International Journal of Medical Toxicology & Legal Medicine Volume 27, No. 1, 2024
e-ISSN: 0974-4614
p-ISSN: 0972-0448

Article Submitted: 12-03-2024; Revised: 20-04-2024; Accepted: 10-05-2024

Comparison of Cellular Immune Responses to Inactivated Virus Platform COVID-19 Vaccines between Young Adult and Elderly Populations: Implications for Vaccination Strategies

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Abstract

Introduction: The COVID-19 pandemic, driven by the SARS-CoV-2 virus, has significantly impacted global health, with the elderly population being particularly vulnerable to high morbidity and mortality. Vaccination has emerged as a critical strategy in controlling virus spread and reducing disease burden, especially among high-risk populations. However, vaccine efficacy in the elderly is a concern due to immunosenescence, which involves the deterioration of immune function with age.

Objective: This study aimed to compare the cellular immune response to the inactivated virus platform COVID-19 vaccine between elderly (aged ≥60 years) and young adults (aged 30-40 years), focusing on changes in T cell populations post-vaccination COVID-19.

Methods: A prospective cohort study design was used to compare immune responses between 40 elderly and 39 young adults who had received the booster-2 series of the inactivated virus COVID-19 vaccine and were eligible for a booster dose. Blood samples were collected before vaccination and four weeks after the booster-2 to analyze CD4+ and CD8+ T cell subsets using flow cytometry.

Results: The study revealed significant differences in the immune responses between the two age groups. Elderly individuals showed a lesser increase in naïve and memory T cells compared to younger adults, indicating a diminished response to the booster vaccination.

Conclusion: The findings suggest that vaccination strategies may need to be tailored to enhance immune responses in the elderly, potentially involving adjusted doses or vaccine formulations. This study provides a scientific basis for optimizing COVID-19 vaccination protocols for the elderly and highlights the challenges of immunosenescence.

Keywords: COVID-19, vaccination, elderly, young adults, cellular immunity, immunosenescence.

1. Introduction :

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has give impact significant global health , with population elderly become the most vulnerable groups to high morbidity and mortality (1). Vaccination has appear as a key strategy in control virus spread and reduce burden disease , especially among population risky high(2,3). However , effectiveness vaccine in the population elderly become attention special Because exists phenomenon immunosenescence, i.e decline function system associated immunity with aging (4).

Immunosenescence, the aging process of the immune system, has drastic impacts to the lives of older people. This process not only leads to low immunogenicity of vaccines but also enhances autoimmune reactions and cancer development and makes people more vulnerable to infections and severe complications from them(5). Thus, the origin of immunosenescence is associated with processes that occur in the course of age-related changes to the production of blood cells. Another way in which the immune system of older people becomes compromised is by a relative increase in myeloid cells and a relative decrease in lymphocytes(6). Thirdly, it is a fact that thymic involution results in a reduction of the naïve functional T cells. These alterations are imposed as a sequential series and each of them diminishes the variety of the T cell receptors thus weakening the immune capacity to effectively counter new antigens(7). The model of immunosenescence suggests that elderly individuals struggle to develop the appropriate immune response to new diseases, leading to pathogen-induced catastrophes. This model is relevant in understanding COVID-19, as elderly individuals may experience worse outcomes than young ones. Researchers also anticipate that spike antigens in COVID-19 vaccines may provide inadequate coverage for frail elderly individuals, as they may not have the same immune response to new diseases as young individuals (8).

Inactivated virus platform COVID-19 vaccine has Lots used in various countries because convenience production and distribution (9). Although vaccine has show effectiveness in reduce infection weight and mortality , more deep understanding about response the immunity it induces , especially in the population elderly , still limited (10,11). Cellular immune responses, involving CD4+ and CD8+ T cells, play a crucial role in long-term protection against viral infections and vaccine effectiveness (12,13).

Previous studies have shown that antibody responses to COVID-19 vaccination in the elderly tend to be lower and decline more rapidly compared to younger populations (14). However, research on post-vaccination cellular immune responses in the elderly population is still limited, especially in the context of inactivated virus platform vaccines (15). A better understanding of differences in cellular immune responses between elderly and young adult populations may provide important insights for the development of more effective and tailored vaccination strategies for different age groups (16).

This study aims to compare cellular immune responses to the inactivated virus platform COVID-19 vaccine between elderly populations (aged ≥60 years) and young adults (aged 30-40 years). We evaluated changes in CD4+ and CD8+ T cell populations, including naïve, memory, and senescent subpopulations, as well as pro-inflammatory and anti-inflammatory cytokine production post-vaccination. It is hoped that the results of this research will provide a scientific basis for optimizing COVID-19 vaccination protocols in the elderly population, as well as provide insight into the mechanisms of immunosenescence that influence vaccine effectiveness.

2. Method:

Research Design

This prospective cohort study compares the cellular immune responses to an inactivated virus platform COVID-19 vaccine between two age groups: elderly individuals (aged ≥ 60 years) and young adults (aged 30-40 years). Sampling was carried out at two time points: before administration of the booster dose (baseline) and 4 weeks after administration of second booster.

Ethical Considerations

This research has received approval from the Ethics Committee [Health Research Ethics Committee of RSUP National DR. Cipto Mangunkusumo Faculty of Medicine, Universitas Indonesia) with protocol number [KET-626/UN2.F1/ETIK/PPM.00.02/2023]. All procedures were performed in accordance with the Declaration of Helsinki and applicable research ethical guidelines.

Research Subjects

Seventy-nine subjects were recruited for this study, comprising 40 elderly individuals (aged 60-85 years) and 39 young adults (aged 30-40 years). Inclusion criteria were subjects who had completed the primary series of an inactivated virus platform COVID-19 vaccine and were eligible for the second booster dose. Exclusion criteria included a history of

confirmed COVID-19 infection, immunosuppressive conditions, and use of immunosuppressant medications. All subjects provided informed consent before participating in the study.

Vaccination Procedures

All subjects received a second booster dose of an inactivated virus platform COVID-19 vaccine, following national guidelines. The vaccines administered were Sinovac, Coronavax, Zifivax, or Sinopharm, each given at a standard dose of 0.5 mL intramuscularly.

Sample Collection

Venous blood samples (10 mL) were collected from each subject at two time points: baseline (before booster administration) and 4 weeks post-administration of the second booster. Peripheral Blood Mononuclear Cells (PBMCs) were isolated using the Ficoll-Paque density gradient centrifugation method and stored in liquid nitrogen until analysis.

Flow Cytometry Analysis

Isolated PBMCs were analyzed using flow cytometry to evaluate T cell subpopulations. The antibody panel used included markers CD3, CD4, CD8, CD28, and CD57. Subpopulations analyzed included naïve T cells (CD28+CD57-), memory T cells (CD28-CD57-), and senescent T cells (CD28-CD57+). Flow cytometric analysis was performed using a BD FACSCanto II flow cytometer, and data were analyzed using FlowJo software.

Statistical Analysis

Data were analyzed using SPSS version 26 software. The Shapiro-Wilk normality test was used to assess data distribution. Differences between age groups and between time points were analyzed using paired t-tests for normally distributed data or Wilcoxon signed-rank tests for non-normally distributed data. A two-way ANOVA test with repeated measures was used to compare changes in cellular immune responses between age groups over time. A p value < 0.05 was considered statistically significant.

3. Results:

The subjects of this research comprised 40 elderly people (60–85 years) and 39 young people (30–40 years). The main sociodemographic and clinical characteristics of the studied sample of subjects are presented in Table 1. There was a significant gender difference between young people and the elderly, with senescence cytotoxic T cells in young adults ($p<0.000$), naïve cytotoxic T cells in the young adult group ($p<0.05$), and memory helper T cells in the elderly ($p<0. 0$). No individual had a Charlson Comorbidity Index score greater than 0, indicating that the recruits had a low prevalence of comorbidities. The lack of substantial morbidity and mortality variations across different age groups mitigates the impact of confounding variables that might jeopardize the validity of the comparative immune response evaluation performed in this investigation.

Table 1. sociodemographic and clinical characteristics of the studied sample of subjects

Variable	Subject	
	N	%
Gender		
Male	22	28
Female	57	72
Age (years)		
30 – 40 (young adult)	39	49
>60 (elderly)	40	51
Education		
Low	79	100
High	0	0

Blood Pressure		
Normal	74	94
Hypertension	5	6
BMI		
< 18.5 (underweight)	0	0
>18.5-24,99 (ideal weight)	70	88
> 25,00-29,99 (overweight)	5	6
> 30 (obese)	4	5

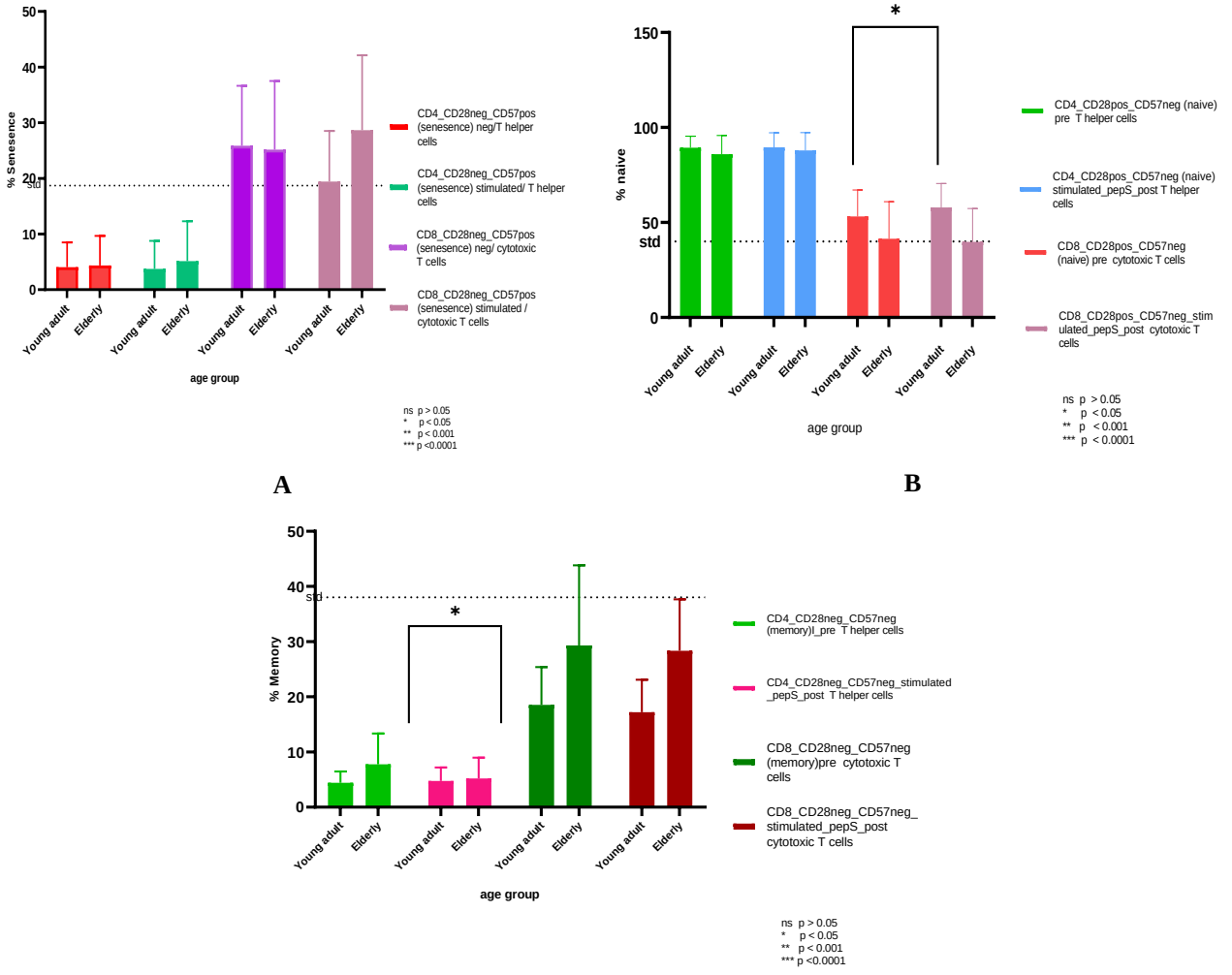

Figure 1. A) Distribution of Senescent T Cells in Different Age Groups Post-COVID-19 Vaccination. B) Distribution of Naïve T Cells in Different Age Groups Post-COVID-19 Vaccination. C) Distribution of Memory T Cells in Different Age Groups Post-COVID-19 Vaccination.

Senescent CD4+ T Cells (CD28-CD57+)

Senescent CD4+ T cells are identified by negative expression of the CD28 co-stimulatory receptor and positive staining for the CD57 isoenzyme, which points to cellular aging and diminished clonal expansion of the T cells. These cells are more of a poor support for the immune response and are characteristic of immunosenescence. Monitoring the levels of senescent CD4+ T cells after vaccination could establish measures of how much the aging immune system continues to develop non-functional T cells that could have a negative impact on the immune response provoked by the recently introduced vaccine. In the elderly group, the percentage of senescent CD4+ T cells rose by 4.35 ± 5.33% before the booster to 5.14 ± 7.16% after the booster, although this was this was not a statistically significant difference ($p = 0.18$). On the other hand, senescent CD4+ T cells were significantly reduced in the young adult group from 4.05 ± 4.43 to 3.74 ± 5. They recorded a 4% increase in the train frequencies, again, though not a very significant improvement ($p = 0.44$). Consequently, the booster vaccination seems not to sufficiently work towards reducing the pile-up of senescent T cells in both ages, which could have implications for the fact that a booster vaccination does not suffice to reverse the impacts of aging on the immune system (1).

Senescent CD8+ T Cells (CD28-CD57+)

As seen in senescent CD4 T cells, senescent CD8 T cells exhibit loss of expression of CD28 and induction of CD57. Infected T-cells have, therefore, reduced cytotoxicity, which is important for directly eliminating virus-infected cells. The increase in the number of senescent cells, such as CD8+ T cells, that express senescence-associated markers is a central feature of immunosenescence that results in a decreased capacity to eliminate pathogens. Measuring these cells will help to determine the ability of the elderly immune system to cope with viral pressures, especially after a vaccination, which is invaluable for evaluating the potential of vaccines in an aging population. It was also noted that there was a decrease in senescent CD8 + T cell percent, approximately 6 percent, among young adults. 87 ± 10.76% to 19.44 ± 9. In the post-booster phase, the rate was 8% as compared to a mere 0.5% before boosting ($p < 0.05$). That could simply mean that booster vaccination in the young elicits a better cytotoxic T cell response in relation to this virus. Conversely, the elderly group recorded a nonsignificant rise in senescent CD8+ T cells, which were initially at 25.17 ± 12.35% to 28.66 ± 13.45% ($p = 0.16$), and suggest that the concept of booster vaccines may be ineffective in combating age-related immunosenescence (2).

Naïve CD4+ T Cells (CD28+CD57-)

Naïve CD4+ T cells could be described as being important in the response to new pathogens. They have not been exposed to the specific antigen; hence, they are capable of recognizing new pathogens and responding to them. In immunosenescence, naïve T cell differentiation and survival are reduced, which greatly reduces the immune system's capability as a natural defense against new infections and diseases, including those induced by vaccination. It’s important to assess the levels of naïve CD4+ T cells after vaccination in order to understand whether the immune system will be able to generate new responses if the organism is exposed to new pathogens, for example, in elderly people. The naïve CD4+ T cells have also been preserved in both groups similarly to that of CD3+CD4+ T cells, with no changes in both groups ($p = 0.24$ in the elderly group and $p = 0$). This stability indicates that the booster dose might not lead to a potentially significant difference in the regeneration of naïve T cells, which are fundamental to interfacing with new antigens. This is especially true for persons of a ripe old age; their capacity to produce naïve T cells may be compromised in favor of recalled memory T cells, thus making them less responsive to new pathogens (4).

Naïve CD8+ T Cells (CD28+CD57-)

Similar to CD4+ T cells, naïve CD8+ T cells play an important role in eliciting responses against new viral infections. These cells play an important role in the generation of cytotoxicity in order to kill affected cells. Unlike earlier in a person’s life, when a large number of naïve CD8+ T cells are available, the ability to respond to new infections reduces and might affect the efficacy of vaccines. It will be apparent that the ability of naïve CD8 + T cells to change after vaccination allows us to evaluate the immune system’s ability to respond to new forms of viruses, which is important in combination with an aging population. In the other group, which consists of young adults, the percentage of naïve CD8+ T cells was increased after the booster from 53. 20 ± 13. 85 to 57. 94 ± 12. 55, $p = 0. 03$. It is in this regard that one may be able to hazard a guess that the increased levels could be a result of a better adaptive immunity response among the young. However, no DN cone difference in naïve CD8+ T cells was observed (41. 42±19. 50% to 39. 81±17. 54%, $p = 0.67$), which may explain why the immunodominance of cytotoxic T cell responses fails in the elderly (9).

Memory CD4+ T Cells (CD28-CD57-)

Memory CD4+ T cells are produced following an initial immune response and afford long-term immunity by virtue of the ability to 'remember' previous infections. Sometimes this maintenance degrades with aging, and the resulting stiffness in the system can be deadly to immune protection, including that offered by vaccines. A determination of the quantity of functional memory CD4+ T cells after vaccination shows how optimized the elderly immune system is to mount a quick and effective response to encounters with existing pathogens. In the elderly group post-booster, there was a remarkable reduction in the ratio of memory CD4+ T cells from 7%. (77 ± 5.57%) to 5.22 ± 3. P = 0.0001 a. The difference with the baseline assessment was statistically significant at 76% (p = 0.02). Such a reduction may, therefore, be indicative of a decline in memory T cell populations, which are required for long-term immune responses in the elderly. On the other hand the young adults showed no changes in memory CD4 + T cells by the booster (4. 43± 2. 03 % to 4. 74± 2. 43 % p = 0. 45) suggesting a more heightened memory response to the booster (10).

Memory CD8+ T Cells (CD28-CD57-)

Memory CD8+ T cells are important in the long-term immune response and act quickly in case of re-infections or booster vaccinations. These cells are required for the maintenance of cytotoxic responses that are long-term. Signs of immunosenescence include the inability to sustain good memory CD8+T cell populations, thereby diminishing the efficiency of immune protection as time goes by. Evaluation of these cells after vaccination allows to identify the duration of immunity after a vaccination in elderly people and, thus, to draw conclusions regarding the further vaccination of this category of population. We did not observe any differences in the trend of memory CD8+ T cells between any of the two groups with respect to their ages. Elderly and female participants had a statistically significantly lower percentage of adherence with the following antihypertensive medications compared to the young/middle-aged group and males, respectively: 29. 30 ± 14. 49% to 28. 33 ± 9. 14% (p = 0.14) in the group of young adults and to 7% (p = 0.57) in the group of elderly people. 54 ± 6. 84% to 17. 19 ± 5. 90% (p = 0. 11). Based on information obtained from the study, it can be concluded that memory CD8+ T cells are not as volatile to booster vaccination as naïve CD8+ T cells are in both age groups; however, a slight decrease in the frequency of memory CD8+ T cells is recorded in both groups. Future studies should unravel the impact of such a decrease on the efficiency and duration of the vaccine boost (12).

Table 2. Cellular Immune response

Variable	Group age	Mean ± SD		P value
		Before	After	
CD4_CD28neg_CD57pos (senescence) / T helper cells	Young adult	4.05 ± 4.43	3.74 ± 5.04	0.44
	elderly	4.35 ± 5.33	5.14 ± 7.16	0.18
CD8_CD28neg_CD57pos (senesce)/ cytotoxic T cells	Young adult	25.87 ± 10.76	19.44 ± 9.08	**0,000**
	elderly	25.17 ± 12.35	28.66 ± 13.45	0.16
CD4_CD28pos_CD57neg (naïve)/ T helper cells	Young adult	89.35 ± 6.02	89.55 ± 7.62	0.81
	elderly	85.95 ± 9.83	87.87 ± 9.43	0.24
CD8_CD28pos_CD57neg (naïve)/ cytotoxic T cells	Young adult	53.20 ± 13.85	57.94 ± 12.55	**0.03**
	elderly	41.42 ± 19.50	39.81 ± 17.54	0.67
CD4_CD28neg_CD57neg (memory)/ T helper cells	Young adult	4.43 ± 2.03	4.74 ± 2.43	0.45
	elderly	7.77 ± 5.57	5.22 ± 3.76	**0.02**
CD8_CD28neg_CD57neg (memory)/ cytotoxic T cells	Young adult	18.54 ± 6.84	17.19 ± 5.90	0.11
	elderly	29.30 ± 14.49	28.33 ± 9.33	0.69

Discussion:

The present study offers useful data for understanding the variation of cellular immune responses to inactivated virus platform COVID-19 vaccines in elderly and young adult volunteers. In the present study, we want to underline the several aspects of immune response differences between young and elderly people that are necessary for understanding vaccination strategies.

Perhaps the most revealing of these differences in expression was seen in CD8+ T cells. The young adults' CD8+ T results also displayed a clear reduction in senescent CD8+ T cells post-boost vaccination and a rise in naïve CD8+ T cells.

Conversely, the elderly group showed no such fluctuations in the total number of these cells or any related increases or decreases in the rate of proliferation. Before we get to that, it suggests that booster vaccines may be more effective in generating or eliciting new CD8+ T-cells in younger adults than the elderly (1). This may be due to the fact that the elderly population is immunocompromised due to immunosenescence, a condition where the ability to produce naïve T cells is reduced and instead there is an increase in senescent cells (2). Another significant difference was recorded in memory CD4+ T cell populations. Among the elderly, the frequency of memory CD4+ T cells decreased after booster as compared to the initial frequency, and this was not the case for young adults. These differences in the creation and preservation of immunological memory between both populations might have effects on the longevity of protective immunity due to vaccination, with a possible rise in immune longevity in elderly people (4).

Surprisingly, both age groups exhibited similar levels of maintenance of the naïve CD4+ T cell count, and no change was detected after booster. This implies that the booster vaccination may offer a rather limp response in the production of new CD4+ T cells, irrespective of the age of the subject (9). Hence, these results can be significant for further COVID-19 vaccination, especially in relation to elderly people. Differences in cellular immune response seen in the elderly and that of the young imply that new strategies for immunization may be needed to achieve the best results in elderly persons (10,17). That could entail changing the vaccine dose, for example, for the elderly, inventing vaccines targeted specifically to older individuals, or fine-tuning the adjuvants for a better T cell reaction in older people; utilizing mixed vaccine approaches is more efficient in eliciting cellular immune responses in the elderly (8).

However, it should be noted that this research has some limiting factors that might have affected the results obtained. What is more, one has to remember that the number of participants in both studies was quite limited, which weakens the possibility of generalizing the conclusions. Further, the four-week follow-up did not enable evaluation of the immune responses of the subjects after the intervention. In addition, this study did not investigate the association between cellular immune responses and the clinical outcome of COVID-19 infection. Nevertheless, the present study has provided some useful insights on age differences in vaccine immune responses that can be incorporated into a fast-increasing database of knowledge. A large sample size and longer follow-up studies should be done to replicate this finding and assess its practical consequences. Furthermore, conducting research on whether elderly people require a different approach to vaccination, which would increase the likelihood of protecting them from COVID-19, is also significant.

Limitations

Limitations of this study include a relatively small and potentially non-representative sample size, which may lead to biased results. Additionally, the study may not have fully controlled for confounding variables such as pre-existing immunity and differences in health status across age groups. Variations in vaccine administration, including timing and dosage, could introduce variability in immune responses observed. The follow-up duration might also be insufficient to capture long-term immune responses, potentially affecting the generalizability of the findings to other inactivated virus vaccines or populations outside the studied age groups. Lastly, the study may not account for the impact of emerging SARS-CoV-2 variants, which could differently affect vaccine efficacy in young and elderly populations. Future studies with larger, more diverse populations, longer follow-up periods, and standardized vaccine administration protocols are recommended to address these limitations and further explore the impact of emerging variants.

4. Conclusion:

In this study, the strong and significant variations in immune mobile responses to the inactivated virus platform COVID-19 vaccine for the elderly population and young adults are depicted. More response dynamic of mature young, with decline CD8+ T cells senescence and increase naïve CD8+ T cells after booster. On the contrary, the elderly had relative preservation of the CD8+ T cells and a reduction in memory CD4+ T cells. These observations help understand the necessity of appropriate vaccination and immunoprophylaxis management in elderly patients, which, most likely, demands different approaches. More study is required while designing and testing immunizations that could counter the impacts of immunosenescence in elderly individuals. Last but not least, considering the disparity in the cellular immune response to SARS-CoV-2, vaccination remains a very effective means of preventing COVID-19-related mortalities and severe disease in all age groups, including the elderly (16). Hence, the issues of vaccination coverage and adherence to booster shots should remain one of the priorities of the COVID-19 pandemic mitigation measures.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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