Nailfold capillaroscopy findings of a multicentric multi-ethnic cohort of patients with idiopathic inflammatory myopathies

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Abstract

Objective

To assess nailfold video capillaroscopic (NVC) abnormalities and their association with clinical features, myositis-specific autoantibodies (MSA), and myositis-associated antibodies (MAA) in a large multi-ethnic cohort of patients with idiopathic inflammatory myopathies (IIM).

Methods

We recruited 155 IIM patients from three centres in Mexico, Spain, and the USA. We evaluated the clinical and laboratory features of the patients and performed semiquantitative and quantitative analyses of the NVC. Each NVC study was defined as having a normal, non-specific, early systemic sclerosis (SSc), active SSc, or late SSc pattern. Twenty-three patients had at least one follow-up NVC when disease control was achieved. Quantitative variables were expressed as medians and interquartile range (IQR) and were compared with the Kruskal-Wallis, the Mann-Whitney U-test, and the Wilcoxon test for paired medians. Associations between qualitative variables were assessed with the χ^2 test.

Results

Most patients were women (68.3%), Hispanic (73.5%), and had dermatomyositis (DM) (61.2%). Fourteen patients (9%) had a normal NVC. A non-specific abnormality pattern was the most frequent (53.9%), and was associated with joint involvement, interstitial lung disease, Jo1 autoantibodies, anti-synthetase syndrome, and immune-mediated necrotising myopathy. The SSc pattern was observed mostly in DM and overlap myositis and was associated with cutaneous features and anti-TIF-1g autoantibodies. After treatment, there was a decrease in the capillaroscopic score, the capillary diameter, and the number of avascular areas, and an increase in capillary density and bushy capillary number.

Conclusion

NVC abnormalities are related to the diagnosis, clinical features, disease activity, and autoantibodies of patients with IIM.

Key words

Nailfold video capillaroscopy, idiopathic inflammatory myopathies, non-specific abnormalities, systemic sclerosis pattern, Jo1, TIF-1g, Mi2, MDA5

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Introduction

Idiopathic inflammatory myopathies (IIM) are a group of systemic autoimmune diseases with increasing incidence after the coronavirus disease 2019 (COVID-19) pandemic (1). Microvascular abnormalities are frequent in IIM, especially in dermatomyositis (DM) (2) and anti-synthetase syndrome (AS) (3). Many different clinical features have been associated with vasculopathy in IIM, such as digital ulcers in anti-MDA5-positive DM, and Raynaud's phenomenon (RP), which is observed in approximately 11% of patients with IIM (3), and is especially frequent in AS (93%) (3). In addition, loss and enlargement of capillaries are found in muscle biopsies from patients with DM (4), indicating that microvascular damage is an important pathogenic factor in IIM.

Among the methods to assess the capillary abnormalities in autoimmune diseases, the nailfold video capillaroscopy (NVC) is a widely available, non-invasive, and inexpensive tool. Capillaroscopic abnormalities have been reported in up to 100% of patients with IIM[5]. Many previous studies have described capillaroscopic abnormalities in patients with IIM; nonetheless, the classification of this group of diseases has considerably evolved in recent decades with the discovery of myositis-specific (MSA) and myositis-associated autoantibodies (MAA). These autoantibodies define disease phenotypes and are associated with specific clinical features. The capillaroscopic characteristics of the distinctive clinical phenotypes of IIM and their differences according to the positivity for MSA and MAA have not been previously described in a large cohort of patients with IIM, which is the aim of the present study.

Methods

We recruited 155 adult IIM patients from three centres in the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), Bethesda, Maryland, USA (n=41), the Vall d'Hebron Hospital, Barcelona, Spain (n=81) and the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico (n=33). Three patients from NIAMS had myositis due to graft versus host disease (GVHD). The rest of the patients were classified as having an IIM according to the 2017 ACR/EULAR criteria (6). For the diagnosis of AS we used Connor's criteria (7). Patients with immune-mediated necrotising myopathy (IMNM) and sporadic inclusion body myositis (sIBM) were classified according to the 2003 European Neuromuscular Centre (ENMC) criteria (8) and Lloyd's criteria (9) respectively. Overlap myositis (OM) was diagnosed if the patients had myositis associated with another connective tissue disease, as previously described (10). The study was approved by the three institutions' Ethics and Research Committees and all patients signed an informed consent at their recruitment.

The patients were clinically assessed by three specialists (ASO, IPF, and JTR), who also performed the NVC using an Optilia Video Capillaroscope (Optilia Instruments AB, Sollentuna, Sweden). We examined the nailfold capillaries of the second to fifth fingers of both hands, at a room temperature of 22-25ºC and took two representative photographs per finger. We analysed the images using an ImageJ macro designed by SMB to facilitate their evaluation. According to the standard report of the NVC abnormalities in IIM (11), we performed semi-quantitative and quantitative analyses of the following parameters per mm: the capillaries' density, shape, and apical diameter; the number of dilated, giant, and bushy capillaries; haemorrhages, thrombosis, and avascular areas. Dilated capillaries were defined as those with an apical diameter >20 micrometres (12) and giant capillaries as those having an apical diameter >50 micrometres (13). The avascular areas were defined as the absence of capillaries within an apical distance of 500 micrometres between two consecutive capillaries (12). After the global assessment of the mentioned parameters, we defined the following capillaroscopic patterns (13), which are shown in Figure 1:

1. Normal: ≥7 capillaries/mm, with a hairpin, tortuous and crossing shapes, apical diameter ≤20 micrometres, and absent haemorrhages, or avascular areas.

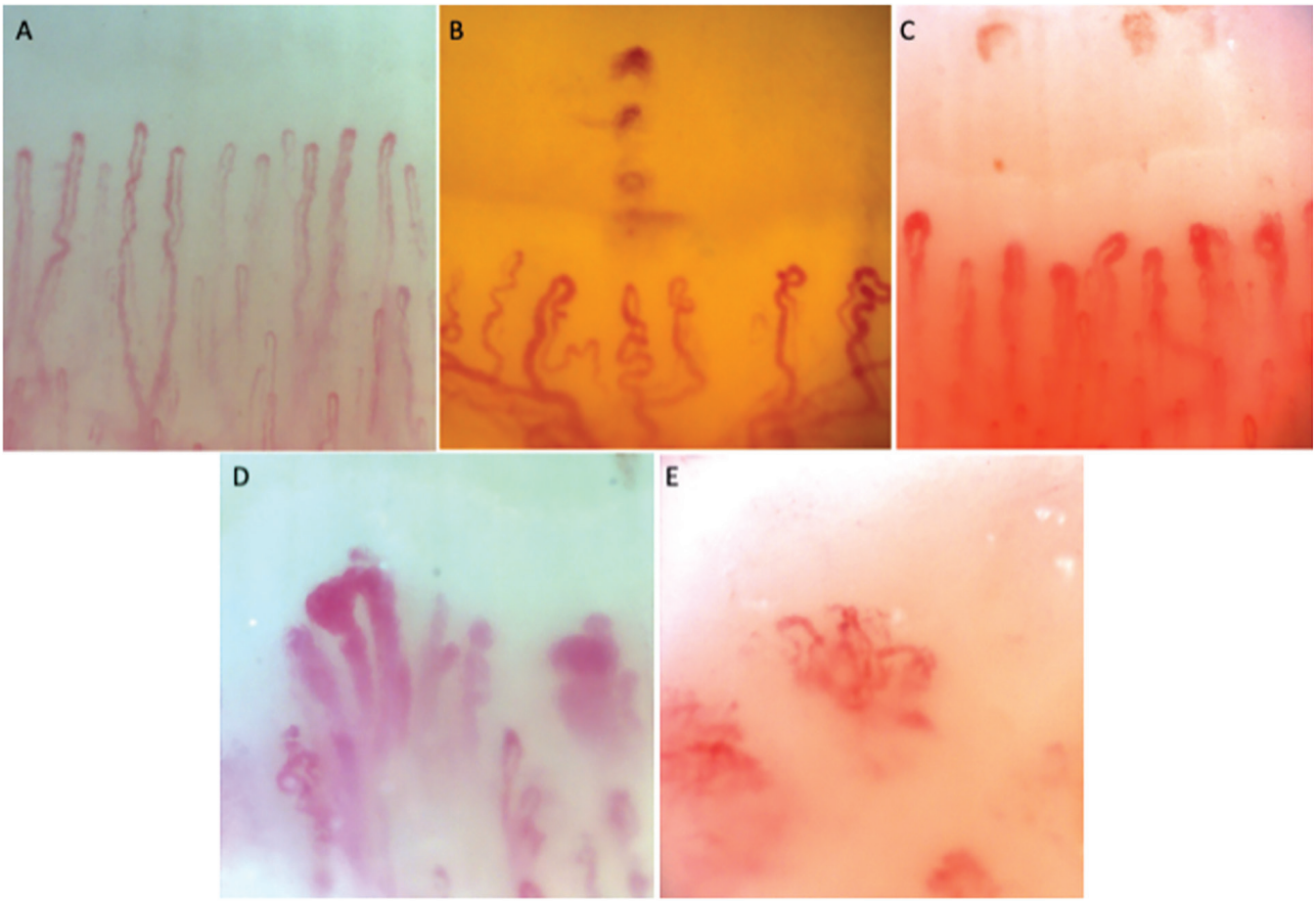

Fig. 1. NVC patterns found in patients with IIM.
(**A**) Normal; (**B**) non-specific abnormalities; (**C**) early systemic sclerosis (SSc) pattern; (**D**) active SSc pattern; (**E**) late SSc pattern.

2. Non-specific abnormalities: decreased capillary density, dilated capillaries, abnormal morphology, and haemorrhages.
3. Early systemic sclerosis (SSc) pattern: Normal capillary density, giant capillaries, normal morphology, and few haemorrhages.
4. Active SSc pattern: Lowered capillary density (4-6 capillaries/mm), giant capillaries, abnormal morphology, and haemorrhages.
5. Late SSc pattern: severely decreased capillary density (≤3 capillaries/mm), abnormal morphology without giant capillaries nor haemorrhages.

For the semiquantitative analysis, we scored the capillary loss as follows (14):
0:≥ 7 capillaries/mm
1: 4-6 capillaries/mm
2: ≤3 capillaries/mm
The number of avascular areas, microhaemorrhages, and thrombosed, dilated, giant, or abnormally shaped capillaries was given a score as following (14):
0: 0 abnormalities/mm
1: 1 abnormality/mm
2: ≥2 abnormalities/mm
These scores were determined per image and an average score per patient was calculated for the capillary loss and each of the mentioned abnormalities. A total capillaroscopy score per patient was calculated by adding the scores of the capillary loss, microhaemorrhages, dilated, giant, thrombosed, and capillaries with abnormal morphology (14). Twenty-three patients (DM=15, AS=3, IMNM=2, PM=1, OM=2) had at least one follow-up NVC. In this group of patients, we compared the capillaroscopic parameters during high disease activity and after immunosuppressive therapy, with low disease activity. From the medical charts, we registered the clinical and laboratory features and the type and dose of immunosuppressive therapy. We assessed the MSA and MAA with the EUROIMMUN EUROLINE kit (Medizinische Labordiagnostika AG, Lubeck, Germany) or by ELISA.

Statistical analysis
We expressed the quantitative variables as medians with interquartile range (IQR) and compared them using the Kruskal-Wallis and the Mann-Whitney U tests. We compared the paired medians with the Wilcoxon test for the patients with follow-up NVC. We assessed correlations between quantitative variables with the Spearman Rho test using the Benjamini-Hochberg correction for multiple comparisons. We compared the capillaroscopic patterns with the clinical phenotypes of IIM, the clinical features, and the autoantibodies using the χ^2 test or Fisher's exact test as appropriate. To assess the relationship between the capillaroscopic patterns and the clinical features of the MSA and MAA, we compared the proportion of patients with each capillaroscopic pattern according to the

Table I. Demographic and clinical features of each cohort of patients with IIM.

	USA n=41	Mexico n=33	Spain n=81	Total n=155
Age in years, median (IQR)	60 (41-70)	42 (33-53)	50 (37-62)	NA
Female, n (%)	24 (58.5)	19 (57.5)	63 (77.7)	106
Months since disease diagnosis, median (IQR)	28 (13-88)	6 (1-12)	24 (0-48)	NA
Cutaneous features, n (%)	19 (46.3)	26 (78.7)	33 (40.7)	78
Heliotrope rash, n (%)	3 (7.3)	4 (15.1)	43 (53.0)	50
Gottron's papules, n (%)	8 (19.5)	14 (42.4)	52 (64.1)	74
Mechanic's hands, n (%)	2 (4.8)	5 (12.1)	19 (23.4)	26
Periungual changes, n (%)	6 (14.6)	11 (33.3)	39 (48.1)	56
V-sign, n (%)	2 (4.8)	13 (39.3)	33 (40.7)	48
Shawl sign, n (%)	1 (2.4)	13 (39.3)	31 (38.2)	45
Malar rash, n (%)	2 (4.8)	19 (57.5)	7 (8.6)	28
Calcinosis, n (%)	3 (7.3)	3 (9.0)	14 (17.2)	20
Skin ulcers, n (%)	1 (2.4)	6 (18.1)	2 (2.4)	9
Myositis, n (%)	35 (85.3)	31 (93.9)	26 (32.0)	92
Dysphagia, n (%)	10 (24.3	12 (36.3)	30 (37.0)	52
Joint involvement, n (%)	9 (21.9)	9 (27.2)	5 (6.1)	23
Raynaud's phenomenon, n (%)	6 (14.6)	11 (33.3)	24 (29.6)	41
Interstitial lung disease, n (%)	6 (14.6)	16 (48.4)	33 (40.7)	55
Cancer, n (%)	0 (0)	1 (3.0)	10 (12.3)	11

presence or absence of every clinical feature or the positivity or negativity of the MSA and MAA using the Fisher's exact test. The statistical analysis was performed using the R software and the Prism Graphpad software.

Results

Of the 155 patients included in the study, one hundred and six (68.4%) were women, and the median (IQR) age ay disease onset was 50 (37-63) years. The most frequent diagnosis was DM, observed in 95 (61.2%) of patients. One hundred and fourteen patients (73.5%) were Hispanic, 27 (17.5%) were White, 11 (7.1%) were Black, and 3 (1.9%) had Asian/Pacific Islander ethnicity. There were no differences in the capillaroscopic parameters according to the different ethnicities. In Table I, we summarise the demographic features of the IIM patients and depict the proportion of patients with every clinical feature in each cohort. At the time of capillaroscopic assessment, the average time since disease diagnosis was 17 months (6–42), and 96 patients (61.9%) had active disease according to the physician's judgment. The median score of disease activity measured with a 0–10 visual analog scale was 2 (0–4). One hundred and one patients (65.1%) were treated with prednisone, 19 (12.2%) with methotrexate, 4 (2.5%) with antimalarials, 24 (15.4%) with calcineurin inhibitors, 7 (4.5%) with rituximab, 13 (8.3%) with azathioprine, 27 (17.4%) with mycophenolate mofetil, and 34 (21.9%) with intravenous immunoglobulin.

According to the NVC features, we studied the capillaroscopy patterns in our patients as well as the association of those patterns with the different clinical phenotypes of IIM. Only 14 patients (9%) had a normal NVC, including the three patients with GVHD myositis. The most frequent capillaroscopy pattern was the presence of non-specific abnormalities (53.9%). Table II shows the association between each capillaroscopic pattern and the different IIM clinical phenotypes. The normal pattern was more frequent in patients with sIBM and GVHD. Non-specific abnormalities were mostly observed in patients with AS and IMNM; whilst the SSc pattern was present mainly in patients with DM and OM. Among patients with an SSc pattern, the most frequent was the active variant (Table II).

In Table III, we depict the proportion of patients with at least one of the capillaroscopic abnormalities in each cohort. The presence of bushy/ramified and dilated capillaries was more frequent in the Mexican than the USA cohort (72.7% *vs*. 48.7%, $p<0.05$, and 87.8% *vs*. 48.7%, $p<0.001$ respectively) (Table III). As shown in Figure 2, patients with DM, AS, and OM had more prominent capillaroscopic abnormalities and a higher capillaroscopic score. In comparison to patients with IMNM, sIBM, and PM, subjects with DM, AS, and OM had a lower number of capillaries (Fig. 2). The highest capillary diameter

Table II. Capillaroscopic patterns according to the clinical phenotypes of patients with IIM.

	Total n=155 (100%)	DM n=95 (61.2%)	AS n=26 (16.7%)	IMNM n=12 (7.7%)	sIBM n=7 (4.5%)	PM n=2 (1.2%)	OM n=10 (6.4%)	GVHD n=3 (1.9%)
Normal	14/155 (9.0%)	3/95 (3.1%)***	1/26 (3.8%)	1/12 (8.3%)	6/7 (85.8%)	0/2 (0.0%)	0/10 (0%)	3 (100.0%)
Non-specific abnormalities	82 /155 (53.9%)	43/95 (45.2%)	21/26 (80.7%)***	10/12 (83.3%)	1/7 (14.2%)	2/2 (100%)	5/10 (50.0%)	0 0%)
SSc-pattern (early, active or late)	59/155 (38.0%)	49/95 (51.5%)	4/26 (15.3%)	1/12 (8.3%)	0/7 (0.0%)	0/2 (0.0%)	5/10 (50.0%)	0 (0%)
Early pattern	4/59 (6.7%)	1/49 (2.0%)	0/4 (0.0%)	1/1 (100.0%)	0/0 (0.0%)	0 (0.0%)	2/5 (40.0%)	0 (0%)
Active Pattern	50/59 (84.7%)	43/49 (87.7%)	4/4 (100.0%)	0/1 (0.0%)	0/0 (0.0%)	0 (0.0%)	3/5 (60.0%)	0 (0%)
Late pattern	5/59 (8.4%)	5/49 (10.2%)	0/4 (0.0%)	0/1 (0.0%)	0/0 (0.0%)	0 (0.0%)	0/5 (0.0%)	0 (0%)

The *p*-value represents the comparison of the prevalence of each capillaroscopic pattern in each clinical phenotype *vs*. the prevalence in the rest of the patients of the row: *$p<0.05$, **$p<0.01$, ***$p<0.001$.

SSc: systemic sclerosis; DM: dermatomyositis; AS: anti-synthetase syndrome; IMNM: immune-mediated necrotizing myopathy; sIBM: sporadic inclusion body myositis; PM: polymyositis; OM: overlap myositis; GVHD: graft versus host disease.

Table III. Proportion of patients with each capillaroscopic finding in the three cohorts of IIM.

	USA n=41	Mexico n=33	Spain n=81	Total n=155
Bushy/ramified capillaries, n (%)*¶	20 (48.7)	24 (72.7)	69 (85.1)	113 (72.9%)
Dilated capillaries, n (%)***¶	20 (48.7)	29 (87.8)	75 (92.5)	124 (80%)
Giant capillaries, n (%)	9 (21.9)	9 (27.2)	38 (46.9)	56 (36.1%)
Microhaemorrhages, n (%)	14 (34.1)	19 (57.7)	57 (70.3)	90 (58%)
Avascular areas, n (%)	12 (29.2)	9 (27.2)	34 (41.9)	55 (35.5%)
Thrombosis, n (%)	3 (7.3)	4 (12.1)	3 (3.7)	10 (6.5%)

*p<0.05, **p<0.01, ***p<0.001.
¶Mexico *vs*. USA.

was observed in patients with DM and OM. Bushy and dilated capillaries were mostly observed in patients with DM, AS, and OM (Fig. 2).

Table IV shows the proportion of patients with each capillaroscopic pattern according to the clinical features of IIM. The SSc pattern was more frequent in patients with cutaneous features and the pattern showing non-specific abnormalities was more frequently observed in patients with joint involvement and interstitial lung disease. There was no association between the capillaroscopic parameters and other clinical features, except for a lower number of capillaries in patients with calcinosis (4.5 (2.3–6.1) *vs*. 5.9 (4.3–7.5), p=0.024). We did not find a significant correlation between the capillaroscopic abnormalities and the laboratory or clinical parameters of disease activity (data not shown).

Next, we compared the proportion of patients with each capillaroscopic pattern according to their MSA and MAA status (Table V). The pattern showing non-specific abnormalities was more frequent in patients with anti-Jo1+ autoantibodies, the early SSc pattern was associated with the presence of anti-Ro52 autoantibodies and the active SSc pattern was mostly observed in patients with anti-Mi2 and anti-TIF-1γ autoantibodies (Table V).

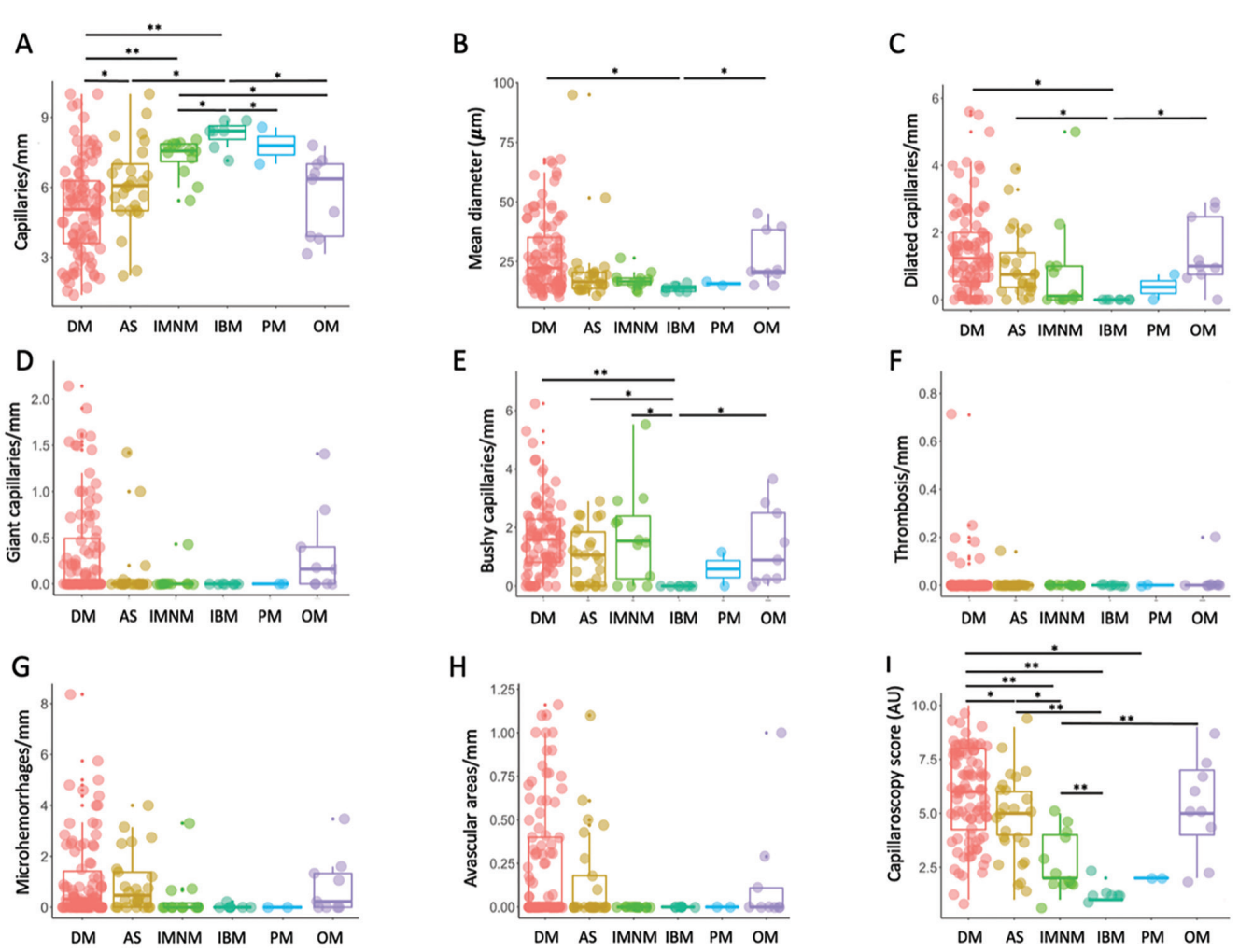

Fig. 2. Capillaroscopic abnormalities observed in patients with IIM according to their diagnosis. Patients with DM, OM, and AS had a lower number of capillaries (**A**). Patients with DM and OM had the highest capillary diameter (**B**) and dilated and bushy capillaries were mostly observed in DM, AS, and OM (**C, E**). Patients with DM, AS, and OM had the highest total capillaroscopic score (**I**). There were no statistically significant differences in the number of giant capillaries (**D**), thrombosis (**F**), microhaemorrhages (**G**), and avascular areas (H). *p<0.05, **p<0.01, *p<0.001.

Table IV. Proportion of patients with each capillaroscopic pattern according to the clinical features of IIM.

	Normal	Non-specific abnormalities	SSc pattern (early, active or late)	Early SSc pattern	Active SSc pattern	Late SSc pattern
Cutaneous features (n=78)	4 (5.1%)	33 (42.3%)**	41 (52.5%)***	0 (0.0%)	37 (90.2%)***	4 (9.7%)
Heliotrope rash (n=50)	0 (0.0%)***	24 (48.0%)	26 (52.0%)*	1 (3.8%)*	23 (88.4%)***	2 (7.6%)
Gottron's papules (n=74)	0 (0.0%)***	33 (44.5%)*	41 (54.4%)***	1 (2.4%)	37 (90.2%)***	3 (7.3%)
Mechanic's hands (n=26)	1 (3.8%)	15 (57.6%)	10 (38.4%)	0 (0.0%)	10 (100.0%)***	0 (0.0%)
Periungual changes (n=56)	0 (0.0%)***	23 (41.0%)*	33 (58.9%)***	1 (3.0%)	29 (87.7%)***	3 (9.0%)
V-sign (n=48)	0 (0.0%)***	18 (37.5%)**	30 (62.5%)***	1 (3.3%)	28 (93.3%)***	1 (3.3%)
Shawl sign (n=45)	0 (0.0%)**	17 (37.7%)*	28 (62.2%)***	1 (3.5%)	26 (92.8%)	1 (3.5%)
Malar rash (n=28)	2 (7.1%)	13 (46.2%)	13 (46.4%)	0 (0.0%)	11 (84.6%)	2 (15.3%)
Calcinosis (n=20)	0 (0.0%)*	10 (50%)	10 (50%)	0 (0.0%)	8 (80.0%)	2 (20.0%)
Skin ulcers (n=9)	0 (0.0%)	5 (55.5%)	4 (44.4%)	0 (0.0%)	3 (75.0%)	1 (25.0%)
Myositis (n=92)	10 (10.8%)	50 (54.3%)	32 (34.7%)	3 (9.3%)	26 (81.2%)	3 (9.3%)
Dysphagia (n=52)	3 (5.7%)	27 (51.9%)	22 (42.3%)	2 (9.0%)	19 (86.3%)	1 (4.5%)
Joint involvement (n=23)	1 (4.3%)	18 (78.2%)*	4 (17.9%)*	0 (0.0%)	3 (75.0%)*	1 (25.0%)
RP (n=41)	0 (0.0%)**	23 (56.0%)	18 (43.9%)	2 (11.1%)	15 (83.3%)	1 (5.5%)
ILD (n=55)	3 (5.4%)	35 (63.3%)*	17 (30.9%)	2 (11.7%)	15 (88.2%)	0 (0.0%)*
Cancer (n=11)	0 (0.0%)	5 (45.4%)	6 (54.5)	0 (0.0%)	6 (100.0%)	0 (0.0%)

The *p*-value represents the comparison of the prevalence of each capillaroscopic pattern in each clinical feature *vs*. the prevalence in the rest of the patients of the row: *$p<0.05$, **$p<0.01$, ***$p<0.001$.
SSc: systemic sclerosis; RP: Raynaud's phenomenon; ILD: interstitial lung disease.

Table V. Proportion of patients with each capillaroscopic pattern according to the positivity of the MSA and the MAA.

Antibody	Normal	Non-specific abnormalities	SSc pattern (early, active or late)	Early pattern	Active pattern	Late pattern
Myositis specific antibodies (MSA)						
Jo1 (n=18)	1 (5.5%)	14 (77.7%)*	3 (16.6%)*	0 (0.0%)	3 (100.0%)	0 (0.0%)
PL7 (n=5)	0 (0.0%)	4 (80.0%)	1 (20.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
PL12 (n=4)	0 (0.0%)	3 (75.0%)	1 (25.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
EJ (n=2)	0 (0.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
OJ (n=1)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mi2 (n=9)	0 (0.0%)	3 (33.3%)	6 (66.6%)	0 (0.0%)	6 (100.0%)*	0 (0.0%)
MDA5 (n=16)	0 (0.0%)	7 (43.7%)	9 (56.2%)	0 (0.0%)	8 (88.8%)	1 (11.1%)
NXP2 (n=14)	0 (0.0%)	8 (57.1%)	6 (42.8%)	0 (0.0%)	5 (83.3%)	1 (16.1%)
TIF-1y (n=17)	1 (5.8%)	6 (35.2%)	10 (58.8%)	0 (0.0%)	10 (100%)*	0 (0.0%)
SAE (n=4)	0 (0.0%)	0 (0.0%)*	4 (100.0%)**	1 (25.0%)	2 (50.0%)	1 (25.0%)
SRP (n=5)	1 (20.0%)	3 (60.0%)	1 (20.0%)	1 (100.0%)	0 (0.0%)*	0 (0.0%)
HMGCR (n=8)	0 (0.0%)	8 (100%)**	0 (0.0%)**	0 (0.0%)	0 (0.0%)*	0 (0.0%)
NT5c1A (n=4)	4 (100.0%)***	0 (0.0%) *	0 (0.0%)*	0 (0.0%)	0 (0.0%)	0 (0.0%)
Myositis-associated antibodies (MAA)						
Ro52 (n=39)	3 (7.6%)	22 (56.4%)	14 (35.8%)	3 (21.4%)*	9 (64.2%)	2 (14.2%)
Ro60 (n=10)	0 (0.0%)	5 (50.0%)	5 (50.0%)	0 (0.0%)	4 (80.0%)	1 (20.0%)
La (n=2)	0 (0.0%)	1 (50.0%)	1 (50.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
PM/Scl (N=9)	0 (0.0%)	5 (55.5%)	4 (44.4%)	0 (0.0%)	4 (100.0%)	0 (0.0%)
Ku (n=2)	0 (0.0%)	1 (50.0%)	1 (50.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)

The *p* value represents the comparison of the prevalence of each capillaroscopic pattern in each MSA and MAA group *vs*. the prevalence in the rest of the patients of the row: **$p<0.05$, **$p<0.01$, ***$p<0.001$.

Finally, we assessed the quantitative features of the NVC according to the MSA and the MAA status. We did not find any statistically significant differences among the patients with different AS autoantibodies, but our analysis was limited due to the low frequency of OJ and EJ-positive patients. Therefore, we compared the quantitative capillaroscopic parameters among patients with positive DM-associated antibodies. Anti-Mi2-positive DM patients had a lower number of capillaries (4.2 (3.8–4.3) *vs*. 5.9 (4.2–5.8), $p=0.03$), a higher number of avascular areas (0.3 (0.1-0.7) *vs*. 0.0 (0.0–0.2), $p=0.0009$), giant capillaries (0.3 (0.0–0.8) *vs*. (0.0 (0.0–0.2), $p=0.012$), and thrombosis (0.0 (0.0–0.1) *vs*. 0.0 (0.0–0.0), $p=0.03$) in comparison to patients with the rest of DM-associated antibodies. Subjects with anti-MDA5-positive DM had a higher number of dilated capillaries (1.5 (0.9–1.8) *vs*. 0.9 (0.1–1.1), $p=0.03$). SAE-1+ DM patients had a higher number of avascular areas (0.8 (0.5–0.9) *vs*. 0.0 (0.0–0.2), $p=0.019$) in

Table VI. Comparison of the quantitative capillaroscopic parameters among the different MSA and MAA.

	Capillaries/ mm, median (IQR)	Diameter (mM), median (IQR)	Normal capillaries/ mm, median (IQR)	Bushy/ ramified capillaries/ mm, median (IQR)	Dilated capillaries/ mm, median (IQR)	Giant capillaries/ mm, median (IQR)	Microhae-morrhages / mm, median (IQR)	Avascular areas/mm, median (IQR)	Thrombosis/ mm, median (IQR)	Capillaro-scopic score, median (IQR)
Myositis specific antibodies (MSA)										
Jo1 (n=18)	5.9 (5.0-6.9)	17.7 (13.5-20.6)	4.6 (3.1-6.1)	0.5 (0.0-1.6)	0.9 (0.2-2.1)	0.0 (0.0-0.0)	0.2 (0.0-0.6)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	4.0 (2.0-5.0)
PL7 (n=5)	5.6 (3.6-8.5)	19.8 (14.9-59.6)	2.2 (1.1-6.0)	1.1 (0.5-2.1)	1.1 (0.4-2.7)	0.0 (0.0-0.7)	1.2 (0.3-2.6)	0.0 (0.0-0.1)	0.0 (0.0-0.0)	5.0 (2.5-6.5)
PL12 (n=4)	4.6 (2.7-7.6)	17.9 (13.8-43.6)	3.2 (1.3-4.8)	1.1 (0.6-1.6)	0.9 (0.7-1.8)	0.0 (0.0-0.7)	1.6 (0.3-2.7)	0.5 (0.1-0.9)	0.0 (0.0-0.1)	5.0 (3.5-7.2)
Mi2 (n=9)	4.2 (3.8-4.3)	35.2 (16.8-46.8)	0.4 (0.3-3.6)	1.0 (0.2-1.8)	1.4 (0.5-2.5)	0.3 (0.0-0.8)	0.5 (0.0-2.8)	0.3 (0.1-0.7)	0.0 (0.0-0.1)	6.0 (4.0-7.0)
MDA5 (n=16)	5.0 (3.1-8.3)	26.4 (14.1-44.2)	1.6 (0.7-4.6)	0.8 (0.5-1.5)	1.5 (0.9-1.8)	0.1 (0.0-0.9)	0.7 (0.0-2.4)	0.0 (0.0-0.2)	0.0 (0.0-0.0)	4.5 (2.2-7.0)
NXP2 (n=14)	5.4 (3.8-7.3)	24-0 (16.5-31.0)	2.4 (1.8-3.3)	1.6 (1.1-2.0)	0.8 (0.1-2.0)	0.0 (0.0-0.1)	0.2 (0.0-1.6)	0.1 (0.0-0.4)	0.0 (0.0-0.0)	5.0 (3.7-6.2)
TIF-1y (n=17)	5.5 (3.3-6.8)	21.4 (13.7-48.0)	1.7 (0.5-5.4)	1.0 (0.6-2.2)	1.1 (0.4-1.6)	0.1 (0.0-0.9)	0.3 (0.0-1.9)	0.0 (0.0-0.8)	0.0 (0.0-0.0)	6.0 (2.0-7.0)
SAE (n=4)	2.0 (1.7-6.4)	30.9 (20.0-58.2)	0.1 (0.0-5.3)	1.7 (0.4-2.3)	0.7 (0.5-4.3)	0.3 (0.0-0.8)	0.2 (0.1-1.9)	0.8 (0.5-0.9)	0.0 (0.0-0.0)	6.0 (5.2-6.7)
SRP (n=5)	7.8 (7.1-7.9)	17.9 (12.5-23.4)	5.0 (3.1-6.0)	1.4 (0.0-2.2)	0.1 (0.0-2.9)	0.0 (0.0-0.2)	0.0 (0.0-1.6)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1 (0.5-3.5)
HMGCR (n=8)	7.5 (7.1-7.8)	16.6 (15.8-18.0)	5.6 (4.3-6.8)	1.5 (0.5-2.7)	0.0 (0.0-0.7)	0.0 (0.0-0.0)	0.0 (0.0-0.4)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	2.0 (1.0-2.5)
NT5c1A (n=4)	8.6 (7.4-8.8)	13.0 (12.3-15.5)	5.8 (4.6-6.4)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Myositis-associated antibodies (MAA)										
Ro52 (n=39)	5.9 (4.8-7.8)	17.3 (13.5-21.4)	4.1 (2.2-6.1)	1.0 (0.1-1.6)	0.8 (0.2-1.7)	0.0 (0.0-0.1)	0.3 (0.0-2.2)	0.0 (0.0-0.1)	0.0 (0.0-0.0)	4.0 (2.0-6.0)
Ro60 (n=10)	5.0 (1.8-5.9)	21.5 (15.1-40.8)	2.1 (0.1-4.0)	1.7 (0.8-2.5)	0.7 (0.4-1.8)	0.0 (0.0-0.4)	0.5 (0.1-1.5)	0.0 (0.0-0.6)	0.0 (0.0-0.0)	6.0 (4.0-6.2)
PM/Scl (n=9)	3.9 (2.8-6.1)	27.0 (23.4-39.4)	1.2 (0.5-2.0)	2.1 (1.6-2.8)	1.1 (0.8-2.2)	0.2 (0.0-0.7)	0.3 (0.0-1.0)	0.0 (0.0-0.5)	0.0 (0.0-0.0)	5.0 (3.5-7.0)

comparison to the rest of the patients with positive DM-associated antibodies. Regarding the MAA, patients with positive anti-PM/Scl autoantibodies had a higher number of bushy or ramified capillaries (2.1 (1.6–2.8) *vs*. 1.1 (0.1–1.3), p=0.033) in comparison to patients with negative PM/Scl antibodies. The quantitative capillaroscopic parameters in each subgroup of MSA and MAA are summarised in Table VI.

The comparison of NVC parameters in the 23 patients during the follow-up (inactive disease) compared to the first visit (active disease) is shown in Figure 3. We observed that coinciding with the improvement of disease activity, there was an increase in the capillary density (4.6 (3.6–6.0) *vs*. 5.8 (4.5–6.8), p<0.0001) and a decrease in the number of avascular areas (0.2 (0-0-0.45) *vs*. 0.0 (0.0–0.15), p=0.019) and the total capillaroscopic score (6 (3–6) *vs*. 4 (3-5), p=0.015). There was a trend towards a statistically significant increase in the number of bushy capillaries (1.8 (0.46–2.9) *vs*. 1.9 (0.7–2.8), p=0.06) and a decrease in the apical diameter of the capillaries (22.7 (18.4–45.1) *vs*. 18.8 (15.3–25.3), p=0.06) when the patients were seen during a time of decreased disease activity.

Discussion

In this multicentric multi-ethnic cohort analysis of the NVC abnormalities of patients with IIM, we observed an association between the non-specific capillaroscopic pattern and the diagnosis, clinical features, and positivity for anti-Jo1 autoantibodies in AS patients, as well as with the diagnosis of IMNM. We confirmed the association between the SSc pattern and the DM clinical features, as well as the improvement of the capillaroscopic abnormalities after treatment. Taken together, our findings suggest a role for capillaroscopic assessment in monitoring disease activity (2). Of note, nailfold capillaroscopic assessment in patients with IIM is one of the potential items for classification criteria of skin-predominant DM (15), highlighting its importance in the differential diagnosis of IIM.

Initial capillaroscopic analyses of IIM patients showed that they had a lower number of capillaries with a larger apical diameter and a higher number of ramified capillaries in comparison to healthy controls (16). When patients with IIM were classified as having PM or DM, the most frequently reported pattern in patients with PM was the non-specific (17), whilst DM patients had a higher amount of abnormalities (18), including giant capillaries (17).

Selva O'Callaghan *et al*. evaluated 53 patients with IIM classified as PM, DM, and IBM and found capillaroscopic abnormalities in 43% of the patients (19). Nonetheless, when any capillaroscopic abnormality is considered, nearly all patients with IIM had an abnormal NVC (5), which is similar to our findings. We found that only 9% of patients had a normal NVC, including the three patients with GVHD myositis.

Some previous studies with small sample sizes have described capillaroscopic abnormalities according to the clinical phenotype of patients with IIM. In patients with AS, the most frequent finding was a decreased capillary density (16) and tortuosities (20). Other studies have shown a scleroderma pattern in 35.3% of patients with AS, ramified capillaries in 50%, and giant capillaries in 26.2% of patients. The capillaroscopic abnormalities were associated with the presence of ILD and the presence of anti-Jo1 autoantibodies (21), which is similar to our results. According to our data, a pattern of non-specific abnormalities with decreased capillary density and tortuous bushy capillaries is characteristic of AS.

In patients with DM, previous studies have shown a higher number of microhaemorrhages and dilated capillaries (19). A systematic review described a scleroderma pattern in 63.6-88.9% of adult DM patients, especially in subjects with less than 6 months of disease duration (5, 22). According to the cur-

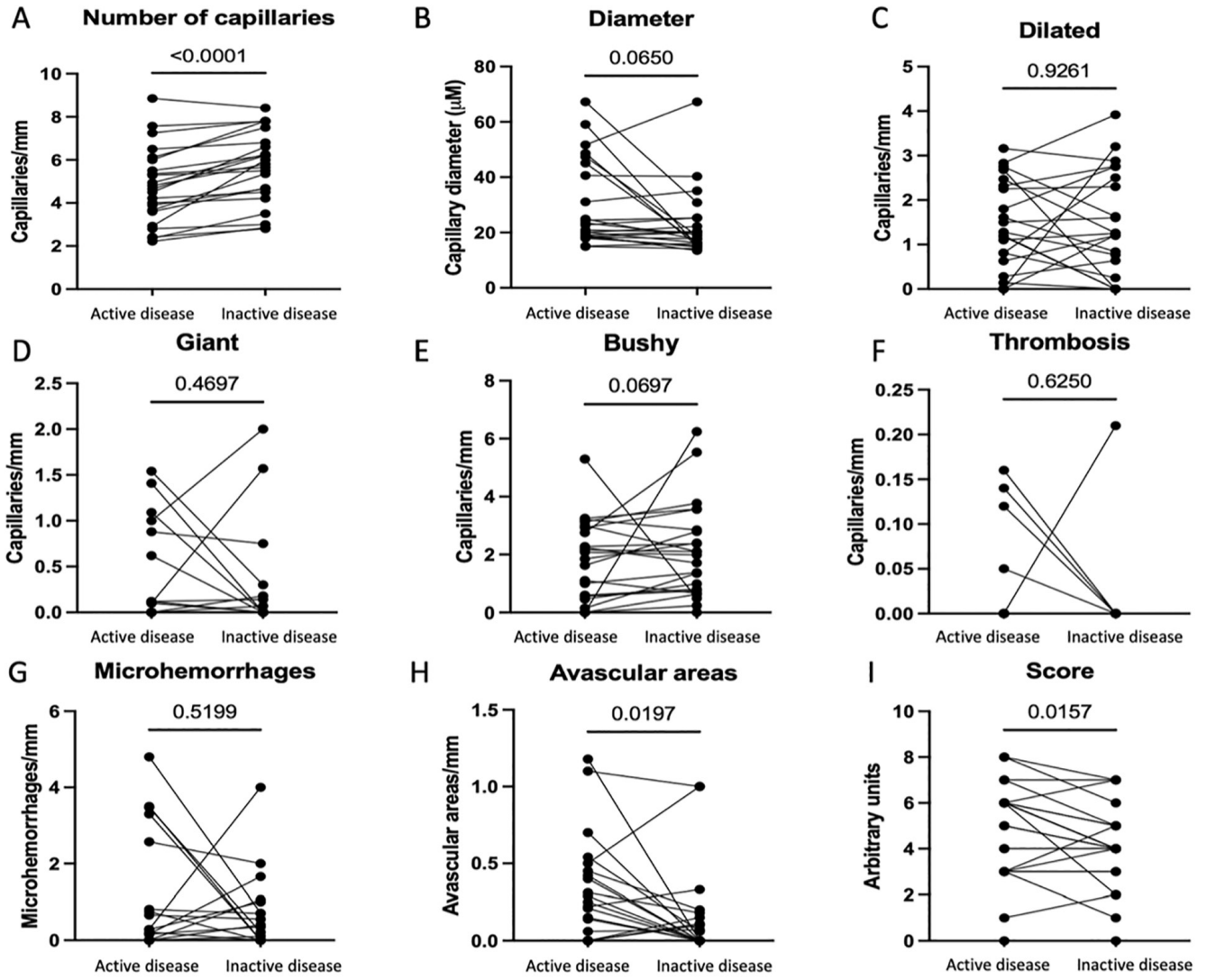

Fig. 3. Comparison of the capillaroscopic abnormalities in patients with IIM and active *vs*. inactive disease. During inactive disease, we observed an increased capillary density (**A**), a higher number of bushy capillaries (**E**), with smaller diameter (**B**), and a decrement in the number of avascular areas (**H**) and in the total capillaroscopic score (**I**). There were no statistically significant differences in the number of dilated (**C**), and giant (**D**) capillaries, nor in the number of thrombosis (**F**) or microhaemorrhages (**H**).

rent study, the most frequently reported scleroderma pattern is the active (46%), while early and late patterns were reported in 24% and 4%, respectively (22). Also, previous studies have shown that giant capillaries and avascular areas were more prominent in patients with DM and OM and were absent in AS and IMNM (14), which is similar to our results.

It has been shown that patients with DM have dynamic capillaroscopic abnormalities, with decreased capillary density at disease onset and ramified capillaries in patients with long-term disease (18). According to our results, a decrement in the capillary score, and capillary diameter, and an increase in the capillary density with the disappearance of microhaemorrhages is observed after treatment of patients with DM (22-25). This suggests that neovascularisation in IIM may be a sign of recovery from the previous vasculopathy, as this feature has been observed in long-standing disease (5).

The association between capillaroscopic abnormalities and certain clinical features has been controversial in the literature. For instance, previous studies and ours have shown no association between RP (16) and muscular and extra-muscular disease activity (14). On the other hand, capillaroscopic abnormalities have been associated with cancer, RP (19), global disease activity, myositis intention to treat index (MITAX), and cutaneous, muscular, constitutional, and pulmonary disease activity (5, 20, 22, 24-26). The many different methods used to evaluate the disease activity in patients with IIM might explain these discordances. In our cohort, the myositis disease activity assessment tool (MDAAT) and the MITAX were not systematically assessed. Nonetheless, our results coincide with the study by Soubrier *et al*. (14), who included a small sample of IIM patients with different clinical phenotypes without finding associations between the muscular and extra-muscular disease activity and capillaroscopic findings.

Earlier studies did not find an association between capillaroscopic abnormalities, MSA, and MAA in DM patients (19). Nonetheless, in a study of 48 IIM patients including 17 DM patients, 8 OM, 12 with AS, and 6 with IMNM, it was observed that the presence of autoantibodies recognising MDA5, SAE, and TIF-1γ was associated with giant capillaries (14). This is similar to our results since we found that the active pattern was associated with anti-TIF-1γ positivity. Our study is the first to describe a more prominent nailfold vasculopathy in patients with anti-Mi2 antibodies, including increased avascular areas and thrombosis. The current study is also the first to report a higher number of avascular areas in patients with anti-SAE1-positive DM. Our findings confirm that capillaroscopic features contribute to the clustering of patients with IIM according to their diagnosis, clinical characteristics, and autoantibodies.

The strengths of our study are its multicentric and multi-ethnic nature, with a large number of patients who were carefully classified according to the currently described clinical phenotypes. Our quantitative and semi-quantitative analysis considered the positivity for MSA and MAA. Also, we included patients with sIBM and IMNM, who were underrepresented in previous studies. The main limitation of our study is that many measurements of disease activity such as the MMT8, HAQ-DI, MDAAT, and MITAX were not available for analysis. Also, the prevalence of some MSA (*e.g.* EJ and OJ) and MAA (*e.g.* Ku) was low and precluded the possibility of showing statistically significant differences.

In summary, NVC abnormalities are related to the diagnosis, clinical features, clinical evolution, MSA, and MAA of patients with IIM. These findings can be extrapolated to patients with different ethnicities and help cluster subjects with distinctive clinical phenotypes.

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