Stratification in systemic sclerosis according to autoantibody status versus skin involvement: a study of the prospective EUSTAR cohort

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STRATIFICATION IN SYSTEMIC SCLEROSIS ACCORDING TO AUTO-ANTIBODIES STATUS VERSUS SKIN INVOLVEMENT: A PROSPECTIVE STUDY OF EUSTAR COHORT

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Research in context

Evidence before this study

There is growing evidence that the current subclassification of systemic sclerosis (SSc) into cutaneous subtype does not capture the heterogeneity of SSc. We wondered whether a stratification by antibodies (that are searched in routine practice) would not allow a better stratification of SSc patients. We searched MEDLINE databases between January 1960 and June 2019 using the terms "(systemic, scleroderma or systemic sclerosis) [MesH] AND classification AND cutaneous AND antibody". Seventy articles could be identified, of which 4 corresponded to our question. In two observational cross-sectional studies, some outcomes were more associated with antibody status in particular lung involvement, whereas some others were more associated with cutaneous subtype. Another small-size cross-sectional study suggested to combine cutaneous involvement and antibody status, whereas highlighting the pitfalls of the current subclassification, another work suggested a stratification in 6 different clusters integrating organ damages, which could be difficult to perform in routine practice. Therefore, the respective performance of a subclassification of SSc patients into antibodies status, cutaneous form or a combination of both remained unknown, particularly regarding disease progression.

Added value of this study

In our longitudinal cohort of more than 10,000 European patients with analysis of a considerable number of events (on average three visits per patient), we could clearly demonstrate the superiority of a model based on auto-antibody status to diagnose the majority of severe organ damages. Moreover, we showed for the first time that the antibody status is more performant to predict overall survival and disease progression over 4-years follow-up.

Implications of all the available evidence

Altogether the results of this study combined with available evidence are of paramount importance, as they may change clinical practice with the proposal of classification according to autoantibodies and not according to skin subtype. This easily performed subclassification using autoantibodies specific status could help the clinicians to risk-stratify their patients and to adapt disease monitoring in routine practice. Moreover these results could have implications in designing clinical trials with enrichment of patients according to their antibody status, which could help in identifying effective drugs in this devastating disease.

ABSTRACT

Objective: To compare the performances of stratification into LeRoy's cutaneous subtypes versus autoantibody status in systemic sclerosis.

Methods: Patients from the EUSTAR database were classified either as (i) limited cutaneous subtype, diffuse cutaneous subtype or sine scleroderma or (ii) according to specific systemic sclerosis autoantibodies or (iii) according to cutaneous subtype and autoantibodies. The respective performance of each model to predict overall survival (OS), progression-free survival (PFS), disease progression and different organ involvements was assessed. The three models were compared by the area under the curve (AUC) and the net reclassification improvement (NRI). Missing data were imputed through multiple imputation using chain equations.

Results: 10'711 patients were included: 1647/10709 (15.4%) of males, mean age: 54.4±13.8 years and mean disease duration: 7.9±8.2 years. In the prospective analysis (n= 7'823 to 7'830), there was no difference in AUC for OS (0.82 [0.81-0.84] for the cutaneous-only model vs. 0.837 [0.82-0.85] for the antibody-only model vs. 0.84 [0.83-0.86] for the combined model) or for PFS (0.70 [0.690-0.71] vs. 0.708 [0.70-0.718]) vs. 0.71 [0.70-0.72]). However, the NRI at 4 years showed a significant improvement in prediction of OS (0.57 [0.46-0.71] vs. 0.29 [0.19-0.39]) and disease progression (0.36[0.29-0.46] vs. 0.21[0.14-0.28]) using the antibody-only model as compared to the cutaneous-only model. The antibody-only model performed better than the cutaneous-only model to diagnose renal crisis (AUC: 0.72 [0.70-74] vs. 0.66[0.64-0.68]) 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 diagnosis of digital ulcers and elevated sPAP, but performed poorly for cardiac involvement.

Conclusion: Auto-antibody-alone model outperforms the cutaneous-only subsetting for risk-stratifying systemic sclerosis patients in the EUSTAR cohort. Physicians should be aware of these findings at the time of decision making for their patient management.

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IRB approval: Each participating center obtained approval of the local ethics committee and all registered patients granted their informed consent.

KEY WORDS: systemic sclerosis; auto-antibodies, cutaneous subtype, classification.

INTRODUCTION

Risk-stratification is key in a heterogeneous disease like systemic sclerosis. Patients with systemic sclerosis are so far primarily sub-classified into diffuse cutaneous systemic sclerosis, limited cutaneous systemic sclerosis and sine scleroderma subtypes according to the extent of skin involvement (1). Accumulating evidences support that the actual classification is inadequate to capture disease heterogeneity (2, 3). Therefore, there is a need to improve the subclassification of the patients to improve decision making for the management and follow-up. This fits with the current development of precision medicine, which must be investigated in a severe disease like systemic sclerosis (4, 5).

Several factors may drive the pitfalls of the current "skin" classification: the modified Rodnan skin score (mRSS) requires training and should be performed by the same assessor to reduce the variability (6, 7), which is not always possible in clinical practice. For a correct classification of a new patient, one should wait until the peak of skin thickness is reached, which could need several years (8).

Antinuclear antibodies (ANA) are detected in more than 90% of systemic sclerosis-patients and are present several years before disease onset (9-11). Among them, three predominant and specific antibodies are observed: anti-centromere (ACA), anti-Scl70, and anti-RNA polymerase III (anti-RNA pol III) antibodies (12). In a preliminary cross-sectional study of the EULAR Scleroderma Trials and Research (EUSTAR) group on 3'656 patients, autoantibody status was more closely associated with clinical manifestations than cutaneous subsets (10). However, there was no longitudinal analyses and since the latter report, the database has grown to >20'000 patients. Altogether, the respective performance of a subclassification of systemic sclerosis patients into antibodies 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 autoantibody status versus combination of cutaneous subtypes and autoantibody status according to (i) disease progression and survival and (ii) organ involvements in a large international multicenter cohort of systemic sclerosis patients.

METHODS

Study design

The ongoing EUSTAR database is a multicenter online database that contains prospectively collected data from more than 20,000 systemic sclerosis patients in more than 180 international centers (list of co-authors in Appendix pages 1-2). The structure of the database, the minimum essential data set and the inclusion criteria have been described in detail previously (13). Each patient's annually scheduled visit for medical purposes is recorded providing longitudinal observational data. Participating centers are expert centers only, and each EUSTAR center is trained by EUSTAR-specific courses including the definitions for disease entities as, e.g., scleroderma renal crisis (14). Each participating center obtained approval of the local ethics committee.

We interrogated the EUSTAR database on the 26th of July 2019, providing information on 16'939 patients (registered since 2010 corresponding to the start of the online version). Inclusion criteria were availability of the data regarding systemic sclerosis related antibody status (12). We surveyed participating centres to record information on anti-pol III RNA status that was missing from the first database extract. Patients with two positive antibodies and patients with one missing data in systemic sclerosis-related autoantibodies were excluded. In all, 10'711 were included (Figure 1). Patients were stratified either as (i) limited cutaneous systemic sclerosis, diffuse cutaneous systemic sclerosis or sine scleroderma (based on the recording made by the treating physician) or (ii) according to autoantibodies as follows (1) no specific autoantibodies, (2) isolated ANA, (3) ACA, (4) anti-Scl70 and (5) anti-RNA pol III antibodies or (iii) according to cutaneous subset and auto-antibodies (combined model). As an exploratory analysis, we also assessed the performance of a stratification of the cutaneous subset according to mRSS (14/51≤ diffuse mRSS, limited 1≤mRSS<14, sine scleroderma mRSS: 0/51) (15). Our models were also assessed in incident patients (disease duration < 1

year) and in patients with an early disease < 4 years. Stratification was performed at baseline without change over time for the prospective analysis. For the longitudinal analysis, stratification was performed at each visit according to the skin form and antibody status recorded in the database at the date of the visit.

Disease characteristics

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

Outcome measures and definitions

Lung fibrosis was defined as ground glass opacities or traction bronchiectasis or reticular or "honey combing" on chest high-resolution computed tomography (HRCT).

Patients with at-least one follow-up visit were included in the prospective analysis. Overall survival was defined as the time from the first visit until last follow-up or death (any cause).

Progression-free survival was defined as the time from the first visit until worsening of (i) dermal fibrosis (≥ 5 points and 25% of increase in mRSS) (8), and/or (ii) of lung involvement (decrease of ≥ 10% in forced vital capacity (FVC) or ≥15% in the diffusing capacity for carbon monoxide (DLCO) in patients with known lung fibrosis (16, 17) or occurrence of lung fibrosis *de novo*) and/or (iii) elevated systolic pulmonary artery pressure (sPAP) >45 mm Hg by echocardiography used as a surrogate marker for pulmonary arterial hypertension (18) and/or (iv) of renal crisis *de novo* and/or (v) death. Disease progression was defined as the time from the first visit until progression-free survival without death. The occurrence of the following outcomes were assessed during the follow-up (10, 13, 19): digital ulcers (current or

previous), upper gastro-intestinal (GI) or/and lower GI involvement, renal crisis, heart dysfunction defined by left ventricular ejection fraction LVEF<50% on transthoracic echocardiography, lung fibrosis (on HRCT), restrictive lung fibrosis (defined by lung fibrosis on HRCT and reduced FVC below 70%) and systolic pulmonary artery pressure (sPAP) >45 mm Hg on echography (18).

Statistical Analysis

The data collected were described using the number and the percentage (%) for qualitative variables. Mean and standard deviation (SD) were used for quantitative variables. The performance of each outcome was assessed using mixed effect logistic regressions models for organ involvement and Cox proportional hazards regressions models for overall survival, progression-free survival and disease progression with the covariates of interest: antibodies status and cutaneous subtypes. The Odd-Ratio (OR) or Hazard ratio (HR) and their 95% confidence intervals (95% CI) 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 the receiver operating characteristic (ROC) curves (AUC) of the three models. AUC shows the strength of discrimination between methods. AUC takes a value in the interval [0 - 1], where a random classifier has a score of around 0.5, 0.7 to 0.8 is considered acceptable, 0.8 to 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, the net reclassification index (NRI), which is based on reclassification tables constructed separately for participants with and without events, has been proposed and was shown to offer incremental information over the AUC for the prediction models (21). The NRI assesses the improvement of an added model in comparison with a base model. To circumvent the issues related to threshold determination,

252 the continuous NRI was used. It is interpreted as the net percentage of persons reclassified
253 upwards (improved reclassification) and downwards (worse reclassification) for events (NRI-
254 event) and non-events (NRI non-event) separately with a range of -100% to 100%. NRI event
255 and NRI non-event provide information on how the new risk model (potentially) improves
256 prediction for events and, separately, for non-events. The NRI event and non-event can be
257 interpreted as the net change in the proportion of subjects assigned a more appropriate risk
258 under the new model. Overall NRI is the sum of the NRI-event and NRI non-event and can be
259 interpreted as a unitless statistic. A positive overall NRI means an upward "movement"
260 (improvement in reclassification) and a negative NRI a downward "movement " (worsening
261 in reclassification) (22). The maximum value of the overall NRI is 2 indicate better
262 discrimination and the minimum value is -2 indicate poor discrimination. To capture small
263 changes not detected using AUC, the NRI of our different predictive models, as post-hoc
264 analysis was assessed (23). NRI and AUC were evaluated at two and four years (from
265 database entry, i.e. first visit) for overall survival, progression-free survival and disease
266 progression. Multiple imputation chain equation was performed to account for the missing
267 data in covariates. The number of multiple imputations was set to twenty five with 5 iterations
268 for prognostic analysis and sixteen with 5 iterations for longitudinal analysis (24). There was
269 no cut-off for imputation in regard to missing values. Our models were adjusted upon
270 imputation by covariates that could possibly influence the outcomes according to the literature
271 and the Nelson Aalen estimator of the cumulative hazard with death status for the prognostic
272 analysis. The results were aggregated by pooling the estimates obtained on each imputed data
273 set according to Rubin's rules. We used confidence intervals for our models as it was shown
274 that even small NRI values (<0.01) might produce statistically significant p values (22, 25,
275 26). Therefore it was suggested that statistical testing should be avoided for the NRI measure.
276 Confidence intervals provide precision estimates and are preferable, not only for the overall

NRI, but also for its components (22, 25, 26). Statistical analyses were carried out using R Project for Statistical Computing, Version 3.5.2 software (The R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org/).

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RESULTS

In all, 10'711 patients from 159 centers, fulfilling the 2013 criteria for systemic sclerosis (12) (Strobe Checklist in appendix pages 3-4 and Figure 1) were included: 1'647/10'709 (15.4%) males, mean age (± SD): 54.4 (± 13.8) years and mean disease duration: 7.9 (± 8.2) years. 6'533/10'176 (64.2%) had limited cutaneous systemic sclerosis, 2'895/10'176 (28.4%) diffuse cutaneous systemic sclerosis and 748/10'176 (7.4%) systemic sclerosis sine scleroderma. Of the 10'711 patients, 9'176/9'643 (95.2%) were ANA positive: 2'707/9'643 (28.1%) isolated ANA, 3'512/9'643 (36.4%) ACA, 2'658/9'643 (27.6%) anti-Scl 70 and 299/9'643 (3.1%) anti RNA pol III antibodies (Table 1).

During a median [95%CI] follow-up of 56 months [55-58], a median number of three visits per patients was recorded (number of events during the longitudinal follow-up in Appendix page 5).

After four years, 777/7'823 deaths (9.9%) were recorded, 2'875/7'829 progression-free survival (36.7%) and 2'340/6'467 disease progression (36.2%). The comparison of patients with missing follow up could suggest a milder disease (Appendix page 6).

Overall survival and progression-free survival differed according to antibody 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 (Tables 2 and Appendix pages 7-15). Using the NRI, the antibody only model outperformed the cutaneous only model to predict survival

(0.57 [0.46-0.71] vs. 0.29 [0.19-0.39]) (NRI event: 0.21 [0.1 ; 0.34] vs. -0.02 [-0.11 ; 0.07] and NRI non-event 0.36 [0.34; 0.38] vs. 0.31 [0.28 ; 0.33]) and disease progression (0.36 [0.29-0.46] vs. 0.21 [0.14-0.28]) (NRI event: 0.22 [0.15 ; 0.28] vs. -0.17 [-0.22 ; -0.1] and NRI non-event: 0.14 [0.08-0.18] vs. 0.40 [0.36-0.43]) at 4 years (Tables 3 and Appendix pages 7-15). The combined model had similar performances as the antibody only model (Appendix pages 7-15). The results were similar at 2 years (Appendix page 16).

We aimed to delineate the respective performance of the models in predicting each organ involvement in longitudinal analyses (NRI event and non-event in Appendix pages 17-18). The antibody only model better predicted digital ulcers as compared to the cutaneous only model using NRI (but not AUC) (0.31 [0.29-0.33] vs. 0.24 [0.22-0.26]) with the highest association with anti-Scl70 antibodies (OR: 3.57 [2.68-4.75], $p<0.0001$) (Tables 2-3 and Appendix pages 17-20). However, improvements in NRI global were explained by the NRI non-event (Appendix pages 17-18).

The antibody only model outperformed the cutaneous only model in predicting renal crisis (AUC: 0.72 [0.70-74] vs. 0.66 [0.64-0.69]) with the highest association with anti-RNA pol III (OR: 7.47 [1.63-34.24], $p= 0.010$) (Table 2 and Appendix pages 21-22). Similarly, the antibody only model outperformed the cutaneous only model in predicting lung fibrosis (AUC 0.72 [0.72-72] 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-Scl70 antibodies (OR: 9.29 [8.17-10.55] and 7.92 [5.37-11.69], respectively, $p<0.0001$ for both) (Table 2 and Appendix pages 23-26). This was confirmed using the NRI (Table 3 and Appendix pages 17-18). In particular, the NRI event (for presence of lung fibrosis or restrictive lung fibrosis) of antibody only model largely outperformed the NRI event of the cutaneous only model (which were negative).

There was no difference in AUC in predicting the occurrence at least at one visit of upper GI involvement, but the NRI showed improvement using cutaneous only model (Tables 2-3,

Appendix pages 17-18 and pages 27-28). This improvement was explained by better detection of non-events (NRI event negative, NRI non-event positive).

The two models had similar performances in assessing occurrence of intestinal involvement, heart dysfunction defined by LVEF < 50% or elevated sPAP by echocardiography at at-least one visit (Tables 2-3 and Appendix pages 17-18 and pages 29-35).

The combined model showed similar performances as the antibody only model in all the studied outcomes, except for digital ulcers, which were better diagnosed using the combined model using AUC but not NRI. The combined model showed better performances to diagnose elevated sPAP by echocardiography and upper GI involvements than the antibody only model using NRI, but not AUC. However this improvement was explained by a better detection of non-events (NRI non-event) (Tables 2-3 and Appendix pages 7-35). In the exploratory analysis, there was no change using mRSS instead of the cutaneous subset (Appendix page 26 and 35). In incident patients with a disease duration < 1 year and in patients with early disease duration < 4 years, the predictors were essentially the same but there was no difference between the models (Appendix pages 36-48).

DISCUSSION

A more accurate risk-stratification of the patients is required in such a dreadful disease as systemic sclerosis, and recently 10% of international systemic sclerosis experts underlined pitfalls of the actual cutaneous-based subclassification (27). Here we showed that stratifying systemic sclerosis patients according to autoantibodies better predicts (i) overall survival and disease progression and (ii) the different organ damages than a stratification according to cutaneous subtype. The antibody only models is easily and widely available through the large dissemination of antibody assays. Moreover auto-antibody testing is usually done for classifying the disease as it is a part of the 2013 criteria (12) and antibodies are usually mutually exclusive in a single patient (28), which is giving an easy picture for each patient. Accurate and objective measurements with a high reproducibility qualify them therefore as suitable biomarkers.

The direction was shown in a previous EUSTAR study on 3'656 patients, where 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 monocentric study on 551 patients, combining cutaneous involvement and antibody status predicted more accurately the different outcomes than cutaneous subset or antibody status alone (29). Consistently Nihtyanova et al. suggested a subclassification into seven groups associating autoantibody specificity and skin involvement in their monocentric cohort of 1'325 patients (30). In our multicentric cohort, the combined model obtained similar performances for most of the outcomes as the autoantibodies model, but better performances for digital ulcers, for GI involvements and elevated sPAP. However, this improvement was mostly explained by a better detection of non-events. Moreover heart involvement was poorly diagnosed 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 provides 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 (i) monitoring adapted according to autoantibody status rather than cutaneous subtype, (ii) treatment strategies stratified according to autoantibody status (e.g. more aggressive treatment in high-risk patients), and (iii) enrichment in clinical trials in severe and progressive forms on the basis of their autoantibodies status (e.g. positivity for anti-Scl70 antibodies), in whom the effect of treatment will be easier to demonstrate. A recent EUSTAR data-based study proposed six homogenous clusters to stratify systemic sclerosis-patients (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 be easily performed in routine practice, which limits its application as a suitable circulating marker.

Although the progression of disease according to antibody type was consistent with published data, patients without antibodies or with isolated ANA had a worse overall survival. This surprising finding should be treated with caution as the number of patients without any antibodies was small (<5% of our cohort). One may suggest that these patients could represent specific systemic sclerosis forms, maybe paraneoplastic forms (32, 33). Furthermore, the interpretation of the survival curves must be done 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 main systemic sclerosis autoantibodies and excluded rarer autoantibodies. Our aim was to improve systemic sclerosis stratification, therefore, we focused only on systemic sclerosis specific autoantibodies performed in routine practice by systemic sclerosis centers. Future works are needed to determine if a stratification

according to antibodies status could be valuable in systemic sclerosis and overlap syndromes with non-specific systemic sclerosis auto-antibodies, i.e anti-RNP, anti-Ku … Furthermore, due to missing data we could not specifically study the impact of the location of skin fibrosis on the prognosis. In addition, our model did not perfectly predict all outcomes. More advanced clustering statistics could be used in the future to further explore the data and further improve patient stratification. The use of NRI in prediction models is a matter of debates (34). NRI provides information that the AUC does not give. Each index evaluates performance differently and provides different information. NRI detects smaller changes than the AUC (21) and allows to quantify the improvement in classification, which can be valuable for a clinical use (35). Therefore, the combination of the two indexes to assess our models increases the robustness of our analysis. Contrary to NRI event and non-event which present a simple interpretation, the overall NRI is less so because of the implicit weighting by the event rate: sum of two fractions with different denominators (29). It is worth noting that for most of the longitudinal results on different organ damage, the AUC and NRI showed better performance for the antibody-based model, highlighting that antibody status could better stratify systemic sclerosis patients as compared to cutaneous subtype for severe organ damage. For the prospective analysis, NRI shows superiority of antibody based stratification for overall survival and progression-free survival. This difference was not observed using the AUC. One may argue that the NRI able of detecting smaller changes could better demonstrate the superiority of the antibody-based model. Another explanation would be related to the negative points of the AUC which is its insensitivity in comparing models when the reference model performs well. This could explain the fact that the AUC is not different between our three models while the NRI detects a difference. To confirm these hypotheses and our stratification, validation in other prospective cohort will be needed. We included in our longitudinal analysis only patients with a least one follow-up. The characteristics of the

patients lost to follow-up suggested a milder disease, which may introduce some bias into our prospective study. However, these patients were included in the longitudinal analysis for all the different outcomes and our prospective models were adjusted for different disease characteristics. Moreover, as the sample size remains very large, the methodology robust with multiple outcomes studied and multiple imputations, we do believe that our results are reliable. Since EUSTAR cohort includes mainly white Caucasians, our results could not be generalizable to other ethnicities.

Our study has several strengths: data were derived from a large, multicenter cohort, with an extensive list of clinical, laboratory and diagnostic parameters. The data are collected prospectively using standardized forms. To minimize the impact of missing data on our results, we contacted each center to obtain some missing information regarding autoantibodies status and performed multiple imputations. Furthermore, unlike previous cross-sectional clinical studies, we performed longitudinal analyses studying the occurrence of each outcome at several visits (30'000 to 40'000 events per outcome). To decrease potential bias related to changes of the skin fibrosis over time, an exploratory analysis using the mRSS was performed and led to similar results. We confirmed the association of known factors for severe organ involvement (e.g. anti-RNA pol III for renal crisis; anti-Scl70 and male sex for lung fibrosis (36) and DLCO<60% for PAH) supporting the validity of our models. These results are also in line with the clinical practice where e.g. anti-RNA pol III antibodies will particularly guide our search for renal crisis.

Altogether, we show that the autoantibody status outperforms the common cutaneous subsetting to risk-stratify systemic sclerosis patients in EUSTAR cohort. This easily performed subclassification using autoantibodies specific status can be used by the clinicians to risk-stratify their patients and to adapt disease monitoring in routine practice.

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Sritharan N, Boubaya M, Bloch-Queyrat C performed the statistical analysis

Muriel Elhai, Marouane Boubaya and Nanthara Sritharan verified the data and had access to raw data.

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564 Table 1: Characteristics of the included patients at baseline

	General population (n=10711)
Age, years	54·4 ± 13·8
n patients with available data	10699/10711 (0·4%)
Disease duration, years	7·9 ± 8·2
N patients with available data	9140/10711 (14·7%)
Sex	
Male	1647/10709 (15·4%)
Female	9062/10709 (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	6533/10176 (64·2%)
diffuse	2895/10176 (28·4%)
sine SSc	748/10176 (7·4%)
Antibody status	
No antibody	467/9643(4·8%)
isolated ANA	2707/9643 (28·1%)
ACA	3512/9643 (36·4%)
anti-Scl70	2658/9643 (27·6%)
anti-RNA pol III	299/9643 (3·1%)
Joint synovitis	1363/10472 (13%)
Tendon friction rubs	744/10377 (7·2%)
Joint contractures	2600/10448 (24·9%)
Muscular involvement	2309/10342 (22·3%)
CRP≥10 mg/L	258/2210 (11·7%)
Digital ulcers	
current	451/4073(11·1%)
previous	1035/4073 (25·4%)
Upper GI involvement	6273/10411 (60·3%)
Intestinal involvement	2510/10587 (23·7%)
Scleroderma renal crisis	207/10547 (2%)
LVEF<50%	102/5203(2%)
Systolic PAP>45 mmHg by echocardiography	333/4770 (7%)
Lung fibrosis	2030/5066 (40·1%)
Lung fibrosis + FVC<70%	448/6489 (6·9%)
DLCO<60%	2261/7874 (28·7%)
Immunosuppression	2526/8397 (30·1%)
Steroids treatment	2264/7441 (30·4%)
Steroids dosage, mg ,N patients with available data	2·8 ± 6, 6860/7441
Steroids≥10mg/day	732 (10·7%)
Scleroderma pattern on capillaroscopy	3873/4452 (87%)

Data are presented as n patients /n available data, ANA, antinuclear antibodies; ACA, anticentromere; anti-Scl70: anti-topoisomerase 1; anti-RNA pol III: anti-RNA polymerase III; CRP: c-reactive protein; GI: gastro-intestinal; LVEF: left ventricular ejection fraction; PAH: pulmonary arterial hypertension (diagnosed on right heart catheterization); PAP: pulmonary arterial pressure; lung fibrosis diagnosed on high resolution computed tomography; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; Immunosuppressive drugs include methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, anti-TNF alpha, rituximab, tocilizumab and abatacept. The different outcomes are diagnosed according to EUSTAR definitions. Values are mean±SD or numbers (%) of observations.

Table 2: AUC 95% CI of the different models for diagnosis of the different outcomes (longitudinal and prospective analysis)

Outcome	Cutaneous only model	Antibody only model	Combined model
Survival at 4 years	0·824 [0·809 ; 0·841]	0·837 [0·822 ; 0·851]	0·841 [0·827 ; 0·856]
Progression-free survival at 4 years	0·701 [0·690 ; 0·712]	0·708 [0·696 ; 0·718]	0·710 [0·698 ; 0·720]
Disease progression at 4 years	0·676 [0·665 ; 0·687]	0·683 [0·671 ; 0·694]	0·685 [0·672 ; 0·695]
Digital ulcers	0·632 [0·627;0·637]	0·637 [0·631;0·642]	0·649 [0·644;0·655]
Upper gastro-intestinal involvement	0·577 [0·571;0·583]	0·566 [0·561;0·571]	0·583 [0·578;0·589]
Intestinal involvement	0·569 [0·562;0·574]	0·570 [0·563;0·576]	0·577 [0·571;0·582]
Renal crisis	0·664 [0·643;0·685]	0·719 [0·696;0·742]	0·729 [0·708;0·752]
LVEF<50%	0·665 [0·642;0·689]	0·650 [0·626;0·673]	0·649 [0·625;0·674]
Lung fibrosis	0·653 [0·647;0·659]	0·719 [0·715;0·724]	0·722 [0·717;0·726]
Restrictive lung fibrosis	0·711 [0·701;0·721]	0·759 [0·749;0·766]	0·766 [0·758;0·773]
Elevated sPAP by echocardiography	0·761 [0·752;0·772]	0·762 [0·752;0·774]	0·763 [0·753;0·775]

AUC: area under the curve; GI: gastro-intestinal; LVEF: left ventricular ejection fraction; lung fibrosis diagnosed on high resolution computed tomography; restrictive lung fibrosis was considered in cases of lung fibrosis with FVC<70%; PAH: pulmonary arterial hypertension (defined as systolic pulmonary arterial pressure ≥45 mmHg). 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 the first time until worsening of dermal fibrosis (≥ 5 points and 25% of increase in modified Rodnan skin score and/or of lung fibrosis (decrease of ≥ 10% in FVC or ≥15% in the diffusing capacity for carbon monoxide (DLCO) in patients with known lung fibrosis or lung fibrosis and/or elevated sPAP (systolic pulmonary artery pressure) >45 mm Hg used as a surrogate marker for pulmonary hypertension and/or of renal crisis de novo.

Table 3: Absolute NRI 95% CI for the 3 models for the longitudinal and prospective analysis

Outcome	Cutaneous only model	Antibody only model	Combined model
Survival at 4 years	0·29 [0·19 ; 0·39]	0·57 [0·46 ; 0·71]	0·50 [0·40 ; 0·62]
Progression-free survival at 4 years	0·23 [0·16 ; 0·32]	0·36 [0·28 ; 0·43]	0·36 [0·29 ; 0·45]
Disease progression at 4 years	0·21 [0·14 ; 0·28]	0·36 [0·29 ; 0·46]	0·36 [0·28 ; 0·48]
Digital ulcers	0·24 [0·22 ; 0·26]	0·31 [0·29 ; 0·33]	0·32 [0·30 ; 0·34]
Upper gastro-intestinal involvement	0·11 [0·1 ; 0·13]	0·05 [0·03 ; 0·07]	0·17 [0·15 ; 0·19]
Intestinal involvement	0·07 [0·05 ; 0·09]	0·08 [0·06 ; 0·11]	0·09 [0·07 ; 0·11]
Renal crisis	0·46 [0·37 ; 0·53]	0·56 [0·49 ; 0·62]	0·52 [0·43 ; 0·58]
LVEF<50%	0·28 [0·21 ; 0·35]	0·17 [0·09 ; 0·24]	-0·08 [-0·13 ; -0·04]
Lung fibrosis	0·30 [0·28 ; 0·32]	0·55 [0·53 ; 0·57]	0·55 [0·53 ; 0·57]
Restrictive lung fibrosis	0·41 [0·37 ; 0·46]	0·61 [0·59 ; 0·64]	0·62 [0·59 ; 0·64]
Elevated sPAP by echocardiography	-0·03 [-0·07 ; 0·02]	-0·006 [-0·06 ; 0·04]	0·13 [0·08 ; 0·17]

NRI: net reclassification improvement. 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 the first time until worsening of dermal fibrosis (≥ 5 points and 25% of increase in modified Rodnan skin score), and/or of lung fibrosis (decrease of ≥ 10% in FVC or ≥15% in the diffusing capacity for carbon monoxide (DLCO) in patients with known lung fibrosis or lung fibrosis and/or elevated sPAP (systolic pulmonary artery pressure) >45 mm Hg used as a surrogate marker for pulmonary hypertension and/or of renal crisis de novo.

FIGURE LEGENDS

Figure 1. Flow chart for inclusion of patients in the analysis and number of patients analyzed for each outcome. GI: gastro-intestinal, LVEF: left ventricular ejection fraction, PAH: pulmonary arterial hypertension, lung fibrosis diagnosed on high resolution computed tomography, restrictive lung fibrosis was considered if forced vital capacity was below 70%, OS: overall survival, PFS: progression-free survival, DP: disease progression.

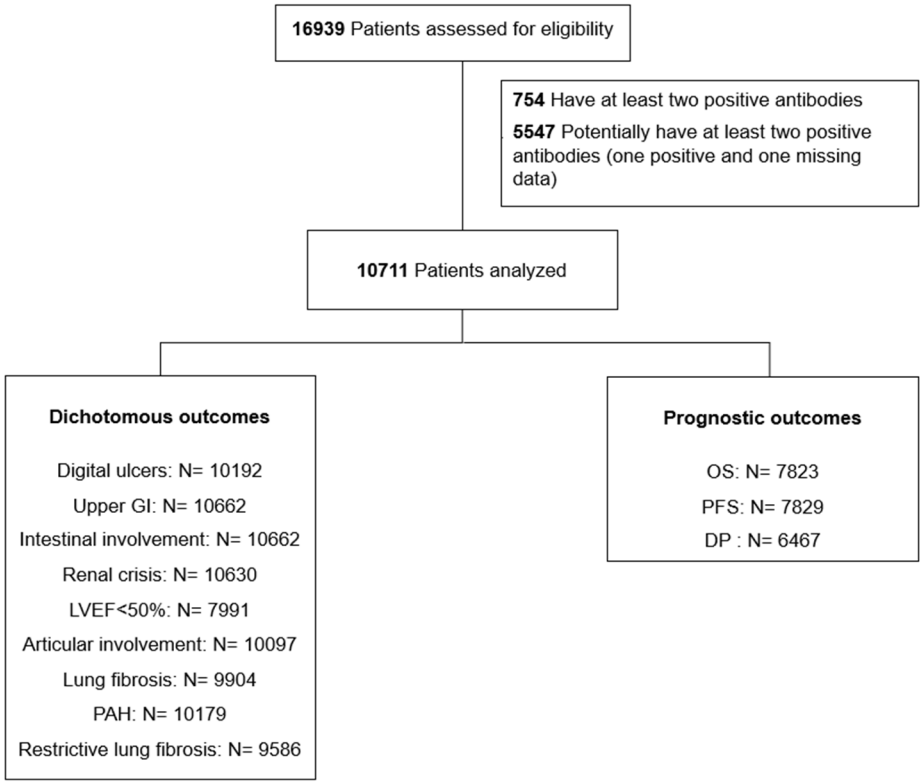
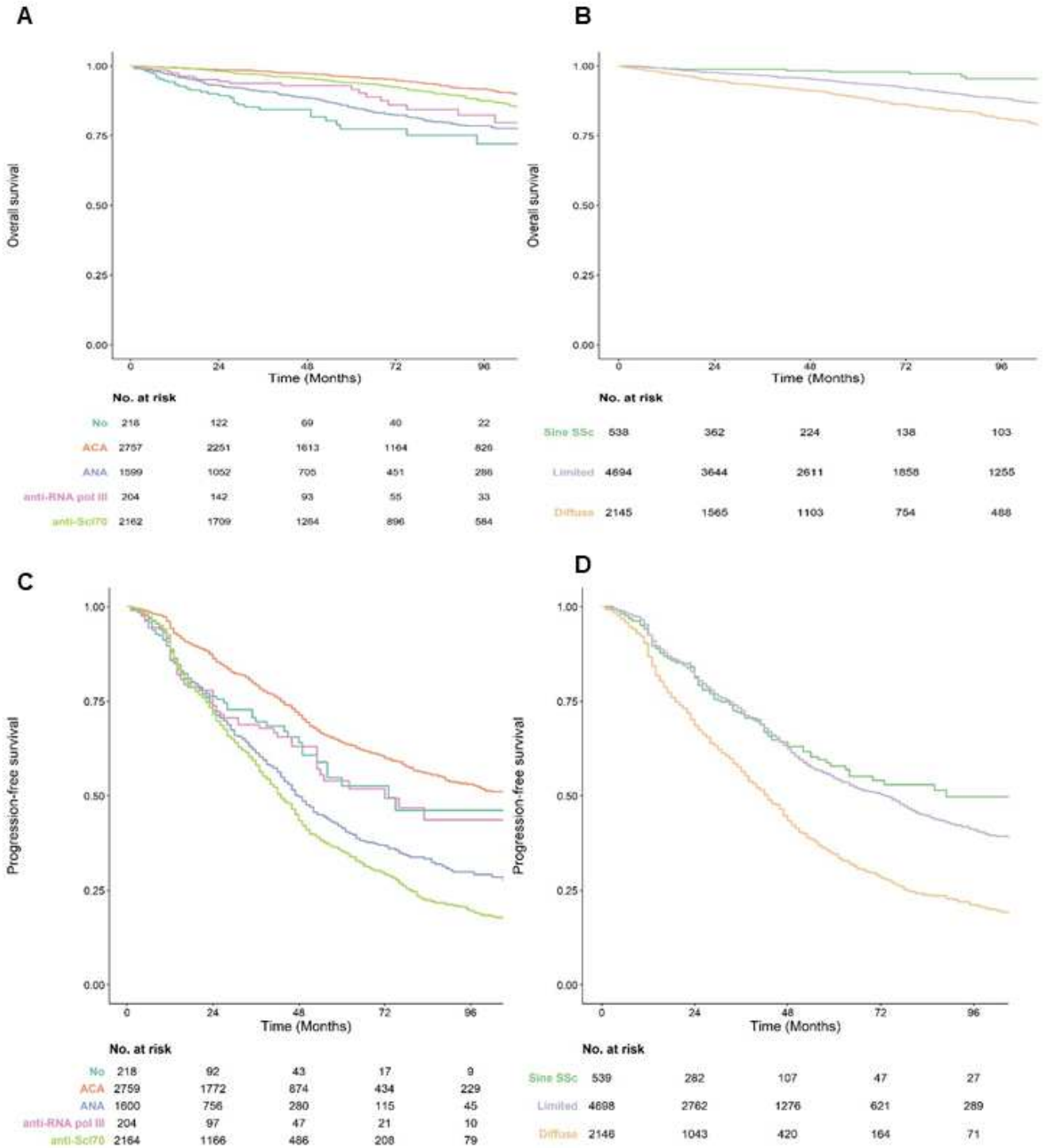


Figure 2: Kaplan-Meier survival curves for overall survival and progression-free survival: (A) Overall survival according to auto-antibodies (no specific autoantibodies, isolated ANA, ACA (anticentromere) antibodies, anti-Scl70 antibodies and anti-RNA polymerase III antibodies) Log rank test $p < 0.0001$. (B) Overall survival according to cutaneous subtype (sine scleroderma, limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis), Log rank test $p < 0.0001$. (C) progression-free survival according to auto-antibodies(no specific autoantibodies, isolated ANA, ACA antibodies, anti-Scl70 antibodies and anti-RNA polymerase III antibodies), Log rank test $p < 0.0001$. (D) Progression-free survival (PFS) according to cutaneous subtype (sine scleroderma, limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis). PFS was defined as

the time from the first visit until worsening of dermal fibrosis (≥ 5 points and 25% of increase in modified Rodnan skin score), or lung fibrosis (decrease of ≥ 10% in forced vital capacity or ≥15% in the diffusing capacity for carbon monoxide in patients with known lung fibrosis or



pulmonary arterial hypertension or renal crisis de novo or death, Log rank test $p < 0.0001$

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