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Article type : Brief Report

## ***Arthritis & Rheumatology***

### *Brief Report*

# **Ulnar Artery Occlusion and severity markers of vasculopathy in Systemic sclerosis: a multicenter cross-sectional study**

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**Running heading:** ulnar artery occlusion and vascular parameters in SSc

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Systemic sclerosis, Scleroderma, Digital Ulcers, vasculopathy, Ulnar artery.

**Abstract**

**Objective:** to evaluate the association of ulnar artery occlusion (UAO) assessed by Doppler Ultrasonography (dUS) with the severity markers of systemic sclerosis (SSc)

**Methods:** 204 unselected patients fulfilling 2013 ACR/EULAR classification criteria for SSc were included in this cross-sectional multicenter study. All patients benefit from bilateral hand dUS evaluating the presence of UAO and clinical/paraclinical visceral evaluation according to current guidelines. Univariable and multivariable ordinal regression models were conducted, grading the severity of UAO as “no UAO”, “only one UAO” and “UAO on both hands” and assessing its association with clinical features of SSc.

**Results:** UAO was found in 76 patients (37.3%) and was bilateral in 49 (24.0%). UAO as an ordinal event was significantly associated with disease duration, history of fingertip ulcers, telangiectasia, higher Rodnan skin score, worse DLCO values, higher tricuspid jet velocity, late capillaroscopic pattern and positivity for anti-centromere antibodies (ACA) (univariable analysis). In the adjusted multivariable ordinal model, UAO was less frequent in women (OR=0.35 [0.15-0.83];  $p=0.017$ ) and in patients with steroids (OR=0.24 [0.09-0.62];  $p=0.0034$ ). Significant association with UAO was persistent in multivariable analyses for history of fingertip ulcers (OR=2.55 [1.24-5.21];  $p=0.011$ ), higher Rodnan skin score (OR=1.65 [1.06-2.56];  $p=0.025$ ), lower DLCO values (OR=0.85 [0.78-0.94];  $p=0.0015$ ) and positivity of ACA (OR=2.89 [1.36-6.11];  $p=0.0056$ ).

**Conclusion:** UAO may represent a relevant severity marker of the vasculopathy in SSc. Its predictive value for the onset of severe vascular manifestations such as pulmonary arterial hypertension and its association with mortality remain to be determined in longitudinal studies.

**Introduction**

Systemic sclerosis (SSc) is a rare chronic autoimmune disorder characterized by vascular hyper-reactivity and fibrosis of the skin and internal organs such as lungs (1). Microangiopathy is considered as the earliest pathological process in the pathogenesis of SSc. The natural history of SSc vasculopathy includes an early inflammatory phase characterized by perivascular infiltrates associated with a proliferation of endothelial cells, pericytes and vascular smooth muscle cells. The second phase is characterized by altered neo-angiogenesis and unbalanced compensatory vasculogenesis in response to chronic ischemia which is responsible for abnormal vascular remodeling (2). This fibroproliferation results in microvessel obliterations that underlie the main vascular complications of SSc such as ischemic digital ulcers (DU) and pulmonary arterial hypertension (PAH). The alteration of microvessels is considered as the hallmark of the disease but large vessels can also be involved. Ulnar artery is especially affected and up to 25% of SSc

patients may suffer from ulnar artery occlusion (UAO), a macrovascular feature which is far more frequent in SSc than in the general population (3,4). Biopsy samples of occluded ulnar arteries in SSc show circumferential luminal narrowing, media thickening and fragmentation of the internal elastic lamina leading to a total occlusion of the artery by an acellular material (5). The histological aspect of UAO is therefore concordant with the mechanisms underlying microangiopathy, suggesting that macrovascular involvement and vasculopathy of small vessels may represent the broad spectrum of the same vascular dysfunction in SSc.

In a recent review in *Arthritis & Rheumatology*, Allanore and colleagues called for an identification of a new vascular phenotype in SSc (2). They especially stressed the need for further studies to clarify whether there is a continuum between peripheral vasculopathy promoting DU and some other vascular-related complications of the disease (2). The accurate definition of an ischemic DU is still a matter of debate (6,7) and other mechanisms such as skin fibrosis, micro-traumatism or calcinosis may be involved in their pathogenesis. DU may therefore not be the most reliable vascular parameter in SSc. PAH and renal crisis are unquestionable vascular manifestations of SSc, but they remain less frequent than DU, limiting their direct use to easily sketch a uniform vascular phenotype. UAO is supposed to be directly linked to the vascular remodeling characterizing the disease. The value of UAO as a relevant severity marker of the general vasculopathy in SSc is still an issue (3). Previous studies addressing this question present several limitations in the literature: limited sample size precluding robust multivariable analyses, single-center studies with possible center bias, various definitions of UAO with different clinical and/or imaging techniques or heterogeneous inclusion criteria with most studies based on classifications older than the 2013 set of criteria (8).

The objective of this brief report was therefore to evaluate the association of UAO assessed by Doppler Ultrasonography (dUS) with the severity markers of the vasculopathy, through a large cross-sectional multicenter study within well-characterized populations of SSc patients fulfilling 2013 ACR/EULAR classification criteria.

## **Patients and Methods**

### *Patients*

Two-hundred and four unselected patients fulfilling ACR/EULAR 2013 classification criteria for SSc (8) were included in this multicenter observational cross-sectional study. This study was approved by local ethics committee (Approval number 15.09 and DC-2008-642) and complied with the French national requirements of the Commission Nationale Informatique et Liberté (CNIL). Non-opposition and informed consent were obtained from all patients.

### *Ultrasound evaluation*

The same trained operator performed all dUS evaluations in each center as previously described (3). Ulnar artery blood flow was measured on the wrist using a transverse view of the Guyon's canal including pisiform bone. UAO was defined as an abolition of blood flow assessed by dUS. Radial artery was also evaluated before its entry in the anatomical snuffbox, using a palmar longitudinal view. US measurements were performed using the MyLab™ Class C system

equipped with a 6-18 MHz linear-array probe in Rennes and a Philips HD15™ ultrasound system equipped with a 3-12 MHz linear-array probe in Lille.

#### *Clinical assessment*

Standard demographic, clinical and biological parameters were evaluated at the time of dUS, according to current guidelines. Echocardiography and pulmonary function tests were performed following standardized procedures (9) and 21 patients benefited from right heart catheterization (RHC) as defined by the ESC/ERC guidelines (10).

#### *Statistical methods*

A cross-sectional description of our population, by UAO status, was firstly conducted giving size (%) for categorical variables and mean  $\pm$  standard deviation or median (25<sup>th</sup> percentile, 75<sup>th</sup> percentile) for quantitative parameters. When deemed appropriate, quantitative parameters were natural-log transformed and standardized for Z-score calculation (Rodnan's score, NT-proBNP). We performed usual Fisher's exact test, ANOVA or Kruskal-Wallis test to compare the three different groups (no occlusion/unilateral/bilateral occlusion).

Assuming that bilateral UAO may constitute a more severe state of SSc macrovascular involvement than unilateral UAO, the whole information was exploited by keeping this parameter as ternary: no UAO vs unilateral vs bilateral, using multivariable ordinal regression model. Nominal and scale effects were individually tested for each variable. Initial candidates as independent parameters were age, sex, smoking history, center, SSc duration since first non-Raynaud's phenomenon symptom, DU history, telangiectasia, Rodnan's score, NT-proBNP, Diffusion capacity for carbon monoxide (DLCO), treatment by PDE5 inhibitors (IPDE5), steroids, diabetes mellitus, hypertension, dyslipidemia and positivity for anti-centromere antibodies (ACA). As Capillaroscopic evaluation was not systematically performed in all patients in this observational study, in order to conserve a large sample size, we did not integrate capillaroscopic findings in the multivariable analyzes. We finally proposed the multivariable models after backward/forward stepwise selection of the candidates, using an  $\alpha=0.05$  as the selective threshold. All analyses were performed using R software version 3.5.0 and the ordinal package.

## **Results**

#### *General clinical features*

Patients' clinical characteristics depending on their status for UAO are summarized in Table 1. The prevalence of UAO (one or both occluded) was 37.3%. UAO was bilateral in 49 patients (24,0%). Only one patient had radial artery occlusion. The following severity markers of vasculopathy differed significantly between patients with or without UAO: disease duration, history of DU, presence of skin telangiectasia, DLCO values, tricuspid regurgitant jet, right atrium area (RAA) $>15$  cm<sup>2</sup>, presence of a late capillaroscopic pattern and treatment by IPDE 5 (Table 1).

In the univariable logistic regression models (Supplementary Table 1 and 2), the association of bilateral UAO with PAH on RHC did not reach statistical significance (OR=2.82, 95%CI [0.82; 9.69],  $p=0.099$ ). Bilateral UAO was associated with higher NT-proBNP values (OR=1.45, 95%CI [1.04; 2.03],  $p=0.03$ ).

#### *Ordinal associations*

In univariable analysis (Table 2), UAO considered as ordinal event (“no occlusion/unilateral/bilateral occlusion”) was significantly associated with the following vascular parameters: history of fingertip DU, the presence of skin telangiectasia, late capillaroscopic pattern, lower DLCO values, higher TR jet velocity, treatment by IPDE5, and positivity for ACA.

In multivariable analysis (Table 3), UAO considered as an ordinal event was significantly associated with male gender, a history of fingertip DU, higher Rodnan skin score, lower DLCO values and ACA.

A history or a current treatment by steroids was protective for UAO both in univariable analysis and in multivariable ordinal regression models (Tables 2 & 3). This result persisted using logistic regression models in sensitivity analyses both on UAO (uni- or bilateral) and bilateral UAO (Supplementary Table 3).

#### **Discussion**

As the question of defining a new unified vascular phenotype is arising in SSc, the search for authentic and relevant new severity markers of the vasculopathy appears to be central. In this multicenter study, we highlighted the univariable association of UAO with key severity markers of vasculopathy such as the late capillaroscopic pattern according to Cutolo’s classification, the presence of skin telangiectasia, altered DLCO measures and the history of fingertip ischemic DU. Using a multivariable ordinal approach allowing us to grade the severity of UAO as “no UAO”, “only one UAO” and “UAO on both hands” in the same model, we pointed out new associations such as the association of UAO with ACA.

Interestingly, although we did not observe any significant association of UAO with PAH on RHC, UAO was associated with almost all available items included in the DETECT study, which has explored relevant clinical and biological parameters predicting the presence of PAH on RHC (9). Only higher uric acid levels were not associated with UAO in our work and data concerning the presence of right axis deviation on ECG were not evaluated in our study. Higher NT-proBNP values were associated with bilateral UAO in univariable analysis although only with a statistical trend in the ordinal regression model ( $p=0.085$ ). Taken together these considerations support the hypothesis that UAO and PAH may share some underlying mechanisms and may participate in drawing a common vascular profile. The absence of a significant association of UAO with PAH on RHC might be explained by a lack of statistical power, given the low prevalence of PAH in our study. This observational study was conducted in “real-world” conditions and according to the French recommendations for the management and detection of SSc-associated PAH. Therefore, all patients systematically benefited from echocardiography to

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detect signs of PAH as part of the routine assessment. The higher values of TR jet velocity in the UAO group and the association of a more frequent right atrium area above 15cm<sup>2</sup> with UAO may suggest that some patients with UAO could have undiagnosed PAH in this study. The risk of false negative of echocardiography does exist and the conditions of this study could not tackle this issue (9). The longitudinal follow-up of patients with UAO will shed light on this question and the predictive value of UAO in determining the future onset of PAH should be evaluated in longitudinal studies. The association of lower DLCO values with UAO also strengthened the relevance of UAO as a severity marker of SSc vasculopathy since there was no association of UAO with interstitial lung disease (ILD), highlighting that the mechanisms of the decreased DLCO in patients with UAO involved more likely pulmonary vasculopathy rather than lung fibrosis and/or ILD. As previously demonstrated, UAO was not associated with tobacco use, diabetes mellitus, hypertension or dyslipidemia (11). These results strengthened the hypothesis that UAO would be more likely the consequence of SSc associated endothelial dysfunction, rather than an arteriosclerotic process. Regarding vasculopathy, the association of UAO with fingertip DU is also consistent with all previous studies from other teams, in single-center studies assessing this association (11,12). We only included fingertip DU considering that this localization may more accurately reflect an ischemic origin. However, recent studies question the relevance of such hypothesis, arguing that all types of DU may have a part of ischemic etiology (6). This is one of the limitations of our study. A global assessment of all types of DU may offer new perspectives in the future. Nonetheless, our work strengthens the message of previous studies suggesting the need for assessing macrovascular hand involvement in patients with DU in SSc (11,12). As UAO seemed to be more frequent in one center (Rennes) in univariable analysis, we included the center in the multivariable models to limit a center effect in our results. Capillaroscopic evaluation was not systematically performed in all patients in this observational study. Consequently, due to missing data and in order to conserve a large sample size, we did not integrate capillaroscopic findings in the multivariable models. This is one limitation of our study, but capillaroscopic evaluation was included in the univariable models.

Two other main results arise from the multivariable ordinal approach. Firstly, the ordinal association of UAO and ACA has never been reported to date. This consideration concerning antibodies also strengthens a possible common vascular profile of patients with PAH and UAO, as an association of PAH and ACA has been reported in several nationwide registries (2,13). Functional antibodies such as anti-endothelial antibodies (i.e. Anti-ETAR antibody or Anti-AT1R antibody) were not evaluated in our work. The association of such antibodies with UAO has already been evaluated before in a single center study in 79 patients with SSc (11). This study did not find any association of UAO with functional antibodies but found a trend towards an association of UAO with ACA ( $p=0.108$ ) and a possible protective value of anti-Topoisomerase I antibodies ( $p=0.075$ ) (11). Our result concerning ACA is consistent with these data and is all the more robust since, besides the univariable and multivariable analyses presented, it persisted in sensitivity analyses with usual multivariable logistic regressions, especially for bilateral UAO (see Supplementary Table 2 for detail). Large observational studies have suggested that the natural history of DU in patients with ACA or anti-Topoisomerase I antibodies might not be the same, DU occurring more lately in anti-centromere positive patients (14,15). This hypothesis is concordant with our results since UAO tended to be associated with longer disease duration in our study, supporting this concept of late vascular complications in ACA positive patients, and

more frequent and early complications in patients with anti-Topoisomerase I antibodies. In our study, disease duration was based on the first non-RP symptom, which is considered as the most consensual way of calculating the duration of SSc. A disease duration based on RP occurrence may offer new insights, since for some authors, this may serve as a better marker for duration of vascular disease. Nonetheless, in order to stay comparable with the vast majority of the literature, first non-RP symptom was considered as the beginning of the disease in our work. The precise links between UAO occurrence and the natural history of the vasculopathy therefore needs to be further explore in longitudinal studies, especially including patients with early SSc.

Another interesting result is the inversed association of UAO with the current or previous use of steroid therapy, which is also steady in sensitivity analyses, suggesting a possible protective effect of steroids on the development of UAO. The first hypothesis would be that steroids are prescribed to patients with early dcSSc or patients with ILD, and that these specific indications might appear as confounding factors. Nonetheless, there was no positive or negative association of dcSSc or ILD with UAO in our work, and the result on the possible protective value of steroids on UAO persisted in the multivariable ordinal regression after adjustment on such confounding factors. Some authors have suggested that immunosuppressive strategies might have their place in the management of SSc vasculopathy in the future. Immunosuppressive strategies may indeed be relevant at the early inflammatory stage of SSc vasculopathy (2). However, considering the cross-sectional design of our study, we cannot assert any causality between steroids use and this lower prevalence of UAO. This result should be interpreted with extreme caution and only longitudinal studies, evaluating UAO before the beginning of steroids and assessing the risk of UAO occurrence could properly address this question.

Beyond the issue of a unified vascular profile in SSc, the exact place of macrovascular involvement and, more specifically, of UAO in the management of DU treatment strategy is still to determine. US is a non-invasive, non-irradiating, easy to use and widely accessible tool. Quantitative US parameters such as resistive indices of ulnar or radial arteries may also improve hand artery evaluation in SSc. Although there is still a need to standardize and further evaluate the validity of US macrovascular evaluation of the hand according to the OMERACT filter (16), promising early results of therapeutic pilot studies involving the presence of UAO in their inclusion strategies may help to better set the place of these macrovascular features of SSc in the future (17).

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**Table 1. Characteristics of the population according to OAU status: none, unilateral or bilateral. n=204**

OAU status	None occluded n <sub>1</sub> = 128	One occluded n <sub>2</sub> = 27	Both occluded n <sub>3</sub> = 49	p-value	Pop. Size (n <sub>1</sub> /n <sub>2</sub> /n <sub>3</sub> )
<b>Clinical features</b>					
Sex (female)	103 (80.5 %)	21 (77.8 %)	34 (69.4 %)	0.29	NMD
Age (years)	54.5 (46-66)	62 (54-71)	62 (56-68)	<b>0.0053</b>	NMD
Smoking (current or past)	48 (37.5 %)	14 (51.9 %)	17 (34.7 %)	0.32	NMD
Diabetes mellitus	4 (3.1 %)	0 (0 %)	3 (6.1 %)	0.52	NMD
Hypertension	35 (27.3 %)	5 (18.5 %)	14 (28.6 %)	0.62	NMD
Dyslipidemia	26 (20.3 %)	5 (18.5 %)	15 (30.6 %)	0.31	NMD
Disease duration since first non-RP symptom (years)	3 (0.8-10)	6 (3-11)	6 (4-17)	<b>0.0042</b>	NMD
Diffuse cutaneous SSc	37 (28.9 %)	10 (37 %)	15 (30.6 %)	0.70	NMD
History of digital ulcer	46 (35.9 %)	19 (70.4 %)	34 (69.4 %)	<b>&lt;0.0001</b>	NMD
Active digital ulcer	17 (13.4 %)	9 (33.3 %)	11 (22.4 %)	<b>0.034</b>	127/27/49
Interstitial lung disease	49 (38.3 %)	12 (44.4 %)	20 (40.8 %)	0.82	NMD
Renal crisis	4 (3.1 %)	0 (0 %)	0 (0 %)	0.61	NMD
Skin telangiectasia	86 (67.2 %)	21 (77.8 %)	42 (85.7 %)	<b>0.04</b>	NMD
Rodnan's skin score <sup>a</sup> (Z-score)	-0.2 ± 1.1	0.3 ± 0.8	0.3 ± 0.8	<b>0.0034</b>	126/27/49
<b>Biology</b>					
NT-proBNP <sup>a</sup> (Z-score)	-0.1 ± 1.0	-0.2 ± 0.7	0.3 ± 1.2	0.079	116/26/43
Uric acid (mg/L)	50.4 ± 17.2	51.3 ± 12.1	56.3 ± 20.0	0.15	117/24/45
Creatinine (mg/L)	8.4 ± 6.2	8.1 ± 1.5	8.5 ± 1.9	0.94	124/27/48
<b>Cardiopulmonary metrics</b>					
PAH on RHC ( <i>n/n RHC (% on the entire population)</i> )	6/9 RHC (4.7 %)	0/5 RHC (0 %)	5/7 RHC (10.2 %)	0.16	(128/27/49)
DLCO (% predicted)	66 ± 17.5	57.6 ± 18.5	56.4 ± 18.3	<b>0.0028</b>	120/24/48
TR jet velocity (m.s <sup>-1</sup> )	<b>2.6 ± 0.5</b>	<b>2.7 ± 0.4</b>	<b>2.8 ± 0.5</b>	<b>0.043</b>	<b>88/20/34</b>
LVEF (%)	65 (60-65)	65 (60-65)	65 (60-65)	0.18	119/25/46
RAA > 15 cm <sup>2</sup>	29 (31.5 %)	4 (19 %)	18 (50 %)	<b>0.044</b>	92/21/36
RAA > 18 cm <sup>2</sup>	12 (13 %)	1 (4.8 %)	7 (19.4 %)	0.32	92/21/36
<b>Capillaroscopy</b>					
Abnormal	87 (88.8 %)	17 (85 %)	35 (92.1 %)	0.65	98/20/38
Early pattern	21 (21.4 %)	2 (10 %)	3 (7.9 %)	0.13	98/20/38
Active pattern	50 (51 %)	7 (35 %)	12 (31.6 %)	0.084	98/20/38
Late pattern	16 (16.3 %)	8 (40 %)	20 (52.6 %)	<b>&lt;0.0001</b>	98/20/38
<b>Treatments<sup>#</sup></b>					
IS <sup>#</sup>	34 (26.6 %)	7 (25.9 %)	10 (20.4 %)	0.69	NMD
Platelet-lowering agents	43 (33.6 %)	9 (33.3 %)	17 (34.7 %)	1	
Anticoagulants	11 (8.6 %)	0 (0 %)	7 (14.3 %)	0.084	
Calcium channel blockers	82 (64.1 %)	18 (66.7 %)	34 (69.4 %)	0.81	
Bosentan	16 (12.5 %)	6 (22.2 %)	10 (20.4 %)	0.24	
IPDE 5	3 (2.3 %)	1 (3.7 %)	6 (12.2 %)	<b>0.023</b>	
IPDE 5 and/or Bosentan	17 (13.3 %)	6 (22.2 %)	10 (20.4 %)	0.30	
Steroids <sup>#</sup>	48 (37.5 %)	7 (25.9 %)	8 (16.3 %)	<b>0.017</b>	
Steroids and/or IS <sup>#</sup>	55 (43 %)	8 (29.6 %)	13 (26.5 %)	0.093	
<b>Antibodies</b>					
Anti-centromere	52 (40.6 %)	11 (40.7 %)	33 (67.3 %)	<b>0.0049</b>	NMD
Anti-Topoisomerase I	35 (27.3 %)	11 (40.7 %)	10 (20.4 %)	0.16	
Anti-RNA polymerase III	8 (6.2 %)	1 (3.7 %)	0 (0 %)	0.22	

Results with  $p < 0.05$  are highlighted in bold

DLCO, Diffusion capacity for carbon monoxide; IPDE 5, Inhibitor of phosphodiesterase type 5; IS, immunosuppressive therapy; LVEF, Left Ventricular Ejection Fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NMD, no missing data; PAH, Pulmonary Arterial Hypertension; PASP, Pulmonary artery systolic pressure; RAA, Right Atrium Area; RP, Raynaud's phenomenon; SSc, Systemic sclerosis; TR, tricuspid regurgitant jet. <sup>a</sup>Natural log-transformed <sup>#</sup>All treatments are presented as "current treatment at the time of US evaluation", only steroids and IS are recorded as "current or history of treatment by steroids and/or IS".

**Table 2. Association between clinical and biological parameters and UAO (Ordinal event “no occlusion/unilateral/bilateral occlusion” as dependent parameter)**

	Univariate ordinal regression model		
	Data available	OR (95% CI)	<i>p</i> -value
<b>Clinical features</b>			
Sex (Female/Male)	204	0.61 [0.32; 1.17]	0.14
Age (+1 year)	204	<b>1.03 [1.01; 1.06]</b>	<b>0.0018</b>
Smoking history (y/n)	204	1.04 [0.59; 1.83]	0.90
Diabetes mellitus (y/n)	204	1.67 [0.36; 7.79]	0.51
Hypertension (y/n)	204	0.95 [0.50; 1.80]	0.88
Dyslipidemia (y/n)	204	1.51 [0.79; 2.90]	0.21
Centre (Rennes/Lille)	204	<b>2.13 [1.21; 3.76]</b>	<b>0.0092</b>
Duration (Z-score, +1 SD)	204	<b>1.66 [1.23; 2.24]</b>	<b>0.0010</b>
Diffuse SSc (y/n)	204	1.15 [0.63; 2.08]	0.65
History of digital ulcer (y/n)	204	<b>3.84 [2.12; 6.95]</b>	<b>&lt;0.0001</b>
Active digital ulcer (y/n)	203	1.93 [0.99; 3.78]	0.054
Interstitial lung disease (y/n)	204	1.14 [0.65; 2.00]	0.65
Telangiectasia (y/n)	204	<b>2.42 [1.21; 4.84]</b>	<b>0.012</b>
Rodnan skin score <sup>a</sup> (Z-score, +1 SD)	202	<b>1.67 [1.23; 2.27]</b>	<b>0.0011</b>
<b>Biology</b>			
NT-proBNP <sup>a</sup> (Z-score, +1 SD)	185	1.30 [0.96; 1.76]	0.085
Uric acid (+1 mg/L)	186	1.02 [1.00; 1.03]	0.073
Creatinine (+1 mg/L)	199	1.00 [0.94; 1.06]	0.97
<b>Cardiopulmonary metrics</b>			
DLCO (+5% predicted)	192	<b>0.87 [0.80; 0.95]</b>	<b>0.001</b>
TR jet velocity (m.s <sup>-1</sup> )	142	<b>2.27 [1.16; 4.42]</b>	<b>0.016</b>
<b>Capillaroscopy (y/n)</b>			
Early pattern	156	<b>0.35 [0.12; 0.97]</b>	<b>0.044</b>
Active pattern	156	<b>0.47 [0.24; 0.92]</b>	<b>0.027</b>
Late pattern	156	<b>4.60 [2.29; 9.26]</b>	<b>&lt;0.0001</b>
<b>Treatments (y/n)</b>			
IS <sup>#</sup>	204	0.78 [0.4; 1.49]	0.44
Platelet-lowering agents	204	1.03 [0.58; 1.86]	0.91
Calcium channel blockers	204	1.22 [0.68; 2.21]	0.50
IPDE 5	204	<b>4.88 [1.36; 17.52]</b>	<b>0.015</b>
IPDE 5 and/or Bosentan	204	1.64 [0.80; 3.36]	0.17
Steroids <sup>#</sup>	204	<b>0.40 [0.21; 0.77]</b>	<b>0.0063</b>
Steroids and/or IS <sup>#</sup>	204	<b>0.51 [0.28; 0.93]</b>	<b>0.029</b>
<b>Antibodies (y/n)</b>			
Anti-centromere	204	<b>2.24 [1.28; 3.94]</b>	<b>0.005</b>
Anti-Topoisomerase I	204	0.89 [0.48; 1.65]	0.71

Results with  $p < 0.05$  are highlighted in bold

DLCO, Diffusion capacity for carbon monoxide; IPDE 5, Inhibitor of phosphodiesterase type 5; IS, immunosuppressive therapy; LVEF, Left Ventricular Ejection Fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NMD, no missing data; PAH, Pulmonary Arterial Hypertension; PASP, Pulmonary artery systolic pressure; SSc, Systemic sclerosis; TR jet, tricuspid regurgitant jet

<sup>a</sup> Natural log-transformed <sup>#</sup> All treatments are presented as “current treatment at the time of US evaluation”, only steroids and IS are recorded as “current or history of treatment by steroids and/or IS”.

**Table 3. Association of clinical and biological parameters with UAO, modeled as an ordinal parameter. Ordinal regression models, univariable and multivariable approaches. n=175<sup>a</sup>**

	Univariable approach		Adjusted model	
	OR [95% CI]	<i>p</i> -value	OR [95% CI]	<i>p</i> -value
Sex (Female/Male)	0.52 [0.26-1.07]	0.075	<b>0.35 [0.15-0.83]</b>	<b>0.017</b>
History of digital ulcer (y/n)	1.60 [0.73-3.52]	0.24	<b>2.55 [1.24-5.21]</b>	<b>0.011</b>
Rodnan skin score (Z-score, +1 SD)	<b>1.60 [1.14-2.24]</b>	<b>0.0070</b>	<b>1.65 [1.06-2.56]</b>	<b>0.025</b>
DLCO (+5% predicted)	<b>0.88 [0.80-0.95]</b>	<b>0.0021</b>	<b>0.85 [0.78-0.94]</b>	<b>0.0015</b>
History or current treatment with steroids (y/n)	<b>0.40 [0.19-0.82]</b>	<b>0.013</b>	<b>0.24 [0.09-0.62]</b>	<b>0.0034</b>
Anti-centromere antibodies (y/n)	<b>2.23 [1.21-4.10]</b>	<b>0.010</b>	<b>2.89 [1.36-6.11]</b>	<b>0.0056</b>

Results with  $p < 0.05$  are highlighted in bold.

CI: Confidence interval; DLCO, Diffusion capacity for carbon monoxide; IPDE 5, Inhibitor of phosphodiesterase type 5; NT-proBNP, N-terminal pro-brain natriuretic peptide; OR: odds-ratio; SSc, Systemic sclerosis, UAO : Ulnar Artery Occlusion

<sup>a</sup> Analyses performed on the population without missing data for all potential confounding parameters selected: sex, age, center, smoking history, duration of SSc, history of digital ulcer, telangiectasia, Rodnan's score, DLCO, NT-proBNP value, treatment by IPDE5, history or current treatment by steroids, diabetes mellitus, hypertension, dyslipidemia and anticentromere antibodies.