



Short Communication

Mortality-related health metrics in systemic autoimmune diseases: an epidemiological analysis of a nationwide register-based cohort

Mucong Li ^{a,b,c,d,1}, Chanyuan Wu ^{a,b,c,d,1}, Peng Yin ^{e,1}, Junyan Qian ^{a,b,c,d}, Jiuliang Zhao ^{a,b,c,d}, Qian Wang ^{a,b,c,d}, Dong Xu ^{a,b,c,d}, Jinmei Su ^{a,b,c,d}, Xiaomei Leng ^{a,b,c,d}, Wenjie Zheng ^{a,b,c,d}, Xinping Tian ^{a,b,c,d}, Yan Zhao ^{a,b,c,d}, Alí Duarte-García ^f, Mengtao Li ^{a,b,c,d,*}, Xiaofeng Zeng ^{a,b,c,d,*}, Maigeng Zhou ^{e,*}

^a Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100730, China

^b National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Ministry of Science & Technology, Beijing 100730, China

^c State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Beijing 100730, China

^d Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Beijing 100730, China

^e National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 100032, China

^f Division of Rheumatology, Mayo Clinic, Rochester, 55905, USA

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Systemic autoimmune diseases (sAIDs) are a spectrum of diseases with multi-organ involvement that share similar clinical manifestations [1]. The capacity for diagnosis and treatment of sAIDs is closely associated with the level of regional development, especially health care service delivery [2]. With increasing incidence and prevalence [3,4,5], sAIDs have become global health concern as leading causes of death in young adults and substantial contributors to premature death [6]. To date, increasing health resources have been invested in sAID related clinical settings and research. However, few studies have provided an integrated overview of the mortality burden of various sAIDs, leaving an enormous care gap in resource allocation between developed and deprived regions [7]. To address this challenge, establishment of large-scale and integrated sAID registries by rheumatology specialists is a priority. In this study, we used the Chinese Rheumatism Data Center (CRDC) registry, a nationwide multicentre cohort for sAIDs across Chinese mainland, to provide an integrated atlas of mortality-related health metrics, including fatality rates, survival probabilities, causes of death, and standardized mortality ratios (SMRs) of eight sAIDs and illustrate the associations between disease burdens of sAIDs and area-level socioeconomic indicators.

The CRDC registry is a nationwide multicentre cohort for sAIDs across all of 31 provinces, municipalities, and autonomous regions

(hereinafter referred to as 31 provincial regions) in Chinese mainland. The registry was founded in 2011, aiming to continuously collect information of prevalent patients with all sAIDs. Patient recruitment and registration in the CRDC rely on unique national identification numbers [8]. Mortality data were collected using national identification numbers linked to the Nation Mortality Surveillance System (NMSS) of the China Center for Disease Control and Prevention. The NMSS has been previously validated, and is widely used in evaluating the burden of various diseases. Between January 2011 and December 2021, a total of 157,335 patients with eight sAIDs were registered in the CRDC; of these, 156,862 patients with valid national identification numbers were eligible for inclusion in our study (Texts S1–S4, Fig. S1 online). The CRDC collaboration has received ethical approval from Peking Union Medical College Hospital (PUMCH-S-191 and PUMCH-S-478). Signed informed consent forms were obtained from all patients. The overall population comprised 87,132 patients with rheumatoid arthritis (RA), 44,658 with systemic lupus erythematosus (SLE), 11,668 with primary Sjögren's syndrome (SS), 4864 with idiopathic inflammatory myopathies (IIM), 4065 with systemic sclerosis (SSc), 1762 with Behçet's disease (BD), 1558 with Takayasu's arteritis (TAK), and 1155 with anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV). Six of the eight sAIDs were female-predominant; and the gender differences were subtle in BD and AAV. The median years of disease duration in all patients was 5.16 (3.08–9.00) years, respectively. A total of 6426 deaths were confirmed, with the overall average age at death being 61.17 (15.77) years (Table 1). Sensitivity analysis demonstrated

* Corresponding authors.

E-mail addresses: mengtao.li@cstar.org.cn (M. Li), zengxfpumc@163.com (X. Zeng), zhoumaigeng@ncncd.chinacdc.cn (M. Zhou).

¹ These authors contributed equally to this work.

Table 1
Characteristics of overall CRDC registry and deceased patients.

CRDC registry	Overall (n = 156,862)	RA (n = 87,132)	SLE (n = 44,658)	SS (n = 11,668)	IIM (n = 4864)	SSc (n = 4065)	BD (n = 1762)	TAK (n = 1558)	AAV (n = 1155)
Age at first diagnosis (years), mean ± SD	43.64 (15.51)	48.46 (13.90)	32.53 (13.19)	48.47 (13.34)	47.70 (14.82)	47.37 (13.29)	37.25 (12.86)	31.64 (12.33)	57.07 (15.97)
Gender (%)									
Male	16.15	20.05	8.20	4.89	27.49	16.31	46.54	14.06	51.60
Female	83.85	79.95	91.80	95.11	72.51	83.69	53.46	85.94	48.40
Disease duration (years), median (IQR) ^a	5.16 (3.08, 9.00)	5.25 (3.25, 9.25)	6.00 (3.25, 10.15)	3.91 (2.50, 5.91)	3.75 (2.08, 6.08)	5.08 (2.84, 8.50)	4.67 (2.67, 6.98)	4.84 (3.08, 7.50)	3.08 (1.42, 4.83)
Deceased patients									
Overall	(n = 6426)	(n = 3274)	(n = 1509)	(n = 361)	(n = 564)	(n = 465)	(n = 49)	(n = 54)	(n = 150)
Age at first diagnosis (years), mean ± SD	55.10 (16.69)	61.03 (13.11)	40.74 (17.60)	59.70 (13.58)	56.73 (12.73)	53.45 (13.46)	45.23 (15.47)	38.18 (12.97)	67.29 (11.32)
Gender (%)									
Male	31.75	40.10	14.25	13.02	38.65	23.66	61.22	20.37	64.00
Female	68.25	59.90	85.75	86.98	61.35	76.34	38.78	79.63	36.00
Age at time of death (years), mean ± SD	61.17 (15.77)	68.31 (10.80)	46.85 (16.96)	64.04 (13.24)	59.13 (12.57)	58.30 (12.38)	49.12 (15.03)	43.31 (13.02)	69.35 (11.06)

CRDC: Chinese Rheumatism Data Center; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SS: Sjögren's syndrome; IIM: idiopathic inflammatory myopathies; SSc: systemic sclerosis; BD: Behçet's disease; TAK: Takayasu's arteritis; AAV: ANCA-associated vasculitis; SD: standard deviation.

^a Disease duration is from the index date to the last follow-up, the time of death, or Dec 31, 2021, whichever occurred first.

that data imputation did not change the demographic and clinical characteristics of patients (Table S2 online).

Fatality rates in patients with the eight investigated sAIDs are presented in Fig. S2 (online). The fatality rates in total, male, and female patients with all sAIDs were 4.10%, 8.05%, and 3.33% respectively. AAV, IIM, and SSc had the highest fatality rates in the registry at over 10%. The fatality rates of RA, TAK, SLE, SS, and BD were approximately 3%–4%. The fatality rates of male patients with sAIDs were higher than those of female patients in all the above mentioned diseases (significant in these sAIDs except for TAK, Table S3 online). Fig. S3 (online) displays the survival probabilities of patients with eight sAIDs. Within 10 years after the index date, patients with AAV (75.30%), IIM (83.32%), and SSc (84.80%) had relatively lower survival rates (Fig. S3 online). In seven of the eight sAIDs (RA, SLE, SS, IIM, SSc, TAK, and AAV), female patients had a significantly lower risk of death than their male counterparts with the same disease duration. Furthermore, a period characterized by notably high mortality in the early phase of disease (within one year of sAID diagnosis) was observed in both IIM and AAV.

The principal immediate and underlying causes of death in patients with sAIDs are shown in Fig. 1a (Table S4 online). Regarding the immediate causes of death, cardiovascular diseases (44.72%), respiratory diseases (16.40%), malignant neoplasms (13.62%), respiratory infections (6.99%), and digestive diseases (3.67%) were the leading causes of death in patients with RA of both genders. Proportionally more immediate causes of death were disease-related, and the distribution of the immediate causes of death varied between male and female patients with other sAIDs. In male patients, the immediate causes of death were as follows, in descending frequency: cardiovascular diseases (30.68%), respiratory diseases (19.39%), malignant neoplasms (16.50%), musculoskeletal diseases (11.14%), and genitourinary diseases (6.47%). In female patients, the immediate causes of death were cardiovascular diseases (31.63%), respiratory diseases (16.45%), musculoskeletal diseases (16.08%), malignant neoplasms (10.60%), and genitourinary diseases (6.73%). Regarding the immediate causes of death of each sAID, cardiovascular disorders led to more than half of deaths in TAK and BD. Respiratory diseases (in IIM, SS, AAV and SSc) and malignancy (in IIM) explained approximately 20% of deaths in the corresponding diseases. The rank of underlying causes of death in patients with sAIDs was broadly similar to that of the immediate causes of death in each sAID. Notably, musculoskeletal diseases accounted for more underlying causes of death than immediate causes of death, implying that sAIDs themselves or their complications are vital accelerators of death in patients with sAIDs (Table S5 online).

Generally, patients with sAIDs had a significant higher all-cause mortality risk in comparison with the overall population, with the overall age-, gender-, and calendar year-adjusted SMR of all sAIDs patients being 1.48 (95% confidence interval [CI] 1.44–1.51; male patients, SMR 1.42, 1.36–1.48; female patients, SMR 1.51, 1.46–1.55). The age-, gender-, and calendar year-adjusted SMR of total patients was highest for TAK (5.45, 95%CI 4.00–6.91), followed by IIM (5.08, 4.66–5.50), SSc (4.94, 4.49–5.39), SLE (3.50, 3.32–3.68), AAV (2.97, 2.50–3.45), BD (2.27, 1.64–2.91), and SS (1.53, 1.37–1.69) (Fig. 1b). sAIDs posed a higher threat to men with IIM (SMR 5.10, 95%CI 4.43–5.78), AAV (3.08, 2.46–3.69), and SS (1.73, 1.23–2.22); women had a higher risk with TAK (5.87, 4.11–7.62), SSc (5.01, 4.49–5.54), SLE (3.66, 3.46–3.86), and BD (2.28, 1.26–3.31). With respect to RA, the mortality risk of patients was generally comparable to that of the overall population (SMR 0.96, 95%CI 0.93–1.00). SMRs of patients with complete data regarding the time of the first confirmed diagnosis are provided in Fig. S4 (online). Overall, data imputation yielded similar findings in the SMRs.

The results in Table S6 (online) suggest that a higher human development index (HDI) was associated with increased mortality risks in patients with both RA (SMR ratio 12.24 for a 1-unit increase in HDI, $P < 0.001$) and SLE (SMR ratio 5.15 for a 1-unit increase in HDI, $P = 0.080$) compared with the region-specific general population. With respect to economic factors, we found that

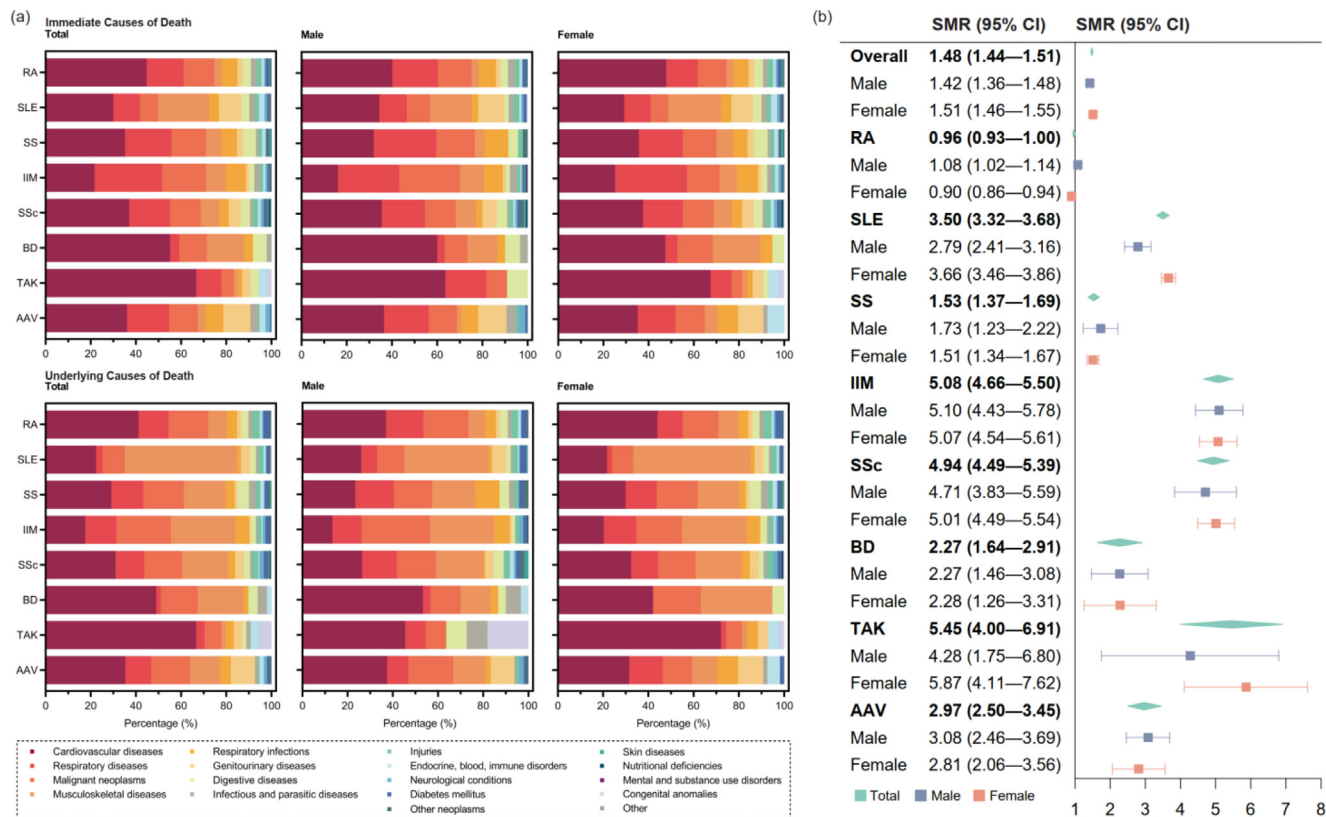


Fig. 1. Causes of death and standardized mortality ratios of systemic autoimmune diseases. (a) Immediate and underlying causes of death in total, male, and female patients with 8 systemic autoimmune diseases are presented. Classification of cause of death was referred to WHO methods and data sources for country-level causes of death 2000–2019, with corresponding international classification of diseases (ICD)-10 codes listed in supplemental contents. Detailed data are available in Table S4 (online). (b) Point estimates and 95% CIs of standardized mortality ratios (SMRs) in total, male, and female patients are presented for 8 systemic autoimmune diseases. SMRs were adjusted for age, gender, and calendar year. RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SS: Sjögren's syndrome; IIM: idiopathic inflammatory myopathies; SSc: systemic sclerosis; BD: Behçet's disease; TAK: Takayasu's arteritis; AAV: ANCA-associated vasculitis; SMR: standardized mortality ratio.

both gross domestic product (GDP) per capita (SMR ratio 1.22 for a 10,000 USD increase, $P = 0.005$) and national health expenditures per capita (SMR ratio 2.63 for a 1000 USD increase, $P = 0.039$) were significantly positively related to a relatively higher excess mortality risk in SLE than in the region-specific general population. A similar result for GDP per capita was also found in RA (SMR ratio 1.17 for a 10,000 USD increase, $P = 0.100$), although the association was marginally significant. Moreover, we identified that the average education level had a positive correlation with excess deaths in patients with both RA (SMR ratio 1.15 for a 1-year increase, $P = 0.019$) and SLE (SMR ratio 1.11 for a 1-year increase, $P = 0.037$). As for health care delivery, more medical institutions (SMR ratio 0.95 for one additional medical institution per 10,000 residents, $P = 0.005$) and hospital beds (SMR ratio 0.35 for one additional hospital bed per 100 residents, $P = 0.131$) were protective factors against excess mortality in SLE, but not in RA. Notably, patients with RA or SLE in regions with more health staff tended to have near-significant more excess mortality (RA: SMR ratio 1.89 for one additional health staff per 100 residents, $P = 0.142$; SLE: SMR ratio 1.58 for one additional health staff per 100 residents, $P = 0.149$).

The predominance of AAV, IIM, and SSc as leading lethal sAIDs in our cohort is in accordance with recent studies on the background of high-income countries and regions [6,9]. In our cohort, it was speculated that 75%–85% of patients with AAV, IIM, and SSc could survive to 10 years from the index date, whereas approximate 95% and more patients with the other five sAIDs survived for the same period. These low fatality rates and high survival probabilities are broadly similar to the results of previous studies; however, patients with all sAIDs in our cohort showed slightly better outcomes owing to a relatively younger mean age (43.63 years) [10–

13]. Notably, the fatality rates and survival probabilities of all eight sAIDs were higher in male than in female patients. These results were commensurate with the results of previous studies [10,12].

In the present study, causes of death were analyzed in view of multimorbidity, a patient-centered concept, rather than sAID-related comorbidity, a disease-based concept that is often used in cohort studies on sAIDs [14,15]. Mortal outcomes in sAIDs are multifaceted. In most sAIDs, a flare of disease and multiple organ involvement (especially cardiovascular and respiratory diseases) were the main causes of death. While in RA, cardiovascular diseases accounted for nearly half of the immediate causes of death, followed by respiratory diseases and infections (nearly a quarter), malignancy, and digestive diseases. These causes of death covered more than 80% of deaths, indicating that the long-term use of glucocorticoid and immunosuppressant agents may be related to an accumulated risk of cardiovascular events, infection, and cancer. Our description of the prevalence of severe multimorbidity in various sAIDs highlights the important need for the screening and prevention of these comorbidities owing to both disease flares and treatments.

The excess death risk in sAIDs is parallel to that in some populations with type 1 and 2 diabetes [16,17]. The current study findings showed an overall 0.5- and 0.53- to 4.45-fold excess mortality in patients with seven of the eight sAIDs in comparison to the age- and gender-adjusted general population. These results are generally in line with reports of single sAID in developed countries and regions [6,9]. In RA, patients had a similar mortality risk compared with the general population. These unexpected results may, to some extent, be in accordance with the clinical experience in China and other low-to-middle income countries (LMICs), and also with reports from hospital-based registries in developed countries

and regions [18,19], suggesting that the mortality gap between patients with RA and the general public is narrowing and tends to be disappearing.

Our study has several limitations. Although the CRDC registry has included sAIDs since 2011, we did not evaluate trends in the mortality burden of sAIDs owing to the limited study period and population size. However, this allowed for homogeneity of the inclusion criteria and avoided potential bias. In this study, we mainly focused on health care accessibility. Individual-level socioeconomic indicators (e.g., socioeconomic status, disease activity, and medication) were not included in the analysis, which may influence medical choices and may be potential confounders leading to referral bias. Moreover, we only explored the relationships between socioeconomic indicators and RA and SLE owing to the limited number of patients with other sAIDs. Further research should simultaneously focus on the impacts of both area- and individual-level socioeconomic indicators, and should incorporate more sAIDs, to examine the interactions among these factors and assess their impacts on the mortality burdens of sAIDs.

To the best of our knowledge, our study relied on the largest nationwide registry-based cohort of more than 150,000 patients with sAIDs confirmed in rheumatology admissions or clinics. This comparative study was the first attempt to thoroughly examine the mortality-related health metrics of eight sAIDs at the same time. We observed that mortality risk (up to 4.5 times) in patients with sAIDs can be in substantial excess versus general population. Treatment-related adverse events were partially attributable to cardiovascular events, infection, and cancer in most RA deaths whereas disease flares and multiple organ involvement were the main causes of death in other sAIDs. Additionally, our study provides a systematic account revealing that the mortality burden of sAIDs has a complicated relationship with the level of regional development. The underestimated mortality burden of sAIDs is becoming a serious problem in China, and is generalizable to a broader range of other LMICs. Advances in the prognosis of common chronic diseases have brought the disease burden of sAIDs to the forefront globally. An increasing mortality burden associated with sAIDs indicates relatively insufficient capacity-building in the diagnosis and treatment, unequal distribution of healthcare, and ineffective health knowledge disseminations in LMICs.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author contributions

Chanyuan Wu, Peng Yin, Mengtao Li, Xiaofeng Zeng and Maigeng Zhou developed the study concept and drafted analyses plan. Junyan Qian, Jiuliang Zhao, Qian Wang, Dong Xu, Jinmei Su, Xiaomei Leng, Wenjie Zheng, Xinping Tian and Yan Zhao collected data and provided administrative, technical, or material support.

Mucong Li, Chanyuan Wu and Peng Yin conducted analysis and prepared results. Mucong Li and Chanyuan Wu wrote the first draft of the paper. Duarte-García Alí provided critical review. All authors contributed to the final version of the Article and have seen and approved the final version. Mengtao Li, Xiaofeng Zeng and Maigeng Zhou had full access to all of the data in the study and verified the data. Mengtao Li, Xiaofeng Zeng and Maigeng Zhou are responsible for the integrity of the data, accuracy of the data analysis, and decision to submit the manuscript, and act as guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scib.2024.12.021>.

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