Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2024;49(1):71-80
DOI: 10.17826/cumj.1382804

RESEARCH

Comparison of nailfold capillaroscopy findings in COVID-19 survivors with and without rheumatic disease: a case-control study

Romatizmal hastalığı olan ve olmayan COVID-19 hastalarında tırnak dibi kapilleroskopi bulgularının karşılaştırılması: vaka-kontrol çalışması

Hüseyin Kaplan[1], Gizem Cengiz[1], Senem Şaş[2], Hasan Kara[1]

[1] Erciyes University, Kayseri, Turkey
[2] Ağrı Training and Research Hospital, Ağrı, Turkey

Abstract

Purpose: The aim of this study was to evaluate the nailfold capillaroscopy (NFC) findings of patients with rheumatic disease and healthy controls (HCs) who survived coronavirus disease 2019 (COVID-19).

Materials and Methods: This study included patients with axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), and rheumatoid arthritis (RA) who recovered from COVID-19 and HCs. NFC was performed for all participants. NFC findings of the three groups [patients with COVID-19 (group 1), HCs with COVID-19 (group 2), and HCs without COVID-19 (group 3)] were compared.

Results: A total of 142 individuals (group 1, n = 42; group 2, n = 50; group 3, n = 50) were included in the study. Hospitalization and oxygen therapy were more common in group 1 than in group 2. The median time from a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive real-time polymerase chain reaction (RT-PCR) test to NFC was 10.3 (6.3–24.4) weeks in group 1 and 17.1 (6.1–44.9) weeks in group 2. All NFC findings did not differ among the groups except for capillary ramifications, which were higher in group 1 than in groups 2 and 3. Underlying rheumatic disease was the only predictor that was significantly associated with capillary ramifications.

Conclusion: The NFC findings of COVID-19 survivors with and without rheumatic disease were substantially similar to those of HCs who did not have COVID-19. Capillary ramifications may result from an underlying rheumatic disease in patients with axSpA, PsA, and RA.

Keywords: Capillaries, COVID-19, microcirculation, nailfold capillaroscopy

Öz

Amaç: Bu çalışmanın amacı **k**oronavirüs hastalığı 2019 (COVİD-19) sonrası hayatta kalan romatizmal hastalığı olan hastaların ve sağlıklı kontrollerin tırnak dibi kapilleroskopisi bulgularını değerlendirmektir.

Gereç ve Yöntem: Bu çalışmaya, COVİD-19'dan sonra iyileşen aksiyal spondiloartrit (akSpA), psoriatik artrit (PsA) ve romatoid artrit (RA) hastaları ve sağlıklı kontroller dâhil edildi. Tüm katılımcılara tırnak dibi kapilleroskopisi uygulandı. Üç grubun [COVID-19 geçiren romatizmal hastalar (grup 1), COVİD-19 geçiren sağlıklı kontroller (grup 2) ve COVİD-19 geçirmeyen sağlıklı kontroller (grup 3)] tırnak dibi kapilleroskopi bulguları karşılaştırıldı.

Bulgular: Çalışmaya grup 1'de 42, grup 2'de 50 ve grup 3'te 50 olmak üzere toplam 142 kişi dâhil edildi. Hastaneye yatış ve oksijen tedavisi oranları grup 1'de grup 2'ye göre daha sıktı. Pozitif bir şiddetli akut solunum sendromu koronavirüs-2 (SARS-CoV-2)-real-time polimeraz zincir reaksiyonu (RT-PCR) testinden tırnak dibi kapilleroskopisine kadar geçen ortalama süre grup 1'de 10,3 (6,3–24,4) hafta ve grup 2'de 17,1 (6,1–44,9) haftaydı. Grup 1'de grup 2 ve 3'e göre daha yüksek oranda olan kapiller dallanmalar dışında, tüm kapilleroskopik bulgular gruplar arasında farklılık göstermedi. Altta yatan romatizmal hastalık kapiller dallanmalarla anlamlı şekilde ilişkili olan tek prediktördü.

Sonuç: Romatizmal hastalığı olan ve olmayan, COVİD-19'dan sağ kurtulanların tırnak dibi kapilleroskopi bulguları, sağlıklı kontrollerle büyük ölçüde benzerdi. AkSpA, PsA ve RA hastalarında kapiller dallanmalar altta yatan romatizmal hastalığın bir sonucu olabilir.

Anahtar kelimeler: Kapiller damarlar, COVID-19, mikrosirkülasyon, tırnak dibi kapilleroskopi

Address for Correspondence: Hüseyin Kaplan, Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Erciyes University, Kayseri, Turkey E-mail: hkaplan_87@hotmail.com
Received: 30.10.2023 Accepted: 03.02.2024

INTRODUCTION

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in December 2019 and rapidly spread worldwide[1]. The disease has various clinical manifestations, ranging from flu-like symptoms to life-threatening complications that require hospitalization in an intensive care unit[2]. It can even result in the most devastating consequence, death[3].

The vascular endothelium has several physiological functions (barrier integrity, vascular tone control, tissue hemostasis, oxidative stress, inflammation, etc.) and forms the innermost layer of the blood vessels[4]. Angiotensin-converting enzyme 2, which is considered an important target of SARS-CoV-2, is highly expressed by endothelial cells in the lung, kidney, heart, and intestine. Based on histopathological evidence, COVID-19 is a microvascular and/or endothelial disease associated with endothelial dysfunction. Multiorgan involvement by SARS-CoV-2 is also considered to result from endothelial dysfunction. Moreover, some evidence shows that endothelial dysfunction, which is associated with poor prognosis in COVID-19, may be a therapeutic option[4,5].

Nailfold capillaroscopy (NFC) is commonly used in rheumatology to assess connective tissue diseases[2]. The importance of NFC in the differentiation of primary and secondary Raynaud's phenomenon is well known. Notably, as part of the 2013 American College of Rheumatology (ACR)/ European Alliance of Associations for Rheumatology (EULAR) systemic sclerosis classification criteria, abnormal nailbed capillaroscopy has taken a place. This application noninvasively examines nailfold capillaries parallel to the skin surface, thereby providing information on their microcirculation and morphology[2,6]. Since the COVID-19 pandemic began, several studies evaluating patients diagnosed with COVID-19 using NFC have found microvascular abnormalities[6,7]. However, the significance of the various NFC-detected changes in COVID-19 remains ambiguous[8].

The presence of a concomitant systemic rheumatic disease in individuals infected with SARS-CoV-2 was associated with an increased risk of death. For this increase,the type of rheumatic disease, disease duration, disease activity, and treatments are important[9]. Qualitative and quantitative capillaroscopic changes occur in patients with Raynaud's phenomenon secondary to connective tissue diseases[10]. Therefore, we planned to perform NFC to evaluate patients with spondyloarthritis (SpA) and rheumatoid arthritis (RA) who recovered after contracting COVID-19 and had no history of Raynaud's phenomenon. The main objective of this study was to examine the NFC findings in COVID-19 survivors who attended the rheumatology outpatient clinic for routine control of primary rheumatic diseases. We hypothesized that COVID-19 survivors with rheumatic disease would have microvascular findings different from those of healthy controls (HCs) who survived COVID-19, both of whom would have microvascular findings different from those of HCs who had not experienced COVID-19, on the basis of the possibility that patients with rheumatic disease have a more severe course of COVID-19. Therefore, patients with SpA and RA were assessed by NFC during their outpatient clinic visits and the NFC findings were compared with those of HCs with and without COVID-19.

MATERIALS AND METHODS

Study population

This cross-sectional study was conducted between September 2021 and March 2022 in the rheumatology outpatient clinic of Gevher Nesibe Hospital, Erciyes University. Patients aged 18–65 years who met one of the classification criteria of the Assessment of Spondyloarthritis International Society for axial spondyloarthritis (axSpA)[11], ClASsification criteria for Psoriatic ARthritis (CASPAR) for psoriatic arthritis (PsA)[12], and ACR/ EULAR classification criteria for RA[13] and who had a SARS-CoV-2-positive real-time polymerase chain reaction (RT-PCR) test were included in the study. Patients were not required to be followed up by us or at our center during the COVID-19 course. A history of COVID-19 confirmed by a SARS-CoV-2-positive RT-PCR result at any health center was sufficient for inclusion in the study. Demographic features (age, height, weight, and sex), smoking status, disease- and treatment-related data (disease types, disease duration, and medications), COVID-19 course, and COVID-19 vaccination data of all patients were recorded. According to previous studies[14], long COVID was defined as symptoms lasting >3 months

after the initial onset of symptoms. Specific conditions related to COVID-19, such as hyperinflammatory response, thrombotic events, and medications, were not evaluated because the information was based on patient declarations and we or our center did not follow up all patients during the COVID-19 course. To compare the data from the patients, HCs with and without SARS-CoV-2 RT-PCR positivity were also enrolled in the study. Three groups were created: patients with COVID-19 (group 1), HCs with COVID-19 (group 2), and HCs without COVID-19 (group 3). The exclusion criteria were as follows: age <18 or >65 years, presence of Raynaud's phenomenon, a diagnosis of other rheumatic disease (except for axSpA, PsA, and RA), digital trauma, smoking or caffeine consumption in the last 6 h, and incomplete COVID-19 and/or vaccination data. Participants were assessed by physicians involved in conducting this study that are specialists in rheumatology.

Power analysis (G*power 3.1 program) was used to determine the sample size of the study. Considering the statistical parameters in the reference study[15], 47 individuals must be recruited for each group, with a test power of 0.80, α of 0.05 first type error level, and β of 0.20 second type error level. The primary study sample included 50 participants in each group. However, after the initial analysis of the dataset, eight patients with rheumatic disease were dropped because of missing information on the scales and/or insufficient image quality. Thus, the study sample comprised 42 participants in group 1, 50 participants in group 2, and 50 participants in group 3.

This study was approved by the Erciyes University Clinical Research Ethics Committee on September 22, 2021 (Approval Number: 2021/615). The study also performed in accordance with the Declaration of Helsinki and written informed consent was obtained from all participants.

NFC examination

NFC was performed using a digital microscope [Dino-Lite Capillary Scope 500 Pro (MEDL4N5)] at 200x magnification. Before NFC, individuals were asked if they had used cigarettes and/or consumed caffeine in the previous 6 h and if they had a history of digital trauma in the previous 2 weeks. After the patients/HCs had been kept at 22 °C for 15 min, three images were taken for each finger, and 24 images were taken from the four fingers of the hands, except the thumbs, for each participant. The NFC examination was performed by Associate Professor Gizem Cengiz, a specialist in rheumatology and has a capillaroscopy certificate.

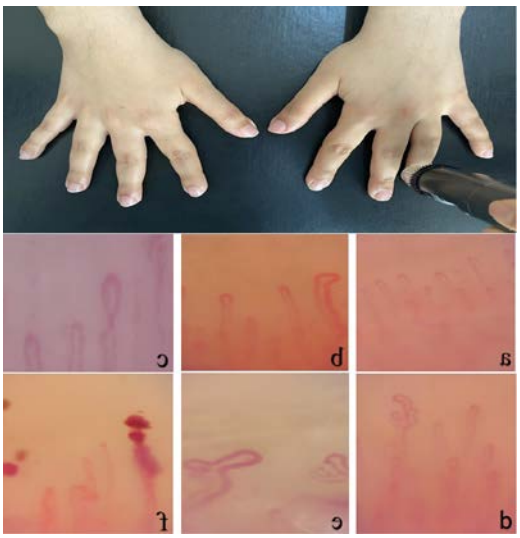

Figure 1. Methodology of NFC and various NFC findings. a) normal capillaries, b) enlarged capillaries, c) giant capillaries, d) capillary ramification, e) avascular area, and f) microhemorrhage.

As previously described[16-19], the images were analyzed for the following items:

a) Capillary density: capillaries per 1 mm in the distal row of the nailfold (<7 is considered "lower capillary density").

b) Microhemorrhages: red and/or black masses due to hemosiderin deposits.

c) Capillary loop diameter: <20 μm indicates normal capillaries; 20–50 μm indicates enlarged capillaries; and >50 μm indicates giant capillaries.

d) Capillary ramifications: branching or bushy capillaries originating from a single capillary.

e) Avascular areas: distance between two distal capillary loops >500 μm

Figure 1. Shows representative images of the NFC application and different capillary characteristics.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 23.0 (IBM Corp., Armonk, NY,

USA). The normality of the data distribution was evaluated using the Shapiro–Wilk test. Descriptive statistics for categorical variables are expressed as numbers and percentages, whereas those for numerical variables are expressed as the mean ± standard deviation or median (Q1–Q3).

For continuous variables containing participants' demographic characteristics and data obtained from the NFC examination, two independent group comparisons were made using the Mann–Whitney U test, and more than two independent group comparisons were made with the one-way analysis of variance (post hoc test: Tukey's honestly significant difference) or the Kruskal–Wallis test (post hoc test: Dunn), depending on the presence or absence of normality. Pearson's chi-square or Fisher's exact test was used to compare categorical data consisting of participants' demographic characteristics, COVID-19-related parameters, and/or components obtained during the NFC examination. Bonferroni correction was performed to adjust for multiple comparisons. Univariate logistic regression analysis was used to identify the predictor(s) associated with capillary ramifications. All p-values < 0.05 were considered statistically significant.

RESULTS

A total of 142 individuals (group 1, n = 42; group 2, n = 50; group 3, n = 50) were included in the study. No difference in age and sex was found among the groups ($p > 0.05$). Body mass index (BMI) was significantly higher in group 1 than in groups 2 and 3 ($p < 0.001$). Other demographic features of the three groups and the clinical and treatment-related data of the patients are shown in Table 1.

Table 1. Demographic features of the three groups and clinical and treatment-related data of the patients

Variable	Group 1 (n = 42)	Group 2 (n = 50)	Group 3 (n = 50)	*p*-value
Age, years	41.1 ± 9.8	40.9 ± 10.8	39.9 ± 13.4	0.427
Female, n (%)	31 (73.8)	36 (72)	31 (62)	0.404
BMI, kg/m²	31.3 ± 6.1[a]	26.5 ± 4.8[b]	24.9 ± 4.0[b]	<0.001*
Current smokers, yes, n (%)	9 (21.4)	7 (14.0)	7 (14.0)	0.548
Disease duration, years	9 (4–14)	-	-	-
Disease types, n (%)				
AxSpA	18 (42.9)	-	-	
PsA	6 (14.2)	-	-	-
RA	18 (42.9)	-	-	
Medications, n (%)				
Regular NSAIDs only	3 (7.1)	-	-	
csDMARD monotherapy	6 (14.3)	-	-	
csDMARD combination	5 (11.9)	-	-	-
bDMARD monotherapy	18 (42.9)	-	-	
bDMARD and csDMARD combination	10 (23.8)	-	-	

*p < 0.05

Continuous variables are expressed as mean ± SD or median (Q1–Q3) and categorical variables as n (%).

A statistically significant difference between the groups is indicated by different lowercase letters in one row.

axSpA, axial spondyloarthritis; bDMARD, biological disea-modifying antirheumatic drugs; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; NSAIDs, nonsteroidal anti-inflammatory drugs; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Asymptomatic recovery from COVID-19 was reported by a patient in group 1. Although all participants in group 2 experienced COVID-19 in quarantine at home, 7 (16.7%) patients in group 1 had a history of hospitalization. None of the patients in groups 1 and 2 were hospitalized in the intensive care unit. When the COVID-19 symptoms of the patients and those of the HCs were compared, only nausea/vomiting was significantly higher in group 1 than in group 2 ($p = 0.003$). The rates of both general vaccination and Sinovac subtype vaccination ($p = 0.878$ and $p = 0.155$, respectively) were similar in all three groups. However, the vaccination rates with BioNTech ($p = 0.010$) were significantly higher in group 2 than in group 1, and the vaccination rates with the combination of BioNTech and Sinovac ($p = 0.002$) were significantly higher in groups 2 and 3 than in group 1 (Table 2).

Table 2. COVID-19-related clinical and vaccination data of patients and healthy controls

Variable	Group 1 (n = 42)	Group 2 (n = 50)	Group 3 (n = 50)	*p*-value
Disease course of COVID-19, n (%)				
Asymptomatic	1 (2.3)[a]	0 (0)[a]	-	
Symptomatic (at home)	34 (81)[a]	50 (100)[b]	-	0.005*
Symptomatic (in hospital)	7 (16.7)[a]	0 (0)[b]	-	
Symptoms of COVID-19 infection, n (%)				
Fever	19 (40)	20 (45.2)	-	0.768
Arthralgia/myalgia	33 (78.6)	41 (83.7)	-	0.724
Headache	30 (71.4)	36 (72)	-	0.952
Loss of taste and/or smell	22 (52.4)	22 (44)	-	0.554
Cough	29 (69)	28 (56)	-	0.285
Throat ache	17 (40.5)	29 (58)	-	0.143
Dyspnea	14 (33.3)	10 (20)	-	0.225
Anorexia	15 (35.7)	16 (32)	-	0.878
Sweating	23 (54.8)	31 (62)	-	0.624
Chest pain	8 (19)	8 (16)	-	0.914
Nausea/vomiting	14 (33.3)[a]	4 (8)[b]	-	0.003*
Eye redness	13 (31)	14 (28)	-	0.936
Diarrhea	3 (7.1)	8 (16)	-	0.218
Stuffy nose	15 (35.7)	23 (46)	-	0.432
Stomachache	8 (19)	10 (20)	-	0.909
Long COVID, yes, n (%)	11 (26.2)	7 (14)	-	0.228
COVID-19 pneumonia, yes, n (%)	5 (11.9)	6 (12)	-	0.989
Oxygen therapy, yes, n (%)	7 (16.7)[a]	0 (0)[b]	-	0.003*
Vaccination, yes, n (%)	39 (92.9)	46 (92)	45 (90)	0.878
Vaccine types, n (%)				
Sinovac	23 (54.8)	32 (64)	37 (74)	0.155
BioNTech	28 (66.7)[a]	45 (90)[b]	43 (86)[a, b]	0.010*
Sinovac + BioNTech	11 (26.2)[a]	28 (56)[b]	30 (60)[b]	0.002*

*p < 0.05; A statistically significant difference between the groups is indicated by different lowercase letters in one row.; Continuous variables are expressed as mean ± SD or median (Q1–Q3) and categorical variables as n (%).; COVID-19, coronavirus disease 2019.

Table 3. NFC findings in the patients and healthy controls

Variable	Group 1 (n = 42)	Group 2 (n = 50)	Group 3 (n = 50)	*p*-value
Time from the SARS-CoV-2-positive RT-PCR test to NFC, weeks	10.3 (6.3–24.4)	17.1 (6.1–44.9)	-	0.535
Capillary density, number/linear 1 mm	8 (8–9)	8 (8–9.25)	9 (8–10)	0.490
Loop diameter, μm	16.2 (14.7–21.3)	15.8 (13.5–17.3)	15.7 (12.9–17.4)	0.219
Microhemorrhages, yes, n (%)	5 (11.9)	1 (2)	3 (6)	0.151
Enlarged capillaries, yes, n(%)	13 (31)	12 (24)	9 (18)	0.349
Giant capillaries, yes, n(%)	0 (0)	0 (0)	1 (2)	0.396
Capillary ramifications, yes, n(%)	9 (21.4)[a]	3 (6)[b]	3 (6)[b]	0.024*
Avascular areas, yes, n(%)	0 (0)	1 (2)	0 (0)	0.396

*p < 0.05; Continuous variables are expressed as median (Q1–Q3) and categorical variables as n (%).; A statistically significant difference between the groups is indicated by different lowercase letters in one row.; NFC, nailfold capillaroscopy; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

The median time from a SARS-CoV-2-positive RT-PCR test to NFC was 10.3 (6.3–24.4) weeks in group 1 and 17.1 (6.1–44.9) weeks in group 2 (p = 0.535). All capillaroscopic findings did not differ among the groups (for all; p > 0.05), except for capillary ramifications (p = 0.024), which were higher in group 1 than in group 2 and 3 (Table 3). We also did not find any significant differences in the NFC findings

among the groups according to the COVID-19 pneumonia status (for all; p > 0.05) (Table 4). Candidate predictors that were estimated to be associated with capillary ramifications were evaluated using the logistic regression model. In the univariate logistic regression analyses, the underlying rheumatic disease was the only predictor that was significantly associated with capillary ramifications [odds ratio (OR), 4.273; 95% confidence interval (CI), 1.075–16.990, p = 0.039] (Table 5).

Table 4. Comparison of NFC findings between the groups according to the COVID-19 pneumonia status

Variable	COVID-19 without pneumonia (n = 81)	COVID-19 with pneumonia (n = 11)	*p*-value
Time from the SARS-CoV-2-positive RT-PCR test to NFC, weeks	12.1 (6.2–33.4)	19.6 (9–54.3)	0.304
Capillary density, number/linear 1 mm	8 (8–9)	9 (8–9)	0.230
Loop diameter, µm	16.1 (14.2–19.1)	14.8 (13.3–16.8)	0.119
Microhemorrhages, yes, n (%)	5 (6.2)	1 (9.1)	0.545
Enlarged capillaries, yes, n(%)	24 (29.6)	1 (9.1)	0.349
Giant capillaries, yes, n(%)	0 (0)	0 (0)	-
Capillary ramifications, yes, n(%)	9 (11.1)	3 (27.3)	0.153
Avascular areas, yes, n(%)	1 (1.2)	0 (0)	0.880

Continuous variables are expressed as median (Q1–Q3) and categorical variables as n (%).; COVID-19, coronavirus disease 2019; NFC, nailfold capillaroscopy; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 5. Identification of potential predictor(s) associated with capillary ramifications

Variable	OR	95% CI		*p*
Age	0.988	0.941	1.037	0.620
Sex (Ref. Female)	0.524	0.140	1.960	0.337
BMI	1.046	0.957	1.144	0.323
Disease duration	0.929	0.820	1.053	0.252
Smoking (Ref. No)	0.341	0.043	2.729	0.311
Number of comorbidities	1.255	0.604	2.609	0.543
HT (Ref. No)	0.464	0.049	4.362	0.502
DM (Ref. No)	9.143	0.724	115.459	0.087
CHD (Ref. No)	4.000	0.225	71.118	0.345
Thyroid disorders (Ref. No)	1.800	0.255	10.045	0.616
COPD (Ref. No)	1.208	0.110	13.249	0.877
Groups (Ref. Group 3)				
Group 2	1.000	0.192	5.210	1.000
Group 1	4.273	1.075	16.990	0.039*
Course of COVID-19 (Ref. Followed at home)				
Followed in the hospital	3.000	0.512	17.570	0.223
Long COVID (Ref. No)	1.444	0.348	5.989	0.612
COVID-19 pneumonia (Ref. No)	3.042	0.681	13.587	0.145
Oxygen therapy (Ref. No)	3.040	0.519	17.801	0.218
Vaccine types (Ref. Unvaccinated)				
Sinovac	0.585	0.199	1.721	0.330
BioNTech	3.431	0.431	27.339	0.244
Sinovac + BioNTech	0.917	0.314	2.681	0.875
Time from the SARS-CoV-2-positive RT-PCR test to NFC	0.991	0.961	1.023	0.582

*p < 0.05; BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; HT, hypertension; NFC, nailfold capillaroscopy; OR, odds ratio; Ref, reference; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

DISCUSSION

This study evaluated the NFC findings of patients with rheumatic disease (axSpA, PsA, and RA) and HCs who survived COVID-19 and compared their results with those of HCs who had no history of COVID-19. Differences in microvascular findings were noted among the three groups. However, no significant differences were found in the capillary evaluation results among the groups, except for a higher rate of capillary ramifications in the rheumatic group. Our results also showed that capillary ramifications were caused by underlying rheumatic diseases. To the best of our knowledge, this is the first study to compare patients with rheumatic diseases and HCs in terms of NFC findings in the period following COVID-19.

Because endothelial dysfunction is an important pathophysiological factor in COVID-19, attempts have been made to detect capillary changes due to COVID-19 using NFC, which can assess microcirculation at the capillary level[2]. Navarro et al.[20] highlighted the changes in nail blood vessels caused by COVID-19 in dermoscopy in 12 patients. Sulli et al.[21] examined videocapillaroscopic microvascular changes in adult COVID-19 survivors and reported that no specific pattern is associated with COVID-19; however, capillary loss may be a prominent distinguishing feature. Similarly, Karahan et al.[19] found that patients with COVID-19 had a lower capillary density than HCs, and those who died of COVID-19 had a lower capillary density than those who survived. In addition, the systemic vascular effects of the virus are evidenced by changes such as capillary thrombosis, microhemorrhages, and angiogenesis detected during COVID-19, which disappeared in controls 3 months after discharge[22]. In the present study, the NFC findings did not differ among the groups, except for capillary ramifications. Because patients with rheumatic disease required hospital admission and oxygen therapy more often than HCs, the capillary ramifications found more frequently in these patients may be attributed to hypoxia, hypercoagulability, and hyperinflammation, as stated by Çakmak et al.[6] in patients with multisystem inflammatory syndrome in children. Nausea/vomiting, which was detected at a higher rate in group 1 (patients with rheumatic disease) and has been associated with more severe COVID-19 in previous studies[23], may also provide indirect evidence to support this finding. In addition, underlying rheumatic diseases may have caused ramifications, as shown in our logistic regression analyses. Because this study was conducted in patients with rheumatic disease whose COVID-19 symptoms had completely resolved, even if not before COVID-19, microvascular abnormalities may occur later depending on the severity of COVID-19, as Natalello et al.[2] mentioned. We were unable to detect a reduction in capillary density, which appears to be a common finding in previous studies[19, 21] that have evaluated people with COVID-19. The finding that both our patients and HCs had a relatively mild COVID-19 may be a factor. Although the aforementioned studies mostly evaluated people who were followed up in intensive care units, and/or had even died, none of the patients in our study had a history of intensive care unit admission.

In systemic rheumatic diseases, the immune dysfunction inherent in the disease and the disease-modifying antirheumatic drugs (DMARDs) used in its treatment may affect the course of COVID-19[24]. Comorbidities, which tend to increase in rheumatic diseases, correlate with severe COVID-19[25]. On the contrary, with the onset of the COVID-19 pandemic, a concern was that the biological treatments used for rheumatic diseases could lead to a severe COVID-19 because of a reduction in immunity[26]. However, in the cytokine storm associated with the pathological immune response in some individuals with COVID-19, biological DMARDs [e.g., interleukin (IL)-6 inhibitors, IL-1 inhibitors, janus kinase inhibitors, and tumor necrosis factor inhibitors] have subsequently become important treatment options [27]. In this study, the rate of COVID-19-related hospitalization was higher in patients with rheumatic diseases than in HCs. This study, which was started approximately 17 months after the declaration of the COVID-19 pandemic, consisted of individuals who, by chance, did not need intensive care unit admission. The better COVID-19 outcomes of these patients may be related to the following findings: 1) some of the study volunteers contracted COVID-19 after vaccination; 2) age, which is a risk factor for severe COVID-19[26], was relatively low in all the groups; and 3) 92.9% of patients with rheumatic disease use DMARDs, which are considered to have a beneficial effect[27]. Sulli et al.[21] found that even in people with severe COVID-19, antivirals and biologics (such as IL-6 receptor antagonists) have a protective effect on capillary density. As the time from a SARS-CoV-2-positive RT-PCR test to NFC exceeded 10 weeks in both patients and HCs, the capillaroscopic changes shown to return three months after COVID-19 by

Rosei et al.[22] may be another factor contributing to the similarity of capillary findings among the study groups. Further studies are needed to determine the conditions under which COVID-19 induces capillary changes or whether the resulting changes are reduced.

Obesity is associated with microvascular dysfunction[28]. Maranhão et al.[29] demonstrated microvascular hemodynamic changes in patients with obesity using dynamic nailfold videocapillaroscopy. In contrast, microvascular dysfunction in patients with obesity contributes to the development of obesity-associated microangiopathy, hypertension, and insulin resistance[30]. In the present study, BMI was higher in patients with rheumatic disease, where capillary ramifications were significantly higher, than in the other HC group. However, BMI was not a predictor associated with ramifications according to logistic regression analysis. Unfortunately, microvascular hemodynamic measurements were not examined in this study because of the lack of measurement capability of our device.

Another important finding of this study was the significant differences in the COVID-19 vaccine types between the rheumatic and HC groups. This difference had no significant effect on the capillary ramifications in the regression analysis. The different distribution rates of the vaccine subtypes among the study groups might have been influenced by factors such as differences in the dates of arrival of the vaccines in our country according to their types and the change in the time of access to the vaccines, depending on the population at risk[31].

The strength of this study is that it compares NFC findings between COVID-19 survivors (patients with rheumatic disease and HCs) and HCs without a history of COVID-19. In addition, this study contributes to the literature by including NFC data collected at later time points after recovery from COVID-19. In addition to these, individuals with connective tissue diseases and those with Raynaud's phenomenon were not included. Conversely, the most important limitation of the study is the lack of prepandemic images for comparison with current NFC findings. Second, patients with rheumatic disease without COVID-19 were not included as a control group. In addition, only PsA patients with psoriatic spondylitis were included in the study. Distal interphalangeal predominant arthritis, symmetric polyarthritis, and asymmetric oligoarthritis subtypes in which characteristic NFC changes are more commonly reported[32], and arthritis mutilans were excluded. Therefore, our results do not include all patients with PsA, and the results might be different if all PsA subtypes were included. The time after COVID-19 diagnosis did not statistically significantly differ between the groups; however, the interval was quite long, and patients with an elapsed time of up to 44 weeks were included.

In conclusion, this study showed that the NFC findings of COVID-19 survivors with and without rheumatic disease were substantially similar to those of HCs who never had COVID-19. Capillary ramifications may be a result of underlying rheumatic disease in patients with axSpA, PsA, and RA. Further studies are needed to determine the mechanisms of capillaroscopic changes suggested to be caused by COVID-19 and whether they are reversible. Investigations into how NFC abnormalities, which have been linked to both COVID-19 and COVID-19 severity in previous studies, change in the subsequent period may make our results more meaningful. One way to do so might be to repeat the NFC examination at certain time points for people who had NFC images taken during active COVID-19. In addition, more advanced devices that can measure microvascular hemodynamic changes may provide better results.

Author Contributions: Concept/Design : HK, GC, SŞ; Data acquisition: HK, GC, SŞ, HK; Data analysis and interpretation: HK, GC; Drafting manuscript: HK, GC, SŞ, HK; Critical revision of manuscript: GC, SŞ; Final approval and accountability: HK, GC, SŞ, HK; Technical or material support: -; Supervision: GC, HK; Securing funding (if available): n/a.
Ethical Approval: Ethical approval was obtained from the Erciyes University Faculty of Medicine Clinical Research Ethics Committee with the decision dated 22.09.2021 and numbered 2021/615.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

REFERENCES

1. Ambrosino P, Calcaterra I, Molino A, Moretta P, Lupoli R, Spedicato GA et al. Persistent endothelial dysfunction in post-acute COVID-19 syndrome: a case-control study. Biomedicines. 2021;9:957.
2. Natalello G, De Luca G, Gigante L, Campochiaro C, De Lorenzis E, Verardi L et al. Nailfold capillaroscopy findings in patients with coronavirus disease 2019: Broadening the spectrum of COVID-19 microvascular involvement. Microvasc Res. 2021;133:104071.
3. Warren AM, Zolfaghari K, Fresnedo M, Bennett M, Pogue J, Waddimba A et al. Anxiety sensitivity, COVID-19 fear, and mental health: results from a

United States population sample. Cogn Behav Ther. 2021;50:204-16.
4. Xu S-w, Ilyas I, Weng J-p. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. Acta Pharmacol Sin. 2023;44:695-709.
5. Liu N, Long H, Sun J, Li H, He Y, Wang Q et al. New laboratory evidence for the association between endothelial dysfunction and COVID-19 disease progression. J Med Virol. 2022;94:3112-20.
6. Çakmak F, Demirbuga A, Demirkol D, Gümüş S, Torun SH, Kayaalp GK et al. Nailfold capillaroscopy: a sensitive method for evaluating microvascular involvement in children with SARS-CoV-2 infection. Microvasc Res. 2021;138:104196.
7. Hadeler E, Morrison B, Tosti A. A review of nail findings associated with COVID-19 infection. J Eur Acad Dermatol Venereol. 2021;35:e699-e709.
8. Mondini L, Confalonieri P, Pozzan R, Ruggero L, Trotta L, Lerda S et al. Microvascular alteration in COVID-19 documented by nailfold capillaroscopy. Diagnostics (Basel). 2023;13:1905.
9. Fragoulis GE, Bournia V-K, Sfikakis PP. Different systemic rheumatic diseases as risk factors for COVID-19-related mortality. Clin Rheumatol. 2022;41:1919-23.
10. Sundaray S, Mishra S, Dash SC, Sundaray NK. Nailfold videocapillaroscopy in connective tissue diseases with Raynaud's phenomenon in an Indian population. Rambam Maimonides Med J. 2022;13:e0003.
11. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis. 2009;68:ii1-44.
12. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54:2665-73.
13. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham III CO et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-81.
14. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis (Lond). 2021;53:737-54.
15. Graceffa D, Amorosi B, Maiani E, Bonifati C, Chimenti MS, Perricone R, Di Carlo A. Capillaroscopy in psoriatic and rheumatoid arthritis: a useful tool for differential diagnosis. Arthritis. 2013;2013:957480.
16. Smith V, Herrick AL, Ingegnoli F, Damjanov N, De Angelis R, Denton CP et al. Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. Autoimmun Rev. 2020;19:102458.
17. Sulli A, Secchi ME, Pizzorni C, Cutolo M. Scoring the nailfold microvascular changes during the capillaroscopic analysis in systemic sclerosis patients. Ann Rheum Dis. 2008;67:885-7.
18. Manfredi A, Sebastiani M, Cassone G, Pipitone N, Giuggioli D, Colaci M et al. Nailfold capillaroscopic changes in dermatomyositis and polymyositis. Clin Rheumatol. 2015;34:279-84.
19. Karahan S, Aydin K, Cetinkaya A, Sirakaya HA. Nailfold videocapillaroscopy in patients with COVID-19-associated pneumonia in intensive care units. J Coll Physicians Surg Pak. 2022;32:455-60.
20. Navarro L, Andina D, Noguera-Morel L, Hernández-Martín A, Colmenero I, Torrelo A. Dermoscopy features of COVID-19-related chilblains in children and adolescents. J Eur Acad Dermatol Venereol. 2020;34:e762-64.
21. Sulli A, Gotelli E, Bica PF, Schiavetti I, Pizzorni C, Aloè T et al. Detailed videocapillaroscopic microvascular changes detectable in adult COVID-19 survivors. Microvasc Res. 2022;142:104361.
22. Rosei CA, Gaggero A, Famà F, Malerba P, Chiarini G, Nardin M et al. Skin capillary alterations in patients with acute SarsCoV2 infection. J Hypertens. 2022;40:2385-93.
23. Ebrahim Nakhli R, Shanker A, Sarosiek I, Boschman J, Espino K, Sigaroodi S et al. Gastrointestinal symptoms and the severity of COVID-19: Disorders of gut–brain interaction are an outcome. Neurogastroenterol Motil. 2022;34:e14368.
24. Sachdeva S, Manaktala P, Malik FA, Gupta U, Desai R. COVID-19 in patients with rheumatic diseases: Is there a need to worry?. J Clin Rheumatol. 2022;28:e401-6.
25. FAI²R/SFR/SNFMI/SOFREMIP/CRI/IMIDIATE consortium and contributors. Severity of COVID-19 and survival in patients with rheumatic and inflammatory diseases: data from the French RMD COVID-19 cohort of 694 patients. Ann Rheum Dis. 2021;80:527-38.
26. Fredi M, Cavazzana I, Moschetti L, Andreoli L, Franceschini F; Brescia Rheumatology COVID-19 Study Group. COVID-19 in patients with rheumatic diseases in northern Italy: a single-centre observational and case–control study. Lancet Rheumatol. 2020;2:e549-56.
27. Santos CS, Férnandez XC, Morales CM, Álvarez ED, Castro CÁ, Robles AL et al. Biological agents for rheumatic diseases in the outbreak of COVID-19: friend or foe?. RMD Open. 2021;7:e001439.
28. Kraemer-Aguiar L, Maranhao P, Sicuro F, Bouskela E. Microvascular dysfunction: a direct link among BMI, waist circumference and glucose homeostasis in young overweight/obese normoglycemic women?. Int J Obes (Lond). 2010;34:111-7.

29. Maranhão PA, de Souza MdGC, Kraemer-Aguiar LG, Bouskela E. Dynamic nailfold videocapillaroscopy may be used for early detection of microvascular dysfunction in obesity. Microvasc Res. 2016;106:31-5.
30. De Jongh RT, Serné EH, IJzerman RG, De Vries G, Stehouwer CD. Impaired microvascular function in obesity: implications for obesity-associated microangiopathy, hypertension, and insulin resistance. Circulation. 2004;109:2529-35.
31. Cengiz B, Sayılır MÜ, Zengin NY, Küçük ÖN, Soylu AR. Does the COVID-19 vaccination rate change according to the education and income: a study on vaccination rates in cities of Turkey between 2021-September and 2022-February. Vaccines (Basel). 2022;10:1933.
32. Lambova SN, Müller-Ladner U. Capillaroscopic pattern in inflammatory arthritis. Microvasc Res. 2012;83:318-22.