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Short Communication

Comparison of inflammatory mediator cytokine responses to inactivated virus platform COVID-19 vaccines between elderly and young adult populations

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has encouraged global vaccine research, yet vaccine effectiveness in the elderly remains a concern due to immunosenescence. The aim of this study was to compare the cytokine response elicited by an inactivated virus-based COVID-19 vaccine between elderly and young adults, focusing on key cytokines involved in cellular and humoral immunity: tumor necrosis factor-alpha (TNF-α), interleukin (IL)-2, IL-6, IL-10, and interferon-gamma (IFN-γ). A cross-sectional study was conducted in the Jakarta-Bogor region of Indonesia from January 2023 to December 2023. The study population was divided into two age cohorts: elderly (60–85 years) and younger adults (30–40 years). Blood samples were collected twice, after the first booster dose and four weeks after the second booster dose. Serum cytokine concentrations were measured using Luminex assays with microparticles conjugated to monoclonal antibodies against TNF-α, IL-2, IL-6, IL-10, and IFN-γ. Comparisons of the cytokine levels were conducted using Student's t-tests or Mann-Whitney U tests as appropriate. A total of 74 individuals were included, with 37 each in the elderly and young adult groups. The results showed significant differences in cytokine responses between the two age groups. After the first booster, the levels of IL-6 and IFN-γ were significantly higher in young adults compared to the elderly. After the second booster, the levels of IL-6 were still significantly higher in the young adult group compared to the elderly group (p=0.001). Data indicated that after the second booster dose, the levels of TNF-α increased significantly in the young adult group only (p=0.004), while the levels of IL-2 (p=0.040) and IFN-γ (p=0.006) increased in the elderly group only compared to after the first dose. IL-10 levels increased in both groups (both had p=0.020). This study highlights that young adults had stronger pro-inflammatory responses, while the elderly relied more on IL-2 and IFN-γ for T-cell immunity, suggesting the need for vaccination strategies for the elderly to optimize immune responses.

Keywords: COVID-19 vaccine, elderly, cytokine response, immunosenescence, inactivated virus vaccine

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the SARS-CoV-2 virus, has profoundly affected global public health and poses a significant mortality risk [1]. Vaccination has

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become a key strategy in curbing the pandemic, with various vaccines developed, including those using inactivated viruses. These vaccines work by triggering an immune response, engaging both humoral and cellular immunity [2]. While humoral immunity focuses on antibody production, cellular immunity is essential for long-term protection and the destruction of infected cells [2]. A critical aspect of cellular immunity is the synthesis and regulation of cytokines, which play a central role in orchestrating immune responses. Key cytokines involved in the immune response to vaccination include tumor necrosis factor-alpha (TNF-α), interleukin (IL)-2), IL-6, IL-10, and interferon-gamma (IFN-γ) [3]. TNF-α is vital for antiviral defense and the activation of immune cells, while IFN-γ enhances local antiviral responses and stimulates immune activity[5]. IL-2 supports T cell proliferation, IL-6 functions as both a pro-inflammatory and anti-inflammatory mediator, and IL-10 acts as an immunosuppressant, preventing excessive immune reactions [6,7,8]. The careful modulation of these cytokines during vaccination is crucial, as it directly influences the vaccine's ability to provide effective immune protection [4].

The effectiveness of COVID-19 vaccines is well established, but the immunogenicity in elderly populations is influenced by immunosenescence [5,6]. This phenomenon, characterized by a decline in immune cell function, particularly T cells, along with changes in immune cell composition and increased chronic inflammation, reduces the effectiveness of vaccines in older adults [7]. Despite this, there is limited information on monitoring cytokine responses as a marker of COVID-19-related inflammation following vaccination with inactivated virus-based vaccines, especially in the elderly [8]. Closing this knowledge gap is essential for developing optimal vaccination strategies to boost immunity in this age group [9,10]. Therefore, the aim of this study was to compare the cytokine responses, specifically TNF-α, IL-2, IL-6, IL-10, and IFN-γ, to an inactivated virus-based COVID-19 vaccine between elderly and young adult populations.

Methods

Study design and setting

A cohort study was conducted in Bogor City, Bogor Regency, and East Jakarta, Indonesia, from January 2023 to December 2023. This study focused on elderly individuals who had regularly received vaccinations following their initial doses of the inactivated virus-based COVID-19 vaccine. The study population was divided into two age cohorts, elderly participants and younger adults, enabling a comparative analysis between the two groups.

This study was carried out across three distinct administrative regions in Indonesia's greater Jakarta-Bogor metropolitan area. The study sites encompassed healthcare facilities in East Jakarta, specifically the public health centers (*Puskesmas*) in the Pulo Gadung district, as well as various vaccination centers throughout both Bogor City and the broader Bogor Regency area. Despite their geographical proximity within the metropolitan region, these three locations represent separate administrative divisions, with Pulo Gadung in East Jakarta situated approximately 60 kilometers from Bogor City, which is administratively distinct from the surrounding Bogor Regency.

Periodic serum samples were collected from participants after their first booster dose, followed by a second collection occurring four weeks after their second booster dose. All sample analyses were conducted at the Integrated Laboratory of Universitas Indonesia in Jakarta, Indonesia. The study protocol was approved by the Ethics Committee of the Faculty of Medicine at Universitas Indonesia.

Sampling strategy

The sample size was determined using an equation to compare the difference between two proportions, taking into account the study's test parameters and statistical power. The goal was to assess whether there is a measurable difference in vaccine efficacy between the elderly group, estimated at 40%, and young adults, estimated at 72%. A 5% significance level and 80% power were applied in the hypothesis testing, leading to a calculated minimum sample size of 37 participants for each group. Purposive sampling was employed in the participant recruitment process.

Participants

This study recruited participants from three geographical locations in Indonesia: Bogor City, Bogor Regency, and East Jakarta. The study population comprised two distinct age groups: elderly individuals aged 60–85 years and a group of young adults aged 30–40 years. All participants had received the inactivated virus-based COVID-19 vaccine, CoronaVac (Sinovac Biotech, Beijing, China), and were scheduled for multiple sample collections throughout the study period. Eligibility criteria for participation were not restricted by comorbidity status, allowing both healthy individuals and those with controlled comorbid conditions to be included. Additionally, all participants were required to have completed their initial CoronaVac vaccination series prior to enrollment.

Several exclusion criteria were established to ensure participant safety and data integrity. The study excluded individuals with active COVID-19 infections and those who had recovered from COVID-19 within the previous three months. Participants were also excluded if they had primary immunodeficiency or had experienced an anaphylactic reaction to either the first dose of the COVID-19 vaccine or any of its components. Additionally, individuals with food allergies or controlled asthma were not eligible for participation. Throughout the study, participants retained the right to withdraw their consent, and anyone who chose to do so was excluded from further participation.

Data collection

The Bogor City Health Office provided a comprehensive list of vaccination centers in the study area, facilitating the identification of potential participants. Trained personnel at these centers conducted eligibility screenings based on standardized protocols. After meeting the inclusion criteria and providing written informed consent, participants underwent assessment through interviews and physical examinations, and the blood was collected. A structured interview was conducted to collect demographic information and medical history, including Charlson Morbidity Index (CMI) comorbidities and COVID-19 exposure history. The physical examination measured blood pressure and body weight. Vaccination status was verified through official vaccination cards and cross-referenced with healthcare facility records. At the same time, baseline blood samples were collected. The blood was collected at two-time points: after the administration of the first dose and four weeks after the second booster dose.

Statistical analysis

Characterization was done using a Luminex 200 flow cytometer (Luminex, Austin, USA), and the data were analyzed using the Statistical Package for the Social Science (SPSS) version 21 (SPSS Inc., Chicago, USA). The Shapiro-Wilk test was applied to assess data normality. Comparisons of participants' attributes across different age groups were conducted using Student's t-test for independent samples when the data followed a normal distribution or the Mann-Whitney U test when they did not. A repeated measures analysis of variance (ANOVA) was used to evaluate differences in inflammatory cytokine immune responses between the elderly and young adults over time. Statistical significance was set at $p<0.05$.

Results

Characteristics of the participants

A total of 37 individuals were included in each study group, and the characteristics of the participants are presented in **Table 1**. The young adult group had predominantly females (81.1%) than the elderly group (59.5% Female). The education level was similar in the two groups, with all participants having a low education level (elementary and junior high school) and none of the participants had a higher educational degree. The elderly group had a higher hypertension proportion (27.0%) than young adults (16.2%). Body mass index (BMI) distributions revealed that the majority of participants in both groups were of normal weight (75.7% of young adults; 81.1% of elderly), and the proportion of overweight individuals was comparable between the two groups (13.5% of young adults; 16.2% of elderly). Interestingly, none of the participants in either group were categorized as underweight. In the assessment of comorbidity patterns based on the

Charlson Comorbidity Index (CCI), none of the assessed comorbidities were present in either the young adult or the elderly groups (**Table 1**).

Table 1. Characteristics of the young adults and the elderly (n=74)

Characteristic	Study groups			
	Young adult (n=37)		Elderly (n=37)	
	Frequency	Percentage	Frequency	Percentage
Sex				
Male	7	18.9	15	40.5
Female	30	81.1	22	59.5
Age (year), mean±SD	35±2.79		64.84±4.56	
Education				
Low level (elementary and junior high school)	37	100.0	37	100.0
High (bachelor, master, or doctoral degree)	0	0.0	0	0.0
Blood pressure				
Normal	31	83.8	27	73.0
Hypertension	6	16.2	10	27.0
Body mass index (BMI) (kg/m²)				
<18.5 (underweight)	0	0.0	0	
>18.5–24.99 (ideal weight)	28	75.7	30	81.1
>25.00–29.99 (overweight)	5	13.5	6	16.2
>30 (obese)	4	10.8	1	2.7
Charlson Comorbidity Index (CCI)				
Myocardial infarction	0	0.0	0	0.0
Congestive heart failure	0	0.0	0	0.0
Peripheral vascular disease	0	0.0	0	0.0
Dementia	0	0.0	0	0.0
Chronic lung disease	0	0.0	0	0.0
Diabetes without complications	0	0.0	0	0.0
Chronic kidney disease	0	0.0	0	0.0
Solid tumor	0	0.0	0	0.0
Leukemia	0	0.0	0	0.0
Lymphoma	0	0.0	0	0.0
Liver Disease	0	0.0	0	0.0
AIDS	0	0.0	0	0.0

Comparison of inflammatory cytokine levels between elderly and young adults

Serum levels of TNF-α, IL-2, IL-6, IL-10, and IFN-γ were measured in both groups and the results are presented in **Table 2**. For TNF-α, there was a significant increase in the young adults, from 210.06±230.16 pg/mL before vaccination to 361.63±322.07 pg/mL after vaccination (p=0.004) (**Table 2**). In the elderly group, TNF-α levels increased from 256.28±215.99 pg/mL pre-vaccination to 313.49±235.58 pg/mL post-vaccination, but this change was not statistically significant (**Table 2**). No significant differences in TNF-α levels were found between the two age groups, either before or after vaccination (**Figure 1**).

For IL-2, young adults showed a non-significant rise from 48.73±23.88 pg/mL to 61.58±25.29 pg/mL, while the elderly experienced a significant increase from 39.64±32.24 pg/mL to 55.45±40.96 pg/mL (p=0.040) (**Table 2**). However, no significant differences were observed between the age groups at either time point (**Figure 2**).

Table 2. Comparison of cytokine inflammatory mediators (tumor necrosis factor-alpha (TNF-α), interleukin (IL)-2, IL-6, IL-10, interferon-gamma (IFN-γ)) among groups

Cytokine	Group	Mean±SD (pg/mL)		p-value
		After first booster	Four weeks after second booster	
TNF-α	Young adult	210.96±239.16	361.63±322.07	0.004*
	Elderly	256.28±215.99	313.49±235.58	0.240
	p-value	0.452	0.508	
IL-2	Young adult	48.78±23.88	61.58±25.29	0.080
	Elderly	39.64±32.24	55.45±40.96	0.040*
	p-value	0.235	0.508	
IL-6	Young adult	10638±16425.64	10479.26±6044	0.230
	Elderly	3591.48±1990.20	3938±1726.85	0.380
	p-value	0.019*	0.001*	
IL-10	Young adult	42.01±32.41	91.52±94.29	0.020*
	Elderly	64.97±68.66	107.66±83.85	0.020*

Cytokine	Group	Mean±SD (pg/mL)		*p*-value
		After first booster	Four weeks after second booster	
	p-value	0.123	0.493	
IFN-γ	Young adult	189.67±213.73	186.48±110.63	0.920
	Elderly	66.76±51.13	147.72±155.30	0.006*
	p-value	0.003*	0.289	

*Statistically significant at $p<0.05$

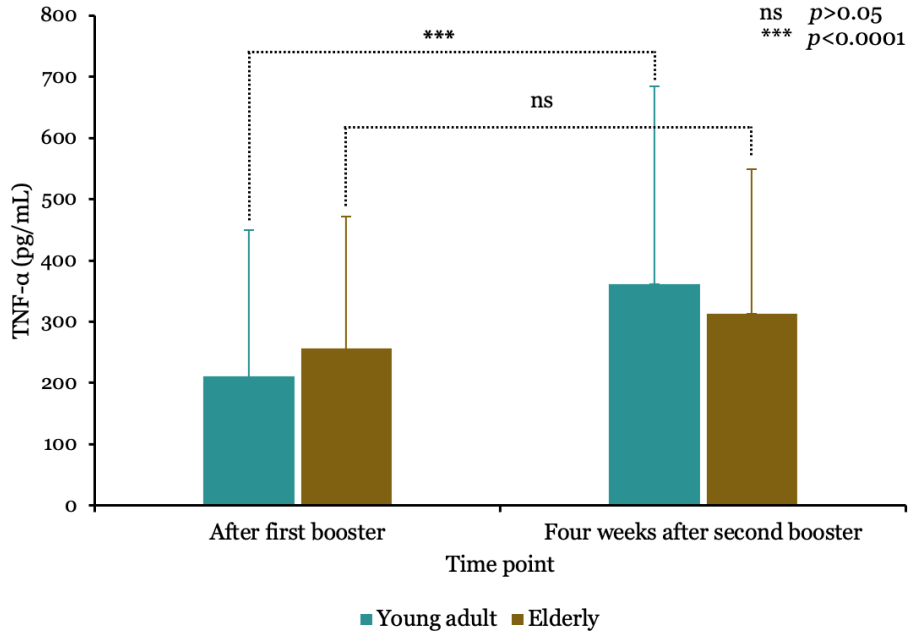

Figure 1. Comparison of tumor necrosis factor-alpha (TNF-α) levels in young adults and the elderly before and after vaccination with inactivated virus-based COVID-19 vaccine.

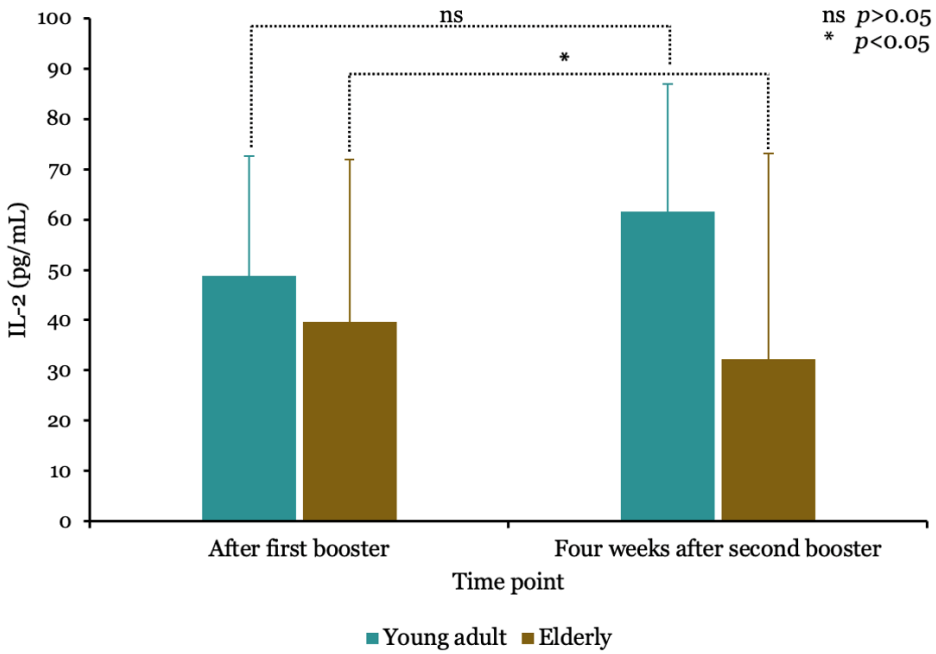

Figure 2. Comparison of interleukin (IL)-2 levels in young adults and the elderly before and after vaccination with inactivated virus-based COVID-19 vaccine.

The IL-6 levels showed significant differences between the groups. In young adults, IL-6 levels did not change significantly, a reduction from 10638±16425.64 pg/mL to 10479.26±6044 pg/mL (**Table 2**). In comparison to the elderly, levels increased from 3591.48±1990.20 pg/mL to 3938±1726.85 pg/mL (**Table 2**). Notably, IL-6 levels were significantly different between the

groups both before and after vaccination (p=0.019 and p=0.001, respectively), with young adults showing consistently higher levels (**Figure 3**).

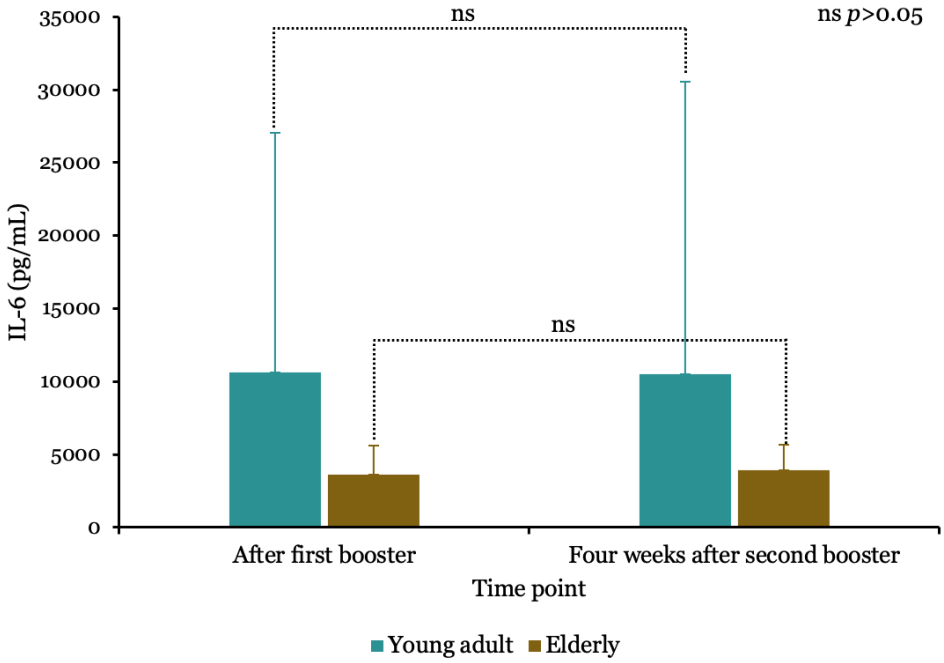

Figure 3. Comparison of interleukin (IL)-6 levels in young adults and the elderly before and after vaccination with inactivated virus-based COVID-19 vaccine.

For IL-10, both groups experienced significant increases. In young adults, IL-10 rose from 42.01±32.41 pg/mL to 91.52±94.29 pg/mL, while in the elderly, it increased from 64.97±68.66 pg/mL to 107.66±83.85 pg/mL, with both p=0.020 (**Table 2**). However, no statistically significant differences were observed between the two groups at either time point (**Figure 4**).

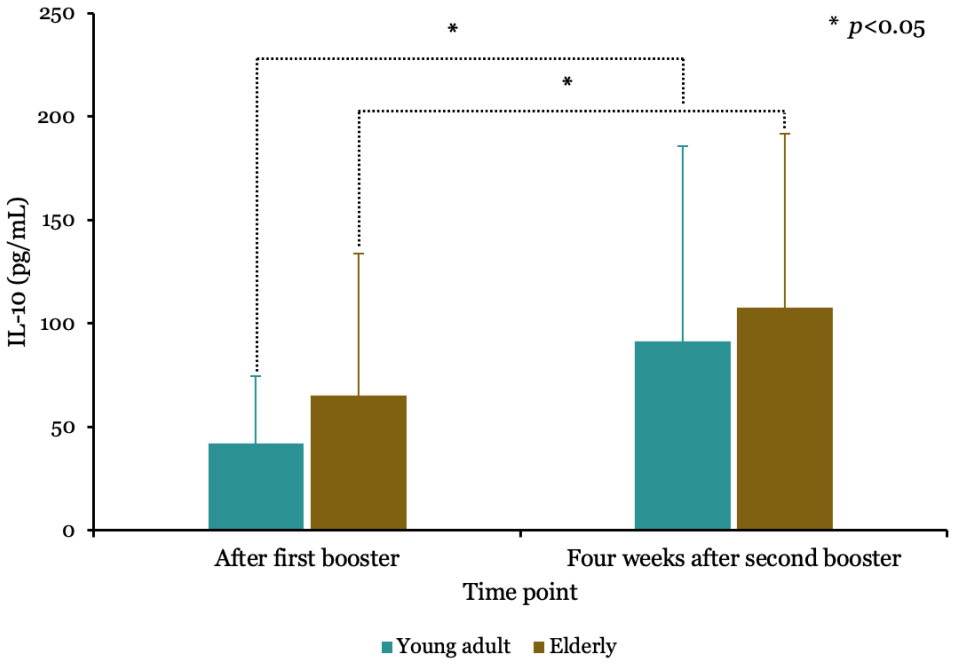

Figure 4. Comparison of interleukin (IL)-10 levels in young adults and the elderly before and after vaccination with inactivated virus-based COVID-19 vaccine.

IFN-γ levels also differed significantly between the groups. In young adults, there was a slight decrease from 189.67±213.73 pg/mL to 186.48±110.63 pg/mL, whereas the elderly group

showed a significant increase from 66.76±51.13 pg/mL to 147.72±155.30 pg/mL (p=0.006) (**Table 2**). Pre-vaccination, the mean antibody levels were significantly higher in young adults compared to the elderly (p=0.003), but this difference diminished post-vaccination (p=0.289), suggesting that the elderly had a more robust response to the vaccine (**Figure 5**).

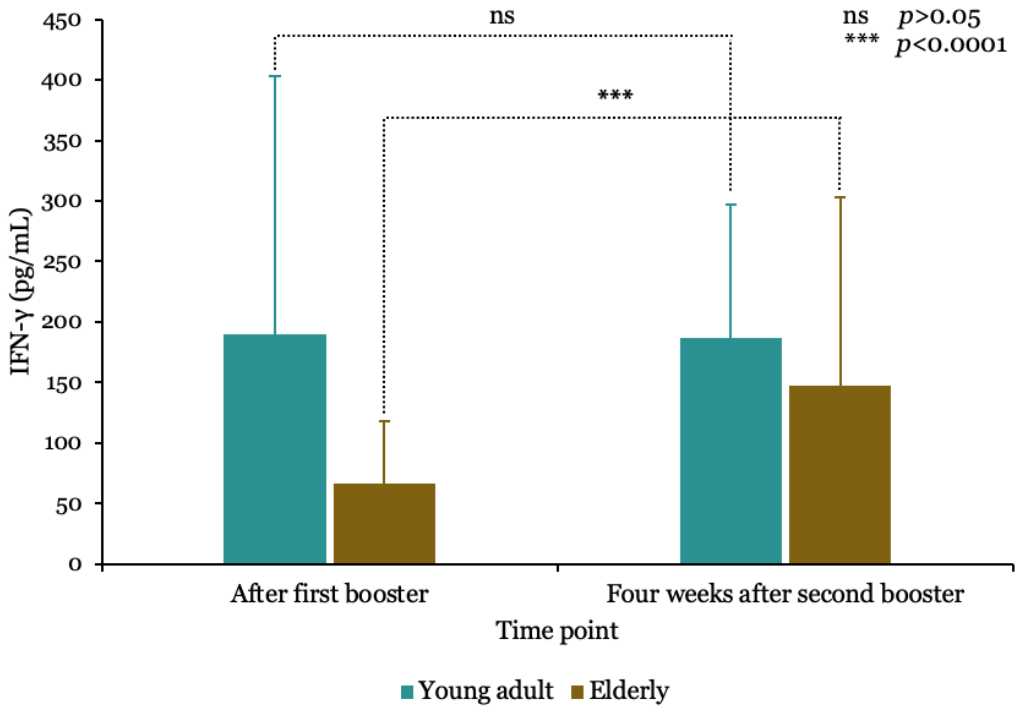

Figure 5. Comparison of interferon-gamma (IFN)-γ levels in young adults and the elderly before and after vaccination with inactivated virus-based COVID-19 vaccine.

Discussion

This study highlights age as a key factor influencing differential immune responses to an inactivated COVID-19 vaccine, providing valuable insights into its effectiveness across different age groups. Young adults exhibited a predominant TNF-α response, whereas elderly individuals showed elevated levels of IL-2, IL-10, and IFN-γ, suggesting a shift toward T-cell-mediated immunity, characteristic of immunosenescence. Notably, there was no significant difference between the two groups in IL-6 responses, indicating that immune regulation during aging is not always straightforward.

The elderly group also exhibited a significantly reduced pro-inflammatory response, particularly evident in lower TNF-α and IL-6 levels compared to young adults. This finding aligns with the broader understanding of immunosenescence, where aging reduces the ability to mount strong inflammatory responses, which are critical for effective antiviral defense [16,17]. The muted TNF-α response in the elderly is especially significant, given that this cytokine plays a central role in initiating and sustaining the inflammatory processes necessary for combating infections [18]. These results are consistent with the findings of a previous study that reported significantly lower TNF-α levels in long-term care facility residents compared to young healthcare workers, even after receiving booster immunizations [19].

Our results showed that the inactivated virus-based vaccine stimulated significantly higher levels of IL-2, IL-10, and IFN-γ in elderly individuals compared to younger adults. IL-2 plays a key role in the growth and maturation of T cells [6], while IL-10 acts as an anti-inflammatory cytokine that helps regulate immune responses by preventing excessive inflammation that could lead to tissue damage [7]. IFN-γ is a critical cytokine for antiviral defense, as it activates macrophages and supports the generation of the T helper type 1 (Th1) response [8]. These cytokines are essential for T cell proliferation and antiviral defenses, indicating that cellular immunity remains functional in older adults, even as humoral (antibody-mediated) responses may decline with age [20]. Interestingly, our findings on elevated IFN-γ levels in the elderly

contrast with those of another study that reported lower IFN-γ levels in elderly LTCF residents compared to younger healthcare workers, even after booster doses [19]. However, both studies align in showing elevated IL-10 after vaccination, demonstrating that vaccines can still elicit strong anti-inflammatory responses in the elderly [14]. Additionally, similar to the previously mentioned study, we found that IL-2 levels increased in elderly participants post-vaccination, suggesting that T cell activation is preserved in this population [14].

The reduced IL-6 response in the elderly is typical of immunosenescence, which refers to the decline in the immune system's ability to regulate and control inflammation [21]. This reduction may potentially slow the development of immunological memory and protective immunity in the elderly population, which is crucial for vaccine-induced immunity [22]. This finding is in accordance with a previous study, which demonstrated that while IL-6 levels in LTCF residents were higher after receiving a booster vaccination, they remained comparatively lower than those of residents under 65 years of age [19].

The findings of this study highlight the importance of developing tailored vaccination strategies for elderly populations. Although inactivated virus vaccines can still elicit immune responses, the lower TNF-α levels observed in the elderly emphasize the need to strengthen their pro-inflammatory pathways. This may be accomplished by incorporating vaccine adjuvants specifically designed to enhance inflammatory responses or by adjusting booster schedules to maintain immune activation for a longer duration [23,24]. The preservation of cellular immunity, as demonstrated by increased IL-2 and IFN-γ levels, presents a promising opportunity to improve vaccine efficacy in older adults. Strategies that focus on boosting T cell responses, rather than relying solely on antibody production, may prove more effective in this population.

Some limitations of our study must be considered, which also highlight directions for future studies. First, the sample size was not fully representative, and we only analyzed five cytokines, meaning other important immune responses may have been overlooked. Additionally, the absence of long-term immunological memory data limits our understanding of changes in the elderly population over time. Future studies should address these issues by enrolling a broader sample that includes individuals of various ages and both sexes, expanding the range of immunological markers analyzed, conducting repeated measurements to determine the duration of vaccine-induced immunity in elderly populations, and investigating adjuvants or boosters specifically designed for immunosenescent individuals to enhance vaccine efficacy in the elderly.

Conclusion

This study demonstrated that COVID-19 vaccines based on inactivated viruses elicited age-dependent cytokine responses. Younger individuals produced higher levels of pro-inflammatory cytokines, while older adults exhibited enhanced cellular immunity, primarily mediated by IL-2 and IFN-γ. These findings underscore the need for tailored vaccination strategies for the elderly, such as using adjuvants or adjusting booster dose schedules, to optimize immune responses and address immunosenescence.

Ethics approval

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.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

How to cite

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