Nailfold Videocapillaroscopy in Patients with COVID-19-associated Pneumonia in Intensive Care Units

Samet Karahan[1], Kaniye Aydin[2], Ali Cetinkaya[3] and Hatice Aslan Sirakaya[3]

[1]*Department of Internal Medicine, Division of Rheumatology, Kayseri City Education and Research Hospital, Kayseri, Turkey*
[2]*Department of Internal Medicine, Intensive Care Unit, Kayseri City Education and Research Hospital, Kayseri, Turkey*
[3]*Department of Internal Medicine, Kayseri City Education and Research Hospital, Kayseri, Turkey*

ABSTRACT

Objective: To compare patients with COVID-19 in intensive care units (ICUs) to healthy controls using nailfold videocapillaroscopy (NVC), offering standardised findings about micro-circulation.

Study Design: A descriptive, cross-sectional study.

Place and Duration of Study: Medical Intensive Care Unit, Kayseri City Education and Research Hospital, Kayseri, Turkey between January and May 2021.

Methodology: The NVC parameters-capillary morphology, loop diameter, capillary density, dilated capillaries, giant capillaries, avascular areas, microaneurysms, and micro-hemorrhages of 32 patients with COVID-19 and 29 controls were recorded.

Results: The most common capillary morphology in the COVID-19 group (18/32, 56.2%) was serpentine, which also characterised some (6/29, 20.7%) patients in the non-COVID-19 group ($p < 0.001$). The median capillary loop diameter was 77.78 ± 3.63 µm in the COVID-19 group and 71.67 ± 2.19 µm in the non-COVID-19 group ($p=0.030$). Mean capillary density was 6.41 ± 1.21/1 mm in the COVID-19 group and 8.55 ± 1.12/1 mm in the non-COVID-19 group ($p < 0.001$). The COVID-19 group had significantly more enlarged capillaries ($p = 0.001$), giant capillaries ($p = 0.025$), avascular areas ($p = 0.028$), micro-aneurysms ($p < 0.001$), and micro-hemorrhages ($p = 0.011$). Mean capillary density was 5.50 ± 0.19/1 mm among deceased patients with COVID-19, but 6.71 ± 0.25/1 mm among survivors ($p = 0.011$).

Conclusion: NVC findings differed between patients with COVID-19 and controls, and capillary density was less among deceased patients with COVID-19 than survivors.

Key Words: *Capillaries, COVID-19, İntensive care unit, Micro-circulation, Nailfold videocapillaroscopy.*

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INTRODUCTION

Thrombotic events associated with COVID-19 are common, potentially life-threatening complications. Among them, arteriovenous thrombosis and severe endothelial damage are especially common in a series of autopsies.[1] Various causes of such endothelial damage have been identified, with neutrophil extracellular traps (NETs), molecular mimicry, thrombotic microangiopathic damage, and lymphocytic vasculitis ranging from endothelial swelling and endothelitis to fibrinoid necrosis and thrombosis as frequently defined entities.[2-5] Although severe vascular endothelial damage has been shown to play a leading role in COVID-19-related morbidity and mortality, it remains unclear which patients have or will develop the damage.

Correspondence to: Dr. Samet Karahan, Department of Internal Medicine, Division of Rheumatology, Kayseri City Education and Research Hospital, Kayseri, Turkey
E-mail: doktorsamet@yahoo.com

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Nailfold videocapillaroscopy (NVC) is a specific, validated, non-invasive method used in the context of connective tissue diseases (CTDs). Although NVC generally provides vital information about the quality of the vascular blood supply in end organs such as the nailfold,[6] its most important application is with patients with systemic sclerosis (SSc). In particular, NVC aids diagnosis by distinguishing primary from secondary Raynaud's phenomenon and provides important information about the long-term outcomes of patients with micro-circulation disorders such as microhemorrhages, avascular areas, and giant capillaries.[7] Beyond that, NVC is an easy-to-learn, readily accessible, inexpensive, non-invasive procedure that offers standardised findings about abnormalities in micro-circulation.

The aim of this study was to compare patients in intensive care units (ICUs) with COVID-19-associated lung involvement, but without documented thromboembolism to patients without COVID-19, using the results of NVC.

METHODOLOGY

Between January and May 2021, 39 patients with COVID-19-related pneumonia followed in the medical ICUs of Kayseri City

Education and Research Hospital, were consecutively enrolled in the study (*i.e.* COVID-19 group). Some patients in the COVID-19 group needed intensive care; whereas, others were followed up in COVID-19 clinics and required intensive care after their health had deteriorated. In that group, NVC was performed by a specialist in the first 24 hours of admission to ICU and before any vasopressors were used.

The NVC findings of patients in the COVID-19 group were compared with NVC findings observed in a population of 35 PCR-negative patients without COVID-19 (19 males, 16 females) who applied to the internal medicine outpatient clinic for a routine control (*i.e.*, non-COVID-19 group).

Patients with any past or present diagnosis of Raynaud's phenomenon, with malignancies and CTDs were excluded. To further eliminate the possibility of autoimmunity, antinuclear antibodies (ANA), rheumatoid factor (RF), and anti-cyclic citrullinated peptides were assessed in both the groups; and the individuals who tested positive, were also excluded. Patients who had received low molecular weight heparin (LMWH) during follow-up in COVID-19 clinics prior to admission to the ICU were also excluded.

NVC with 200× magnification was performed using a digital microscope (Dino-Lite Capillary Scope 200, Naarden, the Netherlands). A certified rheumatologist performed the procedure with the room temperature between 22 and 24°C. Patients in the non-COVID-19 group were asked not to smoke or consume caffeine for at least six hours before the test. The second through fifth fingers of both hands were examined, and measurements were taken by looking at three regions of each nailfold: medial, lateral, and midline. Eight capillaroscopic parameters in each region were recorded: (a) capillary morphology (*i.e.*, normal, serpentine, or branched, with serpentine or tortoise morphology defined as limbs crossing themselves or each other more than twice), (b) capillary loop diameter (*i.e.*, µm diameter at the apical margin of a capillary loop), (c) capillary density (*i.e.*, number of capillaries in a 1-mm length of the distal row of each finger), (d) enlarged capillaries or capillary dilatation (*i.e.*, capillary diameter between 20 and 50 µm), (e) giant capillaries (*i.e.*, capillary diameter greater than 50 µm), (f) avascular area (*i.e.*, distance between two capillary loops greater than 500 µm), (g) microaneurysms (*i.e.*, irregular enlargement and circumscribed increasing of the capillary loop diameter), and (h) microhemorrhages (*i.e.*, hemosiderin deposits with red and/or black images in the distal areas).[8-12] Three images (*i.e.*, medial, lateral, and midline) were recorded for each finger, and 24 images were obtained from each patient.

For capillary morphology, the most common morphology in each finger was noted, and the average predominant capillary morphology of eight fingers was recorded as that patient's morphology. For capillary density and capillary loop diameter, the average of 24 data points obtained from eight fingers was recorded for each patient. For the remaining parameters, patients were considered to be positive if they were positive in at least two fingers and at least two regions of the lateral, medial, and midline areas of the finger. Figure 1 illustrates the method and some pathological findings of the patients.

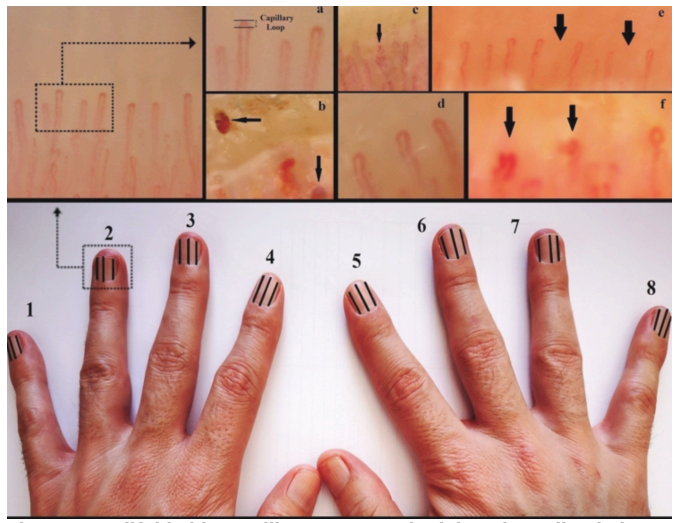

Figure 1: Nailfold videocapillaroscopy methodology is outlined above. Pictures of some NVC findings of the patients are shown above: (a) capillary loop measurement site, (b) microhemorrhage, (c) capillaries in serpentine (tortiose) morphology, (d) enlarged capillaries (capillary diameter between 20 and 50 µm), (e) avascular areas (two consecutive capillary loop distances of more than 500 µm), (f) giant capillaries (capillary diameter greater than 50 µm).

Demographic data of the patients and their comorbid diseases, laboratory parameters, and acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores were recorded. GRAM-risk scores on admission to the hospital were calculated for a clinical risk score to predict the occurrence of critical illness in patients with COVID-19.[13] The need for mechanical ventilators and 28-day mortality rates were also recorded after NVC. All patients or their next of kin provided written informed consents to participate, and the study was approved by the Ethics Committee of Kayseri City Education and Research Hospital (Date: October 12, 2020, No. 228). The study was conducted in accordance with the Declaration of Helsinki.

Statistical analyses were performed using the SPSS version 25.0 (IBM, Armonk, NY, USA), with p values of less than 0.05 considered to indicate significance. Rates of prevalence between the groups were compared using the Chi-square test or Fisher's Exact test. To compare groups of continuous data, the authors used the Mann–Whitney U-test for data without normal distribution and Student's *t*-test for normally distributed data. Spearman's correlation coefficient (r_s) was used to evaluate correlations of other parameters with capillary density. Categorical variables were reported as numbers and percentages; whereas, continuous variables were reported as mean ± standard deviation (SD) if normally distributed; or medians with interquartile range (IQR) if not normally distributed. The Shapiro-Wilk test was used to check whether the data were in normal distribution.

RESULTS

The COVID-19 group contained 32 patients, whose mean age was 61.69 ± 5.86 years, 20 of whom (62.5%) were males and 12

(37.5%) were females. The non-COVID-19 group contained 29 patients, whose mean age was 60.8 6 ± 7.05 years, 17 of whom (58.6%) were males and 12 (41.4%) were females (p = 0.623 for age, p = 0.757 for gender). No differences in demographic data were noted between the groups, as summarised in Table I along with the groups' clinical data.

Table I: Demographic data between COVID-19 and non-COVID-19 groups.

	COVID-19 (n=32)	Non-COVID-19 (n=29)	p-value
Age, years, mean ± S.D.	61.69 ± 7.05	60.86 ± 7.05	0.623
Age ≥65 years, No (%)	9 (28.1)	9 (31)	0.803
Gender, male, No. (%)	20 (62.5)	17 (58.6)	0.757
Gender, female, No. (%)	12 (37.5)	12 (41.4)	0.757
BMI, kg/m^2, mean ± S.E.M.	29.2 ± 0.9	28.3 ± 0.9	0.239
Race, non-Caucasian, No. (%)	1 (3.1)	1 (3.4)	0.729
Current smoking, No (%)	10 (31.3)	6 (20.7)	0.234
Co-morbidities, No. (%)			
DM	8 (25.81)	12 (42.86)	0.167
HT	17 (53.1)	14 (48.3)	0.705
ASHD	8 (25)	8 (27.6)	0.819
Asthma / COPD	3 (9.4)	6 (20.7)	0.213
CKD	2 (6.3)	0	0.493
CHF	1 (3.1)	1 (3.4)	0.729
Hypothyroidism	2 (6.3)	3 (10.3)	0.662
Antihypertensive drugs, No (%)			
ACE Inhibitors / ARBs,	10 (31.3)	11 (37.9)	0.583
CCBs	5 (15.6)	4 (13.8)	0.840
Others	8 (25)	7 (24.1)	0.937

COVID: Coronavirus disease, SD: Standard deviation, BMI: Body mass index, SEM: Standard error of mean, DM: Diabetes mellitus, HT: Hypertension, ASHD: Atherosclerotic heart disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, CHF: Congestive heart failure, ACE: Angiotensin converting enzyme, ARB: Angiotensin receptor blockers, CCB: Calcium channel blockers. Statistical tests: Mann-Whitney U-test, Student t-test, Chi-square test or Fishers' Exact test.

Among patients with COVID-19, the 28-day mortality rate was 8/32 (25%). The demographic and clinical characteristics of deceased and surviving patients with COVID-19 appear in Table II. The mean age of surviving patients with COVID-19, 16/24 of whom (66.7%) were males, was 61.96 ± 7.30 years.

By comparison, the mean age of patients who died, half of whom were males, was 60.88±6.62 years (p = 0.713). The mean body mass index (p = 0.744) and number of comorbidities of the patients, who died and ones who survived, were not significantly different, either (p = 0.453 and p = 0.453, respectively). Peripheral O_2 saturations at admission to the ICU were lower among the deceased (80.0 ± 0.4 *vs*. 83.4 ± 0.1, p <0.001), whose respiratory rates were also higher (25.4 ± 0.3 *vs*. 21.7 ± 0.1, p <0.001). Likewise, the APACHE-II, SOFA, and COVID-19 GRAM-risk scores of the deceased were also high (17.50 ± 5.86 *vs*. 10.29 ± 4.90, p = 0.002; 4.38 ± 0.6 *vs*. 2.92 ± 0.3, p = 0.018; 196.0 ± 29.8 *vs*. 138.0 ± 26.0, p <0.001, respectively).

The most common capillary morphology in the COVID-19 group was serpentine morphology, as observed in 18/32 patients (56.2%). However, serpentine morphology also appeared in 6/29 patients (20.7%) in the non-COVID-19 group (p <0.001). Although the median capillary loop diameter was 77.78 ± 3.63 µm in the COVID-19 group and 71.67 ± 2.19 µm in the non--COVID-19 group (p = 0.030), the mean capillary density differed significantly between the groups: 6.41 ± 1.21/1 mm in the COVID-19 group and 8.55 ± 1.12/1 mm in the non-COVID-19 group (p <0.001). Moreover, enlarged capillaries, giant capillaries, avascular areas, microaneurysms, and microhemorrhages were all significantly more numerous in the COVID-19 group than in the non-COVID-19 group (p = 0.001, p = 0.025, p = 0.028, p <0.001, and p = 0.011, respectively). A detailed analysis of those NVC data in patients with and without COVID-19 is provided in Table III a.

Table III b allows a comparison of the NVC parameters of deceased and surviving patients with COVID-19. As shown, the only significant statistical difference between the groups concerned capillary density; the mean capillary density was 5.50 ± 0.19 among the deceased but 6.71 ± 0.25 among survivors (p = 0.011). Although the mean loop diameter was less among the deceased, the between-group difference was not statistically significant (74.59±9.34 for deceased patients, 85.44 ± 3.68 for survivors, p=0.074), nor was the number of patients with avascular areas, which were detected in 4/8 deceased patients (50%) and in 4/24 survivors (16.7%, p=0.082).

Capillary density negatively correlated with D-dimer (r_s = –0.411, p = 0.020) and APACHE-II score (r_s = –0.0379, p = 0.033), while loop diameter negatively correlated with D-dimer (r_s = –0.672, p <0.001) and GRAM-risk score (r_s = –0.377, p=0.034).

DISCUSSION

This study's primary finding was a set of certain differences in NVC findings, as a sign of microvascular blood supply, between patients with COVID-19-related pneumonia in ICUs and patients without COVID-19. Among patients with COVID-19, capillary loop diameter was higher, capillary density was lower, and capillaries were wider. Avascular areas, microaneurysms, and microhemorrhagic capillaries were more numerous in patients with COVID-19 as well. Among other important findings, capillary density was lower among patients who had died from COVID-19 than among survivors, and capillary density was negatively correlated with D-dimer.

In their study addressing the endothelial, thrombotic, and immune mechanisms of COVID-19, Natalelloa *et al*. used NVC among patients at the time of acute infection and who had recovered from the disease.[14] Abnormal NVC findings were detected in 65% of patients, and more hemosiderin deposits indicating microthrombus and hemorrhaging were found in patients currently ill with COVID-19. By contrast, enlarged capillaries, the loss of capillaries, meandering capillaries, and empty dermal papillae were more numerous among patients who had recovered. However, Natalello *et al*. did not examine critically ill patients or compare the data of patients who had died within 28 days with the data of those who survived. Due to the lack of data regarding mortality rate, the increased frequency of avascular areas among survivors could be deceptive.

Micro-circulation *(i.e*., vessels less than 100 µm in diameter) plays an important role in supplying oxygen to cells, namely by providing tissue perfusion.[15] For that reason, micro-circulation is critical for patients in intensive care, and its disruption has been associated with poor outcomes.[16,17]

Table II: Demographic and clinical characteristics of enrolled COVID-19 group patients.

	All population n = 32	Survived n = 24	Deceased n = 8	p-value
Age, years, mean ± S.D.	61.69 ± 7.05	61.96 ± 7.30	60.88 ± 6.62	0.713
Sex, Male, No. (%)	20 (62.5)	16 (66.7)	4 (50)	0.433
Sex, Female, No. (%)	12 (37.5)	8 (33.3)	4 (50)	0.433
BMI (kg/m^2), mean ± S.E.M.	30.1 ± 0.8	30.2 ± 0.9	29.7 ± 1.7	0.744
Number of comorbidities	1.6 ± 0.2	1.5 ± 0.3	2.0 ± 0.6	0.453
Parameters at ICU presentation				
Peripheral O_2 saturation (%), mean ± S.E.M.	82.5 ± 0.3	83.4 ± 0.1	80.0 ± 0.4	<0.001
Respiratory rate (breaths/min), mean ± S.E.M.	22.7 ± 0.3	21.7 ± 0.1	25.4 ± 0.3	<0.001
Laboratory values				
Neutrophil (/mm^3), mean ± S.D.	8,567 ± 4,973	7,557 ± 4,932	11,597 ± 3,950	0.045
Lymphocyte (/mm^3), mean ± S.E.M.	1,028 ± 310	1,081 ± 410	868 ± 220	0.556
Hemoglobin (g/dL), mean ± S.D.	12.8 ± 2.1	12.8 ± 2.2	12.9 ± 1.6	0.908
Platelet (10^3 /mm^3), mean ± S.D.	212.4 ± 124.4	222.4 ± 128.5	182.6 ± 113.7	0.443
Creatinine (mg/dL), mean ± S.E.M.	1.07 ± 0.14	0.84 ± 0.08	1.76 ± 0.41	0.184
ALT (UI/L), mean ± S.E.M.	53.3 ± 8.4	46.0 ± 8.5	75.1 ± 21.1	0.145
LDH (UI/L) , mean ± S.E.M.	546.5 ± 51.7	433.8 ± 29.1	884.8 ± 131.0	0.001
Bilirubin, direct (mg/dL), mean ± S.E.M.	0.30 ± 0.02	0.30 ± 0.03	0.28 ± 0.04	1.000
CRP (mg/L), mean ± S.E.M.	84.2 ± 11.0	75.1 ± 11.1	111.6 ± 28.3	0.364
D-dimer (ng/mL), mean ± S.E.M.	3,339 ± 551	2,333 ± 489	6,359 ± 1,136	0.004
Ferritin, (ng/mL), mean ± S.E.M.	1,209 ± 252	1,180 ± 305	1,294 ± 452	0.571
Procalcitonin (ng/mL), mean ± S.E.M.	0.39 ± 0.26	0.38 ± .026	0.39 ± 0.13	0.034
Lactates, (mmol/L), mean ± S.E.M.	1.72 ± 0.13	1.52 ± 0.12	2.30 ± 0.30	0.017
Vasopressor, No (%)	6 (18.8)	1 (4.2)	5 (62.5)	0.002
Hemodialysis, No (%)	1 (3.1)	1 (4.2)	0	0.557
Mechanical ventilator, No (%)	10 (31.3)	3 (12.5)	7 (87.5)	<0.001
Risk scores				
APACHE II, mean ± S.D.	12.09 ± 5.97	10.29 ± 4.90	17.50 ± 5.86	0.002
SOFA, mean ± S.E.M.	3.28 ± 0.3	2.92 ± 0.3	4.38 ± 0.6	0.018
COVID-GRAM, mean ± S.D.	152.6 ± 36.8	138.0 ± 26.0	196.0 ± 29.8	<0.001

COVID: Coronavirus disease, SD: Standard deviation, BMI: Body mass index, S.E.M.: Standard error of mean, O^2: Oxygen, ALT: Alanine amino transferase, LDH: Lactic dehydrogenase, CRP: C-reactive protein, APACHE II: Acute Physiology And Chronic Health Evaluation II, SOFA: Sequential organ failure assessment, COVID-GRAM: COVID-Gram Critical Illness Risk Score. Statistical tests: Mann-Whitney U-test, Student t-Test, Chi-Square test or Fisher's Exact test.

Table III (a): NVC findings in the COVID-19 and non-COVID-19 groups.

	COVID-19 (n=32)	Non-COVID-19 (n = 29)	p-value
Capillary morphology			
Normal, N (%)	12 (37.5)	23 (79.3)	<0.001
Serpentine (Tortiose), No. (%)	18 (56.2)	6 (20.7)	<0.001
Branched, No. (%)	2 (6.3)	0	0.171
Loop diameter, µm, mean ± S.E.M.	77.78 ± 3.63	71.67 ± 2.19	0.030
Capillary density, pcs/1 mm, mean ± S.D.	6.41 ± 1.21	8.55 ± 1.12	<0,001
Enlarged capillaries, No. (%)	14 (43.8)	2 (6.9)	0.001
Giant capillaries, No. (%)	6 (18.8)	0	0.025
Avascular areas, No. (%)	8 (25)	1 (3.4)	0.028
Microaneurysms, No. (%)	20 (62.5)	3 (10.3)	<0.001
Microhemorrhages, No. (%)	7 (21.9)	0	<0.001

Table III (b): NVC findings in the survived and non-survived patients of COVID-19 group.

	COVID-19 Survived (n=24)	COVID-19 Deceased (n=8)	p-value
Capillary morphology			
Normal, No. (%)	11 (45.8)	1 (12.5)	0.091
Serpentine (Tortiose), No. (%)	12 (50)	6 (75)	0.217
Branched, No. (%)	1 (4.2)	1 (12.5)	0.843
Loop diameter, µm, mean ± S.E.M.	85.44 ± 3.68	74.59 ± 9.34	0.074
Capillary density, pcs/1 mm, mean ± S.E.M.	6.71 ± 0.25	5.50 ± 0.19	0.011
Enlarged capillaries, No. (%)	11 (45.8)	3 (37.5)	0.504
Giant capillaries, No. (%)	5 (20.8)	1 (12.5)	0.524
Avascular areas, No. (%)	4 (16.7)	4 (50)	0.082
Microaneurysms, No. (%)	15 (62.5)	5 (62.5)	0.657
Microhemorrhages, No. (%)	6 (25)	1 (12.5)	0.423

NVC: Nailfold videocapillaroscopy, COVID: Coronavirus disease, SEM: Standard error of mean, pcs: pieces, SD: Standard deviation. Statistical tests: Chi-Square test or Fisher's Exact test, Mann-Whitney U-test / Student t-Test.

The early evaluation of micro-circulation, which can be assessed sublingually with specially developed tools, may contribute to reducing the rate of mortality in patients with a high risk of death. Studies on micro-circulation in COVID-19 have presented inconsistencies, especially in data regarding capillary density. Rovas *et al*., for example, found severe changes in the micro-circulation in patients with COVID-19.[18] In their observational, cross-sectional, multicentre study, 23 patients with moderate-to-severe or critical COVID-19 were analysed and their data compared with the data of 15 healthy volunteers. Among the patients, vascular density had dropped by up to 90%, particularly in capillaries 4-6 µm in diameter, and correlated with D-dimer levels (r_s = –0.43, p = 0.04). According to the results of the MicroDAIMON study conducted by Damiani *et al*, among 97 critically ill patients without COVID-19, the mean perfused vascular density was 19.3 ± 4.4 mm/mm^2.[17] The perfused vascular density in patients with COVID-19 in this study was considerably lower than in that study. Despite those studies showing decreases in capillary density, Kanoore Edul *et al.* compared the capillary density of patients with COVID-19 with previously reported normal values and found that the density was higher among the patients.[19] All patients in that study were intubated and mechanically ventilated, and their D-dimer levels did not correlate with total or perfused vascular density. In addition, Carsetti *et al.* performed the sublingual micro-circulatory evaluation of nine patients critically ill with COVID-19 and who had undergone veno-venous extracorporeal membrane oxygenation (ECMO); and among their results, capillary density had been altered.[20] In that study,

total vascular density was 16.81 mm/mm^2 (14.46–18.6) and perfused vascular density 15.3 mm/mm^2 (14.09–17.96). The present authors noted that those values among patients with COVID-19 undergoing ECMO were less than the ones recorded in the microDAIMON study. However, they also acknowledged that the capillary densities were similar to densities found by the same study group in another group of patients with COVID-19 who had not undergone ECMO.[21] Lastly, Hutchings *et al*. compared the microvascular parameters of 30 mechanically ventilated patients with COVID-19, 33 patients with septic shock, and 12 healthy volunteers; and found that total vessel density and perfused vessel density were higher among patients with COVID-19 than among the controls.[22]

In the present work, the authors evaluated the micro-circulation in patients with COVID-19-related pneumonia by using NVC, which is inexpensive, readily available, non-invasive, and easy to perform. Given the valuable data presented above and the analyses performed, microvascular evaluation and NVC can help predict microvascular alterations in patients with COVID-19 in ICUs. Upon admission to an ICU, patients at risk of death or mechanical ventilation can be identified with that non-invasive, inexpensive examination, and more intensive anti-coagulation can be applied when necessary.

The strength of this study included a comparison of patients with and without COVID-19 and an analysis of correlations between NVC findings and some clinical and laboratory parameters. In addition, the patients who underwent NVC, and used unfractioned or LMWH or vitamin K antagonists before examination, were excluded from the sample. The exclusion of patients with a history of Raynaud's phenomenon and rheumatological disease such as SSc, rheumatoid arthritis, and SLE, all of which are CTDs, also ranked among the study's strength.

By contrast, conducting the study in a small population and in a single-centre was an important limitation, as was its cross-sectional design. Not re-evaluating patients in the ICU with NVC post-recovery or determining whether NVC findings had improved were other limitations. The reason for those particular limitations was the relatively high number of patients who died; and of survivors who did not remember their days in the ICU, which was perceived to be a highly traumatic experience for them and justified their refusal to receive control NVC testing. In fact, only three of the surviving 24 patients consented to control NVC.

CONCLUSION

NVC findings differed between patients with COVID-19 and controls, and capillary density was less among deceased patients with COVID-19 than survivors.

ETHICAL APPROVAL:

The study was approved by the Ethics Committee of Kayseri City Education and Research Hospital (Date: October 12, 2020, No. 228). The study was conducted in accordance with the Declaration of Helsinki, a statement of ethical principles for medical research involving human subjects.

PATIENTS' CONSENT:

Consents for participation in this study were obtained from all the patients or patients' relatives.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

SK, KA: Concept, design, definition of intellectual content, patient treatment and follow-up, literature search, data acquisition, manuscript preparation, manuscript editing.
AC, HAS: Patient treatment and follow-up, manuscript editing.

DATA SHARING STATEMENT:

All of the individual participant's data were collected during the trial; and after deidentification will be available (including data dictionaries) for researchers who provide a methodologically sound proposal.

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