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autoimmune disease, conventional, fracture, disease-modifying antirheumatic drug, biologic

**Abstract**

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Material and methods
Individuals aged >18 years with a newly diagnosed autoimmune disease between 2003 and 2014 were identified from Taiwan's National Health Insurance Research Database. Multivariate Cox proportional hazards regression was employed to identify risk factors associated with fractures.

Results
Among 68,296 patients (mean age 51.9±15.4 years; 78.4% female), rheumatoid arthritis was the most common autoimmune disease. During a mean follow-up of 5.6±3.5 years, 10,709 (15.7%) patients had fractures. Independent predictors included female sex, age ≥65 years, prior fractures, comorbidities (osteoporosis, hypertension, diabetes mellitus, hyperlipidemia, cerebrovascular disease, chronic obstructive pulmonary disease, hypogonadism and menopause/postmenopause, end-stage renal disease, alcoholism), and glucocorticoid use >1.67 mg/day prednisone equivalent. The fracture risk was lower in patients with systemic lupus erythematosus, systemic sclerosis, vasculitis, pemphigus, Sjögren's syndrome, polymyositis/dermatomyositis and inflammatory bowel disease compared to those with rheumatoid arthritis. The use of conventional DMARDs, biologic DMARDs (TNF-α and IL-6 inhibitors and selective T-cell co-stimulatory modulator), and vitamin D–containing supplements was independently associated with a reduced fracture risk.

Conclusions
Both general and disease-specific factors contributed to fracture risk. The lower fracture risk among patients treated with DMARDs and vitamin D highlights the benefits of controlling inflammation and optimizing bone health. These findings provide robust, large-scale epidemiologic evidence from a Taiwanese population and underscore the importance of minimizing glucocorticoid exposure.

# Epidemiology and risk factors for fractures among patients with autoimmune diseases: a nationwide population-based study

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**Running title:** Risk factors for fractures with autoimmune diseases

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Numbers of Tables: 4
Numbers of Figures: 1
Numbers of Supplementary materials: 2

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## Introduction

Osteoporosis is characterized by low bone mass with microarchitectural disruption, skeletal fragility and a consequent increase in the risk of fractures, particularly of the hip and vertebrae. Autoimmune diseases are a group of disorders in which the immune system attacks healthy cells, causing inflammation in one or more organs. Systemic types of autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) affect multiple organs, while organ-specific types such as inflammatory bowel disease (IBD) target a single organ. Previous studies have reported that osteoporosis and fractures are more prevalent in patients with autoimmune diseases than in healthy individuals [1-3]. Contributing factors include the autoimmune disease per se [4], rheumatic disease-related factors including physical disability, and the long-term use of glucocorticoids [5], which reduces bone formation, increases bone resorption, and impairs calcium metabolism.

Conventional DMARDs (cDMARDs) treat autoimmune diseases by broadly modulating the immune system, thereby reducing chronic inflammation and slowing disease progression [6]. Pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6, play central roles in the pathogenesis of autoimmune diseases and disrupt bone homeostasis by increasing receptor activator of nuclear factor κB ligand expression and decreasing osteoprotegerin levels, thereby promoting osteoclastic bone loss [7, 8]. Biologic DMARDs (bDMARDs) target specific cytokines and have been shown to be effective in treating autoimmune diseases [9, 10]. By reducing inflammation, bDMARDs can theoretically preserve bone mass; however, studies investigating their effects on fracture risk are limited and the results have been conflicting [11-14].

Identifying modifiable risk factors in high-risk patients is therefore essential to optimize preventive strategies. Considering ethnic and racial differences in the prevalence of autoimmune diseases, this study aimed to comprehensively evaluate associations between demographic, disease-related, and treatment-related factors including the use of glucocorticoids, cDMARDs, and

bDMARDs with the risk of fractures in a large cohort of Taiwanese patients with autoimmune diseases.

## Material and methods

### Data source and study subjects

Data were obtained from the Health and Welfare Data Science Center. The National Health Insurance Research Database (NHIRD) contains complete detailed registry and claims data on medical service utilization for all enrollees in the National Health Insurance (NHI) program. The Taiwan NHI used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for medical diagnosis from 2000–2015. The ICD-9-CM codes of diseases and Anatomical Therapeutic Chemical codes of medications investigated in this study are shown in Supplementary Table I and Supplementary Table II, respectively. The Institutional Review Board of our institute waived the requirement for informed consent for this study (2019-07-016BC & 2019-08-004BC).

Patients with certain autoimmune diseases are defined as having a catastrophic illness by the Bureau of NHI. They may apply for a catastrophic illness certificate which exempts them from co-payments for related treatments. Certification requires a thorough evaluation by experts who confirm the diagnosis based on clinical findings, laboratory tests, and imaging according to established criteria. This retrospective cohort study enrolled patients aged >18 years in the catastrophic illness database who were newly diagnosed with an autoimmune disease including RA, SLE, systemic sclerosis (SSc), vasculitis, pemphigus, Sjögren's syndrome, polymyositis/dermatomyositis (PM/DM) and IBD between 2003 and 2014. The exclusion criteria were patients aged ≤18 years and those with pre-existing autoimmune diseases. The date of autoimmune disease onset was defined as the date of application for a catastrophic illness certificate. All patients were followed from the date of diagnosis with an autoimmune disease until the first diagnosis of fracture, death, or 31 December 2015, the end of the study period.

### Outcome

The primary outcome was the occurrence of a new clinical fracture after the diagnosis of an autoimmune disease. Fractures were defined as patients who had at least two outpatient or one inpatient visits for a fracture (ICD-9-CM 805-829). Fractures were grouped into eight categories: (1) vertebra; (2) hip/femur; (3) upper extremity (humerus, radius and ulna); (4) wrist and hand; (5) sternum/rib/clavicle/scapula; (6) lower leg (patella, tibia, fibula and ankle); (7) foot; and (8) pelvis and others.

**Covariates**

Variables potentially related to fractures including demographic factors (age and sex) and other comorbidities including osteoporosis, hyperthyroidism, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, obesity, malnutrition, testicular hypogonadism, menopause/postmenopause and alcoholism were retrieved. End-stage renal disease (ESRD) was confirmed by catastrophic illness certificates with the ICD-9-CM code 585. A history of prior fractures was identified as a fracture that occurred 3 years prior to the index date using the same definition as for the index fracture. The patients were categorized into younger (<65 years) and older (≥65 years) groups.

**Glucocorticoids, cDMARDs and bDMARDs**

Data on the use of systemic (oral or intravenous) glucocorticoids including betamethasone, dexamethasone, methylprednisolone, paramethasone, prednisolone, triamcinolone, hydrocortisone, and cortisone were extracted. Glucocorticoid exposure was calculated as the mean of the daily dosage of prednisone equivalent. Based on the median dose of mean daily prednisolone, we categorized mean daily prednisolone dosage into two groups: 0-1.67 mg/day and >1.67 mg/day. We also extracted data on the use of cDMARDs including sulfasalazine, methotrexate, leflunomide, azathioprine, cyclosporine, penicillamine, hydroxychloroquine, and cyclophosphamide, and

bDMARDs including TNF-α inhibitors, IL-6 inhibitor (tocilizumab) and selective T-cell co-stimulatory modulator (abatacept).

**Bone-protective medications and statins**

Data on the use of bone-protective medications including bisphosphonates, calcium, vitamin D, calcium combined with vitamin D supplements, and statins were also collected.

**Statistical analysis**

Continuous variables were presented as mean values with standard deviations, and categorical variables were presented as counts and percentages. Cumulative incidence was estimated using the Kaplan-Meier method. Univariate and multivariate Cox proportional hazards model analyses were performed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk factors associated with fractures. Variables with a p value < 0.05 in the univariate analysis were entered into the multivariate model. A p value < 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS version 21.0 (IBM Inc., Armonk, NY, USA).

## Results

### Demographic and clinical features

Table I summarizes the baseline characteristics of 68,296 patients with autoimmune diseases, including 53,564 (78.4%) females and 14,732 (21.6%) males (female-to-male ratio 3.6:1). The mean age at first autoimmune disease diagnosis was 51.9±15.4 years, and 21.7% of the patients were aged ≥65 years. Among the included patients, RA was the most common autoimmune disease. Overall, 30,443, 10,669, 1545, 1951, 1097, 18,599, 1684 and 2308 patients were diagnosed with RA, SLE, SSc, vasculitis, pemphigus, Sjögren's syndrome, PM/DM and IBD, respectively. During a follow-up period of 5.6±3.5 years, 10,709 (15.7%) patients were diagnosed with a new fracture, corresponding to a fracture incidence of 28.2 per 1000 person-years. A total of 389 patients had fractures at multiple sites, resulting in 11,141 fracture locations (Table II). Vertebral fractures were the most common (3565, 32.0%), followed by upper extremity (2096, 18.8%), hip/femur (1317, 11.8%), lower leg (1113, 10.0%), sternum/rib/clavicle/scapula (1030, 9.2%), foot (1020, 9.2%), wrist and hand (682, 6.1%), and pelvis and others (318, 2.9%). Figure 1 shows the Kaplan-Meier curve for the cumulative incidence of fractures during follow-up, with 4.0%, 6.6%, 8.9%, 13.3%, and 23.8% of the patients experiencing symptomatic fractures at 1, 2, 3, 5, and 10 years, respectively. In addition, 4616 (6.8%) of the patients had a fracture prior to the diagnosis of an autoimmune disease. The most prevalent comorbidities were hypertension (15.8%), diabetes mellitus (6.7%), hyperlipidemia (6.5%), chronic obstructive pulmonary disease (5.2%), coronary artery disease (5.1%), and osteoporosis (4.0%).

### Glucocorticoids and types of DMARDs

The mean daily doses of glucocorticoids in prednisone equivalent were higher in the fracture group than in the non-fracture group (4.4±9.7 mg/day vs 3.7±8.1 mg/day, $p<0.001$). Overall, 61,923 (90.7%) and 6627 (9.7%) patients were prescribed at least one cDMARD and bDMARD, respectively (Table III). Among the cDMARDs, hydroxychloroquine, methotrexate and sulfasalazine

were prescribed in 78.5%, 39.3% and 35.6% of the patients, respectively. TNF-α inhibitors were the most frequently prescribed bDMARD. A higher proportion of the patients without fractures received cDMARDs, including methotrexate, leflunomide, azathioprine, cyclosporine, penicillamine, hydroxychloroquine and cyclophosphamide, and bDMARDs including TNF-α inhibitor, IL-6 inhibitor and selective T-cell co-stimulatory modulator treatment.

**Bone-protective medications and statins**

Overall, 12,956 (19.0%) patients received any kind of bone-protective medication, of which calcium supplements were the most common (12.7%), followed by calcium combined with vitamin D preparations (5.2%) and bisphosphonates (4.2%). The prescription rate of statins was 18.4% (Table III).

**Univariate and multivariate analyses of the risk factors for fractures**

The results of the univariate and multivariate analyses of the risk factors for fractures are shown in Table IV. In univariate analysis, female sex, age at autoimmune disease onset ≥65 years, fracture in the 3 years prior to autoimmune disease onset, osteoporosis, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypogonadism and menopause/postmenopause, ESRD, alcoholism, mean dosage of glucocorticoids >1.67 mg/day, bisphosphonate therapy, and calcium with vitamin D were correlated with fractures. The patients with SLE, SSc, vasculitis, pemphigus, PM/DM and IBD had a significantly lower risk of fractures compared to those with RA. In addition, the patients with hyperthyroidism and those who used cDMARDs (sulfasalazine, methotrexate, leflunomide, azathioprine, cyclosporine, penicillamine, hydroxychloroquine and cyclophosphamide), bDMARDs (TNF-α inhibitors, IL-6 inhibitor and selective T-cell co-stimulatory modulator), vitamin D alone, and statins also had a significantly lower risk of fractures.

In multivariate logistic analysis, the independent risk factors for fractures were female sex (HR, 1.414; 95% CI, 1.342-1.491), age at autoimmune disease onset ≥65 years (HR, 2.366; 95% CI, 2.260-2.478), fracture in the 3 years prior to autoimmune disease onset (HR, 3.265; 95% CI, 3.102-3.437), osteoporosis (HR, 1.456; 95% CI, 1.362-1.557), hypertension (HR, 1.209; 95% CI, 1.149-1.272), diabetes mellitus (HR, 1.293; 95% CI, 1.211-1.380), hyperlipidemia (HR, 1.176; 95% CI, 1.098-1.259), cerebrovascular disease (HR, 1.125; 95% CI, 1.032-1.225), chronic obstructive pulmonary disease (HR, 1.171; 95% CI, 1.094-1.253), hypogonadism and menopause/postmenopause (HR, 1.104; 95% CI, 1.018-1.197), ESRD (HR, 1.356; 95% CI, 1.012-1.818), alcoholism (HR, 1.712; 95% CI, 1.299-2.256) and mean dosage of glucocorticoids >1.67 mg/day (HR, 1.873; 95% CI, 1.793-1.956). Compared with RA, SLE (HR, 0.488; 95% CI, 0.450-0.530), SSc (HR, 0.523; 95% CI, 0.435-0.630), vasculitis (HR, 0.570; 95% CI, 0.498-0.653), pemphigus (HR, 0.437; 95% CI, 0.364-0.526), Sjögren's syndrome (HR, 0.791; 95% CI, 0.746-0.838), PM/DM (HR, 0.661; 95% CI, 0.573-0.762) and IBD (HR, 0.414; 95% CI, 0.357-0.481) were associated with a lower risk of fractures. In addition, hyperthyroidism (HR, 0.827; 95% CI, 0.703-0.973), use of cDMARDs including sulfasalazine (HR, 0.753; 95% CI, 0.716-0.792), methotrexate (HR, 0.771; 95% CI, 0.732-0.813), leflunomide (HR, 0.831; 95% CI, 0.775-0.890), azathioprine (HR, 0.663; 95% CI, 0.620-0.709), cyclosporine (HR, 0.885; 95% CI, 0.815-0.961), hydroxychloroquine (HR, 0.634; 95% CI, 0.604-0.665), and cyclophosphamide (HR, 0.822; 95% CI, 0.742-0.911), bDMARDs including TNF-α inhibitors (HR, 0.664; 95% CI, 0.610-0.723), IL-6 inhibitor (HR, 0.224; 95% CI, 0.143-0.353), and selective T-cell co-stimulatory modulator (HR, 0.433; 95% CI, 0.310-0.604), vitamin D (HR, 0.626; 95% CI, 0.521-0.753), calcium with vitamin D (HR, 0.845; 95% CI, 0.785-0.908), and statins (HR, 0.542; 95% CI, 0.513-0.572) were inversely associated with the risk of fractures.

## Discussion

The World Health Organization's fracture risk assessment tool (FRAX) is widely used to predict the 10-year probability of a hip fracture or major osteoporotic fracture in the general population based on bone mineral density at the femoral neck as well as age, sex and multiple clinical factors. However, previous studies have shown that FRAX may underestimate fractures risk in individuals exposed to a glucocorticoid dose higher than 7.5 mg/day of prednisolone or equivalent [15] and those with diabetes [16]. Patients with autoimmune diseases have systemic inflammation due to immune dysregulation, long-term glucocorticoid exposure, and metabolic dysregulation such as diabetes, all of which contribute to a substantially increased fracture risk [17, 18]. Accurately identifying these risk factors is essential for optimizing preventive strategies and guiding treatment approaches.

Autoimmune diseases are known to disproportionately affect women, which may partially explain the higher fracture risk observed in this population. In the current study, the female predominance observed in SLE, RA, SSc, vasculitis, pemphigus, Sjögren's syndrome, and PM/DM reflects the inherent sex distribution of these autoimmune diseases rather than selection bias. Consistent with previous studies, we found that female sex, advanced age, and a history of prior fractures were strongly associated with fracture occurrence. In addition, vertebrae, upper extremity and femur were the most common fracture locations, which is consistent with previous reports [19].

In this study, the prevalence of comorbidities was high, and osteoporosis, hypertension, diabetes mellitus, cerebrovascular disease, chronic obstructive pulmonary disease, hypogonadism and menopause/postmenopause, ESRD and alcoholism were all associated with a higher risk of fractures, aligning with previous epidemiological findings [20, 21]. Notably, we also found that hyperlipidemia was associated with an increased risk of fractures, whereas statin use decreased this risk, supporting the hypothesis that statins may promote osteogenesis by enhancing osteoblast differentiation and reducing osteoclast activity [22-24]. However, hyperthyroidism was associated with a lower fracture

risk, which is inconsistent with earlier reports [25], possibly due to confounding by differences in disease severity and therapeutic management in our cohort.

Glucocorticoids are extensively used as the mainstay of therapy for many autoimmune diseases, and osteoporotic fractures have been reported in up to 30-50% of patients treated with long-term glucocorticoids [26, 27]. In our study, the patients who received a mean daily glucocorticoid dose >1.67 mg/day prednisone equivalent had an approximately 1.87-fold higher risk of fractures. Glucocorticoids accelerate bone loss directly by inhibiting osteoblastogenesis, increasing osteoblast apoptosis and inducing osteoclastogenesis [28], and indirectly by reducing intestinal calcium absorption and increasing renal calcium wasting, thereby leading to a negative calcium balance and secondary hyperparathyroidism. In addition, long-term glucocorticoid therapy may lead to suboptimal serum 25(OH) vitamin D concentrations [29] and secondary hypogonadotropic hypogonadism [30], thereby exacerbating bone loss and skeletal fragility.

Previous studies have reported that patients with autoimmune diseases including RA [31], SLE [32], SSc [33], ankylosing spondylitis [34], PM/DM [35], and psoriasis [36] have higher rates of osteoporosis and fractures than the general population. In this study, we found that the incidence of fractures was higher in the RA patients than in those with other autoimmune diseases (32.0 vs 24.9 per 1000 person-years, respectively) even though their average glucocorticoid dose was significantly lower than that in the patients with other autoimmune diseases (3.1±5.3 vs 4.4±10.2 mg/day). Therefore, we speculate that other RA-specific factors may be involved in the high risk of osteoporosis and fractures. First, pro-inflammatory cytokines involved in the pathogenesis of RA such as TNF-α, IL-6 and IL-17 play relevant roles in upregulating osteoclastogenic cytokines [37]. Second, decreased physical activity, long duration of RA, older age, postmenopausal status, and sarcopenia all have deleterious effects on bone mass. Third, RA-specific anti-citrullinated

protein/peptide antibodies participate in bone destruction by mediating osteoclast differentiation and inflammation [38].

Previous studies have reported the development of methotrexate osteopathy in children receiving high-dose methotrexate therapy for acute lymphoblastic leukemia, as well as in adult patients undergoing low-dose methotrexate therapy for various autoimmune diseases. However, growing evidence indicates that low-dose methotrexate does not have a detrimental effect on bone in the absence of the concomitant use of glucocorticoids [39]. Hydroxychloroquine is a crucial background treatment for most patients with SLE. Both in vivo and in vitro studies have demonstrated that hydroxychloroquine inhibits osteoclastic activity, which may have a favorable effect on bone mineral density [40]. In addition, sulfasalazine has been shown to enhance mesenchymal stem cell osteogenic differentiation [41], while azathioprine does not appear to induce osteoporosis as a prominent side effect [42]. Reduced $1,25(OH)_2$ vitamin D production and secondary hyperparathyroidism resulting from calcineurin inhibitor–associated nephrotoxicity have been proposed as mechanisms that contribute to cyclosporine-induced bone loss after transplantation, whereas its use in rheumatic diseases is not typically associated with increased fracture risk [43]. In our cohort, cDMARDs including sulfasalazine, methotrexate, leflunomide, azathioprine, cyclosporine, hydroxychloroquine and cyclophosphamide were all associated with a decreased risk of fractures.

From a pathophysiological point of view, biologic therapies may control disease activity, lower inflammation status and decrease the use of glucocorticoids, and are considered to have potentially beneficial effects on osteoporosis and fractures. In the current study, the use of bDMARDs including TNF-α inhibitors, IL-6 inhibitor and selective T-cell co-stimulatory modulator was associated with a reduced risk of fractures. bDMARDs may exert a protective effect by simultaneously suppressing inflammation and inhibiting osteoclastogenesis mediated by pro-inflammatory cytokines [7, 44].

However, the results of previous studies on the effect of bDMARD therapy on the risk of fractures have been inconsistent. Several studies have reported that bDMARDs show promise in counteracting hand bone [45] and spine bone loss [11, 12, 46], and Chen et al. [47] reported that abatacept had a better bone mineral density-preserving effect than cDMARDs and TNF-α inhibitors in patients with RA. However, another study reported that although bDMARDs had beneficial effects on bone mineral density, they did not seem to substantially reduce the incidence of fractures [14]. In addition, a meta-analysis showed that while bDMARDs did not decrease the risk of fractures in patients with RA, SLE and IBD, they significantly decreased the risk of fractures in patients with psoriasis and psoriatic arthritis [13]. Epidemiological evidence suggests that vitamin D deficiency is highly prevalent in patients with autoimmune diseases and related to disease development and severity [48]. In our cohort, only 19.0% of patients were prescribed calcium or vitamin D supplements. The low prescription rate of vitamin D likely due to restrictions in the NHI program, which only covers the cost of these supplements for specific patient groups, such as those with renal insufficiency. Records of self-paid or out-of-pocket vitamin D and calcium supplements are not included in the NHIRD. Our findings suggest that vitamin D supplementation may confer protective effects against fractures, highlighting the need for clinicians to monitor vitamin D status and consider supplementation to protect bone health in this high-risk population. Although bisphosphonates have proven efficacy in preventing osteoporotic fractures, long-term use carries a small risk of atypical femur fractures [49, 50]. Overall, the benefits of bisphosphonate therapy generally outweigh potential harms [51]. In this cohort, bisphosphonate use was not associated with a significant reduction in fracture risk. Clinicians should tailor bone-protective strategies based on the fracture risk profile of individual patients.

A strength of this study is its comprehensive assessment of comorbidities and treatments on fracture risk in patients with autoimmune diseases using a large, nationally representative cohort. However, several limitations should be acknowledged. First, fractures were determined using ICD-9-

CM codes which only capture symptomatic fractures, whereas asymptomatic vertebral fractures were likely undiagnosed. Second, as a retrospective cohort study using claims data, detailed clinical information such as X-rays, calcium measurements, anti-citrullinated protein/peptide antibodies, disease activity and patient lifestyle factors such as caffeine intake, dietary habits, body mass index, physical activity, family history, and treatment adherence was unavailable. Third, the 25(OH) vitamin D test is not covered by the NHI program and must be self-paid. Therefore, we could not evaluate the impact of 25(OH) vitamin D levels on fractures. Fourth, the NHI guidelines restrict the prescription of bDMARDs for specific patients with active disease who have received a full dose of cDMARDs, which may have influenced the treatment patterns in our cohort.

In conclusion, this large, nationwide cohort study showed that female sex, age ≥65 years, a prior fracture, RA, or a mean glucocorticoid dose >1.67 mg/day prednisone equivalent had a higher risk of fractures. In contrast, treatment with cDMARDs, bDMARDs, bone-protective medications including vitamin D alone or combined with calcium, and statins was associated with a lower fracture risk. These findings highlight the importance of targeted fracture prevention strategies for high-risk patients with autoimmune diseases. In particular, low-dose glucocorticoid therapy combined with DMARD treatment and adequate vitamin D supplementation may help reduce their fracture risk. Future prospective research should evaluate interventions to reduce fracture risk and further clarify optimal glucocorticoid and DMARD regimens in patients with autoimmune diseases.

## Conflict of Interest

The authors declare no conflict of interest.


## Funding Source

The research was supported by a grant from Taipei Veterans General Hospital (V112C-133).

## Acknowledgements

This work was supported by a grant from Taipei Veterans General Hospital (V112C-133). We also thank Chang-Yi Tsai for her contribution to the preparation of the graphical abstract.


## Ethical approval

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital, and the need for informed consent was waived.

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**Legends**

Figure 1

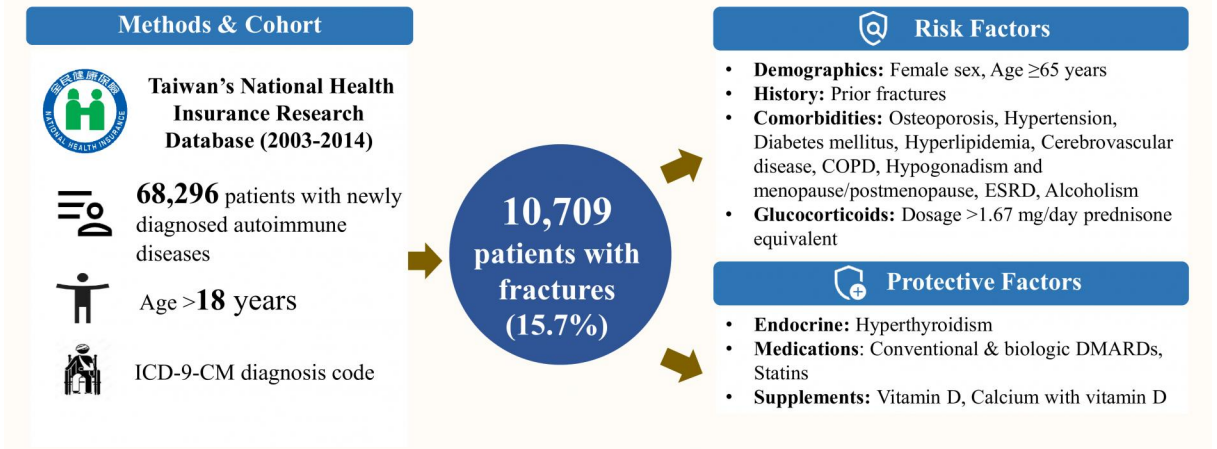
Kaplan-Meier curve for the cumulative incidence of fractures in patients with autoimmune diseases. The cumulative incidence of fractures was 4.0% at 1 year, 13.3% at 5 years, and 23.8% at 10 years.

Graphical abstract

This graphical abstract shows factors associated with fractures in patients with autoimmune diseases based on nationwide population data.

*ICD-9-CM - International Classification of Diseases, Ninth Revision, Clinical Modification, COPD - chronic obstructive pulmonary disease, ESRD - end-stage renal disease, DMARD - disease-modifying antirheumatic drug, RA - rheumatoid arthritis.*

# Epidemiology and risk factors for fractures among patients with autoimmune diseases: a nationwide population-based study




## Conclusions

Glucocorticoid dosage >1.67 mg/day prednisone equivalent was associated with a higher risk, and RA was associated with a higher risk compared to the other autoimmune diseases. Conventional or biologic DMARDs and vitamin D-containing supplements were associated with a reduced risk.

Table I Demographic and clinical characteristics of the patients with autoimmune diseases with and without fractures

| Variables | Total n=68296 | Fracture n=10709 | Without fracture n=57587 |
|---|---|---|---|
| Female | 53564 (78.4%) | 8846 (82.6%) | 44718 (77.1%) |
| Age at onset of autoimmune disease (years) | 51.9±15.4 | 59.9±14.3 | 50.4±15.2 |
| Age at autoimmune disease ≥65 years | 14854 (21.7%) | 4317 (40.3%) | 10537 (18.3%) |
| History of previous fracture | 4616 (6.8%) | 1968 (18.4%) | 2648 (4.6%) |
| Autoimmune disease | | | |
| RA | 30443 (44.6%) | 5682 (53.1%) | 24761 (43.0%) |
| SLE | 10669 (15.6%) | 1112 (10.4%) | 9557 (16.6%) |
| SSc | 1545 (2.3%) | 187 (1.7%) | 1358 (2.4%) |
| Vasculitis | 1951 (2.9%) | 252 (2.4%) | 1699 (3.0%) |
| Pemphigus | 1097 (1.6%) | 129 (1.2%) | 968 (1.7%) |
| Sjögren's syndrome | 18599 (27.2%) | 2918 (27.2%) | 15681 (27.2%) |
| PM/DM | 1684 (2.5%) | 223 (2.1%) | 1461 (2.5%) |
| IBD | 2308 (3.4%) | 206 (1.9%) | 2102 (3.7%) |
| Comorbidity | | | |
| Osteoporosis | 2727 (4.0%) | 1147 (10.7%) | 1580 (2.7%) |
| Hyperthyroidism | 919 (1.3%) | 149 (1.4%) | 770 (1.3%) |
| Hypertension | 10777 (15.8%) | 2899 (27.1%) | 7878 (13.7%) |
| Diabetes mellitus | 4545 (6.7%) | 1230 (11.5%) | 3315 (5.8%) |
| Hyperlipidemia | 4448 (6.5%) | 1120 (10.5%) | 3328 (5.8%) |
| Coronary artery disease | 3513 (5.1%) | 987 (9.2%) | 2526 (4.4%) |
| Cerebrovascular disease | 2154 (3.2%) | 608 (5.7%) | 1546 (2.7%) |
| Chronic obstructive pulmonary disease | 3533 (5.2%) | 990 (9.2%) | 2543 (4.4%) |
| Obesity | 132 (0.2%) | 28 (0.3%) | 104 (0.2%) |
| Malnutrition | 133 (0.2%) | 20 (0.2%) | 113 (0.2%) |
| Hypogonadism and menopause/postmenopause | 2558 (3.7%) | 682 (6.4%) | 1876 (3.3%) |
| End-stage renal disease | 244 (0.4%) | 46 (0.4%) | 198 (0.3%) |
| Alcoholism | 224 (0.3%) | 51 (0.5%) | 173 (0.3%) |

*Data are presented as mean ± SD or n (%).*

*RA - rheumatoid arthritis, SLE - systemic lupus erythematosus, SSc - systemic sclerosis, PM/DM - polymyositis/dermatomyositis, IBD - inflammatory bowel disease.*

Table II Distribution of fractures by anatomical site

| **Fracture location** | **n (%)** |
|---|---|
| Vertebra | 3565 (32.0%) |
| Hip/Femur | 1317 (11.8 %) |
| Upper extremity | 2096 (18.8%) |
| Wrist and hand | 682 (6.1%) |
| Sternum/rib/clavicle/scapula | 1030 (9.2%) |
| Lower leg | 1113 (10.0%) |
| Foot | 1020 (9.2%) |
| Pelvis and others | 318 (2.9%) |
| **Total** | **11141 (100%)** |

*Data are presented as n (%).*
*Percentages are calculated for the total number of fracture locations.*

Table III Pharmacological treatments of the patients with autoimmune diseases with and without fractures.

| Variables | Total n=68296 | Fracture n=10709 | Without fracture n=57587 |
|---|---|---|---|
| Glucocorticoid | | | |
| Mean dosage of daily glucocorticoids (mg/day) | 3.8±8.4 | 4.4±9.7 | 3.7±8.1 |
| Mean dosage of glucocorticoids >1.67 mg/day | 34157 (50%) | 5863 (54.7%) | 28294 (49.1%) |
| cDMARD | | | |
| Sulfasalazine | 24290 (35.6%) | 3886 (36.3%) | 20404 (35.4%) |
| Methotrexate | 26853 (39.3%) | 4033 (37.7%) | 22820 (39.6%) |
| Leflunomide | 8030 (11.8%) | 1141 (10.7%) | 6889 (12.0%) |
| Azathioprine | 12226 (17.9%) | 1250 (11.7%) | 10976 (19.1%) |
| Cyclosporine | 5360 (7.8%) | 692 (6.5%) | 4668 (8.1%) |
| Penicillamine | 1622 (2.4%) | 226 (2.1%) | 1396 (2.4%) |
| Hydroxychloroquine | 53643 (78.5%) | 8032 (75.0%) | 45611 (79.2%) |
| Cyclophosphamide | 3682 (5.4%) | 422 (3.9%) | 3260 (5.7%) |
| bDMARD | | | |
| TNF-α inhibitor | 6062 (8.9%) | 686 (6.4%) | 5376 (9.3%) |
| IL-6 inhibitor | 712 (1.0%) | 19 (0.2%) | 693 (1.2%) |
| Selective T-cell co-stimulatory modulator | 619 (0.9%) | 35 (0.3%) | 584 (1.0%) |
| Bone-protective medication | | | |
| Bisphosphonate | 2872 (4.2%) | 919 (8.6%) | 1953 (3.4%) |
| Calcium | 8672 (12.7%) | 1769 (16.5%) | 6903 (12.0%) |
| Vitamin D | 864 (1.3%) | 116 (1.1%) | 748 (1.3%) |
| Calcium with vitamin D | 3585 (5.2%) | 837 (7.8%) | 2748 (4.8%) |
| Statin | 12587 (18.4%) | 1737 (16.2%) | 10850 (18.8%) |

*Data are presented as mean ± SD or n (%).*

*cDMARD - conventional disease-modifying antirheumatic drug, bDMARD - biologic disease-modifying antirheumatic drug, TNF-α - tumor necrosis factor-α, IL - interleukin.*

Table IV Univariate and multivariate Cox regression analyses of risk factors for fractures in the patients with autoimmune diseases

| Variables | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| Female | 1.249 (1.188-1.313) | <0.001 | 1.414 (1.342-1.491) | <0.001 |
| Age at autoimmune disease ≥65 years | 3.482 (3.349-3.620) | <0.001 | 2.366 (2.260-2.478) | <0.001 |
| History of previous fracture | 4.760 (4.533-5.000) | <0.001 | 3.265 (3.102-3.437) | <0.001 |
| Autoimmune disease | | | | |
| RA | 1 (Reference) | | 1 (Reference) | |
| SLE | 0.547 (0.513-0.583) | <0.001 | 0.488 (0.450-0.530) | <0.001 |
| SSc | 0.715 (0.618-0.827) | <0.001 | 0.523 (0.435-0.630) | <0.001 |
| Vasculitis | 0.634 (0.559-0.719) | <0.001 | 0.570 (0.498-0.653) | <0.001 |
| Pemphigus | 0.686 (0.576-0.816) | <0.001 | 0.437 (0.364-0.526) | <0.001 |
| Sjögren's syndrome | 0.978 (0.935-1.022) | 0.319 | 0.791 (0.746-0.838) | <0.001 |
| PM/DM | 0.837 (0.732-0.957) | 0.009 | 0.661 (0.573-0.762) | <0.001 |
| IBD | 0.528 (0.460-0.607) | <0.001 | 0.414 (0.357-0.481) | <0.001 |
| Comorbidity | | | | |
| Osteoporosis | 2.722 (2.560-2.894) | <0.001 | 1.456 (1.362-1.557) | <0.001 |
| Hyperthyroidism | 0.808 (0.688-0.950) | 0.010 | 0.827 (0.703-0.973) | 0.022 |
| Hypertension | 2.000 (1.917-2.087) | <0.001 | 1.209 (1.149-1.272) | <0.001 |
| Diabetes mellitus | 1.922 (1.812-2.040) | <0.001 | 1.293 (1.211-1.380) | <0.001 |
| Hyperlipidemia | 1.455 (1.367-1.548) | <0.001 | 1.176 (1.098-1.259) | <0.001 |
| Coronary artery disease | 1.877 (1.758-2.004) | <0.001 | 1.034 (0.963-1.110) | 0.357 |
| Cerebrovascular disease | 2.108 (1.942-2.288) | <0.001 | 1.125 (1.032-1.225) | 0.007 |
| Chronic obstructive pulmonary disease | 1.816 (1.701-1.938) | <0.001 | 1.171 (1.094-1.253) | <0.001 |
| Obesity | 1.113 (0.768-1.613) | 0.572 | | |
| Malnutrition | 1.232 (0.794-1.910) | 0.351 | | |
| Hypogonadism and menopause/postmenopause | 1.253 (1.160-1.355) | <0.001 | 1.104 (1.018-1.197) | 0.017 |
| End-stage renal disease | 1.727 (1.293-2.307) | <0.001 | 1.356 (1.012-1.818) | 0.041 |
| Alcoholism | 1.581 (1.201-2.081) | <0.001 | 1.712 (1.299-2.256) | <0.001 |
| Mean daily dosage of glucocorticoids >1.67 mg/day | 1.285 (1.237-1.335) | <0.001 | 1.873 (1.793-1.956) | <0.001 |
| cDMARD | | | | |
| Sulfasalazine | 0.872 (0.839-0.908) | <0.001 | 0.753 (0.716-0.792) | <0.001 |
| Methotrexate | 0.820 (0.788-0.852) | <0.001 | 0.771 (0.732-0.813) | <0.001 |
| Leflunomide | 0.739 (0.695-0.786) | <0.001 | 0.831 (0.775-0.890) | <0.001 |
| Azathioprine | 0.532 (0.502-0.564) | <0.001 | 0.663 (0.620-0.709) | <0.001 |
| Cyclosporine | 0.645 (0.597-0.696) | <0.001 | 0.885 (0.815-0.961) | 0.004 |
| Penicillamine | 0.752 (0.659-0.858) | <0.001 | 0.866 (0.735-1.021) | 0.087 |
| Hydroxychloroquine | 0.704 (0.674-0.736) | <0.001 | 0.634 (0.604-0.665) | <0.001 |
| Cyclophosphamide | 0.600 (0.544-0.661) | <0.001 | 0.822 (0.742-0.911) | <0.001 |

| | | | | |
|---|---|---|---|---|
| bDMARD | | | | |
| TNF-α inhibitor | 0.584 (0.540-0.631) | <0.001 | 0.664 (0.610-0.723) | <0.001 |
| IL-6 inhibitor | 0.147 (0.094-0.230) | <0.001 | 0.224 (0.143-0.353) | <0.001 |
| Selective T-cell co-stimulatory modulator | 0.342 (0.246-0.477) | <0.001 | 0.433 (0.310-0.604) | <0.001 |
| Bone-protective medication | | | | |
| Bisphosphonate | 2.100 (1.963-2.247) | <0.001 | 1.032 (0.961-1.109) | 0.385 |
| Calcium | 1.039 (0.987-1.094) | 0.142 | | |
| Vitamin D | 0.716 (0.596-0.860) | <0.001 | 0.626 (0.521-0.753) | <0.001 |
| Calcium with vitamin D | 1.120 (1.043-1.202) | 0.002 | 0.845 (0.785-0.908) | <0.001 |
| Statin | 0.715 (0.679-0.753) | <0.001 | 0.542 (0.513-0.572) | <0.001 |

*RA - rheumatoid arthritis, SLE - systemic lupus erythematosus, SSc - systemic sclerosis, PM/DM - polymyositis/dermatomyositis, IBD - inflammatory bowel disease, cDMARD - conventional disease-modifying antirheumatic drug, bDMARD - biologic disease-modifying antirheumatic drug, TNF-α - tumor necrosis factor-α, IL - interleukin, HR - hazard ratio, CI - confidence interval.*

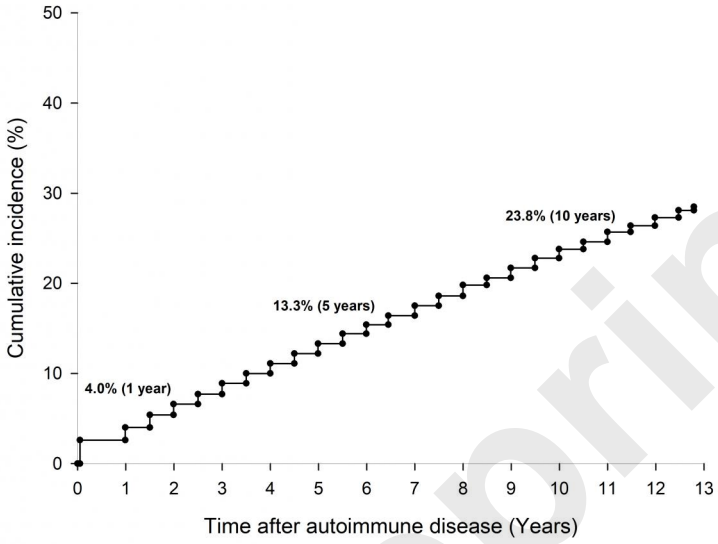





Figure 1