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The evaluation of gastrointestinal involvement and nutritional status in systemic sclerosis: identifying risk factors for malnutrition in a cross-sectional study

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ABSTRACT

Aims: Gastrointestinal (GI) involvement is frequently observed in Systemic sclerosis (SSc). Considering the effect of GI involvement on SSc patients, the risk of malnutrition might be increased. The study aimed to evaluate GI involvement and the risk for malnutrition and to demonstrate the relationship between disease-related features and risk factors for malnutrition in SSc patients.

Methods: SSc-related clinical features and disease severity evaluated with Physician Global Assessment (PGA) were recorded. Detailed GI symptoms and the impact of GI involvement on patients were assessed with the UCLA SCTC GIT 2.0 questionnaire. Nutritional status was evaluated with Body Mass Index (BMI) and the Malnutritional Universal Screening Tool (MUST).

Results: 104 SSc patients were involved in the study. Mean age of patients with SSc was 52.24±12.82 years. GI involvement was found in 85.7% of patients. 76% of patients had GI symptoms. The median BMI of patients was 25.3 (9) kg/m² with 4.8% of patients categorized as underweight. The assessment of risk for malnutrition using MUST showed 74% of patients at low risk, 16% at moderate risk, and 9.6% at high risk. No important association was detected between risk groups for malnutrition and UCLA GIT 2.0 score. A significant association was found between moderate to high risk for malnutrition and dcSSc (OR 3.12, %95 CI:1.26-7.73; P=0.01), the presence of GI symptoms (OR 5.32, %95 CI:1.16-24.36; P=0.03), the decrease in oral aperture (OR 0.35, %95 CI:0.15-0.79; p:0.02), and severity of the disease investigated by PGA score (OR 1.52, %95 CI:1.09-2.13; p=0.01).

Conclusion: GI involvement is a common manifestation in SSc patients. Approximately 26% of patients were at moderate to high risk for malnutrition. Several SSc-specific clinical features, including disease severity, the presence of GI symptoms, dcSSc, and a decrease in oral aperture were related to a higher risk for malnutrition.

Keywords: Gastrointestinal involvement, malnutrition, MUST score, risk factors, systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is a chronic rheumatologic disease characterized by multisystem involvement with elevated morbidity and mortality rates. The primary pathogenetic mechanisms in SSc involve a dysregulation of the immune system, resulting in exaggerated inflammation, vasculopathy, and consequent augmented extracellular matrix synthesis, culminating in fibrosis.[1-3] In SSc, major organ involvements such as pulmonary, cardiac, or gastrointestinal (GI) systems are frequently observed, those play a pivotal role in contributing to disease-specific manifestations and serve as crucial determinants of both disease severity and progression of the disease.

The GI tract is the second most frequently affected site following the skin, with an incidence reported in 80%-90% of SSc patients.[4,5] SSc has the potential effect on any part of the GI tract, thereby contributing to a highly heterogeneous presentation of disease-related symptoms ranging from reflux symptoms such as regurgitation or heartburn sensation to diarrhea or fecal incontinence. Given that pulmonary and heart involvement stand as the primary cause of SSc-related mortality, therapeutic interventions, and clinical approaches predominantly prioritize these manifestations.[6] Therefore, GI involvement might be failed to notice leading to a lack of thorough assessment and proper treatments. Apart from its high incidence, GI involvement can cause a substantial decline in quality of life and functional capacity in SSc patients. GI involvement is reported as the major determinant of health quality in SSc patients.[7] Furthermore, severe GI disease, including malabsorption, need for hyperalimentation, pseudo-obstruction, and

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intestinal bacterial overgrowth, affects 8% of SSc patients. Moreover, severe GI disease is observed in the very early disease (disease duration<2 years) and is associated with higher mortality rate.[8,9]

The presence of GI involvement in SSc poses a risk for the development of malnutrition due to symptoms associated with the involvement, such as early satiety or distension, and dysmotility-related complications, particularly in intestinal bacterial over-growth leading to malabsorption.[10] Besides, the chronic course of SSc, coupled with its multisystem involvement and disease severity, might also contribute to the development of malnutrition. The objective of the study was to evaluate GI involvement and risk for malnutrition in SSc patients and to determine the impacts of SSc-related features on risk for malnutrition.

METHODS

This study was cross-sectional and conducted at the Department of Rheumatology, Gazi University Hospital. Patients who met the ACR/EULAR 2013 criteria of SSc were included.[11] Participants who supplied informed written consent by the principles delinated in the Declaration of Helsinki were incorporated into the study. The study received approval from Gazi University Hospital Ethics Committee (Date: 05.10.2020, Decision No: 664).

Sociodemographic information and clinical characteristics of SSc patients were derived from both medical records and interviews conducted with patients. Gastrointestinal (GI) involvement was evaluated with the presence of related symptoms, including reflux, dysphagia, early satiety, diarrhea, bloating, and constipation, based on self-reported information provided by patients and any evidence of esophageal involvement (esophageal dysmotility, as a reported by manometry).[12] Besides severe GI disease defined as the presence of hyperalimentation, small intestinal bacterial overgrowth or pseudo-obstruction was investigated.[9] The definition of microstomia was as an interincisal distance measuring less than 40 mm.[13]

The UCLA SCTC GIT 2.0 questionnaire is a measure to evaluate the impact of SSc-related GI symptoms on health-related quality of life and to assess the severity of GI involvement in SSc patients.[14] UCLA GIT 2.0 includes seven subscales related to GI manifestations and all subscales are scored from 0.0 to 3.0 except diarrhea (0.0-2.0) and constipation (0.0-2.5), and the total score is computed as the sum of all subscales, excluding constipation, divided by 6 yielding a range from 0.0 to 2.83 (higher scores reflect worse HRQOL). The Turkish-validated version of this measurement was utilized in the study 15. Moreover, participants underwent assessment using the Health Assessment Questionnaire (HAQ) and the Physician Global Assessment (PGA; scale: 0-10) to assess disease severity.[16]

Nutritional status and malnutrition were assessed by using body mass index (BMI) and the Malnutritional Universal Screening Tool (MUST). According to BMI value, patients were classified into different categories: underweight, normal weight, overweight, and obese.

The MUST which demonstrates the risk for malnutrition is calculated by adding all scores of BMI (>20=0, 18.5-20=1, <18.5=2), weight loss (unplanned weight loss in 3-6 months, <5%=0, 5-10%=1, <10%=2), and acute disease effect (no oral intake for more than five days=2). A score of 2 or higher means a high risk for malnutrition, necessitating intervention. A score of 1 signifies moderate risk for malnutrition, recommending observation and a score of 0 means low risk for malnutrition.[17]

Statistical Analysis

SPSS was used to analyse the data of study. In accordance with the distribution, numeric data were expressed as mean±standard deviation (SD) or median with interquartile range (IQR). Comparisons between groups were analyzed with One-Way ANOVA, Kruskal Wallis Test, The Student's T test, and Man Whitney U Test. The variables, which were found a statically meaningful difference ($p<0.05$) between malnutrition risk groups, were included in univariate regression analyses. Univariate regression analyses were employed to identify risk factors for malnutrition in SSc patients and results were exhibited as an odds ratio (OR) with 95% confidence intervals (95% CI). The Spearmen test was used to calculate correlation coefficients and assess their significance for the association between non-normally distributed variables.

RESULTS

One hundred four patients (92.3% female and 64.4% lcSSc) were enrolled. The mean age of patients was 52.24±12.82 years and the median disease duration of patients was 5 (8) years. The patients' characteristics were shown in **Table 1**. The assessment of disease severity indicated a mean PGA score of 4.70±1.52. The median score of HAQ was 0.625 (1.125) in patients.

GI involvement was observed in 87.5% of SSc patients, 76% of whom had GI symptoms. The predominant GI symptoms included reflux symptoms (heartburn or regurgitation) in 60.6% of patients, dysphagia in 51.9%, and early satiety in 47.1%. Other less frequent symptoms were bloating/distention (24%), constipation (12.7%), and diarrhea (8%). Approximately five percent

of patients exhibited severe GI symptoms. (**Table 2**). The median oral aperture among patients was measured at 36.5 (10) mm and microstomia was present in two-thirds of patients. The median UCLA GIT total score was 0.214 (0-2.11)

Table 1. Baseline patients' characteristics

Age, years, mean±SD	52.24±12.82
Gender, Female, n (%)	96 (92.3)
Smoking, ever, n (%)	29 (28)
Disease duration, years, median (IQR)	5 (8)
Disease subset, lcSSc/dcSSc, n (%)	67 (64.4)/37 (35.6)
mRSS, median (IQR)	13 (12)
Telangiectasia, n (%)	65 (62.5)
Digital ulcer history, n (%)	48 (46.1)
Musculoskeletal involvement, n (%)	57 (54.8)
Interstitial lung disease, n (%)	60 (57.7)
Pulmonary arterial hypertension, n (%)	10 (9.6)
Heart involvement, n (%)	26 (25)
Renal crisis, n (%)	7 (6.7)
Anti-topoisomerase I positivity, n (%)	60 (57.7)
Anti-centromere positivity, n (%)	21 (20.2)
HAQ score, median (IQR)	0.625 (1.125)
PGA score, mean±SD	4.70±1.52

dcSSc: diffuse cutaneous systemic sclerosis; HAQ: health assessment questionnaire; IQR: interquartile range; lcSSc: limited cutaneous systemic sclerosis; mRSS: modified Rodman skin score; PGA: physician global assessment.

Table 2. Features of gastrointestinal involvement and nutritional status in SSc patients

Oral aperture, mm, median (IQR)	36.5 (10)
Microstomia, n (%)	66 (63.5)
Gastrointestinal involvement, n (%)	91 (87.7)
Esophageal involvement, n (%)	83 (79.8)
Gastrointestinal symptoms, n (%)	79 (76)
Severe gastrointestinal symptoms, n (%)	5 (4.8)
UCLA GIT, total score, median (min-max)	0.214 (0-2.11)
UCLA GIT-reflux score, median (min-max)	0.375 (0-2.62)
UCLA GIT-distention score, median (min-max)	0.5 (0-3)
UCLA GIT-fecal soilage score, median (min-max)	0 (0-3)
UCLA GIT-diarrhea score, median (min-max)	0 (0-2)
UCLA GIT-social functioning score, median (min-max)	0.16 (0-1.83)
UCLA GIT-emotional well-being score, median (min-max)	0 (0-2.88)
UCLA GIT-constipation, median score (min-max)	0 (0-2.25)
Nutritional status	
BMI kg/m², median (IQR)	25.3 (9)
Underweight, n (%)	5 (4.8)
Normal, n (%)	45 (43.3)
Overweight, n (%)	26 (25)
Obese, n (%)	28 (26.8)
MUST Score, median (IQR)	0.39 (1)
Low risk, n (%)	77 (74)
Medium risk, n (%)	17 (16.3)
High risk, n (%)	10 (9.6)

BMI: body mass index; IQR: interquartile range; MUST: Malnutritional Universal Screening Tool; UCLA GIT: The University of California Los Angles Scleroderma Gastrointestinal tract questionnaire.

The examination of nutritional status in the study demonstrated that the median BMI of patients was 25.3 (9) kg/m². The assessment of risk for malnutrition using MUST showed 74% of patients at low risk, 16% at moderate risk, and 9.6% at high risk The evaluation of patients' characteristics in terms of risk for malnutrition was presented in **Table 3**. The comparison of disease subsets between risk groups for malnutrition displayed that the frequency of dcSSc in patients with moderate and high risk for malnutrition was %58 and 50%, respectively. The ratio of dcSSc was statistically lower in patients at low risk for malnutrition (28.6%) than patients at moderate risk for malnutrition (p=0.03). There were not any remarkable differences in the frequency of organ involvement, except renal crises, between risk groups for malnutrition (p>0.05). The renal crisis was frequently detected in patients with high risk in contrast to patients with low risk (p=0.02). Besides, patients at high risk for malnutrition had significantly increased HAQ scores meaning more disease-related disability, and more severe disease than in patients at low risk (p=0.03; p=0.004, respectively).

The median oral aperture of SSc patients in the moderate-risk group was 3.3 (0.9) mm which was prominently lower in comparison to patients with low risk for malnutrition (3.8 (0.7) mm; p=0.01). GI symptoms were more prevalent in patients at high risk for malnutrition in contrast to patients at low risk for malnutrition (p=0.04). The median UCLA GIT 2.0 score of patients was 0.18 (0-2.11) at low risk 0.28 (0-1.45) at moderate risk and 0.39 (0-1.1) at high risk for malnutrition. Despite the higher scores observed in the moderate and high-risk groups, there was no significant association to be found between risk groups and UCLA GIT 2.0 score.

The association between the MUST risk score and clinical variables was elucidated through regression analyses, with unadjusted crude OR being reported. An important association was displayed between moderate to high risk for malnutrition and dcSSc (OR=3.12, %95 CI:1.26-7.73; P=0.01), the presence of GI symptoms (OR=5.32, %95 CI:1.16-24.36; P=0.03), the decrease in oral aperture (OR=0.35, %95 CI:0.15-0.79; P=0.02), and disease severity investigated by PGA score (OR=1.52, %95 CI:1.09-2.13; p=0.01). There was not any important correlation between the MUST risk score and UCLA GIT 2.0 total and subscale scores (UCLA GIT total, r=0.019 p=0.85; UCLA GIT-reflux, r=0.035 p=0.73; UCLA GIT-distention, r=-0.012 p=0.90; UCLA GIT-fecal soilage, r=-0.027 p=0.78; UCLA GIT-social functioning, r=0.15 p=0.13; UCLA GIT-diarrhea, r=-0.013 p=0.89; UCLA GIT-emotional well-being, r=0.049 p=0.62; UCLA GIT-constipation, r=0.035 p=0.73).

Table 3. The assessment of clinical features in SSc patients in terms of risk for malnutrition

MUST	Low Risk n=77	Moderate Risk n=17	High Risk n=10	p	p1	p2	p3
Age, years, mean±SD	53.9±12.8	48.35±15.5	46±8	0.72	0.15	0.05	0.60
Disease duration, years, median (IQR)	5 (7)	5 (9)	2 (6)	0.26	0.62	0.14	0.13
Disease subset, dcSSc, n (%)	22 (28.6)	10 (58.7)	5 (50)	0.04	0.03	0.27	0.70
mRSS, median (IQR)	12 (11)	16 (16)	14.5 (22)	0.37	0.27	0.30	0.84
Telangiectasia, n (%)	48 (62.3)	12 (70.6)	5 (50)	0.55	0.81	0.49	0.41
Digital ulcer history, n (%)	37 (48.7)	7 (41.2)	6 (10)	0.77	0.77	0.74	1.00
Musculoskeletal involvement, n (%)	37 (48.7)	12 (70.6)	8 (80)	0.06	0.17	0.09	0.68
Interstitial lung disease, n (%)	44 (57.1)	10 (58.8)	6 (60)	0.99	1.00	1.00	1.00
Pulmonary arterial hypertension, n (%)	8 (11.4)	0	2 (20)	0.31	0.59	0.60	0.19
Heart involvement, n (%)	21 (29.2)	1 (6.3)	4 (40)	0.12	0.10	0.48	0.12
Renal crisis, n (%)	3 (4.1)	1 (6.3)	3 (30)	0.01	0.55	0.02	0.26
Anti-topoisomerase I positivity, n (%)	43 (55.8)	11 (64.7)	6 (60)	0.82	0.73	1.00	1.00
Anti-centromere positivity, n (%)	16 (20.8)	4 (23.5)	1 (10)	0.74	0.75	0.68	0.62
HAQ, median (IQR)	0.56 (1.06)	0.62 (1.73)	1.43 (1.69)	0.08	0.23	0.03	0.51
PGA, median (IQR)	5 (2)	5 (3)	6 (2)	0.02	0.41	0.004	0.10
Oral aperture, mm, median (IQR)	3.8 (0.7)	3.3 (0.9)	3.4 (1)	0.03	0.01	0.21	0.59
Microstomia, n (%)	46 (59.7)	12 (70.6)	8 (80)	0.45	0.37	0.49	1.00
Gastrointestinal involvement, n (%)	65 (84.4)	16 (94.1)	10 (100)	0.25	0.45	0.34	1.00
Esophageal involvement, n (%)	60 (77.9)	14 (82.4)	9 (90)	0.55	0.72	0.68	1.00
Gastrointestinal symptoms, n (%)	54 (70.1)	15 (88.2)	10 (100)	0.05	0.12	0.04	0.52
Severe gastrointestinal symptoms, n (%)	4 (5.2)	0 (0)	1 (10)	0.48	1.00	0.47	0.37
UCLA GIT, total score, median (min-max)	0.18 (0-2.11)	0.28 (0-1.45)	0.39 (0-1.1)	0.87	0.61	0.82	0.80

p1: low risk vs moderate risk p2: low risk vs high risk p3: moderate risk vs high risk
dcSSc: diffuse cutaneous systemic sclerosis; HAQ: health assessment questionnaire; IQR: interquartile range; lcSSc: limited cutaneous systemic sclerosis; mRSS: modified Rodman skin score; MUST: Malnutritional Universal Screening Tool; PGA: physician global assessment; UCLA GIT: The University of California Los Angles Scleroderma Gastrointestinal tract questionnaire.

DISCUSSION

The majority of SSc patients suffer from GI involvement which can lead to detrimental consequences, such as esophageal stricture, pseudobstruction or malnutrition, and markedly impairment of health related quality of life. The primary aim of treatment modalities and clinical approaches to GI involvement is usually to relieve the symptoms and sustain adequate nutritional status. Although the exact pathogenesis of GI involvement in SSc is obscure, clinical and animal studies are implicated in vascular damage, inflammation, fibrosis, and muscular atrophy which result in hypomobility, the hallmark of GI involvement. Furthermore, recent studies have revealed that autonomic nerve dysfunction contributes to one of the mechanisms underlying dysmotility in GI involvement.[18,19]

In our study, the incidence of GI involvement was found to be 87.5% and upper GI symptoms were found to be more prominent in SSc patients. The cohort study which included 69% of lcSSc patients, similar to our study sample has demonstrated that the predominant GIT complaint is upper GIS symptoms (94%), the most common of ones are reflux and distention, evaluated using SSc-GIT 1.0.5 The EUSTAR database which is the most extensive SSc cohort has shown that upper GI symptoms are more frequently observed than lower GI symptoms, compatible with our results.[20] Besides, our study revealed that 5% of SSc patients had severe GI disease which is related to increased morbidity and mortality.[9]

In SSc, dysmotility is one of the main mechanisms responsible for serious GI manifestations such as reflux esophagitis, gastroparesis, small intestinal bacterial overgrowth, or pseudo-obstructions, all of which might be potential leading causes of malnutrition.[18,21] Beyond severe involvement, various symptoms and associated complications of GI involvement can contribute to the predisposition of malnutrition in SSc patients. In our cohort, SSc patients were found to have a notable frequency of malnutrition risk with 25.6% classified as having moderate (16%) to high (9.6%) risk for malnutrition and %5 patients with underweight. The Canadian SSc cohort with a large number patient size has demonstrated that 30% of patients are at moderate to high risk for malnutrition and the number of GI symptoms is related to higher risk for malnutrition.[22] Similarly, GI symptoms were reported in 76% of SSc patients and the presence of these symptoms was found to be a predictor of higher risk for malnutrition in our study. Nonetheless, our study reported that the UCLA GIT 2.0 total score which reflects the severity of GIS involvement and its related symptoms, did not exhibit a significant increase

in patients at moderate to high risk for malnutrition. The study assessing GI symptoms and nutritional status in SSc has demonstrated a meaningful correlation was not detected between MUST score and UCLA GIT 2.0 total or subscale scores, similar to our results.[23] However, a recent study has indicated that malnourished SSc patients have significantly worse GI symptoms evaluated using UCLA GIT 2.0.[24]

Although dcSSc is considered as a predictor of major organ involvements such as ILD or renal disease, it is noteworthy that GIS involvement is frequently observed in both lcSSc and dcSSc patients.[4] In our study, patients with dcSSc were markedly frequent within the moderate and high-risk group for malnutrition, and a significant association was found between dcSSc and higher risk for malnutrition in SSc. Similar to our result, the Canadian cohort group has reported the relationship between dcSSc and a higher risk for malnutrition.[22] In contrast previous study including ninety-eight SSc patients has shown that mRSS scores are increased in patients with high risk for malnutrition whereas disease subsets are similar between risk groups.[25] In addition disease subset, renal crises/involvement was significantly frequent in patients at high risk for malnutrition in comparison to patients at low risk while there was no detected meaningful association between renal crisis and higher risk for malnutrition in our study. An interesting finding from our study was no obvious effect of major organ involvement on risk for malnutrition.

In the literature, a few clinical studies have detected that disease severity is considered as an independent risk factor for malnutrition.[22,26,27] The results of our study, consistent with prevailing previous reports, emphasized that the disease severity assessed with PGA was a predictor for malnutrition risk. Besides, patients with moderate to higher risk for malnutrition had worse health quality in our study. Microstomia, a common manifestation of SSc, can affect nutritional status in SSc patients through leading to chewing problems, dental health problems, and loss of teeth. Microstomia and a decrease in oral aperture are considered as risk factors for the development of malnutrition in SSc.[22,25] Interestingly, the frequency of microstomia was similar in low and moderate to high risk groups for malnutrition whereas a decrease in oral aperture was significantly related to moderate to high risk for malnutrition in our cohort.

Limitations

The main limitation was a lack of information on treatments related to GI involvement in the study. Therefore, we could not analyze the effect of GI-related treatment on symptoms or nutritional status. Another limitation was the absence of an investigation of laboratory findings related to malnutrition such as hemoglobin, serum folate, vitamin B12, and albumin. Besides, we did not evaluate patients according to localization of GI involvement due to the need of further investigation to detect the definitive localization. Also, we did not perform multivariate analyses to determine the independent risk factors for malnutrition because of the imbalance in the sample size of the groups.

CONCLUSION

In SSc, GI involvement and malnutrition may be overlooked possibly due to a predominant focus on other major organ involvements with their substantial their heavy burdens. However, the evaluation of GI involvement and malnutrition can be facilitated through the straightforward and practical approach of questioning the symptoms and using the MUST score.[10] Furthermore, special attention might be needed to be directed towards patients exhibiting specific features, such as dcSSc, GI symptoms, severe disease, and a decrease in oral aperture for the development of malnutrition.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Gazi University Hospital Ethics Committee (Date: 05.10.2020, Decision No: 664).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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