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A composite biomarker score to predict modified Rodnan skin score in systemic sclerosis: insight from autologous stem cell transplantation international scleroderma trial

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Abstract

Background Skin fibrosis is a cardinal manifestation of systemic sclerosis (SSc) and is routinely measured by modified Rodnan skin score (mRSS), which is however limited by its operator-dependence and may not reflect the complex disease biology at the cutaneous compartment. A recent high dimensional multi-omic analysis identified 3 serum proteins independently associated with mRSS: tenascin C (TENC), cartilage oligomeric matrix protein (COMP), and collagen type IV alpha 1 (COL4A1). The aim of our study was to evaluate the relationship between these analytes as cross-sectional and dynamic biomarkers for skin involvement, as well as to capture potential correlations with type of immunosuppressive treatment.

Methods We selected 21 patients from 2 Dutch centres who participated in the Autologous Stem Cell Transplantation International Scleroderma trial - a phase 3, multicentre, randomized study comparing autologous stem cell transplantation (HSCT) to cyclophosphamide (CYC) in diffuse cutaneous (dc)SSc. Serum concentrations of the three analytes were measured with ELISAs at baseline, 12 and 24 months. We employed linear mixed-effects models to assess cross-sectional correlation between mRSS, analyte concentrations and time. A multivariable linear regression model (independent of time) was used to formulate a composite biomarker score to predict mRSS.

Results There were 11 patients in the CYC arm, and 10 to the HSCT arm. Serum concentrations of COMP and COL4A1, but not TENC, showed significant correlation with mRSS at the mixed model; COL4A1 correlation with mRSS remained significant at multivariable analysis ($\beta = 0.01$, $p = 0.001$). We derived a composite biomarker formula score to predict mRSS with good performance at Bland Altman plot. As dynamic biomarkers, only changes in concentrations of COMP were associated with mRSS change ($r = 0.013$; $p = 0.012$). It is notable that there was greater reduction in COL4A1 concentration at 24 months in the HSCT group compared with CYC (-81 ng/mL vs. -27.4 ng/mL in CYC group; $p = 0.029$).

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Conclusion Our composite biomarker score showed a moderate cross-sectional correlation with mRSS and potentially complement mRSS in the assessment of skin activity. The differential variations for serum COL4A1 across treatment groups warrant further evaluation as a predictive marker of immunotherapeutic response in dcSSc.

Keywords Systemic sclerosis, Diffuse cutaneous systemic sclerosis, Skin fibrosis, Modified rodnan skin score, Stem cell transplantation, Cyclophosphamide, Biomarker

Introduction

Skin fibrosis is a cardinal manifestation of systemic sclerosis (SSc) and is measured by the modified Rodnan skin score (mRSS). This semi-quantitative score is routinely used in clinical practice to assess disease severity and response to treatment, and mRSS is a frequent outcome in clinical trials of diffuse cutaneous (dc)SSc [1]. However, mRSS has limitations, being operator-dependent and grading skin involvement only based on skin thickening, rather than capturing the various alterations that can be present in the cutaneous compartment.

Recent studies have harnessed growing understanding of pathophysiology of SSc skin and to identify circulating biomarkers that correlate with mRSS, aiming to discover additional or improved tools to quantify skin involvement in clinical practice. A recent high dimensional multi-omic analysis carried out in a well characterized SSc cohort (BIOlogical Phenotyping of diffuse SYstemic sclerosis - BIOPSY -cohort) identified four serum proteins independently associated with mRSS and with earlier and more severe SSc phenotypes [2]. These proteins were tenascin C (TNC), cartilage oligomeric matrix protein (COMP), collagen type IV alpha 1 (COL4A1), and spondin 1 (SPON1). Integrating the normalized plasma protein expression values of the four analytes, a composite score to predict mRSS was derived, with a statistically significant correlation between predicted and actual mRSS [2]. Further, Roblin et al. explored a composite score using the same four proteins whose serum concentrations were measured by commercially available enzyme-linked immunosorbent assays (ELISA). For this study, the same BIOPSY cohort and a new validation cohort, the Molecular Determinants to Improve Scleroderma (SSc) treatment (MODERNISE), were employed [3]. Due to technical difficulties in measuring its concentration, SPON1 was not included in the derived composite score, which comprised TENC, COMP and COL4A1 [3]. Whilst there was correlation of the composite marker and its components with mRSS, and some association with underlying treatment, the results of this study were inconclusive, potentially due to the limited variability in mRSS and modest impact of standard immunosuppressive treatment in the included cohorts [3].

We designed this study using the same approach in an independent cohort from the ASTIS trial – a phase 3, multicentre, randomized study comparing autologous stem cell transplantation (HSCT to cyclophosphamide (CYC) in dcSSc patients – characterized by a greater range of mRSS and high percentage of patients receiving intense immunosuppressive treatment. The aim of our study was to evaluate the relationship between the serum concentration of the analytes as cross-sectional and dynamic biomarkers for skin involvement in this cohort, as well as to determine potential correlations with type of immunosuppressive treatment.

Methods

Cohort

We selected patients from two Dutch centres who participated in the ASTIS trial (Leiden University Medical Centre and Amsterdam University Medical Centre). Inclusion criteria are for ASTIS trial are presented elsewhere [4]. In short, patients of 18 to 65 years of age with dcSSc and maximum disease duration of 4 years were included, with minimum mRSS of 15, and involvement of heart, lungs, or kidneys with no major organ dysfunction. The protocol for HSCT comprised the initial mobilization with CYC and CD34 + cells harvesting, with subsequent conditioning regimen with CYC and anti-thymocyte globulin, followed by CD34 + cells reinfusion. Patients in the CYC treatment group received 12 monthly CYC pulses [4].

All the sera were collected upon obtaining written informed patient consent during time of ASTIS trial enrolment. Collected sera were aliquoted and stored at − 80 °C and subsequently shipped to Centre for Rheumatology, Royal Free UCL for the experiments. For all patients, samples at baseline, 12 months and 24 months after randomisation were available. This study was done in compliance with the Declaration of Helsinki [5].

ELISA

Concentrations of candidate proteins were determined using commercial ELISA kits from Cusabio (Houston, TX, USA) for COL4A1 (CSB-EL005741HU: 1:100 dilution), R&D Systems (Minneapolis, MN, USA) for COMP (DCMP0: 1:100 dilution), Abcam (Cambridge, UK) for TNC (ab213831: 1:200 dilution). Protein concentrations were measured at baseline, 12 months and 24 months for all samples. Two 96-wells plates were used for each analyte, and each sample was run in duplicate, including standards. The researcher who performed the experiments (SR) was blinded from clinical and treatment data until completion of the assays.

Statistical analysis

All statistical analyses were performed with STATA-18 software package. Continuous variables were expressed as median and interquartile range (IQR), while categorical variables were expressed as frequencies. Comparison between continuous variables was done through Mann-Whitney or Kruskal-Wallis test, as appropriate, while comparison between categorical variables was done through Fisher exact test. We employed linear mixed-effects models to test for cross-sectional correlation between mRSS (dependent variable), target analyte concentrations and time (independent variables), including their fixed effects. We tested an interaction term between time and the different analytes; as it was not statistically significant, it was not retained in the final model. A multivariable linear regression model (independent of time) was used to formulate a new composite biomarker score to predict mRSS, and Bland Altman plot was employed to determine the agreement between the predicted mRSS and the actual mRSS. Ramsey Regression Equation Specification Error Test (RESET) was employed to test for nonlinearity. Univariable linear regression and Spearman's test were used to visualize cross-sectional correlation between target analyte and mRSS and to test for dynamic correlation of target analyte's serum concentration (independent variable) and mRSS (dependent variable), accounting for differences in serum concentration and in mRSS between baseline and 12 months and baseline and 24 months. A p value < 0.05 was considered statistically significant. Visualization of linear regressions, dot plots, and Bland Altman plot were done with GraphPad PRISM software.

Table 1 Demographic and clinical characteristics of the cohort stratified per treatment group

	CYC group ($n=11$)	HSCT group ($n=10$)	Total ($n=21$)	*P* value*
Male sex (%)	3 (27%)	4 (40%)	7 (33.3%)	0.659
Median age at baseline (years, IQR)	48 (44–56)	48 (40–53)	48 (41–55)	0.291
Median disease duration (months, IQR)	12 (9–23)	8 (4–22)	10 (5–25)	0.526
Scl70 positivity (%)	10 (90.1%)	6 (60%)	16 (76.2%)	0.149
History of smoking (%)	10 (90.1%)	3 (30%)	13 (62%)	0.024
Previous cyclophosphamide (%)	2 (18.2%)	3 (30%)	5 (23.8%)	0.635
ILD (%)	8 (72.7%)	10 (100%)	18 (85.7%)	0.214
PH (%)	0	0	0	1
Cardiac involvement	1 (9.1%)	1 (10%)	2 (9.5%)	1
Renal involvement	1 (9.1%)	1 (10%)	2 (9.5%)	1
Median mRSS at baseline (IQR)	21 (18.5–26.5)	18 (16–30)	21 (16–29)	0.596
mRSS at 12 months	16 (11.5–22)	8.5 (6.25–11.5)	12 (7–16)	0.048
mRSS at 24 months	8 (4.5–19.5)	5 (0.5–6)	6 (2–12)	0.117
FVC (% predicted) at baseline	84 (75–93.5)	77 (72.5–86)	83 (72–90)	0.503
FVC (% predicted) at 12 m	86 (76–102.5)	84 (79.8–73)	86 (78–102)	0.986
FVC (% predicted) at 24 m	88 (76.5–93.5)	86.5 (74.3–102.5)	88 (75–98)	0.877

CYC Cyclophosphamide, *HSCT* Hematopoietic stem cell transplant, *ILD* Interstitial lung disease, *PH* Pulmonary hypertension, *mRSS* modified Rodnan skin score, *FVC* Forced vital capacity

*Referred to the comparison between the two treatment groups

Results

Patient characteristics

The study cohort was composed of 21 patients, 14 (66.7%) of whom were females, and 18 (85.7%) with positive Scl70 antibodies. Median age at baseline was 48 years (IQR 41–55), with a disease duration at baseline of 10 months (IQR 5–25). Ten patients were treated with HSCT, and 11 received treatment with twelve monthly cyclophosphamide (CYC) pulses. The demographic, clinical and treatment characteristics of the cohort, stratified by treatment group, are depicted in Table 1. There was a marked decrease in mRSS over time in both groups, with a median baseline mRSS of 21/51, decreasing to 12/51 at 12 months and to 6/51 at 24 months in the whole group ($N=21$).

Performance as cross-sectional biomarkers

We first evaluated the individual biomarkers as cross-sectional predictors of mRSS, including all the 3 timepoints (i.e. baseline, 12 months and 24 months), using a linear mixed-effect model.

Median serum TENC concentration were 74 ng/mL (51.5–84.7) at baseline, 46.3 ng/mL (38.3–62.7) at 12 months and 54.8 ng/mL (36.3–62.7) at 24 months. TENC did not show a statistically significant correlation with mRSS ($\beta=0.04$, 95% confidence interval [CI] −0.05–0.14; $p=0.362$).

Median serum COMP concentrations were 765 ng/mL (457–1157) at baseline, 604ng/mL (518–934) at 12 months, 622 ng/mL (505–865) at 24 months. Serum COMP concentrations showed a significant correlation with mRSS ($\beta=0.01$, 95% CI 0.001–0.02; $p=0.026$).

Median serum COL4A1 concentrations were 128 ng/mL (107–184) at baseline, 80 ng/mL (65–121) at 12 months, and 84 ng/mL (66–130) at 24 months. Serum COL4A1 concentrations showed a significant correlation with mRSS ($\beta=0.07$, 95% CI 0.02–0.11; $p=0.007$). Figure 1 shows the univariable linear regression of the three analytes considering all timepoints.

At the multivariable analysis, correlation between COL4A1 and mRSS retained statistical significance ($\beta=0.06$; 95% CI 0.003–0.11; $p=0.036$) while COMP lost its statistical significance ($\beta=0.01$; 95% CI −0.001–0.013;

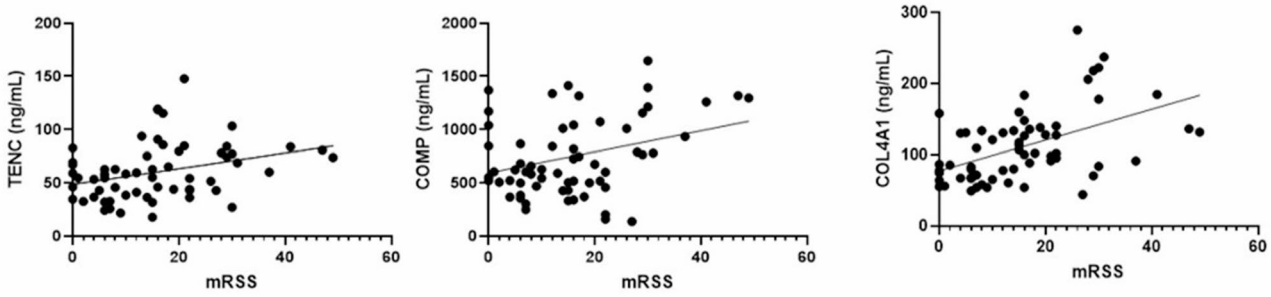

Fig. 1 Cross-sectional correlation with univariable regression of individual analytes (TENC, COMP, COL4A1) and mRSS

$p = 0.141$). Finally, TENC as expected showed a non-significant correlation with mRSS (β= −0.02; 95% CI −0.11–0.07; $p = 0.699$).

To formulate a generalizable prediction equation for mRSS, we performed a multivariable linear regression analysis. Here, serum concentrations of COL4A1 once again showed a significant correlation with mRSS (β = 0.1, 95% CI 0.04–0.15; $p = 0.001$), while a non-significant correlation was detected for both TENC (β = 0.06, 95% CI −0.05–0.16, $p = 0.306$) and COMP (β = 0.005, 95% CI −0.03–0.01; $p = 0.203$). The linear regression model explained approximately 26% of the variance in mRSS (adjusted $R^2 = 0.2598$). We subsequently derived an integrated composite biomarker formula to predict mRSS, with a statistically significant correlation between predicted and actual mRSS ($r = 0.31$, $p < 0.0001$). Model assumptions were checked: the Ramsey RESET test for nonlinearity was not significant ($p = 0.137$), and fractional polynomial analysis suggested that all predictors could be kept linear. Residual plots did not reveal systematic deviations from linearity or constant variance. Therefore, the linear model was retained for subsequent analysis. The refined formula is depicted below and in Fig. 2 with associated Bland Altman plot.

Predicted mRSS = (0.0557*TENC) + (0.0048*COMP) + (0.0952*COL4A1) −2.08

Performance as dynamic biomarkers

The three analytes were assessed as dynamic biomarkers for cutaneous involvement, comparing the change in serum concentration from baseline to 24 months. Median change in TENC concentration was −16.7 ng/mL (−28.3, −6.7), with a non-significant negative correlation with mRSS changes ($r = -0.03$; $p = 0.634$). Median change in COMP concentration was −42.8 ng/mL (−277.1, 151.6), with a significant positive correlation with mRSS trajectory, both at linear regression ($r = 0.013$; $p = 0.012$) and at Spearman's test (rho = 0.473; $p = 0.0371$). Median change in COL4A1 concentration was −58.2 ng/mL (−94.1, −14.1), with a non-significant correlation with mRSS changes ($r = 0.059$; $p = 0.097$). At multivariable linear regression, change in COMP concentration remained statistically significant with a positive correlation with mRSS response ($r = 0.12$; $p = 0.036$).

No significant correlation between changes in concentration of serum analytes and mRSS at 12 months was detected.

Differential response according to treatment

Dynamics in serum analytes in both treatment arms were analysed. The median change in mRSS at 24 months was −15.5 (−23, −14) in the HSCT group and −14 (−14.5, −4.5) in the CYC group, with non-significant difference between the two treatment groups ($p = 0.069$). We demonstrated that compared to CYC group, a statistically significant greater decrease in COL4A1 concentrations in the HSCT group (−81 ng/mL in HSCT group vs. −27.4 ng/mL in CYC group; $p = 0.029$), as depicted in Fig. 3, while no significant difference was detected for TENC and COMP. Interestingly, all patients in the HSCT had a mRSS reduction of more than 5 points at 24 months (further defined as responders), while four CYC patients did not. Moreover, responders (10 HSCT patients and 7 CYC patients) showed a significantly greater reduction in COL4A1 concentrations at 24 months than non-responders (−63.9 ng/mL and −8.5ng/mL), respectively; $p = 0.04$).

Correlation with other clinical outcomes

A total of 18/21 patients (85.7%) had interstitial lung disease (ILD) at baseline. Median predicted forced vital capacity (FVC) was 83% (IQR 72–90) at baseline, 86% (78–102) at 12 months, and 88% (75–98) at 24 months. Kruskall-Wallis test did not identify a significant difference in FVC at all 3 timepoints ($p = 0.47$). At linear mixed model, TENC showed a statistically significant negative correlation with FVC (β= −0.11, 95% CI −0.22 – −0.01; $p = 0.047$). This did not apply to the other analytes, which both showed a negative correlation with FVC, but not statistically significant: β= −0.01 (95% CI −0.02–0.01; $p = 0.154$) for COMP and β= −0.05 (95% CI −0.11–0.01; $p = 0.068$) for COL4A1.

Five patients (19%) experienced major organ involvement or death during follow up (3 and 2 respectively). No

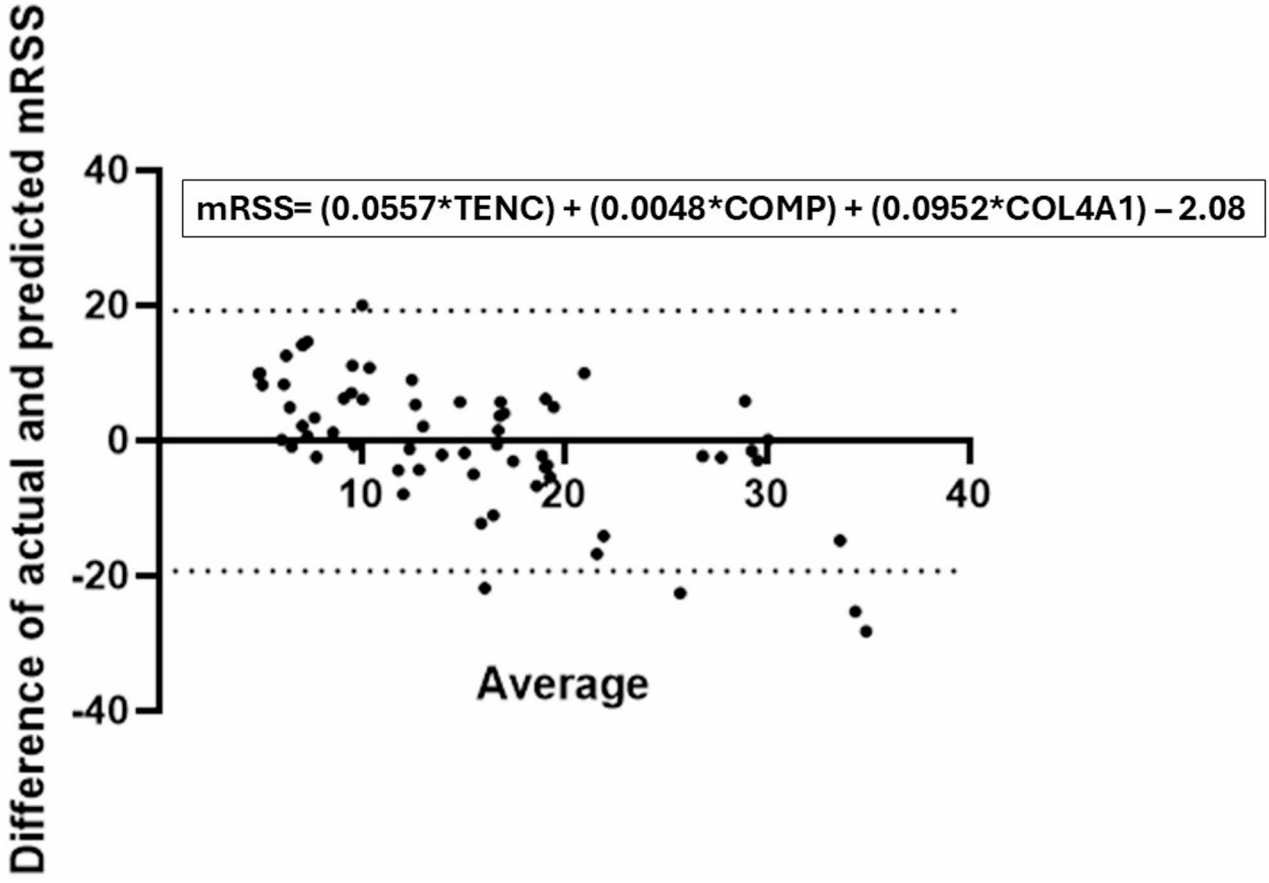

Fig. 2 Bland Altman plot of predicted and actual mRSS, showing better conformity for mRSS less than 20. At the top, the derived formula for predicted mRSS based on serum concentration of TENC, COMP and COL4A1

significant correlation between this composite outcome and target analytes concentrations (both at baseline and considering their variation overtime) was detected.

Discussion

In this study we derived an updated composite biomarker score to predict skin involvement in SSc as measured by mRSS in a unique cohort of early dcSSc receiving high-intensity immunosuppressive therapy.

Serum levels of COMP and COL4A1 correlated with mRSS cross-sectionally, while the correlation with TENC was not statistically significant. Out of the three analytes, COL4A1, a fibrillar collagen molecule synthesised by endothelial cells and pericytes and mainly involved in angiogenesis [6], displayed the greatest level of correlation, which was maintained after correction for the other biomarkers' levels at multivariable analysis.

Our newly derived composite biomarker score showed a moderate correlation with mRSS. However, the agreement between predicted and observed mRSS was associated with wide confidence intervals, thus underscoring that our composite biomarker might be more useful if employed in conjunction with mRSS rather than as its surrogate.

Interestingly, only COMP displayed a significant correlation with mRSS changes overtime. COMP is a matricellular protein regulated by transforming growth factor β (TGFβ). It identifies a subpopulation of SSc fibroblasts whose abundance correlates with extent of cutaneous involvement and its serum concentrations have already been reported as elevated in SSc patients, correlating with mRSS [7, 8]. Our findings of COMP as a dynamic biomarker are in line with the previous evidence reporting a four-gene biomarker, which included COMP, as predictive of mRSS and correlating with mRSS changes overtime (although this was tested in only 5 patients) in dcSSc [9]. However, the level of correlation between COMP and mRSS variations was not strong in our study which could indicate that its activity is not restricted only to the cutaneous compartment. Previous studies showed that COMP is highly expressed in patients with SSc-ILD and is associated with overall mortality in early SSc [10, 11]. The poor performance of TENC and COL4A1 as dynamic biomarkers may reflect, similarly to COMP, the low specificity of these proteins for the cutaneous

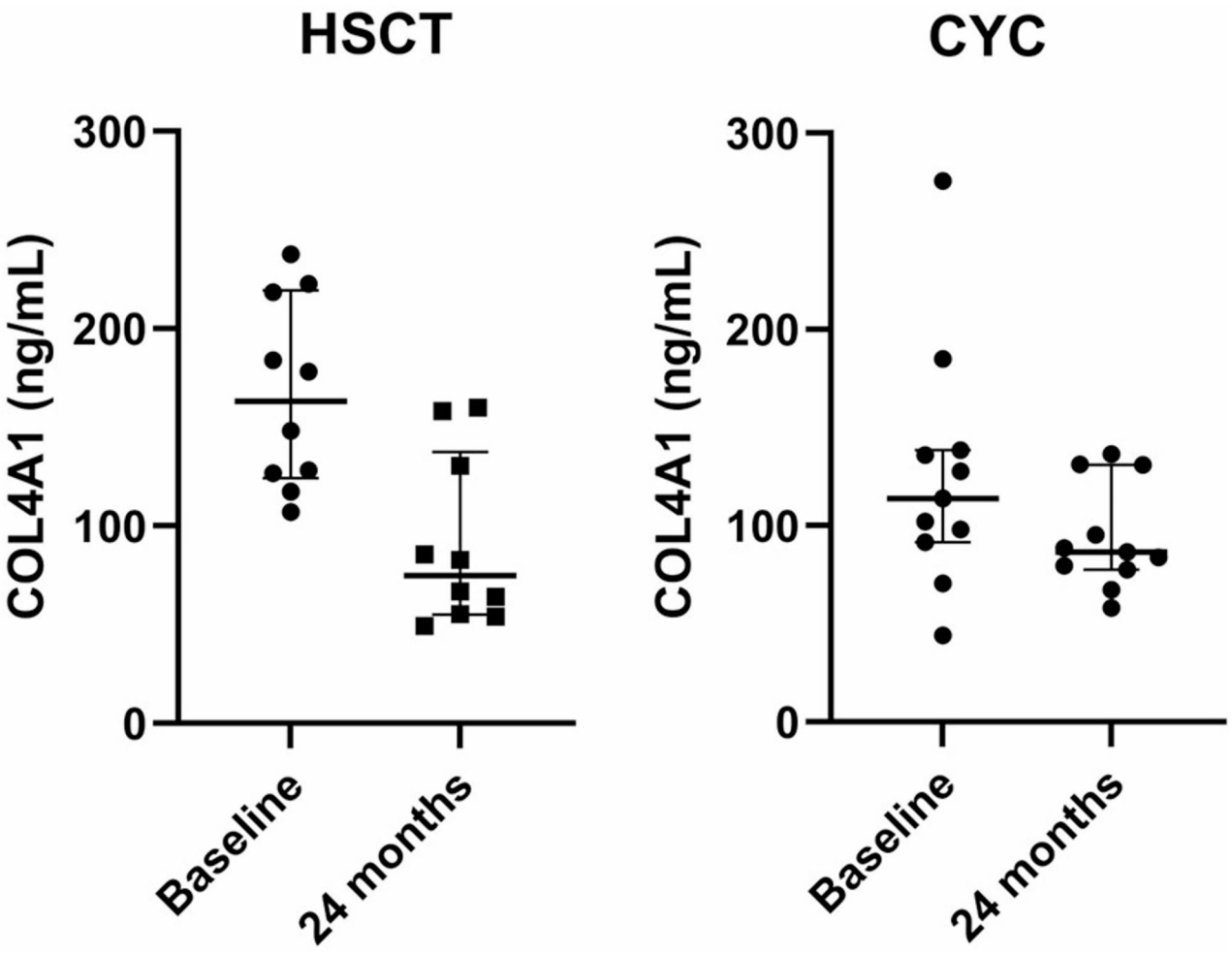

Fig. 3 Changes in COL4A1 serum concentrations at 24 months in cyclophosphamide (CYC) group vs. autologous hematopoietic stem cell transplantation (HSCT) group

compartment. Indeed, we documented an inverse relationship between TENC levels and FVC, indicating its correlation with severity of ILD. Also, it may signify that, rather than dynamic biomarkers, these analytes could perform better in defining a 'signature' for cutaneous and systemic involvement, potentially helpful to better characterize disease activity across a SSc cohort.

In the third part of our study, we looked at treatment-specific changes in serum analytes' concentrations. Whilst serum levels of TENC and COMP did not differ across the 2 treatment groups; there was a greater reduction in COL4A1 levels at 24 months in the HSCT group compared to CYC treated patients. This likely reflects a more profound effect on microvascular axis by HSCT, as already shown by several studies focusing on improvement in nailfold capillaroscopy and microvascular damage in skin histology [12–14]. Although our limited sample size (only two deaths, in the CYC group) precluded survival analysis, the observed reduction in COL4A1 concentration—occurring around two years post-treatment—parallels the improved survival seen in HSCT versus cyclophosphamide phase 3 trials (ASTIS and SCOT) [4, 15], suggesting that decreased COL4A1 may reflect reduced overall disease activity.

We acknowledge several limitations to our study. First, the small sample size limits the statistical significance of our findings, even though our cohort, characterized by a wide mRSS range and exposure to high dose immunosuppression, represents the ideal sample to test for our hypothesis. Further, our findings reflect the challenges in moving from techniques such as gene expression profiling, transcriptomic, or proteomic-based approaches, very sensitive and with a greater analytical range, to ELISA-based protein quantification, which better reflects future clinical practice. As in our previous analysis, the level of correlation between serum analytes and mRSS was lower with ELISA-based techniques than with a multi-omics approach [2, 3]. Second, the formula to predict mRSS is derived from a multivariable linear regression which is based on the incorrect assumption that all observations

are independent. However, deriving the formula from our mixed model would not have made it generalizable as time should have been included as a variable. Third, our analysis was not powered to assess links with clinically meaningful outcomes other than changes in mRSS. Further research in a larger cohort with longer follow-up time will help determining whether early reduction in COL4A1 concentrations is correlated with a real survival benefit. Fourth, since immune reconstitution after HSCT can take longer than 24 months, it is possible that including more longitudinal samples we could capture potential later changes [16]. Finally, our cohort included prevalently patients with early disease, with a baseline median disease duration of only 10 months, thereby our results may not be generalizable to longer disease duration periods.

Conclusion

This newly derived composite biomarker score showed a moderate level of cross-sectional correlation with cutaneous involvement in SSc and may be useful as a complementary tool to better characterize extent of skin fibrosis in clinical practice and trials. This score did not perform well as a dynamic biomarker of skin fibrosis. The differences for serum COL4A1 across treatment groups, with greater reduction in the HSCT group, warrants further evaluation of the role of this protein as a predictive marker in dcSSc.

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Authors' contributions
SR performed the experiments and data analysis. BAA and CK assisted with the experiments. ER and MK assisted with data analysis. SR, VHO, CD, and JS wrote the main manuscript text and prepared the figures. AEV, JKDVB, JMvL and JS provided the serum samples for the experiments and clinical data. CPD and JS designed and directed the study. All authors reviewed and approved the manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Informed consent was provided by all patients upon participation to ASTIS trial.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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