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Prolong Exposure of NSAID in Patients With RA Will Decrease the Risk of Dementia

A Nationwide Population-Based Cohort Study

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Abstract: Rheumatoid arthritis (RA), a chronic, systemic inflammatory disorder, primarily affects joints. Several studies have indicated that early inflammation, cardiovascular disease, and depression in patients were associated with a considerably increased risk of dementia. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for treating RA. NSAIDs facilitate alleviating RA-associated chronic pain, inflammation, and swelling. Therefore, we conducted this nationwide study for evaluating the association between the dementia risk and NSAID treatment in patients with RA.

The RA cohort comprised patients aged 20 years and older who were newly diagnosed with RA between 2000 and 2011, with data obtained from the Registry of Catastrophic Illnesses Patient Database (RCIPD). Patients without RA were frequency matched with the RA cohort at a 1:4 ratio according to age, sex, and year of RA diagnosis. The relative risks of dementia were estimated using Cox proportional hazard models.

The risk of dementia in the RA cohort was not significantly higher than that in the non-RA cohort (adjusted HR [hazard ratio] = 0.95, 95% confidence interval [CI] = 0.87–1.02). Regarding the duration of NSAID treatment, the risk of dementia was significantly lower when the RA cohort used NSAIDs for >2191 days (HR = 0.56, 95% CI = 0.45–0.68).

A longer duration of NSAID treatment possibly reduces the risk of dementia. Additional studies are warranted for verifying the association of dementia risk with NSAID treatment in patients with RA.

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Abbreviations: RA = rheumatoid arthritis, NSAIDs = nonsteroidal anti-inflammatory drugs, HR = hazard ratio, RCIPD = Registry of Catastrophic Illnesses Patient Database, AD = Alzheimer disease, NHI = National Health Insurance, NHIRD = NHI Research Database, CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, CHF = congestive heart failure, TNF = tumor necrosis factor.

INTRODUCTION

Rheumatoid arthritis (RA), a chronic and systemic inflammatory disease, can cause severe disability and increase the mortality rate because of deformed and painful joints.[1,2] Previous studies have indicated an increased risk of cerebrovascular and neurodegenerative diseases and depression in patients with RA.[3–6] Furthermore, early inflammation, cardiovascular diseases, and depression in patients were associated with an increased risk of dementia.[7–10] Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for treating RA, and several studies suggest that NSAIDs reduce the risk of Alzheimer disease (AD) or dementia in patients with RA.[11–14] However, the association between RA and dementia remains unclear. Therefore, in this nationwide study, we evaluated the risk of dementia in and effect of NSAID treatment on patients with RA.

METHODS

Data Source

The National Health Insurance (NHI) program was implemented on March 1, 1995, and covers ~99% of the Taiwanese population (~23.74 million).[15] The National Health Research Institutes audits and releases the NHI Research Database (NHIRD), described in detail in previous studies,[16,17] for

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research purposes. Diseases were classified on the basis of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. This study analyzed depersonalized secondary data; thus, no informed consent was required. This study was exempted from review by the Institutional Review Board of China Medical University (CMUH104-REC2-115).

Patients

We used the Registry for Catastrophic Illness Patient Database (RCIPD), a subset of the NHIRD, for identifying patients with RA (ICD-9-CM 714) aged 20 years. The date of the first diagnosis of RA between 2000 and 2011 served as the index date. The NHI RCIPD was established for tracking patients with major or catastrophic illnesses, including cancer, end-stage renal disease, mental illness, congenital illness, and several autoimmune diseases such as RA. The application for a catastrophic illness card is scrutinized through peer review, and patients having this card can be exempted from copayment. We excluded patients with a history of dementia (ICD-9-CM 290, 294.1, and 331.0) before the index date and those with incomplete data on age and sex. Patients without RA (non-RA cohort) were randomly selected from the NHIRD and were frequency-matched with the RA cohort at a 1:4 ratio according to age (in 5-y intervals), sex, and year of RA diagnosis by using the same exclusion criteria.

Outcome and Comorbidities

The outcome variable was the development of dementia during follow-up. All patients were followed until the occurrence of dementia; death; withdrawal from the NHI program; or December 31, 2011. Baseline comorbidities for each patient included diabetes (ICD-9-CM 250), hypertension (ICD-9-CM 401-405), hyperlipidemia (ICD-9-CM 272), coronary artery disease (CAD: ICD-9-CM 410-414), head injury (ICD-9-CM 310.2, 800, 801, 803, 804, 850, 851, 853, and 854), depression (ICD-9-CM 296.2, 296.3, 296.82, 300.4, and 311), stroke (ICD-9-CM 430-438), chronic obstructive pulmonary disease (COPD: ICD-9-CM 491, 492, and 496), and congestive heart failure (CHF: ICD-9-CM 428).

Statistical Analysis

We used the chi-square test for determining the categorical differences in demographic variables and comorbidities between the RA and non-RA cohorts and compared the mean age and follow-up period between the cohorts by using Student's *t* test. We calculated the incidence (per 1000 person-y) of dementia by using different risk factors and calculated the relative risk of dementia between the cohorts by using demographic variables. Univariate and multivariate Cox proportional hazards regression analyses were used for estimating the risk of dementia associated with RA. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox model. The multivariate model was adjusted for sex, age, and comorbidities, revealing a significant difference with the univariate model. We also evaluated the effect of the duration of NSAID use ($\leq$730, 731–1460, 1461–2190, and >2190 d) on the risk of dementia among patients with RA. All analyses were conducted using SAS statistical software (Version 9.4 for Windows; SAS Institute, Inc, Cary, NC). A 2-tailed *P* value of 0.05 was considered statistically significant.

TABLE 1. Characteristics of Patients Between Patients With Rheumatoid Arthritis and Patients Without Rheumatoid Arthritis

	Rheumatoid Arthritis				
	Yes (N = 33,229)		No (N = 132,916)		
	n	%	n	%	*P* Value
Age, y					0.99
20–34	3131	9.42	12,524	9.42	
35–49	99,30	29.9	39,720	29.9	
50–64	12,594	37.9	50,376	37.9	
≥ 65	7574	22.8	30,296	22.8	
Mean (SD)*	53.9	14.2	53.3	14.2	<0.001
Gender					0.99
Female	25,796	77.6	103,184	77.6	
Male	7433	22.4	29,732	22.4	
Comorbidity					
Diabetes	2846	8.56	11,487	8.64	0.65
Hypertension	10,790	32.5	41,353	31.1	<0.001
Hyperlipidemia	6645	20.0	26,569	20.0	0.97
CAD	5349	16.1	19,660	14.8	<0.001
Head injury	1261	3.79	4705	3.54	0.03
Depression	2428	7.31	6794	5.11	<0.001
Stroke	876	2.64	3942	2.97	0.001
COPD	4165	12.5	11,309	8.51	<0.001
CHF	1138	3.42	3245	2.44	<0.001

Chi-square test; *t test.
CAD = coronary artery disease, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease.

RESULTS

Our study included 33,229 and 132,916 patients in the RA and non-RA cohorts, respectively. In the RA cohort, 39.3% of patients were aged <49 years and 77.6% of them were women (Table 1). The mean age of the RA and non-RA cohorts was 53.9 ± 14.2 years and 53.3 ± 14.2 years, respectively. The RA cohort had a higher prevalence of preexisting comorbidities, namely hypertension, coronary artery disease (CAD), head injury, depression, stroke, chronic obstructive pulmonary disease (COPD), and congestive heart failure (CHF) (all $P < 0.05$).

During the mean follow-up period of 6.65 years and 6.70 years for the RA and non-RA cohorts, respectively, the overall incidence of dementia was non-significantly higher (0.89-fold) in the RA cohort than in the non-RA cohort (3.34 vs 3.74 per 1000 person-y), with an adjusted HR of 0.95 (95% CI = 0.87–1.02) after adjustment for age, sex, and comorbidity (Table 2). The incidence of dementia increased with increasing age and comorbidities.

In the multivariate Cox model, compared with patients aged ≤ 49 years, the risk of dementia was 10.7-fold higher in patients aged 50 to 64 years (95% CI = 8.48–13.5) and

TABLE 2. The Incidence (Per 1000 Person-Years) and Risk Factors for Dementia

Variable	Event	PY	Rate[†]	Crude HR[‡] (95% CI)	Adjusted HR[§] (95% CI)
Rheumatoid arthritis					
No	3330	890,627	3.74	1.00	1.00
Yes	737	220,985	3.34	0.89 (0.82, 0.97)*	0.95 (0.87, 1.02)
Age, y					
≤ 49	77	467,625	0.16	1.00	1.00
50–64	914	427,455	2.14	13.2 (10.5, 16.7)**	10.7 (8.48, 13.5)**
65+	3076	216,532	14.2	94.7 (75.5, 118.7)**	61.3 (48.7, 77.2)**
Sex					
Female	3011	879,092	3.43	1.00	1.00
Male	1056	232,520	4.54	1.36 (1.27, 1.46)**	1.01 (0.94, 1.09)
Comorbidity					
Diabetes					
No	3349	1,035,168	3.24	1.00	1.00
Yes	718	76,444	9.39	3.21 (2.96, 3.48)**	1.29 (1.19, 1.41)**
Hypertension					
No	1361	789,774	1.72	1.00	1.00
Yes	2706	321,838	8.41	5.12 (4.79, 5.46)**	1.45 (1.35, 1.56)**
Hyperlipidemia					
No	2693	911,050	2.96	1.00	1.00
Yes	1374	200,562	6.85	2.45 (2.29, 2.61)**	1.03 (0.96, 1.11)
CAD					
No	2561	961,355	2.66	1.00	1.00
Yes	1506	150,257	10.0	3.97 (3.72, 4.23)**	1.17 (1.08, 1.25)**
Head injury					
No	3826	1,080,912	3.54	1.00	1.00
Yes	241	30,700	7.85	2.48 (2.18, 2.83)**	1.62 (1.42, 1.85)**
COPD					
No	3205	1,026,794	3.12	1.00	1.00
Yes	862	84,818	10.2	3.62 (3.36, 3.91)**	1.32 (1.22, 1.43)**
Stroke					
No	3641	1,088,582	3.34	1.00	1.00
Yes	426	23,030	18.5	6.19 (5.60, 6.85)**	1.91 (1.72, 2.12)**
CHF					
No	3754	1,090,752	3.44	1.00	1.00
Yes	313	20,859	15.0	4.94 (4.40, 5.54)**	1.29 (1.14, 1.45)**
Depression					
No	3678	1,062,926	3.46	1.00	1.00
Yes	389	48,685	7.99	2.58 (2.32, 2.87)**	1.73 (1.55, 1.93)**

CHF = congestive heart failure, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, PY = person-years

[†] Rate = incidence rate, per 1000 person-years.

[‡] Crude HR = relative hazard ratio.

[§] Adjusted HR = multivariable analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease (CAD), head injury, stroke, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and depression.

* $P < 0.01$.

** $P < 0.001$

61.3-fold higher in those aged ≥ 65 years (95% CI = 48.7–77.2). The risk of dementia was higher in patients with diabetes (HR = 1.29, 95% CI = 1.19–1.41), hypertension (HR = 1.45, 95% CI = 1.35–1.56), CAD (HR = 1.17, 95% CI = 1.08–1.25), head injury (HR = 1.62, 95% CI = 1.42–1.85), COPD (HR = 1.32, 95% CI = 1.22–1.43), stroke (HR = 1.91, 95% CI = 1.72–2.12), CHF (HR = 1.29, 95% CI = 1.14–1.45), and depression (HR = 1.73, 95% CI = 1.55–1.93). The dementia incidence increased with age in both cohorts; however, the relative risk of dementia in the age-specific RA and non-RA cohorts was significantly lower for older patients (HR = 0.89; 95% CI = 0.71–0.97; Table 3).

Table 4 presents the risk of dementia stratified according to the duration of NSAID treatment. Compared with patients with RA who used NSAIDs for ≤730 days, the risk of dementia was significantly lower in those who used NSAIDs for >2191 days (HR = 0.56, 95% CI = 0.45–0.68).

DISCUSSION

In this nationwide retrospective cohort study, we enrolled all Taiwanese patients with RA over a 10-year follow-up period. The study explored the risk of dementia in patients with RA and evaluated the effects of NSAIDs on reducing the aforementioned risk. The major finding was that a longer duration of NSAID treatment reduced the risk of dementia in patients with RA.

We observed that the prevalence of hypertension, CAD, stroke, and depression was significantly higher in the RA cohort than in the non-RA group (Table 1). This finding was consistent with that of previous studies stating that patients with RA have a higher risk of cardiovascular and cerebrovascular diseases.[18,19] Diabetes, hypertension, CAD, head injury, COPD, stroke, CHF, and depression are also known risk factors for dementia (Table 2).[7,20,21]

The tumor necrosis factor (TNF) plays a crucial role in the pathogenesis of RA.[22,23] Previous studies have indicated that the dysregulation of TNF production is implicated in AD.[24,25] A characteristic of AD is β-amyloid aggregation, and deposition of β-amyloid activates glial cells, subsequently inducing TNF production.[26–28] However, we did not observe any significant association between the risk of dementia and development of RA, possibly because of the effect of the NSAID treatment. In the present study, we enrolled all patients with RA having severe disabilities in Taiwan from the RCIPD during 2000 and 2011. The major symptom of RA is pain,[29] and the main aim of the treatment for RA is to reduce the symptoms.[30] In the RA and non-RA cohorts, NSAID treatment had unequal probabilities of causing the reverse result (HR = 0.95, 95% CI = 0.87–1.02); however, this difference was not significant. This finding can be explained by the results presented in Table 4. A longer duration of NSAID treatment reduces the risk of dementia, particularly in the patient group administered NSAIDs for >2191 days. Because of the limitation of the NHIRD, the risk of dementia in patients with RA remains unclear and warrants experimental studies.

Cigarette smoking is a risk factor for both RA and dementia, but information on smoking is unavailable in the NHIRD. Therefore, COPD has been used widely as a proxy variable for cigarette smoking in previous studies.[31,32] Furthermore, the lack of clinical data, such as data from blood tests, electroencephalograms, and neuroimaging, was the main limitation of this NHIRD-based study. Nevertheless, we identified patients with RA according to ICD-9-CM codes, which are recorded by well-trained physicians. Finally, the NSAID treatment might have a low potency because patients with RA and dementia were less likely to receive the treatment. This factor might have caused the efficacy of NSAIDs in preventing the development of dementia to be underestimated.

TABLE 3. Incidence and Hazard Ratio of Dementia Between Patients With Rheumatoid Arthritis and Without Rheumatoid Arthritis

	Rheumatoid Arthritis							
	Yes			No				
Outcome	Event	PY	Rate†	Event	PY	Rate†	Crude HR‡ (95% CI)	Adjusted HR§ (95% CI)
Gender								
Female	547	175,450	3.12	2464	703,642	3.50	0.89 (0.81, 0.98)*	0.93 (0.85, 1.03)
Male	190	45,535	4.17	866	186,985	4.63	0.91 (0.78, 1.06)	0.98 (0.83, 1.14)
Age, y								
20–49	18	94,579	0.19	59	373,045	0.16	1.19 (0.70, 2.01)	1.04 (0.61, 1.77)
50–64	184	84,683	2.17	730	342,772	2.13	1.03 (0.88, 1.22)	0.98 (0.83, 1.15)
≥ 65	535	41,723	12.8	2541	174,809	14.5	0.90 (0.82, 0.98)*	0.89 (0.71, 0.97)*
Comorbidity‖								
No	119	115,912	1.03	633	510,719	1.24	0.82 (0.67, 0.99)*	0.88 (0.72, 1.07)
Yes	618	105,073	5.88	2697	379,907	7.10	0.83 (0.76, 0.91)**	0.95 (0.87, 1.03)

CI = confidence interval, HR = hazard ratio, PY = person-years.

† Rate = incidence rate per 1000 person-years;

‡ Crude HR = relative hazard ratio;

§ Adjusted HR = hazard ratio adjusted for age, and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, head injury, stroke, COPD, congestive heart failure, and depression;

‖ Comorbidity = patients with any one of the comorbidities (including diabetes, hypertension, hyperlipidemia, coronary artery disease, head injury, stroke, COPD, congestive heart failure, and depression) were classified as the comorbidity group

* $P < 0.05$.

** $P < 0.001$.

TABLE 4. Incidence and Adjusted Hazard Ratio of Dementia Stratified by Duration of NSAID in Patients With Rheumatoid Arthritis

NSAID exposed	N	Event	PY	Rate[†]	Crude HR[‡] (95% CI)	Adjusted HR[§] (95% CI)
Duration on NSAID						
≤ 730 days	9191	155	48,230	3.21	1 (reference)	1 (reference)
731–1460 days	8366	172	45,286	3.80	1.22 (0.98, 1.52)	0.96 (0.77, 1.19)
1461–2190 days	5882	136	38,771	3.51	1.04 (0.83, 1.31)	0.81 (0.64, 1.02)
> 2191 days	9790	274	88,698	3.09	0.63 (0.52, 0.77)***	0.56 (0.45, 0.68)***

CI = confidence interval, HR = hazard ratio, NSAID = Nonsteroidal anti-inflammatory drugs, PY = person-years.
[†] Rate = incidence rate per 1000 person-years
[‡] Crude HR = relative hazard ratio
[§] Adjusted HR = hazard ratio adjusted for age, and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, head injury, stroke, COPD, congestive heart failure, and depression
*** $P < 0.001$

This study has several strengths. First, we conducted the longitudinal and nationwide study design by population-based data and NHIRD records in the present study. Both of study and control cohorts were with low loss to follow-up. We enrolled all patients with RA aged ≥20 years from 2000 to 2011 in Taiwan without sampling. Second, the frequencies of clinical visits were different between the patients with and without RA because of differences in disease severity. However, this potential bias might not occur over an 11-year follow-up period. Third, we adjusted for many confounders for determining the risk of dementia in patients with RA, namely diabetes, hypertension, hyperlipidemia, CAD, head injury, depression, stroke, COPD, and CHF, which were risk factors for both RA and dementia. In addition, NHIRD covers ∼99% of the Taiwanese population, due to the reimbursement policy, Taiwan government is the single-buyer. The medical reimbursement specialists and peer review scrutinized all insurance claims based on the standard diagnosed criteria. If these doctors or hospitals make wrong diagnoses or coding, they will be punished with a lot of penalties. Therefore, the diagnostic criteria of dementia based on ICD-9 codes in this study were highly reliable.

In summary, our findings reveal no significant association between the risk of dementia and RA. Nevertheless, it is suggested that prolonged use of NSAIDs reduces the risk of dementia in patients with RA. Because of the limitations of the NHIRD, it is necessary to conduct an experimental study determining the mechanism underlying the association of dementia risk with NSAID treatment in patients with RA.

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