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Nailfold videocapillaroscopy findings are associated with IIM subtypes and IFN activation

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Abstract

Objective This study aimed to characterize nailfold videocapillaroscopy (NVC) features in patients with different subtypes of Idiopathic inflammatory myopathy (IIM) and to investigate the correlations between NVC findings, myositis-specific antibody (MSA) subtypes, disease activity, cytokine profiles, and interferon-stimulated gene (ISG) expression levels.

Methods This cross-sectional observational single-center study included 55 IIM patients, categorized into MDA5 (+), anti-aminoacyl-tRNA-synthetase antibodies (ARS) (+), and MSA(-) groups based on their MSA profiles. Demographic data, laboratory tests, and NVC assessments were systematically collected and analyzed. The relative expression of type I ISGs in whole blood, as well as serum cytokine and chemokine profiles, were measured. Statistical analyses were performed to explore correlations between NVC scores and clinical parameters, including serum biomarkers.

Results NVC abnormalities were observed in most IIM patients, with significant differences in NVC features among the MSA subgroups. The MDA5(+) group exhibited significantly higher scores for capillary dilation ($P < 0.01$), giant capillaries ($P < 0.05$), microhemorrhages ($P < 0.01$), and abnormal capillary morphology ($P < 0.05$) compared to the ARS (+) group. ISG expression and cytokine levels were upregulated in IIM patients, with active disease patients showing significantly higher levels of certain ISGs and cytokines compared to clinically stable patients. Notably, specific NVC score dimensions were positively correlated with the levels of certain ISGs and cytokines. For example, microhemorrhage, capillary dilation, and capillary density all had significantly positive correlations with MX1, IFI27, IP-10, RANTES, and GROα ($P < 0.05$). And giant capillary is also related to levels of IFI27, SDF-1α, IP-10, RANTES, and GROα ($P < 0.05$).

Conclusion IIM patients exhibit distinct NVC abnormalities, which vary across different MSA subtypes. NVC findings have potential clinical value in screening disease activity and interferon pathway activation in IIM patients.

Keywords Nailfold videocapillaroscopy, Idiopathic Inflammatory myopathy, Type I interferon, Myositis-specific antibody

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Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of systemic autoimmune diseases primarily characterized by chronic inflammatory lesions in the skin and muscles, but they can also affect vital organs such as the lungs and heart. These conditions are difficult to treat, are prone to relapse, and often have a poor prognosis. The clinical presentation of IIM is highly heterogeneous [1, 2], with significant variability in clinical manifestations, pathological features, affected organs, and prognosis depending on the specific myositis-specific autoantibodies (MSAs) present in the patient. For example, patients with positive aminoacyl-tRNA synthetase antibodies (ARS) often present with mechanic's hands, Raynaud's phenomenon, and arthritis, which are frequently accompanied by interstitial lung disease (ILD). Although these patients generally respond well to immunosuppressive therapy, they are prone to relapse. In contrast, those positive for anti-MDA5 antibodies typically present clinically amyopathic dermatomyositis (CADM) with mild muscle involvement and more severe skin manifestations, often accompanied by rapidly progressive interstitial lung disease, which has a very high mortality rate [3]. Currently, rheumatologists face challenges such as unclear pathogenesis and difficulties in disease assessment, which hinder the development of precise treatment strategies. Exploring new classification methods and disease assessment techniques for IIM is a pressing clinical need.

Nailfold videocapillaroscopy (NVC) is a noninvasive imaging technique that allows for the direct observation of capillary networks in the skin, providing a quantitative analysis of capillary abnormalities. Studies have demonstrated the importance of NVC results in evaluating connective tissue diseases characterized by vascular pathology, particularly systemic sclerosis (SSc) and connective tissue diseases associated with Raynaud's phenomenon [4]. NVC has become an integral part of the classification criteria for SSc [5], offering valuable information for differential diagnosis, disease activity monitoring, and prognosis prediction. The IIM also exhibits microvascular abnormalities, although the most common changes are endothelial damage and microhemorrhages caused by inflammatory cell infiltration [6], rather than the fibrosis and vasoconstriction observed in SSc. Recent studies have described the NVC characteristics of IIM subtypes, such as dermatomyositis (DM), anti-synthetase syndrome (ASS), and myositis overlap syndrome. Capillary dilation, disorganization, and decreased density are more commonly observed in DM patients, with 62% of ASS patients showing abnormal NVC findings [7].

Interferons (IFNs) are divided into three types: I, II, and III. Type I interferons, including IFN-α, IFN-β, IFN-ω, IFN-κ, and IFN-ε, play crucial roles in upregulating MHC-I expression, activating natural killer (NK) cells, promoting the survival of activated T cells, and supporting the maturation of dendritic cells, thereby contributing to antiviral defenses [8]. Many rheumatic diseases involve persistent activation of type I IFN pathways. Studies have shown that the expression levels of interferon-stimulated genes (ISGs) can more sensitively indicate disease activity in patients with DM than can existing clinical indicators [9, 10], suggesting that ISGs could serve as valuable markers for precise IIM classification, disease assessment, and prognosis [11]. Type I IFN activation has also been shown to cause endothelial damage [12], leading to vascular abnormalities associated with DM, which may be detectable by NVC. Additionally, serum cytokine levels can provide insights into the pathways and extent of inflammation at the protein level.

This study aims to examine the NVC characteristics of different IIM subtypes—specifically ARS (+), anti-MDA5(+), and MSA (-)—and explore their correlation with clinical features, ISGs, and cytokine levels. The goal of this study was to evaluate the potential clinical value of NVC as a noninvasive, quantitative, convenient, and intuitive tool for disease assessment.

Methods

Participants

This is a cross-sectional observational study that enrolled adult patients (aged 18–70 years) with IIM attending the Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Beijing, China, between January and April 2022. The inclusion criteria were based on the 1975 Bohan & Peter criteria for polymyositis (PM) and DM, the 2002 Sontheimer criteria for CADM, or the 2010 Solomon criteria for ASS. Eligible patients tested positive for anti-MDA5 or any anti-ARS antibodies or were negative for all MSAs. Patients with other concurrent rheumatic autoimmune diseases, vascular diseases (e.g., systemic lupus erythematosus, diabetes, vasculitis), active infections, or conditions preventing nailfold videocapillaroscopy examination, such as nailfold ulceration, were excluded. This study was approved by the Ethics Committee of Peking Union Medical College Hospital and conforms to the ethical guidelines of the 1975 Declaration of Helsinki (institutional review board approval number: JS-2038). All patients provided written informed consent upon recruitment.

The clinical information collected included demographics (age, sex, lifestyle factors such as alcohol intake and smoking history), comorbidities (e.g., coronary heart disease, stroke, malignancy), and clinical symptoms and organ involvement related to IIMs. Laboratory findings, including complete blood counts; liver and kidney function tests; and erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), immunoglobulin, ferritin, muscle enzymes, MSAs, and myositis-associated antibodies,

were recorded. Additionally, details of the medications administered at the time of recruitment, including corticosteroids and immunosuppressants, were also collected. Manual Muscle Testing 8 (MMT8) [13], Myositis Disease Activity AssessmentVisual Analogue Scale (MYOACT), and Myositis Intention-to-Treat Activity Index (MITAX) [14, 15] are also evaluated in our study. Disease activity was categorized on the basis of the MITAX, focusing on seven domains including cutaneous, muscle, constitutional, skeletal, gastrointestinal, pulmonary, and cardiovascular. Grades A and B (scored 3 or higher) of any single domain are defined as "active disease," whereas grades C, D, and E (scored less than 3) in all domains are considered as "stable".

Nailfold videocapillaroscopy examination

NVC was performed by a medical nailfold capillary microscope and analyzed by the software connected with this equipment (TR-8000D, Tongren Medical Electronic Technology Co., Ltd. Xuzhou, China). Patients were required to rest in a room at a temperature of 20–25 °C for 15 min before the examination, and the capillary status of eight fingers (excluding thumbs) was assessed. Vegetable oil was applied to the nailfold to increase the resolution. Each nailfold was divided into four 1 mm × 1 mm regions, and four consecutive images were captured. If anatomical reasons, such as severe curvature or deformity, prevented the acquisition of all four images, at least two images from the central 1 mm × 1 mm region were captured.

The NVC images were semi-quantitatively scored according to these six dimensions [16]: capillary density (the number of capillary loops per millimeter length, ≥ 7/mm means normal in adults), capillary dilation (capillary loop diameter > 20 μm), giant capillary (capillary loop diameter > 50 μm), microhemorrhage (hemosiderin deposits visible near the capillaries), abnormal capillary morphology (abnormal branching of capillary loops, with at least one branch or two crossings), and disorganized capillary arrangement (capillaries lose their normal shape and polarity, no longer parallel to the limb's distal end). An often-used semiquantitative score is used to evaluate NVC characteristics (0 = normal, 1 = < 33% of capillary alterations/reduction, 2 = 33–66% of capillary alterations/reduction, 3 = > 66% of capillary alterations/reduction). The average score across six NVC dimensions is first computed for each individual finger image. The mean scores for all fingers are then averaged to obtain a subject's overall mean NVC score. Moreover, the scleroderma pattern is defined according to giant capillaries, decreased density, abnormal morphology, and hemorrhage [5]. All NVC images were acquired, evaluated, and scored by a single trained investigator (M.T.).

Interferon-stimulated genes

Peripheral blood RNA was extracted and reverse transcribed into cDNA, followed by real-time quantitative PCR (RT–qPCR) to measure the expression levels of eight ISGs, namely, *ISG15*, *IFIT1*, *IFI27*, *IFI44L*, *SIGLEC1*, *RSAD2*, *MX1*, and *IFI44*, with β-actin used as the reference gene. Additionally, the expression levels of these genes were measured in age- and sex-matched healthy controls for comparison. For each patient and healthy control, the relative expression levels of the eight ISGs were calculated, and the mean relative expression (M_{HD}) and standard deviation (SD_{HD}) of the healthy controls were determined. ISG activation in this study was defined as: the expression levels of at least four of the eight ISGs exceeding M_{HD} + 2 SD_{HD} or the expression levels of at least two of the eight ISGs exceeding M_{HD} + 4 SD_{HD} [17].

Cytokines and chemokines

Serum samples from patients were collected, and the levels of 34 cytokines and chemokine panels (including MIP-1α, SDF-1α, IL-27, IL-1β, IL-2, IL-4, IL-5, IP-10, IL-6, IL-7, IL-8, IL-10, eotaxin, IL-12p70, IL-13, IL-17 A, IL-31, IL-1RA, RANTES, IFN-γ, GM-CSF, TNF-α, MIP-1β, IFN-α, MCP-1, IL-9, TNF-β, GRO-α, IL-1α, IL-23, IL-15, IL-18, IL-21, and IL-22) were measured via a multiplex liquid–phase chip analysis system.

Statistical analysis

Categorical variables are described as counts (percentages), and group differences are compared via the Pearson chi-square test or Fisher's exact test. Continuous variables with a normal distribution are presented as the mean ± standard deviation (SD), with differences between groups analyzed via Student's t test. Continuous variables that are not normally distributed are described as medians (interquartile ranges), with group comparisons made via the rank-sum test. Spearman's rank correlation test was employed to assess correlations between continuous variables. A P value of < 0.05 was considered to indicate statistical significance. Histogram plots are used to describe and compare variables of different groups. Statistical analyses were performed by IBM SPSS 23.0 and STATA 15.0, and figures were generated via GraphPad Prism 9.0.2.

Results

Baseline demographics and clinical characteristics

A total of 55 patients were included in this study. Among them, 19 patients were in the ARS (+) group, 25 were in the MDA5 (+) group, and 11 were in the MSA (-) group.

All three groups were predominantly composed of middle-aged women, with significant differences in diagnoses. Notably, no cases of PM were found in the MDA5 (+) group, whereas DM (37%) and CADM (11%) were

less common in the ARS (+) group. There were no significant differences in smoking history or comorbidities among the groups (Table 1).

In terms of clinical presentation, 63% of ARS (+) patients had elevated muscle enzymes, which was significantly higher than that in the other two groups. Additionally, the prevalence of mechanic's hands was higher in the ARS (+) group (53%) than in the MDA5 (+) group (24%) and the MSA (-) group (9%). In contrast, characteristic DM rashes, including heliotrope rash (16% vs. 72%), Gottron's papules (21% vs. 80%), Gottron's sign (16% vs. 68%), and the "V" sign (5% vs. 60%), were less common in the ARS (+) group than in the MDA5 (+) group.

The prevalence of ILD was significantly higher in the MDA5 (+) and ARS (+) groups compared to the MSA (-) group (88% vs. 74% vs. 18%, $p < 0.01$). These findings are consistent with the typical clinical patterns associated with the three MSA subtypes. Laboratory tests revealed that white blood cell (WBC), platelet (PLT), CK, and CRP levels were significantly higher in the ARS (+) group than in the other two groups. This finding reflects differences in muscle involvement and suggests potential differences in the inflammatory status among the groups at baseline. In terms of treatment, all patients received glucocorticoid therapy. Among conventional synthetic disease-modifying antirheumatic drugs (DMARDs), calcineurin inhibitors (including cyclosporine A and tacrolimus), cyclophosphamide, and methotrexate were the most commonly used. Additionally, a subset of patients received targeted synthetic DMARDs, such as JAK inhibitors, while one MSA (-) patient was treated with tocilizumab. No significant differences in treatment regimens were observed among the groups, indicating a broadly similar therapeutic approach across the patient cohorts. No significant differences were found in the other laboratory parameters or disease activity assessments (Table 1).

NVC findings in IIM patients

Abnormal NVC patterns were observed among the IIM patients (Fig. 1), with significant differences in NVC characteristics across the different MSA groups. Notably, the distinctions between the MDA5 (+) group and the ARS (+) group were particularly pronounced. Compared with the ARS (+) group, the MDA5 (+) group had significantly higher scores for irregular capillary enlargement, giant capillaries, and nailfold microhemorrhages. In contrast, NVC findings in the MSA (-) group were more heterogeneous, with patterns falling between those of the MDA5 (+) and ARS (+) groups. The MSA (-) group presented significantly higher scores for abnormal capillary morphology compared to the ARS (+) group, although no significant differences were found in other dimensions (Fig. 2). Sixteen patients (67.3%) met the criteria for the scleroderma pattern and were distributed as follows: 10 out of 25 (40%) in the MDA5 (+) group, 1 out of 19 (5.3%) in the ARS (+) group, and 5 out of 11 (45.5%) in the MSA (-) group. The prevalence of the scleroderma pattern was significantly higher in the MDA5(+) group ($p<0.05$) and MSA(-) group ($p<0.05$), compared to the ARS (+) group. However, no significant correlation was observed between the presence of the scleroderma pattern and disease activity.

Among IIM patients, elevated ISG expressions were observed, particularly for ISG15, MX1, and IFI27, although no significant differences in the relative expression levels of the eight ISGs were detected across the different MSA groups. The proportions of IFN activation in the MDA5 (+) group, ARS (+) group, and MSA (-) group were 10 (40%), 3 (16%), and 3 (27%), respectively. Notably, the proportion of IFN activation in the MDA5 (+) group was significantly higher than that in the ARS (+) group (40% vs. 11%, $p = 0.04$), suggesting more pronounced IFN activation in MDA5 (+) IIM patients. While serum levels of 34 cytokines and chemokines were measured in all enrolled patients, 19 of these, including IFN-α and IFN-β, were below the detection limit in more than 90% of patients. Therefore, only the remaining 14 were included in the analysis. Despite the elevation of serum cytokine and chemokine levels in IIM patients, no significant differences were found across the MSA groups (Table 2).

NVC, ISG, and cytokine expression in relation to disease activity in IIM patients

Given the differences in disease behavior, the inflammatory response, and immune activation between the active and stable phases of IIM, we categorized patients on the basis of disease activity to explore associations between NVC patterns, ISG expression, cytokine profiles, and both MSA types and disease activity.

Comparison of NVC patterns by disease activity

When comparing NVC semiquantitative scores by disease activity and MSA group, positively correlated trends without statistical significance were found between NVC abnormalities (capillary density, dilation, and microhemorrhage) and disease activity in the MDA5 (+) and ARS (+) groups. However, a significant difference was observed only in capillary density between active and stable ARS (+) patients. No clear trends were observed in the MSA (-) group regarding NVC scores or disease activity.

Correlation between NVC scores, ISG expressions, and cytokine/chemokine profiles

The semi-quantitative NVC scores are significantly associated with certain ISG or cytokine/chemokine levels. The analysis revealed significant positive correlations between NVC microhemorrhage and MX1 ($r = 0.41$,

Table 1 Demographics, clinical features, and laboratory findings of IIM patients

	MDA5 (+) (*n* = 25)	**ARS (+) (*n* = 19)**	**MSA(-) (*n* = 11)**
Female, n (%)	18 (72)	13 (68)	10 (91)
Age, mean (SD)	45.5 (12.4)	49.4 (13.4)	43.5 (10.3)
Age of disease onset, mean (SD)	44.3 (11.8)	43.9 (12.4)	38.4 (12.8)
BMI, median (IQR)	23.4 (20.8, 26.7)	24.7 (24.2, 25.4)	23.2 (21.4, 24.8)
Diagnosis, n (%)			
DM	13 (52)	7 (37)	8 (73)
PM	0 (0)	6 (32)	2 (18)
CADM	11 (44)	2 (11)	1 (9)
Don't meet Bohan/Peter criteria	1 (4)	4 (21)	0 (0)
Smoking history, n(%)	5 (20)	4 (21)	1 (9)
Clinical Manifestations, n (%)			
Muscle			
Muscle weakness	10 (40)	8 (42)	7 (64)
Elevated muscle enzyme	14/25 (56)	12/19 (63)	4/11 (36)
Abnormal EMG	13/16 (81)	7/14 (50)	3/7 (43)
Abnormal muscle biopsy	7/9 (78)	3/5 (60)	1/4 (25)
Rash			
Heliotrope sign	18 (72)	3 (16)	7 (64)
Gottron rash	20 (80)	4 (21)	3 (27)
Gottron papule	17 (68)	3 (16)	3 (27)
V sign	15 (60)	1 (5)	6 (55)
Mechanic's hands	6 (24)	10 (53)	1 (9)
Raynaud phenomenon	3 (12)	2 (11)	1 (9)
ILD	22 (88)	14 (74)	2 (18)
Arthritis	9 (36)	3 (16)	1 (9)
Lab tests, median (IQR)			
WBC($\times 10^9$/L)	6.2 (5.1, 8.5)	10.2 (8.7, 13.0)	7.0 (5.2, 9.2)
NEUT($\times 10^9$/L)	3.8 (3.2, 4.9)	7.9 (7.3, 10.0)	4.5 (2.8, 8.3)
HGB (g/L)	139.0 (134.0, 147.0)	141.0 (133.0, 147.5)	141.0 (134.0, 146.0)
PLT($\times 10^9$/L)	213.5 (167.5, 277.0)	273.5 (234.0, 325.0)	212.5 (194.5, 231.0)
ALT (U/L)	25.0 (20.0, 43.0)	23.0 (14.0, 29.0)	13.0 (10.0, 37.0)
ALB (g/L)	42.0 (39.0, 45.0)	43.0 (40.0, 45.0)	43.5 (42.0, 45.0)
AST (U/L)	24.0 (16.0, 35.0)	23.0 (16.0, 34.0)	18.0 (16.0, 23.0)
LDH (U/L)	230.0 (178.0, 290.0)	231.0 (192.0, 280.0)	204.0 (157.0, 272.0)
Cr (μmol/L)	63.0 (60.0, 65.5)	58.0 (51.0, 79.0)	73.0 (69.0, 76.0)
CK (U/L)	44.0 (31.0, 61.0)	96.5 (56.5, 290.5)	76.5 (52.0, 89.5)
Ferritin (ng/mL)	80.5 (53.0, 231.0)	90.4 (40.5, 141.0)	90.0 (34.0, 200.0)
ESR (mm/h)	14.5 (3.5, 35.5)	13.0 (7.0, 23.0)	9.0 (3.0, 9.0)
CRP (mg/l)	0.9 (0.5, 2.5)	3.5 (0.9, 17.4)	0.6 (0.2, 1.7)
IgG (g/L)	11.8 (10.8, 14.1)	12.9 (10.9, 14.0)	10.4 (9.3, 15.7)
IgA (g/L)	1.8 (1.5, 2.7)	2.8 (2.2, 3.9)	2.4 (2.2, 2.7)
IgM (g/L)	1.2 (0.9, 1.5)	1.0 (0.6, 1.7)	0.8 (0.7, 1.1)
Treatment, n(%)			
Glucocorticoid	25 (100)	19 (100)	11 (100)
CYC	10 (40)	7 (37)	4 (36)
CNI (CsA or TAC)	18 (72)	10 (53)	7 (64)
CYC + CNI	8 (32)	5 (26)	2 (18)
MMF	0 (0)	3 (16)	0 (0)
MTX	4 (16)	1 (5)	1 (9)
JAKi	4 (16)	7 (37)	1 (9)
TCZ	0 (0)	0 (0)	1 (9)
Disease Activity			

Table 1 (continued)

	MDA5 (+) (*n* = 25)	ARS (+) (*n* = 19)	MSA(-) (*n* = 11)
MYOACT, median (IQR)	3.0 (2.0, 5.0)	2.0 (1.0, 2.5)	1.0 (0.0, 8.0)
MMT8, median (IQR)	171.0 (145.6, 308.5)	239.5 (80.0, 488.7)	82.5 (80.0, 188.7)
Active disease by MITAX, n (%)	10 (40)	8 (42)	4 (36)

Data are shown as n (%) for categorical variables, mean (SD) for normally distributed continuous variables, and median (IQR) for not normally distributed continuous variables

BMI, body mass index. DM, dermatomyositis. PM, polymyositis. CADM, clinically amyopathic dermatomyositis. ILD, interstitial lung disease. WBC, white blood cell. HGB, hemoglobin. PLT, platelet. ALB, albumin. LDH, lactate dehydrogenase. CK. creatine kinase. ESR, erythrocyte sedimentation rate. CRP, C-reactive protein. CYC, cyclophosphamide. CNI, calcineurin inhibitor. CsA, cyclosporine A. TAC, tacrolimus. MMF, mycophenolate mofetil. MTX, methotrexate. JAKi, Janus kinase inhibitor, including tofacitinib and baricitinib. TCZ, tocilizumab. MYOACT, myositis disease activity assessment visual analogue scale. MMT8, manual muscle test. MITAX, myositis intention-to-treat activity index

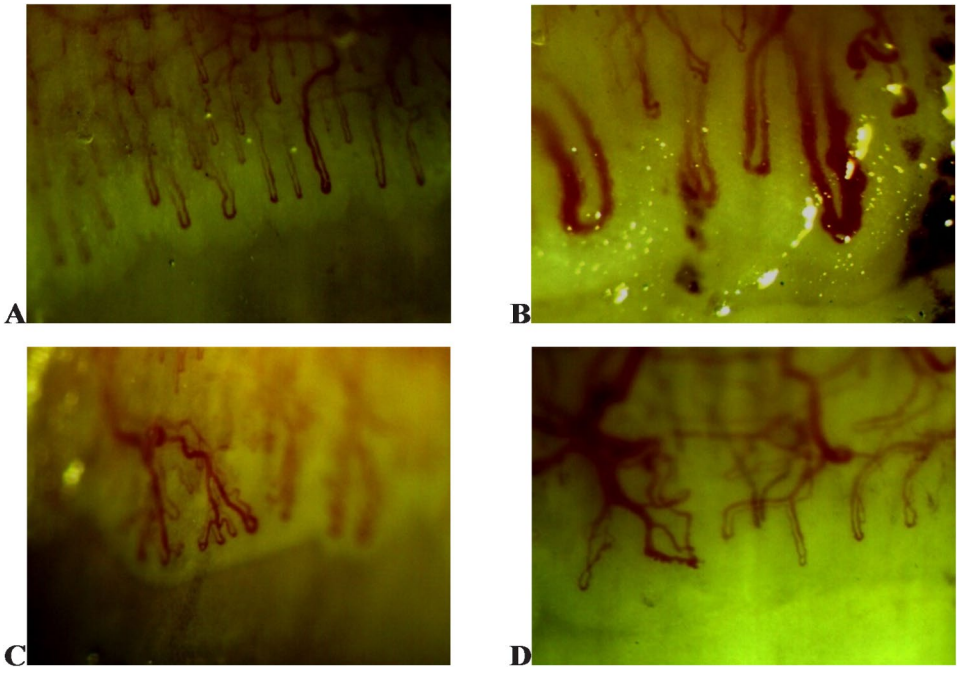

Fig. 1 Different nailfold videocapillaroscopy findings in IIM patients. (**A**) Normal nailfold capillaries. (**B**) Density-decreased and dilated capillaries and hemorrhages. (**C**) Abnormal morphology. (**D**) Disorganized arrangement

$P<0.01$), ISG15 ($r=0.32$, $P<0.05$), IFI27 ($r=0.50$, $P<0.01$); capillary dilation and MX1 ($r=0.37$, $P<0.01$), IFI27 ($r=0.45$, $P<0.01$); and capillary density and MX1 ($r=0.37$, $P<0.01$), IFI27 ($r=0.40$, $P<0.01$). Interestingly, capillary morphological abnormalities showed significant negative correlations with several ISGs, including IFIT1 (r = -0.40, $P<0.01$), RSAD2 (r = -0.35, $P<0.05$), ISG15 (r = -0.35, $P<0.05$), SIGLEC1 (r = -0.31, $P<0.05$), and IFI44L (r = -0.35, $P<0.05$). Regarding cytokine/chemokine levels, IP-10 was significantly positively correlated with capillary density ($r=0.46$, $P<0.01$), dilation ($r=0.44$, $P<0.01$), giant capillary ($r=0.44$, $P<0.01$), microhemorrhage ($r=0.55$, $P<0.01$), and disorganized capillary arrangement ($r=0.46$, $P<0.01$). Similar findings were observed for RANTES and GROα (Table 3).

Discussion

In this cross-sectional study involving 55 IIM patients, we characterized the NVC features in patients with different MSA subtypes, including the MDA5(+), ARS (+), and MSA (-) groups, and identified significant differences in NVC patterns between these groups. Moreover, we observed positive correlations between NVC scores, ISG expression levels, and the levels of certain cytokines.

Our study revealed that patients in the MDA5(+) group had more severe NVC abnormalities, including higher scores for capillary dilation, giant capillaries, and microhemorrhages, than did those in the ARS (+) group, where abnormalities were milder. This finding is consistent with previous research showing prominent vascular changes in anti-MDA5(+) patients [18, 19]. Although prior studies reported more capillary morphological abnormalities in ASS patients, ARS (+) group in our study exhibited

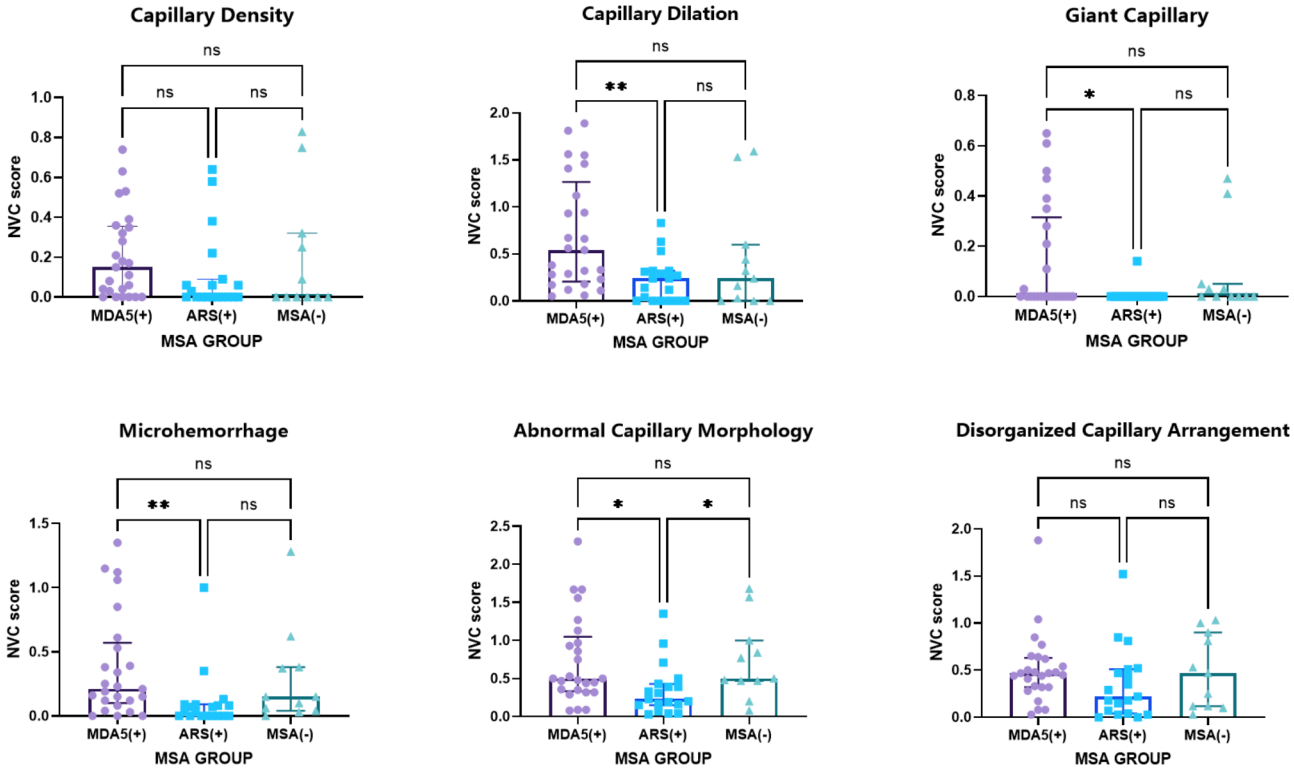

Fig. 2 Semiquantitative NVC Scores in Different MSA Groups across Various Evaluation Dimensions. NVC, nailfold videocapillaroscopy. MSA, myositis-specific autoantibody. NS, no significance. ARS, aminoacyl-tRNA synthetase antibody. *, $P<0.05$. **, $P<0.01$

Table 2 ISGs and cytokine/chemokine levels in IIM patients across MSA groups

	MDA5 (+) ($n=25$)	ARS (+) ($n=19$)	MSA (-) ($n=11$)	*P*
IFIT1	1.0 (0.6, 1.7)	2.0 (1.2, 3.0)	0.7 (0.2, 2.0)	MDA5 (+) vs. ARS (+), $P<0.05$
IFI44	0.7 (0.4, 1.0)	1.3 (0.6, 3.0)	0.7 (0.1, 1.0)	MDA5 (+) vs. ARS (+), $P<0.05$
RSAD2	1.2 (0.7, 1.8)	2.1 (1.1, 2.9)	0.7 (0.5, 2.1)	MDA5 (+) vs. ARS (+), $P<0.05$
MX1	4.3 (1.1, 12.0)	1.3 (0.5, 6.7)	0.5 (0.1, 5.7)	
ISG15	2.2 (0.6, 10.5)	1.2 (0.9, 5.4)	1.0 (0.3, 2.8)	
SIGLEC1	1.6 (1.1, 2.9)	2.0 (1.3, 3.8)	0.3 (0.2, 1.8)	ARS (+) vs. MSA(-), $P<0.05$
IFI44L	1.0 (0.4, 1.2)	1.4 (0.8, 3.0)	1.1 (0.1, 2.2)	MDA5 (+) vs. ARS (+), $P<0.05$
IFI27	2.5 (0.6, 45.6)	0.6 (0.2, 25.5)	0.5 (0.3, 5.5)	
IFN activation	10 (40%)	3 (16%)	3 (27%)	
SDF-1α, pg/ml	392.4 (303.5, 551.9)	398.2 (331.0, 543.5)	496.8 (457.5, 551.2)	
IP-10, pg/ml	15.9 (7.7, 25.4)	19.7 (11.1, 44.9)	16.9 (10.0, 44.4)	
IL-7, pg/ml	0.6 (0.4, 1.0)	1.2 (0.7, 1.5)	0.6 (0.5, 1.5)	
Eotaxin, pg/ml	16.9 (11.2, 27.0)	20.6 (8.1, 28.6)	17.6 (10.8, 27.8)	
IL-17 A, pg/ml	1.1 (1.1, 1.1)	1.1 (1.1, 3.6)	1.1 (1.1, 2.3)	
IL-1RA, pg/ml	42.4 (28.9, 192.8)	85.2 (12.9, 339.3)	41.8 (20.9, 50.9)	
RANTES, pg/ml	20.3 (13.1, 41.5)	22.7 (17.0, 35.5)	29.2 (14.3, 43.0)	
TNF-α, pg/ml	1.8 (1.8, 1.8)	1.8 (1.8, 1.8)	1.8 (1.8, 1.8)	
MIP-1β, pg/ml	47.5 (32.0, 65.7)	49.0 (18.3, 79.9)	46.7 (35.5, 60.0)	
MCP-1, pg/ml	16.5 (5.1, 75.7)	19.5 (8.7, 67.4)	20.8 (14.4, 41.7)	
GRO-α, pg/ml	0.7 (0.7, 0.7)	0.7 (0.7, 0.7)	0.7 (0.7, 0.7)	
IL-1α, pg/ml	0.3 (0.3, 0.3)	0.3 (0.3, 0.3)	0.3 (0.3, 0.6)	
IL-18, pg/ml	5.6 (5.6, 27.0)	12.7 (5.6, 20.2)	5.6 (5.6, 10.0)	
IL-21, pg/ml	4.8 (4.8, 4.8)	4.8 (4.8, 4.8)	4.8 (4.8, 4.8)	
IL-22, pg/ml	6.8 (6.8, 6.8)	6.8 (6.8, 6.8)	6.8 (6.8, 6.8)	

Table 3 Correlations between NVC scores and ISG and cytokine/chemokine levels

r	Capillary density	Capillary Dilation	Giant capillary	Microhemorrhage	Abnormal Capillary Morphology	Disorganized Capillary Arrangement
ISG						
IFIT1	-0.09	-0.14	0.01	-0.12	-0.40**	-0.08
IFI44	-0.22	-0.23	-0.09	-0.21	-0.29*	-0.16
RSAD2	-0.06	-0.12	0.00	-0.12	-0.35*	-0.09
MX1	0.37**	0.42**	0.27	0.41**	-0.15	0.21
ISG15	0.24	0.26	0.24	0.32*	-0.35*	0.09
SIGLEC1	-0.11	-0.10	-0.04	-0.10	-0.31*	-0.16
IFI44L	-0.23	-0.24	-0.11	-0.13	-0.35*	-0.15
IFI27	0.40**	0.45**	0.35*	0.50**	-0.11	0.28
Cytokine/chemokine						
SDF-1α	0.18	0.26	0.37**	0.37*	-0.07	0.14
IP-10	0.46**	0.44**	0.44**	0.55**	-0.02	0.46**
IL-7	0.30*	0.20	0.18	0.28	0.09	0.26
Eotaxin	0.15	0.05	0.06	0.09	0.10	0.15
IL-17 A	0.23	0.22	0.45**	0.26	-0.03	0.13
IL-1RA	0.24	0.28	0.32*	0.43**	-0.17	0.26
RANTES	0.33*	0.41**	0.39**	0.42**	-0.04	0.29*
TNF-α	0.07	0.07	0.04	0.16	0.05	0.14
MIP1β	0.05	0.06	0.17	0.17	-0.07	0.15
MCP-1	0.20	0.24	0.23	0.24	-0.13	0.07
GROα	0.29*	0.26	0.36*	0.39**	-0.14	0.31*
IL-1α	0.00	-0.04	0.08	0.05	-0.07	0.12
IL-18	0.08	0.20	0.09	0.21	-0.12	0.11
IL-21	-0.05	0.02	0.10	0.01	-0.11	-0.03
IL-22	-0.04	0.03	0.11	0.01	-0.11	-0.03

* $P<0.05$, ** $P<0.01$

only mild abnormal capillary morphology without significant differences in semiquantitative scoring [7]. The MSA (-) group demonstrated high heterogeneity in NVC features, which has not been previously reported. Our study included a high proportion of MDA5(+) patients, consistent with other Chinese IIM cohorts [20, 21].

Several studies have explored the relationship between NVC changes and disease activity in the IIM. In juvenile dermatomyositis (JDM), NVC characteristics were found to be correlated with 20 out of 26 clinical or laboratory indicators of disease activity, and another study showed that NVC abnormalities in IIM patients could improve with treatment [22, 23]. Our study similarly revealed trends toward higher NVC scores in the active disease groups for MDA5(+) and ARS (+) patients, although these trends did not reach statistical significance, likely because of our small sample size. Previous studies have shown that the scleroderma pattern can be observed in 69.0–84% of IIM patients, with a significantly higher prevalence in DM patients [24, 25]. Scleroderma pattern is also found to be associated with disease activity [26]. In our study, MDA5 (+) IIM patients have a higher prevalence of scleroderma pattern than the other two groups. However, our study revealed no significant correlation between the scleroderma pattern and disease activity. These findings suggest that the scleroderma pattern may reflect the similarity of pathogenesis of vascular damage in SSc and MDA5 (+) IIM.

We also observed elevated expression of several ISGs in IIM patients, with notable type I IFN activation, especially in the MDA5(+)-IIM group, where the proportion of patients with IFN activation was significantly higher than that in the ARS (+) and MSA (-) groups. This finding supports the established role of type I IFN activation in MDA5(+) IIM and aligns with the findings of previous studies [27]. Furthermore, a higher proportion of patients with active disease demonstrated IFN activation, reinforcing the connection between type I IFN pathways and disease activity in the IIM.

In terms of cytokine and chemokine profiles, our study revealed elevated serum levels of multiple cytokines in DM patients, with significantly increased levels of IP-10, eotaxin, IL-1RA, RANTES, MCP-1, and IL-18 in the active disease group. Our research group previously reported elevated levels of MIP-1α, IP-10, IL-8, IL-1RA, MCP-1, GRO-α, and IL-22 in DM patients compared with healthy controls, suggesting the activation of these cytokines and pathways in DM. IP-10, IL-1RA, and

MCP-1 are particularly useful markers for distinguishing active from stable DM patients, which is consistent with the findings of this study [28]. However, we did not observe elevated serum IFN-α/β levels, which contrasts with the ISG results. This discrepancy could be due to the paracrine or autocrine nature of IFN action, the relatively mild disease severity in our cohort, or insufficient IFN activation to cause measurable serum increases. The increase in IP-10 suggests the possible involvement of IFN-γ activation.

Interestingly, this is the first study revealing a significant positive correlation between NVC scores—capillary density, capillary dilation, and microhemorrhage—and the expression of ISGs, particularly MX1, IFI27, and ISG15. Additionally, five out of the six NVC dimensions, with the exception of capillary morphology, were significantly positively correlated with different cytokine levels. These results suggest that NVC could serve as a surrogate marker for ISG and cytokine activation, suggesting potential clinical utility in the management of IIM. Further large-scale studies are warranted to confirm these associations and explore the prognostic value of NVC.

NVC results are evaluated in qualitative, semi-quantitative, and quantitative methods [29]. Qualitative evaluation primarily determines whether the findings align with a scleroderma pattern, which can be further categorized into early, active, and late stages [5]. This study adopted the semi-quantitative scoring system proposed by Sulli et al. [16], which assesses NVC features across six dimensions and has been widely used in previous research [25, 30]. In addition, some studies have employed direct quantitative assessments, such as measuring capillary density and counting giant capillaries within a defined length. Notably, in patients with JDM, those with higher disease activity tend to have lower capillary density, suggesting that quantitative assessment may offer a more precise evaluation of this aspect [24, 30, 31].

This study has several limitations. The relatively small sample size, influenced by time constraints and the pandemic, may have limited the statistical power of some analyses. Larger cohorts are needed to validate our findings. NVC image acquisition and scoring were manually performed by a single investigator, ensuring consistency but introducing potential observation bias. Manual measurements may also have inaccuracies, highlighting the need for automated analysis tools [32]. Additionally, in our study, the average disease duration in the MDA5(+) group was significantly shorter than the other two groups. Previous studies revealed a reduction in giant capillaries after 30 months of follow-up in DM patients, accompanied by an increase in capillary morphological abnormalities [30]. Therefore, the differences in giant capillaries in the MDA5 group may be partly attributed to the shorter disease duration. Future studies should include disease duration-matched IIM subgroups to better compare NVC features. Moreover, NVC abnormalities have been reported in other conditions, such as connective tissue disease-ILD and interstitial pneumonia with autoimmune features, in addition to SSc and IIM, warranting further investigation in similar studies.

This study is the first to explore NVC features across different antibody subtypes of IIM and their relationships with ISG and cytokine profiles. We found significant differences in NVC patterns among MSA subgroups and revealed a significant correlation between NVC abnormalities and ISG and cytokine levels. These findings highlight the potential of NVC as a noninvasive tool to screen immune dysregulation and vascular changes in the IIM, with possible implications for disease monitoring and management.

Conclusions

IIM patients have different NVC patterns across different MSA subtypes. NVCs are significantly correlated with IFN activation and certain elevated cytokines/chemokines. This study suggests potential use of NVC as a noninvasive tool for screening vascular abnormalities, and ISG and cytokine/chemokine activation in IIM patients.

Abbreviations

ARS	Aminoacyl-tRNA-synthetase antibodies
ASS	Anti-synthetase syndrome
BMI	Body mass index
CADM	Clinically amyopathic dermatomyositis
CK	Creatine kinase
CRP	C-reactive protein
DM	Dermatomyositis
DMARD	Disease-modifying antirheumatic drug
EMG	Electromyogram
ESR	Erythrocyte sedimentation rate
IFN	Interferon
ILD	Interstitial lung disease
IIM	Idiopathic inflammatory myopathy
ISG	Interferon-stimulated gene
JDM	Juvenile dermatomyositis
MITAX	Myositis intention-to-treat activity index
MMT8	Manual muscle test
MSA	Myositis-specific antibody
MYOACT	Myositis disease activity assessment visual analogue scale
NVC	Nailfold videocapillaroscopy
PM	Polymyositis
RT–qPCR	Real-time quantitative PCR
SD	Standard deviation
SSc	Systemic sclerosis

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Author contributions

M.T. conducted the NVC evaluations, analyzed the data, and wrote the main manuscript. J.S. and Y.P.carried out the basic experiments. S.Z., C.W., J.L., and Q.W. enrolled patients and performed clinical evaluations. Q.W. also designed this study, and provided fundings. Q.W., M.L., and X.Z. supervised this study and revised the final manuscript. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Peking Union Medical College Hospital and conforms to the ethical guidelines of the 1975 Declaration of Helsinki (institutional review board approval number: JS-2038). Informed consent was obtained.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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