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Cellular and humoral immune responses after a third dose of SARS-CoV-2 mRNA vaccine in lung transplant recipients in Japan

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ABSTRACT

Background: Lung transplant (LTx) recipients are at higher risk of infection with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). There is an increasing demand for additional analysis regarding the efficacy and safety of after the initial series of mRNA SARS-CoV-2 vaccines in Japanese transplant recipients.

Method: In this open-label, nonrandomized prospective study carried out at Tohoku University Hospital, Sendai, Japan, LTx recipients and controls received third doses of either the BNT162b2 or the mRNA-1273 vaccine, and the cellular and humoral immune responses were analyzed.

Results: A cohort of 39 LTx recipients and 38 controls participated in the study. The third dose of SARS-CoV-2 vaccine promoted much greater humoral responses at 53.9 % of LTx recipients than after the initial series at 28.2 % of patients without increasing the risk of adverse events. However, still fewer LTx recipients responded to the SARS-CoV-2 spike protein with the median IgG titer of 129.8 AU/mL and with the median IFN-γ level of 0.01 IU/mL when compared to controls with those of 7394 AU/mL and 0.70 IU/mL, respectively.

Conclusion: Although the third dose of mRNA vaccine in LTx recipients was effective and safe, impaired cellular and humoral responses to SARS-CoV-2 spike protein were noted. Given lower antibody production and establishing vaccine safety, repeating the administration of mRNA vaccine will lead to robust protection in such a high-risk population (jRCT1021210009).

1. Background

Lung transplant (LTx) recipients are at a higher risk of infection with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and consequent death [1,2]. However, it has been shown that in administering an mRNA SARS-CoV-2 vaccine, the efficacy of the first and second doses of the vaccine (hereinafter referred to as "the initial series") is considerably limited in recipients who have undergone LTx [3,4] as well as solid-organ transplant (SOT) [5,6], raising the need for the further investigation of immune-response from the cellular and humoral standpoints and vaccine safety in such a high-risk population. Despite several studies documenting the efficacy of administering a third dose of mRNA SARS-CoV-2 vaccine (hereinafter referred to as a "booster") to SOT recipients [7,8], detailed analysis with respect to different races and ethnicities and from various countries will be of significance given the current wave of COVID-19 being still far from over. Under the unique transplant circumstances in Japan, with a severe donor shortage and a limited number of transplantations [9,10], there is an increasing demand for additional analysis regarding the efficacy and safety of further vaccinations after the initial series of mRNA SARS-CoV-2 vaccines in the Japanese population. Thus, the primary aim of study was to evaluate cellular and humoral immune responses in LTx recipients who received boosters in a Japanese transplant center. A secondary aim was to determine the safety of the boosters by comparing LTX recipients and healthy controls.

2. Methods

2.1. Study design

This is an open-label, nonrandomized prospective study carried out at Tohoku University Hospital (TUH), Sendai, Japan. The primary study protocol, which was approved in June 2021 [3], was

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revised in March 2022 and approved by the institutional review board at Tohoku University Graduate School of Medicine (2021-1-142). Written informed consent was obtained from LTx recipients and controls. The study protocol was disclosed at the Japan Registry of Clinical Trials (jRCT1021210009) in June 2021 and revised in March 2022. The LTx recipients and controls were recruited from June to December 2022 and followed up until the end of January 2023. All methods were performed in accordance with the Declaration of Helsinki.

2.2. Participants

The inclusion criteria for LTx recipients were patients who had undergone LTx at TUH and who [1] were at a point at least six months after LTx, [2] had no history of reverse transcription polymerase chain reaction (RT–PCR)-confirmed SARS-CoV-2 infection, [3] had received a SARS-CoV-2 mRNA vaccine twice and [4] were at least 20 years old. The inclusion criteria for controls were healthy volunteers who [1] had no history of transplantation or immunosuppressive therapy, [2] had no history of RT–PCR-confirmed SARS-CoV-2 infection, [3] had received a SARS-CoV-2 mRNA vaccine twice and [4] were at least 20 years old. After enrolling in the study, LTx recipients and controls received the booster in the form of either the BNT162b2 vaccine (Pfizer Inc.) or the mRNA-1273 vaccine (Moderna, Inc.) according to the recommended schedule by the Japanese Ministry of Health, Labour and Welfare. Blood samples were collected before and at least four weeks after booster administration, when clinical data were reviewed by coauthors (Fig. 1). Details of the questionnaire for adverse events within seven days of booster administration had been previously described [3], and immunosuppression [11], histocompatibility testing [12], anti-microbial prophylaxis [13] and overall management [14] with respect to LTx recipients had been previously documented.

2.3. Cellular and humoral immune responses

The cellular immune response to SARS-CoV-2 was evaluated by the SARS-CoV-2 QuantiFERON research-use-only (RUO) assay (QIAGEN, Tokyo, Japan), according to the manufacturer's protocol [15]. Whole blood samples were incubated in an Ag1 tube that contained CD4+ T-cell epitopes from the S1 subunit of the spike protein, an Ag2 tube with both CD4+/CD8+ T-cell epitopes derived from the S1 and S2 subunits of the spike protein, a Nil tube (negative control) and a Mitogen tube (positive control) at 37 °C for 16 to 24 h. Plasma was collected after centrifugation at 3000 rpm for 15 min. Plasma IFN-γ concentrations were analyzed by QuantiFERON ELIZA RUO (QIAGEN, Tokyo, Japan) and measured at LSI Medience Corporation, Sendai, Japan. Participants who had an IFN-γ level $\geq$ 0.15 IU/mL in Ag2 tube were defined as responders for the cellular immune response to SARS-CoV-2. Undetectable IFN-γ (<0.07 IU/mL) was calculated as 0.01 IU/mL for the statistical analysis. The humoral immune response was evaluated by SARS-CoV-2 IgG II Quant (Abbott, Tokyo) as previously described [3]. Participants who had the SARS-CoV-2 S1 subunit of the spike protein IgG $\geq$ 50 AU/mL were regarded as responders according to the manufacturer's protocol. Undetectable IgG (<6.8 AU/mL) was calculated as 1.0 AU/mL for the statistical analysis.

2.4. Data collection and analysis

Data on LTX recipients and controls or responders and non-responders with respect to IgG or IFN-γ were presented as fractions (percentages) or medians (interquartile range [IQR]). Differences between groups were compared with the chi-square or Fisher's exact tests for categorical variables and Mann-Whitney tests for continuous variables. Differences in IgG titer or IFN-γ level across groups were compared by means of the Mann–Whitney *U* test. Spearman's coefficient (r) was calculated for testing bivariate correlations of IgG titers with IFN-γ levels. Statistical significance was set at $p < 0.05$. Statistical analyses and graphing were performed using GraphPad Prism 9.0 (GraphPad Software, Inc., La Jolla, CA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [16].

3. Results

3.1. Characteristics of LTx recipients and controls

The cohort consisted of 39 LTx recipients and 38 controls (Table 1). The median age of the LTx recipients was 52 (IQR 45–59), and 24 out of 39 (61.5 %) were female. After administration of the booster, nearly half of the recipients (56.4 %) had received the BNT162b2 vaccine more than twice. In LTx recipients, the booster promoted much greater humoral responses than those after the initial series, the fraction of SARS-CoV-2 IgG responders being 28.2 % before booster administration, which increased to 53.9 % after administration. In contrast, all controls became seropositive after the second vaccination [3] and were already SARS-CoV-2 IgG responders prior to booster administration (p.< 0001). With respect to cellular immune response, 25.6 % of LTx recipients were SARS-CoV-2 IFN-γ responders, while the fraction was 89.5 % in controls ($p < 0.0001$).

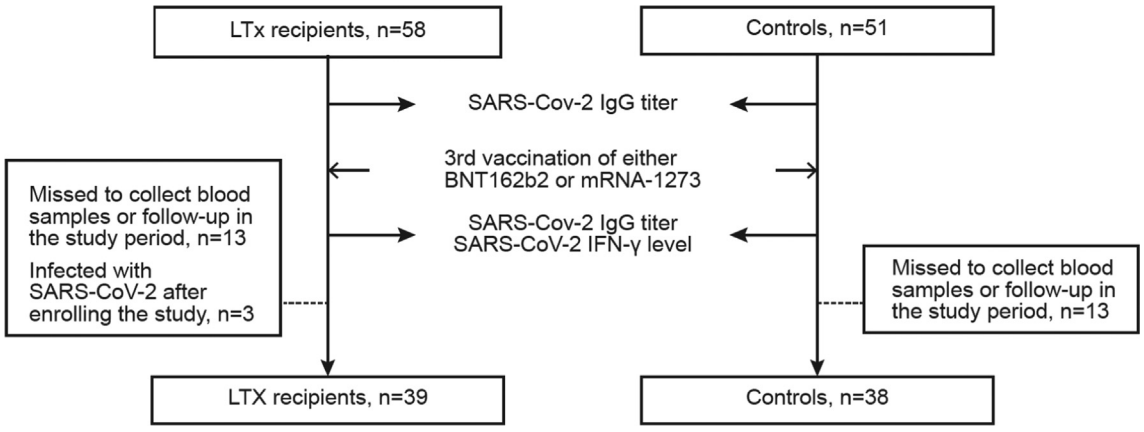

Fig. 1. Study flow. LTx: lung transplant.

Table 1
Characteristics of lung transplant recipients and controls in the study.

	LTx recipients (n = 39)	Controls (n = 38)	p value
Age - years (IQR)	52 (45–59)	43 (29–47)	0.0001
Femal sex - no. (%)	24 (61.5)	33 (86.8)	0.0183
Vaccine type - no. (%)			0.0047
BNT162b2 vaccine dominant	22 (56.4)	33 (86.8)	
mRNA-1273 vaccine dominant	17 (43.6)	5 (13.2)	
Dasys from 3rd vaccine to blood sampling - days (IQR)	95 (74–130)	139 (122–166)	0.0022
SARS-CoV-2 IgG responder before 3rd vaccine -no. (%)	11 (28.2)	38 (100.0)	0.0001
SARS-CoV-2 IgG responder after 3rd vaccine -no. (%)	21 (53.9)	38 (100.0)	0.0001
SARS-CoV-2 IFN-γ responder after 3rd vaccine -no. (%)	10 (25.6)	34 (89.5)	0.0001

LTx: lung transplant; IQR: interquartile.

The SARS-CoV-2 IgG titer and IFN-γ level of LTx recipients and controls were compared. In LTx recipients, the median IgG titer before booster administration was 8.3 AU/mL (IQR 1.0–61.4), increasing to 129.8 AU/mL (IQR 1.0–1340) after administration, whereas in controls it was 1408 AU/mL (IQR 597.8–2405) before administration, increasing to 7394 AU/mL (IQR 4097–13500) after administration (Fig. 2A). Likewise, cellular immune response after administration exhibited a significant difference: in LTx recipients, the median IFN-γ level was 0.01 IU/mL (0.01–0.18), and in controls ($p < 0.0001$) it was 0.70 IU/mL (IQR 0.26–1.50) (Fig. 2B). A strong correlation between IgG titer (AU/mL) and IFN-γ level (IU/mL) ($r = 0.620$) was not observed in either LTx recipients or controls (Fig. 2C).

3.2. Differences between responders and non-responders in LTx recipients

The characteristics of SARS-CoV-2 IgG responders and non-responders in LTx recipients are shown in Table 2. SARS-CoV-2 IgG responders tended to be younger, at a median age of 49 (IQR 38–57), than non-responders, at 56 (IQR 50–59). Gender, LTx indication and vaccine type were not significantly different between responders and non-responders. Despite higher mycophenolate ACU in non-responders after the second vaccination [3], a significant difference in mycophenolate AUC was not observed between the responders and non-responders after booster administration ($p = 0.856$). While in LTx recipients, 42.9 % of SARS-CoV-2 IgG responders were IFN-γ responders, a mere 5.6 % of IgG non-responders produced IFN-γ against S1 and S2 subunits of the SARS-CoV-2 spike protein ($p = 0.011$).

The characteristics of SARS-CoV-2 IFN-γ responders and non-responders in LTx recipients were analyzed from the standpoint of cellular immunity (Table 3). There were no differences in age, gender, LTx indication or vaccine type in IFN-γ responders and non-responders. IFN-γ responders were found in older transplantations rather than recent ones, the median years since LTx being 12.5 vs 4.0, respectively ($p = 0.0088$). A trend was observed in SARS-CoV-2 IFN-γ responders with a higher fraction of IgG responders: 60 % of IFN-γ responders were IgG responders before booster administration (vs 17.2 % in IFN-γ non-responders, $p = 0.0167$) and 90 % of IFN-γ responders were IgG responders after booster administration (vs 41.4 % in IFN-γ non-responder, $p = 0.0106$).

3.3. Adverse events after booster administration

As previously reported [17,18], vaccinated-site pain (55.3 %) and fatigue (52.6 %) were most common in local and systemic adverse events, respectively, in healthy individuals. Overall, similar trends in adverse events were observed in LTx recipients compared to controls: vaccinated-site pain occurred in 38.5 % of LTx recipients and fatigue in 25.6 %. Importantly, LTx recipients had significantly fewer episodes of lymphadenopathy, fever, fatigue and myalgia than controls ($p < 0.05$ in all events). There were no LTx recipients who exhibited reduced lung function after booster administration during the follow-up period. No hospital admissions or deaths occurred during the study period.

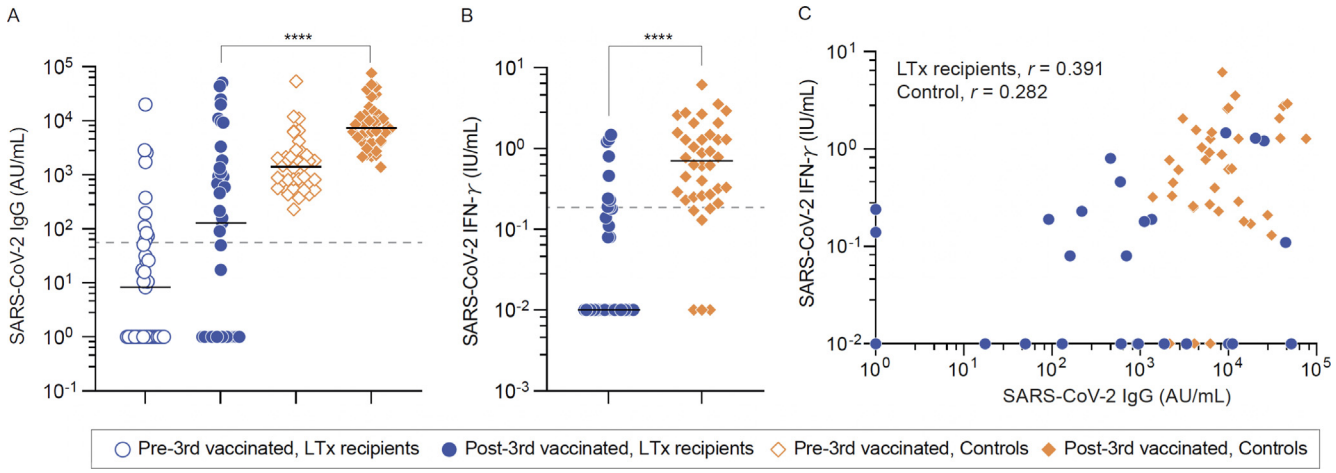

Fig. 2. Trend of cellular and humoral immune responses in participants (lung transplant recipients shown by blue circles and controls shown by orange diamonds) before and after a third dose of SARS-CoV-2 vaccine. A. IgG titers of participants before and after vaccination. B. IFN-γ level of participants after vaccination. C. Spearman's coefficient (r) was calculated for between IFN-γ level and IgG titers. LTx: lung transplant; ****$p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Characteristics of IgG responders and non-responders with respect to a third dose of SARS-CoV-2 vaccine in lung transplant recipients.

	SARS-CoV-2 IgG responder (n = 21)	SARS-CoV-2 IgG non-responder (n = 18)	p value
Age - years (IQR)	49 (38–57)	56 (50–59)	0.0484
Femal sex - no. (%)	11 (52.4)	13 (72.2)	0.3230
Underlying disorder - no. (%)			0.7161
Obstructve	9 (42.9)	8 (44.4)	
Vascular	6 (28.6)	4 (22.2)	
Suppurative	3 (14.3))	2 (11.1)	
Fibrosis	2 (9.5)	4 (22.2)	
Allogenic	1 (4.8)	0 (0.0)	
Transplant type - no. (%)			0.9990
Single	11 (52.4)	10 (55.6)	
Double	10 (47.6)	8 (44.4)	
Years since transplant - years (IQR)	6 (3–12)	6 (2–10)	0.7319
Tacrolimus concentration - ng/mL (IQR)	8.8 (6.5–10.5)	8.0 (5.0–10.0)	0.4811
Mycophenolate AUC - μg ▫ h/mL (IQR)	33.4 (17.1–43.0)	33.8 (23.7–43.0)	0.8563
Sirorimus use - no. (%)	4 (19.1)	4 (22.2)	0.9990
Days from 3rd vaccine to 3rd sample - days (IQR)	95 (67–126)	92 (81–179)	0.7435
Vaccine type - no. (%)			0.2599
BNT162b2 vaccine dominant	15 (71.4)	15 (83.3)	0.4642
mRNA-1273 vaccine dominant	6 (28.6)	3 (16.7)	
SARS-CoV-2 IgG responder before 3rd vaccine -no. (%)	11 (52.4)	0 (0.0)	0.0002
SARS-CoV-2 IFN-γ responder after 3rd vaccine -no. (%)	9 (42.9)	1 (5.6)	0.0106

BNT162b2 vaccine dominant, vaccinated with BNT162b2 three times or BNT162b2 twice and mRNA-1273 once; mRNA-1273 vaccine dominant, vaccinated with mRNA-1273 three times or mRNA-1273 twice and BNT162b2 once; IQR: interquartile.

Table 3
Characteristics of IFN-γ responders and non-responders with respect to a third dose of SARS-CoV-2 vaccine in lung transplant recipients.

	SARS-CoV-2 IFN-γ responder (n = 10)	SARS-CoV-2 IFN-γ non-responder (n = 29)	p value
Age - years (IQR)	49 (38–57)	55 (46–59)	0.2969
Femal sex - no. (%)	6 (60.0)	18 (62.1)	0.9999
Underlying disorder - no. (%)			0.2990
Obstructve	3 (30.0)	14 (48.3)	
Vascular	4 (40.0)	6 (20.7)	
Suppurative	1 (10.0)	4 (13.8)	
Fibrosis	1 (10.0)	5 (17.2)	
Allogenic	1 (10.0)	0 (0.0)	
Transplant type - no. (%)			0.4646
Single	4 (40.0)	17 (58.6)	
Double	6 (60.0)	12 (41.4)	
Years since transplant - years (IQR)	12.5 (6–15)	4 (2–9)	0.0088
Tacrolimus concentration - ng/mL (IQR)	8.2 (5.2–10.5)	8.4 (6.1–10.4)	0.6981
Mycophenolate AUC - μg ▫ h/mL (IQR)	33.3 (15.2–41.9)	33.6 (26.2–43.6)	0.5576
Sirorimus use - no. (%)	2 (20.0)	6 (20.7)	0.9999
Days from 3rd vaccine to 3rd sample - days (IQR)	112 (83–160)	95 (71–129)	0.2974
Vaccine type - no. (%)			0.1970
BNT162b2 vaccine dominant	6 (60.0)	24 (82.8)	
mRNA-1273 vaccine dominant	4 (40.0)	5 (17.2)	
SARS-CoV-2 IgG responder before 3rd vaccine -no. (%)	6 (60.0)	5 (17.2)	0.0167
SARS-CoV-2 IgG responder after 3rd vaccine -no. (%)	9 (90.0)	12 (41.4)	0.0106

BNT162b2 vaccine dominant, vaccinated with BNT162b2 three times or BNT162b2 twice and mRNA-1273 once; mRNA-1273 vaccine dominant, vaccinated with mRNA-1273 three times or mRNA-1273 twice and BNT162b2 once; IQR: interquartile; AUC: area under plasma concentration time curve.

4. Discussion

Cellular and humoral response after the booster administration in LTx recipients were investigated in a Japanese transplant center. The booster promoted much greater humoral responses in LTx recipients than after the initial series without increasing the risk of adverse events. However, with respect to IgG and IFN-γ, still fewer LTx recipients responded to the SARS-CoV-2 spike protein than did the controls. SARS-CoV-2 IgG responders accounted for 53.9 % with the median IgG titer of 129.8 AU/mL and IFN-γ responders for 25.6 % with the median IFN-γ level of 0.01 IU/mL after booster administration. These trends were observed in LTx recipients in other studies [19,20] and the outcomes were consistent with other organ transplant recipients [21,22]. Given the high immunosuppressive regimen that hampers the immune response to vaccination [7] and impaired humoral response that affects neutralizing antibodies and protection against SARS-CoV-2 infection [23], LTx recipients remain at risk of breakthrough COVID19 even after vaccination. However, in the context of vaccine safety, no life-threatening episodes were observed in LTx recipients, such as a reduction in lung function or hospital admission, and there were fewer adverse events than in healthy controls after booster administration (Fig. 3), this outcome being better than expected. Recent studies demonstrated that repeating SARS-CoV-2 vaccination increased antibody titer and changed the fraction of responders from 10.6 % of participants after the first vaccination to 35.1 % after the second, 48.5 % after booster administration, and 65.1 % after administration of a second booster [24]. With those features in

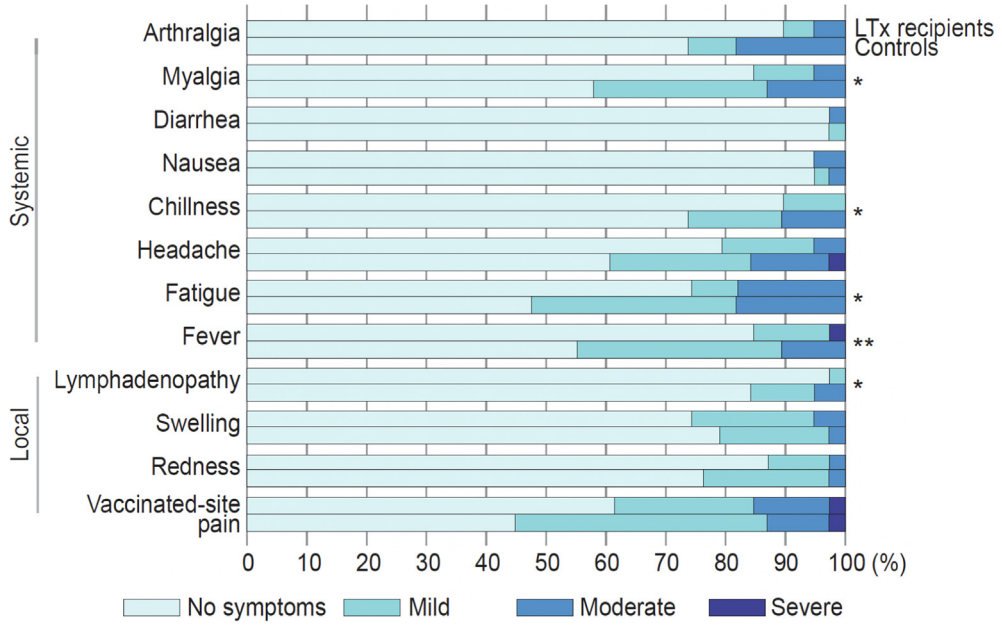

Fig. 3. Percentages of various adverse events in lung transplant recipients and controls after a third dose of SARS-CoV-2 vaccine. LTx: lung transplant; *p < 0.05; **p < 0.01.

mind, repeating SARS-CoV-2 mRNA vaccination by administering a second or third booster could bring about better humoral response in LTx recipients and lead to whole or partial protection against SARS-CoV-2 infection.

Although, in LTx recipients, 90 % of IFN-γ responders achieved antibody response after booster administration, a mere 42.5 % of IgG responders had detectable IFN-γ response to the SARS-CoV-2 spike protein (Fig. 2C); in other words, 57.5 % lacked a cellular response. The data was consistent with other studies reporting that a reduced T-cell function in SOT recipients was associated with a discordance between cellular and humoral immune responses, where SARS-CoV-2 IgG was confirmed despite undetectable cellular responses [25]. These data suggested that antibodies specific to the SARS-CoV-2 spike protein would be produced, at least partially, in a T-cell-independent manner [26,27]. Given the need for post-transplant maintenance immunosuppression including calcineurin inhibitors, antimetabolites, corticosteroids and other medications [11,12,28], most of which suppress T-cell function rather than B-cell activity with antibody production, it is conceivable that SOT recipients' cellular immunity would be weaker than their humoral immunity. Although the cellular immunity to SARS-CoV-2 in SOT recipients is still undetermined, current evidence indicates that antibodies have a protective role with respect to the SARS-CoV-2 spike protein [29,30]. Since the data obtained in the present study indicate little correlation between IgG titer and IFN-γ level and a discordance between cellular and humoral immune responses, it seems the optimal indications of protection against SARS-CoV-2 in SOT recipients still rely on the antibody titers. That being said, a further study should be conducted to ascertain the role of cellular immunity to SARS-CoV-2 in such a high-risk population.

In view of such dominant roles of humoral immunity against SARS-CoV-2 beyond impaired cellular response but still insufficient IgG production after vaccination in SOT recipients, passive immunization may be a reasonable and also unique approach to protect SOT recipients from prevailing respiratory viruses. In a multicenter, double-blind, randomized, placebo-controlled trial [31] tixagevimab/cilgavimab, which combines monoclonal antibodies that neutralize non-overlapping epitopes of the receptor-binding domain of the SARS-CoV-2 spike protein, has been shown to reduce the risk of symptomatic COVID-19 in adults with an inadequate response to mRNA vaccines. Although tixagevimab/cilgavimab may not be able to adequately neutralize all variants of the current circulating SARS-CoV-2 virus with respect to SOT recipients [32] and should be administered at an appropriate dosage [33], high-dose tixagevimab/cilgavimab resulted in a lower incidence of breakthrough COVID-19 [34] and hospital admission [35]. The current wave of COVID-19 is still far from over and in the meantime, prophylaxis with monoclonal antibodies could be a potential option to reduce the risk of COVID-19 in SOT recipients.

This analysis has some limitations that warrant discussion. Because of the small sample size, the data did not permit in-depth investigation, such as evaluating clinical factors associated with SARS-CoV-2 IgG or IFN-γ non-responders. In a meta-analysis [8], LTx recipients with antimetabolite exhibited a poor antibody response. Additionally, the discordance between IgG and IFN-γ production requires detailed analysis. To this end, a future multicenter study involving a larger cohort, for instance after administration of a second or third booster, is needed. This would allow multivariate analysis with respect to the clinical risk factors associated with poor IgG or IFN-γ responders and the difference in cellular and humoral response in the Japanese population.

In conclusion, cellular and humoral immune responses after the administration of a third dose of mRNA vaccine to Japanese LTx recipients were investigated through a nonrandomized prospective study. In the recipients, this booster vaccination promoted better humoral responses than those after the initial series of vaccinations without increasing the risk of adverse events. However, fewer LTx recipients than healthy individuals exhibited sufficient IgG response and even lower IFN-γ response to the SARS-CoV-2 spike protein even after administration of the booster. Given the lower antibody production in LTx recipients and the importance of establishing vaccine safety for such recipients, repeated administration of mRNA vaccine and, additionally, prophylaxis monoclonal antibodies will lead to robust protection against SARS-CoV-2.

5. Ethics approval and consent to participate.

All methods were performed in accordance with the Declaration of Helsinki. The study protocol was approved in March 2022 by the institutional review board Tohoku University Graduate School of

Medicine (2021-1-142). Written informed consent was obtained from all participants prior to entering the study. The study protocol was disclosed at the Japan Registry of Clinical Trials (jRCT1021210009) in June 2022.

6. Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

7. Authors' contributions

UM and TH are the guarantor of this manuscript, responsible for statistical analysis and has full access to all data in the study. MA and MH gathered information from the medical chart and the database. TK contributed the data analysis and interpretation. YO 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. All authors have read and approved the manuscript.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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