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Humoral response to SARS-CoV-2 vaccination in haemodialysis patients and a matched cohort

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ABSTRACT

Objectives SARS-CoV-2 vaccination is a crucial intervention for infection control; however, the immune response to vaccination in dialysis patients has been reported to be moderate compared with healthy adults. There are few studies available on humoral response in immunised dialysis patients compared with well-matched control group, we conducted a prospective cohort study measuring SARS-CoV-2 antibody titres in Fukushima Prefecture, Japan since September 2021.

Participants We compared the titres of both anti-SARS-CoV-2 S1 IgG and neutralising antibodies of 65 haemodialysis patients (dialysis group) with 500 residents in Soma, Fukushima (control group).

Methods Coarsened exact matching was used to balance sex, age and days from the second dose between dialysis and control groups.

Results Significant differences in the titres of anti-SARS-CoV-2 S1 IgG and neutralising antibodies were observed between the dialysis and control groups; anti-SARS-CoV-2 S1 IgG: 168.35 (4.48–1074.29) AU/mL and 269.81 (4.72–945.96) AU/mL in dialysis and control groups, p=0.02, neutralising antibodies: 35.77 (2.94–826.06) AU/mL and 62.22 (0.00–535.57) AU/mL, p=0.007, respectively).

Conclusions We observed significantly reduced anti-SARS-CoV-2 S1 antibody and neutralising antibodies in haemodialysis patients compared with cohorts matched for duration after vaccination. Patients receiving haemodialysis should be carefully monitored for immunological responses to the vaccination and COVID-19 infection.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We compared the anti-SARS-CoV-2 S1 IgG and neutralising antibodies titres of the dialysis group with the control group.
⇒ Coarsened exact matching method was used to balance sex, age and days from second dose between dialysis and control groups.
⇒ We evaluated the initial measurement of anti-SARS-CoV-2 antibodies as a preliminary study and did not assess longitudinal changes in antibody titres over time.
⇒ Detailed characteristics of dialysis patients such as duration of dialysis and their epidemiology were not available in this study.

INTRODUCTION

Patients receiving haemodialysis are at high risk of SARS-CoV-2 infection and mortality.[1 2] Patients with end-stage renal disease are susceptible to infection due to their immunocompromised state, and infection has been the second most common cause of mortality. Regular visits to the dialysis centre could increase the risk of SARS-CoV-2 infection due to limited capacity for air ventilation, close proximity and limited ability to physically distance.[3] In Japan, 5471 dialysis patients were infected with SARS-CoV-2, and 519 died, accounting for 9.5% of mortality, as of 18 March 2022.[4] The COVID-19 mortality in dialysis patients was higher than in the general population in Japan (0.44% as of 24 March 2022). Thus, preventative measures for the SARS-CoV-2 outbreak should be taken for dialysis patients.

SARS-CoV-2 vaccination is a crucial element for infection control; however, the immune response to vaccination in dialysis patients was reported to be moderate to less than healthy adults.[5] Significant decreases in the titre of anti-spike protein and neutralising antibodies of SARS-CoV-2 were observed in dialysis patients compared with healthy individuals.[6–9] However, few studies on humoral response in immunised dialysis patients compared with the well-matched control group. Age, sex and the postvaccination period were reported to be dependent variables of anti-SARS-CoV-2 antibody titres.[10 11] We conducted a prospective cohort study measuring SARS-CoV-2 antibodies in Fukushima Prefecture, Japan, since September 2021.[12–14] We present the preliminary results of the humoral response in dialysis patients, along with a comparison

with volunteer residents obtained by coarsened exact matching (CEM).

METHODS

Study design and population

This study was part of prospective cohort study. The public health office of Soma City (Fukushima Prefecture, Japan) broadly informed the residents of this study to understand their immunisation status as an infection control measurement. Five hundred residents voluntarily participated in the study. Sixty-five patients treated with haemodialysis in a hospital in Soma were also recruited in this study. All dialysis patients were outpatients receiving treatment at a hospital-associated clinic. All participants received a survey asking their age, sex, dates of vaccination with SARS-CoV-2, adverse reaction after vaccination, prescribed medication and history of the disease. The inclusion criteria for this study were the completion of the primary administration of the SARS-CoV-2 vaccine.

Serological assay

IgG antibody levels against the SARS-CoV-2 spike protein (S1) and neutralising activity were measured as secondary immune status outcome after second dose vaccination. IgG antibody titres against the SARS-CoV-2 N-protein were used to determine the previous status of COVID-19 infection. Collection of blood samples from all the participants was performed between 14 September and 25 September 2021. After serum isolation at blood collection sites, all frozen serum (−20°C) was shipped and evaluated in a central laboratory at the University of Tokyo.

All serological assays were performed using the CLIA assay with iFlash 3000 (YHLO Biotech, Shenzhen, China) and iFlash-2019-nCoV series (YHLO Biotech, Shenzhen, China) as reagents. The measurement was performed according to the manufacturer's instructions between 22 September 2021 and 28 October 2021. The validation process for quality control was conducted daily before measurement. The cut-off values of the anti-S1 and N antibodies and the neutralising activity were 10 AU/mL, which were the official cut-off values of the manufacturer. For neutralising activity, AU/mL×2.4 was used to convert to International Units (IU/mL). For IgG, AU/mL×1.0 was used to convert to binding antibody units (BAU/mL). The neutralising activity was set to 500 AU/mL if the activity was above 500 AU/mL due to the upper limit of the measurement. The results of similar antibody tests performed in this region can be found elsewhere.[15–17]

Statistical analysis

The CEM method was used to balance sex, age and days from second dose between dialysis and control groups.[18] CEM was performed using the MatchIt package.[19] Sex, age and days passed since the second dose were binned by Sturge's method if the variable were continuous. Thirteen subclasses were obtained with both haemodialysis patients and healthy controls. Weights were assigned to each subclass of haemodialysis patients or healthy controls to ensure the same ratio of haemodialysis patients and healthy controls is maintained within each subclass to the overall matched cohort. These weights were also applied when performing linear regression. The standardised mean differences were less than 0.1 on all matched variables. We compared the characteristics of the haemodynamic patients (dialysis group) with the residents of Soma (control group). The two-group comparison was performed with the Mann-Whitney U and Fisher's exact tests for continuous and categorical variables, respectively. The missing data were excluded from the individual analysis. Multivariable linear regression models were employed to predict log 10 of anti-SARS-CoV-2 S1 IgG and neutralising antibodies with participant characteristics of the participant group, such as sex, age and days between blood collection and second vaccination for the matched cohort. Linearity and heteroscedasticity were confirmed by plotting the residual against the fitted values. Normality on residuals were confirmed by QQ plot. Cook's distance was less than 0.5 for all points. All analyses were performed using STATA IC (V.15) except for the CEM obtained by R package MatchIt package (V.4.3.2) of R (V.4.1.1).[20] Violin and dot plots were constructed using the R package ggplot2 (V.3.3.2). Statistical significance was considered if the two-sided p values were less than 0.05.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

A total of 65 patients receiving haemodialysis and 500 residents were included in this study (table 1) (online supplemental table S1 for missing data). Although all participants in this study received two doses of vaccination (most patients received BNT162b2), no participants received third doses at blood collection.

In the entire cohort, dialysis patients were older (median age 69 and 47 years in the dialysis and control groups, respectively) and had a lower proportion of females (30.8% and 51.4%) when compared with controls. The time between the second vaccination and the blood collection for antibody measurement overlapped between dialysis patients and the control (105 and 117 days). The dialysis group exhibited a lower proportion of postvaccination adverse events of pain, malaise, fever ≥37.5°C when compared with controls (table 2).

After matching the CME for age, sex and time after the second administration of primary vaccination, we obtained 49 dialysis patients and 89 participants for further analysis (table 1 and figure 1). In the matched cohort, significantly higher proportions of hypertension, diabetes and cardiovascular disease were observed in the dialysis group compared with the control (p<0.001, <0.001 and<0.01). The dialysis group exhibited a significantly

Table 1 Participant characteristics

Variables	Entire cohort		Matched cohort	
	Dialysis patients (n=65)	Control (n=500)	Dialysis patients (n=49)	Control (n=89)
Age, years (range)	69 (48–89)	47 (13–90)	70 (50–90)	71 (49–88)
Sex, Female	20 (30.8)	257 (51.4)	13 (26.5)	44 (49.4)
Vaccine				
BNT162b2	65 (100)	498 (99.6)	47 (95.9)	88 (98.9)
Unknown	2 (0.3)	2 (0.4)	2 (4.1)	1 (1.1)
Days (range) between dates of the second vaccination and blood collection	105 (70–112)	117 (15–170)	105 (72–112)	107 (75–113)
Days (range) between the first and second vaccination	21 (20–39)	21 (11–49)	21 (21–39)	21 (17–33)
Medical history				
COVID-19	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
Hypertension	58 (89.2)	123 (24.6)	44 (89.8)***	49 (55.1)
Hyperlipidaemia	7 (10.8)	46 (9.2)	4 (8.2)	17 (19.1)
Bronchial asthma	1 (1.5)	29 (5.8)	1 (2.0)	3 (3.4)
Diabetes	32 (49.2)	28 (5.6)	27 (55.1)***	11 (12.4)
Cardiovascular disease	13 (20.0)	25 (5.0)	11 (22.4)**	6 (6.7)
Gout	6 (9.2)	21 (4.2)	4 (8.2)	7 (7.9)
Anaphylaxis	1 (1.5)	7 (1.4)	1 (2.0)	1 (1.1)
Respiratory disease	5 (7.7)	7 (1.4)	3 (6.1)	4 (4.5)
Rheumatoid arthritis	2 (3.1)	6 (1.2)	1 (2.0)	2 (2.2)
Mental illness	1 (1.5)	5 (1.0)	0 (0.0)	1 (1.1)
Medications				
Antihistamines	10 (15.6)	29 (5.8)	7* (14.3)	3 (3.4)
NSAIDs	1 (1.5)	26 (5.2)	1 (2.0)	4 (4.5)
Steroids	2 (3.1)	9 (1.8)	2 (4.1)	2 (2.2)
Acetaminophen	5 (7.7)	6 (1.2)	4 (8.2)	1 (1.1)
Immunosuppressants	0 (0.0)	6 (1.2)	0 (0.0)	2 (2.2)
Antitumour agents	1 (1.5)	4 (0.8)	1 (2.0)	3 (3.4)
Biological therapeutics	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)

Median (range) or number (percentage) values are shown for continuous or categorical variables, respectively. The Mann-Whitney U test or Fisher's exact test were performed in the matched cohort.
*p<0.05, **<0.01 and ***<0.001.
NSAIDs, non-steroidal anti-inflammatory drugs.

lower proportion of postvaccination adverse events of pain, malaise compared with the control (p<0.001 and <0.01)

Titres of SARS-CoV-2 antibodies

None and two study participants showed the SARS-CoV-2 N-IgG antibody above the cut-off value in the dialysis and control groups, respectively. In the entire cohort, the significantly lower titres of SARS-CoV-2 S1-IgG were observed in dialysis patients compared with the control (median (range); 168.35 (4.48–1074.29) AU/mL and 286.66 (4.72–3556.17) AU/mL in dialysis and control groups, respectively, p<0.001) (figure 2). The levels of neutralising antibodies in dialysis patients were also significantly lower than those of the control (36.94 (2.94–36.94) AU/mL and 79.97 (0.00–2826.06) AU/mL, p<0.001).

After CME matching, significant differences in the titres of both anti-SARS-CoV-2 S1 IgG and neutralising antibodies were observed between the dialysis and control groups in the matched cohort (figure 2); anti-SARS-CoV-2 S1 IgG: 168.35 (4.48–1074.29) AU/mL and 269.81 (4.72–945.96) AU/mL in dialysis and control groups, p=0.02,

Table 2 Postvaccination adverse events

Variables	Entire cohort		Matched cohort	
	Dialysis patients (n=65)	Control (n=500)	Dialysis patients (n=49)	Control (n=89)
Adverse reaction				
Pain	2 (3.1)	304 (60.9)	1 (2.0)***	32 (36.0)
Fatigue	4 (6.2)	256 (51.3)	3 (6.1)**	23 (25.8)
Joint pain	23 (35.4)	168 (33.7)	18 (36.7)*	16 (18.0)
Fever (≥37.5℃)	3 (4.6)	166 (33.3)	2 (4.1)	8 (9.0)
Headache	5 (7.7)	158 (31.7)	2 (4.1)	3 (3.4)
Fever (<37.5℃)	5 (7.7)	68 (13.6)	3 (6.1)	3 (3.4)
Dizziness	0 (0.0)	21 (4.2)	0 (0.0)	1 (1.1)
Diarrhoea	0 (0.0)	15 (3.0)	0 (0.0)	1 (1.1)
Nausea	3 (4.6)	15 (3.0)	2 (4.1)	0 (0.0)

The number (percentage) is shown. In the matched cohort, statistical significance with Fisher's exact test.
*p<0.05, **<0.01 and ***<0.001.

neutralising antibodies: 35.77 (2.94–826.06) AU/mL and 62.22 (0.00–535.57) AU/mL, p=0.007, respectively). Participants with SARS-CoV-2 N-IgG antibody above the cut-off value were not included in the matched cohort of the dialysis and control groups.

Predictors of anti-SARS-CoV-2 antibodies in the matched cohort

Multivariate linear regression was performed to predict the log10 of SARS-CoV-2 antibody titres with the participant group, sex, age and duration of postvaccination using the matched cohort. In the models for both anti-SARS-CoV-2 S1 IgG and neutralising antibodies, dialysis and age were identified as independent predictors (a model for the log10 SARS-CoV-2 S1 IgG titre: p<0.05 and <0.001 for the dialysis group and age, respectively, a model for the Log_{10} neutralising antibodies titre: p<0.01 and <0.001 for the dialysis group and age) (table 3). The dialysis group showed negative values of β coefficients in both two models (β coefficient (95% CI): −0.187 (−0.334 to −0.039) and −0.237 (−0.400 to −0.075) for the models of Log10 SARS-CoV-2 S1 IgG and neutralising antibodies titres, respectively).

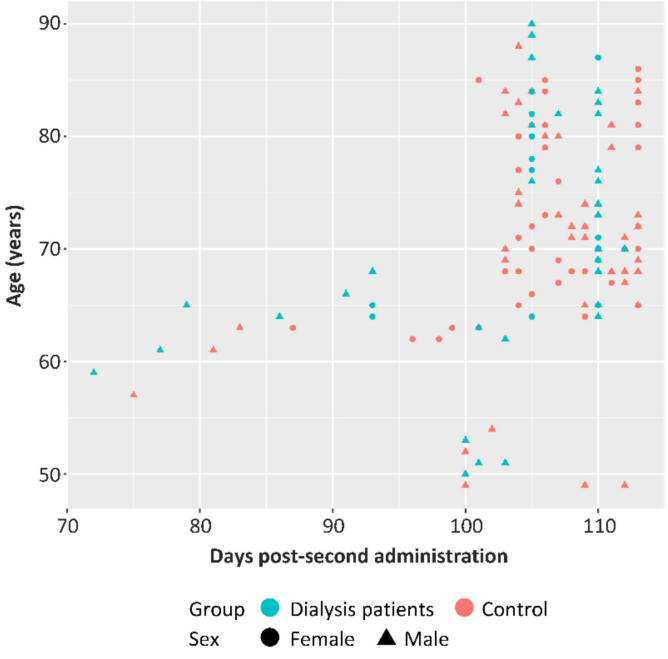

Figure 1 Distribution of age, sex and days postprimary vaccination in the matched cohort. Days postsecond vaccination (x axis) and age (y axis) are shown.

Variables to predict the log10 titres of anti-SARS-CoV-2 S1 IgG and neutralising antibodie are shown by multiple linear regression models. The anti-SARS-CoV-2 S1 IgG models and neutralising antibodies exhibited a weak fit of 0.258 (p<0.001) and 0.291 (p<0.001) for adjusted R^2 values, respectively. When analysing the neutralising antibody titre of log10, a participant in the control group was excluded because he had a neutralising antibody of 0. The day range between the first and second vaccination was not included in the regression variable, since most participants in both the matched cohort of dialysis patients and the control group had 21 days between the first and second vaccination, and the variation in values was small.

DISCUSSION

In this study, we demonstrated that patients undergoing haemodialysis had significantly lower titres of anti-SARS-CoV-2 S1 IgG and neutralising antibodies after the vaccination after matching for age, sex and postvaccination duration. The findings suggest that haemodialysis patients should be carefully monitored for their immunisation status.

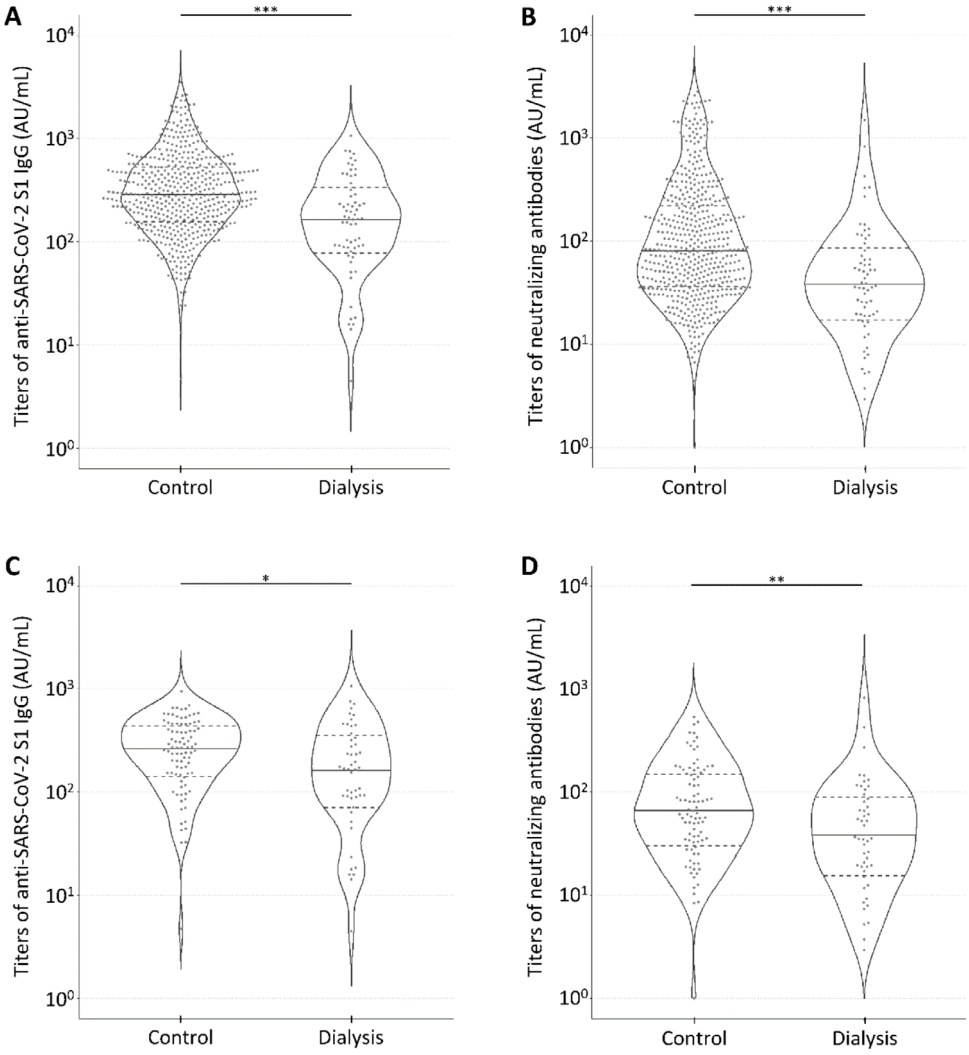

Figure 2 Histograms of SARS-CoV-2 antibody titres. The violin and dot plots of anti-SARS-CoV-2 S1 IgG titres (A and C for the overall and matched cohorts) and the neutralising antibodies (B and D for overall and matched cohorts) are shown. Solid and dashed lines in the violin plot indicate median and the IQR, respectively.

Our findings showing significantly lower anti-SARS-CoV-2 antibody titres in dialysis patients were consistent with previous studies.[9] We performed CME matching to correct the influence of age, sex and period after the completion of primary vaccination on anti-SARS-CoV-2 antibody titres. The dialysis showed a significant negative impact on antibody titres even after the matching. The weaker humoral response to SARS-CoV-2 vaccination

Table 3 Multiple linear regression to predict antibody titres in matched cohorts

Dependent variable	Variables	β coefficients	95% CI	P value
Log_{10} SARS-CoV-2 S1 IgG titre				
	Dialysis group	–0.187	–0.334 to –0.039	0.013
	Sex-male	–0.161	–0.322 to 0.000	0.051
	Age	–0.013	–0.021 to –0.006	<0.001
	Days postvaccination	0.003	–0.005 to 0.011	0.47
Log_{10} Neutralising antibody titre				
	Dialysis group	–0.237	–0.400 to –0.075	0.005
	Sex-male	–0.145	–0.323 to 0.032	0.11
	Age	–0.017	–0.026 to –0.009	<0.001
	Days postvaccination	0.006	–0.003 to 0.015	0.19

and the higher mortality of COVID-19 in dialysis patients support the enhancement of the regimen of SARS-CoV-2 vaccination. To date, the public recommendation by the Centers for Disease Control and Prevention in the USA defines the primary series of vaccination and two boosters for moderately and severely immunosuppressed adults.[21] In Japan, however, the Ministry of Health, Labour and Welfare kept the definition of a booster after the primary series of vaccination.[22] Thus, it is necessary to review the vaccination regimen corresponding to the risk of severe COVID-19 in Japan. It is noteworthy that significant differences in the medical history of hypertension, diabetes and cardiovascular disease were observed between the matched cohorts in this study, which might be confounders of antibody titres.

There are several limitations in this study. First, the small cohort size and a single institute study cause statistical underpower and unknown bias. Second, we evaluated the initial measurement of anti-SARS-CoV-2 antibodies as a preliminary study and did not assess longitudinal changes in antibody titres over time. The short range of postvaccination periods may miss statistical significance. Third, in this study, detailed characteristics of dialysis patients, such as duration of dialysis and epidemiology, were not found. Fourth, there might be a recall bias due to the survey asking for previous medical histories and medications of the participants. Fifth, there is heterogeneity in medical history in the control group, as we saw more than 10% prevalence of hypertension, hyperlipidaemia and diabetes. Sixth, there were no participants in the dialysis group who showed positive IgG antibody titres against the SARS-CoV-2 N protein; therefore, this study could not assess the correlation between SARS-CoV-2 antibody levels and actual infections/severity of the COVID-19 disease. Lastly, the absence of SARS-CoV-2 infection in these cohorts makes it impossible to discriminate the titres associated with the prevention of SARS-CoV-2 infection. More studies are warranted to assess the correlation between antibody titres and actual clinical outcomes, as reported in healthy adults.[23 24]

CONCLUSIONS

We observed significantly reduced anti-SARS-CoV-2 S1 antibody and neutralising antibodies in haemodialysis patients compared with cohorts matched for duration after vaccination. Patients receiving haemodialysis should be carefully monitored for immunological responses to vaccination and COVID-19 infection.

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Contributors All authors conceived and designed the study, and take responsibility for the integrity of the data and the accuracy of data analysis. TZ and MT wrote the manuscript. MT designed the research. TN, MK, CY, TK and YK performed the research. FO and YN analysed the data. KS, JK and RS played an important role in interpreting the results. All authors critically reviewed the manuscript for important intellectual content and provided final approval of the manuscript.

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Competing interests YK and MT received a research grant from Pfizer Health Research Foundation for research not associated with this work.

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

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

Ethics approval This study was approved by the institutional review boards of Hirata Central Hospital (Fukushima Prefecture, Japan) (approval number: 2021-0611-1) and Fukushima Medical University (Fukushima Prefecture, Japan) (2021-116). Written consent was obtained from all study participants or their family agents when the cognitive function of the participants was significantly impaired. This study was conducted in accordance with Ethical Guidelines for Life Science and Medical Research Involving Human Subjects in Japan.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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