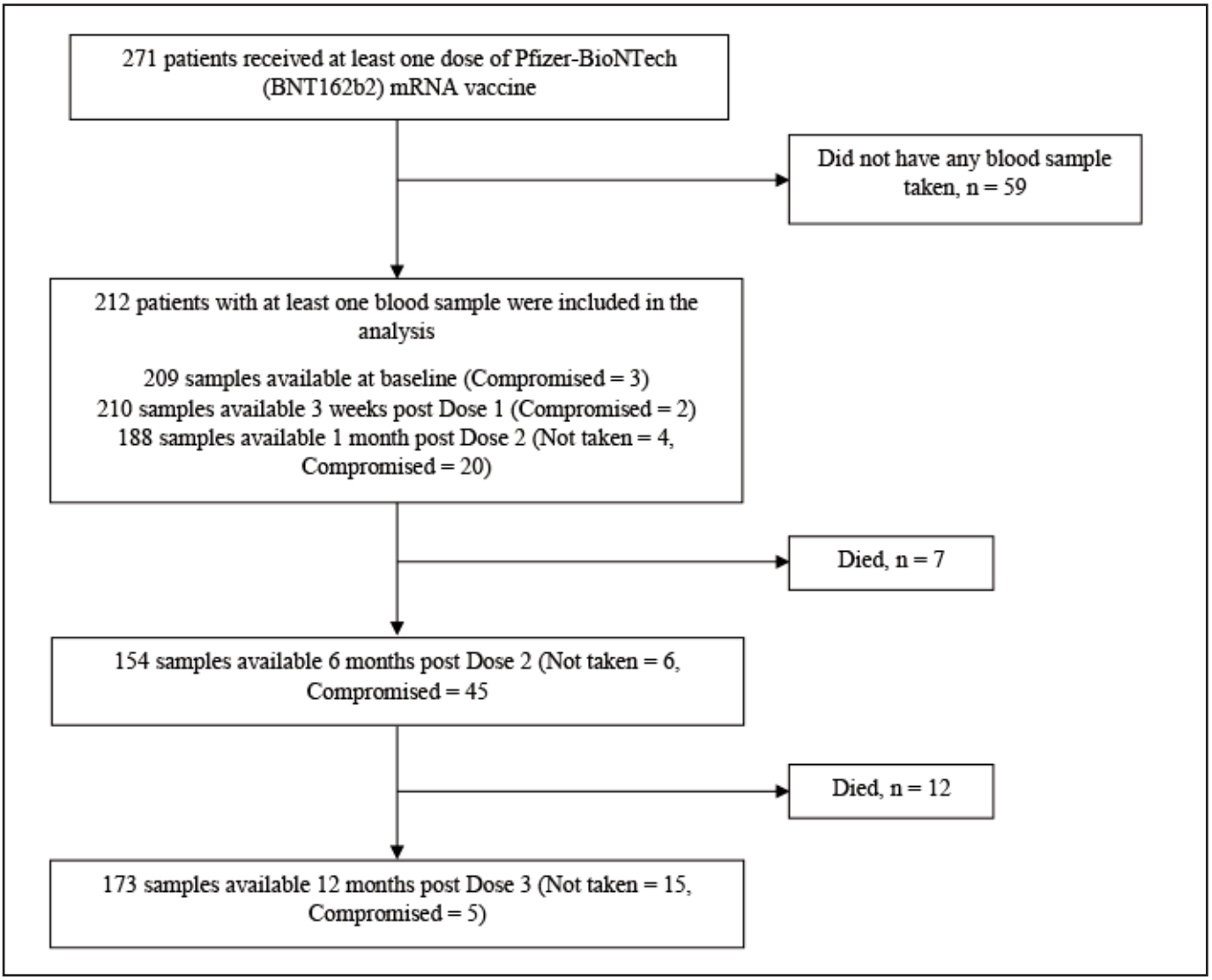

Fig. 2: Sample availability at each scheduled time point

second dose. The median level was reduced to 174.5 BAU/ml by the sixth month (mean 23.5 weeks). However, after the third dose, median nAb levels remained consistently high until the last observed sample 12 months later.

DISCUSSION

Patients with ESRD have compromised immune systems and comorbidities thus they are at a higher risk of severe COVID-19, and possibly reduced vaccine-induced antibody responses compared to the general population.[14,15]

We observed an almost complete seropositivity rate (98.4%) in our samples after two doses of the Pfizer- BNT162b2 vaccine compared to just one dose. Additionally, we found that patients with prior SARS-CoV-2 exposure had higher median nAb titres after the first dose of the vaccine, although this difference was not statistically significant. This finding is consistent with a study examining antibody responses after multiple doses of the same vaccine,[16] reinforcing the understanding that prior infection can prime the immune system, but vaccination provides a significant boost in antibody levels regardless of prior exposure. With two doses, the antibody titer levels in all patients reached the maximum detectable limit, further justifying the importance of completing the full vaccination course.

We also observed a waning in median nAb titres six months after the second dose, nevertheless levels were amplified and remained consistently high after the third (booster) dose. This supports the rationale behind booster dose recommendations, particularly for vulnerable populations, as emphasised by the "Coronavirus Disease 2019 (COVID-19)" (2023).[17] Our findings provide real-world evidence supporting this vaccination strategy in haemodialysis patients.

The occurrence of breakthrough infections is consistent with the understanding that while vaccination significantly reduces the risk, it does not completely eliminate the possibility of an infection. Breakthrough infection occurred in 29.3% of our patients, which was higher compared to other

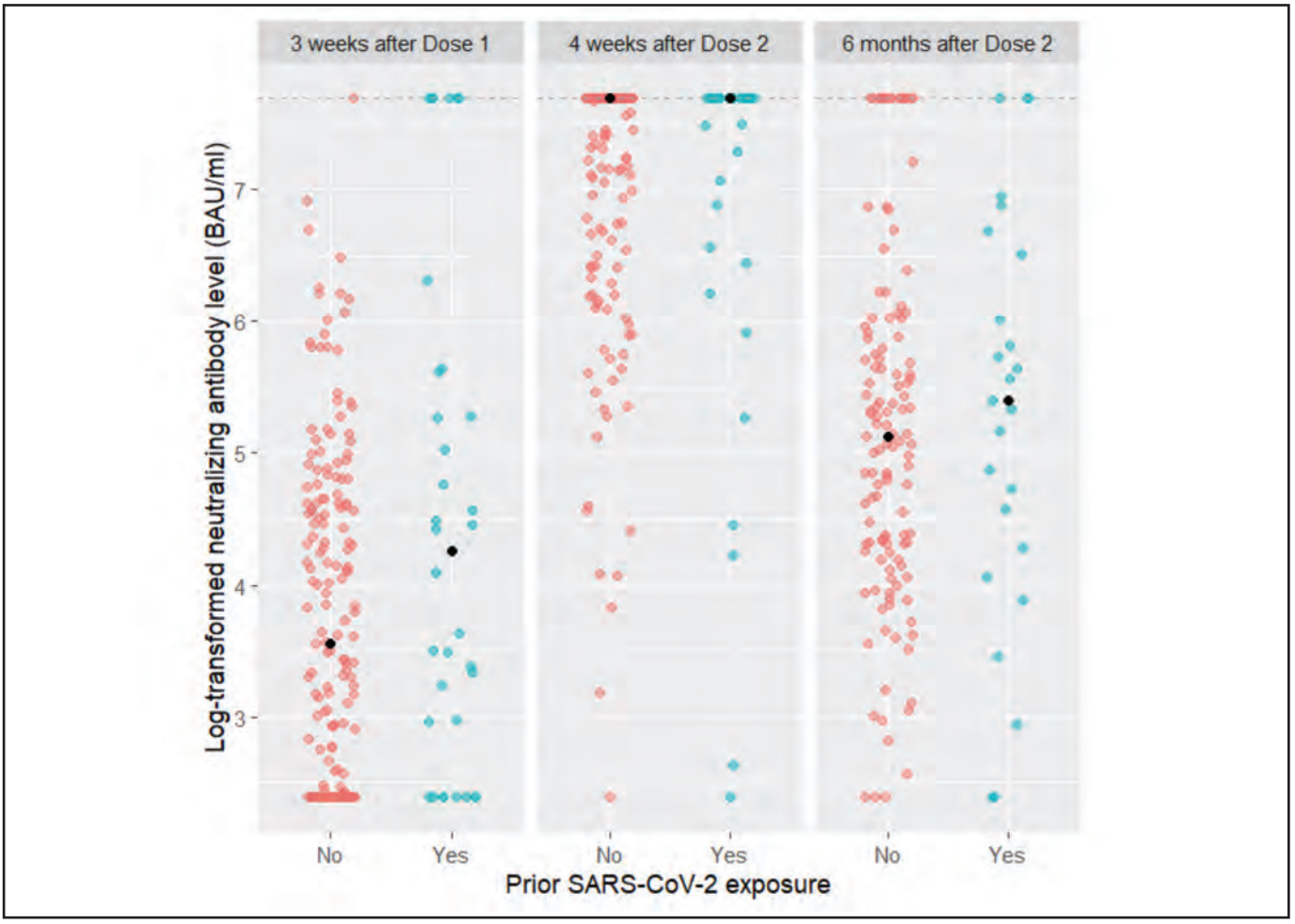

Fig. 3: Log-transformed neutralising antibody levels (BAU/ml) levels after doses 1 and 2 for those with and without prior exposure to SARS-CoV-2. The black circle indicates the median of the log-transformed antibody levels. The dotted grey line indicates the upper detection limit of the assay

studies in haemodialysis patients.[18,19] This discrepancy may be attributed to the study period and emergence of new variants that were either more contagious or more deadly. In mid to late 2021, the COVID-19 epidemic in Malaysia was dominated by the Delta variant before it was displaced by the highly transmissible Omicron variant in January 2022.[20] Most of the breakthrough infections in our cohort occurred after the third dose, coinciding with the period when the highly infective Omicron variant was widespread, which may explain the higher incidence rate observed.[21] Furthermore, this may reflect changes in individual behaviour and public practices following the relaxation of Malaysia's Movement Control Order (MCO). Nevertheless, there were no serious complications except in two cases where the patients died.

Limitations of the study

Our study has a few weaknesses. Firstly, breakthrough infection status was based on self-report. Infections were reported and documented, accompanied by test results, thus the likelihood of a false positive is reduced. If patients had symptoms during his clinic visit, his status would then be assessed by his treating nephrologist. Nonetheless, there may be particularly mild or asymptomatic cases that may have been missed. However, this limitation is unlikely to substantially affect the outcome of the study as the presence of asymptomatic infections itself may reflect an expected effect of vaccination which is known to attenuate disease severity even when infection is not fully prevented.

Secondly, blood-taking was done at fixed intervals rather than to the occurrence of breakthrough infections therefore we were unable to correlate levels of the antibody titres during the infection. Lastly, we did not conduct viral genotyping, therefore we were unable to determine which SARS-CoV-2 variants were responsible for the infections. Consequently, we could not assess whether immune responses differed depending on which variant patients were exposed to during the study.

CONCLUSION

Our results contribute to the growing body of evidence supporting the immunogenicity of this vaccine in haemodialysis patients. The high seropositivity rates and the sustained antibody levels after the booster dose underscore the importance of this vaccine in protecting this vulnerable population.

However, the occurrence of breakthrough infections highlights the need for continued monitoring, preventive measures, and further research to optimize vaccination strategies in haemodialysis patients.

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