RESEARCH ARTICLE

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Prolonged Capillary Refill Time Indicates Early Nailfold Capillaroscopy in Systemic Sclerosis

ABSTRACT

Objective: Systemic sclerosis (SSc) is a progressive connective tissue disorder that features vascular injury and persistent fibrosis with an autoimmune background. The hypoxic state at the capillary caused by SSc can be assessed with several methods. This study thus investigated the capillary refill time (CRT) effectivity in evaluating peripheral circulation in SSc patients.

Methods: This prospective, case-control study was conducted with SSc patients and gender and age-matched healthy controls. The CRT measurements were performed by a rheumatologist unaware of patients' records with a smartphone camera in the optimized test ambiance. A video processing software was then applied for the captured videos.

Results: 61 patients with SSc and 60 controls participated in this study. According to disease involvement, the patients were then divided into diffuse cutaneous SSc (dSSc) and limited cutaneous SSc. Mainly, CRT was prolonged in the patient group than in the control group. CRT was also prolonged in patients with pathological capillaroscopy patterns in the nail fold capillaroscopy (NFC), below 50 years old, or whose disease duration was over three years. Per disease involvement, patients in the dSSc group with pathologic NFC had prolonged CRT results and higher pulmonary artery pressure levels. The use of CRT for NFC positivity in patients with SSc was practicable (AUC: 0.717;95% CI 0.714-0.942; 83.95% accuracy; 67.9% sensitivity, 100% specificity, 100% positive predictive value, 21.7% negative predictive value, P=0.015).

Conclusions: CRT is markedly prolonged in patients with SSc. Evaluating CRT with the NFC positivity may provide pulmonary progression predictable, notably in dSSc patients.

Keywords: Capillaroscopy, Capillary Refill Time, Pulmonary Hypertension, Systemic Sclerosis.

Uzamış Kapiller Dolum Süresi, Sistemik Sklerozlu Hastalarda Tırnak Yatağı Kapillaroskopisinin Erken Yapılmasını Vurgular

ÖZET

Amaç: Sistemik skleroz (SSk), otoimmün bir arka planda vasküler hasar ve kalıcı fibrozisi içeren ilerleyici bir bağ dokusu hastalığıdır. SSk'nin kapillerdeki sebep olduğu hipoksik durum çeşitli yöntemlerle değerlendirilebilir. Bu çalışma bu nedenle, SSk hastalarında periferik dolaşımı değerlendirmede kapiller dolum zamanının (KDZ) etkinliğini değerlendirmiştir.

Gereç ve Yöntem: Bu prospektif, vaka-kontrol çalışması, SSk hastaları ile cinsiyet ve yaşça eşleştirilmiş sağlıklı kontrollerle yürütülmüştür. KDZ ölçümleri, hasta kayıtlarından bilgisi olmayan bir romatolog tarafından bir akıllı telefon kamerası ile uygun hale getirilmiş bir test ortamında yapıldı. Kayıt edilen videolar için bir video yazılımı uygulandı.

Bulgular: 61 SSk hastası ve 60 kontrol bu çalışmaya katıldı. Hastalık tutulumuna göre hastalar diffüz kutanöz SSk (dkSSk) ve limitli kutanöz SSk olarak ikiye ayrıldı. Esasen, KDZ hasta grubunda kontrol grubuna göre uzamıştı (p = 0.003). KDZ, tırnak yatağı kapilleroskopisi (TYK) patolojik paternde olan 50 yaş altındaki ya da hastalık süresi 3 yıldan fazla olan hastalarda uzamıştı. Hastalık tutulumuyla beraber, TYK'si patolojik olan dkSSk grubundaki hastalarda KDZ sonuçları uzamıştı ve pulmoner arter basıncı seviyeleri daha yüksekti. SSk'lı hastalarda TYK pozitifliği için KDZ kullanımı uygulanabilirdi (AUC: 0.717;95% CI 0.714-0.942; 83.95% doğruluk; 67.9% duyarlılık, 100% özgüllük, 100% pozitif prediktif değer, 21.7% negatif prediktif değer, P=0.015).

Sonuç: SSk'lı hastalarda KDZ belirgin şekilde uzamaktadır. KDZ'nin TYK pozitifliği ile değerlendirilmesi, özellikle dkSSk hastalarında pulmoner progresyonun öngörülebilir olmasını sağlayabilir.

Anahtar Kelimeler: Kapilleroskopi, Kapiller Dolum Zamanı, Pulmoner Hipertansiyon, Sistemik Skleroz.

INTRODUCTION

Systemic Sclerosis (SSc) is an autoimmune disease in which excessive connective tissue increase influences the entire human body (1). Intense fibroblastic activity and excessive collagen production were identified in the disease (2). SSc manifests a heterogeneous organ involvement and severity. The skin is primarily affected; cardiac, pulmonary, gastrointestinal (GI) tract, renal, digital, and musculoskeletal involvements may also be detected (3). The first disruption in the skin is edema, followed by thickening and hardening due to excessive collagen production (2, 4). Raynaud's phenomenon (RP), which is reversible vasospasm due to functional changes in the digital arteries of the extremities, can be the first clinical sign (1, 5). Pallor, paresthesia, pain, augmented edema appearing in the fingers in the form of attacks, and the progression of angiopathies secondary to collagen deposition led to ischemic ulcers and atrophies in the fingers (1, 6). The formation of digital ulcers indicates a worse course in disease progressions, such as cardiovascular worsening and decreased survival (7, 8). Like cardiologic involvement, musculoskeletal, renal, and pulmonary complications are also prognostic (3).

Evaluating digital involvements among cutaneous manifestations is crucial in SSc patients. In physical examination, possible clues such as swollen puffy fingers, non-pitting edema of the hands, skin thickening, perioral skin tightening, loss of fingertip tissue, tendon friction rubs, calcinosis cutis, cutaneous hyperpigmentation and telangiectasias, abnormal nail fold capillaroscopy (NFC) can be detected (9, 10). NFC is an uncomplicated, invivo technique that can predict the SSc prognosis and mediate the effects of autoantibodies (11, 12). In addition, NFC, where the fourth or fifth finger is usually selected in practice, is mainly used to distinguish the RP origin (13). Evaluating the architecture of the skin capillaries can point out the morphology, density, size, microhemorrhages, avascularity, and neoangiogenesis (14). Therfore, a pathological NFC consisted of dilated and giant capillaries, hemorrhages, disorganized vascular arrays, ramified/bushy capillaries, and capillary losses (15).

Capillary refilling time (CRT), which is ancient but functional use, is a physical examination method that can evaluate skin arterioles at the bedside. CRT effectively assesses inconvenient circumstances of the peripheral vascular bed's fullness (16). In CRT, mainly, the filling rate of the arteriole and capillary system is observed. A time of > 2 s is considered one means of proving circulatory disorder (17). However, some situations reduce the reliability of CRT, such as age, ambient light, ambient temperature, observer reliability, and applied pressure; therefore, the examination takes effort, attention, and time (16, 18).

There is no conventional method other than NFC to evaluate the digital involvement at the micro-level in patients with SSc. A test such as CRT, which can predict peripheral tissue perfusion, has not yet been applied in patients with SSc. The evaluations and results of our study thus contribute to NFC findings and determine CRT's role in the prognosis of SSc.

MATERIAL AND METHODS

Our prospective case-control study was conducted with SSc patients diagnosed according to 2013 ACR/EULAR Classification Criteria for Scleroderma (19) and an age-matched control group. The local ethics committee approved the study method (2020/96), and the participants signed informed consent forms were collected prior to the study. The patients' demographic features and laboratory parameters were noted simultaneously. Those over 18 years of age who had at least a hemoglobin (Hb) level of 10 gr/dL did not take drugs or food that can cause vascular response (decongestant, caffeine, or tea intake) within the preceding 24 h were included in the study. At the same time, those with nail bed impropriety (cosmetic application, manicure, onychomycosis) and smoking were excluded.

The patients were categorized into two groups based on the SSc disease severity (20). Accordingly, patients with a clinical evaluation (objectively documented RP plus anyone: SSc-type nail fold capillary pattern/SSc selective autoantibodies or a subjective RP plus both: SSc-type nail fold capillary pattern and SSc selective antibodies) were rated as limited cutaneous (lSSc); and those with criteria for lSSc plus proximal cutaneous changes were rated as diffuse cutaneous (dSSc) involvement. Likewise, the control group consisted of age-matched healthy individuals with no comorbidities.

NFC assessments were performed after patients were kept at room temperature in a sitting position for at least 15 minutes. Mainly the 4th and 5th, though all fingers were evaluated. After the immersion oil (Mr Salt-E, Chrystal distribution, CA, USA) was applied, the procedure was performed with a capillaroscope (AM4113T-R4-70x magnification, Dino-Lite digital microscope, Class B, Taiwan). Findings of NFC in 20x magnification were accepted as the presence of neoangiogenesis, capillary elongation/tortuosity (>4 times the average width), reduced capillary density (<7 capillaries/mm), avascular area (the absence of two or more consecutive loops), hemorrhage (positivity), giant loops (> 50 µm) and abnormal blood flow (21).

The CRT measurements were made with materials (a smartphone, freeware software, physical

programming platform) found easily in ordinary outpatient clinic conditions. The patients who obtained the CRT course were unaware of the laboratory results and NFC findings. Firstly, the body temperatures were taken from all participants to obtain proper conditions for the CRT measurements, and results were considered normal between 36.5 - 38 Celcius (22). Next, the patient and control group were matched by age not to cause an age deflection effect. Then, all measurements were made between 9 - 10 am to keep the optimum light level; furthermore, the measurement area's light exposure was set to a brightness level of 300-500 lux via a photometric application (Lux-Meter) already installed the smartphone. Finally, we designed a 3D measurement platform and a manufacturing procedure with Ultimaker Cura to standardize each evaluation. The middle finger was preferred for CRT measurement, as it has the most extended terminal phalanx between the fingers and thus has more blood supply. In addition, the measurements were performed by only one rheumatologist to avoid measurement technique variations.

The images were recorded twice with a regular smartphone placed on a focused tray on the platform to observe the finger placement area. The chosen finger to be measured was placed in the appropriate position. Adequate pressure was applied to the nail root with a transparent, flat plastic tool until whitening was achieved, then the plastic tool was immediately pulled from the smartphone's camera frame after 5 s. All stages were recorded in mp4 video format via the same smartphone placed on the platform. The images were evaluated by using the color threshold filter of the VLC media player software (ver. 3.0.5) to determine the observed blood flow in the images. The time between the blood flow disappeared and the nail color completely re-regulated was recorded on the screen in ms. The average result of the two measurements for each finger was recorded as the current CRT value. All the equipment used for CRT measurement is presented in Figure 1.

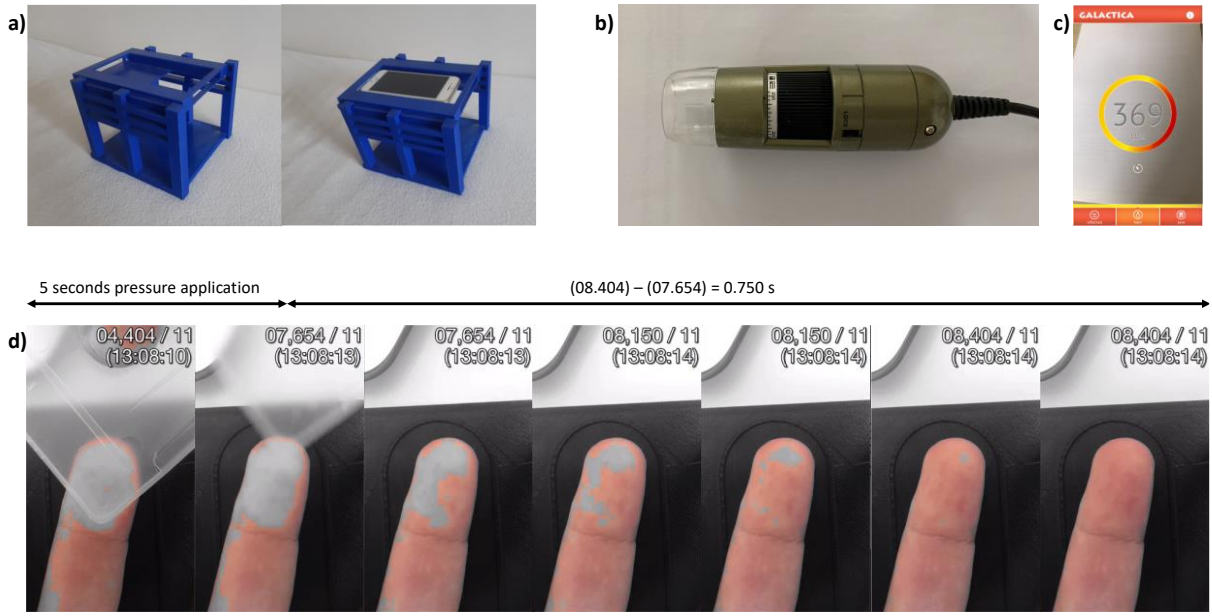


Figure 1. The pieces of equipment used for CRT measurement, a) A smartphone placed on a 3D designed measurement platform; b) Digital microscope (Dino-Lite); c) Photometric application (Lux-Meter); d) Sequential snapshots from the evaluated video with VLC player in color threshold filter mode.

Statistical Analysis: We used SPSS ver. 22 (SPSS Inc., Chicago, IL, USA) for the statistical analyses. The Pearson correlation was used to correlate normally distributed data, whereas, in non-normal data, Spearman correlation was used. The Chi-square test was preferred in categorical data evaluation. We also used independent t-tests to compare the CRT results between the patients with SSc and the control group. In continuous data pinpointing comparisons with CRT and in comparisons according to disease severity, an independent t-test was used in normal distributions and the Mann–Whitney U-test in non-normal distributions. The area under the receiver-operating characteristics (ROC) curve (AUC) and 95% confidence intervals (CI) were used to assess the ability of each CRT of the patient and control groups to the NFC distinction. In all calculations, a p-value of 0.05 was accepted as significant.

RESULTS

This study included a total of 61 out-patients (mean age 48.78±12.56 years) and 60 controls (mean age 49.33 ± 12.75 years). The longest measurement among all CRTs was 5,736 s. Again, 33.1% of all measured CRTs were prolonged. Meanwhile, 95% of those were in the patient group. None of the participants were smoking. Two cases in the lSSc and one in the dSSc group had a level of

Hb below 10 gr/dL; they were excluded from the study. The remained demographic, laboratory, and characteristic features of the patients with SSc subgroups are detailed in Table 1. The control group was also matched by gender to the patient group (56 female, four male). Only 3.3% of the CRTs in the control group were measured as prolonged. The mean CRT results in the control group were 1.315±0.33. No laboratory procedure was performed in the control group, except for fingertip oxygen saturation measurement. The mean oxygen saturation level in the control group was above 96%.

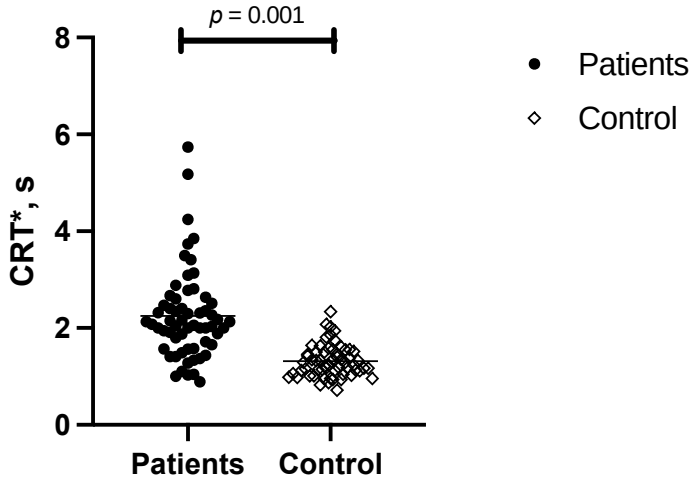
Table 1. Demographic, characteristics features and laboratory results of the SSc patients.

	All patiens (n = 61)	lSSc (n = 24)	dSSc (n = 37)	*P* value
Demographic & Clinics				
Gender, F/M (n)	57/4	23/1	34/3	0.484
Age, (year)	48.78±12.56	48.37±8.70	49.05±14.64	0.768
SSc (year)	4.23±2.38	4.1±2.42	4.32±2.39	0.738
Dispnea, n (%)	17 (27.9)	1 (4.2)	16 (43.2)	**0.001**
Involvement				
Joint, n (%)	13 (21.3)	2 (8.3)	11 (29.7)	**0.046**
Cutaneus, n (%)	53 (86.9)	21 (87.5)	32 (86.5)	0.909
Extra-cutaneus, n (%)	38 (62.3)	13 (54.2)	25 (67.6)	0.291
Renal, n (%)	1 (1.6)	1 (4.2)	0 (0)	0.393
GI, n (%)	38 (62.3)	13 (54.2)	25 (67.6)	0.291
Digital ulcer, n (%)	3 (4.9)	0 (0)	3 (8.1)	0.272
Laboratory results				
WBC, $x10^9$/L	7.1 (5.75-8)	7.1 (6.02-8)	7.2 (5.6-7.95)	0.819
ANC, $x10^9$/L	4.3 (3.1-4.9)	4.3 (3.32-5.12)	4.1 (2.95-4.9)	0.555
ALC, $x10^9$/L	1.85 (1.55-2.5)	1.87 (1.62-2.5)	1.8 (1.5-2.5)	0.762
Plt count, $x10^9$/L	288 (243-338)	289 (256-346)	284 (242-334)	0.631
Hb, gr/dL	13.02±1.28	12.67±1.25	13.25±1.28	0.077
Esr, mm/h	16 (5-28)	16.5 (6.75-26.5)	16 (4.14-31.5)	0.492
CRP, mg/L	4.48 (2.04-10.4)	3.96 (1.83-13.5)	4.83 (2.5-9.75)	0.900
(+) ANA, n (%)	57 (93.4)	21 (87.5)	36 (97.3)	0.290
(+) anti-Scl-70, n (%)	18 (29.5)	0 (0)	18 (48.6)	**0.001**
(+) anticentromere, n (%)	21 (34.4)	12 (50)	9 (24.4)	**0.039**
(+) RF, n (%)	3 (4.9)	3 (12.5)	0 (0)	0.056
(+) NFC, n (%)	56 (91.8)	22 (91.7)	34 (91.9)	0.660
(+) RP, n (%)	58 (95.1)	22 (91.7)	36 (97.3)	0.556
mPAP, mmHg	27 (25-30)	27 (25-29)	28 (24-30.5)	0.667
Abnormal Thoraks CT,n(%)	23 (37.7)	0 (0)	23 (62.2)	**0.001**
NSIP, n (%)	21 (34.4)	2 (8.3)	19(51.4)	**0.001**
UIP, n (%)	3 (4.9)	0 (0)	3 (8.1)	0.272
CRT, ms	2.248±0.927	2.347±1.019	2.184±0.871	0.585
Treatment				
HCQ, n (%)	60 (98.3)	23 (95)	37 (100)	0.210
ISx Treatment, n (%)	32 (44.3)	10 (41.6)	22 (59.5)	**0.004**
AZA, n (%)	12 (19.6)	7 (29.1)	5 (13.5)	0.133
CP, n (%)	6 (9.8)	1 (4.1)	5 (13.5)	0.231
RIX, n (%)	4 (6.5)	2 (8.3)	2 (5.4)	0.651
MMF, n (%)	3 (4.9)	0 (0)	3 (8.1)	0.152

P values are the comparison of lSSc and dSSc groups. (Chi-square test or Mann-Whitney U test); The mean data are given as mean ± standard deviation. The median data are presented as median and 25-75% quartiles. Data are the number, n (%), or n/N (%); **ALC**, Absolute lymphocyte count; **ANA**, Antinuclear antibody; **ANC**, Absolute neutrophil count; **anti-Scl-70**, Anti-topoisomerase I; **AZA**, Azathioprine; **CENB** , Centromeric protein B; **CP**, Cyclophosphamide; **CRP**, C-reactive protein; **CRT**, Capillary refill time, **CT**, Computed tomography; **dSSc**, Diffuse cutaneous systemic sclerosis; **ESR**, Erithrocyte sedimentation rate; **GI**, Gastrointestinal; **Hb**, Hemoglobin; **HCQ**, Hydroxychloroquine; **lSSc**, Limited cutaneous systemic sclerosis; **ISx**, Featured immunosuppressive treatments; **MMF,** Mycophenolate mofetil; **mPAP**, Mean pulmonary artery pressure; **NFC**, Nailfold capillaroscopy; **NSIP**, Non-specific interstitial pneumonia; **Plt**, Platelet; **RF**, Rheumatoid factor; **RIX**, Rituximab; **RP**, Raynaud's phenomenon; **UIP**, Usual interstitial pneumonia; **WBC**, White blood cell.

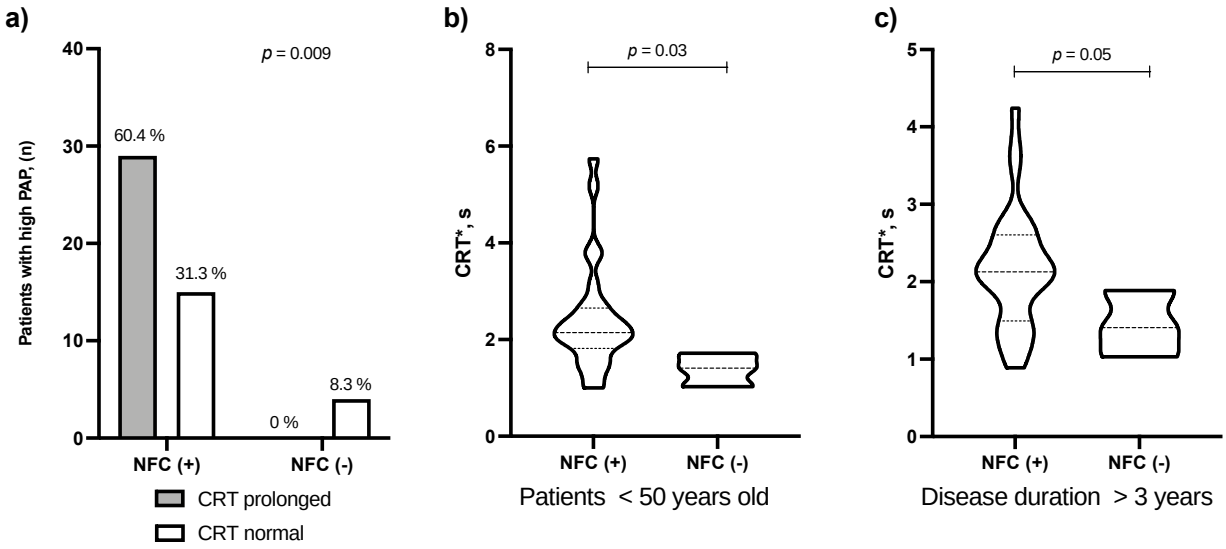
There was significant increase in CRT measurements in the patient group compared to the control group ($p = 0.001$, $F = 18.894$, $\eta = 0.353$) (Figure 2). Unlike, age and gender comparison did not reveal statistical significance between both groups. Among the correlated results, besides CRT and NFC positivity, which was statistically significant ($p = 0.003$), CRT also showed statistical

significance with RP (p = 0.022) and receiving immunosuppressive treatment (p = 0.042). Other remarkable findings were graphically shown in Figure 3. Accordingly, all patients with positive NFC and prolonged CRT had higher pulmonary artery pressure (PAP) levels (>24 mmHg) (Figure 3a) (23). Moreover, a Mann-Whitney U test revealed a difference in CRT in those under 50 years of age who had positive NFC (p = 0.030, η= 0.152) (Figure 3b). There is also evidence of CRT prolongation in all patients with more than three years of disease and positive NFC (p = 0.005, η= 0.125) (Figure 3c).



***CRT,** Capillary refill time

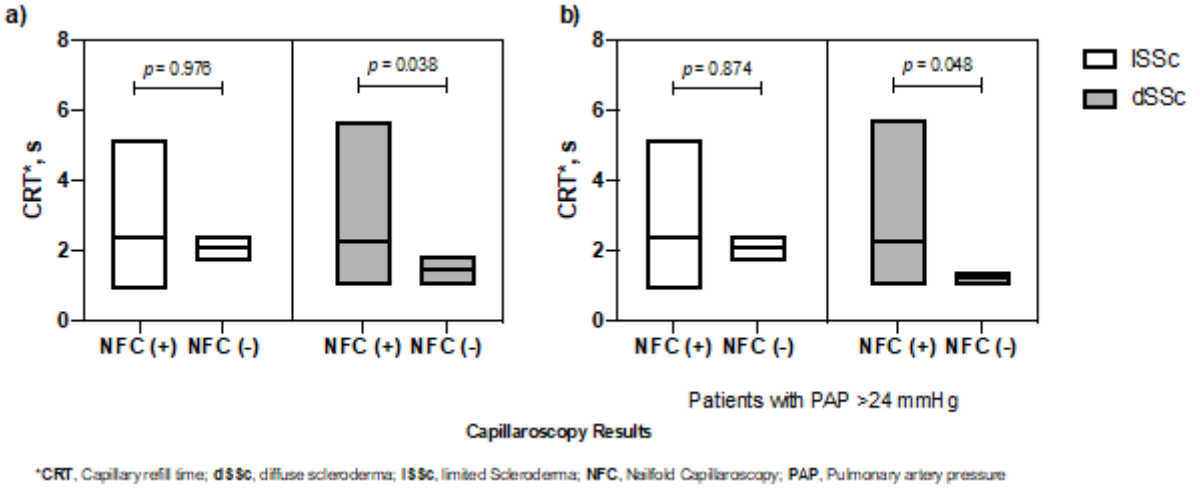
Figure 2. CRT distribution of all participants.



*** CRT**, Capillary refill time; **NFC**, Nail fold capillaroscopy; **PAP**, Pulmonary artery pressure

Figure 3 a) Distributions of categorized CRT results and the nailfold capillaroscopy (NFC) positivity in SSc patients with high pulmonary artery pressure levels, **b**) CRT variations in SSc patients below 50 years of age with positive NFC, **c**) CRT changes in the NFC positive SSc patients with a disease duration of more than three years.

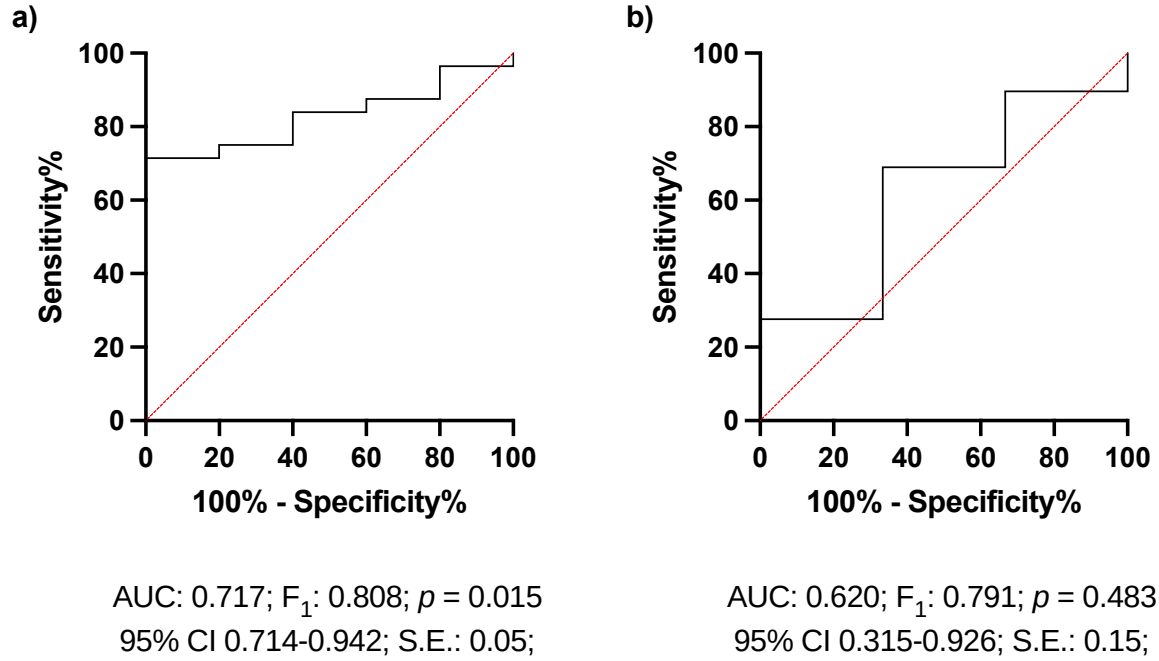
In subgroup analysis, CRT measurements did not reveal a statistical significance between the dSSc and lSSc groups (p = 0.585). Similarly, the lack of statistical significance persisted between CRT and capillaroscopy, computed tomography scans of thorax evaluations. However, CRT was significantly prolonged in the dSSc group with positive NFC testing (p = 0.038) (Figure 4a). In addition, those with a positive NFC in the dSSc group had longer CRTs at high PAP levels (p = 0.048) (Figure 4b).



*CRT, Capillary refill time; dSSc, diffuse scleroderma; lSSc, limited Scleroderma; NFC, Nailfold Capillaroscopy; PAP, Pulmonary artery pressure

Figure 4. **a**) CRT comparisons in the dSSc and lSSc patients with nail fold capillaroscopy assessments, **b**) CRT diversions in dSSc and lSSc patients with pulmonary hypertension.

The evaluations for the discrimination significance of CRT measurement were given in Figure 5. Accordingly, CRT had a fair distinctiveness between NFC positive and negative subgroups with 83.95% accuracy (67.9% sensitivity, 100% specificity, 100% positive predictive value, 21.7% negative predictive value, 0.717 ROC AUC) (Figure 5a). Conversely, NFC had a poor prediction on the RP positivity (65.5% sensitivity, 100% specificity, 100% positive predictive value, 13% negative predictive value, 0.620 ROC AUC, 82.7% accuracy) (Figure 5b).



*AUC, Area under the curve; CI, Confidence interval; F_1, F_1 score; S.E., Standart Error

Figure 5. ROC curve analysis for indicative value of CRT, **a)** In patients with pathological capillaroscopy patterns in the nail fold capillaroscopy, **b)** In patients with positive Raynaud's phenomenon.

Among the correlations; CRT was positively correlated with the NFC positivity (p = 0.02, r = 0.384), RP (p = 0.22, r = 0.292), whereas platelet count was negatively correlated with the NFC positivity (p = 0.033, r = -0.273), RP (p = 0.022, r = -0.293) and skin ulceration (p = 0.014, r = -0.314), CRT was negatively correlated with receiving immunosuppressive therapy (p = 0.043, r = -0.26), and absolute lymphocyte count was positively correlated with GI involvement (p = 0.029, r = -0.28), were remarkable.

DISCUSSION

In this prospective, case-control study, we evaluated CRT measurements in patients with SSc. We found a significant CRT prolongation compared to the control group. CRT results were significantly prolonged, especially in those with a positive capillaroscopy. There was no difference between both dSSc and lSSc subgroups per disease severity. However, the CRP was also detected prolonged in higher PAP levels, <50 years of age, and >3 years disease duration. Since SSc is a progressive disorder, predicting an involvement before target-organ damage will favor the patient. The NFC is one of the implements prominently used in arterial involvements linked to mortality (12). An early evaluation of microangiopathy in SSc patients demonstrates the importance of capillaroscopy; however, specified optical magnification is required for the evaluation, which is not ubiquitous (24). At this point, CRT is a free method that can be performed at the bedside, does not consume much time, but requires attention. Our study detected significant CRT prolongation in patients with positive capillaroscopy. Whether the CRT was not an objective evaluation tool that would not be wholly replaced with NFC, it may be eligible to make NFC more emphasis in patients with prolonged CRTs.

The hand involvement was common in the SSc progression. There have already been implemented and novel located devices that can evaluate the peripheral circulatory system in this regard (25). Since the NFC only defines the anatomical structures of the nail fold, a dynamic device that also evaluates the functional nail fold state, such as oxygenation, was featured to take the pole position. Thermography, Photoplethysmo-graphy, Photoacoustic and high-frequency ultrasound, and laser-assisted imaging such as Laser Doppler Flowmetry, Laser Doppler Perfusion, Laser speckle contrast analysis were some of the prominent functional measures (26-28). However, the common problem was that the imaging could be technically limited in patients with significant digital contractures. Unfortunately, these multifunctional devices can be found in well-equipped health centers. As a result, functional measurement methods were not as objective as capillaroscopy, which is not affected by other physical dilemmas but requires significant experience; instead of considering them as an alternative to capillaroscopy, it should be a goal to prioritize the NFC when these tests are unfavorable.

Once genetic and environmental factors lead to endothelial damage in SSc patients, the apoptosis in endothelial cells would become inevitable via the anti-endothelial antibodies produced by B lymphocytes against the inflammation site (6). Secondary to impaired vasculogenesis, proliferative or destructive but obliterative vasculopathy mainly caused tissue hypoxia. Therefore, determining tissue hypoxia in the early stage of the disease was substantial. An examination approach such as CRT, which has proven itself in various cases, may also be used for a hypoxic setting (29-31). Without absolute objectivity, the CRT evaluates peripheral circulation in a fundamental approach in 2 s. Nevertheless, CRT was measured to be prolonged more per decade increase due to decreased vascular compliance (32).

Similarly, as age advances, the destruction of endothelial cells increases, and their regeneration ability weakens (33). Our study found that CRT results were significantly prolonged in patients below 50 years of age or whose disease duration was over three years. Taken together, this demonstrates that advancing age harms the capillaries similar to SSc. In addition, it may be possible to comment as follows; the CRT prolongation might be practical below 50 years old in SSc patients with positive NFC; however, the time gap in the NFC elongation was closed with the negative effect of increasing age on capillaries beyond the 50s.

A typical CRT can estimate adequate superior vena cava oxygen saturation. A long-term study formalized this issue; a CRT of $\leq$ 2 s was associated with the superior vena cava oxygen saturation of 70% (34). SSc patients with cardiac involvement or pulmonary artery hypertension secondary to pulmonary involvement worsened the central venous pressure levels were clinically presented with dyspnea. Based on this pathogenesis, our study also evaluated the potential relationship between PAP levels and CRT positivity. As a result, we noticed that CRT prolongation was statistically significant in dSSc patients with a PAP level of >20 mmHg compared to the lSSc subgroup. Surprisingly, these patients with pulmonary hypertension also had NFC positivity. These results may partly explain that dyspnea leading to local hypoxemia can trigger RF, which induces hypoxemia at peripheral tissues. While there was no statistical difference in CRT measurements between subgroups, CRT may predict PHT in patients with SSc, based on the difference when PAP level is >20 mmHg in the dSSc subgroup.

Unfortunately, this study could not encompass the entire cutaneous SSc involvements by CRT alone. However, CRT will already be prolonged in both groups since RP and nail fold involvement are diagnostic criteria in both dSSc and ISSc groups. If CRT measurements had been measured with a more sensitive and technologically dynamic method, the errors during application would have been minimized. However, the study was methodized via an ordinary smartphone to create awareness in medical practice without sophisticated devices. Nevertheless, we declared that CRT could not be equivalent to capillaroscopy. Another issue is that the platform used for focusing

was a 3D-printed instrument that could not be easily and rapidly manufactured. However, as smartphones can auto-focusing, using the platform is not indispensable.

In conclusion, CRT has been found relatively prolonged in patients with SSc. Additionally, detecting CRT prolongation was highly prevalent in SSc patients with positive capillaroscopy. To the best of our knowledge, no data was found on the association between SSc and CRT. Our study findings propose that appropriate time should be allocated for CRT measurement in SSc patients to manage the proper approach for early capillaroscopy, even though there was no physical clue for the nail fold involvement. Further studies may investigate whether capillary refill time can be an alternative to predict underlying connective tissue disease in patients with Raynaud's phenomenon in centers where capillaroscopy is unavailable.

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