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CLINICAL STUDY

Baseline capillaroscopy provides no evidence of microvascular changes to predict long-COVID syndrome

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ABSTRACT

BACKGROUND: Long-COVID refers to a variety of symptoms that continue for at least 4 weeks following the onset of acute COVID-19 infection. "Microclots/microvasculopathy" is a potential cutting-edge theory. Nailfold capillaroscopy is a non-invasive method used to assess microvascularity. In this study, we aimed to compare baseline characteristics and capillaroscopic findings of patients with and without long-COVID syndrome.

METHODS: Baseline clinical characteristics of 53 patients who tested positive for SARS-CoV-2 were recorded. At the time of COVID-19 diagnosis, patients underwent nailfold capillaroscopy. One year later, patients were rescreened for long-COVID symptoms. Comparisons were made between patients with and without long-COVID syndrome in terms of their baseline characteristics and capillaroscopic findings.

RESULTS: There were 35 individuals (66%) with long-COVID syndrome. The most common symptoms related to long-COVID were fatigue (43.4%), myalgia (34%), arthralgia (20.8%), dyspnea (20.8%). In total, 22 patients (41.5%) had abnormal capillaroscopy findings. Like other baseline characteristics, the proportion of patients with abnormal capillaroscopic findings (40% vs 44%, p=0.76) was similar between patients with and without long-COVID syndrome.

CONCLUSION: Microvasculopathy and microthrombotic vascular damage are among the strongest hypotheses discussed in this regard. Our results may suggest that factors, rather than baseline microvasculopathy, may drive pathophysiological mechanism underlying the poorly understood long-COVID syndrome *(Tab. 2, Ref. 35)*.

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KEY WORDS: COVID-19, microangiopathy, nailfold capillaroscopy, long-COVID, post-COVID.

Introduction

There are increasing reports of prolonged or persistent symptoms following acute COVID-19 (1). These physical symptoms are common and typically include fatigue, shortness of breath, chest pain, and cough. Headache, arthralgia, dysgeusia, myalgia, and diarrhea have also been reported. Common psychological and cognitive symptoms include poor concentration, insomnia, anxiety and depression. The time to symptom resolution may depend primarily on preexisting risk factors, the severity of the acute illness, and the spectrum of initial symptoms. While some of these processes are similar to recovery from a viral illness, critical illness and/or sepsis, some aspects are specific to COVID-19 (2). After COVID-19 infection, prolonged symptoms are common, even in patients with less severe illness and who have never been hospitalized (2, 3, 4). Recently, new terms such as "long-COVID, post-COVID" have been coined to describe the persistence of symptoms developed during acute infection without a reasonable explanation by an alternative diagnosis (3, 5). Recently, NICE recommended time limits for defining long-COVID syndrome. This classification consists of acute COVID-19 (symptoms lasting up to 4 weeks), ongoing symptomatic COVID (symptoms lasting between 4 and 12 weeks), and post-COVID (symptoms that develop during or after infection and last longer than 12 weeks). According to NICE, the term "long-COVID" includes the subgroups of ongoing symptomatic COVID and post-COVID (6). It is well known that acute covid infection and autoimmune diseases have similar pathophysiological features and some of anti-rheumatic drugs have been used successfully in treatment. Similarly, long-COVID shares similar symptoms and is considered a mimicker of autoimmune diseases and thus poses a diagnostic and management challenge (7). The most recent estimate of people living with long-COVID worldwide is over 65 million, and this number is growing with no clear diagnostic or treatment options (4, 8). The incidence, prevalence, persistence,

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pathophysiological background of long-COVID and its impact on patients remain unclear. Among the pathophysiological hypotheses, the most widely discussed are immune dysregulation, neuroinflammation, microthrombotic vascular damage, impaired cellular energy production caused by mitochondrial dysfunction, and microvasculopathy and neuronal damage caused by coagulopathy and endothelial damage (9, 10, 11).

Capillaroscopy is a widely used non-invasive method to evaluate microvasculopathy by examining the nail capillary bed (12). Capillaroscopy as a bedside, easily applicable method may help detect dysfunctional endothelial activation and microvasculopathy in patients with COVID-19 (13, 14, 15). In patients with COVID-19, capillaroscopic changes representing microvascular damage were observed in the acute and follow-up periods (14, 15). Furthermore, hyperinflammatory response was more frequently observed in patients with capillaroscopic changes (15).

The pathophysiology of long-COVID is not yet fully understood. Although microvascular damage is one of the hypotheses, capillaroscopic changes, which are indirect indicators of microvascular damage, have not been studied in long-COVID syndrome. Current knowledge on this topic is largely lacking. In this study, we aimed to assess whether there are baseline microvascular changes in long-COVID patients thus compared the baseline characteristics and capillaroscopic findings of patients with and without long-COVID syndrome.

Materials and methods

Patients selection

Fifty-three patients who tested positive for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (RT-PCR) from nasopharyngeal or oropharyngeal swabs and had a baseline capillaroscopic examination were included. Patients younger than 18 years, pregnant women, those with comorbidities or chronic medication use, or with recent hand trauma were excluded. Baseline characteristics were collected with attention to the smoking habit, baseline COVID-19 symptoms, and pulmonary involvement (ground glass opacity, focal infiltration, focal opacity assessed by computerized tomography). Laboratory tests such as lymphocyte count, hemoglobin, platelet count, creatinine, liver function tests, lactate dehydrogenase, ferritin, fibrinogen, INR, troponin I, creatinine kinase, D-dimer and C-reactive protein were assessed at enrolment using standard methods. COVID-19 therapies, including favipravir, antiaggregants, anticoagulants (low-molecular-weight heparin) and immunomodulatory drugs (glucocorticoids, anakinra, IL-6 receptor antagonist-tocilizumab), and capillaroscopic findings were recorded at baseline. The study was approved by the Ministry of Health and *** Ethics Committee (E1-23-3382).

Abnormal capillaroscopy

Between 30/04/2020-01/06/2020, the same trained rheumatologist performed the capillaroscopic evaluation in all patients, using an optical probe equipped with a 200× magnification lens and connected to image analysis software (Dino-Lite). The clinician performed the procedure by taking precautions appropriate to the conditions of transmission (16). Two images of the central area of the nail bed of the fingers (thumbs excluded) were obtained for each subject.

We used the definitions proposed by Ingegnoli et al (17) to identify abnormal capillary examination findings in capillaroscopic COVID-19 patients. Morphological abnormality was defined as giant capillary or >50% tortuous or >10% elongated capillary or bleeding area or neoangiogenesis or avascular areas plus the presence of another capillaroscopic abnormality.

A patient's capillaroscopic examination was defined as abnormal if there was more than 1 morphologic abnormality in at least 2 different nail bed examination.

Long-COVID Screening

Patients were re-evaluated by telephone interview for symptoms of long-COVID 1 year after complete recovery of the initial diagnosis (8). Cough, sputum, hemoptysis, dyspnea, palpitation, fever, fatigue, wheezing, syncope, myalgia, arthralgia, sore throat, dysgeusia, dysosmia, earache, anorexia, diarrhea, nausea, vomiting, abdominal pain, weight loss, confusion, headache, attention deficit, memory loss, anxiety, depression, sleep disturbance, hair loss symptoms and history of thrombosis were checked. These symptoms were categorized and recorded as symptoms present before COVID, symptoms that began during and continued after the acute COVID period, and symptoms that developed in the post-COVID period. Individuals with any of the long-COVID-related symptoms, that were not present prior to COVID-19 infection, were considered to have the disease. Patients were divided into two subgroups according to whether they had long-COVID syndrome and baseline characteristics and capillaroscopic findings were compared according to long-COVID status. In addition, each long-COVID related symptom was compared between patients grouped by whether they had abnormal capillaroscopic findings.

Statistical analysis

SPSS 24.0 (IBM Corp., Armonk, NY, USA) was used. The conformity of variables to normal distribution was examined visually (histograms and probability plots) and analytically (Shapiro–Wilk test). Continuous data were described as mean (±standard deviation, SD) or median (interquartile range, IQR) and categorical variables as percentages. Chi-square test was used to compare categorical variables. Student t test or Mann–Whitney U (where appropriate) test was used to compare continuous variables. $p<0.05$ was considered statistically significant.

Results

We analyzed a total of 53 hospitalized COVID-19 patients. Most patients were male (72%) with a mean age of 37.8±11.4 years. During the acute COVID-19 infection period 51 patients underwent thorax computed tomography, revealing ground glass opacity in 82.4%, focal patchy infiltration in 4%, and normal findings in 12%. Common COVID-19 symptoms during the acute infection included cough 70%, fever 43%, dyspnea 32%, myalgia 30%,

sore throat 25%, arthralgia 21%, headache 15%, anosmia 13%, nausea/vomiting 12%, diarrhea 8%, dysgeusia 6%, weakness 6% and abdominal pain 4%. Out of 53 patients, 2 (3.7%) developed thrombosis, with one case of pulmonary thromboembolism and one case of sinus vein thrombosis. The median length of hospital stay was 7 (3–25) days. In total, 22 patients (41.5%) had at least 1 of the abnormal capillaroscopy changes described above.

Of the 53 patients, 35 (66%) had at least one long-COVID symptom. Most patients with long-COVID were male (74%) with a mean age of 39±11.6. Fatigue (43.4%) was the most common

Tab. 1. Baseline Characteristics of COVID-19 patients with and without long-COVID.

	Without long-COVID (n=18)	With long-COVID (n=35)	p
Male, n (%)	12 (66.7)	26 (74.3)	0.56
Age, year, mean (SD)	35.4 (10.9)	39 (11.6)	0.28
Smoking, n (%)			0.90
Current	4 (22.2)	5 (14.3)	
Ex-smoker	1 (5.6)	2 (5.7)	
Never	7 (39)	16 (45.7)	
Capillary density, mean±SD	8.8 (1.3)	9.2 (1.4)	0.32
Abnormal Capillaroscopy, n (%)	8 (44)	14 (40)	0.76
Fever, n (%)	7 (38.9)	16 (45.7)	0.63
Cough, n (%)	13 (72.2)	24 (68.6)	0.78
Dyspnea, n (%)	3 (16.7)	14 (40.0)	0.08
Arthralgia, n (%)	3 (16.7)	8 (22.9)	0.73
Myalgia, n (%)	4 (22.2)	12 (34.3)	0.36
Headache, n (%)	5 (27.8)	3 (8.6)	0.10
Sore throat, n (%)	5 (27.8)	8 (22.9)	0.74
Anosmia, n (%)	3 (16.7)	4 (11.4)	0.68
Dysgeusia, n (%)	1 (5.6)	2 (5.7)	0.99
Stomachache, n (%)	0	2 (5.7)	0.54
Nausea/vomiting, n (%)	0	6 (17.1)	0.08
Diarrhea, n (%)	1 (5.6)	3 (8.6)	0.99
Lymphocyte, median (IQR)	1395 (1137.5 to 1770)	1510 (990 to 1940)	0.78
Hemoglobin, median (IQR)	14.1 (12.9 to 15)	14.2 (13.8 to 15)	0.62
Platelets, median (IQR)	201500 (176000 to 235250)	221000 (165000 to 247500)	0.95
Creatinine, median (IQR)	0.8 (0.7 to 0.9)	0.8 (0.7 to 1.0)	0.99
Aspartate aminotransferase, median (IQR)	18.5 (13.2 to 30.8)	21 (15.5 to 28.5)	0.54
Alanine aminotransferase, median (IQR)	25.5 (16.2 to 29.8)	25 (19 to 41)	0.41
Lactate dehydrogenase, median (IQR)	225 (196.8 to 270.5)	210 (186 to 258)	0.45
Creatinine kinase, median (IQR)	95 (54 to 112)	91 (64 to 125)	0.60
C-reactive protein, median (IQR)	9 (5 to 15.2)	8.(3.5 to 31.5)	0.81
Ferritin, median (IQR)	120.5 (28.8 to 163.5)	142 (73.2 to 274.8)	0.25
Fibrinogen, median (IQR)	3 (2.8 to 3.6)	3.5 (2.7 to 4.2)	0.42
D-dimer, median (IQR)	0.4 (0.3 to 0.5)	0.4 (0.2 to 0.8)	0.51
INR, median (IQR)	1 (1.0 to 1.1)	1 (1.0 to 1.1)	0.71
Troponin I, median (IQR)	2.5 (2.5 to 2.5)	2.5 (2.5 to 4)	0.12
Thorax computerized tomography, n (%)			
Ground glass opacity or	13 (76)	32 (94)	0.08
Focal infiltration/opacity or Thrombosis			
Normal findings	4 (24)	2 (6)	
Hyperinflammatory response, n (%)	1 (5.6)	4 (11.4)	0.49
Thrombosis, n (%)	0	2 (5.7)	0,30
Length of stay in hospital, day, median (IQR)	7.5 (6-10)	7 (6-10)	0.92
COVID-19 treatments			
Favipiravir, n (%)	2 (11.1)	12 (34.3)	0.10
Glucocorticoid, n (%)	1 (5.6)	0	0.34
Tocilizumab, n (%)	1 (5.6)	2 (5.7)	0.99
Anakinra, n (%)	0	3 (8.6)	0.54
Acetylsalicylic acid/dipyridamole, n (%)	0	2 (5.7)	0.54
Low molecular weight heparin, n (%)	11 (61.1)	23 (65.7)	0.74

IQR – Interquartile range, COVID-19 – Coronavirus disease-2019, SD – Standard deviation, INR – International normalized rate

long-COVID symptom, followed by myalgia (34%), arthralgia (20.8%), dyspnea (20.8%), cough (18.9%), hair loss (15%), headache (13.2%), and sleep disturbance (13%). Baseline characteristics of patients with and without long-COVID syndrome are shown in Table 1. Among the patients with long-COVID syndrome, 21 (60%) had normal and 14 (40%) had abnormal capillaroscopy findings. Capillary densities were similar between groups. The percentage of each capillaroscopic finding, including the presence of hemorrhages, pericapillary edema, empty dermal papilla, avascular area, neoangiogenesis, branching capillary, bushy capillary and ramified capillary, were similar between groups. Baseline characteristic, including demographics, smoking history, symptoms, laboratory results, imaging results, length of hospital stay, and treatment used were comparable between groups. However, in patients with long-COVID syndrome, we found a trend towards more dyspnea, more nausea/vomiting, and abnormal thorax computed tomography in the acute infection period. The proportions of patients having abnormal capillaroscopy findings were comparable between groups.

All symptoms associated with long-COVID were similar in frequency in patients with and without abnormal capillaroscopy (Tab. 2).

Discussion

In April 2020, shortly after the start of the pandemic, anecdotal patient reports began to emerge of previously healthy individuals who experienced prolonged symptoms and did not fully recover from infection with SARS-CoV-2. These patients coined the term "long-COVID" (18). In July 2021, "long-COVID" was added as a recognized condition that may result in disability under the Americans with Disabilities Act (19). COVID-19 infection is still a cause for concern and long-COVID syndrome continues to affect many patients with increasing prevalence. There are reports that long-COVID is associated with labor shortages. The most recent estimate of people living with long-COVID worldwide is over 65 million, and this number is growing with no clear diagnostic or treatment options (20). Therefore, understanding its pathophysiology is important for managing its clinical course and determining treatment strategies. Our study is the first in the literature that examined the relationship between the presence of long-COVID, and baseline characteristics and capillaroscopic findings, in the acute infection period and one of a few to evaluate the prevalence of long-COVID syndrome in the 1-year period following acute COVID-19 infection (21). At least one long-COVID symptom was observed in 66% of patients one year after acute infection. Although we found some trends, there was no significant difference between patients with and without long-COVID syndrome in terms of capillaroscopic findings and baseline characteristics including demographics, smoking history, symptoms, laboratory results, imaging results, length of hospital stay, and treatment used.

It is a fact that the long-COVID syndrome will become more common and may lead to a decrease in the quality of life and loss of work ability in affected individuals. The prevalence of symptoms persisting after acute infection can be as high as 87% in hospitalized patients (22, 23). In a cohort of non-hospitalized patients, fatigue was reported in 37% of patients (24). More than 200 symptoms affecting multiple organ systems have been described (1). Shortness of breath, fatigue, sleep disturbance and psychological problems, including anxiety, depression, post-traumatic stress disorder, and difficulty concentrating, are the most reported persistent symptoms in studies (22, 25). No clear relationship has been reported between the severity and diversity of symptoms during the acute infection period and the development of long-COVID syndrome. In patients with long-COVID syndrome, we only found a trend towards more dyspnea, more nausea/vomiting, and abnormal thorax computerized tomography in the acute infection period.

It is not yet known how long the symptoms defined as long-COVID will persist and what changes in symptom diversity and severity will be observed over time. Although it is defined as a period of 12 weeks to 12 months, most incidence studies have been conducted for a maximum period of 24 weeks. In these 25 observational studies, the frequency of long-COVID symptoms ranged from 4.7% to 80% (26). In a 6-month retrospective cohort study of 273,618 people recovering from COVID-19, the frequency of long-COVID was 42.34% (27). No matter whether they had been hospitalized or not, according to recent systematic review and metanalysis, 45% of COVID-19 survivors still had a variety of unresolved symptoms at 4 months (21). In our study, we questioned hospitalized patients about their symptoms one year after full recovery. Our research is one of the few studies that evaluated the frequency of long- COVID symptoms after one year. Our long-COVID symptom frequency was found to be 66%,

Tab. 2. Comparison of COVID-19 patients with and without capillaroscopic abnormalities.

	All patients	Abnormal capillaroscopy, n=22	Normal capillaroscopy, n=31	p
Long-COVID syndrome clinical features				
Fatigue, n (%)	23 (43.3)	11 (50)	12 (39)	0.41
Myalgia, n (%)	18 (34)	9 (41)	9 (29)	0.37
Arthralgia, n (%)	11 (20.7)	6 (27)	5 (16)	0.49
Dyspnea, n (%)	11 (20.7)	6 (27)	5 (16)	0.49
Cough, n (%)	10 (19)	4 (18)	6 (19.3)	0.99
Hair loss, n (%)	8 (15)	4 (18)	4 (13)	0.70
Headache, n (%)	7(13)	2 (9)	5 (16)	0.68
Sleep disorder, n (%)	7 (13)	4 (18)	3 (9.6)	0.43
Long-COVID syndrome, n (%)	35 (66)	14 (64)	21 (68)	0.76

which is in line with the literature. The fact that the prevalence of long-COVID symptoms in the 12th month after COVID-19 was similar or higher to the rates in the 4th-6th month, is an indication that the symptoms continue longer than predicted.

The fact that long-COVID symptoms also occur in patients who are not hospitalized suggests that they cannot be explained solely by the severity of the acute infection. The strongest pathophysiological theory proposed in this regard is neuronal damage caused by an increased inflammatory response in combination with vascular abnormalities such as microvascular dysfunction and endothelial activation (28). Therefore, numerous studies have been conducted to understand the microvascular events underlying the pathophysiology of long-COVID and some biomarkers like nitric oxide bioavailability, oxidative stress, proinflammatory cytokines, have been studied (29, 30). Nailfold capillaroscopy is a simple method of detecting microvascular changes in capillaries. In nailfold capillaroscopy examinations performed in patients with COVID-19 in the acute and post-acute phases, abnormal capillaroscopy findings were found in patients with COVID-19 compared to healthy controls (14, 15, 31, 32). In one of these studies, 41% of 54 patients hospitalized for COVID-19 had abnormal capillaroscopic findings. Patients with abnormal capillaroscopic findings were found to have an increased frequency of hyperinflammatory response and use anti-cytokine drugs (15). In pediatric patients, capillaroscopic abnormalities have also been shown in COVID-19 infection, and during the long follow-up period, especially in patients who developed an inflammatory response (33, 34). Several clinical trials demonstrating changes in NVC have been collected in a review, emphasizing the need for further studies to understand the true severity of each change in NVC (35). So, if there is an association between hyperinflammation and endothelial dysfunction and abnormal capillaroscopic findings, is there an association between abnormal capillaroscopic findings and long-COVID syndrome? In our study, we did not find a statistically significant increase in the frequency of abnormal capillaroscopic findings in patients with long-COVID syndrome. Moreover, all symptoms associated with long-COVID were similar in frequency in patients with and without abnormal capillaroscopy.

Our study represents the inaugural investigation exploring the hypothesis that microvascular status may play a crucial role in the pathophysiology of long-COVID. As the first study of its kind, while our study provides valuable insights, readers should interpret the findings with attention to the potential limitations. The primary limitation of our study is the relatively small number of patients included in the analysis. Second limitation arises from the unavoidable difference in the number of patients between the two study groups. This discrepancy results from the sequential nature of our study design, where capillaroscopy was performed initially, followed by the evaluation of long-COVID status after a one-year interval. Another notable limitation is the absence of control capillaroscopic evaluations before acute COVID-19 infection and during the assessment of long-COVID syndrome. Performing capillaroscopy during COVID-19 infection and one year after in patients with known recent capillaroscopy findings before COVID may overcome this limitation, but due to the changing COVID-19 epidemiology, it seems very difficult to overcome this limitation in similar studies to be performed in larger populations.

In conclusion, we found a 66% prevalence of long-COVID syndrome at 1-year follow-up after acute COVID-19. We did not find a statistically significant increase in the frequency of baseline abnormal capillaroscopic findings in patients with long-COVID syndrome. Moreover, all symptoms associated with long-COVID were found to be similar in frequency in patients with and without abnormal capillaroscopy. Capillaroscopy findings at the time of COVID-19 diagnosis are not predictive of which patients will ultimately develop long-COVID syndrome. Considering that abnormal capillaroscopic findings are an indirect indicator of microvascular pathology, the results of our study may suggest that the hypothesis of microcirculatory dysfunction alone may be insufficient to explain the pathophysiology underlying the long-COVID syndrome. However, it should be noted that capillaroscopy is an indirect indicator for this and further studies in larger groups of patients are needed.

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