Dear Editor:

The older population is the main victim of the coronavirus disease 2019 (COVID-19) pandemic [1]. Many studies have shown that residents at long-term care facilities (LTCF) have been greatly affected by COVID-19 [2], indicating a requirement of a comprehensive strategy to protect the elderly for normalization of social functions. Here, we aimed to assess the immune response after a third-dose mRNA vaccine booster among older Japanese people. Our results suggest an importance of antibody titter to establish a treatment priority in the vulnerable population.

To investigate the antibody titres against SARS-CoV-2 among older individuals, 23 facilities (12 day-care centres [DCC] and 11 LTCFs) responded to our call to participate. Each participant received either two doses of BNT162b2 or mRNA-1273 vaccines at least six months prior. For comparing the titres with those of younger generations, we collected data from the nursing care staff at the DCCs and LTCFs. Additionally, our previous data of healthcare workers was used [3]. Mokobio SARS-CoV-2 IgM & IgG Quantum Dot immunoassay (Mokobio Biotechnology R&D Centre Inc., MD, USA) was used for the point-of-care fingertip whole blood sampling test. In this study, we defined non-responders as those whose post-booster antibody titres were less than 1,000 U/mL at any test time after vaccination (<3 months). This was based on neutralizing activity against the wild-type virus and immune evasion of the Omicron variant as explained in our previous literature [3]. Post-booster antibody titres were analysed by

stratifying according to age, sex, living status, and vaccine type. A logistic regression model was used for the multivariate analysis. The institutional review board of Okayama University Hospital approved this study (No. 2112-044), and written informed consent was obtained from all the participants.

Data of 1,046 older adults were eligible for the analysis. The median age of the population was 86 years, with a female predominance (66.3%). Among the participants, 67.2% resided at LTCFs. The proportion of receiving vaccine boosters after two doses of BNT162b2 (59.2%) was higher than that of mRNA-1273 (40.2%) vaccine administration. Then, we incorporated data of nursing care staff working at DCCs and LTCFs, and the healthcare workers at hospitals to demonstrate the distribution of post-booster antibody titres by age as compared with COVID-19 survivors at the facility with the cluster [3]. Of the 1,771 people, we excluded those examined 1 to 9 days after the booster dose (N=415), and a total of 1,356 individuals were analysed.

Antibody titres were widely distributed in each age group (**Fig. 1**). The invalid (too high for measurement) testing rate was over 10% in those aged <60 years. With age, it decreased to 5.4% in septuagenarians, 4.7% in octogenarians, and 3.2% in nonagenarians. Based on the finding, we regarded those with antibody titres less than 250 U/mL as poor responders, which corresponds to two-fold the LD50 concentration level *in vitro*. The number and proportion of non-responders increased with age: 2 (0.9%) septuagenarians, 23 (5.4%) octogenarians, and 29 (9.4%)

nonagenarians. Moreover, the antibody titers of COVID-19 survivors one month after the cluster event was apparently higher than those after the post third-dose vaccination. Despite the extremely high age of these groups (median ages of those two times-vaccinated and three times-vaccinated were 86.5 years and 88 years, respectively), the invalid testing rates were 39.3% and 47.1%, respectively, and no non-responders were detected.

Further, we investigated the explanatory factors for third-dose vaccine responsiveness among the older population (**Table 1**). To exclude data derived from those shortly after the booster vaccination, we included only data from 10 days after vaccination (N=982). The proportions of responders aged <70 years (81.4%), 70–79 years (septuagenarians, 80.5%), 80–89 years (octogenarians, 72.7%), and ≥90 years (over nonagenarians, 66.3%) decreased with age. Univariate analysis suggested that men, commuters to DCC, and ≥50 days after the booster were significantly associated with the vaccine responsiveness. A result of the multivariate analysis did not show significant differences in age group, sex, and living status; while, the third-dose vaccination with mRNA-1273 was associated with a significantly higher response rate than BNT162b2 (75.8% vs. 70.6%: odds ratio [95% CI]; 1.37 [1.00 – 1.89]). In comparison with the group of the 10–19 days period, the vaccine response rate in those with a longer period after vaccination (≥50 days) was significantly lower (77.2% vs. 63.0%: odds ratio [95% CI]; 0.55 [0.33 – 0.92])

Older people are at increased risk of developing severe COVID-19. According to a population-based seroprevalence study in Switzerland, the fatality risk for those aged ≥65 years was approximately 5.6%, significantly higher than that of the younger generation (<0.001%) aged under 50 years [4]. In the United States, the number of deaths among people aged ≥ 65 years is presumably 97 times higher than that among people aged 18–29 years [5]. This can be explained by immunosenescence and multimorbidity of underlying diseases among the elderly [6, 7]. People age not only physically but also immunologically, and they lose the capability to respond to foreign antigens [6]. Experts in immune aging indicate that the oldest old (nonagenarians and centenarians) population can be classified into high-performing and low-performing individuals based on genetic variants that advantageously function for healthy aging [8, 9]. Notably, there were apparent non-responders to the third booster, although the multivariate analysis indicated that age was not associated with vaccine response rate. This may be explained by the low-performing properties of these individuals. Our data suggested mRNA-1273 booster was significantly associated with the vaccine responders. Consistently, a randomized control study concluded that, in comparison with BNT123b2, mRNA-1273 booster vaccination can trigger a stronger neutralizing activity against the Omicron variant in older people [10].

Collectively, to reduce the number of COVID-19 victims among the older people, the establishment of a triage system for non-responders against vaccination is warranted. The

fingertip whole blood sampling test as a point-of-care testing was useful to identify the non-responder individuals in LTCF. Henceforward, serological testing protocols and an elderly-oriented booster schedule should be discussed to lessen the clinical burden of the disease and facilitate social normalization.

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Author Contribution

HH and MN conceived and designed the study; HH, TH, and MN were responsible for blood sampling; HH performed the statistical analysis and documented the manuscript; TY, ST, and FO supervised the study; all authors interpreted the results, critiqued the manuscript, and gave final approval to the submitted manuscript.

Data Availability Statement

Data in detail will be available if requested to the corresponding author.

Competing interests: None to report.

Declaration: This manuscript has not been published previously in any language, in whole or in part, and is not currently under consideration elsewhere. We have read and understood your journal's policies and believe that neither the manuscript nor the study violates any of them.

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Figure legend

Fig. 1. Distribution of post-third-dose antibody titres of 1,356 individuals in comparison with COVID-19 survivors

Antibody data of healthcare workers, nursing care staff, and older people examined 10 days or after the vaccine booster was administered. In addition, the antibody titres of COVID-19 survivors who were infected in a cluster event at a long-term care facility were provided by vaccination doses. The lowest values in each younger age group were 317.9 U/mL in <30 years; 392.3 U/mL, 30–39 years; 320.7 U/mL, 40–49 years; 258.5 U/mL, 50–59 years; and, 284.6 U/mL, 60–69 years.