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Summary

Background The current subclassification of systemic sclerosis into cutaneous subtypes does not fully capture the heterogeneity of the disease. We aimed to compare the performances of stratification into LeRoy's cutaneous subtypes versus stratification by autoantibody status in systemic sclerosis.

Methods For this cohort study, we assessed people with systemic sclerosis in the multicentre international European Scleroderma Trials and Research (EUSTAR) database. Individuals positive for systemic-sclerosis autoantibodies of two specificities were excluded, and remaining individuals were classified by cutaneous subtype, according to their systemic sclerosis-specific autoantibodies, or both. We assessed the performance of each model to predict overall survival, progression-free survival, disease progression, and different organ involvement. The three models were compared by use of the area under the curve (AUC) of the receiver operating characteristic and the net reclassification improvement (NRI). Missing data were imputed.

Findings We assessed the database on July 26, 2019. Of 16 939 patients assessed for eligibility, 10 711 patients were included: 1647 (15·4%) of 10 709 were male, 9062 (84·6%) were female, mean age was 54·4 (SD 13·8) years, and mean disease duration was 7·9 (SD 8·2) years. Information regarding cutaneous subtype was available for 10 176 participants and antibody data were available for 9643 participants. In the prognostic analysis, there was no difference in AUC for overall survival (0·82, 95% CI 0·81–0·84 for cutaneous only *vs* 0·84, 0·82–0·85 for antibody only *vs* 0·84, 0·83–0·86 for combined) or for progression-free survival (0·70, 0·69–0·71 *vs* 0·71, 0·70–0·72 *vs* 0·71, 0·70–0·72). However, at 4 years the NRI showed substantial improvement for the antibody-only model compared with the cutaneous-only model in prediction of overall survival (0·57, 0·46–0·71 for antibody only *vs* 0·29, 0·19–0·39 for cutaneous only) and disease progression (0·36, 0·29–0·46 *vs* 0·21, 0·14–0·28). The antibody-only model did better than the cutaneous-only model in predicting renal crisis (AUC 0·72, 0·70–0·74 for antibody only *vs* 0·66, 0·64–0·69 for cutaneous only) and lung fibrosis leading to restrictive lung function (AUC 0·76, 0·75–0·77 *vs* 0·71, 0·70–0·72). The combined model improved the prediction of digital ulcers and elevated systolic pulmonary artery pressure, but did poorly for cardiac involvement.

Interpretation The autoantibody-only model outperforms cutaneous-only subsetting for risk stratifying people with systemic sclerosis in the EUSTAR cohort. Physicians should be aware of these findings at the time of decision making for patient management.

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Introduction

Risk stratification is key in the management of a heterogeneous disease like systemic sclerosis. People with systemic sclerosis are primarily classified into having diffuse cutaneous systemic sclerosis, limited cutaneous systemic sclerosis, and sine scleroderma subtypes according to the extent of skin involvement.[1] Accumulating evidence supports that this classification is inadequate to capture disease heterogeneity.[2,3] The subclassification of people with systemic sclerosis must be improved to enhance decision making for disease management and follow up. This proposal fits with the current development of precision medicine, which must be investigated in a severe disease like systemic sclerosis.[4,5]

Several factors might drive the pitfalls of the current skin classification: use of the modified Rodnan skin score (mRSS) requires training and should be done by the same assessor to reduce variability,[6,7] which is not always possible in clinical practice. For the correct classification of a person with a new diagnosis of systemic sclerosis, clinicians should wait until the peak of skin thickness is reached, which could take several years.[8]

Antinuclear antibodies are detected in more than 90% of people with systemic sclerosis and are present several

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See Online for appendix

Research in context

Evidence before this study

There is growing evidence that the current subclassification of systemic sclerosis by cutaneous subtype does not fully capture the heterogeneity of the disease . We aimed to investigate whether stratification by autoantibodies (that are assessed in routine practice) would allow better classification of patients with systemic sclerosis. We searched MEDLINE databases between Jan 1, 1960, and June 1, 2019, and used the terms "(scleroderma or systemic sclerosis [MesH]) AND classification AND cutaneous AND antibody". 70 articles were identified, of which four were relevant. In two cross-sectional studies, some outcomes were more associated with antibody status (eg, lung involvement), whereas others were more associated with cutaneous subtype. Another small cross-sectional study suggested using the combination of cutaneous involvement and antibody status for patient stratification, highlighting the pitfalls of the current skin-based subclassification, and another study on the EUSTAR database suggested stratification in six different clusters integrating organ damage, which could be difficult in routine clinical practice. Therefore, the performance of the subclassification of people with systemic sclerosis by auto-antibody status, cutaneous subtype, or a combination of both remains unknown, particularly regarding disease progression.

Added value of this study

We used a longitudinal cohort of more than 10 000 European people with systemic sclerosis with analysis of multiple outcomes (with, on average, three visits per patient). In this cohort, we could clearly show the difference of using a model based on autoantibody status to predict the majority of incidents of severe organ damage. To our knowledge, we show for the first time that the antibody status is a better predictor of overall survival and disease progression over 4 years than is cutaneous subtype.

Implications of all the available evidence

The results of this study, combined with available evidence, could change clinical practice from classification by cutaneous subtype to autoantibodies. This easily performed subclassification using autoantibody status could help clinicians to risk stratify their patients and to adapt disease monitoring in routine practice. These results could also have implications in the design of clinical trials, with enrichment of patients according to their antibody status, which could help to identify effective treatments for this disease.

years before disease onset.[9–11] Among these antibodies, three predominant and specific antibodies are observed: anti-centromere, anti-topoisomerase-1, and anti-RNA polymerase III antibodies.[12] In a preliminary cross-sectional study of the European Scleroderma Trials and Research (EUSTAR) group in 3656 people with systemic sclerosis, autoantibody status was more closely associated with clinical manifestations than was cutaneous subset.[10] However, no longitudinal analyses were done in that study and, since its publication, the EUSTAR database has grown to include over 20 000 people with systemic sclerosis. Altogether, the performance of the subclassification of people with systemic sclerosis by autoantibody status, cutaneous form, or a combination of both remains to be determined, particularly in terms of longitudinal data.

Therefore, we aimed to compare the performances of stratification into cutaneous subtypes versus auto-antibody status versus the combination of cutaneous subtypes and autoantibody status according to disease progression and survival, and organ involvements in a large international multicentre cohort of people with systemic sclerosis.

Methods

Study design

For this cohort study we used data from the ongoing EUSTAR database, a multicentre online database that contains prospectively collected data from more than 20 000 people with systemic sclerosis in more than 180 international centres. The structure of the database, its minimum essential dataset, and its inclusion criteria have been described in detail previously.[13] Each patient's annually scheduled visit for medical purposes is recorded to produce longitudinal observational data. Each EUSTAR centre is trained with EUSTAR-specific courses, including the definitions for different disease entities such as scleroderma renal crisis.[14] Each participating centre obtained approval from their local ethics committee and all registered patients granted their written informed consent.

On July 26, 2019, ME, NS, and MB assessed the EUSTAR database, which provides information on people with systemic sclerosis who had been registered since 2010, corresponding to the start of the online version of the database. The sole inclusion criterion was the availability of data on systemic sclerosis-related antibody status.[12] We surveyed participating centres to record information on anti-RNA polymerase III antibody status that was missing from the first database extract. Patients who were positive for systemic sclerosis-specific autoantibodies of two different specificities were excluded, as were patients positive for one autoantibody and with missing data (due to the potential for positivity for autoantibodies of two different specificities). Patients were classified either as having limited cutaneous systemic sclerosis, diffuse cutaneous systemic sclerosis, or sine scleroderma (based on the recording made by the treating physician); or according to autoantibodies as having no specific autoantibodies, isolated anti-nuclear antibodies, anticentromere antibodies,

anti-topoisomerase-1, or anti-RNA polymerase III antibodies; or according to their cutaneous subset and autoantibodies (ie, combined model). As an exploratory analysis, we also assessed the performance of a stratification of the cutaneous subset according to mRSS (diffuse mRSS: ≥14 of 51; limited mRSS: 1–13 of 51; sine scleroderma mRSS: 0 of 51).[15] Our models were also assessed in incident patients (ie, those with a disease duration of <1 year) and in patients with early disease (ie, those with a disease duration of <4 years, including incident patients). Stratification was done at baseline without change over time for the prospective analysis. For the longitudinal analysis, stratification was done at each visit according to the skin subtype and antibody status on the day, which was recorded in the database.

Disease characteristics

Disease duration was defined as the time from the onset first non-Raynaud's symptom. Immunosuppressive therapies included methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, tumour necrosis factor inhibitors, rituximab, tocilizumab, and abatacept.

Outcome measures and definitions

Lung fibrosis was defined as ground glass opacities, traction bronchiectasis, or reticulation or honeycombing on chest high-resolution CT.

Patients who had at least one follow-up visit were included in the prognostic analysis. Overall survival was defined as the time from the first visit until the most recent follow-up or death from any cause.

Progression-free survival was defined as the time from the first visit until death or disease progression. Disease progression was defined as the time from first visit until worsening of dermal fibrosis (≥5 points and 25% increase in mRSS),[8] worsening of lung fibrosis (decrease of ≥10% in forced vital capacity or ≥15% in diffusing capacity for carbon monoxide [DLCO]) in patients with known lung fibrosis,[16,17] de-novo lung fibrosis, elevation of systolic pulmonary artery pressure of more than 45 mm Hg on echocardiography (a surrogate marker for pulmonary arterial hypertension),[18] or new renal crisis. In the longitudinal analysis, the occurrence of the following outcomes was assessed during follow-up:[10,13,19] digital ulcers (current or previous), upper gastrointestinal or lower gastrointestinal involvement, renal crisis, heart dysfunction (defined by a left ventricular ejection fraction of less than 50% on transthoracic echocardiography), lung fibrosis (on high-resolution CT), restrictive lung fibrosis (defined by lung fibrosis on high-resolution CT and reduced forced vital capacity below 70%), and systolic pulmonary artery pressure of more than 45 mm Hg on echography.[18]

Statistical analysis

The data collected were described using the number and the percentage for categorical variables. Mean and SD were used for quantitative variables. The performance of each outcome was assessed using mixed effects logistic regression models for organ involvement and Cox proportional hazards regression models for overall survival, progression-free survival, and disease progression with the covariates of interest: autoantibody status and cutaneous subtypes. The odds ratio (OR) or hazard ratio (HR) and their 95% CIs were reported. Survival data are shown as Kaplan-Meier survival plots. All tests were two-sided at a 0·05 significance level. We assessed the improvement in discrimination by comparing the area under curve (AUC) of the receiver operating characteristic (ROC) of the three models. AUC shows the strength of discrimination between methods. AUC takes a value between 0 and 1, where a random classifier has a score of around 0·5, 0·7–0·8 is considered acceptable, 0·8–0·9 is considered excellent, and 1 is considered as perfect classifier.[20] However, the performance of the AUC as an accurate measurement of a model has been a matter of debate, particularly in detecting small changes.[21] Therefore, we also used the net reclassification index (NRI), which is based on reclassification tables constructed separately for participants with and without events and was shown to offer incremental information over the AUC for the prediction models.[21] The NRI assesses the improvement of an added model compared with a base model. To circumvent the issues related to threshold determination, the continuous NRI was used, which is interpreted as the net proportion of people reclassified upwards (improved reclassification) and downwards (worse reclassification) for events (NRI event) and non-events (NRI non-event) separately with a range of –1 to 1. NRI events and NRI non-events give information on

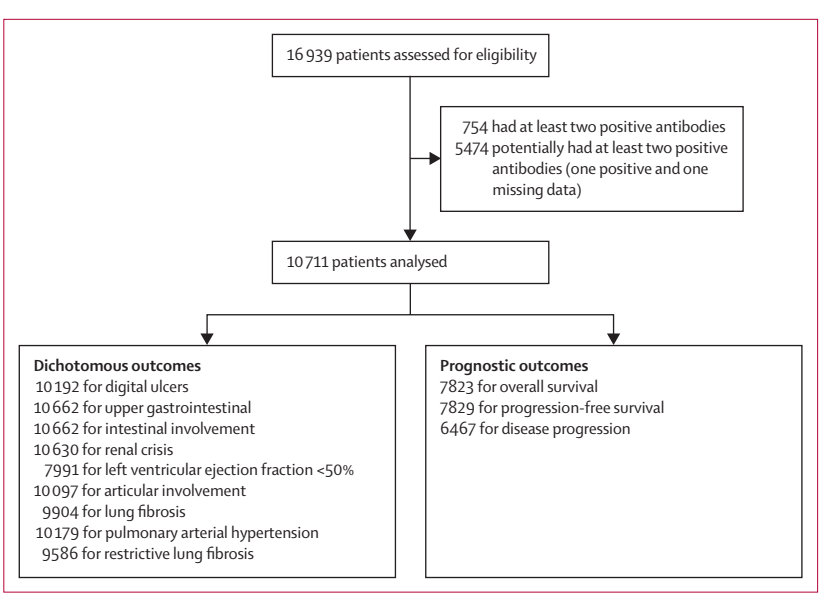

Figure 1: **Flow chart for inclusion of patients in the analysis and number of patients analysed for each outcome**

	Study population (N=10 711)
Age	
Mean, years	54·4 (13·8)
Patients with available data	10 669/10 711 (99·6%)
Disease duration	
Mean, years	7·9 (8·2)
Patients with available data	9140/10 711 (85·3%)
Sex	
Male	1647/10 709 (15·4%)
Female	9062/10 709 (84·6%)
Ethnicity	
White	8163/8787 (92·9%)
Asian	216/8787 (2·5%)
Black	161/8787 (1·8%)
Other	247/8787 (2·8%)
Cutaneous subsets based on LeRoy's criteria	
Limited cutaneous systemic sclerosis	6533/10 176 (64·2%)
Diffuse cutaneous systemic sclerosis	2895/10 176 (28·4%)
Sine scleroderma	748/10 176 (7·4%)
Autoantibody status	
No autoantibodies	467/9643 (4·8%)
Isolated antinuclear antibodies	2707/9643 (28·1%)
Anticentromere antibodies	3512/9643 (36·4%)
Anti-topoisomerase-1 antibodies	2658/9643 (27·6%)
Anti-RNA polymerase III antibodies	299/9643 (3·1%)
Joint synovitis	1363/10 472 (13·0%)
Tendon friction rubs	744/10 377 (7·2%)
Joint contractures	2600/10 448 (24·9%)
Muscular involvement	2309/10 342 (22·3%)
(Table 1 continues in next column)	
(Continued from previous column)	
C-reactive protein ≥10 mg/L	258/2210 (11·7%)
Digital ulcers	
Current	451/4073 (11·1%)
Previous	1035/4073 (25·4%)
Scleroderma pattern on capillaroscopy	3873/4452 (87·0%)
Upper gastrointestinal involvement	6273/10 411 (60·3%)
Intestinal involvement	2510/10 587 (23·7%)
Scleroderma renal crisis	207/10 547 (2·0%)
Left ventricular ejection fraction <50%	102/5203 (2·0%)
Pulmonary arterial hypertension*	333/4770 (7·0%)
Lung fibrosis	2030/5066 (40·1%)
Restrictive lung fibrosis†	448/6489 (6·9%)
Diffusing capacity for carbon monoxide <60%	2261/7874 (28·7%)
Immunosuppressive treatment‡	2526/8397 (30·1%)
Glucocorticoid treatment	2264/7441 (30·4%)
Glucocorticoid dosage	
Mean, mg	2·8 (6·0)
Patients with available data	6860/7441 (92·2%)
Glucocorticoids ≥10 mg per day	732/6860 (10·7%)

Data are mean (SD) or n/N (%). Lung fibrosis was diagnosed on high-resolution CT. *Systolic pulmonary arterial pressure >45 mm Hg by echocardiography. †Lung fibrosis and forced vital capacity <70%. ‡Immunosuppressive drugs include methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, anti-TNFs, rituximab, tocilizumab, and abatacept. The different outcomes are diagnosed according to EUSTAR definitions.

Table 1: **Characteristics of the included patients at baseline**

how the new risk model could improve prediction for events and for non-events, separately. The presence of the NRI event and non-event can be interpreted as the net change in the proportion of patients assigned a more appropriate risk under the new model. Overall NRI is the sum of the NRI event and NRI non-event and can be interpreted as a unitless statistic. A positive overall NRI means an upward movement (improvement in reclassification) and a negative NRI a downward movement (worsening in reclassification).[22] The maximum value of the overall NRI is 2, which indicates better discrimination, and the minimum value is –2, which indicates poor discrimination. To capture small changes not detected using AUC, the NRI of our different predictive models was assessed in a post-hoc analysis.[23] NRI and AUC were evaluated at 2 years and 4 years (from database entry—ie, first visit) for overall survival, progression-free survival, and disease progression. A multiple imputation chain equation was done to account for the missing data in covariates. The number of multiple imputations was set to 25 with five iterations for prognostic analysis, and 16 with five iterations for longitudinal analysis.[24] There was no cut off for imputation for missing values. Our models were adjusted upon imputation by covariates (appendix pp 7–15, 19–48) that could, according to the literature, influence the outcomes and the Nelson Aalen estimator of the cumulative hazard with death status for the prognostic analysis. The results were aggregated by pooling the estimates obtained from each imputed dataset according to Rubin's rules. We used confidence intervals for our models as it was shown that even small NRI values (<0·01) might produce statistically significant p values.[22,25,26] Statistical testing was therefore avoided for the NRI measure. Confidence intervals provide precision estimates and are preferable, not only for the overall NRI, but also for their components.[22,25,26] Statistical analyses were carried out using R Project for Statistical Computing (version 3.5.2) software .

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

On July 26, 2019, 16 939 people in the EUSTAR database were assessed for eligibility and 10 711 participants from 159 centres who fulfilled the 2013 criteria for systemic

sclerosis were included (figure 1).[12] Mean age was 54·4 (SD 13·8) years and mean disease duration was 7·9 (SD 8·2) years. 1647 (15·4%) of 10709 were men and 9062 (84·6%) were women. Of 10176 people with data on skin subtype available, 6533 (64·2%) had limited cutaneous systemic sclerosis, 2895 (28·4%) had diffuse cutaneous systemic sclerosis, and 748 (7·4%) had systemic sclerosis sine scleroderma. Of the 9643 patients with data on antibody status, 9176 (95·2%) were positive for antinuclear antibodies, 2707 (28·1%) had isolated antinuclear antibodies, 3512 (36·4%) had anticentromere antibodies, 2658 (27·6%) had anti-topoisomerase-1, and 299 (3·1%) anti-RNA polymerase III antibodies (table 1).

During a median follow-up of 56 months (95% CI 55–58), a median number of three visits per patient was recorded. The total number of organ-specific events during follow up, as well as the number of events disaggregated by sex, are in the appendix (p 5). After 4 years, 777 (9·9%) deaths were recorded among the 7823 patients with available data, 2875 (36·7%) of 7829 had progression-free survival, and 2340 (36·2%) of 6467

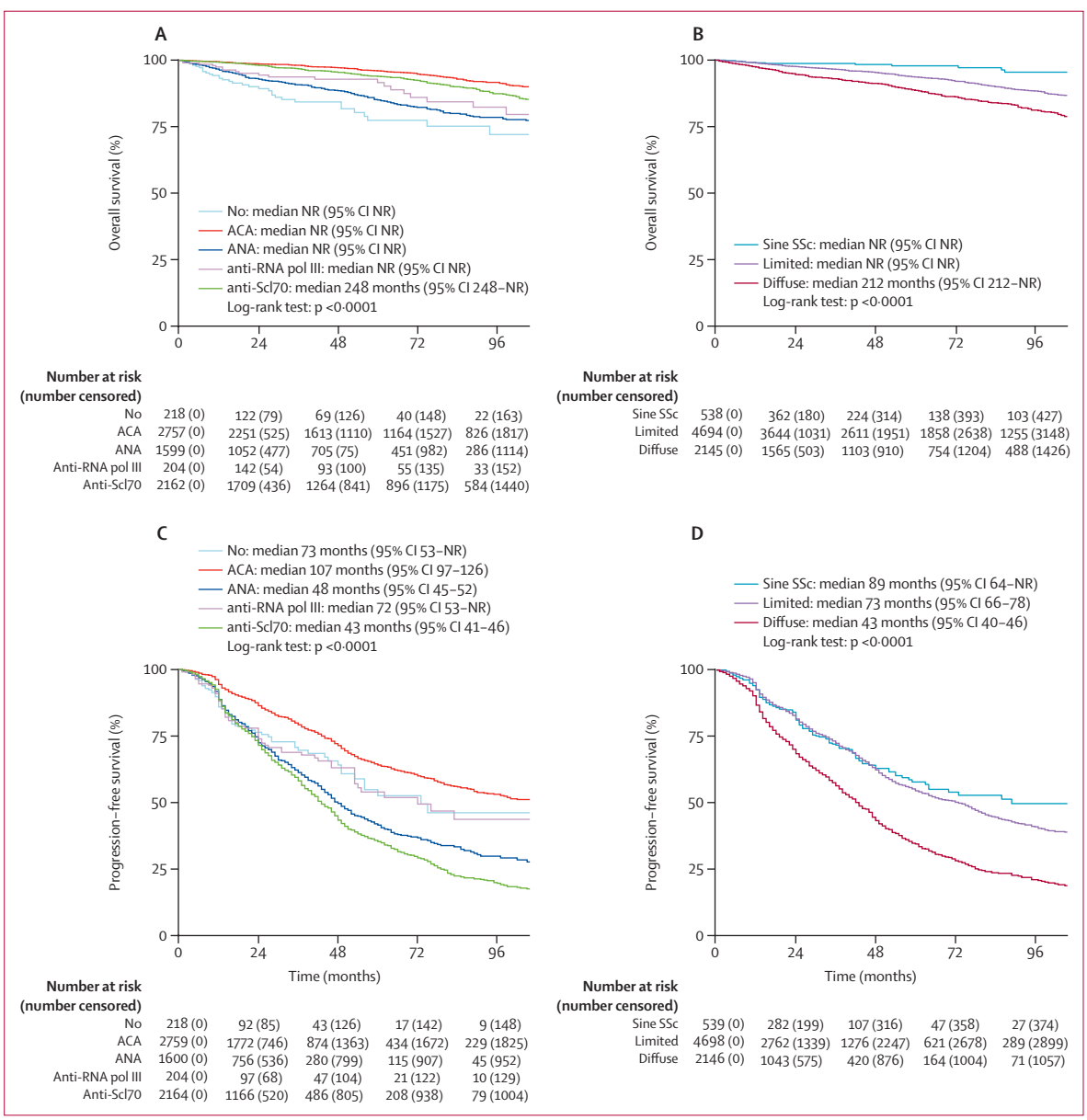

Figure 2: **Kaplan-Meier curves for overall survival and progression-free survival**
(A) Overall survival according to autoantibodies. (B) Overall survival according to cutaneous subtype. (C) Progression-free survival according to autoantibodies. (D) Progression-free survival according to cutaneous subtype. ACA=anticentromere antibodies. ANA=isolated antinuclear antibodies. anti-RNA pol III=anti-RNA polymerase III. anti-Scl70=anti-topoisomerase-1. Diffuse=diffuse cutaneous systemic sclerosis. Limited=limited cutaneous systemic sclerosis. No=no specific antibodies. NR=not reached. Sine SSc=sine scleroderma.

had disease progression. Comparison of patients with and without missing follow-up could suggest a milder disease in those who were lost to follow-up (appendix p 6). Overall survival and progression-free survival differed according to autoantibody profiles and cutaneous forms (p<0·0001 in log-rank test; figure 2).

Using AUC, we did not detect any difference in overall survival, progression-free survival, and disease progression between the three models (table 2; appendix pp 7–15). Using the NRI at 4 years, the antibody-only model (0·57, 95% CI 0·46 to 0·71) outperformed the cutaneous-only model (0·29, 0·19 to 0·39) for prediction of survival (NRI event 0·21, 0·10 to 0·34 for antibody-only *vs* –0·02, –0·11 to 0·07 for cutaneous-only; NRI non-event 0·36, 0·34 to 0·38 *vs* 0·31, 0·28 to 0·33) and disease progression (0·36, 0·29 to 0·46 for the antibody-only model *vs* 0·21, 0·14 to 0·28 for the cutaneous-only model; NRI event 0·22, 0·15 to 0·28 *vs* –0·17, –0·22 to –0·1; NRI non-event 0·14, 0·08 to 0·18 *vs* 0·40, 0·36 to 0·43; table 3; appendix pp 7–15). The combined model performed similar to the antibody-only model. The results were similar at 2 years (appendix p 16).

We aimed to assess the performance of the models in predicting the involvement of each organ in longitudinal analyses (appendix pp 17–18). The antibody-only model better predicted digital ulcers compared with the cutaneous-only model using NRI (0·31, 95% CI 0·29–0·33 for antibody-only *vs* 0·24, 0·22–0·26 for cutaneous-only), but not AUC (tables 2, 3; appendix pp 17–18), with the highest association with anti-topoisomerase-1 (Scl70) antibodies (OR 3·57, 95% CI 2·68–4·75; p<0·0001; appendix pp 19). However, improvements in NRI global were explained by the NRI non-event (appendix pp 17–18).

The antibody-only model outperformed the cutaneous-only model in predicting renal crisis (AUC 0·72, 95% CI 0·70–0·74 for antibody-only *vs* 0·66, 0·64–0·69 for cutaneous-only) with the highest association with anti-RNA polymerase III (OR 7·47, 95% CI 1·63–34·24; p=0·010) (table 2; appendix pp 21–22). Similarly, the antibody-only model outperformed the cutaneous-only model in predicting lung fibrosis (AUC 0·72, 95% CI 0·72–0·72 *vs* 0·65, 0·65–0·66) and restrictive lung fibrosis (AUC 0·76, 0·75–0·77 *vs* 0·71, 0·70–0·72), which were associated with anti-topoisomerase-1 antibodies (OR 9·29, 95% CI 8·17–10·55 for lung fibrosis and 7·92, 5·37–11·69 for restrictive lung fibrosis, p<0·0001 for both; table 2; appendix pp 23–26). This was confirmed using the NRI (table 3; appendix pp 17–18). In particular, the NRI event (for the presence of lung fibrosis or restrictive lung fibrosis) of the antibody-only model outperformed the NRI event of the cutaneous-only model (which was negative).

There was no difference in AUC in predicting the occurrence at least at one visit of upper gastrointestinal involvement, but the NRI showed improvement using the cutaneous-only model compared with the antibody-only model (tables 2, 3; appendix pp 17–18, 27–28). This improvement was explained by better detection of non-events (ie, NRI event negative or NRI non-event positive).

The two models had similar performance in assessing the occurrence of intestinal involvement, heart dysfunction defined by a left ventricular ejection fraction of less than 50%, or pulmonary arterial hypertension (defined as elevated systolic pulmonary artery pressure) by echocardiography in at least one visit (tables 2, 3; appendix pp 17–18, 29–34).

The combined model had a similar performance to that of the antibody-only model in all the studied outcomes, except for digital ulcers, which were better predicted in the combined model using AUC but not NRI. The combined model had better performance in the prediction of elevated systolic pulmonary artery pressure by echocardiography and upper gastrointestinal involvements than the antibody-only model using NRI, but not AUC. However, this improvement was explained by a better detection of NRI non-events (tables 2, 3;

	Cutaneous-only model (95% CI)	Antibody-only model (95% CI)	Combined model (95% CI)
Survival at 4 years	0·82 (0·81–0·84)	0·84 (0·82–0·85)	0·84 (0·83–0·86)
Progression-free survival at 4 years	0·70 (0·69–0·71)	0·71 (0·70–0·72)	0·71 (0·70–0·72)
Disease progression at 4 years	0·68 (0·67–0·69)	0·68 (0·67–0·69)	0·69 (0·67–0·70)
Digital ulcers	0·63 (0·63–0·64)	0·64 (0·63–0·64)	0·65 (0·64–0·66)
Upper gastrointestinal involvement	0·58 (0·57–0·58)	0·57 (0·56–0·57)	0·58 (0·58–0·59)
Intestinal involvement	0·57 (0·56–0·57)	0·57 (0·56–0·58)	0·58 (0·57–0·58)
Renal crisis	0·66 (0·64–0·69)	0·72 (0·70–0·74)	0·73 (0·71–0·75)
Left ventricular ejection fraction <50%	0·67 (0·64–0·69)	0·65 (0·63–0·67)	0·65 (0·63–0·67)
Lung fibrosis	0·65 (0·65–0·66)	0·72 (0·72–0·72)	0·72 (0·72–0·73)
Restrictive lung fibrosis	0·71 (0·70–0·72)	0·76 (0·75–0·77)	0·77 (0·76–0·77)
Pulmonary arterial hypertension	0·76 (0·75–0·77)	0·76 (0·75–0·77)	0·76 (0·75–0·78)

Lung fibrosis was diagnosed on high-resolution CT. Restrictive lung fibrosis was considered in patients with lung fibrosis and forced vital capacity <70%. Pulmonary arterial hypertension is defined as systolic pulmonary arterial pressure >45 mm Hg.

Table 2: **Area under curve for the receiver operating characteristic of the different models for diagnosis of the different outcomes (longitudinal and prognostic analysis)**

	Cutaneous-only model (95% CI)	Antibody-only model (95% CI)	Combined model (95% CI)
Survival at 4 years	0·29 (0·19 to 0·39)	0·57 (0·46 to 0·71)	0·50 (0·40 to 0·62)
Progression-free survival at 4 years	0·23 (0·16 to 0·32)	0·36 (0·28 to 0·43)	0·36 (0·29 to 0·45)
Disease progression at 4 years	0·21 (0·14 to 0·28)	0·36 (0·29 to 0·46)	0·36 (0·28 to 0·48)
Digital ulcers	0·24 (0·22 to 0·26)	0·31 (0·29 to 0·33)	0·32 (0·30 to 0·34)
Upper gastrointestinal involvement	0·11 (0·10 to 0·13)	0·05 (0·03 to 0·07)	0·17 (0·15 to 0·19)
Intestinal involvement	0·07 (0·05 to 0·09)	0·08 (0·06 to 0·11)	0·09 (0·07 to 0·11)
Renal crisis	0·46 (0·37 to 0·53)	0·56 (0·49 to 0·62)	0·52 (0·43 to 0·58)
Left ventricular ejection fraction <50%	0·28 (0·21 to 0·35)	0·17 (0·09 to 0·24)	–0·08 (–0·13 to –0·04)
Lung fibrosis	0·30 (0·28 to 0·32)	0·55 (0·53 to 0·57)	0·55 (0·53 to 0·57)
Restrictive lung fibrosis	0·41 (0·37 to 0·46)	0·61 (0·59 to 0·64)	0·62 (0·59 to 0·64)
Pulmonary arterial hypertension	–0·03 (–0·07 to 0·02)	–0·01 (–0·06 to 0·04)	0·13 (0·08 to 0·17)

Table 3: **Absolute net reclassification improvement for the three models for the longitudinal and prognostic analysis**

appendix pp 7–34). In the exploratory analysis, there was no change using mRSS instead of the cutaneous subset (appendix p 26, 35). In incident patients and patients with early disease duration, the predictors were essentially the same and there was no difference between the models (appendix pp 36–48).

Discussion

A more accurate risk stratification of patients is required in such a life-threatening disease as systemic sclerosis. In 2018, 10% of international systemic sclerosis experts identified issues with cutaneous-based subclassification.[27] Here, we showed that stratifying patients with systemic sclerosis according to autoantibodies better predicts overall survival and disease progression, and the different organ damages than does stratification according to cutaneous subtype. The antibody-only model is easily and widely available through the large dissemination of antibody assays. Moreover, autoantibody testing is usually done for disease classification as it is a part of the 2013 criteria,[12] and systemic sclerosis-specific autoantibodies of different specificities are usually mutually exclusive in a single patient.[28] Therefore, accurate and objective measurements with a high reproducibility qualify autoantibodies as suitable biomarkers.

In a previous EUSTAR study of 3656 people with systemic sclerosis, some disease manifestations were more associated with the cutaneous form, whereas digital ulcers, lung fibrosis, and pulmonary hypertension were more associated with autoantibodies.[13]

In a multicentre study[29] in 551 people with systemic sclerosis, the combination of cutaneous involvement and autoantibody status predicted different outcomes more accurately than did cutaneous subset or autoantibody status alone. Nihtyanova and colleagues[30] suggested a subclassification into seven groups by autoantibody specificity and skin involvement in their single centre cohort of 1325 people with systemic sclerosis. In our multicentric cohort, the combined model performed similarly for most of the outcomes compared with the autoantibody-only model, but performed better for digital ulcers, gastrointestinal involvement, and elevated systolic pulmonary artery pressure. However, this improvement was mostly explained by the better detection of non-events in the combined model. Moreover, heart involvement was poorly predicted using the combined model.

Because of the difficulties in interpreting the combined model, and the broadly similar performance of the combined and antibody-only models, we believe that the use of the antibody-only model is more advantageous, is simpler in routine practice, and gives excellent-to-acceptable model performance for overall survival, disease progression, and all organ damages. This better stratification of patients could lead to changes in clinical practice, with monitoring adapted according to autoantibody status rather than cutaneous subtype; treatment strategies stratified according to autoantibody status (eg, more aggressive treatment in high-risk patients); and enrichment in clinical trials for severe and progressive forms based on patients' autoantibody status (eg, positivity for anti-topoisomerase-1 antibodies), in whom the effect of treatment is likely to be easier to show. A 2019 study that made use of EUSTAR data proposed six homogenous clusters to stratify people with systemic sclerosis,[31] confirming that the subclassification based on cutaneous involvement could not capture the complete heterogeneity of the disease. Although interesting and opening new pathological hypotheses, this comprehensive clustering cannot easily be done in routine clinical practice, which limits its application as a suitable risk stratification approach.

Although the progression of disease according to autoantibody type was consistent with published data, people with systemic sclerosis without autoantibodies or with isolated antinuclear antibodies had worse overall survival. This finding should be treated with caution as the number of patients without any autoantibodies was small (<5% of our cohort). These patients could represent specific systemic sclerosis forms, perhaps including paraneoplastic forms.[32,33] Furthermore, the survival curves must be interpreted with caution as they are not adjusted for the different characteristics of the disease, unlike the multivariate models.

Our study has several limitations. We assessed only the main systemic sclerosis autoantibodies and excluded rarer autoantibodies. Our aim was to improve systemic sclerosis stratification, therefore we only focused on systemic sclerosis-specific autoantibodies tested for in routine practice by systemic sclerosis centres. Future research is needed to determine whether stratification according to antibody status could be valuable in patients with systemic sclerosis and overlapping syndromes with non-specific systemic sclerosis autoantibodies (eg, anti-RNP, or anti-Ku). Furthermore, due to missing data we could not specifically study the effect of the location of skin fibrosis on prognosis. In addition, our model did not perform well for all outcomes. In future, more advanced clustering statistics could be made use of to further explore the data and improve patient stratification.

The use of NRI in prediction models is a matter of debate.[34] NRI gives information that the AUC does not. Each index evaluates performance differently and provides different information. NRI detects smaller changes than the AUC[21] and allows the improvement in classification to be quantified, which can be valuable for clinical use.[35] Therefore, the combination of the two indexes to assess our models increases the robustness of our analysis. Contrary to the simplicity of NRI event and non-event, the overall NRI is more complex because of the implicit weighting by the event rate (ie, the sum of two fractions with different denominators).[29] For most of the longitudinal results on different organ damage, the

AUC and NRI performed better for the antibody-based model, highlighting that antibody status could better stratify people with systemic sclerosis compared with cutaneous subtype for severe organ damage. For the prognostic analysis, NRI shows superiority of antibody-based stratification for overall survival and progression-free survival. This difference was not observed using the AUC, perhaps due to the NRI's ability to detect smaller changes, which could better show the superiority of the antibody-based model. Another explanation would be related to the limitations of the AUC, including its insensitivity in comparing models when the reference model does well. This insensitivity could explain why the AUC is not different between our three models whereas the NRI detects a difference. To confirm these hypotheses and our stratification, validation in other prospective cohorts will be needed. In our longitudinal analysis we included only patients with a least one follow-up. The characteristics of the people with systemic sclerosis who were lost to follow-up suggested a milder disease, which might introduce some bias into our study. However, these individuals were included in the longitudinal analysis for all the different outcomes, and our models were adjusted for different disease characteristics. Moreover, as the sample size remains very large and the method robust with multiple outcomes studied and multiple imputations, we do believe that our results are reliable. Since the EUSTAR cohort includes mainly White individuals, our results are not generalisable to other races.

This study has several strengths. Data were derived from a large, multicentre cohort, with an extensive list of clinical, laboratory, and diagnostic variables. Data were collected prospectively by use of standardised forms. To minimise the effect of missing data on our results, we contacted each centre to obtain some missing information regarding autoantibody status and did multiple imputations. Furthermore, unlike previous cross-sectional clinical studies, we did longitudinal analyses studying the occurrence of each outcome across several visits (30 000 to 40 000 events per outcome). To decrease the potential bias related to changes in skin fibrosis over time, an exploratory analysis using the mRSS was done and produced similar results. We confirmed the association of known factors for severe organ involvement (eg, anti-RNA polymerase III for renal crisis; anti-topoisomerase-1 and male sex for lung fibrosis,[36] and DLCO <60% for pulmonary arterial hypertension) supporting the validity of our models. These results are also in line with clinical practice in which, for example, anti-RNA polymerase III antibodies will particularly guide our search for renal crisis.

Altogether, we show that the autoantibody status outperforms the use of common cutaneous subsets to risk stratify people with systemic sclerosis in the EUSTAR cohort. The subclassification of autoantibody-specific status is easily done and can be used by the clinicians to risk stratify their patients and to adapt disease monitoring in routine practice.

Contributors

ME, NS, MB, and YA formulated the study hypotheses and contributed to its design, literature search, composition of the tables and figures and redaction of the first draft and subsequent iterations of the manuscript. AB-G, ES, EH, JdV-B, GR, JHWD, ER, FDG, FAM, DEF, CdlP, A-MH-V, AG, OD, and YA conceived and launched the EUSTAR database, collected data in their respective countries and offered critical comments regarding the manuscript. ME, NS, MB, AB-G, ES, EH, JdV-B, GR, JHWD, ER, FDG, FAM, DEF, CdlP, A-MH-V, AG, OD, CB-Q, and YA did the data analysis and data interpretation. NS, MB, and CB-Q did the statistical analysis. ME, MB, and NS verified the data and had access to raw data. ME, MB, NS, and YA had final responsibility for the decision to submit for publication. All authors have finally approved the submitted version to be published.

Declaration of Interests

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Data sharing

No additional unpublished data from the study are available.

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