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Lupus in the community versus referral centres: Disease phenotype and severity and implications for clinical care and rheumatology training

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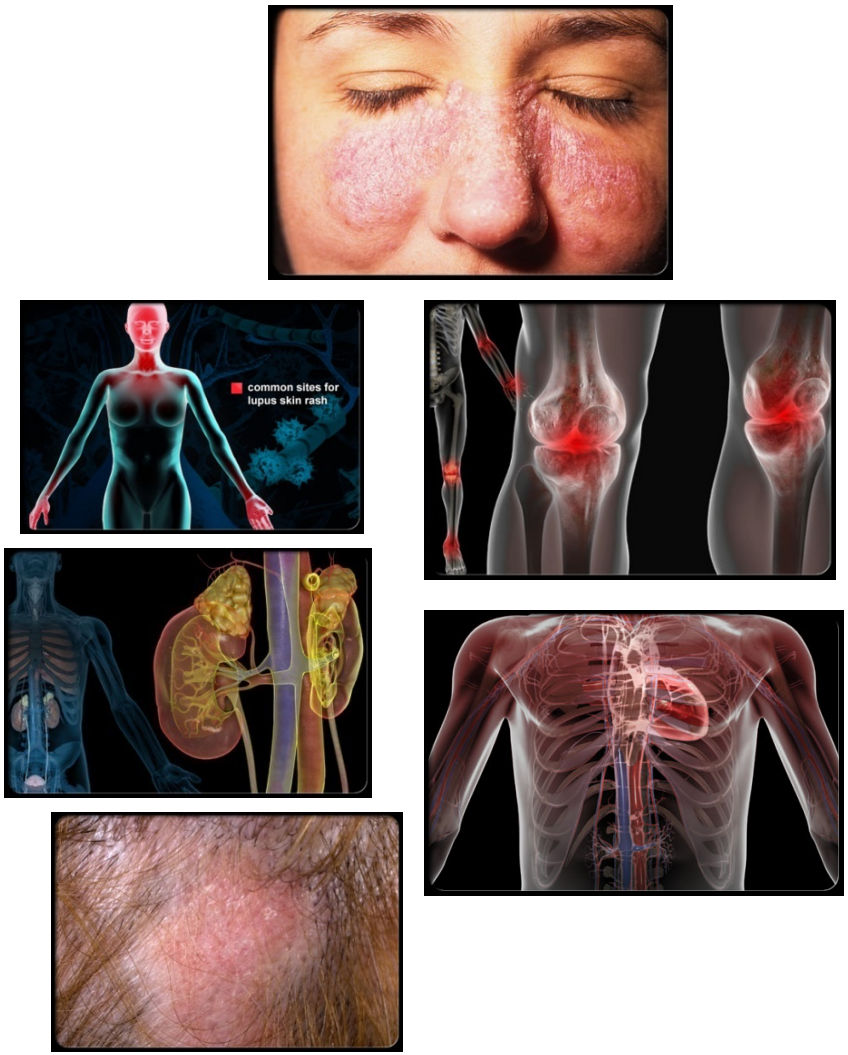
Background

- Systemic lupus erythematosus (SLE) is a *rare* multisystem disease with wide heterogeneity in clinical manifestations and severity
- Most scientific reports originate from **tertiary referral centres** for SLE
- Potential of referral bias for the most severe forms of the disease



Background

- **Greece**:
  - Tertiary referral centres for SLE
  - Non-tertiary centres
  - Extended network of private-based rheumatologists

- Whether the phenotype of SLE across different levels of healthcare is the same, is not clear

Aim of the study

- To assess and quantitate the differences in disease phenotype and severity between lupus in the community versus the disease seen in major centres.

Patients and methods

vs.

"Attikon" SLE cohort (*Athens*)

- **Tertiary referral centre for SLE** (> 10^6 target population)
  - Referrals for lupus nephritis, neuropsychiatric SLE
- *Cross-sectional analysis*
  - Demographics
  - Manifestations
  - Comorbidities
  - Therapies
  - Activity-Damage
- *Longitudinal analysis*
  - Patterns of disease activity over time and damage accrual

"Leto" SLE cohort (*Crete*)

- **Population-based cohort study** (~ $6x10^5$ total population)

Crete

- ✓ *Southernmost Mediterranean island*
- ✓ *0,6 million people*
- ✓ *Isolated geographically*
- ✓ *Stable and genetically homogenous*
- ✓ *Mixed urban-rural*
- ✓ *One single rheumatology referral unit*

Project: Irini Gergianaki – George Bertsias

Case finding of ‘potential’ SLE cases

Multiple sources

Dept of Rheumatology, Clinical Immunology and Allergy
University Hospital of Heraklion
Crete

Capture Recapture analysis

Slide courtesy I. Gergianaki

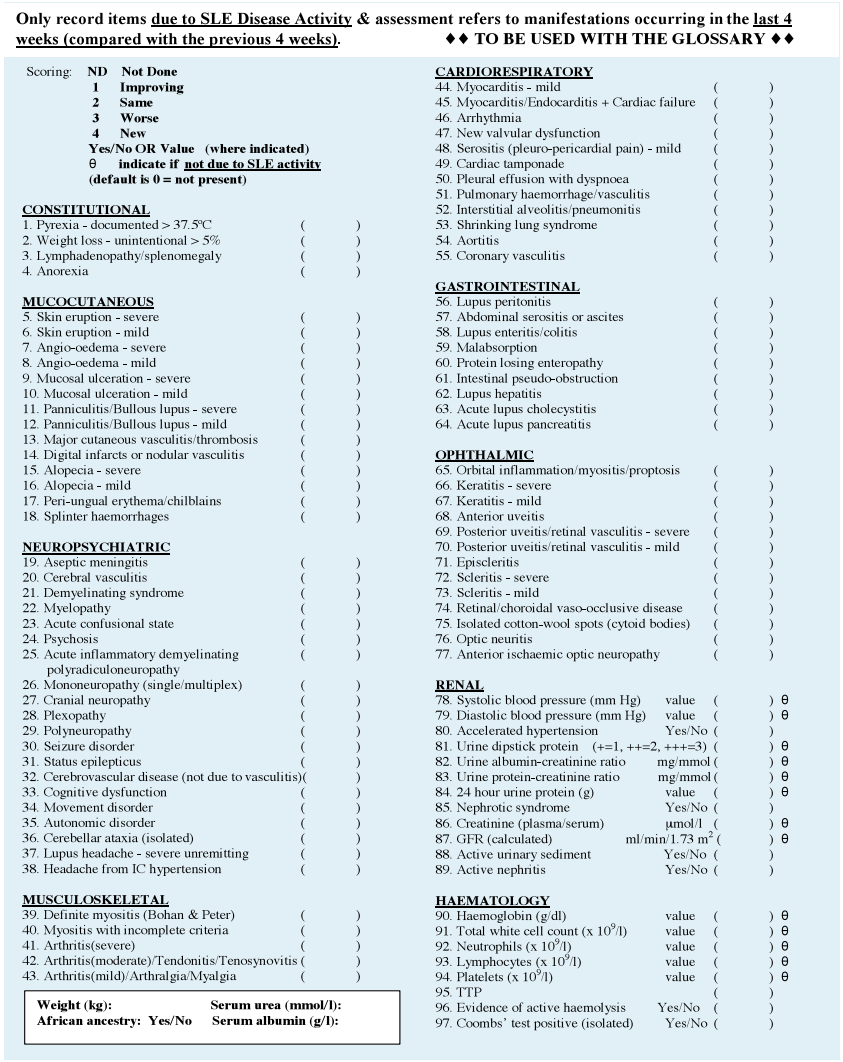
S.Sam Lim et al, Population-based Lupus Registries. Arthritis Rheum 2009 Oct;10(61):1462-66

Categorization of disease severity

- Disease is categorized as
  - **severe**
  - **moderate**
  - **mild**

    based on:

  1. physician assessment
  2. the presence of BILAG group A (severe), B (moderate) or C/D/E (mild) manifestations at any time during the course of the disease.



Only record items due to SLE Disease Activity & assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks). **♦♦ TO BE USED WITH THE GLOSSARY ♦♦**

Scoring: **ND Not Done**
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
θ indicate if not due to SLE activity
(default is 0 = not present)

CONSTITUTIONAL
1. Pyrexia - documented > 37.5ºC ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS
5. Skin eruption - severe ( )
6. Skin eruption - mild ( )
7. Angio-oedema - severe ( )
8. Angio-oedema - mild ( )
9. Mucosal ulceration - severe ( )
10. Mucosal ulceration - mild ( )
11. Panniculitis/Bullous lupus - severe ( )
12. Panniculitis/Bullous lupus - mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia - severe ( )
16. Alopecia - mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL
39. Definite myositis (Bohan & Peter) ( )
40. Myositis with incomplete criteria ( )
41. Arthritis(severe) ( )
42. Arthritis(moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis(mild)/Arthralgia/Myalgia ( )

Weight (kg): **Serum urea (mmol/l):**
African ancestry: Yes/No **Serum albumin (g/l):**

CARDIORESPIRATORY
44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Serositis (pleuro-pericardial pain) - mild ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL
56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC
65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis - severe ( )
67. Keratitis - mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis - severe ( )
70. Posterior uveitis/retinal vasculitis - mild ( )
71. Episcleritis ( )
72. Scleritis - severe ( )
73. Scleritis - mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

RENAL
78. Systolic blood pressure (mm Hg) value ( ) θ
79. Diastolic blood pressure (mm Hg) value ( ) θ
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) θ
82. Urine albumin-creatinine ratio mg/mmol ( ) θ
83. Urine protein-creatinine ratio mg/mmol ( ) θ
84. 24 hour urine protein (g) value ( ) θ
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( ) θ
87. GFR (calculated) ml/min/1.73 m^2 ( ) θ
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

HAEMATOLOGY
90. Haemoglobin (g/dl) value ( ) θ
91. Total white cell count (x 10^9/l) value ( ) θ
92. Neutrophils (x 10^9/l) value ( ) θ
93. Lymphocytes (x 10^9/l) value ( ) θ
94. Platelets (x 10^9/l) value ( ) θ
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

Results

Demographics

vs.

"Attikon" SLE cohort (*Athens*)		"Leto" SLE cohort (*Crete*)
225 (ongoing)	**Number of patients (n)**	**850**
9/1	**Female/Male ratio**	13/1
77/23	**Urban/Rural inhabitance, %**	57/43
38.3 (15.2)	**Age at SLE diagnosis (years), mean (SD)**	43.0 (15.0)
41.5	**Current smoking, %**	30.0
25.3	**Obesity (BMI>30), %**	30.0

Results

Comparison of clinical manifestations

Manifestation, n (%)	"Leto" population cohort	"Attikon" tertiary cohort	*p-value*
Photosensitivity	703 (**85**)	123 (**58**)	**<0.0001**
Malar rash	480 (**58**)	85 (**39**)	**<0.0001**
Discoid rash	99 (**12**)	19 (**9**)	0.61
Mucosal ulcers	394 (**48**)	49 (**23**)	**<0.0001**
Arthritis	753 (**91**)	175 (**81**)	**0.0012**
Serositis	124 (**15**)	45 (**21**)	0.086
Nephritis	104 (**13**)	36 (**17**)	0.149
1ary NPSLE	67 (**8**)	**40 (18)**	**<0.0001**
Haematological	248 (**30**)	**79 (37)**	0.067

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Serology			
Low C3/C4	176 (**21**)	81 (**47**)*	**<0.0001**
Anti-dsDNA (+)	190 (**23**)	69 (**37**)*	**0.0003**
aPL (+)	118 (**14**)	35 (**31**)*	**0.0008**

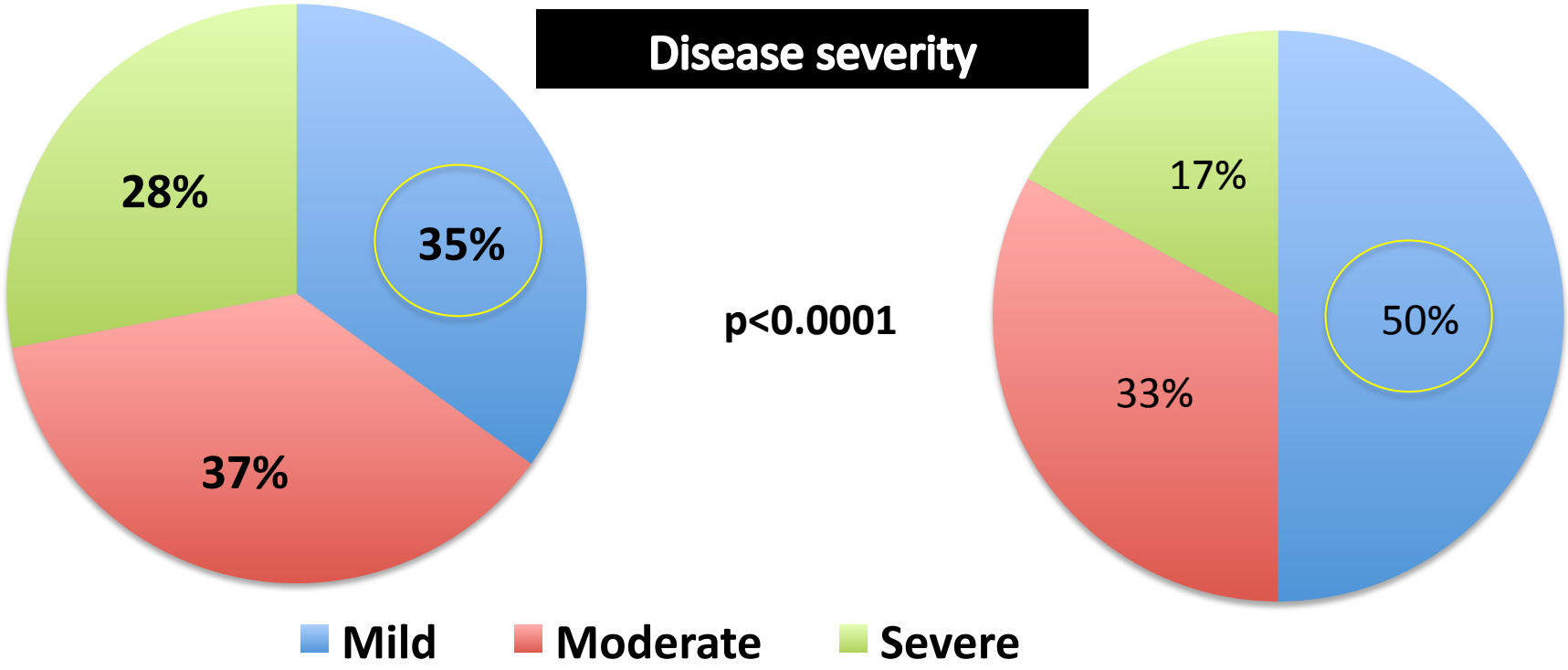
* In pts available, at the time of analysis

Results

Patterns of disease severity

"Attikon" SLE cohort (*Athens*)

"Leto" SLE cohort (*Crete*)



Results

Comparison of damage accrual

Key points

- In a population-based SLE study, SLE patients more frequently had mucocutaneous and musculoskeletal manifestations – severe manifestations were more prevalent in an SLE cohort of a tertiary centre.
- At the community level, clinical phenotype of SLE may encompass milder forms of the disease
  - Underrecognized by tertiary referral centres
  - Lupus nephritis may not be as common as traditionally considered
- Implications for:
  - **Clinical training**: Rheumatology fellows need to recognize milder forms of the disease.
  - **Community**: SLE is not by default a severe or life threatening disease

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