The relevance of cluster analyses to stratify systemic lupus erythematosus: increased mortality with heavier treatment

Sirs,

Systemic lupus erythematosus (SLE) is probably one of the most heterogeneous systemic disease, and it still represents a challenge for the clinician both in terms of diagnosis and treatment (1).

In this context, cluster analyses could be of great value to better evaluate the heterogeneity of the disease, and to improve the effectiveness of patient-tailored treating strategies. However, this kind of statistical approach is not frequently reported for SLE.

The first analyses focused on autoantibody profile clustering at baseline, and identified clinical settings with a possible relationship with outcome (2, 3).

Recently, Pego-Reigosa *et al*. applied a cluster analysis to a large cohort of Spanish patients with systemic lupus erythematosus (SLE) (4). These authors identified three SLE clusters, with different amount of damage, starting from clinical manifestations during the course of the disease. Cardiovascular and musculoskeletal manifestations were the two dominant forms of damage in two different clusters showing the highest mortality.

These data are consistent with cluster analysis in our single-centre SLE cohort, presented at the 2016 European Lupus Meeting (5). We performed a two-step cluster analysis, with log-likelihood distance measure and automatically determined number of clusters, followed by analysis of variance or chi squared test with post hoc correction for multiple comparisons, in a cohort of 366 patients with SLE followed for a mean of 5.3±3.9 years in our Clinic. The cohort consisted of 323/366 (88.3%) females, with mean age at SLE diagnosis of 38.6±15.0 years.

The following variables were introduced in the model: fulfilment of ACR 1997 revised criteria for SLE (6), clinical manifestations (articular involvement differentiated in arthralgia or synovitis, serositis, mucocutaneous, haematological, renal and cerebral involvement and presence of antiphospholipid syndrome, flare/year, serologic profile (anti-dsDNA, anticardiolipin and antibeta2GPI antibodies and lupus anticoagulant) and treatment employed at the last follow-up, including the use of glucocorticoids and immunosuppressors. Cyclophosphamide was used in the induction phase of SLE in 26 patients, but none of them was taking this drug at the last follow-up.

This analysis divided SLE patients into three clusters, characterised by the following dominant features:

Cluster 1
Chronic use of glucocorticoids and more-than one immunosuppressor employed, and arthritis, absence of antiphospholipid syndrome and CNS involvement.

Cluster 2
Antiphospholipid syndrome, and articular, mucocutaneous and CNS (mainly ischaemic lesions) involvement.

Cluster 3
Mucocutaneous involvement and absence of major organ involvement (Fig. 1; Table I).

No difference in age and SLE duration was noticed among the three clusters. Notably, both the presence of nephritis and the histological class did not differentiate between the first two clusters. The low number of this type of involvement may underestimate the role of nephritis in our cohort (50/366, 13.6%).

Mortality and number of SLE flares per year were significantly higher in cluster 1 (mortality by Chi square test: p=0.013; cluster 1 *versus* cluster 2, 20/145 (13.8%) *versus* 4/79 (5%), p=0.06, cluster 1 *versus* cluster 3, 20/145 (13.7%) *versus* 6/113 (5.3%) p=0.027 by post hoc test; flare/years cluster 1 *versus* cluster 2, mean (95%CI) 0.91 (0.62–1.20) *versus* 0.44 (0.29-0.60) p=0.02; cluster 1 *versus* cluster 3, mean (95%CI) 0.91 (0.62–1.20) *versus* 0.28 (0.19–0.37), p<0.0001).

Overall, our findings appear concordant with those reported by Pego-Reigosa, where mortality was higher in that cluster with more damage accrual. In fact, we disclosed a higher mortality in cluster 1, *i.e.* in SLE requiring more glucocorticoids and heavier immunosuppression, consistent with a more severe disease causing damage with time. Such patients showed also arthritis, which mirrors a state of chronic systemic inflammation and increased cardiovascular risk (7). Limitations to these conclusions were the absence of the cause of mortality, and the damage score.

Secondly, mortality and number of flares per year were higher in the cluster 1 irrespectively of the serological profile. Conversely, the serological profile was also relevant at baseline to disclose SLE patients with a higher mortality (8). We then suggest that cluster analyses performed both at diagnosis and in the follow-up may be complementary to better stratify SLE.

Surprisingly, the antiphospholipid syndrome, which was absent in cluster 1, did not affect mortality. It might be due to a high rate of minor neurologic events (*i.e.* ischaemic lesions at MRI observed in 16/62 patients). However, it could also suggest that the treatment of SLE, rather than the association of antiphospholipid syndrome, may be of greater importance to affect the outcome of SLE itself.

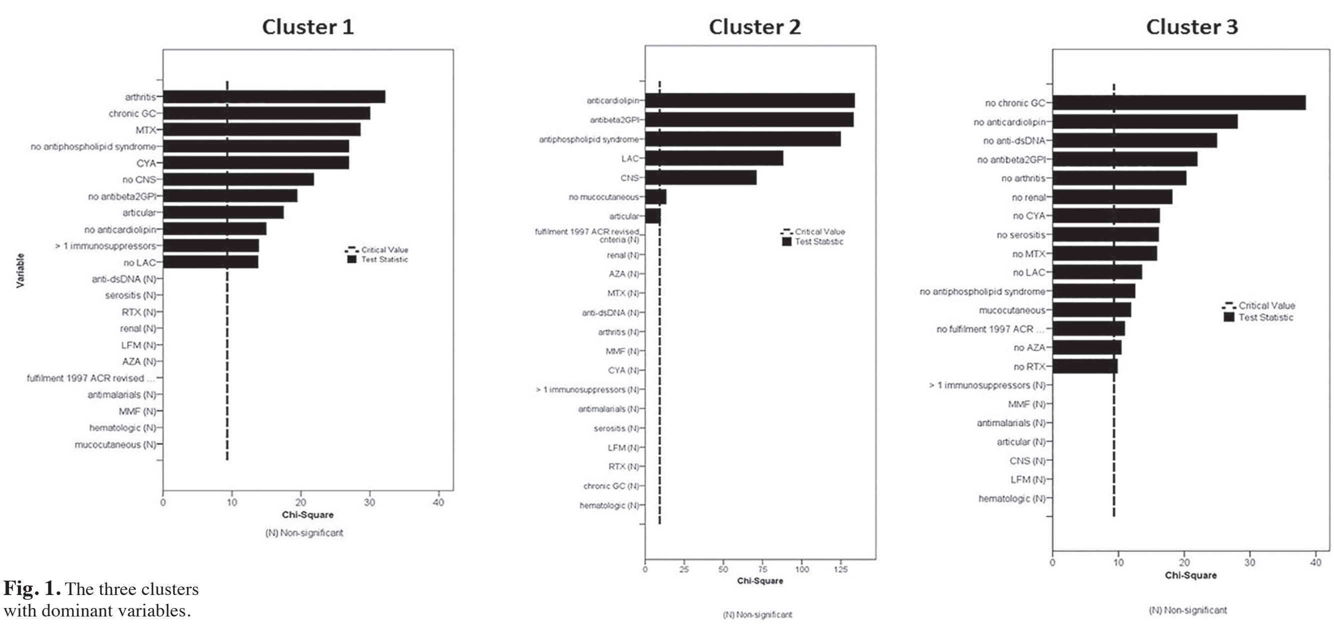

Fig. 1. The three clusters with dominant variables.

Table I. Cluster distribution (n=351; 15 excluded cases) and comparisons.

Feature, n (%)	Cluster 1 n=145 (41%)	Cluster 2 n=83 (24%)	Cluster 3 n=123 (35%)	*p*-value 1 *vs.* 2	*p*-value 1 *vs.* 3	*p*-value 2 *vs.* 3
Fulfilment of 1997 ACR revised criteria	117 (77)	71 (86)	73 (59)	ns	0.004	<0.0001
Arthralgias	134 (92)	53 (64)	87 (71)	<0.0001	<0.0001	NS
Arthritis	89 (61)	23 (28)	23 (19)	<0.0001	<0.0001	NS
Mucocutaneous	104 (72)	46 (55)	107 (87)	0.0018	0.012	<0.0001
Haematological	89 (61)	50 (60)	69 (56)	NS	NS	NS
Renal	29 (20)	20 (24)	1 (0,8)	NS	<0.0001	<0.0001
CNS	11 (8)	53 (64)	21 (17)	<0.0001	NS	<0.0001
Serositis	40 (28)	18 (22)	5 (4)	NS	<0.0001	0.003
Antiphospholipid syndrome	1 (0,7)	52 (63)	6 (5)	<0.0001	NS	<0.0001
Anti-dsDNA	61 (42)	34 (41)	12 (10)	NS	<0.0001	<0.0001
ACLA	26 (18)	77 (93)	13 (11)	<0.0001	NS	<0.0001
Antibeta2GPI	8 (5)	59 (71)	4 (3)	<0.0001	NS	<0.0001
LAC	24 (17)	65 (78)	19 (15)	<0.0001	NS	<0.0001
Antimalarials	68 (47)	35 (42)	74 (60)	NS	NS	0.034
Methotrexate	37 (25)	3 (4)	0 <0.0001	<0.0001	NS	
Cyclosporine A	37 (25)	4 (5)	0 <0.0001	<0.0001	NS	
Azathioprine	26 (18)	19 (23)	5 (4)	NS	0.003	0.0003
Mofetil mycophenolate	17 (12)	14 (17)	5 (4)	NS	NS	NS
Rituximab	18 (12)	8 (10)	0 NS	0.0003	0.0026	
Chronic prednisone ≥5 mg/day	67 (46)	23 (28)	2 (2)	0.002	<0.0001	<0.0001
>1immunosuppressor	18 (12)	1 (1)	0 0.001	<0.0001	NS	

NS: not significant; CNS: central nervous system; ACLA: anticardiolipin antibody; GPI, glycoprotein I; LAC: lupus anticoagulant.

All these observations may be relevant in the light of novel treatments, such as belimumab or others, having the potential to reduce the damage accrual in SLE (9, 10). Overall, the concept of a better long-term control of SLE with less glucocorticoids and immunosuppressors is again reinforced.

Key messages

- Cluster analysis is a key step to simplify SLE complexity.
- Chronic glucocorticoids and immunosuppressors affect the long-term outcome of SLE.

G. De Marchi*, *MD*
L. Quartuccio*, *MD, PhD*
F. Zuliani, *MD*
M. Bond, *MD*
S. De Vita, *MD*

**These authors contributed equally to this work.*

Rheumatology Clinic, Department of Medical and Biological Sciences, Azienda Ospedaliero-Universitaria "S. Maria della Misericordia", Udine, Italy.

Address correspondence to:
Prof. Salvatore De Vita, MD,
Rheumatology Clinic, Department of Medical and Biological Sciences, Azienda Ospedaliero-Universitaria "S. Maria della Misericordia", Piazzale Santa Maria della Misericordia 15, 33100 Udine, Italy.
E-mail: salvatore.devita@asuiud.sanita.fvg.it

Competing interests: none declared.

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