

Research article

Trajectories of disease severity and their clinical outcome in real-world patients with systemic lupus erythematosus

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ABSTRACT

Objective: Systemic lupus erythematosus (SLE) is characterised by variability of disease activity patterns over time. This study aimed to investigate the trajectories of SLE disease severity patterns, identify clinical and demographic variables, and assess the association between trajectories of SLE disease severity and all-cause mortality.

Methods: A retrospective cohort of newly diagnosed patients with SLE was established using the Korean nationwide healthcare claims information database between 1st January 2008 and 31st December 2016. Using group-based trajectory modelling (GBTM), they were clustered based on the trajectory of SLE disease severity patterns during a two-year follow-up from the cohort entry date. We performed Cox proportional hazards models to compare the mortality between trajectories of SLE disease severity patterns.

Results: A total of 8901 patients with SLE were included in the analysis from 2008 to 2016. Five distinct SLE disease severity trajectories were identified as optimal: consistently severe (4.6 %), mild-then-moderate (11.6 %), moderate-then-mild (15.1 %), consistently moderate (30.4 %), and consistently mild (38.3 %). Patients with consistently mild disease severity were more likely to be older; those with consistently severe disease severity were more likely to be male with more comorbidities than other groups. Compared to the consistently mild disease severity, the other trajectory groups showed a higher risk of all-cause mortality.

Conclusion: Through GBTM, dynamic two-year severity trajectories of newly diagnosed SLE were identified. Patients' demographics and comorbidities attributed to changes in SLE severity trajectories, which may inform evidence for clinical decision-making.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease known for its variable severity, diverse clinical manifestations and unpredictable course marked by variable disease exacerbation (flares) and remission periods [1]. SLE's adjusted global prevalence and incidence are 50–100 and 0.3–31.5 per 100,000 persons per year, respectively [1]. While curative therapy

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remains elusive, the treatment focus for SLE is on achieving remission or low disease activity and preventing flares. The European League Against Rheumatism (EULAR) recommends initiating management with hydroxychloroquine and glucocorticoids before considering immunosuppressive agents and biologics for persistently active or refractory disease [2].

Immunosuppressives and biologics have significantly improved long-term prognosis [3,4]. However, persistently high disease activity and medication-related adverse events impact the health-related quality of life for individuals with SLE [5,6]. Prognosis in SLE is multifactorial, tied to treatment and disease activity [7]. High disease activity over time correlates with poor outcomes, including irreversible organ damage and increased mortality [8,9]. Conversely, consistently low disease activity is associated with lower damage-related morbidity and fewer flares [10].

Recognition of the extreme variability in disease activity patterns within and between individuals with SLE is crucial [11]. A recent prospective observational study in Greece, using SLEDAI-2K and PGA, conducted group-based trajectory modelling (GBTM) to identify clusters following similar patterns of disease activity in individuals with SLE on belimumab treatment [12]. However, individuals receiving SLE treatments other than belimumab were not evaluated, thus limiting the evidence on factors influencing these patterns in real-world clinical settings. Based on a nationwide population-based study, investigating these factors could identify clinical strategies for monitoring high-risk patients, contribute to personalized care and evaluate long-term prognosis. Hence, the present study aimed to investigate distinct disease severity trajectories, identify associated clinical and demographic variables and assess their association with mortality in patients newly diagnosed with SLE.

2. Material and methods

2.1. Data source

We conducted a retrospective population-based cohort study using the nationwide healthcare claims information database managed by the National Health Insurance Service (NHIS) in Korea. The NHIS-National Health Information Database (NHIS-NHID) includes information on the entire population of Korea (over 50 million individuals). All citizens are covered and receive healthcare services [13]. The NHIS has established the rare and intractable disease (RID) registration system in Korea for certain rare diseases, including SLE [14]. The RID code is reliable because a diagnosis has to be certified by physicians through uniform criteria distributed by the NHIS [14]. The NHIS-NHID main sections cover sociodemographic variables, mortality and health services, including admission, ambulatory care, disease diagnosis and pharmaceutical services. All diagnoses are coded based on the International Classification of Diseases 10th Revision (ICD-10) established by the World Health Organisation [13]. The Institutional Review Board (IRB) of Hanyang University Hospital exempted this study from IRB review because we used existing publicly available data, and patient information could not be identified directly or through identifiers linked to the subjects. (No. HYUH 2020-05-041-001).

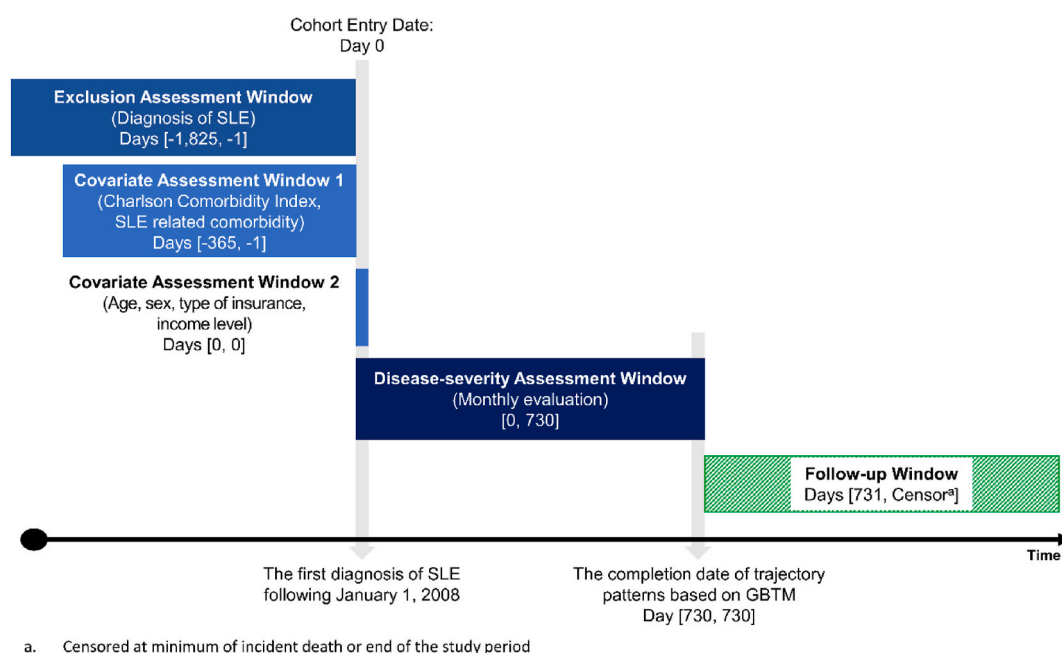


Fig. 1. Study design diagram. Abbreviations: SLE, systemic lupus erythematosus; GBTM, group-based trajectory modelling.

2.2. Study design & study population

The study population included patients diagnosed with SLE between 1st January 2008 and 31st December 2016. The cohort entry date corresponded to the first diagnosis of SLE, based on the identification of ICD-10 code (M32) and RID code (V136). To ensure the study population comprised only newly diagnosed with SLE, we excluded patients with prior diagnosis for at least five years before the cohort entry date (Fig. 1). The study excluded patients with observation periods of less than two years following the cohort entry date to cluster longitudinal patterns of disease severity for two years.

2.3. Covariates

Baseline demographic characteristics, such as age, sex, geographic region, type of insurance, type of institution and household income, were determined at the cohort entry date. Chronic comorbid conditions were detected during the one-year baseline before the cohort entry date based on the Charlson Comorbidity Index (CCI) [15]. Additionally, we investigated SLE-related comorbidities and opportunistic infections, including antiphospholipid antibody syndrome, avascular necrosis, tuberculosis, hypertension and hyperlipidaemia.

SLE disease severity was defined as mild, moderate and severe based on the pre-specified algorithm developed by Garris [16]. Based on SLE-related conditions and medication combinations, the algorithm was defined to classify SLE disease severity using administrative claims data [16]. Severe SLE was defined as either a diagnosis of severe SLE-related condition or treatment with rituximab, cyclophosphamide (CYC) or high-dose oral corticosteroid (CS) ≥ 60 mg/day (prednisone-equivalent) [16]. Moderate SLE was classified as either diagnosis of moderate SLE-related condition or treatment with an immunosuppressive agent (azathioprine, leflunomide, methotrexate, mizoribine, mycophenolate, tacrolimus) or oral CS ≥ 7.5 to < 60 mg/day. Patients were assigned mild SLE if they did not meet the criteria of moderate or severe disease [16].

2.4. Analysis

2.4.1. Identification of disease severity trajectories

We used GBTM to identify clusters of individuals with similar trajectories of disease severity patterns over two years following the cohort entry date. We defined a two-year evaluation period based on the previously reported median (IQR) time of 14.4 (5.1–18.7) months from the diagnosis of SLE to the first disease flare, as observed in a previous prospective cohort study involving 210 patients [17]. The assigned SLE disease severity was the highest disease severity experienced by the patient each month from the cohort entry date. For a two-year period, we imputed monthly longitudinal missing measurements, resulting from the complete taking of prescribed medications and the absence of healthcare service utilization, using the last observation carried forward method. In GBTM, finite mixture modelling, maximum likelihood estimation was applied to longitudinal data for determining the trajectory shape for each group and the probabilities of each individual belonging to specific trajectory groups [18]. We conducted GBTM based on a censored normal distribution from the disease severity patterns of patients with SLE [19]. To identify the optimal number of trajectories, we evaluated trajectory models with 2–6 groups based on the statistical indices, the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) [20]. To ensure the adequacy and utility of the trajectories, we also considered the clinical diversity of trajectories while avoiding overly complex trajectories.

2.4.2. Profile of disease severity trajectory groups

We evaluated whether the characteristics differed across SLE disease severity trajectories and assessed their associations with the trajectories. Patient demographics and disease characteristics for each trajectory were described and compared using analysis of variance (ANOVA) for continuous variables and chi-square or Fisher's exact tests for categorical variables. Multivariable multinomial logistic regression analysis was used to assess for adjusted odds ratios (aORs) and their 95 % confidence intervals (CIs) of patient characteristics associated with each SLE disease severity trajectory.

We also evaluated the mortality in each SLE disease severity trajectory to assess the robustness of trajectories based on GBTM. The mortality was defined as the occurrence of all-cause mortality after the end of the clustering with two years follow-up from the cohort entry date. The incidence rates (IR) per 100 person-years and their 95 % CI were calculated based on a Poisson distribution. We used Cox proportional hazards models to obtain hazard ratios (HR) and 95 % CIs to compare the mortality risks between trajectories of SLE disease severity patterns. We constructed GBTM using the crimCV package in R Statistical Software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria). All other analyses were performed with SAS 9.4 for Windows (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Characteristics of the study population

Among 17,393 patients with SLE from January 2008 to December 2016, the study identified 8901 patients who were first diagnosed with SLE (Fig. 2). Based on AIC and BIC measurement (Supplementary Table 1) and the clinical diversity, five distinct SLE disease severity trajectories were identified as optimal (Fig. 3): 'Group 1' was consistently severe disease severity: 405 (4.6 %), 'Group 2' was mild-then-moderate disease severity: 1034 (11.6 %), 'Group 3' was moderate-then-mild disease severity: 1346 (15.1 %), 'Group

4' was consistently moderate disease severity: 2709 (30.4 %) and 'Group 5' was consistently mild disease severity: 3407 (38.3 %) (Fig. 3).

Among 8901 patients with SLE, severity in the first month of SLE diagnosis were classified as 3285 (36.9 %) patients in mild disease severity, 4053 (45.5 %) patients in moderate disease severity, and 1563 (17.6 %) patients in severe disease severity (Supplementary Table 2). When comparing trajectory groups, patients with consistently severe disease (Group 1) showed a higher prevalence of severe disease severity (74.3 %) in the first month of SLE diagnosis. Compared to patients with the trajectory of moderate-than-mild disease (Group 3), those with constantly moderate disease (Group 4) showed a higher prevalence of immunosuppressant use in the first month (31.8 % in Group 4 vs 16.5 % in Group 3) and the last month (68.2 % in Group 4 vs 2.2 % in Group 3). Monthly distribution of classified trajectories among patients identified as severe according to the algorithm during the two-year study period is shown in Fig. 4. Among patients in severe status assessed in the first month following the cohort entry date, GBTM clustering classified 19.3 % as consistently severe and 58.3 % as consistently moderate. Patients assessed as severe monthly over a two-year period were clustered as consistently severe, ranging from 19.3 % to 60.2 %.

3.2. Factors associated with different severity trajectories

The baseline characteristics in patients with SLE were significantly different according to the five SLE disease severity trajectory groups (Supplementary Table 3). Patients with consistently severe disease were more likely to be younger than patients with consistently mild disease severity, and patients with consistently moderate disease severity were the youngest among trajectory groups. Males were significantly more likely than females to exhibit either consistently severe (aOR 1.72, 95 % CI 1.32–2.26) or consistently moderate disease severity (aOR 1.33, 95 % CI 1.14–1.56) than consistently mild disease severity (Fig. 5). Patients with Medicaid as their insurance type were significantly less likely than health insurance to exhibit consistently severe (aOR 0.43, 95 % CI 0.29–0.64), mild-then-moderate (aOR 0.55, 95 % CI 0.42–0.72), moderate-then-mild (aOR 0.26, 95 % CI 0.19–0.35) and consistently moderate disease severity (aOR 0.19, 95 % CI 0.15–0.25) than consistently mild disease severity. Patients with severe or moderate disease severity were more likely to have comorbidities before SLE diagnosis than other trajectory groups. Patients diagnosed with rheumatic disease other than SLE before the cohort entry date were significantly less likely to exhibit consistently severe disease (aOR 0.61, 95 % CI 0.47–0.79) than consistently mild disease severity. Moreover, these patients were significantly more likely to exhibit mild-then-moderate than consistently mild disease severity (aOR 1.36, 95 % CI 1.17–1.57). Patients with consistently severe or moderate disease severity were relatively more likely to have hypertension (aOR 2.90, 95 % CI 2.21–3.80 and aOR 1.77, 95 % CI 1.52–2.06), mild liver disease (aOR 1.38, 95 % CI 1.09–1.74 and aOR 1.53, 95 % CI 1.36–1.72), diabetes with chronic complications (aOR 1.93, 95 % CI 1.20–3.10 and aOR 1.07, 95 % CI 0.77–1.50), chronic pulmonary disease (aOR 1.16, 95 % CI 0.92–1.46 and aOR 1.22, 95 % CI 1.08–1.38) and hyperlipidaemia (aOR 1.31, 95 % CI 0.95–1.82 and aOR 1.45, 95 % CI 1.20–1.77) than consistently mild disease severity.

3.3. Mortality in the five SLE severity trajectory groups

The risk of all-cause mortality hazard ratio for the five SLE disease severity trajectory groups is shown in Table 1. IRs per 100 person-year (95 % CI) of mortality were 1.15 (0.79–1.67) in the consistently severe group, 0.83 (0.63–1.08) in the mild-then-moderate

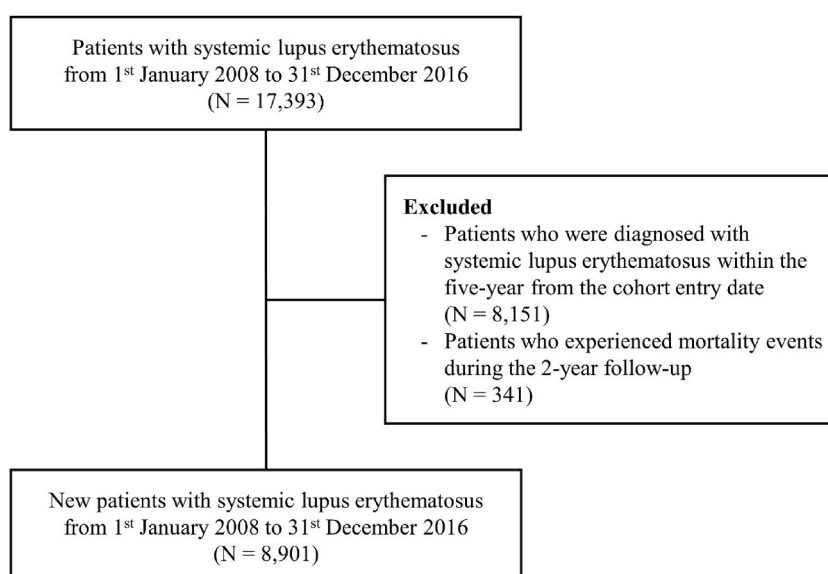


Fig. 2. Flowchart of selection of the study population.

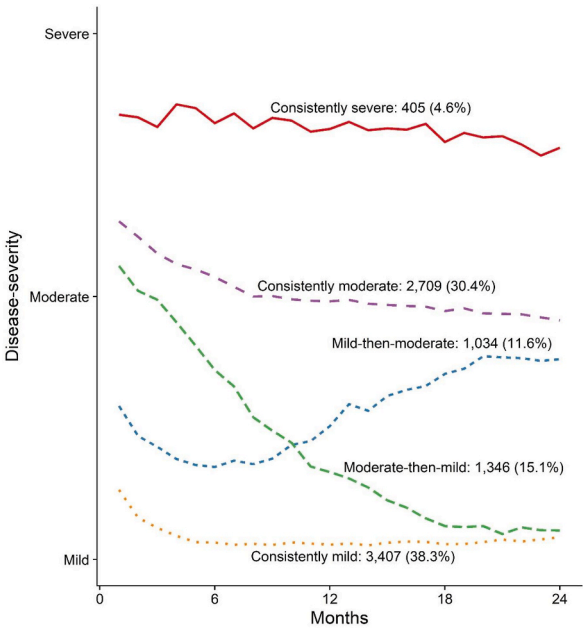


Fig. 3. Trajectories of disease severity in patients with systemic lupus erythematosus based on group-based trajectory modelling.

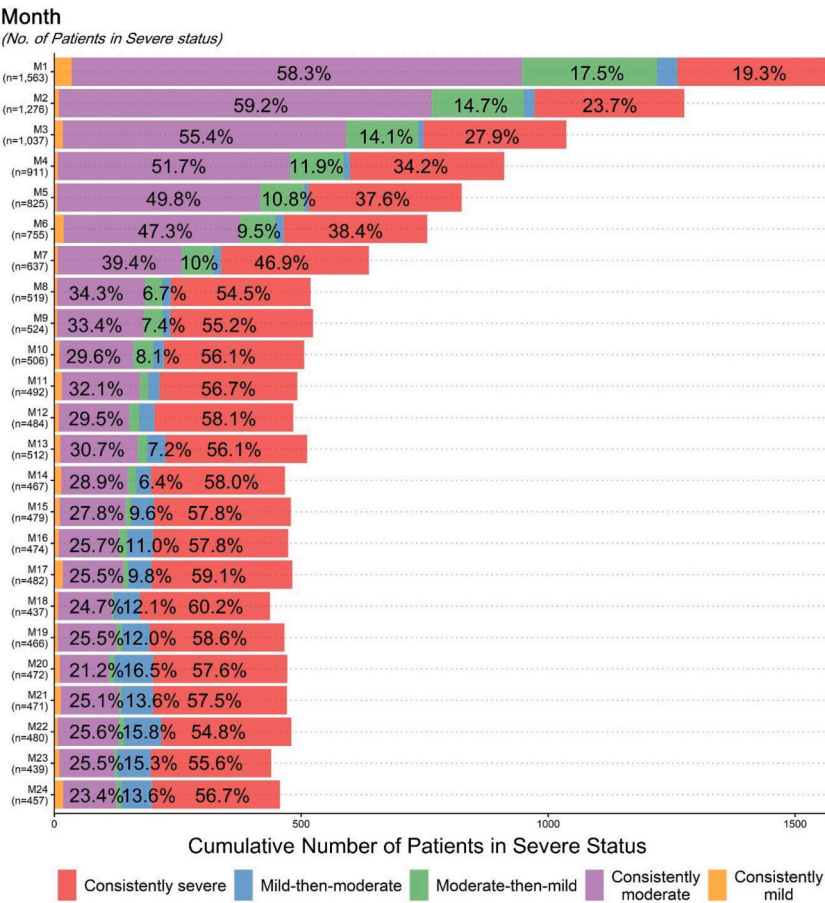


Fig. 4. Monthly distribution of patients with severe status across classified trajectories over a two-year study period.

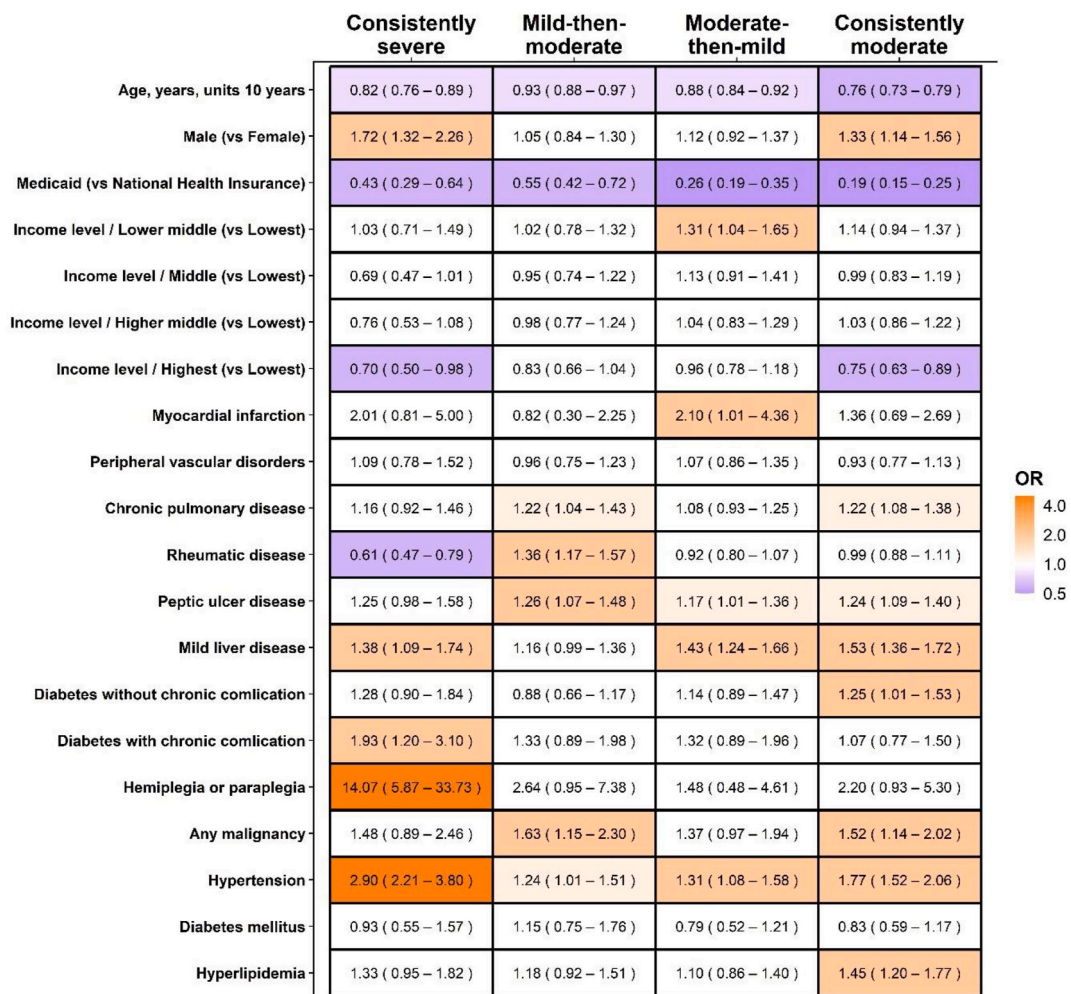


Fig. 5. The adjusted odds ratios for baseline characteristics associated with the different trajectory groups using multinomial logistic regression (Reference: consistently mild).

group, 0.68 (0.53–0.88) in the moderate-then-mild group, 0.87 (0.74–1.02) in the consistently moderate group and 0.35 (0.28–0.44) in the consistently mild group. The adjusted HR of all-cause mortality in the consistently severe group was 2.54 (1.59–4.06) compared to the consistently mild group. The other trajectory groups also had significantly higher risk of all-cause mortality (HR (95 % CI): 2.28 (1.58–3.29) in the mild-then-moderate group, 1.81 (1.26–2.59) in the moderate-then-mild group, 2.45 (1.79–3.37) in the consistently moderate group) compared to the consistently mild group. Fig. 6 shows the time to cumulative mortality according to the five SLE disease severity trajectories.

Table 1
All-cause mortality according to the five SLE severity trajectory groups.

Group	No. of death	Person-year ^a	IR ^b (95%CI)	Crude HR (95%CI)	Adjusted HR ^c (95%CI)
Consistently severe	27	2352	1.15 (0.79–1.67)	3.42 (2.21–5.31)	2.54 (1.59–4.06)
Mild-then-moderate	53	6406	0.83 (0.63–1.08)	2.39 (1.68–3.40)	2.28 (1.58–3.29)
Moderate-then-mild	59	8637	0.68 (0.53–0.88)	1.94 (1.38–2.72)	1.81 (1.26–2.59)
Consistently moderate	141	16,263	0.87 (0.74–1.02)	2.54 (1.92–3.36)	2.45 (1.79–3.37)
Consistently mild	76	21,658	0.35 (0.28–0.44)	Reference	Reference

^a Person-years were calculated from the completion date of the clustering of trajectory patterns over two years.

^b Incidence rate per 100 person-year.

^c Adjusted for age, sex, range of Charlson Comorbidity Index, SLE-related comorbidities, region, type of insurance, type of institution, income level, IR, incidence rate; CI, confidence interval; HR, hazard ratio.

4. Discussion

We clustered individuals with similar trajectories of disease severity patterns, combining SLE-related conditions and medications, two years from diagnosis of SLE in Korean patients with SLE. Trajectories of SLE disease severity were classified into the following five distinct clusters: consistently severe disease severity, mild-then-moderate disease severity, moderate-then-mild disease severity, consistently moderate disease severity and consistently mild disease severity. Based on five distinct SLE disease severity trajectories, patients with consistently mild disease severity were likely to be older with lower comorbidity before SLE diagnosis. Evaluation of the association between all-cause mortality and five disease severity trajectories showed that the risk of all-cause mortality in the other groups (groups 1 to 4) increased significantly compared to the consistently mild disease severity. Furthermore, moderate-then-mild disease severity, compared to the consistently mild group, was comparatively lower among the other trajectory groups.

This finding was consistent with other studies that severe or moderate disease severity was likely to be associated with younger age, male sex, higher comorbidity and higher risk of all-cause mortality. In a prospective cohort study of 202 patients with SLE over two years, patients diagnosed with SLE before the age of 25 years had more flares based on the SLEDAI-2K score [21]. In the LUMINA (LUpus in MInorities, NAture versus Nurture) study, males showed early damage in the disease course and tended to have a poorer long-term prognosis [22]. Furthermore, a study involving 1412 male patients with SLE in the Dallas-Fort Worth Metropolitan Statistical Area showed that despite a relatively lower prevalence among males, the severity of the disease was higher in males [23]. Another study reported that diabetes mellitus (8.5 % in mild, 13.0 % in moderate, 20.0 % in severe), liver disease (3.9 % in mild, 6.1 % in moderate, 9.9 % in severe) and hypertension (33.3 % in mild, 39.6 % in moderate, 49.8 % in severe) were significantly higher in patients with severe or moderate SLE than with mild SLE [24]. Moreover, 126 (21.5 %) patients with rheumatoid arthritis showed mild severity, 285 (25.1 %) exhibited moderate severity, and 111 (21.9 %) showed severe severity during the one-year after SLE diagnosis [24]. Furthermore, in a study using the US public health data from Medicaid, diabetes (10.4 % in mild, 16.5 % in moderate, 21.5 % in severe), hypertension (25.3 % in mild, 38.8 % in moderate, 52.2 % in severe) and hyperlipidaemia (12.5 % in mild, 16.8 % in moderate, 18.8 % in severe) were observed [25].

To improve low disease activity in SLE and prevent flares according to different disease severity patterns, comprehensive monitoring of SLE disease activity over time is important in patients with SLE. Previous studies based on a prospective cohort monitored SLE severity using a questionnaire over a defined follow-up period and described well the association between severe disease severity and poor clinical outcomes [21,22]. Previous studies based on an observational cohort evaluated the association between the severity of severe SLE disease and poor clinical outcomes in the highest severity group of SLE disease severity measured over one year [26,27]. However, no study has examined patient characteristics and the association with changes in SLE disease severity over time based on an observational cohort representing a real-world setting. In clinical practice, it is crucial to identify patients at risk of SLE exacerbations over time so that these high-risk patients can be offered individualized SLE disease severity management. Therefore, particular attention is needed to manage patients with SLE who have characteristics that indicate the potential for disease exacerbation patterns over time.

We used GBTM on longitudinal data to identify distinct SLE disease severity trajectories in patients with SLE. GBTM provides informative insights into the grouping of subjects presenting with similar baseline values and longitudinal patterns of change [18]. The previous study found insights into the predictors of hydroxychloroquine (HCQ) nonadherence and diverse behavioural patterns in patients with SLE according to the classification of HCQ users into distinct groups using GBTM [28]. The other study using GBTM provided more informative patterns of medication use over time by determining various patterns of opioid use post-total-joint-replacement in patients with rheumatoid arthritis [29]. To assess the SLE disease severity in patients with SLE, we used the algorithm for determining SLE disease severity that combined SLE-related conditions and medications based on indicators used to measure disease severity in the clinical setting from a previous study [16]. To reflect accounting for the variation in the SLE disease process, we considered monthly SLE disease severity during the two years from the cohort entry date.

The present study had several strengths. To the best of our knowledge, this is the first study to examine the baseline characteristics and assess the risk of all-cause mortality according to clustered disease severity trajectories over time in patients with SLE based on GBTM. Our study also has high generalisability since it used a nationwide representative population in Korea. Furthermore, we used a highly valid definition of patients with SLE by using the ICD-10 and the RID codes.

However, the study had several potential limitations, including concerns about the validity of the algorithm for determining disease severity. In addition, laboratory data for disease severity were not available, as we used claims data. However, we reviewed the ICD-10-based algorithm through the consensus of expert clinical opinion based on the ICD-9-based definition performed to assess SLE disease severity and the severity of SLE flares from the previous study. This retrospective study cannot exclude the possibility of residual confounding risk factors and accurately measure medication adherence using claims data. Nevertheless, our primary objective was to investigate clinical strategies for monitoring high-risk patients, contribute to personalized care, and evaluate prognosis. There were unclustered trajectories, including mild-then-severe and severe-then-mild. Despite their clinical importance in elucidating potential factors associated with exacerbations (flares) and remission, the trajectories were not feasible due to the relatively small number of patients included in their trajectories. Nevertheless, we identified five distinct SLE disease severity trajectories and the best model among those with different numbers of trajectories using AIC and BIC measurements. Further studies with long-term follow-up in a larger real-world population are necessary to overcome these drawbacks.

5. Conclusion

In conclusion, through GBTM, dynamic two-year severity trajectories of newly diagnosed SLE was identified. Patients'

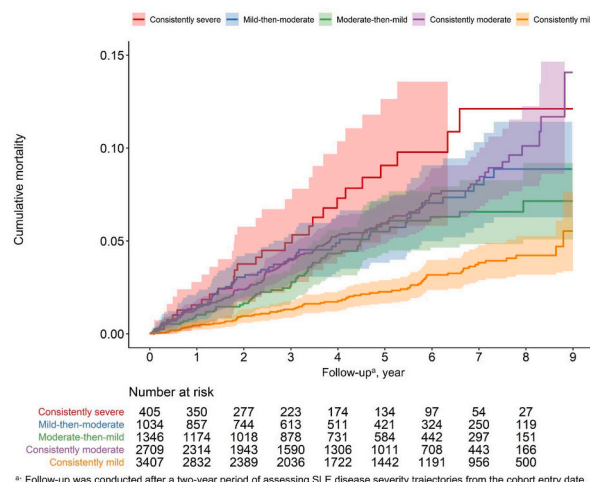


Fig. 6. Cumulative mortality among the five SLE severity trajectories.

demographics and comorbidities attributed to changes in SLE severity trajectories, which may inform evidence for clinical decision-making. Future studies with long-term follow-up in a larger real-world population should identify unclustered trajectories.

Compliance with ethical standards

This study protocol was exempted from review by the Institutional Review Board of Hanyang University Hospital (No. HYUH 2020-05-041-001). The informed consent was waived since we used existing publicly available data, and patient information could not be identified directly or through identifiers linked to the subjects (approved on May 11, 2022).

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Data availability statement

The data underlying this article were provided by the National Health Insurance Service by permission. Data can only be shared upon permission of the National Health Insurance Service; <https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do> (accessed on 13 September 2024).

CRediT authorship contribution statement

Seung-Hun You: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Eun Jin Jang:** Conceptualization, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Soo-Kyung Cho:** Conceptualization, Investigation, Validation, Writing – review & editing. **Yoon-Kyoung Sung:** Conceptualization, Funding acquisition, Investigation, Validation, Writing – review & editing. **Sun-Young Jung:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2024.e38705>.

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