Geriatrik Bilimler Dergisi / Journal of Geriatric Science
Available online at:
Doi: 10.47141/geriatrik.1276791

ARAŞTIRMA MAKALESİ/ORIGINAL ARTICLE

# Another Face of the Post-COVID Syndrome in Elderly Patients: Increased Frailty Due to Systemic Inflammation

# Yaşlı Hastalarda Post-COVID Sendromunun Bir Diğer Yüzü: Sistemik Enflamasyona Bağlı Artan Kırılganlık

Gülbahar Darılmaz Yüce [1]
Funda Salgür[2]
Samra Kamilova[3]
Özgün Çiçek[4]
Matin Iskandarov[4]
Meriç Yavuz Çolak[5]
Gaye Ulubay[1]
M. Şule Akçay[1]

[1]Başkent University Faculty of Medicine, Department of Chest Diseases, Ankara, Türkiye
[2]Başkent University Faculty of Medicine, Department of Family Medicine, Ankara, Türkiye
[3]Başkent University Faculty of Medicine, Department of General Surgery, Ankara, Türkiye
[4]Başkent University Faculty of Medicine, Department of Internal Diseases, Ankara, Türkiye
[5]Başkent University Faculty of Medicine, Department of Biostatistics, Ankara, Türkiye

**Correspondence:**
Gülbahar DARILMAZ YÜCE, Başkent University Faculty of Medicine, Department of Chest Diseases, Ankara, Türkiye,
E-mail: yucegulbahar@yahoo.com.tr,
Phone: +90 312 223 73 33

**Cite This Article:** Yüce GD, Salgür F, Kamilova S, Çiçek Ö, Iskandarov M, Çolak MY, Ulubay G, Akçay Ş. YAnother Face of the Post-COVID Syndrome in Elderly Patients: Increased Frailty Due to Systemic Inflammation . Geriatrik Bilimler Dergisi 2023;6(2) Doi: 10.47141/geriatrik.1276791

**Received:** 05.04.2023
**Accepted:** 08.08.2023

## ABSTRACT

**Aim:** COVID-19 is known to be a condition that creates long-term morbidity and mortality in older adults. There is not enough information yet about the relationship between COVID-19 and frailty. In our study, we investigated whether COVID-19 increases frailty, a condition that can be counted among its long-term effects.

**Materials and Methods:** The study included 73 patients over the age of 65 who were hospitalized in the Başkent University Medical Faculty Hospital COVID-19 Isolation Service, with positive COVID-19 PCR test. Patients were categorized as mild-moderate, severe, and critical pneumonia requiring intensive care unit admission. The FRAIL Frailty scale was applied to the patients on the first day of hospitalization. The FRAIL Frailty scale was applied again at the 3rd month follow-up after discharge. FRAIL index were compared on the first day of hospitalization and 3 months after discharge due to COVID-19.

**Results:** 58.9% of the patients participating in our study were male and 41.1% were female. Their mean age was 77.48±7.68 years. The mean FRAIL score was 1.34±0.12 on the first day of hospitalization and 2.24±0.12 after discharge. The mean change in FRAIL score between the first day of hospitalization and after discharge was 60.3% and was statistically significant ($p<0.001$). The change was the highest in the intensive care unit group, with 95% ($p<0.001$).

**Conclusion:** COVID-19 increases systemic inflammation, leading to increased frailty. Elderly patients should be evaluated for frailty during and after COVID-19.

**Keywords:** COVID-19, Long-COVID, Aged, Frail Elderly, Hospitalization

## ÖZ

**Amaç:** COVID-19'un yaşlı yetişkinlerde uzun süreli morbidite ve mortalite yaratan bir durum olduğu bilinmektedir. COVID-19 ve kırılganlık ilişkisi hakkında henüz yeterli bilgi yoktur. Çalışmamızda COVID-19'un uzun vadeli etkileri arasında sayılabilecek bir durum olan kırılganlığı arttırıp arttırmadığını araştırdık.

**Gereç ve Yöntemler:** Çalışmaya Başkent Üniversitesi Tıp Fakültesi Hastanesi COVID-19 İzolasyon Servisi'nde yatan 65 yaş üstü, COVID-19 PCR testi pozitif olan 73 hasta dahil edildi. Hastalar hafif-orta pnömoni, ağır pnömoni ve yoğun bakım ünitesine yatış gerektiren ciddi pnömoni olarak kategorize edildi. Hastalara yatışının ilk gününde FRAIL Frailty ölçeği uygulandı. Taburculuk sonrası 3. ay kontrolünde tekrar FRAIL Frailty ölçeği uygulandı. Hastaneye yatışın ilk günü ve taburculuk sonrası 3. ay kontrol FRAIL indeksleri karşılaştırıldı.

**Bulgular:** Çalışmamıza katılan hastaların %58,9'u erkek, %41,1'i kadındı. Ortalama yaşları 77,48±7,68 idi. Ortalama FRAIL skoru yatışın ilk günü 1,34±0,12 iken taburculuk sonrası 2,24±0,12 idi. İlk ve son FRAIL skorları arasındaki ortalama değişim %60,3 idi ve istatistiksel olarak anlamlıydı ($p<0,001$). FRAIL skorundaki değişim en fazla %95 ile yoğun bakım grubunda oldu ($p<0,001$).

**Sonuç:** COVID-19 sistemik inflamasyonu arttırarak kırılganlığın artmasına neden olur. Yaşlı hastalar COVID-19 sırasında ve sonrasında kırılganlık açısından değerlendirilmelidir.

**Anahtar Kelimeler:** COVID-19, Uzun Süreli COVID, Yaşlı, Kırılgan Yaşlı, Hastaneye Yatış

## INTRODUCTION

During the COVID-19 pandemic frail elderly people showed higher mortality rates than the general population (1). In aging the gradual development of chronic subclinical systemic inflammation, also called inflammatory aging, and acquired immune system impairment are observed (2).

The term "prolonged COVID-19 syndrome" or "post-COVID-19 syndrome" has also been used for conditions such as persistent symptoms, permanent organ damage, and continued systemic inflammation after COVID-19. Post-COVID-19 syndrome is thought to be a physical, functional, mental and psychological multisystem disease (3). It has been reported that the post-COVID-19 syndrome is more likely to occur among women and older adults (4). It has been reported that the prevalence of post-COVID-19 syndrome in the elderly is approximately 9.3% and the most common symptoms reported 90 days after recovery are fatigue, myalgia and shortness of breath, and depression and anxiety are frequently observed. It is now known that COVID-19 is a condition with long-term consequences that affect many systems by triggering systemic inflammation (3). Studies have shown that many proinflammatory cytokines such as interleukin 6, C-reaktif protein and tumor necrosis factor (IL-6, CRP, TNF), which increase in COVID-19, are also independently associated with frailty (5,6).

Frailty is a common and important geriatric syndrome characterized by age-related declines in physiological reserve and function of multiple organ systems, leading to increased susceptibility to adverse health outcomes (7,8,9). Frailty is defined as a syndrome by the presence of three or more of five phenotypic criteria (weakness as measured by low grip strength, slowness with slow walking speed, low physical activity level, low energy or self-reported fatigue, and weight loss). In Western countries, the prevalence of frailty is 10.7% (7). Multisystem pathophysiological processes, including chronic inflammation and immune activation, play a role in the pathogenesis of frailty syndrome (8,9).

There is not enough research yet on the relationship between the long-term effects of COVID-19 and frailty. For this reason, in our study, we investigated whether COVID-19 increases frailty, which is a condition that can be listed among the long-term effects of COVID-19.

## MATERIAL AND METHODS

A total of 143 patients, 70 of whom were excluded from the study diagnosed with laboratory-confirmed COVID-19, who were followed up and treated at the hospital between June 2020 and July 2022 in the COVID-19 isolation ward of University Medical Faculty Hospital were included in this prospective cohort study. Patients under the age of 65, patients (n=12) who were discharged from the hospital or taken to the normal ward assuming that they did not have COVID-19 infection based on their COVID-19 polymerase chain reaction (PCR), thoracic computerized tomography (CT), and clinical course, patients (n=53) who were unable to answer the FRAIL scale, and patients (n=5) who died during the study were excluded from the study. Patients with bacterial or fungal agents isolated from the respiratory tract and patients who developed secondary bacterial or fungal pneumonia were excluded from the study, and only the relationship between COVID-19 pneumonia and frailty was investigated. The study was continued with 73 patients who completed follow-up.

Demographic characteristics, symptoms, laboratory data, radiological findings and treatment strategies of the patients were

recorded. According to national COVID-19 guidelines, patients were categorized as mild-moderate, severe, and critical pneumonia requiring intensive care unit (ICU) admission (10). According to the guideline, patients with symptoms such as fever, muscle/joint pains, cough and sore throat, respiratory rate <30/minute, oxygen saturation in room air (SpO2) above 90%, and mild pneumonia findings on chest X-ray or tomography should be mild-moderate, patients with tachypnea (≥30/minute) and SpO2 level below 90% and bilateral diffuse pneumonia findings on chest X-ray or tomography were considered as severe pneumonia. Patients with dyspnea, respiratory rate≥30/minute, PaO2/FiO2<300, increased oxygen demand, SpO2<90% or PaO2<70 mmHg despite 5 L/minute oxygen therapy, hypotension (systolic blood pressure<90 mmHg), tachycardia >100/minute, kidney damage, liver damage, confusion, bleeding diathesis, immunosuppression, troponin elevation and arrhythmia, lactate>2 mmol, capillary return disorder and cutis marmaratus were considered as critical pneumonia requiring ICU admission. The FRAIL scale was given to the patients on the first day of hospitalization by the COVID-19 inpatient ward physician. While the FRAIL scale was applied on the first day of hospitalization, the answers to the questions were asked for 15 days before the symptoms and signs of COVID-19 appeared. The FRAIL scale was reapplied by the physician at the outpatient clinic visits at the 3rd month after discharge. FRAIL index were compared on the first day of hospitalization (FRAIL 1) and the 3rd month after discharge (FRAIL 2) due to COVID-19. The FRAIL scale is a quick screening tool for frailty that takes a few minutes to answer (11). The word 'FRAIL' is an acronym, with each letter representing a frailty criterion (F=Fatigue, R=Resistance: climb one flight of stairs, A=aerobic exercises: walk one block, I=Illness: 5 or more, L=Loss of weight: >5% of body weight in the last year). Each of these parameters is scored either 0 or 1. The total score was between 0 and 5. Based on the total score, the patient is considered 0: Normal, 1–2: Prefrail, 3–5: Frail (11). In our study, those with an increase in the FRAIL index were identified as the group with the change, and those without an increase in the FRAIL index were identified as the group with no change. Comparisons were made between the group with change and the group with no change.

**Ethical Approval:** This study was approved by the Başkent University Medical and Health Sciences Research Board (approval number KA22/167, 22/72 and date March 30, 2020). This study was carried out in accordance with the Helsinki Declaration.

## Statistical Analysis

Study data were analyzed with SPSS 25.0 software and G-Power software was used to determine sample size. The suitability of the data distribution to the normal distribution was evaluated with the Kolmogrov Smirnov test. For the comparison of quantitative variables, when the parametric test assumptions were met, "One-way analysis of variance" was used to compare the variables belonging to 3 independent patient groups, and "One-way analysis of variance" was used when the assumptions were not met. Kruskall-Wallis analysis of variance" was used. In group comparisons of time-dependent measurements, "Paired t-test" was used when parametric test assumptions were met, and "Wilcoxon sign-rank test" was used when assumptions were not met. Relations between variables in the study "Pearson correlation test" and "Spearman correlation test" In the

comparison of the fragility values of the three patient groups at the end of hospitalization and at the end of the 3rd month, a minimum of 66 patients were determined for an effect size of 0.20, a minimum power of 80%, and an error level of 0.05, and 73 patients were included in the study.

## RESULTS

58.9% of the patients participating in our study were male and 41.1% were female. Their mean age was 77.48±7.68 years. There was chronic obstructive pulmonary disease (COPD) in 20.5% of the patients, asthma in 5.5%, type 2 diabetes mellitus (DM) in 39.7%, chronic kidney disease (CKD) in 23.3%, cancer (CA) in 13.7%, chronic liver disease (CLD) in 1.4%, hypertension (HT) in 69.9%, coronary artery disease (CAD) in 53.4%, Alzheimer's or dementia in 8.3%, and a history of transplantation in 2.7%.

Of the patients included in the study, 19.2% had mild-moderate pneumonia, 53.4% had severe pneumonia, and 27.4% had critical pneumonia, which was followed up and treated in the ICU. The most common complaint of the patients at the time of admission to the hospital was fatigue (71.2%). This was followed by shortness of breath with 58.9% and fever with 56.2%. Typical radiological findings supporting COVID-19 were present in 87.7% of patients at the time of admission to the hospital.

The mean score of the FRAIL scale in patients was 1.34±0.12 on the first day of hospitalization due to COVID-19, and 2.24±0.12 at the 3rd month follow-up after discharge. The change in the mean FRAIL scale score was found to be 60.3% and it was statistically significant (Wilcoxon signed rank test p<0.001). When the results of the FRAIL scale were classified as normal, prefrail and frail, 24.7% of the patients were normal, 60.3% were prefrail, 15.1% were frail at hospitalization, and these values increased after 3 month toward frailty, resulting in 5.5% normal, 53.4% prefrail, and 41.1% frail patients. In the control visits after the disease, it was observed that the frailty of these patients increased and only 5.5% of the patients could be classified as normal based on their FRAIL score. The percentage of frail patients has increased after COVID-19. We observed that the frailty of normal and prefrail patients increased after the disease, making these patients classified as frail (Mc Nemar Bowker test p<0.001) (Table I).

**Table I.** FRAIL index changes admission and postdischarge

| | Frailty on admission | Frailty 90-day postdischarge | Change | | p |
|---|---|---|---|---|---|
| | | | % | (n) | |
| FRAIL index (mean) | 1.34 ±0.12 | 2.24±0.12 | 60.3 | 44 | <0.001* |
| Normal % | 24.7 | 5.5 | 22.2 | 4 | <0.001** |
| n | 18 | 4 | | | |
| Prefrail % | 60.3 | 53.4 | 61.4 | 27 | |
| n | 44 | 39 | | | |
| Frail % | 15.1 | 41.1 | 100 | 11 | |
| n | 11 | 30 | | | |

*Wilcoxon signed-rank test
**Mc Nemar Bowker test
p<0.05, significant

Changes were detected in 14.3% of 14 patients with mild-moderate pneumonia, 59% of 39 patients with severe pneumonia, and 95% of 20 patients followed in the ICU, and the changes were significant according to Chi. Square Test (p<0.001) (Table II).

**Table II.** Variability according to the clinical status of the patients

| Clinical status | | Variability | | Total | p |
|---|---|---|---|---|---|
| | | No Change | Change | | |
| Mild-Moderate | n | 12 | 2 | 14 | <0.001 |
| | % | 85.7 | 14.3 | 100.0 | |
| Severe | n | 16 | 23 | 39 | |
| | % | 41.0 | 59.0 | 100.0 | |
| Critical | n | 1 | 19 | 20 | |
| | % | 5.0 | 95.0 | 100.0 | |
| Total | n | 29 | 44 | 73 | |
| | % | 39.7 | 60.3 | 100.0 | |

p<0.05, significant

An increase in frailty was observed in 75% of those who need nasal $O_2$, 93.3% of those who need high-flow oxygen therapy (HFOT), 100% of those who need noninvasive mechanical ventilation (NIMV), and 100% of those who need invasive mechanical ventilation (IMV). We found that the need for nasal $O_2$, HFOT, NIMV, and IMV, which are parameters indicating the severity of the disease, was higher in the group with increased frailty and this was statistically significant (p=0.001, p=0.003, p=0.003, p=0.060, respectively). Corticosteroids were used for treating 73.3% of the patients with change, and the need for corticosteroid was significantly higher in the group with change than in the group with no change (p=0.002). When the patients were evaluated according to sputum, deep tracheal aspirate, urine and blood culture results in terms of secondary bacterial and fungal infection; *Candida albicans, Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli* were detected in urine, *Staphylococcus epidermidis* in blood, *Candida albicans* in sputum. In terms of culture positivity, there was no difference between the groups with and without changes in the FRAIL index (p=0.246). The median of peripheral oxygen saturation values at hospital admission was 92 in the group with change and 95 in the group with no change (p<0.001), the median was 93 at hospital discharge in the group with the change, and 94 in the group with no change (p<0.049) (Table III).

**Table III.** Comparison of those with a change and those with no change in the FRAIL index

| | | Those with a change in the FRAIL index | | Those with no change in the FRAIL index | | p |
|---|---|---|---|---|---|---|
| **WBC (thousand/µL)** | | 8.28±1,25 | | 7.28±3.54 | | 0.143 |
| **Neutrophil (thousand/µL)** | | 6.47±3.56 | | 5.04±3.09 | | 0.038 |
| **NLR** | | 5.93±3,28 | | 4.31±3,20 | | 0.013 |
| **Lymphocyte (thousand/µL)** | | 1.19±0.61 | | 1.30±0.62 | | 0.423 |
| **BUN (mg/dL)** | | 26.95±18.49 | | 2.55±20.87 | | 0.910 |
| **Creatine (mg/dL)** | | 1.42±1.31 | | 1.40±0.84 | | 0.382 |
| **CRP (mg/L)** | | 87.08±65.07 | | 48.64±42.07 | | 0.010 |
| **PCT (µg/L)** | | 1.81±7.84 | | 0.72±2.75 | | 0.700 |
| **D-dimer (mg/L)** | | 2.03±2.91 | | 1.93±1.62 | | 0.607 |
| **LDH (U/L)** | | 270.06±106.05 | | 286.21±146.99 | | 0.714 |
| **HS Troponin-I (ng/L)** | | 152.09±670.03 | | 59.3±214.37 | | 0.631 |
| **CK-MB (µg/L)** | | 2.03±3.52 | | 2.36±3.41 | | 0.664 |
| **Ferritin (µg/L)** | | 492.49±648.55 | | 317.87±387.91 | | 0.248 |
| **Admission $SpO_{2*}$**<br>**mean**<br>**median(min-max)** | | 90.59±4.46<br>92 (90–98) | | 94.15±2.40<br>95 (75–97) | | 0.001 |
| **Discharge $SpO_{2*}$**<br>**mean**<br>**median(min-max)** | | 92.55±2.78<br>93(85–97) | | 94.18±2.04<br>94(89–98) | | 0.049 |
| | | n | % | n | % | |
| **Nasal-$O_2$ requirement** | Yes | 39 | 75 | 13 | 25 | 0.001 |
| | No | 5 | 23.8 | 16 | 72.6 | |
| **HFOT requirement** | Yes | 14 | 93.3 | 1 | 6.7 | 0.003 |
| | No | 30 | 51.7 | 28 | 48.3 | |
| **NIMV requirement** | Yes | 11 | 100 | 0 | 0 | 0.003 |
| | No | 33 | 53.2 | 29 | 46.8 | |
| **IMV requirement** | Yes | 5 | 100 | 0 | 0 | 0.060 |
| | No | 39 | 57.4 | 29 | 42.6 | |

**Table III.** ( Countinued) Comparison of those with a change and those with no change in the FRAIL index

| | | n | % | n | % | |
|---|---|---|---|---|---|---|
| **Steroid requirement** | Yes | 34 | 73.9 | 12 | 26.1 | 0.002 |
| | No | 10 | 37 | 17 | 63 | |
| **Bacterial infection** | Yes | 11 | 73.3 | 4 | 26.7 | 0.246 |
| | No | 33 | 56.9 | 25 | 43.1 | |

¿hi-Square test *Mann–Whitney U test O2: Oxygen, HFOT: High Flow Oxygen Therapy, NIMV: Noninvasive Mechanical Ventilation, IMV: Invasive Mechanical Ventilation, SpO2: Oxygen Saturation, WBC: leukocytes, NLR: neutrophil/lymphocyte ratio, BUN: blood urea nitrogen, CRP: C-reactive protein, PCT: procalcitonin, LDH: lactate dehydrogenase, HS: high sensitive, CK-MB: creatine kinase-myocardial band p<0.05, significant

The mean length of hospital stay was 8.37±4.30 days and the median length of hospital stay was 6.5 (min:4-max:19) days in the group with no change, and the mean length of hospital stay was 8.60±4.88 days and the median length of hospital stay was 7 days (min:4-max:25) in the group with the change, and the difference was not statistically significant (p=0.921). The mean ICU length of stay was 8.0±4.20 days and the median ICU length of stay was 8 (min:8-max:8) days in the group with no change, and the mean ICU length of stay was 7.05±4.06 days and the median ICU length of stay was 7 (min:2-max:13) days in the group with the change, and the difference was not statistically significant (p=0.80).

It was observed that neutrophil counts and neutrophil-lymphocyte ratio (NLR) of patients with a change in the FRAIL index were higher than those without changes in frailty (p=0.038 and p=0.013, respectively). We observed that the neutrophil count and high NLR increased frailty in the elderly with COVID-19 infection. The mean CRP value in patients with a change in the FRAIL index was 87.08±65.07 and it was shown that high CRP played a role in frailty (p= 0.010) (Table III). The mean D-Dimer value at admission was 1.98 ±2.47 in all COVID-19 patients and was high for all age groups. There was no difference in mean D-Dimer values between groups with and without changes in the frail index (p=0.607).

According to Kruskal-Wallis test, there was no significant difference between clinical states in terms of FRAIL 1 score (p=0.329) (Table IV). There was a significant difference between clinical states in terms of FRAIL 2 score (p<0.001). Post hoc testing was performed to identify the group or groups that caused the difference, and it was determined that the situation causing the difference was the clinical situation (Figure 1). The difference between mild and moderate pneumonia was p=0.002, the difference between mild and severe pneumonia was p<0.001, the difference between moderate and severe pneumonia was p=0.008, and the difference between the three groups was p<0.001.

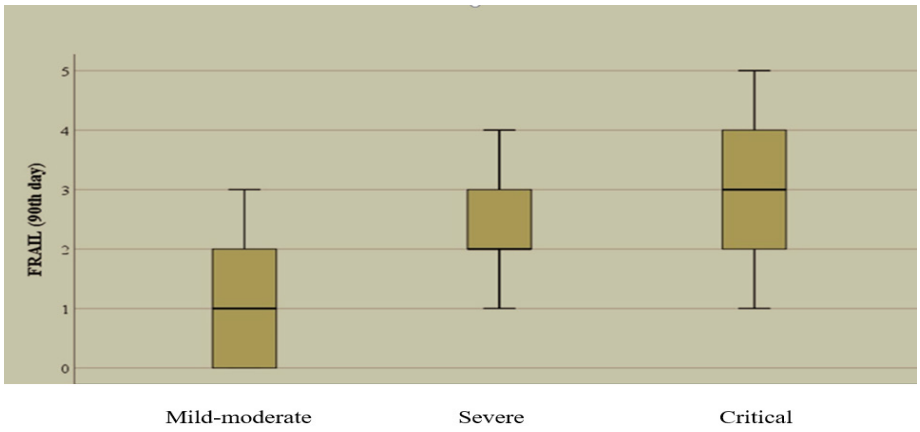


**Figure 1.** FRAIL scores according to the clinical status of the patients after discharge (ICU: Intensive care unit)

**Table IV.** Frailty degree of patients according to their clinical status

| | | Mild-Moderate | | Severe | | Critical | | p |
|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | |
| **Admission frailty** | Normal | 6 | 8.2 | 7 | 9.6 | 5 | 6.8 | 0.329 |
| | Prefrail | 7 | 9.6 | 24 | 32.9 | 13 | 17.8 | |
| | Frail | 1 | 1.4 | 8 | 11 | 2 | 2.7 | |
| **Frailty 90-day postdischarge** | Normal | 4 | 5.4 | 0 | 0 | 0 | 0 | 0.001 |
| | Prefrail | 9 | 12.3 | 23 | 31.5 | 7 | 9.5 | |
| | Frail | 1 | 1.3 | 16 | 21.9 | 13 | 17.8 | |

p<0.05. significant

ICU: Intensive care unit

## DISCUSSION

Frailty has been associated with a higher risk of developing serious illness among elderly COVID-19 patients (12). In our study, we found an increase in the mean FRAIL score in all patients, change in the FRAIL score, and an increase in the percentage of frail patients after COVID-19. This finding showed that COVID-19 is a cause of frailty or a condition that increases existing frailty.

COVID-19 has left a global burden for long-term care, with its short- and long-term effects. The medium and long-term effects of COVID-19 on fatigue, resistance, aerobic exercises, number of illnesses and weight loss in elderly patients are not fully known. In previous studies, it has been shown that hospitalizations due to pneumonia cause a significant physical deterioration in elderly patients (13). Viral infections may also exacerbate the impairment in age-related immunological responses through overstimulation of inflammatory pathway activity. Additionally, viral infections cause the overexpression of oxidative stress. Therefore, chronic viral infections may accelerate aging. Coronaviruses use host factors for replication; these factors are also associated with mechanisms associated with aging (14). It has been shown that chronic Cytomegalovirus (CMV) infection is associated with frailty and inflammation increases this effect (15). The increased immune response and inflammation that occur in acute situations may continue for a long time after the removal of the agent. It has been shown that persistent systemic inflammation, in which the systemic proinflammatory state lasts for at least 3 months in patients who are followed up in the ICU due to viral infection and recover, is associated with poorer physical recovery (16). It has been suggested that the increased inflammatory state plays a key role in the pathogenesis of frailty, directly or indirectly, through pathophysiological processes. Serum levels of white blood cell, neutrophil, monocyte counts and proinflammatory cytokines IL-6 and CRP increase in frail older adults (17,18). IL-6, which has been shown to be elevated in COVID-19, is a transcription factor and signal converter that affects adaptive immunity, skeletal muscle functions, appetite, and cognition (19,20). In our study, it was observed that high neutrophil count, high NLR and increase in CRP, whose prognostic values in COVID-19 were noted in the elderly with COVID-19 infection (20,21), are factors that increase frailty.

It is known that D-Dimer levels are high in COVID-19 (20). It has been shown in previous studies that there is a proven relationship between frailty and coagulation markers (factor VIII, fibrinogen and D-dimer) (22). In our study, it was observed that the mean D-Dimer level was higher than normal in the COVID-19 patients included in the study. We could not show that it was higher in the group with increased frailty. We think that our results may not have reflected this relationship, as blood samples collected at admission were used for D-dimer levels in our study.

Chronically elevated cortisol levels are implicated in the pathogenesis of many age-related psychiatric and somatic disorders, including depression, memory deficits, cognitive impairment, obesity, cardiovascular

disease, diabetes, and osteoporosis (23). Additionally, an increase in inflammatory burden and the cytokines known to increase during COVID-19, such as IL-6, IL-1, and TNF-α (24), are well-known activators of the pituitary-adrenal axis, and stimulation of this axis causes high cortisol levels. In our study, it was observed that more corticosteroids were used during and after the disease in the group with increased frailty. In our study, the mean age of the patients was 77.48±7.68 years. Therefore, we think that age may be a factor in the increase in frailty. However, our patient groups were different in terms of their pre-and post-COVID-19 frailty, with the frailty being greater in post-COVID-19. Therefore, we believe that the increase in frailty was related to the systemic corticosteroids used during the infection and the age factor.

In a multicenter study, it was reported that 40% of ICU survivors had increased frailty within one year, while disability-related frailty developed in critically ill survivors (25). In our study, we found that there was a higher increase in frailty (95%) of patients hospitalized in the ICU, and that frailty was higher in patients who needed respiratory support therapy (nasal $O_2$, HFOT, NIMV, and IMV). Peripheral oxygen saturation values measured at hospital admission and discharge were lower in the group with increased frailty. It is known that frailty and respiratory impairment is associated (26).

It has also been shown in previous studies that there is an increase in frailty in elderly patients who survive after COVID-19 (27,28). In particular, dyspnea has been reported to be an important risk factor for post-COVID-19 frailty (29).

Apart from hospitalization due to viral pneumonia, systemic inflammation, increased coagulation, systemic corticosteroid use, intensive care admission, and advanced age, sarcopenia may also have contributed to the increase in frailty in our patients. Sarcopenia is defined as the loss of muscle mass and strength that can occur rapidly after the age of 50, and chronic inflammation also contributes to sarcopeniaing (8). Malnutrition plays a key role in the pathogenesis of frailty and sarcopenia. Elderly patients with COVID-19 often show low food intake on hospitalization. This contributes to sarcopeniaing and frailty (24). Therefore, the nutrition of elderly patients with COVID-19 is of great importance in preventing frailty. We believe that it may be important to designate specific nutrition programs to address this.

COVID-19 is a disease that caused frailty due to systemic inflammation. After COVID-19, elderly patients may exhibit temporary or permanent neurological, cardiovascular and musculoskeletal disorders. This is a reversible condition (25). For this reason, early recognition of frailty with frailty assessment, and prevention or reduction of frailty through interventions for frailty syndrome must be ensured.

### Limitations of the Study

Study data in terms of vaccination status are lacking, as a group of patients included in the study were included in the study before their COVID-19 vaccinations.

## CONCLUSION

Our study showed that frailty increases after COVID-19. For this reason, it is important to assess frailty, especially in elderly patients, during and after COVID-19, and to start anti-inflammatory therapy, functional, nutritional, neuromotor, respiratory and cardiac rehabilitation at the earliest period, and novel studies are needed on this subject.

## ACKNOWLEDGEMENT

### Conflict of Interest

The authors declare that they have no conflict of interest.

### Financial Support

This study was funded by the Başkent University Research Fund (Project no: KA22/167).

### Ethical Declaration

This study was approved by the Başkent University Medical and Health Sciences Research Board (approval number KA22/167, 22/72 and date March 30, 2020).

### Authors Contributions

Concept: GDY, Design: GDY, FS, MYÇ, Data collection and entry: SK, ÖÇ, MI, Analysis and interpretation: FS, GDY, MYÇ, Literature search: GDY, FS, ÖÇ, SK, MI, Writing: GDY, Critical review: GU, MŞA, MYÇ, GDY, FS.

## REFERENCES

1. Marengoni A, Zucchelli A, Vetrano DL, et al. Beyond Chronological Age: Frailty and Multimorbidity Predict In-Hospital Mortality in Patients With Coronavirus Disease 2019. J Gerontol A Biol Sci Med Sci. 2021;76(3):38-15.

2. Fulop T, Witkowski JM, Olivieri F, et al. The integration of inflammaging in age-related diseases. Semin. Immunol. 2018; 40:17–35.

3. PS, Madhavan S, Pandurangan V. Prevalence, Pattern and Functional Outcome of Post COVID-19 Syndrome in Older Adults. Cureus. 2021;13(8):17189.

4. Cabrera Martimbianco AL, Pacheco RL, Bagattini ÂM, et al. Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review. Int J Clin Pract. 2021;75(10):14357.

5. Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents. 2020;34(2):327-331.

6. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet. 2013;381(9868):752-62.

7. Escourrou E, Herault M, Gdoura S, Stillmunkés A, Oustric S, Chicoulaa B. Becoming frail: a major turning point in patients' life course. Fam Pract. 2019 Mar 20;36(2):231-236. doi: 10.1093/fampra/cmy043.

8. Chen X, Mao G, Leng SX. Frailty syndrome: an overview. Clin Interv Aging. 2014;9:433-41.

9. Li H, Manwani B, Leng SX. Frailty, inflammation, and immunity. Aging Dis. 2011;2(6):466-73.

10. T.R. Ministry of Health, General Directorate of Public Health, COVID-19 (SARS-CoV-2 Infection) Adult Patient Treatment [e-book]. 2021. [Internet]. Available from: https://covid19.saglik.gov.tr/TR-66301/covid-19-rehberi.html. Accessed: 09.06.2022 (in Turkish)

11. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging. 2012;16(7):601-8.

12. Ma Y, Hou L, Yang X, et al. 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(1):274.

13. Martín-Salvador A, Torres-Sánchez I, Sáez-Roca G, et al. Age group analysis of psychological, physical and functional deterioration in patients hospitalized for pneumonia. Arch Bronconeumol. 2015;51(10):496-501.

14. Salimi S, Hamlyn JM. COVID-19 and Crosstalk With the Hallmarks of Aging. J Gerontol A Biol Sci Med Sci. 2020;75(9):34-41.

15. Schmaltz HN, Fried LP, Xue QL, et al. Chronic cytomegalovirus infection and inflammation are associated with prevalent frailty in community-dwelling older women. J Am Geriatr Soc. 2005;53(5):747-54.

16. Griffith DM, Lewis S, Rossi AG, et al; RECOVER Investigators. Systemic inflammation after critical illness: relationship with physical recovery and exploration of potential mechanisms. Thorax. 2016;71(9):820-9.

17. Langmann GA, Perera S, Ferchak MA, et al. Inflammatory Markers and Frailty in Long-Term Care Residents. J Am Geriatr Soc. 2017;65(8):1777-1783.

18. Leng SX, Xue QL, Tian J, et al. Associations of neutrophil and monocyte counts with frailty in community-dwelling disabled older women: results from the Women's Health and Aging Studies I. Exp Gerontol. 2009;44(8):511-6.

19. Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Annu Rev Med. 2000;51:245-70.

20. Henry BM, de Oliveira MHS, Benoit S, et al Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020;58(7):1021-1028.

21. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol. 2020;92(10):1733-1734.

22. Walston J, McBurnie MA, Newman A, et al. Cardiovascular Health Study. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch Intern Med. 2002;162(20):2333-41.

23. Varadhan R, Walston J, Cappola AR, et al. Higher levels and blunted diurnal variation of cortisol in frail older women. J Gerontol A Biol Sci Med Sci 2008; 63:190.

24. Chen B, Liu W, Li M, et al. Frailty Pathogenesis, Assessment, and Management in Older Adults With COVID-19. Front Med (Lausanne). 2021;8:694367.

25. Brummel NE, Girard TD, Pandharipande PP, et al. Prevalence and Course of Frailty in Survivors of Critical Illness. Crit Care Med. 2020;48(10):1419-1426.

26. Khan KT, Hemati K, Donovan AL. Geriatric Physiology and the Frailty Syndrome. Anesthesiol Clin. 2019;37(3):453-474.

27. Ferrara MC, Zarcone C, Tassistro E, et al; STORM Long-COVID Team. Frailty and long-COVID: is COVID-19 responsible for a transition in frailty status among older adults who survived hospitalization for COVID-19? Aging Clin Exp Res. 2023 Feb;35(2):455-461.

28. Covino M, Russo A, Salini S, et al. Long-Term Effects of Hospitalization for COVID-19 on Frailty and Quality of Life in Older Adults ≥80 Years. J Clin Med. 2022 Sep 29;11(19):5787.

29. Müller I, Mancinetti M, Renner A, et al. Frailty assessment for COVID-19 follow-up: a prospective cohort study. BMJ Open Respir Res. 2022 Apr;9(1):e001227.