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Comorbidity clusters and their relationship with severity and outcomes of index diseases, in a large multicentre systemic lupus erythematosus cohort

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ABSTRACT

Objective Patients with SLE have a well-known increased risk of major comorbidities, although they are also very heterogeneous in terms of the prevalence of comorbid conditions. The relationships of such comorbidities with the outcomes and the severity of index diseases are less known. We aimed to evaluate the interactions between comorbid conditions, in a large multicentre SLE cohort, and their impact on severity and outcomes, using a cluster analysis.

Methods Data on 14 cumulative comorbidities were derived from patients with SLE (American College of Rheumatology (ACR)-97 criteria) who had been included in the retrospective phase of the RELESSER (Spanish Society of Rheumatology National Register of SLE). The Severity Katz Index and the SLICC/ACR Damage Index were calculated. Unsupervised cluster analysis was performed to better characterise the relationships between comorbidities in a large multicentre cohort of patients with SLE. For intercluster differences testing, analysis of variance and Tukey tests were used to compare continuous numerical variables; a Kruskal-Wallis test to discrete variables and the χ^2 (or Fisher's exact test) were used for categorical ones.

Results A total of 3658 patients with SLE were included. Men accounted for 9.6% of patients. The mean (SD) age was 45.9 years, and 93% were Caucasian. Four clusters, with markedly different comorbidity profiles and outcomes, were identified: in cluster 2 (n=516), patients were grouped around depression (100% of the cases); in cluster 3 (n=418) around serious infections (100%); and in cluster 4 (n=388) around cardiovascular events (also 100%). However, in cluster 1, the largest one (n=2336), no patient had any of the three defining comorbidities of the other clusters, and this cluster was associated with the best outcomes.

Conclusions Cluster analysis identifies well-differentiated subsets of patients with SLE in terms of their comorbidities. The most relevant comorbidities in SLE tend to aggregate in the most severe patient subsets.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Comorbidities are frequent in patients with SLE and have an important impact on main outcomes, including survival. However, the distribution of the most relevant comorbidities in SLE cohorts is heterogeneous, and the relationship between the comorbidities and the index disease is less known.

WHAT THIS STUDY ADDS

⇒ This study identifies subsets of patients aggregating on the basis of main comorbidities and analyse the relationships of the clusters with the severity of SLE and outcomes of the disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study underscores the importance of paying closer attention to more severe cases of SLE, particularly with respect to the potential occurrence of such serious comorbidities as depression, severe infection and CV events.

INTRODUCTION

SLE is a systemic autoimmune disease characterised by a remarkable diversity of clinical

and immunopathological presentations. The survival of patients with SLE has improved significantly over the past few decades and the major cause of death is no longer active lupus, but rather comorbidities such as cardiovascular (CV) disease, infection or malignancy.[1] Although patients with SLE have a well-known increased risk of all these comorbidities, as well as others such as osteoporosis and/or depression, compared with the general population,[2] which often complicate the disease course. They are also very heterogeneous in terms of those comorbidities. The role of coexisting conditions in the outcomes, and the interaction between comorbid conditions and the index disease, is less understood.[3] Furthermore, comorbid conditions are associated with emergency department visits, hospitalisations and medical expenses of patients with SLE.[4] Therefore, it is not surprising that the proper management of comorbidities has long been considered an integral part of the holistic management of SLE.[5]

Due to the heterogeneity of disease courses and outcomes, different approaches have been used to identify subsets of patients with SLE. Cluster analysis has been shown to be a good statistical tool, revealing relationships between variables, grouping them where associations and patterns in data exist without need of a prior hypothesis (namely, 'unsupervised analysis').

Several studies have successfully used cluster analysis in cohorts of patients with SLE, furthering knowledge in diverse areas and/or dominances of the disease, such as clinical characteristics, autoantibodies.[6–9] Along these lines, our own group has published a cluster analysis of organ damage carried out using a large multicentre registry from Spain, RELESSER (Spanish Society of Rheumatology Lupus Registry), revealing unexpected associations such as a musculoskeletal cluster and mortality.[10 11] Even though damage in SLE, such as measured by the SLICC/American College of Rheumatology (ACR) Damage Index (SDI), includes comorbidity-derived damage, it is, in fact, a mixture of organ damage related to cumulative disease activity, treatment toxicities and comorbidities. Given the good performance of cluster analysis when used for organ damage in SLE, we decided to conduct a study employing a similar approach, although in this case to explore relationships and associations between clinical characteristics, therapies and comorbidities in SLE in the same multicentre cohort, while also trying to identify homogeneous subgroups. Furthermore, we aimed to determine the relationships of the index diseases with severity and outcomes.

PATIENTS AND METHODS

Data were derived from the retrospective cross-sectional phase of RELESSER (ie, RELESSER-TRANS). The population of RELESSER-TRANS was comprised of 4219 unselected adult patients with a clinical diagnosis of SLE made by an expert physician. For this analysis, only patients who fulfilled the ACR-97 SLE classification criteria were included.

Table 1 Frequency of comorbidities in the cohort

Comorbidity	N/total available (%)
Thyroiditis	288/3487 (8.3)
Peptic ulcer	128/3351 (3.8)
Severe hepatopathy	38/3626 (1.0)
Obstructive pulmonary disease	98/3609 (2.7)
Diabetes mellitus	179/3600 (5.0)
Cardiovascular event	388/3539 (11.0)
Cardiac arrhythmia	150/3603 (4.2)
Pulmonary embolism	122/3611 (3.4)
Dementia	26/3583 (0.7)
Malignancy	212/3597 (5.9)
Serious infection	705/3658 (19.3)
End-stage renal disease	98/3519 (2.8)
Osteoporosis	260/3543 (7.3)
Depression	610/3576 (17.1)

Only comorbidities present at baseline—that is, at the entrance in the register—were considered. Definitions of variables and comorbidities, as well as the global characteristics of the registry, have been previously published elsewhere. These correspond to the cumulative data regarding damage (using SDI), severity (using the Katz Severity Index) (KSI),[12] treatments for SLE and comorbidities (both, using the Charlson Index, and separately considered), at the time of the last clinical visit noted in the register.[13] A total of 14 comorbidities were considered for this study (table 1). The definitions of the comorbidities that characterised each subgroup were as follows: severe infection, when resulting in hospitalisation or death; CV events, including any of the following: congestive heart failure, myocardial infarction, stroke or peripheral arteriopathy. Depression was considered present if such a diagnosis appeared in the patient's medical record or if she/he had been treated with antidepressants. The remaining definitions of the comorbidities encompassed in the study have been published previously.[13] Refractory disease was defined as previously published,[13] namely: ineffectiveness of cyclophosphamide, or two or more other immunosuppressants (mycophenolate mofetil, methotrexate, azathioprine or leflunomide), or the need to use rituximab or to carry out a splenectomy.

Statistical approach

The non-hierarchical partitioning method ('k-means' algorithm) was applied, with groups 2, 3, 4 and 5. Only comorbidities equal to, or more than, 5% of prevalence were considered for the cluster groups definition. To measure the degree of similarity between the comorbidity patterns in two patients, Euclidean distance was used. Briefly, the algorithm first selects the initial centres for each cluster, assigning those patients to the cluster with

the nearest centre. Afterwards, the cluster centres are recalculated using all patients; these are then reassigned to the nearest centre in terms of Euclidean distance. One plot of the sum of squares within clusters (SSDG: Sum of Squared Distances of the Group centroid; cluster homogeneity criterion) versus the number of clusters was built (online supplemental material figure 1S). For choosing the number of clusters, we used the values from the plot where an 'elbow' appeared. While either three or four groups seemed a reasonable choice, we eventually decided to use four clusters for the comparative analyses, on the basis of its clinical plausibility. Any missing values related to the comorbidities were imputed as absent (ie, comorbidity not present), yet the percentages of missing values for each comorbidity were all under 5%, with the sole exception of peptic ulcer.

Analysis of variance and Tukey tests were used to compare continuous numerical variables. The Kruskal-Wallis test was used to compare discrete numerical variables (KSI and SDI), and the χ^2 test to compare the frequencies of the categorical variables (or Fisher's exact test when the conditions of the χ^2 test were not met).

All analyses were carried out using R Statistical Software, V.3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was considered present when p value<0.05.

Patient involvement

Patients were not involved in the design and conduct of this research

RESULTS

The study population comprised 3658 patients who fulfilled four or more ACR-97 SLE classification criteria. Men accounted for 9.6% (n=353) of the patients. The mean age on enrolment in the register was 45.9 years, and 93% of patients were Caucasian.

The median of the Severity Katz Index was 2 (IQR: 1–3) and the median SDI was 1 (IQR: 0–2). As specifically defined for the register, 24.5% of the patients were refractory to the therapy at least once and 54.6% were hospitalised at least once.

The median of the Charlson Index was 2 (IQR: 1–3). The distribution of the most important comorbidities compiled from RELESSER is displayed in table 1, and the treatments for those comorbidities are shown in table 2.

Four clusters which differed markedly in comorbidity profiles and outcomes were identified (table 3).

One subgroup was clustered around depression, which was present in 100% of the cases within that group (cluster 2). Another cluster (cluster 3) comprised patients with one or more serious infections and also had a 100% cumulative incidence rate. Finally, cluster 4, which centred on CV events, similarly had a 100% incidence rate.

Interestingly, in cluster 1, no patient had any of the three defined comorbidities found in the other clusters (namely, infection, depression and CV events). Actually, almost all of the evaluated comorbidities occurred less frequently in this cluster (table 3). This cluster can be reliably characterised as the less severe cluster, on the basis of less damage, lower severity index, lower refractoriness and lower mortality. Fortunately, it was the numerically largest group, involving 2336 patients (63.9%), and as expected, the disease duration was shortest in this patient subset.

Cluster 2 (100% depression) was associated with greater use of non-steroidal anti-inflammatory drugs (NSADs) (79%) and, remarkably, it was not the most severe patient subset. It is also worth mentioning its association with the female sex (table 3).

Cluster 3 (100% serious infection) featured the greatest percentage of patients who had been treated with glucocorticoids or with high intensity immunosuppression, that is, cyclophosphamide or mycophenolate. Interestingly, most patients from this subset were considered refractory to treatment (table 3). Cluster 4 (100% CV event) was the one most strongly associated with mortality, with 90/388 deaths (25.2%), and was the cluster that exhibited the highest damage, according to SDI. No differences between clusters were found in terms of deaths due to SLE.

Table 2 Treatments for comorbidities

Treatment	N/total (%)
Acetylsalicylic acid	1091/2935 (37.2)
Oral anticoagulants	494/3425 (14.4)
Antidiabetics	143/3389 (4.2)
Statins	843/3318 (25.4)
Diuretics	726/3279 (22.1)
Calcium and/or vitamin D	2256/3353 (67.3)
Antiresorptives	830/3348 (24.8)

DISCUSSION

We have been able to identify four well-differentiated clusters of comorbidities in a large multicentre cohort of patients with SLE. Cluster 2 was defined by the presence of depression in 100% of the patients, cluster 3 by serious infection, also occurring in 100% of the cases, and cluster 4 by CV events, also in 100% of the patients. Finally, Cluster 1, the numerically largest, was characterised by the absence of these 'index' comorbidities, corresponding to 63.8% of the overall.

Our results suggest that the distribution of comorbidities is not random in SLE. We demonstrate that certain comorbidities may be associated with clinical disease severity patterns, in terms of organ damage, treatment refractoriness and mortality and certain sociodemographic factors, which further supports the complex nature of comorbidities in SLE and their inter-relationships.

To the best of our knowledge, this approach to evaluating comorbidities in SLE has been used only once

Table 3 Clusters of comorbidities and associated outcomes

	Cluster 1(d) n=2336 (63.9%)	Cluster 2(a) n=516 (14.1%)	Cluster 3(b) n=418 (11.4%)	Cluster 4(c) n=388 (10.6%)	P value
Age at diagnosis, mean (SD)	34.3 (13.8)[a,c]	36.6 (14.8)[b,c,d]	32.7 (14.9)[a,c]	40.9 (17.6)[a,b,d]	<0.001
Age at last visit, mean (SD)	44.8 (14.1)[a,b,c]	49.8 (14.1)[b,c,d]	46.7 (14.3)[a,c,d]	46.7 (14.3)[a,b,d]	<0.001
Male N (%)	214 (9.2)[a,c]	25 (4.8)[b,c,d]	51 (12.2)[a]	63 (16.3)[a,d]	<0.001
Caucasian N (%)	2088 (92.3)	482 (96.2)	382 (92.9)	357 (94.7)	0.083
Time with SLE (months), mean (SD)	129.2 (95.9)[a,b,c]	159.3 (101.4)[d]	170.3 (100.3)[d]	169 (113)[d]	<0.001
Diagnostic delay (month), mean (SD)	30.1 (51.8)[b,c]	37.3 (57.9)[b]	20.5 (38.0)[a,c,d]	39.3 (66.5)[b,d]	<0.001
Thyroiditis, N (%)	192 (8.2)[a]	50 (9.7)[b,d]	21 (5.0)[a]	25 (6.4)	0.037
Peptic ulcer, N (%)	55 (2.4)[a,b,c]	24 (4.7)[d]	18 (4.3)[c,d]	31 (8.0)[b,d]	<0.001
Severe hepatopathy, N (%)	15 (0.6)[b,c]	7 (1.4)	8 (1.9)[d]	8 (2.1)[d]	0.011
Obstructive pulmonary disease, N (%)	33 (1.4)[a,b,c]	23 (4.5)[d]	17 (4.1)[d]	25 (6.4)[d]	<0.001
Diabetes, N (%)	82 (3.5)[b,c]	24 (4.7)[c]	24 (5.7)[c,d]	24 (5.7)[a,b,d]	<0.001
CV event, N (%)	0 (0.0)[c]	0 (0.0)[c]	0 (0.0)[c]	388 (100)[a,b,d]	<0.001
Cardiac arrhythmia, N (%)	53 (2.3)[b,c]	17 (3.3)[c]	19 (4.5)[c,d]	61 (15.7)[a,b,d]	<0.001
Pulmonary embolism, N (%)	57 (2.4)[b,c]	17 (3.3)	25 (6.0)[d]	23 (5.9)[d]	<0.001
Dementia, N (%)	5 (0.2)[a,c]	7 (1.4)[d]	3 (0.7)[c]	11 (2.8)[b,d]	<0.001
Malignancy, N (%)	110 (4.7)[a,c]	46 (8.9)[d]	25 (6.0)	31 (8.0)[d]	0.001
Serious infection, N (%)	0 (0.0)[a,b,c]	122 (23.6)[b,c,d]	418 (100)[a,c,d]	165 (42.5)[a,b,d]	<0.001
End-stage renal disease, N (%)	27 (1.2)[b,c]	11 (2.1)[b,c]	26 (6.2)[a,d]	34 (8.8)[a,d]	<0.001
Osteoporosis, N (%)	79 (3.4)[a,b,c]	71 (13.8)[d]	41 (9.8)[c,d]	69 (17.8)[b,d]	<0.001
Depression, N (%)	0 (0.0)[a,c]	516 (100)[b,c,d]	0 (0.0)[a,c]	94 (24.4)[a,b,d]	<0.001
NSAID, N (%)	1577 (73.6)[a,b,c]	390 (79.3)[b,c,d]	258 (64.7)[a,d]	238 (64.0)[a,d]	<0.001
Glucocorticoids, N (%)	1890 (86.0)[a,b,c]	451 (91.3)[b,d]	400 (98.0)[a,c,d]	354 (93.2)[b,d]	<0.001
Methotrexate or leflunomide, N (%)	346 (15.9)[a,b]	108 (21.9)[c,d]	85 (21.2)[c,d]	55 (14.7)[a,b]	0.001
Azathioprine, N (%)	580 (26.7)[a,b,c]	186 (37.6)[b,d]	214 (53.1)[a,c,d]	160 (42.9)[b,d]	<0.001
Cyclophosphamide or mycophenolate, N (%)	501 (23.5)[a,b,c]	145 (29.7)[b,c,d]	216 (54.3)[a,c,d]	139 (37.4)[a,b,d]	<0.001
Antimalarials, N (%)	1869 (85.4)[b,c]	433 (86.9)[b,c]	317 (78.3)[a,c,d]	263 (71.1)[a,b,d]	<0.001
Rituximab, N (%)	110 (5.0)[a,b,c]	37 (7.5)[b,d]	48 (12.1)[a,d]	31 (8.2)[d]	<0.001
Severity Katz Index, mean (SD)	2.3 (1.4)[a,b,c]	2.8 (1.8)[b,c,d]	3.5 (1.8)[a,d]	3.5 (2)[a,d]	<0.001
Refractory lupus, N (%)	442 (18.9)[a,b,c]	137 (26.6)[b,c,d]	192 (45.9)[a,c,d]	127 (32.7)[a,b,d]	<0.001
Lupus nephritis, N (%)	568 (25.0)[b,c]	142 (28.0)[b,c]	214 (51.4)[a,c,d]	168 (44.0)[a,b,d]	<0.001
SDI, mean (SD)	0.7 (1)[a,b,c]	1.3 (1.8)[b,c,d]	1.6 (1.8)[a,c,d]	3.3 (2.5)[a,b,d]	<0.001
Hospitalisation due to lupus, N (%)	1012 (44.6)[a,b,c]	303 (59.9)[b,c,d]	341 (82)[a,c,d]	298 (77.4)[a,b,d]	<0.001
Death, N (%)	46 (2.2)[a,b,c]	27 (5.6)[b,c,d]	45 (11.6)[a,c,d]	90 (25.2)[a,b,d]	<0.001
Death due to lupus, N (%)	14 (36.8)	8 (40.0)	8 (19.5)	24 (30.4)	0.27

Regarding age, the p value for the comparison between groups 1 and 3 is 0.0498. For age at last visit, the p value for the comparison between groups 1 and 3 is 0.0498 (χ^2). For peptic ulcer, the p value for the comparison between groups 2 and 4 is 0.053 (χ^2) or 0.048 (Fisher). For refractory lupus, the p value for the comparison between groups 2 and 4 is 0.051 (χ^2) or 0.046 (Fisher).
a, b, c and d (superindex) mean signicantly different from cluster 2, 3, 4 and 1, respectively.
ACR, American College of Rheumatology; CV, cardiovascular; NSAID, non-steroidal anti-inflammatory drug; SDI, SLICC/ACR Damage Index.

before.[14] A cluster analysis was carried out by the group of Bersias in Crete, Greece. Their statistical method for building the clusters consisted of hierarchical agglomerative clustering. Their study involved a rather small cohort as compared with our own, which included 399 patients. In contrast with our findings, they identified five clusters of comorbidities. Cluster 1 included most of the patients (n=227) and was characterised by increased prevalence of thyroid disease and obesity, dyslipidaemia and mental comorbidities. Cluster 2 (n=46) exhibited a high frequency of metabolic risk factors; Cluster 3 (n=43) of gastrointestinal, skin, allergic and haematologic

diseases; and Cluster 4 (n=45) of metabolic risk factors, CV, respiratory and mental disorders. Cluster 5 included a minority (n=6) of patients with SLE with a relatively higher prevalence of osteoporosis, malignancies, neurologic, infectious and kidney disorders. The five clusters did not differ in terms of disease duration. Clusters 2 and 5 included patients with high frequencies of biopsy-proven nephritis and were comprised of the more severe patients. However, the relationships between the clusters and the main SLE outcomes were not elucidated, and several clusters consisted of small patient cohorts, in one case as few as six patients, thus compromising the reliability of the analysis. Differences in the definition of variables and the types of comorbidities included, as well as the statistical procedures used for cluster analysis, might explain such divergent results.

In our study, we observed a high prevalence of depression, consistent with previous reports from our country.[15] Interestingly, despite the lack of any aggregation among the most severe clusters, no patients in Cluster 1, the least severe, suffered from depression. Given its association with mortality, in the general population as well as in SLE,[16 17] depression should be considered a potentially serious comorbidity, and perhaps should be actively assessed in the most severe patients, given that it is often overlooked.[15] As expected, a lesser percentage of males were found in this cluster. Interestingly, the use of NSADs was higher in this cluster, suggesting the possibility of a greater prevalence of pain, with or without arthritis, a well-known factor related to depression in the general population, though not specifically investigated in SLE to date.[18]

Interestingly, the profile associated with depression in our analysis corresponds to patients not very severe, indicating a not strong relationship between severity and depression. Obviously, further studies on the subject are needed to confirm this hypothesis.

All Cluster 3 patients had serious infections that were treated, unsurprisingly, with immunosuppressants (such as azathioprine, cyclophosphamide or mycophenolate) and glucocorticoids as well as rituximab, which proved consistent with the higher percentage of refractory patients in this cohort. Interestingly, the frequency of lupus nephritis was the highest in this cluster, perhaps related to the higher use of immunosuppressors. Worth underscoring is the increased risk of hospitalisation compared with the other groups. This reflects, in turn, the well-known and increased risk for serious infections associated with hospitalisation.[19 20]

Cluster 4, 100% of which patients experienced a CV event, was the one most associated with organ damage, as measured by SDI. This is due to the fact that CV events are one of the items included in the SDI index. Nevertheless, it was the cluster most closely associated with mortality, amounting to no less than 25%. This is in line with the majority of more recent studies that have shown CVD to be the main cause of death in patients with SLE.[21–23] Beyond the comorbidities that defined the clusters identified in our study (namely, depression, serious infection and CV events), all of which are widely recognised as quite frequent comorbidities in SLE,[2 14 24] it is worth noting the high prevalence of thyroiditis, that is, 8.3%, a figure higher than what has been reported in the general population.[25] Likewise, diabetes mellitus was found in 5% of patients, perhaps resulting from the frequent use of glucocorticoids in this population. Nevertheless, one recent study found a reduced incidence of diabetes in an Asian cohort, a somewhat striking result and one for which the authors admit that they cannot venture any explanation.[26] In any case, our study is not focused on the prevalence of such comorbidities, and this study lacked a control group, precluding the availability of any solid data in this regard.

Our study has strengths but is not without some drawbacks. First of all, it is affected by the limitations inherent to any retrospective study, which impose certain objective restrictions on the amount of data that can be inferred. Regarding comorbidities, the imputation of missing values can lead to underestimations of their prevalence. However, by taking into account the relevance of the comorbidities examined in our cluster analyses, we believe that this possibility is probably low. The large number of patients involved, in tandem with the relatively high number of comorbidities collected, allowed us to make a robust cluster analysis and explore their clinical significance—that is, linking the clusters to the most relevant outcomes of SLE. On the other hand, the differences in disease duration between the clusters may have had an influence on the prevalence of comorbidities in all of the clusters. Nonetheless, such information remains clinically useful, in the sense that the longer the duration of the disease, the greater the likelihood that comorbidities will develop. Finally, it should also be noted that our study is mainly restricted to a Caucasian population. Last, but not least, a prospective validation of the clusters would strengthen the value of these results.

In summary, cluster analysis identifies well-differentiated subgroups of patients with SLE in terms of comorbidities. The most relevant comorbidities tend to aggregate in the most severe patient subsets.

These data underscore the importance of paying closer attention to more severe cases of SLE, particularly with respect to the potential occurrence of such serious comorbidities as depression, severe infection and CV events.

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