Clinical and Experimental Nephrology (2023) 27:660–671
https://doi.org/10.1007/s10157-023-02348-8

ORIGINAL ARTICLE

Anti-SARS-CoV-2 IgG antibody titer after BNT162b2 mRNA COVID-19 vaccination in Japanese patients who underwent renal replacement therapy, hemodialysis, peritoneal dialysis, and kidney transplantation

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Received: 18 November 2022 / Accepted: 5 April 2023 / Published online: 24 April 2023

Abstract

Background Coronavirus disease (COVID-19) vaccination is recommended for patients undergoing renal replacement therapy (RRT), including hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation (KT). However, the difference in the immune response between RRT patients and healthy individuals after mRNA vaccines remains uncertain.

Methods This retrospective observational study evaluated the anti-severe-acute-respiratory-syndrome-coronavirus-2 (anti-SARS-CoV-2) IgG antibody acquisition, titers and their changes, normal response rate (reaching titers of healthy individuals), factors associated with a normal response, and effectiveness of booster vaccination in Japanese RRT patients.

Results Most HD and PD patients acquired anti-SARS-CoV-2 IgG antibodies after the second vaccination; however, their antibody titers and normal response rates (62–75%) were low compared with those of healthy subjects. Approximately 62% of KT recipients acquired antibodies, but the normal response rate was low (23%). Anti-SARS-CoV-2 IgG antibody waning occurred in the control, HD, and PD groups, while negative or very low titers remained in KT recipients. Third booster vaccination was effective in most HD and PD patients. However, the effect was mild in KT recipients – only 58% reached a normal response level. Multivariate logistic regression analyses demonstrated that younger age, higher serum albumin level, and RRT other than KT were significantly associated with a normal response after the second vaccination.

Conclusions RRT patients, particularly KT recipients, exhibited poor vaccine responses. Booster vaccination would be beneficial for HD and PD patients; however, its effect in KT recipients was mild. Further COVID-19 vaccinations using the latest vaccine or alternative procedures should be considered in RRT patients.

Keywords COVID-19 · SARS-CoV-2 · Vaccine · Hemodialysis · Peritoneal dialysis · Kidney transplantation

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide causing coronavirus disease (COVID-19) which has led to severe physical conditions, resulting in death or sequelae [1]. Various vaccines have been developed to suppress the increase in cases of severe disease and death. The BNT162b2 mRNA COVID-19 and mRNA-1273 SARS-CoV-2 vaccines are newly developed mRNA vaccines that have demonstrated high effectiveness, resulting in a decrease in COVID-19 aggravation and death [2].

Patients with end-stage kidney disease (ESKD) who undergo renal replacement therapy (RRT) often have multiple risk factors that result in a high risk of death. These include aging, diabetes mellitus (DM), hypertension, chronic kidney

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diseases, lung diseases, and heart diseases. Patients with these conditions and those who are undergoing immunosuppressive therapy or anti-cancer therapy exhibit severe COVID-19. In Japan, aging is a remarkable factor in dialysis patients, with the average age being 69.4 years [3]. Thus, Japanese patients undergoing RRT—including hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation (KT)—are at a high risk of developing severe COVID-19. The mortality rate because of COVID-19 in dialysis patients has ranged between 10 and 32% in various countries, including Japan, which is much higher than the latest mortality rate in the general Japanese population (0.2%) [3, 4]. The mortality rate of KT recipients with COVID-19 as of Dec 2021 was 6.0% in Japan [5], which is lower than that of dialysis patients. However, their mortality and aggravation rates are higher than those of the general population [3]. Therefore, appropriate COVID-19 prevention through vaccination is important for patients undergoing RRT.

However, sufficient antibody titers and vaccination effectiveness are not easily acquired in RRT patients because of their immunocompromised condition. To date, two brief reports by Matsunami et al. have shown the response rate, antibody titers, antibody waning after two doses of COVID-19 vaccine, and effectiveness of the third booster vaccine in RRT patients in Japan [6, 7]. However, no studies have analyzed anti-SARS-CoV-2 antibody positivity together with the acquisition status of antibody titers equivalent to those in healthy subjects (normal vaccine response) as main outcomes. To prevent infection and/or aggravation of COVID-19 by the Omicron variant, an estimated antibody titer of approximately tenfold that for the conventional type of COVID-19 is required [8, 9]. Considering the spread of the Omicron variant, the exclusive analysis of anti-SARS-CoV-2 antibody positivity would be insufficient given the inability to predict the vaccine's preventive ability against SARS-CoV-2 variants. Therefore, an analysis concerning a sufficient normal vaccine response is important and may uncover the potential high-risk compromised condition of RRT patients. Moreover, the clinical factors associated with a normal vaccine response in RRT patients are still unclear.

Herein, we aimed to investigate the anti-SARS-CoV-2 IgG antibody acquisition status, antibody titers and their changes, normal vaccine response rate, factors associated with a normal response, and effectiveness of booster vaccination in Japanese RRT patients.

Materials and methods

Study design and patients

This retrospective observational study evaluated anti-SARS-CoV-2 IgG antibody titers 3 and 6 months after the second vaccination in ESKD patients undergoing HD, PD, or KT. All maintenance HD patients treated at the Kashiwabara Clinic between January and December 2021 were enrolled. The data of 80 among the 95 patients who had received two vaccinations were analyzed (Fig. 1). All PD patients who were treated at Shinshu University Hospital between January and December 2021 were enrolled. The data of all 21 PD patients who received two vaccinations were analyzed (Fig. 1). All recipients who underwent KT at Shinshu University Hospital and those treated continuously between January and December 2021 were enrolled. Of the 41 patients, the data of 39 who received two vaccinations were analyzed (Fig. 1). Thus, the data of 140 RRT patients were analyzed 3 months after the second vaccination. The serum samples of 47 healthy medical staff members of Shinshu University Hospital were analyzed for the control group. Six months after the second vaccination, the number of participants in the control, HD, PD, and KT groups were 40, 58, 19, and 37, respectively (Fig. 1). No participants were diagnosed with COVID-19 until 6 months after the second vaccination (February 2022). Furthermore, we evaluated the effects of a third booster vaccination in patients with insufficient/non-response.

Vaccination

All patients received two intramuscular injections of 30 µg BNT162b2 mRNA COVID-19 Vaccine (BioNTech-Pfizer BNT162b2). The second vaccination was performed 3 weeks after the first. The third vaccination with intramuscular injections of 30 µg BNT162b2 mRNA COVID-19 Vaccine or 50 µg mRNA-1273 Vaccine (Moderna) was administered after more than 5 months.

Data collection and antibody titer assessment

Blood samples were obtained from the residuals of regular blood tests approximately 3 and 6 months after the second vaccination. Blood samples from the control group were obtained 90 and 180 days after the second vaccination. Other clinical data were collected from medical records. Blood samples of HD patients were obtained at the first HD session of the week, and those of PD patients and KT recipients were obtained during their regular examinations.

Anti-SARS-CoV-2 IgG antibody titers were evaluated using ARCHITECT SARS-CoV-2 IgG II Quant (Abbott Co., Abbott Park, IL, USA) in cooperation with LSI Medience Co. (Tokyo, Japan). This method measures IgG levels against the SARS-CoV-2 spike S1 subunit, highly correlated with neutralizing antibodies [10, 11].

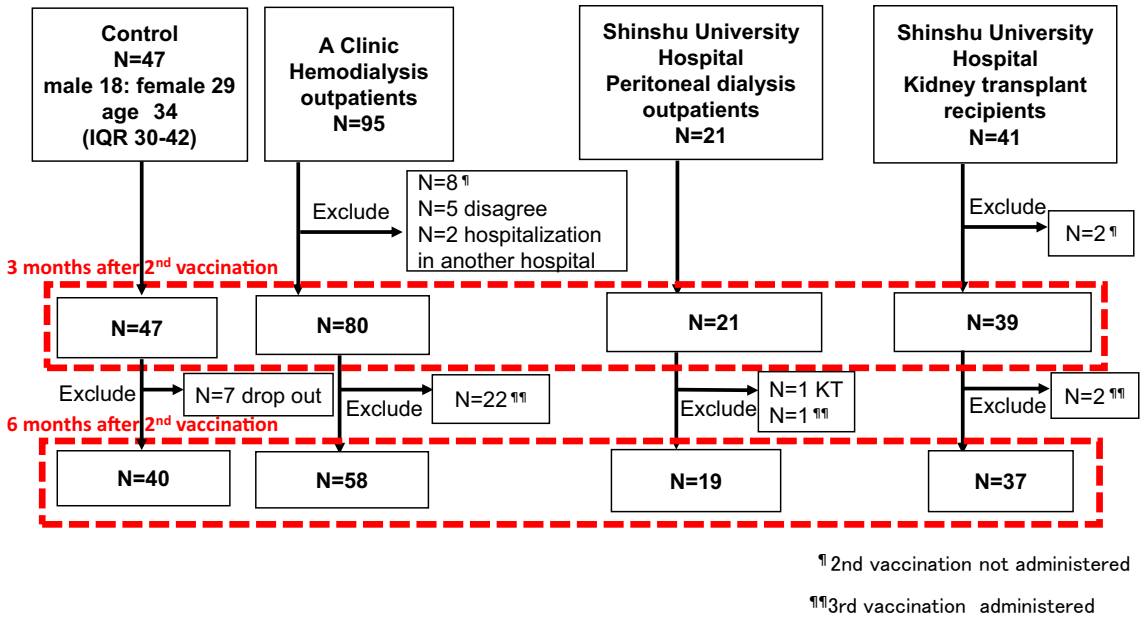

Fig. 1 Study flow. A total of 204 patients and controls were enrolled. Of the 47 controls, 7 were excluded 6 months after the second vaccination. Fifteen of the 95 HD patients were excluded at 3 months, and 22 were excluded at 6 months after the second vaccination. Two of the 21 PD patients were excluded 6 months after the second vaccination. Two of the 41 KT recipients were excluded at 3 months, and 3 were excluded at 6 months after the second vaccination. The number of participants in each group (control, HD, PD, and KT) at 3 months was 47, 80, 21, and 39, respectively. The number of participants in each group (control, HD, PD, and KT) at 6 months was 40, 58, 19, and 37, respectively

Definitions

We defined antibody positivity as an anti-SARS-CoV-2 IgG antibody titer > 50 AU/mL, according to the package insert. A previous study revealed that almost the entire healthy general population could obtain sufficient amounts of IgG antibodies and its clinical efficacy with two doses of the BNT162b2 mRNA COVID-19 Vaccine [1]. Therefore, we defined the lowest anti-SARS-CoV-2 IgG antibody titer in the control group at 3 months after the second vaccination as the cut-off for an insufficient response level. Other definitions are provided in the supplemental method.

Statistical analyses

Continuous variables are presented as medians and interquartile ranges (IQRs), and categorical variables as numbers and percentages. The Mann–Whitney U and Kruskal–Wallis tests were used to compare continuous variables between two and multiple groups, respectively. The chi-square and Fisher exact probable tests were used to compare categorical variables between two and multiple groups, respectively. Multiple comparisons of continuous variables among the four groups were performed using the Mann–Whitney U test with Bonferroni correction. The factors, including age, sex, days from vaccination, serum albumin level, KT, and adverse events, that were significantly associated with a normal response rate were examined using univariate and multivariate logistic regression analyses. Statistical significance was set at $p < 0.05$. Analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [12].

Results

Patient characteristics

Background data for the three RRT groups (HD, PD, and KT) are presented in Table 1. Age, duration of RRT, and comorbidities, including DM, hypertension, cardiovascular disease, and the cause of ESKD, significantly differed among the three groups (Table 1). Laboratory data, including total protein level, serum albumin level, albumin/globulin ratio, blood urea nitrogen (BUN) level, creatinine level, lymphocyte count, hemoglobin level, and platelet count, also significantly differed among the three groups. In the control group, the median age was 34 years (IQR: 30–42), and the male-to-female ratio was 18:29.

Table 1 Background clinical data of patients who underwent three types of renal replacement therapy (hemodialysis, peritoneal dialysis, and kidney transplantation)

	HD patients		PD patients		KT recipients		p-value
	n = 80		n = 21		n = 39		
Age	70	(63–78)	52	(37–63)	44	(36–63)	< 0.001
Male (%)	60	(75.0)	15	(71.4)	22	(56.4)	0.12
BMI (kg/m^2)	22.9	(20.5–26.3)	21.8	(19.9–27.7)	21.1	(19.6–25.1)	0.48
Smoking history (%)	44	(55.0)	11	(52.4)	15	(38.5)	0.26
ACE-I/ARB use	42	(52.5)	14	(66.7)	15	(38.5)	0.11
Duration of follow-up from RRT (months)	85	(50–461)	30	(14–56)	48	(22–102)	< 0.001
Complications							
Diabetes mellitus (n, %)	36	(45.0)	7	(33.3)	7	(18.0)	0.011
Hypertension (n, %)	78	(97.5)	18	(85.7)	34	(87.2)	0.03
Malignancy (n, %)	15	(18.8)	3	(14.3)	5	(12.8)	0.77
Cardiovascular disease (n, %)	37	(46.3)	6	(28.6)	5	(12.8)	0.002
Cause of end-stage kidney disease							
Diabetic kidney disease (n, %)	35	(43.8)	6	(28.6)	4	(10.3)	< 0.001
Chronic glomerulonephritis (n, %)	19	(23.8)	3	(14.3)	13	(33.3)	< 0.001
Nephrosclerosis (n, %)	12	(15.0)	3	(14.3)	5	(12.8)	< 0.001
Polycystic kidney disease (n, %)	4	(3.8)	3	(14.3)	1	(2.6)	< 0.001
Unknown, others (n, %)	11	(13.8)	6	(28.6)	16	(41.0)	< 0.001
Use of immunosuppressants							
PSL + FK + MMF	0	(0.0)	1	(4.8)	27	(69.2)	–
FK + MMF	0	(0.0)	0	(0.0)	1	(2.6)	–
PSL + FK + MZR	0	(0.0)	0	(0.0)	1	(2.6)	–
FK + MMF	0	(0.0)	0	(0.0)	1	(2.6)	–
PSL + CYA + EVR + LEF	0	(0.0)	0	(0.0)	1	(2.6)	–
PSL + FK + EVR	0	(0.0)	0	(0.0)	2	(5.1)	–
PSL + FK + EVR + MMF	0	(0.0)	0	(0.0)	1	(2.6)	–
PSL + EVR + MMF	0	(0.0)	0	(0.0)	1	(2.6)	–
PSL + CYA + MMF	0	(0.0)	0	(0.0)	1	(2.6)	–
PSL + FK + AZA	0	(0.0)	0	(0.0)	1	(2.6)	–
mPSL + FK + MMF	0	(0.0)	0	(0.0)	2	(5.1)	–
Other	1	(1.3)	0	(0.0)	0	(0.0)	–
Laboratory data							–
TP (g/dL)	6.2	(5.8–6.4)	6.3	(5.4–6.6)	6.7	(6.5–7.1)	< 0.001
Alb (g/dL)	3.5	(3.3–3.7)	3.3	(2.6–3.6)	4.2	(4.1–4.4)	< 0.001
A/G ratio	1.33	(1.21–1.50)	1.06	(0.96–1.24)	1.68	(1.55–1.96)	< 0.001
BUN (mg/dL)	56.6	(46.6–66.2)	52.6	(49.2–58.7)	20.9	(16.1–25.4)	< 0.001
Cre (mg/dL)	9.9	(7.4–11.9)	10.6	(9.6–12.4)	1.4	(1.1–1.6)	< 0.001
WBC ($\times 10^3$/μL)	5.30	(4.10–6.55)	6.00	(5.57–6.59)	5.90	(5.15–6.54)	0.19
NEU ($\times 10^3$/μL)	3.97	(2.89–5.09)	3.76	(3.50–4.66)	3.50	(3.19–4.50)	0.83
LYM ($\times 10^3$/μL)	1.01	(0.82–1.35)	1.13	(1.00–1.32)	1.50	(1.02–1.94)	0.004
Hb (g/dL)	11.0	(10.2–11.7)	11.1	(10.2–11.6)	12.8	(11.25–14.1)	< 0.001
Plt ($\times 10^4$/μL)	19.1	(14.2–22.5)	20.4	(18.4–25.7)	24.3	(21.1–29.1)	< 0.001
CRP (mg/dL)	N.D	–	0.09	(0.05–0.30)	0.03	(0.01–0.05)	–

Continuous variables are presented as medians and interquartile ranges, and categorical variables are presented as numbers (n) and percentages (%). Continuous variables were compared among the three RRT groups using the Kruskal–Wallis test, and categorical variables were compared using Fisher's exact probability test. Statistical significance was set at $p < 0.05$

ACE-I angiotensin-converting enzyme inhibitor, *A/G ratio* albumin globulin ratio, *Alb* albumin, *ARB* angiotensin II receptor blocker, *AZA* azathioprine, *BMI* body mass index, *BUN* blood urea nitrogen, *Cre* creatinine, *CRP* C-reactive protein, *CyA* cyclosporin A, *EVR* everolimus, *FK* tacrolimus, *Hb* hemoglobin, *HD* hemodialysis, *KT* kidney transplantation, *LEF* leflunomide, *LYM* lymphocyte count, *MMF* mycophenolate mofetil, *mPSL* methylprednisolone, *MZR* mizoribine, *NEU* neutrophil count, *N.D.* not done, *PD* peritoneal dialysis, *Plt* platelet count, *PSL* prednisolone, *RRT* renal replacement therapy, *TP* total protein, *WBC* white blood cell count

Comparisons of anti-SARS-CoV-2 IgG antibody acquisition, antibody titers, and their changes after the second vaccination among the groups

We compared the anti-SARS-CoV-2 IgG antibody acquisition rate, antibody titers, and their changes after the second vaccination among the control, HD, PD, and KT groups (Table 2 and Fig. 2). Days from vaccination at 3 and 6 months differed slightly among the groups (Table 2). The antibody titer differed significantly among the four groups at 3 and 6 months. In the control group, the antibody acquisition rate was 100% 3 months after the second vaccination, and the median titer was 4970 (3420–7295) AU/mL. Six months after the second vaccination, the antibody acquisition rate was maintained at 100%; however, the median titer decreased significantly to 970 (667–1458) AU/mL, indicating antibody waning. The median waning ratio of antibody titers (antibody titers in 6 months/those in 3 months) was 19.3%. In HD patients, the antibody acquisition rate was 98.8% 3 months after the second vaccination. The median titer was 935 (491–2270) AU/mL, which was significantly lower than that in the control group. Six months after the second vaccination, the antibody acquisition rate remained at 96.6%; however, the median titer decreased significantly to 332 (151–641) AU/mL. The median waning ratio of the antibody titers was 26.4%. In PD patients, the antibody acquisition rate was 95.2% 3 months after the second vaccination. The median titer was 569 (362–819) AU/mL, which was significantly lower than that in the control group. Six months after the second vaccination, the antibody acquisition rate slightly decreased to 89.5%, and the median titer decreased to 214 (159–353) AU/mL. The median waning ratio of the antibody titers was 36.0%. In KT recipients, the antibody acquisition rate was only 61.5% 3 months after the second vaccination, and the median titer was extremely low at 97 (9–332) AU/mL. Six months after the second vaccination, the antibody acquisition rate was 56.8%, and the low median titer did not

Table 2 Comparison and changes in anti-SARS-CoV-2 IgG antibody titers, antibody acquisition rate, and normal response rate 3 and 6 months after the second vaccination in the RRT groups

After 3 months	Control (n = 47)	HD patients (n = 80)	PD patients (n = 21)	KT recipients (n = 39)	RRT group difference
Days from vaccination (days)	90	88 (71–107)	113 (70–144)*	106 (56–128)	n.s
IgG antibodies (AU/mL)	4970 (3420–7295)	935 (491–2270)***	569 (362–819)***	97 (9–332)***	B', C''
Antibody acquisition rate (n, %)	47 (100.0)	79 (98.8)	20 (95.2)	24 (61.5)***	B, C''
Normal response rate (n, %)	47 (100.0)	60 (75.0)***	13 (61.9)***	9 (23.1)***	B, C''
Insufficient response rate (n, %)	0 (0.0)	19 (23.8)***	7 (33.3)***	15 (38.5)***	n.s
Non-response rate (n, %)	0 (0.0)	1 (1.2)	1 (4.8)	15 (38.5)***	B, C''
Insufficient/non-response rate (n, %)	0 (0.0)	20 (25.0)***	8 (38.1)***	30 (76.9)***	B, C''
After 6 months	Control (n = 40)	HD patients (n = 58)	PD patients (n = 19)	KT recipients (n = 37)	RRT group difference
Days from vaccination (days)	180	194 (179–203)***	186 (164–234)	173 (152–200)	C
IgG antibodies (AU/mL)	970 (667–1458)	332 (151–641)***	214 (159–353)***	119 (11–239)***	C''
Antibody acquisition rate (n, %)	40 (100.0)	56 (96.6)	17 (89.5)	21 (56.8) ***	C''
Normal response rate (n, %)	36 (90.0)	21 (36.2)***	2 (10.5)***	6 (16.2)***	n.s
Insufficient response rate (n, %)	4 (10.0)	35 (60.3)***	15 (78.9)***	15 (40.5)*	n.s
Non-response rate (n, %)	0 (0)	2 (3.4)	2 (10.5)	16 (43.2)***	C''
Insufficient/non-response rate (n, %)	4 (10.0)	37 (63.8)***	17 (89.5)***	31 (83.8)***	n.s
	Control (n = 40)	HD patients (n = 58)	PD patients (n = 19)	KT recipients (n = 37)	RRT group difference
IgG antibodies of 6 months/3 months after vaccination (%)	19.3 (14.8–27.9)	26.4 (17.5–37.3)	36.0 (28.5–52.8)**	100 (59.1–102.7)***	B'', C''

* vs. control at each time point: *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$; comparison among RRT groups (HD vs. PD, PD vs. KT, KT vs. HD) at each time point: HD vs. PD: A'', $p < 0.001$, A', $p < 0.01$, A, $p < 0.05$; PD vs. KT: B'', $p < 0.001$, B', $p < 0.01$, B, $p < 0.05$; HD vs. KT: C'', $p < 0.001$, C', $p < 0.01$, C, $p < 0.05$: n.s. represents no significant difference ($p \geq 0.05$)

Continuous variables are presented as medians and interquartile ranges, and categorical variables are presented as numbers (n) and percentages (%). Continuous variables were compared between the two groups using the Mann–Whitney U test, and categorical variables were compared using the chi-square test. Statistical significance was set at $p < 0.05$

HD hemodialysis, *IgG* immunoglobulin G, *KT* kidney transplantation, *PD* peritoneal dialysis, *RRT* renal replacement therapy, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

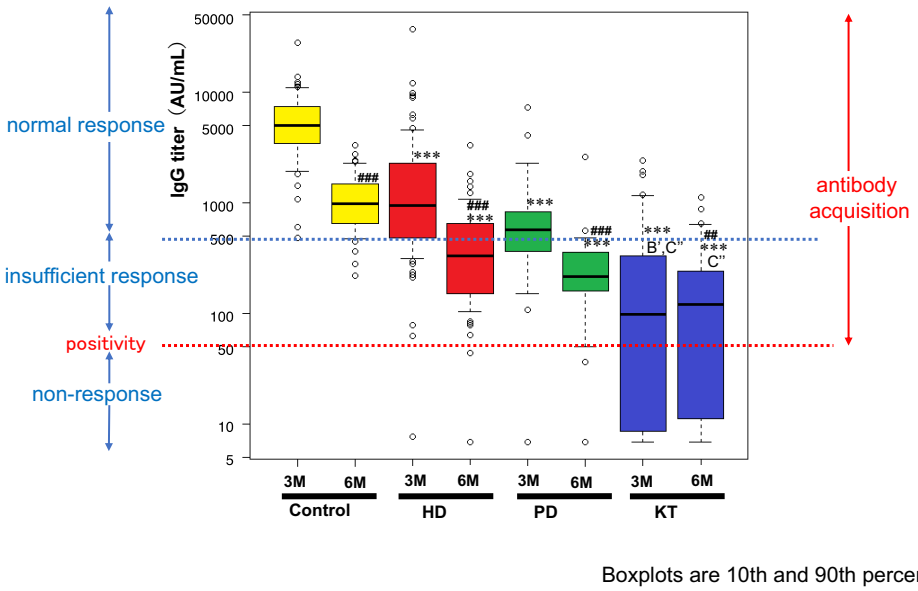

Fig. 2 Anti-SARS-CoV-2 IgG antibody titers at 3 months and 6 months after the second vaccination in the control, HD, PD, and KT groups. Multiple comparisons were performed among the groups using the Mann–Whitney U test. In addition, the anti-SARS-CoV-2 IgG antibody titer was compared using the Wilcoxon signed-rank sum test between 3 months (3 M) and 6 months (6 M) in each group. * vs. control at each time point: *, $p<0.05$, **, $p<0.01$, ***, $p<0.001$; # vs. 3 M titers of each group: #, $p<0.05$, ## $p<0.01$, ### $p<0.001$; comparison among RRT groups (HD vs. PD, PD vs. KT, KT vs. HD) 3 months and 6 months after the second vaccination: HD vs. PD: A'', $p<0.001$, A', $p<0.01$, A, $p<0.05$; PD vs. KT: B'', $p<0.001$, B', $p<0.01$, B, $p<0.05$; HD vs. KT: C'', $P<0.001$, C', $p<0.01$, C, $p<0.05$

change (119 [11–239] AU/mL). The median waning ratio of the antibody titers was 100.0% (Table 2).

Throughout the observation period, the antibody titers in the RRT group were significantly lower than those in the control group, indicating a poor vaccine response in the RRT group, especially in KT recipients. Seventeen RRT patients could not obtain anti-SARS-CoV-2 IgG antibodies 3 months after the second vaccination. Among them, one HD patient underwent chemotherapy for multiple myeloma, one PD patient was treated with immunosuppressive therapy for systemic lupus erythematosus, and the other 15 were KT recipients.

Comparisons in normal response rate after the second vaccination among the groups

We considered an insufficient vaccine response that did not reach normal vaccine response levels as possibly clinically important. Therefore, we defined the lowest anti-SARS-CoV-2 IgG antibody titer in the control group 3 months after the second vaccination (474 A/mL) as the cut-off for a "normal response." This cut-off was approximately tenfold that for "positivity." This normal response titer level was estimated to be essential for the prevention of infection and/or aggravation of COVID-19 by the Omicron variant. Three months after the second vaccination, the normal response rates in HD, PD, and KT patients were 75%, 62%, and 23%, respectively. Furthermore, 6 months after the second vaccination, the normal response rates in HD, PD, and KT patients were 36%, 11%, and 16%, respectively.

Comparison of adverse events after the second vaccination among the groups

Among the RRT groups, the antibody titer, antibody acquisition rate, and normal response rate in KT recipients were significantly lower than those in HD or PD patients; no significant difference was detected between HD and PD patients (Fig. 2 and Table 2). Similarly, the incidence rate and severity of adverse events were extremely low and mild, respectively, in KT recipients, whereas these were identical in HD and PD patients (Supplementary Fig. 1).

Analyses of associated factors of normal vaccine response in RRT patients

To investigate the clinical factors that were significantly associated with a normal vaccine response, we performed univariate and multivariate logistic regression analyses of the data of all RRT patients (N = 140). Univariate logistic regression analyses indicated that a long duration of follow-up after RRT; the RRT type, such as HD and KT; high BUN and creatinine levels; a short period from vaccination; and a high frequency of adverse events after

vaccination were significantly associated with a normal response (Table 3). Among them, we considered that the RRT type strongly confounded the period between RRT and follow-up and the BUN and creatinine levels. Subsequently, we conducted multivariate analyses using clinical factors suggested by other literature and the candidate factors determined through univariate analyses. Multivariate logistic regression analyses including age, male sex, days from vaccination, albumin level, adverse events after vaccination, and KT status, indicated that younger age, high serum albumin level, and RRT other than KT were significantly associated with a normal response (Table 4).

Table 3 Univariate analyses of the clinical factors associated with a normal response (N = 140)

Clinical factors	OR	95% CI	p-value
Age	1.00	(0.98–1.02)	0.82
Male (n, %)	1.35	(0.65–2.79)	0.42
BMI (kg/m^2)	1.02	(0.95–1.10)	0.52
Smoking history (n, %)	1.00	(0.51–1.96)	1.00
ACE-I/ARB use (n, %)	1.33	(0.68–2.61)	0.41
Duration of follow-up from RRT (months)	1.01	(1.00–1.01)	0.016
Diabetes Mellitus (n, %)	1.66	(0.81–3.40)	0.17
HD (n, %)	5.18	(2.50–10.70)	< 0.001
PD (n, %)	1.18	(0.45–3.05)	0.74
KT (n, %)	0.12	(0.05–0.27)	< 0.001
TP (g/dL)	0.83	(0.47–1.48)	0.54
Alb (g/dL)	0.58	(0.30–1.10)	0.10
A/G ratio	0.37	(0.14–1.02)	0.06
BUN (mg/dL)	1.05	(1.03–1.07)	< 0.001
Cre (mg/dL)	1.26	(1.15–1.38)	< 0.001
WBC (× 10^3/μL)	1.00	(0.82–1.22)	0.97
NEU (× 10^3/μL)	1.15	(0.90–1.47)	0.26
LYM (× 10^3/μL)	0.73	(0.44–1.21)	0.22
Hb (g/dL)	0.87	(0.70–1.08)	0.21
Plt (× 10^4/μL)	0.96	(0.92–1.00)	0.07
Days from vaccination (days)	0.99	(0.98–0.99)	0.018
AE (n, %)	2.56	(1.28–5.11)	0.008

The clinical factors associated with a normal response were investigated using univariate logistic regression analyses. Statistical significance was set at $p < 0.05$

ACE-I angiotensin-converting enzyme inhibitor, *AE* adverse events after vaccination, *A/G ratio* albumin globulin ratio, *Alb* albumin, *ARB* angiotensin II receptor blocker, *BMI* body mass index, *BUN* urea nitrogen, *CI* confidence interval, *Cre* creatinine, *HD* hemodialysis, *Hb* hemoglobin, *KT* kidney transplantation, *LYM* lymphocyte count, *NEU* neutrophil count, *OR* odds ratio, *PD* peritoneal dialysis, *Plt* platelet count, *RRT*: renal replacement therapy, *TP* total protein, *WBC* white blood cell count

Table 4 Multivariate analyses of the clinical factors associated with a normal response (all RRT patients, N = 140)

Clinical factors	OR	95% CI	p-value
Age	0.97	(0.94–1.00)	0.044
Male (n, %)	0.84	(0.32–2.16)	0.71
Days from vaccination (days)	0.99	(0.98–1.00)	0.22
KT (n, %)	0.01	(0.00–0.07)	< 0.001
Alb (g/dL)	3.85	(1.29–11.50)	0.016
AE (n, %)	0.80	(0.31–2.06)	0.64

The clinical factors associated with a normal response were investigated using multivariate logistic regression analyses. Statistical significance was set at $p < 0.05$

AE adverse events after vaccination, *Alb* albumin, *CI* confidence interval, *KT* kidney transplantation, *OR* odds ratio

Effect of booster vaccination in RRT patients with insufficient/non-response after the second vaccination

Since the current results indicated that RRT patients are prone to exhibit a poor vaccine response, we investigated the effect of the third booster vaccination on the insufficient/non-response group (Fig. 3 and Table 5). In the HD and PD groups with insufficient/non-response, 92.9% (13 of 14 cases) achieved normal response levels by booster vaccination, and only one HD patient failed to acquire antibodies. The median antibody titer was 6275 (2160–12,600) AU/mL. In the KT recipient group with insufficient/non-response, the third booster vaccination increased the antibody titer to 1335 (49–4855) AU/mL, significantly lower than that in the HD and PD groups. Approximately 73.1% (19 of 26 recipients) acquired antibodies, 57.7% (15 of 26 recipients) reached the normal response level, 15.4% (4 of 26 recipients) were at an insufficient level, and 26.9% (7 of 26 recipients) failed to acquire antibodies. The insufficient/non-response rate was significantly higher in KT recipients (42.3%).

During the follow-up period 6–10 months after the second vaccination (February to June 2022), three dialysis patients with insufficient/non-response (1 HD and 2 PD patients) developed COVID-19. In contrast, none of the patients with a normal response developed COVID-19. One HD patient (63-year-old male) had mild symptoms and was followed-up without special treatment. One PD patient (37-year-old female) required remdesivir and steroid treatment, noninvasive positive pressure ventilation, and continuous hemodiafiltration in the intensive care unit for severe respiratory failure symptoms. Another PD patient (68-year-old male) with a history of interstitial pneumonia was treated with sotrovimab and steroids. All patients recovered without any sequelae.

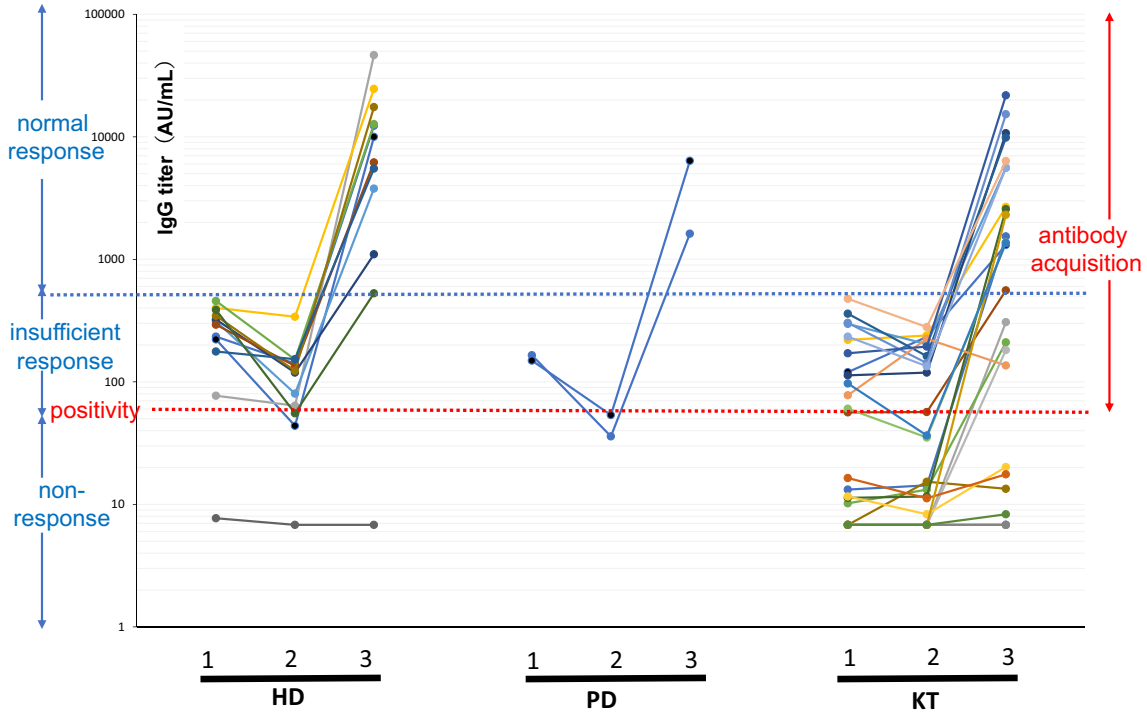

Fig. 3 The effects of the third booster vaccination against insufficient/non-response patients. Changes in antibody titer after the third vaccination are indicated in patients with insufficient/non-response (n = HD 12, PD 2, KT 26). 1: 3 months after the second vaccination, 2: 6 months after the second vaccination, 3: 3 months after the third vaccination

Table 5 The antibody titers, antibody acquisition rate, and normal response rate 3 months after the third vaccination in RRT patients with insufficient/non-response after the second vaccination

3 months after the third vaccination	HD and PD patients (n = 14)		KT recipients (n = 26)		p-value
Age	73	(65–77)	48	(38–64)	< 0.001
Male (%)	10	(71.4)	14	(53.8)	0.33
Days after third vaccination (days)	106	(97–114)	98	(86–105)	0.06
IgG antibodies (AU/mL)	6275	(2160–12,600)	1335	(49–4855)	0.013
Antibody acquisition rate (n, %)	13	(92.9)	19	(73.1)	0.22
Normal response rate (n, %)	13	(92.9)	15	(57.7)	0.07
Insufficient response rate (n, %)	0	(0.0)	4	(15.4)	0.30
Non-response rate (n, %)	1	(7.1)	7	(26.9)	0.22
Insufficient/non-response rate (n, %)	1	(7.1)	11	(42.3)	0.030

Continuous variables are presented as medians and interquartile ranges, and categorical variables are presented as numbers (n) and percentages (%). Continuous variables were compared between the two groups using the Mann–Whitney U test, and categorical variables were compared using the chi-square test. Statistical significance was set at $p < 0.05$

HD hemodialysis, *IgG* immunoglobulin G, *KT* kidney transplantation, *PD* peritoneal dialysis

Discussion

The anti-SARS-CoV-2 IgG antibody titer and normal response rate in the RRT groups were significantly lower than those in the control group at both 3 and 6 months after the second vaccination. In particular, KT recipients exhibited extremely low titers, very low antibody acquisition, and normal response rates. The normal response rates in each RRT group were markedly lower than the antibody acquisition rates, uncovering the potential high-risk compromised condition of RRT patients that has not been revealed in previous studies that exclusively analyzed the antibody acquisition. Significant antibody waning was detected in control, HD, and PD patients from 3 to 6 months after the second vaccination, and a low titer remained in KT recipients. The booster third vaccination effectively increased the titers in HD and

PD patients to a sufficient level; however, the effects were mild in KT recipients, and many KT recipients failed to achieve sufficient antibody levels. These findings indicate that RRT patients, particularly KT recipients, have poor vaccine responses.

In this study, the titer and normal response rates after the second vaccination were significantly lower in HD and PD patients than those in the control group, and marked antibody waning was detected in both groups. Generally, humoral responses, such as antibody acquisition and maintenance of antibody titers after mRNA vaccination, time-dependently decreased. Moreover, the anti-SARS-CoV-2 IgG antibody titer was reported to decrease significantly earlier in HD patients than in healthy controls [13]. These findings indicate that mRNA vaccination for COVID-19 may be less effective in HD and PD patients. However, a sufficient increase in the titer of anti-SARS-CoV-2 IgG antibodies was reported after the third vaccination in HD patients [14]. This study also detected the beneficial effects of booster vaccination, which increased the antibody titers to a normal response level, in Japanese HD and PD patients, supporting the results of previous studies [7, 14]. Aggressive vaccination may be required more frequently in HD and PD patients than in healthy participants to maintain sufficient antibody titers.

This current study demonstrated that the antibody titers and acquisition rate after COVID-19 vaccination were markedly lower in KT recipients than in dialysis patients and healthy populations, supporting the results of previous studies [6, 7, 15]. Furthermore, our analyses stratified by normal response, insufficient response, and non-response revealed the very low normal response rate and poor booster vaccination effects, highlighting the severe immunocompromised status in KT recipients, and clearly demonstrated the different immune response in RRT patients after mRNA vaccination. The analyses of clinical factors associated with a normal response demonstrated that the strongest associated factor was the RRT type (KT). The poor effectiveness of vaccination in KT recipients may be because of immunosuppressive therapy. The current study could not detect a significant relationship between the type of immunosuppressants and antibody titers after vaccination. However, 71% of KT recipients with non-response regardless of booster vaccination (5 of 7 recipients) had a history of various infectious diseases (2 recipients, severe cytomegalovirus infection requiring hospitalization; 1 recipient, refractory herpes zoster; 1 recipient, non-tuberculous mycobacterial disease; 1 recipient, BK virus infection), indicating a severe immunosuppressed status as a result of immunosuppressants. Many previous studies have reported that the use of rituximab could be associated with decreasing antibody acquisition after COVID-19 vaccination [16]. Rituximab depletes B cells and is reported to suppress antibody production markedly after the administration of many types of vaccines [17–19]. Mycophenolate mofetil (MMF) is also reported to reduce the antibody acquisition rate significantly after COVID-19 vaccination in solid organ transplant recipients [20]. Therefore, countermeasures in terms of COVID-19 vaccination are essential for patients who are administered these immunosuppressants. Clinical guidance from the American College of Rheumatology (ACR) recommends that the first COVID-19 vaccine should be administered 4 weeks before rituximab infusion [21]. ERA-EDTA recommends that the COVID-19 vaccine should be administered more than 6 months after rituximab infusion [22]. These recommendations indicate the importance of a sufficient interval between rituximab infusion and vaccination. MMF causes a dose-dependent reduction in antibody acquisition rate. Patients administered MMF < 1000 mg/day present a five-fold humoral immune response compared with those administered MMF > 1000 mg/day [23]. Discontinuation of MMF helps seroconversion in seronegative organ transplant recipients regardless of two doses of the COVID-19 vaccine [24]; therefore, the ACR recommends that MMF should be discontinued until 1–2 weeks after COVID-19 vaccination [21]. Given the balance between the risks of infection or aggravation of COVID-19 and immune rejection of the transplanted kidney, the optimal timing of COVID-19 vaccination and dosage of immunosuppressants should be carefully considered.

The previous prospective studies of COVID-19 mRNA vaccination in patients receiving dialysis demonstrated that immunosuppressive treatment, longer dialysis period, lower serum hemoglobin and albumin levels, and lower leukocyte counts were all predictors of normal response to vaccination [25, 26]. Our multivariate analyses indicated that younger age and high serum albumin levels were the remaining associated factors after adjusting for RRT type (KT or non-KT), supporting the results of previous studies. These findings suggest that younger age and good nutritional status are important to elicit a normal vaccine response regardless of RRT type. A previous study has reported that adverse events may reflect immune reactions and be associated with the acquired antibody titers after mRNA vaccination [27]. In the current study, univariate analyses showed that the occurrence of adverse events after vaccination might be a factor significantly associated with a normal vaccine response; however, the association disappeared in the multivariate analysis. Although adverse events were significantly less frequent in KT recipients than in HD and PD patients, probably due to immunosuppressive therapy, a significant relationship between adverse events and antibody titers was not detected when stratified by RRT type, even in the KT group. The current study indicated that the RRT type

is strongly associated with the occurrence of adverse events, whereas the relationship between the existence/severity of adverse events and vaccine response remains unclear.

Recently, the efficiency of vaccination and virus affinity of antibodies have been weakened against mutated variants of SARS-CoV-2, such as the Delta and Omicron variants [28]. The preventive effect of the BNT162b2 mRNA COVID-19 Vaccine against alpha-type COVID-19 is approximately 95%; however, the effects on the Delta-type COVID-19 have decreased to 88% [29]. Furthermore, the titer of neutralizing antibodies against the Delta-type COVID-19 is approximately 60% that against the original type (Wuhan) of COVID-19 in Japan [30]. The preventive effect against the Omicron variants is further reduced—only 1/10 of the neutralizing antibodies against the Omicron variants are produced [8, 9]. Regarding the Centaurus variants (BA.2.75 strain), which are feared to be prevalent, escape from neutralizing antibodies has been reported to be stronger than with other Omicron variants [31]. Therefore, a high antibody titer is essential for preventing COVID-19 by novel variants, including the Omicron and Centaurus variants. In this study, only patients with insufficient/non-response developed COVID-19, supporting our hypothesis. The current study demonstrated that RRT patients, especially KT recipients, are prone to exhibit insufficient/non-response. Several reports have indicated that enough neutralizing antibodies cannot be obtained with three rounds of mRNA vaccination in KT recipients and that a small percentage of KT recipients acquire neutralizing antibodies against the Omicron variants [32, 33]. These findings suggest that conventional COVID-19 vaccines may be ineffective against the novel virus variants, especially in KT recipients. Improved vaccines against the Omicron variants have been developed and applied clinically. RRT patients should be actively vaccinated with these latest vaccines. However, these new vaccines may not produce effective neutralizing antibodies in KT recipients. The current study indicated that half of KT recipients acquired sufficient antibody titers after booster vaccination, suggesting the importance of repeated booster vaccination [34]. However, booster vaccinations may be less effective in KT recipients who are strongly immunosuppressed, such as patients in the early period of post-transplantation or rejection treatment. For these KT recipients, prophylactic methods other than vaccination, such as anti-SARS-CoV-2 monoclonal antibodies (neutralizing antibody drugs such as AZD7442 [tixagevimab–cilgavimab]), should be considered [35].

Limitations

First, this was a retrospective observational study, and the timing of the evaluation of the anti-SARS-CoV-2 IgG antibody titer was not unified. As anti-SARS-CoV-2 IgG antibodies decrease in a time-dependent manner, this may influence the current results. Second, we evaluated only humoral immunological responses in this study. Vaccination affects cellular immunological responses to pathogens. A comparison of cellular immunological responses among each RRT group is needed. Third, we could not evaluate the factors associated with a normal vaccine response in each RRT group using multivariate logistic regression analyses because of the small sample size. Fourth, we were unable to completely exclude RRT patients with asymptomatic COVID-19, because we did not perform mandatory PCR tests to rule out asymptomatic infection. Fifth, we evaluated the efficacy of the conventional type of COVID-19 vaccine and could not evaluate that of specific mRNA vaccines against the Omicron variant.

Nevertheless, we believe that our research has various strengths given that we could investigate the "pure" effect of two mRNA vaccine doses and the natural course of antibody waning in RRT patients. Most RRT patients did not have COVID-19 during the data collection period and they received two or three doses of the newly developed mRNA vaccines at the same time and after the same interval. At present, conducting similar research investigating the "pure" effect of the mRNA vaccine is impossible because so many people have already had COVID-19 and have received multiple vaccines at different intervals. When the need arises to develop a novel mRNA vaccine for another pathogen in the future, our research will be useful for predicting the antibody acquisition status and normal vaccine response in RRT patients.

The technology of mRNA vaccination is progressing; for example, a clinical trial of mRNA vaccination for solid cancer has been started by BioNTech and Moderna, and the Phase I trial has been completed [36]. We believe that many newly invented mRNA vaccines will be used in the future, and our study will be useful for predicting their efficacy in RRT patients.

Conclusion

The anti-SARS-CoV-2 spike protein IgG antibody titer and the normal vaccine response in HD and PD patients were low 3 months after the second vaccination, and antibody waning occurred after 6 months. In KT recipients, the antibody acquisition rate, normal vaccine response rate, and antibody titers were extremely low after the second vaccination. Booster vaccination was effective in HD and PD patients, but might be less effective in KT recipients. Further vaccinations using the latest vaccines or alternative procedures should be considered to protect RRT patients from COVID-19.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10157-023-02348-8.

Acknowledgements None.

Authors' contributions RI and MH designed the study. RI, AY, and MH collected the data. RI, DA, and YY performed the statistical analyses. RI and MH drafted the manuscript. SK, KH, and YK revised the manuscript. All the authors have read and approved the final version of the manuscript.

Funding No funding was received for this study.

Availability of data and material The data used in this study are available from the corresponding author upon request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional review board of the ethical committee at which the study was conducted (IRB approval number 5425) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The requirement for written informed consent was waived owing to the study's retrospective nature.

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