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# Nailfold capillaroscopy abnormalities as predictors of mortality in patients with systemic sclerosis

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**Key words:** systemic sclerosis, Raynaud's phenomenon, capillaroscopy, mortality

## ABSTRACT

**Objective.** *Peripheral microangiopathy is a hallmark of systemic sclerosis (SSc) and can be early detected by nailfold capillaroscopy (NFC). This study aimed to examine whether more severe peripheral microangiopathy at NFC are predictive factor for death in SSc patients.*

**Methods.** *135 SSc patients who performed NFC between June 2001 and July 2009 were included. The following NFC parameters were evaluated: number of capillary loops/mm, avascular score (scored from 0 to 3), and number of enlarged and giant capillary loops. Univariate and multivariate regression models were used to analyse the association of mortality with NFC and clinical parameters.*

**Results.** *At the time of the analysis (August 2010), 123 patients were alive, and 12 were dead. By univariate analysis, male gender, forced vital capacity <75% predicted, higher number of giant capillary loops, and an avascular score >1.5 on NFC were associated with a significantly increase risk of death. By multivariate analysis, an avascular score >1.5 was the only independent predictor of death (hazard ratio 2.265). Survival rates from diagnosis at 1, 5 and 10 years were lower in patients with avascular score >1.5 (97%, 86%, and 59%, respectively) compared with those with avascular score ≤1.5 (97%, 97%, and 91% respectively) (p=0.009 by log rank test).*

**Conclusion.** *Avascular scores higher than 1.5 at NFC was an independent predictor of death in SSc, suggesting that NFC can be useful for predicting SSc outcome.*

## Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease characterised by widespread cutaneous and visceral fibrosis, small-vessel vasculopathy, and presence of autoantibodies against sev-

eral cellular antigens. It is a heterogeneous disease with respect to the extent of skin involvement and internal organ severity, ranging from limited cutaneous SSc, with less serious involvement of the internal organs, to diffuse cutaneous SSc, characterised by extensive skin involvement and often rapidly progressive visceral involvement (1, 2). Although survival in SSc has improved in recent decades, SSc is still associated with significant morbidity and mortality rates (3-6). Previous studies have reported increased mortality in patients with older age, male sex, diffuse cutaneous SSc, and severe involvement of lungs, heart and kidneys (1-8).

Small-vessel vasculopathy, characterised by increased vasoconstriction, endothelial cell injury, and fibrotic intimal hyperplasia, is an early and prominent event in SSc. Structural changes in the peripheral microcirculation can be easily detected by nailfold capillaroscopy (NFC), a noninvasive and well established method for early diagnosis of SSc (9-11). Patients with SSc exhibit a typical pattern at NFC, designated "SD pattern", and characterised by enlargement of capillary loops, loss of capillaries, variable degree of microhaemorrhage, disruption of the orderly appearance of the capillary bed and distortion of capillaries (10, 12). Although previous studies have shown that NFC abnormalities correlate with more severe disease (13, 14), the influence of NFC abnormalities as a predictor of mortality in SSc has been investigated by a few studies in a restricted number of patients (15, 16). The aim of this study was to determine whether the degree of peripheral microangiopathy evaluated by nailfold capillaroscopy is a predictive factor for mortality in a large sample of patients with SSc.

## Materials and methods

This was a retrospective study including all SSc patients who attended the

Competing interests: none declared.

Rheumatology Division at the Federal University of São Paulo and underwent NFC between June 2001 and July 2009. NFC data were derived from the Capillaroscopy Database started in 2001 which contains demographic, capillaroscopic and laboratory information of all patients undergoing NFC examination in our centre. Consecutive patients who underwent NFC up to July 2009 and who fulfilled the criteria of the American College of Rheumatology (ACR) for SSc (17), and were under follow-up at our scleroderma unit were included. Medical appointments were scheduled within one to 4 months. Patients with overlap symptoms to other connective diseases such as systemic lupus erythematosus, and rheumatoid arthritis were excluded from the study. SSc patients with associated Sjögren's syndrome were included.

#### Data collection

The data set was locked for analysis in August 2010, so that the minimum follow-up since NFC was 12 months. Information about demographic characteristics, disease features, and immunosuppressive treatment were collected. The date of SSc diagnosis was considered as the time of the diagnosis for each patient, whether the diagnosis was made at our Hospital or at the referring institution. The time between first symptoms (Raynaud's phenomenon in the majority of patients) and diagnosis was also recorded. The disease was classified as diffuse cutaneous or limited cutaneous SSc as previously described (18).

Data about pulmonary function tests were collected and a forced vital capacity (FVC) <75% of the predicted values was considered abnormal. Pulmonary arterial hypertension (PAH) was defined by pulmonary arterial systolic pressure (PASP) >40mmHg, estimated on Doppler echocardiography.

All NFC procedures were performed in a stereomicroscope (Olympus SZ40) under 10-25 x magnification according to the protocol proposed by Andrade *et al.* (9). A transparent ruler is incorporated to the right eyepiece of the stereomicroscope, allowing reproducible measurements of capillary width and

of the number of capillary loops/mm. All the ten digits of the hands were examined. The following parameters were analysed in all patients: (1) number of capillary loops/mm, (2) avascular score, (3) number of enlarged loops (over four times the normal afferent, transition, and efferent limbs width), and (4) number of giant capillary loops (10 or more times the normal width of capillary limbs). The avascular score was assessed according to Lee's method (19), in which a deletion area is defined as the absence of two or more consecutive loops. Each finger was rated from 0 to 3: grade 0 = no avascular area; 1 = one or two discrete avascular areas; 2 = more than two discrete avascular areas; 3 = extensive and confluent avascular areas. For each patient the NFC parameters were calculated as the average obtained in all analysed fingers. All NFC exams were performed by the same observer, blinded for the patient conditions, and with extensive experience in the method.

Antinuclear antibodies (ANA) were determined by indirect immunofluorescence using HEp-2 cell as substrate. Anti-centromere antibodies (ACA) were identified by the typical pattern on the indirect immunofluorescence HEp-2 cell assay and anti-topoisomerase I (anti-Scl-70) antibodies were determined by the double immunodiffusion method against rabbit thymus extract.

The following variables were evaluated in the analysis of prognostic factors: age at diagnosis, gender, extent of skin sclerosis, FVC, PASP on echocardiogram, ANA, ACA and anti-topoisomerase antibodies, immunosuppressive treatment, and NFC parameters. The vital status (alive or deceased) was verified by reviewing medical records to determine the last follow up or by phone contact. Patients were classified as alive if they were followed up to or after August 2010. For patients deceased in the hospital, the causes of death recorded on the discharge summary were documented. For patients who did not die in our hospital the primary cause of death in the death certificates was obtained by telephone interview.

#### Statistical analysis

Comparison between groups was performed using Student's *t*-test or Mann-Whitney test for continuous variables and chi-square test or Fisher's exact test for categorical data. A *p*-value <0.05 was considered significant. The association between variables and mortality were assessed using univariate Cox proportional hazards models. Subsequently, a multivariate model was built including all variables found to be significant in univariate analysis (*p*≤0.10). Kaplan-Meier curve was constructed to estimate survival according to the avascular score on NFC. Comparison of survival curve was conducted using the log-rank test.

#### Results

A total of 205 SSc patients attended the Rheumatology Division at UNIFESP to perform NFC between June 2001 and July 2009. At the time of the analysis (August 2010), 123 patients were alive and 12 were deceased. The remaining 70 patients had unknown mortality status and were consequently excluded from the analysis.

The major clinical, laboratory, and NFC features of the 135 patients, alive and deceased, are summarised in Table I. The mean duration of follow up from diagnosis was 6.49±4.40 years (range 1–22 years), with no difference between patients who died during the follow up period and those who did not (*p*=0.776). The overall mean age at diagnosis was 48.15±14.31 years, with no difference between the 123 patients who were alive and the twelve deceased patients (49.21±14.07 vs 47.02±14.53 years, *p*=0.623). Similarly, alive and deceased patients did not differ with respect to the interval between the first symptom and diagnosis (*p*=0.162). As expected there was a predominance of the female gender among the 135 SSc patients (82%). However, among the 12 patients who died, the proportion of males (41%) was significantly higher comparing to the patients who were alive (18%) (*p*=0.046). Seventy-three patients were classified as limited cutaneous SSc, and 62 as diffuse cutaneous SSc, with no difference in the proportion of deaths in these two

groups ( $p=0.767$ ). ANA and ACA were positive in 88% and 18% of the 135 patients, respectively. Data for anti-Scl-70 antibodies were available for 93 patients, with a prevalence of 15%. The frequency ANA, ACA and anti-Scl-70 antibodies was similar between alive and deceased patients. There was no difference in the frequency of use of immunosuppressive treatment (cyclophosphamide and azathioprine) between the two groups. Cyclophosphamide was used by 21 patients (17 alive and 4 deceased), and azathioprine was used by 10 patients (9 alive and 1 deceased) (Table I).

The typical NFC scleroderma pattern (SD pattern) was observed in 11 deceased patients (91%) and in 99 alive patients (80%) ( $p=0.307$ ). The analysis of NFC individual parameters demonstrated a significantly higher number of giant capillary loops and a significantly higher avascular score in the 12 patients who died compared to the alive patients ( $p=0.01$  and  $p=0.002$ , respectively). An avascular score higher than 1.5 was found in 75% of the patients who had died and in 30% of the patients who were alive ( $p=0.004$ ) (Table I).

#### Causes of death

Immediate causes of death were pulmonary arterial hypertension ( $n=3$ ), pulmonary fibrosis ( $n=1$ ), association of pulmonary fibrosis and pulmonary arterial hypertension ( $n=1$ ), SSc myocardial involvement ( $n=1$ ), acute myocardial infarction ( $n=1$ ), pneumonia ( $n=1$ ), septicemia ( $n=2$ ), and sudden death ( $n=1$ ). For one patient the cause of death was unknown and death certificate was not available.

#### Predictors for survival

By univariate analysis, male gender, FVC <75% predicted, higher number of giant capillary loops, and avascular score higher than 1.5 on NFC were associated with a significantly increased risk of death (Table II). In the multivariate model, a significantly increased risk of death was associated independently with avascular score higher than 1.5 (hazard ratio [HR] 2.265, 95% confidence interval [95% CI]: 1.02-11.77,

**Table I.** Demographic parameters, autoantibodies, and nailfold capillaroscopy abnormalities in 135 patients with systemic sclerosis according to vital status.

	All patients (n=135)	Alive (n=123)	Deceased (n=12)	Alive vs. deceased
Age at diagnosis, years	48.15 ± 14.31	49.21 ± 14.07	47.02 ± 14.53	0.62
Gender, number of males (%)	25 (18%)	20 (16%)	5 (41%)	<b>0.04</b>
Years between first symptoms and diagnosis	4.64 ± 4.58	4.42 ± 4.77	4.12 ± 2.79	0.16
Years of followup (from diagnosis)	6.49 ± 4.40	6.64 ± 4.46	5.10 ± 3.84	0.78
Limited disease subtype (%)	73 (54%)	67 (54%)	6 (50%)	0.77
FVC (% predicted) (n=93)	88.51 ± 17.08	89.71 ± 16.18	78.42 ± 22.13	0.09
FVC <75% predicted (n=93) (%)	18 (19%)	15 (17%)	3 (33%)	0.24
PASP >40 mmHg (n=100) (%)	15 (15%)	12 (13%)	4 (36%)	0.07
Positive ANA (%)	119 (88%)	109 (89%)	10 (83%)	0.64
Positive ACA (%)	24 (18%)	21 (17%)	3 (25%)	0.45
Positive Anti-Scl-70 (n=93) (%)	14 (15%)	12 (14%)	2 (22%)	0.62
NFC with SD pattern (%)	110 (82%)	99 (80%)	11 (91%)	0.31
Number of capillaries/mm	7.73 ± 1.95	7.78 ± 1.97	7.28 ± 1.67	0.33
Number of enlarged capillary loops	3.37 ± 3.37	3.24 ± 3.23	4.76 ± 4.55	0.29
Number of giant capillary loops	0.18 ± 0.55	0.13 ± 0.32	0.74 ± 1.49	<b>0.01</b>
Avascular score	1.12 ± 0.97	1.03 ± 0.94	1.94 ± 0.92	<b>0.002</b>
Avascular score >1.5 (%)	47 (35%)	38 (30%)	9 (75%)	<b>0.004</b>
Immunosuppressive treatment	31 (23%)	26 (19%)	5 (41%)	0.11

Except where indicated otherwise, values are the mean ± SD. FVC: forced vital capacity; PASP: pulmonary arterial systolic pressure; ANA: antinuclear antibodies; ACA: anti-centromere antibody; NFC: nailfold capillaroscopy.

**Table II.** Univariate analysis of predictors of mortality in patients with systemic sclerosis.

Parameters	Hazard ratio	95% CI	p-value
Age at diagnosis	0.995	0.96-1.03	0.78
Male gender	3.679	1.06-12.76	<b>0.04</b>
Disease subtype	1.396	0.44-4.41	0.57
FVC < 75% predicted	3.654	0.87-15.38	<b>0.08</b>
PASP > 40 mmHg	0.477	0.14-1.65	0.24
ANA	2.206	0.48-10.21	0.31
ACA	0.713	0.19-2.67	0.62
Anti-Scl70	0.534	0.11-2.58	0.43
Number of capillaries/mm	0.887	0.65-1.17	0.36
Number of enlarged capillary loops	1.071	0.93-1.23	0.33
Number of giant capillary loops	2.109	1.39-3.19	<b>&lt;0.001</b>
Avascular score >1.5	4.791	1.29-17.73	<b>0.02</b>
Immunosuppressive treatment	0.429	0.13-1.36	0.15

ANA antinuclear antibodies; ACA: anti-centromere antibody; FVC: forced vital capacity; PASP: pulmonary arterial systolic pressure; CI: confidence interval.

**Table III.** Multivariate analysis of predictors of mortality in patients with systemic sclerosis.

Parameters	Hazard ratio	95% CI	p-value
Male versus female gender	0.539	0.69-1.55	0.38
FVC <75% vs. ≥75% predicted	1.039	0.45-8.99	0.36
Number of giant capillary loops	0.318	1.04-3.04	0.37
Avascular score >1.5 vs. ≤1.5	2.265	1.02-11.77	0.04

CI: confidence interval.

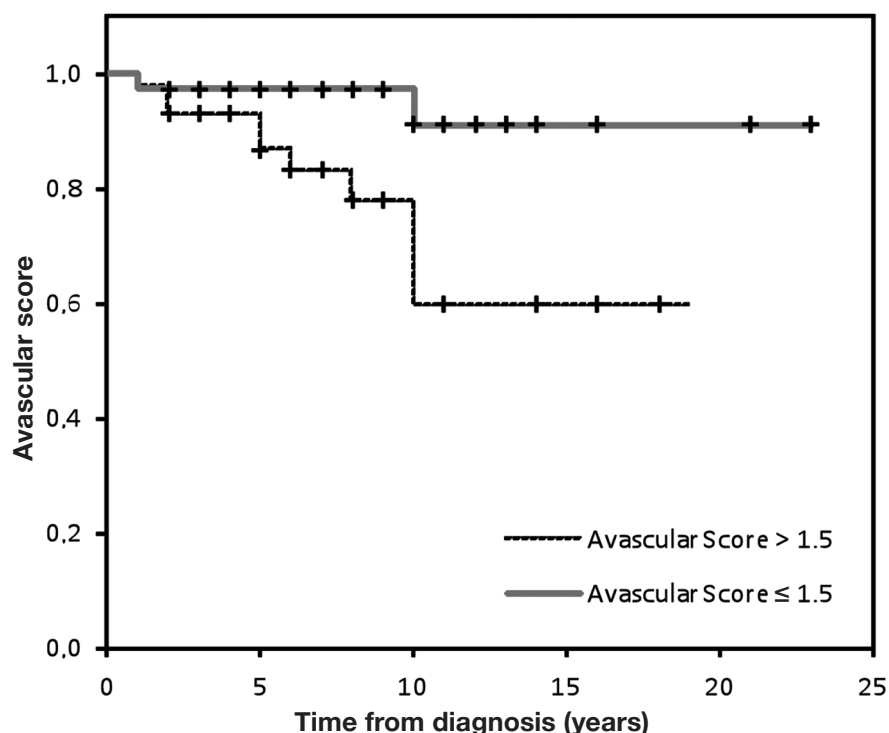
$p=0.04$ ) (Table III). Survival rates from SSc diagnosis were 97%, 86%, and 59% at 1, 5 and 10 years, respectively, among patients with avascular score higher than 1.5 compared with survival rates of 97%, 97%, and 91% at 1, 5 and

10 years, respectively, among those with avascular score ≤1.5 ( $p=0.009$  by log rank test) (Fig. 1). Survival rates in the 135 SSc patients were 97%, 93%, and 78% at 1, 5 and 10 years, respectively.

## Discussion

Although some studies have shown an improvement in patient's survival over the last years SSc remains a devastating disease with poor prognosis (4, 8, 20). A recent meta-analysis of cohort studies evaluating the mortality in SSc patients reported no significant change in mortality ratios over the past 40 years (21). The present study originally showed reduced survival in SSc patients with more severe peripheral microangiopathy as analysed by NFC. Patients with higher degree of capillary loss (avascular score above 1.5) had a two-fold increase in mortality rates in comparison to those with a reduced amount of avascular score.

Only two other studies evaluated the association of NFC parameters and mortality in SSc. Simeón *et al.* (16), showed that an active pattern on NFC was associated with shorter survival by univariate analysis, but not on multivariate analysis. Similarly, Scussel-Lonzetti *et al.* performed an analysis of a cohort of 309 French Canadian patients and found that the degree of capillary loss was associated with increased mortality rate by univariate analysis, but this was not an independent predictive factor for mortality (15). However, the degree of capillary loss was associated with more extensive skin involvement (15). Heterogeneity in SSc patient selection and differences in NFC methodology could explain these minor divergences in the literature. The present study utilised a reproducible NFC methodology, comprehending several microangiopathic parameters assessed in quantitative and semiquantitative fashion. The absolute number of enlarged and giant capillaries, and the avascular score were determined in each finger and the mean value for all 10 fingers was used for the analyses. In contrast, Siméon *et al.* (16), used a qualitative classification proposed by Maricq *et al.* (22), who classified the NFC abnormalities in two major nailfold capillary patterns, namely the "active" (extensive loss of capillaries and minimal capillary enlargement) and the "slow" (capillary enlargement and/or extremely enlarged capillaries with no or minimal capillary loss) pattern. Scussel-Lonzetti *et al.* (15), used semi-



**Fig. 1.** Kaplan-Meier survival curve from diagnosis of systemic sclerosis comparing patients with an avascular score higher than 1.5 on nailfold capillaroscopy with those with an avascular score  $\leq 1.5$  ( $p=0.009$  by log rank test).

quantitative scores for both capillary dilatation and capillary loss, which may convey some degree of subjectivity to the assessment. The methodology used in the present study has been developed with the aim to grant objectivity to the NFC exam by relying in quantitative and semiquantitative parameters with clearly defined criteria, and has shown good intra and inter-observer reproducibility (9, 23). The present results suggest that the assessment of objective NFC parameters was able to show the association of more severe degrees of nailfold microangiopathy with higher risk of mortality. In addition, we have recently shown that NFC is a reliable and reproducible method in comparison to the videocapillaroscope method for the evaluation of the microangiopathy in patients with RP (23).

Interestingly, several studies have previously shown association between NFC and more severe disease. Most previous results report on a positive correlation between the degree of abnormalities at NFC, mostly the severity of capillary loss, and the extent of cutaneous and visceral involvement in SSc (13, 14, 24, 25). We have shown

previously that higher degrees of capillary loss at NFC were associated with the diffuse form of SSc, the number of involved organs, and the presence of anti-Scl-70 antibodies (14), factors that have been associated with higher mortality in several studies. The present finding of poor prognosis in patients with higher degree of capillary loss at NFC emphasises the importance of the method for the identification of patients with more severe disease.

In the present study we did not find association between mortality and other parameters including age at diagnosis, disease subtype, and presence of anti-topoisomerase I antibodies. Male gender was associated with higher risk of mortality in univariate analysis, but not in multivariate analysis. Some previous studies have indicated an association between mortality and older age at diagnosis (8), SSc-related autoantibodies (6), and diffuse skin involvement disease (26), but other studies could not confirm all these associations (1, 27). In a recent multiethnic early systemic sclerosis (SSc) cohort, older age at diagnosis, but not diffuse cutaneous disease or the presence of anti-Scl-70



antibodies were significant predictors of mortality (1). Capillaroscopy data was not available in this study.

The main limitations of the present study are the retrospective design and the lack of whole data on visceral involvement and treatment. Nonetheless we were interested in determining whether NFC variables could be a significant determinant of mortality in a cohort of SSc patients and there was a structured Capillaroscopy Database available that conferred a considerable degree of confidence for the retrospective analysis. Further prospective studies including other important parameters in SSc prognosis are necessary for the confirmation of NFC microangiopathy as an independent predictor of mortality in SSc patients. In addition, patients were recruited from a tertiary centre and we cannot exclude a referral bias toward patients with more severe disease.

In the current study, survival from the time of diagnosis was only 59% at 10 years in patients with an avascular score higher than 1.5 comparing with 91% at 10 years in patients with an avascular score  $\leq 1.5$ . The ten-year survival was 78% among all patients evaluated. The survival rates reported in different studies vary widely, depending on the characteristics of the population of each cohort (8, 28). Differences in the proportion of patients with different clinical subsets, frequency of autoantibodies, and ethnic variability are reasons why these results are difficult to compare (4). Mayes *et al.* (8), studied the prevalence, incidence and survival of SSc in a large US sample, and showed an absolute survival of 77% at 5 years, and 55% at 10 years. Factors negatively affecting survival included male sex and older age at diagnosis. Steen and Medsger (4), showed a 10-year cumulative survival of 67% in the 1990s, comparing to 54% in the 1970s. Another recent study, involving Canadian patients who were followed between 1994 and 2004, showed a 10-year survival of 82% (26). Finally, an Italian study of 1012 patients showed a 10-year survival of 76% among patients recruited between 1986 and 1999 (2). To our knowledge this is the first

cohort evaluating survival in patients with SSc in Latin America. Our results suggest that despite different ethnicity and geographic environment, Brazilian SSc patients have similar survival rates in comparison to European and North American patients. However, the mortality rates observed in this study might be underestimated by the fact that 70 of the original 205 patients had unknown vital status.

The analysis of the clinical and demographic findings of the 135 Brazilian patients disclosed epidemiological features similar to those registered in the literature in that there was female predominance, disease onset around 45 year old in average, and presence of SD pattern on NFC in more than 80% of the patients (2, 10). The high prevalence of patients with diffuse cutaneous disease (46%) is probably related to a referral bias since all patients were recruited from a tertiary centre.

Our findings are particularly relevant at a time when early diagnosis of SSc is being proposed (29). The microangiopathic abnormalities evaluated by NFC tend to occur at early stages of the disease, sometimes when only Raynaud's phenomenon is present and there is no involvement of major organs. Thus, NFC is considered a very important diagnostic tool for the early diagnosis of SSc (30, 31). Moreover, previous studies have focused on risk factors evaluated when the disease is well established, with the involvement of organs like the kidneys, lungs and heart. Not surprisingly, the presence of any major organ involvement is associated with decreased survival (4). The early detection of patients with higher risk of mortality, before the involvement of the major organs, could have practical implication for these patients.

In conclusion, our data suggests that higher degree of devascularisation on NFC was significantly associated with higher risk of mortality, suggesting that NFC can be used as prognostic marker in SSc. The demonstration that a non-invasive and low cost tool such as NFC could detect SSc patients with poorer prognosis can have important practical implication for therapeutic decision of these patients. Further prospective

studies are warranted to evaluate NFC parameters as predictors of disease outcome in patients with early disease.

## References

1. ASSASSI S, DEL JUNCO D, SUTTER K *et al.*: Clinical and genetic factors predictive of mortality in early systemic sclerosis. *Arthritis Rheum* 2009; 61: 1403-11.
2. FERRI C, VALENTINI G, COZZI F *et al.*: Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine* (Baltimore) 2002; 81: 139-53.
3. MEDSGER TA JR, MASI AT, RODMAN GP, BENEDEK TG, ROBINSON H: Survival with systemic sclerosis (scleroderma): a life-table analysis of clinical and demographic factors in 309 patients. *Ann Intern Med* 1971; 75: 369-76.
4. STEEN VD, MEDSGER TA: Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 2007; 66: 940-4.
5. BRYAN C, HOWARD Y, BRENNAN P, BLACK C, SILMAN A: Survival following the onset of scleroderma: results from a retrospective inception cohort study of the UK patient population. *Br J Rheumatol* 1996; 35: 1122-6.
6. IOANNIDIS JPA, VLACHOYIANNPOULOS PG, HAIDICH AB *et al.*: Mortality in systemic sclerosis: an international meta-analysis of individual patient data. *Am J Med* 2005; 118: 2-10.
7. ABU-SHAKRA M, LEE P: Mortality in systemic sclerosis: a comparison with the general population. *J Rheumatol* 1995; 22: 2100-2.
8. MAYES MD, LACEY JV JR, BEEBE-DIMMER J *et al.*: Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum* 2003; 48: 2246-55.
9. ANDRADE LEC, GABRIEL JRA, ASSAD RL, FERRARI JAL, ATRA E: Panoramic nailfold capillaroscopy: a new reading method and normal range. *Semin Arthritis Rheum* 1990; 20: 21-31.
10. MARICQ KR, LEROY EC, D'ANGELO WA *et al.*: Diagnostic potential of *in vivo* capillary microscopy in scleroderma and related disorders. *Arthritis Rheum* 1980; 23: 183-9.
11. HUDSON M, MASETTO A, STEELE R, ARTHURS E, BARON M, CANADIAN SCLERODERMA RESEARCH GROUP: Reliability of widefield capillary microscopy to measure nailfold capillary density in systemic sclerosis. *Clin Exp Rheumatol* 2010; 28 (Suppl. 62): 36-41.
12. SULLI A, SECCHI ME, PIZZORNI C, CUTOLO M: Scoring the nailfold microvascular changes during the capillaroscopic analysis in systemic sclerosis patients. *Ann Rheum Dis* 2008; 67: 885-7.
13. CARAMASCHI P, CANESTRINI S, MARTINELLI N *et al.*: Scleroderma patients nailfold videocapillaroscopic patterns are associated with disease subset and disease severity. *Rheumatology* 2007; 46: 1566-9.
14. SATO LT, KAYSER C, ANDRADE LE: Nailfold capillaroscopy abnormalities correlate with cutaneous and visceral involvement in systemic sclerosis patients. *Acta Reumatol Port* 2009; 34: 219-27.

15. SCUSSEL-LONZETTI L, JOYAL F, RAYNAULD JP *et al.*: Predicting mortality in systemic sclerosis: analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. *Medicine* (Baltimore) 2002; 81: 154-67.
16. SIMEÓN CP, ARMADANS L, FONOLLOSA V *et al.*: Mortality and prognostic factors in Spanish patients with systemic sclerosis. *Rheumatology* 2003; 42: 71-5.
17. SUBCOMMITTEE FOR SCLERODERMA CRITERIA OF THE AMERICAN RHEUMATISM ASSOCIATION DIAGNOSTIC AND THERAPEUTIC CRITERIA COMMITTEE: Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980; 23: 581-90.
18. LEROY EC, BLACK C, FLEISCHMAJER R *et al.*: Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202-5.
19. LEE P, LEUNG FY, ALDERDICE C, ARMSTRONG SK: Nailfold capillary microscopy in the connective tissue diseases: a semi-quantitative assesment. *J Rheumatol* 1983; 10: 930-8.
20. ANTON JM, CASTRO P, ESPINOSA G *et al.*: Mortality and long term survival prognostic factors of patients with systemic autoimmune diseases admitted to an intensive care unit: a retrospective study. *Clin Exp Rheumatol* 2012; 30: 338-44.
21. ELHAI M, MEUNE C, AVOUAC J, KAHAN A, ALLANORE Y: Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. *Rheumatology* 2012; 51: 1017-26.
22. MARICQ HR, SPENCER-GEEN G, LEROY EC: Skin capillary abnormalities as indicators of organ involvement in scleroderma (systemic sclerosis), Raynaud's syndrome and dermatomyositis. *Am J Med* 1976; 61: 862-70.
23. SEKIYAMA JY, CAMARGO CZ, ANDRADE LEC, KAYSER C: Comparison of wide-field nailfold capillaroscopy and videocapillaroscopy in the assessment of the microcirculation in patients with Raynaud's phenomenon [abstract]. *Arthritis Rheum* 2011; 63: S570.
24. JOYAL F, CHOQUETTE D, ROUSSIN A, LEVINGTON C, SENÉCAL JL: Evaluation of the severity of systemic sclerosis by nailfold capillary microscopy in 112 patients. *Angiology* 1992; 43: 203-10.
25. BREDEMEIER M, XAVIER RM, CAPOBIANCO KG *et al.*: Nailfold capillary microscopy can suggest pulmonary disease activity in systemic sclerosis. *J Rheumatol* 2004; 31: 286-94.
26. AL-DHAHER FF, POPE JE, OUIMET JM: Determinants of morbidity and mortality of systemic sclerosis in Canada. *Semin Arthritis Rheum* 2010; 39: 269-77.
27. MATHAI SC, HUMMERS LK, CHAMPION HC *et al.*: Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: impact of interstitial lung disease. *Arthritis Rheum* 2009; 60: 569-77.
28. SILMAN AJ: Scleroderma: demographics and survival. *J Rheumatol* 1997; 48 (Suppl.): 58-61.
29. AVOUAC J, FRANSEN J, WALKER UA *et al.*: Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. *Ann Rheum Dis* 2011; 70: 476-81.
30. SPENCER-GREEN G: Outcomes in primary Raynaud phenomenon: a meta-analysis of the frequency, rates, and predictors of transition to secondary diseases. *Arch Intern Med* 1998; 158: 595-600.
31. HERRICK AL, CUTOLO M: Clinical implications from capillaroscopic analysis in patients with Raynaud's phenomenon and systemic sclerosis. *Arthritis Rheum* 2010; 2: 2595-604.