Gastrointestinal disorders in systemic sclerosis: cluster analysis and prognosis from a French prospective cohort

C. Mollière[1], A.F. Guédon[1], N. Kapel[2], F. de Vassoigne[3], F. Graiess[4], P. Senet[5], C. Cacciatore[1], C. McAvoy[1], O. Fain[1], S. Rivière[1], A. Mekinian[1]

[1]Department of Internal Medicine, Hôpital Saint-Antoine (APHP), Sorbonne University, Paris; [2]Functional Coprology Department, Assistance Publique Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Paris; [3]Tumorothèque d'Hématologie Saint-Antoine, APHP, Hôpital Saint-Antoine, Sorbonne University, Paris; [4]Department of Radiology, Hôpital Saint-Antoine (APHP), Sorbonne University, Paris; [5]Department of Dermatology, Hôpital Tenon (APHP), Sorbonne University, Paris, France.

Abstract

Objective

The gastrointestinal tract (GIT) is frequently involved in systemic sclerosis (SSc) and is responsible for alteration of quality of life. Many complications can occur, including chronic intestinal pseudo-obstruction, digestive haemorrhage and small-intestinal bacterial overgrowth. Since early development of organ failure is associated with poor prognosis, we need to identify risk factors associated with severe GIT involvement to prevent severe forms of the disease.

Methods

We conducted an observational prospective study, which included 90 SSc patients from December 2019 to September 2021. We collected questionnaires about digestive manifestations and quality of life, blood and stool samples, and performed imaging. At inclusion and throughout the study we assessed the occurrence of malnutrition and severe GIT disorders. We performed statistical analysis to highlight eventual risk factors associated with digestive manifestations, including hierarchical cluster analysis.

Results

A majority of our patients had gastro-oesophageal manifestations (93.3%), followed by intestinal manifestations (67.8%) and anorectal manifestations (18.9%). We found a correlation between anorectal disorders and cardiac disease, and between gastro-oesophageal involvement and impaired pulmonary function tests. Smoking was significantly associated with occurrence of severe GIT disorders. Malnutrition was frequent and associated with more cardiac and pulmonary disease. Cluster analysis identified three groups of patients, including one cluster with cardiac and digestive involvement.

Conclusion

GIT manifestations are frequent and severe in SSc. Smoking appears to be associated with severe disease. Anorectal manifestations may be associated with cardiac disease, but we need more studies to validate these results.

Key words

systemic sclerosis, gastrointestinal

Chloé Mollière, PhD
Alexis F. Guédon, PhD
Nathalie Kapel, PhD
Frédéric de Vassoigne, MSc
Farouk Graiess, PhD
Patricia Senet, MD, PhD
Carlotta Cacciatore, PhD
Chloé McAvoy, MSc
Olivier Fain, MD, PhD
Sébastien Rivière, PhD
Arsène Mekinian, MD, PhD

Please address correspondence to:
Arsène Mekinian
Service de Médecine Interne,
Hôpital Saint-Antoine (APHP),
184 rue de Faubourg Saint-Antoine,
75012 Paris, France.
E-mail: arsene.mekinian@aphp.fr

Received on May 14, 2024; accepted in revised form on July 25, 2024.

Competing interests: none declared.

Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterised by alteration of conjunctive tissue and vascular obliteration, leading to fibrosis of the skin and multi-organ dysfunction (1, 2).

The gastrointestinal tract (GIT) is the second most involved organ after the skin in SSc (3) and every segment from the mouth to the anus can be affected (4). GIT manifestations occur in 70-90% of patients with SSc (5-7). Among GIT manifestations, oesophageal involvement is the most common manifestation and concerns about 80% of the patients (8). Other GIT manifestations often reported include gastroparesis, nausea, bloating, abdominal pain, constipation, diarrhoea and anorectal manifestations such as anal incontinence or rectal prolapse (9). GIT disorders in SSc can be complicated by digestive haemorrhage secondary to vascular lesions such as small bowel angiodysplasia (10) or gastric antral vascular ectasia (GAVE) (11), which is associated with a higher mortality (12). Due to intestinal dysmotility, chronic intestinal pseudo-obstruction (CIPO) (13, 14) and small intestinal bacterial overgrowth (SIBO), concerning 30-62 % of the patients (15), are responsible for malnutrition and associated with mortality in 50% of the cases (16,17). Malnutrition is frequent in SSc and seems to be associated with more aggressive disease progression (18, 19). GIT disorders can also be complicated, in case of severe constipation, by diverticulosis and sometimes intestinal perforation and peritonitis (19, 20). Finally, GIT involvement seems to be responsible for 10% of death in SSc (18).

Identification of risk factors associated with GIT manifestations in SSc would allow to better identify patients susceptible to develop a GIT involvement. In a recent multicentric prospective study of 834 patients, authors identified several risk factors of severe GIT manifestations including positivity of anti-centromeres antibodies (ACA), smoking status and steroids use, whereas calcium channel blockers appear to be protective (21).

In this study, we evaluated the prevalence of GIT manifestations in SSc and analysed in cluster independent analysis the risk factors associated with severe GIT involvement and overall prognosis.

Patients and methods

Study design

We conducted a prospective observational study in Saint-Antoine and Tenon Hospitals (Paris, France) which included 90 patients followed for SSc according to ACR/EULAR 2013 (American College of Rheumatology/ European League Against Rheumatism) classification criteria (22) from 26 December 2019 to 14 September 2021. Patients were consecutively included during their hospitalisation or visit in the Department of Internal Medicine during the study period. This investigation was conducted in compliance with the protocol of Good Clinical Practices and Declaration of Helsinki principles. Patients gave written informed consent to the use of their data.

Data collection and outcomes

General data about the disease (demographics, date of SSc diagnosis corresponding to the first non-Raynaud symptom reported, subset of SSc, cardiovascular risk factors, associated diseases, various organ involvements, autoantibody status, specific treatments) were extracted from a database previously constituted. Various organ involvements included interstitial lung disease, evaluated by computed tomography (CT)-scan, cardiac disease (defined by presence of diastolic ventricular dysfunction or arrhythmia or atrioventricular block or pericarditis), pulmonary hypertension (confirmed by right-heart catheterisation), history of sclerodermic renal crisis and articular involvement.

For gastrointestinal involvement, we collected digestive symptoms reported by the patient by oral interrogation and by UCLA-SCTC GIT 2.0 Instrument and s-HAQ questionnaires, and we performed stool and blood samples and intestinal imaging (CT-scan and/or MRE). The UCLA-SCTC GIT 2.0 Instrument is a seven-item scale including reflux, distention/bloating, diarrhoea, faecal soilage, constipation, emotional well-being, and social

functioning capturing SSc-related GIT symptoms and their severity based on the frequency of occurrence. The total UCLA GIT score is the sum of all scales (except constipation) and ranges from 0 to 2.83 providing an estimation of the severity of GIT involvement. S-HAQ questionnaire is a validated score used to evaluate quality of life of patients. The measurement of faecal calprotectin was performed using the automated LIAISON Calprotectin assay (DiaSorin Inc., Italy) and testing was performed following the manufacturer's instructions on the DiaSorin LIAISON XL (DiaSorin Inc.). Faecal calprotectin over 50 μg/g was considered as abnormal. Severe gastrointestinal events were defined as follow: malnutrition (as defined by the Haute Autorité de Santé: Body Mass Index <18.5 kg/m² or 22 kg/m² in adult older than 70 years old, or albumin <35 g/l or loss of weight >10% within 6 months or >5% within 1 month), occurrence of a composite criteria including small intestinal bacterial overgrowth, chronic intestinal pseudo-obstruction or digestive haemorrhage.

Statistical analysis

Continuous variables were expressed as medians (interquartile ranges [IQR]), and qualitative variables were expressed as numbers (proportions). Qualitative variables and quantitative variables were compared using Fisher and Kruskal-Wallis tests, respectively. Cumulative incidence curves of outcomes were generated using Kaplan-Meier and compared using the logrank-test. We used Cox model to obtain Hazard Ratio (HR). Proportional hazards assumptions were checked using Schoenfeld residuals. We considered the date of the signed consent as the inclusion date and the date of last hospital contact or the outcome occurrence date as the last follow-up date. Two-sided testing was used, with $p<.05$ considered statistically significant. All analyses were performed using R software 4.2.2 version for Mac (Foundation for Statistical Computing, Vienna, Austria). Finally, we used factor analysis of mixed data (FAMD), handling missing data by using multiple imputation, with the R missMDA package v1.18 (24). Then we performed hierarchical cluster analysis based on FAMD coordinates by using Euclidean distance. We used three different methods to determine the optimal number of clusters. All methods suggested three clusters (Supplementary Fig. S1).

Results

Cohort description

We included 90 patients in this study, with 76 female sex (84.4%), a median age of 55.7 years (IQR 44.3-64.4), 64 limited cutaneous SSc (lcSSc) (71.1%) and 26 diffuse cutaneous SSc (dcSSc) (28.9%). Median disease duration was 93 months (IQR 23-217). Demographic and disease characteristics are summarised in Table I.

Almost all patients (96%) complaint at least with one of gastrointestinal symptoms (Table I), 3 patients had a history of chronic intestinal pseudo-obstruction (3.3%) and 5 were treated by cyclical courses of antibiotics for small intestinal bacterial overgrowth (5.6%). Finally, 84 patients (93.3%) were classified in "gastro-oesophageal involvement" group defined by the presence of reflux or dysphagia, 61 patients (67.8%) in "intestinal involvement" group defined by the presence of constipation and/or diarrhoea or chronic intestinal pseudo-obstruction or small intestinal bacterial overgrowth and 17 patients (18.9%) in "anorectal involvement" group defined by the presence of anal incontinence. UCLA-SCTC GIT 2.0 scores are in Table I. Albumin was under 35 g/l for 10 patients (11.1%). Faecal calprotectin (n=54 patients) showed a median at 37.5 μg/g (IQR 15.25-94.50); between 50 and 150 μg/g for 12 patients (13.3%) and greater than 150 μg/g for 6 patients (6.7%). Thirty-five patients had an MRE and only two showed a moderate parietal thickening of small bowel wall without stenosis and global jejunal dysmotility without bowel parietal thickening. Thirty-five patients had a CT scan including 18 abnormal findings (20%): 1 patient had a pseudo-occlusion with intestinal distension (measured to 28 mm; no MRE available for this patient) and 17 had an oesophageal dilatation.

Comparison of patients by segments of GIT involved

We compared features of patients in "gastro-oesophageal involvement", "intestinal involvement" and "anorectal involvement" groups (Suppl. Tables S1-S3) and according to the number of digestive segments involved (Table II). Patients with gastro-oesophageal involvement (Suppl. Table S1) had a significantly higher UCLA "reflux" score than patients without gastro-oesophageal involvement (0.38 *vs*. 0.0, p=0.011), higher faecal calprotectin levels (44.50 *vs*. 6.50 μg/g, p=0.007), and modified Rodnan skin score (8 *vs*. 3, p=0.034). Interestingly, almost all parameters of pulmonary function tests were significantly worse in patients with gastro-oesophageal involvement (Suppl. Table S1). Patients with intestinal involvement (Suppl. Table S2) had more reflux (81.7 *vs*. 55.2%, p=0.017), more dysphagia (33.9 *vs*. 10.3%, p=0.035) and more anal incontinence (27.1 *vs*. 3.6%, p=0.022) than patients without intestinal involvement. The quality of life of patients with intestinal involvement was significantly altered, as attested by higher UCLA "emotional well-being" score (0.44 *vs*. 0.22, p=0.03), UCLA "social functioning" score (0.33 *vs*. 0.0, p=0.001) and s-HAQ score (0.2 *vs*. 0.0, p=0.04). Patients with anorectal involvement (Suppl. Table S3) had more cardiac manifestations (47.1 *vs*. 13.7%, p=0.006). All items constitutive to the UCLA score were significantly higher in patients with anorectal involvement with quality of life significantly altered in this group. The prevalence of cardiac disease significantly increased with the number of digestive segments involved (50% *vs*. 18.2% *vs*. 7.7% *vs*. 0% with 3, 2, 1 or 0 digestive segments involved respectively, p=0.006) (Table II).

Cluster analysis

Clustering of individuals based on the selected variables yielded a number of 3 clusters (Fig. 1A-B). Results are presented in Table III. Cluster 1, "mild limited cutaneous systemic sclerosis" (n=25) was only composed of lcSSc patients, more frequent anti-centromeres antibodies (88% *vs*. 34.6%, p<0.001

Table I. Demographic and disease characteristics at inclusion.

	Overall n=90	
Age, year median (IQR)	55.7	(44.3-64.4)
Female, n (%)	76	(84.4)
Smoking, n (%)	31	(34.4)
Body mass index (kg/m²), median (IQR)	24.2	(20.7-27.8)
Body mass index <18.5 kg/m², n (%)	10	(11.1)
Arterial hypertension, n (%)	26	(28.9)
Diabetes, n (%)	6	(6.7)
Limited cutaneous SSc, n (%)	64	(71.1)
Disease duration, months median (IQR)	93	(23-217)
Associated diseases:		
Sjögren's syndrome, n (%)	14	(15.6)
Autoimmune thyroiditis, n (%)	6	(6.7)
Primary biliary cholangitis, n (%)	6	(6.7)
Raynaud, n (%)	88	(97.8)
mRSS, median (IQR)	7.5	(3.8-12.3)
Digital ulcers, n (%)	44	(48.9)
Active digital ulcers, n (%)	14	(15.6)
Telangiectasia, n (%)	53	(58.9)
Interstitial lung disease*, n (%)	33	(36.7)
Cardiac disease∞, n (%)	18	(20)
Pulmonary hypertension£, n (%)	4	(4.4)
Articular involvement, n (%)	33	(36.7)
Scleroderma renal crisis history, n (%)	1	(1.1)
Serum creatinine (µmol), median (IQR)	60.5	(53.3-74.3)
Anti-nuclear antibodies, n (%)	81	(90)
Anti-Scl70 antibodies, n (%)	26	(28.9)
Anti-centromere antibodies, n (%)	32	(35.6)
Anti-RNA POL3 antibodies, n (%)	7	(7.8)
Anti-PM/SCL antibodies, n (%)	3	(3.3)
Treatment:		
Steroids, n (%)	23	(25.6)
IS treatment without steroids°, n (%)	30	(33.3)
Calcium channel blockers, n (%)	62	(68.9)
Bosentan, n (%)	7	(7.8)
Sildenafil, n (%)	7	(7.8)
Proton pump inhibitors, n (%)	73	(81.1)
Reflux, n (%)	65	(72.2)
Dysphagia, n (%)	23	(25.6)
Vomiting, n (%)	8	(8.9)
Abdominal pain, n (%)	28	(31.1)
Diarrhoea, n (%)	36	(40)
Constipation, n (%)	44	(48.9)
CIPO, n (%)	3	(3.3)
SIBO, n (%)	5	(5.6)
Anal incontinence, n (%)	17	(18.9)
Gastro-oesophageal involvement, n (%)	84	(93.3)
Intestinal involvement, n (%)	60	(66.7)
Anorectal involvement, n (%)	17	(18.9)
UCLA reflux, median (IQR)	0.38	(0.12-0.62)
UCLA distension/bloating, median (IQR)	0.75	(0.25-1.50)
UCLA diarrhoea, median (IQR)	0.00	(0.00-1.00)
UCLA faecal soilage, median (IQR)	0.00	(0.00-0.00)
UCLA constipation, median (IQR)	0.25	(0.00-0.50)
UCLA social functioning, median (IQR)	0.17	(0.00-0.50)
UCLA emotional well-being, median (IQR)	0.44	(0.11-0.69)
UCLA total score, median (IQR)	0.42	(0.16-0.71)
s-HAQ, median (IQR)	0.15	(0.00-0.70)
Albumin (g/l), median (IQR)	41	(36.8-43.0)
Calprotectin (µg/g), median (IQR)	37.5	(15.3-94.5)
Abnormal MRE, n (%)	2	(2.2)
Abnormal CT-scan, n (%)	18	(20)

*Interstitial lung disease: evaluated by CT-scan.
∞Cardiac disease: presence of diastolic ventricular dysfunction or arrhythmia or atrioventricular block or pericarditis.
£Pulmonary hypertension: measured by right-heart catheterisation.
°Including cyclophosphamide, mycophenolate mofetil, rituximab and methotrexate.
IS: immunosuppressive; mRSS: modified Rodnan skin score.

and 6.1%, $p<0.001$ in cluster 2 and 3, respectively). They had less frequent intestinal (44%) or anorectal involvement (4%) than cluster 2 (88.9% and 59.3%, $p=0.003$ and $p<0.01$, respectively). They also had a better diffusing capacity for carbon monoxide (median [IQR]: 78.50 [70.25, 84.00], $p<0.001$) compared to cluster 2 (median [IQR]: 53.00 [47.25, 60.25], $p=0.085$). Those patients had less frequent immunosuppressive treatments (8% *vs*. 37%, $p=0.031$ and 68.4%, $p<0.001$ in cluster 2 and 3, respectively).

Cluster 2 "SSc with cardiac and digestive involvement" (n = 27) have more frequent intestinal (88.9%) or anorectal involvement (59.3%) than cluster 1 (44% and 4%, $p=0.002$ and $p<0.001$, respectively) and cluster 3 (65.8% and 0.0%, $p=0.07$ and $p<0.001$, respectively). Patients from cluster 2 had more frequent heart involvement (44.4% *vs*. 4%, $p=0.002$ and 13.2%, $p=0.01$ as compared to cluster 1 and 3 respectively), higher BNP levels (median [IQR]: 91.0 [27.0, 244.5] *vs*. 44.0 [20.0, 85.0], $p=0.03$ and 27.0 [19.0, 42.0], $p=0.01$ compared to cluster 1 and cluster 3 respectively). They also had higher troponin levels than cluster 1 (median [IQR]: 8.5 [3.0, 21.5] *vs*. 3.0 [2.0, 8.0], $p=0.04$) and more frequent pericardial effusion (26.9% *vs*. 0.0% $p<0.01$).

Cluster 3 "SSc with cutaneous and pulmonary involvement" (n = 38) included 19 patients (50%) with diffuse cutaneous systemic sclerosis. They had higher modified Rodnan skin score (10 *vs*. 7 as compared to cluster 2, and 3 as compared to cluster 1, $p<0.001$), more interstitial lung disease compared to cluster 1 (61.1% *vs*. 20%, $p<0.001$). They also had more frequent immunosuppressive treatments than cluster 2 (68.4% *vs*. 37%, $p=0.02$).

Regarding survival analyses, we did not find any difference regarding time to severe digestive outcome survival between clusters (5-years cumulative outcome events [95%CI: 9.1% [0.0; 24.6] in cluster 1, 9.1% [0.0, 20.3] in cluster 2 and 9.66% [0.0; 21.6] in cluster 3, global logrank test: 0.80).

Finally, UCLA "emotional well-being" score was significant elevated in cluster 2 (0.67 *vs*. 0.28, p 0.009 as compared

Table II. Characteristics of patients according to the number of digestive segments involved.

	Number of digestive segments involved				*p*^
Overall n=90	0 (n=4)	1 (n=26)	2 (n=44)	3 (n=16)	
Female, n (%)	4 (100)	22 (84.6)	35 (79.5)	15 (93.8)	0.458
Age, year median (IQR)	68.9 (59.3-70.8)	56.7 (49.5-64.5)	52.4 (42.0-62.0)	61.5 (45.6-68.8)	0.253
Arterial hypertension, n (%)	2 (50)	8 (30.8)	12 (27.3)	4 (25)	0.780
Diabetes, n (%)	0 (0.0)	4 (15.4)	2 (4.5)	0 (0.0)	0.178
Smoking, n (%)	2 (50)	10 (38.5)	13 (29.5)	6 (37.5)	0.765
lcSSc, n (%)	4 (100)	21 (80.8)	27 (61.4)	12 (75)	0.175
BMI, median (IQR)	25.5 (24.1-26.1)	25.6 (22.3-28.9)	23.1 (20.1-27.4)	22.4 (20.7-28.1)	0.521
Digital ulcers, n (%)	0 (0.0)	11 (42.3)	26 (59.1)	7 (43.8)	0.099
Active digital ulcers, n (%)	0 (0.0)	3 (11.5)	4 (9.1)	5 (31.2)	0.121
Telangiectasia, n (%)	2 (50)	15 (57.7)	27 (61.4)	9 (56.2)	0.959
mRSS, median (IQR)	3 (0.0-6.3)	6.5 (2.5-10.0)	9 (5.0-15.5)	8 (2.5-11.5)	0.168
Interstitial lung disease*, n (%)	0 (0.0)	10 (38.5)	18 (40.9)	5 (31.2)	0.408
Cardiac disease∞, n (%)	0 (0.0)	2 (7.7)	8 (18.2)	8 (50)	**0.006**
Pulmonary hypertension£, n (%)	0 (0.0)	1 (10)	2 (15.4)	1 (12.5)	0.960
Articular involvement, n (%)	0 (0.0)	9 (34.6)	20 (46.5)	4 (25.0)	0.167
Scleroderma renal crisis history, n (%)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0.477
Anti-centromere antibodies, n (%)	3 (75)	11 (45.8)	12 (30.0)	6 (37.5)	0.258
Anti-Scl70 antibodies, n (%)	0 (0.0)	8 (33.3)	15 (37.5)	3 (18.8)	0.287
Anti-RNA POL3 antibodies, n (%)	0 (0.0)	3 (12.5)	4 (10.0)	0 (0.0)	0.474
Anti-PM/SCL antibodies, n (%)	0 (0.0)	0 (0.0)	2 (5.0)	1 (6.2)	0.658
Reflux, n (%)	0 (0.0)	15 (57.7)	37 (86.0)	13 (81.2)	**<0.001**
Dysphagia, n (%)	0 (0.0)	3 (11.5)	16 (38.1)	4 (25.0)	0.06
Vomiting, n (%)	0 (0.0)	0 (0.0)	7 (16.7)	1 (6.2)	0.108
Abdominal pain, n (%)	1 (25.0)	6 (23.1)	9 (21.4)	12 (75.0)	**0.001**
Diarrhoea, n (%)	0 (0.0)	0 (0.0)	22 (51.2)	13 (81.2)	**<0.001**
Constipation, n (%)	0 (0.0)	4 (15.4)	27 (62.8)	13 (81.2)	**<0.001**
POIC, n (%)	0 (0.0)	0 (0.0)	1 (2.4)	2 (12.5)	0.163
SIBO, n (%)	0 (0.0)	0 (0.0)	2 (4.8)	3 (18.8)	0.077
Anal incontinence, n (%)	0 (0.0)	0 (0.0)	1 (2.4)	16 (100)	**<0.001**
UCLA reflux, median (IQR)	0 (0.0-0.0)	0.25 (0.12-0.47)	0.31 (0.12-0.75)	0.62 (0.25-0.75)	0.046
UCLA distension/bloating, median (IQR)	0.25 (0.25-0.25)	0.25 (0-0.50)	0.75 (0.25-1.5)	1.38 (0.94-1.75)	**0.001**
UCLA diarrhoea, median (IQR)	0 (0.0-0.0)	0 (0.0-0.0)	0 (0.0-1.0)	1.0 (0.38-1.50)	**<0.001**
UCLA faecal soilage, median (IQR)	0 (0.0-0.0)	0 (0.0-0.0)	0 (0.0-0.0)	1.0 (1.0-1.0)	**<0.001**
UCLA constipation, median (IQR)	0 (0.0-0.0)	0 (0.0-0.25)	0.25 (0.0-0.50)	0.44 (0.25-1.0)	**0.008**
UCLA social functioning, median (IQR)	0.08 (0.04-0.13)	0.17 (0.0-0.29)	0.17 (0.0-0.37)	0.67 (0.29-0.87)	**0.002**
UCLA emotional well-being, median (IQR)	0 (0.0-0.0)	0.28 (0.0-0.44)	0.33 (0.11-0.50)	0.78 (0.53-1.0)	**0.001**
UCLA total, median (IQR)	0.06 (0.05-0.06)	0.19 (0.11-0.30)	0.44 (0.21-0.62)	0.95 (0.75-1.04)	**<0.001**
s-HAQ, median (IQR)	0 (0.0-0.0)	0.05 (0.0-0.46)	0.12 (0.0-0.69)	0.48 (0.24-0.92)	**0.026**
Albumin (g/l), median (IQR)	41.1 (37.7-41.1)	41.4 (38.8-42.3)	41.0 (35.4-43.1)	37.6 (33.9-42.8)	0.685
Calprotectin (µg/g), median (IQR)	3.0 (1.5-4.5)	24.5 (14.3-84.5)	76.0 (19.0-118.0)	37.0 (8.0-86.0)	0.050
Steroids, n (%)	0 (0.0)	8 (30.8)	13 (30.2)	9 (56.2)	0.111
IS treatment without steroids, n (%)	0 (0.0)	13 (50.0)	18 (40.9)	7 (43.8)	0.306
Calcium channel blockers, n (%)	4 (100)	19 (73.1)	28 (65.1)	11 (68.8)	0.510
Bosentan, n (%)	0 (0.0)	0 (0.0)	5 (11.6)	2 (12.5)	0.275
Sildenafil, n (%)	0 (0.0)	3 (11.5)	2 (4.7)	2 (12.5)	0.591
Proton pump inhibitors, n (%)	0 (0.0)	22 (84.6)	37 (86.0)	14 (87.5)	**<0.001**

*Interstitial lung disease: evaluated by CT-scan.
∞Cardiac disease: presence of diastolic ventricular dysfunction or arrhythmia or atrioventricular block or pericarditis.
£Pulmonary hypertension: measured by right-heart catheterisation.
°Including cyclophosphamide, mycophenolate mofetil, rituximab and methotrexate.
^Global comparison of each group. Qualitative variables and quantitative variables were compared using Fisher and Kruskal-Wallis tests, respectively.
IS: immunosuppressive; mRSS: modified Rodnan skin score.

to cluster 1; 0.67 *vs*. 0.22, $p<0.001$ as compared to cluster 3), suggesting a worse quality of life in cluster 2 comparing to cluster 1 and 3.

Outcome and risk factors of severe GIT involvement

Median time of follow up was 17 months (IQR 12-21). At the end of the follow up, 6 patients had died: from cardiogenic shock (n=2), neuroendocrine cancer (n=1), SARS-CoV-2 infection (n=1) and from unknown cause (n=2). There were 28 patients (31.1%) with malnutrition and 9 patients (10 %) with at least one episode of digestive haemorrhage, small intestinal bacterial overgrowth or chronic intestinal pseudo-obstruction. Patients with malnutrition had more frequently diffuse cutaneous SSc (79% *vs*. 53.6%, $p=0.027$), more interstitial lung disease (57.1% *vs*. 27.4%, $p=0.013$) and more cardiac disease (39.3% *vs*. 11.3%, $p=0.005$)

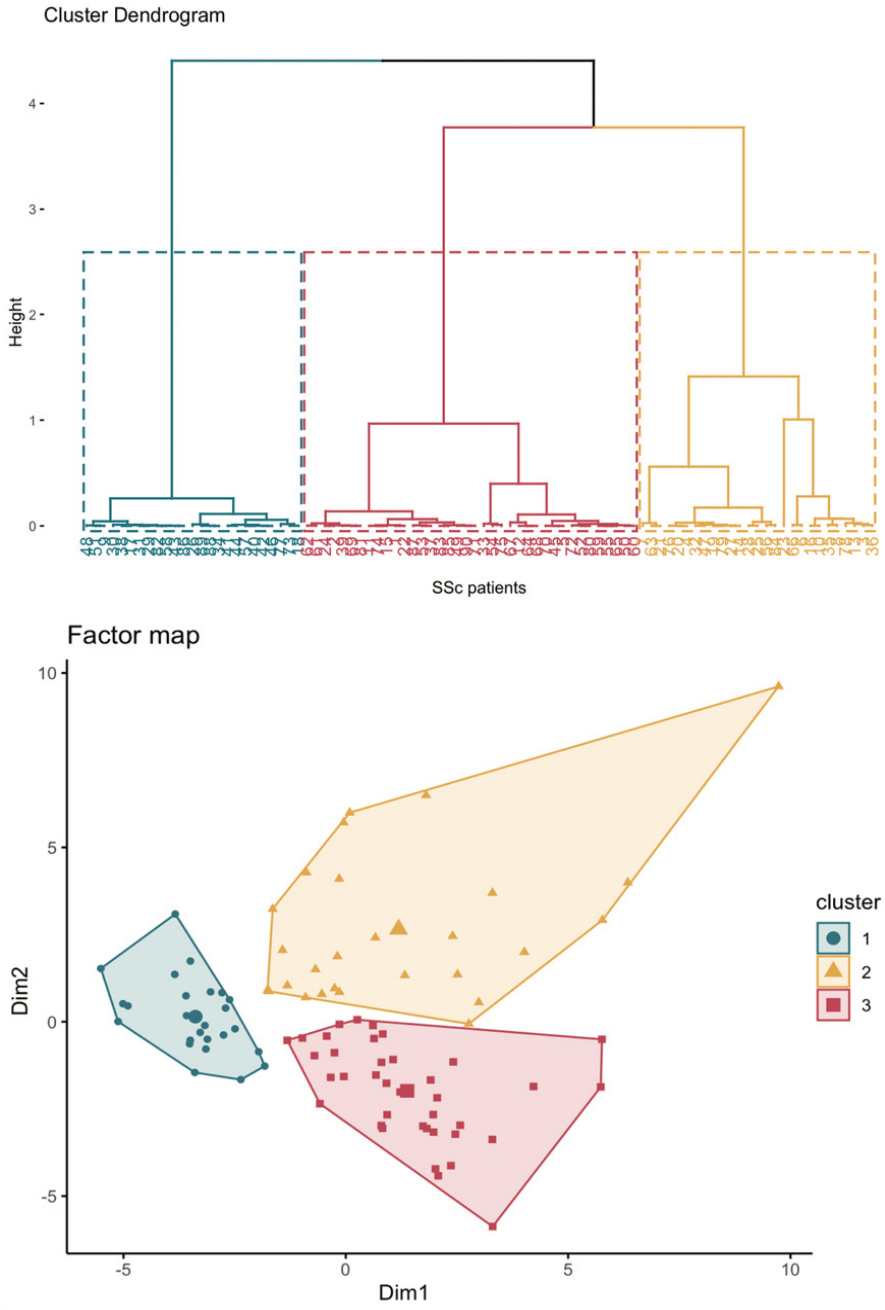

Fig. 1. Unsupervised analysis of patients with SSc.
(**A**) The hierarchical clustering on principal components analysis of patients with SSc revealed three clusters (variables included are listed in the supplementary material). (**B**) Factor map showing the individuals used to generate the dendrogram.

(Suppl. Table S4). No patient without malnutrition died at the end of follow-up whereas 4 patients with malnutrition died (p=0.013). Bivariate analysis of factors associated with the occurrence of severe GIT events showed a higher proportion of smokers (77.8% *vs*. 29.6%, p=0.012) and a smaller BMI (18.6 *vs*. 24.25 kg/m², p=0.027) as compared to patients without composite criteria outcome (Suppl. Table S5). Smoking was associated with a significantly higher risk for the composite of digestive haemorrhage or chronic intestinal pseudo-obstruction or small intestinal bacterial overgrowth (adjusted HR 11.87, p=0.024, 95% CI 1.38-102.25).

Discussion

Most of our patients suffered from digestive impairment and the gastro-oesophageal involvement was predominant (93.3%). These results are concordant with the prevalence of oesophageal involvement reported in literature (8). As previously reported in several studies, we found that intestinal and anorectal involvements are associated with altered quality of life (6, 25). In this study, we identified several phenotypes of GIT involvements using cluster unsupervised analysis. Indeed, we identified 3 phenotypes which distinguish lcSSc with anti-centromeres antibodies, more intestinal and anal GIT profile composed with heart involvement, and cluster of patients with lung disease and diffuse SSc associated with anti-Scl70 antibodies. Interestingly, the first patients' profile with prevalent gastro-oesophageal involvement have also more frequent impaired lung functional tests. Indeed, some authors have described a correlation between reflux and interstitial lung disease, mainly by inhalation of gastric liquid (26, 27). Gastro-oesophageal involvement was significantly associated with increased faecal calprotectin, although faecal calprotectin remains normal in most patients (28, 29). Furthermore, smoking was significantly associated with occurrence of severe digestive outcomes (including digestive haemorrhage, CIPO, or SIBO) in Cox regression model analysis. In a recent study (21), smoking has already been described as a risk factor of severe digestive involvement in SSc. Moreover, as reported in previous study (19), malnutrition was associated with higher mortality. More recently, the authors worked on an original approach using the phenome-wide association study (PheWAS) to explore the contributors to gastrointestinal disorders in SSc (30). Interestingly, they also found a correlation between reflux and interstitial lung disease.

This study has several limitations, as the classification in each digestive segment involved group was difficult since one symptom can concern different segments of the GI tract. Many data analysed here are based on symptoms, which are subjective, these symptoms can be encountered in general populations and are fluctuating over time. The collection of symptoms through a questionnaire may constitute a bias.

Table III. Unsupervised cluster analysis of patients with systemic sclerosis.

Overall n = 90	Cluster 1 (n = 25)	Cluster 2 (n = 27)	Cluster 3 (n = 38)	*p*^
Female, n (%)	23 (92)	24 (88.9)	29 (76.3)	0.182
Smoking, n (%)	8 (32)	12 (44.4)	11 (28.9)	0.413
Body mass index (kg/m²), median (IQR)	25.6 (21.5-29.1)	23.1 (20.7-27.7)	23.7 (20.7-28.2)	0.304
Arterial hypertension, n (%)	9 (36)	8 (29.6)	9 (23.7)	0.57
Diabetes, n (%)	3 (12)	0 (0.0)	3 (7.9)	0.206
Limited cutaneous SSc, n (%)	25 (100.0)	20 (74.1)	19 (50.0)	**<0.001**
Raynaud, n (%)	25 (100.0)	27 (100.0)	36 (94.7)	0.247
mRSS, median (IQR)	3 (0.0-6.0)	7 (3.0-15.0)	10 (8.0-17.0)	**<0.001**
Digital ulcers, n (%)	4 (16.0)	16 (59.3)	24 (63.2)	**0.001**
Active digital ulcers, n (%)	1 (4.0)	7 (25.9)	6 (15.8)	0.093
Telangiectasia, n (%)	16 (64.0)	17 (63.0)	20 (52.6)	0.586
Interstitial lung disease*, n (%)	2 (8.0)	9 (33.3)	22 (57.9)	**<0.001**
Cardiac disease∞, n (%)	1 (4.0)	12 (44.4)	5 (13.2)	**0.001**
Pulmonary hypertension £, n (%)	0 (0.0)	1 (7.7)	3 (18.8)	0.529
Articular involvement, n (%)	7 (28.0)	9 (34.6)	17 (44.7)	0.386
Scleroderma renal crisis history, n (%)	0 (0.0)	0 (0.0)	1 (2.6)	0.501
Anti-Scl70 antibodies, n (%)	2 (8.0)	4 (15.4)	20 (60.6)	**<0.001**
Anti-centromere antibodies, n (%)	22 (88.0)	9 (34.6)	2 (6.1)	**<0.001**
Treatment:				
Aspirin, n (%)	0 (0.0)	7 (26.9)	1 (2.6)	**0.001**
Statin, n (%)	1 (4.0)	9 (34.6)	1 (2.6)	**0.001**
Steroids, n (%)				
IS treatment with steroids°, n (%)				
Reflux, n (%)	16 (64.0)	23 (85.2)	26 (70.3)	0.202
Dysphagia, n (%)	3 (12.0)	8 (30.8)	12 (32.4)	0.162
Vomiting, n (%)	0 (0.0)	2 (7.7)	6 (16.2)	0.089
Abdominal pain, n (%)	2 (8.0)	15 (57.7)	8 (21.6)	**<0.001**
Diarrhoea, n (%)	3 (12.0)	17 (65.4)	14 (37.8)	**<0.001**
Constipation, n (%)	10 (40.0)	19 (70.4)	14 (37.8)	**0.023**
CIPO, n (%)	0 (0.0)	3 (11.5)	0 (0.0)	**0.026**
SIBO, n (%)	0 (0.0)	4 (15.4)	1 (2.8)	**0.037**
Anal incontinence, n (%)	1 (4.0)	16 (61.5)	0 (0.0)	**<0.001**
Gastro-oesophageal involvement, n (%)	20 (80.0)	27 (100.0)	37 (97.4)	**0.007**
Intestinal involvement, n (%)	11 (44.0)	24 (88.9)	25 (65.8)	**0.003**
Anorectal involvement, n (%)	1 (4.0)	16 (59.3)	0 (0.0)	**<0.001**
UCLA reflux, median (IQR)	0.25 [0.16, 0.44]	0.62 [0.19, 0.81]	0.25 [0.00, 0.62]	0.096
UCLA distension/bloating, median (IQR)	0.25 [0.25, 1.00]	1.00 [0.62, 1.75]	0.75 [0.25, 1.00]	0.117
UCLA diarrhoea, median (IQR)	0.00 [0.00, 0.00]	0.50 [0.00, 1.00]	0.00 [0.00, 0.50]	**0.005**
UCLA faecal soilage, median (IQR)	0.00 [0.00, 0.00]	1.00 [0.00, 1.00]	0.00 [0.00, 0.00]	**<0.001**
UCLA constipation, median (IQR)	0.25 [0.00, 0.50]	0.38 [0.12, 0.88]	0.00 [0.00, 0.38]	**0.024**
UCLA social functioning, median (IQR)	0.17 [0.00, 0.17]	0.50 [0.08, 0.75]	0.17 [0.00, 0.33]	**0.04**
UCLA emotional well-being, median (IQR)	0.28 [0.00, 0.61]	0.67 [0.44, 1.00]	0.22 [0.00, 0.44]	**0.001**
UCLA total score, median (IQR)	0.22 [0.11, 0.46]	0.73 [0.54, 0.97]	0.28 [0.19, 0.57]	**<0.001**
s-HAQ, median (IQR)	0.00 [0.00, 0.10]	0.55 [0.18, 1.10]	0.20 [0.05, 0.70]	**<0.001**
Albumin (g/l), median (IQR)	41.3 [40.0, 43.0]	40 [34.4, 42.1]	38.9 [36.1, 42.6]	0.276

*Interstitial lung disease: evaluated by CT-scan.
∞Cardiac disease: presence of diastolic ventricular dysfunction or arrhythmia or atrioventricular block or pericarditis.
£Pulmonary hypertension: measured by right-heart catheterisation.
°Including cyclophosphamide, mycophenolate mofetil, rituximab and methotrexate.
^Global comparison of each group. Qualitative variables and quantitative variables were compared using Fisher and Kruskal-Wallis tests, respectively.
IS: immunosuppressive; mRSS: modified Rodnan skin score.

However, the validated UCLA-SCTC GIT 2.0 score was correlated with digestive symptoms reported and this can improve the validity of the study. Furthermore, no difference was noted on occurrence of digestive symptoms depending on the disease duration in our study. In our study, 20 patients were included less than one year after their diagnostic of SSc. It would have been interesting to see if these patients are more affected by digestive disorders than the others. During the follow-up, we collected data about occurrence of malnutrition, death or severe gastrointestinal disorders and thus the number of patients who developed new digestive symptoms could not be analysed. A better evaluation, which could be based on questionnaire related tools, should be used to better detect the gastrointestinal involvement in SSc.

In the future, studies on the microbiota could improve our understanding of GIT in SSc, as it has already been performed in other autoimmune/inflammatory diseases like familial Mediterranean fever (31), inflammatory bowel disease (IBD) (32–34) or systemic lupus erythematosus (35).

Conclusion

Gastrointestinal disorders are frequent in systemic sclerosis and are responsible for mortality and altered of quality of life. This study reported the gastrointestinal manifestations in a cohort of 90 patients with SSc, with a predominance of gastro-oesophageal involvement and for the first time described a cluster analysis allowing classification of various clinical GIT phenotypes. Futures studies are necessary in particular to correlate with the microbiota changes.

Take home messages

- Gastrointestinal disorders are frequent in systemic sclerosis and are associated with bad quality of life. Little is known in literature about risk factors associated with severe digestive impairment.
- Smoking seems to be associated with severe digestive involvement in systemic sclerosis.
- Gastro-esophageal manifestations are associated with impaired pulmonary function tests.
- We found a correlation between cardiac involvement and anorectal disorders.
- Cluster analysis identified three groups of patients, including one cluster with cardiac and digestive involvement.

References

1. SILVER RM: Clinical aspects of systemic sclerosis (scleroderma). *Ann Rheum Dis* 1991; 50 (Suppl. 4): 854-61. https://doi.org/10.1136/ard.50.suppl_4.854
2. DI BATTISTA M, LEPRI G, CODULLO V *et al*.: Systemic sclerosis: one year in review 2023. *Clin Exp Rheumatol* 2023; 41(8): 1567-74. https://doi.org/10.55563/clinexprheumatol/ki76s5
3. SJOGREN RW: Gastrointestinal motility disorders in scleroderma. *Arthritis Rheum* 1994; 37(9): 1265-82. https://doi.org/10.1002/art.1780370902
4. JAOVISIDHA K, CSUKA ME, ALMAGRO UA, SOERGEL KH: Severe gastrointestinal involvement in systemic sclerosis: report of five cases and review of the literature. *Semin Arthritis Rheum* 2005; 34(4): 689-702. https://doi.org/10.1016/j.semarthrit.2004.08.009
5. JAEGER VK, WIRZ EG, ALLANORE Y *et al*.: Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR study. *PloS One* 2016; 11(10): e0163894. https://doi.org/10.1371/journal.pone.0163894
6. OMAIR MA, LEE P: Effect of gastrointestinal manifestations on quality of life in 87 consecutive patients with systemic sclerosis. *J Rheumatol* 2012; 39(5): 992-96. https://doi.org/10.3899/jrheum.110826
7. SHREINER AB, MURRAY C, DENTON C, KHANNA D: Gastrointestinal manifestations of systemic sclerosis. *J Scleroderma Relat Disord* 2016; 1(3): 247-56. https://doi.org/10.5301/jsrd.5000214
8. DELLA ROSSA A, VALENTINI G, BOMBARDIERI S *et al*.: European multicentre study to define disease activity criteria for systemic sclerosis. I. Clinical and epidemiological features of 290 patients from 19 centres. *Ann Rheum Dis* 2001; 60(6): 585-91. https://doi.org/10.1136/ard.60.6.585
9. JAFFIN BW, CHANG P, SPIERA H: Fecal incontinence in scleroderma. Clinical features, anorectal manometric findings, and their therapeutic implications. *J Clin Gastroenterol* 1997; 25(3): 513-17. https://doi.org/10.1097/00004836-199710000-00006
10. IIO S, OKA S, SUMIOKA A *et al*.: Characteristics and treatment outcomes of small-bowel angioectasia in systemic sclerosis patients: a retrospective observational study. *Intern Med* 2022; 61(5): 615-22. https://doi.org/10.2169/internalmedicine.8034-21
11. YAMAMOTO M, TAKAHASHI H, AKAIKE J *et al*.: Gastric antral vascular ectasia (GAVE) associated with systemic sclerosis. *Scand J Rheumatol* 2008; 37(4): 315-16. https://doi.org/10.1080/03009740801998754
12. DUCHINI A, SESSOMS SL: Gastrointestinal hemorrhage in patients with systemic sclerosis and CREST syndrome. *Am J Gastroenterol* 1998; 93(9): 1453-6. https://doi.org/10.1111/j.1572-0241.1998.00462.x
13. VALENZUELA A, LI S, BECKER L *et al*.: Intestinal pseudo-obstruction in patients with systemic sclerosis: an analysis of the Nationwide Inpatient Sample. *Rheumatology* 2016; 55(4): 654-58. https://doi.org/10.1093/rheumatology/kev393
14. MECOLI C, PUROHIT S, SANDORFI N, DERK CT: Mortality, recurrence, and hospital course of patients with systemic sclerosis-related acute intestinal pseudo-obstruction. *J Rheumatol* 2014; 41(10): 2049-54. https://doi.org/10.3899/jrheum.131547
15. PITTMAN N, RAWN SM, WANG M, MASETTO A, BEATTIE KA, LARCHÉ M: Treatment of small intestinal bacterial overgrowth in systemic sclerosis: a systematic review. *Rheumatology* 2018; 57(10): 1802-11. https://doi.org/10.1093/rheumatology/key175
16. BHARADWAJ S, TANDON P, GOHEL T *et al*.: Gastrointestinal manifestations, malnutrition, and role of enteral and parenteral nutrition in patients with scleroderma. *J Clin Gastroenterol* 2015; 49(7): 559-64. https://doi.org/10.1097/mcg.0000000000000334
17. PREIS E, FRANZ K, SIEGERT E *et al*.: The impact of malnutrition on quality of life in patients with systemic sclerosis. *Eur J Clin Nutr* 2018; 72(4): 504-10. https://doi.org/10.1038/s41430-018-0116-z
18. FORBES A, MARIE I: Gastrointestinal complications: the most frequent internal complications of systemic sclerosis. *Rheumatology* 2009; 48 Suppl 3: iii36-39.
19. BARON M, HUDSON M, STEELE R *et al*.: Canadian Scleroderma Research Group. Malnutrition is common in systemic sclerosis: results from the Canadian scleroderma research group database. *J Rheumatol* 2009; 36(12): 2737-43. https://doi.org/10.3899/jrheum.090694
20. GEIRSSON AJ, WOLLHEIM FA, AKESSON A: Disease severity of 100 patients with systemic sclerosis over a period of 14 years: using a modified Medsger scale. *Ann Rheum Dis* 2001; 60(12): 1117-22. https://doi.org/10.1136/ard.60.12.1117
21. VAN LEEUWEN NM, BOONSTRA M, FRETHEIM H *et al*.: Gastrointestinal symptom severity and progression in systemic sclerosis. *Rheumatology* 2022; 61(10): 4024-34. https://doi.org/10.1093/rheumatology/keac118
22. VAN DEN HOOGEN F, KHANNA D, FRANSEN J *et al*.: Classification Criteria for Systemic Sclerosis: An ACR-EULAR Collaborative Initiative. *Arthritis Rheum* 2013; 65(11): 2737-47. https://doi.org/10.1002/art.38098
23. JAMART C, LEVESQUE H, THIETART S *et al*.: Iloprost duration for digital ulcers in systemic sclerosis: French retrospective study at two centers and literature review. *front med* 2022; 9: 878970. https://doi.org/10.3389/fmed.2022.878970
24. JOSSE J, HUSSON F: missMDA: a package for handling missing values in multivariate data analysis. *J Stat Softw* 2016; 70: 1-31. https://doi.org/10.18637/jss.v070.i01
25. FRANCK-LARSSON K, GRAF W, RÖNNBLOM A: Lower gastrointestinal symptoms and quality of life in patients with systemic sclerosis: a population-based study. *Eur J Gastroenterol Hepatol* 2009; 21(2): 176-82. https://doi.org/10.1097/meg.0b013e32831dac75
26. SAVARINO E, BAZZICA M, ZENTILIN P *et al*.: Gastroesophageal reflux and pulmonary fibrosis in scleroderma: a study using pH-impedance monitoring. *Am J Respir Crit Care Med* 2009; 179(5): 408-13. https://doi.org/10.1164/rccm.200808-1359oc
27. ZHANG XJ, BONNER A, HUDSON M *et al*.: Association of gastroesophageal factors and worsening of forced vital capacity in systemic sclerosis. *J Rheumatol* 2013; 40(6): 850-58. https://doi.org/10.3899/jrheum.120705
28. MARIE I, LEROI AM, MENARD JF, LEVESQUE H, QUILLARD M, DUCROTTE P: Fecal calprotectin in systemic sclerosis and review of the literature. *Autoimmun Rev* 2015; 14(6): 547-54. https://doi.org/10.1016/j.autrev.2015.01.018
29. LUNDGREN D, EKLÖF V, PALMQVIST R, HULTDIN J, KARLING P: Proton pump inhibitor use is associated with elevated faecal calprotectin levels. A cross-sectional study on subjects referred for colonoscopy. *Scand J Gastroenterol* 2019; 54(2): 152-57. https://doi.org/10.1080/00365521.2019.1566493
30. MACLEAN RH, AHMED F, ONG VH, MURRAY CD, DENTON CP: A phenome-wide association study of drugs and comorbidities associated with gastrointestinal dysfunction in systemic sclerosis. *J Rheumatol* 2023;5 0(7): 907-15. https://doi.org/10.3899/jrheum.220990
31. DESHAYES S, FELLAHI S, BASTARD JP *et al*.: Specific changes in faecal microbiota are asso-

ciated with familial Mediterranean fever. *Ann Rheum Dis* 2019;78(10):1398-404. https://doi.org/10.1136/annrheumdis-2019-215258

32. EOM T, KIM YS, CHOI CH, SADOWSKY MJ, UNNO T: Current understanding of microbiota- and dietary-therapies for treating inflammatory bowel disease. *J Microbiol* 2018; 56(3): 189-98. https://doi.org/10.1007/s12275-018-8049-8
33. SEKSIK P, RIGOTTIER-GOIS L, GRAMET G *et al*.: Alterations of the dominant faecal bacterial groups in patients with Crohn's disease of the colon. *Gut* 2003; 52(2): 237-42. https://doi.org/10.1136/gut.52.2.237
34. MANICHANH C, RIGOTTIER-GOIS L, BONNAUD E *et al*.: Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. *Gut* 2006; 55(2): 205-11. https://doi.org/10.1136/gut.2005.073817
35. HEVIA A, MILANI C, LÓPEZ P *et al*.: Intestinal dysbiosis associated with systemic lupus erythematosus. *mBio* 2014; 5(5): e01548-01514. https://doi.org/10.1128/mbio.01548-14