Functional and Biomarker-Based Prognostic Factors in Systemic Sclerosis

Doctoral (PhD) Thesis

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1. INTRODUCTION

Systemic sclerosis (SSc) is a rare, heterogeneous systemic autoimmune disease characterized by microvascular dysfunction, immune dysregulation, and progressive fibrosis affecting the skin and internal organs. Despite its low prevalence, SSc is associated with the highest disease-specific mortality among connective tissue diseases, largely due to pulmonary and cardiac involvement. The etiology of SSc is multifactorial, involving genetic susceptibility, environmental exposures, and epigenetic mechanisms. The pathophysiological cascade is initiated by endothelial injury, followed by immune activation and sustained inflammation, ultimately leading to excessive extracellular matrix deposition and fibrosis. Clinically, the disease often begins with Raynaud's phenomenon and progresses to involve the skin and multiple organ systems, including the lungs, heart, gastrointestinal tract, and kidneys. Disease course and prognosis are highly variable, and reliable prognostic markers remain an unmet clinical need. Skin involvement plays a central role in disease classification and prognosis. Based on its extent, SSc is categorized into limited (lcSSc) and diffuse cutaneous (dcSSc) subsets, with dcSSc generally associated with more aggressive progression and earlier internal organ involvement after the first episode of the Raynaud's phenomenon. The modified Rodnan Skin Score (mRSS) is widely used as a surrogate marker of disease severity. Visceral involvement is a major determinant of outcome. The SSc-associated interstitial lung disease (SSc-ILD) is one of the most frequent and severe complications, while pulmonary arterial hypertension (PAH),

cardiac involvement, and renal crisis significantly contribute to morbidity and mortality. In addition to organ damage, patients experience substantial impairment in functional capacity and quality of life.

Oral involvement, particularly reduced mouth opening ability (MOA) or microstomia, represents an important yet often underappreciated manifestation of SSc. The reported prevalence varies widely due to differences in measurement methods and definitions. Mouth opening ability has most commonly been assessed using interincisal distance (ID); however, additional parameters - such as interlabial distance (LD) and intercommissural width - have also been proposed. The lack of standardized measurement approaches and validated cut-off values limits comparability across studies and hinders clinical applicability. Importantly, microstomia is not only a functional problem but may also reflect overall disease severity. Previous studies have demonstrated associations between reduced mouth opening and more extensive skin involvement, vasculopathy, and internal organ manifestations. Furthermore, decreased oral aperture has been linked to impaired quality of life, affecting nutrition, speech, and oral hygiene. Longitudinal data suggest that while mouth opening remains relatively stable in most patients, progressive reduction may indicate worsening disease. Emerging evidence also points to a potential association between reduced oral aperture and survival, particularly in dcSSc, raising the possibility that microstomia may serve as a simple, clinically accessible prognostic marker.

Given the heterogeneity of SSc, there is a growing need for reliable biomarkers that reflect disease activity, organ involvement, and prognosis. Among the candidates investigated, serum CC Motif Chemokine Ligand 18 (seCCL18) has emerged as a promising biomarker, particularly in relation to fibrotic processes. The seCCL18 is predominantly produced by alternatively activated macrophages within fibrotic tissues and reflects both macrophage-driven inflammation and extracellular matrix turnover. Elevated seCCL18 levels have been consistently associated with systemic sclerosis–related interstitial lung disease (SSc-ILD), one of the leading causes of mortality in SSc. Several studies have demonstrated that high baseline seCCL18 concentrations are predictive of ILD progression, particularly when assessed by decline in forced vital capacity (FVC) and are associated with reduced survival. In addition, seCCL18 has been proposed as a diagnostic biomarker for SSc-ILD. Its levels also appear to be modifiable by immunosuppressive and biologic therapies, suggesting a potential role in monitoring treatment response. Although the strongest evidence relates to pulmonary involvement, elevated seCCL18 levels may also reflect broader disease activity and severity. Its association with mortality further highlights its potential utility in risk stratification.

2. AIMS

Study I – Oral Aperture Parameters in SSc

- To evaluate oral aperture parameters used to assess MOA in SSc and analyze their associations with clinical characteristics and functional measures, including contractures (CCs), extensive contractures (extCCs), Health Assessment Questionnaire (HAQ-DI), and Hand Anatomic Index (HAI)
- To introduce and assess novel oral aperture measurement approaches alongside established methods, and to identify simple, objective, and reproducible parameters suitable for routine clinical practice
- To establish normal reference values based on a healthy Hungarian control population and compare oral aperture parameters between patients with SSc and healthy controls (HCs)
- To investigate whether reduced mouth opening capacity is associated with long-term survival and its potential role as a prognostic indicator in SSc

Study II – seCCL18 as a Biomarker of Multiorgan Involvement and Survival

- To determine the seCCL18 levels in patients with SSc and compare them with healthy controls
- To assess the association between elevated seCCL18 levels and organ involvement, particularly pulmonary, cardiac, and gastrointestinal and musculoskeletal manifestations

- To evaluate the relationship between seCCL18 levels and disease activity using the revised activity index created by the European Scleroderma Trials and Research Group (EUSTAR and EUSTAR-AI)
- To examine the association between seCCL18 levels and long-term survival and clinical outcomes in SSc

3. PATIENTS AND METHODS

Two single-center studies were conducted in a tertiary EUSTAR center at the University of Pécs, in accordance with the Declaration of Helsinki and with appropriate ethical approvals (Study I: Regional and Institutional Research Ethics Committee, Medical Center, University of Pécs Approval No. 2720/2006 and 4906/2013; Hungarian National Ethics Committee IF-6720-6/2015; Study II: Hungarian National Ethics Committee Approval No. 30636-3/2017/EKU). All participants provided written informed consent.

Study I was a prospective cohort study including 131 patients with systemic sclerosis (SSc) and 63 age- and sex-matched healthy controls (HCs). Clinical, functional, and laboratory data were collected using standardized protocols. Oral aperture parameters - interincisal distance (ID), labial distance (LD), opened (OW) and closed width (CW) - were measured, and derived parameters (oral area and circumference – OA, OC) were calculated. Using the ID, LD, OW, CW, OA, and OC measurements obtained from the HCs, the lower limit of normal (LLN) for each parameter was defined as the HC mean minus two standard deviations (mean − 2 SD). In patients with SSc,

values falling below the LLN were classified as reduced and defined as microstomia. Associations with clinical characteristics, functional indices (HAQ-DI, HAI), and survival were analyzed.

Study II was a cross-sectional study with longitudinal follow-up including 151 patients with SSc and 47 HCs. Serum CCL18 (seCCL18) levels were measured by ELISA. Elevated seCCL18 levels were defined as values exceeding the mean + 2 SD of healthy controls (>130 ng/mL). Detailed clinical assessments including laboratory analysis covered multiorgan involvement such as pulmonary, cardiac, gastrointestinal, and musculoskeletal manifestations, according to standardized criteria and EUSTAR recommendations.

In both studies, disease activity was assessed using validated indices (EScSG-AI, Pecs-AI, EUSTAR-AI), and organ involvement was defined using established clinical and instrumental criteria.

Survival analyses were performed using national and institutional databases. Statistical analyses included non-parametric tests, correlation analyses, and Kaplan–Meier analysis and Cox regression models, with results expressed as hazard ratios and 95% confidence intervals.

4. RESULTS

4.1 Study I – Oral Aperture Parameters and Prognosis in SSc

4.1.1 Oral Aperture Parameters of SSc Patients and Healthy Controls

At baseline, HCs showed significantly higher MOA values than SSc patients across all assessed parameters (ID, LD, OW, OA, OC), except for CW (all $p<0.01$).

Microstomia, defined as values falling below the mean - 2SD of HCs in at least one of the six assessed oral aperture parameters, was present in 56.5% of the total SSc cohort. Reduced ID was found in 45% (n = 59) of patients, reduced LD in 37% (n = 49), reduced CW in 2% (n = 3), reduced OW in 5% (n = 6), reduced OA in 10% (n = 13), and reduced OC in 19% (n = 25).

Patients with decreased OA exhibited significantly lower ID values compared to those with preserved OA, despite decreased ID (median (IQR) ID: 20 (14;25) mm vs. 29 (25;30) mm, $p < 0.01$). In HCs, all mouth-opening parameters were significantly lower in females than in males. Among SSc patients, females had significantly lower CW, OA, and OC values compared to males. When stratified by sex, both female and male SSc patients showed reduced MOA parameters compared to sex-matched HCs, except for CW.

Comparison of SSc subtypes revealed that only ID differed significantly between groups, with lower values in dcSSc than in lcSSc (median (IQR): 30 (22;37) mm vs. 35 (30;40) mm, $p < 0.01$).

Although reduced ID was more frequent in dcSSc, decreased LD and OA were similarly prevalent in both subgroups.

Disease duration did not show any correlation with MOA parameters in the overall SSc cohort or in dcSSc. However, in lcSSc, ID showed a weak negative correlation with disease duration (rho = - 0.235, $p < 0.05$). When stratified by disease duration (≤2 vs. >2 years), ID, LD, and OC were lower in early SSc compared to HCs across all groups. No significant differences were observed between early and longer disease duration groups for ID, LD, OW, or CW; however, OA and OC were reduced in patients with disease duration >2 years.

Microstomia was more frequent in patients with disease duration >2 years compared to early SSc (61% vs. 37%, $p < 0.05$). Reduced ID was already present in early SSc in approximately one-third of patients (34.5%) and occurred more frequently in dcSSc than in lcSSc ($p < 0.05$). Decreased LD was observed in 24.1% of patients with early SSc.

4.1.2 Oral Aperture and Clinical Parameters

In SSc patients with disease duration > 2 years (n = 102), ESR showed a weak negative correlation with ID (rho = - 0.203, $p < 0.01$).

Within the dcSSc subgroup with disease duration > 2 years (n = 32), ID showed a moderate positive correlation with body mass index (BMI) (rho = 0.445, $p = 0.011$) and a moderate negative correlation with mRSS (rho = -0.423, $p = 0.016$). Within the same subgroup, LD was moderately negatively correlated with ESR (rho = -0.492,

p = 0.04), and OA also showed a moderate correlation with ESR (rho = 0.430, p = 0.014).

4.1.3 Oral Aperture and Functional Impairment in SSc

Patients with microstomia exhibited a greater number of contractures compared to those with preserved oral aperture parameters.

When individual MOA parameters were evaluated, SSc patients with reduced ID, LD, or OC had significantly more contractures than those with values within the normal range. Moreover, the number of extCCs was increased in patients presenting decreased ID, LD, OA, or OC.

Correlation analysis between vertical and calculated oral parameters (ID, LD, OA, OC) and the number of CCs, as well as extCCs, also supported these associations (rho ranging from -0.279 to -0.394, $p<0.01$). Among dcSSc patients, lower ID, LD, OA, OC were associated with a higher number of CCs, whereas in lcSSc only reduced LD showed such an association. In dcSSc, decreased ID or OA was also linked to a higher frequency of extCCs, while in lcSSc reduced LD was associated with increased extCC numbers. Subgroup-specific correlation analyses supported these findings.

In patients with short disease duration, no association was observed between MOA parameters and the number of CCs or extCCs. In contrast, in patients with disease duration >2 years, decreased MOA parameters were associated with higher numbers of both CCs and extCCs. Reduced LD was consistently associated with increased CC and extCC numbers in both SSc subsets in this group. Among patients

with disease duration >2 years, weak-to-moderate negative correlations were found between MOA parameters (ID, LD, OA, OC) and CCs and extCCs (rho between -0.288 and -0.470, $p < 0.05$). Similar correlations were observed in lcSSc patients (rho between –0.267 and -0.471, $p < 0.05$).

HAI values indicated worse hand function in patients with microstomia compared to those with preserved MOA (median (IQR): 1.81 (1.39;2.9) vs. 2.55 (1.81;3.23), $p < 0.05$). When MOA parameters were analyzed separately, decreased LD, OA, and/or OC were associated with lower HAI values, indicating more pronounced impairment in small joint mobility. In dcSSc, decreased OA was associated with lower HAI (median (IQR): 0.6 (0.3;2.0) vs. 1.8 (1.4;2.5), $p < 0.05$), while in lcSSc reduced LD was associated with lower HAI values (median (IQR): 1.7 (1.1;2.6) vs. 2.8 (2.0;3.36), $p < 0.05$). No association was observed in early disease; however, in patients with disease duration >2 years, decreased LD, OA, and/or OC were associated with lower HAI values. Correlation analyses further confirmed these relationships.

In the overall SSc cohort, lower ID, LD, OA, and OC values were each associated with significantly higher HAQ-DI scores. Patients with reduced ID had a median HAQ-DI of 1.13 (0.63–1.88) compared with 0.88 (0.16–1.47) in those with preserved ID ($p < 0.01$). Similarly, decreased LD, OA, and OC were accompanied by higher disability scores (LD: 1.50 (1.06–2.00) vs. 0.75 (0.13–1.38), $p < 0.001$;

OA: 1.75 (1.44–2.19) vs. 1.00 (0.38–1.50), $p < 0.001$; OC: 1.50 (1.19–2.00) vs. 0.88 (0.25–1.50), $p < 0.001$).

A similar pattern was observed in patients with disease duration >2 years. Reduced values of all four MOA parameters were associated with significantly worse functional status, reflected by higher HAQ-DI scores (ID: 1.13 (0.75–1.88) vs. 0.88 (0.38–1.50), $p < 0.05$; LD: 1.50 (1.13–2.00) vs. 0.88 (0.25–1.38), $p < 0.001$; OA: 1.75 (1.40–2.28) vs. 1.00 (0.50–1.50), $p < 0.01$; OC: 1.50 (1.13–2.00) vs. 1.00 (0.38–1.50), $p < 0.01$). Among patients with early disease, those with moderate-to-severe disability (HAQ-DI >1) exhibited significantly lower OA and OC values than patients with HAQ-DI ≤1 (OA: 1287 (1106–1544) vs. 1593 (1384–1962) mm^2, $p < 0.05$; OC: 127 (120–139) vs. 148 (131–157), $p < 0.05$).

Correlation analyses further supported the association between microvascular impairment and disability. In the overall SSc cohort, HAQ-DI showed weak-to-moderate inverse correlations with all MOA parameters (rho = −0.316 to −0.475, all $p < 0.01$). These relationships were more pronounced in dcSSc, where moderate-to-strong negative correlations were observed (rho = −0.477 to −0.679, $p < 0.05$). In lcSSc, significant but weaker correlations were found only for LD, OA, and OC (rho = −0.371 to −0.395, $p < 0.01$). Among patients enrolled within 2 years of disease onset, HAQ-DI correlated negatively with all four MOA parameters (rho = −0.386 to −0.508, $p < 0.05$), while in dcSSc patients with disease duration >2 years, OA

and OC demonstrated particularly strong inverse associations with disability (rho = −0.653 and −0.697, respectively; $p < 0.05$).

4.1.4 Oral Aperture and Disease Activity

Disease activity assessed by Pecs-AI was higher in patients with reduced LD (57% vs. 39%, $p < 0.05$), particularly in lcSSc patients with longer disease duration.

In the total cohort, weak but significant negative correlations were observed between MOA parameters (ID, LD, OA, OC) and disease activity (rho ranging from -0.181 to -0.273, $p < 0.05$). These associations were more evident in lcSSc patients with longer disease duration (rho ranging from -0.332 to -0.360, $p < 0.01$). In contrast, no significant association was found between MOA parameters and EScSG-AI.

4.1.5 Survival Analysis

During follow-up, reduced MOA parameters - particularly LD, OA, and OC - were associated with poorer survival in univariate analyses ($p < 0.05$–0.01). Kaplan–Meier analysis identified several factors associated with poorer survival, including dcSSc subtype, male sex, FVC < 80%, DLCO < 80%, HAQ-DI ≥ 1, low hematocrit (female < 35%, male < 40%), ESR > 30 mm/h, presence of malignancy either prior to or during follow-up, as well as decreased LD, OA, and OC at baseline.

In multivariate Cox regression analysis, decreased OA (<941 mm²) remained an independent predictor of mortality (HR 2.742, 95% CI 1.152–6.530, $p < 0.05$). Additional independent predictors included male sex (HR 4.171, 95% CI 1.668-10.430, $p < 0.01$), ESR >30 mm/h (HR 2.604, 95% CI 1.325-5.118, $p < 0.01$), higher HAQ-DI (HR 2.019, 95% CI 1.313-3.105, $p < 0.01$), age at disease onset (HR 1.039, 95% CI 1.015-1.063, $p < 0.01$), whereas higher DLCO (HR 0.978, 95% CI 0.958-0.997, $p < 0.05$) and higher BMI (HR 0.913, 95% CI 0.852-0.978, $p < 0.05$) were related to favorable outcomes. Details are shown in Table 1.

Table 1. Univariate and multivariate survival analysis of 131 systemic sclerosis patients

Univariate survival analysis (Kaplan-Meier)		
Risk factor	**Overall mortality risk**	**p**
	Log Rank chi-square	
ESR>30 mm/h	18.853	<0.001
Low hematocrit (female<35%, male<40%)	11.888	<0.001
Malignancies (current or in history)	11.156	<0.01
Decreased OA	8.787	<0.01
Decreased OC	7.641	<0.01
HAQ-DI score ≥1	6.926	<0.01
FVC<80%	6.855	<0.01
Male sex	6.617	<0.05
DLCO<80%	6.148	<0.05
DcSSc subgroup	5.428	<0.05
Decreased LD	4.046	<0.05
BMI<18.5	3.790	0.05
Low albumin	3.742	0.05
Multivariate survival analysis (Cox Proportional Hazards Model)		
	HR (95% CI)	**p**
Male sex	4.171 (1.668-10.430)	<0.01
Decreased oral area (<941 mm^2)	2.742 (1.152-6.530)	<0.05
ESR >30mm/h	2.604 (1.325-5.118)	<0.01
HAQ-DI	2.019 (1.313-3.105)	<0.01
Age at disease onset	1.039 (1.015-1.063)	<0.01
DLCO%	0.978 (0.958-0.997)	<0.05
BMI	0.913 (0.852-0.978)	<0.05

Legend: ESR: erythrocyte sedimentation rate; malignancies: coexistent malignancies and malignancies diagnosed during follow-up; OA: oral area (decreased: OA<941mm2); OC: oral circumference (decreased: OC<115mm); LD: vertical interlabial distance at maximally opened mouth (decreased: LD<37mm); HAQ-DI: Health Assessment Questionnaire - Disability Index; FVC: forced vital capacity; DLCO: diffusing capacity of the lungs for carbon monoxide; BMI: Body Mass Index in kg/m^2

4.2 Study II – Serum CCL18 as a Biomarker of Multiorgan Involvement and Survival

4.2.1 Baseline Characteristics and Organ Manifestations

DcSSc was associated with a higher prevalence of SSc-ILD (72.3% vs. 57.4%, $p = 0.008$), DUs ($p = 0.015$), and tendon friction rubs (TFRs) ($p = 0.008$). In contrast, lcSSc patients were older ($p = 0.002$), had longer disease duration ($p=0.001$), and more frequent myocardial involvement ($p = 0.026$) and left ventricular diastolic dysfunction ($p = 0.020$).

4.2.2 Serum CCL18 Levels

The seCCL18 levels were significantly higher in SSc patients than in HCs (median (IQR); SSc: 95.6 (64.7;130.0) vs. HC: 71.0 (56.5;97.4) ng/mL, $p < 0.01$), both in early ($\leq$3 years, $p = 0.047$) and long-standing disease ($p < 0.001$). Elevated levels (>130 ng/mL) were present in 24.5% of patients.

No significant difference was observed between dcSSc and lcSSc subsets; however, higher seCCL18 levels were detected in early dcSSc compared to HCs (116.9 (71.0;164.3) vs. 71.0 (56.5;97.4) ng/mL, $p = 0.016$). The seCCL18 showed only a weak correlation with age (rho = 0.326, $p < 0.01$) and was independent of disease duration.

4.2.3 Pulmonary Involvement and Functional Capacity

Elevated seCCL18 levels were strongly associated with pulmonary involvement. Patients with elevated levels had a higher prevalence of

SSc-ILD (81.1% vs. 60.5%, p = 0.022), reduced FVC <70% (16.7% vs. 3.5%, p = 0.006), and reduced DLCO <70% (80.6% vs. 54.4%, p = 0.005).

Patients with SSc-ILD had significantly higher seCCL18 levels compared to those without ILD (105.8 (76.4;134.0) vs. 79.2 (49.1;106.6) ng/mL, p<0.001). Patients with elevated seCCL18 levels (>130 ng/mL) had significantly lower mean FVC% (94 ± 21 vs. 104 ± 19, p = 0.006), DLCO% (59 ± 16 vs. 66 ± 18, p = 0.015), and TLC% (104 ± 19 vs. 115 ± 19, p = 0.002) than those with normal seCCL18 levels (≤130 ng/mL), indicating more severe pulmonary impairment.

Among patients with SSc-ILD, elevated seCCL18 was associated with further reductions in mean FVC% (91.0 ± 19.1 vs. 102.3 ± 22.4, p = 0.019) and TLC% (100.3 ± 17.6 vs. 111.6 ± 21.1; p = 0.012).

4.2.4 Non-Pulmonary Organ Involvement

Elevated seCCL18 was associated with several non-pulmonary manifestations. Higher seCCL18 levels were observed in patients with arterial hypertension (106.9 ± 40.6 vs. 93.4 ± 44.7 ng/mL, p = 0.042), myocardial disease (104.8 ± 41.8 vs. 83.8 ± 44.2 ng/mL, p = 0.008), left ventricular diastolic dysfunction (107.1 ± 40.5 vs. 84.5 ± 45.0 ng/mL, p < 0.001), and esophageal involvement (110.7 ± 38.3 vs. 93.3 ± 43.1 ng/mL, p = 0.009).

Musculoskeletal involvement, including small joint CCs (64.9 % vs. 44.1 %, p = 0.029) and TFRs (51.4 % vs. 27.4 %, p=0.007), was more

frequent in patients with elevated seCCL18. In lcSSc, elevated seCCL18 was also associated with DUs (44.4 vs. 20.4%, $p = 0.049$).

Elevated seCCL18 levels were associated with increased inflammatory activity, including CRP >5 mg/L (51.4 % vs. 19.3 %, $p < 0.001$) and ESR >28 mm/h (37.8 % vs. 18.4 %, $p = 0.015$), and showed moderate correlations with both CRP (rho = 0.441, $p < 0.001$) and ESR (rho = 0.422, $p<0.001$). ATA positivity was also more frequent in patients with elevated seCCL18 (40.5 % vs. 21.9 %, $p = 0.026$).

In the dcSSc subgroup, elevated seCCL18 levels were associated with a higher prevalence of CRP >5 mg/L (42.1% vs. 17.2%, $p = 0.023$) and ESR >28 mm/h (42.1% vs. 15.6%, $p = 0.014$).

In the lcSSc subgroup, patients with elevated seCCL18 levels more frequently exhibited ATA positivity (27.8% vs. 6.0%, $p = 0.014$), anti-RNAP III positivity (22.2% vs. 4.1%, $p = 0.040$), and CRP >5 mg/L (61.1% vs. 22.0%, $p = 0.002$).

In contrast, gastroesophageal reflux disease (GERD) and sicca symptoms were more common among patients with normal seCCL18 levels, the latter particularly in the lcSSc subgroup (79.8% vs. 59.5%, $p = 0.013$ and 66.7% vs. 45.9%, $p = 0.025$, respectively). Patients with elevated seCCL18 levels were more likely to receive immunosuppressive therapy at baseline (67.6% vs. 42.1%, $p = 0.007$).

4.2.5 Disease Activity

According to EUSTAR-AI, 51% of patients had an active disease. Elevated seCCL18 levels were associated with a higher proportion of active disease (73% vs. 44%, p = 0.002).

Patients with active SSc had significantly higher seCCL18 levels compared to those with inactive disease (109.2 ± 46.5 vs. 90.3 ± 37.2 ng/mL, p = 0.009). This association was particularly seen in dcSSc (89% vs. 56%; p = 0.008), while a similar trend was observed in lcSSc (55.5% vs. 28%; p = 0.036).

4.2.6 Survival Analysis

The study cohort included 151 patients, of whom 147 were eligible for survival analysis, as four patients were excluded due to insufficient follow-up data. During a median follow-up of approximately 7 years, 22/147 (15%) of patients died. Elevated baseline seCCL18 levels were associated with poorer survival in univariate analysis, alongside other established clinical and functional prognostic factors. (Log Rank = 6.218, p = 0.013) (Table 2).

In multivariate Cox regression analysis, seCCL18 remained an independent predictor of mortality (HR 1.789, 95% CI 1.133–2.824, p = 0.013). Additional independent predictors included reduced DLCO (HR 1.942 per 10% decrease, 95% CI 1.321–2.857, p < 0.001) and reduced 6MWT performance (HR 1.249 per 10% decrease, 95% CI 1.046–1.490, p = 0.014) (Table 2).

Table 2. Univariate analysis and multivariate Cox regression (backward stepwise) analysis of 147 SSc patients

Univariate analysis (Kaplan-Meier)		
	Log Rank Chi-Square	**p**
Elevated seCCL18 (>130ng/ml)	6.218	**0.013**
SSc-ILD	7.069	**0.008**
DLCO<80%	6.047	**0.014**
Arrhythmia (ECG or Holter monitor)	6.659	**0.010**
Six Minute Walk Test below lower limit of normal	14.459	**<0.001**
Small joint contractures (joint <75% range of motion)	8.061	**0.005**
Subcutaneous calcinosis	4.393	**0.036**
Low BMI (<18.5kg/m2) or weight loss (10% in 1 year) due to malabsorption	4.186	**0.041**
Multivariate Cox regression (backward stepwise)		
	Overall mortality risk HR (95% CI)	**p**
Six Minute Walk Test Reference (per 10% decrease)	1.249 (1.046-1.490)	**0.014**
seCCL18 (per 1-SD increment)	1.789 (1.133-2.824)	**0.013**
Decreasing DLCO (per 10% decrease)	1.942 (1.321-2.857)	**<0.001**

HR: Hazard Ratio; CI: confidence interval; mRSS: modified Rodnan Skin Score; DLCO: diffusing capacity for carbon monoxide in %, CRP: C-reactive protein in mg/l; ESR: erythrocyte sedimentation rate in mm/h; PAH: pulmonary arterial hypertension. Variables removed: gender (p = 0.709), age at diagnosis (p = 0.482), BMI (p = 0.212), dcSSc subtype (p = 0.649), PAH (p = 0.104), CRP (p = 0.912), ESR (p = 0.384), presence of small joint contractures (p = 0.863), mRSS per 10 points increment (p = 0.158). The seCCL18 levels were standardized, and the results represent one standard deviation increase in the seCCL18 levels. Results of the multivariate analysis are presented as hazard ratios (HR) with 95% confidence intervals (CI). Statistically significant p-values (p < 0.05) are indicated in bold.

5. DISCUSSION

Study I

In this study, we comprehensively evaluated oral aperture parameters in SSc, focusing on their clinical relevance and prognostic significance. Although microstomia is a well-recognized manifestation of SSc, there is currently no standardized approach for its assessment. The ID is the most evaluated parameter; however, other measures, including LD, may provide additional clinically relevant information.

We assessed both conventional parameters (ID, LD, OW, CW) and newly introduced composite measures (OA, OC) and compared them with values obtained from a healthy Hungarian age-, and sex-matched control group. MOA parameters were significantly reduced in SSc patients, and microstomia was present in more than half of the cohort. Importantly, decreased mouth opening was already detectable within the first two years of disease onset, suggesting that it may represent an early manifestation of SSc. While reduced ID was more common in dcSSc, decreases in LD and OA were similarly frequent in both dcSSc and lcSSc, indicating that microstomia is also a relevant feature in lcSSc.

MOA parameters were associated with both inflammatory activity and structural and/or functional damage. In patients with longer disease duration, LD and OA showed negative correlations with ESR, suggesting that reduced mouth opening may reflect ongoing

inflammation. In addition, moderate-to-strong associations were observed between MOA parameters and joint damage, including contractures and impaired hand function and functional status. Notably, LD demonstrated consistent associations with both structural and functional impairment across both SSc subsets, whereas ID showed such associations mainly in dcSSc. These findings indicate that LD provides additional clinical value, particularly in identifying lcSSc patients at increased risk of joint involvement.

All decreased MOA parameters were associated with higher values of HAQ-DI, reflecting overall functional disability and worse performance, both in early and later disease stages. Although no relationship was found with EScSG-AI, decreased LD was associated with active disease based on Pecs-AI, especially in lcSSc. This association may be explained by the broader composition of the Pecs-AI, which incorporates more comprehensively the functional, cutaneous, and pulmonary components.

Importantly, this study is the first to demonstrate the prognostic significance of microstomia in SSc using multivariate analysis. Reduced LD, OA, and OC were associated with worse survival, and OA emerged as an independent predictor of mortality. These findings indicate that oral aperture parameters, particularly OA, may reflect not only functional impairment but also overall disease burden and prognosis.

Some established prognostic factors were not confirmed in our cohort, which may be explained by the relatively low frequency of certain

organ manifestations and the longer disease duration at inclusion, potentially resulting in a selection bias toward milder cases. In addition, only baseline organ involvement was assessed, which may have led to underestimation of their impact.

Despite these limitations, the inclusion of a healthy control group represents a major strength, allowing for more accurate determination of reference values. Overall, our findings demonstrate that reduced MOA is a frequent and clinically relevant feature of SSc, associated with functional impairment, joint damage, and disease activity. Among the examined parameters, LD and OA appear to be the most informative, reflecting disability and prognosis, respectively.

Study II

In this study, we investigated the clinical significance of seCCL18 levels in a well-characterized SSc cohort. Our findings confirm that seCCL18 is a relevant biomarker reflecting key pathogenic processes in SSc, particularly macrophage-driven inflammation and fibrosis.

Elevated seCCL18 levels were observed in a substantial proportion of patients (n=37/151, 24.5 %) even with a relatively long median disease duration and were associated with more severe organ involvement, impaired pulmonary function, and worse clinical outcomes. Importantly, seCCL18 elevation appeared to be independent of disease subset and duration, suggesting that it reflects underlying disease activity rather than cumulative damage.

A strong association was found between seCCL18 levels and SSc-ILD, as well as with reduced pulmonary function parameters. Notably, elevated seCCL18 was also observed in lcSSc patients with SSc-ILD, indicating that its relevance is not limited to the dcSSc subtype. These findings suggest that seCCL18 may serve as a biomarker of pulmonary fibrosis across the entire SSc spectrum.

Beyond pulmonary involvement, elevated seCCL18 levels were associated with cardiac, musculoskeletal and gastrointestinal involvement, indicating that this biomarker reflects a broader disease activity and inflammatory disease burden, suggesting that it may capture ongoing pathological processes even in long-standing disease.

Interestingly, certain manifestations, such as GERD and sicca symptoms, were more frequent in patients with normal seCCL18 levels. This may reflect alternative pathogenic mechanisms, including non-fibrotic processes such as smooth muscle atrophy, neuropathy, or receptor-mediated dysfunction.

Importantly, this study is the first to systematically evaluate the relationship between seCCL18 and both disease activity and a wide range of non-pulmonary organ manifestations. In addition, elevated baseline seCCL18 was identified as an independent predictor of mortality, supporting its potential role as a prognostic biomarker.

Some well-known prognostic factors were not confirmed in this cohort, likely due to the relatively long disease duration and improved management strategies, which may attenuate the impact of traditional

risk factors. In addition, the cross-sectional design limits the assessment of longitudinal changes in seCCL18 and their relationship with disease progression. In addition, large multicenter investigations are required to establish clinically relevant cut-off values and validate the utility of seCCL18 at the individual patient level.

Nevertheless, this study has several strengths, including the well-characterized cohort, minimal loss to follow-up, and comprehensive assessment of organ involvement. The findings support the clinical relevance of seCCL18 as a marker of disease severity, activity, and prognosis.

In conclusion, seCCL18 appears to be a promising biomarker reflecting multi-organ involvement and adverse outcomes in SSc. Its measurement may contribute to improved risk stratification and patient management, particularly in identifying individuals at higher risk of progressive disease. However, further prospective multicenter studies are required to validate its clinical utility and establish standardized cut-off values.

6. SUMMARY

The present doctoral work investigated two complementary aspects of SSc: clinically measurable functional impairment related to microstomia (Study I) and the seCCL18 as a circulating biomarker reflecting underlying disease mechanisms and organ involvement (Study II). Although methodologically distinct, both approaches

aimed to improve the assessment of disease severity, activity, and prognosis, thereby supporting more precise risk stratification.

In Study I, reduced mouth opening ability (MOA) was identified as a frequent and clinically relevant manifestation affecting both dcSSc and lcSSc subsets, already detectable in the early phase of the disease. Key parameters, particularly reduced LD and OA, were associated with structural joint damage, higher HAQ-DI, and disease activity, indicating that they reflect both functional impairment and ongoing inflammation. Notably, OA emerged as an independent predictor of long-term mortality, suggesting that simple clinical measurements may also provide prognostic information.

In Study II, elevated seCCL18 levels were associated with more severe organ involvement, especially SSc-ILD, impaired pulmonary function, and reduced survival. Beyond pulmonary manifestations, seCCL18 was also linked to cardiac, musculoskeletal, and gastrointestinal involvement, as well as overall disease activity (EUSTAR-AI), indicating that it reflects a broader fibrotic and inflammatory disease burden. These findings support its role as a biomarker of ongoing disease activity, even in long-standing SSc.

Together, the results demonstrate a convergence between clinical phenotype and underlying pathophysiology. While MOA parameters provide a direct measure of functional impairment and structural damage, seCCL18 reflects systemic fibrotic activity at the molecular level. Both approaches identify patients with more severe disease,

higher activity, and worse prognosis, suggesting that they capture complementary aspects of disease burden.

Importantly, disease severity in SSc cannot be adequately described by a single domain. Reduced MOA reflects disability and joint involvement, whereas elevated seCCL18 indicates multiorgan involvement and adverse outcomes. Their parallel associations with disease activity and survival suggest that they represent different manifestations of a shared process characterized by persistent inflammation and progressive disease. From a clinical perspective, combining functional assessment (LD, OA) with biomarker evaluation (seCCL18) may improve identification of high-risk patients and support more individualized management and a possible development of a new SSc activity index. Both studies highlight the need for longitudinal assessments, as reduced MOA parameters and elevated baseline seCCL18 levels were both associated with disease activity and adverse outcomes.

In conclusion, functional clinical parameters and circulating biomarkers provide complementary information on disease severity and prognosis in SSc. Their integration may enhance risk stratification and contribute to a more comprehensive understanding of disease heterogeneity. Further large-scale prospective studies are needed to validate these findings and define their role in clinical practice.

7. NEW RESULTS

Study I

- This study demonstrated for the first time that oral area (OA) is an independent predictor of long-term mortality in SSc
- This study showed that composite oral aperture parameters (OA and OC) provide additional clinical and prognostic information beyond conventional measures (ID, LD)
- This study demonstrated that LD has added value over ID in identifying lcSSc patients at higher risk of structural joint involvement

Study II

- This study is the first to systematically analyze the relationship between seCCL18 and EUSTAR-AI as well as a broad spectrum of non-pulmonary organ manifestations
- This study demonstrated that seCCL18 is associated not only with SSc-ILD but also with multiorgan involvement, including cardiac, musculoskeletal and gastrointestinal manifestations
- This study showed that seCCL18 reflects overall disease activity (EUSTAR-AI) even in patients with long-standing SSc
- This study confirmed and extended previous findings by demonstrating that seCCL18 is an independent predictor of mortality in a well-characterized EUSTAR cohort

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9. LIST OF PUBLICATIONS RELATED TO THE SUBJECTS INCLUDED IN THE THESIS

Papers

Papers upon which this thesis relies:

- **Filipánits, K.**, Nagy, G., Varjú, C., Czirják, L., Minier, T. (2024). Microstomia is associated with functional impairment and is a poor prognostic factor in systemic sclerosis - a single center observational study with survival analysis. BMC Oral Health, 24(1), 1390. https://doi.org/10.1186/s12903-024-05178-6. **Q1, IF: 3.1**

- **Filipánits, K.**, Nagy, G., Jász, D. K., Minier, T., Simon, D., Erdő-Bonyár, S., Berki, T., Kumánovics, G. (2026). Serum CCL18 May Reflect Multiorgan Involvement with Poor Outcome in Systemic Sclerosis. Biomolecules, 16(1), 136. https://doi.org/10.3390/biom16010136. **Q1, IF: 4.8**

Papers closely related to the topic of the thesis:

- Erdő-Bonyár, S., Rapp, J., Subicz, R., Böröcz, K., Szinger, D., **Filipánits, K.**, Minier, T., Kumánovics, G., Czirják, L., Berki, T., & Simon, D. (2024). Disturbed Complement Receptor Expression Pattern of B Cells Is Enhanced by Toll-like Receptor CD180 Ligation in Diffuse Cutaneous Systemic Sclerosis. International Journal of Molecular Sciences, 25(17), 9230. https://doi.org/10.3390/ijms25179230. **Q1, D1, IF: 4.9**

- Erdő-Bonyár, S., Rapp, J., Subicz, R., **Filipánits, K.**, Minier, T., Kumánovics, G., Czirják, L., Berki, T., Simon, D. (2024). Toll-like Receptor Homologue CD180 Ligation of B Cells Upregulates Type I IFN Signature in Diffuse Cutaneous Systemic Sclerosis. International Journal of Molecular Sciences, 25(14), 7933. https://doi.org/10.3390/ijms25147933. **Q1, D1, IF: 4.9**

- Kéringer, P., Kovács, K. T., Nagy, G., Ágoston-Szabó, Á., **Filipánits, K.**, Kiss, F. I., Szabó, A., Kumánovics, G. (2025). Patient-reported gastrointestinal involvement is associated with reduced quality of life and disability in systemic sclerosis. Journal of Scleroderma and Related Disorders, 10(3), 597-605. https://doi.org/10.1177/23971983251345284.
  Q3, IF: 1.2

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- Minier, T., Lóránd, V., Bálint, Z., Komjáti, D., Németh, B., **Filipánits, K.**, Kovács, A., Nagy, G., Varjú, C., Czirják, L., & Kumánovics, G. (2020). Decreased oral aperture is a poor prognostic factor in systemic sclerosis. Journal of Scleroderma and Related Disorders, 5(Suppl 1). https://doi.org/10.1177/2397198319898367

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Posters

- Minier, T., Lóránd, V., Bálint, Z., Komjáti, D., Németh, B., **Filipánits, K.**, Kovács, A., Nagy, G., Varjú, C., Czirják, L., Kumánovics, G. (2020). Decreased oral aperture is a poor prognostic factor in systemic sclerosis. 6th Systemic Sclerosis World e-Congress, 2020.07.11–13., online, P.176.

Oral Presentations

- **Filipánits, K.**, Minier, T. (2022). The impact of the disease activity and disease related damage on the long-term survival in systemic sclerosis – results of a single center prospective cohort. XX. Rheumatology Resident and Specialist Conference, 2022.03.31–04.01., Pécs (online), Oral presentation. [Hungarian]

- **Filipánits, K.**, Nagy, G., Varjú, C., Kovács, A., Komjáti, D., Kisné Bálint, Z., Czirják, L., Kumánovics, G., Minier, T. (2022). The impact of the disease activity on the long-term survival in systemic sclerosis – results of a single center prospective cohort. Annual Conference of the Hungarian Association of Rheumatologists, 2022.09.22–24., Sopron, Hungary, Oral presentation. [Hungarian]

10. LIST OF PUBLICATIONS NOT DIRECTLY RELATED TO THE SUBJECTS INCLUDED IN THE THESIS

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- Hamar, Á., **Filipánits, K.**, Váradi, A., Váradi-Rácz, R., Gellén, H. O., Futács, K., Urbán, P., Kovacs, G. L., & Gombos, K. (2022). Diagnostic accuracy of SARS-CoV-2 Panbio™ rapid antigen diagnostic tests in a 4,440-case clinical follow-up. Frontiers in Medicine, 9, 908127. https://doi.org/10.3389/fmed.2022.908127

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Published Abstracts

- **Filipánits K**., Nagy G., Komjati D., et al. POS1270 The impact of overlap syndromes on the scleroderma clinical trial consortium damage index (SCTC-DI) in systemic sclerosis. Annals of the Rheumatic Diseases 2023, 82:979. https://doi.org/10.1136/annrheumdis-2023-eular.1363

- **Filipánits, K.**, Fekete, A., László, K., Horváth-Sarródi, A., Pintér, E., Duga, Zs., Reglődi, D. (2024). Nurturing exceptional talent: The Romhányi György College for Advanced Studies enhancing development in gifted medical students. Multidiszciplináris Egészség és Jóllét, 2(Suppl. 1), 31.

- Peresztegi, M. Zs., **Filipánits, K.**, Czopf, L., Németh, T., Szántó, Z., Tamás, A. (2024). Enhancing clinical training in undergraduate medical education through near-peer teaching at the University of Pécs Medical School. Multidiszciplináris Egészség és Jóllét, 2(Suppl. 1), 37–38.

- Tamás, A., **Filipánits, K.**, Németh, T., Sebők, J., Peresztegi, M. Zs., Czopf, L. (2024). Empowering medical students: Near-peer teaching initiatives at the University of Pécs Medical School, Hungary. Multidiszciplináris Egészség és Jóllét, 2(Suppl. 1), 40.

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- **Filipánits, K.**, Nagy, G., Varjú, C., Kovács, A., Komjáti, D., Kisné Bálint, Z., Czirják, L., Kumánovics, G., Minier, T. (2022). Clinical characteristics of patients with overlap syndromes associated with systemic sclerosis – results from a single tertiary care center. 7th Systemic Sclerosis World e-Congress, 2022.03.09–11., online, P.164.

- Minier, T., **Filipánits, K.**, Nagy, G., Varjú, C., Kovács, A., Komjáti, D., Kisné Bálint, Z., Czirják, L., Kumánovics, G. (2022). The impact of the overlap syndromes on the global disease activity indicators in systemic sclerosis – results from a single tertiary care center. 7th Systemic Sclerosis World e-Congress, 2022.03.09–11., online, P.165.

- Minier, T., **Filipánits, K.**, Nagy, G., Kovács, A., Komjáti, D., Kisné Bálint, Z., Kumánovics, G., Czirják, L., Varjú, C. (2022). Extent of damage based on the Scleroderma Clinical Trials Consortium damage index – results from a single tertiary EUSTAR center. 7th Systemic Sclerosis World e-Congress, 2022.03.09–11., online, P.166.

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- **Filipánits, K.**, László, K., Horváth-Sarródi, A., Pintér, E., Duga, Zs., Németh, T., Czopf, L., Tamás, A., Reglődi, D. (2024). A viable concept to support gifted medical students to accelerate their development: The Romhányi György College for Advanced Studies. 23rd Thai Medical Education Conference (TMEC), 2024.02.04–07., Bangkok, Thailand.

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- **Filipánits, K.**, Kumánovics, G. (2025). Innovative rheumatology teaching at the University of Pécs Medical School: Recipient of the EULAR Best Undergraduate Teaching Concept Award. APLAR Congress 2025, 2025.09.03–07., Fukuoka, Japan.

- **Filipánits, K.**, Tüske, F., Minier, T., Kumánovics, G. (2026). Investigation of the relationship between the 6-minute walk test and global disease activity in systemic sclerosis. 24th European Congress of Internal Medicine (ECIM 2026), 2026.03.25–28., Vienna, Austria.

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- **Filipánits, K.**, Czopf, L., Peresztegi, M. Zs., Németh, T., Tamás, A. (2023). Leveraging the potential of an online survey creator for enhanced digital organization management of near-peer teaching at the University of Pécs Medical School. AMSE 2023 Conference: The Digital Transformation for Healthcare Professions: Patient Care, Education and Research, 2023.10.05., Iași, Romania.

- **Filipánits, K.**, Kumánovics, G. (2025). The EULAR Best Undergraduate Teaching Concept Award. EULAR 2025, 2025.06.11–14., Barcelona, Spain.

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11. SCIENTOMETRICS

Scientific papers (MTMT-ID: 10083832)

Total: 7 (all English-language)

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