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Undifferentiated connective tissue disease at risk of systemic sclerosis: A weighted score to identify patients who will evolve

Undifferentiated connective tissue disease at risk of SSc (UCTD-risk-SSc) [1], otherwise referred to as very early-early SSc [2] is a condition charactherised by Raynaud's phenomenon (RP) and either SSc marker autoantibodies or distinct capillaroscopic alterations or both [2]. This condition has been reported to evolve into SSc satisfying ACR/EULAR criteria [3] in 50% of cases [4]. At present, it remains to be established how to predict such evolution.

In order to address this topic, 102 UCTD-SSc-risk patients unfulfilling at admission the 2013 ACR/EULAR classification criteria [3] neither presenting any manifestation indicative of SSc sine scleroderma [5] were prospectively enrolled from November 1st, 2000 and followed up, as previously outlined [4] for 1–12 years (median 3 years) to December 31st, 2017. Out of them, 96 were females; the median age at admission was 44 years (range 16–73); the median disease duration from RP was 3 years (range 1–31). At baseline, 72 were IF-ANA positive; 65 presented a serum SSc marker autoantibody (16 anti-Scl70, 46 anticentromere; 2 anti-Th/To; 1 anti-Pm-Scl); 81, at nailfold videocapillaroscopy, showed megacapillaries only; 3 of them also had avascular areas; 33 were found to have a DLCO < 80% of predicted value, indicative of preclinical lung involvement; 21 an inverted E/A ratio, indicative of preclinical heart involvement [4]; any of these alterations being detected in 49.

During follow-up, 46/102 patients evolved to definite SSc. At Cox regression univariate analysis, a baseline IF-ANA titer ≥1: 320 (HR 9.69; 95% CI 3.01–31.17; $p = .0001$), anti-Scl-70 positivity (HR 2.92; 95% CI 1.52–5.63; $p = .001$), ACA positivity (HR 2.27 95% CI 1.23–4.18; $p = .008$), presence of avascular areas as detected by videocapillaroscopy (HR 4.45; 95% CI 1.35–14.63; $p = .01$), and preclinical heart and/or lung involvement (HR 1.91; 95% CI 1.06–3.45; $p = .03$) were found to significantly predict evolution to SSc. Interestingly, none of the 30 ANA-negative patients of the 37 diagnosed as UCTD-risk-SSc because of the presence of megacapillaries evolved to definite SSc versus 2 of the 7 ANA-positive patients ($p = .03$).

Table 1 shows the variables that predicted evolution to definite SSc and the relative weight that we assigned to each of them on a 10-point scale depending on the respective β values. Fig. 1 shows the results of the ROC analysis conducted to identify the score with the highest sensitivity and specificity. A score > 2.75 predicted evolution to SSc in patients affected by UCTD-risk-SSc with a sensitivity of 91.3% (< 1 of 10 patients who would evolve to SSc would not be captured) and a 73.2% specificity (about 3 of 10 non-evolving patients would be considered at risk of evolution). Notably, a score of 4.25 (i.e., ANA ≥1:320 plus ACA positivity) had a specificity as high as 100%.

Table 1
Indipendent predictors of evolution into definite SSc based on multivariate regression. Relative weight in a 10-point score as derived by the respective regression coefficient[a]

Variable	B	HR	95% CI	*P*	Weight
Anti-Scl70	2.4484	11.57	3.12–42.88	0.0003	3
ANA ≥1:320	1.9359	6.93	1.81–26.51	0.0049	2.75
Avascular areas	1.6166	5.03	1.36–18.59	0.0158	2.25
ACA	1.3672	3.92	1.13–13.59	0.0319	2

[a] β: regression coefficients; ANA: anti-nuclear antibodies; HR: hazard ratio; 95% CI: 95% confidence interval;ACA: anti-centromere antibodies.

Predicting which patients with UCTD-risk-SSc (very-early SSc) will evolve to definite SSc has long been a challenge [6]. Actually, given the lack of definite predictive criteria of evolution to SSc, Bellando Randone and Matucci Cerinic [7] stated that the only feasible clinical strategy in very early SSc is to enroll patients in a strict follow-up program to detect early internal organ involvement in "real time", in order to start an aggressive therapeutic approach.

Here, we describe a 10-point score based on features that are easily identified at admission and predicts evolution to full-blown SSc. Although awaiting validation by studies conducted in other prospective cohorts, the score identified by us can help clinicians in their everyday approach to the patient with UCTD-risk-SSc (very early/early SSc).

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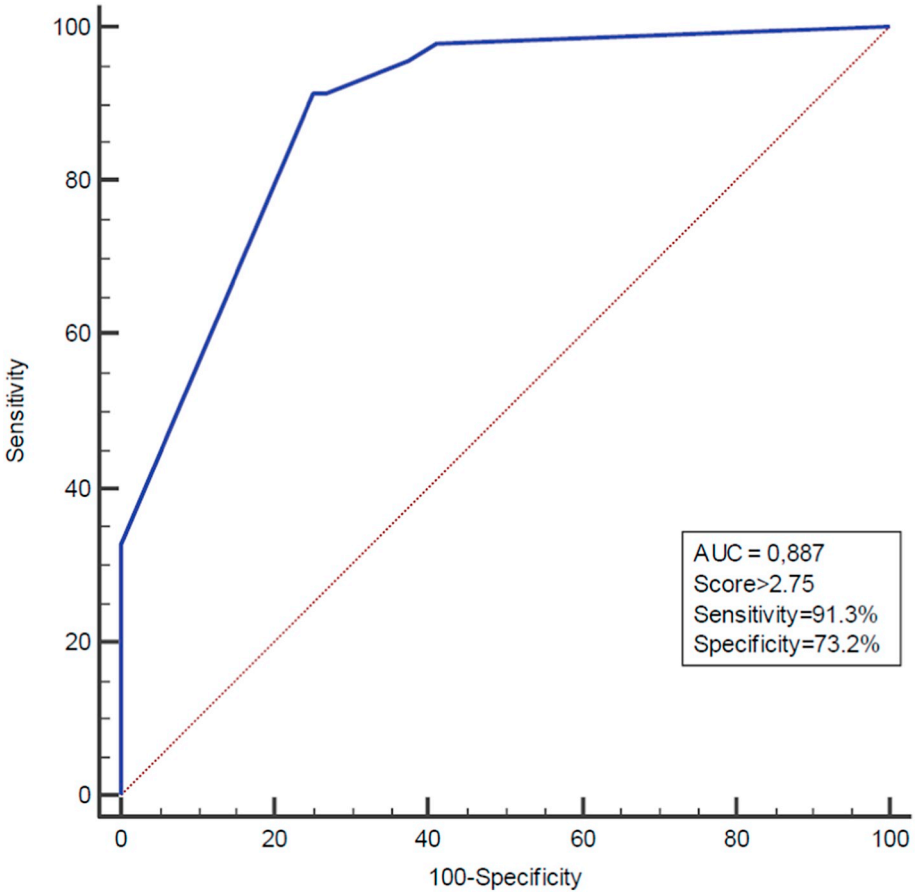

Fig. 1. ROC analysis identify the score with the highest sensitivity and specificity. A score > 2.75 predicted evolution to SSc in patients with UCTD-risk-SSc with 91.3% sensitivity and 73.2% specificity.

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Authors' contributions

AR and AM recruited patients, collected the clinical data and performed the statistical analysis; AB, TG, FB, SF, RI, VM helped with data collection. AS, MB, AC, MD, PA, GMDM, ASp interpreted the data and revised the manuscript. GV designed, coordinated, supervised the study, and wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the University of Campania "L. Vanvitelli" Ethics Committee and by the ASL Roma B Ethics Committee. All enrolled patients consented to attend this cohort signed written.

Consent for publication

Consent for publication has been obtained from all participants.

Declarations of conflicts of interest

None.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Antonella Riccardi[a], Antonella Marcoccia[b], Alessia Borgia[a], Tiziana Guastafierro[b], Francesco Bondanini[b], Serena Fasano[a], Rosaria Irace[a], Valentina Messiniti[a], Alessandro Sanduzzi[c], Marialuisa Bocchino[c], Aldo Ciani[b], Michele D'Alto[c], Paola Argiento[c], Giovanni Maria De Matteis[b], Alberto Spanò[b], Gabriele Valentini[a,*]
[a] *Rheumatology Unit, Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy*
[b] *Centro di Riferimento Interdisciplinare, Interdipartimentale per la diagnosi precoce della Sclerodermia, Sandro Pertini Hospital, Rome, Italy*
[c] *Pneumology and Cardiology Units, Monaldi Hospital, Naples, Italy*
E-mail address: gabriele.valentini@unicampania.it (G. Valentini).

* Corresponding author at: Rheumatology Unit, Department of Precision Medicine, University of Campania "Luigi Vanvitelli", via Sergio Pansini 5, 80131 Naples, Italy.