


## ORIGINAL PAPER

# Humoral response to mRNA-based COVID-19 vaccine in patients with myeloid malignancies

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## Abstract

Data on the response to the COVID-19 vaccine in patients with myeloid malignancy, who are at severe risk in case of infection, have not emerged. In a study of 69 patients with myeloid malignancies, including 46 patients with acute myeloid leukaemia (AML) and 23 patients with myelodysplastic syndrome (MDS), anti-spike SARS-CoV-2 antibody titres were measured 3 months after the second mRNA-based vaccination. Seroconversion rates for AML and MDS were 94.7% and 100% respectively, with no significant difference from healthy controls (HCs). Patients with MDS showed a significantly lower antibody titre than that in HCs or AML patients. In AML patients, the antibody titres were comparable to those in HCs when treatment was completed, but lower in patients under maintenance therapy. The response to COVID-19 vaccine appears to be related to disease and treatment status. Patients with myeloid malignancies may be more responsive to vaccines than patients with lymphoid malignancies.

## KEY WORDS

acute myeloid leukaemia, COVID-19, humoral response, myelodysplastic syndrome, SARS-CoV-2 vaccine

## INTRODUCTION

The end of the SARS-CoV-2 pandemic, the virus responsible for COVID-19, is not foreseen. Vaccination using two subtypes of mRNA-based vaccines, BNT162b2 or mRNA-1273, is an effective public health measure to reduce the risk of infection and severe complications from COVID-19.<sup>1-3</sup> However, patients with haematological malignancies were excluded from pivotal trials.<sup>1,2,4-6</sup> Therefore, data for COVID-19 vaccine responses in patients with haematological malignancies, particularly in patients with myeloid malignancies including acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS), are limited. Unfortunately, recent studies

revealed that patients with haematological malignancies were at the greatest risk of COVID-19-related mortality.<sup>7-14</sup>

However, recent preliminary studies have suggested a low seroconversion rate in vaccinated patients with haematological malignancies compared with that in healthy controls (HCs).<sup>15-21</sup> While a serological response is not the only predictor of immunity, it has been used as a surrogate marker of vaccine efficacy in many vaccination studies in patients with haematological malignancies because a low serological level could make this population more vulnerable to COVID-19.<sup>15-23</sup>

In Japan, the national policy encourages all applicants who wish to receive COVID-19 vaccine including patients with

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malignancies to be vaccinated. In this study, we investigated the antibody titres of COVID-19 in patients with myeloid malignancies who received two doses of the mRNA-based COVID-19 vaccine and compared them with the antibody titres in HCs.

## PATIENTS AND METHODS

### Patients

Previously treated, currently treated, and newly diagnosed AML or MDS patients were included in this study. All patients were vaccinated with two doses of the mRNA-based COVID-19 vaccine (either BNT162b2 or mRNA-1273) and visited the Blood Disorders Center at Aiiiku Hospital between 17 August and 31 December 2021. BNT162b2 and mRNA-1273 were administered 21 and 28 days apart, respectively. Individuals with a known history of COVID-19 were excluded from the cohorts of patients and the HCs. The response criteria in patients with AML and MDS were defined according to European Leukemia Net recommendations<sup>24</sup> and the modified International Working Group (IWG) 2006 response criteria for MDS,<sup>25</sup> respectively. Disease status was determined at the time of the second vaccination.

Considering the age distribution of patients with myeloid malignancies, we recruited health-care workers aged  $\geq 50$  years at Aiiiku Hospital who had received two doses of the BNT162b2 vaccine. They had minimal risk of SARS-CoV-2 transmission from inpatients as our hospital did not accept COVID-19 patients. This study was a prospective observational study (UMIN 000045150) and conducted in compliance with ethical principles based on the Helsinki Declaration and was approved by the institutional review board of Aiiiku Hospital. Informed consent was obtained from all participants in the study.

### Assessment of serological response

Serum samples were obtained 3 months  $\pm$  SD 2 weeks after the second vaccine dose and were evaluated for anti-spike (S) SARS-CoV-2 antibodies using Elecsys Anti-SARS-CoV-2S immunoassay, performed on the Cobas e411 fully automated analyser (Roche Diagnostics, Basel, Switzerland) to the antibody targeting the SARS-CoV-2 S protein receptor-binding domain.<sup>17,26,27</sup> This assay has a minimum measurement value of 0.4 U/ml, with a concentration of  $\geq 0.8$  U/ml considered as a positive result. For individuals with an antibody titre  $< 0.4$  U/ml, it was calculated as 0.4 U/ml for convenience.

### Statistical analysis

The Mann–Whitney *U* test was used to compare medians of antibody titres. Spearman's rank correlation coefficient was used to assess the relationship between two variables. Differences between two groups of categorical data were analysed using

TABLE 1 Patient characteristics

	AML ( <i>n</i> = 46)	MDS ( <i>n</i> = 23)
Age (years), median (range)	67.5 (18–88)	73 (59–87)
Sex, Male/Female	23/23	15/8
On active therapy at the time of vaccination		
Yes	18	17
Chemotherapy	2	0
Hypomethylating agent	13	9
Targeted therapy	3	0
Erythropoiesis-stimulating agents	0	5
Anabolic steroid	0	2
Cyclosporin A	0	1
No	28	6
Treatment off in CR	25	0
Treatment naive	3	6
Status at the time of vaccination		
CR	38	7
Relapse/Refractory	5	10
Previously untreated (Treatment naive)	3	6
HSCT prior to vaccination	3	0
Vaccine subtype		
BNT162b2	35	21
mRNA-1273	11	2
Period from diagnosis to vaccination, months, median (range)	47 (1–206)	36.5 (1–342)

Abbreviations: AML, acute myeloid leukaemia; CR, complete remission; HSCT, allogeneic haematopoietic stem cell transplantation; MDS, myelodysplastic syndrome.

Fisher's exact test. A two-sided  $p < 0.05$  was considered to indicate statistical significance. All statistical analyses were performed with EZR (Jichi Medical University, Saitama, Japan).<sup>28</sup>

## RESULTS

### Characteristics of patients and healthy controls

A total 69 patients with myeloid malignancies, including 46 patients with AML and 23 patients with MDS, were enrolled in this study. The characteristics of the patients are shown in Table 1. HCs included 43 individuals with a median age of 56.0 years (range 50–72) and with a female predominance (69.8%).

### Disease-specific serological responses for AML and MDS

Patients with MDS showed a significantly lower antibody titre than that in HCs: [median 157.0 U/ml [interquartile

range (IQR) 13.2–411.0] vs. 1079.0 (IQR 661.0–1526.0),  $p < 0.0001$ ]; however, there was no significant difference between the antibody titres in HCs and patients with AML [1079.0 (661.0–1526.0) vs. 576.0 (158.3–1708.8) U/ml,  $p = 0.0885$ ] (Figure 1A). The antibody titre in MDS patients was significantly lower than that in AML patients [157.0 (13.2–411.0) vs. 576.0 (158.3–1708.8) U/ml,  $p < 0.01$ ] (Figure 1A).

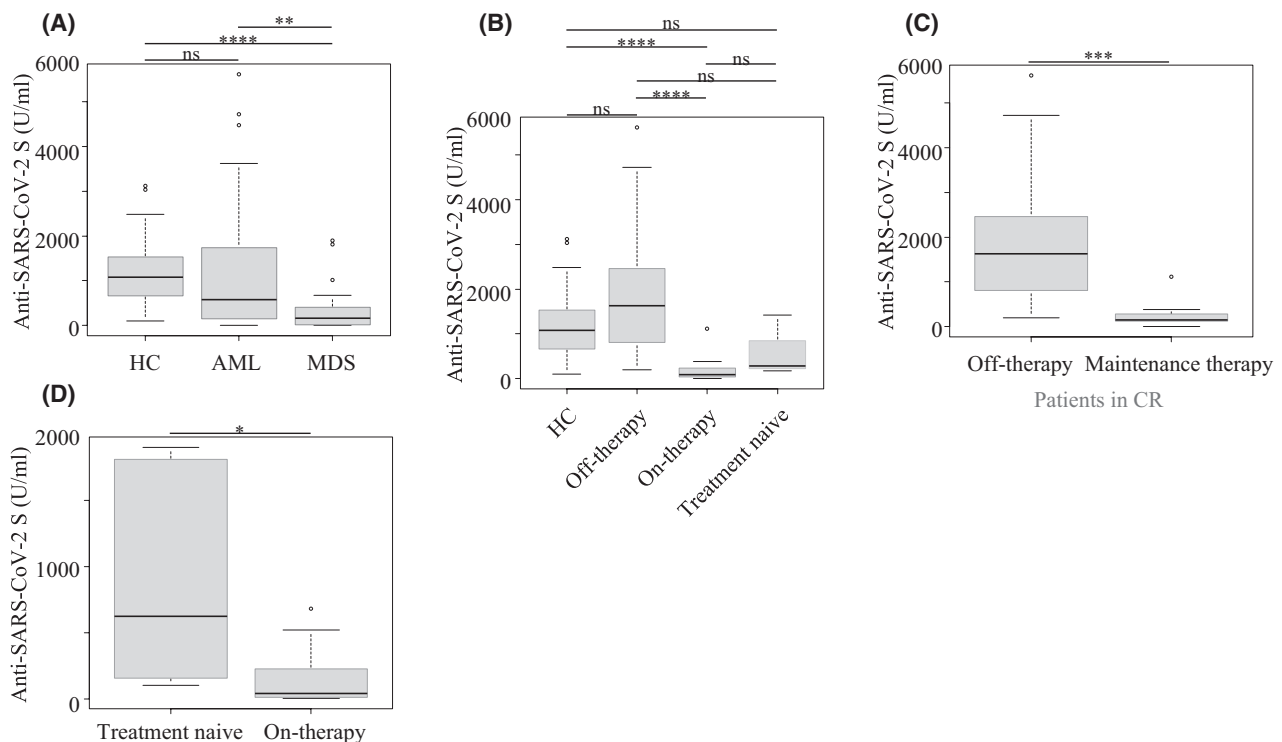
### Factors affecting serological responses in AML patients

Seroconversion rates at 3 months after the second vaccination for patients with AML and HCs were 94.7% and 100%, respectively ( $p = 0.2170$ ). There were 25 AML patients under treatment-free observation in complete remission (CR) after completion of treatment, with a median follow-up period of 61 months. The antibody titre in those patients was comparable to that in HCs [median 1630.0 (806.0–2454.0) vs. 1079.0 (661.0–1526.0) U/ml,  $p = 0.1080$ ] (Figure 1B). Since all of the healthy individuals had been vaccinated with BNT162b2, we analysed only BNT162b2-vaccinated patients. As a result, the antibody titre in BNT162b2-vaccinated AML patients under treatment-free observation was also comparable to those of HCs [813.5 (397.8–1801.8) vs. 1079.0 (661.0–1526.0)

U/ml,  $p = 0.6840$ ] (Figure S1A). On the other hand, AML patients receiving active treatment had a lower antibody titre than that in patients under treatment-free observation [92.2 (37.5–216.3) vs. 1630.0 (806.0–2454.0) U/ml,  $p < 0.0001$ ] and HCs [92.2 (37.5–216.3) vs. 1079.0 (661.0–1526.0) U/ml,  $p < 0.0001$ ] (Figure 1B).

Thirty-eight patients in CR included 25 patients under treatment-free observation, 12 patients under maintenance therapy, and one patient undergoing consolidation therapy. The antibody titre in all of the AML patients in CR was also comparable to that in HCs [816.5 (250.0–2063.5) vs. 1079.0 (661.0–1526.0) U/ml,  $p = 0.6380$ ].

There were 18 patients who were receiving active treatment including five patients in non-CR who were receiving treatment, one patient in CR who was receiving consolidation chemotherapy, and 12 patients in CR who were receiving maintenance therapy. In the 12 patients receiving maintenance therapy, hypomethylating agent (HMA) was administered to nine patients, Am80 in two patients, and FLT3 inhibitor in one patient. The antibody titre in patients undergoing maintenance therapy was significantly lower than that in patients under treatment-free observation [154.0 (126.0–289.0) vs. 1630.0 (806.0–2454.0) U/ml,  $p < 0.001$ ] (Figure 1C). In this regard, there was a significant difference in the period from diagnosis to vaccination between AML patients in CR under treatment-free observation and those



**FIGURE 1** The boxes show the interquartile range, center line shows the median, and whiskers show maximum and minimum values. The dots show individual participants. (A) Anti-SARS-CoV-2 S antibody titres in healthy controls (HCs) ( $n = 43$ ), in patients with acute myeloid leukaemia (AML) ( $n = 46$ ), and in patients with myelodysplastic syndrome (MDS) ( $n = 23$ ). (B) Anti-SARS-CoV-2 S antibody titres in healthy controls ( $n = 43$ ) and AML patients off-therapy ( $n = 25$ ), those with active therapy ( $n = 18$ ), and those who were treatment naive ( $n = 3$ ) at the time of vaccination. (C) Anti-SARS-CoV-2 S antibody titres in patients in complete remission under treatment-free observation ( $n = 25$ ) or those receiving maintenance therapy ( $n = 12$ ) at the time of vaccination. (D) Anti-SARS-CoV-2 S antibody titres in patients with MDS who were treatment naive ( $n = 6$ ) or were receiving active therapy ( $n = 17$ ). \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ; \*\*\*,  $p < 0.001$ ; \*\*\*\*,  $p < 0.0001$ ; ns, not significant.

receiving maintenance therapy [61.0 (48.0–108.0) vs. 18.5 (6.0–32.3) months,  $p < 0.001$ ] (Figure S1B). Furthermore, Spearman's correlation coefficient and  $p$  values were calculated to assess the relationship between duration from diagnosis to vaccination and antibody titres in all of the patients, and a significant correlation was confirmed ( $r = 0.63$ ,  $p < 0.0001$ ), (Figure S1C).

## Factors affecting serological responses in MDS patients

The seroconversion rate at 3 months after the second vaccination for MDS patients was 100%. In contrast to patients with AML, certain treatments were continued in all the MDS patients in CR, and both MDS patients in non-CR and in CR showed significantly lower antibody titres than HCs [non-CR vs. HCs: 26.7 (7.5–98.2) vs. 1079.0 (661.0–1526.0) U/ml,  $p < 0.0001$ ; CR vs. HCs: 169.0 (24.9–381.0) vs. 1079.0 (661.0–1526.0) U/ml,  $p < 0.001$ ].

Patients receiving active therapy had a lower antibody titre than that in treatment-naïve patients [41.0 (10.7–227.5) vs. 623.5 (173.8–1613.3) U/ml,  $p < 0.05$ ] (Figure 1D). The antibody titre was significantly lower in patients currently receiving HMA than in the other patients [11.1 (3.3–73.0) vs. 224.0 (103.0–681.0) U/ml,  $p < 0.01$ ].

## DISCUSSION

This study showed high seroconversion rates in patients with AML and MDS at 3 months after the second vaccination (94.7% and 100%, respectively), in contrast to recent studies showing lower seroconversion rates (39.5–76.0%) in vaccinated patients with haematological malignancies.<sup>15–21</sup> These studies focused mainly on lymphoid malignancies. B-cell depleting therapies such as anti-CD20 antibody agents are known to reduce vaccine efficacy.<sup>18,20,29</sup> In our study of myeloid malignancies, seroconversion rates after vaccination were comparable to healthy individuals. Therefore, patients with myeloid malignancies may have less disease-related immune dysfunction than patients with lymphoid malignancies.<sup>21</sup>

This is one of the first studies on the effect of COVID-19 vaccines focusing on patients with AML and MDS and provides several new findings. First, in AML patients who completed treatment, the antibody titres were comparable to those in HCs. There was a positive correlation between antibody titres and the period from diagnosis to vaccination, indicating that off-therapy AML patients who were in long-term CR regain sufficient humoral immune responses. Such a good vaccine response has not been reported in other haematological malignancies.

Second, the antibody titre in CR patients with AML receiving maintenance therapy was significantly lower than that in CR patients under treatment-free observation. Although several studies have shown that patients with

haematological malignancies receiving active treatment had lower antibody titres after vaccination than those in off-treatment patients,<sup>16,19–21,27</sup> there are insufficient data on the impact of maintenance therapy on vaccine efficacy. In lymphoid malignancies, maintenance therapy with anti-CD20 antibody drugs, Bruton's tyrosine kinase inhibitors, and venetoclax reduced antibody titres.<sup>16,20,24</sup> On the other hand, tyrosine kinase inhibitors do not impair the vaccine response in patients with chronic myeloid leukaemia.<sup>19</sup> Myeloma patients under maintenance therapy with immunomodulatory agents had relatively intact serological responses.<sup>17,21</sup> In our study, there was a significant difference in the period from diagnosis to vaccination between AML patients in CR under treatment-free observation and those receiving maintenance therapy (Figure S1B), and that difference seemed to contribute to the difference in antibody titres. Besides, 75% of the AML patients undergoing maintenance therapy received HMA in our cohort, and lymphopenia is known as an adverse event of HMA.<sup>30</sup> In view of these findings, careful consideration should be given to the positive and negative effects of maintenance therapy in patients with haematological malignancies with regard to COVID-19.<sup>29</sup> However, continuation of HMA maintenance therapy for AML and MDS is often essential. Therefore, maintenance therapy should be continued for patients with myeloid malignancies, with strict measures for preventing infection.

Our study has several limitations. This study included a heterogeneous patient population and the number of patients was small, which made it difficult for us to perform sub-analysis for certain subgroups. Although this study focused on myeloid malignancies, myeloproliferative disorders were not included. This study evaluated only humoral immunity not T-cell immunity nor certain clinical factors that are also important in preventing a severe course of COVID-19.<sup>3,31–33</sup> Although the serological response is used as a surrogate marker of vaccine efficacy in many vaccination studies, preventive antibody titres against SARS-CoV-2 infection are unknown.<sup>15–22</sup> Furthermore, the protective impact of vaccination and its ability to prevent SARS-CoV-2 infection or clinically significant COVID-19 was not studied.

In conclusion, the response to COVID-19 vaccine appears to be related to disease and treatment status. Myeloid malignancies may have less impact than lymphoid malignancies on the vaccine response. AML patients under treatment-free observation in CR could be expected to have a vaccine effect that is comparable to that in healthy individuals. In contrast, since the response to vaccination might be insufficient in AML patients undergoing maintenance therapy, maintenance therapy should be continued with strict measures for prevention of infection even after vaccination.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

## AUTHOR CONTRIBUTIONS

Akio Mori designed the study, analysed the data, and wrote the manuscript. Masahiro Onozawa revised the manuscript. Shihori Tsukamoto, Takashi Ishio, Emi Yokoyama, Koh Izumiyama, Makoto Saito and Masanobu Morioka performed recruitment and treatment of patients and provided a critique of the manuscript. Haruna Muraki performed experiments and provided a critique of the manuscript. Takanori Teshima revised and approved the manuscript. Takeshi Kondo designed and supervised the study and approved the manuscript. All authors read and approved the final manuscript.

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## SUPPORTING INFORMATION

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