

# Seroprevalence of SARS-CoV-2 IgG Antibodies After the Second BNT162b2 mRNA Vaccine in Japanese Kidney Transplant Recipients

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**Research Article**

**Keywords:** SARS-CoV-2, vaccine, kidney transplantation, seropositive, seroprevalence

**Posted Date:** December 9th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-1120488/v1>

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# Abstract

We aimed to evaluate the rate of anti-SARS-CoV-2 IgG seropositivity and investigated factors associated with seropositivity after the second SARS-CoV-2 mRNA vaccination in kidney transplant (KT) recipients. This retrospective study conducted between June 2021 and November 2021 included 106 KT recipients and 127 healthy controls who received the second dose of the BNT162b2 mRNA vaccine at least seven days before the measurement of antibody titers. The titers of immunoglobulin G (IgG) antibodies against the receptor-binding domain of SARS-CoV-2 spike (S) protein were determined. Seropositivity was defined as an anti-SARS-CoV-2 IgG level of  $\geq 15$  units/mL, which was considered as the presence of sufficient neutralizing antibodies. The median ages and the seroprevalence rates of the healthy controls and KT recipients were 68 and 56 years and 98% and 22%, respectively. Univariate logistic regression analysis revealed that age  $>53$  years, rituximab use, mycophenolate mofetil use, and KT vintage  $<7$  years were negatively associated with anti-SARS-CoV-2 IgG seropositivity in KT recipients. Humoral response after the second BNT162b2 mRNA vaccine was greatly hindered by immunosuppression therapy in KT recipients. Older age, rituximab use, mycophenolate mofetil use, and KT vintage may play key roles in seroconversion.

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is a critical disease associated with high mortality rate in kidney transplant (KT) recipients with immunosuppression<sup>1</sup>, for whom SARS-CoV-2 vaccination is recommended for infection prevention. However, several studies reported that KT recipients exhibited a significantly impaired response to standard dose of SARS-CoV-2 mRNA-based vaccination compared to the general population<sup>2-7</sup>. Sufficient data are not available for KT recipients, who were not included in SARS-CoV-2 vaccine clinical trials<sup>8</sup>. Additionally, most studies evaluating immunoglobulin G (IgG) antibody levels against SARS-CoV-2 mRNA vaccines (Pfizer/BioNTech BNT162b2 or Moderna mRNA-1273) were from Western countries. As KT protocols vary across countries and regions, the vaccine efficacy has not been fully validated in KT recipients in Japan. In Japan, ABO blood-type incompatible (ABOi) KT protocols with strong immunosuppression strategies are necessary due to the absence of donor exchange programs and the serious donor shortage<sup>9-13</sup>. Currently, one-third of the recipients undergo ABOi KT with rituximab desensitization<sup>13</sup>. However, the anti-SARS-CoV-2 IgG seropositivity rate after the second SARS-CoV-2 mRNA-based vaccination in patients who undergo ABOi KT with contemporary immunosuppressive strategies remains unknown. Therefore, we measured the titers of immunoglobulin G (IgG) antibodies against the receptor-binding domain of SARS-CoV-2 spike (S) protein and investigated risk factors for inadequate humoral response after the second dose of the Pfizer/BioNTech BNT162b2 mRNA vaccine in KT recipients, including those who underwent ABOi KT.

## Results

The background characteristics of the study cohort are summarized in Table 1. Briefly, the median ages were 68 (IQR: 38-77) and 56 (IQR: 44-65) years in the controls and KT recipients, respectively. Rituximab was administered in 43 (41%) KT recipients, including 24 (23%) ABOi KT recipients and 19 (18%) ABOc KT recipients. Biopsy-proven rejection and viral infections before enrollment in the current study were observed in 10 (9%) and 11 (10%) patients, respectively. Steroids were used in most of all recipients (n=97, 92%), with a median prednisone dose of 5.0 mg. All recipients received combined immunosuppressive therapy including a median of three agents. Everolimus was used in 12 recipients. The median period after KT was 6.3 years. No recipient experienced biopsy-proven rejection or viral events during the current study period.

Table 1  
Background of participants

	Ctrl	Recipients	Seronegative	Seropositive	
		All	<15 U/mL	≥15 U/mL	P value
n	127	106	83	23	
Age, years	68 (38-77)	56 (44-65)	59 (46-66)	44 (38-55)	<0.001
Male, n (%)	91 (72%)	64 (60%)	51 (61%)	13 (57%)	0.81
Seropositive (≥15 U/mL), n	125 (98%)				
Marginal (0.40-15 U/mL), n (%)	127 (100%)	11 (10%)	11 (13%)	0 (0%)	0.196
Age at KT		46 (34-58)	49 (38-60)	34 (27-42)	<0.001
Median KT vintage, years		6 (3-12)	5 (3-9)	12 (7-15)	<0.001
Median dialysis vintage, years		1 (0.3-3)	1 (0.1-3)	2 (0.3-3)	<0.001
Cadaver KT		14 (13%)	11 (13%)	3 (13%)	1.000
Primary kidney disease, n (%)					
Vascular		51 (48%)	41 (49%)	10 (43%)	0.645
Interstitial		4 (3.8%)	4 (4.8%)	0 (0.0%)	0.575
Polycystic kidney disease		3 (2.8%)	1 (1.2%)	2 (8.7%)	0.118
Diabetes		8 (7.5%)	5 (6.0%)	3 (13%)	0.367
Others		14 (13%)	13 (16%)	1 (4.3%)	0.294
ABO blood type incompatible KT, n (%)		24 (23%)	22 (27%)	2 (8.7%)	0.093
Immunosuppressant regimen, n (%)					
Tacrolimus		90 (85%)	73 (88%)	17 (74%)	0.109
Cyclosporine		12 (11%)	8 (10%)	4 (17%)	0.287
Mycophenolate mofetil		89 (84%)	76 (92%)	13 (57%)	<0.001
Azathioprine		9 (8.5%)	3 (3.6%)	6 (26%)	0.003

KT: kidney transplant, eGFR: estimated glomerular filtration rate.

	Ctrl	Recipients	Seronegative	Seropositive	
Everolimus		12 (11%)	8 (9.6%)	4 (17%)	0.287
Steroids		97 (92%)	76 (92%)	21 (91%)	1.000
Rituximab		43 (41%)	38 (46%)	5 (22%)	0.054
Any history of rejection events, n (%)		10 (9.4%)	7 (8.4%)	3 (13%)	0.449
Any history of viral infection events, n (%)		11 (10%)	10 (12%)	1 (4.3%)	0.450
eGFR at vaccination, mL/min/1.73m <sup>2</sup>		44 (35-54)	43 (35-53)	45 (34-59)	<0.001
KT: kidney transplant, eGFR: estimated glomerular filtration rate.					

## Outcomes

The rate of anti-SARS-CoV-2 IgG seroprevalence was significantly lower in the KT recipients than in the controls (22% [23/106] vs. 98% [125/127],  $P < 0.001$ ; Fig. 1A). The rates of marginal anti-SARS-CoV-2 IgG seropositivity were 100% and 32% in the controls and KT recipients, respectively. Although not statistically significant, the anti-SARS-CoV-2 IgG seropositivity was lower in the ABOi KT recipients (8.3%) than in the ABOc KT recipients (26%,  $P = 0.093$ ) (Fig. 1B). The cross-sectional antibody titers are shown in Fig. 1C.

Univariable logistic regression analysis revealed that age (OR 0.94, 95%CI 0.91–0.98,  $P = 0.004$ ), rituximab use (OR 0.33, 95%CI 0.11–0.97,  $P = 0.044$ ), MMF use (OR 0.12, 95%CI 0.04–0.37,  $P < 0.001$ ), and KT vintage (OR 1.10, 95%CI 1.03–1.17,  $P = 0.005$ ) were significantly associated with anti-SARS-CoV-2 IgG seropositivity in KT recipients (Table 2). Based on the optimal cutoff values for age (53 years) and KT vintage (7 years) using the area under the ROC curve (AUC) analysis, the rate of anti-SARS-CoV-2 IgG seropositivity ranged between 10% and 15% among the KT recipients >53 years of age, those with a KT vintage of <7 years, and those who received rituximab or MMF (Fig. 2A). The rates of anti-SARS-CoV-2 IgG seronegativity were higher in those with more than one risk factor. Specifically, the anti-SARS-CoV-2 IgG seroprevalence rates of KT recipients harboring 0, 1, 2, 3, and 4 factors were 88%, 27%, 26%, 10%, and 0%, respectively (Fig. 2B). The AUC for the predictive accuracy of anti-SARS-CoV-2 IgG seropositivity was 0.79 in the model including rituximab use, MMF use, age >53 years, and KT vintage <7 years. Summary of the present study was shown in the visual abstract (Fig. S1).

Table 2  
Univariable logistic regression analysis

Variable	Factors	P value	OR	95%CI
Age at vaccination	Continuous	<i>0.004</i>	0.94	0.91-0.98
Gender	Male	<i>0.669</i>	0.82	0.32-2.08
Diabetes	Yes	<i>0.493</i>	0.63	0.17-2.38
Type of KT	ABOi	<i>0.088</i>	0.26	0.06-1.22
Immunosuppression	Rituximab use	<i>0.044</i>	0.33	0.11-0.97
	MMF use	<i>&lt;0.001</i>	0.12	0.04-0.37
	Everolimus use	<i>0.306</i>	1.97	0.54-7.25
	Cyclosporine use	<i>0.306</i>	1.97	0.54-7.25
	Steroids use	<i>0.968</i>	0.97	0.19-5.01
	3 or more agents use	<i>0.177</i>	0.34	0.07-1.63
Biopsy proven rejection events	Yes	<i>0.507</i>	1.63	0.39-6.87
Any viral infections	Yes	<i>0.306</i>	0.33	0.04-2.74
Renal function (eGFR)	mL/min/1.73m <sup>2</sup>	<i>0.661</i>	1.01	0.97-1.04
KT vintage, years	Continuous	<i>0.005</i>	1.10	1.03-1.17
OR: odds ratio, CI: confidence interval				

## Discussion

In the present retrospective study evaluation humoral response after the second BNT162b2 mRNA vaccination in KT recipients in Japan, we found that only 24% of the KT recipients had anti-SARS-CoV-2 IgG antibody titers of  $\geq 15$  U/mL and that the rate of anti-SARS-CoV-2 IgG seropositivity was 98% in healthy controls. This finding is comparable to previous studies reporting impaired humoral response in KT recipients. However, the rate of anti-SARS-CoV-2 IgG seropositivity varies across the studies, ranging from 4.1–40.3%, due to differences in study population, sample size and measurement methods. Korh et al. and Danthu et al. reported anti-SARS-CoV-2 IgG seroprevalence rates of 22% (5/23) and 4.1% (3/74), respectively, in KT recipients, based on the LIAISON® SARS-CoV-2 Trimetric-S IgG assay (Diasorin, Italy) with a positive cutoff value of 13.0 arbitrary units/mL<sup>3,7</sup>. Kolb et al. reported a seroprevalence of 37% (10/28) using the Anti-SARS-CoV-2 QuantiVac ELISA for spike protein (Euroimmun, Germany) with a positive cutoff value of 35.2 binding antibody units/mL<sup>6</sup>. Benomane et al. and Bertrand et al. reported seroprevalence rates of 40.3% (64/159) and 17.8% (8/45 recipients), respectively, using the ARCHITECT® IgG II Quant test for spike protein (Abbott Laboratories) with a positive cutoff value of 50.0 arbitrary

units/mL<sup>2,5</sup>. Although our observation of impaired humoral response in KT recipients (22%) is consistent with previous studies, the wide range of antibody tests and different cutoffs employed across the studies may contribute to the different results reported by the studies. One study investigated the agreement of three serological tests from Abbott, Roche, and Diasorin<sup>14</sup> and found a good agreement among the three tests (Cohen's kappa, 0.71–0.87). However, that study also reported that the clinical performance of these tests was insufficient in studies with low seroprevalence<sup>14</sup>. Overall, these findings highlight the need for careful interpretation of the results from different tests, especially in KT recipients. Additionally, the efficacy of SARS-CoV-2 vaccines cannot be measured by IgG antibody titers alone<sup>15</sup>. As the determination of protective IgG antibody levels remains unclear, further studies are necessary for optimal methods and cutoff values to determine the efficacy of SARS-CoV-2 mRNA vaccines.

The current study findings suggest that humoral response after SARS-CoV-2 mRNA vaccination is strongly inhibited in KT recipients >53 years of age, those treated with rituximab or MMF, and those with a KT vintage of < 7 years. Interestingly, similar factors were reported to be associated with weaker humoral response in a recent study that investigated the SARS-CoV-2 S IgG antibody in 142 KT recipients using the LIAISON® assay and showed age  $\geq 54$  years, KT vintage  $\leq 8$  years, and treatment with  $\geq 2$  immunosuppressants were significantly associated with seroconversion<sup>16</sup>. These results suggest that combination immunosuppressive therapy may induce strong immunosuppression which might interfere with antiviral antibody production for 7–8 years. Factors that impact antibody response in KT recipients should be further investigated.

Among the immunosuppressive agents, rituximab and MMF exhibited a significant impact on humoral response in not only KT recipients but also patients with other chronic clinical conditions. Several studies reported the negative effects of rituximab and MMF use on anti-SARS-CoV-2 IgG seropositivity in KT recipients<sup>17,18</sup> and in patients with autoimmune inflammatory rheumatic diseases<sup>19</sup>. Kantauskaite et al. showed that MMF-free immunosuppressive regimens were significantly associated with seroconversion (OR 13.25, 95% CI 3.22–54.6,  $P < 0.001$ )<sup>17</sup>. The authors suggested that MMF had a dose-dependent unfavorable effect on antibody titers, such as MMF levels of >1000 mg/day. We also examined the association between anti-SARS-CoV-2 IgG seropositivity and MMF dose and found that the seropositivity was lower in those treated with MMF doses > 1000 mg (6.3%) compared to those who were not treated with MMF (59%) and those treated with 500–1000 mg MMF (16%), which indicated that MMF dose modification might improve immune response to the SARS-CoV-2 vaccine. However, further investigation is warranted to address the balance between rejection and immune acquisition.

Rituximab use was also significantly associated with impaired humoral response in the current study. A multicenter observational study examining SARS-CoV-2 seropositivity in adult patients with autoimmune inflammatory rheumatic diseases ( $n = 686$ ) reported that rituximab use was significantly associated with impaired humoral response to the BNT162b2 mRNA vaccine<sup>19</sup>. As B cell depletion is associated with a lack of serological response, those findings are reasonable regarding the negative impact of rituximab on

humoral response to various vaccines<sup>20</sup>. Therefore, these results emphasize the importance of SARS-CoV-2 vaccination before the administration of MMF and /or rituximab in KT recipients.

The impact of ABOi KT on humoral response to SARS-CoV-2 vaccines should be addressed. Albeit uncommon across the globe, ABOi KT is a common alternative for donor exchange programs in Japan. As it requires extensive immunosuppression including rituximab and therapeutic apheresis, we hypothesized that ABOi KT might also have a great impact on anti-SARS-CoV-2 IgG seropositivity. However, we found that ABOi KT had a limited impact on seropositivity in the present study; this result might be associated with the lower statistical power due to the limited sample size, which should be addressed in future studies.

The major limitations of the present study include the limited sample size and retrospective study design. The IgG antibody titers were determined during the early phase of mass immunization in Japan. ABOi KT and rituximab use in immunologically high-risk recipients might not be common worldwide. Additionally, measurement of antibody titers is one of the several methods to assess immunologic response to vaccination. Despite those limitations, this is the first study evaluated the seroprevalence of SARS-CoV-2 IgG antibodies after the second BNT162b2 mRNA vaccine in Japanese KT recipients.

In conclusion, we confirmed that the rate of anti-SARS-CoV-2 IgG seroconversion was low in KT recipients after the second BNT162b2 mRNA vaccine. However, several outstanding questions remain and further investigation is warranted to determine the duration of immunity under immunosuppressive therapy, the effect of reduced titers on the protective activity of vaccines against breakthrough infections, and the efficacy of third vaccination in KT recipients.

## Methods

This retrospective study was approved by the Ethics Committee of Hirosaki University (2021-089). All participants had previously provided written informed consent for other biomarker studies. Additional informed consent for the current study was waived with approval by the Ethics Committee of Hirosaki University. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul and Helsinki.

### Participants

The current study conducted between June 21, 2021 and November 1, 2021 included 106 KT recipients and 127 healthy controls who received the second BNT162b2 dose at least seven days before the measurement of anti-SARS-CoV-2 antibody titers. The control group included members of the medical staff, medical students, and posttreatment patients with localized cancers who were not actively receiving any treatment. Those with previous SARS-CoV-2 infection and who provided blood samples for titer measurement within the first seven days after the second BNT162b2 dose were excluded. Clinical parameters of age, gender, primary kidney disease, KT vintage (years), dialysis vintage (years), ABO blood

type compatibility, immunosuppressant agents, past history of rejection events, past history of viral events, and renal function were obtained from the medical records.

## **Immunosuppression**

Flow cytometry and Luminex-based single-antigen bead assay were used to select the immunosuppression protocol <sup>21</sup>. Low-dose rituximab (100 mg/m<sup>2</sup> or 100 mg/body) and donor-specific human leukocyte antigen antibodies were administered in recipients of ABOi and ABO blood-type compatible (ABOc) KT, respectively. For ABOc KT recipients, basic immunosuppression included calcineurin inhibitors (CNIs), mycophenolate mofetil (MMF), and steroids. Most KT recipients, i.e., those who underwent KT after February 2002, were treated with induction therapy using the anti-CD25 monoclonal antibody basiliximab on the day of operation and postoperative day 4. Intravenous immunoglobulin was not given in all KT patients due to the lack of insurance coverage. ABOi KT recipients received basic immunosuppressive agents, rituximab and therapeutic apheresis. Low-dose rituximab was administered three weeks before transplantation. Basic immunosuppressive agents (CNIs, MMF, and steroids) were administered seven days before transplantation in all ABOi KT recipients. Several sessions of double-filtration plasmapheresis and one session of plasma exchange were performed on the day before surgery to remove anti-A/B antibodies until the anti-A/B antibody titers decreased to a level of <1:32–1:64. Those with viral infection or malignancies were switched from CNIs or MMF to everolimus.

## **Measurement of anti-SARS-CoV-2 IgG antibody titers**

Cross-sectional blood samples collected for regular evaluation were used to measure the titers of IgG antibodies against the SARS-CoV-2 S receptor-binding domain, and the Elecsys Anti-SARS-CoV-2 S RUO assay (Covas 8000/e 801; Roche Diagnostics, Mèlan, France) was used. According to the manufacturer's data, seropositivity was defined as an anti-SARS-CoV-2 IgG level of  $\geq 15$  U/mL, which was shown to be sufficient for the presence of neutralizing antibodies. Antibody titers between 0.80 and 15 U/mL were defined as marginal values.

## **Outcomes**

In the current study, we compared the rates of anti-SARS-CoV-2 IgG seropositivity as well as the rates of marginal anti-SARS-CoV-2 IgG seropositivity between the controls and KT recipients. We also determined the anti-SARS-CoV-2 IgG seropositivity rate in ABOi KT recipients, and investigated the factors associated with anti-SARS-CoV-2 IgG seropositivity after the second SARS-CoV-2 mRNA vaccination in KT recipients.

## **Statistical analysis**

Qualitative and quantitative variables were described as numbers with percentages and medians with interquartile ranges (IQRs), respectively. The chi-squared, Fisher's exact, Mann-Whitney *U*, and Student's *t*

tests were used for the statistical comparison between the healthy controls and KT recipients. Univariable logistic regression analysis was performed to identify factors associated with anti-SARS-CoV-2 IgG seropositivity after the second SARS-CoV-2 mRNA vaccination, and odds ratio (OR) with 95% confidence interval (CI) were calculated. Predictive accuracy and optimal cutoff values for anti-SARS-CoV-2 IgG levels were evaluated by area under the receiver operating characteristic (ROC) curve analysis. All statistical analyses were performed using BellCurve for Excel 3.10 (Social Survey Research Information, Tokyo, Japan) and GraphPad Prism 7.00 (GraphPad Software, San Diego, CA, USA).

## Declarations

**Author contributions:** Shingo Hatakeyama had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Shingo Hatakeyama

**Acquisition, analysis, or interpretation of data:** All authors

**Drafting of the manuscript:** Shingo Hatakeyama, Tomoko Hamaya

**Critical revision of the manuscript for important intellectual content:** Naoki Fujita, Takuma Narita, Teppei Okamoto

**Statistical analysis:** Shingo Hatakeyama

**Administrative, technical, or material support:** All authors

**Study supervision:** Chikara Ohyama

**Acknowledgments:** The authors would like to thank Yukie Nishizawa, Mitsuharu Miyadate, and Satomi Sakamoto for their invaluable support with data collection.

**Funding:** This work was supported by a Grant-in-Aid for Scientific Research (grant no.: 19H05556, 20K09517, and 21K09339) from the Japan Society for the Promotion of Science.

**Data sharing information:** Our data can be shared on reasonable request. Email: shingoh@hirosaki-u.ac.jp

**Conflicts of interest:** Shingo Hatakeyama received honoraria from Janssen Pharmaceutical K.K. and Pfizer Inc. and supported by a grant from NIPRO Corporation. Chikara Ohyama received honoraria from Astellas Pharma Inc., NIPPON SHINYAKU Company Ltd., AstraZeneca K.K., Janssen Pharmaceutical K.K., Takeda Pharmaceutical Company Ltd., Novartis Pharma K.K., ONO Pharmaceutical Company Ltd., Chugai Pharmaceutical Company Ltd., Sanofi S.A., Bayer AG., Pfizer Inc., Bristol Myers Squibb, Otsuka Pharmaceutical Company Ltd., KISSEI Pharmaceutical Company Ltd., Kyowa Kirin Company Ltd., Daiichi

Sankyo Company Ltd., KANEKA Corporation, and Nipro Corporation. The other authors have no potential conflicts of interest to disclose.

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## Figures

Fig.1

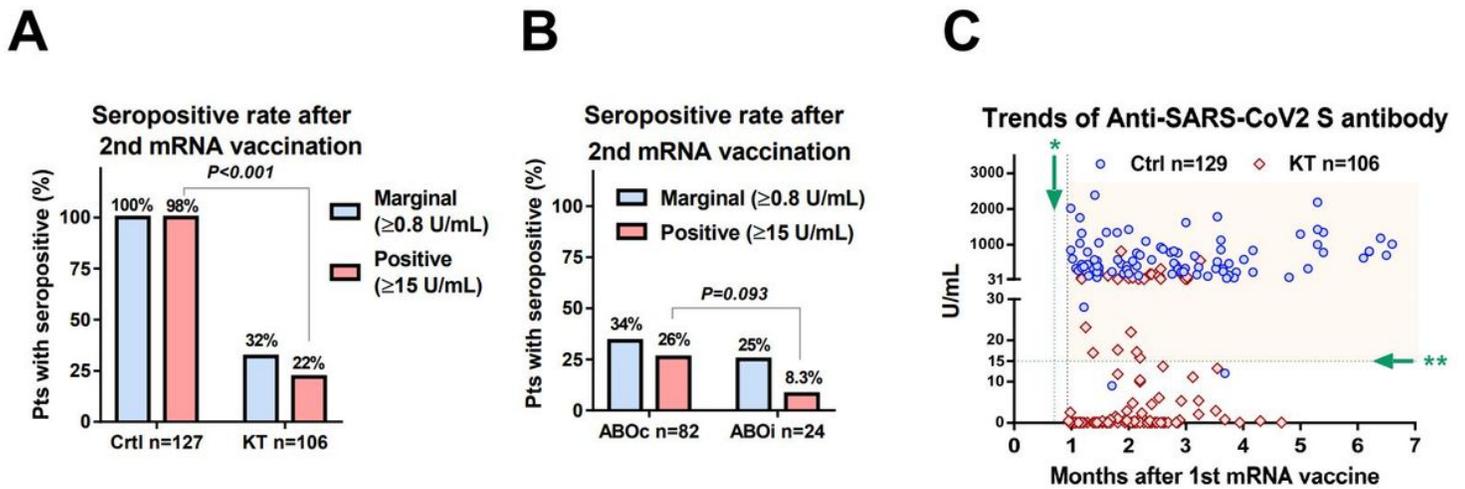


Figure 1

Rate of anti-SARS-CoV-2 IgG seropositivity after the second dose of the BNT162b2 mRNA vaccine A: Comparison of seropositivity rates after the second vaccine dose between the control (Ctrl) and kidney transplant (KT) recipients. Seropositivity and marginal seropositivity were defined as anti-SARS-CoV-2 IgG antibody titers of  $\geq 15$  U/mL and 0.80–15 U/mL, respectively. B: Comparison of seropositivity rates after the second mRNA vaccine dose between the ABO blood-type compatible (ABOc) and ABO blood-type incompatible (ABOi) KT recipients. C: Trends in anti-SARS-CoV-2 IgG antibody titers. \*, Second mRNA vaccination; \*\*, cutoff for the presence of neutralizing antibody

Fig.2

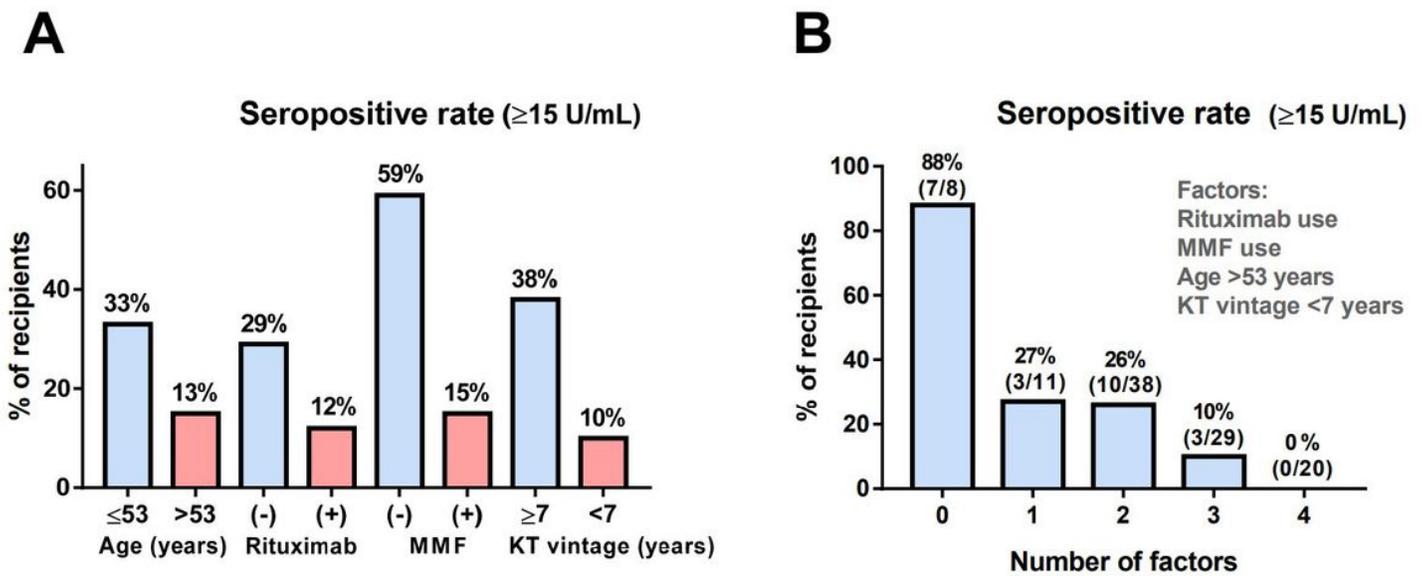


Figure 2

Comparison of rates of anti-SARS-CoV-2 IgG seropositivity based on select factors A: Comparison of anti-SARS-CoV-2 IgG seropositivity based on age ( $\leq 53$  vs.  $> 53$  years), rituximab use (yes vs. no), KT vintage ( $\geq 7$  vs.  $< 7$  years). B: Association between the number of risk factors and the rate of seronegativity

## Supplementary Files

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