Onset age affects mortality and renal outcome of female systemic lupus erythematosus patients: a nationwide population-based study in Taiwan

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Abstract

Objective. The objective of this study was to investigate the impact of disease onset age on mortality and renal survival in female SLE patients.

Methods. This nationwide, population-based, retrospective cohort study used data from the National Health Insurance Research Database of Taiwan. Female patients newly diagnosed with SLE from 2001 to 2004 were identified as the study cohort. A non-SLE group was matched for age, sex and initial diagnosis date (index date) as the comparison cohort. Co-morbidities, mortality rates and end-stage renal disease (ESRD) incidences were compared among SLE patients of different onset age. Hazard ratios with a 95% CI were determined by the Cox proportional hazard model to quantify the mortality rates and ESRD incidences. Juvenile-onset, adult-onset and late-onset SLE patients were categorized according to disease onset age: <18, 18–50 and >50 years old.

Results. In total, 513 juvenile-onset, 3076 adult-onset and 764 late-onset SLE patients were identified. Compared with non-SLE controls, the hazard ratios of mortality were 6.49 (95% CI 3.73, 11.32, P < 0.001) for juvenile-onset, 1.75 (95% CI 1.47, 2.08, P < 0.001) for adult-onset and 3.44 (95% CI 2.76, 4.28, P < 0.001) for late-onset SLE patients. The hazard ratios of incident ESRD were 20.28 (95% CI 12.79, 32.15, P < 0.001) for adult-onset lupus patients and 1.99 (95% CI 1.36, 2.93, P < 0.001) for late-onset patients.

Conclusion. Female patients with late-onset SLE carried a higher risk of mortality than those with adult-onset disease in the presence of co-morbidities. Juvenile-onset SLE patients were at greatest risk of mortality, which is probably due to disease severity.

Key words: systemic lupus erythematosus, age, mortality, co-morbidities, end-stage renal disease.

Introduction

SLE is a systemic autoimmune disease with a broad spectrum of clinical manifestations that predominantly affects young women during childbearing age [1, 2]. The disease onset of SLE can also occur in paediatric and older populations [3]. Late-onset SLE, defined as disease onset at age >50 years, comprises 12–18% of SLE cases [1, 4]. In 15–20% of all SLE patients the diagnosis is made before the age of 18 years [5].

Age at disease onset has a great impact on clinical manifestations of SLE [6]. As the geriatric population increases worldwide, there will be more cases of late-onset SLE in the future. Compared with younger patients,
late-onset SLE patients are reported to have a more insidious disease onset and lower disease severity [7–9]. Therefore, diagnosis of late-onset SLE is often delayed and can be a challenging task for physicians. Lupus nephritis and central nervous system involvement are also less frequently encountered in the late-onset group [10]. In contrast, juvenile-onset lupus nephritis seems to be more severe than late-onset lupus nephritis [11]. A study in China demonstrated that late-onset SLE patients show less active but more chronic lesions in renal pathology, and SLE patients with onset at ≤40 years of age appear to have worse long-term renal outcomes [12]. Conversely, recent epidemiologic studies have shown that late-onset SLE is not benign. Greater accrual damages and higher mortality rates have also been observed in late-onset SLE patients [6, 9, 13–15]. The discrepancy in these studies may be attributable not only to lupus disease activity, but also the consequences of aging or age-related comorbidities. In addition, the main cause of death in elderly lupus patients is not SLE itself, but treatment-related infection, cardiovascular diseases or age-related pathologies [3, 6, 9, 16]. Thus conclusions drawn from available studies are limited by rather small case numbers, heterogeneity of patient groups and lack of matched healthy controls [15].

To answer the critical but unsolved question of whether late-onset lupus patients have higher mortality rates and poorer renal outcomes, we conducted a nationwide, population-based, retrospective cohort study to investigate the impact of disease onset age on renal survival and mortalities in female SLE patients in Taiwan.

Methods

Data source

The data source is the National Health Insurance Research Database (NHIRD) of Taiwan, which includes inpatient and ambulatory care claims from 1996 to 2009. The National Health Insurance Program of the Bureau of National Health Insurance (BNHI) covers >98% of the population in Taiwan. It maintains a computerized comprehensive database comprising all medical claims for ambulatory care services and hospitalizations, thereby facilitating a nationwide population-based cohort study. The NHIRD established a registry system for catastrophic illnesses, a category to which SLE belongs. The BNHI performs routine validation of the diagnoses by reviewing the original medical charts of all patients who apply for a catastrophic illness certificate. The completeness and accuracy of the NHII claims databases are guaranteed by the aforementioned agencies. Because the NHIRD consists of de-identified secondary data released to the public for research purposes, this study was exempted from full review by the Institutional Review Board of Taichung Veterans General Hospital.

Study samples

This retrospective cohort study consisted of a study cohort and a comparison cohort. The study cohort enrolled all female SLE patients [International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM) code 710.0] in Taiwan from the registry of catastrophic illness patients during the period 2001–04. The index date for the study cohort was identified as the date of the first-time ambulatory care visit with a diagnostic code for SLE during that period. To identify new SLE cases, we excluded those who had an index date before 1 January 2001. Also excluded were SLE patients who were followed-up for <3 years. Juvenile-onset SLE patients referred to SLE patients with the onset age <18 years. The adult-onset group indicated the onset age between 18 and 50 years, while subjects with disease that occurred after age 50 years were categorized as late-onset patients. The study cohort enrolled 4353 SLE patients: 513 juvenile onset, 3076 adult onset and 764 late onset.

The comparison cohort was selected from a 1 000 000-person representative sample. Patients having an SLE diagnosis in any claims data during the period 2001–04 were excluded. Patients were then randomly extracted from the registry of beneficiaries (four for every patient in the study cohort) as the comparison cohort and matched to the study cohort for age at SLE onset (i.e. <18, 18–50, >50 years) and year of index date. The date of the first-time ambulatory visit occurring in the year of the index date was selected as the index date for the comparison cohort. Patients with <3 years of ambulatory visits recorded after the index date were excluded. The comparison cohort included 17 412 patients without SLE.

Potential confounders included the insured amount as the economic index, prescription medication and co-morbid medical diseases. Type 2 diabetes mellitus (DM; ICD9-CM code 250), hypertension (codes 401–405), heart failure (code 428), stroke (code 430–438), liver cirrhosis (code 571), glomerulonephritis (codes 582–583), end-stage renal disease (ESRD, code 585), pneumonia (codes 480–486), herpes zoster (code 053), tuberculosis (TB, codes 010–018) and cancers (codes 140–208) were defined as co-morbid medical disorders. If these diagnostic codes were used in two or more ambulatory claims 6 months before and after the index date, they were recorded as co-morbidities. Pharmacologic treatment given at the diagnosis of SLE was included.

Study outcomes

The primary outcome was mortality. The date of death was defined as the ending date of NHI coverage. Ninety-seven per cent of the records had the same date of death and date of end of NHI coverage. Thus the end of NHI coverage was considered as a good proxy for a patient’s survival. All causes of mortality were included in this study. Another primary outcome was ESRD. Patients with ESRD were defined as those undergoing dialysis for at least two consecutive years or receiving renal allograft transplantation. All patients were followed up until the occurrence of endpoints, permanent disenrollment from the NHI or the end of the study (31 December 2009), whichever came first.
Statistical analysis
To examine the unadjusted comparisons, the Pearson $\chi^2$ test was used for categorical variables. Hazard ratios (HRs) of mortality and incident ESRD were determined by a Cox proportional hazards model with a 95% CI. Age, insured amount and co-morbidities were adjusted. Mortality rates and ESRD incidences of the SLE and non-SLE populations were calculated. The denominator was the total number of study cases. The numerator was the cumulative number of death or incident ESRD cases, respectively. All statistical tests were two-sided, conducted at a significance level of 0.05 and reported using $P$-values and/or 95% CIs. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

Results
Demographic data of newly diagnosed female SLE cases during 2001–04
The demographic data, co-morbidities and treatments of newly diagnosed female SLE patients during the period 2001–04 were stratified by age at onset (Table 1). The co-morbidities of type 2 DM, hypertension, heart failure, stroke and liver cirrhosis increased with advancing onset age. However, the prevalence of glomerulonephritis was higher in the juvenile-onset group as compared with adult-onset and late-onset lupus patients.

Comparisons of co-morbidities between SLE patients and non-SLE controls
Compared with non-SLE controls, SLE patients had an increased prevalence of hypertension, heart failure and stroke (Table 2). The prevalence of type 2 DM was significantly increased in adult-onset SLE patients. Infection rates of pneumonia, herpes zoster and TB were all dramatically increased in SLE patients as compared with non-SLE controls. Also, SLE patients of all age groups were at increased risks of malignancy in this study.

Comparisons of mortality risks between SLE patients and non-SLE controls
When compared with non-SLE subjects, juvenile-onset SLE patients carried the highest mortality risks (HR 6.49, 95% CI 3.73, 11.32, $P < 0.0001$; Table 3), followed by the late-onset patients (HR 3.44, 95% CI 2.76, 4.28, $P < 0.0001$). The mortality rates of adult-onset SLE patients were only modestly increased (HR 1.75, 95% CI 1.47, 2.08, $P < 0.0001$). SLE patients of different ages were at greater risk of 1-, 3- and 5-year mortality (Fig. 1A) as compared with non-SLE subjects (Fig. 1B). A J-curve phenomenon was observed in mortality rates of SLE patients, with the highest in the late-onset group and the lowest in the adult-onset group.

Comparisons of incident ESRD risks between SLE patients and non-SLE controls
In this study we demonstrated that the risk of incident ESRD was drastically lower in late-onset SLE patients (HR 1.99, 95% CI 1.36, 2.93, $P < 0.0001$; Table 4) as compared with adult-onset patients (HR 20.28, 95% CI 12.79, 32.15). The ESRD risks seemed to be even higher in the juvenile-onset patients. However, due to a lack of observed events in non-SLE controls, the HR could not be calculated. The J-curve phenomenon was also observed in the ESRD incidence in SLE patients. Compared with non-SLE controls (Fig. 1D), the 1-, 3- and 5-year ESRD incidence was highest in the late-onset group followed by the juvenile-onset group and then the adult-onset SLE patients (Fig. 1C).

Discussion
This study is, to the best of our knowledge, the first population-based cohort study that demonstrates the mortality and incident ESRD risks among female SLE patients of different onset ages with appropriate comparisons with non-SLE controls. To minimize the effects of aging and compare mortality due to SLE alone, an age-matched control was used for comparison. We found that although

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n = 4353)</th>
<th>Age &lt; 18 years (n = 516)</th>
<th>Age 18–50 years (n = 3076)</th>
<th>Age &gt; 50 years (n = 764)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total observation period, mean (s.d.), years</strong></td>
<td>7.33 (1.52)</td>
<td>7.43 (1.40)</td>
<td>7.37 (1.45)</td>
<td>7.08 (1.79)</td>
</tr>
<tr>
<td><strong>Insured amount, n (%), NT$</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 800</td>
<td>1987 (45.7)</td>
<td>496 (96.7)</td>
<td>1115 (36.3)</td>
<td>376 (49.2)</td>
</tr>
<tr>
<td>12 800–19 999</td>
<td>1167 (26.8)</td>
<td>13 (2.5)</td>
<td>892 (29.0)</td>
<td>262 (34.3)</td>
</tr>
<tr>
<td>20 000–31 000</td>
<td>619 (14.2)</td>
<td>4 (0.8)</td>
<td>539 (17.5)</td>
<td>76 (10.0)</td>
</tr>
<tr>
<td>&gt;31 000</td>
<td>580 (13.3)</td>
<td>0 (0.0)</td>
<td>530 (17.2)</td>
<td>50 (6.5)</td>
</tr>
<tr>
<td><strong>Treatment, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>3640 (83.6)</td>
<td>468 (91.2)</td>
<td>2559 (83.2)</td>
<td>613 (80.2)</td>
</tr>
<tr>
<td>CYC</td>
<td>627 (14.4)</td>
<td>112 (21.8)</td>
<td>419 (13.6)</td>
<td>96 (12.6)</td>
</tr>
<tr>
<td>AZA</td>
<td>1029 (23.6)</td>
<td>166 (32.4)</td>
<td>744 (24.2)</td>
<td>119 (15.6)</td>
</tr>
<tr>
<td>HCQ</td>
<td>3244 (74.5)</td>
<td>343 (66.9)</td>
<td>2377 (77.3)</td>
<td>524 (68.6)</td>
</tr>
</tbody>
</table>
The mortality risks were higher in the late-onset SLE patients compared with the adult-onset group, juvenile-onset SLE patients had the greatest mortality risks. Also, incident ESRD risks were lowest in the late-onset SLE patients.

It was reported that ~10% of SLE patients have shorter life expectancies and 5-year mortality rates after diagnosis [17]. The leading causes of mortality in SLE patients with lupus nephritis were infection, cardiovascular diseases and cancers [18]. Our report also showed that the prevalence of pneumonia, herpes zoster, tuberculosis and cancers was significantly increased in SLE patients of different age groups. In the Framingham Heart Study, SLE patients carried a >50-fold risk for cardiovascular diseases as compared with non-SLE controls [19]. Also, arterial hypertension, premature atherosclerosis and increased susceptibility to cerebrovascular accidents were also observed in SLE patients [20–22]. In keeping with previous reports, our study showed that SLE patients had a higher prevalence of hypertension, heart failure and stroke than the non-SLE population. Systemic autoimmune diseases were associated with insulin resistance and type 2 DM, but the link between DM and SLE has not been elucidated [23, 24]. Our study is the first report to reveal the increased prevalence of type 2 DM in adult-onset SLE patients. Type 2 DM may lead to nephropathy, retinopathy and peripheral neuropathy that can complicate the management of SLE patients [24]. Also, treatment of active SLE requires large doses of glucocorticoids, which may interfere with optimized glycaemic control [24]. The relationship between SLE and DM warrants further comprehensive investigations.

Mortality rates in late-onset SLE patients appeared to be higher as compared with adult-onset patients.

Table 2: Comparison of co-morbidities between SLE and non-SLE controls in different age groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>non-SLE</th>
<th>SLE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.09</td>
<td>0.39</td>
<td>0.174</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.05</td>
<td>0.39</td>
<td>0.100</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.05</td>
<td>1.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>0.90</td>
<td>5.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>0.24</td>
<td>39.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.38</td>
<td>15.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>0.19</td>
<td>6.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TB</td>
<td>0.09</td>
<td>0.58</td>
<td>0.055</td>
</tr>
<tr>
<td>Cancers</td>
<td>0.14</td>
<td>2.34</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3: Risks of mortality among female SLE patients compared with non-SLE controls stratified by different age groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18 years</td>
<td>6.49</td>
<td>3.73</td>
<td>11.32</td>
</tr>
<tr>
<td>18–50 years</td>
<td>1.75</td>
<td>1.47</td>
<td>2.08</td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>3.44</td>
<td>2.76</td>
<td>4.28</td>
</tr>
<tr>
<td>Total</td>
<td>2.20</td>
<td>1.93</td>
<td>2.50</td>
</tr>
</tbody>
</table>

Data are presented as percentage. DM: diabetes mellitus, TB: tuberculosis.

The mortality risks were higher in the late-onset SLE patients compared with the adult-onset group, juvenile-onset SLE patients had the greatest mortality risks. Also, incident ESRD risks were lowest in the late-onset SLE patients.
Late-onset female SLE patients carried a higher risk of mortality but a lower risk of incident end-stage renal disease than adult-onset SLE patients when compared with non-SLE controls. Juvenile-onset SLE patients were at the highest risks of mortality and renal failure.

**Rheumatology key messages**

- Juvenile-onset female SLE patients were at the highest risks of mortality and renal failure.
- Late-onset female SLE patients carried a higher risk of mortality but a lower risk of incident end-stage renal disease than adult-onset SLE patients.

**Acknowledgements**

This study is based in part on data obtained from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, and managed by the National Health Research Institutes, Taiwan (registered number NHIRD-99-315). The interpretation and conclusions contained herein do not represent those of the Bureau of National Health Insurance or the National Health Research Institutes, Taiwan.

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

**References**

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