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Original article

Clinical science

Standardized nailfold capillaroscopy in children with rheumatic diseases: a worldwide study

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Abstract

Objectives: To standardly assess and describe nailfold videocapillaroscopy (NVC) assessment in children and adolescents with juvenile rheumatic and musculoskeletal diseases (jRMD) *vs* healthy controls (HCs).

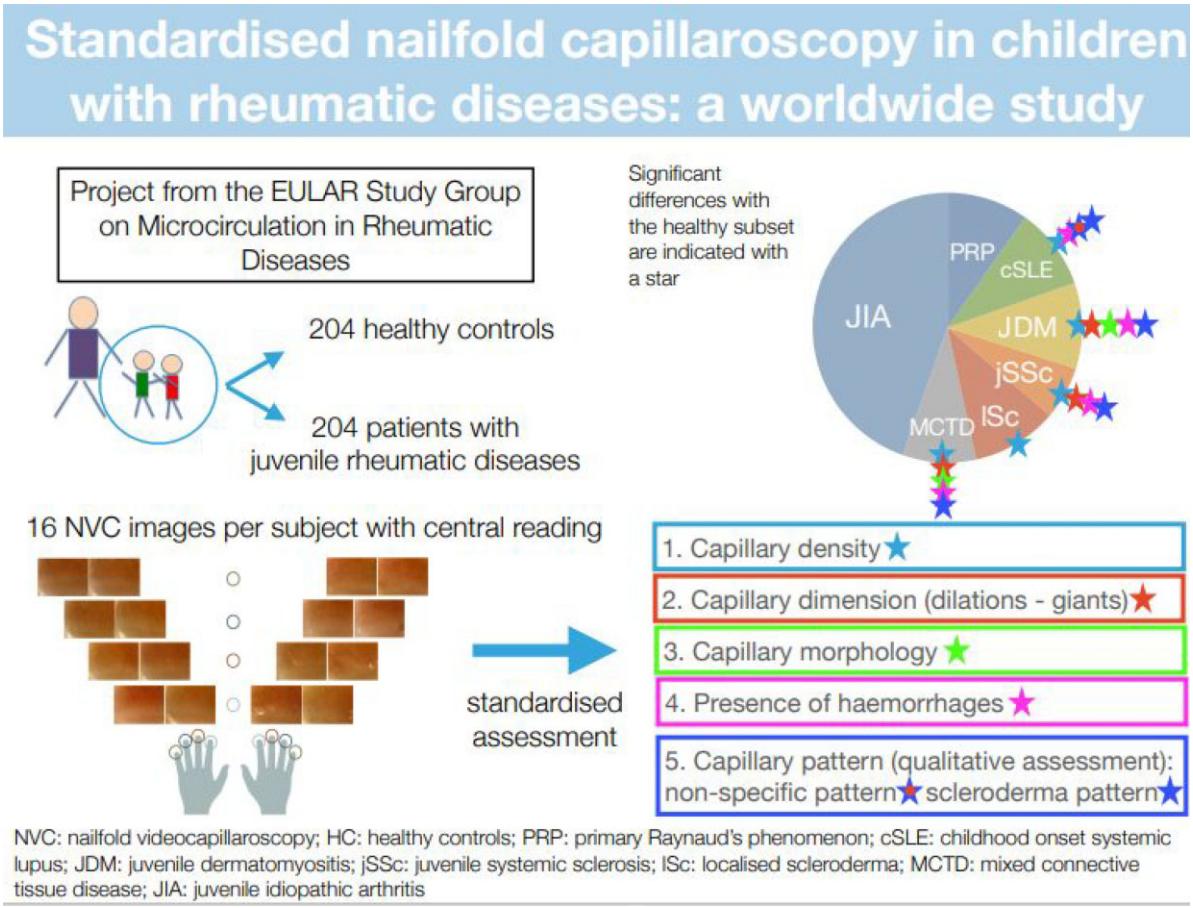
Material and methods: In consecutive jRMD children and matched HCs from 13 centres worldwide, 16 NVC images per patient were acquired locally and read centrally per international consensus standard evaluation of the EULAR Study Group on Microcirculation in Rheumatic Diseases. A total of 95 patients with JIA, 22 with JDM, 20 with childhood-onset SLE (cSLE), 13 with juvenile SSc (jSSc), 21 with localized scleroderma (lSc), 18 with MCTD and 20 with primary RP (PRP) were included. NVC differences between juvenile subgroups and HCs were calculated through multivariable regression analysis.

Results: A total of 6474 images were assessed from 413 subjects (mean age 12.1 years, 70.9% female). The quantitative NVC characteristics were significantly lower or higher in the following subgroups compared with HCs: for density: lower in jSSc, JDM, MCTD, cSLE and lSc; for dilations: higher in jSSc, MCTD and JDM; for abnormal shapes: higher in JDM and MCTD; for haemorrhages: higher in jSSc, MCTD, JDM and cSLE. The qualitative NVC assessment of JIA, lSc and PRP did not differ from HCs, whereas the cSLE and jSSc, MCTD, JDM and cSLE subgroups showed more non-specific and scleroderma patterns, respectively.

Conclusions: This analysis resulted from a pioneering registry of NVC in jRMD. The NVC assessment in jRMD differed significantly from HCs. Future prospective follow-up will further elucidate the role of NVC in jRMD.

Keywords: nailfold capillaroscopy, scleroderma pattern, juvenile rheumatic and musculoskeletal diseases, children, microcirculation

Graphical abstract



Rheumatology key messages

- This study describes international consensus standardized NVC interpretation in a multicentre cohort of children.
- Children and adolescents with jRMD display distinct standard NVC characteristics compared with healthy controls.
- Age is only weakly associated with capillary density and dimension in juvenile healthy controls.

Introduction

Nailfold capillaroscopic examination has proven its worth in the field of rheumatology [1, 2]. In adults, it allows, together with the identification of autoantibodies, discrimination between primary and secondary RP, the latter being related to an underlying CTD [3]. Moreover, its role was formalized, through the incorporation of 'an abnormal nailfold capillaroscopy' as criterion (referring to the scleroderma pattern) in the SSc 2013 classification criteria [4]. Ever since its increased use, assembled efforts have led to the standardization of the capillaroscopic technique and reading in adults [5–8]. In children and adolescents, however, nailfold capillaroscopy is less used and studies are scarce and usually small, using non-standardized methods [9]. The EULAR Study Group on Microcirculation in Rheumatic Diseases thus found it timely to start an international collaborative to collect nailfold capillaroscopic data from children and adolescents with and without juvenile rheumatic and musculoskeletal diseases (jRMD). We hypothesize that through nailfold videocapillaroscopy (NVC), as in adult disease, we may detect microvascular abnormalities, presumably caused by systemic inflammatory immune responses.

This article presents the first data from this collaborative effort, in which the NVC characteristics of an international cohort of children and adolescents are standardly described by implementing international consensus definitions from the EULAR Study Group on Microcirculation in Rheumatic Diseases. The results could serve as a framework for paediatricians to interpret NVC assessments in their rheumatological practices. For researchers, it could provide the prerequisites to further investigate NVC characteristics and clinical correlations in disease-specific studies.

Patients and methods

Study patients and healthy controls

Children and adolescents from 13 different centres worldwide were examined using NVC. All participating centres obtained approval from the local ethics committee (for Belgium: B670201627545) and written informed consent from all participants or representatives were obtained. Details on centre contributions and their approval numbers are found in Supplementary Table S1, available at *Rheumatology* online [7].

Co-investigators were asked to include consecutive patients with RP and/or a definite diagnosis of a jRMD according to the physician's opinion and fulfilling the established classification criteria, irrespective of the disease duration or disease activity status [10–16]. RP was defined as the observation of at least a biphasic colour change after cold exposure [17]. Patients with an indefinite diagnosis or overlap (other than mixed connective tissue disease) were excluded. Additionally, the presence of ANA and, if available, the specifications on extractable nuclear antigen antibodies were documented, as per discretion of the local investigator. Features such as RP, nail biting, recent trauma or presence of interfering skin changes were recorded through a case report form. No records were collected on therapies, with the assumption that all patients were receiving a variety of therapies.

Each jRMD patient with evaluable NVC images was manually matched to a healthy control (HC) of the same gender and age group (age ranges: <5, 5–7, 8–10, 11–14 and 15–18 years) [18]. If no exact age- and gender-matched HC was available, the authors selected an available match that was as close as possible, where priority was given to similar age over same gender. The HCs were provided by different centres. They were mainly recruited at schools, some were siblings of patients or family members of the investigators. No reliable records were collected on the presence of RP in HCs, recruited in circumstances where serological or clinical assessment was unavailable (e.g. in schools).

Capillaroscopic technique, reading and reporting method

Each child was examined with a standardized NVC technique [7]. All fingers, except for the thumbs, were assessed with a ×200 magnification contact lens [Videocap (DS Medica, Milan, Italy), Optilia (Vällingby, Sweden), Inspectis (Kista, Sweden), DinoLite (Taiwan) microscopes, depending on local equipment]. Two adjacent central images per nailfold were captured, coded and saved (set of 16 images per child) and the investigators were asked to place a grid on all images, corresponding to a 1 mm nailfold in real life, using centre-dependent image analysis software (DS Medica, Optilia, Inspectis, DinoLite). It took ∼10 minutes to acquire the 16 images per child. No specific training was given to the investigators, who were all operating in a capillaroscopic expert centre. The NVC images were collected digitally through Web Share and read at Ghent University by a trained observer who was blinded to health or disease status (K.M.) [19]. The graphic viewer IrfanView (version 4.51; https://www.irfanview.com/) was used to correct for image sizes, which varied among centres, and to measure the dimension of the capillaries using the 1 mm grid as a reference. The reading and reporting method followed the capillaroscopic protocol of the EULAR Study Group on Microcirculation in Rheumatic Diseases (Fig. 1) [7, 20]. The quantitative NVC assessment in the 1 mm grid consisted of the following NVC parameters at the image level: the 'capillary density' (the number of capillaries in the distal row); the 'capillary dimension' [the number of dilated capillaries (dilations) having an apical limb diameter of 20–50 μm and the number of giant capillaries (giants), having an apical limb diameter of >50 μm]; the 'capillary morphology' [the number of capillaries with a normal morphology (capillaries with a hairpin shape; once or twice-crossing shape; or tortuous shape, i.e. limbs bend but do not cross; on the condition that the tip is convex) and abnormal morphology (all capillaries whose shape does not correspond to the definition of a normal shape)] [21, 22] and the presence of 'microhaemorrhages' (red or brown amorphous structures in the pericapillary/periungual region).

To obtain the quantitative NVC parameters at the subject level, the means were calculated, except for the two NVC parameters 'giants' and 'microhaemorrhages', which were both reported in a dichotomous way at the subject level as being present or not.

The qualitative NVC assessment consisted of categorizing the capillary pattern at the image level in a 'scleroderma pattern' (a pattern with the presence of giants or the combination of abnormal shapes with an extremely reduced number of capillaries of ≤3 capillaries/linear mm) or a 'non-scleroderma pattern'. The latter included a 'normal pattern' (the capillaries of the distal row are normally shaped, homogeneous in dimension and their density is ≥7/linear mm) and a 'non-specific pattern' [8]. To depict the overall capillary pattern at the

Nailfold Video Capillaroscopic protocol 	IMAGE LEVEL								SUBJECT LEVEL
	Left Hand				Right Hand				
	2nd	3rd	4th	5th	2nd	3rd	4th	5th	
QUANTITATIVE ASSESSMENT *per linear mm*									
N° of capillaries (capillary density)	–	–	–	–	–	–	–	–	Mean capillary density
N° of dilations	–	–	–	–	–	–	–	–	Mean n° of dilations
N° of giants	–	–	–	–	–	–	–	–	Presence: Y/N
N° of abnormal shapes	–	–	–	–	–	–	–	–	Mean n° of abnl shapes
N° microhaemorrhages	–	–	–	–	–	–	–	–	Presence: Y/N
QUALITATIVE ASSESSMENT									
Normal pattern	–	–	–	–	–	–	–	–	Overall capillary pattern
Non-specific pattern	–	–	–	–	–	–	–	–	
Scleroderma pattern	–	–	–	–	–	–	–	–	

Figure 1. Standardized NVC protocol. Images of the second, third, fourth and fifth digits of each hand are assessed according to the standard format to report on capillaroscopic characteristics, including the quantitative (per linear millimetre) and qualitative (the capillary pattern) assessment (image level). To report at the subject level, the capillaroscopic parameters are deduced from all the obtained NVC images from an individual subject by calculating the mean of the capillary density, the mean of the number of dilations and the mean of the number of abnormal shapes (the sum of each NVC parameter divided by the number of assessed images per subject); by describing the presence or absence of the parameters 'giants' and 'microhaemorrhages' in a dichotomous way and by deriving the overall qualitative assessment (details in section 2.2)

subject level, the following rules were applied: as soon as one of the images was categorized as a 'scleroderma pattern' the overall capillary pattern was a 'scleroderma pattern'; when no 'scleroderma pattern' was present (none of the 16 images), the most dominant 'non-scleroderma pattern' depicted the overall capillary pattern. If both the 'normal' and 'non-specific' patterns were equally represented (eight 'normal' patterns and eight 'non-specific' patterns), the 'non-specific pattern' was assigned as overruling the capillary pattern. Examples of the quantitative and qualitative NVC assessments at the image level are given in Fig. 2.

Evaluability and handling of missing data

The evaluability was assessed per image based on the difficulty of the capillaroscopic reading. If all NVC parameters were evaluable, the visibility of that image was considered 'good'. In contrast, an image was scored as 'bad' if any NVC parameter was not evaluable. A bad image was still included for analysis and the concerning unevaluable parameter was then encoded as a missing. A subject was excluded from further analysis if <4 of the 16 images were scored as good.

Statistical analysis

Analyses have been performed using SPSS version 27 (IBM, Armonk, NY, USA) and R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). To assess the matched sample quality (jRMD *vs* HC), an optimal pair propensity score matching method was used that minimizes the overall distance (age and gender) between matched pairs [23]. Descriptive statistics were used to represent demographic features and to describe the NVC parameters per subgroup, with means and S.D.s for continuous variables and proportions for categorical variables. The following six NVC parameters were analysed at the subject level: mean capillary density, mean number of dilations, presence of giants, mean number of abnormal shapes, presence of microhaemorrhages and the capillary pattern. For comparison of these six NVC parameters between disease subgroups and the overall HC group, unmatched multivariable regression analysis was performed, adjusted for age and gender. Raw *P*-values were reported and a Bonferroni correction was applied (α-level set at 0.007, as seven subgroups were compared with the overall HC group) and the corresponding 99.3% CIs are reported. The mean differences (for continuous variables) and the odds ratios (ORs; for categorical variables) were presented compared with the HC subgroup. Additionally, exploratory subgroup analysis in the HC group was done by calculating the Pearson correlation coefficient to quantify the linear relationship between age and the quantitative NVC parameters density, dimension and morphology.

Results

A total number of 6474 NVC images were assessed from 413 subjects, consisting of 120 boys and 293 girls, with a mean age of 12.1 years (S.D. 3.72). In some subjects, <16 NVC images were assessed, due to erroneous storage of the images or because adjacent NVC images were overlapping. Demographics per subgroup are shown in Table 1 and details

Capillaroscopic characteristics	Non-scleroderma pattern				Scleroderma pattern		
	Normal	Non-specific abnormalities			Early	Active	Late
Density (mm)	≥7	↓			≥7	4-6	≤3
Dimension (μm)	Normal		20-50		>50 (giant)	>50 (giant)	-
Abnormal morphology	-			+	-	+	++

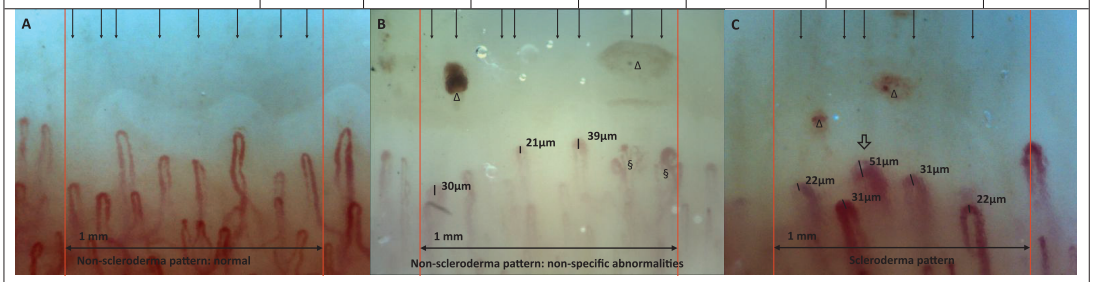


Figure 2. Standardised assessment of NVC images according to the international consensus EULAR Study Group on Microcirculation in Rheumatic Diseases definitions. **(A)** An example of a stereotypical 'normal' pattern. Density: 8 capillaries/linear mm (↓). Dimension: no dilations, no giants. Morphology: no abnormal shapes. Microhaemorrhages: absent. Interpretation: normal pattern (non-scleroderma pattern). **(B)** An example of a 'non-specific' pattern. Density: 8 capillaries/linear mm. Dimension: presence of 3 dilations/linear mm, no giants. Morphology: presence of two abnormal shapes (§). Microhaemorrhages: present. Interpretation: non-specific abnormalities (non-scleroderma pattern). **(C)** An example of a 'scleroderma' pattern. Density: 5 capillaries/linear mm (↓). Dimension: presence of a giant (⇓). Morphology: no abnormal shapes. Microhaemorrhages: present. Interpretation: (active) scleroderma pattern. Adapted from Smith V et al. Standardization of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. Autoimmunity Reviews 2020;19:102458 [7]

on ANA are found in Supplementary Table S2, available at *Rheumatology* online.

Evaluability and matching

In 5912 NVC images (91.3%), all NVC parameters could be assessed. Most subjects had >12 images of good visibility (Supplementary Table S3, available at *Rheumatology* online). From the 209 studied patients, 5 had a bad general visibility (<4/16 good images): in 4 subjects (3 with the systemic form of JIA and 1 with PsA), it was related to a technical problem with the focus of the lens, and in 1 patient with JDM it was inherent to the capillaroscopic abnormalities, in which diffuse microhaemorrhages made it impossible to assess other NVC parameters. Those five subjects were excluded from further analysis (and were not matched).

As such, statistical analyses were performed on 204 patients with jRMD and 204 HCs. An optimal pair propensity score matching method showed no imbalances in gender and a standardized mean difference in age of <0.1, which corresponds to a maximum age difference of 3 years within matched pairs.

Quantitative NVC assessment

Table 2 shows the NVC parameters per subgroup, together with the mean differences and ORs per disease subset *vs* HCs.

Capillary density

The mean capillary density in HCs was 8.5 capillaries/linear mm (s.d. 1.2), which was similar to the mean capillary density from patients with PRP and JIA. In contrast, in patients with MCTD, JDM and juvenile SSc (jSSc), a significantly lower capillary density was seen [7.1 (s.d. 1.3), 6.3 (s.d. 2.0) and 5.2 (s.d. 1.9), respectively; $P < 0.001$].

The density in childhood-onset SLE (cSLE) [7.6 (s.d. 1.3)] and localized scleroderma (lSc) [7.7 (s.d. 1.2)] was significantly lower compared with HCs as well ($P = 0.006$ and $P = 0.005$, respectively). However, the mean difference remained small (<1 capillary/linear mm). The results are shown in Fig. 3A.

Capillary dimension

In HCs, a mean of 0.5 capillary dilations/linear mm (s.d. 0.6) was observed. In lSc and JIA patients, the capillary dimension did not differ from HCs. An increased number of dilated capillaries was seen in PRP [1.0 (s.d. 0.9), $P = 0.008$] and cSLE [0.9 (s.d. 1.1); $P = 0.035$] but was only statistically significantly different from HCs in JDM, MCTD and jSSc, in which a mean of 1.5 (s.d. 1.2), 1.8 (s.d. 1.0) and 1.8 (s.d. 0.6) capillary dilations/linear mm, respectively, were observed ($P < 0.001$) (Table 2, Fig. 3B).

In jSSc, 37.09% of the capillaries were dilated and 15.96% of the capillaries were giants *vs* 5.60% dilations and 0.03% giants in HCs ($P < 0.001$). The same trends were observed in MCTD and JDM with 26.33% and 28.89% of dilated capillaries and 5.03% and 4.76% of giants, respectively ($P < 0.001$).

Capillary morphology

The mean number of abnormal capillary shapes per linear millimetre in HCs was 0.3 (s.d. 0.3) and about the same values were observed in PRP, cSLE, lSc and JIA. JDM and MCTD subjects exhibited significantly more abnormal shapes compared with HCs, being 0.9/linear mm (s.d. 1.0) and 0.6/linear mm (s.d. 0.4) ($P < 0.001$) (Table 2, Fig. 3C).

Of note, although the mean number of abnormal shapes in jSSc [0.5/linear mm (s.d. 0.4)] was not significantly different from HCs (after Bonferroni correction), we found in a post hoc analysis that the proportion of the mean number of abnormal shapes on the mean capillary density (number of abnormal shapes/total number of capillaries) revealed a significant difference (12.15% in jSSc *vs* 3.25% in HCs; $P < 0.001$).

Table 1. Demographics ($N=413$)

Characteristics	HCs ($n=204$)	PRP ($n=20$)	cSLE ($n=20$)	JDM ($n=22$)	jSSc ($n=13$)	lSc ($n=21$)	MCTD ($n=18$)	JIA ($n=95$)				
								OA ($n=22$)	PA ($n=23$)	ERA ($n=20$)	PsA ($n=15$)	JIAS ($n=15$)
Age, mean (S.D.), years	12.0 (3.6)	14.6 (2.1)	13.6 (4.0)	11.4 (3.9)	13.1 (3.6)	11.2 (3.5)	13.5 (3.2)	11.5 (3.8)				
								10.8 (4.1)	11.4 (4.0)	13.6 (2.8)	12.1 (4.4)	9.4 (3.9)
Female, *n* (%)	145 (71.1)	16 (80.0)	14 (70.0)	15 (68.2)	12 (92.3)	14 (66.7)	15 (83.3)	62 (65.2)				
								18 (81.8)	15 (65.2)	11 (55.0)	9 (60.0)	9 (60.0)
Race, *n* (%)												
White	161 (78.9)	17 (85.0)	8 (40.0)	17 (77.3)	5 (38.5)	15 (71.4)	12 (66.7)	19 (86.4)	20 (87.0)	17 (85.0)	13 (86.7)	8 (53.3)
Asian	6 (2.9)	0 (0.0)	3 (15.0)	0 (0.0)	3 (23.1)	1 (4.8)	1 (5.6)	2 (9.1)	0 (0.0)	0 (0.0)	2 (13.3)	6 (40.0)
Black	11 (5.4)	0 (0.0)	5 (25.0)	2 (9.1)	1 (7.7)	1 (4.8)	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Other	26 (12.7)	3 (15.0)	4 (20.0)	3 (13.6)	4 (30.8)	4 (19.0)	5 (27.8)	0 (0.0)	3 (13.0)	3 (15.0)	0 (0.0)	0 (0.0)
Disease duration, mean (S.D.), years	–	1.3 (1.9)	2.4 (2.7)	3.3 (4.2)	2.5 (2.5)	3.8 (3.2)	2.1 (2.8)	6.2 (4.5)	4.5 (3.6)	3.5 (3.7)	4.7 (5.1)	4.2 (4.1)
RP, *n* (%)	4* (2.0)	20 (100)	4 (20.0)	0 (0.0)	13 (100)	2 (9.5)	10 (55.6)	2 (9.1)	1 (4.3)	2 (10.0)	0 (0.0)	1 (6.7)
ANA, *n*/total valid (%)	–	5/20 (25.0)	17/18 (94.4)	13/16 (81.2)	13/13 (100.0)	2/11 (18.2)	14/16 (87.5)	9/17 (40.9)	13/21 (59.1)	6/15 (40.0)	5/10 (50.0)	1/15 (6.7)

* 4/204 (2.0%) of HCs had RP, in which the cause remained undefined (primary or secondary), as no rheumatological workup had been performed in volunteers at schools.
ANA: antinuclear antibodies detected by indirect immunofluorescence screening on Hep-2 cell substrates; ERA: enthesitis-related arthritis; JIAS: juvenile idiopathic arthritis (systemic); PA: polyarthritis.

Presence of microhaemorrhages

Fig. 3D shows the proportions of subjects with microhaemorrhages per subgroup. In 39.2% of the HCs, microhaemorrhages were found. The proportion increased in PRP to 55.0% ($P=0.317$) and was lower in JIA (29.7%; $P=0.134$). Significantly more microhaemorrhages were observed in patients with CTD: cSLE 80.0%, JDM 85.3%, jSSc 84.6% and MCTD 77.8%. The ORs are represented in Table 2.

Qualitative NVC assessment

A normal pattern was observed in 62.7% of HCs and was present in similar proportions in JIA and lSc. The non-specific pattern was the most dominant pattern in PRP (60.0%) and cSLE (75.0%), however, only in cSLE was it statistically significantly different from the proportion in HCs [OR 4.5 (CI 1.2, 22.2), $P=0.002$]. The odds to exhibit a scleroderma pattern were higher in the CTD subsets compared with HCs (Table 2).

A scleroderma pattern was observed in 3/204 HCs (1.5%), in 1/20 PRP patients (5.0%) and in 1/91 JIA patients (1.0%). In all five, clinical signs of an underlying CTD were absent. One of the HCs with a scleroderma pattern had RP (a 16-year-old White girl). Another HC (a 6-year-old Black boy) had a local trauma in the same finger in which giants were observed. In the last 'healthy' child [a 14-year-old boy with mixed ethnicities (White/Black), no explanation for this observed abnormality was given. The boy with PRP, who had a scleroderma pattern, had no ANAs on multiple occasions and no jRMD-related symptoms, but reported on a compulsive habit of nail biting. The boy with JIA, who had a scleroderma pattern, reported nail biting as well.

Exploratory analysis of age-related nailfold capillaroscopic findings in HCs

No age-related increase in capillary density was observed ($R=-0.20$, $P=0.773$) (Fig. 4A). In contrast, the youngest age group (<5 years old) exhibited a significantly higher capillary density compared with the other age groups. The Pearson's correlation coefficient between the capillary density and age, by leaving out the youngest age group, resulted in a significant, although very weak positive correlation ($R=0.14$, $P=0.046$) (Fig. 4B).

There was a mild association between age and the number of capillary dilations, as reflected in a positive, but also small, correlation coefficient ($R=0.18$, $P=0.011$) (Fig. 4C). And there was no association with the number of abnormal shapes ($R=-0.02$, $P=0.758$) (Fig. 4D). No age influence was found for the presence of microhaemorrhages (data not shown).

Discussion

This study is the first multicentre analysis of data from the international paediatric NVC registry set up by the EULAR Study Group on Microcirculation in Rheumatic Diseases. The NVC characteristics of patients with varying jRMD and PRP are described in a standardized way and compared with a large group of HCs. The study reveals that the NVC assessment in CTD, such as jSSc, MCTD, JDM and cSLE, differs significantly from that of HCs. The NVC characteristics from a large sample of JIA patients are comparable to those from HCs.

Table 2. Comparison of the quantitative and qualitative NVC assessment in the different subgroups compared with HCs ($n = 408$)

Characteristics	HC ($n = 204$)	PRP ($n = 20$)	cSLE ($n = 20$)	JDM ($n = 21$)	jSSc ($n = 13$)	lSc ($n = 21$)	MCTD ($n = 18$)	JIA ($n = 91$)
Quantitative assessment								
Density								
Mean capillary density/linear mm, (S.D.)	8.5 (1.2)	8.7 (0.8)	7.6 (1.3)	6.3 (2.0)	5.2 (1.9)	7.7 (1.2)	7.1 (1.3)	8.7 (1.2)
MD (99.3% CI)		0.2 (−0.6, 1.0)	**−0.8 (−1.6, 0.0)**	**−2.1 (−2.9, −1.4)**	**−3.2 (−4.2, −2.2)**	**−0.8 (−1.6, 0.0)**	**−1.4 (−2.3, −0.5)**	0.2 (−0.2, 0.6)
P-value		0.467	**0.006**	**0.001**	**0.001**	**0.005**	**<0.001**	0.229
Dimensions								
Mean number of dilations/linear mm (S.D.)	0.5 (0.6)	1.0 (0.9)	0.9 (1.1)	1.5 (1.2)	1.8 (0.6)	0.4 (0.4)	1.8 (1.0)	0.4 (0.6)
MD (99.3% CI)		0.4 (0.0, 0.9)	0.3 (−0.1, 0.8)	**1.1 (0.6, 1.5)**	**1.3 (0.7, 1.8)**	−0.1 (−0.5, 0.4)	**1.2 (0.8, 1.7)**	−0.1 (−0.3, 0.2)
P-value		0.008	0.035	**<0.001**	**<0.001**	0.675	**<0.001**	0.441
Subjects with giants, *n* (%)	3 (1.5)	1 (5.0)	1 (5.0)	12 (57.1)	11 (84.6)	0 (0.0)	10 (55.6)	1 (1.1)
OR (99.3% CI)		4.5 (0.1, 63.1)	4.4 (0.1, 58.5)	**71.8 (13.2, 627.7)**	**283.7 (33.2, 5229.1)**	1.3 (0.0, 31.0)	**73.3 (12.0, 701.3)**	0.9 (0.0, 11.7)
P-value		0.185	0.188	**<0.001**	**<0.001**	0.869	**<0.001**	0.943
Morphology								
Mean number of abnormal shapes/linear mm, (S.D.)	0.3 (0.3)	0.2 (0.3)	0.3 (0.4)	0.9 (1.0)	0.5 (0.4)	0.4 (0.6)	0.6 (0.4)	0.2 (0.3)
MD (99.3% CI)		0.0 (−0.3, 0.2)	0.1 (−0.2, 0.3)	**0.7 (0.4, 0.9)**	0.2 (−0.1, 0.6)	0.2 (−0.1, 0.4)	**0.3 (0.1, 0.6)**	0.0 (−0.2, 0.1)
P-value		0.675	0.452	**<0.001**	0.043	0.059	**0.001**	0.719
Microhaemorrhages								
Subjects with microhaemorrhages, *n* (%),	80 (39.2)	11 (55.0)	16 (80.0)	17 (85.3)	11 (84.6)	8 (38.1)	14 (77.8)	27 (29.7)
OR (99.3% CI)		1.6 (0.4, 5.9)	**5.2 (1.3, 29.8)**	**6.2 (1.6, 35.4)**	**6.8 (1.2, 80.8)**	1.0 (0.3, 3.5)	**4.6 (1.1, 26.8)**	0.7 (0.3, 1.4)
P-value		0.317	**0.001**	**<0.001**	**0.002**	0.964	**0.003**	0.134
Qualitative assessment								
Scleroderma pattern								
Subjects with a scleroderma pattern, *n* (%)	3 (1.5)	1 (5.0)	3 (15.0)	13 (61.9)	12 (92.3)	0 (0.0)	11 (61.1)	1 (1.1)
OR (99.3% CI)		4.4 (0.1, 61.3)	**11.4 (1.1, 114.8)**	**85.3 (15.8, 748.4)**	**465.9 (45.3, 18977.3)**	1.3 (0.0, 31.3)	**85.7 (14.3, 812.4)**	1.0 (0.0, 12.0)
P-value		0.189	**0.005**	**<0.001**	**<0.001**	0.861	**<0.001**	0.959
Non-scleroderma patterns								
Subjects with a non-specific pattern, *n* (%)	73 (35.8)	12 (60.0)	15 (75.0)	4 (19.0)	1 (7.7)	7 (33.3)	7 (38.9)	24 (26.4)
OR (99.3% CI)		2.2 (0.6, 8.5)	**4.5 (1.2, 22.2)**	0.4 (0.1, 1.8)	0.2 (0.0, 1.4)	1.0 (0.2, 4.0)	1.1 (0.2, 4.0)	0.6 (0.3, 1.4)
P-value		0.096	**0.002**	0.131	0.031	0.957	0.901	0.118
Subjects with a normal pattern, *n* (%)	128 (62.7)	7 (33.3)	2 (10.0)	4 (19.0)	0 (0.0)	14 (66.7)	0 (0.0)	66 (72.5)

The mean differences (MDs) (by multivariable regression analysis, adjusted for the matching factors age and gender) and ORs per subgroup are compared with HCs, showing the raw *P*-values and the Bonferroni corrected CIs. When a significant difference ($P < 0.007$, α-level set at 0.007, as seven subgroups were compared) between the subgroup and the HC group existed, these values are indicated in bold.

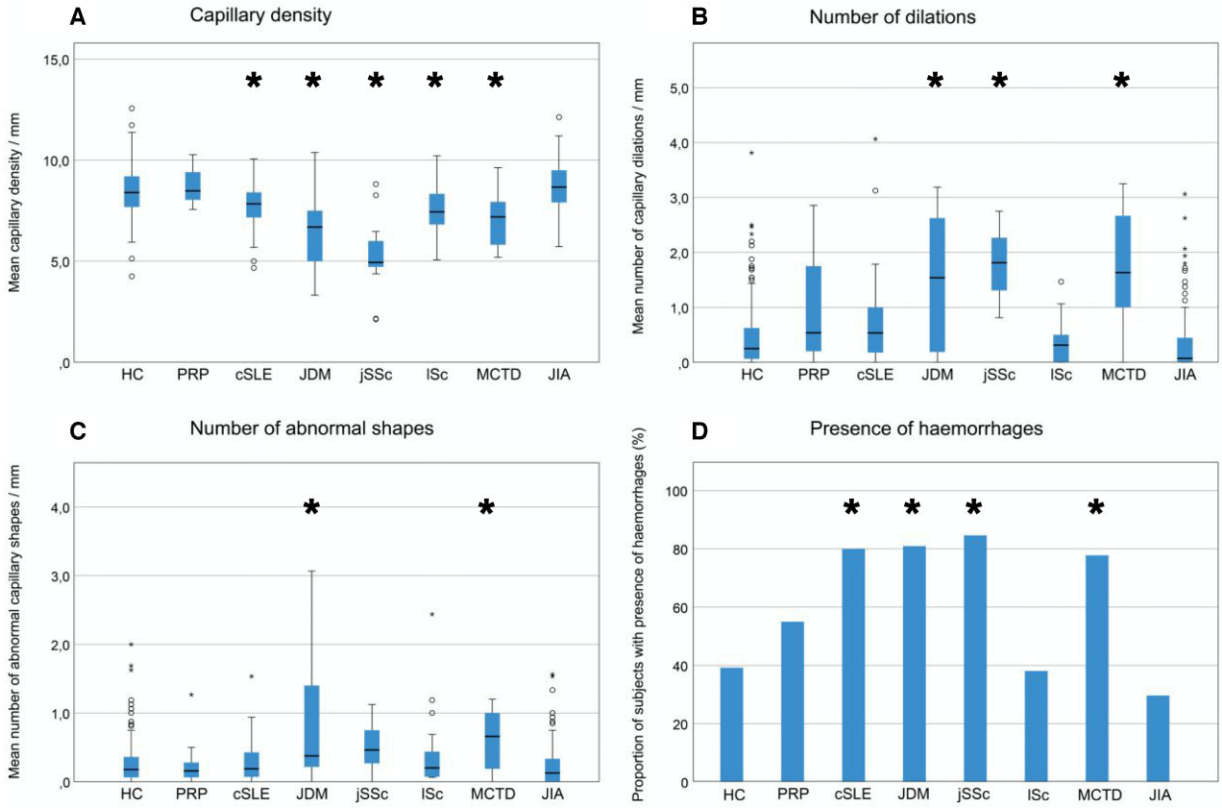


Figure 3. Quantitative NVC assessment per subgroup compared with the HCs. **(A)** Box plot of the mean capillary density per linear millimetre. **(B)** Box plot of the mean number of dilations per linear millimetre. **(C)** Box plot of the mean number of abnormal shapes per linear millimetre. Variations in the subgroups are evidenced by the wide blue boxes and by the presence of outliers (°1.5 × interquartile range) and extreme values (*3 × interquartile range). **(D)** Bar graph of the proportion of subjects with the presence of nailfold microhaemorrhages. The statistically significant differences (by linear regression analysis) between each subgroup and the overall HC subgroup are indicate with an asterisk (*)

This study is the first of its kind, in that the NVC images were assessed quantitatively and qualitatively, according to the standardized international consensus definitions from the EULAR Study Group on Microcirculation in Rheumatic Diseases [7, 20].

The results are in accordance with the few previous publications on this topic in jRMD, in which a lower capillary density was found in jSSc, MCTD and JDM [24–29]. Additionally, we observed a lower capillary density in cSLE and lSc [28–30]. Interestingly, the mean capillary density in HCs was 8.5/linear mm (s.d. 1.2), which is in the normal density range in adults (where the cut-off value is 7/linear mm) and may indicate that the same cut-off values for normality can be used in children [8].

Although Piotto *et al.* [18] previously found a strong correlation between density and age in 100 healthy children (>5 years of age) ($R = 0.796$, $P < 0.001$), we can only at best report that there is a very weak association in our healthy subgroup ($R = 0.14$, $P = 0.046$). Other reports on this topic are more in line with our results [28, 31].

It is novel in the capillaroscopic research of jRMD to report on the capillaroscopic dimension as the mean number of dilations per millimetre [18, 29, 32]. We observed a significantly higher number of dilations and also a higher proportion of subjects with giants in jSSc, MCTD and JDM compared with HCs, consistent with observations in adults [33–35]. In keeping with the findings of Herrick *et al.* [31], our subgroup analysis in HCs revealed a trend for the mean number of dilations per millimetre to increase with age.

So far, no studies with children report on the capillary morphology by using the standardized 'simple' definitions from the EULAR Study Group on Microcirculation in Rheumatic Diseases [5, 7, 18, 32, 34]. Concerning the presence of microhaemorrhages, we observed higher prevalence rates than previously reported in HCs (39% compared with prevalence rates ranging from 10 to 20% in the literature) [28, 32]. It should be kept in mind that, as it stands, no reliable distinction between pathological and non-pathological types of microhaemorrhages can be made, especially in children who are more frequently exposed to (micro)traumatic events [32, 36].

Not unexpectedly, we observed scleroderma patterns in CTDs and non-specific abnormalities as the predominant pattern in cSLE [24, 25, 27, 28, 37–39]. Remarkably, in three of five 'unexpected' cases with a scleroderma pattern, trauma or the compulsive habit of nail biting was noted, which underlines the need for repeated assessments in these cases and careful follow-up.

The consecutive input from centres dispersed across Europe, the American continent and South Asia is a major advantage of our study. Despite the dominance of the White ethnicity within the study population, we obtained images from a relatively larger proportion of JIA patients from the South Asian subcontinent (40%) and from a relatively larger proportion of Black patients among those suffering from cSLE, which reflects data from a real-life world study population. Both diseases are known to have a higher prevalence in these ethnicities [40, 41].

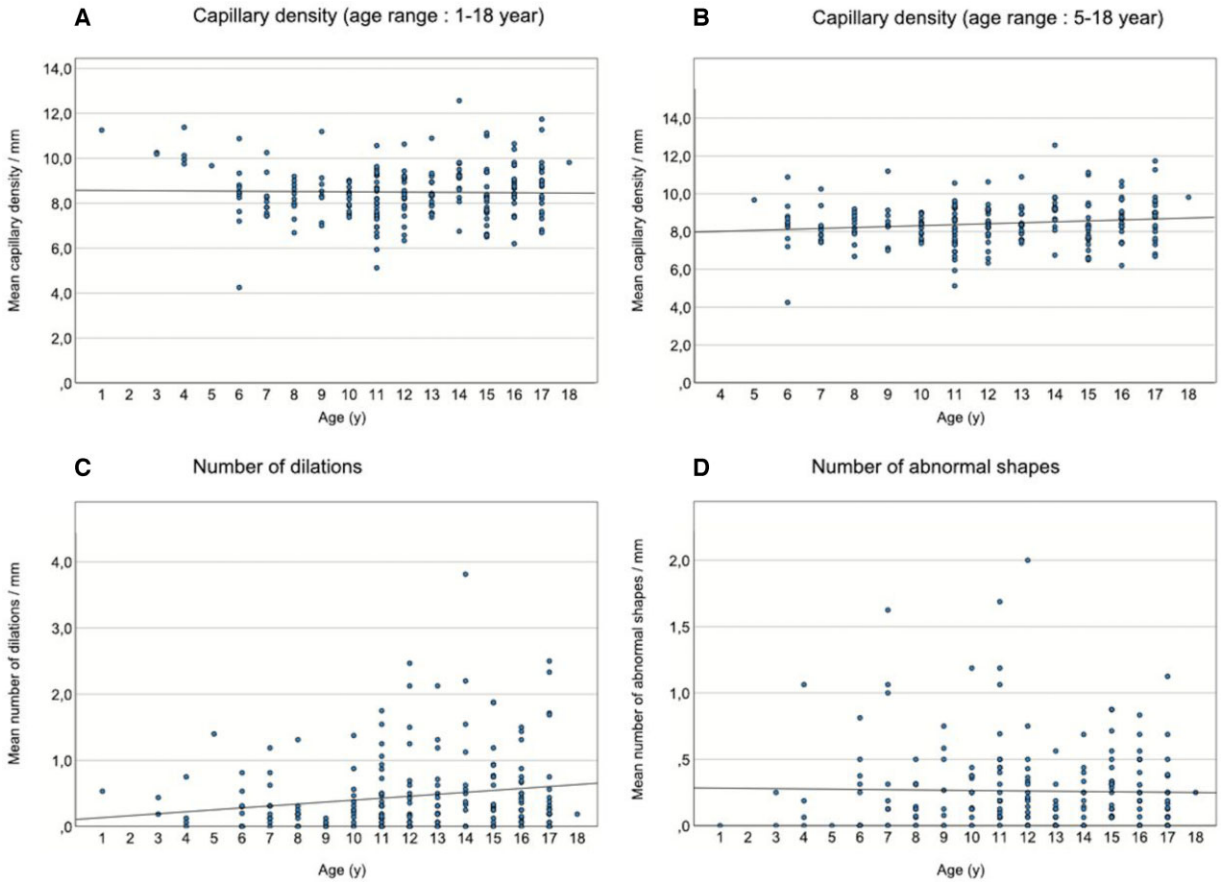


Figure 4. Exploratory analysis of the quantitative NVC assessment in relation to age in the healthy subset. Data are represented in scatter plots and fitted regression lines. **(A)** Capillary density in the total healthy subset ($n = 204$). **(B)** Capillary density in the healthy subset without the youngest group ($n = 197$). **(C)** Mean number of capillary dilations per linear millimetre ($n = 204$). **(D)** Mean number of abnormal shapes per linear millimetre ($n = 204$)

Another advantage of our study is the standardized acquisition of NVC images from different centres with similar magnification (×200) and the centralized reading method. By using the videocapillaroscope, which is considered the gold standard device to obtain reliable nailfold images, and by applying a standardized methodology, we believe that our results add value for the implementation of NVC examinations in clinical practice [7]. While instructions on the NVC technique and capturing method were provided to the operators only by a written study protocol, the high reported general evaluability (97.6% of the jRMD subjects) attests to the applicability of this technique [18, 34]. However, it needs to be kept in mind that, while thoroughly validated in adults, the NVC technique and methodology needs further validation in children and adolescents.

Our study has some limitations linked to its exploratory nature. First, the subgroups of patients with jRMD remain relatively small and no pairwise comparison with age- and sex-matched HCs was performed. Likewise, for the interpretation of the age-related NVC characteristics in the healthy subset, it is important to note that only seven children were <5 years old. Second, inherent to the study design, we did not obtain reliable clinical information from our HCs. Children were mostly recruited at schools, in the absence of their parents. Thus an underlying diagnosis of RP or rheumatic disease might have been missed. Third, our analysis did not correct for centre contributions because we were unable to match all jRMD patients with HCs from the same centre and because samples per subgroup were very small for some centres.

To conclude, this study pioneers the standardized NVC assessment of children and adolescents with jRMD recruited across the world and had the aim of describing their NVC assessment in a detailed and comprehensive manner. Our results support the regular use of NVC in children with PRP, CTD and even lSc. A further step of this international project is to follow children and adolescents prospectively in order to shed light on clinical associations with NVC abnormalities in larger disease-specific samples. The EULAR Study Group on Microcirculation in Rheumatic Diseases further advocates the use of standardized NVC assessments and terminology to improve the accuracy of NVC studies and to facilitate comparisons in the future.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Data availability statement

Data are available within the article or its supplementary materials. Data underlying this study will be shared upon reasonable request to the corresponding author.

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