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Original article

# Causes of Raynaud's phenomenon and the predictive laboratory and capillaroscopy features for the evolution to a definite connective tissue disease

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## Abstract

**Objective.** In patients with RP, capillaroscopy is useful for discriminating primary from secondary causes. There are certain capillaroscopy and lab values as predictive factors leading to a known CTD. We conducted the present study to evaluate the causes of RP in our area and followed the studied subjects to find prognostic factors indicating a definite CTD or remaining a UCTD.

**Methods.** In this retrospective cohort study we included all adult patients with RP who were referred for capillaroscopy from 2010 to 2019. All the patients with primary and secondary RP with follow-up were evaluated for demography, laboratory results and capillaroscopy to find the risk factors of their progression to a CTD.

**Results.** A total of 760 of 776 patients were included, with 679 being female (89.3%) and 81 (10.7%) male. There were 660 subjects (90.8%) with secondary RP [mostly UCTD (48.2%) and then SSc (16.4%)] and 67 (9.2%) with primary RP; 109 patients were followed up and 42 (42%) of those with secondary RP developed a definite CTD. The scleroderma pattern and some capillary changes on capillaroscopy and/or positive ANA had statistically significant differences for CTD transition.

**Conclusion.** We had a small number of patients with primary RP. The most prevalent causes of secondary RP in our patients were UCTD and SSc. Some capillaroscopy and laboratory results alone or in combination could be used as a predictive marker for the transition of patients with UCTD to CTD.

**Key words:** RP, capillaroscopy, UCTD

**Rheumatology key messages**

- We had a small number of patients with primary RP compared with previous studies.
- The most common causes of secondary RP were UCTD, SSc, overlap syndrome and MCTD.
- Certain capillaroscopy and autoantibody results were the risk factors for transition to a definite CTD.

## Introduction

RP is an unusual hypersensitivity characterized by colour changes of the digits on exposure to cold, stress and some drugs. It is classified as primary, with no underlying disease, or secondary, with an associated disease, mostly SSc, idiopathic inflammatory myopathies, SLE, primary SS (pSS), MCTD and UCTD [1, 2].

Capillaroscopy is a useful tool for discriminating primary RP from secondary RP. Moreover, the predictive and prognostic values of capillaroscopy in patients with RP have been confirmed [3–5]. It was shown that after 6.5 years of follow-up, 82% of patients with RP and pathological findings at nailfold capillaroscopy converted to a CTD [4]. Some predictive values have been proposed that can change an early UCTD (defined as systemic autoimmune disease that has similar clinical and serological characteristics of definite CTD but does not fulfil the disease criteria) to a known CTD or remaining as a stable UCTD [6]. The most common predictive factors in the evolution to a definite CTD were having a

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positive ANA test and having a scleroderma pattern on capillaroscopy, including the presence of giant loop and/or capillary loss [5].

We conducted a study on all the patients with RP referred to our capillaroscopy centre and evaluated capillaroscopy, clinical character and lab tests to determine the contributions of the primary and secondary causes of RP. In addition, in their follow-up, we tried to determine the percentage of patients with RP and UCTD differentiated to a definite CTD and predictors of remaining a stable UCTD or becoming a definite CTD.

## Materials and methods

In this retrospective cohort study, we included all patients ≥15 years of age with RP who were referred to the outpatient clinic of the Rheumatology Unit of Hafez Hospital (affiliated with Shiraz University of Medical Sciences as a solo referral centre for capillaroscopy in Fars province, located in southwest Iran) from 2010 to 2019 and fulfilling the international consensus criteria for RP [7]. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.sums.med.rec.1397.294). Informed consent was obtained from each patient prior to capillaroscopy and gathering data.

The inclusion criteria were patients with RP having at least six evaluable nailfolds. RP was diagnosed when the patient had hypersensitivity to cold and episodic distal finger colour changes to white (pallor) or blue (cyanosis) after cold exposure [1, 8].

Primary RP was diagnosed in patients with a history of attacks of acral pallor or cyanosis being entirely reversible; symmetric attacks along with strong and symmetrical peripheral pulses; no skin necrosis, ulcer or gangrene; no secondary causes (based on the patient's history and physical examinations); normal capillaroscopy; negative ANA and normal ESR [1, 7–9].

The patients with a definite CTD or those with a definite reason for their RP were considered as secondary RP. If the patients had signs and symptoms suggestive of a CTD yet did not fulfil the existing classification criteria, we defined them as UCTD [6]. Those with RP without clinical findings of a CTD, but with serological and/or capillaroscopy abnormalities, were defined as suspected secondary RP [3]. We extracted the patients with very early scleroderma [10] from those with suspected secondary RP since they had a uniform clinical presentation and placed them in the category of a defined CTD.

The patients with UCTD and suspected secondary RP were followed. History taking and physical examination were done at the time of inclusion and the available data, including ANA, ENA profiles, complete blood count and ESR, were recorded. If these patients had a follow-up in the clinic during the 9 years, we recorded their last diagnosis and put them in groups of a definite CTD or stable UCTD.

The exclusion criteria were patients with fewer than six available nailfolds, those with other reasons for their colour changes (e.g. erythromelalgia), patients with malignancy, vibration-associated jobs, drug-induced RP and smokers. The clinical data on age, sex and disease duration (from the onset of RP) were collected.

The capillaroscopy with a stereomicroscope [Euromex ST. 1740, ×250 power and video camera Cmex D.C.5000 (5 megapixels); Euromex Microscopen, Arnhem, The Netherlands] was carried out by a rheumatologist involved in this research. Eight fingers of the two hands, excluding the thumbs, were assessed using immersion oil. We reported the distribution [normal, disturbed (capillary disarrangement)], the presence or absence of dilated (20–50 μm) capillaries, capillaries with a dimension ≥30 μm, giant loops (>50 μm; one or multiple), abnormal shapes (like ramification and angiogenesis), the avascular area (intercapillary distance >500 μm), microhaemorrhages [total number; few (2–5) or multiple (>5)], mean capillary number per millimetre [normal (≥7/high power field), decreased (<7/high power field)] and capillary length [normal, elongated (>300 μm)]. Based on the last standardization of nailfold capillaroscopy and international Delphi consensus for reporting the data (2020), the capillaroscopy patterns were reported as normal, scleroderma pattern (early, active, late) and non-specific abnormalities [11, 12]. We also used the term scleroderma-like pattern (a mixture of microvascular abnormalities involved in the scleroderma capillary patterns but which did not fully fit the definition of any of the three aforementioned scleroderma patterns) [13–15].

### Statistical analysis

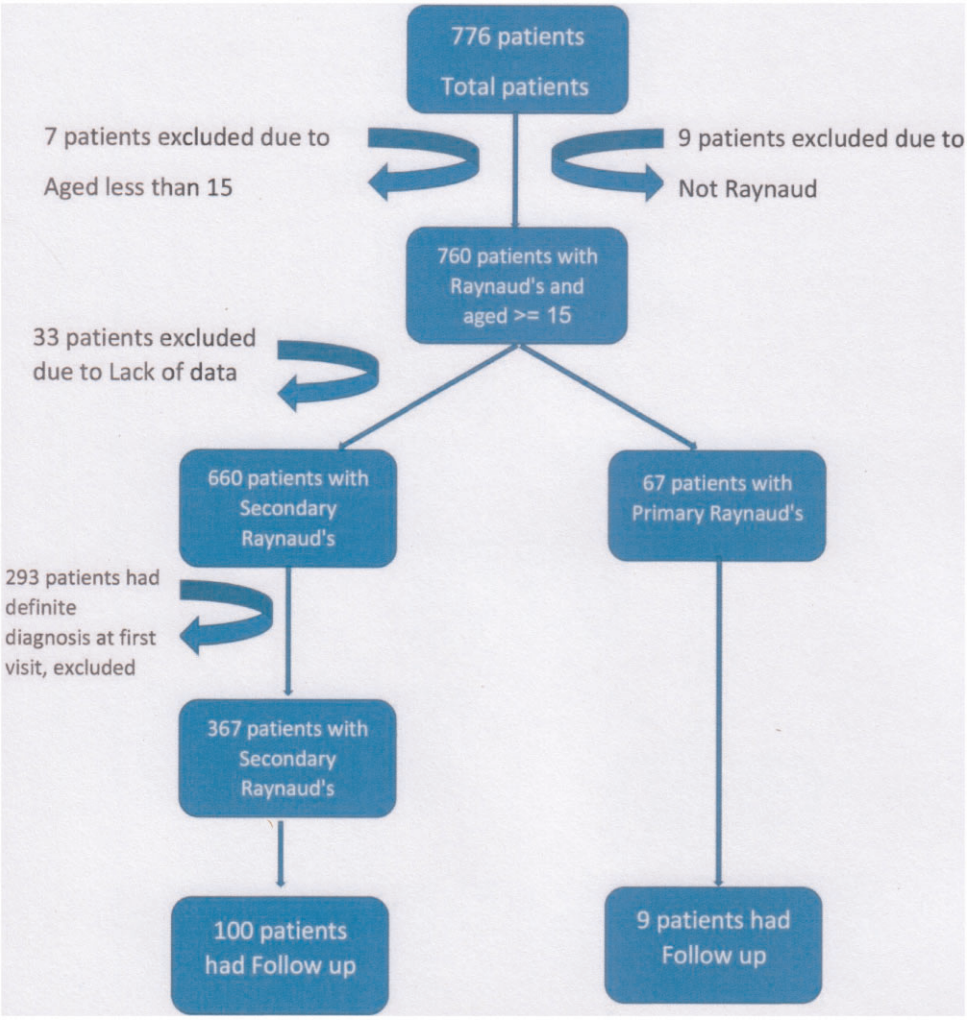
The quantitative and qualitative variables, statistical relationships and comparisons were analysed using chi-square and *t*-test methods with SPSS version 23 software (IBM, Armonk, NY, USA). For all the tests, *P*-values <0.05 were considered to be statistically significant.

## Results

The data from 776 patients were available during the 9 year period. Fig. 1 shows the number of patients and the excluded patients during the study. Among the remaining 760 patients, 81 (10.7%) were male and 679 (89.3%) were female with a mean age of 39.03 years (S.D. 13.22; range 15–81). The mean age at the first RP presentation was 33.45 years (S.D. 13.27; range 4–79). The mean duration of RP was 43.27 months (S.D. 55.63). Due to its high variance (1–360 months), the median was calculated as 24 months.

The patients with primary and secondary RP were mostly females (80.6% of primary and 90.5% of secondary). There were more female cases with secondary RP than with primary RP ($P = 0.012$). The mean age at referral was also higher in those with secondary RP [39.7 years (S.D. 13.2) *vs* 34.87 (12.9); $P = 0.004$].

FIG. 1 Diagram of patients with RP, total number at the study beginning and the excluded patients during the study period




The mean age at the onset of RP and the median RP duration was 32.6 years (S.D. 13.38) and 18 months (age range 13–60 years), respectively, in patients with primary RP and 35.9 years (S.D. 13.17) and 43.7 months (age range 5–79 years), respectively, for patients with secondary RP, with no significant differences ($P = 0.06$ and 0.419, respectively). The mean age of RP presentation was 30.5 years (S.D. 11.12). Of 660 patients with secondary RP, most had UCTD [318 (48.2%)] and 293 (44.4%) had a definite CTD on the first visit, which were mostly SSc (16.4%), overlap syndromes (OSs) (5.8%) and MCTD (5%) (Table 1).

The subjects with suspected secondary RP with a mean follow-up of 24.78 months were 66.7% female and 33.3% male with a mean age at referral of 37.67 years (S.D. 9.65). The mean and median of RP duration were 18.5 months and 18 months, respectively. The age of RP presentation was 35.45 years (S.D. 10.31).

The mean and median RP duration in 109 patients with follow-up during the 9 years of study were 29.31 months (S.D. 19.1) and 24 months, respectively, and the mean time of follow-up of the two groups was 22.45 months (29.46 months for secondary RP and 15.44 months for primary RP).

Among 91 UCTD patients with follow up, 49 patients remained as UCTD (53.8%) and 42 patients (46.2%) developed a definite CTD. Among 49 patients with suspected secondary RP, only nine patients were followed up and all of them remained suspected secondary RP. All the participants with primary RP with a follow-up (nine patients) remained primary RP without differentiation into any CTDs.

Since only one patient existed in each group of RA, very early scleroderma and interstitial lung disease–associated CTD groups, these patients were excluded. The remaining 100 patients (42 patients with newly

**Table 1** Prevalence of patients with secondary RP due to a systemic CTD or UCTD at the first referral

| First referral diagnosis | Number | Percent |
|---|---|---|
| UCTD | 318 | 48.2 |
| Scleroderma | 108 | 16.4 |
| Suspected secondary RP | 49 | 7.4 |
| Overlap | 38 | 5.8 |
| MCTD | 33 | 5 |
| Very early scleroderma | 31 | 4.7 |
| SLE | 29 | 4.4 |
| pSS | 23 | 3.5 |
| Other[a] | 13 | 2 |
| Dermatomyositis | 8 | 1.2 |
| ILD-associated CTD | 3 | 0.5 |
| RA | 3 | 0.5 |
| APS | 2 | 0.3 |
| PM | 1 | 0.2 |
| Anti JO-1 | 1 | 0.2 |
| Total | 660 | 100 |

ILD: interstitial lung disease. [a]Other were 8 smokers, 1 patient with CTS, 1 with cervical rib, 1 with DLE, 1 with drug-induced (propranolol use) and 1 with sclerosis sine scleroderma.

developed definite CTD, 49 with stable UCTD and 9 with suspected secondary RP) were studied during follow-up (Table 2).

The mean follow-up duration was 15.44 months (S.D. 5.24) in primary RP patients and 24.78 months (S.D. 11.37) in patients with suspected secondary RP. There were no significant differences between the patients with a stable UCTD and those who developed a definite CTD based on sex, age at RP onset, RP duration and age at entry to the study ($P = 0.72$, 0.44, 0.61 and 0.2, respectively).

Age at RP onset was significantly different between the groups of patients with a new definite CTD ($P = 0.04$) and the MCTD group was significantly younger (26.71 *vs* 37.4 years compared with other CTD groups). Other features such as sex, age at entry to the study and RP duration were not significantly different between the patients with CTD conversion (SSc, OSs, pSS and MCTD).

On capillaroscopy pattern analysis, there were no differences between the patients with UCTD who converted to a definite disease and those with stable UCTD and no significant differences were observed between converted UCTD disease groups (Table 3). UCTD patients with a scleroderma pattern in capillaroscopy were more differentiated into a CTD ($P < 0.001$) (early and active pattern with *P*-values of 0.015 and 0.02, respectively). However, there were no significant differences between the converted groups.

Non-specific abnormalities were the most prevalent pattern in the patients with UCTD and they mostly remained UCTD ($P = 0.001$). A scleroderma-like pattern was the least common pattern and in those with UCTD and this pattern there were no significant differences

**Table 2** Demographic features of patients with RP and UCTD who developed a definite CTD during the follow-up

| Follow-up diagnosis | Sex, *n* (%) | | Age, years, mean (S.D.) | Duration of RP, months | | Age at RP presentation, years, mean (S.D.) | Follow-up, months, mean (S.D.) | Total, *n* |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | | Mean | Median | | | |
| Scleroderma | 0 | 15 (100) | 37.4 (14.54) | 57.93 | 27 | 33.45 (13.37) | 36.13 (19.98) | 15 |
| Overlap syndrome | 1 (7.7) | 12 (92.3) | 42.31 (9.18) | 30.62 | 24 | 39.75 (7.92) | 41.08 (26.55) | 13 |
| pSS | 0 | 4 (100) | 43.25 (11.92) | 42 | 42 | 39.75 (11.81) | 16.75 (6.39) | 4 |
| MCTD | 2 (28.6) | 5 (71.4) | 26.71 (7.95) | 13.67 | 15 | 27.19 (7.11) | 29 (17.72) | 7 |
| RA | – | 1 | 69 | – | 144 | 57 | 25 | 1 |
| ILD-associated CTD | – | 1 | 24 | – | 4 | 24 | 26 | 1 |
| Very early scleroderma | – | 1 | 31 | – | – | – | 13 | 1 |
| UCTD | 6 (12.2) | 43 (87.8) | 35.67 (12.45) | 34.07 | 18 | 31.93 (12.4) | 29.04 (18.68) | 49 |
| Total | 9 (9.89) | 82 (90.11) | – | – | – | – | – | 91 |

ILD: interstitial lung disease.

**Table 3** Capillaroscopy in stable UCTD patients and those who developed a definite CTD

| Capillaroscopy | | Total ($N = 88$) | Patients with UCTD that converted to a definite CTD disease during follow-up | | | | UCTD converted to a definite CTD, *n* (%) | Stable UCTD ($n = 49$) | *P*-value[¶] |
|---|---|---|---|---|---|---|---|---|---|
| | | | Scleroderma ($n = 15$) | Overlap ($n = 13$) | pSS ($n = 4$) | MCTD ($n = 7$) | | | |
| Capillaroscopy patterns[a] | | | | | | | | | |
| Normal, *n* (%) | | 6 (7.2) | 0 | 1 (16.7) | 0 | 0 | 1 (16.7) | 5 (83.3) | 0.22 |
| *P*-value* | | | 0.61 | | | | | | |
| Scleroderma pattern | Early scleroderma, *n* (%) | 17 (17.6) | 5 (29.4) | 4 (23.5) | 1 (5.9) | 2 (11.8) | 12 (70.6) | 5 (29.4) | 0.015 |
| | *P*-value* | | 1 | | | | | | |
| | Active scleroderma, *n* (%) | 8 (8.2) | 5 (62.5) | 1 (12.5) | 1 (12.5) | 0 | 7 (87.5) | 1 (12.5) | 0.02 |
| | *P*-value* | | 0.15 | | | | | | |
| Non-specific abnormalities, *n* (%) | | 55 (65) | 5 (9.1) | 5 (9.1) | 2 (3.6) | 5 (9.1) | 17 (30.9) | 38 (69.1) | 0.001 |
| *P*-value* | | | 0.41 | | | | | | |
| Scleroderma-like, *n* (%) | | 2 (2) | 0 | 2 (100) | 0 | 0 | 2 (100) | 0 | 0.19 |
| *P*-value* | | | 0.33 | | | | | | |
| Distribution | | | | | | | | | |
| Abnormal, *n* (%) | | 21 (23.8) | 9 (42.9) | 4 (19) | 3 (14.3) | 0 | 16 (76.2) | 5 (23.8) | 0.001 |
| *P*-value* | | | 0.017 | | | | | | |
| Morphology | | | | | | | | | |
| Abnormal[b], *n* (%) | | 16 (18.6) | 3 (18.7) | 5 (31.25) | 1 (6.25) | 2 (12.5) | 11 (68.7) | 5 (31.3) | 0.03 |
| *P*-value* | | | 0.84 | | | | | | |
| Dimension | | | | | | | | | |
| Dilatation $<0.03$, *n* (%) | | 44 (50) | 2 (4.5) | 5 (11.4) | 1 (2.3) | 3 (6.8) | 11 (25) | 33 (75) | $<0.001$ |
| *P*-value* | | | 0.36 | | | | | | |
| Dilatation $\geq 0.03$, *n* (%) | | 37 (42) | 12 (32.5) | 7 (18.9) | 3 (8.1) | 4 (10.8) | 26 (70.3) | 11 (29.7) | $<0.001$ |
| *P*-value* | | | 0.46 | | | | | | |
| Giant loop[c] | | | | | | | | | |
| One, *n* (%) | | 7 (7.2) | 2 (28.6) | 2 (28.6) | 0 | 2 (28.6) | 6 (85.8) | 1 (14.2) | 0.04 |
| *P*-value* | | | 0.78 | | | | | | |
| Multiple, *n* (%) | | 21 (21.6) | 9 (42.9) | 4 (19) | 2 (9.5) | 0 | 15 (71.4) | 6 (28.6) | 0.004 |
| *P*-value* | | | 0.03 | | | | | | |
| Capillary density | | | | | | | | | |
| Decreased $<7$, *n* (%) | | 13 (13.5) | 7 (53.8) | 2 (15.4) | 1 (7.7) | 1 (7.7) | 11 (84.6) | 2 (15.4) | 0.002 |
| *P*-value* | | | 0.261 | | | | | | |

(continued)

**Table 3** Continued

| Capillaroscopy | Total (*N* = 88) | Patients with UCTD that converted to a definite CTD disease during follow-up | | | | UCTD converted to a definite CTD, *n* (%) | Stable UCTD (*n* = 49) | *P*-value[¶] |
|---|---|---|---|---|---|---|---|---|
| | | Scleroderma (*n* = 15) | Overlap (*n* = 13) | pSS (*n* = 4) | MCTD (*n* = 7) | | | |
| Drop-out[d] | | | | | | | | |
| Yes, *n* (%) | 6 (6.2) | 2 (33.3) | 0 | 1 (16.7) | 1 (16.7) | 4 (66.7) | 2 (33.3) | 0.4 |
| *P*-value* | | 0.282 | | | | | | |
| Haemorrhages | | | | | | | | |
| Yes (2–5), *n* (%) | 20 (22.7) | 0 | 3 (15) | 0 | 1 (5) | 4 (20) | 16 (80) | 0.01 |
| *P*-value* | | 0.19 | | | | | | |
| Yes >5, *n* (%) | 25 (28.4) | 9 (36) | 4 (16) | 4 (16) | 2 (8) | 19 (76) | 6 (24) | <0.001 |
| *P*-value* | | 0.05 | | | | | | |
| Elongation[e] | | | | | | | | |
| Yes, *n* (%) | 28 (33) | 4 (14.3) | 2 (7.2) | 3 (10.7) | 3 (10.7) | 12 (42.9) | 16 (57.1) | 0.85 |
| *P*-value* | | 0.126 | | | | | | |
| Blood flow | | | | | | | | |
| Stasis (slowing), *n* (%) | 6 (6.2) | 1 (16.7) | 2 (33.3) | 0 | 2 (33.3) | 5 (83.3) | 1 (16.7) | 0.08 |
| *P*-value* | | 0.43 | | | | | | |
| Microthrombosis, *n* (%) | 1 (1) | 0 | 0 | 0 | 0 | 0 | 1 (100) | 1 |
| *P*-value* | | — | | | | | | |

*P*-values comparing the difference between capillaroscopy variables frequency between the two groups of patients including UCTD patients who converted to definite CTD during the follow-up and patients who remained UCTD during the study (*P*-value[¶]) and between patients who differentiated into definite diseases (*P*-value*) were considered significant if <0.05. [a]Late scleroderma capillaroscopy pattern was ignored in the evaluation since no data existed among patients with follow-up during the study period. [b]Abnormal morphology includes meandering, ramification, bushy, arborization, branching (neo-angiogenesis) and bizarre capillaries. [c]Giant loop: capillary diameter >0.05 mm. [d]Drop-out: avascular areas >0.5 mm in distal row or two capillary losses. [e]Elongation: length >0.3 mm.

between the total converted UCTD and stable UCTD and also converted groups.

The patients with normal capillary distribution mostly remained UCTD and those with capillary disarrangement were more converted into a definite CTD ($P = 0.001$), mostly SSc (42.9%; $P = 0.017$). The subjects with abnormal morphology were also more converted into a definite CTD, with no significant differences between the groups ($P = 0.84$). Those with capillary dilatation $<0.03$ mm (more prevalent dimension) mostly remained UCTD (75%; $P < 0.001$), but those with capillary dilatation $\geq 0.03$ mm converted more often into a definite CTD (70.3%; $P < 0.001$), but without significant differences between the groups. The patients without any giant loop mostly remained UCTD (70%) and those with at least one giant loop mostly converted into a definite CTD (85.8% and 71.4%, respectively). Only the presence of multiple giant loops was a risk factor of differentiation into SSc (42.9%). The participants with normal capillary density mostly remained UCTD (62.2%) and those with decreased capillary density mostly converted into a definite CTD (84.6%) without specific disease differentiation. Those with two to five total haemorrhages mostly remained UCTD (80%) and the patients with more than five total haemorrhages had more conversion into a definite CTD (76%) without a significant differentiation into a specific CTD ($P = 0.01$ and $<0.001$, respectively). The UCTD patients with a normal or scleroderma-like capillaroscopy pattern, normal morphology and dimensions, increased elongation, avascular area, stasis in the blood flow and no capillary haemorrhages did not progress to a definite CTD ($P > 0.05$).

In the assessment of laboratory data, the primary and suspected secondary RP cases were ignored because of the negative lab data in most of them. The 88 remaining patients were included in the analysis (Table 4). aPL antibody tests, due to negativity in all the patients, were not included.

Most (80.5%) patients with UCTD had a positive ANA test and they mostly converted into a definite CTD (52.9%) compared with UCTD patients with a negative ANA test, who mostly remained UCTD (94.1%; $P < 0.001$). RF-negative patients mostly remained UCTD (52.3%) and RF-positive patients mostly converted to a definite CTD (90.9%; $P = 0.01$), mostly to OSs.

The patients with UCTD with negative anti-RO mostly remained UCTD and the positive ones showed more conversion to a definite CTD (71.4% and 76.2%, respectively; $P < 0.001$) without any significant differences in conversion to a CTD. All the snRNP-positive patients converted to MCTD ($P < 0.001$).

Regarding the combination of lab and capillaroscopy results, in RF- [10] and anti-ScL-70- positive patients [4], the analysis could not be interpreted due to the small number of patients. Anti-RO and ACA positivity combined with abnormal capillaroscopy showed no significant differences between the patients with the converted disease and those who remained UCTD (Table 5).

The subjects with UCTD with positive ANA and a scleroderma pattern on capillaroscopy mostly converted to a definite CTD (78.3%), while those with non-specific abnormalities mostly remained UCTD (60%; $P = 0.003$ and 0.01, respectively), without any significant differences among the subgroups. The patients with positive ANA and a capillary diameter $<0.03$ mm mostly remained UCTD (65.5%) and those with a diameter $\geq 0.03$ mm mostly converted to a definite disease ($P = 0.01$ and 0.002, respectively).

The cases with positive ANA and no giant loops mostly remained UCTD (61.4%) and those with multiple giant loops mostly converted to a definite CTD ($P = 0.002$ and 0.01, respectively). Additionally, the patients with positive ANA and more than five haemorrhages mostly converted to a definite disease (81.8%), mainly (40.9%) SSc ($P = 0.004$ and 0.04, respectively).

## Discussion

In this study we evaluated the causes, manifestations, capillaroscopy and laboratory features of 727 patients with RP and found the factors associated with their progression with primary RP and UCTD to a definite CTD. There were 67 primary RP (9.2%), 49 suspected secondary RP (6.7%) and 660 secondary RP patients, including 293 CTD (40.3%) and 318 UCTD (43.8%) cases. The number of primary RP patients was greater than our patients in all previous articles; the highest number was seen in the study by Hirschl *et al.* [16] (83.7%) and the lowest was seen in the study by De Angelis *et al.* [17] (68.6%). There were also 210 patients (35.8%) in the work of Koenig *et al.* [18], 143 (74.9%) in the work of Trombetta *et al.* [19] and 129 (44.8%) in the work of Ingegnoli *et al.* [5]. The small number of patients with primary RP in our study might be related to climate differences (lower latitudes and warmer weather in our country compared with higher latitudes and colder weather in the studies conducted in other countries; four studies in Italy [5, 17, 19, 20], one in Serbia [3], one in Switzerland [4], one in Austria [16] and one in Canada [18]). We did not find any articles on primary RP prevalence in Middle Eastern countries, which have weather conditions similar to our country.

In all the categories of our patients with RP, the dominant gender was female. The patients with primary RP had a lower mean age at presentation compared with the secondary RP group [34.87 years (S.D. 12.9; range16–61) and 39.7 (13.2; 15–81), respectively]. In a systematic review and meta-analysis done by Garner *et al.* [21] on 33 articles about PR, the studies were mostly conducted in Europe, the USA, Japan, New Zealand and Israel, with a wide range of ages at onset for primary RP (15–84 year-old, mean $\geq$18 and 53 in three studies), although we know primary RP is usually presented in young ages. Furthermore, in a prospective case–control study in an Italian cohort on 132 primary RP patients by Prete *et al.* [22], the mean age was reported to be 46.33 years (S.D. 15.8).

**Table 4** Laboratory variables in stable UTCD patients and those who developed a definite CTD

| Lab tests | Total ($N = 88$) | Patients with UCTD who developed a new definite CTD during follow-up | | | | Total UCTD converted into CTD | UCTD ($n = 49$) | *P*-value¶ |
|---|---|---|---|---|---|---|---|---|
| | | Scleroderma ($n = 15$) | Overlap ($n = 13$) | pSS ($n = 4$) | MCTD ($n = 7$) | | | |
| ANA | | | | | | | | |
| Positive, *n* (%) | 70 (80.5) | 15 (21.4) | 12 (17.2) | 4 (5.7) | 6 (8.6) | 37 (52.9) | 33 (47.1) | <0.001 |
| *P*-value* | | 0.6 | | | | | | |
| dsDNA | | | | | | | | |
| Positive, *n* (%) | 4 (5.8) | 0 | 1 (25) | 0 | 0 | 1 (25) | 3 (75) | 0.62 |
| *P*-value* | | 1 | | | | | | |
| RF | | | | | | | | |
| Positive, *n* (%) | 11 (20) | 1 (9.1) | 4 (36.4) | 3 (27.2) | 2 (18.2) | 10 (90.9) | 1 (9.1) | 0.01 |
| *P*-value* | | 0.01 | | | | | | |
| C3 | | | | | | | | |
| Low, *n* (%) | 1 (1.4) | 0 | 0 | 0 | 0 | 0 | 1 (100) | 1 |
| *P*-value* | | - | | | | | | |
| C4 | | | | | | | | |
| Low, *n* (%) | 4 (5.8) | 1 (25) | 0 | 0 | 1 (25) | 2 (50) | 2 (50) | 0.62 |
| *P*-value* | | 0.59 | | | | | | |
| SCL-70 | | | | | | | | |
| Positive, *n* (%) | 4 (6.1) | 2 (50) | 1 (25) | 0 | 0 | 3 (75) | 1 (25) | 0.29 |
| *P*-value* | | 0.7 | | | | | | |
| ACA | | | | | | | | |
| Positive, *n* (%) | 19 (44.2) | 4 (21.05) | 4 (21.05) | 2 (10.5) | 0 | 10 (52.6) | 9 (47.4) | 0.32 |
| *P*-value* | | 0.66 | | | | | | |
| Anti-RO/SSA | | | | | | | | |
| Positive, *n* (%) | 21 (30) | 4 (19.1) | 8 (38.1) | 1 (4.7) | 3 (14.3) | 16 (76.2) | 5 (23.8) | <0.001 |
| *P*-value* | | 0.64 | | | | | | |
| Anti-LA/SSB | | | | | | | | |
| Positive, *n* (%) | 3 (4.5) | 0 | 1 (25) | 0 | 2 (75) | 3 (100) | 0 | 0.06 |
| *P*-value* | | 0.15 | | | | | | |
| SnRNP | | | | | | | | |
| Positive, *n* (%) | 14 (20) | 0 | 0 | 0 | 6 (42.9) | 6 (42.9) | 8 (57.1) | 0.8 |
| *P*-value* | | <0.001 | | | | | | |
| Sm | | | | | | | | |
| Positive, *n* (%) | 4 (5.7) | 0 | 0 | 0 | 2 (50) | 2 (50) | 2 (50) | 1 |
| *P*-value* | | 0.11 | | | | | | |
| Anti-CCP | | | | | | | | |
| Positive, *n* (%) | 2 (5.6) | 1 (50) | 1 (50) | 0 | 0 | 2 (100) | 0 | 0.48 |
| *P*-value* | | 1 | | | | | | |
| CRP | | | | | | | | |
| Positive ≥6, *n* (%) | 5 (6.8) | 0 | 1 (20) | 0 | 1 (20) | 2 (40) | 3 (60) | 1 |
| *P*-value* | | 0.41 | | | | | | |
| ESR | | | | | | | | |
| High ≥20, *n* (%) | 25 (31.3) | 4 (16) | 6 (24) | 1 (4) | 3 (12) | 14 (56) | 11 (44) | 0.18 |
| *P*-value* | | 0.57 | | | | | | |

**P*-values comparing the difference between lab test variables, frequency between the two groups of patients including UCTD patients converted to definite CTD during the follow-up and the patients who remained UCTD during the study (*P*-value¶) and between patients who differentiated into definite diseases (*P*-value*) were considered significant if <0.05. SM: anti-Smith antibody.

The mean age at RP onset [32.6 years (S.D. 13.3) in primary RP *vs* 35.9 (13.1) in secondary RP] and the RP duration were not significantly different between the groups. In the study by Pavlov-Dolijanovic *et al.* [3], the patients with primary RP were also mostly female (89%), with a mean age at onset of 38.1 years. Based on the meta-analysis by Ingegnoli *et al.* [23], primary RP patients were mostly female (88.1%), with a mean age at presentation of 43.1 years and a mean age at onset of 34.1 years.

**Table 5** Combination of ANA and capillaroscopy in stable UCTD patients and those who developed a definite CTD

| ANA and capillaroscopy | Total ($N = 88$) | Patients with UCTD who developed a definite CTD during follow-up | | | | Total UCTD converted to CTD | UCTD ($n = 49$) | *P*-value¶ |
|---|---|---|---|---|---|---|---|---|
| | | Scleroderma ($n = 15$) | Overlap ($n = 13$) | pSS ($n = 4$) | MCTD ($n = 7$) | | | |
| ANA positive and capillaroscopy pattern | | | | | | | | |
| Scleroderma, *n* (%) | 23 (26.7) | 10 (43.5 | 4 (17.4%) | 2 (8.7) | 2 (8.7) | 18 (78.3) | 5 (21.7) | 0.003 |
| *P*-value* | | | 0.316 | | | | | |
| Early scleroderma, *n* (%) | 15 (17.5) | 5 (33.3) | 3 (20) | 1 (6.7) | 2 (13.3) | 11 (73.3) | 4 (26.7) | 0.07 |
| *P*-value* | | | 0.953 | | | | | |
| Active scleroderma, *n* (%) | 8 (9.3) | 5 (62.5) | 1 (12.5) | 1 (12.5) | 0 | 7 (87.5) | 1 (12.5) | 0.06 |
| *P*-value* | | | 0.241 | | | | | |
| Non-specific, *n* (%) | 40 (46.5) | 5 (12.5) | 5 (12.5) | 2 (5) | 4 (10) | 16 (40) | 24 (60) | 0.01 |
| *P*-value* | | | 0.613 | | | | | |
| ANA positive and morphology | | | | | | | | |
| Normal shape, *n* (%) | 72 (83.7) | 12 (16.6) | 8 (11) | 3 (4) | 5 (7) | 28 (38.8) | 44 (61.2) | 0.019 |
| *P*-value* | | | 0.08 | | | | | |
| Abnormal shape, *n* (%) | 14 (16.3) | 3 (21.4) | 5 (35.7) | 1 (7.15) | 1 (7.15) | 10 (71.4) | 4 (28.6) | 0.12 |
| *P*-value* | | | 0.643 | | | | | |
| ANA positive and dimension | | | | | | | | |
| $<0.03$ mm, *n* (%) | 29 (45.3) | 2 (6.9) | 5 (17.25) | 1 (3.45) | 2 (6.9) | 10 (34.5) | 19 (65.5) | 0.01 |
| *P*-value* | | | 0.39 | | | | | |
| $\geq 0.03$ mm, *n* (%) | 35 (54.7) | 12 (34.3) | 6 (17.1) | 3 (8.6) | 4 (11.4) | 25 (71.4) | 10 (28.6) | 0.002 |
| *P*-value* | | | 0.42 | | | | | |
| ANA positive and giant loop | | | | | | | | |
| Negative | 44 (62.9) | 4 (9.1) | 7 (15.9) | 2 (4.5) | 4 (9.1) | 17 (38.6) | 27 (61.4) | 0.002 |
| *P*-value* | | | 0.274 | | | | | |
| One loop, *n* (%) | 6 (8.6) | 2 (33.3) | 1 (16.7) | 0 | 2 (33.3) | 5 (83.3) | 1 (16.7) | 0.2 |
| *P*-value* | | | 0.425 | | | | | |
| Multiple loops, *n* (%) | 20 (28.5) | 9 (45) | 4 (20) | 2 (10) | 0 | 15 (75) | 5 (25) | 0.01 |
| *P*-value* | | | 0.064 | | | | | |
| ANA positive and total haemorrhages | | | | | | | | |
| 2–5, *n* (%) | 15 (40.5) | 0 | 3 (20) | 0 | 0 | 3 (20) | 12 (80) | 0.004 |
| *P*-value* | | | 0.08 | | | | | |
| $>5$, *n* (%) | 22 (59.5) | 9 (40.9) | 3 (13.6) | 4 (18.2) | 2 (9.1) | 18 (81.8) | 4 (18.2) | 0.001 |
| *P*-value* | | | 0.04 | | | | | |

*P*-values comparing the difference between combined ANA positive and capillaroscopy variables (those showing a significant difference in Table 3 analysis), frequency between the two groups of patients including UCTD patients who converted to definite CTD during the follow-up and the patients who remained UCTD during the study (*P*-value¶) and between patients who differentiated into definite diseases (*P*-value*) were considered significant if $<0.05$.

At baseline of our study, 293 patients (44.4%) had a definite CTD, including 36.9% with SSc, 13% OSs, 11.3% MCTD, 10.6% very early scleroderma, 9.9% SLE, 7.9% pSS, 3% DM/PM, 1% interstitial lung disease–associated CTD, 1% RA, 0.7% APS, 0.3% anti-JO1 syndrome and 4.4% other diagnoses (smokers, CTS, cervical rib, DLE and drug-induced, such as with propranolol use).

In total, 109 patients were followed up during our study period. There were nine primary RP and nine suspected secondary RP patients, all without transitions to a definite diagnosis. Since different studies have shown that patients with primary RP develop a definite CTD at a rate of 1–2%/year, the short follow-up duration of our patients with primary RP (15 months) and the small number of them might be the reasons behind this result.

We followed 91 patients with UCTD; 49 patients (53.8%) remained UCTD during 29.04 months and 42 (46.2%) with the mean follow-up of 26.7 months developed a definite CTD, mostly SSc, OSs, MCTD and pSS. There were no significant differences between those who remained UCTD and the CTD transition patients with respect to sex, age at RP onset, RP duration and age at study entry. The only exception was the younger age of patients in the MCTD group (26.71 years *vs* 37.4 in patients who had CTD conversion). Meli *et al.* [4] and Trombetta *et al.* [19], in line with our study, reported no significant differences regarding sex, age and RP duration between the patients who developed CTD and those who did not; thus these demographic parameters were not predictive of CTD evolution.

Ingegnoli *et al.* [23], in a meta-analysis, showed that among patients with secondary RP, 28.6% developed CTD, mostly (71.8%) SSc. In our study, 46% of patients with secondary RP developed CTD, which is higher than that reported in previous studies. Furthermore, the patients with UCTD with a scleroderma pattern on capillaroscopy mostly developed a definite CTD and patients with a non-specific abnormality on capillaroscopy mostly remained UCTD.

Our UCTD patients with capillary disarrangement, abnormal morphology, capillary diameter $\geq$0.03 mm, giant loops, decreased capillary density and more than five total haemorrhages on capillaroscopy had significant transitions to a definite CTD. Among them, only the cases with capillary disarrangement, those with multiple giant loops and the presence of more than five total haemorrhages when accompanied by a positive ANA test more commonly developed SSc.

In the study by Meli *et al.* [4] on 1024 patients with RP over 10 years, the presence of giant loop, avascular area and irregularity in capillaries were predictors of CTD development. Ingegnoli *et al.* [20] also reported that the presence of giant loops, microhaemorrhages and decreased capillary number had a significant prognostic role in the conversion to SSc. A difference in our study is the lack of significant differences concerning the avascular area, which may be explained by the small number of avascular areas in our patients with CTD transition (only six patients).

Trombetta *et al.* [19] implied that patients with a capillary diameter $>$30 μm had earlier transitions to SSc. Even though our study suggested that the presence of a capillary diameter $\geq$30 μm increased the chance of CTD transition, it did not increase the development of a specific CTD.

In our research, 49% of the UCTD patients remained stable and 42% had a CTD transition. García-González *et al.* [24] showed that among 98 patients with UCTD, 62% remained stable UCTD, 24% had remission and 14% developed into definite CTD during 11 years. The presence of cytopenia, anti-RO positivity and abnormal capillaroscopy was more common in their converted CTD group; high ANA titre and ACA positivity were also correlated with definite CTD development. We also noticed that the presence of ANA, RF and anti-RO/SSA in patients with UCTD can lead to a definite CTD, but not ACA positivity. The follow-up of our patients with ACA positivity was only 2.8 years (S.D. 1.8; range 4–78 months) and this may be the reason behind the difference in our results. The patients with RF positivity had a further conversion to OS, and those with positive snRNP, who became a definite CTD, all became MCTD.

The patients with UCTD with positive ANA combined with a scleroderma pattern of capillaroscopy, capillary diameter $\geq$0.03 mm, the presence of multiple giant loops and more than five haemorrhages mostly developed a definite CTD. Those with positive ANA combined with non-specific abnormalities, capillary diameter $<$0.03 mm, the absence of giant loops and those with two to five haemorrhages mostly remained UCTD. Ingegnoli *et al.* [5] showed that decreased capillary number ($<$7 loops/mm), giant loops and ANA increased the chance of SSc.

Based on our findings, CTD transition requires at least 17 months of follow-up for pSS, 36.5 months for SSc and 41 months for OSs to be recognized. Therefore it is recommended that the follow-up period for RP should be at least 3–5 years, a period during which, as shown by Herrick and Wigley [25], patients can develop a CTD.

Our study revealed that patients with UCTD with a scleroderma pattern of capillaroscopy developed more definite CTD compared with those with non-specific abnormalities that mostly remained UCTD. The subjects with capillary disarrangement, abnormal morphology, capillary diameter $\geq$0.03 mm, one giant loop, decreased capillary density and more than five total haemorrhages significantly transitioned to a definite CTD. In addition, the presence of ANA, RF and anti-RO/SSA in our patients with UCTD was a risk factor leading to a definite CTD. A combination of positive ANA and scleroderma pattern, capillary diameter $\geq$0.03 mm, the presence of multiple giant loops and more than five haemorrhages led to a definite CTD. The patients with positive ANA and more than five total haemorrhages were mostly converted to SSc.

Regarding the limitations of our study, we should mention the small number of patients with follow-up in the primary RP group and the short mean follow-up duration (27 months), which precluded the correct evaluation of CTD differentiation during the study. Studies with a longer duration are suggested for confirmation of the low and high important risk factors.

## Conclusion

Our study sheds light on the low incidence of primary RP in our patients. The most common causes of secondary RP were UCTD, SSc, OSs and MCTD. In accordance with previous studies, some capillaroscopy features and autoantibody results (like ANA, RF and anti-RO) alone or in combination (positive ANA combined with the scleroderma pattern, capillary diameter $\geq$0.03 mm, presence of even one giant loop and more than five total haemorrhages) could be taken into account as a risk factor for transition of patients with UCTD to a definite CTD.

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## Data availability statement

All data and materials in this article are available from the corresponding author on reasonable request.

## References


1 Wigley FM, Flavahan NA. Raynaud's phenomenon. N Engl J Med 2016;375:556–65.

2 Devulder J, van Suijlekom H, van Dongen R *et al.* 25. Ischemic pain in the extremities and Raynaud's phenomenon. Pain Pract 2011;11:483–91.

3 Pavlov-Dolijanovic S, Damjanov NS, Stojanovic RM, Vujasinovic Stupar NZ, Stanisavljevic DM. Scleroderma pattern of nailfold capillary changes as predictive value for the development of a connective tissue disease: a follow-up study of 3,029 patients with primary Raynaud's phenomenon. Rheumatol Int 2012;32:3039–45.

4 Meli M, Gitzelmann G, Koppensteiner R, Amann-Vesti BR. Predictive value of nailfold capillaroscopy in patients with Raynaud's phenomenon. Clin Rheumatol 2006;25: 153–8.

5 Ingegnoli F, Boracchi P, Gualtierotti R *et al.* Improving outcome prediction of systemic sclerosis from isolated Raynaud's phenomenon: role of autoantibodies and nail-fold capillaroscopy. Rheumatology (Oxford) 2010;49: 797–805.

6 Mosca M, Tani C, Vagnani S, Carli L, Bombardieri S. The diagnosis and classification of undifferentiated connective tissue diseases. J Autoimmun 2014;48–49:50–2.

7 Maverakis E, Patel F, Kronenberg DG *et al.* International consensus criteria for the diagnosis of Raynaud's phenomenon. J Autoimmun 2014;48–49:60–5.

8 Wigley FM. Clinical practice. Raynaud's phenomenon. N Engl J Med 2002;347:1001–8.

9 Pauling JD, Hughes M, Pope JE. Raynaud's phenomenon—an update on diagnosis, classification and management. Clin Rheumatol 2019;38:3317–30.

10 Bellando-Randone S, Matucci-Cerinic M. Very early systemic sclerosis. Best Pract Res Clin Rheumatol 2019; 33:101428.

11 Smith V, Herrick AL, Ingegnoli F *et al.* Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. Autoimmun Rev 2020;19:102458.

12 Ingegnoli F, Herrick AL, Schioppo T *et al.* Reporting items for capillaroscopy in clinical research on musculoskeletal diseases: a systematic review and international Delphi consensus. Rheumatology (Oxford) 2020;60:1410–8.

13 Lambova SN, Muller-Ladner U. The role of capillaroscopy in differentiation of primary and secondary Raynaud's phenomenon in rheumatic diseases: a review of the literature and two case reports. Rheumatol Int 2009;29:1263–71.

14 Cortes S, Cutolo M. Capillaroscopic patterns in rheumatic diseases. Acta Reumatol Port 2007;32:29–36.

15 Maricq HR, Harper FE, Khan MM, Tan EM, LeRoy EC. Microvascular abnormalities as possible predictors of disease subsets in Raynaud phenomenon and early connective tissue disease. Clin Exp Rheumatol 1983;1: 195–205.

16 Hirschl M, Hirschl K, Lenz M *et al.* Transition from primary Raynaud's phenomenon to secondary Raynaud's phenomenon identified by diagnosis of an associated disease: results of ten years of prospective surveillance. Arthritis Rheum 2006;54:1974–81.

17 De Angelis R, Del Medico P, Blasetti P, Cervini C. Raynaud's phenomenon: clinical spectrum of 118 patients. Clin Rheumatol 2003;22:279–84.

18 Koenig M, Joyal F, Fritzler MJ *et al.* Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. Arthritis Rheum 2008;58: 3902–12.

19 Trombetta AC, Smith V, Pizzorni C *et al.* Quantitative alterations of capillary diameter have a predictive value for development of the capillaroscopic systemic sclerosis pattern. J Rheumatol 2016;43:599–606.

20 Ingegnoli F, Boracchi P, Gualtierotti R *et al.* Prognostic model based on nailfold capillaroscopy for identifying Raynaud's phenomenon patients at high risk for the development of a scleroderma spectrum disorder: PRINCE (prognostic index for nailfold capillaroscopic examination). Arthritis Rheum 2008;58: 2174–82.

21 Garner R, Kumari R, Lanyon P, Doherty M, Zhang W. Prevalence, risk factors and associations of primary Raynaud's phenomenon: systematic review and meta-analysis of observational studies. BMJ Open 2015;5: e006389.

22 Prete M, Favoino E, Giacomelli R *et al.* Evaluation of the influence of social, demographic, environmental, work-related factors and/or lifestyle habits on Raynaud's phenomenon: a case–control study. Clin Exp Med 2020;20: 31–7.

23 Ingegnoli F, Ughi N, Crotti C, Mosca M, Tani C. Outcomes, rates and predictors of transition of isolated Raynaud's phenomenon: a systematic review and meta-analysis. Swiss Med Wkly 2017;147:w14506.

24 García-González M, Rodríguez-Lozano B, Bustabad S, Ferraz-Amaro I. Undifferentiated connective tissue disease: predictors of evolution into definite disease. Clin Exp Rheumatol 2017;35:739–45.

25 Herrick AL, Wigley FM. Raynaud's phenomenon. Best Pract Res Clin Rheumatol 2020;34:101474.