

Figure 2. Kaplan–Meier curves illustrating cumulative survival by disease onset pattern. Patients with RP-first onset show better survival compared to those with simultaneous or NRP-first onset. Tick marks indicate censored observations. Differences were assessed using the log-rank test. NRP, non-Raynaud’s phenomenon onset; RP, Raynaud’s phenomenon onset; SG, Simultaneous group onset.

and reduced 10-year survival.^{10,11} More recently, another Italian study examined the sine scleroderma subset in the SPRING registry, showing a longer RP-to-diagnosis interval in ssSSc than in lcSSc and dcSSc.¹² Comparably, two analysis of the international EUSTAR registry are in line with our data. While Hügler *et al.*²⁸ demonstrated that late-onset SSc was associated with a higher prevalence of pulmonary hypertension and cardiac dysfunction, but milder cutaneous involvement and worse survival, Jaeger *et al.*²⁹ confirmed that age and timing of symptom onset influenced the risk and time of onset of major organ manifestations, including ILD and PAH. These observations are consistent with our results and support the face validity of our patient stratification system based on mode of onset. Unlike these earlier works, our study broadens the framework by introducing a distinct “Simultaneous onset” group, integrated age at RP and NRP onset, explored its relationship with antibody profiles and clinical phenotypes, and performed survival analyses adjusted for comorbidities. These aspects extend previous findings and highlight the potential of onset patterns as a practical tool for patient stratification in real-life.

The Spanish Scleroderma Registry reported that approximately 17% of patients presented with NRP onset, which was associated with a higher

likelihood of developing dcSSc and an increased risk of severe outcomes, including early visceral involvement, ILD, and PAH. Interestingly, our cohort revealed a markedly lower proportion of patients with NRP-first onset (2.2%). This discrepancy may reflect differences in study design, patient selection, or data collection methods, particularly regarding the timing and characterization of early symptoms. Notably, the inclusion in our study of a distinct “Simultaneous onset” group, representing patients who developed RP and NRP symptoms within the same year, may have contributed to a more refined classification. This intermediate category potentially encompassed individuals who, in other cohorts, might have been classified under the NRP group, thereby explaining the lower prevalence observed in our data.

By distinguishing the simultaneous group, our classification captures the heterogeneity of SSc onset more effectively and identifies a subset of patients with a particularly aggressive clinical course. This approach strengthens early risk stratification and supports tailored management strategies aimed at improving outcomes. Interestingly, a similar approach has been applied in other connective tissue diseases. In antisynthetase syndrome (aSyS), the temporal sequence of clinical

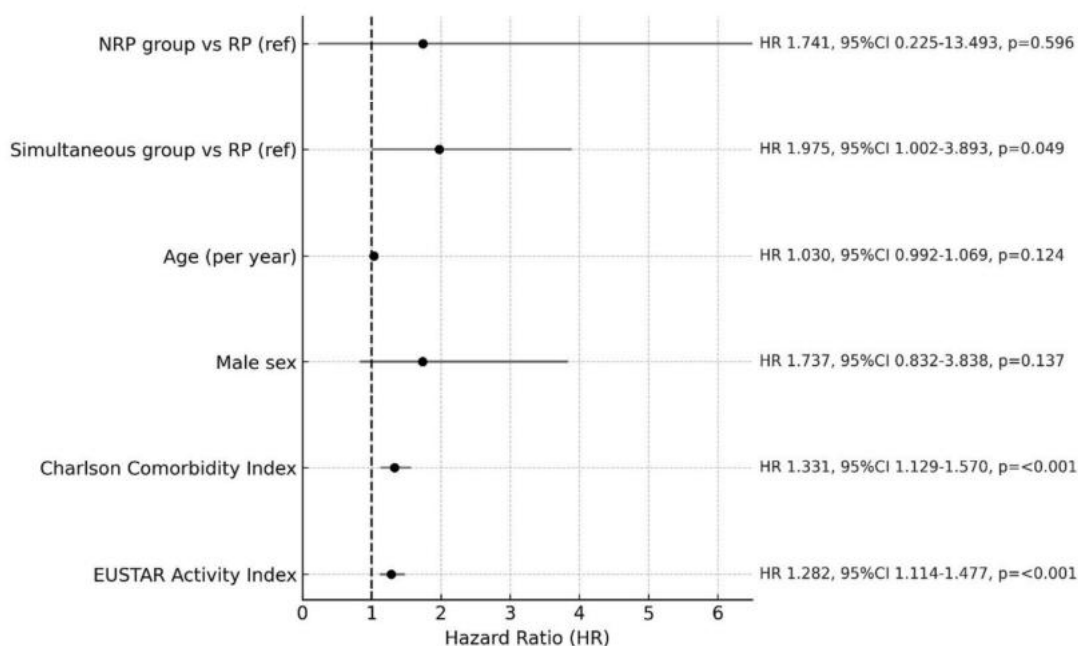


Figure 3. Prognostic factors related to mortality in a Cox regression model. EUSTAR, European Scleroderma Trial and Research; NRP, non-Raynaud's phenomenon; RP, Raynaud's phenomenon.

features at onset has been linked to specific phenotypes and outcomes. In large international cohorts, earlier onset of aSyS-ILD was associated with more severe disease courses and worse pulmonary outcomes.^{30,31} Although the pathogenetic mechanisms and target organs differ from SSc, these findings reinforce the notion that the timing of symptom onset is a clinically relevant stratification tool across autoimmune connective tissue diseases, supporting our approach to clustering patients into groups with different mode of onset.

While NRP onset has been associated with the presence of dcSSc,³² evidence regarding its direct impact on survival remains limited. The absence of robust survival studies hampers the ability to fully evaluate the prognostic significance of NRP onset and its role in long-term outcomes.

In contrast, more is known about age-related differences in RP onset. Indeed, older age at onset is associated with ACA positivity and lcSSc, while younger onset more commonly linked to dcSSc and ATA antibodies.^{28,33–35} However, late-onset patients also face worse outcomes, including higher rates of organ involvement such as ILD, PAH, and cardiac complications.³⁶

In the present study, the division of patients into the RP, simultaneous, and NRP onset subgroups

identify more clearly the different clinical–prognostic SSc scenarios observable in real life because of the different timing of RP onset.

It allows us to reveal significant differences in the distribution of clinical manifestations and autoantibody profiles, supporting the role of RP-NRP onset pattern in the disease stratification. The RP group was characterized by a younger mean age at RP onset and a higher prevalence of ACA, frequently associated with a milder clinical endotype, including a lower frequency of dcSSc, ILD, and dyspnea. These findings are consistent with previous observations that lcSSc is often associated with a longer interval between the onset of RP and the appearance of the first NRP sign or symptom.^{11,32}

The patients in the simultaneous group represented the largest part of our cohort (58.8%) and presented a more severe disease endotype, characterized by a higher prevalence of ATA, dcSSc, and esophageal involvement.

In contrast, the NRP group demonstrated a higher prevalence of cardiopulmonary complications, including higher sPAP, a higher rate of PAH, and lower FVC values. These findings suggest that NRP onset may identify a subgroup of patients at increased risk for severe organ

complications. This highlights the crucial role of non-rheumatologists who often are the first healthcare contact for these patients, making their role in identifying early signs of SSc. Raising awareness of these clinical patterns among primary care providers and other specialists might indeed improve early diagnosis and timely referral.

Moreover, our data revealed that the age at onset of RP and NRP symptoms may also significantly influence the disease endotype. Consistent with previous studies,²⁸ we confirmed that onset of both RP and NRP in younger ages were associated with higher prevalence of ATA positivity, severe skin, and vascular involvement. Conversely, older RP onset and older NRP onset (respectively, >56 and >59 years in our cohort), were characterized by milder cutaneous features but associated with more severe cardiopulmonary involvement and increased prevalence of PAH.³⁷ Similar data were showed by the EULAR Scleroderma Trials and Research (EUSTAR) group in a previous work in which they demonstrated that late-onset SSc was an independent risk factor for pulmonary hypertension.²⁸ The demographic and clinical findings from the Italian cohort described by Ferri *et al.* also underscore these age- and endotype-related outcomes. In their study of 1012 Italian SSc patients, significant differences in survival rates and organ involvement were observed based on cutaneous subset and age of onset.¹⁰

Other studies identified an older age at the time of SSc diagnosis being linked to poorer outcomes, including an increased risk of mortality,^{38–41} mainly due to a more aggressive disease course,⁴² as well as to the impact of biological age itself. Specifically, some authors identified that the risk of death increases by 5% for every 1-year increase in age at time of diagnosis.³ Age-related survival and disease characteristics further highlighted that both older RP and NRP onset groups had lower 5-year survival rates. For older patients, our findings align with other cohort studies showing a higher prevalence of cardiac complications such as conduction blocks, left ventricular diastolic dysfunction, and increased sPAP.^{28,33,34,39,43–45} which remained significant after adjustment for sex, antibody status, and SSc subtype.

Our study additionally demonstrated that the clinical onset of SSc in terms of RP-NRP patterns of presentation may represent an additional

independent risk factor for mortality in SSc, in line with the data previously reported by the Spanish Scleroderma Study Group.²⁷ Although the survival curves showed comparable mortality rates across the RP, simultaneous, and NRP groups, we observed a significantly higher mortality risk in the simultaneous group compared to the RP group after adjustment for demographic and disease characteristics acting as confounders. This finding further underlines the association between a short-term, simultaneous RP-NRP timing in the onset of SSc and a more aggressive disease endotype, which adds up to the previously known predictors of mortality.

Given the impact that the RP-NRP pattern of onset carries on both disease presentation and prognosis, we tried to identify which features were associated with each specific group, specifically focusing on demographic and autoantibody data. Indeed, based on the results of our multinomial regression models, clinicians may apply these predictive factors to assist in the early identification of patients who may benefit from earlier referral to an SSc specialist center for further evaluation and management. In fact, patients exhibiting characteristics associated with a higher likelihood of belonging to the RP group (e.g., female sex, ACA positivity, early RP onset) may have a more stable disease course. In contrast, patients who are more likely to fall into the NRP or simultaneous groups (e.g., older age of RP onset, male sex, ATA, or ARA positivity) should be prioritized for early referral and closer surveillance to mitigate the risk of severe disease progression (see Figure 4).

Our study benefits from the large sample size and comprehensive data from a national registry, allowing robust subgroup analysis and supporting the potential clinical implications of our results. In terms of risk stratification and personalized management, the timing of RP onset and age of first NRP symptoms may indeed guide risk assessment, helping clinicians identify patients at greater risk for severe disease or mortality. Importantly, onset timing could also serve as a simple, readily available marker to be incorporated into future risk stratification tools or even contribute to refinement of classification criteria, complementing the current emphasis on RP as an entry symptom. In particular, the identification of simultaneous onset at diagnosis could be used as an early “red flag” to prioritize closer monitoring and timely therapeutic intervention (e.g., HRCT,

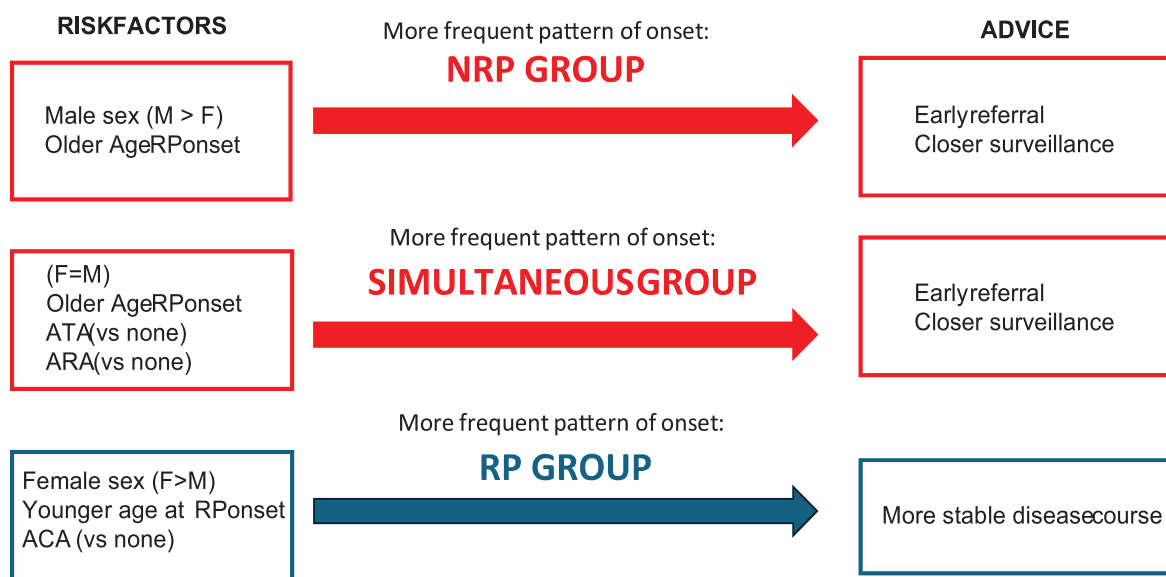


Figure 4. Classification of onset groups (NRP, Simultaneous, RP) based on risk factors, predominant clinical characteristics, and management recommendations. Risk factors include sex, age at RP onset, and the presence of autoantibodies (ATA, ARA, ACA). The arrows indicate the most frequent patterns of onset, with corresponding advice for each group highlighted. ACA, anti-centromere antibodies; ARA, anti-RNA polymerase III antibodies; ATA, anti-topoisomerase I antibodies; NRP, non-Raynaud's phenomenon; RP, Raynaud's phenomenon.

PFT, echocardiography), and timely therapeutic intervention. Similarly, NRP-first onset may identify patients requiring an analogous intensive approach. Conversely, RP-first onset at a younger age may indicate a more indolent course, allowing for a less intensive but still regular follow-up. Beyond individual management, onset timing and age could be integrated into simple clinical algorithms or future prediction models to stratify patients at diagnosis, optimize use of healthcare resources, and inform tailored treatment strategies. This information could also support patient counseling by providing early prognostic insights and may help stratify subgroups in clinical trials, facilitating the design of studies focused on high-risk patients. Further validation in international cohorts will be essential to determine whether these patterns can be robustly translated into practical decision-making tools and incorporated into long-term management pathways.

Limitations

Notwithstanding, several limitations must be acknowledged in our analysis. First, the cross-sectional design of our study does not allow conclusions on causality and limits the ability to evaluate disease progression over time. Longitudinal data analysis is therefore necessary to confirm and refine these associations, as well as

to support the potential clinical implications. Second, the retrospective nature of the study and the use of complete cases without missing data for all inferential and regression analysis may contribute to a potential selection bias. A further limitation of our study is that no a priori power analysis was performed to calculate the sample size, as this was a retrospective, post hoc, registry-based analysis of prospectively collected data.

Third, only about half of the cohort had available survival data, and the median follow-up of 24 months limits the ability to capture late events, possibly introducing informative censoring and bias in survival estimates. In addition, treatment exposure was not included in regression or survival models because of incomplete longitudinal data, which may have influenced organ outcomes and mortality estimates. This limitation is further compounded by small numbers of deaths recorded and the lack of cause-specific mortality data in the SPRING registry, which reduces the precision of our survival analyses.

Moreover, the age at RP onset was patient-reported and therefore subject to recall bias especially when RP preceded SSc diagnosis by several years. This limitation may also affect the simultaneous group, in which we were unable to ascertain whether RP or NRP occurred first within the

same year. This may introduce uncertainty in classification, suggesting that some cases might have been misclassified within this category. Additionally, the lack of detailed information for RP and NRP onset date may have improperly assigned certain patients to the RP or NRP groups, given their onset being recorded in two consecutive calendar years, while still potentially within 12 months from each other.

In addition, the limited size of the NRP group (corresponding to 2.2% of the overall population) and the in our median short-term observation may limit the generalizability of our findings.

Finally, longitudinal analyses in larger international cohorts, overcoming the abovementioned limitations are planned to support our results and confirm whether the prognostic impact of RP-NRP onset timing persists over extended periods, particularly in the NRP group.

Conclusion

In conclusion, our study highlights the importance of stratifying SSc patients not only using cutaneous subset and autoantibody patterns but also based on the age of RP/NRP onset and the RP/NRP pattern of presentation. We identified significant heterogeneity in disease manifestations and outcomes across different patterns of onset, further supporting the need for personalized management approaches in SSc, with a focus on early identification and risk stratification to optimize clinical outcomes. Further longitudinal studies are required to confirm these associations and refine strategies for early intervention and monitoring.

Declarations

Ethics approval and consent to participate

The study was approved by the coordinating ethics committee of AOU Careggi, Florence, Italy (Ref. OSS 15.010), and by the ethics committees of all participating centers. Written informed consent was obtained from all participants before enrollment in the SPRING-SIR registry.

Consent for publication

Not applicable.

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Competing interests

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Availability of data and materials


The data that support the findings of this study were derived from the SPRING-SIR Registry of the Italian Society for Rheumatology. Data from the SPRING-SIR Registry are not publicly available due to institutional and ethical restrictions, but may be accessed upon reasonable request to the Italian Society of Rheumatology and subject to approval by the SPRING-SIR Steering Committee.

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Supplemental material

Supplemental material for this article is available online.

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