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ORIGINAL RESEARCH

# Evaluation of Capillaroscopy Findings in Patients Presenting with Raynaud's Phenomenon (RP): A Retrospective Study*

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**ABSTRACT**

Raynaud's phenomenon (RP) is a discoloration of the fingers due to abnormal vasoconstriction in the digital arteries and cutaneous arterioles in response to cold or emotional stress. The study included patients who presented to a tertiary rheumatology clinic with RP between September 2022 and April 2023 and underwent nailfold capillaroscopy (NFC). Of the included patients, 34 (57.6%) were diagnosed with inflammatory rheumatic disease (IRD) and 25 (42.4%) with primary RP. When analysing antibodies, the most common antibody was antinuclear antibody (ANA) (n=39, 66.1%), and most of them were positive with a low titer (n=22, 37.3%). When comparing patients with and without IRD, the capillary density of ≥7 per 1 millimetre was sufficient in all patients in the group without IRD. There was a decrease in capillary density (<7) in 13 (38.24%) patients in the IRD group. When the sizes of capillaries were evaluated, a significant difference was found between the groups in terms of giant capillaries (>50 µm) (p=0.005). In the IRD group, 14 (41.18%) patients had a scleroderma (SCL) pattern and 20 (58.82%) had a non-SCL pattern. In the non-IRD group, all but two patients had a non-SCL pattern. Age, ANA positivity, high ANA titer, presence of giant capillaries and SCL pattern had a positive significant discriminatory effect (p<0.05) in distinguishing between patients with and without IRD. NFC assessment is an important tool in the diagnosis of IRDs such as systemic sclerosis. Advanced age, SCL pattern, giant capillaries and ANA positivity should be warning signs of secondary RP.

**Keywords: İnflammatory rheumatic disease. Capillaroscopy. Raynaud's Phenomenon. Systemic sclerosis.**

**Raynaud Fenomeni (RF) ile Başvuran Hastaların Kapilleroskopi Bulgularının Değerlendirilmesi: Retrospektif Çalışma Raynaud Fenomeni (RF) ve Kapilleroskopi**

**ÖZET**

Raynaud fenomeni (RF), soğuğa veya duygusal strese karşı dijital arterlerde ve kutanöz arteriyollerdeki anormal vazokonstriksiyona bağlı olarak gelişen parmaklardaki renk değişikliğidir. Çalışmaya Eylül 2022-Nisan 2023 tarihleri arasında üçüncü basamak bir romatoloji polikliniğine RF ile başvurup tırnak kıvrımı kapilleroskopisi (TKK) yapılan hastalar dahil edildi. Dahil edilen hastaların 34 (%57,6)'üne inflamatuvar romatizmal hastalık (İRH) tanısı konulduğu, 25 (%42,4)'inin ise primer RF olarak kabul edildiği belirlendi. Antikorlar değerlendirildiğinde, en sık saptanan anti-nükleer antikor (ANA) (n=39, %66,1) olup, çoğunluğu düşük titrede pozitifti (n=22, %37,3). İRH saptanan ve saptanmayan hastalar karşılaştırıldığında, İRH olmayan gruptaki hastaların tamamında kapiller dansite her 1 milimetrelik alanda ≥7 olup yeterliydi. İRH grubundaki hastaların 13'ünde kapiller dansitede azalma (<7) mevcuttu. Kapillerlerin boyutları değerlendirildiğinde, gruplar arasında dev kapiller (>50 µm) açısından anlamlı farklılık saptandı (p=0,005). İRH grubundaki hastaların 14'ünde SCL paterni, 20 (%58,82)'sinde ise non-SCL paterni saptanmıştı. İRH olmayan gruptaki hastaların sadece ikisi hariç tamamında non-SCL paterni saptanmıştı. Yaş, ANA pozitifliği, yüksek titre ANA pozitifliği, dev kapiller görülmesi ve SCL paterninin İRH olan ve olmayan hastaları ayırmada pozitif anlamlı ayırıcı (p<0,05) etkisi gözlenmiştir. TKK değerlendirmesi, sistemik skleroz gibi İRD'lerin tanısında önemli bir araçtır. İleri yaş, SCL paterni, dev kapiller ve ANA pozitifliği sekonder RF açısından uyarıcı olmalıdır.

**Anahtar Kelimeler: İnflamatuvar romatizmal hastalık. Kapilleroskopi. Raynaud fenomeni. Sistemik skleroz.**

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Raynaud's phenomenon (RP) is a discoloration of the fingers due to abnormal vasoconstriction of the digital arteries and cutaneous arterioles in response to cold or emotional stress. Initially a white discoloration (vasoconstriction), followed by a blue discoloration (cyanosis due to deposits of deoxygenated blood) and finally a red discoloration (hyperemia after ischemia).[1,2] The overall prevalence of RP is usually between 3 and 5%, although high rates of up to 21% have also been reported.[1,2] A primary RP can be

diagnosed if no underlying cause for the RP can be found. If there is an underlying pathology, in particular connective tissue diseases (CTDs), this is referred to as secondary RP.[3] Primary RP usually occurs at a young age and is 4-20 times more common in women than in men.[4] It presents with symmetric attacks, digital ulcers or trophic lesions are not seen. Capillaroscopic examination shows normal findings. In contrast, secondary RP occurs in middle age, with asymmetric attacks, digital ulcers and gangrene, positive autoantibody formation and abnormal findings on capillaroscopic examination.[4]

In primary RP, there is a functional defect in the arteriovenous anastomoses, which play a role in thermoregulation, whereas in secondary RP, tissue ischemia is observed, which is due to both a disturbance in thermoregulation and structural defects in the nutritional capillaries. Thus, while excessive vasospasm develops after exposure to cold in primary RP, structurally intact feeding capillaries prevent tissue ischemia and thus ischemic damage in primary RP.[5]

Nailfold capillaroscopy (NFC) is a non-invasive, inexpensive and easy-to-use imaging technique that can be used to assess the microcirculation of the nailfold.[6] It is frequently used in rheumatology practice to differentiate between primary and secondary RP and is also included in the ACR/EULAR classification criteria for systemic sclerosis (SSc) published in 2013.[7] It has been used for many years as an auxiliary method in the detection of rheumatic diseases that affect the microcirculation, such as Sjogren's syndrome (SJS), rheumatoid arthritis, systemic lupus erythematosus (SLE) and idiopathic inflammatory myositis, especially SSc among the CTDs.[8]

Structural microvascular abnormalities are one of the main features of SSc related to the pathophysiologic process. With NFC imaging, the column of red blood cells in the capillaries is visualised.[9] In imaging, capillaries consist of an arterial and a venous part and an apical ring that connects the two parts. The arterial part is narrower than the venous part, and the ratio of venous to arterial diameters is about 1.2-1.5/1.[4]

The NFC technique with ×200 magnification, which captures at least two contiguous areas of 1 mm in the nailfold in the middle of the finger, is the gold standard for performing capillaroscopy. The images can be evaluated qualitatively or semi-quantitatively with the NFC. Quantitative assessment includes capillary density (normal, >7/mm per capillary), morphology (normal, capillaries in the shape of a hairpin or once or twice cross-shaped or curved, provided they are convex), width of the apical part (normal, <20 micrometres (μm)) and the presence of haemorrhage areas (normal, absent). In the early phase of the scleroderma (SCL) pattern, the number of capillaries is adequate (>7/mm per capillary), the morphology is normal and there is little or no haemorrhage. The most striking feature of the early SCL pattern is giant capillaries (apical diameter >50 μm). The early SCL pattern is important for the early diagnosis of SSc. In the active phase of the SCL pattern, the number of capillaries is reduced (4-6 per mm) and their morphology is impaired. Areas of haemorrhage are more or absent, and giant capillaries (apical diameter >50 μm) are other detectable findings. In the late phase of the SCL pattern, the capillary density is greatly reduced (< 4 per mm), avascular areas are visible and the morphology is clearly deteriorated. Hemorrhagic areas and giant capillaries are not to be expected.[9]

In secondary RP due to CTDs such as SLE and SJS, which are not part of the scleroderma spectrum, findings in the form of normal patterns or non-specific abnormalities may occur when assessing NFC. Non-specific abnormalities are defined as isolated findings such as enlarged capillaries (apical diameter 20-50 μm), few areas of hemorrhage, partial reduction in the number of capillaries and partial deterioration of morphology. If numerous abnormalities or several different abnormalities occur in a patient, this may indicate an underlying CTD. The fact that non-specific abnormalities can also occur in primary RP can lead to difficulties in the differential diagnosis of primary RP and secondary RP.[9]

In our study, we aimed to evaluate the capillaroscopic findings of patients admitted to our rheumatology outpatient clinic with RP, whether these patients were diagnosed with inflammatory rheumatic disease (IRD) on the basis of clinical, laboratory and imaging procedures and whether the capillaroscopic findings had a significant differential effect with regard to the diagnosis of IRD.

## Material and Method

Patients who presented with RP and underwent capillaroscopy at Bursa Uludag University Faculty of Medicine between September 2022 and April 2023 were included in our study. Capillaroscopic findings, clinical and demographic data, laboratory characteristics, autoantibodies (rheumatoid factor, anti-cyclic citrullinated peptide, anti-nuclear antibody (ANA), ANA profile), diagnosis of IRD, diagnosis of primary or secondary RP and presence of lung involvement were recorded. ANA values of 1/320 and below were classified as low positive titers, values above 1/320 titers as high positive titers (Ethics Committee approval date: December 4, 2024; protocol code: 2024-19-18).

A total of 78 patients underwent capillaroscopy during the six-month period; however, 19 of the patients were excluded from the study because clear images could

not be obtained during the capillaroscopic examination for reasons such as the use of nail polish, inappropriate ambient temperature and excessive nailfold skin thickness on the examined fingers. Of the 59 patients included in the study, the third, fourth and fifth toes of both hands were examined at 200x magnification. Cedar oil was used in the examination of all patients to make the capillaries more visible. The examination was carried out after a waiting period of 15-20 minutes in a room with a normal temperature of approx. 20-22°C. The previously acquired images were evaluated by a rheumatologist trained and certified in capillaroscopy, who was blinded to the diagnostic information provided by the patients. Number (per mm), size (apical width) and morphology of capillaries, presence or absence of avascular areas and hemorrhagic areas were determined and recorded as SCL or non-SCL pattern. Patients who were found to have an SCL pattern were categorized into early, active or late phase depending on the findings. Patients classified as non- SCL pattern were categorized as normal or non-specific abnormalities according to the findings of the NFC.

Those who presented with RP and were diagnosed with secondary RP and IRD and those who were diagnosed with primary RP and no IRD were compared as two separate groups with regard to clinical, demographic, laboratory and capillaroscopic findings.

*Statistical Analysis*

The compatibility of the continuous variables with the normal distribution was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as n (%). When comparing two groups, the Independent Sample t-Test was used for continuous variables with normal distribution. The Chi-square test was used for the comparison of categorical variables. Univariate logistic regression analysis was performed to determine the factors that may be associated with the distinction between patients with IRD and those without IRD. Multivariate logistic regression analysis was performed for the significant variables after the univariate logistic regression analysis. The SPSS (IBM SPSS for Windows, Ver.28) package program was used for the statistical data calculations. $p<0.05$ was accepted as the statistical significance level.

## Results

The mean age of the patients (n=59) was 51.17 years (±SD:14.72) and almost all were female (n=56, 94.9%).

It was found that 34 (57.6%) of the patients were diagnosed with IRD during follow-up, while 25 (42.4%) were not diagnosed with IRD and were recognised as primary RP. In the evaluation of the 34 patients diagnosed with IRD, the most common diagnoses were SSc (n=9, 26.5%) and SJS (n=9, 26.5%). Of the patients with a diagnosis other than CTDs (other IRDs), one was diagnosed with ankylosing spondylitis and the other with psoriatic arthritis. When antibodies were evaluated, ANA was the most commonly detected antibody (n=39, 66.1%), and the majority were positive at low titers (n=22, 37.3%). In the ANA profile panel, anti-SSA (n=11, 18.6%) was the most frequently detected antibody (Table I).

**Table I.** Clinical, Demographic and Laboratory Characteristics of Patients Presenting with Raynaud's Phenomenon

| | |
|---|---|
| **Age (years)** | 51.17 (±SD:14.72) |
| **Gender, n(%)** | |
| Female | 56 (94.9) |
| Male | 3 (5.1) |
| **Diagnosis, n(%)** | |
| No IRD | 25 (42.4) |
| Yes IRD | 34 (57.6) |
| **IRD** | 34 (100) |
| SSc | 9 (26.5) |
| SJS | 9 (26.5) |
| RA | 5 (14.7) |
| SLE | 3 (8.8) |
| UCTD | 5 (14.7) |
| MCTD | 1 (2.9) |
| Other IRD | 2 (5.9) |
| **Lung involvement, n(%)** | 5 (8.5) |
| **RF positivity, n(%)** | 7 (11.9) |
| **Anti-CCP positivity, n(%)** | 5 (8.5) |
| **ANA positivity, n(%)** | 39 (66.1) |
| **ANA 1/100, n(%)** | 17 (28.8) |
| **ANA 1/320, n(%)** | 5 (8.5) |
| **ANA 1/1000, n(%)** | 12 (20.3) |
| **ANA 1/3200, n(%)** | 3 (5.1) |
| **ANA 1/10000, n(%)** | 2 (3.4) |
| **ANA positivity with low titer, n(%)** | 22 (37.3) |
| **ANA positivity with high titer, n(%)** | 17 (28.8) |
| **Anti-SSA, n(%)** | 11 (18.6) |
| **Anti-SSB, n(%)** | 5 (8.5) |
| **Anti-SCL, n(%)** | 7 (11.9) |
| **Anti-Centromere, n(%)** | 10 (16.9) |
| **RNP, n(%)** | 3 (5.1) |
| **PM-SCL, n(%)** | 2 (3.4) |

***ANA,*** anti-nuclear antibody; ***Anti-CCP,*** anti cyclic citrullinated peptide; ***IRD,*** inflammatory rheumatic disease; ***MCTD,*** mixed connective tissue disease; ***PM-SCL***, Poliomyositis/scleroderma antibody; ***RA,*** *rheumatoid arthritis*; ***RF,*** rheumatoid factor; ***RNP,*** U1-ribonucleoproteins; ***SJS,*** systemic sjogren's syndrome; ***SLE,*** systemic lupus erythematosus; ***SSc,*** systemic sclerosis; ***UCTD,*** undifferentiated connective tissue disease.

When comparing patients with and without IRD, it was found that the patients in the group without IRD were younger (p=0.002). Although ANA positivity was found in almost all patients (n=31, 91.18%) in the IRD group ($p<0.001$), there was no significant difference between the groups in terms of low titer

ANA positivity (p>0.05). High titer ANA positivity was detected in approximately half of the patients in the IRD group (n=16, 47.06%) (p<0.001). When assessing capillary density, capillary density was ≥7 per 1 millimeter (mm) in all patients in the non-IRD group. In 13 patients in the IRD group, capillary density decreased (<7). When assessing the size of the capillaries, there was no significant difference between the two groups with regard to normal capillaries (<20 µm) and enlarged capillaries (20-50 µm) (p>0.05), while a significant difference was found with regard to giant capillaries (>50 µm) (p=0.005). There was no significant difference between the groups in terms of abnormal morphology and hemorrhage (p>0.05). The SCL pattern was detected in 14 patients in the IRD group. In the non-IRD group, all patients had a non-SCL pattern, with the exception of two patients with an SCL pattern. In the IRD group, 20 (58.82%) patients had a non-SCL pattern, of which seven were normal and 13 had non-specific abnormalities. In SSc, one of the most common IRDs, the SCL pattern was found in eight patients (88.88%), while it was found in three (33.33%) of the SJS patients (Table II).

**Table II.** Comparison of Demographic, Laboratory and Capillaroscopic Characteristics of Patients with and without IRD Presenting with Raynaud's Phenomenon

| | No IRD n (%) 25 (42.4) | IRD n (%) 34 (57.6) | p |
|---|---|---|---|
| **Age (years)** | 44.36 (±SD: 13.98) | 56.18 (±SD: 13.33) | ***0.002*** *t* |
| **Gender** | | | |
| Female | 24 (96.00) | 32 (94.11) | >0.05 $\chi^2$ |
| Male | 1 (4.00) | 2 (5.89) | |
| **Lung involvement** | 0 (0.00) | 5 (14.71) | ***0.045*** $\chi^2$ |
| **RF positivity, n(%)** | 0 (0,00) | 7 (20.59) | ***0.016*** $\chi^2$ |
| **Anti-CCP positivity, n(%)** | 0 (0.00) | 5 (14.70) | ***0.045*** $\chi^2$ |
| **ANA positivity, n(%)** | 8 (32.00) | 31 (91.18) | ***<0.001*** $\chi^2$ |
| **ANA positivity with low titer, n(%)** | 7 (28.00) | 15 (44.12) | 0.206 $\chi^2$ |
| **ANA positivity with high titer, n(%)** | 1 (4.00) | 16 (47.06) | ***<0.001*** $\chi^2$ |
| **Capillary density (/mm)** | | | |
| **≥7** | 25 (100.00) | 21 (61.76) | ***<0.001*** $\chi^2$ |
| **4-6** | 0 (0.00) | 12 (35.29) | ***<0.001*** $\chi^2$ |
| **≤3** | 0 (0.00) | 1 (2.95) | >0.05 $\chi^2$ |
| **Dimension (µm)** | | | |
| **<20** | 11 (44.00) | 10 (29.41) | 0.247 $\chi^2$ |
| **20-50** | 12 (48.00) | 10 (29.41) | 0.145 $\chi^2$ |
| **>50** | 2 (8.00) | 14 (41.18) | ***0.005*** $\chi^2$ |
| **Abnormal morphology** | 11 (44.00) | 22 (64.70) | 0.113 $\chi^2$ |
| **Haemorrhage** | 7 (28.00) | 16 (47.06) | 0.138 $\chi^2$ |
| **Non-SCL pattern** | 23 (92.00) | 20 (58.82) | ***0.014*** $\chi^2$ |
| Normal | 5 (20.00) | 7 (20.59) | 0.956 $\chi^2$ |
| Non-specific abnormality | 18 (72.00) | 13 (38.24) | ***0.010*** $\chi^2$ |
| **SCL pattern** | 2 (8.00) | 14 (41.18) | ***0.005*** $\chi^2$ |
| Early | 2 (8.00) | 0 (0.00) | 0.175 $\chi^2$ |
| Active | 0 (0.00) | 12 (35.29) | ***<0.001*** $\chi^2$ |
| Late | 0 (0.00) | 2 (5.88) | >0.05 $\chi^2$ |

***ANA,*** anti-nuclear antibody; ***CCP,*** anti-cyclic citrullinated peptide; ***IRD,*** inflammatory rheumatic disease; ***RF,*** rheumatoid factor; ***SCL,*** scleroderma ***t,*** Independent Samples t Test; ***χ2,*** chi-square test; ***p <0.05***:statistical significance level.

The univariate logistic regression analysis performed to evaluate the factors that might be effective in discriminating between patients with and without IRD showed a positive significant differential effect (p<0.05) for age, ANA positivity, ANA high titer positivity, giant capillary and SCL pattern. On the other hand, the non-SCL pattern had a negative significant differential effect. In the multivariate analysis, only ANA positivity had a positive significant differential effect (p<0.05) (Table III).

**Table III.** Factors Associated with the Differentiation of Patients with IRD from Patients without IRD

| | Univariate Logistic Regression | | | Multivariate Logistic Regression | | |
|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** |
| **Age** | 1.065 | 1.020-1.112 | **0.004** | | | |
| **ANA positivity** | 21.958 | 5.136-93.871 | **<0.001** | 21.958 | 5.136-93.871 | **<0.001** |
| **ANA positivity with high titer** | 21.333 | 2.585-176.084 | **0.004** | | | |
| **Capillary dimension >50 µm** | 8.050 | 1.628-39.800 | **0.011** | | | |
| **Non-SCL pattern** | 0.195 | 0.049-0.779 | **0.021** | | | |
| **SCL-pattern** | 8.050 | 1.628-39.800 | **0.011** | | | |

***ANA,*** anti-nuclear antibody; ***CI,*** *confidence interval*; ***OR,*** Odds ratio*;* ***p <0.05,*** statistical significance level.

## Discussion and Conclusion

When evaluating the capillaroscopic findings of patients with RP in our study, SSc and SJS were the most common IRD diagnoses, and SS-A and ANA high titer positivity were important for the diagnosis of IRD. Although the non-SCL pattern is an expected finding, especially in patients with a primary RP diagnosis, it can also be found in patients with IRD (58.82% of our patients with IRD). ANA positivity is an important marker for differentiating between patients with an IRD diagnosis and those without an IRD diagnosis.

Only three of our patients were male, the majority were female. In addition, the patients in the primary RP group without an IRD diagnosis were younger than the patients in the secondary RP group with an IRD diagnosis, and our results are consistent with the literature.[2,4,10]

RP is common in SSc and its prevalence can reach 95%. Therefore, the detection of microvasculopathy by NFC is important for the early diagnosis of CTDs, especially SSc, in patients with RP and is included in the SSc classification criteria.[7,10] When assessing our patients with regard to the diagnosis of CTD, SSc (26.5%) and SJS (26.5%) were the most common diagnoses. The preponderance of patients with SSc is to be expected as the prevalence of RP in patients with

SSc is high. On the other hand, the rate of SJS patients was similar to that of SSc. In the separate evaluation of the capillaroscopic findings of patients with SJS, an SCL pattern was found in 33.3% of these patients. In the study conducted by Corominas et al.[11] the SCL pattern was found in 10.2% of patients with primary SJS. In another study by Capobianco et al.[12] this rate was 11.5%. In the study conducted by Bernardino et al.[10] it was determined that patients who were previously evaluated with NFC were most frequently followed up with the diagnoses of SSc, mixed connective tissue disease (MCTD) and SLE. The small number of patients could be one of the main factors for the difference of our results from those in the literature.

ANA positivity is an important diagnostic marker in CTDs. One study reported that ANA positive patients had significantly longer RP times compared to ANA negative SSc patients. In this study, 90% of SSc patients were also classified as ANA-positive.[13] Another study reported that ANA and SS-A positivity are risk factors for differentiation to a CTD such as SJS and SSc in patients investigated with RP and followed up as undifferentiated connective tissue disease (UCTD)[14]. In our study, ANA positivity, especially ANA high-titer positivity, was found more frequently in the IRD group.

In our study, there was no significant difference between the secondary RP group with IRD and the primary RP group without IRD in terms of haemorrhage, the presence of abnormal morphology and enlarged capillaries. Again, although there was a significant difference between the groups in terms of non-SCL pattern, most patients in the secondary RP group with IRD had a non-SCL pattern, and the majority of these patients had non-specific abnormalities. The SCL pattern, decrease in the number of capillaries and giant capillaries were conspicuous in the patients in the secondary RP group diagnosed with IRD.

The NFC assessment has a high sensitivity and specificity in SSc patients. In addition, similar microvasculopathic changes may occur in other CTDs, and assessment of NFC may become important for early diagnosis.[15] RP is a common finding in patients with SSc, and as there may be a correlation between NFC findings and systemic involvement, monitoring of NFC findings may become important. [10]

In a study conducted in patients with SJS, nonspecific abnormalities were found in 27.2% of patients, while the SCL pattern was found in 10.2%. In other cases, normal capillaroscopic findings were reported.[11] The study by Thomson et al.[16] reported that during follow-up of 86 patients with abnormal capillaroscopic findings, SSc was found in 79 patients, dermatomyositis (DM) in four patients, and antisynthetase syndrome in three patients. Of 71 patients with normal NFC findings at baseline, only four developed SSc during follow-up. For the diagnosis of SSc, the NFC showed a sensitivity of 95% and a specificity of 91%. In our study, SCL pattern and giant capillaries were conspicuous in patients in the secondary RP group who were diagnosed with IRD.

In a study involving 3029 patients with primary RP, the association between NFC findings and the presence of CTD was investigated. Patients were followed up at 6-month intervals for an average of 4.8 years, and NFC findings in the 6 months prior to diagnosis were evaluated. At the end of follow-up, 1123 (37.1%) patients were diagnosed with CTD. The study found that SCL pattern was significantly associated with the development of SSc, DM, SSc overlap and MCTD.[17] In our study, an SCL pattern was present in two of the patients accepted as primary RP. As we had no follow-up data on these patients, it was not possible to determine whether they developed CTD in the future.

In the study by Shenavandeh et al.[14] it was reported that UCTD patients who were ANA positive patients with SCL pattern, enlarged capillaries, giant capillaries and more than five hemorrhage areas on capillaroscopy differentiated into CTD during follow-up. Another study by Szabo et al.[18] found mild avascularity and, in a few cases, enlarged capillaries in patients with primary RP. Another study by Ziegler et al.[3] also reported specific differences in microvascular structure between patients with primary RP and healthy controls. In summary, it was concluded that primary RP may not be entirely benign and may be associated with microcirculatory vasculopathy. In patients with non-rheumatic diseases such as diabetes mellitus, glaucoma, essential hypertension and anorexia nervosa or chronic smokers, findings such as reduced capillary density, haemorrhages, enlarged capillaries and avascular areas may be observed, even if there is no underlying CTD. It has also been reported that COVID-19 infection can cause non-specific changes and hemorrhages.[15] In our study, although no avascular area was found in the capillaroscopic examinations of patients who were not diagnosed with IRD and accepted as primary RP, the rates of hemorrhage and dilated capillaries were similar to those in the secondary RP group, and there was no significant difference between the groups. Since our study was not a prospective study, we could not make a comparison regarding capillaroscopic findings and diagnosis at follow-up of patients in this primary RP group.

The main limitations of our study are the small number of patients and the lack of follow-up data due to the cross-sectional design. We included patients from the first period after the start of recording NFC findings. In later evaluations, however, there were also

patients whose diagnosis was not yet clear. We have therefore chosen this time period to include patients with definitive diagnoses. However, in our study, the findings referred to as nonspecific abnormalities were by no means rare in patients in the primary RP group. In addition, two patients had giant capillaries. Other important limitations were the lack of a healthy control group and the fact that comorbidities such as diabetes mellitus, which can cause capillaroscopic changes, were not recorded.

NFC assessment, in combination with other clinical and laboratory findings, is an important, non-invasive and easily reproducible method for the diagnosis of IRD, especially SSc. A considerable degree of non-specific abnormalities can be detected in patients with primary RP, and it is important to monitor these patients with NFC for future IRD diagnosis. Advanced age, SCL pattern, giant capillaries and ANA positivity should be warning signs of secondary RP.

**Ethics Committee Approval Information:**
Approving Committee: Bursa Uludag University Health Research Ethics Committee
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**Researcher Contribution Statement:**
Idea and design: S.M., B.Y., B.N.C.; Data collection and processing: S.M., A.E.; Analysis and interpretation of data: S.M., A.E.; Writing of significant parts of the article: S.M., B.Y., B.N.C., H.E.D., Y.P.
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