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ORIGINAL ARTICLE

Association of the Charlson Comorbidity Index With Mortality in Systemic Lupus Erythematosus

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Objective. **To investigate whether comorbidity as assessed by the Charlson Comorbidity Index (CCI) is associated with mortality in a long-term followup of systemic lupus erythematosus (SLE) patients.**

Methods. **Data were collected from 499 SLE patients attending the Lupus Clinic at the McGill University Health Center, Montreal, Quebec, Canada, and 170 SLE patients from the Department of Rheumatology at Lund University Hospital, Lund, Sweden. This included data on comorbidity, demographics, disease activity, the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), and antiphospholipid antibody syndrome (APS). Variables were entered into a Cox proportional hazards survival model.**

Results. **Mortality risk in the Montreal cohort was associated with the CCI (hazard ratio [HR] 1.57 per unit increase in the CCI, 95% confidence interval [95% CI] 1.18–2.09) and age (HR 1.04 per year increase in age, 95% CI 1.00–1.09). The CCI and age at diagnosis were also associated with mortality in the Lund cohort (CCI: HR 1.35, 95% CI 1.13–1.60; age: HR 1.09, 95% CI 1.05–1.12). Furthermore, the SDI was associated with mortality in the Lund cohort (HR 1.40, 95% CI 1.19–1.64), while a wide CI for the estimate in the Montreal cohort prevented a definitive conclusion (HR 1.20, 95% CI 0.97–1.48). We did not find a strong association between mortality and sex, race/ethnicity, disease activity, or APS in either cohort.**

Conclusion. **In this study, comorbidity as measured by the CCI was associated with decreased survival independent of age, lupus disease activity, and damage. This suggests that the CCI may be useful in capturing comorbidity for clinical research in SLE.**

INTRODUCTION

Mortality in systemic lupus erythematosus (SLE) has improved over the past decades, although long-term survival remains decreased compared to the general population (1,2). Early recognition of patients with an increased risk of adverse outcomes may be of great importance in determining treatment and risk factor management. Prognostic studies have suggested several factors associated with a less favorable outcome in lupus, including a variety of clinical factors, such as disease activity (3–9). Other factors, such as socioeconomic factors and ethnicity, may also be of importance in long-term outcome (10,11). Early organ damage as measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (ACR) Damage Index (SDI) (12) has been reported to be associated with mortality (13,14), although not consistently (15). As well as being a measure of damage, the SDI could be considered a means of measuring comorbidity, since items cover many important comorbid states, such as cardiac and respiratory diseases, diabetes mellitus, and malignancies. However, since it was designed as a measure of damage, not comorbidity, the SDI captures only events that have occurred after SLE diagnosis.

The Charlson Comorbidity Index (CCI) was developed with the aim of identifying conditions associated with increased mortality, in order to facilitate prognostic studies (16). The CCI was developed using a cohort of hospitalized

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individuals. Factors associated with mortality over a 1-year followup period were included in the index and weighted according to impact on mortality. The index consists of 19 items, rendering a summary score that is principally cumulative. The validity of this index was then confirmed in a cohort of breast cancer patients during a 10-year followup (16). A review on comorbidity measurements, including the CCI, is given by de Groot et al (17). The CCI has been used in prognostic studies in various diseases to adjust for comorbid conditions (18–23). In SLE, 1 study has been performed using hospital discharge registries, suggesting an increased mortality in lupus patients with a higher CCI score at admission (24). However, the impact of the CCI on overall mortality has not been studied in long-term prospectively followed SLE cohorts. This is the aim of the present study.

PATIENTS AND METHODS

The impact of the CCI on mortality in SLE was tested in a long-term followup SLE cohort from Canada, the Montreal Lupus Cohort (MLC), based at the McGill University Health Center (n = 499), and in a long-term followup SLE cohort from Southern Sweden, the Lund Lupus Cohort (LLC; n = 170) (1,25). The study was performed in accordance with the Declaration of Helsinki and was approved by the local ethics boards at McGill University and Lund University.

MLC. All patients in the MLC fulfilled 4 or more ACR classification criteria for SLE (26). These patients constitute part of an established cohort that is evaluated annually and for which data have been collected for research purposes on a yearly basis since 1978. The CCI was obtained at annual visits for patients still active in followup in 2006 and 2007 (56%), and the data were verified through medical record review. For the other patients (44%), data were retrieved through medical record review only.

Measures of the SLE Disease Activity Index (SLEDAI) (9) and SDI scores (12), as well as data on demographics, smoking history, years of education, and the presence or absence of the antiphospholipid syndrome (APS) according to the revised APS criteria (27), were obtained at yearly visits.

LLC. This population-based inception cohort includes only patients residing within a defined health care district in Southern Sweden at the time of SLE diagnosis, spanning the years 1981 to 2006. The details concerning capture of SLE cases in this district are previously described (25). In this cohort, data on the CCI were collected through medical record review, whereas data on annual SDI scores, demographics, and APS were collected at annual visits and confirmed through medical record review. SLEDAI scores were generated from charts at the time of diagnosis and at the first visit each subsequent year until the end of followup. Data on smoking and education levels were not available.

In both cohorts, classification of individual items in the CCI in this study was done without attribution to underlying cause, similar to the SDI. Deaths were confirmed through hospital records and/or vital statistics registry linkage.

Statistical methods. Descriptive statistics were compiled for each variable of interest, including means, SDs, or proportions, as required. Cox proportional hazards models were run to estimate the associations of potential predictor variables on mortality. A variety of models were run in order to assess for confounding. Hazard ratios (HRs) were calculated as the exponential of the model coefficients for each variable, and reported with 95% confidence intervals (95% CIs). As longitudinal data were available for the CCI, SDI, and SLEDAI, we entered these into our survival model as time-dependent covariates.

RESULTS

In the MLC, the median age at diagnosis was 31 years (range 8–80 years) and the median followup time was 13 years (range 1–50 years). Mortality in the MLC was 16% at the end of followup. In the LLC, the median age at diagnosis was 47 years (range 15–88 years) and the median disease duration was 13 years (range 0–27 years). The mortality at the end of followup in the LLC was 27%. The cumulative mortality was 1.2 per 100 patient-years in the MLC and the corresponding figure in the LLC was 2.1. The female to male ratio was 9:1 and 8.5:1 in the MLC and LLC, respectively.

The distribution of the ACR classification criteria for SLE (26), of ethnicity, and of CCI comorbidities in the MLC and LLC is shown in Tables 1, 2, and 3, respectively. On the CCI, all patients scored 1 for SLE (connective tissue disease, therefore the lowest possible score was 1). The mean CCI score at the end of followup in the MLC was 2.0 (range 1–13) and for the LLC was 2.3 (range 1–10). In the MLC, 56% of patients had a score of 1 at the end of followup, while the corresponding figure in the LLC was 49%. The mean SDI score at the end of followup was

Table 1. Distribution of American College of Rheumatology classification criteria for systemic lupus erythematosus in the MLC and LLC*

	MLC (n = 499)	LLC (n = 170)
Malar rash	228 (46)	80 (47)
Discoid lupus erythematosus	66 (13)	58 (34)
Photosensitivity	228 (46)	110 (65)
Oral ulcers	182 (36)	36 (21)
Arthritis	404 (81)	139 (82)
Serositis	228 (46)	78 (46)
Glomerulonephritis	196 (39)	42 (25)
Seizures/psychosis	56 (11)	16 (9)
Hematologic	323 (65)	107 (63)
Immunologic	309 (62)	114 (67)
ANA	474 (95)	169 (99)

* Values are the number (percentage). MLC = Montreal Lupus Cohort; LLC = Lund Lupus Cohort; ANA = antinuclear antibody.

Table 2. Distribution of ethnic groups in the MLC and LLC*

	MLC (n = 499)†	LLC (n = 170)
White	363 (73)	167 (98)
African American	50 (10)	0 (0)
Asian	48 (10)	2 (1)
American Indian	7 (1)	0 (0)
Other	23 (5)	1 (1)

* Values are the number (percentage). MLC = Montreal Lupus Cohort; LLC = Lund Lupus Cohort.
† Data were not available for 8 patients in the MLC.

2.5 (range 0–15) in the MLC and 2.0 (range 0–13) in the LLC, and the mean time-adjusted SLEDAI score was 2.8 (range 0–48) in the MLC and 1.8 (range 0–12) in the LLC.

In the univariate analysis, the HR for the SDI only was 1.48 per unit increase (95% CI 1.37–1.60) and for the CCI only was 1.89 per unit increase (95% CI 1.70–2.09). In multivariate analyses, the CCI and age at diagnosis were associated with mortality in the MLC (CCI: HR 1.57 per unit increase, 95% CI 1.18–2.09; age: HR 1.04 per year increase, 95% CI 1.00–1.09) (Table 4). The CCI and age at diagnosis were also associated with mortality in the LLC (CCI: HR 1.35, 95% CI 1.13–1.60; age: HR 1.09, 95% CI 1.05–1.12) (Table 4). The SDI was associated with mortality in the LLC (HR 1.40, 95% CI 1.19–1.64), with a similar trend, although not significant, in the MLC (HR 1.20, 95% CI 0.97–1.48). APS, sex, and disease activity were not clearly associated with mortality in either cohort, although the wide 95% CIs preclude definitive conclusions. A similar finding was noted for race/ethnicity in the MLC, while race/ethnicity in the LLC was not studied due to the low percentage of nonwhites (1.7%). In the MLC, data on smoking history and years of education were available for 78.2% and 61.7% of the patients, respectively. Neither smoking nor education level was strongly associated with mortality. Data on smoking and education level were not available for the LLC. Other data on socioeconomic factors were not available in either cohort.

Table 4. Hazard ratios and 95% confidence intervals in the multivariate adjusted analysis regarding association with mortality in the MLC and LLC*

	MLC	LLC
CCI score	1.57 (1.18–2.09)	1.35 (1.13–1.60)
Age at diagnosis, years	1.04 (1.00–1.09)	1.09 (1.05–1.12)
SDI score	1.20 (0.97–1.48)	1.40 (1.19–1.64)
Ethnicity (white)	2.04 (0.57–7.29)	N/A
APS (yes)	0.90 (0.44–1.83)	0.91 (0.53–1.59)
Sex (male)	1.11 (0.55–2.24)	0.97 (0.67–1.41)
SLEDAI score	1.07 (0.97–1.19)	1.01 (0.95–1.07)

* MLC = Montreal Lupus Cohort; LLC = Lund Lupus Cohort; CCI = Charlson Comorbidity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; N/A = not applicable; APS = antiphospholipid syndrome; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

The number of patients with a metastatic solid tumor in the CCI was 11 in the MLC and 4 in the LLC. A modified CCI without the variable "metastatic solid tumor" was associated with increased mortality (HR per unit increase 1.26, 95% CI 1.07–1.47) in multivariate analysis.

Overall, there were 134 patients (20%) lost to followup, defined as patients with no chart record for >2 years. At the end of followup, unless we had evidence that they were deceased, all patients were censored as being alive at the time point of the last record in the chart.

A possible difference in the relative importance of the

Table 3. Distribution of Charlson Comorbidity Index scores in the MLC and LLC*

	MLC (n = 499)	LLC (n = 170)	Both cohorts (n = 669)	Score per item
Acute myocardial infarction	24 (4.8)	23 (13.5)	47 (7.0)	1
Congestive heart failure	30 (6.0)	30 (17.6)	60 (9.0)	1
Peripheral vascular disease	25 (5.0)	10 (5.9)	35 (5.2)	1
Cerebrovascular disease	57 (11.4)	24 (14.1)	81 (12.1)	1
Dementia	3 (0.6)	9 (5.3)	12 (1.8)	1
Chronic pulmonary disease	78 (15.6)	27 (15.9)	105 (15.7)	1
Connective tissue disease	499 (100)	170 (100)	669 (100)	1
Ulcer disease	29 (5.8)	14 (8.2)	43 (6.4)	1
Mild liver disease	17 (3.4)	2 (1.2)	19 (2.8)	1
Diabetes mellitus	16 (3.2)	8 (4.7)	24 (3.6)	1
Hemiplegia	7 (1.4)	6 (3.5)	13 (1.9)	2
Moderate or severe renal disease	26 (5.2)	1 (0.6)	27 (4.0)	2
Diabetes mellitus with end organ damage	1 (0.2)	3 (1.8)	4 (0.6)	2
Any tumor	40 (8.0)	13 (7.6)	53 (7.9)	2
Leukemia	0 (0)	2 (1.2)	2 (0.3)	2
Lymphoma	10 (2.0)	2 (1.2)	12 (1.8)	2
Moderate or severe liver disease	2 (0.4)	2 (1.2)	4 (0.6)	3
Metastatic solid tumor	11 (2.2)	4 (2.4)	15 (2.2)	6
AIDS	0 (0)	0 (0)	0 (0)	6

* Values are the number (percentage) unless otherwise indicated. MLC = Montreal Lupus Cohort; LLC = Lund Lupus Cohort; AIDS = acquired immunodeficiency syndrome.

SDI and CCI on mortality in different age groups was explored in the MLC. Results, although not conclusive, were indicative of an age–SDI interaction, with a stronger effect on mortality in the age group >50 years at diagnosis, while the CCI was seemingly more important in younger age groups (data not shown). The age structure in the LLC did not allow for investigation of this question.

DISCUSSION

In this study, we could demonstrate an association between comorbidity, measured by the CCI, and mortality in 2 cohorts of long-term prospectively followed SLE patients. Importantly, the association with mortality was independent of age, disease activity, and the SDI.

The impact of comorbidity, such as cardiovascular disease and malignancies, on prognosis in SLE is well recognized. Adjusting for various comorbid conditions associated with prognostic studies of SLE is often important, but may be difficult. Therefore, the application of a well-established instrument for recording comorbidity, such as the CCI, may be of value in SLE outcome studies, including evaluation of treatment effects and biomarkers of prognosis.

In a study by Ward in a hospital-based SLE cohort using the hospital diagnosis registry, the CCI was shown to be associated with mortality at the time of discharge (24). In this study, Ward also developed and tested an SLE-specific comorbidity index that had a similar predictive ability of mortality as the CCI. The use of an SLE-specific comorbidity instrument, however, has some limitations, in that it precludes comparisons of the effects of comorbidity in SLE with other diseases. In addition, the lupus-specific index was tested in a short-term followup SLE cohort in a hospital setting. For these reasons, we chose to use the CCI in this study, although further studies using the SLE-specific comorbidity index in the study by Ward are of great interest.

There are some differences in our findings between the 2 SLE cohorts in our study. In part, this may reflect more severe cases in the MLC, due to it being in a tertiary care center, while the LLC is a population-based cohort, thus excluding severe cases referred from outside centers. Furthermore, the LLC includes predominantly white patients, while the MLC consists of patients with a mixture of races/ethnicities. Another important issue is age at diagnosis, which was higher in the LLC. Despite these differences, the CCI was associated with mortality in both cohorts.

Another difference between the cohorts was that of data retrieval for the CCI, which was solely based on medical record review in the LLC, but based on annual patient visits for the majority of patients in the MLC. Several studies have been performed using CCI data collected through medical record review, including the first confirmatory study by Charlson et al (16,20). Nevertheless, there is a potential bias in data collection from medical record review that possibly could result in slightly lower CCI scores, but one would suspect that this would only bias toward the null effect in terms of finding a true relationship between the CCI and mortality. Therefore, our results, at least in terms of the LLC, likely reflect conservative estimates.

The findings regarding the SDI in this study support a relationship with mortality, as noted in several studies (13,14). As expected, the SDI score correlated with the CCI score in our cohorts ($r = 0.48$, 95% CI 0.46–0.50). When analyzing the differences in SDI and CCI scores, 69% of the patients had a score difference of 1 or 0. For 5.8% of the patients, a score difference of 5 or more was seen. The SDI includes a larger set of variables than the CCI, and although a number of variables are shared, the definitions are generally not the same. The agreement of a positive or negative score for comparable items in the 2 indices was generally good (>90%). However, when excluding the patients with a score of 0 in both indices, which constitute the majority, differences were found with agreement varying from 41% to 83%. For instance, the agreement between a positive score in the variable "myocardial infarction" in both the SDI and the CCI was 74%, and a comparison between a positive score in either of the variables "glomerular filtration rate <50%" or "end-stage renal disease" in the SDI and the variable "moderate or severe renal disease" in the CCI revealed an agreement of 41%. These findings indicate that the item definitions, as well as the time point of SLE diagnosis in relation to development of comorbid conditions, are of importance for the results. As mentioned in the Introduction, since it was designed as a measure of damage, not comorbidity, the SDI captures only events that have occurred after SLE diagnosis. In contrast, the CCI captures all cumulative comorbidity. Furthermore, the variables in the SDI do not carry the same weights as the CCI in terms of impact on mortality. Results suggest that both the CCI and the SDI may be included in SLE mortality studies.

We did not find a strong association between higher SLEDAI scores and mortality, probably because the SLEDAI was measured only once yearly, thus underestimating disease activity over time. Disease activity measured as time-adjusted SLEDAI scores has been reported by Ibañez et al to correlate with mortality in SLE (28). However, in that study, the SLEDAI was scored at least twice yearly, making it more likely that episodes of increased disease activity were captured.

In conclusion, we report that the CCI is associated with mortality in 2 independent, long-term, prospectively followed SLE cohorts independent of age, disease activity, and damage. This suggests that the CCI may be useful in capturing comorbidity for clinical research in SLE.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Jönsen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Jönsen, Clarke, Sturfelt, Pineau.

Acquisition of data. Jönsen, Clarke, Bernatsky, Nived, Bengtsson, Sturfelt, Pineau.

Analysis and interpretation of data. Jönsen, Clarke, Joseph, Belisle, Bernatsky, Nived, Bengtsson, Sturfelt, Pineau.

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