Immunogenicity of the third and fourth BNT162b2 mRNA COVID-19 boosters and factors associated with immune response in patients with SLE and rheumatoid arthritis

Theerada Assawasaksakul, Seelwan Sathitratanaacheewin, Preeyaporn Vichaiwattana, Nasamon Wanlapakorn, Yong Poovorawan, Yingyos Avihingsanon, Nawaporn Assawasaksakul, Wonngarm Kittanamongkolchai

ABSTRACT

Objectives To evaluate the safety and immunogenicity of third and fourth BNT162b2 boosters in patients with SLE and rheumatoid arthritis (RA).

Methods Patients with SLE and RA aged 18–65 years who completed a series of inactivated, adenoviral vector, or heterogenous adenoviral vector/mRNA vaccines for at least 28 days were enrolled. Immunogenicity assessment was done before and day 15 after each booster vaccination. The third BNT162b2 booster was administered on day 1. Patients with suboptimal humoral response to the third booster dose (antireceptor-binding domain (RBD) IgG on day 15 <2360 BAU/mL) were given a fourth BNT162b2 booster on day 22.

Results Seventy-one patients with SLE and 29 patients with RA were enrolled. The third booster raised anti-RBD IgG by 15-fold, and patients with positive neutralising activity against the Omicron variant increased from 0% to 42%. Patients with positive cellular immune response also increased from 55% to 94%. High immunosuppressive load and initial inactivated vaccine were associated with lower anti-RBD IgG titre. Fifty-four patients had suboptimal humoral responses to the third booster and 28 received a fourth booster dose. Although anti-RBD IgG increased further by sevenfold, no significant change in neutralising activity against the Omicron variant was observed. There were two severe SLE flares that occurred shortly after the fourth booster dose.

Conclusions The third BNT162b2 booster significantly improved humoral and cellular immunogenicity in patients with SLE and RA. The benefit of a short-interval fourth booster in patients with suboptimal humoral response was unclear.

Trial registration number TCTR20211220004.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The SARS-CoV-2 omicron variant (B.1.1.159) has multiple mutations that have resulted in greater escape from immune protection elicited by COVID-19 vaccines.
⇒ More attenuated immune response to SARS-CoV-2 vaccination has been observed in patients with autoimmune rheumatic diseases. The additional third dose of SARS-CoV-2 vaccine has been recommended in immunocompromised populations.
⇒ Some immunocompromised patients have a suboptimal humoral response to a third booster dose. Factors associated with poor immune response have not been adequately studied.
⇒ Administration of more than three doses has been shown to enhance immune response in some severely immunocompromised patients.

WHAT THIS STUDY ADDS

⇒ The third BNT162b2 booster was well tolerated, and significantly improved both humoral and cellular immunogenicity in patients with SLE and RA previously vaccinated with either inactivated, adenoviral vector, or heterogenous adenoviral vector/mRNA vaccines.
⇒ High intensity of immunosuppressive therapy and initial inactivated vaccine were associated with lower humoral immune response to the third BNT162b2 booster.
⇒ Short interval administration of a fourth BNT162b2 booster in poor humoral immune responders may not offer additional protection against the omicron variant, and flares were observed in patients with SLE.

INTRODUCTION

The newly emerged B.1.1.159 (Omicron) variant of SARS-CoV-2 has become the dominant strain globally. Its multiple mutations have resulted in greater escape from immune protection elicited by COVID-19 vaccines. Recent studies in healthy populations suggested that the third booster dose of mRNA vaccine enhanced protection against
the Omicron variant, although neutralising antibody titres were reduced by sevenfold compared with the ancestral variant.²–⁴

In patients with autoimmune rheumatic diseases, a more attenuated immune response to SARS-CoV-2 vaccination has been observed.⁵ According to a recent study, a third dose of mRNA 1273 vaccine significantly increased antireceptor-binding domain (RBD) titre in transplant recipients compared with placebo. However, in approximately half of the patients who received a booster, the anti-RBD titre remained low (<100 U/mL).⁶ Clinical factors associated with the immunogenicity in immunosuppressed populations have not been adequately studied. Several booster doses may be required to achieve adequate immune protection.⁷ The safety and risk of disease flare associated with repetitive vaccination in patients with autoimmune rheumatic diseases remain unknown.

We aimed to evaluate safety and immunogenicity of the third and fourth BNT162b2 booster doses in patients with SLE and rheumatoid arthritis (RA) previously vaccinated with either adenoviral vector, inactivated or heterogenous adenoviral vector/mRNA regimens. Factors associated with humoral immune response after the third booster dose were also evaluated.

### METHODS

**Trial design**

This is a prospective, single arm, open-labelled study investigating the safety and immunogenicity of third and fourth mRNA vaccine (BNT162b2, Pfizer-BioNTech) booster doses in patients with SLE and RA who have previously been vaccinated with inactivated SARS-CoV-2 COVID-19 vaccine (CoronaVac or COVILO), adenovirus-vectored vaccine (AZD1222, AstraZeneca) or heterologous regimen of AZD1222/BNT162b2.

**Participants**

Eligible patients were aged 18–65 years who met the classification criteria for SLE (American College of Rheumatology (ACR) 1997⁸ or the Systemic Lupus International Collaborating Clinics criteria⁹ or European League Against Rheumatism (EULAR)/ACR classification¹⁰ or RA (2010 ACR and EULAR classification criteria for RA¹¹ and had completed a series of inactivated vaccine (CoronaVac or COVILO), AZD1222 or AZD1222/BNT162b2 for at least 28 days. Intervals between the first and second doses of COVID-19 vaccines were stipulated by vaccine types: 4 weeks for inactivated vaccine, 8–12 weeks for AZD1222/AZD1222 and 4–8 weeks for AZD1222/BNT162b2.

### Figure 1

Schematic diagram of the study. BAU, binding antibody unit; RBD, receptor-binding domain.

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**Blood collection**

- **Day 1:** BNT162b2 (3rd dose)
- **Day 15:** Blood collection
- **Day 22:** BNT162b2 (4th dose), if anti-RBD IgG < 2,360 BAU/mL
- **Day 36:** Blood collection

*Blood collection for immunogenicity assessment: anti-RBD immunoglobulin, anti-RBD IgG (Abbott), anti-nucleocapsid IgG, neutralization activity against SARS-CoV-2 Omicron variants (B.1.1.529) (random subset), and ELISPOT (random subset)*
Exclusion criteria were history of SARS-CoV-2 infection, allergy to a vaccine component, pregnancy, breastfeeding and active disease at enrolment. Recruitment occurred at the rheumatology and nephrology clinic in a tertiary referral centre in Bangkok, Thailand, from 1 August 2021 to 30 November 2021. Consecutive patients meeting eligibility criteria were invited to participate in the study and provided written informed consent.

Procedures
At baseline, demographic information, current medications, disease activity and blood samples for immunogenicity analyses were collected. On day 1, 30 μg of BNT162b2 was administered intramuscularly via the deltoid region. On day 15, blood samples were collected in order to assess immune responses at their peak. On day 22, those with suboptimal humoral response, defined as anti-RBD IgG less than 2360 BAU/mL (16503 AU/mL) after the third booster, were given the fourth BNT162b2 booster at 30 μg. Blood sample collection for immune responses assessment was performed again on day 36 (figure 1).

We chose the anti-RBD IgG (Abbott Diagnostics, Abbott Park, Illinois, USA) cut-off value of 2560 BAU/mL (16503 AU/mL) as it corresponded to vaccine efficacy of 90% for wild type. We aimed for high vaccine efficacy due to the spread of vaccine-resistant variants including Delta (B.1.617.2) and Omicron (B.1.1.529) variants.

Immunogenicity assessment
The humoral responses were measured by serum binding IgG levels against RBD of the SARS-CoV-2 spike protein using the SARS-CoV-2 IgG II Quant assay (Abbott Diagnostics). Values of 50 arbitrary U/mL (AU/mL) were considered positive. The numerical AU/mL is converted to binding antibody unit (BAU) per millilitre (BAU/mL) by multiplying it by 0.142. The SARS-CoV-2 cPassTM surrogate virus-neutralising test (GenScript, Piscataway, New Jersey, USA) was used to evaluate the neutralising activity against the SARS-CoV-2 Omicron variant in a subset of prebooster and postbooster samples. According to the manufacturer’s recommendations, inhibition levels greater than 30% were considered positive. The SARS-CoV-2 IgG assay (Abbott Diagnostics) was used to quantify the nucleocapsid protein of SARS-CoV-2 to evaluate for recent SARS-CoV-2 infection. Positive values were defined as 1.4. The cellular immune responses were measured by human IFN-γ-ELISpot assay (ELISpot) in a random subset of patients. Positive responses were defined as >50 spots per 10⁶ peripheral blood mononuclear cells.

Immunosuppressive treatments
Due to various immunosuppressive treatment regimens used in our cohort and more than half of patients taking two or more immunosuppressive medications, we adopted and modified the Vasudev score to standardise the overall immunosuppressive load. One unit of immunosuppression was assigned for each of the following doses of immunosuppressive medications: prednisone 5 mg/day, mycophenolate mofetil (MMF) 500 mg/day, azathioprine 100 mg/day, cyclosporine 100 mg/day, tacrolimus 2 mg/day, leflunomide 10 mg/day and methotrexate 15 mg/week (table 1). The average dose of immunosuppressive medication during the first 30 days was used for immunosuppressive unit scale calculation. Adjustment of immunosuppressive medications during such periods was not allowed unless clinically indicated.

Safety and reactogenicity assessment
Thanou modified SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus: National Assessment–Systemic Lupus Erythematosus Disease Activity Index) Flare Index was used to determine SLE flares. Disease activity of patients with RA was measured by Disease Activity Score 28 ESR in a subset of patients. The local and systemic reactogenicities were reviewed on day 15 and reviewed again on day 36 in those who received the second booster.

Table 1 Immunosuppressive load calculation scale modified from Vasudev score (9)

<table>
<thead>
<tr>
<th>Immunosuppressive medication</th>
<th>Unit dose</th>
<th>Immunosuppression unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>5 mg/day</td>
<td>1</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>100 mg/day</td>
<td>1</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>100 mg/day</td>
<td>1</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>2 mg/day</td>
<td>1</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>500 mg/day</td>
<td>1</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>15 mg/week</td>
<td>1</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>10 mg/day</td>
<td>1</td>
</tr>
</tbody>
</table>

One unit of immunosuppression was assigned to the corresponding doses of agents.

Statistical analyses
Continuous variables were expressed as mean (SD) or mean (95% CI). Antibody levels were presented as geometric mean titre (GMT) with 95% CI, or median with range when appropriate. Geometric means were computed by natural log transformation of the data points and calculating the mean and 95% CI on the transformed data. The ln-transformed mean and 95% CI were transformed back to the original scale.

Student’s t-test was used to compare the differences between two groups. Multiple groups were compared using one-way analysis of variance, followed by the Bonferroni post hoc test. Pearson or Spearman’s correlation was used to test for associations between two variables.

Univariable and multivariable linear regression was performed to determine the relationship between clinical factors and immune responses after the third booster dose. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using JMP software V.13.2.1 (SAS Institute, Cary, North Carolina, USA),
RESULTS

One hundred patients were enrolled with 71 having SLE and 29 having RA. All of the patients had stable disease. Ninety three per cent of patients were women. The majority of patients with SLE received MMF, and the majority of patients with RA received methotrexate (table 2).

Because ADZ1222 was primarily administered to the elderly in Thailand, it was given to slightly over half of the patients with RA (51.7%) who tended to be relatively older. Vaccine administration was more equally divided among patients with SLE with 38% receiving inactivated vaccines, 36.6% receiving ADZ1222/ADZ1222% and 25.4% receiving AZD1222/BNT162b2. The inactivated vaccine had the longest interval between the second and third booster doses because it was the first vaccine series available in Thailand (table 2).

Humoral immune responses following the third and fourth BNT162b2 booster doses

Anti-RBD IgG

Antinucleocapsid antibodies were undetectable in all prebooster and postbooster serum samples, indicating that no COVID-19 infection occurred during the peri-booster period. After the third booster, the GMT of anti-RBD IgG increased by 15-fold (from 69 (95% CI 42 to 112) BAU/mL to 1034 BAU/mL (95% CI 677 to 1577), p<0.0001) (figure 2A). Patients with anti-RBD IgG levels of more than 2360 BAU/mL increased from 2% to 46% (p<0.0001)

Of 54 patients (39 with SLE and 15 with RA) with suboptimal responses to the third booster vaccine (anti-RBD IgG titre <2360 BAU/mL on day 15), 28 (23 with SLE and 5 with RA) received the fourth BNT162b2 booster on day 22. The remaining patients refused to have another booster dose. The GMT of anti-RBD Ig increased by sevenfold after the fourth booster (88 BAU/mL (range 49–155) to 644 BAU/mL (range 398–1041), p<0.0001),

Table 2

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>SLE (n=71)</th>
<th>RA (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prebooster anti-RBD IgG&gt;2360 BAU/mL, n (%)</td>
<td>2 (2.8)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD) unless otherwise indicated. BAU, binding antibody unit; CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score using 28 joint counts; ESR, erythrocyte sedimentation rate; anti-RBD IgG, antispike receptor-binding domain IgG antibody; MMF, mycophenolate mofetil; RA, rheumatoid arthritis; RBD, receptor-binding domain; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; TNF, tumour necrosis factor.

Table 2

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>SLE (n=71)</th>
<th>RA (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of immunosuppressive medications used, n (%)</td>
<td>0</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>1</td>
<td>13 (18.3)</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>2</td>
<td>51 (71.8)</td>
<td>9 (31.0)</td>
</tr>
<tr>
<td>3</td>
<td>4 (5.6)</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>4</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Overall immunosuppressive load (modified Vasudev score)</td>
<td>2.71 (1.6)</td>
<td>2.78 (2.1)</td>
</tr>
</tbody>
</table>

Initial vaccine regimen, n (%) | Inactivated/inactivated | 27 (38.0) | 6 (20.7) |
| AZD1222/AZD1222 | 26 (36.6) | 15 (51.7) |
| AZD1222/BNT162b2 | 18 (25.4) | 8 (27.6) |

Interval between the second dose of initial vaccine and third BNT162b2 booster (days)

| Inactivated/inactivated | 88 (31) | 94 (44) |
| AZD1222/AZD1222 | 43 (13) | 53 (17) |
| AZD1222/BNT162b2 | 56 (15) | 61 (11) |

Continued
**Figure 2**  Humoral immune response before and after the third and fourth BNT162b2 booster. Optimal humoral response defined as anti-RBD IgG more than 2360 BAU/mL (16503 AU/mL) after the third booster. BAU, binding antibody unit; RBD, receptor-binding domain.
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Table 3  Association between clinical factors and ln(anti-RBD IgG) at day 15 following a third BNT162b2 booster in patients with SLE and RA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
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<tbody>
<tr>
<td></td>
<td>Regression coefficient</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>0.02</td>
<td>−0.01 to 0.05</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>−0.18</td>
<td>−0.44 to 0.66</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>0.3</td>
<td>−0.16 to 0.77</td>
</tr>
<tr>
<td>Initial vaccine regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZD1222/BNT162b2</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>AZD1222/AZD1222</td>
<td>0.02</td>
<td>−0.54 to 0.58</td>
</tr>
<tr>
<td>Inactivated/inactivated</td>
<td>−0.71</td>
<td>−1.31 to −0.12</td>
</tr>
<tr>
<td>Interval between the second dose of initial vaccine and third BNT162b2 booster</td>
<td>0.002</td>
<td>−0.01 to 0.02</td>
</tr>
<tr>
<td>Total immunosuppressive load</td>
<td>−0.41</td>
<td>−0.64 to −0.18</td>
</tr>
</tbody>
</table>

RA, rheumatoid arthritis.

and three patients (11%) had anti-RBD IgG of >2560 BAU/mL (figure 2B).

**Neutralising activity against omicron variant**
We randomly selected 12 patients with SLE from each initial vaccine group (inactivated SARS-CoV2 vaccine, AZD1222/AZD1222 and AZD1222/BNT162b2) to assess for neutralising activity against the Omicron variant (n=36). The level of anti-RBD IgG corresponded with the neutralising activity ($r^2=0.42$, p<0.0001).

Before receiving a third booster dose, none of the patients demonstrated positive neutralising activity against the Omicron variant. After the third booster dose, 15 patients (42%) had positive neutralising activity (>30% inhibition), and the mean percent inhibition increased from 5.1% (95% CI 3.3% to 6.8%) to 28.0% (95% CI 17.7% to 38.4%) (p<0.0001) (figure 2C).

Of 36 patients, 13 were subsequently given the fourth booster dose according to the protocol. The neutralising activity after the third and fourth booster doses was not statistically different (p=0.7). There were only 1 (7.7%) and 2 (15.4%) of the 13 patients who demonstrated positive neutralising activity against the Omicron variant after the third and fourth booster doses, respectively (figure 2D).

**Factors associated with humoral immune response**
The initial inactivated vaccine and high immunosuppressive load were associated with low anti-RBD IgG titre, even adjusting for other covariates including age, sex, diagnosis and vaccine interval between the second and the third booster doses (table 3). Figure 3A–C illustrates the relationship between total immunosuppressive load and type of initial vaccine with anti-RBD IgG levels.

**Cellular immune responses following the third BNT162b2 booster**
The cellular immune response of 47 randomly selected patients was assessed before and 14 days after the third booster dose. Twenty-one, 15 and 11 patients received inactivated vaccines, AZD1222/AZD1222 and AZD1222/BNT162b2 as initial vaccines, respectively. Thirty-four patients (72%) had SLE and the rest had RA.

After a third booster, the proportion of individuals who had a positive ELISpot test increased from 55% to 94%. Before a third booster, those who initially received inactivated vaccines had the lowest rate of positive ELISpot test (31%), followed by AZD1222/AZD1222 (67%) and AZD1222/BNT162b2 (73%) (p=0.05), which increased to 90%, 93% and 100% after the third booster (p=0.4). There was no significant correlation between ELISpot and anti-RBD IgG level after booster ($r(45)=0.22$, p=0.14).

**Safety, reactogenicity and disease activity of BNT162b2 booster**
There was no COVID-19 breakthrough infection up to 90 days following the third booster vaccination. The...
Epidemiology and outcomes

BNT162b2 boosters were well tolerated, and all reactions were mild and transient. The three most common reactions were injection site pain, fatigue and fever (online supplemental figure 3). Anti-RBD IgG levels did not differ between those without adverse reactions and those who had at least one reaction (p=0.4).

Two patients with SLE (8.7%) experienced disease flare after the fourth booster dose. One patient developed rapidly progressive glomerulonephritis from lupus nephritis 1 week after receiving the fourth booster vaccine. MMF also had been withheld a few months before the booster administration due to a history of multiple infections. The other developed severe thrombocytopenia 4 weeks after receiving a booster dose. The patient’s disease had been inactive for several years and she had not been receiving...
immunosuppressive treatment prior to this episode of flare.

**DISCUSSION**

As the Omicron variant continues to spread around the world and display increased immune escape potential, aggregating data to optimise immunisation strategies in autoimmune rheumatic disease populations is crucial. This study found that a third booster dose of BNT162b2 in patients with SLE and RA was well tolerated and elicited a strong humoral immune response against the Omicron variant. However, approximately half of our patients still had a poor response to the third BNT162b2 booster, particularly those who received more intense immunosuppressive treatment or an inactivated vaccine in the initial vaccine series.

By giving a fourth BNT162b2 booster to poor immune responders, anti-RBD IgG increased to a lesser extent compared with the third booster dose (7-fold vs 15 fold), possibly due to the short interval between the third and fourth boosters. Despite the increase of anti-RBD IgG, no discernible increase in neutralising activity against the Omicron variant was observed. In addition, 8.7% of patients with SLE experienced severe flares shortly after the fourth booster dose, whereas other studies found mostly mild to moderate SLE flares (0% to 10.4%) after the initial vaccine series. In an animal model, repeated exposure to the same antigen was shown to induce autoimmunity. Given this uncertainty, the benefit of administering a short interval fourth booster dose should be balanced against the risk of disease activation.

In terms of cellular immunity, a third BNT162b2 booster elicited T-cell responses in nearly all of our patients. Positive cellular immune response rates were comparable across initial vaccine types, even among those who received inactivated vaccines, which are known to induce lower T-cell response. Recent studies have demonstrated that while variants of concern can evade neutralising antibodies, the cell-mediated immune response cross-reacted with the variants of concern. It also confers resilient protection against severe disease as antibody titres wane overtime.

Prior to the booster vaccination, only 2% of patients in our cohort had antibody levels above the target of 2960 BAU/mL. This could be due to the study’s timing of antibody measurement and high target antibody level. Prebooster anti-RBD IgG was measured at day 65 (95% CI 59 to 70) after the second vaccination. As a result, antibodies may decay by half at the time of measurement. Due to the spread of vaccine-resistant RBD, we also aimed for a high anti-RBD IgG cut-off value, which corresponded to vaccine efficacy of 90% for wild type.

It should be noted that there were several limitations to this study. The findings are observational and based on a small sample size, so they should be interpreted with caution. The results may not be generalisable to other autoimmune rheumatic conditions, other immunosuppressive regimens such as B-cell depletion therapy or initial mRNA vaccine series. The immunosuppressive load calculation was adapted from the prior study which was arbitrarily determined.

In conclusion, this study demonstrated that the third BNT162b2 booster was well tolerated and significantly improved humoral and cellular immunogenicity in patients with SLE and RA. The intensity of immunosuppressive therapy and the type of initial vaccine appear to affect the humoral immune response to the third booster. In poor humoral responders, a fourth BNT162b2 booster administered at a short interval may not provide additional protection against the omicron variant. Our finding that severe flares were observed in patients with SLE after the fourth booster is also cause for caution and additional research on the appropriateness of a fourth booster and the timing of such booster in our population.

**Author affiliations**

1 Division of Rheumatology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
2 Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
3 Center of Excellence in Clinical Virology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
4 FRS(T), Thailand, the Royal Society of Thailand, Sanam Sueapa, Dusit, Bangkok, Thailand
5 Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
6 Cardiometabolic Center, BHF Hospital, Bangkok, Thailand
7 Mahachakri Sirindhorn Clinical Research Center, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
8 Renal Immunology and Transplantation Research Unit, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

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**Contributors** TA, SS and WK contributed to the conception and design of the work; acquisition, analysis, interpretation of data; and drafting and revision of the work; accepts full responsibility for the work and/or the conduct of the study, and controlled the decision to publish. PV, NW, YP , YA and NA contributed to data collection by participant(s). P atients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

**Patient consent for publication** Consent obtained directly from patient(s).

**Ethics approval** This study involves human participants and was approved by the institutional review board of the Faculty of Medicine, Chulalongkorn University (COA No. 1425/2021). The participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.
References


