Original Article

Acupuncture treatment is associated with a decreased risk of dementia in patients with rheumatoid arthritis in Taiwan: A propensity-score matched cohort study

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ABSTRACT

Background: The purpose of this study was to understand whether acupuncture can decrease the risk of dementia in patients with rheumatoid arthritis (RA).
Methods: Using the registry from the National Health Insurance Research Database of Taiwan, we carried out a 1:1 propensity-score matched cohort study to analyze patients with RA diagnosed between 2000 and 2010. The patients who received acupuncture therapy were grouped as acupuncture users ($n = 9,919$), while the others were grouped as non-acupuncture users ($n = 19,331$). After propensity-score matching, the final sample included 9,218 matched participants in both groups, and these participants were followed up until the end of 2011. We used a Cox regression model to adjust for age, sex, comorbidiy, and conventional drugs and compared the hazard ratios (HRs) of developing dementia in the acupuncture and non-acupuncture groups.
Results: Acupuncture users tended to be more female-dominant and younger than non-acupuncture users. After propensity-score matching, both groups have comparable demographic characteristics. Acupuncture users had a lower risk of dementia than non-acupuncture users (adjusted HR: 0.55, 95% CI: 0.46–0.66). The cumulative incidence of dementia in the acupuncture group was significantly lower than that in the non-acupuncture group (log-rank test, $p < 0.001$). Patients who received the combinational treatment of conventional drugs and acupuncture had a significantly lower risk of developing dementia (adjusted HR: 0.64, 95% CI: 0.56–0.73) compared to those who only received conventional drugs.
Conclusion: Acupuncture therapy is associated with a reduced risk of dementia in patients with RA. Further clinical and mechanistic studies are needed.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, multi-systemic, autoimmune inflammatory disease of unknown cause. Although there are a variety of systemic symptoms, the characteristic feature of established RA affects the joints in a symmetrical way, which can be persistent inflammatory synovitis and functional loss.[1] It is a progressive disease that may cause cartilage damage and bone erosions and subsequent changes in joint in-

tegrity by synovial inflammation. Despite its destructive potential, the course of RA can be quite variable. Some patients may experience only a mild oligoarticular illness of brief duration with minimal joint damage, but most will have relentless progressive polyarthritis with marked functional impairment.

In addition to joint damage, there are some other systemic conditions in patients with RA, such as musculoskeletal system other than joints (e.g., bone and muscle) and organs (e.g., skin, eye, lung, heart,

kidney, blood vessels, salivary glands, central and peripheral nervous systems, and bone marrow). These conditions occur in 40% of patients with RA.[2,3] There are more and more evidences showing that both local and systemic inflammation may lead to neuroinflammation.[4] The disease activity of RA is associated with impaired cognitive function.[5] Dementia, which is one of the diseases of the nervous system, was found to have a higher incidence in patients with RA than that in patients without RA.[4-8]

Both conventional Western medicine and traditional Chinese medicine (TCM) have been covered by the National Health Insurance program in Taiwan, which was launched in 1995.[9] Our previous study found that 27.3% of RA patients[10] and 29.1% of Alzheimer's disease patients[11] also visited TCM clinics. In Taiwan, approximately 10.9% of adults utilized acupuncture in 2011.[9] It has been shown that treating RA patients with acupuncture improved symptoms in some studies.[12,13] In addition, some studies have reported that there were benefits in treating disorders of the nervous system by acupuncture.[14-16] For example, one clinical trial showed that treatment with acupuncture might have some beneficial effects on improvements in cognitive status and activities in patients with dementia.[17] However, long-term follow-up information on whether acupuncture could affect the incidence of dementia in patients with RA is lacking.

In Taiwan, the extensive National Health Insurance (NHI) program has covered almost everyone in the total population (23 million people) since 1995.[18] All claims' data were collected in the National Health Insurance Research Database (NHIRD). To investigate the association between dementia and acupuncture in patients with RA, we analyzed the registry for catastrophic illness patients of the NHIRD of Taiwan. The potential sampling bias was reduced because this dataset included all clinically and radiographically confirmed RA patients with long-term follow-up.[19] We hypothesized that acupuncture can reduced the incidence of dementia in RA patients. The aim of this study is to explore the protective effect of acupuncture on dementia in patients with RA.

2. Methods

2.1. Data source

We carried out a nationwide, population-based, 1:1 propensity score-matched cohort study by analyzing the registry for the catastrophic illnesses patient database (RCIPD) from the NHIRD, which contained almost all the RA cases. Diagnostic methods were based on the code of The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

In Taiwan, the NHI program covered almost all the necessary Western medical services and TCM services (Chinese herbal remedies, acupuncture/moxibustion, and tuina/manipulative therapies). Patients can choose TCM or Western medicine services freely. Only licensed TCM or Western medicine physicians are qualified for reimbursement. The large-scale real-world data, NHIRD, comprise de-identified information regarding medical care facilities, specialties, sex, birth dates, visit dates, prescriptions, management, cost and diagnosis codes in the ICD-9-CM format.[18,19] The RCIPD is a part of the NHIRD. It was set up for the diseases that required more intensive care and includes approximately 30 disease categories, such as cancer, schizophrenia, end-stage renal disease, lupus, rheumatoid arthritis and cerebral palsy.[20] The patients with RA were distributed for catastrophic illness certificates as long as they received complete clinical and blood evaluation, followed by cautious and routine review by rheumatologists assigned by the National Health Insurance Administration. Thus, the accuracy of the diagnosis of the patients with RA cases in this study has high credibility.

2.2. Study cohort identification

The flow chart for the selection of RA cases is illustrated in Fig. 1. With all 23,000,000 beneficiaries in the NHI program, the patients ($n = 47{,}531$) with a diagnosis of RA (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code: 714.0) in the RCIPD of NHIRD were included in this study. There were 30,454 newly diagnosed RA patients in 2000–2010. After the cases who had missing information for age or sex and less than 18 years old ($n = 814$) and diagnosis date of dementia (ICD-9-CM: 290, 294.1, 331.0–331.2) before the diagnosis date of RA ($n = 390$) were excluded, the patients who received acupuncture therapy were grouped as acupuncture users ($n = 9919$), while the others were grouped as non-acupuncture users ($n = 19{,}331$). We used a 1:1 propensity score match by sex, age (per 5 years), all comorbidities, Charlson comorbidity index (CCI) score,[21] conventional drug use (oral steroid, NSAID, statin), diagnosis year of RA and index year. Thus, the final grouping was 9218 matched cases in both groups and then followed up until the end of 2011.

2.3. Covariate assessment

The demographic characteristics and claims data of this study cohort were collected and analyzed. The comorbidity of these patients was determined by ICD-9-CM codes: diabetes mellitus (250), hypertension (401–415), hyperlipidemia (272), congestive heart failure (402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0), depression (296.2–296.3, 300.4, 311), anxiety (300.0, 300.2, 300.3, 308.3, 308.91), alcoholism (291, 303, 305.00, 305.01, 305.02, 305.03, 790.3 and V11.3), tobacco use (305.1), obesity (278 and A183) and sleep disorders (307.4 and 780.5). Outcome measurement is the event of dementia (ICD-9-CM: 290, 294.1, 331.0–331.2), including vascular dementia (ICD-9-CM: 290.4) and Alzheimer's disease (ICD-9-CM: 331.0), during the follow-up period until the end of 2011. The date of the first acupuncture intervention was defined as the index date. Patients in the non-acupuncture group were randomly assigned a matched index date to minimize the immortal bias. Patients diagnosed as having dementia within one year after their initial diagnosis of RA were excluded from the cumulative incidence of dementia in the Kaplan-Meier curve.

Types of acupuncture and disease categories in the acupuncture cohort

We also identified patients who received acupuncture (treatment code: B41, B42, B43, B44, B45, B46, B80, B81, B82, B83, B84, B85, B86, B87, B88, B89, B90, B91, B92, B93, B94, P27041, P31103, P31206, P32103, P33031, P33032) and electroacupuncture (treatment code: B43, B44, B85, B86, B87, B88, B89, P33032) as previously described.[22] One course of acupuncture treatment usually includes 6 sessions in a month. Disease categories/diagnoses for patients with RA in the acupuncture cohort were identified by the ICD-9-CM codes.

2.4. Statistical analyses

We used standardized mean differences to compare the baseline characteristics of the acupuncture and non-acupuncture groups. Standardized mean differences less than 0.2 indicated that there is no significant difference in the average or distribution between the two groups.[23] Cox proportional hazards regression was used to calculate the HR and 95% CI for each variable. The discrepancy between the two groups in the follow-up development of developing dementia was measured using the Kaplan-Meier method and the log-rank test. SAS 9.4 (SAS Institute, Cary, NC, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria) to perform the statistical analyses and create the figures. $p < 0.05$ in two-tailed tests was considered statistically significant.

2.5. Ethics statement

The NHIRD was provided by the National Health Insurance Administration and managed by Ministry of Health and Welfare, Taiwan. For guarding enrollees' privacy, every offered dataset was deidentified and encrypted. Therefore, it was impossible to recognize individual patients
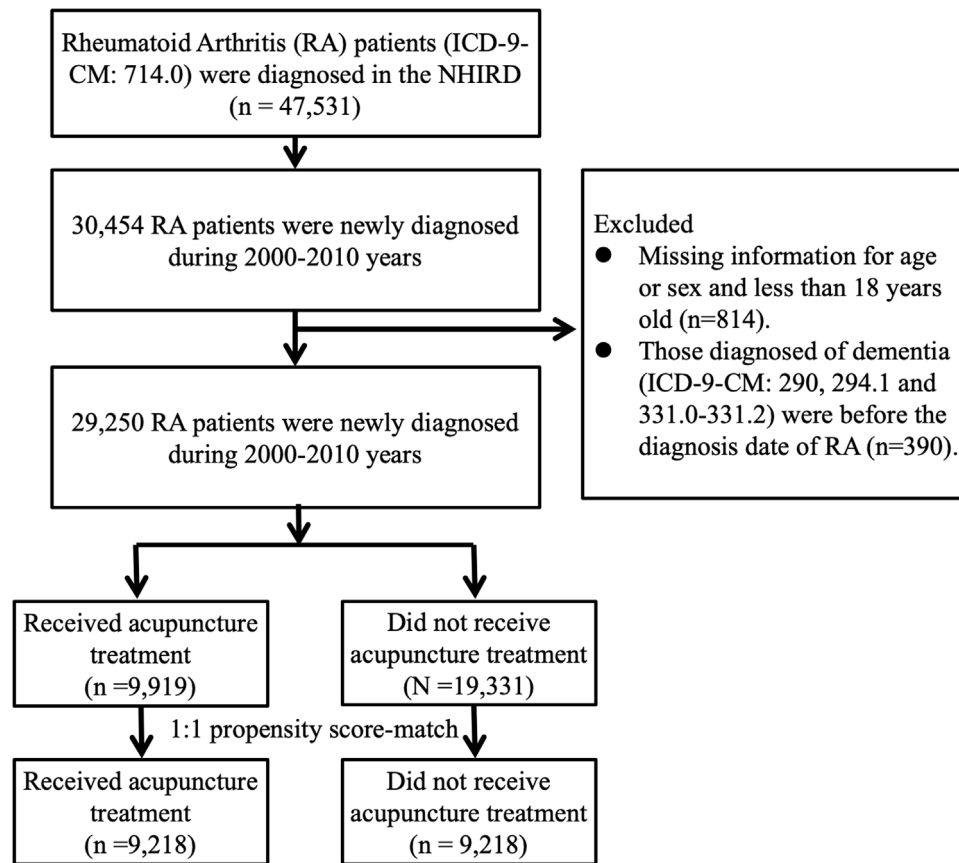
Fig. 1. Recruitment flowchart. Patients with rheumatoid arthritis diagnosed from 2000 to 2010 were recruited. These patients were categorized as acupuncture users or non-acupuncture users according to the inclusion of acupuncture therapies in their treatment. Abbreviations: rheumatoid arthritis (RA); International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM); National Health Insurance Research Database (NHIRD).

by any means. This study was approved by the Research Ethics Committee of China Medical University and Hospital, Taiwan (CMUH104-REC2–115).

3. Results

We identified 30,454 newly diagnosed RA patients in 2000–2010. After excluding missing information for age or sex and less than 18 years old ($n = 814$) and those diagnosed with dementia before the diagnosis date of RA ($n = 390$), a total of 29,250 RA patients were included. Acupuncture users tended to be more female-dominant and younger than non-acupuncture users. Comorbidities varied between the two groups, with more acupuncture users having hyperlipidemia, depression, anxiety, obesity and sleep disorders (Supplementary Table 1).

After further performing 1:1 propensity-score matching by sex, age, all comorbidities, conventional drug use (oral steroids, NSAIDs, statin), the initial diagnostic year of RA, and index year, there were 9,218 patients in both the acupuncture and non-acupuncture treatment groups (Fig. 1).

There were no differences in sex, age, Charlson comorbidity index (CCI) score, conventional drug use, and comorbidity of patients in the two cohorts (Table 1).

In the RA patients, we found that acupuncture users had a lower incidence of dementia compared with patients without acupuncture (adjusted HR: 0.55, 95% CI: 0.46–0.66) (Table 2). The prevalence of dementia increases with age. Compared to the incidence in the 18- to 39-year-old group, the risk was much higher in the 40- to 59-year-old (adjusted HR: 6.62, 95% CI: 2.92–15.0) and > 60-year-old (adjusted HR: 43.9, 95% CI: 19.3–99.9) groups. Furthermore, patients with diabetes (adjusted HR: 1.44, 95% CI: 1.10–1.89), hypertension (adjusted HR: 1.52,

95% CI: 1.24–1.86), hyperlipidemia (adjusted HR: 1.23, 95% CI: 1.01–1.48), congestive heart failure (adjusted HR: 1.39, 95% CI: 1.06–1.83), depression (adjusted HR: 1.66, 95% CI: 1.06–1.83) also had a higher risk of developing dementia than those without these comorbidities. For patients with CCI score 0, patients with subgroups of CCI score 1, CCI score 2, and CCI score ≥ 3, the adjusted HRs of dementia were 1.39, 1.60, and 2.01, respectively.

The patients who took oral steroids (adjusted HR: 0.55, 95% CI: 0.38–0.78), NSAID (adjusted HR: 0.29, 95% CI: 0.14–0.60) or statins (adjusted HR: 0.72, 95% CI: 0.58–0.89) had a significantly lower chance of getting dementia.

Compared with the non-acupuncture cohort, acupuncture users had a lower incidence rate of dementia, especially patients older than 60 years (adjusted HR: 0.50, 95% CI: 0.46–0.65) (Table 3). The incidence of dementia was significantly lower in the acupuncture group when the patients had comorbidities such as diabetes mellitus (adjusted HR: 0.51, 95% CI: 0.31–0.86), hypertension (adjusted HR: 0.48, 95% CI: 0.39–0.60), hyperlipidemia (adjusted HR: 0.52, 95% CI: 0.40–0.68), congestive heart failure (adjusted HR: 0.40, 95% CI: 0.23–0.69), depression (adjusted HR: 0.56, 95% CI: 0.37–0.86), anxiety (adjusted HR: 0.59, 95% CI: 0.43–0.82), or sleep disorder (adjusted HR: 0.52, 95% CI: 0.40–0.67). Among RA patients taking oral steroids (adjusted HR: 0.55, 95% CI: 0.46–0.65), NSAIDs (adjusted HR: 0.55, 95% CI: 0.46–0.66), or statins (adjusted HR: 0.53, 95% CI: 0.37–0.76), the chances of getting dementia in the acupuncture group were also significantly decreased.

To identify the incidence rates of different types of dementia in patients with RA in both cohorts, we further analyzed the incidence rates of vascular dementia and Alzheimer's disease in these patients (Table 4). We found that acupuncture users had a lower incidence rate of vascular

Table 1

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

Variables	Rheumatoid Arthritis				Standardized mean difference
	Received acupuncture				
	No (*n* = 9218)		Yes (*n* = 9218)		
	n	%	n	%	
Sex					
Female	7460	80.9	7488	81.2	0.008
Male	1758	19.1	1730	18.8	0.008
Age group					
18–39	1769	19.2	1489	16.2	0.08
40–59	5448	59.1	6080	66.0	0.142
≥60	2001	21.7	1649	17.9	0.096
Mean±SD (years)	52.7 ± 14.4		52.7 ± 12.9		0.000
Baseline Comorbidity					
Diabetes mellitus	457	4.96	458	4.97	0.000
Hypertension	3114	33.8	3114	33.8	0.000
Hyperlipidemia	2420	26.3	2461	26.7	0.01
Congestive heart failure	349	3.79	341	3.70	0.005
Depression	855	9.28	859	9.32	0.001
Anxiety	2026	22.0	2030	22.0	0.001
Alcoholism	142	1.54	154	1.67	0.01
Tobacco used	37	0.40	42	0.46	0.008
Obesity	96	1.04	99	1.07	0.003
Sleep disorder	3361	36.5	3385	36.7	0.005
Charlson Comorbidity Index (CCI)					
0	5663	61.4	5662	61.4	0.000
1	1945	21.1	1929	20.9	0.004
2	917	9.95	991	10.8	0.026
3+	693	7.52	636	6.90	0.024
Length of days of hospitalization during the study period	13.9	14.9	13.8	14.7	0.001
Conventional drug used					
Oral steroid	8730	94.7	8721	94.6	0.004
NSAID	9166	99.4	9182	99.6	0.025
Statin	1757	19.1	1749	19.0	0.002
Types of acupuncture					
Manual acupuncture	–	–	7954	86.3	
Electroacupuncture	–	–	350	3.80	
Combined manual acupuncture and electroacupuncture	–	–	914	9.92	
Duration between rheumatoid arthritis diagnosis date and the index date, days (mean, median)	(948,700)		(941,653)		0.008
The number of acupuncture courses, (mean, median)	–		(7.73,3.00)		

The means (medians) of the follow-up period were 4.15 (3.63) and 3.56 (2.95) years for the acupuncture cohort and the non-acupuncture cohort, respectively. Each acupuncture course usually includes 6 acupuncture sessions in one month.

dementia than patients not receiving acupuncture (adjusted HR: 0.47, 95% CI: 0.29–0.77).

To compare the differences in the incidence rate of dementia in patients with different types of treatment, we further analyzed the prevalence of dementia in patients who received only conventional treatment, only acupuncture, and both conventional treatment and acupuncture (Table 5). We found that patients who received the combination treatment of conventional drugs and acupuncture had a significantly lower risk of developing dementia (adjusted HR: 0.64, 95% CI: 0.56–0.73).

Based on the Kaplan–Meier curves, we found that the cumulative incidence of dementia in the acupuncture cohort was significantly lower than that in the non-acupuncture cohort (log-rank test, *p* < 0.001) (Fig. 2).

Since that sometimes the patients also received Chinese herbal medicines in the acupuncture clinic, we also identified the commonly prescribed Chinese herbal medicines, including single herbs and herbal formulas. We have also calculated the impact of these herbs and measured the crude HR and adjusted HR of developing dementia (Supplementary Table 2).

4. Discussion

The real-world data from the NHIRD provide evidence consistent with our hypothesis that acupuncture might be beneficial for prevent-

ing the occurrence of dementia in patients with RA. Acupuncture users had a lower incidence of dementia than non-acupuncture users. We discovered that the cumulative incidence of dementia in the acupuncture cohort was significantly lower than that in the non-acupuncture cohort through a Kaplan–Meier analysis. Furthermore, the chances of getting dementia in the acupuncture group also decreased in RA patients taking oral steroids, NSAIDs, or statins. In addition, adjunctive acupuncture therapy and conventional drug use had a significantly lower risk of developing dementia than the use of conventional Western drugs alone.

Aging is the strongest risk factor for dementia. Some studies have shown that approximately 85 percent of dementia individuals are older than 75 years of age.[24,25] It is in substantial agreement with our results that the incidence of dementia increases with age in patients with RA as well.

Among the baseline comorbidities we investigated, diabetes, hypertension, and depression had a higher risk of developing dementia. Furthermore, these three comorbidities were included in nine potentially modifiable risk factors of dementia reported by the Lancet Commission recently.[26] We found that receiving acupuncture showed benefits in preventing dementia in RA patients with comorbidities such as diabetes mellitus, hypertension, hyperlipidemia, depression, or anxiety. Taken together, receiving acupuncture in RA patients with DM or hypertension might be important for preventing the occurrence of dementia.

Table 2

Cox model with hazard ratios and 95% confidence intervals of dementia associated with received acupuncture and covariates among rheumatoid arthritis patients.

Variables	No. of event (n = 546)	Crude* HR	(95% CI)	p-value	Adjusted† HR	(95% CI)	p-value
Received acupuncture							
No	331	1.00	reference		1.00	reference	
Yes	215	0.56	(0.47, 0.67)	<0.001	0.55	(0.46, 0.66)	<0.001
Sex							
Female	437	1.00	reference		1.00	reference	
Male	109	1.09	(0.88,1.34)	0.43	0.97	(0.78, 1.20)	0.78
Age group							
18–39	6	1.00	reference		1.00	reference	
40–59	164	7.78	(3.45, 17.6)	<0.001	6.62	(2.92, 15.0)	<0.001
≥60	376	67.8	(30.3, 151.8)	<0.001	43.9	(19.3, 99.9)	<0.001
Baseline Comorbidity (ref=no comorbidity)							
Diabetes mellitus	67	3.23	(2.50,4.18)	<0.001	1.44	(1.10, 1.89)	0.008
Hypertension	360	4.28	(3.58,5.11)	<0.001	1.52	(1.24, 1.86)	<0.001
Hyperlipidemia	226	2.29	(1.93, 2.72)	<0.001	1.23	(1.01, 1.48)	0.04
Congestive heart failure	62	4.16	(3.20, 5.43)	<0.001	1.39	(1.06, 1.83)	0.02
Depression	87	2.27	(1.80, 2.86)	<0.001	1.66	(1.30, 2.14)	<0.001
Anxiety	161	1.81	(1.51, 2.18)	<0.001	1.16	(0.95, 1.42)	0.15
Alcoholism	8	1.15	(0.57, 2.32)	0.69	1.88	(0.88, 4.02)	0.10
Tobacco used	1	0.65	(0.09, 4.60)	0.66	0.33	(0.04, 2.69)	0.30
Obesity	4	0.87	(0.32, 2.31)	0.77	0.81	(0.30, 2.17)	0.67
Sleep disorder	249	1.87	(1.58, 2.21)	<0.001	1.11	(0.92, 1.34)	0.29
Charlson Comorbidity Index (CCI)							
0	221	1.00	reference		1.00	reference	
1	138	1.91	(1.54, 2.36)	<0.001	1.39	(1.12, 1.72)	0.003
2	97	2.80	(2.21, 3.56)	<0.001	1.60	(1.25, 2.05)	<0.001
3+	90	4.59	(3.59, 5.86)	<0.001	2.01	(1.53, 2.63)	<0.001
Conventional drug used							
Oral steroid	513	0.73	(0.51, 1.04)	0.08	0.55	(0.38, 0.78)	0.001
NSAID	538	0.16	(0.08, 0.32)	<0.001	0.29	(0.14–0.60)	<0.001
Statin	128	1.25	(1.03, 1.52)	0.03	0.72	(0.58, 0.89)	0.003

Crude HR* represented relative hazard ratio.

Adjusted HR† represented adjusted hazard ratio: mutually adjusted for received acupuncture, length of days of hospitalization during the study period, age, sex, diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, depression, anxiety, alcoholism, tobacco used, obesity, sleep disorder, Charlson Comorbidity Index, oral steroid, NSAID and statin in Cox proportional hazard regression.
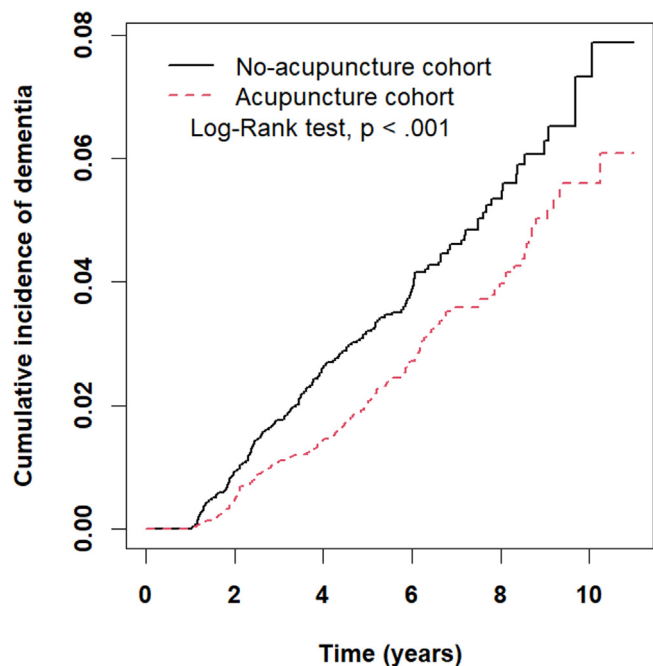
Fig. 2. Cumulative incidence of dementia between the acupuncture cohort and the non-acupuncture cohort. The cumulative incidence of dementia in the acupuncture cohort was significantly lower than that in the non-acupuncture cohort (log-rank test, p < 0.001).

The definitive mechanism of acupuncture treatment remains unclear.[27] Nevertheless, since acupuncture was often used to treat disorders of the nervous system (e.g., traumatic brain injury,[28] stroke,[29] cerebral palsy,[20] and epilepsy[30]) and psychological systems (e.g., depressive disorder,[31] insomnia[32] and anxiety[33]), it seems reasonable that acupuncture could reduce the incidence of dementia in patients with RA in this study. On the other hand, some studies showed anti-inflammatory effects of acupuncture.[34,35] Acupuncture could not only relieve pain through endorphin,[36] adenosine[37] and orexin[38] but also reduce inflammation through dopamine.[39] Since there was a connection between chronic inflammation and dementia,[8] the decrease in the incidence of dementia in patients with RA might be due to the anti-inflammatory effects of acupuncture. Additionally, taking oral steroids reduces the incidence of dementia in this study. This might be considered additional evidence of inflammation associated with dementia.

Among two different types of dementia of patients with RA, the incidence was reduced by acupuncture in vascular dementia, but not Alzheimer's disease. This result might suggest that the effect of acupuncture came from improving cardiovascular function. This is compatible with other studies of acupuncture.[15-17,20]

This study provided valuable information regarding the prevention of and clinical recommendation for dementia in patients with RA. Furthermore, it could provide directions for future clinical trials for treating patients with RA. The strength of this study included the following three points of view: (1) based on a review of the literature and our knowledge, this study is the first large-scale research to investigate the association between dementia and acupuncture of patients with RA. (2) All patients with catastrophic illness certificates of RA were included in this study. All patients were confirmed to be diagnosed by rheuma-

Table 3

Incidence rates, hazard ratios and confidence intervals of dementia in rheumatoid arthritis patients who received and did not receive acupuncture in the stratification of sex, age, comorbidities and conventional drug used.

Variables	Rheumatoid Arthritis Patients Received Acupuncture						Compared with non-acupuncture users	
	No (n = 9218)			Yes (n = 9218)			Crude HR (95% CI)	Adjusted HR (95% CI)
	Event	Person years	IR†	Event	Person years	IR†		
Total	331	32,771	10.1	215	38,228	5.62	0.56(0.47, 0.67)***	0.55(0.46, 0.65)***
Sex								
Female	266	26,788	9.93	171	30,994	5.52	0.56(0.46, 0.68)***	0.57(0.47, 0.69)***
Male	65	5984	10.9	44	7235	6.08	0.56(0.39, 0.83)**	0.47(0.32, 0.70)***
Age group								
18–39	5	6811	0.73	1	6262	0.16	0.21(0.03, 1.83)	0.17(0.02, 1.65)
40–59	87	20,246	4.30	77	25,649	3.00	0.70(0.51, 0.95)*	0.67(0.49, 0.91)**
≥60	239	5714	41.8	137	6317	21.7	0.52(0.42, 0.65)***	0.50(0.40, 0.62)***
Baseline Comorbidity								
Diabetes mellitus								
No	289	31,515	9.17	190	36,568	5.20	0.57(0.47, 0.68)***	0.55(0.46, 0.67)***
Yes	42	1256	33.4	25	1660	15.1	0.44(0.27, 0.73)**	0.51(0.31, 0.86)*
Hypertension								
No	103	22,963	4.49	83	25,969	3.20	0.71(0.54, 0.95)*	0.70(0.52, 0.94)*
Yes	228	9809	23.2	132	12,259	10.8	0.47(0.38, 0.58)***	0.48(0.39, 0.60)***
Hyperlipidemia								
No	194	25,281	7.67	126	29,045	4.34	0.57(0.45, 0.71)***	0.57(0.45, 0.71)***
Yes	137	7491	18.3	132	12,259	10.8	0.53(0.41, 0.69)***	0.52(0.40, 0.68)***
Congestive heart failure								
No	289	31,857	9.07	195	37,048	5.26	0.58(0.49, 0.70)***	0.56(0.47, 0.68)***
Yes	42	915	45.9	20	1180	16.9	0.37(0.22, 0.64)***	0.40(0.23, 0.69)***
Depression								
No	278	30,367	9.15	181	35,207	5.14	0.56(0.47, 0.68)***	0.55(0.45, 0.66)***
Yes	53	2404	22.1	34	3021	11.3	0.53(0.35, 0.82)**	0.56(0.37, 0.86)**
Anxiety								
No	238	26,714	8.91	147	31,058	4.73	0.53(0.44, 0.66)***	0.52(0.43, 0.65)***
Yes	93	6057	15.4	68	7170	9.48	0.62(0.46, 0.85)**	0.59(0.43, 0.82)**
Alcoholism								
No	326	32,379	10.1	212	37,737	5.62	0.56(0.47, 0.67)***	0.55(0.46, 0.65)***
Yes	5	392	12.8	3	491	6.11	0.49(0.12, 2.07)	0.42(0.06, 3.18)
Tobacco used								
No	331	32,684	10.1	214	38,123	5.61	0.56(0.47, 0.66)***	0.54(0.46, 0.65)***
Yes	0	87.4	0.00	1	104	9.57	–	–
Obesity								
No	330	32,500	10.2	212	37,911	5.59	0.56(0.47, 0.66)***	0.54(0.45, 0.64)***
Yes	1	271	3.69	3	317	9.45	2.75(0.29, 26.4)	–
Sleep disorder								
No	175	22,949	7.63	122	26,089	4.68	0.61(0.49, 0.77)***	0.57(0.45, 0.72)***
Yes	156	9823	15.9	93	12,139	7.66	0.49(0.38, 0.64)***	0.52(0.40, 0.67)***
Charlson Comorbidity Index (CCI)								
0	128	21,203	6.04	93	23,985	3.88	0.64(0.49, 0.84)**	0.62(0.47, 0.81)***
1	83	7013	11.8	55	7794	7.06	0.60(0.43, 0.85)**	0.58(0.41, 0.82)**
2	64	2809	22.8	33	4242	7.78	0.35(0.23, 0.54)***	0.36(0.23, 0.55)***
3+	56	1747	32.1	34	2206	15.4	0.49(0.32, 0.76)**	0.51(0.33, 0.79)**
Drug used								
Oral steroid								
No	19	1406	13.5	14	1725	8.12	0.65(0.32, 1.29)	0.65(0.31, 1.38)
Yes	312	31,365	9.95	201	36,503	5.51	0.56(0.47, 0.66)***	0.55(0.46, 0.65)***
NSAID								
No	6	62	96.1	2	94	21.3	0.35(0.07, 1.76)	–
Yes	325	32,709	9.94	213	38,134	5.59	0.57(0.48, 0.67)***	0.55(0.46, 0.66)***
Statin								
No	252	26,162	9.63	166	30,799	5.39	0.57(0.47, 0.69)***	0.56(0.46, 0.68)***
Yes	79	6609	12.0	49	7429	6.60	0.54(0.38, 0.77)***	0.53(0.37, 0.76)***

Abbreviation: IR, incidence rates, per 1000 person-years; HR, hazard ratio; CI, confidence interval.

Adjusted HR: adjusted for accepted acupuncture, length of days of hospitalization during the study period, age, sex, diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, depression, anxiety, alcoholism, tobacco used, obesity, sleep disorder, Charlson Comorbidity Index, oral steroid, NSAID and statin in Cox proportional hazards regression.

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

tologists with clinical and blood sample evaluations. Because NHIRD covered more than 99% of the Taiwanese population, the potential selection bias was thus minimized (3) The medical insurance of the NHI system provided a low-cost and convenient medical service that covered almost all residents in Taiwan.[40] In addition, more than 90% of medical institutions, including hospitals and clinics at all levels, are covered in the NHI program.[40] All RA patients were waived of co-payment when they visited rheumatologist or TCM doctors for the treatment of RA in the NHI program. Thus, people are not faced with differences in price when choosing Chinese medicine or Western medicine.

However, this study has some limitations. First, in patients receiving acupuncture treatment, the method of acupuncture is not standardized,

Table 4

Incidence rates, hazard ratio and confidence intervals of vascular dementia and Alzheimer's disease for rheumatoid arthritis patients who received and did not receive acupuncture in the stratification of sex, age, comorbidities and conventional drugs used.

Outcome	Rheumatoid Arthritis Patients Received Acupuncture						Compared with non-acupuncture users	
	No (*n* = 9218)			Yes (*n* = 9218)			Crude HR	Adjusted HR
	Event	Person years	IR†	Event	Person years	IR†	(95% CI)	(95% CI)
Vascular dementia	42	32,808	1.28	25	38,240	0.65	0.50 (0.30, 0.081)**	0.47 (0.29, 0.77)**
Alzheimer's disease	25	32,805	0.76	19	38,238	0.50	0.63 (0.35, 1.15)	0.63 (0.35, 1.15)

Abbreviation: IR, incidence rates, per 1000 person-years; HR, hazard ratio; CI, confidence interval.
Adjusted HR: adjusted for received acupuncture, length of days of hospitalization during the study period, age, sex, diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, depression, anxiety, alcoholism, tobacco used, obesity, sleep disorder, Charlson Comorbidity Index, oral steroid, NSAID and statin use in Cox proportional hazards regression.
* p:<0.05.

Table 5

Cox model with hazard ratios and 95% confidence intervals of dementia associated with receiving only conventional Western drugs, only acupuncture or both acupuncture and conventional Western drugs among rheumatoid arthritis patients.

Variables	n	No. of event (*n* = 543)	Crude*			Adjusted†		
			HR	(95% CI)	p-value	HR	(95% CI)	p-value
Treatment								
Only conventional Western drugs used	9201	328	1.00	reference		1.00	reference	
Only acupuncture used	63	1	3.15	(0.44, 22.4)	0.2521	0.54	(0.06, 5.25)	0.6149
Combined Western drugs and acupuncture	9205	214	0.56	(0.47–0.67)	<0.0001	0.64	(0.56–0.73)	<0.0001

Crude HR* represented relative hazard ratio;.
Adjusted HR† represented adjusted hazard ratio: mutually adjusted for accepted acupuncture, length of days of hospitalization during the study period, age, sex, diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, depression, anxiety, alcoholism, tobacco used, obesity, sleep disorder, Charlson Comorbidity Index, oral steroid, NSAID and statin in Cox proportional hazard regression.

including position and duration of treatment. Instead, the data reflects a real-world practice in the clinics. Second, since there were no disease severity and imaging data in the NHIRD, we were unable to evaluate the impact of disease severity on outcomes from this study although we have matched the two cohorts by a propensity-score matching method. Third, the mechanism of action of acupuncture remains unclear. Thus, we look forward to future clinical trials and mechanistic studies to explore the mechanisms and clinical efficacy of the preventive effect of acupuncture on dementia in patients with RA based on this study.

In conclusion, our present study suggests that acupuncture treatment is associated with a reduced risk of dementia in patients with RA in Taiwan. This valuable information could provide some ideas for future clinical and mechanistic studies.

Author contributions

Conceptualization and methodology: HRY, PKM and CLL. Software: CLL. Validation: HHL, MCH, CLL, MYW and HRY. Formal analysis: CLL. Investigation: HHL, MCH, YCL, CLL, PKM, MYW, HRY. Resources: HHL and HRY. Writing—original draft: HHL, MCH, MYW, PKM and HRY. Writing—review and editing: PKM, MYW and HRY. Supervision and project administration: HRY.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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Ethical statement

This study was approved by the Research Ethics Committee of China Medical University and Hospital, Taichung, Taiwan (CMUH104-REC2–115). The patient consent was exempted for the total anonymity of all research data in this study.

Data availability

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

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2024.101086.

Supplementary Table 1. Characteristics of rheumatoid arthritis patients according to whether they received acupuncture prior to propensity score matching.

Supplementary Table 2. Hazard Ratios and 95% confidence intervals of dementia risk associated with type of Chinese herbal medicines among RA patients.

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