# ORIGINAL RESEARCH

# Frailty as a Significant Predictor of COVID-19 Among Vaccinated Older Adults

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## Abstract

**Objective:** To investigate polymerase chain reaction (PCR) confirmed symptomatic coronavirus disease-2019 (COVID-19) infection incidence in vaccinated older adults.

**Materials and Methods:** This prospective study comprised 483 adults aged 60 years and older, all vaccinated with 2 doses of inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine. All participants had their anti-SARS-CoV-2 immunoglobulin G antibody titers checked and were simultaneously evaluated by comprehensive geriatric assessment, including frailty. We defined the overall survival time as the period from the date of blood collection for antibody responses through the event date [i.e., PCR confirmed (COVID-19) diagnosis] (if any), the time of the last visit or at the termination of data collection (November 25, 2021), whichever occurred first. Individuals who were vaccinated with the 3rd dose of any type were censored at the time of vaccination and removed from further follow-up.

**Results:** The incidence of symptomatic COVID-19 was significantly higher in the frail group, with a cumulative incidence of 7.1% and 2.2% in the frail and non-frail groups, respectively (p=0.02). In Cox regression analysis, the clinical frailty scale (CFS) score was found to be a significant predictor for breakthrough COVID-19 infection [hazard ratio =3.2 (95% confidence interval =1.0-9.9), p=0.04].

**Conclusion:** High CFS scores among vaccinated older adults should be considered as an easy-to-assess, high-risk marker for predicting breakthrough COVID-19 infection.

**Keywords:** SARS-CoV-2, Sinovac, CoronaVac, older people, frailty

## Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in late 2019. The World Health Organization declared the pandemic on March 11, 2020 (1). SARS-CoV-2 causes a wide variety of clinical conditions, from pneumonia to multi-organ failure. In older adults, symptoms and course of COVID-19 may be different from those in young individuals; hospitalization and mortality rates may be higher; and the efficacy and effectiveness of the COVID-19 vaccine may be lower because of immunosenescence, which may not be explained solely by biological aging (2).

Frailty is defined as a clinical syndrome of decreased reserve to stressors and is strongly associated with increased disability, hospitalization, and mortality rates (3). Frail older adults have a poor prognosis for COVID-19, and some guidelines recommend routine evaluation of frailty status in COVID-19 patients (4). The majority of studies published so far have examined the

relationship between frailty and the relevant course of COVID-19 only in unvaccinated individuals.

This prospective cohort study was a continuation of an earlier cohort study showing that frailty affects seroconversion in older adults, especially those 90 days and more after the second dose of vaccination (5). This study was conducted to investigate the occurrence and risk factors of breakthrough COVID-19 infections among those fully vaccinated (i.e., 2 doses) with the inactivated SARS-CoV-2 vaccine.

## Materials and Methods

The study was conducted with 483 individuals, aged 60 years and older, who were subsequently admitted to the geriatric outpatient clinic from April 1, 2021, through July 1, 2021, for any reason and agreed to participate in the study. All participants were recruited from those vaccinated 2 doses of inactivated SARS-CoV-2 vaccine in the national COVID-19 mass vaccination program. At least 28 days following full vaccination, vaccine-induced anti-spike immunoglobulin G (IgG) antibody levels were measured, and a comprehensive geriatric evaluation was performed for each participant. Findings till this point have been published (5). The same cohort was further followed up until November 25, 2021, for breakthrough infections (if any) and related risk factors. Individuals reporting any other vaccine in the month preceding data collection and those receiving chemotherapy, immunosuppressive therapy, or regular dialysis treatment were excluded from the study.

For comprehensive geriatric assessment, the Katz activities of daily living (ADL) scale (6), Lawton-Brody instrumental ADL (7), mini-mental state examination (MMSE) (8), Yesavage's geriatric depression scale (YGDS) (>5 points were defined as depression) (9), Charlson comorbidity index (CCI) (10), strength, assistance walking, rising from a chair, climbing stairs, and falls (SARC-F) questionnaire (11), mini nutritional assessment-short form (MNA-SF) (scores ≥12 points were defined as normal, scores <11 malnutrition and risk of malnutrition) (12), 4m walking test for gait speed measurement (where values below 0.8 m/sec were evaluated in favor of low physical performance), and handgrip strength (HGS) test (where the low HGS was described as HGS <16 kg for women and <27 kg for men) were performed successively (13). Information was also collected on post-vaccination side effects (fever, myalgia, headache) and polypharmacy (≥5 drug usage) (if any).

Frailty status was evaluated using the clinical frailty scale (CFS), as validated earlier in the Turkish population by Özsürekçi et al. (14). CFS was performed 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).

Participants were later grouped as "frail" (CFS >4) and "non-frail" (CFS ≤4), based on the total scores obtained from the CFS (14). The CFS scores of all participants were determined by the same specialist physician who had previously been trained.

Blood samples were collected at least 28 days after the second dose of Sinovac's SARS-CoV-2 inactivated vaccine (CoronaVac). SARS-CoV-2 spike-specific antibody IgG levels were quantitatively measured using a Siemens Atellica IM sCOVG kit with a measuring interval between 0.50 and 150.00 Index (U/mL) for all cohort members. Individuals with IgG value ≥1.0 were defined as "seropositive", while any value <1 was reported as "seronegative". 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 (15). Technical methods are detailed in a previous study (5).

The primary dependent variable (event in survival models) was defined as contracting symptomatic COVID-19, as confirmed by reverse transcription-polymerase chain reaction. In the survival analysis, 3 groups were determined according to the end of the follow-up period. The follow-up period started from the date when the blood sample was obtained for antibody testing for all participants. The study was completed for the first group at the time of symptomatic COVID-19, for the second group at the time of the 3rd dose of anti-SARS-CoV-2 vaccine, and for the third group at the time of November 25, 2021 (as patients in the third group did not receive their third dose of vaccines or did not have symptomatic COVID-19 until the end of the follow-up period).

The study's ethics approval was obtained from the Hacettepe University Clinical Research Ethics Committee [approval number: 2021/29-09 (KA 21129), date: 14.12.2021]. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

### Statistics

Data collected were analyzed using SPSS v.22.0 (IBM). Categorical variables are presented as counts and percentages (n/%). The chi-square test or Fisher's exact test were used for intergroup comparisons. The Kruskal-Wallis test was used to compare numerical parameters with more than two categorical data. The distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. Measures of central tendency and dispersion are presented as mean (± standard deviation) or median [interquartile range (IQR)], as appropriate. Bonferroni correction was used in a post hoc analysis, as needed. Kaplan-Meier analysis was used to estimate the probability of

outcomes of interest, considering the time to event/censoring. Univariate effects of variables on survival were investigated using the log-rank test. The full (initial) Cox regression model included all potential confounders besides frailty (the main exposure) and seropositivity at baseline; the most explanatory multivariate model was presented as the final model. Variables with p<0.2 were determined as candidates by the chi-square test. In terms of the multicollinearity problem, the final model was created by considering the correlation status and model fit. The omnibus test result was used to evaluate the model fit, and the multivariate model omnibus test p-value was 0.18. A 5% type 1 error was used to infer statistical significance in all analyses.

## Results

Of the 483 recruited participants, the CFS scores were completed for 465 individuals; thus, the sample size was 483 for descriptive and 465 for frailty-associated analyses. Of the participants, 99 (21.2%) were considered "frail". The median (IQR) age was 72 (11) years; 295 (61.1%) were female. The median follow-up time was 64 (58) days, with a range of 1-234 days. The time from the second dose of vaccination to the measurement of antibody response ranged from 28 to144 days with a median (IQR) of 74 (52) days. The number of seropositive participants was 328 (70.2%) in the study group, and the median (IQR) serum spike IgG levels were 2.1 (4.5) AU/mL and 46.1 (104.5) BAU/mL.

**Table 1. Demographic features according to the frailty status**

| | FRAIL n=99 (21.2%) | Robust n=366 (78.7%) | p-value |
|---|---|---|---|
| Age (year) | 75.5 (12) | 71 (10) | <0.001 |
| Female gender [n (%)] | 61 (61.6%) | 224 (61.2%) | 0.51 |
| Comorbidities [n (%)] | | | |
| DM | 40 (40.4%) | 151 (41.3%) | 0.90 |
| HT | 77 (77.8%) | 261 (71.3%) | 0.25 |
| HL | 24 (24.2%) | 111 (30.3%) | 0.26 |
| CHF | 11 (11.1%) | 28 (7.7%) | 0.30 |
| CAD | 33 (33.3%) | 85 (23.2%) | 0.05 |
| AF | 16 (16.2%) | 34 (9.3%) | 0.06 |
| Hypothyroidism | 13 (13.1%) | 72 (19.7%) | 0.14 |
| CKD | 13 (13.1%) | 12 (3.3%) | <0.001 |
| CA | 11 (11.1%) | 44 (12%) | 0.48 |
| Rheumatological disease | 9 (9.1%) | 32 (8.7%) | 0.84 |
| Depression | 9 (9.1%) | 25 (6.8%) | 0.51 |
| COPD-Asthma | 10 (10.1%) | 37 (10.1%) | 0.58 |
| Basic ADL | 5 (4) | 6 (0) | <0.001 |
| Instrumental ADL | 4.5 (5.25) | 8 (0) | <0.001 |
| MMSE | 24 (6.25) | 28 (4) | <0.001 |
| Geriatric depression scale | 5 (6) | 2 (4.5) | <0.001 |
| Charlson comorbidity index | 1 (2) | 1 (2) | <0.001 |
| CFS | 5 (1) | 3 (1) | <0.001 |
| SARC-F | 5 (3) | 1 (2) | <0.001 |
| MNA-SF | 12 (4) | 14 (2) | <0.001 |
| Polypharmacy [n (%)] | 73 (73.7%) | 193 (53.2%) | 0.001 |
| Handgrip strength (kg) | 16.1 (7.05) | 21.1 (12.1) | <0.001 |
| Gait speed (m/sec) | 0.52 (0.42) | 0.90 (0.30) | <0.001 |
| Presence of adverse reactions [n (%)] | 12 (12.5%) | 25 (6.9%) | 0.07 |
| SARS-CoV-2 Spike IgG serum level (AU/mL) | 1.69 (4.67) | 2.15 (4.80) | 0.31 |
| SARS-CoV-2 Spike IgG serum level (BAU/mL) | 36.8 (101.8) | 46.8 (104.5) | 0.31 |
| Seropositivity [n (%)] | 62 (62.6%) | 266 (72.7%) | 0.06 |
| COVID-19 diagnosis confirmed by PCR positivity [n (%)] | 7 (7.1%) | 8 (2.2%) | 0.02 |

DM: Diabetes mellitus, HT: Hypertension, HL: Hyperlipidemia, CHF: Chronic hearth failure, CAD: Coronary artery disease, AF: Atrial fibrillation, CKD: Chronic kidney disease, CA: Cancer history, COPD: Chronic obstructive pulmonary disease, ADL: Activities of daily living, MMSE: Mini-mental status examination, CFS: Clinical frailty scale, SARC-F: Strength, assistance walking, rising from a chair, climbing stairs, and falls, MNA-SF: Mini nutritional assessment-short form, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, IgG: Immunoglobulin G, COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction

Participants were compared by their frailty status. Accordingly, ADL scores, MMSE, YGDS, CCI, CFS, SARC-F, MNA-SF, prevalence of polypharmacy, HGS test, and gait speed were significantly different among frail participants versus those considered as non-frail (p<0.001). Rates of adverse vaccine reactions were relatively higher in the frail group, but the difference was not statistically significant (p=0.07). Polymerase chain reaction (PCR)-confirmed COVID-19 incidence was significantly higher in the frail group (n=7, 7.1%) than in the non-frail group (n=8, 2.2%), (p=0.02) (Table 1). There was no significant association between frailty and serum anti-spike IgG levels (p=0.31) or seropositivity rates (p=0.06).

During the follow-up period, PCR-confirmed COVID-19 infection was detected in 15 participants (3.1%). Eight adults diagnosed with symptomatic COVID-19 infection later received a third dose of COVID-19 vaccine. The other 7 patients with a COVID-19 diagnosis did not have a third COVID-19 vaccine before the end of data collection. Of the 15 incident COVID-19 cases, 10 had mild disease and were treated at home; 3 patients were hospitalized in COVID clinics and 2 patients required intensive care unit (ICU). Computerized tomography findings were in 4 of the patients followed in the hospital. Four patients required non-invasive mechanical ventilation and one patient required invasive mechanical ventilation. While a patient followed in the ICU died, the others were discharged with full recovery. The fatality rate for COVID-19 was 6.7% (n=1) and the mortality rate from all other causes throughout the data collection period (up to 8 months total) was 2.3% (n=11).

Kaplan-Meier survival curves comparing the risk of symptomatic COVID-19 infection across age groups, seropositivity, and frailty did not suggest any statistically significant difference across groups. However, divergence in curves was prominent in all Graphics (1–3) after day 150.

Breakthrough COVID-19, in Cox regression, was found to be statistically significantly associated with the CFS score [hazard ratio =3.2 (95% confidence interval =1.0-9.9), p=0.04)], controlling for age, gender, MNA-SF score, CCI, and seropositivity at baseline (Table 2).

## Discussion

In this study, two findings are remarkable assets to the literature: 1) Frailty is associated with symptomatic breakthrough COVID-19 infections in vaccinated older people, adjusting for vaccine-induced seropositivity; 2) CFS can be used as a high-risk marker for symptomatic breakthrough COVID-19 infections, controlling for age, gender, CCI, MNA-SF score, and anti-SARS-CoV-2 antibody titers. The study confirmed that vaccine-induced seropositivity is highly protective against symptomatic breakthrough COVID-19 infections in older adults vaccinated with two doses of the inactivated CoronaVac vaccine.

Unfortunately, the rather short follow-up period warrants further research on the protective effect of CoronaVac over longer periods.
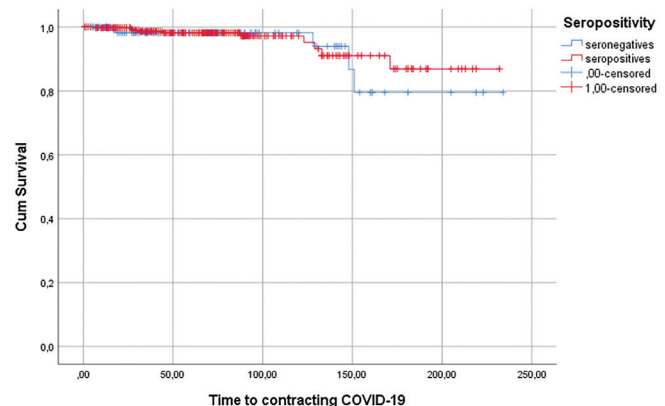


**Graphic 1.** Kaplan-Meier analysis of the seropositive group and seronegative group (p=0.66, log-rank test)

*COVID-19: Coronavirus disease-2019, Cum: Cummulative*
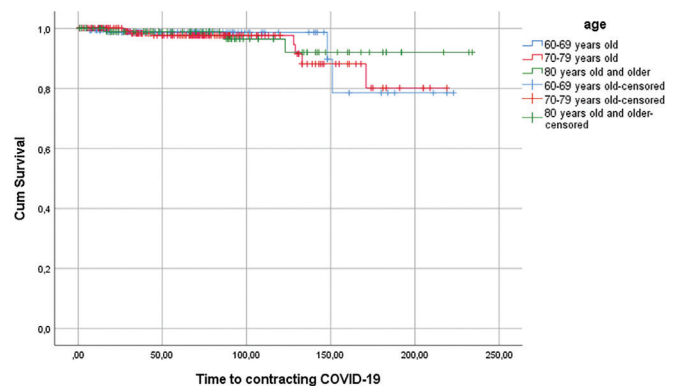


**Graphic 2.** Kaplan-Meier analysis of the age groups (p=0.79, log-rank test)

*COVID-19: Coronavirus disease-2019, Cum: Cummulative*
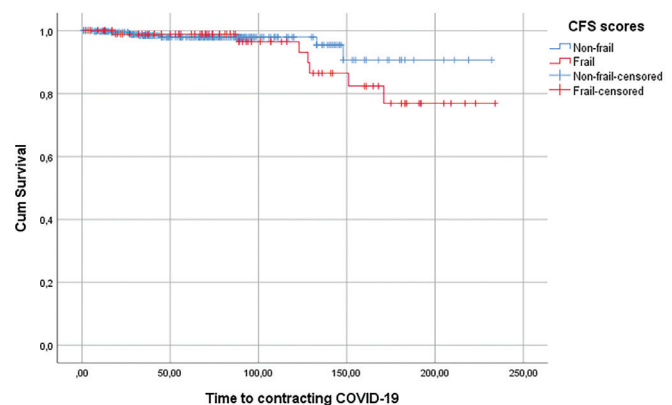


**Graphic 3.** Kaplan-Meier analysis of the frail group and robust group (p=0.73, log-rank test)

*COVID-19: Coronavirus disease-2019, Cum: Cummulative*

| Table 2. Risk factors for contracting COVID-19 in the regression analysis | | | | |
|---|---|---|---|---|
| | Univariate | | Multivariate | |
| Risk factor | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Age | 0.98 (0.91-1.05) | 0.54 | 0.95 (0.88-1.03) | 0.26 |
| Female gender | 0.56 (0.20-1.56) | 0.26 | 0.44 (0.15-1.28) | 0.17 |
| CFS score | 1.76 (0.61-5.07) | 0.29 | 3.2 (1.0-9.9) | 0.04 |
| MNA-SF score | 1.30 (0.91-1.86) | 0.14 | 1.45 (0.99-2.14) | 0.05 |
| CCI | 1.02 (0.75-1.39) | 0.88 | 1.02 (0.75-1.38) | 0.65 |
| Seropositivity | 0.78 (0.26-2.29) | 0.65 | 0.73 (0.24-2.22) | 0.58 |
| HR: Hazard ratio, CI: Confidence interval, COVID-19: Coronavirus disease-2019, CFS: Clinical frailty scale, MNA-SF: Mini nutritional assessment-short form, CCI: Charlson comorbidity index | | | | |

Frailty is a multifactorial clinical condition, and tests performed to assess frailty have been developed on 2 basic frailty models: the biological frailty model and the cumulative deficit model (16). CFS is a reliable cumulative deficit screening tool to identify frailty and is easy to use in both outpatient and inpatient clinics, including emergency departments and ICUs (3). In this study, frailty was ascertained by CFS. The diagnosis of COVID-19 confirmed by PCR positivity was found to be significantly higher in the frail group. Meta-analyses showed that frail patients were more susceptible to COVID-19, and even that each 1-point increase in the CFS score was associated with a 12% increase in mortality (3). In our study, frail patients were older and had lower overall geriatric assessment scores. Similarly, vaccine-induced antibody levels were negatively associated with frailty but did not reach statistical significance. Previous studies have shown higher rates of hospitalization, morbidity, and mortality in men (17). Similarly, women had better COVID-19-free survival rates in our study. Accordingly, in the survival analysis of the model, the potential association between frailty and symptomatic COVID-19 infection in vaccinated older adults, age, geriatric assessment scores, and seropositivity were adjusted for as potential confounders.

In a recent study, frailty was a better predictor of poor prognosis in COVID-19 patients than comorbidities, and the authors recommended early frailty assessment to improve outcomes (18). Hewitt et al. (19) showed that frailty was a better predictor than age for survival in hospitalized patients diagnosed with COVID-19. Mortality rates in hospitalized COVID-19 patients were found to be higher in the frail group in another study that used the hospital frailty risk score for frailty assessment (20). In our study, a 1-point increase in the CFS score resulted in a 3.2-fold increased risk of COVID-19. We found frailty, but not biological age, as a predictor of PCR-confirmed COVID-19 infection among fully vaccinated older adults. Age, gender, CCI scores, and vaccine-induced antibody responses did not reveal any significant evidence for risk stratification. However, the COVID-19 diagnostic risk was positively associated with the MNA-SF scores, although close not significant at alpha 0.05. This has led us to emphasize the importance of malnutrition in older adults. Although COVID-19 itself can cause malnutrition, the presence of malnutrition also increases the risk of COVID-19 (21). Malnutrition was associated with an increased risk of transfer to the ICU in COVID-19 patients in an earlier study, emphasizing the importance of early nutritional screening in older people during the pandemic (22).

In our study, the prevalence of COVID-19 was 3.1%, and most patients presented with mild diseases. Of the infected participants, only one patient died because of COVID-19. In a short report published in our country, vaccination with the inactivated COVID-19 vaccine provided 90% protection from death (23). As of November 25, 2021, in Turkey, 12,840 deaths were reported out of 467,730 PCR-confirmed COVID-19 cases (24). This corresponds to a fatality rate of 2.7%. The fatality rate in our study population was 6.7% among the vaccinated. The inability to detect all COVID-19-related deaths at the national level may explain the inconsistency of observed versus expected fatality rates. The absence of national COVID-19 fatality data with breakdown by age, gender, comorbidity, etc., and the burden of variations in circulating variants over time hinder our ability to apprehend the magnitude of the fatality rate of 6.7% among vaccinated older adults, corresponding to the "expected" rate among their unvaccinated counterparts.

In both efficacy and effectiveness studies, the length of follow-up time is crucial to differentiate the potential effects of the vaccine, durability of vaccine-induced immunity, types of circulating variants, compliance with public preventive measures, daily case numbers, and the possibility of exposure to infected individuals. The shorter the follow-up time, the more likely it is that the true protective effect of COVID-19 vaccines can be established. In this study, the median follow-up was approximately 2-4 months after full vaccination, with the median (IQR) serum spike IgG level being 2.1 (4.5) AU/mL and 46.1 (104.5) BAU/mL. More precise results could be obtained with longer follow-ups, but the national mass vaccination campaign motivated all elderly individuals to receive a third

dose of the COVID-19 vaccine starting from July 1, 2021, which negatively affected our long-term follow-up. Therefore, our results for frailty on symptomatic breakthrough infection should be considered as "short-term" effects, and studies on longer follow-up times are warranted for conclusive answers.

The strengths of the study should also be highlighted. In the literature, most studies examining the relationship between the course of COVID-19 and frailty in older adults were conducted before the vaccination period. Because we evaluated the participants with known antibody responses in this study, we had the opportunity to show that the clinical frailty score may be superior to the antibody response in demonstrating the risk of contracting COVID-19.

## Study Limitations

The findings of our study must be interpreted in light of several limitations. First, in our cohort, only symptomatic patients had a chance to be tested; thus, all events in the analysis were dependent on symptomatic COVID-19 cases. We may have missed cases who had asymptomatic disease after or were symptomatic, yet did not provide PCR samples. Second, given that the study included only those who presented to the geriatric outpatient clinic (for prescription, medical report, routine check-ups, or acute disease), the study findings may not be generalized to all vaccinated older adults. Third, in Turkey, the first 2 doses of vaccine were administered with the inactive vaccine by the national healthcare program, but personal preferences were at the forefront in the $3^{rd}$ and $4^{th}$ doses of vaccines; therefore, we could not continue the follow-up period after the $2^{nd}$ dose of vaccination. Fourth, the actual time from the second dose of vaccination to the measurement of antibody response ranged between 28 and 144 days, which yields widely variable follow-up times for a given individual, which in turn affects COVID risk. Fifth, although patients on chemotherapy or immunosuppressive therapy were excluded, patients with immunosuppressive states or those who were not actively taking these therapies but had pre-existing diseases (such as malignancy in remission) were included, which may also affect vaccine response. Also, in the analysis, subgroup analysis of independent variables suggested a divergence after approximately day 150. This corresponds to the fall (September through November) in our timeline when national COVID-19 case numbers were inclining and delta variants became prominent in the population (24). These might have made the differences more prominent across groups. Similarly, variations in behavioral factors across subgroups and/or overtime need to be assessed in future studies for their potential role in breakthrough infections. Finally, the sample size of the population and especially the events were very small, with only 15 cases of COVID-19.

## Conclusion

To the best of our knowledge, this is the first study investigating the outcome of older adults with known vaccine-induced antibody response after 2 doses of inactivated SARS-CoV-2 vaccination. We only found CFS scores as a significant predictor of breakthrough COVID-19 infection, controlling for age, gender, and seropositivity. High CFS scores among vaccinated older adults should be considered an easy-to-assess, high-risk marker for predicting breakthrough COVID-19 infection. Frail older people should be prioritized in COVID-19 vaccination campaigns, with the highest effective vaccine type at hand, and booster doses should be given earlier. Such an approach will not only maximize individual health among older adults but also COVID-19-related morbidity and mortality rates in populations.

## Ethics

**Ethics Committee Approval:** The study's ethics approval was obtained from the Hacettepe University Clinical Research Ethics Committee [approval number: 2021/29-09 (KA 21129), date: 14.12.2021].

**Informed Consent:** Informed consent was obtained.

## Authorship Contributions

Surgical and Medical Practices: M.H., F.A., B.Ç., M.G.H., Concept: A.O.B., C.B., B.B.D., M.C., S.Ü., M.G.H., Design: A.O.B., A.S., C.B., B.B.D., M.C., S.Ü., M.G.H., Data Collection or Processing: A.O.B., F.A., M.G.O., Z.Ş., S.C., Analysis or Interpretation: M.H., A.S., F.A., S.C., B.Ç., Literature Search: M.G.O., Z.Ş., S.C., B.Ç., Writing: M.H., B.Ç., M.G.H.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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## References

1. World Health Organization. Coronavirus disease 2019 (COVID-19): situation report-22. February 10, 2020. Accessed 11 Feb 2020.

2. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934-943.

3. Pranata R, Henrina J, Lim MA, Lawrensia S, Yonas E, Vania R, Huang I, Lukito AA, Suastika K, Kuswardhani RAT, Setiati S. Clinical frailty scale and mortality in COVID-19: A systematic review and dose-response meta-analysis. Arch Gerontol Geriatr 2021;93:104324.

4. National Institute for Health and Care Excellence. NICE updates rapid COVID-19 guideline on critical care. March 25, 2020.https://www.nice.org.uk/news/article/nice-updates-rapid-covid-19-guideline-on-critical-care.

5. Okyar Baş A, Hafizoğlu M, Akbiyik F, Güner Oytun M, Şahiner Z, Ceylan S, Ünsal P, Doğu BB, Cankurtaran M, Çakir B, Ünal S, Halil MG. Antibody response with SARS-CoV-2 inactivated vaccine (CoronaVac) in Turkish geriatric population. Age Ageing 2022;51:afac088.

6. Arik G, Varan HD, Yavuz BB, Karabulut E, Kara O, Kilic MK, Kizilarslanoglu MC, Sumer F, Kuyumcu ME, Yesil Y, Halil M, Cankurtaran M. Validation of Katz index of independence in activities of daily living in Turkish older adults. Arch Gerontol Geriatr 2015;61:344-350.

7. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179-186.

8. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.

9. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17:37-49.

10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-383.

11. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16-31.

12. Guigoz Y, Lauque S, Vellas BJ. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. Clin Geriatr Med 2002;18:737-757.

13. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

14. Özsürekci C, Balcı C, Kızılarslanoğlu MC, Çalışkan H, Tuna Doğrul R, Ayçiçek GŞ, Sümer F, Karabulut E, Yavuz BB, Cankurtaran M, Halil MG. An important problem in an aging country: identifying the frailty via 9 Point Clinical Frailty Scale. Acta Clin Belg 2020;75:200-204.

15. https://cdn0.scrvt.com/39b415fb07de4d9656c7b516d8e2d907/b2406e708bf287c5/506564e9207f/UnderstandingSARS-CoV-2-IgG-Immunity-Thresholds-and-the-Process-of-Standardization.pdf

16. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:146-156.

17. Aw D, Silva AB, Palmer DB. Immunosenescence: emerging challenges for an ageing population. Immunology 2007;120:435-446.

18. Ma Y, Hou L, Yang X, Huang Z, Yang X, Zhao N, He M, Shi Y, Kang Y, Yue J, Wu C. The association between frailty and severe disease among COVID-19 patients aged over 60 years in China: a prospective cohort study. BMC Med 2020;18:274.

19. Hewitt J, Carter B, Vilches-Moraga A, Quinn TJ, Braude P, Verduri A, Pearce L, Stechman M, Short R, Price A, Collins JT, Bruce E, Einarsson A, Rickard F, Mitchell E, Holloway M, Hesford J, Barlow-Pay F, Clini E, Myint PK, Moug SJ, McCarthy K; COPE Study Collaborators. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health 2020;5:444-451.

20. Kundi H, Çetin EHÖ, Canpolat U, Aras S, Celik O, Ata N, Birinci S, Çay S, Özeke Ö, Tanboğa IH, Topaloğlu S. The role of Frailty on Adverse Outcomes Among Older Patients with COVID-19. J Infect 2020;81:944-951.

21. Wierdsma NJ, Kruizenga HM, Konings LA, Krebbers D, Jorissen JR, Joosten MI, van Aken LH, Tan FM, van Bodegraven AA, Soeters MR, Weijs PJ. Poor nutritional status, risk of sarcopenia and nutrition related complaints are prevalent in COVID-19 patients during and after hospital admission. Clin Nutr ESPEN 2021;43:369-376.

22. Bedock D, Bel Lassen P, Mathian A, Moreau P, Couffignal J, Ciangura C, Poitou-Bernert C, Jeannin AC, Mosbah H, Fadlallah J, Amoura Z, Oppert JM, Faucher P. Prevalence and severity of malnutrition in hospitalized COVID-19 patients. Clin Nutr ESPEN 2020;40:214-219.

23. Akpolat T, Uzun O. Reduced mortality rate after coronavac vaccine among healthcare workers. J Infect 2021;83:20-21.

24. https://covid19.saglik.gov.tr/TR-66935/genel-koronavirus-tablosu.html