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ORIGINAL ARTICLE

Rheumatic Disease Comorbidity Index (RDCI), Disease's Parameters, and Quality of Life among Systemic Sclerosis Patients

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ABSTRACT

Background: Comorbidities are common in autoimmune diseases and are associated with adverse outcomes, increased morbidity, and mortality. This research aimed to assess the Rheumatic Disease Comorbidity Index (RDCI) among systemic sclerosis (SSc) patients and to study the disease's parameters and quality of life (QoL) and their relations with RDCI.

Methods: A cross-sectional study included 61 SSc patients attending Rheumatology clinics, Zagazig University Hospitals- Egypt. Demographic, clinical, and laboratory data were recorded. RDCI, disease activity, disease severity, and SSc quality of life (SScQoL) questionnaire were assessed.

Results: About one-third (32.8%) of the SSc patients had more comorbidities (RDCI score > median (2)). There were significant associations between RDCI and disease activity, disease severity, SScQoL, arthritis, GIT manifestations, other co-morbidities, liver disorders, and renal stones (P= 0.013*, 0.008*, 0.001**, 0.013*, 0.01*, 0.030*, 0.004*, & 0.040*, respectively) and patients with these parameters were (6.4, 4.5, 7.7, 6.4, 7.0, 7.9, 5.9, & 4.4, respectively) times more likely to have more comorbidity of RDCI. RDCI showed significant positive correlations with disease activity (r=+0.364, P=0.004*), disease severity (r=+0.268, P=0.037*), and SScQoL scores (r=+0.661, P≤0.001**). On logistic regression model, disease severity (>6), lower QoL (SScQoL >17), and liver disorders were independent predictors for developing more comorbidities.

Conclusion : Significant positive correlations exist between RDCI score and SSc activity, severity, and SScQoL scores. Higher disease severity, lower QoL, and liver disorders are independent predictors for developing more comorbidities (RDCI >2) in SSc. RDCI can be a crucial method for assessing comorbidities in SSc.

Key Points :

- About one-third (32.8%) of the included SSc patients have RDCI score > median (2).
- RDCI shows significant positive correlations with disease activity, disease severity, and lower quality of life among SSc patients.

Keywords: Systemic sclerosis; disease activity; disease severity; Quality of Life; Rheumatic Disease Comorbidity Index.

INTRODUCTION

Systemic sclerosis (SSc) is a chronic systemic connective tissue disorder characterized by fibrosis of the skin and internal organs [1]. Disease manifestations result from a pathological triad of inflammation, vasculopathy, and fibrosis [2]. Systemic sclerosis is a complex heterogeneous disease. In addition to the disease burden, the bidirectional influence between the disease itself and comorbidities may lead to higher morbidity and mortality rates [3].

Recent studies within the European Scleroderma Trial and Research Group (EUSTAR) cohort revealed that most deaths were directly associated with SSc. However, a significant proportion of the mortality rate was also comorbidity-linked [2]. Comorbidity is defined as the "existence or occurrence of any additional entity during the clinical course of a patient with the index disease under study" [4].

Awareness of comorbidities is essential as comorbidities affect disease activity, prognosis, mortality rate, quality of life (QoL), treatment choice, responsiveness to treatment, side effects, patient compliance, and medical costs [5,6]. Recently, greater attention has been focused on recognizing and managing comorbidities in autoimmune diseases [7].

A number of comorbidity instruments have been created to evaluate comorbidities in patients with rheumatic disease. The Rheumatic Disease Comorbidity Index (RDCI) was developed to quantify the comorbidity burden and assess the association of this burden with long-term health outcomes of rheumatic disorders [8].

The Rheumatic Disease Comorbidity Index (RDCI) was created to quantify the comorbidity burden and assess the association of this burden with long-term health outcomes of rheumatic disorders [8]. RDCI has been widely employed in rheumatoid arthritis (RA) as well as psoriatic arthritis, spondyloarthritis, gout, lupus, vasculitis, and osteoporosis due to its efficacy, feasibility, and flexibility [9, 10, 11].

In contrast to other systemic autoimmune diseases, the data regarding the clinical expression as well as the impact of comorbidities in SSc using RDCI are still limited [12]. This indicates the crucial need for awareness, prompt diagnosis, and effective therapies not only for SSc but also for associated comorbidities.

Therefore, the current research was designed to assess the RDCI among SSc patients and to study the disease's parameters and QoL and their relations with RDCI.

METHODS:

A cross-sectional study was carried out in the follow-up and the inward units at the Rheumatology and Rehabilitation Department at Zagazig University Hospitals in Egypt for one year from November 2023 to October 2024.

The study was approved by the Institutional Review Board (IRB) (ZU-IRB#11162) at the Faculty of Medicine, Zagazig University, Egypt in compliance with the 1964 Helsinki Declaration, which is the Code of Ethics of the World Medical Association for Research including people. Written informed consents were gathered from all participants.

All the eligible patients involved in the study were >16 years old and diagnosed to have SSc if they met the American College of Rheumatology/ European League Against (ACR/EULAR) classification criteria for SSc [13]. LeRoy et al., classified the disease to diffuse cutaneous systemic sclerosis (dcSSc) or limited cutaneous systemic sclerosis (lcSSc) [14]. On the other hand, the study excluded patients with histories of other

autoimmune diseases, scleroderma mimics, malignancy, infection, significant cognitive impairment, or pregnancy. Moreover, patients with histories of previous aesthetic intervention for their face were excluded.

The total sample size was calculated using the open epi -I program, assuming that the incidence of coronary arteriosclerosis among SSc patients according to Mok et al., was 17,2% [15] and throughout the study period, there were a total of 83 patients, so the sample was 61 SSc patients at a 95% confidence level.

Data were collected from clinical consultations including history taking, general, musculoskeletal, mucocutaneous, and systemic examinations. Additionally, the skin thickness was examined using the modified Rodnan skin score (mRSS) which includes seventeen body surface areas on a 0–3 scale with a maximum of 51 [16].

The SSc activity was assessed based on the Revised European Scleroderma Trials and Research Group (EUSTAR) Activity Index (RAI). RAI is a 10-point activity index that is weighted. Diffusing capacity of the lung for carbon monoxide (DLCO) % predicted <70%=1.0, mRSS >18=1.5, digital ulcers=1.5, tendon friction rubs=2.25, C-reactive protein >1 mg/dL=2.25, and Δ-skin=1.5 (Δ=patient viewed worsening during the preceding month) constitute this measure. Patients with active disease were identified using a cut-off of ≥2.5 [17].

The SSc severity was determined depending on the Revised Medsger Severity Scale (MSS). The Revised MSS was created as an organ-specific indicator of the overall impact of SSc on organ function. Both reversible and irreversible aspects of SSc are combined in the MMS, detecting activity and damage. It includes nine organs. The disease severity in every organ system varies from zero to four, with four denoting end-stage disease [18].

The comorbidities in SSc were assessed according to the Rheumatic Disease Comorbidity Index (RDCI). RDCI consists of 11 current or previous comorbid conditions (other than disease manifestations), involving pulmonary disorders, myocardial infarction (MI), other cardiovascular diseases (CVD), stroke, hypertension, diabetes, spine/hip/leg fracture, depression, gastrointestinal tract (GIT) ulcer, other GIT disorders, and cancer. RDCI scores are calculated from the particular variables applying the original formula: 2 × lung disease + (2 × [heart attack, other cardiovascular diseases, or stroke] or 1 × hypertension) + fracture + depression + diabetes + cancer + (ulcer or stomach symptom). Its range is from 0 to 9 [19]. Comorbidities other than items of RDCI were also detected.

The translated Arabic version of the SScQoL questionnaire was used to assess the SSc-associated quality of life (SScQoL). The SScQoL questionnaire is a self-administered questionnaire that comprises 29 questions. The overall score ranges from 0 to 29. Each item's response is marked 1 or 0 based on the "yes" or "no" response, accordingly. A lower quality of life is reflected in a higher score. The five categories that correlate to the Function, Disability, and Health International Classification are derived from a summary of the 29 questions. Six questions (1, 12, 14, 15, 22, and 25) are part of the function (participation restriction), which also asks about emotional (personal elements). Sleep (personal variables) and 13 questions (2, 3, 4, 5, 6, 7, 8, 17, 18, 19, 24, 27, and 29) Social (restrictions on participation), two questions (9 and 20) 6 [20].

Laboratory investigations including antinuclear antibodies (ANA), complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lipid profile, and liver and kidney functions were done. High-resolution computed tomography (HRCT), pulmonary

functiontests (PFTs), and echocardiography (ECHO) were applied for all patients.

Statistical analysis

The Statistical Package for Social Science (SPSS) software (Version 20.0. Armonk, NY: IBM Corp.) was used to code, enter, present, and analyze the gathered data. Quantitative variables were expressed as the mean ± standard deviation (SD) (and median with range for not normally distributed data) while the qualitative variables were expressed as a number and percentage. The chi-square test ($\chi 2$) or Fisher's exact test was used to assess and detect the relation between different qualitative variables. Regression analysis was used to determine the independent factors affecting the RDCI. Spearman correlation (r) was used to correlate RDCI with disease activity, disease severity, and SScQoL questionnaire. If the significant probability (P value) was ≤ 0.05* and ≤0.001**, the results were defined as statistically significant and highly statistically significant, respectively.

RESULTS

This research involved 61 SSc patients with a higher proportion of them females (91.8%), had ages ≤47 years old (50.8%), and had disease duration≤5 years (55.5%). The demographic and clinical characteristics are shown in (Table 1).

On assessing the laboratory, HRCT, ECHO, and PFT characters, the higher percentage of the studied patients had normal hemoglobin (Hb) (68.9%), abnormal ESR (91.8%), abnormal CRP (85.2%), +ve ANA (96.7%), abnormal HRCT (72.1%) with (37.7%) ground glass opacity, abnormal ECHO (63.9%) with (34.4%) Left ventricular diastolic dysfunction (LVDD), and abnormal PFT (67.2%) with (29.5%) mild restriction (Table 2).

In terms of RDCI, disease activity, disease severity, and SScQoL questionnaire, the mean RDCI was 1.95±1.4 with a median of 2.0(0.0-5.0) and about one-third (32.8%) of the included SSc patients had more comorbidities > median (2) with the lower percent of them had pulmonary disorders (9.8%) (other than SSc manifestations), MI (3.3%), other CVD (27.9%), stroke (6.6%), hypertension (29.5%), diabetes (13.1%), spine/hip/leg fracture (4.9%), depression (29.5%), GIT ulcer (0.0%), other GIT disorders (23%), and cancer (6.6%). Also, the mean disease activity was 3.36±1.6 with a median of 3.75(0.0-6.75) and more than two-thirds (68.9%) of patients had activity ≥ 2.5 & the mean disease severity was 6.31±2.1 with (45.9%) of them were more severe > median (6). Regarding the SScQoL questionnaire, the mean total score was 16.3±4.5 with nearly half (49.2%) of patients having more impairment of quality of life > median (17). The means of individual sections were 3.7±1.59 with a median of 4.0(0.0-6.0) for function, 7.46±2.59 for emotion, 0.89±0.78 with median 1.0(0.0-2) for sleep, 3.07±1.38 with median 3.0(1.0-6.0) for social, and 1.16±0.66/ with median 1.0(0.0-2) for pain (Table 3).

The association of RDCI with demographic and clinical factors revealed a significant association between arthritis, GIT manifestations, other co-morbidities, liver disorders, renal stones and RDCI where SSc patients with arthritis, GIT, other co-morbidities, liver disorders, and renal stones were (6.4, 7.0, 7.9, 5.9, & 4.4) times more likely to have more comorbidities, respectively (Table 4).

In addition, the association of RDCI with laboratory, HRCT, ECHO, PFT factors, disease activity, disease severity, and SScQoL questionnaire illustrated statistically significant associations between disease activity, disease severity, SScQoL score, and

RDCI. SSc patients with higher disease activity (RAI ≥ 2.5), higher disease severity (Revised MSS >6), and more impairment of quality of life (SScQoL >17) were (6.4, 4.5, & 7.7) times more likely to have more comorbidity of RDCI, respectively (Table 5).

The best-fitting logistic regression model for identifying the independent variables influencing the RDCI among the studied patients showed that liver disorders, disease severity (Revised MSS >6), and more impairment of QoL (SScQoL >17) were statistically significant independent predictors to have more comorbidities (RDCI >2) (Table 6).

Finally, the correlation of RDCI with disease activity, disease severity, as well as SScQoL score among the studied patients demonstrated that there was a highly statistically significant positive correlation between RDCI & SScQoL scores (r=+0.661, P≤0.001**) and there was a statistically significant positive correlation between RDCI & disease activity (r=+0.364, P=0.004*) and with disease severity (r=+0.268, P=0.037*) (Figure 1).

Table 1: Demographic and clinical characteristics of the studied SSc patients (n=61).

characteristics	No (%)
Age (years)(mean ± SD) ≤ Median (47) > Median (47)	44.5±10.5 31(50.8%) 30(49.2%)
Sex Male Female	 5.0(8.2%) 56(91.8%)
Disease duration (years)(mean ± SD) / Median (Range) ≤ Median (5) > Median (5)	6.97±5.5/ 5(1-23) 34(55.7%) 27(44.3%)
Type Limited Diffuse	 16(26.2%) 45(73.8%)
mRSS (mean ± SD) / Median (Range) Less skin tightness ≤ Median (16) More skin tightness > Median (16)	17.1±6.5/ 16(6-34) 32(52.5%) 29(47.5%)
Cutaneous manifestations Raynaud's phenomenon Ulceration Gangrene Pitting scars Calcinosis Telangiectasia	 61(100%) 27(44.3%) 19(31.1%) 46(75.4%) 5.0(8.2%) 12(19.7%)
Arthritis	42(68.9%)
Friction rub	4.0(6.6%)
Chest Dyspnea Cough	48(78.7%) 46(75.4%) 22(36.1%)
Heart	14(23.0%)

characteristics	No (%)
Palpitation Chest pain Orthopnea	11(18.0%) 3.0(4.9%) 7.0(11.5%)
GIT Dyspepsia Heartburn/GERD Dysphagia Constipation/Diarrhea	50(83.6%) 10(16.4%) 26(42.6%) 29(47.5%) 10(16.4%)
Other comorbidities: Hypothyroidism Liver disorders - Hepatomegaly - Fatty liver - HCV - Liver cirrhosis Hyperlipidemia Convulsions Renal stones	48(78.7%) 8.0(13.1%) 14(23.0%) 4.0(6.6%) 5.0(8.2%) 2.0(3.3%) 3.0(4.9%) 9.0(14.8%) 2.0(3.3%) 2.0(3.3%)
Treatment mycophenolate mofetil Vasodilators Endoxan Azathioprine Methotrexate Corticosteroids	 26(42.6%) 61(100%) 7.0(11.5%) 22(36.1%) 7.0(11.5%) 37(60.7%)

SD: Standard deviation, SSc: Systemic sclerosis, mRSS: modified Rodnan skin score, GIT: gastrointestinal tract, GERD: gastroesophageal reflux disease, HCV: hepatitis C virus.

Table 2: Laboratory, HRCT, ECHO, and PFT characteristics of the studied SSc patients (n=61).

Characters	No (%)
WBC ($x10^3/mm^3$) (mean ± SD) Hb (g/dl) (mean ± SD) Platelets ($x10^3/mm^3$) (mean ± SD)	7.9±2.74 12.2±1.2 287±77.6
ESR (mm/h) (mean ± SD) / Median (Range) CRP (mg/dl) (mean ± SD) / Median (Range)	32.6±18.6/ 27(3-95) 11.1±13.2/ 5.8(0.40-54)
ALT (IU/L) (mean ± SD) / Median (Range) AST (IU/L) (mean ± SD) / Median (Range)	23.3±15.1/ 19(5-80) 23.5±9.3/ 21(10-48)
Creatinine (mg/dL) (mean ± SD) BUN (mg/dL) (mean ± SD) / Median (Range) Creatinine Clearance (mL/min) (mean ± SD) Total protein in urine (mg/24hr) (mean ± SD) / Median (Range)	0.68±0.23 15.5±11.6/ 12.9(0.58-77) 98.1±33.2 201±246/ 138(48-1764)
ANA -ve	 2.0(3.3%)

Characters	No (%)
+ve	59(96.7%)
HRCT	
Normal	17(27.9%)
Abnormal	44(72.1%)
- Ground glass opacity	23(37.7%)
- Honeycombing	19(31.1%)
- Other CT finding	17(27.9%)
ECHO	
Normal	22(36.1%)
Abnormal	39(63.9%)
- Valve lesion	12(19.7%)
- LVDD	21(34.4%)
- PAH	5.0(8.2%)
- Others	
• No	53(86.9%)
• Cardiomegaly	5.0(8.2%)
• Pericardial effusion	3.0(4.9%)
PFT	
Normal	20(32.8%)
Abnormal	41(67.2%)
- Mild restriction	18(29.5%)
- Moderate restriction	10(16.4%)
- Severe restriction	5.0(8.2%)
- Restriction + Obstructive	8.0(13.1%)
FVC (mean ± SD)	73.1±16.9
FEV1 (mean ± SD)	70.2±20.2
FEV1/FVC ratio (mean ± SD)	94.1±19.8

SD: Standard deviation, SSc: Systemic sclerosis, HRCT: high-resolution computed tomography, PFT: pulmonary function tests, ECHO: echocardiography, ANA: antinuclear antibodies, LVDD: Left ventricular WBC: white blood cell, Hb: Hemoglobin, ERS: diastolic dysfunction, PAH: Pulmonary arterial erythrocyte sedimentation rate, CRP: C-reactive hypertension, FVC: Forced vital capacity, FEV1: protein, ALT: alanine transaminase, AST: aspartate forced expiratory volume exhaled in the first second transaminase, BUN: blood urea nitrogen,

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Table 3: RDCI, SSc disease activity, SSc disease severity, and SScQoL among the studied patients (n=61).

Characters	No (%)
RDCI (mean ± SD)/ Median (Range)	1.95±1.4/ 2.0(0.0-5.0)
Less comorbidity ≤ Median (2)	41(67.2%)
More comorbidity > Median (2)	20(32.8%)
Items of RDCI:	
- Pulmonary disorders	6.0(9.8%)
- MI	2.0(3.3%)

Characters	No (%)
- Other CVD	17(27.9%)
- Stroke	4.0(6.6%)
- Hypertension	18(29.5%)
- Diabetes	8.0(13.1%)
- Spine/hip/leg fracture	3.0(4.9%)
- Depression	18(29.5%)
- GIT ulcer	0.0(0.0%)
- Other GIT disorders	
• Cholecystitis	4.0(6.6%)
• Gallbladder stone	5.0(8.2%)
• Anal fissure	2.0(3.3%)
• Piles	3.0(4.9%)
- Cancer	4.0(6.6%)
Disease activity* (mean ± SD)/ Median (Range)	3.36±1.6/ 3.75(0.0-6.75)
Inactive <2.5	19(31.1%)
Active ≥ 2.5	42(68.9%)
Disease severity** (mean ± SD)	6.31±2.1
Less severe ≤ Median (6)	33(54.1%)
More severe > Median (6)	28(45.9%)
SScQoL questionnaire (mean ± SD)	16.3±4.5
Less impairment ≤ Median (17)	31(50.8%)
More impairment > Median (17)	30(49.2%)
Items of SScQoL questionnaire:	
Function (mean ± SD) / Median (Range)	3.7±1.59/ 4.0(0.0-6.0)
Emotional (mean ± SD)	7.46±2.59
Sleep (mean ± SD) / Median (Range)	0.89±0.78/ 1.0(0.0-2)
Social (mean ± SD) / Median (Range)	3.07±1.38/ 3.0(1.0-6.0)
Pain (mean ± SD) / Median (Range)	1.16±0.66/ 1.0(0.0-2)

SD: Standard deviation, SSc: Systemic sclerosis, RDCI: Rheumatic Disease Comorbidity Index, SScQoL: SSc quality of life, CVD: cardiovascular diseases, GIT: gastrointestinal tract.

*Disease activity assessment in SSc was done using the Revised European Scleroderma Trials and Research Group (EUSTAR) Activity Index (RAI).

**Disease severity assessment in SSc was done using the Revised Medsger Severity Scale (MSS).

Table 4: Relation of the RDCI with demographic and clinical factors among the studied patients (n=61).

Factors	More comorbidity (n=20) No (%)	Less comorbidity (n=41) No (%)	P value	OR 95% CI
Age (years)				
≤ Median (47)(n=31)	8.0(25.8%)	23(74.2%)	[a]0.238	Ref
> Median (47)(n=30)	12(40.0%)	18(60.0%)		2(0.65-5.69)
Sex				
Male(n=5)	2.0(40.0%)	3.0(60.0%)	[b]0.720	1.5(0.22-9.18)
Female(n=56)	18(32.1%)	38(67.9%)		Ref
Disease duration (years)				
≤ Median (5)(n=34)	10(29.4%)	24(70.6%)	[a]0.529	Ref

Factors	More comorbidity (n=20) No (%)	Less comorbidity (n=41) No (%)	P value	OR 95% CI
> Median (5)(n=27)	10(37.0%)	17(63.0%)		1.4(0.49-4.14)
Type Limited(n=16) Diffuse (n=45)	 5.0(31.2%) 15(33.3%)	 11(68.8%) 30(66.7%)	 [a]0.879	 Ref 1.1(0.32-3.75)
mRSS Less tightness≤16 (n=32) More tightness>16(n=29)	 9.0(28.1%) 11(37.9%)	 23(71.9%) 18(62.1%)	 [a]0.415	 Ref 1.6(0.54-4.58)
Digital Ulceration -ve(n=34) +ve(n=27)	 9.0(26.5%) 11 (40.7%)	 25(73.5%) 16(59.3%)	 [a]0.238	 Ref 1.9(0.65-5.63)
Digital Gangrene -ve(n=42) +ve(n=19)	 12(28.6%) 8.0(42.1%)	 30(71.4%) 11(57.9%)	 [a]0.297	 Ref 1.8(0.59-5.64)
Pitting scars -ve(n=15) +ve(n=46)	 4.0(26.7%) 16(34.8%)	 11(73.3%) 30(65.2%)	 [b]0.561	 Ref 1.5(0.41-5.35)
Calcinosis -ve(n=56) +ve(n=5)	 18(32.1%) 2.0(40.0%)	 38(67.9%) 3.0(60.0%)	 [b]0.720	 Ref 1.4(0.22-9.18)
Telangiectasia -ve(n=49) +ve(n=12)	 16(32.7%) 4.0(33.3%)	 33(67.3%) 8.0(66.7%)	 [b]0.964	 Ref 1.0(0.27-3.94)
Arthritis -ve(n=19) +ve(n=42)	 2.0(10.5%) 18(42.9%)	 17(89.5%) 24(57.1%)	 [a]0.013*	 Ref 6.4(1.31-31.2)
Friction rub -ve(n=57) +ve(n=4)	 18(31.6%) 2.0(50%)	 39(68.4%) 2.0(50.0%)	 [b]0.448	 Ref 2.2(0.28-16.6)
Chest -ve(n=13) +ve(n=48)	 4.0(30.8%) 16(33.3%)	 9.0(69.2%) 32(66.7%)	 [b]0.861	 Ref 1.2(0.30-4.22)
Heart -ve(n=47) +ve(n=14)	 13(32.7%) 7.0(50.0%)	 34(72.3%) 7.0(50.0%)	 [b]0.118	 Ref 2.7(0.77-8.93)
GIT -ve(n=11) +ve(n=50)	 0.0(0.0%) 20(40.0%)	 11(100%) 30(60%)	 [b]0.01*	 Ref 7(0.83-58.5)
Other comorbidities -ve(n=13) +ve(n=48)	 1.0(7.7%) 19(39.6%)	 12(92.3%) 29(60.4%)	 [b]0.030*	 Ref 7.9(0.94-65.6)
Hypothyroidism -ve(n=53) +ve(n=8)	 17(32.1%) 3.0(37.5%)	 36(67.9%) 5.0(62.5%)	 [b]0.761	 Ref 1.3(0.28-5.95)

Factors	More comorbidity (n=20) No (%)	Less comorbidity (n=41) No (%)	P value	OR 95% CI
Liver disorders -ve(n=47) +ve(n=14)	 11(23.4%) 9.0(64.3%)	 36(76.6%) 5.0(35.7%)	 [b]0.004*	 Ref 5.9(1.63-21.3)
Hyperlipidemia -ve(n=52) +ve(n=9)	 17(32.7%) 3.0(33.3%)	 35(67.3%) 6.0(66.7%)	 [b]0.970	 Ref 1.1(0.23-4.62)
Convulsions -ve(n=59) +ve(n=2)	 19(32.2%) 1.0(50.0%)	 40(67.8%) 1.0(50.0%)	 [b]0.598	 Ref 2.1(0.13-35.6)
Renal stones -ve(n=59) +ve(n=2)	 18(30.5%) 2.0(100%)	 41(69.5%) 0.0(0.0%)	 [b]0.040*	 Ref 4.4(0.38-52.3)

[a]Chi square test, [b]Fisher's exact test, Statistically significant (P≤0.05*), Highly statistically significant (P≤0.001**), OR: Odds ratio, CI: Confidence interval, RDCI: Rheumatic Disease Comorbidity Index, mRSS: modified Rodnan skin score, GIT: gastrointestinal tract.

Table 5: Relation of the RDCI with laboratory, HRCT, ECHO, PFT factors, SSc disease activity, SSc disease severity, and SScQoL questionnaire among the studied patients (n=61).

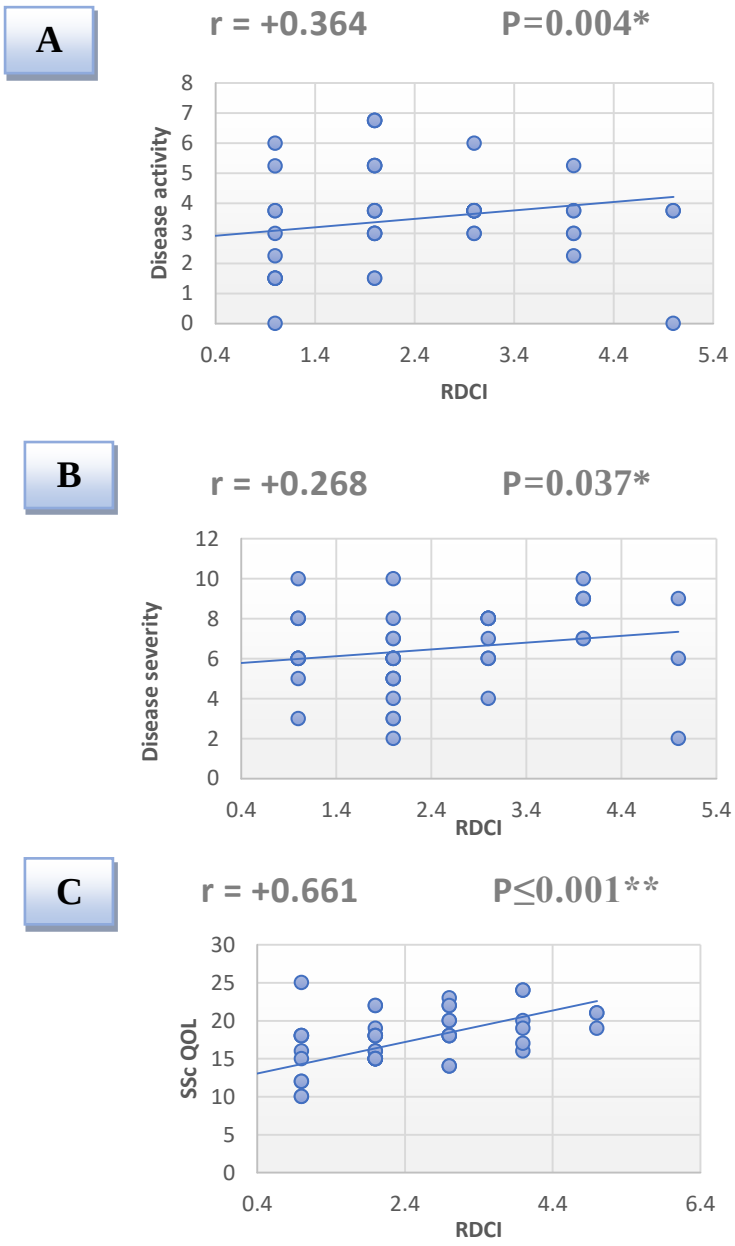
Factors	More comorbidity (n=20) No (%)	Less comorbidity (n=41) No (%)	P value	OR 95% CI
Hb Normal(n=42) Abnormal(n=19)	 12(28.6%) 8.0(42.1%)	 30(71.4%) 11(57.9%)	 [a]0.297	 Ref 1.8(0.59-5.64)
ESR Normal(n=5) Abnormal(n=56)	 1.0(20.0%) 19(33.9%)	 4.0(80.0%) 37(66.1%)	 [b]0.525	 Ref 2.1(0.22-19.7)
CRP Normal(n=9) Abnormal(n=52)	 2.0(22.2%) 18(34.6%)	 7.0(77.8%) 34(65.4%)	 [b]0.465	 Ref 1.9(0.35-9.87)
HRCT Normal(n=17) Abnormal(n=44)	 5.0(29.4%) 15(34.1%)	 12(70.6%) 29(65.9%)	 [a]0.727	 Ref 1.2(0.37-4.19)
ECHO Normal(n=22) Abnormal(n=39)	 4.0(18.2%) 16(41.0%)	 18(81.8%) 23(59.0%)	 [a]0.068	 Ref 3.1(0.89-11.1)
PFT Normal(n=20) Abnormal(n=41)	 5.0(25.0%) 15(36.6%)	 15(75.0%) 26(63.4%)	 [a]0.366	 Ref 1.7(0.53-5.72)
Disease activity Inactive <2.5(n=19) Active ≥ 2.5(n=42)	 2.0(10.5%) 18(42.9%)	 17(89.5%) 24(57.1%)	 [a]0.013*	 Ref 6.4(1.31-31.2)
Disease severity Less severe ≤ 6(n=33) More severe >6(n=28)	 6.0(18.2%) 14(50.0%)	 27(81.8%) 14(50.0%)	 [a]0.008*	 Ref 4.5(1.42-14.3)
SScQoL questionnaire Less impairment ≤17(n=31) More impairment >17(n=30)	 4.0(12.9%) 16(53.3%)	 27(87.1%) 14(46.7%)	 [a]0.001 **	 Ref 7.7(2.17-27.6)

[a]Chi square test, [b]Fisher's exact test, Statistically significant (P≤0.05*), Highly statistically significant (P≤0.001**), OR: Odds ratio, CI: Confidence interval, SSc: Systemic sclerosis, RDCI: Rheumatic Disease Comorbidity Index, HRCT: high-resolution computed tomography, PFT: pulmonary function tests, ECHO: echocardiography, SScQoL: SSc quality of life, Hb: Hemoglobin, ERS: erythrocyte sedimentation rate, CRP: C-reactive protein.

Table (6): Logistic regression determining the independent factors affecting the RDCI among the studied SSc patients (n=61).

Independent factors	B *coefficient*	S.E.	P value	Exp(B)	95% C.I. for EXP(B)	
					Lower	Upper
+ve Arthritis	2.199	1.138	0.053	9.015	0.969	83.910
+ve Liver disorders	2.382	0.999	0.017*	10.822	1.526	76.732
+ve Renal stones	22.658	28420	0.999	6921395887	0.000	-
Disease severity >6	2.981	1.046	0.004*	19.699	2.538	152.911
More impairment of QoL (SScQoL score>17)	2.950	1.109	0.008*	19.099	2.174	167.805
Constant	-26.534	28420	0.999	0.000	-	-

Chi-square test for model coefficient =41.414, P-value≤0.001**, SE: Standard Error, CI: Confidence interval, Variable(s) entered on the equation: arthritis, GIT disorders, other co-morbidity, liver disorders, renal stones, Disease activity, Disease severity, and SScQoL. RDCI: Rheumatic Disease Comorbidity Index, SSc: Systemic sclerosis, QoL: quality of life, SScQoL: SSc quality of life.



Statistically significant (P≤0.05*), Highly statistically significant (P≤0.001**), RDCI: Rheumatic Disease Comorbidity Index, SScQoL: SSc quality of life, SSc: Systemic sclerosis.

Figure 1: Correlation of RDCI with SSc disease activity (A), SSc disease severity (B), and SScQoL questionnaire score (C) among the studied patients (n=61).

DISCUSSION

Comorbidities have an impact on patients' quality of life and potentially increase mortality rates [6]. The data about the role of using RDCI for the assessment of comorbidities in SSc are still limited [21]. Highlighting the association between these comorbidities and the disease parameters is crucial in SSc patients as this may affect the disease course. This study was conducted to assess the RDCI among patients with SSc and to study the disease's parameters and QoL and their relations with RDCI.

When applying RDCI on SSc patients involved in the current study, a clear variability in the comorbidity distribution could be observed. More comorbidities (RDCI> median 2) were detected in about one-third of SSc patients with depression, hypertension, and cardiovascular abnormalities had higher percentages than other disorders. Thombs BD, et al. found that depression was a highly frequent comorbidity in SSc with a prevalence that ranged from 51% to 65%, and this psychological disorder was connected to pain in SSc patients [22]. Moreover, patients with SSc commonly suffer from depression due to cosmetic deformities, such as tight, glossy skin, a beaked nose, face telangiectasias, and the disappearance of the lips' vermillion border [23]. These studies' findings were in concordance with our study where a significant number of patients suffered from diffuse skin tightness, Raynaud's phenomenon, pitting scars, and arthritis. Similarly, another study reported increasing the rate of Raynaud's phenomenon 12 months after SSc diagnosis when compared to index periods before the disease diagnosis [24]. All these manifestations can cause pain and contribute to the limitation of function leading to depression. Another noteworthy finding by Panopoulos and his colleagues was that patients with diffuse SSc had a higher rate of depression than those with RA [12].

Previous cohorts reported an increased risk of cardiovascular diseases in SSc patients when compared to healthy controls [24, 25]. This high frequency of cardiovascular comorbidities can be attributed to the endothelial cell layer of the microcirculation which is known to sustain damage through various mechanisms, such as ischemia-reperfusion injury, immune-mediated cytotoxicity, and infection-induced apoptosis. Additionally, endothelial dysfunction in SSc is largely caused by elevated levels of vasoconstrictive endothelin [26].

In the present study, more than two-thirds of patients suffered from comorbidities other than those included in the RDCI, with liver disorders more evident than other comorbidities. In line with a previous study done by Orlandi et al., they found a high rate of comorbidities in patients with SSc [21]. Another Egyptian study found a higher frequency of liver abnormalities in SSc patients than in controls [27]. This increased rate of hepatic involvement may be attributed to the higher prevalence of fatty liver and viral hepatitis C among the Egyptian population [28, 29].

In the study of the hand, the association of RDCI with demographic and clinical factors showed that patients with SSc suffering from arthritis, GIT manifestations, other co-morbidities, liver disorders, or renal stones were significantly associated with RDCI. Also, they were more likely to have comorbidities encompassed in RDCI. Additionally, liver disorders were significant independent predictors for having higher RDCI scores. Gastrointestinal manifestations occur in about 70–90% of SSc patients, making it the most common visceral organ implicated in this disease [30]. Impaired gastrointestinal function and a worse functional status in individuals with SSc are intimately linked to a higher risk of psychological diseases like depression which

is one of the conditions included in RDCI [3, 30]. Furthermore, the higher rate of hepatic disorders and its substantial relation to RDCI in the present study highlights the significance of prompt detection and better management of this common comorbidity. Arthritis is a common feature of SSc and can lead to physical limitation which is an important risk factor for comorbidities included in RDCI like fractures (due to osteoporosis) and depression [31, 22].

On the other hand, this research did not find any significant association between the other clinical factors or demographic data and RDCI. Many previous studies documented that the older age, male sex, and longer disease duration in SSc patients were associated with worse outcomes and poor survival [32]. This can partially explain the absence of a significant association between the demographic data and RDCI in our findings as the majority of the study population were females (91.8%), a higher proportion with disease duration ≤5 years and the mean age was 44.5±10.5.

Furthermore, other rheumatic disease-related parameters such as the serological profile may influence comorbidities [33]. Our study reported a high percentage of patients with elevated inflammatory markers and positive ANA. However, there was no association between these laboratory findings and RDCI.

The results of our study demonstrated a significant association and significant positive correlation between disease activity and RDCI among SSc patients. Interestingly, a study by Ziade N et al. mentioned that the higher prevalence of cardiovascular and osteoporosis (with subsequent fracture risk) comorbidities in chronic rheumatic diseases is explained by the disease activity itself [34]. In contrast to our findings, a large Italian SSc cohort revealed that comorbidities, using the Charlson comorbidity index (CCI), did not have a significant association to the disease activity in patients with SSc, despite demonstrating a high comorbidity burden on SSc patients and could contribute to worse disease outcome [21]. This means that the prognosis may be impacted by comorbidities and disease activity independently. Therefore, comprehensive monitoring of disease activity is needed as the presence of comorbidities and disease activity may impact the response to therapy and worsen the disease course.

Also, our study documented a significant association and significant positive correlation between disease severity and RDCI in patients with SSc. The logistic regression model showed that higher disease severity (Revised MSS >6) was an important contributor for developing more comorbidities of RDCI. As far as we know, no previous studies illustrated the direct relationship between the severity of SSc and RDCI. However, several research results detected significant associations between some parameters of severe disease and those included in RDCI (such as stroke and cancer). In a recent cohort on U. S. SSc patients, Ying D. and his colleagues found that atrial fibrillation, as one of the parameters of severe SSc, was associated with an increased risk of stroke comorbidity [35]. Similarly, an interesting study by Lama Sakr revealed that interstitial lung disease (ILD), lower forced vital capacity (FVC), and lower DLCO were more common among SSc patients with lung cancer when compared to those without cancer [36]. Severe lung fibrosis is thought to start a precancerous cascade, with atypical epithelial regeneration alterations, thus increasing the risk of lung cancer [3, 37].

Regarding the SScQoL, the current results revealed a significant association and significant positive correlation between impaired QoL and RDCI in SSc patients. In addition, a lower QoL in those patients was detected as an independent factor for developing comorbidities assessed using RDCI. Many studies stated that comorbidities

could negatively affect the physical function and health-related quality of life (HRQoL) of the patients [38]. In a previous study, there was a strong relationship between comorbidities like depression and lower QoL [22]. In addition, our results were close to the reported findings in other autoimmune diseases. Spaetgens B et al. observed a significant independent impact of co-morbidities on HRQoL in patients with gouty arthritis [39]. Another study stated that depression, as a comorbid disorder, showed a strong association and correlation with low quality of life of patients with RA, systemic lupus erythematosus, and fibromyalgia [40]. Finally, early identification and management of the comorbidities in patients with SSc is of paramount importance to improve the QoL in those patients.

This study is limited by a small sample size and single-center study. So, the data can't be generalized.

CONCLUSION

A higher RDCI score in SSc is associated with higher disease activity, higher disease severity, lower quality of life, presence of other comorbidities, renal stones, and liver disorders. There are significant positive correlations between RDCI score and disease activity, disease severity, and SScQoL scores. Higher disease severity (Revised MSS >6), lower quality of life (SScQoL >17), and liver disorders are important contributors for developing more comorbidities (RDCI >2) in SSc. RDCI can be a fundamental method for the assessment of the association between comorbidities and SSc parameters and outcomes. This implies that improving patient survival and quality of life requires proper management of comorbidities and control of disease activity as well as severity.

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