RHEUMATOLOGY

Rheumatology 2021;60:5329–5336
doi:10.1093/rheumatology/keab401
Advance Access publication 5 May 2021

Original article

Relevance of gastrointestinal manifestations in a large Spanish cohort of patients with systemic lupus erythematosus: what do we know?

Beatriz Tejera Segura[1], Irene Altabás González[2,3], Iñigo Rúa-Figueroa[4], Natalia Pérez Veiga[3], Victor Del Campo Pérez[5], Alejandro Olivé-Marqués[6], María Galindo[7], Jaime Calvo[8], Juan Gabriel Ovalles-Bonilla[9], Antonio Fernández-Nebro [10,11,12], Raúl Menor-Almagro[13], Eva Tomero[14], Natividad del Val del Amo[15], Esther Uriarte Isacelaya[16], Víctor Manuel Martínez-Taboada [17], Jose L. Andreu[18], Alina Boteanu[19], Javier Narváez[20], Atusa Movasat[21], Carlos Montilla[22], Jose Miguel Senabre Gallego[23], Blanca Hernández-Cruz[24], Mariano Andrés[25], Eva Salgado[26], Mercedes Freire[27], Sergio Machín García[1], Clara Moriano[28], Lorena Expósito[29], Clara Pérez Velásquez[30], M. L. Velloso-Feijoo[31], Ana Paula Cacheda[32], Nuria Lozano-Rivas[33], Gema Bonilla[34], Marta Arévalo[35], Inmaculada Jiménez[36], Víctor Quevedo-Vila[37], Francisco J. Manero-Ruiz[38], Paloma García de la Peña Lefebvre[39], Tomás Ramón Vázquez-Rodríguez[40], Jesús Ibañez-Rua[41], Tatiana Cobo-Ibañez[42] and Jose María Pego-Reigosa[2,3]

[1]Rheumatology Department, Hospital Universitario Insular de Gran Canaria, Islas, Canarias, [2]Rheumatology Department, Complejo Hospitalario Universitario de Vigo, Vigo, Galicia, [3]Rheumatology & Immuno-Mediated Diseases Research Group (IRIDIS), Galicia Sur Health Research Institute (IIS Galicia Sur), Vigo, [4]Rheumatology Department, Hospital Universitario de Gran Canaria Dr Negrin, Las Palmas de Gran Canaria, Islas Canarias, [5]Department of Statistics and OR, Vigo University, Vigo, [6]Rheumatology Department, Germans Trías i Pujol University Hospital, Badalona, Cataluña, [7]Rheumatology Department, 12 de Octubre University Hospital, Madrid, [8]Rheumatology Department, Hospital Araba, Araba, [9]Rheumatology Department, Hospital Gregorio Marañón, Madrid, [10]Instituto de Investigación Biomédica de Málaga—IBIMA, [11]Rheumatology Department, Hospital Regional Universitario de Málaga, [12]Department of Medicine, Universidad de Málaga, Málaga, [13]Rheumatology Department, Hospital de Jerez, Jerez de la Frontera, [14]Rheumatology Department, Hospital Universitario de la Princesa, Madrid, [15]Rheumatology Department, Navarra Hospital, Pamplona, [16]Rheumatology Department, Hospital Universitario de Donostia, San Sebastián, País Vasco, [17]Rheumatology Department, Hospital Marqués de Valdecilla, Santander, [18]Rheumatology Department, Puerta de Hierro-Majadahonda Hospital, [19]Rheumatology Department, Hospital Ramon y Cajal, Madrid, [20]Rheumatology Department, Hospital de Bellvitge, Hospitalet Llobregat, Cataluña, [21]Rheumatology Department, Hospital Universitario Príncipe de Asturias, Madrid, [22]Rheumatology Department, Salamanca Clinic University Hospital, Salamanca, [23]Rheumatology Department, Hospital Marina Baixa, Alicante, [24]Rheumatology Department, Virgen Macarena Hospital, Sevilla, [25]Rheumatology Department, Hospital General Universitario de Alicante, Elche, Alicante, [26]Rheumatology Department, Hospital Universitario de Orense, [27]Rheumatology Department, Hospital Juan Canalejo de La Coruña, A Coruna, Galicia, [28]Rheumatology Department, Hospital Universitario de León, León, [29]Rheumatology Department, Hospital Universitario de Canarias, La Laguna, Tenerife, [30]Rheumatology Department, Hospital Universitario de Basurto, País Vasco, [31]Rheumatology Department, Hospital Universitario de Valme, Sevilla, [32]Rheumatology Department, Hospital Son Llatzer, Mallorca, Islas Baleares, [33]Rheumatology Department, Hospital Universitario Virgen de la Arrixaca, Murcia, [34]Rheumatology Department, La Paz University Hospital, Madrid, [35]Rheumatology Department, Consorci Sanitari Parc Taulí, Sabadell, Cataluña, [36]Rheumatology Department, Hospital Clínico San Cecilio, Granada, [37]Rheumatology Department, Hospital de Monforte, Monforte, [38]Rheumatology Department, Hospital Universitario Miguel Servet, Zaragoza, [39]Rheumatology Department, Hospital Universitario HM Sanchinarro, Madrid, [40]Rheumatology Department, Hospital Universitario de Lugo, Lugo, [41]Rheumatology Unit, Clinica POVISA, Vigo and [42]Rheumatology Department, Hospital Universitario Infanta Sofía, Madrid, Spain

Submitted 14 February 2021; accepted 28 April 2021

Correspondence to: Beatriz Tejera Segura, Rheumatology Department, Hospital Universitario Insular de Gran Canaria, Avenida Marítima del Sur, s/n CP 35016, Las Palmas de Gran Canaria, Spain. E-mail: btejerasegura@gmail.com

Abstract

Objective. SLE can affect any part of the gastrointestinal (GI) tract. GI symptoms are reported to occur in

CLINICAL SCIENCE

Rheumatology key messages

- GI damage has not been explored much in patients with SLE and is associated with a worse prognosis.
- Older age, high daily dose of glucocorticoids and higher SDI were associated with GI damage.
- The presence of oral ulcers reduced the risk of developing GI damage by 33%.

>50% of SLE patients. To describe the GI manifestations of SLE in the RELESSER (Registry of SLE Patients of the Spanish Society of Rheumatology) cohort and to determine whether these are associated with a more severe disease, damage accrual and a worse prognosis.

Methods. We conducted a nationwide, retrospective, multicentre, cross-sectional cohort study of 3658 SLE patients who fulfil ≥4 ACR-97 criteria. Data on demographics, disease characteristics, activity (SLEDAI-2K or BILAG), damage (SLICC/ACR/DI) and therapies were collected. Demographic and clinical characteristics were compared between lupus patients with and without GI damage to establish whether GI damage is associated with a more severe disease.

Results. From 3654 lupus patients, 3.7% developed GI damage. Patients in this group (group 1) were older, they had longer disease duration, and were more likely to have vasculitis, renal disease and serositis than patients without GI damage (group 2). Hospitalizations and mortality were significantly higher in group 1. Patients in group 1 had higher modified SDI (SLICC Damage Index). The presence of oral ulcers reduced the risk of developing damage in 33% of patients.

Conclusion. Having GI damage is associated with a worse prognosis. Patients on a high dose of glucocorticoids are at higher risk of developing GI damage which reinforces the strategy of minimizing glucocorticoids. Oral ulcers appear to decrease the risk of GI damage.

Key words: systemic lupus erythematosus, gastrointestinal disease, damage

Introduction

Gastrointestinal (GI) manifestations are fairly common in patients with SLE and can be the initial presentation of the disease. GI symptoms are diverse, heterogeneous and, in many cases, non-specific. The prevalence and incidence of GI manifestations varies widely, depending on what symptoms were included in analyses, whether examinations were performed routinely or only in symptomatic patients [1]. Among the GI manifestations of SLE, nausea, vomiting and anorexia are the most common while abdominal pain, diarrhoea and abdominal distension sometimes presents as symptoms of serious GI involvements, which can result from SLE itself, infections or complications of the treatment [2, 3].

Many GI manifestations are not weighted in the SLE Disease Activity Index (SLEDAI) and sometimes may be underestimated [4]. Additionally, in contrast with other autoimmune diseases, such as systemic sclerosis, GI disease activity is less frequent among patients with SLE. However, SLE activity involving the GI system can be severe and life threatening.

Besides, several key points remained unclear concerning GI involvement in SLE. Firstly, the variety of its terminology, such as GI vasculitis (mesenteric vasculitis), lupus enteritis and intestinal pseudo-obstruction implies the uncertainty of the underlying pathophysiology. Secondly, large cohorts describing GI disease activity and GI comorbidities are lacking so treatment strategies are based on clinical experience from other connective tissue disorders [5]. RELESSER (Registry of SLE Patients of the Spanish Society of Rheumatology) is a large and well characterized cohort, that allows us to study in detail the GI manifestations associated with SLE itself but also, the gastrointestinal comorbidity and other clinical variables related to it [6].

The aims of our study are:

- To describe GI manifestations in terms of activity, damage and comorbidities among SLE patients in the RELESSER cohort.
- To compare patients with and without GI damage and determine which factors were associated with GI damage.

Patients and methods

RELESSER registry and study design

Data were obtained from RELESSER, which is a hospital-based registry that consists of two stages. The first is a cross-sectional stage (RELESSER-TRANS), the main objective of which is to describe in detail the characteristics of those patients diagnosed with SLE in Spain. This is followed by a second longitudinal follow-up stage over time involving repeated yearly visits (RELESSER-PROS).

The current study is a retrospective study in which all adult patients in the RELESSER-TRANS Registry were investigated for the presence of GI symptoms. It includes data from 3654 patients who fulfilled at least

four ACR 1997 SLE criteria [7], from rheumatology departments of 45 Spanish hospitals. Data collection was accumulated up until the first visit. The recruitment period was set at 10 months. In order to minimize missing data ('missing values') and optimize the representation, a pre-screening visit was established 3 months before the start of enrolment period, which allowed us to complete the census of patients in each hospital, recovering SLE patients not identified as such and supplementing the local databases, making missing values recoverable. The first patient was included on 27 October 2011 and the last on 13 August 2012, with effective inclusion having a duration of 10 months. The methodologic and general characteristics of the RELESSER Registry have been previously published in more detail [6]. The study protocol was approved by the institutional Ethics Committee of the Hospital Universitario Doctor Negrín and subsequently by the local Ethics Committee of all participating centres that required it. All participants gave written informed consent and their clinical records and information were anonymous. Patients' confidential information was protected in accordance with Spanish law [8]. This study was conducted in accordance with the principles of the Declaration of Helsinki [9].

Outcomes and definitions

GI manifestations analysed in this study included the group associated with activity as defined in SLEDAI-2K [10] (SLE Disease Activity Index) or BILAG (British Isles Lupus Assessment group) [11] indexes, those associated with damage as defined in Systemic Lupus International Collaborating Clinics/ACR Damage index (SLICC/ACR DI) criteria [12], and others (GI comorbidity not included in SLICC/ACR DI). The Katz Index [13] is a simple and helpful measure of disease severity (not just activity) which has been measured in the RELESSER cohort although it is not widely used in clinical practice. It includes 10 items, which include activity and damage manifestations. The maximum score possible is 13. The prevalence of inflammatory bowel disease and coeliac disease was also explored and compared with the general Spanish population.

GI involvement was considered as primary when it was directly related to SLE activity and secondary when it was due to damage or comorbidity.

Renal disease was defined as haematuria, pyuria, proteinuria >0.5 g/24 h and/or presence of haematic cylinders. The antiphospholipid syndrome was defined as the presence of thrombosis and/or recurrent foetal loss or pregnancy morbidity in patients with antiphospholipid antibodies.

Statistical analysis

Numerical variables were expressed as mean (s.d) or median and interquartile range (IQR), depending on whether the distribution was normal or not. In order to establish differences between patients with GI damage and non-GI damage, we define group 1 (SLE patients with GI damage) and group 2 (SLE patients without GI damage). Differences between both groups were analysed using χ^2 tests for categorical variables or Fisher's exact test when expected frequencies were small, Student's *t test* for normal continuous variables and Mann–Whitney *U* test for non-normally distributed variables.

Univariate linear and multivariate logistic regression analyses were performed to explore the relationships of demographics and different SLE clinical manifestations with the presence of GI damage (dependent variable). The selection of variables in the model was made while taking into account their individual association, the multicollinearity between different variables, and its importance as a confounding factor that justified the inclusion as an adjustment variable. In the multivariable analysis, other variables originally introduced in the model were: age at last assessment (years), duration of SLE (years), serositis activity, antiphospholipid syndrome (APS), thrombotic APS, renal activity, antimalarial drugs, at least one immunosuppressant, steroids, oral ulcers and modified SLICC index. Modified SDI (SLICC Damage Index) was calculated excluding GI damage items.

Statistical significance was assumed as $P < 0.05$. All analyses were performed with R Statistical Software, version 4.0.2. (R Foundation for Statistical Computing, Vienna, Austria).

Results

From 3654 SLE patients, 49.3% ($n = 1691$) developed GI symptoms associated with SLE activity, 3.7% ($n = 131$) developed GI damage and 10.2% ($n = 315$) developed other GI manifestations (Table 1).

GI damage and disease activity

Patients in group 1 (patients with GI damage) were older (53.1 (S.D.) 15.1 *vs* 46.6 (S.D.) 14.8 years; $P < 0.001$), they had longer disease duration (16.4 (S.D.) 8.9 *vs* 11.7 (S.D.) 8.3 years; $P = 0.001$) and were more likely to have vasculitis [14.1%, $n = 18$ *vs* 8.7%, $n = 293$; odds ratio (OR) 1.71, $P = 0.056$], renal disease (56.1%, $n = 69$ *vs* 42.4%, $n = 1342$; OR 1.73, $P = 0.003$) and serositis (40.5%, $n = 51$ *vs* 28.5%, $n = 293$; OR 1.7, $P = 0.005$) than patients without GI damage (group 2) (Table 2).

With regard to treatment, there were statistically significant differences between both groups in terms of glucocorticoids (96.9%, $n = 127$ *vs* 88.6%, $n = 2902$; OR 4.07, $P = 0.001$), AZA (44.2%, $n = 57$ *vs* 33.9%, $n = 1066$; OR 1.62, $P = 0.01$), mycophenolate mofetil (23.7%, $n = 31$ *vs* 14.9%, $n = 482$; OR 1.67 $P = 0.009$) and CYC (37.4%, $n = 49$ *vs* 21.8%, $n = 710$; OR 2.14, $P < 0.001$). The use of hydroxychloroquine was more common in group 2 (83.4%, $n = 2719$ *vs* 75.2%, $n = 97$; OR 0.6, $P = 0.022$) (Table 2).

Table 1 Gastrointestinal manifestations in the RELESSER cohort

	Total (%)
GI manifestations associated with SLE activity	1691 (49.3)
Oral ulcers	1603/3464 (46.3)
Lupus hepatitis	91/3510 (2.6)
Abdominal serositis	60/3517 (1.7)
Protein-losing enteropathy	18/3508 (0.5)
Autoimmune hepatitis	6/3564 (0.2)
GI damage	131 (3.7)
Infarction of bowel resection, spleen, liver	101/3563 (2.8)
Pancreatic insufficiency	12/3562 (0.3)
Stricture or upper GI tract surgery	12/3562 (0.3)
Mesenteric insufficiency	6/3562 (0.2)
Chronic peritonitis	6/3562 (0.2)
Other GI manifestations	315 (10.2)
Gastroduodenal ulcers	128/3283 (3.9)
Splenomegaly	118/3475 (3.4)
HCV infection	48/3359 (1.4)
Hepatopathy	35/3543 (1.0)
GI solid tumours	11/3564 (0.3)
Inflammatory bowel disease	7/3564 (0.2)
Coeliac disease	4/3564 (0.1)

GI damage and its association with severity

Hospitalizations and mortality were significantly higher in group 1, suggesting that having GI damage is linked to a worse prognosis. Moreover, patients in group 1 had higher modified SDI (2, IQR 1–4 *vs* 1, IQR 0–2; $P < 0.001$). Similarly, Katz Index was higher in this group (3, IQR 2–4 *vs* 2, IQR 1–3 *vs*; $P < 0.001$). Interestingly, patients with associated antiphospholipid syndrome appear to be at increased risk of developing damage-associated GI manifestations (19.5%, $n = 25$ *vs* 13.7%, $n = 465$; OR 1.53, $P = 0.068$) although the difference was not statistically significant. Nonetheless, we did find a significant statistical difference between GI damage and thrombotic APS (OR 1.66, $P = 0.046$) (Table 2).

In terms of mortality, there were 23 patients (0.65%) who died and had GI disease associated with damage. When comparing this group of SLE patients with the ones who had non-damage GI disease, there was a relation between GI disease associated with damage and death ($P < 0.001$).

In the multivariable analysis, older age, high daily dose of glucocorticoids (≥30 mg prednisone) and higher SDI remained significant. Interestingly, even though the prevalence of oral ulcers was not very dissimilar in both groups in the univariate analysis, the multivariable analysis revealed that the presence of oral ulcers reduced the risk of developing GI damage by 33% (Table 3).

Other GI manifestations

The development of other GI manifestations in the RELESSER cohort was rare, the most common being splenomegaly followed by gastroduodenal ulcers. In this respect, we did not analyse whether any of these manifestations could be related to adverse effects of the medications.

Interestingly, the prevalence of coeliac disease in RELESSER was 0.1% ($n = 4$) which is lower than in Spanish population (0.2%) with statistically significant differences ($P = 0.001$). Besides, the prevalence of inflammatory bowel disease – that is, Crohn's disease and ulcerative colitis – is significantly lower in SLE than in Spanish population (0.2 *vs* 0.39%, $P = 0.002$).

Less than 2% of patients ($n = 48$) developed chronic viral C hepatitis. Similarly, the presence of GI solid tumour was extremely rare among SLE patients with <1% of patients affected ($n = 11$).

Discussion

The GI manifestations in SLE do not seem to be as well characterized as other clinical manifestations in this condition. In our study, a descriptive analysis of these manifestations in a large cohort of SLE patients is performed in addition to demonstrating their association with a worse outcome of the disease. In general, both active gastrointestinal manifestations and those associated with damage are rare.

GI manifestations associated with damage were not very prevalent in the RELESSER cohort, in line with what was observed in other international cohorts [14, 15]. However, suffering GI damage according to SDI was associated with suffering greater organ damage and this result was maintained after adjusting for confounding factors. This finding has not been shown in other studies, although GI involvement in SLE is possibly underestimated in many of them.

Currently, there are no studies that determine whether the GI manifestations in SLE are more severe in patients with associated APS. In our study, patients with associated thrombotic APS appeared to be at increased risk of developing damage-associated GI manifestations with statistically significant differences. However, when obstetric plus thrombotic APS were taken into account together, statistical significance was not reached. Antiphospholipid antibodies and thrombosis have been described during episodes of mesenteric vasculitis, but this prevalence is variable and has only been described in case series [16–19].

Patients with vasculitis, serositis and renal involvement had a higher risk of developing gastrointestinal involvement associated with damage in the univariate analysis. In the case of renal disease, there were statistically significant differences in all items, between patients with GI manifestations associated to damage and without this disease. This finding suggests that even in patients with SLE who present features of incipient lupus nephritis in urinary sediment, there may be a greater risk of developing severe GI manifestations. Certainly, greater disease activity could imply a greater risk of developing organic manifestations of any kind; however, to the

TABLE 2 Demographics and clinical characteristics of SLE patients with and without GI damage: cumulative data since the diagnosis

	SLE patients with GI damage (Group 1)	SLE patients without GI damage (Group 2)	*P*-Value	OR (95% CI)
Gender (Women)	122/131 (93.1)	3095/3427 (90.3)	0.363	1.45 (0.73, 2.89)
Age at diagnosis of SLE mean (S.D.)	37.0 (17.4)	35.1 (14.6)	0.399	—
Age at the last visit mean (S.D.)	53.1 (15.1)	46.6 (14.8)	**<0.001**	—
Disease duration (years) mean (S.D.)	16.4 (8.9)	11.7 (8.3)	**<0.001**	—
Ethnicity – Caucasian	122/127 (96.1)	3103/3336 (93.0)	0.853	1.83 (0.74, 4.53)
Antiphospholipid syndrome	25/128 (19.5)	465/3400 (13.7)	0.068	1.53 (0.98, 2.4)
Thrombotic APS	22/391 (5.6)	117/3446 (3.4)	**0.046**	1.66 (0.97, 2.67)
Neuropsychiatric disease	35/126 (27.8)	754/3222 (23.4)	0.284	1.26 (0.85, 1.87)
Organic brain syndrome	7/129 (5.4)	96/3385 (2.8)	0.102	1.97 (0.89, 4.32)
Lupus headache	8/128 (6.2)	204/3378 (6.0)	0.850	1.04 (0.5, 2.15)
Craneal nerve disorder	16/129 (12.4)	129/3329 (3.9)	**<0.001**	3.51 (2.02, 6.1)
Seizure	8/131 (6.1)	231/3380 (6.8)	0.861	0.89 (0.43, 1.84)
Psychosis	1/131 (0.8)	80/3398 (2.4)	0.370	0.32 (0.04, 2.31)
Visual disturbance	6/128 (4.7)	129/3366 (3.8)	0.636	1.23 (0.53, 2.85)
CVA	11/129 (8.5)	186/3405 (5.5)	0.166	1.61 (0.85, 3.05)
Vasculitis	18/128 (14.1)	293/3354 (8.7)	**0.056**	1.71 (1.02, 2.85)
Musculoskeletal disease	97/130 (74.6)	2658/3373 (78.8)	0.275	0.79 (0.53, 1.18)
Myositis	5/128 (3.9)	126/3365(3.7)	0.813	1.04 (0.42, 2.6)
Arthritis	95/130 (73.1)	2644/3384 (78.1)	0.195	0.76 (0.51, 1.13)
Renal disease	69/123 (56.1)	1342/3162 (42.4)	**0.003**	1.73 (1.21, 2.49)
Hematuria	51/120 (42.5)	966/3227 (29.9)	**0.004**	1.73 (1.2, 2.5)
Pyuria	37/118 (31.4)	690/3159 (21.8)	**0.018**	1.63 (1.1, 2.43)
Proteinuria > 0'5gr/24 h	57/130 (43.8)	1037/3367 (30.8)	**0.003**	1.75 (1.23, 2.5)
Urinary casts	43/127 (33.9)	677/3260 (20.8)	**<0.001**	1.95 (1.34, 2.85)
Skin disease	104/126 (82.5)	2855/3377 (84.5)	0.531	0.86 (0.54, 1.38)
New rash	88/127 (69.3)	2226/3394 (65.6)	0.446	1.18 (0.81, 1.74)
Alopecia	36/126 (28.6)	1222/3372 (36.2)	0.089	0.7 (0.48, 1.04)
Malar rash	69/131 (52.7)	1863/3392 (54.9)	0.655	0.91 (0.64, 1.3)
Discoid lupus	25/129 (19.4)	702/3360 (20.9)	0.741	0.91 (0.58, 1.42)
Oral ulcers	53/129 (41.1)	1550/3335 (46.5)	0.243	0.8 (0.56, 1.15)
Serositis	51/126 (40.5)	953/3339 (28.5)	**0.005**	1.7 (1.18, 2.45)
Pleurisy	40/127 (31.5)	769/3360 (22.9)	**0.032**	1.55 (1.06, 2.27)
Pericarditis	32/128 (25.0)	534/3369 (15.9)	**0.010**	1.77 (1.17, 2.67)
Laboratory tests	115/130 (88.5)	3017/3395 (88.9)	0.887	0.96 (0.55, 1.66)
Increased DNA binding	96/129 (74.4)	2454/3345 (73.4)	0.840	1.06 (0.71, 1.58)
Low complement	105/130 (80.8)	2624/3373 (77.8)	0.453	1.2 (0.77, 1.87)
Fever (SLEDAI)	4/129 (3.1)	132/3389 (3.9)	0.818	0.79 (0.29, 2.17)
Hematologic disease	88/129 (68.2)	2267/3336 (68.0)	1	1.01 (0.69, 1.48)
Thrombocytopenia	37/129 (28.7)	755/3283 (23.0)	0.137	1.35 (0.91, 1.99)
Leukopenia	73/127 (57.5)	2041/3356 (60.8)	0.460	0.87 (0.61, 1.25)
Treatments (ever used)				
Antimalarials	97/129 (75.2)	2719/3260 (83.4)	**0.022**	0.6 (0.4, 0.91)
Glucocorticoids	127/131 (96.9)	2902/3274 (88.6)	**0.001**	4.07 (1.5, 11.08)
Maximum dose				
≤ 10 mg/d	8/122 (6.6)	442/2742 (16.1)	**<0.001**	4.07 (1.5, 11.08)
10–30 mg/d	30/122 (24.6)	878/2742 (32.0)		
>30–60 mg/d	33/122 (27.0)	687/2742 (25.1)		
>60 mg/d	51/122 (41.8)	735/2742 (26.8)		
MTX	18/131 (13.7)	548/3255 (16.8)	0.404	0.79 (0.47, 1.3)
AZA	57/129 (44.2)	1066/3245 (32.9)	**0.010**	1.62 (1.13, 2.31)
Mycophenolate	31/131 (23.7)	482/3231 (14.9)	**0.009**	1.77 (1.17, 2.68)
CYC	49/131 (37.4)	710/3250 (21.8)	**<0.001**	
At least one immunosuppressor (IS)	91/131 (69.5)	1729/3230 (53.5)	**<0.001**	2.14 (1.49, 3.07)
Rituximab	14/131 (10.7)	208/3253 (6.4)	0.068	1.98 (1.35, 2.88)
Abatacept	0/130 0	10/3244 (0.3)	1	1.75 (0.99, 3.1)-
Anti-TNF	2/130 (1.5)	64/3235 (2.0)	0.974	0.77 (0.19, 3.2)
At least one biological drug	16/129 (12.4)	248/3198 (7.8)	0.066	1.68 (0.98, 2.89)

(continued)

Table 2 Continued

	SLE patients with GI damage (Group 1)	SLE patients without GI damage (Group 2)	*P*-Value	OR (95% CI)
Modified SLICC/SDI median (IQR)	2 (1–4)	1 (0–2)	**<0.001**	—
Katz Index	3 (2–4)	2 (1–3)	**<0.001**	–
Hospitalizations (any)	93/130 (71.5)	1829/3377 (54.2)	**<0.001**	2.13 (1.44, 3.13)
Number of hospitalizations	3 (1–5)	2 (1–3)	**<0.001**	—
Death	23/131 (17.6)	179/3433 (5.2)	**<0.001**	3.92 (2.43, 6.32)

Modified SLICC/SDI was calculated excluding gastrointestinal damage items. IQR: interquartile range; CVA: Cerebrovascular Accident. P value < 0.05 in bold.

Table 3 Variables independently associated with GI damage

Variables	Odds ratio	95% CI	*P*-value
Age at the last clinic evaluation	1.02	1.01-1.04	**<0.001**
Glucocorticoids			
≤ 10 mg/d	1.23	0.37–4.73	0.751
10–30 mg/d	2.61	1.01–8.88	**0.074**
>30–60 mg/d	3.04	1.17–10.40	**0.035**
>60 mg/d	4.14	1.61–14.05	**0.008**
Oral ulcers	0.67	0.45–0.98	**0.044**
Modified SLICC	1.26	1.16–1.36	**<0.001**

Variables originally introduced in the model: age at last assessment (years), duration of SLE (years), serositis activity, APS, thrombotic APS, renal activity, antimalarial drugs, at least one immunosuppressant, steroids, oral ulcers and modified SLICC index.

best of our knowledge, this is the first study that shows an association between specific activity items and more risk of developing GI damage. Other studies have shown that when SLE is active there is a higher risk of developing GI manifestations in general but not specifically those associated with damage [3, 5].

Patients with GI manifestations associated with damage had higher numbers of hospitalizations and mortality from any cause. Nevertheless, it could not be established whether the cause of hospitalization was due to GI morbidity. Similarly, it is not known whether the cause of death was due to SLE or other associated disease such as neoplasms or infections. The highest percentage of mortality from GI manifestations in SLE is attributed to mesenteric vasculitis with series describing up to 50% mortality and complicated pancreatitis with 45% mortality [20–22]. In others, such as in intestinal pseudo-obstruction, mortality is <20% [20, 23]. On the other hand, in an autopsy study of SLE patients it was found that 60–70% had evidence of peritonitis but only 10% had a clinical diagnosis before death [24].

Case reports and case series indicate an infrequent association between inflammatory bowel disease and SLE. Nonetheless, some authors exposed that overlapping symptoms could make differentiating the two diagnosis challenging [17, 25]. In our cohort, the prevalence of inflammatory bowel disease was significantly lower than in the Spanish general population. Other observational studies have shown a prevalence of ulcerative colitis at 0.4% which is comparable to general population controls [26]. With regard to Crohn disease, the prevalence has been estimated at 0.3–0.7% of patients with SLE in some case series [25, 26]; however, it is not clear whether there is a possible association between both diseases [27]. The prevalence of coeliac disease in our cohort was 0.1%, which is lower than in the Spanish general population (0.2%) with statistically significant difference ($P = 0.001$). Prior investigations have revealed a possible association between SLE and coeliac disease [17]. Coeliac disease seems to have a tendency to coexist with other autoimmune conditions, including rheumatoid arthritis and type 1 diabetes, among others [28]. There seems to be overlap in disease presentation as well as autoantibody positivity, as manifest through high ANA titres and human leucocyte antigen serotypes. Results from epidemiologic study identified and increased prevalence of coeliac disease in an SLE population compared with age-matched and sex-matched controls (0.8% compared with 0.2%) [29]. Nonetheless, more data is needed to confirm these findings.

With regard to treatment, there was a higher percentage of patients treated with hydroxychloroquine in the group of patients without GI manifestations associated with damage, suggesting the protective role of this drug. However, this association was lost in the multivariate analysis. The protective role of hydroxychloroquine against accrual damage in SLE has already been suggested [30].Different doses of glucocorticoids were associated with the presence of GI manifestations associated with damage even after the adjusted analysis.

While it is well established that glucocorticoids are associated with organ damage [31–34], there are no previous studies in the literature that have found this association specifically with GI manifestations.

Oral ulcers affect 25–50% of SLE patients in different cohorts [5, 17]. In our series, 46.3% of patients developed oral ulcers. Interestingly, although the prevalence of oral ulcers was similar in both groups of patients, we found that their presence appeared to reduce the risk against the development of GI damage in the multivariable analysis. These results must be validated by prospective cohorts before establishing an accurate relationship. In other publications, the relationship of mucosal lesions with systemic activity has been disputed. Some studies have found an association of oral ulcers with clinical systemic activity according to defined guidelines on the basis of history and physical examination, although this did not correlate with significant changes in titres of serum complement (C3) or anti-DNA antibodies. It has also been suggested that patients with oral ulcers have a higher mortality that those without oral ulcers but this has not been confirmed by further studies [35]. Sultan *et al.* [1] have not found evidence of increased lupus activity in those patients with recurrent mouth ulcers.

The current study has some limitations. First, its cross-sectional retrospective design that does not allow conclusions to be drawn on causality with respect to the relationship between GI manifestations and damage, which should be the object of future longitudinal studies. Second, most patients in the RELESSER cohort are Caucasian so other ethnic groups are not well represented, which makes it difficult to extrapolate the results of the present study.

In conclusion, having GI damage is associated with clinical involvement of other target organs in SLE and with a worse prognosis. Patients on a high dose of glucocorticoids are at a higher risk of developing GI damage, which reinforces the strategy of minimizing glucocorticoids. Oral ulcers are common in SLE and appear to decrease the risk of GI damage.

Acknowledgements

We would like to thank Norman Jiménez-Otero, from the Rheumatology & Immuno-Mediated Diseases Research Group (IRIDIS), Galicia Sur Health Research Institute (IIS Galicia Sur) for his support.

Funding: The RELESSER Registry was partially funded by GlaxoSmithKline (GSK), Roche, Union Chimique Belge (UCB), Lilly and Novartis.

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1 Sultan SM, Ioannou Y, Isenberg DA. A review of gastrointestinal manifestations of systemic lupus erythematosus. Rheumatology 1999;38:917–32.

2 Hallegua DS, Wallace DJ. Gastrointestinal manifestations of systemic lupus erythematosus. Curr Opin Rheumatol 2000;12:379–85.

3 Li Z, Xu D, Wang Z *et al.* Gastrointestinal system involvement in systemic lupus erythematosus. Lupus 2017;26:1127–36.

4 Fawzy M, Edrees A, Okasha H, El Ashmaui A, Ragab G. Gastrointestinal manifestations in systemic lupus erythematosus. Lupus 2016;25:1456–62.

5 Mok CC. Investigations and management of gastrointestinal and hepatic manifestations of systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2005;19:741–66.

6 Rúa-Figueroa I, López-Longo FJ, Calvo-Alén J *et al.* National registry of patients with systemic lupus erythematosus of the Spanish Society of Rheumatology: objectives and methodology. Reumatol Clin 2014;10:17–24.

7 Hochberg M. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.

8 Organic Law 15/1999 of December 13, 1999 on the Protection of Personal Data. Official State Gazette 1999; num.298, 43088–99.

9 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191–4.

10 Ibañez D, Gladman D, Urowitz M. Summarizing disease features over time: II. Variability measures of SLEDAI-2K. J Rheumatol 2007;34:336–40.

11 Gordon C, Sutcliffe N, Skan J, Stoll T, Isenberg DA. Definition and treatment of lupus flares measured by the BILAG index. Rheumatology 2003;42:1372–9.

12 Petri M, Orbai AM, Alarcón GS *et al.* Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.

13 Katz JD, Senecal JL, Rivest C, Goulet JR, Rothfield N. A simple severity of disease index for systemic lupus erythematosus. Lupus 1993;2:119–23.

14 Frodlund M, Reid S, Wetterö J *et al.* The majority of Swedish systemic lupus erytemathosus patients are still affected by irreversible organ impairment: factors related to damage accrual in two regional cohorts. Lupus 2019;28:1261–72.

15 Taraborelli M, Cavazzana I, Martinazzi N *et al.* Organ damage accrual and distribution in systemic lupus erythematosus patients followed-up for more than 10 years. Lupus 2017;26:1197–204.

16 Gladman DD, Goldsmith CH, Urowitz MB *et al.* The Systemic Lupus International Collaborating Cinics/

American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison. J Rheumatol 2000;27:373–6.

17 Brewer BN, Kamen DL. Gastrointestinal and hepatic disease in systemic lupus erythematosus. Rheum Dis Clin A Am 2018;44:165–75.

18 Alves SC, Fasano S, Isenberg DA. Autoimmune gastrointestinal complications in patients with systemic lupus erythematosus: case series and literature review. Lupus 2016;25:1509–19.

19 Janssens P, Arnaud L, Galicier L *et al.* Lupus enteritis: from clinical findings to therapeutic management. Orphanet J Rare Dis 2013;8:67.

20 Tian XP, Zhang X. Gastrointestinal involvement in systemic lupus erythematosus: Insight into pathogenesis, diagnosis and treatment. World J Gastroenterol 2010;16: 2971–7.

21 Kwok SK, Seo SH, Ju HJ *et al.* Lupus enteritis: clinical characteristics, risk factor for relapse and association with anti-endothelial cell antibody. Lupus 2007;16:803–9.

22 Medina F, Ayala A, Jara LJ *et al.* Acute abdomen in systemic lupus erythematosus: the importance of early laparotomy. Am J Med 1997;103:100–5.

23 Ceccato F, Salas A, Góngora V *et al.* Chronic intestinal pseudo-obstruction in patients with systemic lupus erythematosus: report of four cases. Clin Rheumatol 2008;27:399–402.

24 Takeno M, Ishigatsubo Y. Intestinal manifestations in systemic lupus erythematosus. Intern Med 2006;45:41–2.

25 Yamashita H, Ueda Y, Kawaguchi H *et al.* Systemic lupus erythematosys complicated by Crohn's disease: a case report and literature review. BMC Gastroenterol 2012;12:174.

26 Shor DB, Dahan S, Comaneshter D, Cohen AD, Amital H. Does inflammatory bowel disease coexist with systemic lupus erythematosus? Autoimmun Rev 2016; 15:1034–7.

27 Katsanos KH, Voulgari PV, Tsianos EV. Inflammatory bowel disease and lupus: a systematic review of the literature. J Crohns Colitis 2012;6:735–42.

28 Denham JM, Hill ID. Celiac disease and autoimmunity: review and controversies. Curr Allergy Asthma Rep 2013;13:347.

29 Dahan S, Shor DB, Comaneshter D *et al.* All disease begins in the gut: celiac disease co-existence with SLE. Autoimmun Rev 2016;15:848–53.

30 Fessler BJ, Alarcón GS, McGwin G *et al.* Systemic lupus erythematosus in Three Ethnic Groups. XVI. Association of hydroxychloroquine use with reduced risk of damage accrual. Arthritis Rheum 2005;52:1473–1480.

31 Bruce IN, O'Keeffe AG, Farewell V *et al.* Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort. Ann Rheum Dis 2015;74: 1706–16.

32 Pego-Reigosa JM, Lois-Iglesias A, Rúa-Figueroa I *et al.* Relationship between damage clustering and mortality in systemic lupus erythematosus in early and late stages of the disease: cluster analyses in a large cohort from the Spanish Society of Rheumatology Lupus Registry. Rheumatology 2016;55:1243–50.

33 Petri M, Purvey S, Fang H, Magder LS. Predictors of organ damage in systemic lupus erythematosus: the Hopkins' Lupus cohort. Arthritis Rheum 2012;64: 4021–4028.

34 Segura BT, Bernstein BS, McDonnell T *et al.* Damage accrual and mortality over long-term follow-up in 300 patients with systemic lupus erythematosus in a multi-ethnic British cohort. Rheumatology 2020;59: 524–533.

35 Jonsson R, Heyden G, Westberg N, Nyberg G. Oral mucosal lesions in systemic lupus erythematosus – a clinical, histopathological and immunopathological study. J Rheumatol 1984;11:38–42.