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Acupuncture decreased the risk of ischemic stroke in patients with rheumatoid arthritis: a nationwide propensity score-matched study

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Acupuncture decreased the risk of ischemic stroke in patients with rheumatoid arthritis: a nationwide propensity score-matched study

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Abstract

Objectives: The purpose of this study was to demonstrate that acupuncture is beneficial for decreasing the risk of ischemic stroke (IS) in patients with rheumatoid arthritis (RA).

Design: This is a propensity score-matched cohort study.

Setting: This is a nationwide population-based study.

Participants: The patients with RA diagnosed between 1 January 1997 and 31 December 2010 through the National Health Insurance Research Database.

Interventions: The patients who were administered acupuncture therapy from the initial date of RA diagnosis of rheumatoid arthritis to 31 December 2010 were included in the acupuncture cohort. Patients who did not receive acupuncture treatment during the same time interval were regarded as the no-acupuncture cohort.

Primary outcome measures: A Cox regression model was used to adjust for age, sex, comorbidities, and types of drugs used. We compared the subhazard ratios (SHRs) of IS between these two cohorts through competing-risks regression models.

Results: After a 1:1 propensity score match, a total of 23,226 patients were identified. The basic characteristics of these patients were similar. A lower cumulative incidence of ischemic stroke was found in the acupuncture cohort (log-rank test, $p < 0.001$). In the end, 341 patients in the acupuncture cohort (5.95 per 1,000 person-years) and 605 patients in the no-acupuncture cohort (12.4 per 1,000 person-years) experienced an ischemic stroke (adjusted SHR, 0.57; 95% CI, 0.50–0.65). The advantage of lowering ischemic stroke incidence through acupuncture therapy in RA patients was independent of sex, age, types of drugs used, and comorbidities.

Conclusions: This study showed the beneficial effect of acupuncture in reducing the incidence rate of ischemic stroke in patients with RA.

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Strengths and limitations of this study:

- Our research disclose the possible long-term effect from acupuncture in stroke prevention which could not be investigated from clinical trial.
- The causality could not be proved directly as clinical trial through our study design.

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Introduction

The rheumatoid arthritis (RA) is one of the common rheumatoid diseases, and demonstrated as polyarthritis in the joints, mainly synovial inflammation, and morning stiffness.[1] The bone erosion, joint deformity and loss of functional abilities are the long-term complication from RA. When it comes to chronic process, the inflammation status could be noted in the whole body: pericarditis, myocarditis, pleuritis, interstitial lung fibrosis, osteoporosis, and cardiovascular diseases (CVD).[2-5] Comorbidities from CVD are the major cause to develop death in the RA patients, such as stroke.[6-11] Comparing to general population, stroke is more common noted in the RA patients.[12] The prevalence of RA in the global and Asia are 460 per 100,000 population and 15.8 of 100,000 people, respectively.[13-15] But the risk to develop ischemic stroke in Asian RA patients (hazard ratio (HR), 1.32) is similar with the Caucasian group (HR 1.29).[16-17]

Trying to disclose the agents to prevent stoke is an essential issue to clinical doctors and patients.[18] The common prescriptions to treat RA are Nonsteroidal anti-inflammatory drugs (NSAIDs), steroid, conventional disease-modifying antirheumatic drugs (DMARDs), and biological agents such as etanercept, infliximab (TNF-α inhibitor) and anakinra (IL-1 inhibitor).[3,5,19] And steroid, DMARDs such as methotrexate (MTX), and infliximab have found their advantages in the prevention of ischemic stroke in the RA patients.[18] But some of them could bring the complications in the bone marrow to cause thrombocytopenia.[20] The alternative intervention to control RA and lower complication from treatment itself become a well-discussion topic.

In lots of countries and regions, such as Taiwan, Germany, Hong Kong, and China, acupuncture therapy is widely used to control pain when patients have musculoskeletal and immune problems, including RA.[21-25] A previous cohort study

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founded that approximately 27.3% of RA patients in Taiwan ever consulted traditional Chinese medicine (TCM) service, and 23.6% of these patients had received acupuncture.[26] Furthermore, secondary stoke prevention is also noted from acupuncture therapy in the Taiwanese.[27] And the hypothesis in the acupuncture to lower stoke rate is similar with agents to treat RA: anti-inflammation. Thus, we want to investigate the relationship between acupuncture intervention and incidence of ischemic stroke in RA patients.

In Taiwan, the records of medical services are saved in the database of National Health Insurance: National Health Insurance Research Database (NHIRD). The service of NHI is from 1995 until now and the coverage rate in the Taiwanese is more than 99% population.[28] In other words, the medical data in the NHIRD is long and large enough to demonstrate a national wide population research. And sampling bias could be prevented when study process through such a large-scale database.[29] We use NHIRD to investigate the long-term effect of ischemic stroke prevention in patients with RA have accepted acupuncture treatment.

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Materials and Methods

Data sources

A nationwide, population-based 1:1 propensity score-matched cohort study via data analysis derived from the NHIRD was performed. The database used in this study was the Registry for Catastrophic Illness Patients Database (RCIPD), which is part of the NHIRD. The personal information was removed from the NHIRD. It was not possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research The RCIPD enrolled all patients with a catastrophic illness, which was proven by pathological, laboratory, and clinical diagnoses by both specialists and a regular review. This real-world database consists of datasets including demographic characteristics, outpatient and inpatient visits, diagnostic codes, assessments, remedies, procedures and medical expenses for reimbursement. The diagnoses were coded by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Patients with a diagnosis of RA are issued catastrophic illness certificates and receive free medical services for health complications. Thus, the RCIPD is a comprehensive database for the investigation of all RA patients in Taiwan. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH104-REC2-115).

Study subjects and variables

We used both ambulatory and inpatient medical records to identify RA treatments that were linked with the RCIPD from 1997 to 2010 to identify a study population (n=47,809) for follow-up until the end of 2011 (**Fig. 1**). Newly diagnosed RA patients (n=36,277) with the diagnosis of ICD-9-CM code 714.0 were included. We excluded patients (n=1,793) who were younger than 18 years, who had

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incomplete data on age or sex, who had an interruption in health insurance services during the follow-up period, and who had a diagnosis of ischemic stroke (ICD-9-CM: 433-438) before the index date. Finally, 34,484 patients newly diagnosed of RA were included. Patients who received acupuncture therapy from the initial RA diagnosis to 31 December 2010 were included in the acupuncture cohort (n=12,266). We used a propensity score approach to minimize confounders in the analysis of acupuncture therapy. A one-to-one propensity score match was conducted by age (per 5 years), sex, comorbidities, and types of drugs used (oral steroid, NSAID, statin, all DMARDs), RA diagnosis year and index year by multiple logistic regression analysis. And the definition of drugs used is patient with ≥28 cumulative use days. The numbers of participants in both the acupuncture and no-acupuncture cohorts were the same (n=11,613). The index date was defined as the first time that patients received acupuncture therapy which was given randomly to no-acupuncture cohort according to the acupuncture cohort. The immortal time was defined as the period from the initial diagnosis of RA to the index date.

Covariate assessment

The patients were divided into three groups by age (18–39 years, 40–59 years, and ≥ 60 years). ICD-9-CM codes of comorbidities that appeared more than one time in the outpatient or inpatient records before the primary diagnosis of RA were taken into consideration; such comorbidities included diabetes mellitus (DM; ICD-9-CM code 250), hypertension (HTN; ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), congestive heart failure (ICD-9-CM codes 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, and 428.0), anxiety (ICD-9-CM codes 300.0, 300.2, 300.3, 308.3, and 308.91), depression (ICD-9-CM 296.2–296.3, 300.4, 311), alcoholism (ICD-9-CM codes 291, 303, 305.00–305.03,

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790.3, and V11.3), tobacco use (ICD-9-CM code 305.1), obesity (ICD-9-CM codes 278 and A183), and atrial fibrillation (ICD-9-CM 427.3). The events of ischemic stroke (ICD-9-CM: 433-438) were compared between acupuncture and non-acupuncture cohort of RA patients.

Types of acupuncture and disease categories in the acupuncture cohort

We identified the different acupuncture types by the treatment codes, including manual acupuncture of the TCM type (B41, B42, B45, B46, B80, B81, B82, B83, B84, B90, B91, B92, B93, B94, P27041, P31103, and P32103) and electroacupuncture (B43, B44, B86, B87, B88, and B89) as previously described.[30]

Statistical analyses

The standardized mean difference (SMD) was used to compare the baseline characteristics of the acupuncture and no-acupuncture cohorts as previously described.[30] A negligible difference in mean values or proportions between the two cohorts was defined as less than 0.1 standard deviation (SD). A competing-risks regression models was performed to estimate the crude and adjusted subhazard ratios (SHRs) of acupuncture therapy, age, sex, comorbidities, and types of drugs used. The Kaplan-Meier method and the log-rank test were conducted to find the difference between the two cohorts in the development of ischemic stroke. We used SAS 9.4 (SAS Institute, Cary, NC, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria) to perform statistical analyses and create the figures. Statistical significance was defined as $p < 0.05$ in two-tailed tests.

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Results

We used 1:1 propensity-score matching by sex, age, all comorbidities, drugs (oral steroid, NSAID, statin, all DMARDS), the RA diagnosis year and index year to enroll an equal number (n=11,613) of RA patients in the acupuncture cohort and non-acupuncture cohort (**Fig. 1**). The baseline characteristics of both cohorts are presented in **Table 1**, with similar distributions of sex, age, comorbidities, and prescriptions. Most participants were female in both cohorts, and most patients were middle-aged (40-59 years). The most common comorbidity was HTN; more than 38% of patients had this problem. In patients with RA, 18% had DM, 28% had hyperlipidemia, 6% had congestive heart failure, 24% had anxiety, and 10% had depression. There were no differences in the proportions of alcoholism, tobacco dependence, and obesity between the two cohorts. NSAIDs were the most common prescriptions in both the cohorts, 76% included patients were on these medications. In the participants of the two cohorts, 55% used oral steroids, and 5% used statin agents. Most patients (87%) were treated by manual acupuncture, with electroacupuncture having been used in 3% of the participants, and the other 10% of patients having had combined manual acupuncture and electroacupuncture treatments. The mean duration between RA diagnosis and the first acupuncture treatment was approximately 1,065 days. The mean number of acupuncture visits was 9.83.

During the follow-up period, 946 patients developed ischemic stroke (**Table 2**). The incidence of ischemic stroke in RA patients increased with age, with older patients having had a higher risk. The adjusted SHRs of the 40–59-year-old group and the over 60 years old group were 5.99 and 14.7, respectively. The patients with comorbidities of DM, HTN and congestive heart failure had a higher risk of ischemic stroke. The adjusted SHRs of the patients with DM, HTN and congestive heart failure were 1.58, 2.10 and 1.31, respectively. The cumulative incidence of ischemic stroke

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was significantly lower in the acupuncture cohort (log-rank test, $p < 0.001$, **Fig. 2**).

Table 3 shows the 341 patients in the acupuncture cohort (5.95 per 1000 person-years) and the 605 patients in the non-acupuncture cohort (12.4 per 1000 person-years) who developed ischemic stroke (adjusted SHR, 0.57; 95% CI, 0.50–0.65). Both males and females were observed to experience the benefit of ischemic stroke prevention, with an adjusted SHR of 0.58 in the female group (95% CI, 0.49–0.67) and an adjusted SHR of 0.54 in the male group (95% CI, 0.41–0.70). The age subgroups ≥40 years old had a lower risk of ischemic stroke after acupuncture therapy (adjusted SHR, 0.54; 95% CI, 0.44–0.66 in the 40-59-year-old group; adjusted SHR, 0.58; 95% CI, 0.48–0.69 in the over 60 years old group). Acupuncture decreased the risk of ischemic stroke in most patients with comorbidities. Coprescriptions with either steroids, statins, or DMARDs did not change the positive results of acupuncture therapy.

The results from un-matching analysis were also provided to prevent possible sampling bias from our 1:1 propensity-score matching in **Supplementary Table 1**and **2**. And the final results analyzed by competing-risks regression models are compatible with the results after 1:1 propensity-score matching.

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Discussion

As far as we know, this is the first study to show that acupuncture therapy is beneficial for ischemic stroke prevention in the RA patients. RA is one of the common disease categories among acupuncture visits in Taiwan.[31] We previously found that 23.6% of RA patients had received acupuncture.[26] In the present study, we showed that the benefit of acupuncture therapy in reducing the risk of ischemic stroke was independent of sex, age, and comorbidities.

Although patients with RA have been known to have high risk for the development of stroke, there is an unmet need to improve the preventive measures for patients with RA.[32] Inflammation is a consistent and independent predictor of CVD in RA.[33] TNF-α is a cytokine that mediates inflammation reactions.[34] A high level of TNF-α has been observed in RA patients, and it has been found that TNF-α can induce pannus formation and subsequent bone destruction.[35] By interrupting TNF-α expression and production by inflammatory cells, TNF-α inhibitors can efficiently control the inflammatory process.[36] Biological agents targeting cytokines may decrease CVD risk in RA.[37] Therefore, it is interesting to know whether if acupuncture fit the niche to reduce the inflammation in RA patients.

There are a couple evidences and potential explanations about the effects and mechanisms of acupuncture. Acupuncture has been reported to be effective in treating neuropathy,[38] relieving pain[39] and attenuating cardiovascular disease[40] in different clinical trials. Previous clinical studies revealed that acupuncture reduced the amounts of tender joints, relieved morning stiffness and joint pain, enhanced physical activity, and improved quality of life in patients with RA.[41,42] In the analysis of blood and synovial fluid of the RA patients, acupuncture was found to reduce TNF-α and vascular endothelial growth factor to improve the inflammation of RA.[43] In animal

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studies, acupuncture reduced inflammation in collagen-induced arthritis model.[44-46] Furthermore, acupuncture was found not only have analgesic effect through beta-endorphin,[47] adenosine[48] and orexin,[49] but also reduce inflammation through dopamine.[50] On the other hand, unstable blood pressure and lipid profiles are the two risk factors of ischemic stroke, and acupuncture therapy has the advantage of controlling both HTN and dyslipidemia.[51,52] If acupuncture relieved the morning stiffness and join pain, the patients might also benefit from increasing daily activities, which might also reduce the risk of stroke.[53]

Our study had some limitations. For example, we could not identify the number and specific affected joints from the data of the RCIPD. Thus, we use prescriptions for RA treatment to be variables which could represent the severity of RA. After performing 1:1 propensity score matching, the differences between the two cohorts was minimizing. And, we had similar percentages of patients who used NSAIDs, steroid agents, statins, and DMARDs. The second limitation was that the RCIPD did not provide data on height, weight, and exercise status. We tried to define a diagnosis of alcoholism, tobacco use, and obesity to represent these personal characteristics and lifestyles; then, through 1:1 propensity score matching, we attempted to eliminate or minimize confounders. The distribution of patients with different habits was similar, and these parameters did not change the significant effect of ischemic stroke prevention in patients with RA. Additionally, the RCIPD database could not offer information of acupoints for RA treatment. The selection of acupoints depends on the diagnosis and the experience of the TCM doctors. The variable prescriptions of acupuncture could also stem from the different complaints, comorbidities and wishes of the patients. Because of the standard TCM program training in medical schools, most TCM doctors in Taiwan know the concepts of basic acupoints. Further clinical trials with standardized acupoints should be conducted based on the findings of this

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Conclusions

Our study demonstrates that the ischemic stroke risk could be reduced by acupuncture treatment in patients with RA in Taiwan. It also offers important ideas for more comprehensive studies in the future.

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Competing interests

The authors declare that they have no conflicts of interest.

Authors' contributions

CYH and MCH contributed equally. MCH contributed to conception of the study, participated in the interpretation of clinical data and drafted the manuscript. CYH contributed to conception of the study, participated in the interpretation of clinical data and drafted the manuscript. HHL participated in the interpretation of clinical data and drafted the manuscript. CLL performed the statistical analysis. GZ drafted the manuscript. MYW contributed to design of the study, participated in the interpretation of clinical data and drafted the manuscript. YCL supervised the project, participated in the interpretation of clinical data and drafted the manuscript. HRY supervised the project, contributed to conception and design of the study and finalized the manuscript. MYW and HRY contributed equally as co-corresponding authors.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Table 1.Characteristics of rheumatoid arthritis patients according to whether they received acupuncture treatment.

Variable	Rheumatoid Arthritis				Standardized mean difference
	Acupuncture treatment				
	No (n = 11613)		Yes (n = 11613)		
	n	%	n	%	
Sex					
Women	9499	81.8	9478	81.6	0.01
Men	2114	18.2	2135	18.4	0.01
Age group					
18-39	1839	15.8	1588	13.7	0.06
40-59	6684	57.6	7330	63.1	0.11
≥ 60	3090	26.6	2695	23.2	0.08
Mean ± SD (years)	54.9±14.5		54.8±13.2		0.01
Baseline Comorbidity					
Diabetes mellitus	2176	18.7	2126	18.3	0.01
Hypertension	4507	38.8	4416	38.0	0.02
Hyperlipidemia	3267	28.1	3273	28.2	0.001
Congestive heart failure	741	6.38	723	6.23	0.006
Depression	1256	10.8	1248	10.8	0.002
Anxiety	2880	24.8	2841	24.5	0.008
Alcoholism	208	1.79	221	1.90	0.008
Tobacco use	70	0.60	77	0.66	0.008
Obesity	130	1.12	135	1.16	0.004
Atrial fibrillation	741	6.38	715	6.16	0.009
Drugs used					
Oral steroid	6489	55.6	6495	55.9	0.001
NSAID	8823	76.0	8882	76.5	0.012
Statin	5592	5.10	593	5.11	0.000
Conventional DMARDS					
Hydroxychloroquine	5670	48.8	5663	48.8	0.001
Sulfasalazine	4295	37.0	4323	37.2	0.005
Methotrexate	9	0.08	10	0.09	0.003
Leflunomide	867	7.47	872	7.51	0.002
D-penicillamine	131	1.13	1298	1.11	0.002
Azathioprine	208	1.79	223	1.92	0.01
Mycophenolate	5	0.04	5	0.04	0.000

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Cyclosporine	555	4.78	544	4.68	0.004
Biological DMARDs					
Conventional DMARDS					
Hydroxychloroquine	5670	48.8	5663	48.8	0.001
Etanercept	625	5.38	629	5.42	0.002
Adalimumab	198	1.70	193	1.66	0.003
Types of acupuncture					
Manual acupuncture	-	-	10050	86.5	
Electroacupuncture	-	-	401	3.45	
Combination of both types	-	-	1162	10.0	
Duration from rheumatoid arthritis diagnosis and index, days (mean, median)	(1078.52, 795.0)		(1065.18, 707.0)		0.32
Acupuncture visits (mean, median)	-		(9.83, 3.00)		

The mean (median) follow-up period was 4.93 (4.35) and 4.21 (3.41) years in the acupuncture cohort and the compared cohort, respectively.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

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Table 2. Subhazard ratios and 95% confidence intervals of ischemic stroke associated with acupuncture treatment and covariates among rheumatoid arthritis patients using the competing-risks regression models.

Variable	No. of event (n = 946)	Crude*			Adjusted†		
		SHR	(95% CI)	p-value	SHR	(95% CI)	p-value
Acupuncture treatment							
No	605	1.00	reference		1.00	reference	
Yes	341	0.52	(0.46, 0.60)	<0.001	0.57	(0.49, 0.65)	<0.001
Sex							
Women	714	1.00	reference		1.00	reference	
Men	231	1.44	(1.24, 1.67)	<0.001	1.32	(1.14, 1.54)	<0.001
Age group							
18-39	13	1.00	reference		1.00	reference	
40-59	372	7.17	(4.14, 12.4)	<0.001	5.99	(3.44, 10.4)	<0.001
≥ 60	561	28.1	(16.3, 48.6)	<0.001	14.7	(8.38, 25.7)	<0.001
Baseline Comorbidity (ref = no comorbidity)							
Diabetes mellitus	334	2.64	(2.31, 3.01)	<0.001	1.58	(1.36, 1.82)	<0.001
Hypertension	654	3.96	(3.45, 4.54)	<0.001	2.10	(1.79, 2.47)	<0.001
Hyperlipidemia	371	1.94	(1.70, 2.21)	<0.001	1.08	(0.93, 1.25)	0.30
Congestive heart failure	148	3.18	(2.67, 3.79)	<0.001	1.31	(1.08, 1.59)	0.006

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Depression	120	1.46	(1.21, 1.77)	<0.001	1.12	(0.91, 1.37)	0.28
Anxiety	256	1.40	(1.21, 1.61)	<0.001	0.99	(0.85, 1.16)	0.94
Alcoholism	20	1.48	(0.95, 2.29)	0.08	1.46	(0.88, 2.43)	0.14
Tobacco use	2	0.55	(0.14, 2.20)	0.40	0.32	(0.07, 1.40)	0.13
Obesity	10	1.16	(0.62, 2.17)	0.65	1.10	(0.58, 2.08)	0.77
Atrial fibrillation	50	1.02	(0.77, 1.35)	0.90	0.89	(0.66, 1.19)	0.43
Drugs used							
Oral steroid	1621	0.57	(0.47-0.69)	< 0.0001	0.51	(0.42-0.62)	< 0.0001
NSAID	1726	0.22	(0.11-0.46)	< 0.0001	0.24	(0.11-0.51)	0.0002
Statin	329	1.04	(0.92-1.17)	0.5575	0.65	(0.58-0.74)	< 0.0001
Conventional DMARDS							
Hydroxychloroquine	333	0.47	(0.41, 0.54)	<0.001	0.70	(0.60, 0.81)	<0.001
Sulfasalazine	235	0.47	(0.41, 0.54)	<0.001	0.80	(0.68, 0.94)	0.007
Methotrexate	2	1.88	(0.50, 7.04)	0.35	3.15	(0.84, 11.9)	0.08
Leflunomide	18	0.22	(0.14, 0.35)	<0.001	0.34	(0.22, 0.54)	<0.001
D-penicillamine	11	0.85	(0.46, 1.53)	0.53	1.07	(0.61, 1.88)	0.05
Azathioprine	9	0.39	(0.20, 0.75)	0.004	0.77	(0.40, 1.49)	0.44
Mycophenolate	0	-	-		-	-	
Cyclosporine	35	0.62	(0.44, 0.87)	0.005	1.40	(0.99, 1.98)	0.06
Biological DMARDs							
Etanercept	16	0.27	(0.16, 0.44)	<0.001	0.51	(0.31, 0.83)	0.007
Adalimumab	3	0.18	(0.06, 0.57)	0.003	0.43	(0.14, 1.34)	0.15
Conventional DMARDS							

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Hydroxychloroquine	333	0.47	(0.41, 0.54)	<0.001	0.70	(0.60, 0.81)	<0.001

Crude SHR* represents the relative subhazard ratio;

Adjusted SHR† represents the adjusted subhazard ratio: mutually adjusted for accepted acupuncture, age, comorbidities, and drugs used in competing-risks regression models.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

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Table 3. Incidence rates, subhazard ratios and confidence intervals of ischemic stroke in rheumatoid arthritis patients who received and did not receive acupuncture in the stratification of sex, age, comorbidities and drug used using the competing-risks regression models.

Variables	Rheumatoid arthritis						Compared with non-acupuncture users	
	No (n = 11613)			Yes (n = 11613)			Crude SHR	Adjusted SHR
	Event	Person years	IR†	Event	Person years	IR†	(95% CI)	(95% CI)
Total	605	48836	12.4	341	57273	5.95	0.52(0.45, 0.60)***	0.57(0.50, 0.65)***
Sex								
Women	460	40274	11.4	254	46907	5.41	0.51(0.44, 0.60)***	0.58(0.49, 0.67)***
Men	145	8562	16.9	87	10366	8.39	0.54(0.42, 0.71)***	0.54(0.41, 0.70)***
Age group								
18-39	5	8734	0.57	8	8576	0.93	1.47(0.49, 4.45)	1.45(0.44, 4.76)
40-59	226	29529	7.65	146	37225	3.92	0.53(0.43, 0.66)***	0.54(0.44, 0.66)***
≥ 60	374	10573	35.4	187	11472	16.3	0.55(0.46, 0.65)***	0.58(0.48, 0.69)***
Baseline Comorbidity								
Diabetes mellitus								
No	383	41083	9.32	229	48060	4.76	0.55(0.47, 0.65)***	0.60(0.51, 0.71)***
Yes	222	7753	28.6	112	9213	12.2	0.47(0.38, 0.59)***	0.52(0.41, 0.65)***
Hypertension								
No	184	32174	5.72	108	37634	2.87	0.52(0.41, 0.66)***	0.57(0.45, 0.72)***

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Yes	421	16661	25.3	233	19639	11.9	0.53(0.45, 0.62)***	0.57(0.49, 0.67)***
Hyperlipidemia								
No	366	36970	9.90	209	43496	4.81	0.53(0.45, 0.62)***	0.61(0.51, 0.72)***
Yes	239	11866	20.1	132	13777	9.58	0.51(0.42, 0.63)***	0.51(0.41, 0.63)***
Congestive heart failure								
No	513	46595	11.0	285	54590	5.22	0.51(0.44, 0.59)***	0.55(0.47, 0.64)***
Yes	92	2241	41.1	56	2683	20.9	0.61(0.44, 0.85)***	0.65(0.47, 0.92)***
Depression								
No	523	44638	11.7	303	52396	5.78	0.54(0.47, 0.62)***	0.59(0.51, 0.67)***
Yes	82	4198	19.5	38	4877	7.79	0.43(0.30, 0.64)***	0.48(0.32, 0.72)***
Anxiety								
No	442	38718	11.4	248	46073	5.38	0.51(0.44, 0.60)***	0.56(0.48, 0.66)***
Yes	163	10117	16.1	93	11200	8.30	0.55(0.43, 0.71)***	0.57(0.44, 0.74)***
Alcoholism								
No	596	48177	12.4	330	56529	5.84	0.51(0.45, 0.59)***	0.56(0.49, 0.64)***
Yes	9	659	13.7	11	744	14.8	1.12(0.47, 2.67)	1.25(0.50, 3.09)
Tobacco use								
No	603	48655	12.4	341	57090	5.97	0.52(0.46, 0.60)***	0.57(0.50, 0.65)***
Yes	2	181	11.1	0	182	0.00		
Obesity								
No	598	48412	12.4	338	56737	5.96	0.52(0.46, 0.60)***	0.57(0.50, 0.65)***
Yes	7	424	16.5	3	536	5.60	0.38(0.10, 1.49)	0.40(0.14, 1.19)

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Atrial fibrillation								
No	576	46291	12.4	320	54553	5.87	0.51(0.45, 0.59)***	0.56(0.49, 0.64)***
Yes	29	2545	11.4	21	2720	7.72	0.72(0.43, 1.26)	0.70(0.38, 1.30)
Drugs used								
Oral steroid								
No	318	17828	17.8	166	21844	7.60	0.48(0.41, 0.58)***	0.53(0.44, 0.64)***
Yes	287	31008	9.26	175	35429	4.94	0.56(0.47, 0.68)***	0.59(0.49, 0.72)***
NSAID								
No	216	7329	29.5	105	9509	11.0	0.46(0.37, 0.58)***	0.54(0.43, 0.69)***
Yes	389	41506	9.37	236	47764	4.94	0.55(0.47, 0.64)***	0.56(0.48, 0.66)***
Statin								
No	586	45820	12.8	322	54040	5.96	0.51(0.44, 0.58)***	0.56(0.49, 0.64)***
Yes	19	3016	6.30	19	3233	5.88	0.94(0.50, 1.79)	0.97(0.49, 1.95)
Conventional DMARDS								
No	347	14099	24.6	181	18431	9.82	0.48(0.40, 0.57)***	0.54(0.45, 0.65)***
Yes	258	34736	7.43	160	38842	4.12	0.56(0.46, 0.68)***	0.58(0.47, 0.71)***
Biological DMARDs								
No	591	44821	13.2	336	52599	6.39	0.53(0.46, 0.60)***	0.58(0.50, 0.66)***
Yes	14	4014	3.49	5	4674	1.07	0.28(0.10, 0.79)*	0.26(0.09, 0.80)**

Abbreviation: IR, incidence rate per 1,000 person-years; SHR, subhazard ratio; CI, confidence interval

Adjusted SHR: adjusted for accepted acupuncture, age, sex, comorbidities, and drugs used in the competing-risks regression models.

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*: $p < 0.05$; **: $p < 0.01$; *** $p < 0.001$

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

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Figure legends

Fig. 1 Study population flowchart. A total of 47,809 patients with rheumatoid arthritis were newly diagnosed from 1997 to 2010. Sex, age, comorbidities, types of drugs used, RA diagnosis year and index year were processed via 1:1 matching; subsequently, 11,613 patients were included in the acupuncture and no-acupuncture cohorts.

Fig. 2 The cumulative incidence of ischemic stroke in the acupuncture (dashed line) cohort and the no-acupuncture cohort (solid line). Patients in the acupuncture group had a lower incidence of ischemic stroke (log-rank test, $p < 0.001$).

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Figures

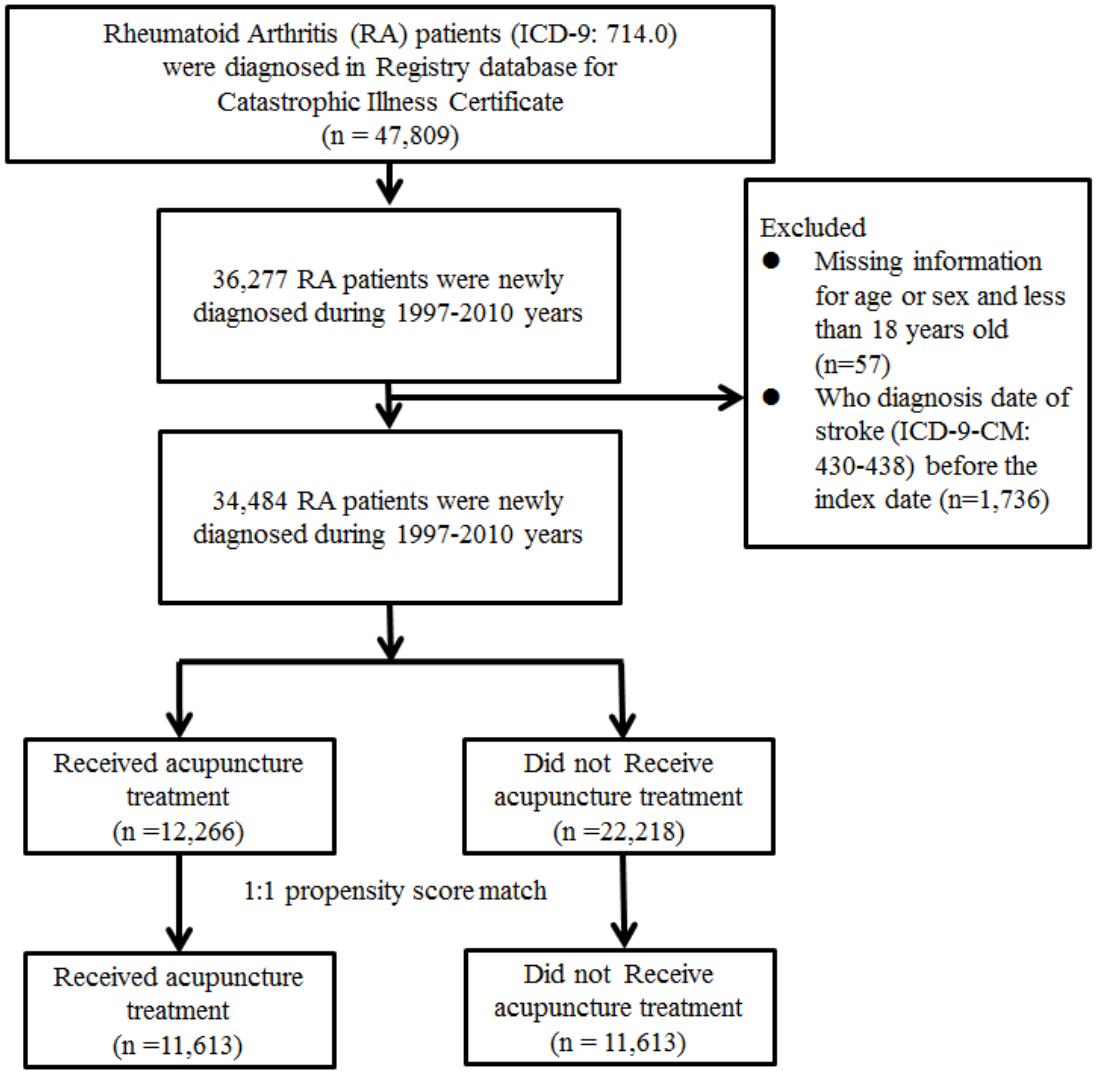

Fig. 1

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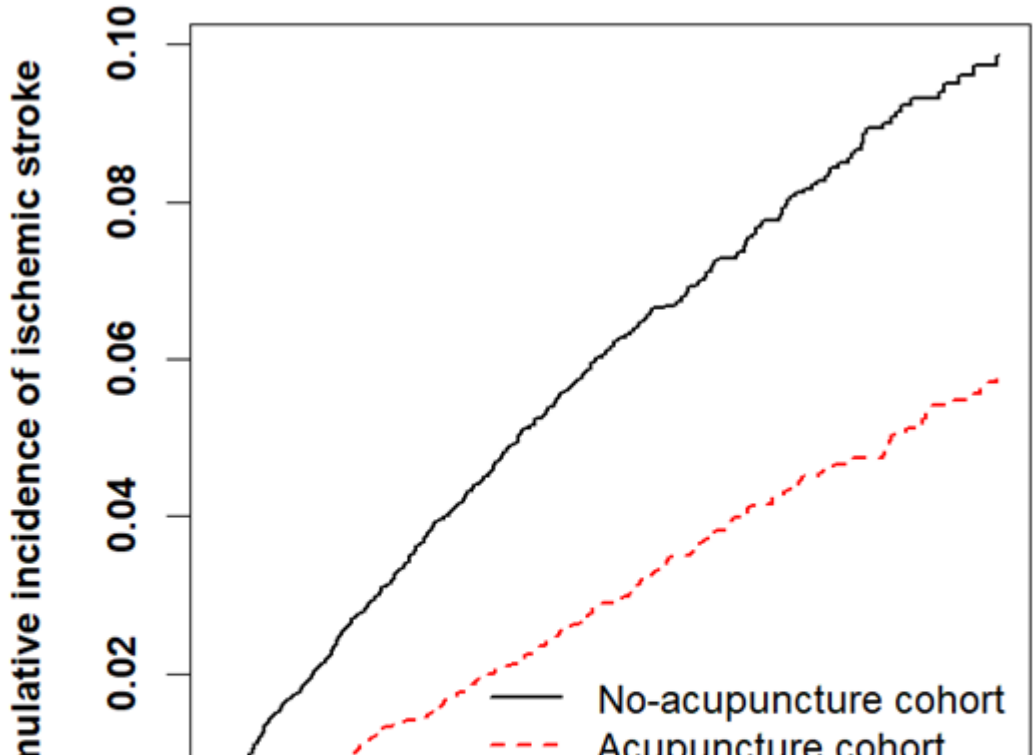

Fig. 2

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Supplement Table 1. Characteristics of rheumatoid arthritis patients according to accept acupuncture in un-matching.

Variable	Rheumatoid Arthritis				Standardised mean difference
	Accepted acupuncture				
	No (n =22218)		Yes (n =12266)		
	n	%	n	%	
Gender					
Women	16702	75.2	10109	82.4	0.18
Men	5516	24.8	2157	17.6	0.18
Age group					
18-39	2994	13.5	1767	14.4	0.03
40-59	12351	55.6	7762	63.3	0.16
≥60	6873	30.9	2737	22.3	0.20
Mean±SD (years)	56.7±14.7		54.3±13.3		0.17
Baseline Comorbidity					
Diabetes mellitus	4117	18.5	2260	18.4	0.003
Hypertension	8857	39.9	4632	37.8	0.04
Hyperlipidemia	5610	25.3	3593	29.3	0.09
Congestive heart failure	1698	7.64	736	6.00	0.07
Depression	1901	8.56	1394	11.4	0.09
Anxiety	4591	20.7	3118	25.4	0.11
Alcoholism	422	1.90	244	1.99	0.01
Tobacco used	146	0.66	84	0.68	0.003
Obesity	188	0.85	163	1.33	0.05
Atrial fibrillation	1102	4.96	845	6.89	0.08
Drug used					
Oral steroid	10814	48.7	6946	56.6	0.16
NSAID	13907	62.6	9532	77.7	0.34
Statin	828	3.73	688	5.61	0.09
Conventional DMARDS					
Hydroxychloroquine	9299	41.9	6059	49.4	0.15
Sulfasalazine	7210	32.5	4606	37.6	0.11
Methotrexate	14	0.06	11	0.09	0.01
Leflunomide	1309	5.89	973	7.93	0.08
D-penicillamine	196	0.88	138	1.13	0.02
Azathioprine	385	1.73	229	1.87	0.01
Mycophenolate	10	0.05	7	0.06	0.01
Cyclosporine	816	3.67	594	4.84	0.06
Biological DMARDs					
Etanercept	941	4.24	706	5.76	0.07

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Adalimumab	345	1.55	202	1.65	0.01
Types of acupuncture					
Manual acupuncture			10604	86.45	
Electroacupuncture			407	3.32	
Combination of manual acupuncture and electroacupuncture			1255	10.23	
Duration between rheumatoid arthritis date and index, days (mean, median)	(981.29, 668.0)		(1047.36, 688.5)		
Acupuncture visits, (mean, meidan)			(10.43, 3.00)		

The mean (median) of follow-up period were 4.96 (4.39) and 4.01 (3.17) years for acupuncture cohort and compared cohort.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

Supplement Table 2. Subhazard ratios and 95% confidence intervals of ischemic stroke associated with accepted acupuncture and covariates among rheumatoid arthritis patients using the competing-risks regression models in un-matching.

Variable	No. of event (n=1441)	Crude*			Adjusted†		
		SHR	(95%CI)	p-value	SHR	(95%CI)	p-value
Accepted acupuncture							
No	1080	1.00	reference		1.00	reference	
Yes	361	0.48	(0.42, 0.53)	<0.001	0.65	(0.58, 0.74)	<0.001

Crude SHR* represented relative subhazard ratio;

Adjusted SHR† represented adjusted subhazard ratio: mutually adjusted for accepted acupuncture, age, gender, comorbidities, and drugs used in competing-risks regression models.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-10
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	9-10
		(*b*) For matched studies, give matching criteria and the number of controls per case	9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9-10*
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	9-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how matching of cases and controls was addressed	11
		(*e*) Describe any sensitivity analyses	11
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-13
		(b) Give reasons for non-participation at each stage	12-13
		(c) Consider use of a flow diagram	12-13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	12-13
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	12-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3-4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Acupuncture decreased the risk of ischemic stroke in patients with rheumatoid arthritis: a nationwide propensity score-matched study

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Secondary Subject Heading:	Rheumatology, Neurology
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Acupuncture decreased the risk of ischemic stroke in patients with rheumatoid arthritis: a nationwide propensity score-matched study

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Abstract

Objectives: The purpose of this study was to demonstrate that acupuncture is beneficial for decreasing the risk of ischemic stroke (IS) in patients with rheumatoid arthritis (RA).

Design: This is a propensity score-matched cohort study.

Setting: This is a nationwide population-based study.

Participants: The patients with RA diagnosed between 1 January 1997 and 31 December 2010 through the National Health Insurance Research Database.

Interventions: The patients who were administered acupuncture therapy from the initial date of RA diagnosis of rheumatoid arthritis to 31 December 2010 were included in the acupuncture cohort. Patients who did not receive acupuncture treatment during the same time interval were regarded as the no-acupuncture cohort.

Primary outcome measures: A Cox regression model was used to adjust for age, sex, comorbidities, and types of drugs used. We compared the subhazard ratios (SHRs) of IS between these two cohorts through competing-risks regression models.

Results: After a 1:1 propensity score match, a total of 23,226 patients were identified. The basic characteristics of these patients were similar. A lower cumulative incidence of ischemic stroke was found in the acupuncture cohort (log-rank test, $p < 0.001$; immortal time: 1,065 days; mean number of acupuncture visits: 9.83). In the end, 341 patients in the acupuncture cohort (5.95 per 1,000 person-years) and 605 patients in the no-acupuncture cohort (12.4 per 1,000 person-years) experienced an ischemic stroke (adjusted SHR, 0.57; 95% CI, 0.50–0.65). The advantage of lowering ischemic stroke incidence through acupuncture therapy in RA patients was independent of sex, age, types of drugs used, and comorbidities.

Conclusions: This study showed the beneficial effect of acupuncture in reducing the incidence rate of ischemic stroke in patients with RA.

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Strengths and limitations of this study:

- Our research disclose the possible long-term effect from acupuncture in stroke prevention which could not be investigated from clinical trial.
- Lower ischemic stroke developed in patients with rheumatoid arthritis after acupuncture therapy.
- The causality could not be proved directly as clinical trial through our study design.

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Introduction

The rheumatoid arthritis (RA) is one of the common rheumatoid diseases, and demonstrated as polyarthritis in the joints, mainly synovial inflammation, and morning stiffness [1]. The bone erosion, joint deformity and loss of functional abilities are the long-term complication from RA. When it comes to chronic process, the inflammation status could be noted in the whole body: pericarditis, myocarditis, pleuritis, interstitial lung fibrosis, osteoporosis, and cardiovascular diseases (CVD) [2-5]. Comorbidities from CVD are the major cause to develop death in the RA patients, such as stroke [6-11]. Comparing to general population, stroke is more common noted in the RA patients [12]. The prevalence of RA in the global and Asia are 460 per 100,000 population and 15.8 of 100,000 people, respectively [13-15]. But the risk to develop ischemic stroke in Asian RA patients (hazard ratio (HR), 1.32) is similar with the Caucasian group (HR 1.29) [16-17].

Trying to disclose the agents to prevent stroke is an essential issue to clinical doctors and patients [18]. The common prescriptions to treat RA are Nonsteroidal anti-inflammatory drugs (NSAIDs), steroid, conventional disease-modifying antirheumatic drugs (DMARDs), and biological agents such as etanercept, infliximab (TNF-α inhibitor) and anakinra (IL-1 inhibitor) [3,5,19].And steroid, DMARDs such as methotrexate (MTX), and infliximab have found their advantages in the prevention of ischemic stroke in the RA patients [18]. But some of them could bring the complications in the bone marrow to cause thrombocytopenia [20]. The alternative intervention to control RA and lower complication from treatment itself become a well-discussion topic.

In lots of countries and regions, such as Taiwan, Germany, Hong Kong, and China, acupuncture therapy is widely used to control pain when patients have musculoskeletal and immune problems, including RA [21-25]. A previous cohort

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study founded that approximately 27.3% of RA patients in Taiwan ever consulted traditional Chinese medicine (TCM) service, and 23.6% of these patients had received acupuncture [26]. Furthermore, secondary stroke prevention is also noted from acupuncture therapy in the Taiwanese [27]. And the hypothesis in the acupuncture to lower stroke rate is similar with agents to treat RA: anti-inflammation. Thus, we want to investigate the relationship between acupuncture intervention and incidence of ischemic stroke in RA patients.

In Taiwan, the records of medical services are saved in the database of National Health Insurance: National Health Insurance Research Database (NHIRD). The service of NHI is from 1995 until now and the coverage rate in the Taiwanese is more than 99% population [28]. In other words, the medical data in the NHIRD is long and large enough to demonstrate a national wide population research. And sampling bias could be prevented when study process through such a large-scale database [29]. We use NHIRD to investigate the long-term effect of ischemic stroke prevention in patients with RA have accepted acupuncture treatment.

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Materials and Methods

Data sources

A nationwide, population-based 1:1 propensity score-matched cohort study via data analysis derived from the NHIRD was performed. The database used in this study was the Registry for Catastrophic Illness Patients Database (RCIPD), which is part of the NHIRD. The personal information was removed from the NHIRD. It was not possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research The RCIPD enrolled all patients with a catastrophic illness, which was proven by pathological, laboratory, and clinical diagnoses by both specialists and a regular review. This real-world database consists of datasets including demographic characteristics, outpatient and inpatient visits, diagnostic codes, assessments, remedies, procedures and medical expenses for reimbursement. The diagnoses were coded by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Patients with a diagnosis of RA are issued catastrophic illness certificates and receive free medical services for health complications. Thus, the RCIPD is a comprehensive database for the investigation of all RA patients in Taiwan. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH104-REC2-115).

Study subjects and variables

We used both ambulatory and inpatient medical records to identify RA treatments that were linked with the RCIPD from 1997 to 2010 to identify a study population (n=47,809) for follow-up until the end of 2011 (**Fig. 1**). Newly diagnosed RA patients (n=36,277) with the diagnosis of ICD-9-CM code 714.0 were included. We excluded patients (n=1,793) who were younger than 18 years, who had

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incomplete data on age or sex, who had an interruption in health insurance services during the follow-up period, and who had a diagnosis of ischemic stroke (ICD-9-CM: 433-438) before the index date. Finally, 34,484 patients newly diagnosed of RA were included. Patients who received acupuncture therapy from the initial RA diagnosis to 31 December 2010 were included in the acupuncture cohort (n=12,266). We used a propensity score approach to minimize confounders in the analysis of acupuncture therapy. A one-to-one propensity score match was conducted by age (per 5 years), sex, comorbidities, and types of drugs used (oral steroid, NSAID, statin, all DMARDs), RA diagnosis year and index year by multiple logistic regression analysis. And the definition of drugs used is patient with ≥28 cumulative use days. The numbers of participants in both the acupuncture and no-acupuncture cohorts were the same (n=11,613). The index date was defined as the first time that patients received acupuncture therapy which was given randomly to no-acupuncture cohort according to the acupuncture cohort. The immortal time was defined as the period from the initial diagnosis of RA to the index date.

Covariate assessment

The patients were divided into three groups by age (18–39 years, 40–59 years, and ≥ 60 years). ICD-9-CM codes of comorbidities that appeared more than one time in the outpatient or inpatient records before the primary diagnosis of RA were taken into consideration; such comorbidities included diabetes mellitus (DM; ICD-9-CM code 250), hypertension (HTN; ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), congestive heart failure (ICD-9-CM codes 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, and 428.0), anxiety (ICD-9-CM codes 300.0, 300.2, 300.3, 308.3, and 308.91), depression (ICD-9-CM 296.2–296.3, 300.4, 311), alcoholism (ICD-9-CM codes 291, 303, 305.00–305.03,

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790.3, and V11.3), tobacco use (ICD-9-CM code 305.1), obesity (ICD-9-CM codes 278 and A183), and atrial fibrillation (ICD-9-CM 427.3). The events of ischemic stroke (ICD-9-CM: 433-438) were compared between acupuncture and non-acupuncture cohort of RA patients.

Types of acupuncture and disease categories in the acupuncture cohort

We identified the different acupuncture types by the treatment codes, including manual acupuncture (B41, B42, B45, B46, B80, B81, B82, B83, B84, B90, B91, B92, B93, B94, P27041, P31103, and P32103) and electroacupuncture (B43, B44, B86, B87, B88, and B89) as previously described.[30]

Statistical analyses

The standardized mean difference (SMD) was used to compare the baseline characteristics of the acupuncture and no-acupuncture cohorts as previously described [30]. A negligible difference in mean values or proportions between the two cohorts was defined as less than 0.1 standard deviation (SD). A competing-risks regression models was performed to estimate the crude and adjusted subhazard ratios (SHRs) of acupuncture therapy, age, sex, comorbidities, and types of drugs used. The Kaplan-Meier method and the log-rank test were conducted to find the difference between the two cohorts in the development of ischemic stroke. We used SAS 9.4 (SAS Institute, Cary, NC, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria) to perform statistical analyses and create the figures. Statistical significance was defined as $p < 0.05$ in two-tailed tests.

Patient and Public Involvement

None

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Results

We used 1:1 propensity-score matching by sex, age, all comorbidities, drugs (oral steroid, NSAID, statin, all DMARDS), the RA diagnosis year and index year to enroll an equal number (n=11,613) of RA patients in the acupuncture cohort and non-acupuncture cohort (**Fig. 1**). The baseline characteristics of both cohorts are presented in **Table 1**, with similar distributions of sex, age, comorbidities, and prescriptions. Most participants were female in both cohorts, and most patients were middle-aged (40-59 years). The most common comorbidity was HTN; more than 38% of patients had this problem. In patients with RA, 18% had DM, 28% had hyperlipidemia, 6% had congestive heart failure, 24% had anxiety, and 10% had depression. There were no differences in the proportions of alcoholism, tobacco dependence, and obesity between the two cohorts. NSAIDs were the most common prescriptions in both the cohorts, 76% included patients were on these medications. In the participants of the two cohorts, 55% used oral steroids, and 5% used statin agents. Most patients (87%) were treated by manual acupuncture, with electroacupuncture having been used in 3% of the participants, and the other 10% of patients having had combined manual acupuncture and electroacupuncture treatments. The mean duration between RA diagnosis and the first acupuncture treatment was approximately 1,065 days. The mean number of acupuncture visits was 9.83.

During the follow-up period, 946 patients developed ischemic stroke (**Supplementary Table 1**). The incidence of ischemic stroke in RA patients increased with age, with older patients having had a higher risk. The adjusted SHRs of the 40–59-year-old group and the over 60 years old group were 5.99 and 14.7, respectively. The patients with comorbidities of DM, HTN and congestive heart failure had a higher risk of ischemic stroke. The adjusted SHRs of the patients with DM, HTN and congestive heart failure were 1.58, 2.10 and 1.31, respectively. The

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cumulative incidence of ischemic stroke was significantly lower in the acupuncture cohort (log-rank test, $p < 0.001$, **Fig. 2**).

Supplementary Table 2 shows the 341 patients in the acupuncture cohort (5.95 per 1000 person-years) and the 605 patients in the non-acupuncture cohort (12.4 per 1000 person-years) who developed ischemic stroke (adjusted SHR, 0.57; 95% CI, 0.50–0.65). Both males and females were observed to experience the benefit of ischemic stroke prevention, with an adjusted SHR of 0.58 in the female group (95% CI, 0.49–0.67) and an adjusted SHR of 0.54 in the male group (95% CI, 0.41–0.70). The age subgroups ≥40 years old had a lower risk of ischemic stroke after acupuncture therapy (adjusted SHR, 0.54; 95% CI, 0.44–0.66 in the 40-59-year-old group; adjusted SHR, 0.58; 95% CI, 0.48–0.69 in the over 60 years old group). Acupuncture decreased the risk of ischemic stroke in most patients with comorbidities. Coprescriptions with either steroids, statins, or DMARDs did not change the positive results of acupuncture therapy.

The results from un-matching analysis were also provided to prevent possible sampling bias from our 1:1 propensity-score matching in **Supplementary Table 3** and **4**. And the final results analyzed by competing-risks regression models are compatible with the results after 1:1 propensity-score matching.

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Discussion

As far as we know, this is the first study to show that acupuncture therapy is beneficial for ischemic stroke prevention in the RA patients. RA is one of the common disease categories among acupuncture visits in Taiwan [31]. We previously found that 23.6% of RA patients had received acupuncture [26]. In the present study, we showed that the benefit of acupuncture therapy in reducing the risk of ischemic stroke was independent of sex, age, and comorbidities.

Although patients with RA have been known to have high risk for the development of stroke, there is an unmet need to improve the preventive measures for patients with RA [32]. Inflammation is a consistent and independent predictor of CVD in RA [33]. TNF-α is a cytokine that mediates inflammation reactions [34]. A high level of TNF-α has been observed in RA patients, and it has been found that TNF-α can induce pannus formation and subsequent bone destruction [35]. By interrupting TNF-α expression and production by inflammatory cells, TNF-α inhibitors can efficiently control the inflammatory process [36]. Biological agents targeting cytokines may decrease CVD risk in RA [37]. Therefore, it is interesting to know whether if acupuncture fit the niche to reduce the inflammation in RA patients.

There are a couple evidences and potential explanations about the effects and mechanisms of acupuncture. Acupuncture has been reported to be effective in treating neuropathy [38], relieving pain [39] and attenuating cardiovascular disease [40] in different clinical trials. Previous clinical studies revealed that acupuncture reduced the amounts of tender joints, relieved morning stiffness and joint pain, enhanced physical activity, and improved quality of life in patients with RA [41,42]. In the analysis of blood and synovial fluid of the RA patients, acupuncture was found to reduce TNF-α and vascular endothelial growth factor to improve the inflammation of RA [43]. In

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animal studies, acupuncture reduced inflammation in collagen-induced arthritis model [44-46]. Furthermore, acupuncture was found not only have analgesic effect through beta-endorphin [47], adenosine [48] and orexin [49], but also reduce inflammation through dopamine [50]. On the other hand, unstable blood pressure and lipid profiles are the two risk factors of ischemic stroke, and acupuncture therapy has the advantage of controlling both HTN and dyslipidemia [51,52]. If acupuncture relieved the morning stiffness and join pain, the patients might also benefit from increasing daily activities, which might also reduce the risk of stroke [53].

Our study had some limitations. For example, we could not identify the number and specific affected joints from the data of the RCIPD. Thus, we use prescriptions for RA treatment to be variables which could represent the severity of RA. After performing 1:1 propensity score matching, the differences between the two cohorts was minimizing. And, we had similar percentages of patients who used NSAIDs, steroid agents, statins, and DMARDs. The second limitation was that the RCIPD did not provide data on height, weight, laboratory data or exercise status. We tried to define a diagnosis of alcoholism, tobacco use, and obesity to represent these personal characteristics and lifestyles; then, through 1:1 propensity score matching, we attempted to eliminate or minimize confounders [54]. The distribution of patients with different habits was similar, and these parameters did not change the significant effect of ischemic stroke prevention in patients with RA. And the algorithm for risk to develop cardiovascular events, such as the Framingham Risk Score is hard to form, because of lacking the above information. Additionally, the RCIPD database could not offer information of acupoints for RA treatment. The selection of acupoints depends on the diagnosis and the experience of the TCM doctors. The variable prescriptions of acupuncture could also stem from the different complaints, comorbidities and wishes of the patients. Because of the standard TCM program

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training in medical schools, most TCM doctors in Taiwan know the concepts of basic acupoints, such as LI11, ST36, and SP9 (**Supplementary Fig. 1**) [55,56]. Further clinical trials with standardized acupoints should be conducted based on the findings of this study. And the difference of treatment results among various types of interventions could not be found from our database which did not belong to our result measure. The evidence of treatment dose of acupuncture therapy is still establishing, thus we did not discuss the topic in here.

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Conclusions

Our study demonstrates that the ischemic stroke risk could be reduced by acupuncture treatment in patients with RA in Taiwan. It also offers important ideas for more comprehensive studies in the future.

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Ethics Approval Statement

The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH104-REC2-115).

Competing Interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Competing interests

The authors declare that they have no conflicts of interest.

Authors' contributions

CYH and MCH contributed equally. MCH contributed to conception of the study, participated in the interpretation of clinical data and drafted the manuscript. CYH contributed to conception of the study, participated in the interpretation of clinical data and drafted the manuscript. HHL participated in the interpretation of clinical data and drafted the manuscript. CLL performed the statistical analysis. GZ drafted the manuscript. MYW contributed to design of the study, participated in the interpretation of clinical data and drafted the manuscript. YCL supervised the project, participated in the interpretation of clinical data and drafted the manuscript. HRY supervised the project, contributed to conception and design of the study and finalized the manuscript. MYW and HRY contributed equally as co-corresponding authors.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Table 1.Characteristics of rheumatoid arthritis patients according to whether they received acupuncture treatment.

Variable	Rheumatoid Arthritis				Standardized mean difference
	Acupuncture treatment				
	No (n = 11613)		Yes (n = 11613)		
	n	%	n	%	
Sex					
Women	9499	81.8	9478	81.6	0.01
Men	2114	18.2	2135	18.4	0.01
Age group					
18-39	1839	15.8	1588	13.7	0.06
40-59	6684	57.6	7330	63.1	0.11
≥ 60	3090	26.6	2695	23.2	0.08
Mean ± SD (years)	54.9±14.5		54.8±13.2		0.01
Baseline Comorbidity					
Diabetes mellitus	2176	18.7	2126	18.3	0.01
Hypertension	4507	38.8	4416	38.0	0.02
Hyperlipidemia	3267	28.1	3273	28.2	0.001
Congestive heart failure	741	6.38	723	6.23	0.006
Depression	1256	10.8	1248	10.8	0.002
Anxiety	2880	24.8	2841	24.5	0.008
Alcoholism	208	1.79	221	1.90	0.008
Tobacco use	70	0.60	77	0.66	0.008
Obesity	130	1.12	135	1.16	0.004
Atrial fibrillation	741	6.38	715	6.16	0.009
Drugs used					
Oral steroid	6489	55.6	6495	55.9	0.001
NSAID	8823	76.0	8882	76.5	0.012
Statin	5592	5.10	593	5.11	0.000
Conventional DMARDS					
Hydroxychloroquine	5670	48.8	5663	48.8	0.001
Sulfasalazine	4295	37.0	4323	37.2	0.005
Methotrexate	9	0.08	10	0.09	0.003
Leflunomide	867	7.47	872	7.51	0.002
D-penicillamine	131	1.13	1298	1.11	0.002
Azathioprine	208	1.79	223	1.92	0.01
Mycophenolate	5	0.04	5	0.04	0.000

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Cyclosporine	555	4.78	544	4.68	0.004
Biological DMARDs					
Conventional DMARDS					
Hydroxychloroquine	5670	48.8	5663	48.8	0.001
Etanercept	625	5.38	629	5.42	0.002
Adalimumab	198	1.70	193	1.66	0.003
Types of acupuncture					
Manual acupuncture	-	-	10050	86.5	
Electroacupuncture	-	-	401	3.45	
Combination of both types	-	-	1162	10.0	
Duration from rheumatoid arthritis diagnosis and index, days (mean, median)	(1078.52, 795.0)		(1065.18, 707.0)		0.32
Acupuncture visits (mean, median)	-		(9.83, 3.00)		

The mean (median) follow-up period was 4.93 (4.35) and 4.21 (3.41) years in the acupuncture cohort and the compared cohort, respectively.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

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Figure legends

Fig. 1 Study population flowchart. A total of 47,809 patients with rheumatoid arthritis were newly diagnosed from 1997 to 2010. Sex, age, comorbidities, types of drugs used, RA diagnosis year and index year were processed via 1:1 matching; subsequently, 11,613 patients were included in the acupuncture and no-acupuncture cohorts.

Fig. 2 The cumulative incidence of ischemic stroke in the acupuncture (dashed line) cohort and the no-acupuncture cohort (solid line). Patients in the acupuncture group had a lower incidence of ischemic stroke (log-rank test, $p < 0.001$).

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Figures

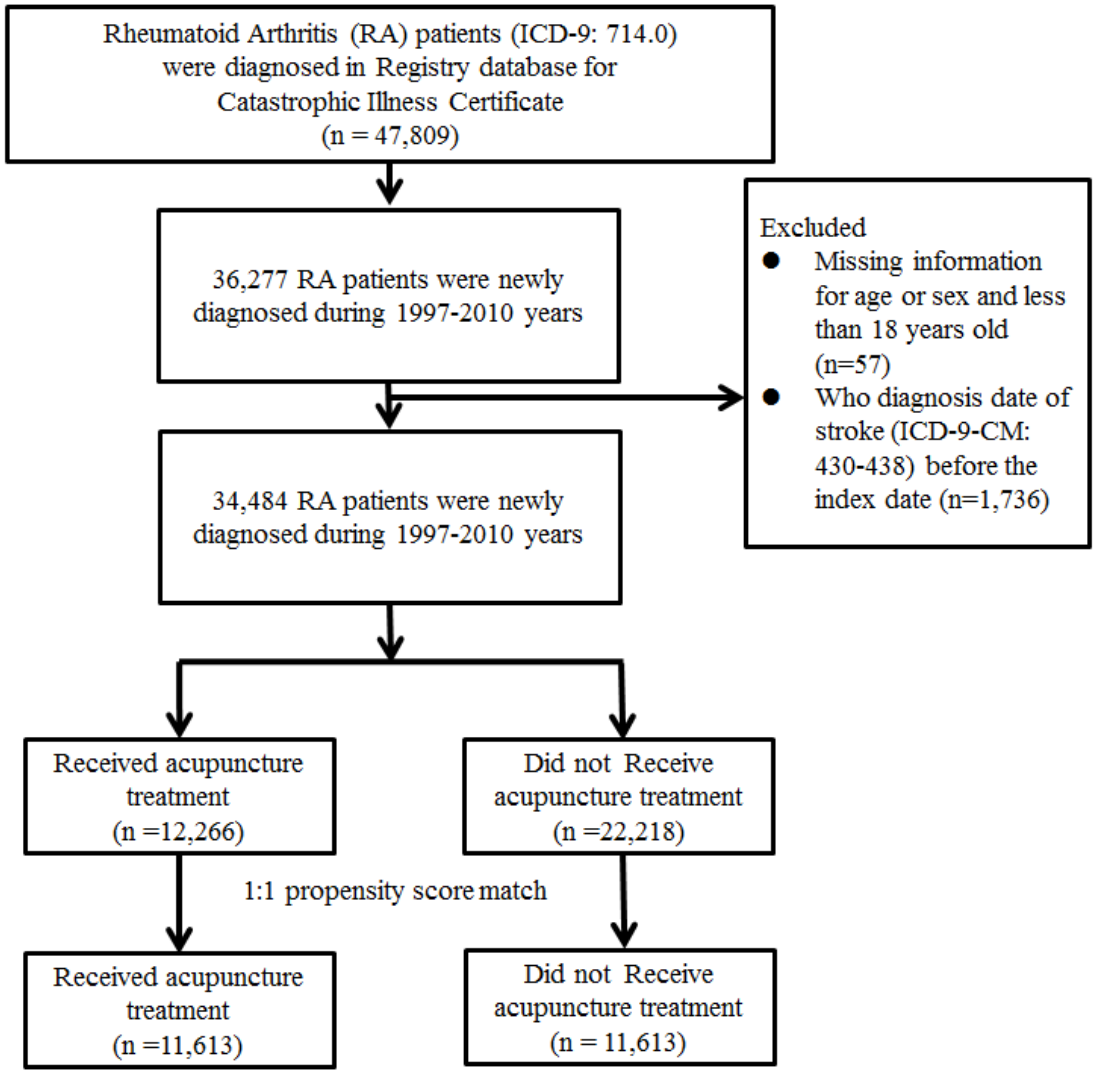

Fig. 1

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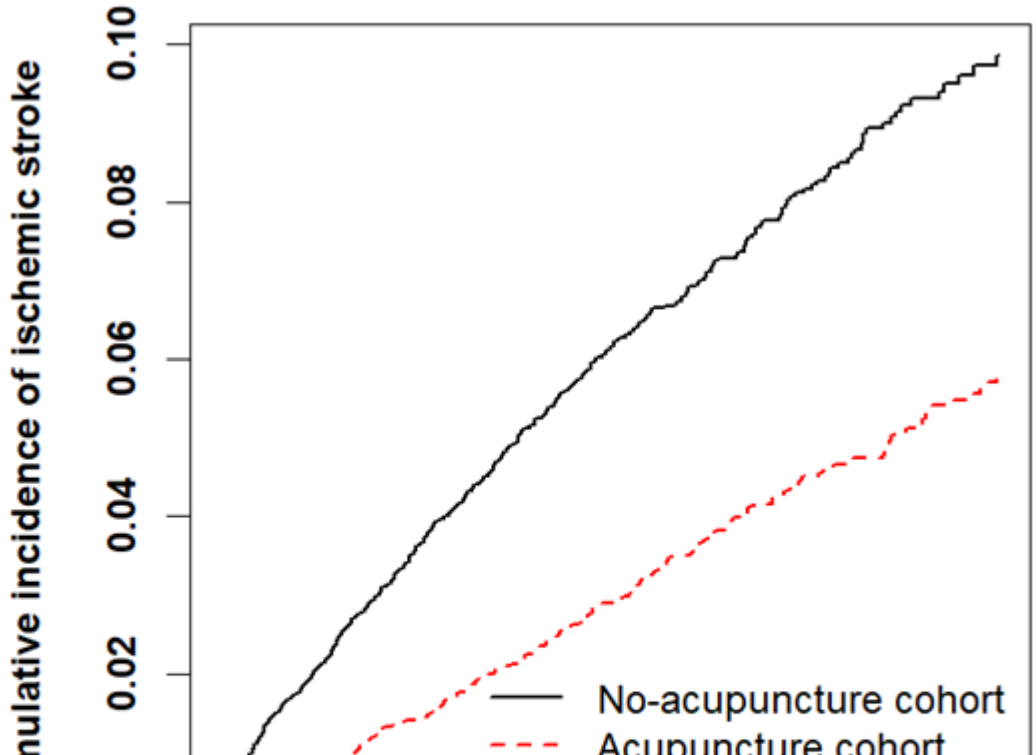

Fig. 2

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Supplementary Table 1. Subhazard ratios and 95% confidence intervals of ischemic stroke associated with acupuncture treatment and covariates among rheumatoid arthritis patients using the competing-risks regression models.

Variable	No. of event (n = 946)	Crude*			Adjusted†		
		SHR	(95% CI)	p-value	SHR	(95% CI)	p-value
Acupuncture treatment							
No	605	1.00	reference		1.00	reference	
Yes	341	0.52	(0.46, 0.60)	<0.001	0.8	(0.49, 0.65)	<0.001
Sex							
Women	714	1.00	reference		1.00	reference	
Men	231	1.44	(1.24, 1.67)	<0.001	1.3	(1.14, 1.54)	<0.001
Age group							
18-39	13	1.00	reference		1.00	reference	
40-59	372	7.17	(4.14, 12.4)	<0.001	5.99	(3.44, 10.4)	<0.001
≥ 60	561	28.1	(16.3, 48.6)	<0.001	14.7	(8.38, 25.7)	<0.001
Baseline Comorbidity (ref = no comorbidity)							
Diabetes mellitus	334	2.64	(2.31, 3.01)	<0.001	1.58	(1.36, 1.82)	<0.001
Hypertension	654	3.96	(3.45, 4.54)	<0.001	2.10	(1.79, 2.47)	<0.001
Hyperlipidemia	371	1.94	(1.70, 2.21)	<0.001	1.08	(0.93, 1.25)	0.30
Congestive heart failure	148	3.18	(2.67, 3.79)	<0.001	1.31	(1.08, 1.59)	0.006
Depression	120	1.46	(1.21, 1.77)	<0.001	1.12	(0.91, 1.37)	0.28
Anxiety	256	1.40	(1.21, 1.61)	<0.001	0.99	(0.85, 1.16)	0.94
Alcoholism	20	1.48	(0.95, 2.29)	0.08	1.46	(0.88, 2.43)	0.14
Tobacco use	2	0.55	(0.14, 2.20)	0.40	0.32	(0.07, 1.40)	0.13
Obesity	10	1.16	(0.62, 2.17)	0.65	1.10	(0.58, 2.08)	0.77
Atrial fibrillation	50	1.02	(0.77, 1.35)	0.90	0.89	(0.66, 1.19)	0.43
Drugs used							
Oral steroid	1621	0.57	(0.47-0.69)	< 0.0001	0.51	(0.42-0.62)	< 0.0001
NSAID	1726	0.22	(0.11-0.46)	< 0.0001	0.24	(0.11-0.51)	0.0002
Statin	329	1.04	(0.92-1.17)	0.5375	0.65	(0.58-0.74)	< 0.0001

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Conventional DMARDS							
Hydroxychloroquine	333	0.47	(0.41, 0.54)	<0.001	0.70	(0.60, 0.81)	<0.001
Sulfasalazine	235	0.47	(0.41, 0.54)	<0.001	0.80	(0.68, 0.94)	0.007
Methotrexate	2	1.88	(0.50, 7.04)	0.35	3.15	(0.84, 11.9)	0.08
Leflunomide	18	0.22	(0.14, 0.35)	<0.001	0.34	(0.22, 0.54)	<0.001
D-penicillamine	11	0.85	(0.46, 1.53)	0.53	1.07	(0.61, 1.88)	0.05
Azathioprine	9	0.39	(0.20, 0.75)	0.004	0.77	(0.40, 1.49)	0.44
Mycophenolate	0	-	-			-	
Cyclosporine	35	0.62	(0.44, 0.87)	0.005	1.41	(0.99, 1.98)	0.06
Biological DMARDs							
Etanercept	16	0.27	(0.16, 0.44)	<0.001	0.51	(0.31, 0.83)	0.007
Adalimumab	3	0.18	(0.06, 0.57)	0.003	0.43	(0.14, 1.34)	0.15
Conventional DMARDS							
Hydroxychloroquine	333	0.47	(0.41, 0.54)	<0.001	0.70	(0.60, 0.81)	<0.001

Crude SHR* represents the relative subhazard ratio;

Adjusted SHR† represents the adjusted subhazard ratio: mutually adjusted for accepted acupuncture, age, sex, comorbidities, and drugs used in competing-risks regression models.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

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Supplementary Table 2.. Incidence rates, subhazard ratios and confidence intervals of ischemic stroke in rheumatoid arthritis patients who received and did not receive acupuncture in the stratification of sex, age, comorbidities and drug used using the competing-risks regression models.

Variables	Rheumatoid arthritis						Compared with non-acupuncture users	
	No (n = 11613)			Yes (n = 11613)			Crude SHR	Adjusted SHR
	Event	Person years	IR†	Event	Person years	IR†	(95% CI)	(95% CI)
Total	605	48836	12.4	341	57273	5.95	0.52(0.46, 0.60)***	0.57(0.50, 0.65)***
Sex								
Women	460	40274	11.4	254	46907	5.41	0.52(0.44, 0.60)***	0.58(0.49, 0.67)***
Men	145	8562	16.9	87	10366	8.39	0.50(0.42, 0.71)***	0.54(0.41, 0.70)***
Age group								
18-39	5	8734	0.57	8	8576	0.93	1.63(0.49, 4.45)	1.45(0.44, 4.76)
40-59	226	29529	7.65	146	37225	3.92	0.51(0.43, 0.66)***	0.54(0.44, 0.66)***
≥ 60	374	10573	35.4	187	11472	16.3	0.53(0.46, 0.65)***	0.58(0.48, 0.69)***
Baseline Comorbidity								
Diabetes mellitus								
No	383	41083	9.32	229	48060	4.76	0.51(0.47, 0.65)***	0.60(0.51, 0.71)***
Yes	222	7753	28.6	112	9213	12.2	0.47(0.38, 0.59)***	0.52(0.41, 0.65)***
Hypertension								
No	184	32174	5.72	108	37634	2.87	0.50(0.41, 0.66)***	0.57(0.45, 0.72)***
Yes	421	16661	25.3	233	19639	11.9	0.53(0.45, 0.62)***	0.57(0.49, 0.67)***
Hyperlipidemia								
No	366	36970	9.90	209	43496	4.81	0.53(0.45, 0.62)***	0.61(0.51, 0.72)***
Yes	239	11866	20.1	132	13777	9.58	0.51(0.41, 0.63)***	0.51(0.41, 0.63)***
Congestive heart failure								
No	513	46595	11.0	285	54590	5.22	0.51(0.44, 0.59)***	0.55(0.47, 0.64)***
Yes	92	2241	41.1	56	2683	20.9	0.61(0.44, 0.85)***	0.65(0.47, 0.92)***
Depression								
No	523	44638	11.7	303	52396	5.78	0.54(0.47, 0.62)***	0.59(0.51, 0.67)***

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Yes	82	4198	19.5	38	4877	7.79	0.43(0.30, 0.64)***	0.48(0.32, 0.72)***
Anxiety								
No	442	38718	11.4	248	46073	5.38	0.57(0.44, 0.60)***	0.56(0.48, 0.66)***
Yes	163	10117	16.1	93	11200	8.30	0.56(0.43, 0.71)***	0.57(0.44, 0.74)***
Alcoholism								
No	596	48177	12.4	330	56529	5.84	0.51(0.45, 0.59)***	0.56(0.49, 0.64)***
Yes	9	659	13.7	11	744	14.8	1.12(0.47, 2.67)	1.25(0.50, 3.09)
Tobacco use								
No	603	48655	12.4	341	57090	5.97	0.46(0.46, 0.60)***	0.57(0.50, 0.65)***
Yes	2	181	11.1	0	182	0.00		
Obesity								
No	598	48412	12.4	338	56737	5.96	0.46(0.46, 0.60)***	0.57(0.50, 0.65)***
Yes	7	424	16.5	3	536	5.60	0.39(0.10, 1.49)	0.40(0.14, 1.19)
Atrial fibrillation								
No	576	46291	12.4	320	54553	5.87	0.51(0.45, 0.59)***	0.56(0.49, 0.64)***
Yes	29	2545	11.4	21	2720	7.72	0.72(0.41, 1.26)	0.70(0.38, 1.30)
Drugs used								
Oral steroid								
No	318	17828	17.8	166	21844	7.60	0.48(0.40, 0.58)***	0.53(0.44, 0.64)***
Yes	287	31008	9.26	175	35429	4.94	0.56(0.46, 0.68)***	0.59(0.49, 0.72)***
NSAID								
No	216	7329	29.5	105	9509	11.0	0.46(0.37, 0.58)***	0.54(0.43, 0.69)***
Yes	389	41506	9.37	236	47764	4.94	0.52(0.47, 0.64)***	0.56(0.48, 0.66)***
Statin								
No	586	45820	12.8	322	54040	5.96	0.51(0.44, 0.58)***	0.56(0.49, 0.64)***
Yes	19	3016	6.30	19	3233	5.88	0.94(0.50, 1.79)	0.97(0.49, 1.95)
Conventional DMARDS								
No	347	14099	24.6	181	18431	9.82	0.48(0.40, 0.57)***	0.54(0.45, 0.65)***
Yes	258	34736	7.43	160	38842	4.12	0.56(0.46, 0.68)***	0.58(0.47, 0.71)***
Biological DMARDs								

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No	591	44821	13.2	336	52599	6.39	0.53(0.46, 0.60)***	0.58(0.50, 0.66)***
Yes	14	4014	3.49	5	4674	1.07	0.23(0.10, 0.79)*	0.26(0.09, 0.80)**

Abbreviation: IR, incidence rate per 1,000 person-years; SHR, subhazard ratio; CI, confidence interval

Adjusted SHR: adjusted for accepted acupuncture, age, sex, comorbidities, and drugs used in the competing risks regression models.

*: $p < 0.05$; **: $p < 0.01$; *** $p < 0.001$

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

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Supplementary Table 3. Characteristics of rheumatoid arthritis patients according to accept acupuncture in un-matching.

Variable	Rheumatoid Arthritis				Standardised mean difference
	Accepted acupuncture				
	No (n =22218)		Yes (n =12266)		
	n	%	n	%	
Gender					
Women	16702	75.2	10109	82.4	0.18
Men	5516	24.8	2157	17.6	0.18
Age group					
18-39	2994	13.5	1767	14.4	0.03
40-59	12351	55.6	7762	63.3	0.16
≥60	6873	30.9	2737	22.3	0.20
Mean±SD (years)	56.7±14.7		54.3±13.3		0.17
Baseline Comorbidity					
Diabetes mellitus	4117	18.5	2260	18.4	0.003
Hypertension	8857	39.9	4632	37.8	0.04
Hyperlipidemia	5610	25.3	3593	29.3	0.09
Congestive heart failure	1698	7.64	736	6.00	0.07
Depression	1901	8.56	1394	11.4	0.09
Anxiety	4591	20.7	3118	25.4	0.11
Alcoholism	422	1.90	244	1.99	0.01
Tobacco used	146	0.66	84	0.68	0.003
Obesity	188	0.85	163	1.33	0.05
Atrial fibrillation	1102	4.96	845	6.89	0.08
Drug used					
Oral steroid	10814	48.7	6946	56.6	0.16
NSAID	13907	62.6	9532	77.7	0.34
Statin	828	3.73	688	5.61	0.09
Conventional DMARDS					
Hydroxychloroquine	9299	41.9	6059	49.4	0.15
Sulfasalazine	7210	32.5	4606	37.6	0.11
Methotrexate	14	0.06	11	0.09	0.01
Leflunomide	1309	5.89	973	7.93	0.08
D-penicillamine	196	0.88	138	1.13	0.02
Azathioprine	385	1.73	229	1.87	0.01
Mycophenolate	10	0.05	7	0.06	0.01
Cyclosporine	816	3.67	594	4.84	0.06
Biological DMARDs					

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Etanercept	941	4.24	706	5.76	0.07
Adalimumab	345	1.55	202	1.65	0.01
Types of acupuncture					
Manual acupuncture			10604	86.45	
Electroacupuncture			407	3.32	
Combination of manual acupuncture and electroacupuncture			1255	10.23	
Duration between rheumatoid arthritis date and index, days (mean, median)	(981.29, 668.0)		(1047.36, 688.5)		
Acupuncture visits, (mean, meidan)			(10.43, 3.00)		

The mean (median) of follow-up period were 4.96 (4.39) and 4.01 (3.17) years for acupuncture cohort and compared cohort.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

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Supplementary Table 4. Subhazard ratios and 95% confidence intervals of ischemic stroke associated with accepted acupuncture and covariates among rheumatoid arthritis patients using the competing-risks regression models in un-matching.

Variable	No. of event (n=1441)	Crude*			Adjusted†		
		SHR	(95%CI)	p-value	SHR	(95%CI)	p-value
Accepted acupuncture							
No	1080	1.00	reference		1.00	reference	
Yes	361	0.48	(0.42, 0.53)	<0.001	0.65	(0.58, 0.74)	<0.001

Crude SHR* represented relative subhazard ratio;

Adjusted SHR† represented adjusted subhazard ratio: mutually adjusted for accepted acupuncture, age, gender, comorbidities, and drugs used in competing-risks regression models.

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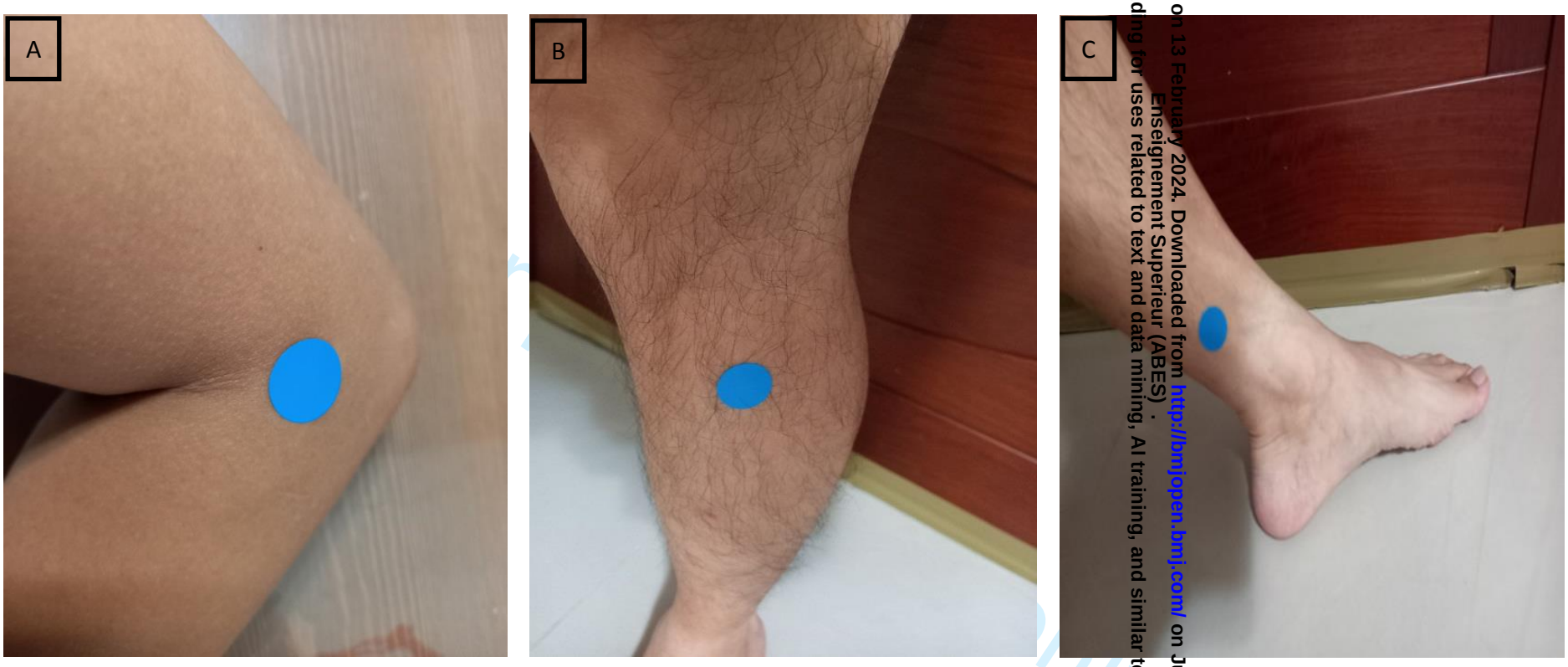

Supplementary Fig. 1. Acupoints of (A)LI11, (B)ST36, and (C)SP9 (blue spot)

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-10
Participants	6	*(*a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	9-10
		(*b*) For matched studies, give matching criteria and the number of controls per case	9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9-10*
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	9-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how matching of cases and controls was addressed	11
		(*e*) Describe any sensitivity analyses	11
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-13
		(b) Give reasons for non-participation at each stage	12-13
		(c) Consider use of a flow diagram	12-13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	12-13
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	12-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3-4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Acupuncture decreased the risk of ischemic stroke in patients with rheumatoid arthritis: a nationwide propensity score-matched study

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Rheumatology, Neurology
Keywords:	Stroke < NEUROLOGY, COMPLEMENTARY MEDICINE, RHEUMATOLOGY

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Acupuncture decreased the risk of ischemic stroke in patients with rheumatoid arthritis: a nationwide propensity score-matched study

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Abstract

Objectives: The purpose of this study was to demonstrate that acupuncture is beneficial for decreasing the risk of ischemic stroke (IS) in patients with rheumatoid arthritis (RA).

Design: This is a propensity score-matched cohort study.

Setting: This is a nationwide population-based study.

Participants: The patients with RA diagnosed between 1 January 1997 and 31 December 2010 through the National Health Insurance Research Database.

Interventions: The patients who were administered acupuncture therapy from the initial date of RA diagnosis of rheumatoid arthritis to 31 December 2010 were included in the acupuncture cohort. Patients who did not receive acupuncture treatment during the same time interval were regarded as the no-acupuncture cohort.

Primary outcome measures: A Cox regression model was used to adjust for age, sex, comorbidities, and types of drugs used. We compared the subhazard ratios (SHRs) of IS between these two cohorts through competing-risks regression models.

Results: After a 1:1 propensity score match, a total of 23,226 patients were identified. The basic characteristics of these patients were similar. A lower cumulative incidence of ischemic stroke was found in the acupuncture cohort (log-rank test, $p < 0.001$; immortal time: 1,065 days; mean number of acupuncture visits: 9.83). In the end, 341 patients in the acupuncture cohort (5.95 per 1,000 person-years) and 605 patients in the no-acupuncture cohort (12.4 per 1,000 person-years) experienced an ischemic stroke (adjusted SHR, 0.57; 95% CI, 0.50–0.65). The advantage of lowering ischemic stroke incidence through acupuncture therapy in RA patients was independent of sex, age, types of drugs used, and comorbidities.

Conclusions: This study showed the beneficial effect of acupuncture in reducing the incidence rate of ischemic stroke in patients with RA.

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Strengths and limitations of this study:

- Our research disclose the possible long-term effect from acupuncture in stroke prevention which could not be investigated from clinical trial.
- Lower ischemic stroke developed in patients with rheumatoid arthritis after acupuncture therapy.
- The causality could not be proved directly as clinical trial through our study design.

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Introduction

The rheumatoid arthritis (RA) is one of the common rheumatoid diseases, and demonstrated as polyarthritis in the joints, mainly synovial inflammation, and morning stiffness [1]. The bone erosion, joint deformity and loss of functional abilities are the long-term complication from RA. When it comes to chronic process, the inflammation status could be noted in the whole body: pericarditis, myocarditis, pleuritis, interstitial lung fibrosis, osteoporosis, and cardiovascular diseases (CVD) [2-5]. Comorbidities from CVD are the major cause to develop death in the RA patients, such as stroke [6-11]. Comparing to general population, stroke is more common noted in the RA patients [12]. The prevalence of RA in the global and Asia are 460 per 100,000 population and 15.8 of 100,000 people, respectively [13-15]. But the risk to develop ischemic stroke in Asian RA patients (hazard ratio (HR), 1.32) is similar with the Caucasian group (HR 1.29) [16-17].

Trying to disclose the agents to prevent stroke is an essential issue to clinical doctors and patients [18]. The common prescriptions to treat RA are Nonsteroidal anti-inflammatory drugs (NSAIDs), steroid, conventional disease-modifying antirheumatic drugs (DMARDs), and biological agents such as etanercept, infliximab (TNF-α inhibitor) and anakinra (IL-1 inhibitor) [3,5,19].And steroid, DMARDs such as methotrexate (MTX), and infliximab have found their advantages in the prevention of ischemic stroke in the RA patients [18]. But some of them could bring the complications in the bone marrow to cause thrombocytopenia [20]. The alternative intervention to control RA and lower complication from treatment itself become a well-discussion topic.

In lots of countries and regions, such as Taiwan, Germany, Hong Kong, and China, acupuncture therapy is widely used to control pain when patients have musculoskeletal and immune problems, including RA [21-25]. A previous cohort

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study founded that approximately 27.3% of RA patients in Taiwan ever consulted traditional Chinese medicine (TCM) service, and 23.6% of these patients had received acupuncture [26]. Furthermore, secondary stroke prevention is also noted from acupuncture therapy in the Taiwanese [27]. And the hypothesis in the acupuncture to lower stroke rate is similar with agents to treat RA: anti-inflammation. Thus, we want to investigate the relationship between acupuncture intervention and incidence of ischemic stroke in RA patients.

In Taiwan, the records of medical services are saved in the database of National Health Insurance: National Health Insurance Research Database (NHIRD). The service of NHI is from 1995 until now and the coverage rate in the Taiwanese is more than 99% population [28]. In other words, the medical data in the NHIRD is long and large enough to demonstrate a national wide population research. And sampling bias could be prevented when study process through such a large-scale database [29]. We use NHIRD to investigate the long-term effect of ischemic stroke prevention in patients with RA have accepted acupuncture treatment.

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Materials and Methods

Data sources

A nationwide, population-based 1:1 propensity score-matched cohort study via data analysis derived from the NHIRD was performed. The database used in this study was the Registry for Catastrophic Illness Patients Database (RCIPD), which is part of the NHIRD. The personal information was removed from the NHIRD. It was not possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research The RCIPD enrolled all patients with a catastrophic illness, which was proven by pathological, laboratory, and clinical diagnoses by both specialists and a regular review. This real-world database consists of datasets including demographic characteristics, outpatient and inpatient visits, diagnostic codes, assessments, remedies, procedures and medical expenses for reimbursement. The diagnoses were coded by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Patients with a diagnosis of RA are issued catastrophic illness certificates and receive free medical services for health complications. Thus, the RCIPD is a comprehensive database for the investigation of all RA patients in Taiwan. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH104-REC2-115).

Study subjects and variables

We used both ambulatory and inpatient medical records to identify RA treatments that were linked with the RCIPD from 1997 to 2010 to identify a study population (n=47,809) for follow-up until the end of 2011 (**Fig. 1**). Newly diagnosed RA patients (n=36,277) with the diagnosis of ICD-9-CM code 714.0 were included. We excluded patients (n=1,793) who were younger than 18 years, who had

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incomplete data on age or sex, who had an interruption in health insurance services during the follow-up period, and who had a diagnosis of ischemic stroke (ICD-9-CM: 433-438) before the index date. Finally, 34,484 patients newly diagnosed of RA were included. Patients who received acupuncture therapy from the initial RA diagnosis to 31 December 2010 were included in the acupuncture cohort (n=12,266). We used a propensity score approach to minimize confounders in the analysis of acupuncture therapy. A one-to-one propensity score match was conducted by age (per 5 years), sex, comorbidities, and types of drugs used (oral steroid, NSAID, statin, all DMARDs), RA diagnosis year and index year by multiple logistic regression analysis. And the definition of drugs used is patient with ≥28 cumulative use days. The numbers of participants in both the acupuncture and no-acupuncture cohorts were the same (n=11,613). The index date was defined as the first time that patients received acupuncture therapy which was given randomly to no-acupuncture cohort according to the acupuncture cohort. The immortal time was defined as the period from the initial diagnosis of RA to the index date.

Covariate assessment

The patients were divided into three groups by age (18–39 years, 40–59 years, and ≥ 60 years). ICD-9-CM codes of comorbidities that appeared more than one time in the outpatient or inpatient records before the primary diagnosis of RA were taken into consideration; such comorbidities included diabetes mellitus (DM; ICD-9-CM code 250), hypertension (HTN; ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), congestive heart failure (ICD-9-CM codes 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, and 428.0), anxiety (ICD-9-CM codes 300.0, 300.2, 300.3, 308.3, and 308.91), depression (ICD-9-CM 296.2–296.3, 300.4, 311), alcoholism (ICD-9-CM codes 291, 303, 305.00–305.03,

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790.3, and V11.3), tobacco use (ICD-9-CM code 305.1), obesity (ICD-9-CM codes 278 and A183), and atrial fibrillation (ICD-9-CM 427.3). The events of ischemic stroke (ICD-9-CM: 433-438) were compared between acupuncture and non-acupuncture cohort of RA patients.

Types of acupuncture and disease categories in the acupuncture cohort

We identified the different acupuncture types by the treatment codes, including manual acupuncture (B41, B42, B45, B46, B80, B81, B82, B83, B84, B90, B91, B92, B93, B94, P27041, P31103, and P32103) and electroacupuncture (B43, B44, B86, B87, B88, and B89) as previously described.[30]

Statistical analyses

The standardized mean difference (SMD) was used to compare the baseline characteristics of the acupuncture and no-acupuncture cohorts as previously described [30]. A negligible difference in mean values or proportions between the two cohorts was defined as less than 0.1 standard deviation (SD). A competing-risks regression models was performed to estimate the crude and adjusted subhazard ratios (SHRs) of acupuncture therapy, age, sex, comorbidities, and types of drugs used. The Kaplan-Meier method and the log-rank test were conducted to find the difference between the two cohorts in the development of ischemic stroke. We used SAS 9.4 (SAS Institute, Cary, NC, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria) to perform statistical analyses and create the figures. Statistical significance was defined as $p < 0.05$ in two-tailed tests.

Patient and Public Involvement

None

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Results

We used 1:1 propensity-score matching by sex, age, all comorbidities, drugs (oral steroid, NSAID, statin, all DMARDS), the RA diagnosis year and index year to enroll an equal number (n=11,613) of RA patients in the acupuncture cohort and non-acupuncture cohort (**Fig. 1**). The baseline characteristics of both cohorts are presented in **Table 1**, with similar distributions of sex, age, comorbidities, and prescriptions. Most participants were female in both cohorts, and most patients were middle-aged (40-59 years). The most common comorbidity was HTN; more than 38% of patients had this problem. In patients with RA, 18% had DM, 28% had hyperlipidemia, 6% had congestive heart failure, 24% had anxiety, and 10% had depression. There were no differences in the proportions of alcoholism, tobacco dependence, and obesity between the two cohorts. NSAIDs were the most common prescriptions in both the cohorts, 76% included patients were on these medications. In the participants of the two cohorts, 55% used oral steroids, and 5% used statin agents. Most patients (87%) were treated by manual acupuncture, with electroacupuncture having been used in 3% of the participants, and the other 10% of patients having had combined manual acupuncture and electroacupuncture treatments. The mean duration between RA diagnosis and the first acupuncture treatment was approximately 1,065 days. The mean number of acupuncture visits was 9.83.

During the follow-up period, 946 patients developed ischemic stroke (**Supplementary Table 1**). The incidence of ischemic stroke in RA patients increased with age, with older patients having had a higher risk. The adjusted SHRs of the 40–59-year-old group and the over 60 years old group were 5.99 and 14.7, respectively. The patients with comorbidities of DM, HTN and congestive heart failure had a higher risk of ischemic stroke. The adjusted SHRs of the patients with DM, HTN and congestive heart failure were 1.58, 2.10 and 1.31, respectively. The

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cumulative incidence of ischemic stroke was significantly lower in the acupuncture cohort (log-rank test, $p < 0.001$, **Fig. 2**).

Supplementary Table 2 shows the 341 patients in the acupuncture cohort (5.95 per 1000 person-years) and the 605 patients in the non-acupuncture cohort (12.4 per 1000 person-years) who developed ischemic stroke (adjusted SHR, 0.57; 95% CI, 0.50–0.65). Both males and females were observed to experience the benefit of ischemic stroke prevention, with an adjusted SHR of 0.58 in the female group (95% CI, 0.49–0.67) and an adjusted SHR of 0.54 in the male group (95% CI, 0.41–0.70). The age subgroups ≥40 years old had a lower risk of ischemic stroke after acupuncture therapy (adjusted SHR, 0.54; 95% CI, 0.44–0.66 in the 40-59-year-old group; adjusted SHR, 0.58; 95% CI, 0.48–0.69 in the over 60 years old group). Acupuncture decreased the risk of ischemic stroke in most patients with comorbidities. Coprescriptions with either steroids, statins, or DMARDs did not change the positive results of acupuncture therapy.

The results from un-matching analysis were also provided to prevent possible sampling bias from our 1:1 propensity-score matching in **Supplementary Table 3** and **4**. And the final results analyzed by competing-risks regression models are compatible with the results after 1:1 propensity-score matching.

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Discussion

As far as we know, this is the first study to show that acupuncture therapy is beneficial for ischemic stroke prevention in the RA patients. RA is one of the common disease categories among acupuncture visits in Taiwan [31]. We previously found that 23.6% of RA patients had received acupuncture [26]. In the present study, we showed that the benefit of acupuncture therapy in reducing the risk of ischemic stroke was independent of sex, age, and comorbidities.

Although patients with RA have been known to have high risk for the development of stroke, there is an unmet need to improve the preventive measures for patients with RA [32]. Inflammation is a consistent and independent predictor of CVD in RA [33]. TNF-α is a cytokine that mediates inflammation reactions [34]. A high level of TNF-α has been observed in RA patients, and it has been found that TNF-α can induce pannus formation and subsequent bone destruction [35]. By interrupting TNF-α expression and production by inflammatory cells, TNF-α inhibitors can efficiently control the inflammatory process [36]. Biological agents targeting cytokines may decrease CVD risk in RA [37]. Therefore, it is interesting to know whether if acupuncture fit the niche to reduce the inflammation in RA patients.

There are a couple evidences and potential explanations about the effects and mechanisms of acupuncture. Acupuncture has been reported to be effective in treating neuropathy [38], relieving pain [39] and attenuating cardiovascular disease [40] in different clinical trials. Previous clinical studies revealed that acupuncture reduced the amounts of tender joints, relieved morning stiffness and joint pain, enhanced physical activity, and improved quality of life in patients with RA [41,42]. In the analysis of blood and synovial fluid of the RA patients, acupuncture was found to reduce TNF-α and vascular endothelial growth factor to improve the inflammation of RA [43]. In

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animal studies, acupuncture reduced inflammation in collagen-induced arthritis model [44-46]. Furthermore, acupuncture was found not only have analgesic effect through beta-endorphin [47], adenosine [48] and orexin [49], but also reduce inflammation through dopamine [50]. On the other hand, unstable blood pressure and lipid profiles are the two risk factors of ischemic stroke, and acupuncture therapy has the advantage of controlling both HTN and dyslipidemia [51,52]. If acupuncture relieved the morning stiffness and join pain, the patients might also benefit from increasing daily activities, which might also reduce the risk of stroke [53].

Our study had some limitations. For example, we could not identify the number and specific affected joints from the data of the RCIPD. Thus, we use prescriptions for RA treatment to be variables which could represent the severity of RA. After performing 1:1 propensity score matching, the differences between the two cohorts was minimizing. And, we had similar percentages of patients who used NSAIDs, steroid agents, statins, and DMARDs. The second limitation was that the RCIPD did not provide data on height, weight, laboratory data or exercise status. We tried to define a diagnosis of alcoholism, tobacco use, and obesity to represent these personal characteristics and lifestyles; then, through 1:1 propensity score matching, we attempted to eliminate or minimize confounders [54]. The distribution of patients with different habits was similar, and these parameters did not change the significant effect of ischemic stroke prevention in patients with RA. And the algorithm for risk to develop cardiovascular events, such as the Framingham Risk Score is hard to form, because of lacking the above information. Additionally, the RCIPD database could not offer information of acupoints for RA treatment. The selection of acupoints depends on the diagnosis and the experience of the TCM doctors. The variable prescriptions of acupuncture could also stem from the different complaints, comorbidities and wishes of the patients. Because of the standard TCM program

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training in medical schools, most TCM doctors in Taiwan know the concepts of basic acupoints, such as LI11, ST36, and SP9 (**Supplementary Fig. 1**) [55,56]. Further clinical trials with standardized acupoints should be conducted based on the findings of this study. And the difference of treatment results among various types of interventions could not be found from our database which did not belong to our result measure. The evidence of treatment dose of acupuncture therapy is still establishing, thus we did not discuss the topic in here.

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Conclusions

Our study demonstrates that the ischemic stroke risk could be reduced by acupuncture treatment in patients with RA in Taiwan. The possible mechanism may reduce pro-inflammatory cytokines through acupuncture therapy which could , attenuates cardiovascular disease, including ischemic stroke. It also offers important ideas for more comprehensive studies in the future.

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Ethics Approval Statement

The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH104-REC2-115).

Competing Interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Health and Welfare, and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of National Health Insurance Administration, Ministry of Health and Welfare, or National Health Research Institutes.

Authors' contributions

CYH and MCH contributed equally. MCH contributed to conception of the study, participated in the interpretation of clinical data and drafted the manuscript. CYH contributed to conception of the study, participated in the interpretation of clinical data and drafted the manuscript. HHL participated in the interpretation of clinical data and drafted the manuscript. CLL performed the statistical analysis. GZ drafted the manuscript. MYW contributed to design of the study, participated in the interpretation of clinical data and drafted the manuscript. YCL supervised the project, participated in the interpretation of clinical data and drafted the manuscript. HRY supervised the project, contributed to conception and design of the study and finalized the manuscript. MYW and HRY contributed equally as co-corresponding authors.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Table 1.Characteristics of rheumatoid arthritis patients according to whether they received acupuncture treatment.

Variable	Rheumatoid Arthritis				Standardized mean difference
	Acupuncture treatment				
	No (n = 11613)		Yes (n = 11613)		
	n	%	n	%	
Sex					
Women	9499	81.8	9478	81.6	0.01
Men	2114	18.2	2135	18.4	0.01
Age group					
18-39	1839	15.8	1588	13.7	0.06
40-59	6684	57.6	7330	63.1	0.11
≥ 60	3090	26.6	2695	23.2	0.08
Mean ± SD (years)	54.9±14.5		54.8±13.2		0.01
Baseline Comorbidity					
Diabetes mellitus	2176	18.7	2126	18.3	0.01
Hypertension	4507	38.8	4416	38.0	0.02
Hyperlipidemia	3267	28.1	3273	28.2	0.001
Congestive heart failure	741	6.38	723	6.23	0.006
Depression	1256	10.8	1248	10.8	0.002
Anxiety	2880	24.8	2841	24.5	0.008
Alcoholism	208	1.79	221	1.90	0.008
Tobacco use	70	0.60	77	0.66	0.008
Obesity	130	1.12	135	1.16	0.004
Atrial fibrillation	741	6.38	715	6.16	0.009
Drugs used					
Oral steroid	6489	55.6	6495	55.9	0.001
NSAID	8823	76.0	8882	76.5	0.012
Statin	5592	5.10	593	5.11	0.000
Conventional DMARDS					
Hydroxychloroquine	5670	48.8	5663	48.8	0.001
Sulfasalazine	4295	37.0	4323	37.2	0.005
Methotrexate	9	0.08	10	0.09	0.003
Leflunomide	867	7.47	872	7.51	0.002
D-penicillamine	131	1.13	1298	1.11	0.002
Azathioprine	208	1.79	223	1.92	0.01
Mycophenolate	5	0.04	5	0.04	0.000

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Cyclosporine	555	4.78	544	4.68	0.004
Biological DMARDs					
Conventional DMARDS					
Hydroxychloroquine	5670	48.8	5663	48.8	0.001
Etanercept	625	5.38	629	5.42	0.002
Adalimumab	198	1.70	193	1.66	0.003
Types of acupuncture					
Manual acupuncture	-	-	10050	86.5	
Electroacupuncture	-	-	401	3.45	
Combination of both types	-	-	1162	10.0	
Duration from rheumatoid arthritis diagnosis and index, days (mean, median)	(1078.52, 795.0)		(1065.18, 707.0)		0.32
Acupuncture visits (mean, median)	-		(9.83, 3.00)		

The mean (median) follow-up period was 4.93 (4.35) and 4.21 (3.41) years in the acupuncture cohort and the compared cohort, respectively.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

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Figure legends

Fig. 1 Study population flowchart. A total of 47,809 patients with rheumatoid arthritis were newly diagnosed from 1997 to 2010. Sex, age, comorbidities, types of drugs used, RA diagnosis year and index year were processed via 1:1 matching; subsequently, 11,613 patients were included in the acupuncture and no-acupuncture cohorts.

Fig. 2 The cumulative incidence of ischemic stroke in the acupuncture (dashed line) cohort and the no-acupuncture cohort (solid line). Patients in the acupuncture group had a lower incidence of ischemic stroke (log-rank test, $p < 0.001$).

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Figures

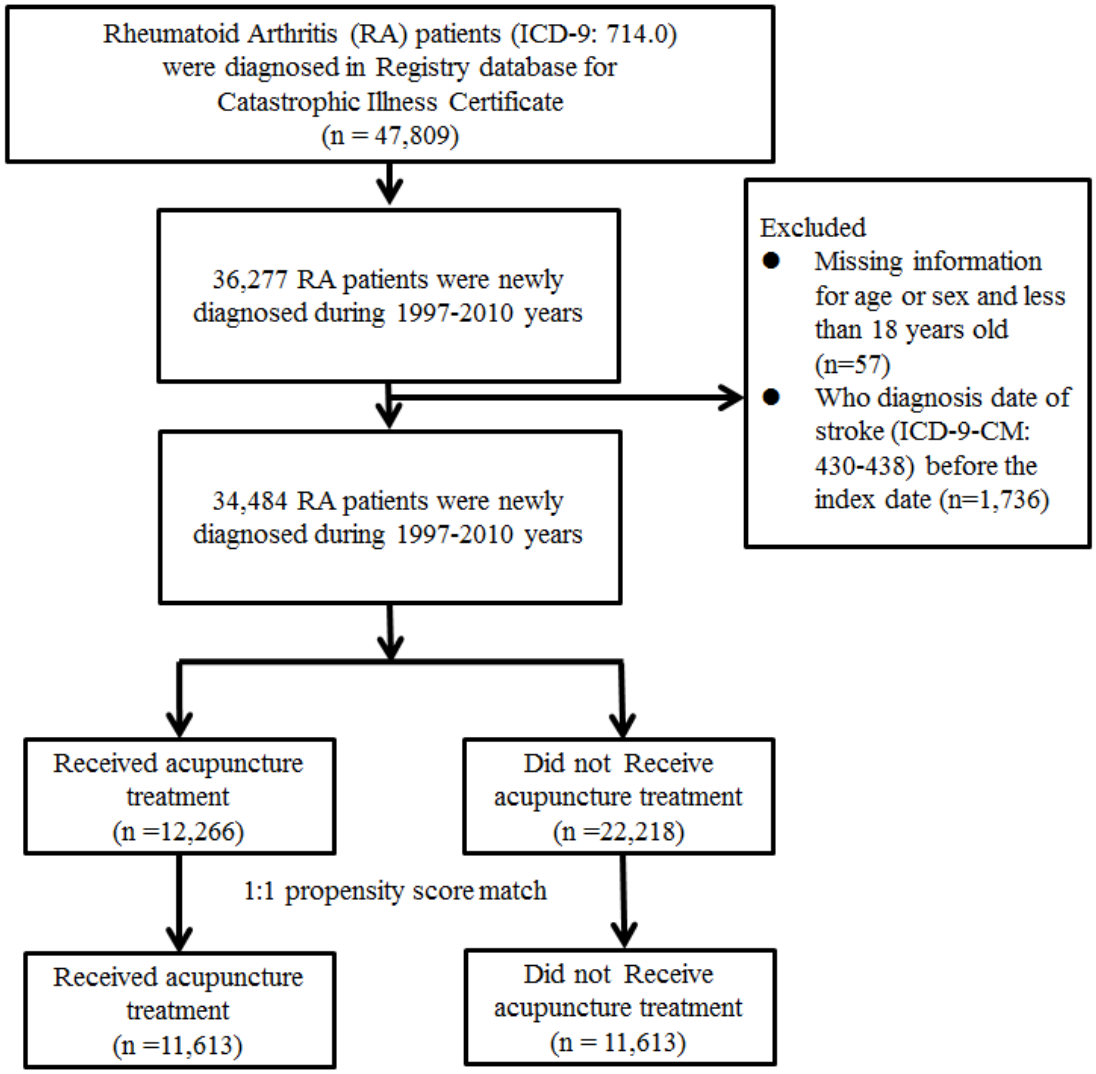

Fig. 1

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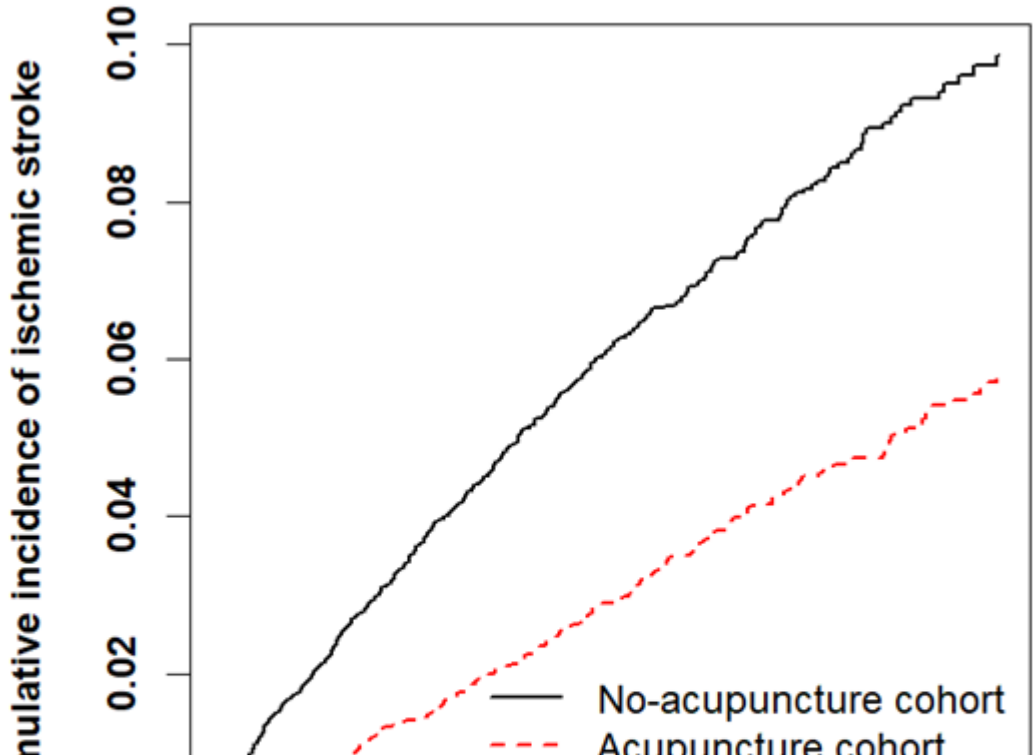

Fig. 2

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Supplementary Table 1. Subhazard ratios and 95% confidence intervals of ischemic stroke associated with acupuncture treatment and covariates among rheumatoid arthritis patients using the competing-risks regression models.

Variable	No. of event (n = 946)	Crude*			Adjusted†		
		SHR	(95% CI)	p-value	SHR	(95% CI)	p-value
Acupuncture treatment							
No	605	1.00	reference		1.00	reference	
Yes	341	0.52	(0.46, 0.60)	<0.001	0.63	(0.49, 0.65)	<0.001
Sex							
Women	714	1.00	reference		1.00	reference	
Men	231	1.44	(1.24, 1.67)	<0.001	1.32	(1.14, 1.54)	<0.001
Age group							
18-39	13	1.00	reference		1.00	reference	
40-59	372	7.17	(4.14, 12.4)	<0.001	5.99	(3.44, 10.4)	<0.001
≥ 60	561	28.1	(16.3, 48.6)	<0.001	14.7	(8.38, 25.7)	<0.001
Baseline Comorbidity (ref = no comorbidity)							
Diabetes mellitus	334	2.64	(2.31, 3.01)	<0.001	1.58	(1.36, 1.82)	<0.001
Hypertension	654	3.96	(3.45, 4.54)	<0.001	2.10	(1.79, 2.47)	<0.001
Hyperlipidemia	371	1.94	(1.70, 2.21)	<0.001	1.08	(0.93, 1.25)	0.30
Congestive heart failure	148	3.18	(2.67, 3.79)	<0.001	1.31	(1.08, 1.59)	0.006
Depression	120	1.46	(1.21, 1.77)	<0.001	1.12	(0.91, 1.37)	0.28
Anxiety	256	1.40	(1.21, 1.61)	<0.001	0.99	(0.85, 1.16)	0.94
Alcoholism	20	1.48	(0.95, 2.29)	0.08	1.46	(0.88, 2.43)	0.14
Tobacco use	2	0.55	(0.14, 2.20)	0.40	0.32	(0.07, 1.40)	0.13
Obesity	10	1.16	(0.62, 2.17)	0.65	1.10	(0.58, 2.08)	0.77
Atrial fibrillation	50	1.02	(0.77, 1.35)	0.90	0.89	(0.66, 1.19)	0.43
Drugs used							
Oral steroid	1621	0.57	(0.47-0.69)	< 0.0001	0.51	(0.42-0.62)	< 0.0001
NSAID	1726	0.22	(0.11-0.46)	< 0.0001	0.24	(0.11-0.51)	0.0002
Statin	329	1.04	(0.92-1.17)	0.5375	0.65	(0.58-0.74)	< 0.0001

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Conventional DMARDS							
Hydroxychloroquine	333	0.47	(0.41, 0.54)	<0.001	0.70	(0.60, 0.81)	<0.001
Sulfasalazine	235	0.47	(0.41, 0.54)	<0.001	0.80	(0.68, 0.94)	0.007
Methotrexate	2	1.88	(0.50, 7.04)	0.35	3.15	(0.84, 11.9)	0.08
Leflunomide	18	0.22	(0.14, 0.35)	<0.001	0.34	(0.22, 0.54)	<0.001
D-penicillamine	11	0.85	(0.46, 1.53)	0.53	1.07	(0.61, 1.88)	0.05
Azathioprine	9	0.39	(0.20, 0.75)	0.004	0.77	(0.40, 1.49)	0.44
Mycophenolate	0	-	-			-	
Cyclosporine	35	0.62	(0.44, 0.87)	0.005	1.41	(0.99, 1.98)	0.06
Biological DMARDs							
Etanercept	16	0.27	(0.16, 0.44)	<0.001	0.51	(0.31, 0.83)	0.007
Adalimumab	3	0.18	(0.06, 0.57)	0.003	0.43	(0.14, 1.34)	0.15
Conventional DMARDS							
Hydroxychloroquine	333	0.47	(0.41, 0.54)	<0.001	0.70	(0.60, 0.81)	<0.001

Crude SHR* represents the relative subhazard ratio;

Adjusted SHR† represents the adjusted subhazard ratio: mutually adjusted for accepted acupuncture, age, sex, comorbidities, and drugs used in competing-risks regression models.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

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Supplementary Table 2.. Incidence rates, subhazard ratios and confidence intervals of ischemic stroke in rheumatoid arthritis patients who received and did not receive acupuncture in the stratification of sex, age, comorbidities and drug used using the competing-risks regression models.

Variables	Rheumatoid arthritis						Compared with non-acupuncture users	
	No (n = 11613)			Yes (n = 11613)			Crude SHR	Adjusted SHR
	Event	Person years	IR†	Event	Person years	IR†	(95% CI)	(95% CI)
Total	605	48836	12.4	341	57273	5.95	0.48(0.46, 0.60)***	0.57(0.50, 0.65)***
Sex								
Women	460	40274	11.4	254	46907	5.41	0.50(0.44, 0.60)***	0.58(0.49, 0.67)***
Men	145	8562	16.9	87	10366	8.39	0.50(0.42, 0.71)***	0.54(0.41, 0.70)***
Age group								
18-39	5	8734	0.57	8	8576	0.93	1.63(0.49, 4.45)	1.45(0.44, 4.76)
40-59	226	29529	7.65	146	37225	3.92	0.51(0.43, 0.66)***	0.54(0.44, 0.66)***
≥ 60	374	10573	35.4	187	11472	16.3	0.53(0.46, 0.65)***	0.58(0.48, 0.69)***
Baseline Comorbidity								
Diabetes mellitus								
No	383	41083	9.32	229	48060	4.76	0.51(0.47, 0.65)***	0.60(0.51, 0.71)***
Yes	222	7753	28.6	112	9213	12.2	0.47(0.38, 0.59)***	0.52(0.41, 0.65)***
Hypertension								
No	184	32174	5.72	108	37634	2.87	0.50(0.41, 0.66)***	0.57(0.45, 0.72)***
Yes	421	16661	25.3	233	19639	11.9	0.53(0.45, 0.62)***	0.57(0.49, 0.67)***
Hyperlipidemia								
No	366	36970	9.90	209	43496	4.81	0.53(0.45, 0.62)***	0.61(0.51, 0.72)***
Yes	239	11866	20.1	132	13777	9.58	0.51(0.41, 0.63)***	0.51(0.41, 0.63)***
Congestive heart failure								
No	513	46595	11.0	285	54590	5.22	0.51(0.44, 0.59)***	0.55(0.47, 0.64)***
Yes	92	2241	41.1	56	2683	20.9	0.61(0.44, 0.85)***	0.65(0.47, 0.92)***
Depression								
No	523	44638	11.7	303	52396	5.78	0.54(0.47, 0.62)***	0.59(0.51, 0.67)***

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Yes	82	4198	19.5	38	4877	7.79	0.43(0.30, 0.64)***	0.48(0.32, 0.72)***
Anxiety								
No	442	38718	11.4	248	46073	5.38	0.57(0.44, 0.60)***	0.56(0.48, 0.66)***
Yes	163	10117	16.1	93	11200	8.30	0.58(0.43, 0.71)***	0.57(0.44, 0.74)***
Alcoholism								
No	596	48177	12.4	330	56529	5.84	0.51(0.45, 0.59)***	0.56(0.49, 0.64)***
Yes	9	659	13.7	11	744	14.8	1.12(0.47, 2.67)	1.25(0.50, 3.09)
Tobacco use								
No	603	48655	12.4	341	57090	5.97	0.52(0.46, 0.60)***	0.57(0.50, 0.65)***
Yes	2	181	11.1	0	182	0.00		
Obesity								
No	598	48412	12.4	338	56737	5.96	0.52(0.46, 0.60)***	0.57(0.50, 0.65)***
Yes	7	424	16.5	3	536	5.60	0.39(0.10, 1.49)	0.40(0.14, 1.19)
Atrial fibrillation								
No	576	46291	12.4	320	54553	5.87	0.51(0.45, 0.59)***	0.56(0.49, 0.64)***
Yes	29	2545	11.4	21	2720	7.72	0.71(0.41, 1.26)	0.70(0.38, 1.30)
Drugs used								
Oral steroid								
No	318	17828	17.8	166	21844	7.60	0.48(0.40, 0.58)***	0.53(0.44, 0.64)***
Yes	287	31008	9.26	175	35429	4.94	0.56(0.46, 0.68)***	0.59(0.49, 0.72)***
NSAID								
No	216	7329	29.5	105	9509	11.0	0.46(0.37, 0.58)***	0.54(0.43, 0.69)***
Yes	389	41506	9.37	236	47764	4.94	0.52(0.47, 0.64)***	0.56(0.48, 0.66)***
Statin								
No	586	45820	12.8	322	54040	5.96	0.51(0.44, 0.58)***	0.56(0.49, 0.64)***
Yes	19	3016	6.30	19	3233	5.88	0.94(0.50, 1.79)	0.97(0.49, 1.95)
Conventional DMARDS								
No	347	14099	24.6	181	18431	9.82	0.48(0.40, 0.57)***	0.54(0.45, 0.65)***
Yes	258	34736	7.43	160	38842	4.12	0.52(0.46, 0.68)***	0.58(0.47, 0.71)***
Biological DMARDs								

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No	591	44821	13.2	336	52599	6.39	0.51(0.46, 0.60)***	0.58(0.50, 0.66)***
Yes	14	4014	3.49	5	4674	1.07	0.22(0.10, 0.79)*	0.26(0.09, 0.80)**

Abbreviation: IR, incidence rate per 1,000 person-years; SHR, subhazard ratio; CI, confidence interval

Adjusted SHR: adjusted for accepted acupuncture, age, sex, comorbidities, and drugs used in the competing risks regression models.

*: $p < 0.05$; **: $p < 0.01$; *** $p < 0.001$

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

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Supplementary Table 3. Characteristics of rheumatoid arthritis patients according to accept acupuncture in un-matching.

Variable	Rheumatoid Arthritis				Standardised mean difference
	Accepted acupuncture				
	No (n =22218)		Yes (n =12266)		
	n	%	n	%	
Gender					
Women	16702	75.2	10109	82.4	0.18
Men	5516	24.8	2157	17.6	0.18
Age group					
18-39	2994	13.5	1767	14.4	0.03
40-59	12351	55.6	7762	63.3	0.16
≥60	6873	30.9	2737	22.3	0.20
Mean±SD (years)	56.7±14.7		54.3±13.3		0.17
Baseline Comorbidity					
Diabetes mellitus	4117	18.5	2260	18.4	0.003
Hypertension	8857	39.9	4632	37.8	0.04
Hyperlipidemia	5610	25.3	3593	29.3	0.09
Congestive heart failure	1698	7.64	736	6.00	0.07
Depression	1901	8.56	1394	11.4	0.09
Anxiety	4591	20.7	3118	25.4	0.11
Alcoholism	422	1.90	244	1.99	0.01
Tobacco used	146	0.66	84	0.68	0.003
Obesity	188	0.85	163	1.33	0.05
Atrial fibrillation	1102	4.96	845	6.89	0.08
Drug used					
Oral steroid	10814	48.7	6946	56.6	0.16
NSAID	13907	62.6	9532	77.7	0.34
Statin	828	3.73	688	5.61	0.09
Conventional DMARDS					
Hydroxychloroquine	9299	41.9	6059	49.4	0.15
Sulfasalazine	7210	32.5	4606	37.6	0.11
Methotrexate	14	0.06	11	0.09	0.01
Leflunomide	1309	5.89	973	7.93	0.08
D-penicillamine	196	0.88	138	1.13	0.02
Azathioprine	385	1.73	229	1.87	0.01
Mycophenolate	10	0.05	7	0.06	0.01
Cyclosporine	816	3.67	594	4.84	0.06
Biological DMARDs					

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Etanercept	941	4.24	706	5.76	0.07
Adalimumab	345	1.55	202	1.65	0.01
Types of acupuncture					
Manual acupuncture			10604	86.45	
Electroacupuncture			407	3.32	
Combination of manual acupuncture and electroacupuncture			1255	10.23	
Duration between rheumatoid arthritis date and index, days (mean, median)	(981.29, 668.0)		(1047.36, 688.5)		
Acupuncture visits, (mean, meidan)			(10.43, 3.00)		

The mean (median) of follow-up period were 4.96 (4.39) and 4.01 (3.17) years for acupuncture cohort and compared cohort.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

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Supplementary Table 4. Subhazard ratios and 95% confidence intervals of ischemic stroke associated with accepted acupuncture and covariates among rheumatoid arthritis patients using the competing-risks regression models in un-matching.

Variable	No. of event (n=1441)	Crude*			Adjusted†		
		SHR	(95%CI)	p-value	SHR	(95%CI)	p-value
Accepted acupuncture							
No	1080	1.00	reference		1.00	reference	
Yes	361	0.48	(0.42, 0.53)	<0.001	0.65	(0.58, 0.74)	<0.001

Crude SHR* represented relative subhazard ratio;

Adjusted SHR† represented adjusted subhazard ratio: mutually adjusted for accepted acupuncture, age, gender, comorbidities, and drugs used in competing-risks regression models.

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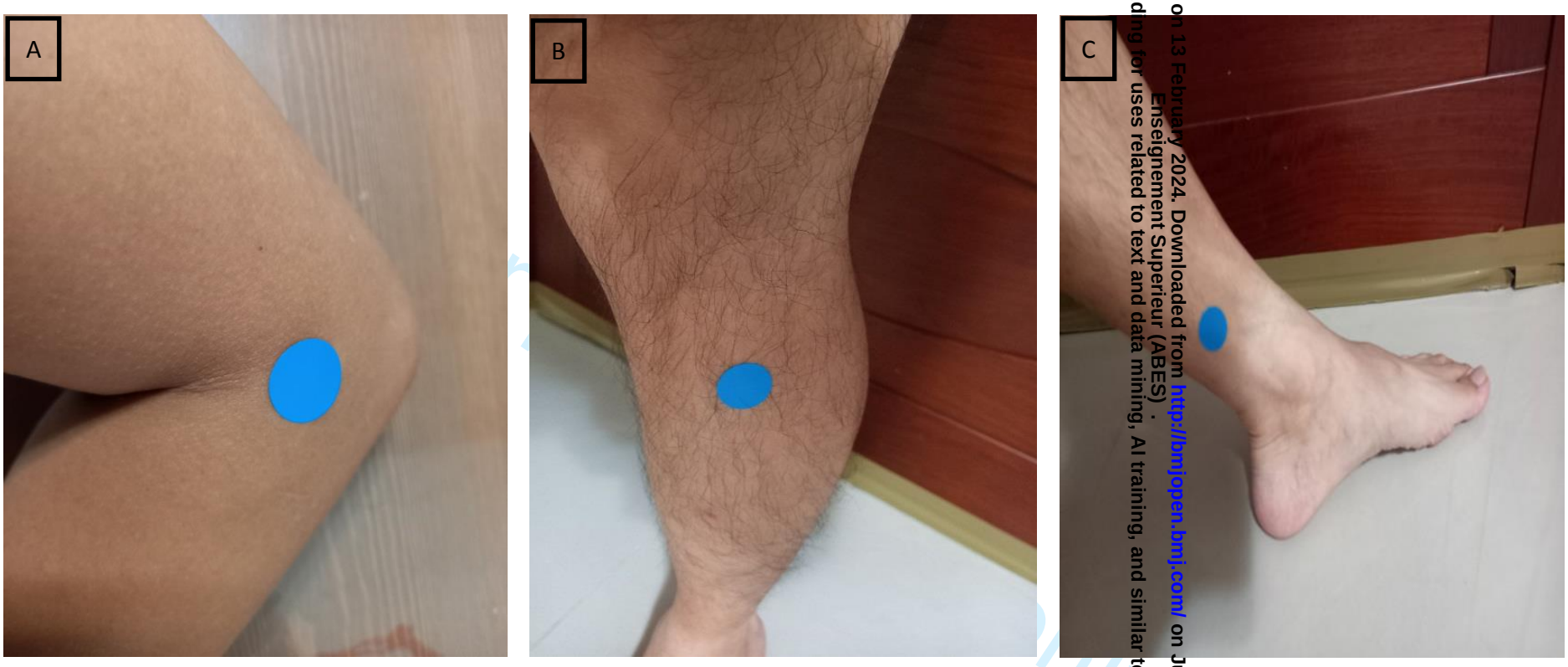

Supplementary Fig. 1. Acupoints of (A)LI11, (B)ST36, and (C)SP9 (blue spot)

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-10
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	9-10
		(*b*) For matched studies, give matching criteria and the number of controls per case	9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9-10*
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	9-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how matching of cases and controls was addressed	11
		(*e*) Describe any sensitivity analyses	11
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-13
		(b) Give reasons for non-participation at each stage	12-13
		(c) Consider use of a flow diagram	12-13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	12-13
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	12-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3-4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The effect of acupuncture on ischemic stroke in patients with rheumatoid arthritis: A nationwide propensity score-matched study

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The effect of acupuncture on ischemic stroke in patients with rheumatoid arthritis: A nationwide propensity score-matched study

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Abstract

Objectives: The purpose of this study was to demonstrate that acupuncture is beneficial for decreasing the risk of ischemic stroke (IS) in patients with rheumatoid arthritis (RA).

Design: This is a propensity score-matched cohort study.

Setting: This is a nationwide population-based study.

Participants: Patients with RA diagnosed between January 1, 1997, and December 31, 2010, through the National Health Insurance Research Database

Interventions: The patients who were administered acupuncture therapy from the initial date of RA diagnosis of rheumatoid arthritis to December 31, 2010, were included in the acupuncture cohort. Patients who did not receive acupuncture treatment during the same time interval constituted the no-acupuncture cohort.

Primary outcome measures: A Cox regression model was used to adjust for age, sex, comorbidities, and types of drugs used. We compared the subhazard ratios (SHRs) of IS between these two cohorts through competing-risks regression models.

Results: After 1:1 propensity score matching, a total of 23,226 patients were identified. The basic characteristics of these patients were similar. A lower cumulative incidence of ischemic stroke was found in the acupuncture cohort (log-rank test, $p < 0.001$; immortal time: 1,065 days; mean number of acupuncture visits: 9.83). In the end, 341 patients in the acupuncture cohort (5.95 per 1,000 person-years) and 605 patients in the no-acupuncture cohort (12.4 per 1,000 person-years) experienced ischemic stroke (adjusted SHR, 0.57; 95% CI, 0.50–0.65). The advantage of lowering ischemic stroke incidence through acupuncture therapy in RA patients was independent of sex, age, types of drugs used, and comorbidities.

Conclusions: This study showed the beneficial effect of acupuncture in reducing the incidence of ischemic stroke in patients with RA.

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Strengths and limitations of this study:

- Our research discloses the possible long-term effect of acupuncture on stroke prevention that could not be investigated in clinical trials.
- Lower ischemic stroke developed in patients with rheumatoid arthritis after acupuncture therapy.
- The causality could not be proven directly through our study design.

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Introduction

Rheumatoid arthritis (RA) is a common rheumatoid disease that manifests as polyarthritis in the joints, mainly synovial inflammation and morning stiffness [1]. Bone erosion, joint deformity and loss of functional abilities are long-term complications of RA. In regard to chronic processes, the inflammation status can be noted in the whole body: pericarditis, myocarditis, pleuritis, interstitial lung fibrosis, osteoporosis, and cardiovascular diseases (CVDs) [2-5]. Comorbidities from CVD, such as stroke, are the major cause of death in RA patients [6-11]. Compared to the general population, stroke is more common in RA patients [12]. The prevalence of RA globally and in Asia is 460 per 100,000 people and 15.8 per 100,000 people, respectively [13-15]. However, the risk of developing ischemic stroke in Asian RA patients (hazard ratio (HR), 1.32) is similar to that in Caucasian populations (HR 1.29) [16-17].

Trying to disclose the agents to prevent stroke is an essential issue for clinical doctors and patients [18]. The common prescriptions to treat RA are nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, conventional disease-modifying antirheumatic drugs (DMARDs), and biological agents such as etanercept, infliximab (TNF-α inhibitor) and anakinra (IL-1 inhibitor) [3,5,19]. Steroids and DMARDs, such as methotrexate (MTX) and infliximab, have advantages in the prevention of ischemic stroke in RA patients [18]. However, some of them could result in complications in the bone marrow that cause thrombocytopenia [20]. Finding alternative interventions to control RA while lowering complications from treatment itself has become a well-discussed topic.

In many countries and regions, such as Taiwan, Germany, Hong Kong, and China, acupuncture therapy is widely used to control pain when patients have musculoskeletal and immune problems, including RA [21-25]. A previous cohort

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study found that approximately 27.3% of RA patients in Taiwan ever consulted traditional Chinese medicine (TCM) services, and 23.6% of these patients had received acupuncture [26]. Furthermore, secondary stroke prevention is also noted to result from acupuncture therapy in the Taiwanese population [27]. The hypothesized mechanism by which acupuncture lowers the stroke rate is similar to that of anti-RA agents: anti-inflammation. Thus, we wanted to investigate the relationship between acupuncture intervention and the incidence of ischemic stroke in RA patients.

In Taiwan, the records of medical services are saved in the database of National Health Insurance: National Health Insurance Research Database (NHIRD). The service of NHI is from 1995 until now, and the coverage rate in the Taiwanese population is more than 99% [28]. In other words, the medical data in the NHIRD cover a long enough time and are large enough to be used for nationwide population research. Sampling bias could be prevented when the study is conducted through such a large-scale database [29]. We used the NHIRD to investigate the long-term effect of ischemic stroke prevention in patients with RA who accepted acupuncture treatment.

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Materials and Methods

Data sources

A nationwide, population-based 1:1 propensity score-matched cohort study via data analysis derived from the NHIRD was performed. The database used in this study was the Registry for Catastrophic Illness Patients Database (RCIPD), which is part of the NHIRD. Personal information was removed from the NHIRD. It was not possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of our research. The RCIPD enrolled all patients with a catastrophic illness, which was proven by pathological, laboratory, and clinical diagnoses by both specialists and a regular review. This real-world database consists of datasets including demographic characteristics, outpatient and inpatient visits, diagnostic codes, assessments, remedies, procedures and medical expenses for reimbursement. The diagnoses were coded by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Patients with a diagnosis of RA are issued catastrophic illness certificates and receive free medical services for health complications. Thus, the RCIPD is a comprehensive database for the investigation of all RA patients in Taiwan. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH104-REC2-115).

Study subjects and variables

We used both ambulatory and inpatient medical records to identify RA treatments that were linked with the RCIPD from 1997 to 2010 to identify a study population (n=47,809) for follow-up until the end of 2011 (**Fig. 1**). Newly diagnosed RA patients (n=36,277) with a diagnosis of ICD-9-CM code 714.0 were included. We excluded patients (n=1,793) as follows: 1) patients who were younger than 18 years;

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patients who had incomplete data on age or sex; 3) patients who had an interruption in health insurance services during the follow-up period, and 4) patients who had a diagnosis of ischemic stroke (ICD-9-CM: 433-438) before the index date. Finally, 34,484 newly diagnosed RA patients were included. Patients who received acupuncture therapy from the initial RA diagnosis to December 31, 2010, were included in the acupuncture cohort (n=12,266). We used a propensity score approach to minimize confounders in the analysis of acupuncture therapy. A one-to-one propensity score match was conducted by age (per 5 years), sex, comorbidities, types of drugs used (oral steroids, NSAIDs, statins, all DMARDs), RA diagnosis year and index year by multiple logistic regression analysis. The definition of drugs used was patients with ≥28 cumulative use days. The numbers of participants in both the acupuncture and no-acupuncture cohorts were the same (n=11,613). The index date was defined as the first time that patients received acupuncture therapy, which was given randomly to patients in the no-acupuncture cohort according to the approach in the acupuncture cohort. The immortal time was defined as the period from the initial diagnosis of RA to the index date.

Covariate assessment

The patients were assigned to three groups by age (18–39 years, 40–59 years, and ≥ 60 years). ICD-9-CM codes of comorbidities that appeared more than once in the outpatient or inpatient records before the primary diagnosis of RA were taken into consideration; such comorbidities included diabetes mellitus (DM; ICD-9-CM code 250), hypertension (HTN; ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), congestive heart failure (ICD-9-CM codes 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, and 428.0), anxiety (ICD-9-CM codes 300.0, 300.2, 300.3, 308.3, and 308.91), depression (ICD-9-CM 296.2–296.3, 300.4, 311),

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alcoholism (ICD-9-CM codes 291, 303, 305.00–305.03, 790.3, and V11.3), tobacco use (ICD-9-CM code 305.1), obesity (ICD-9-CM codes 278 and A183), and atrial fibrillation (ICD-9-CM 427.3). The events of ischemic stroke (ICD-9-CM: 433-438) were compared between the acupuncture and nonacupuncture cohorts of RA patients.

Types of acupuncture and disease categories in the acupuncture cohort

We identified the different acupuncture types by the treatment codes, including manual acupuncture (B41, B42, B45, B46, B80, B81, B82, B83, B84, B90, B91, B92, B93, B94, P27041, P31103, and P32103) and electroacupuncture (B43, B44, B86, B87, B88, and B89) as previously described [30].

Statistical analyses

The standardized mean difference (SMD) was used to compare the baseline characteristics of the acupuncture and no-acupuncture cohorts as previously described [30]. A negligible difference in mean values or proportions between the two cohorts was defined as less than 0.1 standard deviation (SD). Competing-risk regression models were performed to estimate the crude and adjusted subhazard ratios (SHRs) of acupuncture therapy, age, sex, comorbidities, and types of drugs used. The Kaplan–Meier method and the log-rank test were conducted to find the difference between the two cohorts in the development of ischemic stroke. We used SAS 9.4 (SAS Institute, Cary, NC, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria) to perform statistical analyses and create the figures. Statistical significance was defined as $p < 0.05$ in two-tailed tests.

Patient and Public Involvement

None

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Results

We used 1:1 propensity score matching by sex, age, all comorbidities, drugs (oral steroids, NSAIDs, statins, all DMARDs), RA diagnosis year and index year to enroll an equal number (n=11,613) of RA patients in the acupuncture cohort and nonacupuncture cohort (**Fig. 1**). The baseline characteristics of both cohorts are presented in **Table 1**, with similar distributions of sex, age, comorbidities, and prescriptions. In both cohorts, most participants were female, and most patients were middle-aged (40-59 years). The most common comorbidity was HTN; more than 38% of patients had this problem. In patients with RA, 18% had DM, 28% had hyperlipidemia, 6% had congestive heart failure, 24% had anxiety, and 10% had depression. There were no differences in the proportions of alcoholism, tobacco dependence, or obesity between the two cohorts. NSAIDs were the most common prescriptions in both cohorts, and 76% of the included patients were on these medications. In the participants of the two cohorts, 55% used oral steroids, and 5% used statin agents. Most patients (87%) were treated by manual acupuncture, with electroacupuncture having been used in 3% of the participants, and the other 10% of patients having had combined manual acupuncture and electroacupuncture treatments. The mean duration between RA diagnosis and the first acupuncture treatment was approximately 1,065 days. The mean number of acupuncture visits was 9.83.

During the follow-up period, 946 patients developed ischemic stroke (**Supplementary Table 1**). The incidence of ischemic stroke in RA patients increased with age, with older patients having a higher risk. The adjusted SHRs in the 40–59-year-old group and the over 60-year-old group were 5.99 and 14.7, respectively. The patients with comorbidities of DM, HTN and congestive heart failure had a higher risk of ischemic stroke. The adjusted SHRs of the patients with DM, HTN and congestive heart failure were 1.58, 2.10 and 1.31, respectively. The

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cumulative incidence of ischemic stroke was significantly lower in the acupuncture cohort (log-rank test, $p < 0.001$, **Fig. 2**).

Supplementary Table 2 shows the 341 patients in the acupuncture cohort (5.95 per 1000 person-years) and the 605 patients in the nonacupuncture cohort (12.4 per 1000 person-years) who developed ischemic stroke (adjusted SHR, 0.57; 95% CI, 0.50–0.65). Both males and females were observed to experience the benefit of ischemic stroke prevention, with an adjusted SHR of 0.58 in the female group (95% CI, 0.49–0.67) and an adjusted SHR of 0.54 in the male group (95% CI, 0.41–0.70). Patients in the age subgroup ≥40 years old had a lower risk of ischemic stroke after acupuncture therapy (adjusted SHR, 0.54; 95% CI, 0.44–0.66 in the 40-59-year-old group; adjusted SHR, 0.58; 95% CI, 0.48–0.69 in the over 60 years old group). Acupuncture decreased the risk of ischemic stroke in most patients with comorbidities. Coprescriptions with steroids, statins, or DMARDs did not change the positive results of acupuncture therapy.

The results from the nonmatching analysis were also provided to prevent possible sampling bias from our 1:1 propensity score matching in **Supplementary Tables 3** and **4**. The final results analyzed by competing-risk regression models are compatible with the results after 1:1 propensity score matching.

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Discussion

To the best of our knowledge, this is the first study to show that acupuncture therapy is beneficial for ischemic stroke prevention in RA patients. RA is one of the common disease categories among acupuncture visits in Taiwan [31]. We previously found that 23.6% of RA patients had received acupuncture [26]. In the present study, we showed that the benefit of acupuncture therapy in reducing the risk of ischemic stroke was independent of sex, age, and comorbidities.

Although patients with RA have been known to have a high risk for the development of stroke, there is an unmet need to improve preventive measures for patients with RA [32]. Inflammation is a consistent and independent predictor of CVD in RA [33]. TNF-α is a cytokine that mediates inflammatory reactions [34]. A high level of TNF-α has been observed in RA patients, and it has been found that TNF-α can induce pannus formation and subsequent bone destruction [35]. By interrupting TNF-α expression and production by inflammatory cells, TNF-α inhibitors can efficiently control the inflammatory process [36]. Biological agents targeting cytokines may decrease CVD risk in RA [37]. Therefore, it is interesting to know whether acupuncture fits the niche to reduce inflammation in RA patients.

There is some evidence and potential explanations about the effects and mechanisms of acupuncture. Acupuncture has been reported to be effective in treating neuropathy [38], relieving pain [39] and attenuating cardiovascular disease [40] in different clinical trials. Previous clinical studies revealed that acupuncture reduced the number of tender joints, relieved morning stiffness and joint pain, enhanced physical activity, and improved quality of life in patients with RA [41,42]. In the analysis of blood and synovial fluid of RA patients, acupuncture was found to reduce TNF-α and vascular endothelial growth factor to improve the inflammation of RA [43]. In animal

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studies, acupuncture reduced inflammation in a collagen-induced arthritis model [44-46]. Furthermore, acupuncture not only has analgesic effects through beta-endorphin [47], adenosine [48] and orexin [49] but also reduces inflammation through dopamine [50]. On the other hand, unstable blood pressure and lipid profiles are the two risk factors for ischemic stroke, and acupuncture therapy has the advantage of controlling both HTN and dyslipidemia [51,52]. If acupuncture relieves morning stiffness and joint pain, patients might also benefit from increasing daily activities, which might also reduce the risk of stroke [53].

Our study had some limitations. For example, we could not identify the number and specific affected joints from the data of the RCIPD. Thus, we used prescriptions for RA treatment as variables that could represent the severity of RA. After performing 1:1 propensity score matching, the differences between the two cohorts were minimized. We had similar percentages of patients who used NSAIDs, steroid agents, statins, and DMARDs. The second limitation was that the RCIPD did not provide data on height, weight, laboratory data or exercise status. We tried to define a diagnosis of alcoholism, tobacco use, and obesity to represent these personal characteristics and lifestyles; then, through 1:1 propensity score matching, we attempted to eliminate or minimize confounders [54]. The distribution of patients with different habits was similar, and these parameters did not change the significant effect of ischemic stroke prevention in patients with RA. The algorithm for risk of developing cardiovascular events, such as the Framingham Risk Score, is hard to formulate because of the lack of the above information. Additionally, the RCIPD database could not offer information on acupoints for RA treatment. The selection of acupoints depends on the diagnosis and the experience of TCM doctors. The variable prescriptions of acupuncture could also stem from the different complaints, comorbidities and wishes of the patients. Because of the standard TCM program

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training in medical schools, most TCM doctors in Taiwan know the concepts of basic acupoints, such as LI11, ST36, and SP9 (**Supplementary Fig. 1**) [55,56]. Further clinical trials with standardized acupoints should be conducted based on the findings of this study. The difference in treatment results among various types of interventions could not be discovered in our database and was not included as a result measure. The evidence of the treatment dose of acupuncture therapy is still being established; thus, we did not discuss the topic here.

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Conclusions

Our study demonstrates that the ischemic stroke risk could be reduced by acupuncture treatment in patients with RA in Taiwan. The possible mechanism may involve reducing proinflammatory cytokines through acupuncture therapy, thereby attenuating cardiovascular disease, including ischemic stroke. The study also offers important ideas for more comprehensive research in the future.

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Ethics Approval Statement

The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH104-REC2-115).

Competing Interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Database, provided by the National Health Insurance Administration, Ministry of Health and Welfare, and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of the National Health Insurance Administration, Ministry of Health and Welfare, or National Health Research Institutes.

Authors' contributions

CYH and MCH contributed equally. MCH contributed to the conception of the study, participated in the interpretation of clinical data and drafted the manuscript. CYH contributed to the conception of the study, participated in the interpretation of clinical data and drafted the manuscript. HHL participated in the interpretation of clinical data and drafted the manuscript. CLL performed the statistical analysis. GZ drafted the manuscript. MYW contributed to the design of the study, participated in the interpretation of clinical data and drafted the manuscript. YCL supervised the project, participated in the interpretation of clinical data and drafted the manuscript. HRY supervised the project, contributed to the conception and design of the study and finalized the manuscript. MYW and HRY contributed equally as cocorresponding authors.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Table 1. Characteristics of rheumatoid arthritis patients according to whether they received acupuncture treatment

Variable	Rheumatoid Arthritis				Standardized mean difference
	Acupuncture treatment				
	No (n = 11613)		Yes (n = 11613)		
	n	%	n	%	
Sex					
Women	9499	81.8	9478	81.6	0.01
Men	2114	18.2	2135	18.4	0.01
Age group					
18-39	1839	15.8	1588	13.7	0.06
40-59	6684	57.6	7330	63.1	0.11
≥ 60	3090	26.6	2695	23.2	0.08
Mean ± SD (years)	54.9±14.5		54.8±13.2		0.01
Baseline Comorbidity					
Diabetes mellitus	2176	18.7	2126	18.3	0.01
Hypertension	4507	38.8	4416	38.0	0.02
Hyperlipidemia	3267	28.1	3273	28.2	0.001
Congestive heart failure	741	6.38	723	6.23	0.006
Depression	1256	10.8	1248	10.8	0.002
Anxiety	2880	24.8	2841	24.5	0.008
Alcoholism	208	1.79	221	1.90	0.008
Tobacco use	70	0.60	77	0.66	0.008
Obesity	130	1.12	135	1.16	0.004
Atrial fibrillation	741	6.38	715	6.16	0.009
Drugs used					
Oral steroid	6489	55.6	6495	55.9	0.001
NSAID	8823	76.0	8882	76.5	0.012
Statin	5592	5.10	593	5.11	0.000
Conventional DMARDS					
Hydroxychloroquine	5670	48.8	5663	48.8	0.001
Sulfasalazine	4295	37.0	4323	37.2	0.005
Methotrexate	9	0.08	10	0.09	0.003
Leflunomide	867	7.47	872	7.51	0.002
D-penicillamine	131	1.13	1298	1.11	0.002
Azathioprine	208	1.79	223	1.92	0.01
Mycophenolate	5	0.04	5	0.04	0.000

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Cyclosporine	555	4.78	544	4.68	0.004
Biological DMARDs					
Conventional DMARDS					
Hydroxychloroquine	5670	48.8	5663	48.8	0.001
Etanercept	625	5.38	629	5.42	0.002
Adalimumab	198	1.70	193	1.66	0.003
Types of acupuncture					
Manual acupuncture	-	-	10050	86.5	
Electroacupuncture	-	-	401	3.45	
Combination of both types	-	-	1162	10.0	
Duration from rheumatoid arthritis diagnosis and index, days (mean, median)	(1078.52, 795.0)		(1065.18, 707.0)		0.32
Acupuncture visits (mean, median)	-		(9.83, 3.00)		

The mean (median) follow-up periods were 4.93 (4.35) and 4.21 (3.41) years in the acupuncture cohort and the compared cohort, respectively.

Abbreviations: nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs)

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Figure legends

Fig. 1. Study population flowchart

A total of 47,809 patients with rheumatoid arthritis were newly diagnosed from 1997 to 2010; sex, age, comorbidities, types of drugs used, RA diagnosis year and index year were processed via 1:1 matching; subsequently, 11,613 patients were included in the acupuncture and no-acupuncture cohorts

Fig. 2. The cumulative incidence of ischemic stroke in acupuncture (dashed line) cohort and the no-acupuncture cohort (solid line). Patients in the acupuncture group had a lower incidence of ischemic stroke (log-rank test, $p < 0.001$)

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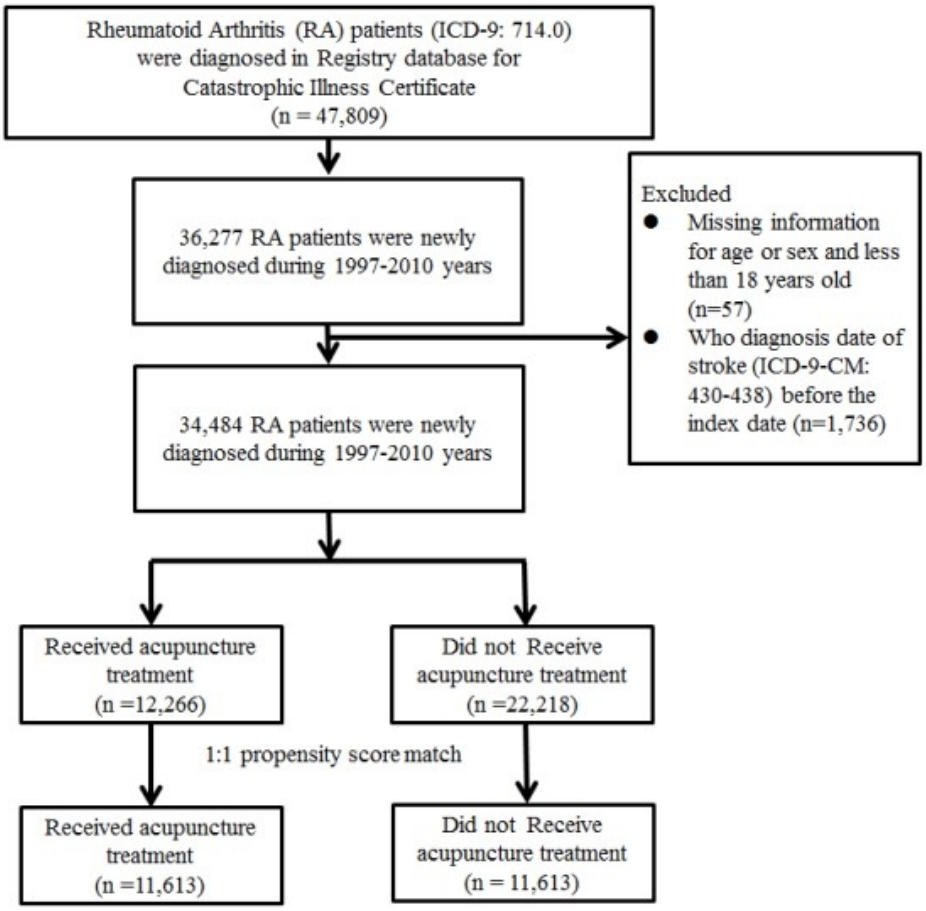

Fig. 1

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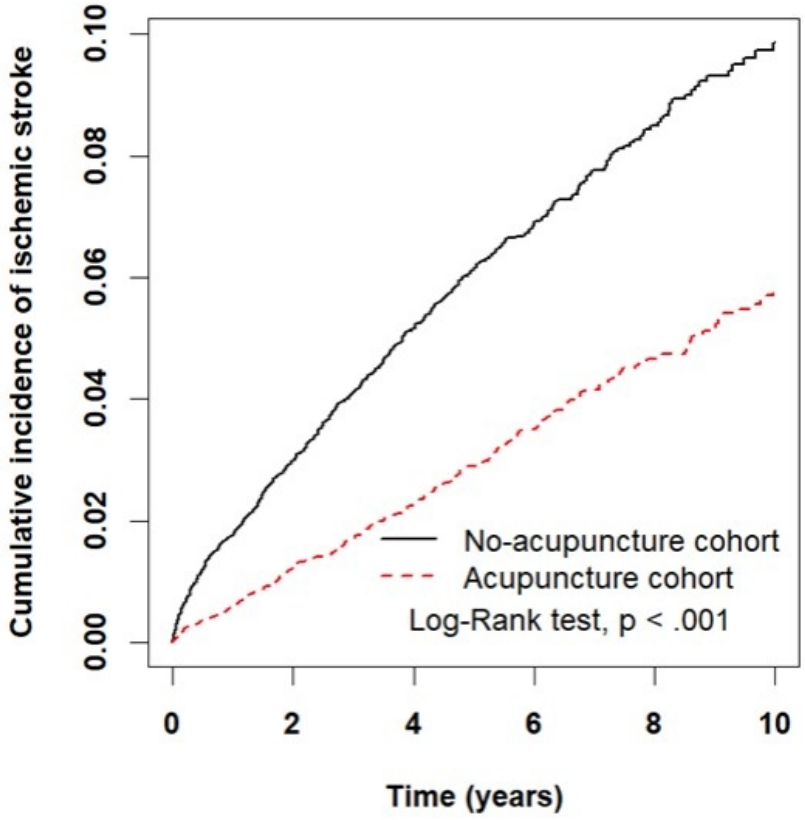

Fig. 2

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Supplementary Table 1. Subhazard ratios and 95% confidence intervals of ischemic stroke associated with acupuncture treatment and covariates among rheumatoid arthritis patients using the competing-risks regression models.

Variable	No. of event (n = 946)	Crude*			Adjusted†		
		SHR	(95% CI)	p-value	SHR	(95% CI)	p-value
Acupuncture treatment							
No	605	1.00	reference		1.00	reference	
Yes	341	0.52	(0.46, 0.60)	<0.001	0.63	(0.49, 0.65)	<0.001
Sex							
Women	714	1.00	reference		1.00	reference	
Men	231	1.44	(1.24, 1.67)	<0.001	1.32	(1.14, 1.54)	<0.001
Age group							
18-39	13	1.00	reference		1.00	reference	
40-59	372	7.17	(4.14, 12.4)	<0.001	5.99	(3.44, 10.4)	<0.001
≥ 60	561	28.1	(16.3, 48.6)	<0.001	14.7	(8.38, 25.7)	<0.001
Baseline Comorbidity (ref = no comorbidity)							
Diabetes mellitus	334	2.64	(2.31, 3.01)	<0.001	1.58	(1.36, 1.82)	<0.001
Hypertension	654	3.96	(3.45, 4.54)	<0.001	2.10	(1.79, 2.47)	<0.001
Hyperlipidemia	371	1.94	(1.70, 2.21)	<0.001	1.08	(0.93, 1.25)	0.30
Congestive heart failure	148	3.18	(2.67, 3.79)	<0.001	1.31	(1.08, 1.59)	0.006
Depression	120	1.46	(1.21, 1.77)	<0.001	1.12	(0.91, 1.37)	0.28
Anxiety	256	1.40	(1.21, 1.61)	<0.001	0.99	(0.85, 1.16)	0.94
Alcoholism	20	1.48	(0.95, 2.29)	0.08	1.46	(0.88, 2.43)	0.14
Tobacco use	2	0.55	(0.14, 2.20)	0.40	0.32	(0.07, 1.40)	0.13
Obesity	10	1.16	(0.62, 2.17)	0.65	1.10	(0.58, 2.08)	0.77
Atrial fibrillation	50	1.02	(0.77, 1.35)	0.90	0.89	(0.66, 1.19)	0.43
Drugs used							
Oral steroid	1621	0.57	(0.47-0.69)	< 0.0001	0.51	(0.42-0.62)	< 0.0001
NSAID	1726	0.22	(0.11-0.46)	< 0.0001	0.24	(0.11-0.51)	0.0002
Statin	329	1.04	(0.92-1.17)	0.5375	0.65	(0.58-0.74)	< 0.0001

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Conventional DMARDS							
Hydroxychloroquine	333	0.47	(0.41, 0.54)	<0.001	0.70	(0.60, 0.81)	<0.001
Sulfasalazine	235	0.47	(0.41, 0.54)	<0.001	0.80	(0.68, 0.94)	0.007
Methotrexate	2	1.88	(0.50, 7.04)	0.35	3.15	(0.84, 11.9)	0.08
Leflunomide	18	0.22	(0.14, 0.35)	<0.001	0.34	(0.22, 0.54)	<0.001
D-penicillamine	11	0.85	(0.46, 1.53)	0.53	1.07	(0.61, 1.88)	0.05
Azathioprine	9	0.39	(0.20, 0.75)	0.004	0.77	(0.40, 1.49)	0.44
Mycophenolate	0	-	-			-	
Cyclosporine	35	0.62	(0.44, 0.87)	0.005	1.41	(0.99, 1.98)	0.06
Biological DMARDs							
Etanercept	16	0.27	(0.16, 0.44)	<0.001	0.51	(0.31, 0.83)	0.007
Adalimumab	3	0.18	(0.06, 0.57)	0.003	0.43	(0.14, 1.34)	0.15
Conventional DMARDS							
Hydroxychloroquine	333	0.47	(0.41, 0.54)	<0.001	0.70	(0.60, 0.81)	<0.001

Crude SHR* represents the relative subhazard ratio;

Adjusted SHR† represents the adjusted subhazard ratio: mutually adjusted for accepted acupuncture, age, sex, comorbidities, and drugs used in competing-risks regression models.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

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Supplementary Table 2.. Incidence rates, subhazard ratios and confidence intervals of ischemic stroke in rheumatoid arthritis patients who received and did not receive acupuncture in the stratification of sex, age, comorbidities and drug used using the competing-risks regression models.

Variables	Rheumatoid arthritis						Compared with non-acupuncture users	
	No (n = 11613)			Yes (n = 11613)			Crude SHR	Adjusted SHR
	Event	Person years	IR†	Event	Person years	IR†	(95% CI)	(95% CI)
Total	605	48836	12.4	341	57273	5.95	0.48(0.46, 0.60)***	0.57(0.50, 0.65)***
Sex								
Women	460	40274	11.4	254	46907	5.41	0.50(0.44, 0.60)***	0.58(0.49, 0.67)***
Men	145	8562	16.9	87	10366	8.39	0.50(0.42, 0.71)***	0.54(0.41, 0.70)***
Age group								
18-39	5	8734	0.57	8	8576	0.93	1.63(0.49, 4.45)	1.45(0.44, 4.76)
40-59	226	29529	7.65	146	37225	3.92	0.51(0.43, 0.66)***	0.54(0.44, 0.66)***
≥ 60	374	10573	35.4	187	11472	16.3	0.53(0.46, 0.65)***	0.58(0.48, 0.69)***
Baseline Comorbidity								
Diabetes mellitus								
No	383	41083	9.32	229	48060	4.76	0.51(0.47, 0.65)***	0.60(0.51, 0.71)***
Yes	222	7753	28.6	112	9213	12.2	0.47(0.38, 0.59)***	0.52(0.41, 0.65)***
Hypertension								
No	184	32174	5.72	108	37634	2.87	0.50(0.41, 0.66)***	0.57(0.45, 0.72)***
Yes	421	16661	25.3	233	19639	11.9	0.53(0.45, 0.62)***	0.57(0.49, 0.67)***
Hyperlipidemia								
No	366	36970	9.90	209	43496	4.81	0.53(0.45, 0.62)***	0.61(0.51, 0.72)***
Yes	239	11866	20.1	132	13777	9.58	0.51(0.41, 0.63)***	0.51(0.41, 0.63)***
Congestive heart failure								
No	513	46595	11.0	285	54590	5.22	0.51(0.44, 0.59)***	0.55(0.47, 0.64)***
Yes	92	2241	41.1	56	2683	20.9	0.61(0.44, 0.85)***	0.65(0.47, 0.92)***
Depression								
No	523	44638	11.7	303	52396	5.78	0.54(0.47, 0.62)***	0.59(0.51, 0.67)***

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Yes	82	4198	19.5	38	4877	7.79	0.43(0.30, 0.64)***	0.48(0.32, 0.72)***
Anxiety								
No	442	38718	11.4	248	46073	5.38	0.57(0.44, 0.60)***	0.56(0.48, 0.66)***
Yes	163	10117	16.1	93	11200	8.30	0.58(0.43, 0.71)***	0.57(0.44, 0.74)***
Alcoholism								
No	596	48177	12.4	330	56529	5.84	0.51(0.45, 0.59)***	0.56(0.49, 0.64)***
Yes	9	659	13.7	11	744	14.8	1.12(0.47, 2.67)	1.25(0.50, 3.09)
Tobacco use								
No	603	48655	12.4	341	57090	5.97	0.52(0.46, 0.60)***	0.57(0.50, 0.65)***
Yes	2	181	11.1	0	182	0.00		
Obesity								
No	598	48412	12.4	338	56737	5.96	0.52(0.46, 0.60)***	0.57(0.50, 0.65)***
Yes	7	424	16.5	3	536	5.60	0.39(0.10, 1.49)	0.40(0.14, 1.19)
Atrial fibrillation								
No	576	46291	12.4	320	54553	5.87	0.51(0.45, 0.59)***	0.56(0.49, 0.64)***
Yes	29	2545	11.4	21	2720	7.72	0.71(0.41, 1.26)	0.70(0.38, 1.30)
Drugs used								
Oral steroid								
No	318	17828	17.8	166	21844	7.60	0.48(0.40, 0.58)***	0.53(0.44, 0.64)***
Yes	287	31008	9.26	175	35429	4.94	0.56(0.46, 0.68)***	0.59(0.49, 0.72)***
NSAID								
No	216	7329	29.5	105	9509	11.0	0.46(0.37, 0.58)***	0.54(0.43, 0.69)***
Yes	389	41506	9.37	236	47764	4.94	0.52(0.47, 0.64)***	0.56(0.48, 0.66)***
Statin								
No	586	45820	12.8	322	54040	5.96	0.51(0.44, 0.58)***	0.56(0.49, 0.64)***
Yes	19	3016	6.30	19	3233	5.88	0.94(0.50, 1.79)	0.97(0.49, 1.95)
Conventional DMARDS								
No	347	14099	24.6	181	18431	9.82	0.48(0.40, 0.57)***	0.54(0.45, 0.65)***
Yes	258	34736	7.43	160	38842	4.12	0.52(0.46, 0.68)***	0.58(0.47, 0.71)***
Biological DMARDs								

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No	591	44821	13.2	336	52599	6.39	0.51(0.46, 0.60)***	0.58(0.50, 0.66)***
Yes	14	4014	3.49	5	4674	1.07	0.22(0.10, 0.79)*	0.26(0.09, 0.80)**

Abbreviation: IR, incidence rate per 1,000 person-years; SHR, subhazard ratio; CI, confidence interval

Adjusted SHR: adjusted for accepted acupuncture, age, sex, comorbidities, and drugs used in the competing risks regression models.

*: $p < 0.05$; **: $p < 0.01$; *** $p < 0.001$

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

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Supplementary Table 3. Characteristics of rheumatoid arthritis patients according to accept acupuncture in un-matching.

Variable	Rheumatoid Arthritis				Standardised mean difference
	Accepted acupuncture				
	No (n =22218)		Yes (n =12266)		
	n	%	n	%	
Gender					
Women	16702	75.2	10109	82.4	0.18
Men	5516	24.8	2157	17.6	0.18
Age group					
18-39	2994	13.5	1767	14.4	0.03
40-59	12351	55.6	7762	63.3	0.16
≥60	6873	30.9	2737	22.3	0.20
Mean±SD (years)	56.7±14.7		54.3±13.3		0.17
Baseline Comorbidity					
Diabetes mellitus	4117	18.5	2260	18.4	0.003
Hypertension	8857	39.9	4632	37.8	0.04
Hyperlipidemia	5610	25.3	3593	29.3	0.09
Congestive heart failure	1698	7.64	736	6.00	0.07
Depression	1901	8.56	1394	11.4	0.09
Anxiety	4591	20.7	3118	25.4	0.11
Alcoholism	422	1.90	244	1.99	0.01
Tobacco used	146	0.66	84	0.68	0.003
Obesity	188	0.85	163	1.33	0.05
Atrial fibrillation	1102	4.96	845	6.89	0.08
Drug used					
Oral steroid	10814	48.7	6946	56.6	0.16
NSAID	13907	62.6	9532	77.7	0.34
Statin	828	3.73	688	5.61	0.09
Conventional DMARDS					
Hydroxychloroquine	9299	41.9	6059	49.4	0.15
Sulfasalazine	7210	32.5	4606	37.6	0.11
Methotrexate	14	0.06	11	0.09	0.01
Leflunomide	1309	5.89	973	7.93	0.08
D-penicillamine	196	0.88	138	1.13	0.02
Azathioprine	385	1.73	229	1.87	0.01
Mycophenolate	10	0.05	7	0.06	0.01
Cyclosporine	816	3.67	594	4.84	0.06
Biological DMARDs					

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Etanercept	941	4.24	706	5.76	0.07
Adalimumab	345	1.55	202	1.65	0.01
Types of acupuncture					
Manual acupuncture			10604	86.45	
Electroacupuncture			407	3.32	
Combination of manual acupuncture and electroacupuncture			1255	10.23	
Duration between rheumatoid arthritis date and index, days (mean, median)	(981.29, 668.0)		(1047.36, 688.5)		
Acupuncture visits, (mean, meidan)			(10.43, 3.00)		

The mean (median) of follow-up period were 4.96 (4.39) and 4.01 (3.17) years for acupuncture cohort and compared cohort.

Abbreviation: Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARD (disease-modifying antirheumatic drugs).

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Supplementary Table 4. Subhazard ratios and 95% confidence intervals of ischemic stroke associated with accepted acupuncture and covariates among rheumatoid arthritis patients using the competing-risks regression models in un-matching.

Variable	No. of event (n=1441)	Crude*			Adjusted†		
		SHR	(95%CI)	p-value	SHR	(95%CI)	p-value
Accepted acupuncture							
No	1080	1.00	reference		1.00	reference	
Yes	361	0.48	(0.42, 0.53)	<0.001	0.65	(0.58, 0.74)	<0.001

Crude SHR* represented relative subhazard ratio;

Adjusted SHR† represented adjusted subhazard ratio: mutually adjusted for accepted acupuncture, age, gender, comorbidities, and drugs used in competing-risks regression models.

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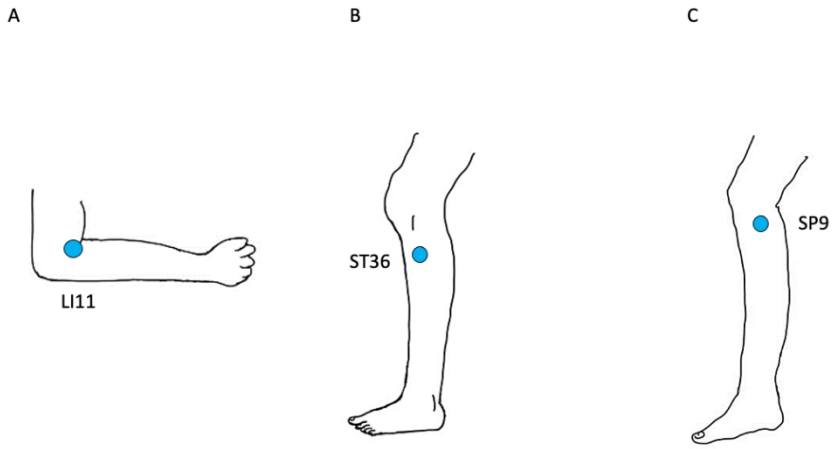

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-10
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	9-10
		(*b*) For matched studies, give matching criteria and the number of controls per case	9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9-10*
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	9-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how matching of cases and controls was addressed	11
		(*e*) Describe any sensitivity analyses	11
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-13
		(b) Give reasons for non-participation at each stage	12-13
		(c) Consider use of a flow diagram	12-13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	12-13
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	12-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3-4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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