RESEARCH PAPER

Antibody response with SARS-CoV-2 inactivated vaccine (CoronaVac) in Turkish geriatric population

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Abstract

Background: Sars-CoV-2 infection influences older individuals at the forefront, and there is still limited data on the COVID-19 vaccine response in the geriatric population. This study aimed to assess antibody response after vaccination with SARS-CoV-2 inactivated vaccine and examine possible factors affecting this response in a geriatric population.
Methods: individuals who have been on at least the 28th day after the second dose of the COVID-19 vaccine were included. Comprehensive geriatric assessment tools and the Clinical Frailty Scale were performed. SARS-CoV-2 spike-specific IgG antibodies were detected and, levels ≥ 1 U/ml were defined as seropositive, <1 U/ml were defined as seronegative.
Results: a total of 497 patients were included and divided into three groups according to the days past after the second dose of the vaccine (Group 1: 28–59 days, Group 2: 60–89 days and Group 3: 90 days and more). Groups included 188, 148 and 171 patients, respectively. Seropositivity rate in each group was 80.9, 73.2 and 57.3%, respectively. In Groups 1 and 2, Charlson Comorbidity Index score was higher in the seronegative group ($P = 0.023$ and $P = 0.011$, respectively). In Group 3, the prevalence of frailty was significantly higher in the seronegative group ($P = 0.002$).
Conclusion: to the best of our knowledge, this is the first study assessing the antibody response after vaccination with Sars-CoV 2 inactivated vaccine in the Turkish geriatric population. Moreover, this is the first study revealing the relationship between antibody response and frailty. Larger studies are needed to confirm the antibody response duration and the association between frailty and COVID-19 vaccine response.

Keywords: SARS-CoV-2, sinovac, coronavac, neutralising antibody, anti-Spike IgG, older people

Key Points

- Seroconversion rate in older adults significantly decreased 90 days after the second dose of vaccine.
- Frailty might play an important role in vaccine response.
- The seropositivity rate was significantly lower in frail geriatric patients after two-dose scheduled inactive SARS-CoV-2 vaccination.

Introduction

Sars-CoV2 infection undoubtedly influenced older individuals at the forefront. Although important steps have been taken worldwide for the treatment and prevention, vaccination is the most powerful weapon to break the chain of transmission.

Sinovac's Coronavac vaccine is an inactivated whole virus vaccine approved by 32 countries, including Turkey, for use in adults ≥ 18 years. [1] Despite the disadvantages (i.e. the integrity of antigens or epitopes that should be verified, limited immunogenicity requiring adjuvants to enhance the immune response), inactivated vaccines are still popular due to their advantages (i.e. non-replicability in the host, non-transmissibility, relatively easy production systems) [2]. Most vaccine studies (prepared by either new or conventional methods; mRNA, adenovirus vector, adjuvant protein or inactivated virus), have not included older patients, especially the frail groups. Therefore, the immune response to vaccines in this special group is not well known [2, 3].

Vaccine response in older adults is not a truly well-understood area [4]. Immunosenescence (qualitative and quantitative deterioration in immune response due to ageing), frailty and multiple chronic diseases make it difficult to predict the vaccine response in the geriatric population. Furthermore, there is insufficient data on the duration of the antibody response. A study conducted on inactivated influenza vaccine reported that seroprotection rates against all three strains in the vaccine had decreased six months after vaccination in older individuals [5]. Therefore, it is essential to highlight the duration of seroprotection after vaccination with inactivated SARS-CoV-2 vaccine in this population.

The aim of this study was to assess antibody response after vaccination with SARS-CoV-2 inactivated vaccine (CoronaVac) and to examine possible factors that may affect this response in a geriatric population aged 60 years and older, who were evaluated in terms of frailty with comprehensive geriatric assessment (CGA).

Materials and methods

Sample size determination

In a study with a dichotomous (yes/no) endpoint (Sars-CoV2 infection) and a study group (older adults) from the community, it was predicted that the risk of COVID-19 infection in the known (older adults) population was 2% and the risk of infection in this population could be reduced by 85% with inactivated vaccine. Thus, 411 people aged 60 or over should be included in the study group with a margin of error of 0.05 (alpha) and power of 90% [6]. Assuming there may be a 20% loss until the end of the study, it was calculated that the sample size should be 493 with 20% excess.

Study design

Four hundred ninety-seven geriatric outpatients, who were 60 years and older and who were on at least the 28th

day after the second dose of the SARS-CoV-2 inactivated vaccine (CoronaVac), and had not met the exclusion criteria were enrolled for the study. Exclusion criteria were determined as any history of Sars-CoV-2 real-time PCR or thorax computer tomography proven or clinically suspected COVID-19 infection (information confirmed from the national database), immunosuppressive treatments, patients with dementia, active oncological treatments and regular dialysis treatment.

Demographic data of the participants (age, gender, education, occupation, where and whom they live with), chronic diseases, medications, polypharmacy, smoking and falls were recorded.

Comprehensive geriatric assessment

CGA was performed using standardised tools, i.e. Mini-Mental State Examination (MMSE), Mini Nutritional Assessment short-form (MNA-SF), Yesavage's Geriatric Depression Scale (YGDS), The Katz Activities of Daily Living (ADL) scale and Lawton-Brody Instrumental Activities of Daily Living (IADL). The patient's functional status was evaluated using the Katz ADL test, evaluating over 6 points by questioning how independently the patient performed basic care and activities related to daily life and the score increased as independence increased [7]. The Lawton Brody scale was performed to evaluate patients' IADLs [8]. The cognitive status of the participants was screened by MMSE. The patients' orientation, memory, attention, calculation, recall, language, motor function and perception skills were assessed with the MMSE. The maximum score of the test is 30 points, and the scores 24 and below were assessed as cognitive impairment [9]. Nutritional screening via MNA-SF was performed and, scores > 11 points were defined as normal, 8–11 points were defined as the risk of malnutrition and ≤7 points were defined as malnutrition [10]. The YGDS was used for depression screening, and patients scoring over five points were assessed clinically for depression [11].

Assessment of frailty

The Clinical Frailty Scale (CFS) was performed to assess frailty. CFS defines clinical frailty by giving a score between 1 and 9 (1: very fit; 2: well; 3: well with the treated comorbid disease; 4: apparently vulnerable; 5: mildly frail; 6: moderately frail; 7: severely frail; 8: very severely frail; and 9: terminally ill) based on the clinical opinion of the physician, and according to accepted definitions, patients were divided into two groups as non-frail (CFS ≤ 4) and frail (CFS > 4) [12]. Turkish validation study of CFS was available, and CFS was found to be a reliable and valid frailty screening tool for community-dwelling older adults in the Turkish population [13].

Muscle strength

Muscle strength was evaluated by handgrip measurements defined via the Takei grip strength dynamometer. The

Table 1. Demographical characteristics and Comprehensive Geriatric Assessments according to groups defined as the days past after the second dose of the vaccine

		Group 1 (28–59 days past after the second dose of vaccination group) (n = 188 (37.8%))	Group 2 (60–89 days past after the second dose of vaccination group) n = 148 (27.8%)	Group 3 (90 and more days past after the second dose of vaccination group) n = 171 (34.4%)	P value
Age, median (IQR)		71 (67–75)	71 (67–73)	75(67–79)	<0.0001[a,c,d]
Female gender, n (%)		111 (56.%)	91 (65.9%)	103 (60.2%)	0.419
Comorbidities	Depression, n (%)	18 (9.6%)	19 (13.8%)	24 (14%)	0.406
	CVD, n (%)	49 (26.1%)	30 (21.7%)	48 (28.1%)	0.438
	HT, n (%)	135 (71.8%)	101 (73.2%)	122 (71.3%)	0.934
	DM, n (%)	84 (44.7%)	53 (38.4%)	67 (39.2%)	0.434
	Atrial fibrillation, n (%)	16 (8.5%)	11 (8.0%)	25 (14.6%)	0.089
	Hypothyroidism, n (%)	34 (18.1%)	28 (20.3%)	28 (16.4%)	0.674
	Congestive heart failure, n (%)	19 (10.1%)	10 (7.2%)	14 (8.2%)	0.643
	Rheumatological diseases, n (%)	20 (10.6%)	9 (6.5%)	15 (8.8%)	0.433
	Malignancy history, n (%)	25 (13.3%)	14 (10.1%)	17 (9.9%)	0.535
	Chronic renal disease, n (%)	8 (4.3%)	9 (6.5%)	8 (4.7%)	0.630
	Pulmonary diseases, n (%)	15 (8.0%)	13 (9.4%)	6 (3.4%)	0.091
Basic ADLs, median (IQR)		6 (6–6)	6 (5–6)	6 (5–6)	0.051
Instrumental ADLs, median (IQR)		8 (8–8)	8 (8–8)	8 (7–8)	0.143
MMSE, median (IQR)		28 (26–30)	28 (25–29)	28 (26–30)	0.177
Geriatric Depression Scale score, median (IQR)		1(0–5)	2 (0–4.5)	2 (0–4)	0.506
Clock drawing test, median (IQR)		5 (3–6)	6 (3–6)	6 (3–6)	0.669
CCI Score, median (IQR)		1 (0–2)	1 (0–2)	1 (0–2)	0.060
CFS score, median (IQR)		3 (3–4)	3 (3–4)	3 (3–4)	0.071
CFS-frailty, n (%)		37 (20.2%)	28 (21.2%)	36 (22%)	0.924
MNA-SF score, median (IQR)		14 (12–14)	14 (12–14)	14 (12–14)	0.138
Malnutrition (MNA < 12)		43 (23.9%)	20 (15.9%)	41 (27.5)	0.066
Number of drugs, median (IQR)		5 (3–7)	5 (3–7)	5 (2–7)	0.744
Polypharmacy, n (%)		110 (59.5%)	75 (54.7%)	100 (58.5%)	0.520
Falls, n (%)		26 (14.6%)	22 (17.7%)	23 (16%)	0.764
HGS, median (IQR)		20 (16–29.3)	20 (17–26.6)	21.2 (17.2–29.7)	0.755
Low HGS, n (%)		60 (38.7%)	32 (28.8%)	47 (36.7%)	0.228
Low gait speed, n (%)		49 (33.8%)	27 (26.5%)	37 (30.1%)	0.465
Gait speed, median (IQR)		0.9 (0.7–1.2)	0.9 (0.7–1.0)	0.9 (0.8–1.1)	0.881
Sars-CoV2 spike IgG serum level U/ml, median (IQR)		4 (1.6–10)	1.78 (0.9–5.3)	1.35 (0.5–3.7)	<0.0001[a,b,c,d]
Sars-CoV2 spike IgG serum level BAU/ml, median (IQR)		79.1 (31.6–166.0)	41.2 (19.8–103.5)	27.0 (10.9–62.3)	<0.0001[a,b,c,d]
Seropositivity, n (%)		152 (80.9%)	101 (73.2%)	98 (57.3%)	<0.0001[a,c,d]

CVD, Cardiovascular diseases; HT, Hypertension; DM, Diabetes Mellitus; ADL, Activities of daily living; MMSE, Mini-mental State Examination; CFS, Clinical Frailty Scale; MNA-SF, Mini Nutritional Assessment short-form. [a]P-value < 0.05 for the comparison between Group 1, 2 and 3. [b]P value < 0.05 for the comparison between Group 1 and 2. [c]P value < 0.05 for the comparison between Group 1 and 3. [d]P value < 0.05 for the comparison between Group 2 and 3.

measurements were made three times with the dominant hand in the sitting position, with the elbow bent at 90° and the hand in the neutral position. The highest of the three repeated measurements was used in the analysis. Cut-off values were taken according to the EWSGOP revised sarcopenia criteria, the low handgrip strength (HGS) for women and men, was described as HGS < 16 kg and <27 kg, respectively [14].

Physical performance

The gait speed measurement was utilised to assess physical performance. In the four-metres walking test, the patient was asked to walk at a normal speed (with the auxiliary device if used) and stop at a specified point, and the elapsed time was recorded in seconds, then the patient's walking speed was

calculated in m/s. Values below 0.8 m/s were evaluated in favour of low physical performance [14].

Assessment of comorbidities

We used the Charlson comorbidity index (CCI) to assess the patients' comorbidities. CCI is a commonly used comorbidity index including 17 comorbidities, and it indicates disease burden with robust estimation of mortality [15, 16].

Detection of SARS-CoV-2 IgG antibody

To measure the level of IgG against SARS-CoV-2, blood samples were drawn from the patients. Serum samples were collected by whole blood centrifugation at 4,000 rpm for 10 min. All samples were stored at –20°C before testing. Atellica IM SARS-CoV-2 IgG (sCOVG) assay (11207386, California, USA) was used to detect IgG against

the SARS-CoV-2 spike protein receptor-binding domain and all samples were run in Atellica IM 1600 analyser (Siemens Healthineers, California, USA). The Atellica IM sCOVG assay is a fully automated two-step sandwich immunoassay using chemiluminescent technology with a measuring interval between 0.50–150.00 Index (U/ml). The result is reported as non-reactive (negative) if the value is <1.00 U/ml, and as reactive (positive) if the value is ≥1.00 U/ml. The analytical sensitivity at the cut-off values for the Atellica IM sCOVG assay was determined using the World Health Organization First International Standard for anti-SARS-CoV-2 immunoglobulin (human) NIBSC code: 20/136. The concentration of the reference standard that corresponds to the cut-off value of 1.00 Index (U/ml) for the assay is 21.80 BAU/ml [17].

Statistical analyses

Statistical analyses were executed by SPSS version 22.0 (IBM). Variables were investigated using visual (histogram, probability plots) and analytic methods to determine whether or not they are normally distributed. Descriptive statistics were presented as mean ± standard deviation for variables with normal distribution, median (IQR) for disproportionate variables and the number of cases and (%) for nominal variables. In terms of median values, when the group number was two, the differences between the groups were investigated by Mann–Whitney U test. When the group number was more than two, the differences between the groups were investigated by the Kruskal–Wallis test. Chi-square test or Fisher exact test were performed for categorical variables to compare the data and Bonferroni correction was performed when necessary. A P value < 0.05 was considered statistically significant.

Results

A total of 497 patients with a median (IQR) age of 72 (67–78) years were enrolled in the study, and 305 (61.4%) patients were female. The median (IQR) number of days after the 2nd dose of vaccine was 72 (45–97) days. The seropositivity rate in the whole sample was 70.6% ($n = 351$).

In order to evaluate the course of the antibody response over time, patients were divided into three groups according to the days past after the second dose of the vaccine (Group 1: 28–59 days, Group 2: 60–89 days and Group 3: 90 days and more), and groups included 188, 148 and 171 patients, respectively.

Patients in Group 3 were significantly older than other groups ($P < 0.0001$). There were no differences between groups in terms of gender, comorbidities, CGAs, frailty and functional status (Table 1).

Seropositivity rate decreased over time, and the rate in each group was 80.9, 73.2 and 57.3%, respectively (Appendix 1). sCOVG serum level median (IQR) binding
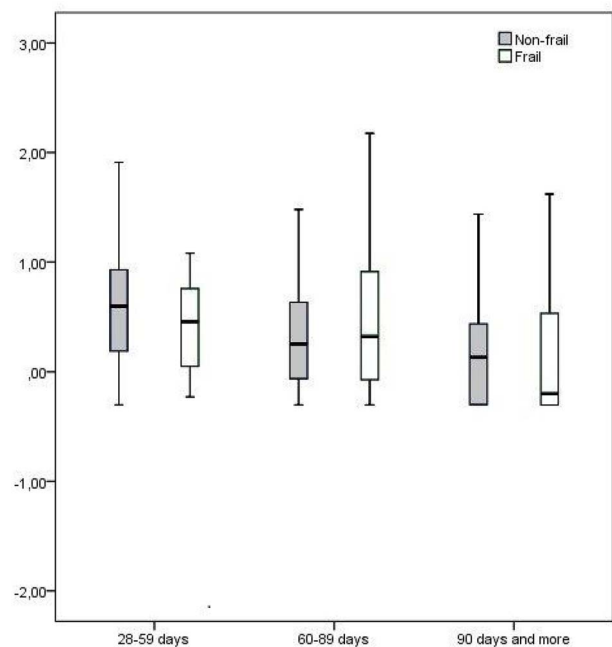
Figure 1. Distribution of antibody titres according to frailty status.

antibody unit (BAU/ml) for each group was 79.1 (31.6–166.0), 41.2 (19.8–103.5) and 27.0 (10.9–62.3), respectively ($P < 0.0001$). In any of the three groups, no significant difference was found between antibody positive and negative groups in terms of age, gender, most comorbidities (exceptions showed in Tables 2 and 3), nutritional status, number of drugs, falls, low HGS, low gait speed, presence of adverse reactions and the scores of Basic ADLs, MMSE, YGDS and clock drowning test (Tables 2–4). Distribution of seropositivity according to the days past after the second dose of the vaccine is given in Supplementary Appendices 1. In Groups 1 and 2, the CCI scores were higher in the seronegative group ($P = 0.023$ and $P = 0.011$, respectively) (Tables 2 and 3). In Group 3, the median (IQR) of IADL, for seropositive and negative groups were 8 (8–8) and 8 (6–8), respectively ($P = 0.025$), and prevalence of frailty was significantly higher in the seronegative group (13.4 vs. 34.3% for seropositive and negative groups, respectively ($P = 0.002$, Table 4). In Figure 1, solely for using in the box blot plot, the logarithmic spike IgG levels were calculated to exclude outliers. These logarithmic spike IgG levels were only used in Figure 1 to show the distribution of seropositivity rate according to the frailty status more comprehensible.

Discussion

Sars-CoV2 infection is a universal challenge and although Sars-CoV2 infection undoubtedly influenced older individuals at the forefront, there is still limited data on the COVID-19 vaccine response in the geriatric population. However, great strides have been made in vaccination since

Table 2. Comparison of seropositive and seronegative individuals in Group 1

		Sars-CoV2 spike IgG antibody positive group $n = 152$ (80.9%)	Sars-CoV2 spike IgG antibody negative group $n = 36$ (19.1%)	P value
Age, median (IQR)		71 (67–76)	72 (68–80.75)	0.272
Female gender n (%)		87 (58%)	22 (61.1%)	0.734
Comorbidities	Depression, n (%)	16 (10.2%)	2 (5.6%)	0.533
	CVD, n (%)	40 (26.7%)	9 (25.0%)	0.838
	HT, n (%)	107 (71.3%)	28 (77.8%)	0.436
	DM, n (%)	65 (43.3%)	19 (52.8%)	0.307
	Atrial fibrillation, n (%)	13 (8.7%)	3 (8.3%)	0.949
	Hypothyroidism, n (%)	27 (18.0%)	7 (19.4%)	0.840
	Congestive heart failure, n (%)	13 (8.7%)	6 (16.7%)	0.215
	Rheumatological diseases, n (%)	13 (8.7%)	7(19.4%)	0.074
	Malignancy history, n (%)	18 (12.0%)	7 (19.4%)	0.276
	Chronic renal disease, n (%)	6 (4.0%)	2 (5.6%)	0.653
	Pulmonary diseases, n (%)	12 (8.0%)	9 (25.0%)	0.008*,**
Basic ADLs, median (IQR)		6 (5.75–6.0)	6 (5.0–6.0)	0.991
Instrumental ADLs, median (IQR)		8 (8–8)	8 (8–8)	0.991
MMSE, median (IQR)		28 (26–30)	27(26–29)	0.377
Geriatric depression scale score, median (IQR)		2(0–5)	1(0–3)	0.204
Clock drawing test, median (IQR)		5 (5–6)	6 (5–6)	0.864
CCI score, median (IQR)		1 (0–2)	2 (1–3)	0.023*
CFS score, median (IQR)		3 (3–4)	3 (3–4)	0.406
CFS-frailty, n (%)		29 (19.7%)	8 (22.2%)	0.738
MNA-SF score, median (IQR)		14 (12.7–14)	14 (11–14)	0.968
Malnutrition (MNA < 12)		32 (22.2%)	11 (30.6%)	0.294
Number of drugs, median (IQR)		5 (3–7)	6 (3–8)	0.200
Polypharmacy, n (%)		88 (59.9%)	22 (61.1%)	0.891
Falls, n (%)		19 (13.2%)	7 (20.6%)	0.285
HGS, median (IQR)		20.0 (16–29.3)	19.9 (16.2–29.4)	0.392
Low HGS, n (%)		45 (35.7%)	15 (51.7%)	0.111
Low gait speed, n (%)		40 (33.6%)	9 (34.6%)	0.922
Gait speed, median (IQR)		0.90 (0.6–1.2)	0.961 (0.7–1.2)	0.826
Sars-CoV2 spike IgG serum level U/ml, median (IQR)		4.6 (2.5–10)	0.56 (0–0.6)	<0.0001*,**,***
Sars-CoV2 spike IgG serum level BAU/ml, median (IQR)		100.3 (55.1–217.3)	12.3 (0.0–14.2)	<0.0001*,**,***

CVD, Cardiovascular diseases; HT, Hypertension; DM, Diabetes Mellitus; ADL, Activities of daily living; MMSE, Mini-mental State Examination; CFS, Clinical Frailty Scale; MNA-SF, Mini Nutritional Assessment short-form. *Significance at $P < 0.05$. **Significance at $P < 0.01$. ***Significance at $P < 0.001$.

the beginning of the pandemic; older adults, who are likely to be among the first to be vaccinated, are often excluded in vaccine studies. Therefore, evaluating the vaccine response in older adults, who are mostly affected by the pandemic and may have many confounding factors like frailty and multiple chronic comorbidities, is essential. In the light of the CGA, including frailty assessment, this study aimed to evaluate the antibody response and factors that may affect it in this particular group. Our findings suggest that antibody response after two doses of the inactivated vaccine decreases, especially after 90 days. Furthermore, to the best of our knowledge, this study is the first revealing comorbidity burden and frailty as important factors for COVID-19 vaccine seroconversion in the geriatric population.

There is still insufficient data for long-term follow-up of antibody response after COVID-19 vaccination not only in older adults but also in all age groups. A recent study on non-immunocompromised healthcare workers showed a significant decline in neutralising antibody titres three months after the second dose of BNT162b2 [18]. In addition, Sinopharm's inactivated COVID-19 vaccine, which has similar technology with Sinovac's Coronavac, also showed decreased antibody production, vaccine effectiveness and mortality reduction, in older adults [19, 20]. Similar to the previous studies, we observed a significant decline in the seroconversion rate over time, particularly if it has been longer than three months after the second dose. These findings may support the concerns about the possible short-lasting humoral immunity response after the two-dose vaccination schedule, and starting with the older population, booster doses may be needed to help to pursue seropositivity.

The BAU/ml is the conversion factor determined using the World Health Organization international standard code to standardise interlaboratory variability due to different reagents. However, few studies evaluating the antibody response of the Sinovac vaccine have used BAU/ml. Therefore, our study aimed to make qualitative and quantitative

Table 3. Comparison of seropositive and seronegative individuals, in Group 2

		Sars-CoV2 spike IgG antibody positive group $n = 101$ (73.2%)	Sars-CoV2 spike IgG antibody negative group $n = 37$ (26.7%)	*P* value
Age, median (IQR)		71 (67–75.2)	71 (66.2–75)	0.723
Female gender		66 (67.3%)	23 (63.9%)	0.707
Comorbidities	Depression, *n* (%)	15 (15.3%)	4 (11.1%)	0.537
	CVD, *n* (%)	20 (20.4%)	10 (27.8%)	0.364
	HT, *n* (%)	76 (77.6%)	25 (69.4%)	0.334
	DM, *n* (%)	38 (38.8%)	15 (41.7%)	0.742
	Atrial fibrillation, *n* (%)	6 (6.1%)	5 (13.9%)	0.165
	Hypothyroidism, *n* (%)	24 (24.5%)	4 (11.1%)	0.091
	Congestive heart failure, *n* (%)	7 (7.1%)	3 (8.3%)	0.728
	Rheumatological diseases, *n* (%)	2 (2.0%)	7 (19.4%)	0.001*,**
	Malignancy history, *n* (%)	7 (7.1%)	7 (19.4%)	0.055
	Chronic renal disease, *n* (%)	6 (6.1%)	8 (3.8%)	0.701
	Pulmonary diseases, *n* (%)	7 (7.1%)	2 (5.6%)	0.745
Basic ADLs, median (IQR)		6 (5–6)	6 (5–6)	0.331
Instrumental ADLs, median (IQR)		8 (8–8)	8 (8–8)	0.261
MMSE, median (IQR)		28 (25–29)	27.5 (25.7–30)	0.914
Geriatric depression scale score, median (IQR)		2 (0–5)	2.5 (0.7–7)	0.697
Clock drawing test, median (IQR)		6 (2.2–6)	6 (3–6)	0.388
CCI score, median (IQR)		1 (0–1)	1.5 (0–3)	0.011*
CFS score, median (IQR)		3 (3–4)	3 (3–4)	0.729
CFS-frailty, *n* (%)		21 (21.9%)	7 (19.4%)	0.761
MNA-SF score, median (IQR)		14 (13–14)	13.5 (12–14)	0.128
Malnutrition (MNA < 8)		13 (14.1%)	7 (20.6%)	0.379
Number of drugs, median (IQR)		5 (3–7)	5 (3–9)	0.719
Polypharmacy, *n* (%)		20 (55.6%)	55 (56.7%)	0.816
Falls, *n* (%)		15 (16.5%)	7 (21.2%)	0.542
HGS, median (IQR)		19.4 (16.9–26.6)	23.5 (17.7–27)	0.035*
Low HGS, *n* (%)		25 (30.9%)	7 (23.3%)	0.437
Low gait speed, *n* (%)		17 (23.3%)	10 (34.5%)	0.248
Gait Speed, median (IQR)		0.9 (0.8–1.1)	0.85 (0.6–0.9)	0.382
Sars-CoV2 spike IgG serum level U/ml, median (IQR)		2.9 (1.6–6.5)	0.57 (0–0.7)	<0.0001*,**,***
Sars-CoV2 spike IgG serum level BAU/ml, median (IQR)		61.9 (37.0–131.8)	12.4 (0.0–15.2)	<0.0001*,**,***

CVD, Cardiovascular diseases; HT, Hypertension; DM; Diabetes Mellitus; ADL, Activities of daily living; MMSE, Mini-mental State Examination; CFS, Clinical Frailty Scale; MNA-SF, Mini Nutritional Assessment short-form. *Significance at $P < 0.05$. **Significance at $P < 0.01$. ***Significance at $P < 0.001$.

evaluations by giving both U/ml and BAU/ml values. Based on a hospital serological study, young healthcare professionals (mean age: 34.4) who received two doses of CoronaVac, tested after 60 days, had significantly lower sCOVG serum levels compared to those who were tested within 60 days of receiving CoronaVac (111.1 ± 62.63 vs. 237.4 ± 160.4 BAU/ml; $P < 0.001$) [21]. In another study conducted on participants who received two doses of CoronaVac with a mean age of 42.3, the median sCOVG serum level collected after 21–49 days after the second dose of vaccine was found to be 128 BAU/ml [22]. In our study, sCOVG serum level median (IQR) BAU/ml for each group was 79.1 (31.6–166.0), 41.2 (19.8–103.5) and 27.0 (10.9–62.3), respectively. Compared to the few studies conducted in young patients, the lower mean BAU values obtained in a geriatric population may be explained via the factors, particularly immunosenescence, that reduce ageing related antibody response. Since this study's primary aim was not to compare the age groups, more randomised controlled studies

comparing older and younger adults are needed to prove this hypothesis.

Vaccine response in the older population is not an entirely well-understood area due to confounders such as immunosenescence (qualitative and quantitative deterioration in immune response due to ageing), frailty and multiple comorbidities [4, 23]. The change of immune organs in older adults is most obvious in thymus; the activity of thymocytes and thymic epithelial cells are reduced, the immune response substances are reduced and therefore immune function is decreased [24]. In addition, the generation of activated B cells and immunoglobulin functionality are important issues [4]. Therefore, immunosenescence may cause alterations in vaccine response in older adults. Frailty is a relatively new concept, providing us an integrative understanding than comorbidities alone of susceptibility to adverse outcomes [25]. Furthermore, recent studies show that immunosenescence is not only a consequence of biological ageing but also a contributor to the variability in

Table 4. Comparison of seropositive and seronegative individuals, in Group 3

		Sars-CoV2 spike IgG antibody positive group $n = 98$ (57.3%)	Sars-CoV2 spike IgG antibody negative group $n = 73$ (42.7%)	P value
Age, median (IQR)		75 (68.7–79)	75 (68–81)	0.744
Female gender		63 (64.3%)	4 (54.8%)	0.208
Comorbidities	Depression, n (%)	16 (16.3%)	8 (11%)	0.320
	CVD, n (%)	29 (29.6%)	19 (26%)	0.608
	HT, n (%)	70 (71.4%)	52 (71.2%)	0.978
	DM, n (%)	34 (34.7%)	33 (45.2%)	0.164
	Atrial fibrillation, n (%)	15 (15.3%)	10 (13.7%)	0.7691
	Hypothyroidism, n (%)	8 (18.4%)	10 (13.7%)	0.414
	Congestive heart failure, n (%)	11 (11.3%)	3 (4.1%)	0.090
	Rheumatological diseases, n (%)	7 (7.1%)	8 (11%)	0.383
	Malignancy history, n (%)	14 (14.3%)	3 (4.1%)	0.052
	Chronic renal disease, n (%)	2 (2%)	6 (8.2%)	0.074
	Pulmonary diseases, n (%)	12 (12.2%)	6 (8.2%)	0.396
Basic ADLs, median (IQR)		6 (5–6)	6 (5–6)	0.232
Instrumental ADLs, median (IQR)		8 (8–8)	8 (6–8)	0.025*
MMSE, median (IQR)		28 (26–29)	28 (24–30)	0.544
Geriatric depression scale score, median (IQR)		2 (1–4)	2 (0–5)	0.769
Clock drawing test, median (IQR)		6 (4–6)	6 (2–6)	0.689
CCI score, median (IQR)		1 (0–2)	1 (0–2)	0.903
CFS score, median (IQR)		3 (3–4)	4 (3–4)	0.028*
CFS-frailty, n (%)		13 (13.4%)	23 (34.3%)	0.002*,**
MNA-SF score, median (IQR)		14 (11.5–14)	14 (12–14)	0.926
Malnutrition (MNA < 12)		25 (28.1%)	16 (26.7%)	0.849
Number of drugs, median (IQR)		4 (2–6.5)	5 (2–7)	0.662
Polypharmacy, n (%)		54 (55.1%)	46 (63%)	0.299
Falls, n (%)		13 (14.3%)	10 (18.9%)	0.469
HGS, median (IQR)		21 (15.0–28.7)	23 (16.1–27.4)	0.419
Low HGS, n (%)		26 (33.3%)	21 (42%)	0.321
Low gait speed, n (%)		23 (30.7%)	14 (29.2%)	0.860
Gait speed, median (IQR)		0.9 (0.8–1.1)	1 (0.8–1.2)	0.864
Sars-CoV2 spike IgG serum level U/ml, median (IQR)		2.4 (1.37–5.39)	0.5 (0.5–0.59)	<0.0001*,**,***
Sars-CoV2 spike IgG serum level BAU/ml, median (IQR)		52.6 (29.8–117.0)	10.9 (10.9–12.6)	<0.0001*,**,***

CVD, Cardiovascular diseases; HT, Hypertension; DM, Diabetes Mellitus; ADL, Activities of daily living; MMSE, Mini-mental State Examination; CFS, Clinical Frailty Scale; MNA-SF, Mini Nutritional Assessment short-form. *Significance at $P < 0.05$. **Significance at $P < 0.01$. ***Significance at $P < 0.001$.

vulnerability seen with frailty [24, 25]. Current studies have revealed the impact of frailty on other vaccine responses. In a study evaluating pneumococcal vaccine response in older adults, frailty has appeared to be a better predictor of immune response than age alone [26]. Moreover, many studies assessing the impact of frailty on influenza vaccine responses disclosed that frailty was strongly associated with antibody response as a measure of vaccine efficacy [24]. Although there is a growing body of evidence showing the relationship between frailty and vaccine response [15, 26], most of the vaccination studies have not included frail older adults as a major limitation. In the first report of inactivated SARS-CoV-2 vaccine, CoronaVac, tested in older adults (aged ≥ 60 years), used a phase 1/2 study design to assess the safety of two different doses (3 μg and 6 μg) and found similar neutralising antibody responses among adults aged 18–59 years received same doses [27]. However, the most important limitation of this study was evaluating the seroconversion rate solely at days 28 and 56 and having no data on patients' comorbidities or compressive geriatric

assessments, including frailty. In another Phase 2 vaccine study conducted on chimpanzee adenovirus vector vaccine developed by AstraZeneca/Oxford University, people aged 60 and older were included, and similar seropositivity on the 28th day was reported in all age groups. Since, this study is not providing a follow up after 28 days and excludes older participants with severe comorbidities and a CFS score of 4 and above, the antibody response in frail older adults has been unknown [28].

In our study, all patients were evaluated in terms of frailty via CFS, a frailty scale most often used for cumulative deficit frailty. Although we observed no relationship between seroconversion and frailty in Groups 1 and 2 after the second dose of vaccine, in Group 3, frailty prevalence with CFS was significantly higher in the seronegative group ($P = 0.002$). Even though most studies in the field of vaccination emphasise that there might be an age-related decrease in antibody response, our study showed no difference between seropositive and negative groups in terms of age, however, frailty seems to be associated with antibody response.

Therefore, frailty might be playing a key role in possible short-lasting humoral immunity response after the two-dose vaccination, clarified after 90 days.

Despite the studies focused on the effect of comorbidities on non-Sars-CoV2 vaccine response [29], there is insufficient data about the impact of comorbidity burden. Although we observed higher scores of CCI in the seronegative subjects of Groups 1 and 2, no relationship was found between seroconversion and CCI in Group 3. In accordance with our findings, in a study with a small group of haemodialysis patients conducted by Torreggiani *et al.*, at the time of the second dose mRNA vaccine (i.e. 3 weeks after the first dose), low neutralising antibody titers were observed in the high CCI scored group [30]. In conclusion, it can be hypothesised that the seroconversion rate, especially in the early period, may be affected by the burden of comorbidity.

The main limitation of our study is the cross-sectional design, which hinders the causal direction of the relationships seen. Another issue that can be considered as a limitation is that the prevaccine antibody status of the patients is not known. Although N-protein IgG measurement is one of the methods that can objectively evaluate whether patients have had COVID-19 before, it was not available to make this measurement for this cross-sectional study. In order to avoid this situation becoming a limitation, patients were evaluated with all suspicious clinical symptoms, contacts with people infected with COVID-19 and rt-PCR and thorax computer tomography results were obtained from the national database since the onset of the pandemic. Patients were excluded from the study in the presence of a suspicious/positive history, symptom or result. In addition, the lack of recurrent antibody measurements of the same patients also causes limitations in the objective evaluation of the real-life course of the antibody response. Furthermore, a follow-up of the patients in terms of COVID-19 infection could provide essential data on the vaccine's effectiveness. Finally, considering that humoral immune response may not be the sole factor affected by immunosenescence, further studies evaluating the effect of cellular immunity on vaccine response may also be needed.

There are also several strengths of the study. This is the first study giving information about the inactive COVID-19 vaccine seroconversion rate proceeding over time in older adults. Another important strength of this study is showing the effect of frailty, an essential component of the assessment of an older individual, on the COVID-19 vaccine response, as a distinctive feature of the study.

In conclusion; to the best of our knowledge, this is the first study assessing antibody response after vaccination with Sars-CoV 2 inactivated vaccine in the Turkish geriatric population. We found that the seropositivity rate was significantly lower in frail geriatric patients after two-dose scheduled vaccination. These findings may support the necessity of a third dose vaccination after two doses of inactive vaccination, especially in the frail older population. Larger sampled randomised controlled trials are needed to confirm the association between frailty and COVID-19 vaccine response.

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