

Increased risk of depression in patients with rheumatoid arthritis: a seven-year population-based cohort study

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OBJECTIVE: Rheumatoid arthritis (RA) is a costly and crippling autoimmune disease that can lead to the development of depression, contributing to suboptimal clinical outcomes. However, no longitudinal studies have identified an association between rheumatoid arthritis and subsequent depression. This study aimed to investigate the incidence and risk factors of depression among RA patients in Taiwan.

METHODS: Using Taiwan's National Health Insurance Research Database, we identified 3,698 newly diagnosed RA patients aged 18 years or older, together with 7,396 subjects without RA matched by sex, age and index date, between 2000 and 2004. The incidence of depression and the risk factors among RA cases were evaluated using Cox proportional-hazard regression.

RESULTS: The incidence of depression was 1.74-fold greater in the RA cohort than in the non-RA cohort (11.80 versus 6.89 per 1,000 person-years; $p < 0.01$). Multivariate analysis showed that RA subjects who were female, were older, or had comorbidities such as stroke, chronic kidney disease, or cancer had a significantly greater risk of depression compared with those without these conditions.

CONCLUSION: This population-based cohort study showed a strong relationship between RA and a subsequent risk of depression. The findings could be beneficial to healthcare providers for identifying individuals with a higher predisposition for depression, thereby possibly facilitating the provision of an appropriate rehabilitation intervention after RA onset to support the patient's adaptation.

KEYWORDS: Rheumatoid Arthritis; Depression; Risk Factor; Cohort Study.

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INTRODUCTION

Rheumatoid arthritis (RA) is a debilitating disease characterized by chronic symmetric polyarthritis involving peripheral small joints that affects 0.3-1.0% of the population worldwide (1). Most individuals first experience RA between 30 and 50 years of age (2). Approximately 20-30%

of these individuals are unable to work within 3 years following diagnosis, which places a tremendous burden on the patients, their families and the healthcare system (3). Accordingly, a report from the American College of Rheumatology Subcommittee showed that RA is responsible for 250,000 hospitalizations and 9 million physician visits each year (4). Additionally, Birnbaum et al. (5) reported that the annual direct medical costs for RA in the US were \$19.3 billion, with the total societal costs (the sum of direct costs and indirect costs) estimated to exceed \$39 billion.

RA not only results in enormous economic losses but also presents a significant public health problem. Recently, RA has been proven to be a major risk factor for many chronic conditions such as cancer, cardiovascular disease, kidney

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dysfunction and respiratory disease (2,6). A review by Sokka et al. reported that RA patients had a 50-60% greater risk of death from all causes compared with individuals without RA (7). Due to the irreversible nature of RA and the poor clinical responses of RA patients, psychiatric disorders, especially depression, are commonly found among RA patients. Indeed, the prevalence of depression among RA patients is estimated to range from 14.8 to 38.8% (8) and patients with RA are five times more likely to experience depression than the general population (9). RA patients suffering from concomitant depression had a 7.2% (\$12,225 vs. \$11,404) increase in medical costs (10) and their likelihood of mortality compared with patients with RA only was more than doubled (11). Therefore, it is important to clarify the factors that may lead to depression and to then incorporate appropriate treatment for these factors into the routine care of RA patients.

Although some studies on depression among RA subjects have been conducted, most have been performed in Western countries (9,12-14). In particular, Chinese patients often consider depression to be a taboo subject and are highly reluctant to openly discuss this problem with others (15). Previous studies of Chinese RA patients have often focused on disease outcomes during pregnancy (16), epidemiological reports (17), or the subsequent risk of cancer following RA onset (18). Consequently, only limited data are available on psychological issues, especially depression, among Asian patients with RA. Of the few studies conducted that have examined factors related to depression among Chinese RA patients, there are major weaknesses such as the absence of a control group, a small sample size, or a cross-sectional design (19,20). To fill this gap in the literature, we conducted a follow-up study to assess the association between RA and the subsequent risk of depression, together with risk factors, in Asian patients using claims data obtained from the National Health Insurance (NHI) of Taiwan. Although this is a preliminary study of depression in RA patients, its findings should assist healthcare providers in identifying potential cases of depression and provide an empirical rationale for initiating more timely and efficient interventions for RA patients.

METHODS

Data sources

All analytic data were retrieved from the Longitudinal Health Insurance Database (LHID), which is maintained by the Bureau of National Health Insurance (BNHI) and provided to scientists in Taiwan for research purposes. In 1995, Taiwan launched a single-payer NHI Program to remove the financial barriers to medical care for all legal residents. At the end of 2010, >99% of Taiwan's population had enrolled in this program (21). The LHID is a subset of the NHI database and contains comprehensive utilization and enrollment information for one million randomly selected NHI beneficiaries, representing 5% of all enrollees in Taiwan in 2000. Because a multistage, stratified, systematic sampling method was used for this study, there were no statistically significant differences regarding sex or age between the sample group and the total number of enrollees (21). This study was approved by the local institutional review board and ethics committee of Buddhist Dalin Tzu Chi Hospital, Taiwan (No. B101030014).

Study subjects

Diagnoses in the patient insurance claims data were coded according to the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM). The LHID records were used to identify adult patients with RA aged ≥ 18 years and newly diagnosed between 2000 and 2004. Patients who were identified with an ICD code of 714.0 comprised the RA cohort. To eliminate errors resulting from misclassification, we selected RA subjects who had at least 2 RA diagnoses in the ambulatory service or those who were admitted to the hospital with a primary RA diagnosis during the 5-year period. This approach was based on the method adopted by former researchers using administrative databases (22,23). The index date was defined as the date of the first RA diagnosis.

Based on gender, age and index date, each RA patient was matched with 2 control-group patients from a reference population not registered with an RA diagnosis. Each subject in the control group was assigned the same index date as the corresponding RA patient. After excluding subjects with a history of depression at baseline, a total of 3,698 RA patients and 7,396 non-RA control subjects were included in the data analysis. Patients were considered to have a history of depression if they had ≥ 2 outpatient visits or at least one inpatient claim of depression (ICD-9-CM codes of 296.2, 296.3, 300.4 or 311) since 1996, when the computerized claims data from the LHID were available, until the date of cohort entry. All subjects were followed up to the end of 2011 to measure the incidence of depression based on the above-mentioned criteria: at least two ambulatory visits or one hospitalization with the diagnosis of depression. The date of their first medical visit due to depression was established as the starting point for their time at risk with depression. Follow-up person-years (PYs) were calculated as the time interval from the entry date to the earliest occurrence of one of the following: a diagnosis of depression, the date of withdrawal from insurance, or December 31, 2011.

Demographic variables and disease characteristics

The demographic variables used in this study included age, gender, income for estimating insurance payment and urbanization level of the subject's residential area. The monthly incomes were divided into 3 levels: \leq New Taiwan Dollar (NTD) 17,880, NTD 17,881-NTD 43,900, and \geq NTD 43,901. Urbanization levels were divided into 3 strata based on population density: urban (levels 1-2), suburban (levels 3-4) and rural (levels 5-7) areas. Level 1 refers to the "most urbanized" and level 7 refers to the "least urbanized" communities (24). Disease characteristics included the presence of a chronic disease such as hypertension (ICD-9-CM 401-405), stroke (ICD-9-CM 430-438), diabetes (ICD-9-CM 250), heart disease (ICD-9-CM 410-429), chronic kidney disease (ICD-9-CM 585) and cancer (ICD-9-CM 140-208). Additionally, medication usage was stratified into two groups according to whether the subjects had received DMARDs or biological agents for more than three months after the index date.

Statistical analysis

The χ^2 test was used to examine differences in demographic variables and disease characteristics between the RA and control cohorts. The depression incidence rate for the 2 cohorts was presented as the number of cases per 1,000



Table 1 - Demographic data and comorbidity comparison of the study subjects.

Variables	Non-RA	RA	p
	N = 7,396 (%)	N = 3,698 (%)	
Age, (years)			0.99
<50	2653 (35.9)	1326 (35.9)	
50–69	3151 (42.6)	1579 (42.7)	
≥70	1592 (21.5)	793 (21.4)	
Mean (SD)	55.76 (15.24)	55.75 (15.24)	0.98
Gender			
Female	4864 (65.8)	2432 (65.8)	
Male	2532 (34.2)	1266 (34.2)	
Monthly income			0.24
Low	2142 (29.0)	1075 (29.1)	
Median	4626 (62.6)	2344 (63.4)	
High	626 (8.5)	279 (7.5)	
Level of urbanization			<0.01
Urban	4226 (57.2)	2055 (55.6)	
Suburban	1150 (15.6)	529 (14.3)	
Rural	2018 (27.3)	1114 (30.1)	
Medication usage			<0.01
Yes	14 (0.2)	414 (11.2)	
No	7382 (99.8)	3284 (88.8)	
Comorbidity			
Hypertension	594 (8.0)	331 (9.0)	0.10
Stroke	62 (0.8)	55 (1.5)	<0.01
Diabetes	267 (3.6)	173 (4.7)	0.01
Heart disease	218 (2.9)	125 (3.4)	0.22
Chronic kidney disease	29 (0.4)	12 (0.3)	0.58
Cancer	32 (0.8)	16 (0.6)	0.12

PYs. A Cox proportional hazards regression analysis was applied to compute the hazard ratio (HR) and 95% confidence interval (CI) of depression for RA compared with the control cohort. The multivariate Cox proportional hazards model was used to identify risk factors that might predict depression and their adjusted hazard ratio (aHR) within the RA cohort. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics and depression incidence between the two cohorts

The distributions of demographic variables and disease characteristics for the RA and control cohorts are shown in Table 1. RA patients were more likely to reside in a rural area ($p < 0.01$), take medications ($p < 0.01$) and be diagnosed with comorbidities such as stroke and diabetes ($p < 0.05$ for both comorbidities).

Among the study sample of 11,094 patients, a total of 905 first episodes of depression occurred - 413 among the RA patients and 492 among the control subjects - during the follow-up of 34,992.62 and 71,449.94 PYs, respectively. The incidence of depression in the RA cohort was greater than

that in the control group (11.80 vs. 6.89 per 1,000 PYs), with an aHR of 1.74 (95% CI 1.48, 1.95; Table 2).

Risk factors of depression in RA subjects

A multivariate Cox proportional-hazard regression analysis was used to estimate the aHR of depression among RA patients based on demographic data and disease characteristics (Table 3). The data showed that age and gender are significantly related to the risk of depression in RA patients. In addition, the risk of depression was 19% greater for subjects aged ≥ 70 years compared with those aged < 18 years (95% CI 1.02-1.38). Compared with male gender, female gender was related to an aHR of 1.77 for depression (95% CI 1.52-2.07). Additionally, the presence of a comorbidity increased the risk of depression, with patients with cancer having the highest risk (aHR: 2.47, 95% CI 1.46-4.20), followed by those with chronic kidney disease (aHR: 2.32, 95% CI 1.10-4.88) and stroke (aHR: 1.84, 95% CI 1.14-2.96).

DISCUSSION

This is the first study to utilize a national administrative database to address the relationship between RA and subsequent depression in an Asian population. Due to the relatively low RA incidence, a large sample size is required to obtain sufficient statistical power for a proper analysis.

Table 2 - Crude and adjusted hazard ratios of depression for RA patients compared with non-RA controls.

Patient group	Event	PY	Incidence	Crude HR (95% CI)	aHR* (95% CI)
Controls	492	71449.94	6.89	1	1
RA patients	413	34992.62	11.80	1.72 (1.51–1.96)	1.74 (1.48-1.95)

Incidence rate is per 1,000 person-years.

*The model was adjusted for age, gender, urbanization level, monthly income, medication usage and comorbidities.



Table 3 - Multivariate analysis of factors related to the risk of depression among RA patients.

Variable	Crude HR (95% CI)	Adjusted HR* (95% CI)
Age, (years)		
<50	1	1
50-69	1.09 (0.91-1.31)	1.13 (0.92-1.37)
≥70	1.20 (1.04-1.39)	1.19 (1.02-1.38)
Gender		
Male	1	1
Female	1.78 (1.52-2.08)	1.77 (1.52-2.07)
Monthly income		
Low	1.16 (0.89-1.52)	1.01 (0.86-1.17)
Median	1.08 (0.84-1.39)	1.07 (0.81-1.41)
High	1	1
Level of urbanization		
Urban	1.14 (0.97-1.33)	1.17 (0.98-1.36)
Suburban	1.06 (0.86-1.31)	1.10 (0.86-1.33)
Rural	1	1
Medication usage		
Yes	1.30 (0.97-1.79)	1.27 (0.94-1.69)
No	1	1
Comorbidity		
Stroke		
No	1	1
Yes	1.65 (1.04-2.64)	1.84 (1.14-2.96)
Hypertension		
No	1	1
Yes	1.07 (0.85-1.34)	1.02 (0.77-1.25)
Diabetes		
No	1	1
Yes	1.09 (0.79-1.51)	1.03 (0.74-1.36)
Heart disease		
No	1	1
Yes	1.17 (0.83-1.65)	1.14 (0.80-1.63)
Chronic kidney disease		
No	1	1
Yes	2.19 (1.04-4.61)	2.32 (1.10-4.88)
Cancer		
No	1	1
Yes	2.29 (1.35-3.88)	2.47 (1.46-4.20)

*Adjusted for all variables in the model.

Previous studies have nearly always been conducted using hospitalized patients, which may limit the number of patients observed and lead to possible selection bias. Therefore, the present population-based data using age- and sex-matched control groups allowed for a better validation of the results than the data obtained in previous studies. Additionally, our cohort study design using nationwide claims-based data allowed us to examine the temporal association between RA and depression risk.

Our study suggests that RA patients have a 74% increased risk of depression compared with similarly aged control subjects in a general population, which is in agreement with the results of prior studies conducted in Western populations (9,12,13,25). Possible explanations for our results include the following. First, RA is a chronic, unremitting disease with no known cure. Severe RA can cause progressive functional impairments that affect community involvement, work, family life and social and recreational activities. These effects may lower the patient's self-esteem and self-efficacy thereby inducing a higher risk for depression (26). Second, the debilitating and continuous physical RA symptoms may trigger "learned helplessness" cognitions, such that one's inability to successfully cope with physical deterioration and life-threatening situations results in increased levels of uncertainty, unpredictability and

ultimately, emotional distress and depression (27). Third, the symptoms manifested by RA are directly associated with experiencing chronic pain and the latter has been linked to increased levels of depression (28). Fourth, tumor necrosis factor- α (TNF- α) and interleukin 1 (IL-1) are the pivotal cytokines involved in RA (29) and these pro-inflammatory agents have been considered as pathogenic factors associated with the mechanism of developing depression (26,30). In fact, a meta-analysis of 22 studies indicated that inflammatory cytokines may regulate adult neurogenesis to induce hippocampal neurogenesis atrophy, which has been implicated as a key contributing factor in the pathophysiology of depression and is a target of novel treatment strategies (31).

The incidence of depression among RA patients in our study was lower than that in a previous report (11.80/1,000 PYs vs. 55.0/1,000 PYs) (25). This variation may be due to methodological discrepancies such as variations in sample sizes and differences in the assessment tools employed. In this previous report (25), the psychiatric diagnosis of depression was made based on a self-administered questionnaire that assessed symptoms only, which may have reduced the accuracy of the data due to recall bias. In addition, due to their conservative Asian culture, Chinese subjects tend to stigmatize psychiatric illness and seldom discuss or openly seek regular psychiatric treatment for this issue (15). Notably, some studies have reported that <20% of RA patients were treated and referred to appropriate psychiatric services after the onset of the disease (19,32). Therefore, it is imperative to implement a standard care process that identifies those groups with a higher predisposition for developing depression in an effort to provide early referral to psychiatric treatment.

With respect to the correlates of depression, the findings from the multivariate analysis indicated that age is positively correlated with the risk of depression. One possibility is that older RA patients have other age-associated functional declines that might aggravate their psychological distress. However, this result is inconsistent with findings reported in 3 other studies (13,14,33). Such conflicting findings may be due to differences among the participants and designs of the various studies. For example, the participants in the latter studies were Westerners, who may have been more open to discussing psychiatric disorders. This openness could possibly have lessened or moderated the effect of age on the risk of depression. Furthermore, most prior studies were conducted using a cross-sectional design that made it difficult to reach clear conclusions. The retrospective cohort-controlled design employed in our study allowed us to make more reliable conclusions concerning the relationship between age and depression among RA patients.

Our study revealed that females are 1.78-fold more likely to suffer from depression than males, which was consistent with the findings of previous reports (12,30). A possible reason for this finding is that women have been shown to be more health-conscious than men and more likely to pursue treatment at the earliest sign of medical irregularity (34), thus increasing the probability of detecting depression. Our results, however, are inconsistent with those of other studies showing only a marginally increased rate of depression in female RA patients (20,32). The contradictory results in these former studies may be due to the low statistical power



resulting from small sample sizes, with only 113 and 200 participants recruited per study.

Regarding the effect of comorbidity on the risk of depression, the present study showed that RA patients with certain comorbidities, including chronic kidney disease, stroke or cancer, have a significantly greater risk of depression. RA patients with hypertension, diabetes mellitus and heart disease showed a tendency to develop depression, but the association failed to reach statistical significance. Despite the lack of comparative studies on the effects of comorbidities, our findings are, nevertheless, in agreement with arguments made in the literature (30) suggesting that comorbidities among RA patients may be associated with a predisposition for developing depression. We speculate that the comorbidities accompanying RA might negatively affect the patients' perceptions of their health status or reduce their ability to withstand therapy-induced side effects and other complications stemming from their condition, thus leading to a higher risk of depression. Furthermore, a recent review article reported that depressive mood may be related to the types of drugs a patient receives such as oncologic medications, corticosteroids or biological agents (35). Therefore, clinicians are encouraged to carefully appraise the effects of a medication prior to using it to treat RA patients with depression. This approach could be beneficial in reducing the risk for depression following an RA diagnosis.

The following limitations merit consideration when considering the findings of this study. First, we did not account for other confounding factors such as the use of tobacco and alcohol, physical activity, body mass index, social networks, religious beliefs and educational level because they were unavailable in the LHID. Accordingly, caution must be exercised when interpreting this study's findings. Nonetheless, a meta-analysis of the depression risk estimate in RA found that RA per se could predict a predisposition toward depression through the activation of pro-inflammatory cytokines (29). Nonetheless, future studies using more specific covariates are recommended to assess whether the present findings can be replicated among other demographically and geographically diverse groups. In addition, the relationship of depression prognostic outcomes among RA patients should be considered. Second, inaccurate diagnoses may have occurred. To minimize this error, we selected subjects with RA or depression only after they were recorded to have at least 2 outpatient visits reporting consistent diagnoses or one inpatient admission. Furthermore, the Taiwan NHI randomly samples claims from hospitals, interviews patients and reviews medical charts to verify the accuracy of medical records. Third, as data regarding RA severity were not available in this claims database, failure to adjust for this factor might have biased the results. However, the multivariate analysis applied considered the impact of several comorbidities with physical impairments, including hypertension, stroke, DM, heart disease, CKD and cancer. Furthermore, we conducted a sensitivity analysis limited to RA subjects without comorbidities and found that these patients with RA still had a significantly higher incidence rate and aHR of depression (11.51 *vs.* 6.49 per 1000 PYs; aHR: 1.78). Thus, the impact of disease severity is unlikely to compromise the results of this study. Despite these methodological concerns, this population-based, retrospective cohort study provides useful information on the

relationship between RA and the subsequent risk of depression among Chinese patients.

In conclusion, this study demonstrates that the RA patients evaluated were 1.74 times more likely to be diagnosed with depression than the general population after adjusting for several potentially influential covariates. The factors leading to an increased risk of depression among RA patients included being female and older, as well as having certain comorbidities such as stroke, chronic kidney disease and cancer. The data from this population-based study allow healthcare providers to further understand the demographic and disease characteristics that may provoke depression among RA patients. The need to routinely observe patients for signs of depression and to institute culturally appropriate interventions should be emphasized.

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■ AUTHOR CONTRIBUTIONS

Lin MC was involved in the study design and participated in providing comments on the manuscript drafts. Guo HR helped in the design of the study, interpretation of the data and manuscript drafting and review. Lu MC contributed to the data analysis and revised the manuscript. Livneh H contributed to the interpretation of the data and provided comments on the final manuscript draft. Lai NS provided administrative support and comments on the manuscript drafts. Tsai TY was responsible for the study conception and design, data analysis, and manuscript drafting.

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