Epidemiology of systemic lupus erythematosus

Guillermo J. Pons-Estel, Manuel F Ugarte-Gil & Graciela S. Alarcón

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Epidemiology of systemic lupus erythematosus

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is a disease distributed worldwide, which occurs in both genders, and across racial/ethnic and age groups; however, higher rates are observed in adults, in women and in non-Caucasians. Genetic, environmental, sociodemographic and methodological issues are responsible not only for these differences but for the variable course and outcome of the disease. Non-Caucasians have a more severe disease with a higher risk for early mortality and damage accrual. Males also have a more severe disease; however, a negative impact of male gender on lupus outcomes has not been firmly established. Childhood-onset is associated with a more severe disease; moreover, it is also associated with higher damage and diminished survival; finally, late-onset lupus is mild but it is associated with higher damage accrual and a diminished survival.

Areas covered: In this review, we discuss the incidence and prevalence of SLE, the impact of age, gender and race/ethnicity in SLE and in the survival of those affected.

Expert commentary: Age, gender and race/ethnicity impact disease expression in SLE patients; despite improvements in survival, mortality in SLE remains almost three times higher than in the general population.

1. Introduction

Systemic lupus erythematosus (SLE) is a complex multisystemic autoimmune disease characterized by a wide spectrum of clinical manifestations, overabundance of immunological and laboratory abnormalities and a variable course and outcome. Epidemiological data available to date derives primarily from descriptive, observational and experimental studies, which have used a set of classification criteria to include patients with similar clinical and laboratory abnormalities. Population-based studies have, for the most part, validated the information from the other studies.

In 1982, the American College of Rheumatology (ACR) developed and validated a set of classification criteria to achieve a consistent definition of SLE for the purpose of both, research and epidemiological surveillance; these criteria were updated, albeit never validated in 1997 [1] and are currently used for case definition [2,3]. In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) group undertook a revision of the ACR criteria with the aim of establishing a more precise and clinical relevant set; in fact, clinical relevance was gained and sensitivity increased but not so specificity when compared with the 1997 revised ACR criteria [4]. While the applicability of this new criteria set is to be defined, different groups have evaluated their performance in classifying real-life patients; these studies have shown that at least the SLICC criteria exhibit similar specificity, better sensitivity and fewer misclassifications than the ACR criteria [5–7]. The SLICC criteria clearly offer some advantages over the ACR criteria as they can classify as lupus patients those with biopsy-proven nephritis in the presence of autoimmunity markers [antinuclear antibodies (ANAs) and/or anti-dsDNA antibodies]. In addition, heightened clinical relevance has been achieved with the inclusion of manifestations such as alopecia and neurological manifestations other than psychosis and seizures. Finally, intangement manifestations have been grouped under acute and chronic cutaneous lupus. In summary, the SLICC classification criteria seem to perform better than the revised 1997 ACR criteria in terms of sensitivity, but at the cost of losing some specificity [8].

2. Lupus worldwide

Using for the most part the ACR criteria (1982 or 1997), the overall incidence rates for SLE have varied from approximately 0.3–23.7 per 100,000 person-years [9,10] whereas prevalence rates have ranged from 6.5 to 178.0 per 100,000. Data for the most salient incidence and prevalence studies are summarized in Table 1. The variations observed in these rates across the world most likely represent differences in patients’ characteristics such as age, gender, ethnic/racial background, socioeconomic status (SES), geographic region and national origin and environmental exposures. However, differences in case
Table 1. Data on systemic lupus erythematosus (SLE) incidence and prevalence around the world.

<table>
<thead>
<tr>
<th>Country/ geographical Area</th>
<th>Case definition (ACR 1982, ACR 1997, or other)</th>
<th>Study type</th>
<th>No. of patients</th>
<th>Ethnic distribution</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Study period</th>
<th>Incidence (cases per 100,000 persons-years) (F/M)</th>
<th>Overall prevalence (cases per 100,000 inhabitants) (F/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Europe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Denmark</td>
<td>Hermansen et al. [14]</td>
<td>ICD-10</td>
<td>1644</td>
<td>All ethnicities</td>
<td>≥18</td>
<td>14%-M</td>
<td>1995–2011</td>
<td>2.3 (4.0/0.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Finland, all regions</td>
<td>Elfving et al. [16]</td>
<td>ACR 1997</td>
<td>566</td>
<td>All ethnicities</td>
<td>≥15</td>
<td>NA</td>
<td>2000–2007</td>
<td>1.7 (2.9/0.5)</td>
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</tr>
<tr>
<td>France, all regions</td>
<td>Arnaud et al. [17].</td>
<td>ICD-10</td>
<td>27,369</td>
<td>All ethnicities</td>
<td>≥15</td>
<td>NA</td>
<td>2010</td>
<td>3.3 (5.5/0.9)</td>
<td>47 (79.1/11.8)</td>
</tr>
<tr>
<td>Germany</td>
<td>Brinks et al. [18]</td>
<td>ICD-10</td>
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<td>All ethnicities</td>
<td>≥15</td>
<td>19.5%-M</td>
<td>2002</td>
<td>NA</td>
<td>36.7 (55.4/15.4)</td>
</tr>
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<td>Germany</td>
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<td>845</td>
<td>All ethnicities</td>
<td>≥15</td>
<td>19.5%-M</td>
<td>2002</td>
<td>NA (1.9/0.9)</td>
<td>NA</td>
</tr>
<tr>
<td>Iceland</td>
<td>Gudmundsson, et al. [21]</td>
<td>ACR 1982</td>
<td>76</td>
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<td>NA</td>
<td>NA</td>
<td>1975–1984</td>
<td>3.3 (5.8/0.8)</td>
<td>35.9 (62.0/7.2)</td>
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<td>Ireland, Northern Italy,</td>
<td>Gourley et al. [22]</td>
<td>NA</td>
<td>415</td>
<td>All</td>
<td>≥18</td>
<td>8.1%-M</td>
<td>1992–1993</td>
<td>NA</td>
<td>25.4 (46.5/4.3)</td>
</tr>
<tr>
<td>Valtrompia</td>
<td>Tsioni1 et al. [25]</td>
<td>ICD-9</td>
<td>201</td>
<td>C</td>
<td>≥16</td>
<td>10.0%-M</td>
<td>1996–2002</td>
<td>2.6</td>
<td>57.9 (100.1/12.0)</td>
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<tr>
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<td>Nossent [26]</td>
<td>ACR 1982</td>
<td>83</td>
<td>C</td>
<td>≥16</td>
<td>12.0%-M</td>
<td>1978–1996</td>
<td>2.6 (4.6/0.6)</td>
<td>44.9</td>
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<tr>
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<td>Nasonov et al. [9]</td>
<td>ACR (NA)</td>
<td>79</td>
<td>C</td>
<td>≥18</td>
<td>2.5%-M</td>
<td>2010</td>
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<td>9 (15.8/0.5)</td>
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<tr>
<td>Sweden, South</td>
<td>Nived et al. [27]</td>
<td>ACR 1982</td>
<td>65</td>
<td>C</td>
<td>NA</td>
<td>NA</td>
<td>1981–1982</td>
<td>4.8 (7.6/2.0)</td>
<td>38.9 (64.8/11.7)</td>
</tr>
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<td>Stahl-Hallengren et al. [28]</td>
<td>ACR</td>
<td>379</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1986–1991</td>
<td>4.1</td>
<td>68.0</td>
</tr>
<tr>
<td>Sweden, South</td>
<td>Jonsson, et al. [29]</td>
<td>NA</td>
<td>39</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1981–1986</td>
<td>4.0 (5.4/1.0)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5939 (Strict)</td>
<td>All ethnicities</td>
<td>13%-M</td>
<td></td>
<td></td>
<td></td>
<td>46 (79/12)</td>
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</table>

(Continued)
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<th>Case definition (ACR 1982, ACR 1997, or other)</th>
<th>Study type</th>
<th>No. of patients</th>
<th>Ethnic distribution</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Study period</th>
<th>Incidence (cases per 100,000 persons-years) (F/M)</th>
<th>Overall prevalence (cases per 100,000 inhabitants) (F/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden, Lund</td>
<td>Ingvarsson et al. [31]</td>
<td>ICD 10</td>
<td>Hospital and clinical records</td>
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<td>All ethnicities</td>
<td>≥15</td>
<td>15%-M</td>
<td>1981–2006</td>
<td>3.9</td>
<td>55</td>
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<tr>
<td>Spain, Lugo</td>
<td>Alonso et al. [32]</td>
<td>ICD-9 ACR 1982</td>
<td>Hospital and clinical records</td>
<td>150</td>
<td>All ethnicities</td>
<td>≥15</td>
<td>15.3%-M</td>
<td>1981–1995</td>
<td>3.6 (5.9/1.1)</td>
<td>17.5 (29.2/5.8)</td>
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<td>Spain, Asturias</td>
<td>Lopez et al. [33]</td>
<td>ICD-9 ACR 1982</td>
<td>Hospital and clinical records</td>
<td>150</td>
<td>All ethnicities</td>
<td>≥15</td>
<td>11.7%-M</td>
<td>1996–2006</td>
<td>2.2 (3.6/0.5)</td>
<td>34.1 (57.9/8.3)</td>
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<td>Turkey, Hava</td>
<td>Cakir et al. et al.</td>
<td>ICD 10</td>
<td>Hospital records</td>
<td>331</td>
<td>All</td>
<td>≥15</td>
<td>7.3%-M</td>
<td>1981–1995</td>
<td>4.4 (8.4/0.6)</td>
<td>51.7 (97.7/7.0)</td>
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<td>Turkey, Thrace</td>
<td>Pamuk et al.</td>
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<td>Hospital records</td>
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<td>All</td>
<td>≥15</td>
<td>0%-M</td>
<td>1981–1982</td>
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<td>UK, England and Wales</td>
<td>Hopkinson et al.</td>
<td>NA</td>
<td>Hospital and clinical records Physicians survey</td>
<td>147</td>
<td>C AC</td>
<td>≥18</td>
<td>6.2%-M</td>
<td>1998–2002</td>
<td>3.8 (6.8/0.5)</td>
<td>27.7 (49.6/3.6)</td>
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<td>UK, Nottingham</td>
<td>Johnson et al.</td>
<td>ACR 1982</td>
<td>Hospital and clinical records Physicians survey</td>
<td>242</td>
<td>C (155) AC (50) AS (36)</td>
<td>≥18</td>
<td>14.0%-M</td>
<td>1999</td>
<td>5.1</td>
<td>64.9</td>
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<td>UK, all countries</td>
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<td>ICD-10 ACR 1982</td>
<td>Clinical practice research datalink</td>
<td>7732</td>
<td>All ethnicities</td>
<td>All</td>
<td>14.0%-M</td>
<td>2010</td>
<td>4.6</td>
<td>97.0</td>
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<td>Nasonov et al. [9]</td>
<td>ACR (NA)</td>
<td>Hospital records</td>
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<td>C</td>
<td>≥18</td>
<td>11.1%-M</td>
<td>1999</td>
<td>5.1</td>
<td>64.9</td>
</tr>
<tr>
<td><strong>North America</strong></td>
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<tr>
<td>USA, California</td>
<td>Fessel [40]</td>
<td>NA</td>
<td>Inpatient and outpatient records Hospitals records</td>
<td>302</td>
<td>NA AA (223) C (79)</td>
<td>All</td>
<td>13.0%-M</td>
<td>1965–1973</td>
<td>7.6</td>
<td>50.8</td>
</tr>
<tr>
<td>USA, Baltimore</td>
<td>Hochberg [41]</td>
<td>ICD-8 ARA 1971</td>
<td>Hospital records</td>
<td>302</td>
<td>AA (223) C (79)</td>
<td>All</td>
<td>13.0%-M</td>
<td>1970–1977</td>
<td>7.6</td>
<td>50.8</td>
</tr>
<tr>
<td>USA, Rochester</td>
<td>Michet et al. [42]</td>
<td>NA</td>
<td>Hospital and clinical records</td>
<td>25</td>
<td>All ethnicities</td>
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<td>NA</td>
<td>1950–1979</td>
<td>1.8 (2.5/0.9)</td>
<td>40 (53.8/19.0)</td>
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<td>USA, Rochester</td>
<td>Uramoto et al. [43]</td>
<td>ACR 1982</td>
<td>Hospital and clinical records</td>
<td>48</td>
<td>Mostly C</td>
<td>All</td>
<td>NA</td>
<td>1980–1992</td>
<td>5.6 (9.4/1.5)</td>
<td>130</td>
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<tr>
<td>USA, Pittsburgh</td>
<td>McCarty et al. [44]</td>
<td>ICD-9 ACR 1982</td>
<td>Hospital and clinical records</td>
<td>191</td>
<td>C, AA, O</td>
<td>All</td>
<td>7.9%-M</td>
<td>1985–1990</td>
<td>2.4</td>
<td>NA</td>
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<tr>
<td>USA, Rural Wisconsin</td>
<td>Naleway et al. [45]</td>
<td>ICD-9 ACR 1982</td>
<td>Hospital and clinical records</td>
<td>117</td>
<td>Mostly C</td>
<td>All</td>
<td>NA</td>
<td>1991–2001</td>
<td>5.1 (8.2/1.9)</td>
<td>78.5 (131.5/24.8)</td>
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<td>USA, Arizona</td>
<td>Balduz et al. [46]</td>
<td>ICD-9 ACR 1982</td>
<td>Hospital and clinical records Population survey</td>
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<td>Mostly H</td>
<td>All</td>
<td>NA</td>
<td>1997</td>
<td>NA</td>
<td>103</td>
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<td>USA, Southeastern Michigan</td>
<td>Somers et al. [47]</td>
<td>ICD-9 ACR 1997 SNOMED US renal data system</td>
<td>Hospital and clinical records Medicaid claims Medicare claims</td>
<td>2139</td>
<td>AA (1219) C (820) H (39)</td>
<td>All</td>
<td>8.5%-M</td>
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<td>5.6 (9.3/1.6)</td>
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<tr>
<td>USA, Olmsted County, Minnesota</td>
<td>Ungprasert et al. [49]</td>
<td>ICD-9 ACR 1997 SLICC</td>
<td>Hospital and clinical records</td>
<td>44 (ACR) 58 (SLICC)</td>
<td>84% C 7% AA 5% AS 2% AI</td>
<td>≥18</td>
<td>NA</td>
<td>1993–2005</td>
<td>ACR 3.7</td>
<td>SLICC 4.9</td>
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<th>Country/geographical Area</th>
<th>Authors [reference]</th>
<th>Case definition (ACR 1982, ACR 1997, or other)</th>
<th>Study type</th>
<th>No. of patients</th>
<th>Ethnic distribution</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Study period</th>
<th>Incidence (cases per 100,000 persons-years) (F/M)</th>
<th>Overall prevalence (cases per 100,000 inhabitants) (F/M)</th>
</tr>
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<tbody>
<tr>
<td>USA, Alaska, Phoenix and Oklahoma</td>
<td>Ferucci et al. [50]</td>
<td>ICD-9 ACR 1997</td>
<td>Indian health service national data warehouse</td>
<td>285</td>
<td>AI (155) AN (130)</td>
<td>18-65</td>
<td>M</td>
<td>2007-2009</td>
<td>7.4 (40.4/-)</td>
<td>178 (271/54)</td>
</tr>
<tr>
<td>USA, 47 States and Washington DC</td>
<td>Feldman et al. [10]</td>
<td>ICD-9</td>
<td>Medicaid analytic extract</td>
<td>34,339</td>
<td>AA (13,236) H (4,767) A (1,452) NA (515) C (12,436)</td>
<td>2000-2004</td>
<td>23.7 (30.5/4.9)</td>
<td>143.7 (192.2/31.8)</td>
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<tr>
<td>USA, Georgia</td>
<td>Lim et al. [149]</td>
<td>ICD-9</td>
<td>Hospital and clinical records</td>
<td>1320</td>
<td>AA p (889) C p (251)</td>
<td>2002-2004</td>
<td>5.6 (9.4/1.7)</td>
<td>74.4 (131.3/14.9)</td>
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<td>Peschken et al. [53]</td>
<td>ACR 1997</td>
<td>Regional arthritis center database</td>
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<td>NA</td>
<td>1993-2002</td>
<td>18.3-25.7</td>
<td>42.3</td>
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<tr>
<td>USA, Georgia</td>
<td>Barnabe et al. [54]</td>
<td>ICD-9</td>
<td>Hospital and clinical records</td>
<td>226</td>
<td>AC (98%)</td>
<td>2000-2010</td>
<td>2.9-25.5</td>
<td>12-90</td>
<td>32.8 (44.7 regression model)</td>
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</tr>
<tr>
<td>Canada, Nova Scotia</td>
<td>Hanly et al. [56]</td>
<td>ICD-9</td>
<td>Quebec health insurance board Hospital and clinical records</td>
<td>2455</td>
<td>NA</td>
<td>1989-2003</td>
<td>3.0</td>
<td>70 (90/40)</td>
<td>70</td>
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<td>Mexico, Southeastern Central America and Caribbean Island</td>
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<td>ACR 1997</td>
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<td>12-90</td>
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<td>AC</td>
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<td>South America</td>
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<td>ACR 1997</td>
<td>Hospital records</td>
<td>75</td>
<td>C (75)</td>
<td>1998-2008</td>
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<td>Brazil, Minas Gerais</td>
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<td>ACR 1997</td>
<td>Hospital records</td>
<td>3</td>
<td>All</td>
<td>2004</td>
<td>NA</td>
<td>98 (110/90)</td>
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<td>ACR 1997</td>
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<td>43</td>
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<td>ACR 1997</td>
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<td>3</td>
<td>All</td>
<td>2011</td>
<td>NA</td>
<td>70</td>
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<tr>
<td>Venezuela, Monagas</td>
<td>Granados et al. [67]</td>
<td>ACR 1997</td>
<td>Hospital and clinical records</td>
<td>1</td>
<td>NA</td>
<td>2011</td>
<td>NA</td>
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(Continued)
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<th>Country/geographical Area</th>
<th>Authors [reference]</th>
<th>Case definition (ACR 1982, ACR 1997, or other)</th>
<th>Study type</th>
<th>No. of patients</th>
<th>Ethnic distribution</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Study period</th>
<th>Incidence (cases per 100,000 person-years) (F/M)</th>
<th>Overall prevalence (cases per 100,000 inhabitants) (F/M)</th>
</tr>
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<tbody>
<tr>
<td>Asia</td>
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<td>Asian-Pacific region</td>
<td>Jakes et al. [68]</td>
<td>ACR 1997</td>
<td>Systematic review</td>
<td>NA</td>
<td>All ethnicities</td>
<td>All</td>
<td>NA</td>
<td>1973–2006</td>
<td>0.9–3.1 (1.4–5.4/0.4–0.8)</td>
<td>4.3–45.3 (7.7–68.4/0.8–7.0)</td>
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<td>China, Anhui</td>
<td>Zou et al. [69]</td>
<td>ACR 1997</td>
<td>Patient evaluation</td>
<td>471</td>
<td>AS</td>
<td>All</td>
<td>8.7%-M</td>
<td>2009–2010</td>
<td>NA</td>
<td>37.6 (70.3/6.4)</td>
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<tr>
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<td>Mok et al. [70]</td>
<td>ACR 1992</td>
<td>Hospital records</td>
<td>442</td>
<td>AS</td>
<td>All</td>
<td>9%-M</td>
<td>2000–2006</td>
<td>3.1 (5.4/0.8)</td>
<td></td>
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<tr>
<td>Iran, Zahedan, Sanandaj</td>
<td>Davatchi et al. [71]</td>
<td>NA</td>
<td>COPCORD</td>
<td>NA</td>
<td>All</td>
<td>≥15</td>
<td>NA</td>
<td>2004–2012</td>
<td>NA</td>
<td>60</td>
</tr>
<tr>
<td>Iran, Tehran</td>
<td>Davatchi et al. [72]</td>
<td>NA</td>
<td>COPCORD</td>
<td>3</td>
<td>All</td>
<td>≥15</td>
<td>0%-M</td>
<td>2004–2005</td>
<td>NA</td>
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<td>Moghimi et al. [73]</td>
<td>NA</td>
<td>COPCORD</td>
<td>NA</td>
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<td>≥15</td>
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<td>2011–2012</td>
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<td>Japan, Okinawa</td>
<td>Iseki et al. [74]</td>
<td>NA</td>
<td>Hospital records</td>
<td>566</td>
<td>AS</td>
<td>NA</td>
<td>9%-M</td>
<td>1972–1991</td>
<td>0.9–2.8 (1.4–4.7/0.4–0.8)</td>
<td>4.3–37.7 (7.7–68.4/0.8–7.0)</td>
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<td>Japan</td>
<td>Kameda [75]</td>
<td>NA</td>
<td>Hospital records</td>
<td>108</td>
<td>AS</td>
<td>NA</td>
<td>NA</td>
<td>1975–1977</td>
<td>1.0</td>
<td>10.8</td>
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<tr>
<td>Kazakhstan</td>
<td>Nasonov et al. [8]</td>
<td>ACR (NA)</td>
<td>Hospital records</td>
<td>52</td>
<td>5 C</td>
<td>≥18</td>
<td>3.8%-M</td>
<td>2010</td>
<td>1.6</td>
<td>20.6</td>
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<tr>
<td>Malaysia, Kuala Lumpur</td>
<td>Wank et al. [76]</td>
<td>ACR 1982</td>
<td>Hospital records</td>
<td>539</td>
<td>AS</td>
<td>All</td>
<td>7%-M</td>
<td>1974–1990</td>
<td>NA</td>
<td>43</td>
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<td>Saudi Arabia, Al-Qaseem</td>
<td>Al-Arfaj et al. [77]</td>
<td>ACR</td>
<td>Community survey</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1992</td>
<td>NA</td>
<td>19.3</td>
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<tr>
<td>South Korea</td>
<td>Ju et al. [78]</td>
<td>ICD-10</td>
<td>Health insurance review</td>
<td>9,000–11,000</td>
<td>All</td>
<td>All</td>
<td>NA</td>
<td>2004–2006</td>
<td>NA</td>
<td>18.8–21.7</td>
</tr>
<tr>
<td>United Arab Emirates, Al</td>
<td>Dhanhani et al. [79]</td>
<td>ICD-9</td>
<td>Hospital records</td>
<td>16</td>
<td>All</td>
<td>NA</td>
<td>18.8%-M-M</td>
<td>2009–2012</td>
<td>8.6 (14.1/3.2)</td>
<td>103 (188.5/20.3)</td>
</tr>
<tr>
<td>Ain region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Australia</td>
<td>Anstey et al. [80]</td>
<td>NA</td>
<td>Hospital records</td>
<td>22</td>
<td>Aborigines</td>
<td>NA</td>
<td>NA</td>
<td>1984–1991</td>
<td>11</td>
<td>52.6 (100.0/5.25)</td>
</tr>
<tr>
<td>Australia</td>
<td>Bossingham [81]</td>
<td>ACR1982</td>
<td>Hospital records</td>
<td>180</td>
<td>Aborigines (26)</td>
<td>All</td>
<td>9.3%-M</td>
<td>1996–1998</td>
<td>NA</td>
<td>45.3 (overall) 92.8 (Aborigines)</td>
</tr>
</tbody>
</table>

ascertainment (self-reported, physician diagnosed, inclusion of serologic tests), study type and time at which the study was conducted may also explain these differences.

Childhood SLE incidence and prevalence rates are considerably lower than adult rates. The annual incidence rate of SLE in children (<16 years) has been reported to be less than 1 per 100,000 persons in studies from Europe and North America [82]. In China, the prevalence of childhood SLE was estimated as 6.3 per 100,000 [83]. Nationwide Medicaid claims data from adult SLE patients reveal the following incidence and prevalence rates by age group (18–29, 30–49, and 50–64) 14.3/27.9/29.7 and 78.9/200.3/292.4 per 100,000 inhabitants, respectively [10].

It is widely known that SLE is much more common in women than in men with a ratio close to 9:1. In the aforementioned Medicaid study the incidence and prevalence of SLE was six times higher in women (30.5 and 192.2, respectively) than in men (4.9 and 31.8, respectively) [10]. Marked differences in incidence and prevalence SLE rates according to ethnic group have been observed. Overall, non-Caucasians experience higher rates than Caucasians. This was nicely illustrated in a population base study performed in the Metropolitan Districts of Birmingham and Solihull, England [38] in 1992. In this study, the overall incidence and prevalence rates were 11.9 and 111.8 for Afro-Caribbeans, 11.5 and 46.7 for Asians and 2.5 and 20.7 for Caucasians [38]. Whereas SES does not appear to impact the incident of SLE, Feldman et al. found that patients with low SES exhibited the highest prevalence rate (167.9 per 100,000) in the Medicaid study [10]. This may suggest that in additional to genetics, occupational (particularly to silica dust), environmental (exposures hazardous wastes and air pollution) and psychosocial stress that are more common in low SES neighborhoods may be responsible for the higher prevalence of SLE in this group of patients.

Several environmental factors may influence SLE occurrence; in a population-based study performed in general residents in rural areas of China, multiple environmental factors, including birth conditions, sweet food, cooking oil, fruit consumption, sunlight exposure, quality of sleep, physical activities, drinking water, residence, negative life events, hepatitis B vaccine, age of menarche, and age at birth of first child were found to affect SLE rates [69].

SLE has been described worldwide, however, it seems to be infrequent in the African continent but surprisingly common in African descendants (Afro-Caribbean, African-American and Afro-Latin-American) around the world. A possible explanation comes from the ‘prevalence gradient’ hypothesis, which suggest that Africans descendants present a genetic background and environmental exposures that are different than in their native countries and predispose them to present higher SLE incidence rates; in turn, African patients living in their native countries may experience competing causes of death which may diminish the incidence of SLE; furthermore, prevalence is affected by reduced survival for patients inadequately treated [84]. It should also be stressed that there are no good quality prevalence data published from West Africa, assumptions are usually made from a United Kingdom study of immigrant women which revealed a SLE prevalence three-times higher among them than in Caucasian but not as high as in patients of Afro-Caribbean origin [85].

It is important to clarify that most of the previous studies differ in their recruitment methodology. While some only use inpatient and outpatient medical records based on the ACR criteria [38] others use international classification of disease (ICD) codes, drugs prescriptions and cause of death registries leading to important variability in SLE prevalence and incident rates [30]. Variations on prevalence rates as a function of the definition used can be appreciated in a Swedish population-based study were the overall prevalence of SLE ranged from 46 and 85 per 100,000 inhabitants depending on the strictness of the case definition used [30]. Similarly, differences can be observed as a function of the criteria used; for example, Ungprasert et al. established that the adjusted incidence in patients living in Olmsted County, Minnesota, was statistically higher using the SLICC than the ACR criteria (4.9 vs. 3.7 per 100,000 person-years, p = 0.004) [49].

Some temporal variation in the incidence and prevalence of SLE has been observed. Uramoto et al. demonstrated in a US population-based study, that SLE has more than tripled over the past 40 years [43]. This increase likely reflects not only an actual increase in disease occurrence but a more accurate ascertainment of cases, the inclusion of milder cases of SLE and the widespread use of antinuclear antibody testing. In contrast to this study, a recent retrospective cohort study utilizing a UK clinical practice research datalink shows a decline in the annual SLE incidence of 1.8% while in contrast the prevalence increase from 64.9 per 100,000 in 1999 to 97.04 in 2012 [39].

The prevalence estimates increased with time during the 1990s. This was suggested to be due to recording a relapsing-remitting disease within a longitudinal database, rather than an actual increase in prevalence [86]. However, one of the incidence studies found a small but non-significant increase in the incidence of SLE in females over time and studies in other European countries have found an increased temporal trend [11,20].

3. Factors that affect the course of SLE

3.1. Impact of age

Age is one of the major factors affecting the clinical manifestations and prognosis of SLE patients. SLE may develop at any age, although its peak incidence occurs during the reproductive age years; in the majority of adult and pediatric cohorts the mean age at diagnosis has varied from 24 to 32 and 12 to 17 years, respectively [87,88].

There is no consensus regarding the appropriate cut off age defining ‘pediatric’ or ‘childhood onset lupus’, with most studies using either 16 or 18 years. Childhood onset lupus (cSLE) represents 10–20% of all SLE cases. As with adults, Caucasian children experience lower SLE incidence and prevalence rates and milder disease, characterized predominantly by malar rash, thrombocytopenia, and a low incidence of renal disease than non-Caucasian children [89].

Clinical manifestations of adult and cSLE are identical, although children, overall, experience a higher frequency of
renal, neurologic and hematologic involvement than their adult counterparts. Renal involvement can be present in 81% of children compared with 46% of adults [90] and is often a presenting feature occurring within 2 years from disease onset in 90% of the patients; histological class distribution of lupus nephritis in children is similar than in adults [91].

cSLE patients show more pronounced disease activity than adults as reported by Ramirez-Gómez et al. in a study comparing Latin American SLE inception cohorts of children (N = 230) and adults (N = 948); the median SLE Disease Activity Index was 13 [interquartile range 8–19] in cSLE and 11 [interquartile range 7–17] in adults and the difference was statistically significant (p < 0.01) [92]. The most pronounced differences in disease activity between adult SLE and cSLE pertain to the renal and neurologic organ systems [93]. Control of disease activity is likely to result in a greater requirement of oral corticosteroids (over 90%), intravenous methylprednisolone and immunosuppressive medications [90,91]. Disease activity and exposure to corticosteroids at high doses and for longer time than in adults contribute to greater damage accrual in cSLE. Brunner et al. compared Canadian children and adult SLE inception cohorts, demonstrating significantly higher mean SLICC damage index scores (SDIs) in the children (1.7 vs. 0.76; p = 0.008). The observed frequency of overall damage in cSLE fluctuates between 39% and 65%, with mean SDI scores of 0.6–2.3 after a median follow-up of 4.1–6.8 years. The most frequently affected organ systems in cSLE are the musculoskeletal, renal, ocular and neuropsychiatric systems [90,91,94].

The 5-year survival rates in juvenile SLE patients in the Western world are now 94–100%; however, the 10-year survival rate remains disappointing at only 81–92% in juvenile SLE [95,96] with lower rates (65%) in Asian patients with associated renal involvement [97]. Moreover, juvenile SLE continues to carry a higher mortality risk than adult SLE which is even evident in adolescents compared to adults as reported in the LUMINA cohort [90].

On the contrary, late-onset lupus (age 50 years and above) tends to have a more insidious onset, the very first manifestations being non-specific (arthralgias, weakness, fatigue, myalgias, weight loss, pyrexia, or loss of cognitive function). Major organ system involvement (renal and neuropsychiatric) is less frequent, lower degrees of disease activity are observed, yet these patients tend to have a poor outcome, in terms of both damage accrual and mortality [98].

3.2. Impact of gender

Lupus is more frequent in females than males, in particular in females of child-bearing age, with a female: male ratio of 8–15:1 [99]. In pre-puberal and late-onset lupus the ratio is 2–8:1 [99]. The SLE clinical phenotype differs some between females and males; males present less frequently arthritis/arthralgia [100–107] although there are some exceptions (among Turkish patients, arthritis was found to be more frequent in male patients [108], photosensitivity [102,104,106–109], malar rash [101,104,107,110], oral ulcers [104,107,110,111], alopecia [102–106,108,112] and Raynaud's phenomenon [102–108,110]; in turn, they present more frequently discoid lesions [101,105,110], subacute cutaneous lesions [101], serositis [107–110,112], renal disease [102–104,106,107,109,113], fever [106], weight loss [106], myositis [102], lymphopenia [104,107,113], and hemolytic anemia [106] whereas the data for hematological and central nervous system manifestations are still controversial [100,103,104,107,110,112,113]. Regarding flares, they were found to be less frequent in males in a study from China [105]. As to serological features, a lower prevalence of anti-Ro [100,105,107,110] and anti-La [107], and a higher prevalence of anti-Smith [104], antisDNA [104,107], Coombs positivity [104], and hypocomplementemia [104,106] have been reported in male SLE patients.

In addition, male patients present a higher frequency of thrombosis [102,104,107], including antiphospholipid antibodies [104,106,107,114], antiphospholipid syndrome [102] and hypertension [104,106,109]; there is, however, some controversial data about a lower frequency of IgM anticardiolipin was found in male patients from the United Kingdom [111].

In addition, as male SLE patients present a higher frequency of kidney involvement, hypertension is not uncommon among them which also conveys a worse prognosis; thus, it would be expected that male patients would present an increased risk of damage and earlier mortality. In fact, in the LUMINA study [114] an association between male gender and early damage occurrence was found; however, that has not been the case for studies emanating from Latin America [106], Greece [110], and China [105]. In the Hopkins Lupus cohort [104], an association between male gender and some SDI components like seizures, myocardial infarction, angina, thrombosis, and kidney involvement was found. Furthermore, kidney damage [105] and cardiovascular involvement were found to be associated with male gender in studies from Asia and Latin America [106]. In terms of mortality, the data are still controversial; in favor of a higher mortality in males are studies from the Hopkins [104], Duke's [115], Germany and Toronto cohorts, and the Carolina Lupus Study [116]. However, data from the United Kingdom [111] and Latin America [106,117] have not confirmed this finding. Whether the phenotypic differences in SLE as a function of gender are due to differences in the genetic load is controversial [118,119].

3.3. Impact of race/ethnicity

Ethnicity is a biological and social construct, including not only genetic ancestry, but also cultural characteristics (language, religion, values, social behaviors, country of origin) yet it is an arbitrary definition [120]. Race is oftentimes used interchangeable with ethnicity but it mainly refers to the biological features of groups of people. Given that there are differences in the clinical characteristics and prognosis among different populations, it is worth evaluating the impact of race/ethnicity in SLE. Genetic ancestry influences the risk for the incidence of SLE; for example, Amerindian ancestry is associated with an increased number of risk alleles for SLE [121], and also with an early age at onset [122], Amerindian and African ancestry are associated with a higher risk for kidney involvement [122,123] and European ancestry with a lower risk [124]. Among
European descendants, Southern Europeans present a higher risk of renal involvement and autoantibody production but with a lower risk of discoid rash and photosensitivity; serositis and autoantibody production is associated with Western European background, compared to Eastern European; finally, Ashkenazi Jewish seem to be protected from the occurrence of neurologic manifestations [125].

Phenotypic differences in SLE between Caucasians and non-Caucasian are depicted in Table 2. In addition, general manifestations are less frequent in Asian patients and Aboriginals from Canada than African descendants [126]. Fever is also less frequent in Mestizo than in African descendants [127]. Cutaneous vasculitis and mononeuritis multiplex are more frequent in Aboriginals from Canada [126]. Asians from Canada have a lower frequency of arthritis and serositis than patients from the other ethnic groups (Caucasians, African descendants, and Canadian Aboriginals) [126]. Seizures occur more frequently in African descendants and tend to be more frequent in Hispanics than in Caucasians; they seem to be less frequent in Asians [128].

Kidney involvement is one of the most worrisome manifestations of SLE, and it is more frequent in Hispanics, Mestizos, African descendants, and Asians [126,127,184,185]; Hispanics and African descendants are also at higher risk of developing end-stage renal disease than Caucasians [186]. Furthermore, response to treatment in lupus nephritis is not uniform across different ethnic groups; for example, in the entire population of the Aspreva Lupus Management Study, mycophenolate and cyclophosphamide groups had similar rates of response, but, Hispanic patients have better rate of response to mycophenolate mofetil than to cyclophosphamide [187].

Hispanics and African descendants experience higher levels of disease activity as compared to Caucasians [188]; furthermore, after disease onset, disease activity declines slowly in Hispanics, followed by African descendants while in Caucasians it declines faster [189]. In addition, non-Caucasians (Hispanics, Asians, and African descendants) experience damage accrual more frequently and of higher magnitude [190–193]. However, this was not bore down in Asians from the SLICC cohort who experience new damage less frequently than European Caucasians [193]. In relation to the pattern of damage, renal damage occurs more frequently in Hispanics, African descendants, and Asians than in Caucasians [184,191,192,194]; integument and diabetes in African descendants [184,190,192], ocular in Hispanics and Caucasians [184]; gastrointestinal and malignancy in Caucasians [184] whereas ocular and cardiovascular damage occur less frequently in Asians, compared to Caucasians [194]. However, socioeconomic factors like health insurance [127,195], education level [127,192], poverty [190,192], helplessness [195] and abnormal illness behaviors [192,195] also impact on damage accrual and could explain, at least in part, the impact of ethnicity on this intermediate outcome.

As to mortality, several cohort studies have reported higher mortality rates among African descendants and Hispanics compared to Caucasians; however, when socioeconomic factors are factored into the analyses, ethnic group is no longer significant [115,171,196]; the exception being the Duke’s cohort in which the rates were still higher in the non-Caucasians after adjusting for SES [197]. In contrast, Asian patients from the Toronto cohort [198] has a similar survival rate than the rest of the members of the cohort (Caucasian, by and large); furthermore, SLE patients from Hong Kong [159] had a survival rate at 5 years of 93% which is similar to the rates observed in Caucasians worldwide. Within ethnic groups there are also some difference; for example, the African descendant Gullah patients from the Sea Islands region of South Carolina, USA have a higher frequency of malar rash and photosensitivity and lower frequency of hematologic involvement than African descendant patients from the PROFILE cohort and the Lupus Multiplex Registry and Repository study [199]. In addition, Hispanics, as defined in the United States (descendants from a Spanish speaking-country) are a heterogeneous group; not surprisingly, therefore, those from Texas (with a large Amerindian ancestral background) have a more severe disease than Hispanics from Puerto Rico, including higher disease activity, more damage accrual, more frequent renal involvement, psychosis and thrombocytopenia but less frequent cutaneous involvement [200]. These data taken together, suggest that even current racial/ethnic group classification is rudimentary to completely explain the differences in the expression and outcome of the disease among populations.

### 3.4. Mortality and survival in SLE

The survival of SLE patients has been improving over the past 60 years with an increase of the five-year survival from around 50% in the 1950s to around 95% in the 2000s [201]. Survival rates for different cohorts are depicted in Table 3. This obvious improvement may relate not only to better management of the disease itself and its associated comorbidities but also to an earlier diagnosis. Noteworthy, however is that the standardized mortality ratio (SMR) for SLE is 2.6–3.0 times higher than in the general population; this is probably related to higher rates of cardiovascular (SMR = 2.3) and renal disease (SMR = 4.7) and of infections (SMR = 5.0) [202,203]. The SMR is even higher in cSLE (18.8) although a breakdown for cardiovascular, renal, and infections causes is not available [204]. A bimodal pattern of mortality has been recognized in SLE since the mid-1970s with patients who die early in the course of the disease do so due to active disease and/or infections while those who die late in the course of the disease do so secondary to cardiovascular disease and oftentimes they have an inactive disease at the time of their death [133].

Several factors have been associated with a higher mortality as already discussed like age at diagnosis, gender, ethnicity, and SES factors.

As to disease-related factors, higher levels of disease activity at diagnosis [152,210,211] and over time [212–217] and the presence of damage, particularly renal, have been associated with increased mortality [127,163,170,211,216–220]. The presence of hematologic disorders [170] (including thrombocytopenia [142,152,159], hemolytic anemia [155,171]), neurological [221], psychiatric [107], pulmonary [107,152] and renal [107,116,152,155,163,166–168] involvement, the antiphospholipid syndrome and of comorbidities including coronary artery
Table 2. Cumulative probability of survival in patients with systemic lupus erythematosus (1955–2016)*.

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
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<th>Ethnic group (%)</th>
<th>Survival (%)</th>
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</thead>
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<td></td>
<td></td>
<td>C</td>
<td>Af</td>
</tr>
<tr>
<td>1955–1964</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merrel and Shulman [129]</td>
<td>USA</td>
<td>99</td>
<td>73</td>
<td>27</td>
</tr>
<tr>
<td>Kellum and Hasenick [130]</td>
<td>USA</td>
<td>299</td>
<td>ND</td>
<td>1964</td>
</tr>
<tr>
<td>1965–1974</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estes and Christian [131]</td>
<td>USA</td>
<td>150</td>
<td>ND</td>
<td>1971</td>
</tr>
<tr>
<td>Jessop and Meyers [132]</td>
<td>South Africa</td>
<td>ND</td>
<td>1973</td>
<td>66</td>
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<td>1975–1984</td>
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<tr>
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<td>Canada</td>
<td>81</td>
<td>ND</td>
<td>1976</td>
</tr>
<tr>
<td>Feinglass et al. [134]</td>
<td>USA</td>
<td>140</td>
<td>ND</td>
<td>1976</td>
</tr>
<tr>
<td>Urman and Rothschild [135]</td>
<td>USA (NYC)</td>
<td>209</td>
<td>ND</td>
<td>1977</td>
</tr>
<tr>
<td>Urman and Rothschild [135]</td>
<td>USA (Connecticut)</td>
<td>156</td>
<td>ND</td>
<td>1977</td>
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<td>Lee et al. [136]</td>
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<td>110</td>
<td>95</td>
<td>4</td>
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<td>Ginzer et al. [137]</td>
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<td>1103</td>
<td>58</td>
<td>32</td>
</tr>
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<td>Feng et al. [138]</td>
<td>Singapore</td>
<td>183</td>
<td>100</td>
<td>1982</td>
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<td>1985–1994</td>
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<td>Malaviya et al. [139]</td>
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<td>181</td>
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<td>1987</td>
</tr>
<tr>
<td>Wallace et al. [140]</td>
<td>USA</td>
<td>609</td>
<td>ND</td>
<td>1989</td>
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<td>Swaeck et al. [141]</td>
<td>Netherlands</td>
<td>110</td>
<td>ND</td>
<td>1989</td>
</tr>
<tr>
<td>Reveille et al. [142]</td>
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N: population; C: Caucasian; Af: African descendant; H: Hispanic; As: Asian; O: other; pub date: publication date; 5-y: 5-year survival; 10-y: 10-year survival; 15-y: 15-year survival; 20-y: 20-year survival.

*Most of the data presented were not derived from inception cohorts; thus, a survival effect bias cannot be ruled out.

bFour years.

From first symptom.
The overall incidence rates of SLE vary from approximately 0.3 to 23.7 per 100,000 person-years whereas prevalence rates range from 6.5 to 178.0 per 100,000. There are, however, temporal, racial/ethnic and gender differences.

The clinical manifestations of adult and children with SLE differ. Younger age at disease onset could be due to a higher genetic load for SLE; thus, younger patients are expected to have a more active disease. Older age on the other hand is associated with less severe disease, yet older SLE patients accrue more damage and experience higher mortality rates. SLE is more frequent in females but male patients tend to have more severe disease manifestations and consequently higher levels of disease activity.

Mortality in SLE has dramatically improved over the years, yet lupus patients have a SMR three times higher than the general population. It is expected that with new and safer treatment strategies, disease manifestations will be better controlled, damage accrual less prominent and that survival rates in SLE will continue to improve.

4. Conclusions

Remarkable disparities worldwide are seen in the incidence and prevalence of SLE. Genetic, environmental, sociodemographic and methodological issues are responsible for the variations observed.

CSLE is a more active disease process than the one in adults with increased predominance of hematological, immunological and renal manifestations and more damage accrual over time (particularly renal). An increase use of corticosteroids (longer time, higher doses) and of immunosuppressive drugs in these patients derives in a higher burden of drug toxicity.

Male SLE patients have severe involvement like lupus nephritis more frequently; conversely, they present cutaneous manifestations and other features such as a milder disease less frequently. However, the association between gender and damage accrual and mortality is not universally accepted.

Non-Caucasian patients tend to be younger at disease onset; they also have an increased risk of severe organ involvement and of damage accrual than Caucasians. Increased mortality rates in non-Caucasian SLE patients seem to be related primarily to SES factors.

Survival in SLE has improved steadily over the past 60 years. Older and younger age at diagnosis, lower SES and lower educational level, and more severe disease, damage included, are associated with higher mortality rates. Comorbidities, including the antiphospholipid syndrome and cardiovascular disease are also associated with higher mortality rates in lupus. Immunosuppressive drugs and high doses of glucocorticoids are associated with higher mortality rates while the use of antimalarials prolongs survival in these patients.

5. Expert commentary

Differences in SLE epidemiology across different populations are multifactorial in origin, with some explanatory variables yet to be discovered. Further genetic and epigenetic SLE studies may shed some light into this. For example, it would be expected that identical SLE twins who are reared apart may experience differences in the expression of their disease which may be explained by different environmental factors. The impact of ethnicity in SLE could be also explained also by genetic and environmental factors; for example, non-Caucasians, by and large, have a lower SES than Caucasian which may be linked to increased rate of infections, and differential access to adequate healthcare.

Younger age at disease onset could be due to a higher genetic load for SLE; thus, younger patients are expected to have a more active disease. Older age on the other hand is associated with less severe disease, yet older SLE patients accrue more damage and experience higher mortality rates. SLE is more frequent in females but male patients tend to have more severe disease manifestations and consequently higher levels of disease activity.

Mortality in SLE has dramatically improved over the years, yet lupus patients have a SMR three times higher than the general population. It is expected that with new and safer treatment strategies, disease manifestations will be better controlled, damage accrual less prominent and that survival rates in SLE will continue to improve.

6. Five years view

In five years, there will be more information about genetic and epigenetic factors associated with the development of SLE and its patterns of disease expression. It is expected that some of these epigenetic factors would be modifiable which will result in reduced damage and mortality.

And, with safer medications, and new treatment strategies, like treat-to-target, damage accrual will decrease and survival will improve. Validation of definitions of possible treatment targets like remission and low disease activity state should be completed worldwide over the next few years.

Key issues

- The overall incidence rates of SLE vary from approximately 0.3 to 23.7 per 100,000 person-years whereas prevalence rates range from 6.5 to 178.0 per 100,000. There are, however, temporal, racial/ethnic and gender differences.
- Childhood onset lupus represents 10–20% of all SLE cases.
- The clinical manifestations of adult and children with SLE are the same; however, children overall, experience a higher frequency of renal, neurologic and hematologic involvement and higher levels of disease activity and damage.
- Male patients exhibit more severe clinical features; however, gender has not been proved to be associated with a worse prognosis.
- Non-Caucasian patients tend to be younger at disease onset and have a more severe disease.
• Lower socioeconomic status, more severe disease, comorbidities and higher doses of glucocorticoids and immune-suppressive drugs are associated with higher mortality rates whereas antimalarials prolong patients’ survival.

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Declaration of interest
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Papers of special note have been highlighted as either of interest (-) or of considerable interest (-) to readers.


In this paper, the authors found that the SLICC criteria perform at least as well as the ACR criteria for the classification of Lupus in the GLADEL and LUMINA cohorts.

- This article reports surprising geographic variation in the prevalence of SLE in Sweden. Also that variation on prevalence rates exists (46–85 per 100,000 inhabitants) as a function of the strictness of the case definition used.
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in systemic lupus erythematosus. A study of 489 Greek


**This paper showed the impact of genetic ancestry.**


- An extensive review of survival and damage in SLE.


- An extensive review and analyses of overall and cause-specific mortality in SLE.


