

Increased Risk of Acute Myocardial Infarction in Systemic Sclerosis: A Nationwide Population-based Study

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ABSTRACT

PURPOSE: Systemic sclerosis is a life-threatening autoimmune disease characterized by vasculopathy, which results in myocardial involvement in an extremely high percentage of patients. Nevertheless, there have been no large-scale epidemiological studies about the risk of acute myocardial infarction in patients with systemic sclerosis. The aims of this study were to evaluate the hazard ratio (HR) and risk factors of acute myocardial infarction in patients with systemic sclerosis, as well as to compare the risks of acute myocardial infarction among systemic sclerosis patients taking different immunosuppressors.

METHODS: The study cohort included 1344 patients with systemic sclerosis and 13,440 (1:10) age-, sex-, and comorbidity-matched controls during the period between 1997 and 2006, from the National Health Insurance Research Database. We compared the risk of acute myocardial infarction between patients with systemic sclerosis and controls and calculated the adjusted HRs for acute myocardial infarction in systemic sclerosis patients taking immunosuppressors and not taking immunosuppressors.

RESULTS: The incidence rates of acute myocardial infarction were 535 and 313 cases per 100,000 person-years for systemic sclerosis cohort and reference cohort, respectively ($P < .001$, unadjusted). After adjusting for age, sex, and underlying medical diseases on Cox proportional hazards model, systemic sclerosis was found to be an independent risk factor for acute myocardial infarction (HR 2.45). Other risk factors included hypertension (HR 2.08) and diabetes (HR 2.14). The multivariate adjusted HR for acute myocardial infarction did not decrease among the systemic sclerosis patients taking systemic steroids, penicillamine, cyclophosphamide, azathioprine, methotrexate, or cyclosporine.

CONCLUSION: Systemic sclerosis is independently associated with an increased risk of acute myocardial infarction. Immunosuppressors do not lower the risk of acute myocardial infarction in our study.

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KEYWORDS: Cardiovascular risk; Coronary artery disease; Immunosuppressor; Myocardial infarction; Systemic sclerosis

Systemic sclerosis is a connective tissue disease characterized by vascular abnormalities and immune dysfunction, leading to fibrosis of skin and internal organs.^{1,2} The

pathogenesis of systemic sclerosis is complex and poorly understood. However, endothelial cell dysfunction is one of the essential factors and culminates in vasculopathy.^{1,3,4}

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Microvascular disease in systemic sclerosis has been well established, with presentation of Raynaud's phenomenon, pulmonary arterial hypertension, and scleroderma renal crisis. However, whether there is macrovascular involvement in systemic sclerosis is still under debate.³⁻⁵

Cardiac involvement is not unusual in systemic sclerosis. Recent studies have demonstrated that cardiac disease occurs in up to 80% of systemic sclerosis patients and is the leading cause of mortality.^{5,6} Systemic sclerosis can affect myocardium, conduction system, cardiac valves, and pericardium.⁷ Myocardial disease is the most prevalent and is postulated to contribute to microvascular ischemia.^{4,6,8} Several case series have found that acute myocardial infarction occurs in systemic sclerosis patients in the absence of significant coronary atherosclerosis, the most critical cause of acute coronary syndrome in the general population, suggesting that microvascular disease plays a role in acute myocardial infarction in systemic sclerosis patients.^{4,9,10} In addition, a previous study has revealed that calcium channel blockers are important in the treatment of microvascular ischemia and in the prevention of systolic dysfunction in systemic sclerosis patients.¹¹ Nonetheless, there have been no large-scale cohort studies conducted on the roles of immunosuppressors, such as systemic steroids, penicillamine, cyclophosphamide, azathioprine, methotrexate, and cyclosporine, in decreasing cardiac complications in patients with systemic sclerosis. Therefore, our study aimed to evaluate the association between systemic sclerosis and acute myocardial infarction using a nationwide Taiwanese population-based dataset and to elucidate the effects of different immunosuppressors on acute myocardial infarction.

METHODS

Data Sources

In this study, published data from the National Health Insurance Research Database (NHIRD) released by the National Health Research Institute of Taiwan was analyzed. Taiwan began its National Health Insurance (NHI) program in 1995 to finance health care for all of its residents. The coverage rate was up to 99% at the end of 2004.¹² There are currently more than 25 million people enrolled in the program, and 92% of all health providers are contracted to the Bureau of NHI.¹³ The database comprises comprehensive information on insured subjects, such as scrambled identification number, date of birth, sex, diagnostic codes in the

format of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and dates of outpatient visits. The accuracy of diagnosis of major diseases in the NHIRD, such as diabetes mellitus, hypertension, and stroke, has been well validated.¹⁴⁻¹⁶ This database is one of the largest nationwide population-based databases

in the world and has been used extensively in many epidemiologic studies.^{17,18} This study was approved by the Institutional Review Board of Taipei Veterans General Hospital.

Study Sample

Between January 1, 1997 and December 31, 2006, we identified all patients diagnosed with systemic sclerosis by the diagnostic code of "systemic sclerosis" (ICD-9-CM code 710.1) from the catastrophic illness database, a subset of the NHIRD. The NHI specifies 31 categories of catastrophic illness (eg, cancers, chronic kidney disease, autoimmune diseases) of which systemic sclerosis is statutorily included. Attending physicians

can apply for a catastrophic illness certificate on behalf of their systemic sclerosis patients according to Department of Health guidelines if there is the presence of Raynaud's phenomenon, typical skin thickening associated with additional extracutaneous features, capillaroscopic abnormalities, and relevant autoantibodies.¹⁹ Applications are reviewed by a committee and approved patients are exempted from copayment.

We excluded patients who had been diagnosed with systemic sclerosis before 1997 ($n = 136$) because this study enrolled only incident systemic sclerosis patients. Patients with myocardial infarction (ICD-9-CM codes 410 and 412) before the diagnosis of systemic sclerosis ($n = 65$) and patients younger than 18 years ($n = 105$) also were excluded. A total of 1344 systemic sclerosis patients were finally included. Systemic treatments, including steroids, penicillamine, cyclophosphamide, azathioprine, methotrexate, and cyclosporine, were further identified in systemic sclerosis patients to evaluate the effects of these immunosuppressors on acute myocardial infarction.

Data from the longitudinal health insurance database 2000 (LHID 2000), a subset of the NHIRD, was used for comparison. The LHID 2000 contains all medical claims data for one million beneficiaries randomly sampled from the Registry of the NHIRD. There are no statistically significant differences in age, sex, or health care costs between the sample group and the original registered population, as reported by the National Health Research Institute of Taiwan.^{20,21} We randomly selected 10 individuals for each

CLINICAL SIGNIFICANCE

- Patients with systemic sclerosis have an increased risk of acute myocardial infarction.
- In addition to macrovascular diseases, microvascular impairment followed by repeated focal ischemia and subsequent widespread fibrosis may be predominantly responsible for myocardial infarction in patients with systemic sclerosis.
- Immunosuppressors, including penicillamine, systemic steroids, cyclophosphamide, azathioprine, methotrexate, and cyclosporine, do not lower the risk of acute myocardial infarction in our study.

systemic sclerosis patient from the LHID 2000 to serve as the control cohort. The controls had no diagnostic codes for systemic sclerosis. In addition, subjects with preexisting myocardial infarction before enrollment were excluded. The age, sex, time of enrollment, and comorbidities such as hypertension (ICD-9 code 401-405), diabetes (ICD-9 code 250), coronary artery disease (ICD-9 code 411-414), dyslipidemia (ICD-9 code 272), atrial fibrillation (ICD-9 code 427.31), peripheral arterial occlusive disease (ICD-9 code 444.2), chronic obstructive pulmonary disease (ICD-9 code 493.2), and chronic kidney disease (ICD-9 code 580-587) were matched between systemic sclerosis and control groups. Comorbid diseases were counted only if the condition occurred in the inpatient setting or in 2 or more outpatient visits. The outcome of acute myocardial infarction was defined by the diagnostic code of "acute myocardial infarction" (ICD-9-CM code 410). Patients coding with this ICD-9 code in Taiwan must fulfill at least 2 of the 3 criteria, including anginal symptoms, typical electrocardiographic changes, and elevated serum cardiac enzyme.

Follow-up began on the date of first diagnosis of systemic sclerosis in the case cohort and on the same day in the matched control cohort and ended on the date of censorship, which was the date of diagnosis of acute myocardial infarction, death, transfer out, or the end of 2009.

Statistical Analysis

We first analyzed the demographic data of the study subjects. Continuous data are presented as mean \pm SD, with comparisons between groups performed by Student *t* test. Categorical data were analyzed by Pearson chi-squared test or Fisher's exact test where appropriate. The acute myocardial infarction-free survival was estimated using the Kaplan-Meier method and compared by log-rank test.

To determine the independent risk factors for acute myocardial infarction, Cox proportional hazards model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) after adjusting for age, sex, and comorbidities including hypertension, diabetes, coronary artery disease, dyslipidemia, atrial fibrillation, peripheral arterial occlusive disease, chronic obstructive pulmonary disease, and chronic kidney disease. The assumption of proportional hazards was confirmed by plotting the graph of the survival function versus the survival time and the graph of the log (-log [survival]) versus the log of survival time. We also calculated the multivariate adjusted HR for acute myocardial infarction in systemic sclerosis patients taking systemic steroids, penicillamine, or other immunosuppressors, including cyclophosphamide, azathioprine, methotrexate, and cyclosporine. Adjusted variables included age, sex, and underlying medical disorders. A 2-tailed *P* value of $<.05$ was considered statistically significant.

Sensitivity analyses were conducted for "frequent user" and "infrequent user" of systemic steroids, penicillamine, or other immunosuppressors, respectively. "Frequent user" was defined as: the duration of immunosuppressor use was

equal to or longer than the median duration of this immunosuppressor. "Infrequent user" was defined as: the duration of immunosuppressor use was less than the median duration of this immunosuppressor. These sensitivity analyses were conducted with the purpose to examine whether the main findings were robust.

Microsoft SQL Server 2000 (Microsoft Corporation, Redmond, Wash) and SPSS statistics analysis package (version 17.0; SPSS for Windows, Chicago, Ill) were used to analyze the data in this study.

RESULTS

A total of 1344 systemic sclerosis patients were identified in this study, including 1017 (75.7%) females and 327 (24.3%) males. The mean age of patients with systemic sclerosis was 50.6 ± 14.4 years. The mean follow-up times were 4.3 ± 2.9 and 4.8 ± 2.8 years in the systemic sclerosis cohort and reference cohort, respectively. The demographic characteristics and comorbid medical diseases of systemic sclerosis patients and controls are listed in **Table 1**. There were no significant differences in age, sex, or medical comorbidities between systemic sclerosis patients and control subjects.

A total of 31 events of acute myocardial infarction occurred in the systemic sclerosis cohort, resulting in an incidence rate of 535 acute myocardial infarctions per 100,000 person-years. In the reference cohort, 203 acute myocardial infarction events occurred, corresponding to an incidence rate of 313 acute myocardial infarctions per 100,000 person-years. There was a significantly increased incidence rate of acute myocardial infarction in systemic sclerosis patients when compared with controls (unadjusted *P* value $<.001$, **Table 1**). The log-rank test showed

Table 1 Characteristics of Case Cohort and Control Cohort

Characteristics	Control (n = 13,440)	Systemic Sclerosis (n = 1344)	<i>P</i> Value
Age, years, mean \pm SD	50.6 \pm 14.4	50.6 \pm 14.4	1.000
Female, n (%)	10170 (75.7)	1017 (75.7)	1.000
Follow-up years, mean \pm SD	4.8 \pm 2.8	4.3 \pm 2.9	$<.001$
Hypertension, n (%)	3121 (23.2)	312 (23.2)	.990
Diabetes, n (%)	1630 (12.1)	163 (12.1)	1.000
CAD, n (%)	2358 (17.5)	236 (17.6)	.978
Dyslipidemia, n (%)	2630 (19.6)	263 (19.6)	1.000
PAOD, n (%)	220 (1.6)	23 (1.7)	.683
AF, n (%)	193 (1.4)	20 (1.5)	.760
CKD, n (%)	1989 (14.8)	199 (14.8)	.988
COPD, n (%)	2711 (20.2)	271 (20.2)	.990
AMI, n (%)	203 (1.5)	31 (2.3)	$<.001$
AMI, incidence rate (events per 100,000 person-years)	203 (313)	31 (535)	$<.001$

AF = atrial fibrillation; AMI = acute myocardial infarction; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; PAOD = peripheral arterial occlusive disease; SD = standard deviation.

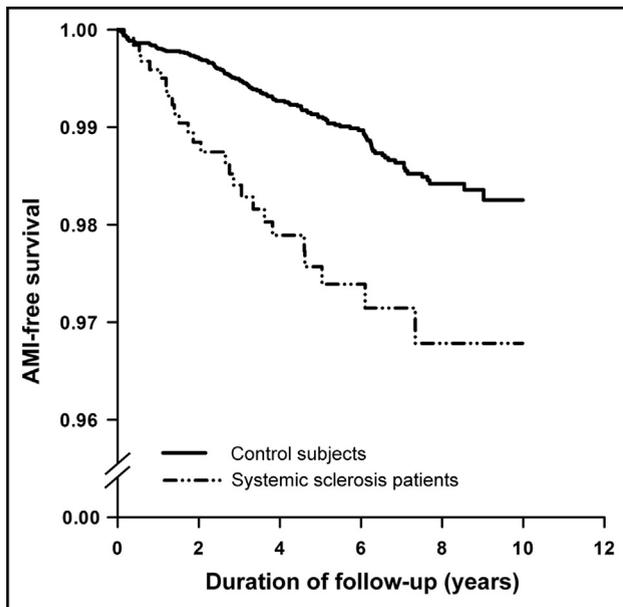


Figure Acute myocardial infarction-free survival of patients with systemic sclerosis and control subjects in Taiwan. AMI = acute myocardial infarction.

significantly lower acute myocardial infarction-free survival in patients with systemic sclerosis when compared with the control group ($P < .001$, **Figure**).

Cox proportional hazards model was used to identify the independent risk factors for acute myocardial infarction. After adjusting for age, sex, and underlying medical comorbidities, the HR for acute myocardial infarction in systemic sclerosis patients was 2.45 (95% CI, 1.60-3.75; $P < .001$) times greater than that for control subjects (**Table 2**). The sex effect was further examined and the results showed that both female and male systemic sclerosis patients were at increased risk of acute myocardial infarction. Additionally, hypertension (HR 2.08; 95% CI, 1.42-3.07) and diabetes (HR 2.14; 95% CI, 1.44-3.18) were independently

associated with acute myocardial infarction, while coronary artery disease (HR 1.13; 95% CI, 0.76-1.67), dyslipidemia (HR 0.95; 95% CI, 0.63-1.41), peripheral arterial occlusive disease (HR 0.82; 95% CI, 0.26-2.61), atrial fibrillation (HR 1.06; 95% CI, 0.43-2.65), chronic kidney disease (HR 0.88; 95% CI, 0.58-1.34), and chronic obstructive pulmonary disease (HR 0.69; 95% CI, 0.46-1.04) were not related to increased HR for acute myocardial infarction (**Table 2**).

We next conducted multivariate analysis to determine the effect of immunosuppressors on acute myocardial infarction in patients with systemic sclerosis. After adjusting for demographic factors and underlying medical diseases, the risk of acute myocardial infarction was similar between patients taking immunosuppressors and patients not taking immunosuppressors. The multivariate adjusted HRs for penicillamine (HR 0.96; 95% CI, 0.39-2.34), systemic steroids (HR 1.41; 95% CI, 0.64-3.09), and other immunosuppressors including cyclophosphamide, azathioprine, methotrexate, and cyclosporine (HR 0.83; 95% CI 0.33-2.11) were presented in **Table 3**. The sensitivity analyses suggested that the primary findings were robust in different definition of immunosuppressors use (**Table 4**).

DISCUSSION

Cardiac involvement is a common presentation in patients with systemic sclerosis.^{3,22} Contraction band myocardial necrosis resulting from ischemia and myocardial fibrosis are the most common pathological findings.^{6,22,23} Despite the evidence of myocardial ischemia, data about the risk of acute myocardial infarction in systemic sclerosis patients remains scarce. A retrospective study conducted in a tertiary medical center demonstrate that the prevalence of acute myocardial infarction is 1.09% (11/1009) in patients with systemic sclerosis.³ Nevertheless, a control group was not available and the relative risk of acute myocardial infarction was unclear in that study. To our knowledge, this is the first population-based prospective study to investigate the

Table 2 Independent Predictors of Acute Myocardial Infarction Identified by Cox Proportional Hazards Model

Predictors	Male		Female		All	
	Crude HR (95% CI)	Adjusted HR* (95% CI)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Crude HR (95% CI)	Adjusted HR† (95% CI)
SSc	2.30 (1.20-4.40)	2.44 (1.27-4.67)	2.53 (1.45-4.44)	2.52 (1.44-4.41)	2.40 (1.57-3.67)	2.45 (1.60-3.75)
Hypertension	4.46 (2.73-7.29)	2.08 (1.20-3.63)	5.61 (3.61-8.74)	2.01 (1.16-3.49)	5.24 (3.78-7.28)	2.08 (1.42-3.07)
Diabetes	3.06 (1.81-5.16)	1.70 (0.95-3.07)	5.41 (3.35-8.73)	2.66 (1.55-4.54)	4.60 (3.23-6.56)	2.14 (1.44-3.18)
CAD	2.86 (1.72-4.75)	1.27 (0.73-2.23)	3.63 (2.26-5.83)	1.02 (0.59-1.78)	3.48 (2.46-4.92)	1.13 (0.76-1.67)
Dyslipidemia	2.26 (1.34-3.82)	1.21 (0.68-2.17)	2.13 (1.28-3.55)	0.79 (0.45-1.38)	2.31 (1.60-3.32)	0.95 (0.63-1.41)
PAOD	2.97 (0.93-9.49)	2.23 (0.68-7.24)	-	-	2.21 (0.70-6.97)	0.82 (0.26-2.61)
AF	2.22 (0.54-9.07)	0.75 (0.18-3.18)	5.29 (1.67-16.80)	1.40 (0.43-4.55)	3.95 (1.62-9.65)	1.06 (0.43-2.65)
CKD	1.79 (1.02-3.15)	0.88 (0.48-1.64)	2.03 (1.15-3.57)	0.87 (0.48-1.55)	2.07 (1.39-3.09)	0.88 (0.58-1.34)
COPD	1.50 (0.88-2.55)	0.68 (0.38-1.22)	1.60 (0.92-2.78)	0.71 (0.40-1.27)	1.72 (1.17-2.53)	0.69 (0.46-1.04)

AF = atrial fibrillation; CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; PAOD = peripheral arterial occlusive disease; SSc = systemic sclerosis.

*Cox proportional hazard regressions were performed to adjust for age and other medical diseases.

†Cox proportional hazard regressions were performed to adjust for age, sex and other medical diseases.

Table 3 Predictors of Acute Myocardial Infarction within the SSc Cohort Identified by Cox Proportional Hazards Model

Characteristics	Crude HR (95% CI)	P Value	Adjusted HR* (95% CI)	P Value	Adjusted HR† (95% CI)	P Value
Female sex	0.37 (0.17-0.81)	.013	0.53 (0.24-1.16)	.113	0.50 (0.22-1.10)	.084
Age	1.08 (1.05-1.12)	<.001	1.08 (1.04-1.11)	<.001	1.07 (1.04-1.11)	<.001
Penicillamine	0.84 (0.35-1.99)	.685	0.97 (0.40-2.33)	.947	0.96 (0.39-2.34)	.929
Systemic steroid	1.39 (0.64-3.03)	.405	1.36 (0.62-2.96)	.441	1.41 (0.64-3.09)	.395
Other immunosuppressors‡	0.59 (0.24-1.47)	.260	0.84 (0.33-2.12)	.709	0.83 (0.33-2.11)	.696

CI = confidence interval; HR = hazard ratio; SSc = systemic sclerosis.

*Cox proportional hazard regressions were performed to adjust for age and sex.

†Cox proportional hazard regressions were performed to adjust for age, sex, and underlying medical diseases.

‡Other immunosuppressors include cyclophosphamide, azathioprine, methotrexate, and cyclosporine.

association between systemic sclerosis and acute myocardial infarction. After adjusting for age, sex, and underlying medical comorbidities, our study disclosed that patients with systemic sclerosis have a 2.45-fold risk for developing acute myocardial infarction compared with the general population.

The etiology of acute myocardial infarction in systemic sclerosis patients can be ascribed to microvascular abnormality or atherosclerotic epicardial disease, such as coronary artery disease. Which one is the primary cause remains a matter of ongoing debate. Our present study revealed that only 12 of 31 acute myocardial infarction patients (38.7%) in the systemic sclerosis group had coronary artery disease, which was not an independent risk factor for acute myocardial infarction in systemic sclerosis patients (HR 1.13; 95% CI, 0.76-1.67). In accordance with our findings, several case series have demonstrated that acute myocardial infarction occurs in systemic sclerosis patients with patent coronary arteries.^{3,24,25} However, controversial results exist. A recent national cohort study in Australia revealed an increased prevalence of coronary heart disease in systemic sclerosis patients.²⁶ The discrepancy may be due to different inclusion criteria for coronary heart disease between studies, such as angina and myocardial infarction that may be due to microvascular ischemia, but not stenosis of the coronary artery itself. As traditional cardiovascular risk factors were less prevalent in the systemic sclerosis cohort in that study, the author claimed that the increased prevalence of coronary heart

disease in systemic sclerosis was likely due to microvascular disease, systemic inflammation, and tissue remodeling.²⁶ Other contrary results are mostly due to small case numbers or subclinical atherosclerosis confined to small coronary arteriole.^{10,27} Given the absence of epicardial coronary atherosclerosis, microvascular impairments, followed by repeated focal ischemia and subsequent widespread fibrosis, may be predominantly responsible for myocardial infarction in systemic sclerosis patients.^{3,4,22}

After adjusting for traditional cardiovascular risk factors, we revealed that comorbid hypertension and diabetes were related to increased risk of acute myocardial infarction in our cohort. Hypertension and diabetes themselves are associated with vascular endothelial cell injury^{4,28,29} and are well-established risk factors for acute myocardial infarction in the general population.^{30,31} Surprisingly, our study revealed that the impact of systemic sclerosis (HR 2.45) on acute myocardial infarction may be even greater than that of hypertension (HR 2.08) or diabetes (HR 2.14) in patients with systemic sclerosis. This intriguing finding may be partially explained by disease-related effect such as malabsorption in systemic sclerosis patients, as several metabolic conditions including diabetes, hypercholesterolemia, and obesity have been found to be less prevalent in systemic sclerosis patients,^{26,32} thus causing less potent effect on acute myocardial infarction.

There is now evidence that calcium channel blockers and angiotensin-converting enzyme inhibitors play a role in the

Table 4 Sensitivity Analyses

Characteristics	n, AMI Event	n, Total	Adjusted HR* (95% CI)	P Value
Frequent penicillamine user	7	504	0.41 (0.13-1.27)	.12
Frequent systemic steroid user	10	330	1.26 (0.48-3.31)	.64
Frequent other immunosuppressors user†	7	256	0.93 (0.31-2.78)	.90
Infrequent penicillamine user	14	501	1.91 (0.72-5.06)	.19
Infrequent systemic steroid user	9	325	1.68 (0.65-4.30)	.28
Infrequent other immunosuppressors user†	2	171	0.74 (0.17-3.22)	.69

AMI = acute myocardial infarction; CI = confidence interval; HR = hazard ratio.

*Cox proportional hazard regressions were performed to adjust for age, sex, and underlying medical diseases.

†Other immunosuppressors include cyclophosphamide, azathioprine, methotrexate, and cyclosporine.

treatment of microvascular ischemia in systemic sclerosis patients.^{11,33} On the contrary, the effects of immunosuppressors on the cardiovascular system are still unclear. Therefore, we elucidated the roles of immunosuppressors in acute myocardial infarction in our study. Although many immunosuppressors have been proven to be effective in different organ systems, for example, systemic steroids for pericarditis^{34,35} and cyclophosphamide for pulmonary disease,³⁶ we failed to demonstrate decreased risks of acute myocardial infarction in patients taking penicillamine, systemic steroids, cyclophosphamide, azathioprine, methotrexate, or cyclosporine. Given the fact that subtle myocardial diseases may be lethal, early diagnosis of latent cardiac involvement followed by timely treatment is imperative. Invasive procedures such as myocardial biopsy have been performed in some studies, but noninvasive techniques may be more appropriate in asymptomatic patients. Cardiac magnetic resonance imaging and ¹²³I-MIBG scintigraphy can be used for identifying myocardial diseases, while Tissue Doppler imaging echocardiography is sensitive for the detection of latent diastolic dysfunction.³⁷⁻³⁹ These novel tools can be useful for early detection of myocardial involvement, prediction of prognosis, and timely treatment of disease.

The strengths of our study included that it was large in scale, with a nationwide systemic sclerosis cohort. In addition, diagnoses were made by board-certified physicians rather than being self-reported by patients. There also were some limitations in the present study. First, personal information, such as lifestyle, body mass index, smoking habit, and laboratory data were not available. To minimize these confounding factors, major medical comorbid diseases were matched between systemic sclerosis patients and control cohort, though this may not have allowed for adequate adjustment for unmeasured confounding. Second, the accuracy of diagnosis might be argued. The diagnoses from the registry-based dataset, including systemic sclerosis, acute myocardial infarction and comorbid diseases, were made and coded by all physicians in Taiwan, rather than by ourselves. However, systemic sclerosis is contained in the catastrophic illnesses in Taiwan and application must be verified by NHI committee. In addition, under the surveillance of the Bureau of NHI, patients diagnosed with acute myocardial infarction in Taiwan must fulfill the criteria of anginal symptoms, typical electrocardiographic changes, or elevated serum cardiac enzyme. Furthermore, our study included only diagnoses made in the inpatient setting or in 2 or more outpatient visits, therefore considerably decreasing the possibility of diagnostic or coding error. Third, the date of systemic sclerosis diagnosis may not represent the disease onset but rather the first time the disease was brought to medical attention. Fourth, the relatively short duration of immunosuppressor use in our patients may limit their effects on acute myocardial infarction prevention. Finally, only a Chinese population was included in this study, and racial differences might exist. Whether these associations can be extrapolated to other ethnic groups requires further survey.

In conclusion, patients with systemic sclerosis are independently at increased risk of acute myocardial infarction.

Owing to frequent myocardial involvement and elevated risk of acute myocardial infarction, which may predict high mortality rate in systemic sclerosis patients, early detection of cardiac diseases is crucial to ensure prompt and timely management. Future studies to evaluate cardiac electromechanical properties are required to further corroborate the etiology of acute myocardial infarction in patients with systemic sclerosis.

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