

Humoral response and safety of the BNT162b2 and mRNA-1273 COVID-19 vaccines in allogeneic hematopoietic stem cell transplant recipients: an observational study

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Abstract

The effectiveness of mRNA COVID-19 vaccines and the optimal timing of vaccine administration in allogeneic hematopoietic stem cell transplantation (Allo-HSCT) recipients remains inadequately investigated. We examine the effectiveness and safety of mRNA COVID-19 vaccines in allo-HSCT recipients. This prospective observational study included 44 allo-HSCT recipients and 38 healthy volunteers. The proportion of subjects acquiring anti-S1 IgG antibodies were considered as the primary endpoint. The occurrence of adverse events after vaccination and objective deterioration of chronic graft-versus-host disease (GVHD) were defined as secondary endpoints. In addition, we compared anti-S1 antibody titers in subgroups based on time interval between transplantation and vaccination. A humoral response to the vaccine was evident in 40 (91%) patients and all 38 healthy controls. The median anti-S1 IgG titers were 395 and 499 BAU/mL in patients and healthy controls, respectively ($p = 0.606$). A short time interval between transplantation and vaccination (≤ 6 months) was associated with low anti-S1 IgG antibody titers. No serious adverse events and deterioration of chronic GVHD were observed. Only one case of new development of mild chronic GVHD was recorded. Messenger RNA COVID-19 vaccines induce humoral responses in allo-HSCT recipients and can be administered safely.

Introduction

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) recipients are at a risk of severe coronavirus disease 2019 (COVID-19), with a 30-day survival rate of 68% if previously unvaccinated [1]. They respond to most conventional vaccines, albeit to a lower extent than healthy individuals during the first few months or years after transplantation. Some conventional vaccines can induce a serological response in allo-HSCT recipients as early as 3–6 months post transplantation. As to COVID-19 vaccines, some societies, such as the American Society of Transplantation and Cellular Therapy and American Society of Hematology, recommend mRNA COVID-19 vaccination as early as three months after allo-HSCT based on the high level of protection afforded to the vaccinated participants and overall safety of the vaccine in clinical trials [2].

The effectiveness of conventional vaccines in allo-HSCT recipients is influenced by complex humoral and cell-mediated immunodeficiencies that evolve over time, transplant procedures, and prevention and treatment of graft-versus-host disease (GVHD) [3]. However, factors associated with humoral response to mRNA COVID-19 vaccines are not well established, and the optimal timing of vaccine administration remains unknown. Moreover, data regarding the safety of mRNA COVID-19 vaccines, including the worsening or newly-development of chronic GVHD, are warranted. Therefore, in the present study, we examined the effectiveness and safety of COVID-19 mRNA vaccines in allo-HSCT recipients and factors associated with an impaired humoral response.

Methods

Study design and participants

This prospective study investigated the efficacy and safety of BNT162b2 and mRNA-1273 COVID-19 vaccines in allo-HSCT recipients admitted to Kobe City Medical Center General Hospital. Patients were recruited between June 2021 and September 2021. Allo-HSCT recipients over the age of 16 years with > 3 months elapsed since transplantation were included in the study. Exclusion criteria were as follows: 1) patients with a known history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and 2) those with comorbidities of autoimmune diseases, including systemic lupus erythematosus, Sjögren's syndrome, inflammatory myositis, mixed connective tissue disease, systemic sclerosis, rheumatic arthritis, polymyalgia rheumatica, psoriatic arthritis, spondyloarthritis, vasculitis syndromes, inflammatory bowel diseases, Guillain–Barré syndrome, multiple sclerosis, and neuromyelitis optica. The control group, comprising healthy volunteers aged ≥ 20 years without a history of COVID-19, in our previous study, in which we investigated vaccine efficacy in patients exposed to anti-CD20 antibodies, also served as the control group in the present study [4]. The study was approved by the Institutional Review Board of Kobe City Medical Center General Hospital (approval no.: zn210708). Informed consent was obtained from all participants.

Procedures

The blood serum samples of study participants were collected 14–90 days after they received the second dose of vaccine. Data on demographics, complete blood count, diagnosis, disease status, and treatment history were extracted from medical records. Details of the treatment history included conditioning regimens, donor type, GVHD prophylaxis, and immunosuppressant intake. In addition, all subjects were enquired about any local or systemic adverse events within 7 days after each vaccine dose through a questionnaire. Adverse events were defined as local pain, redness or edema, axillary lymphadenopathy, fatigue, myalgia, fever, chills, headache, nausea or vomiting, anaphylaxis, and subjective worsening of any chronic GVHD symptoms. To assess the objective deterioration of chronic GVHD signs and symptoms, attending physicians reported National Institutes of Health (NIH) scores for chronic GVHD grading both at the day of inclusion and of blood sampling (genital tract examination was skipped) [5]. The objective deterioration of chronic GVHD was defined as an increase in the sum of the NIH score.

Anti-SARS-CoV-2 antibody titer evaluation

Abbott Architect SARS-CoV-2 IgG Quant II chemiluminescent microparticle immunoassay (Abbott, Sligo, Ireland) was used to detect IgG antibodies to the receptor-binding domain in the S1 subunit of the SARS-CoV-2 spike protein (anti-S1 IgG antibody). Anti-S1 IgG antibody titers are reported as binding antibody unit per mL (BAU/mL) with a range of 7.1–5,680 BAU/mL. Additionally, we examined serum immunoglobulin levels and conducted lymphocyte subset analysis of CD4- and CD8-positive T cells, B cells, and NK cells in collected blood samples.

Endpoints and statistical analysis

The primary endpoint was set as the proportion of subjects acquiring anti-S1 IgG antibodies. According to the manufacturer's instructions, seropositivity against the SARS-CoV-2 spike protein was defined by an anti-S1 IgG antibody titer of > 7.1 BAU/mL. The antibody titer of seronegative patients was set to 0

BAU/mL. We compared anti-S1 IgG antibody titers in subgroups divided by conditioning regimens, donor type, immunosuppressant intake, additional agents for GVHD prophylaxis, and time elapsed between transplantation and vaccination (≤ 6 months and > 6 months). In addition, we compared anti-S1 antibodies in subgroups defined by cutoffs of 700, 80, and 40 mg/dL for IgG, IgA, and IgM, respectively, and a total lymphocyte count of $1.0 \times 10^3/\mu\text{L}$, B cell fraction of 3%, and CD4-positive T cell count of $0.4 \times 10^3/\mu\text{L}$ [4, 6, 7].

Adverse events after vaccination and objective deterioration of chronic GVHD were considered as secondary endpoints. Continuous variables were summarized using medians and interquartile range (IQR; quartiles 1–3), whereas categorical variables were summarized as counts and percentages. Seropositivity rates were compared using chi-square test. Anti-S1 antibody titers between patients and healthy volunteers or among subgroups were compared using the Mann–Whitney *U* test. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using R software (version 4.1.2; R Development Core Team).

Results

Patient characteristics

This study included in total 44 allo-HSCT recipients (20 [45%] men, median age 56 [IQR 40–63] years) and 38 healthy controls (9 [24%] men, median age 28 [IQR 25–40] years). The characteristics of patients and healthy volunteers are listed in **Table 1**. Thirty-eight patients (86%) received BNT162b2, whereas six (14%) received mRNA-1273. The median time from the day of transplantation to the first vaccination was 809 days (IQR: 370–1,500). The number of patients receiving allo-HSCT within ≤ 6 or > 6 months was 5 (11%) and 39 (89%), respectively. Of the 44 patients, 16 (36%) were diagnosed with acute myeloid leukemia or myelodysplastic syndromes, 16 (36%) with lymphomas, 8 (18%) with acute lymphoblastic leukemia, and 4 (9%) with other hematological diseases. Moreover, 41 patients (93%) were in complete remission, 1 was in partial remission, and 2 were on active therapy. Seventeen patients (39%) had one or more chronic GVHD signs or symptoms at inclusion. At vaccination, 20 (45%) patients received one or more immunosuppressive agents.

Immunoassay data revealed that 35 (80%), 36 (82%), and 36 (82%) patients had IgG, IgA, and IgM titers of > 700 mg/dL, > 80 mg/dL, and > 40 mg/dL, respectively, and 39 (89%) patients had a total lymphocyte count of $> 1.0 \times 10^3/\mu\text{L}$, 39 (89%) had B cell fraction of $> 3\%$, and 26 (59%) had a CD4-positive T cell count of $> 0.4 \times 10^3/\mu\text{L}$.

Serological response

Antibody response against the vaccine was evident in 40 (91%) patients and in all 38 healthy controls. The median anti-SARS-CoV-2 IgG titers in patients and healthy controls were 395 (IQR: 76–1,678) BAU/mL and 499 (IQR: 331–826) BAU/mL ($P = 0.606$), respectively (Fig. 1). Details of four seronegative allo-HSCT recipients were as follows: a chronic lymphocytic leukemia patient on ibrutinib for relapse after

allo-HSCT, a T-cell prolymphocytic leukemia patient who had received alemtuzumab before allo-HSCT, an angioimmunoblastic T-cell lymphoma patient who also had B-cell lymphoproliferative disease and received rituximab before allo-HSCT, and an acute myeloid leukemia patient on tacrolimus and prednisolone (35 mg/day) for active chronic GVHD.

In subgroup analysis, a short time interval between transplantation and vaccination (≤ 6 months) was associated with low anti-S1 IgG antibody titers (Fig. 1, **Table 2**). Of note, however, four out of five patients revealed detectable anti-S1 IgG titers, with median titers of 29.2 (IQR: 23.1–67.7) BAU/mL. Even among allo-HSCT recipients, those with longer time intervals between transplantation and vaccination ($n = 39$, > 6 months, median 975 [IQR: 631–1,638] days) exhibited median anti-S1 IgG titers of 590 (IQR: 181–2,079) BAU/mL, which is compatible with those of healthy controls (Fig. 1).

We also conducted an exploratory subgroup analysis and found that lymphocytopenia $\leq 1.0 \times 10^3/\mu\text{L}$, peripheral B cell fraction $\leq 3\%$, hypogammaglobulinemia, immunosuppressant intake at vaccination were associated with impaired humoral response (**Table 2**).

Adverse events

All patients and healthy volunteers reported adverse events after the first and second vaccinations. Local pain at the injection site, fatigue, and fever were common in both groups and were reported in 92%, 50%, and 37% healthy volunteers, respectively, and 77%, 34%, and 14% patients, respectively, after the second dose (Fig. 2). All adverse events were mild and resolved spontaneously.

Deterioration of chronic GVHD

NIH score was recorded by attending physicians on the days of inclusion and blood sampling. Among 17 patients (38.6%) with one or more chronic GVHD signs and NIH score of more than one point at inclusion, only 1 patient had worsened NIH score (5 to 7), 7 had improved NIH score, and 9 had the same NIH score on the day of blood sampling. The patient whose NIH score worsened revealed deteriorated performance status due to lung abscess caused by bacterial infection. Among nine patients whose NIH scores remained stable, one reported subjective worsening of dry eye and limited range of motion, which resolved spontaneously. Among 27 patients (61.3%) whose NIH score at inclusion was zero, only one patient revealed a worsened NIH score (0 to 1) at the time of blood sampling due to a newly developed skin rash that required topical steroid ointment application. Furthermore, another patient reported the occurrence of dry eye within 1 week from vaccination, which resolved spontaneously (Fig. 2).

Discussion

This study prospectively evaluated the humoral response of allo-HSCT recipients to COVID-19 mRNA vaccines BNT162b2 (BioNTech Pfizer) and mRNA-1273 (Moderna). We observed that allo-HSCT recipients respond well to mRNA COVID-19 vaccines. However, vaccination within 6 months from allo-HSCT was associated with low anti-S1 IgG titers. In terms of safety, no additional adverse events were

observed in the allo-HSCT group compared to control group. In addition, no severe development or deterioration of chronic GVHD was reported.

Our study showed a high seropositivity rate in allo-HSCT recipients, compatible with healthy controls. Some previous studies that investigated the effectiveness of mRNA COVID-19 vaccines in allo-HSCT recipients reported a higher seropositivity rate (50–80%) in these patients compared with solid organ transplant recipients (40–60%) or anti-CD20 antibody recipients (< 20% if anti-CD20 antibodies were administered within 6–12 months) [8–13]. However, these studies also indicated that humoral responses of allo-HSCT recipients to mRNA COVID-19 vaccines were weaker than those of healthy individuals [9–13]. Our study revealed a higher seropositivity to mRNA COVID-19 vaccines among allo-HSCT patients than previous reports. This is probably because our study included many patients with a longer time interval between transplantation and vaccination (median duration of 809 [IQR: 370–1,500] days) compared to previous studies. This seems advantageous to expect reconstruction of adaptive immunity to gain seroconversion after vaccination [3]. In addition, the timing of serological assessment after the second dose of allo-HSCT recipients was earlier than that of volunteers (the median 37 versus 79 days, respectively). Therefore, it can result in the lower anti-S1 IgG titers of volunteers due to a decline over time. Our study also revealed that a short time interval between transplantation and vaccination (≤ 6 months) was associated with low anti-S1 IgG antibody titers. Nevertheless, our results are encouraging and support the recommendation of the American Society of Hematology and American Society of Transplantation and Cellular Therapy.

Anti-S1 IgG titers have been reported to be associated with neutralization activity against SARS-CoV-2; however, an observational study has indicated that neutralization activity is absent if anti-S1 antibody levels are low [14]. Among allo-HSCT recipients with a detectable but weak humoral response after the administration of two doses of an mRNA COVID-19 vaccine, an increase in antibody levels after the administration of a third dose has been observed [10]. Therefore, allo-HSCT recipients who received mRNA COVID-19 vaccines early after transplantation would benefit from an additional dose of mRNA COVID-19 vaccines. Keeping up-to-date on vaccination, allo-HSCT recipients should continue strict protective measures, such as wearing masks and social distancing.

In addition to a short time interval between allo-HSCT and vaccination [10, 15, 16], various factors, such as conditioning regimen (e.g., reduced intensity conditioning) [15], donor type (e.g., haploidentical donors) [9, 15, 16], immunosuppressant intake [10, 11, 16–18], GVHD presence [15], hypogammaglobulinemia [14], and lymphocytopenia [9, 10, 14, 16, 19] have been proposed as the potential predictors of impaired humoral response. Our study indicates that immunosuppressive agent use, hypogammaglobulinemia, lymphocytopenia, and low B-cell fraction (< 3%) is associated with impaired humoral response, which is in line with some previous reports. Systematic review and meta-analysis uniting the existing reports would be necessary to establish the predictor of impaired responses.

No serious adverse events were observed in both patients and healthy volunteers in our study. Since mRNA vaccines have a high immunogenicity, there is concern regarding activation of inflammatory

pathways, which might lead to immune-related adverse events, including the deterioration of chronic GVHD [11, 20, 21]. Regarding this concern, previous studies have reported that < 10% of allo-HSCT recipients experienced deterioration or new development of chronic GVHD, most of which were easy to control. In our study, only one case of mild deterioration of existing chronic GVHD and one case of newly developed signs compatible as limited chronic GVHD were recorded. These results are in line with previous studies and encourage the promotion of vaccination in these vulnerable patients.

This study has several limitations. First, the number of patients studied was relatively small. Moreover, allo-HSCT recipients included in this study had a heterogeneous background. The sample size was too small to establish a predictor of the impaired humoral response. In addition, the cohort of healthy individuals for the comparison is not comparable with patients on the two parameters; the age and timing of antibody assessment. Second, we excluded participants with reported COVID-19. Negative results in antigen or nucleic acid amplification tests for SARS-CoV-2 were not requested during inclusion, and the presence of antibodies against the SARS-CoV-2 nucleocapsid protein was not tested. Therefore, our study could have included individuals with asymptomatic infection, which might have interfered with the results [22]. Third, we evaluated only the humoral response to mRNA vaccines and not cell-mediated immune response in these subjects. It has been revealed that both humoral and cellular immunity play critical roles against COVID-19 [23]. Patients receiving anti-CD20 antibodies due to a lack of B cell-mediated humoral immunity have been reported to exhibit cellular response even in seronegative status [24]. Allo-HSCT recipients are in severely immunocompromised status in terms of cellular immunity. Therefore, the evaluation of humoral response alone would be insufficient to draw valid conclusions, and the presence of long-acting T-cell mediated cellular immunity should also be assessed. An observational study in which 66 allo-HSCT recipients were evaluated for both humoral and cellular response to mRNA COVID-19 vaccines reported that seropositivity in 75% of allo-HSCT recipients, but only 19% recipients exhibited cellular response. [24] Unfortunately, we did not address this issue in the present study.

In conclusion, our results suggest that mRNA vaccines are safe and effective for allo-HSCT recipients. In particular, allo-HSCT recipients who underwent transplantation 6 months before vaccination can expect to gain seroconversion after taking mRNA-based COVID-19 vaccines.

Declarations

Acknowledgments

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Author contributions

N.M. and Y.S. initiated the trial, designed the study, and analyzed the data. N.M. wrote the manuscript and Y.S. supervised the statistical analysis and manuscript writing, editing, and review. H.M., S.N., T.N., and

K.S. performed experiments and managed and reported the measurements of anti-SARS-CoV-2 antibodies and other related laboratory data. N.O., D.N., K.K., H.I., R.Y., Y.N., N.H., S.Y., N.Y., A.M., and T.I. collected data and provided patient information. Y.S. and T.I. coordinated the project and edited the manuscript. C.M. provided comments on statistical analysis. A.D. provided comments on epidemiology and infection control. All authors have read and approved the final manuscript.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Clinical trial registration

This study was registered with the University Hospital Medical Information Network (UMIN) in Japan (UMIN000046044).

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Tables

Table 1 and 2 are available in the Supplementary Files section.

Figures

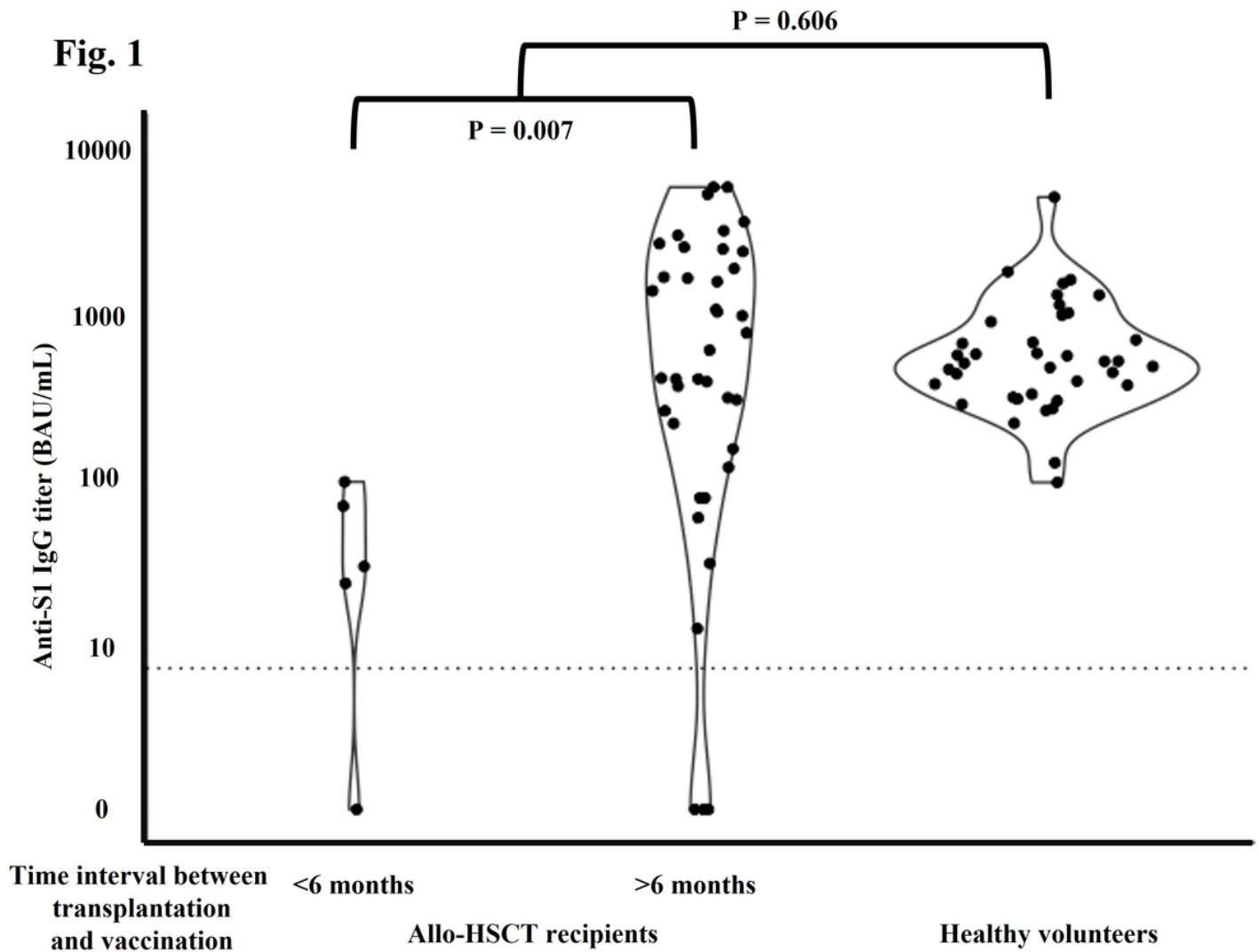


Figure 1

Anti-S1 antibody titers in allo-HSCT recipient subgroup divided by time interval between transplantation and vaccination (<6 months and >6 months) and healthy volunteers. Black dotted lines indicate 7.1 BAU/mL, the cut-off value of serologic reactions according to the manufacturer's instructions. P-value was calculated using the Mann-Whitney *U* test.

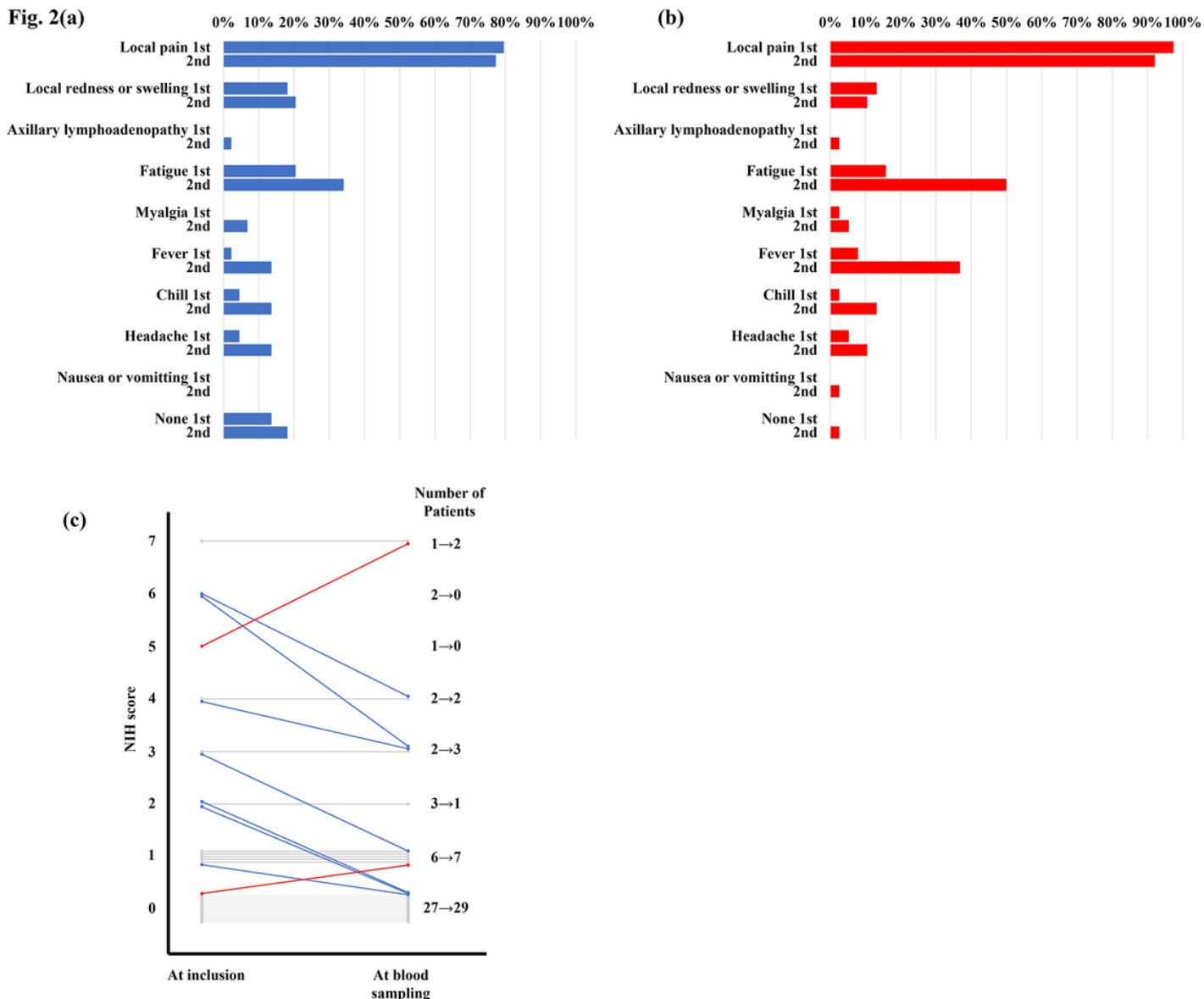


Figure 2

(a and b) Adverse events reported after the first and second dose of mRNA vaccines. The percentage of responders among **(a)** allo-HSCT recipients and **(b)** healthy volunteers declaring one or more adverse events. **(c)** Change in NIH chronic GVHD scores at inclusion (before vaccination) and blood sampling after two doses of vaccines. Among 44 patients, only 2 patients exhibited deteriorated NIH score (red lines). One case exhibited worsened performance status (NIH score five to seven) due to lung abscess caused by bacterial infection and was not relevant to the exacerbation of chronic GVHD. The other (NIH score zero to one) was a case of newly developed skin rash that required topical steroid ointment application. Among other 42 patients, NIH scores of the remaining 42 patients were either stable (gray lines) or improved (blue lines).

Supplementary Files

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- [Table1Nishikubo.xlsx](#)
- [Table2Nishikubo.xlsx](#)