Prevalence and Determinants of Gastrointestinal Manifestations in Patients with Selected Rheumatologic Diseases

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Cite this article as: Kalkan EA, Kalkan Ç, Barutcu S, et al. Prevalence and determinants of gastrointestinal manifestations in patients with selected rheumatologic diseases. *Turk J Gastroenterol.* 2022;33(7):576-586.

ABSTRACT

Background: *Many rheumatic diseases may cause gastrointestinal manifestations. The goal of this study was to analyze the prevalence and predictors of gastrointestinal involvement in patients with rheumatic disorders.*

Methods: *A retrospective chart review was performed for patients with systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis who have consulted due to gastrointestinal symptoms. The relationship between clinical symptoms, gastroscopic/colonoscopic findings, and histopathological results with current drugs and disease duration was evaluated.*

Results: *A total of 364 patients with rheumatic disorders and 740 people as control group were included in the study. Abdominal bloating followed by abdominal pain, regurgitation, and heartburn were reported as the main complaints by more than half of the patients. Most of the patients had gastric mucosal changes expressed as Lanza score, and the presence of major polypharmacy was the most important factor affecting Lanza score (odds ratio: 10, 95% CI: 1.882-54.111, P < .007) followed by disease duration (odds ratio: 1.559, 95% CI: 1.369-1.775, P < .001) and age (odds ratio: 1.069, 95% CI: 1.030-1.109, P < .001). In general, approximately 30% of the patients were positive for Helicobacter pylori infection and 35% showed intestinal metaplasia in histopathological examination. Most of the colonoscopic findings were associated with colonic polyps (n = 81). In multivariate analysis, disease duration was the only factor that affected the presence of colonic lesions (Area Under the Receiver Operating Characteristic (ROC) Curve (AUROC): 0.871, 95% CI: 0.824-0.918, P < .001).*

Conclusion: *Patients with rheumatologic diseases frequently have gastrointestinal manifestations. The most encountered gastrointestinal symptom was abdominal bloating, followed by abdominal pain. Being aware of gastrointestinal manifestations and their determinants may help physicians manage and follow patients with rheumatologic disorders.*

Keywords: *Endoscopy, gastrointestinal, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis*

INTRODUCTION

Connective tissue diseases define chronic inflammatory diseases of the connective tissue and include disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome, and systemic sclerosis (SSc). These diseases are considered as systemic diseases which may have an autoimmune origin that can affect multiple organ systems.[1] All organs of the gastrointestinal (GI) tract can be affected either directly from the disease itself, through associated autoimmune diseases, or as a consequence of the adverse effects of drugs.[2] Gastrointestinal involvement produces substantial morbidity and significantly impairs the quality of life in almost all patients.[3] These patients may refer with non-specific symptoms such as nausea, abdominal pain, bloating, and diarrhea.[4] Symptoms are usually insidious, slow-growing, and may increase or decrease in severity so the involvement of the GI tract can be diagnosed late. To begin appropriate and timely management, for the clinicians, especially a basic overview of the most common rheumatologic diseases and their effects on the GI system is essential. Moreover, GI involvement in patients with rheumatologic disorders is of great importance since GI system damage may influence the course of the disease.[4] Therefore, the goals of this study were to assess the prevalence of GI manifestations and to comprehensively

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Received: ***September 8, 2021*** *Accepted:* ***October 20, 2021*** *Available Online Date:* ***May 11, 2022***

DOI: ***10.5152/tjg.2022.21780***

analyze the determinants that might affect GI symptoms and signs in patients with selected rheumatological disorders.

MATERIALS AND METHODS

Medical records of patients with SLE (n = 146), RA (n = 180), and SSc (n = 38) who were referred to the gastroenterology department for consultation were analyzed. Data were collected regarding patient demographics, GI symptoms, indications for GI interventions, endoscopic findings, and medications used at the time of consultation. In the study, the CV-165/CLV-165 model of the Olympus medical imaging company was used. Gastroscopic and colonoscopic findings (available in 217 patients), histopathological findings, and some major laboratory parameters were also investigated. Seven hundred fifty patients (2 control subjects for 1 patient mainly referring for screening purposes and iron/vit B12 deficiency) from internal medicine outpatient clinic without any known rheumatologic and autoinflammatory diseases were used as a control group.

Definitions

Systemic Lupus Erythematosus

Systemic lupus erythematosus diagnosis was made according to the "Systemic lupus International Collaborating Clinical Classification criteria."[5]

Rheumatoid Arthritis

Rheumatoid arthritis diagnosis was made based on the diagnostic criteria defined by the "American College of Rheumatology/European League Against Rheumatism Collaborative initiative."[6]

Systemic Sclerosis

The diagnosis of SSc was made according to the criteria proposed by the American College of Rheumatology/European League Against Rheumatism Collaborative Initiative.[7]

Main Points

- *The most common gastrointestinal (GI) symptom was abdominal bloating in patients with rheumatologic disorders.*
- *Gastric mucosal damage observed in these patients was associated with major polypharmacy and disease duration.*
- *The clinical implications of GI manifestations of rheumatologic diseases for clinicians should be considered.*

Gastrointestinal Symptoms/Reason for Investigation

Demographic data and GI symptoms of each patient were noted. Besides, the main complaint(s) prompted for clinical investigation were retrieved from the hospital electronic database system and were classified as upper GI complaint, lower GI complaint, iron/vitamin B_{12} deficiency, and for screening purposes.

Gastroscopic Findings and Scores

Esophagogastroduodenoscopy was performed in all patients with targeted biopsies of the gastric body and antrum mucosa. The presence of hiatal hernia, esophagitis, and Barrett's esophagus was noted, and gastric mucosal changes were classified according to the modified Lanza score as follows: Grade 0: no erosions or hemorrhage; Grade 1: 1 or 2 hemorrhages or erosions localized in 1 area of the stomach; Grade 2: 3-5 hemorrhages or erosions localized in 1 area of the stomach; Grade 3: hemorrhages or erosions in 2 areas of the stomach or at least 6 hemorrhages or erosions observed in 1 gastric area, but no one more than 10 in the stomach as a whole; Grade 4: hemorrhages or erosions in 3 or more areas or the stomach; 11 or more hemorrhages or erosions widely spread in the entire stomach; Grade 5: gastric ulcer.[8]

Hiatal hernia was diagnosed when the length between the esophagogastric junction and diaphragmatic pinch was >2 cm.[9] Los Angeles classification was used for the diagnosis and grading of esophagitis.[10] In each exam, 2 biopsies from the gastric antrum, 1 from the incisura angularis, and 2 from the gastric corpus were obtained for histopathological evaluation. Results of histopathological examination of biopsy specimens were assessed for chronic inflammation based on lymphocyte and plasma cell infiltration of the lamina propria, neutrophil activity, atrophy, *Helicobacter pylori* density, and intestinal metaplasia.[11]

Medications

Drugs that the patients have already used at the time of examination were expressed under the title of polypharmacy absent (# of drugs <2), minor polypharmacy (# of drugs 2-4), or major polypharmacy (# of drugs ≥5).[12] The present study complies with the Declaration of Helsinki, and ethics committee or the Ministry of Health has approved the research protocol (E1-20-1156), and written informed consent has been obtained from the subjects.

Statistical Analysis

A descriptive statistical analysis was performed for baseline characteristics. Descriptive statistics are shown as

mean ± standard deviation for variables with normal distribution and as median (min-max) for variables with non-normal distribution. In cases where the number of groups was more than 2, the significance of the difference in terms of averages was investigated with the analysis of variance (ANOVA) test, and the significance of the difference in terms of median values with the Kruskal–Wallis test. When there were 2 groups, for variables showing statistical significance, appropriate post hoc tests were used. Receiver operating characteristic curves were used to describe and compare the ability of disease duration which showed significance for whole variables to predict the presence of special characteristics of intestinal metaplasia, atrophy, and Lanza score. For the variable with a distinctive feature, the cut-off value was calculated according to the index from Youden. In order to find independent risk factors that might affect variables such as intestinal metaplasia, atrophy, Lanza score, and colon findings, multivariable logistic regression analysis was used. In multivariate regression analysis, parameters that might affect univariate test results were defined, and these parameters were used as candidate parameters for multivariate analysis by testing backward method and a result model was established. Odds ratios (ORs), CIs, negative (NPV), and positive predictive values (PPV) for significant parameters were determined. $P < .05$ was considered significant. Statistical analyses were performed with R programming language v. 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). *reportROC* and *ModelGood* libraries were used for diagnostic assessment of biomarkers.

RESULTS

Gastrointestinal Symptoms

Our cohort included a variety of rheumatic diseases, and a total of 364 patients (SLE n = 146, RA n = 180, and SSc n = 38) were included in the study. Of the total patients, 319 (87.6%) were women. Baseline demographic, clinical, endoscopic, and laboratory characteristics of patients and control group are presented in Table 1. The reason for investigation in SLE patients was iron/vitamin B_{12} deficiency in 46% (n = 67), lower GI complaints in 24.7% (n = 36), upper GI complaints in 19.9% (n = 29), and for screening purposes in 9.6% (n = 14). Symptoms/signs that prompted the investigation in RA patients were iron/vitamin B_{12} deficiency in 44.4% (n = 80), screening purposes in 29% (n = 52), lower GI complaints in 15.6% (n = 28), and upper GI complaints in 11.1% (n = 20). In SSc patients, 78.9% (n = 30) had upper GI complaints, 10.6% (n = 4) had iron/vitamin B_{12} deficiency, and 7.9% (n = 3) and 2.6% (n = 1) were investigated due to screening purposes and lower GI complaints, respectively. The most prominent GI symptom was abdominal bloating in patients with SSc (60.5%, n = 23), SLE (53.4%, n = 78), and RA (42.7%, n = 77) and followed by abdominal pain in SSc (47.3%, n = 18), SLE (38.3%, n = 56), and RA 22.2%, n = 40), respectively. Regurgitation was reported in SSc (65.7%, n = 25), SLE (27.3%, n = 40), and RA 26.6%, n = 48) and heartburn in SSc (84.2%, n = 32), SLE (24.6%, n = 36), and RA 21%, n = 38), respectively. In the control group, 54% of patients were investigated due to screening purposes ($P < .001$).

Gastroscopic/Colonoscopic Findings and Scores

Endoscopic examination revealed that 8 (5.5%) patients with SLE, 18 (10%) with RA, and 4 (10.5%) with SSc had hiatal hernia ($P = .039$). In patients with hiatal hernia, esophagitis was seen in 10 (6.8%) patients with SLE, 16 (8.9%) with RA, and 11 (28.9%) with SSc ($P = 0.068$). Endoscopic findings and gastric macroscopic mucosal lesions which was scored according to the modified Lanza score are summarized in Table 1. The gastroscopic findings showed that all the investigated patients had some degree of gastric mucosal changes including 49 (33.5%) of patients with SLE displayed Lanza score 2, 66 (36.6%) of patients with RA had score 3, and 24 (63%) patients with SSc had score 3 and 4, respectively. In the multivariate analysis, the presence of major polypharmacy (# of the drugs ≥5) was found as an independent factor affecting Lanza score (OR: 10.091, 95% CI: 1.882-54.111, $P = 0.007$). However, age (OR: 1.069, 95% CI: 1.030-1.109, $P < .001$) and disease duration (OR: 1.559, 95% CI: 1.369-1.775, $P < .001$) were found to be independent factors affecting Lanza score (Table 2). As for histopathological findings, 40 (27.4%) of patients with SLE, 47 (26.1%) of patients with RA, and 12 (31.6%) with SSc were found to be infected with *H. pylori* infection ($P = 0.787$). In the control group, 124 (16.8%) patients were infected by *H. pylori*. Intestinal metaplasia was observed in 51 (34.9%) of patients with SLE, 69 (38.3%) with RA, and 11 (28.9%) with SSc ($P = 0.517$). In the multivariate analysis, the presence of major polypharmacy (OR: 4.653, 95% CI: 1.990-10.878, $P < .001$), neutrophil activation (OR: 2.677, 95% CI: 1.576-4.547, $P < .001$), and disease duration (OR: 1.231, 95% CI: 1.161-1.309, $P < .001$) were found as independent factors affecting the presence of intestinal metaplasia (Table 3). Determinants of gastric atrophy were found to be disease duration (OR: 1.579, 95% CI: 1.440-1.730, $P < .001$) and neutrophil activation (OR: 2.389, 95% CI: 1.293-4.415, $P = 0.005$) (Table 4).

Table 1. Demographic Characteristics and Gastroscopic/Colonoscopic, Histopathologic, and Laboratory Parameters of Patients

	SLE (n = 146)	RA (n = 180)	SSc (n = 38)	Control Group (n = 740)	*P*
Female/male (%)	133/13 (91.1%/8.9%)	151/29 (83.9%/16.1%)	35/3 (92.1%/7.9%)	654/86 (88.4%/11.6%)	.098
Age, years (mean ± SD)	45.41 ± 13.22	59.69 ± 11.55	46.63 ± 11.88	53.2 ± 9.6	**<.001**
Reason for investigation					
Iron/B12 deficiency	67 (45.9%)	80 (44.4%)	4 (10.6%)	144 (19.5%)	**<.001**
Upper GI system complaints	42 (28.7%)	50 (27.7%)	30 (78.9%)	102 (13.8%)	
Lower GI system complaints	29 (19.9%)	20 (11.1%)	1 (2.6%)	95 (12.8%)	
Screening	14 (9.6%)	52 (28.9%)	3 (7.9%)	399 (53.9%)	
Polypharmacy					
Absent (<2)	25 (17.1%)	37 (20.6%)	12 (1.6%)	690 (93.2%)	**<.001**
Minor (#pharmacy 2-4)	104 (71.2%)	116 (64.4%)	19 (50%)	42 (5.7%)	
Major (#pharmacy ≥5)	17 (11.6%)	27 (15%)	7 (18.4%)	8 (1.1%)	
Most commonly used drugs	Hydroxychloroquine: 104 (71.2%) Glucocorticoids: 91 (63.01%) Azathioprine: 45 (30.8%) Methotrexate: 40 (27.3%) NSAID: 36 (24.6%) Mycophenolate mofetil: 11 (7.5%) Rituximab: 3 (2.05%)	NSAID: 144 (80%) Hydroxychloroquine: 106 (58.8%) Glucocorticoids: 65 (36.1%) Methotrexate: 62 (34.4%) Leflunomid: 47 (26.1%) Salazopyrin: 46 (25.5%) Azathioprine: 30 (16.6%) Rituximab: 24 (13.3%) Adalimumab: 15 (8.3%) Etanercept: 10 (5.5%) Infliximab: 2 (1.1%)	Acetylsalicylic acid: 24 (63.1%) Glucocorticoids: 19 (50%) Hydroxychloroquine: 18 (47.3%) Iloprost: 17 (44.7%) Calcium canal blockers: 13 (34.2%) Colchicine: 6 (15.7%) Bosentan: 5 (13.1%) Azathioprine: 2 (5.2%)	ACE inh/ARB: 247 (33.4%) OAD: 121 (16.4%) Acetylsalicylic Acid: 78 (10.5%) NSAİD: 76 (10.2%) Beta Blockers: 62 (8.4%) CCB: 44 (5.9%) Levothyroxine: 28 (3.8%) SSRI/SNRI: 25 (3.4%) Diuretics: 24 (3.2%)	
GI symptoms	Bloating: 78 (53.4%) Abdominal pain: 56 (38.3%) Regurgitation: 40 (27.3%) Heartburn: 36 (24.6%) Constipation 32 (21.9%) Rectal bleeding 9 (6.2%)	Bloating: 77 (42.7%) Abdominal pain: 40 (22.2%) Regurgitation: 48 (26.6%) Heartburn: 38 (21%) Constipation 36 (20%) Rectal bleeding 13 (7.2%)	Heartburn: 32 (84.2%) Abdominal pain: 18 (47.3%) Regurgitation: 25 (65.7%) Bloating: 23 (60.5%) Constipation: 1 (2.6%)	Bloating: 282 (38.1%) Abdominal pain: 112 (15.1%) Constipation: 94 (12.7%) Regurgitation: 83 (11.2%) Heartburn: 41 (5.5%) Rectal bleeding 19 (2.5%)	
Disease duration [year, (median (min-max)]	4 (1-28)	5 (1-31)	5 (1-30)		**<.001**
Gastroscopic findings					
Modified Lanza Score					
0	7 (4.7%)	0	0	322 (43.5%)	
1	49 (33.5%)	12 (6.6%)	0	295 (39.8%)	
2	39 (26.7%)	32 (17.7%)	10 (26.3%)	63 (8.5%)	
3	23 (15.7%)	66 (36.6%)	12 (31.5%)	38 (5.1%)	
4	17 (11.6%)	54 (30%)	12 (31.5%)	17 (2.3%)	**.039**
5	11 (7.5%)	16 (8.8%)	4 (10.5%)	5 (0.7%)	

(*Continued*)

Table 1. Demographic Characteristics and Gastroscopic/Colonoscopic, Histopathologic, and Laboratory Parameters of Patients (*Continued*)

	SLE (n = 146)	RA (n = 180)	SSc (n = 38)	Control Group (n = 740)	*P*
Hiatal hernia	8 (5.5%)	18 (10%)	4 (10.5%)	36 (4.9%)	.068
Esophagitis	10 (6.8%)	16 (8.9)	11 (28.9%)	8 (1.1%)	.097
Barret's	4 (2.7%)	7 (3.9%)	4 (10.5%)	6 (0.8%)	
Sydney Classification					
Helicobacter pylori	40 (27.4%)	47 (26.1%)	12 (31.6%)	124 (16.8%)	.787
Intestinal metaplasia	51 (34.9%)	69 (38.3%)	11 (28.9%)	68 (9.2%)	.517
Atrophy	56 (38.4%)	77 (42.8%)	16 (42.1%)	54 (7.3%)	.713
Activity	58 (39.7%)	79 (43.9%)	12 (31.6%)	132 (17.8%)	.348
Inflammation	57 (39.1%)	77 (42.7%)	12 (31.6%)	130 (17.6%)	.348
Patients with colonoscopy	102 (69.9%)	104 (57.8%)	11 (28.9%)	412 (55.7%)	**<.001**
Colonoscopic findings (+)	43 (42.1%)	53 (50.9%)	5 (45.5%)	81 (10.9%)	
Polyps	35 (81.3%)	41 (77.3%)	5 (100%)	41 (50.6%)	
Tubular adenoma	31 (88.5%)	37 (90.2%)	5 (100%)	39 (95.1%)	
Villous adenoma	2 (5.7%)	3 (7.3%)		1 (2.4%)	
Tubulovillous adenoma	2 (5.7%)	1 (2.4%)		1 (2.4%)	
Diverticulosis coli	3 (6.9%)	5 (9.4%)		18 (22.2%)	
Inflammatory bowel disease	3 (6.9%)	4 (7.5%)		12 (14.8%)	
Angiodysplasia	2 (4.6%)	3 (5.6%)		10 (12.3%)	
Activity index (SLEDAI/ DAS-28) median (min-max)	2 (0-7)	2.8 (1.1-5.1)			
ALT (U/L) (median (min-max))	24.19 (16-187)	21.46 (17-156)	21.2 (18.5-102.5)	19.8 (16-165)	.11
Albumin (g/dL) (median (min-max))	4 (2.7-4.6)	3.9 (2.4-4.7)	3.9 (3.1-4.8)	3.9 (3-4.7)	.62
Vitamin B12 (pg/mL) (median (min-max))	223 (101-462)	234 (119-561)	228 (114-481)	288 (106-685)	.35
Vitamin D (ng/mL) (median (min-max))	17.1 (3.1-56.9)	16.8 (4.3-57.7)	14.6 (3.6-49.3)	19.3 (8.9-69.7)	.46
Ferritin (ng/mL) (median (min-max))	16 (1-745)	27.5 (2-539)	20.5 (1-272)	24.3 (3-461)	.51

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; SSc, systemic sclerosis; NSAID, non-steroid anti-inflammatory drug; GI, gastrointestinal; ACE Inh, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; OAD, oral antidiabetics; CCB, calcium channel blockers; SSRI, selective serotonin reuptake inhibitors; SNRI, selective noradrenaline reuptake inhibitors.

Table 2. Univariate and Multivariate Analysis of Factors Associated with Modified Lanza Score

	Univariate Analysis					Multivariate Analysis				
Factors	OR	95% CI	*P*	PPV	NPV	OR	95% CI	*P*	PPV	NPV
Age	1.114	1.084-1.145	<.001	93.18 (81.28-97.73)	66.67 (63.50-69.69)	1.069	1.030-1.109	**<.001**	73.68 (66.64-79.69)	81.21 (75.64-85.74)
Gender	0.545	0.253-1.175	.122	-	56.65					
BMI	0.973	0.883-1.071	.571	-	56.65					
Disease duration	1.677	1.491-1.887	<.001	86.24 (79.38-91.07)	87.01 (81.77-90.92)	1.559	1.369-1.775	**<.001**		
Major polypharmacy	27.33	8.19-91.25	<.001	93.18 (81.28-97.73)	66.67 (63.5-69.69)	10.091	1.882-54.111	**.007**		
Hp	0.778	0.442-1.371	.386	-	56.65					
Activity	1.538	0.937-2.526	.089	-	56.65					
Inflammation	1.538	0.937-2.526	.089	-	56.65					

OR, odds ratio; PPV, positive predictive value; NPV, negative predictive value; Hp, *Helicobacter pylori*.

Table 3. Univariate and Multivariate Analysis of Factors Associated with Intestinal Metaplasia

	Univariate Analysis					Multivariate Analysis				
Factors	OR	95% CI	*P*	PPV	NPV	OR	95% CI	*P*	PPV	NPV
Age	1.038	1.021-1.056	<.001	71.05 (55.73-82.71)	68.01 (66.07-70.06)				81.05 (72.85-87.21)	79.93 (76.38-83.05)
Gender	0.667	0.355-1.254	.209		64.01					
BMI	1.022	0.940-1.111	.614		64.01					
Disease duration	1.262	1.194-1.333	<.001	74.26 (66.11-81.01)	78.71 (75.10-81.92)	1.231	1.161-1.306	<.001		
Major polypharmacy	11.745	5.489-25.131	<.001	82.35 (70.12-90.27)	71.57 (69.05-73.95)	4.653	1.990-10.878	<.001		
Hp	1.023	0.633-1.653	.927		64.01					
Activity	2.237	1.444-3.465	<.001		64.01	2.677	1.576-4.547	<.001		
Inflammation	2.237	1.444-3.465	<.001		64.01					

OR, odds ratio; PPV, positive predictive value; NPV, negative predictive value; Hp, Helicobacter pylori.

Table 4. Univariate and Multivariate Analysis of Factors Associated with Gastric Atrophy

	Univariate Analysis					Multivariate Analysis				
Factors	OR	95% CI	*P*	PPV	NPV	OR	95% CI	*P*	PPV	NPV
Age	1.062	1.043-1.081	<.001	66.13 (58.94-72.65)	72.38 (68.12-75.73)				83.46 (77.06-88.34)	83.52 (79.36-87.03)
Gender	1.163	0.612-2.210	.646		59.07					
BMI	1.010	0.931-1.096	.808		59.07					
Duration of disease	1.558	1.426-1.702	<.001	81.16 (74.81-86.20)	83.63 (79.37-87.15)	1.579	1.440-1.730	<.001		
Major polypharmacy	4.743	2.459-9.149	<.001	72.55 (59.71-82.50)	64.22 (61.92-66.45)					
Hp	0.916	0.572-1.468	.715		59.07					
Activity	1.676	1.095-2.564	.017		59.07	2.389	1.293-4.415	.005		
Inflammation	1.676	1.095-2.564	.017		59.07					

OR, odds ratio; PPV, positive predictive value; NPV, negative predictive value; Hp, Helicobacter pylori.

Altogether, 102 (69.9%) patients with SLE, 104 (57.8%) patients with RA, and 11 (28.9%) patients with SSc received colonoscopic examination. The most encountered colonic lesion was polyps in all groups followed by colonic diverticulosis (Table 1). Also, 3 patients with SLE and 4 patients with RA had colonoscopic findings consistent with inflammatory bowel diseases. In the multivariate analysis, disease duration was the only parameter as an independent factor that affects the presence of a colonic lesion (OR: 1.389, 95% CI: 1.262-1.442, $P < .001$, Table 5). As disease duration (years) was found as the only independent risk factor for atrophy, intestinal metaplasia, Lanza score, and colonoscopic findings, we investigated cut-off values for disease duration in predicting the existence of atrophy [AUROC (95% CI): 0.907 (0.875-0.939), cut-off: 5.5, $P < .001$)], intestinal metaplasia [AUROC (95% CI): 0.797 (0.747-0.846), cut-off: 6.5, $P < .001$)], Lanza score [AUROC (95%CI): 0.938 (0.909-0.967), cut-off: 5.5, $P < .001$)], and colonoscopic findings [AUROC (95%CI): 0.871 (0.824-0.918), cut-off: 9.5, $P < .001$)] (Figure 1). Lanza scores 0 and 1 were more common, and hiatal hernia was observed in 36 patients in the control group ($P < .039$).

Medications

Polypharmacy absent (# of drugs <2) was found in 25 (17.1%) of patients with SLE, 37 (20.6%) and 12 (31.5%) of patients with RA and SSc, respectively. Minor polypharmacy (# of drugs 2-4) was found in 104, 116, and 19 patients with SLE, RA, and SSc, respectively. Major polypharmacy (# of drugs ≥ 5) was found in 17, 27, and 7 patients with SLE, RA, and SSc respectively, (p=0.165). The most used drugs were hydroxychloroquine and glucocorticoids in all patient groups (Table 1). Polypharmacy was absent in 93.2% of patients in the control group ($P < .001$).

DISCUSSION

Our study was conducted on 364 patients to assess the prevalence and factors affecting GI manifestations in patients with rheumatologic diseases. We describe here that in systematically evaluated patients with rheumatologic disorders, various GI manifestations are frequent.

Our study evaluated different factors contributing to GI symptoms in these patients. In this study, we observed a high prevalence of GI symptoms among patients with rheumatologic diseases. In our study, half of the SLE patients (53.4%) suffered from abdominal bloating, followed by abdominal pain (38.3%), regurgitation (27.3%), and

Table 5. Univariate and Multivariate Analysis of Factors Associated with Colonoscopic Findings

	Univariate Analysis					Multivariate Analysis				
Factors	OR	95% CI	*P*	PPV	NPV	OR	95% CI	*P*	PPV	NPV
Age	1.067	1.044-1.090	<.001	12.36 (8.4-17.82)	97.09 (95.15-98.27)					
Gender	0.604	0.952-1.148	.142	-	84.63 (75.4-89.8)					
BMI	1.045	0.952-1.148	.350	-	75.55 (74.54-77.45)					
Duration of disease	1.349	1.262-1.442	<.001	70 (58.65-79.33)	84.54 (81.76-86.96)	1.349	1.262-1.442	<.001	70 (58.65-79.33)	84.54 (81.76-86.96)
Major polypharmacy	3.741	2.025-6.912	<.001	-	52.35 (51.55-77.65)					
H. pylori	0.844	0.488-1.462	.546	-	73.47 (71.55-75.78)					
Activation	1.403	0.867-2.271	.168	-	65.58 (55.16-750.42)					
Inflammation	1.403	0.867-2.271	.168	-	69.52 (67.6-83.3)					

BMI, body mass index; OR, odds ratio; PPV, positive predictive value; NPV, negative predictive value; *H. pylori*, *Helicobacter pylori*.

Figure 1. Receiver operating curves for disease duration as a predictor of (1) intestinal metaplasia, (2) gastric atrophy, (3) gastroscopic Lanza score, and (4) colonoscopic findings.

heartburn (24.6%). The prevalence of GI symptoms in SLE patients was found to be between 15% and 75% in previous studies.[13] Gutierrez et al[14] investigated 14 SLE patients by means of esophageal symptoms and reported that 8 patients had mild heartburn and 2 occasional regurgitation. Fawzy et al[15] investigated 40 SLE patients by means of GI manifestations and found prevalence of GI manifestations as 42.5% in SLE patients. The GI manifestations in their patients were reported as acute abdominal pain in 6%, diffuse abdominal pain in 23.5%, epigastric pain in 29%, epigastric pain with vomiting in 23.5%, and epigastric pain with chronic constipation in 6%. In the mentioned study, 11 patients underwent upper GI endoscopy, and esophagitis was found in 2 patients. In our study, esophageal lesions included esophagitis in 8 (6.8%) patients, hiatal hernia in 10 patients, and Barrett's esophagus in 4 patients with SLE. In older studies, esophagitis was reported in 3-5% of patients with SLE.[16] As for gastroscopic findings, we classified gastric findings according to the modified Lanza score. While 49 (33.5%) patients had a Lanza score of 1 (1 or 2 hemorrhages or erosions localized in 1 area of the stomach), no erosions or hemorrhages were observed in 7 patients. Peptic ulcer was observed in 11 (7.5%) patients (Lanza score 5). In patients with SLE, peptic ulcer rate was reported to be 4-21%,[17] and Medina et al[18] reported 3 SLE patients presenting with peptic ulcer disease and perforation out of 55 patients presenting with an acute abdomen. In our study, *H. pylori* infection was identified in 40 (27.4/%) patients with SLE. Sawalha et al[19] investigated 466 patients with SLE with serologic test for the presence

of *H. pylori* infection and 170 (36.4%) of them were found to be positive. They concluded a possible protective role of *H. pylori* infection in delaying the onset of SLE in women in some ethnic groups. Serology does not reliably distinguish between active and past infection; however, in our study, we identified *H. pylori*-positive patients by histopathologic examination. Intestinal metaplasia and atrophy were found in 34.9% and 38.4% of patients, respectively. 102 (70%) of 146 patients had colonoscopy results. Colonoscopy findings were present in 43 (42.1%) of these patients. 35 patients displayed with colonic polyps (31 tubular adenoma), 3 with diverticulosis coli, 3 with inflammatory bowel disease and 2 with angiodysplasia. It is totally 43 patients with colonoscopic findings. In our patients, we did not see colonic carcinoma, inflammatory bowel disease, and malabsorption as reported in previous studies.[20] Hydroxychloroquinine (104 patients, 71.2%) was the most used drug followed by glucocorticoids, and also 104 patients were on minor polypharmacy. This is important because most symptoms are due to adverse reactions to medications.[15]

In this study, 77 (42%) of the patients with RA had abdominal bloating, followed by regurgitation 48 (26.6%), abdominal pain (22.2%), and heartburn (21%). Pagnoux et al[21] found abdominal pain as a major symptom in a very small number of patients with RA. Myasoedova et al[22] investigated 814 patients with RA by means of GI events and found that 32% (n = 261) showed any GI events in a retrospective population-based study. They concluded that there was an increased rate of GI events and GI-related mortality in RA patients. We also analyzed upper endoscopic findings in our study; esophageal lesions included esophagitis in 16 (8.9%) patients, hiatal hernia in 18 patients, and Barrett's esophagus in 7 patients with RA. Gastroscopic findings revealed Lanza score 3 in 66 (36.6%) patients, and peptic ulcer was observed in 16 (8.8%) patients (Lanza score 5). Malone et al[23] investigated 65 patients with RA for the presence of peptic ulcers and found peptic ulcers in 15% of patients concluding this high incidence of peptic ulcer disease was related to drugs used. Schäfer et al[24] investigated the gastroscopic and ileo-colonoscopic results of 458 patients with various rheumatologic disorders retrospectively. They performed 752 endoscopic procedures in 458 patients and found gastritis in 41% and esophagitis in 18% of patients without any histopathologic evaluation. They concluded that endoscopic procedures had an important impact to improve the final diagnosis and treatment of these patients. While *H. pylori* infection was found in 47 (26%) patients, intestinal metaplasia and atrophy were found in 38 (38.3%) and 77 (42.8%) of patients with RA, respectively. Goggin et al[25] searched 52 patients with RA for the presence of *H. pylori* infection and 19 (36.5%) patients were positive for *H. pylori* and concluded that *H. pylori* infection is associated with increased dyspeptic symptoms in RA patients taking non-steroid anti-inflammatory drugs (NSAIDs). Zentilin et al[26] treated 28 *H. pylori*-positive patients and evaluated disease activity at baseline and every 4 months for 2 years. They suggested that *H. pylori* eradication might induce an important improvement in disease activity. On the contrary, Bartels et al[27] searched the relationship between *H. pylori* infection and RA in a large population-based study. They found a comparable prevalence of *H. pylori* in RA patients and healthy subjects and concluded that there was no correlation between *H. pylori* infection and RA. Marcolongo et al[28] investigated RA patients by means of gastric, colonic, and rectal biopsies, and they found chronic superficial and chronic atrophic gastritis in 30% and 62.5% of biopsy specimens, respectively, which was a greater incidence of pathological findings compared to normal subjects or in patients with GI diseases. In total, 104 (57.8%) patients underwent colonoscopic investigation, and we found colonic lesions in 46 patients including polyps in 41 (37 tubular adenoma) and diverticular disease in 5 patients. Although colitis such as ulcerative colitis, drug-induced colitis, and vasculitis associated with RA and secondary amyloidosis were described in RA, our study showed that colonic polyps are also important in the course of the disease.[29] Non-steroidal anti-inflammatory drugs (80%) were the most used medications followed by hydroxychloroquinine (58.8%), and also 116 patients were on minor polypharmacy.

Gastrointestinal system is affected in 90% of patients with SSc, and in 10% of SSc patients, GI symptoms may be the first sign of SSc.[30] In our study, 32 (84.2%) patients had heartburn and 25 (65.7%) had regurgitation, whereas 11 patients had esophagitis and 4 patients had hiatal hernia. *H. pylori* infection was found in 12 (31.6%) of patients. Gastroparesis and gastric antral vascular ectasia are the most common diseases seen in SSc; however, in our patients, we did not see any sign suggesting gastroparesis.[31] Colonic involvement of systemic sclerosis can be seen in between 20% and 50% of patients and impairs health-related quality of life. Eleven patients underwent colonoscopic examination in our study and 5 of them had tubular adenoma. Omair and Lee[32] investigated the effect of GI manifestations on quality of life in 87 patients with SSc and 100 patients with rheumatologic disorders other than SSc as control group. We analyzed factors that

might affect gastric and colonic findings in these patient groups. Multivariate analysis showed that using major polypharmacy (#pharmacy ≥5) was the most important factor affecting Lanza score (OR: 10, $P < .007$) followed by disease duration (OR: 1.559, $P < .001$) and age. It is not surprising to find patients with gastric lesions using major polypharmacy because patients taking chronic aspirin and NSAIDs for rheumatic diseases have a higher than suspected incidence of gastric ulcer and erosions.[33] Gastric atrophy and intestinal metaplasia are 2 important premalignant conditions of the stomach. While disease duration, major polypharmacy, and the presence of activation in the histopathologic examination were the most important factors affecting the presence of intestinal metaplasia, disease duration and presence of activation affected the presence of gastric atrophy. The time span for Lanza score and the presence of gastric atrophy was 5.5 years [AUROC: 0.938, 95% CI: 0.909-0.967, $P < .001$ and AUROC: 907, 95% CI: 0.875-0.939, cut-off: 5.5 years, $P < .001$] and disease duration was the only factor that affected colonic lesion in multivariate analysis [AUROC: 0.871, 95% CI: 0.824-0.918, $P < .001$].

The limitations of this study include, although GI symptoms were evaluated according to a self-reported manner, no symptom scores were available, we only evaluated patients with GI complaints. On the contrary, this study includes a well-characterized rheumatologic diseases population evaluating GI manifestations and has the highest proportion of patients evaluated with gastroscopy/colonoscopy and histopathology.

In conclusion, patients with rheumatologic diseases frequently have GI comorbidity. The most prominent GI symptom was abdominal bloating in this group of patients and followed by abdominal pain. These patients have various degrees of gastric mucosal damage which are associated with major polypharmacy and disease duration. Gastric atrophy and intestinal metaplasia are associated with disease duration, major polypharmacy, and the presence of activation in the histopathologic examination and colonoscopic findings seem to be related with disease duration. Data expressed in this study may help to stratify individual risk of GI manifestations and guide gastroenterologists and/or rheumatologists who are often asked to evaluate patients with symptoms thought to represent an underlying or coexisting rheumatologic disorder.

Ethics Committee Approval: The study was approved by the medical ethics committee of Ministry of Health, Ankara City Hospital (No: E1-20-1156).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.A.K., Ç.K., O.K., İ.S.; Design – E.A.K., Ç.K., İ.S.; Supervision – E.A.K., Ç.K., İ.S.; Resources – E.A.K., Ç.K.; Materials – E.A.K., Ç.K.; Data Collection and/or Processing – E.A.K., Ç.K., İ.S., S.B., O.K., Ö.G., T.K., A.Ş., M.H., E.Ö., İ.A., E.A.; Analysis and/or Interpretation – Ç.K., E.A.K.; Literature Search – E.A.K., Ç.K., İ.S.; Writing Manuscript – E.A.K., Ç.K., İ.S.; Critical Review – E.A.K., Ç.K., İ.S.

Declaration of Interest: The authors have no conflict of interest to declare.

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

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