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Does depression increase the risk of stroke in patients with rheumatoid arthritis? A population-based cohort study

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ABSTRACT

Objectives: Comorbid depression is common and undertreated in patients with rheumatoid arthritis (RA). It remains uncertain whether comorbid depression provoked the risk of poor clinical outcome, stroke in particular, among patients with RA. This work aimed to determine if depression onset during the treatment process increases stroke risk for patients with RA as compared with those with (1) neither RA nor depression, (2) RA only and (3) depression only.

Design: A nationwide, population-based cohort study.

Setting: Taiwan's Longitudinal Health Insurance Database.

Participants: We identified 8045 subjects with a newly diagnosed RA between 1997 and 2010, together with 32 600 subjects without RA matched by age, gender and index date. All subjects were further divided into four groups based on whether they were diagnosed with comorbid depression during the follow-up period.

Main outcome measure: The incidence rate and HR for incident stroke were estimated by the end of 2012 using Cox proportional hazard regression.

Results: We discovered that patients with RA with the comorbid depression exhibited the highest risk of stroke, with an adjusted HR of 2.18 (95% CI 1.87 to 2.54). Those with RA only or those with depression only still had the higher risk of stroke by 43% and 57% as compared with subjects without either condition. Multivariate analysis showed RA subjects who were male or older, incurred the onset of depression, or had comorbidities such as hypertension, diabetes as well as heart disease, had a greater risk of stroke.

Conclusions: This study cleared up the significant association between RA and the subsequent risk of stroke, and further highlighted that the onset of depression within the treatment process may increase stroke risk for RA subjects. Findings could assist healthcare providers to pinpoint individuals with RA with a higher predisposition of stroke, which could facilitate the provision of appropriate rehabilitation.

Strengths and limitations of this study

- The main outcome measures employed in this work are validated due to the application of population-based cohort study, based on a nationwide claim database, thus decreasing recall and selection bias.
- This is the first report to clarify the effect of comorbid depression on the stroke risk among rheumatoid arthritis subjects, which was beneficial for healthcare providers in guiding more effective treatment strategies to improve the clinical outcomes for them.
- Misclassification of diseases and failure to adjust for disease severity might lead to somewhat skewed findings.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease manifested as long-term joint damage, chronic debilitating pain and premature mortality. This disease often affects people 30–50 years of age and results in disability and inability to work, thus posing a heavy burden on patients with RA, their families and the healthcare system.[1] A review of the financial burdens of RA in the USA showed that the annual direct medical costs of RA reached about $9 billion, and the total societal costs (the sum of direct and indirect costs) were estimated to exceed $39 billion.[2]

Despite improvements in the diagnosis and treatment of RA, patients with RA still have a lower life expectancy (6–7 years) when compared with the general population.[3] This increased mortality is primarily due to cardiovascular diseases such as myocardial infarction (MI) or stroke.[4–6] Nevertheless, unlike the studies of RA predicting the onset of MI,[4 7 8] evidence for an association between RA and the development of stroke remains conflicting. A meta-analysis of 15 articles indicated that individuals with RA had a 63% higher risk for MI, but not for stroke (OR=1.14, 95% CI 0.86 to 1.51) when compared with the general population.[4] On

the other hand, a recent Danish study involving 18 247 patients with RA, who were followed for a median of 4.8 years, indicated that those with RA had a 30% higher risk of stroke than a non-RA group.[9] Another meta-analysis of 17 studies reported that patients with RA had a higher predisposition to develop stroke than did non-RA subjects, with a pool risk of 1.91.[8]

One cause for concern is that the former studies did not consider the effect of accompanying psychological factors on the risk of stroke; depression, in particular, which is often underdiagnosed and undertreated.[10] Depression, a well-documented comorbidity among people with chronic diseases, specifically arthritis, may exacerbate functional disabilities, affect adherence to treatment and be a barrier to self-care and self-management behaviours.[11] A recent meta-analysis estimated that the prevalence of depression among patients with RA ranges from 14.8% to 38.8%,[12] and findings from our previous study indicated that patients with RA were nearly twice as likely to experience depression as the general population.[13] Indeed, once patients with RA suffered from concomitant depression, they had a 7.2% increase in medical costs ($12 225 vs $11 404),[14] and their likelihood of mortality more than doubled.[11] Given the alarming rate of depression and the corresponding physical burden on patients with RA, it is imperative to implement effective therapeutic interventions to achieve more favourable therapeutic outcomes, thus serving to extend the life expectancy of patients with RA. Notably, based on former research, the activation of innate inflammatory mechanisms that accompany depressive mood was assumed to affect the susceptibility to development of cardiovascular diseases in addition to the influence of behavioural factors,[15–18] implying that the causative role of depression should not be neglected as determining the association of RA with stroke.

With this growing evidence on the association between RA and subsequent risk of stroke, and the limited information on whether depression serves as a potential factor that affects the relationship between these two conditions, findings from a long-term population-based nationwide study could be useful in allocating medical resources and in instituting fact-based policymaking. Nevertheless, to date, no clinical observations or empirical data have documented this concern. The aim of this cohort study therefore was to determine if patients with RA with the comorbid depression were at an increased risk for stroke as compared with those with (1) neither RA nor depression, (2) RA only and (3) depression only, using claims data from the National Health Insurance (NHI) of Taiwan.

METHODS

Data sources

The data analysed in this cohort study were retrieved from the Longitudinal Health Insurance Database (LHID), maintained by the Bureau of NHI (BNHI) and provided to scientists in Taiwan for research purposes. Taiwan launched a single-payer NHI programme in 1995 in order to remove financial barriers to medical care for all legal residents. At the end of 2010, more than 99% of Taiwan's population had enrolled in this programme.[19] The LHID is a subset of the NHI database, and contains comprehensive usage and enrolment information for one million randomly selected NHI beneficiaries, representing 5% of all enrolees in Taiwan in 2000. As a multistage stratified systematic sampling method was used for this study, there were no statistically significant differences regarding gender or age between the sampled group and the total number of enrolees.[19] This study complied with the guidelines of the Declaration of Helsinki and was approved by the local institutional review board. As the LHID data files contained only de-identified secondary data, the need for informed consent from individual patient consent was waived by the institutional review board.

Study subjects

Diagnoses in the 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 patients with RA in the age bracket of 20–90 years, and newly diagnosed patients between 1997 and 2010. Those who were diagnosed with an ICD-9-CM code of 714.0 comprised the RA cohort. To improve the diagnostic accuracy, we selected only those who had at least three outpatient visits for RA treatment or those patients who were admitted to the hospital with a primary diagnosis of RA during the study period.[13] The year when a patient was newly diagnosed with RA was defined as the index year.

For each case of RA, we randomly selected, from the remaining insured population without RA, four control subjects who were frequency matched to the RA case in terms of gender, age and index year. After the exclusion of subjects with a diagnosis of depression (ICD-9-CM 296.2, 296.3, 300.4 or 311) or stroke (ICD-9-CM 430-438) before the index date, a total of 8045 patients with RA and 32 600 non-RA subjects were included in the data analysis. Occurrence of stroke or depression was defined based on a criterion that indicated at least three outpatient service claims, or at least one inpatient hospitalisation claim, since 1996, when the computerised claims from the LHID became available, until the date of cohort entry. Thereafter, all subjects were followed up until the end of 2012 to measure the incidence of stroke. Only verified strokes that occurred 1 year following the first diagnosis of RA were included in order to render the temporal link between RA and stroke more plausible. We further stratified the RA cohort into two groups based on whether they were diagnosed with comorbid depression between the index date and the follow-up period. In accordance with the same rationale, the non-RA cohort was divided into two groups based on the existence (or non-existence) of

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 stroke, the date of withdrawal from insurance or 31 December 2012, whichever came first.

Demographic characteristics and comorbid conditions

Demographic characteristics analysed in this study included age, gender, monthly income and level of urbanisation of the subject's employment or residential area. Monthly income was grouped into three levels: ≤17 880 New Taiwan Dollars (NT$), 17 881–43 900NT$ and ≥43,901NT$. All 316 cities and townships in Taiwan were classified into seven ordered levels of urbanisation based on various indicators including population density, proportion of residents with college or higher education, percentage of elderly (> 65 years of age) people, proportion of the workforce in agriculture and number of physicians per 10^5 people.[20] Level 1 refers to the 'most urbanised' and level 7 refers to the 'least urbanised' areas. The level of urbanisation was further divided into three strata: urban (levels 1–2), suburban (levels 3–4) and rural (levels 5–7) areas. Baseline comorbid conditions for each subject included hypertension (ICD-9-CM 401-405), diabetes (ICD-9-CM 250), heart disease (ICD-9-CM 410-429), chronic kidney disease (ICD-9-CM 585), tobacco use (ICD-9-CM 305.1), alcohol dependence syndrome (ICD-9-CM 303) and cancer (ICD-9-CM 140-208). The frequency of ambulatory care visits within the study period for each subject was considered to correct for surveillance bias.

Statistical analysis

Intergroup differences were evaluated using the independent-sample t-test or non-parametric Kolmogorov-Smirnov test for continuous variables and the χ^2 test or Fisher exact test for categorical variables. The incidence rate of stroke in the four groups is presented as the number of cases per 1000 PYs. To assess the risk of developing stroke across the four groups, Cox proportional hazards regression model was applied to compute the crude and adjusted HRs and the 95% CIs for stroke among them. We also performed a sensitivity analysis to test the robustness of the findings using asthma, a disease not related to stroke, to replace depression. Finally, a multivariate Cox proportional hazards regression model was then used to identify risk factors that might be related to the incident of stroke and their adjusted HRs within RA cohorts. All analyses were conducted using SAS V.9.3 (SAS Institute, Cary, North Carolina, USA), and p<0.05 was considered statistically significant.

RESULTS

Table 1 shows the distribution of demographic data and comorbid medical disorders for the RA and non-RA cohorts. The RA cohorts were more likely to have a lower monthly income (p=0.001), reside in a rural area (p<0.001), have more visits seeking medical care (p<0.001) and suffer comorbid conditions including hypertension, diabetes, heart disease, chronic kidney disease or alcohol dependence syndrome (all p<0.01).

Of the total sample of 40 645 patients, 4550 had an incident stroke during the follow-up period. The crude and adjusted HRs for stroke in patients with depression only, RA only and both as a group are shown in table 2. Overall, after adjustment for potential confounders, relative to those with neither RA nor depression, subjects with RA and depression exhibited the highest risk of developing a stroke, with an adjusted HRs of 2.18 (95% CI 1.87 to 2.54), followed by those with depression (adjusted HRs=1.57, 95% CI 1.41 to 1.75) and those with RA only (adjusted HRs=1.43, 95% CI 1.12 to 1.55).

Table 3 presents Cox regression model of factors related to the onset of stroke among individuals with RA. Compared with those without depression, those with depression were significantly more likely to develop a stroke (adjusted HRs=1.63, 95% CI 1.37 to 1.92) after adjustment for confounding factors. Results also showed that age was related to the risk of stroke. There was a 5% increase in the risk of stroke for each 1-year increment (95% CI 1.03 to 1.08). Compared with female subjects, male subjects had adjusted HRs of 1.17 for stroke (95% CI 1.03 to 1.28). Additionally, some comorbid conditions including hypertension, heart disease and diabetes increased the risk of stoke with adjusted HRs of 1.51 (95% CI 1.40 to 1.84), 1.48 (95% CI 1.31 to 1.73) and 1.34 (95% CI 1.16 to 1.56), respectively.

In the sensitivity analysis, we compared the risks of stroke across three groups: reference, RA only and RA with asthma. We found that the RA with asthma group had an adjusted HR of 1.18 with a 95% CI of 0.89 to 1.34, which is not statistically significant. This indicates the validity of our methodology.

DISCUSSION

Previous studies of the association between RA and the risk of stroke using hospital-based/community-based populations yielded mixed findings.[4 8 9 21] It is noteworthy that these studies essentially ignored the effect of accompanying depressive symptoms, a common psychological problem among patients with RA, on the relationship between the two diseases. To the best of our knowledge, this was the first population-based, nationwide study which attempted to determine if depression modified the association between RA and stroke, and could therefore help to facilitate the provision of more appropriate interventions to successfully manage rheumatological disorders and prevent the subsequent risk of cardiovascular diseases.

This 15-year follow-up study found that individuals with RA had a 43% greater adjusted risk of stroke when compared with the general population. These findings are in agreement with the results of prior studies

Table 1 Demographic data and comorbidity comparison of the study subjects

Variables	Non-RA cohort N=32 600 (%)	RA cohort N=8045(%)	p Value
Age (years)			0.85
≤40	5378 (16.5)	1331 (16.5)	
41–60	15 569 (47.8)	3814 (47.4)	
60+	11 653 (35.7)	2900 (36.0)	
Mean±SD	55.00±14.63	55.01±14.65	0.94
Gender			0.95
Female	22 461 (68.9)	5540 (68.9)	
Male	10 139 (31.1)	2505 (31.1)	
Monthly income			<0.001
Low	15 218 (46.7)	3513 (43.7)	
Median	15 985 (49.0)	4213 (52.4)	
High	1397 (4.3)	319 (4.0)	
Level of urbanisation			<0.001
Urban	18 839 (57.8)	4485 (55.7)	
Suburban	5311 (16.3)	1258 (15.6)	
Rural	8450 (25.9)	2302 (28.6)	
Comorbidity			
Hypertension	5965 (21.2)	2216 (27.6)	<0.001
Diabetes	2717 (9.6)	1046 (13.0)	<0.001
Heart disease	3054 (10.8)	1273 (15.8)	<0.001
Chronic kidney disease	264 (0.9)	123 (1.5)	<0.001
Cancer	959 (3.4)	268 (3.3)	0.75
Alcohol dependence syndrome	30 (0.1)	18 (0.2)	0.002
Tobacco use	36 (0.1)	10 (0.1)	0.74
Visits seeking medical care			
Mean±SD (median, 25th–75th centile)	234.55±194.08 (185, 97–319)	159.90±155.87 (114, 52–219)	<0.001

RA, rheumatoid arthritis.

Table 2 Crude and adjusted HRs of stroke for those with RA and comorbid depression, those with RA only and those with depression only as compared with those with neither RA nor depression.

Patient group	Event	PY	Incidence	Crude HRs (95% CI)	Adjusted HRs* (95% CI)
Non-RA cohort					
Neither RA nor depression (n=29 925)	3063	245086.81	12.50	1.00	1.00
Depression only (n=2675)	377	24540.32	15.36	1.23 (1.11 to 1.37)	1.57 (1.41 to 1.75)
RA cohort					
RA only (n=6909)	929	55223.83	16.82	1.35 (1.25 to 1.45)	1.43 (1.12 to 1.55)
RA and depression (n=1136)	181	9901.31	18.28	1.48 (1.26 to 1.71)	2.18 (1.87 to 2.54)

*Adjusted for age, gender, level of urbanisation, income, visits seeking medical care and comorbidity.
PY, per 1000 person-years for incidence rate; RA, rheumatoid arthritis.

conducted in Western populations.[8 9] It has been argued that rheumatologic disorders are an overlapping group of conditions that are characterised by chronic inflammation involving connective tissues and organs.[1 6 16] Once inflammation occurs in the body, the vascular endothelial cells secrete proinflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) or interleukin (IL)-6, which activate and attract massive numbers of white cell counts to the damaged region within the lumen of the vessel. Following infiltration into the tunica media, white cell counts absorb oxidised low-density lipoproyein (LDL-C) and become foam cells, consequently accelerating the risk of thromboembolism.[18] In addition, a growing body of evidence has shown that inflammatory cytokines stimulate the production of matrix metalloproteinases as well, and this may cause further injury to the blood–brain barrier, thereby provoking a greater susceptibility to stroke.[22 23]

A noteworthy feature of the current study herein was that once patients with RA were diagnosed with comorbid depression during the treatment process, they exhibited more than double the likelihood of stroke than the general population. We speculate that there are several potential reasons as to why depression

Table 3 Multivariate analysis of factors for the incidence of stroke among patients with RA

	Cox regression model (n=8045)	
Variables	Adjusted HRs*	95% CI
Depression		
No	1	
Yes	1.63	1.37 to 1.92
Age	1.05	1.03 to 1.08
Gender		
Female	1	
Male	1.17	1.03 to 1.28
Monthly income		
Low	1	
Median	0.97	0.85 to 1.10
High	0.85	0.58 to 1.26
Level of urbanisation		
Urban	1	
Suburban	1.10	0.92 to 1.30
Rural	1.06	0.92 to 1.22
Comorbidity		
Hypertension		
No	1	
Yes	1.51	1.40 to 1.84
Diabetes		
No	1	
Yes	1.34	1.16 to 1.56
Heart disease		
No	1	
Yes	1.48	1.31 to 1.73
Chronic kidney disease		
No	1	
Yes	1.02	0.76 to 1.30
Cancer		
No	1	
Yes	1.12	0.84 to 1.47
Visits seeking medical care	0.99	0.98 to 1.01

*Adjusted for all variables in the model.
RA, rheumatoid arthritis.

exacerbates the risk of stroke in these patients. First, the presence of symptoms of depression is likely linked to treatment non-adherence and an increase in unhealthy lifestyles, such as poor nutrition and physical inactivity, and these may contribute to the development of a stroke.[15] Second, symptoms of depression can cause systematic inflammation that worsens the manifestations of RA. Recent studies demonstrated that depressed individuals with RA had higher circulating levels of inflammatory markers such as IL-6, TNF-α and C reactive protein (CRP);[10] all of which play key roles in the pathogenesis of stroke.[18] Additionally, recent research have focused on another signalling pathway, namely, gut-to-brain communication, which suggested that intestinal dysfunction induced by negative moods may cause the activation of immune cells and the production of cytokines in the gut as well, thereby inducing the expression of inflammatory markers, which in turn induce initiation and progression of neurological disorders.[24 25] It is also noteworthy that only one in five patients with depression is estimated to have been treated and referred to appropriate psychiatric services after the onset of RA.[26] The implementation of a standardised psychosocial assessment, and of patient care procedures, as part of routine care, may therefore help in the early referral of high-risk patients for further therapeutic interventions.

This study also indicated that male subjects were at a 1.17-fold greater risk of stroke than female subjects in the RA cohorts. No previous study has examined gender differences in the risk of stroke among patients with RA, which renders a comparison of results impossible. Nevertheless, this is consistent with the observation that male subjects have a higher risk of stroke than female subjects among the general population.[27] There are several possible explanations for this result. First, women appear to have greater health consciousness with regard to stroke prevention than men, and immediately seek medical therapy at the slightest irregularity in well-being, so the onset of chronic diseases may be expected to be lower in women than in men.[28] Second, lifetime exposure to ovarian oestrogens may protect against the risk of stroke for female subjects. Extensive animal experiments and human studies have supported the function of oestrogens as neuroprotectants against neurodegenerative diseases, particularly stroke, through enhancing basal release of nitric oxide to curb coronary thrombosis and atherosclerosis.[27 29] Recently, oestrogenic agents have been suggested as a novel therapeutic approach to treat the neuronal damages associated with global ischaemia.[27 30]

Consistent with the findings of prior studies conducted in the general population,[16 27] age was positively correlated with the risk of stroke among patients with RA. We speculate that with ageing, blood vessels gradually lose elasticity and gain resistance, slowing the flow of blood. Moreover, with poor circulation, fat is prone to accumulate in the abdomen and release free fatty acids into the serum, leading to higher insulin resistance, elevated serum triglycerides and increased levels of LDL-C,[31] thereby resulting in the greater risk of stroke.

Findings of this study indicate that patients with RA and several comorbid conditions such as hypertension, diabetes or heart disease had a significantly greater risk for stroke. Those with chronic kidney disease and cancer showed a tendency for stroke, but the association failed to reach statistical significance. Despite the lack of comparative studies on the effects of comorbid conditions on stroke among patients with RA, our findings are consistent with past arguments made in the literature.[6] The elevated risk of stroke may be attributed to several causes. For example, insulin resistance and hypertension are common cardiovascular risk factors among individuals with RA.[32] Moreover, the functional impairment induced by comorbid conditions may lead to limited physical activity which could, very likely, trigger additional risk of

stroke. Finally, the immunosuppressive therapies used for patients with RA have been found to have deleterious effects. Some review articles indicated that the use of corticosteroids or non-steroidal anti-inflammatory drugs may be related to the risk of cardiovascular events.[6 18] Before prescribing these drugs, rheumatologists should carefully appraise the inherent cerebrovascular or cardiovascular risk among patients with RA.

Several limitations of this study should be considered when interpreting these results. First, we could not account for some potential confounding factors such as social networks, coping modes or educational level because these data were unavailable in the LHID. Future research controlling for those untested variables is needed to better determine if the present findings are replicated across diverse groups of individuals. Second, the identification of exposure and outcome were based on the ICD-9-CM, and misclassification is inevitable. However, we selected only those cases with RA, depression or stroke after they were recorded as having either at least three outpatient visits reporting consistent diagnoses, or one inpatient admission. This approach is likely to minimise such errors. Furthermore, as the approach to coding and the availability of data were similar regardless of the RA and depression status, we believe the misclassification was likely to be random and thus, if indeed occurring, would tend to draw the estimated HRs to the direction of the null values. Second, it should also be noted that the NHI of Taiwan randomly samples claims from hospitals, interviews patients and reviews medical charts to verify the accuracy of medical records. Third, because data regarding the severity of RA were unavailable in these databases. Nonetheless, the multivariate analysis applied in this study considered the impact of several comorbid conditions including hypertension, diabetes, heart disease, chronic kidney disease, tobacco use, alcohol dependence syndrome and cancer. Furthermore, we performed a sensitivity analysis using on those RA subjects without comorbid conditions to test the robustness of our findings and found that depressed RA subjects with no known comorbid condition still had a higher risk of stroke when compared with those without RA and depression, with an adjusted HR of 1.65 (95% CI 1.23 to 2.03). Thus, the impact of disease severity is unlikely to compromise findings of this study. Fourth, evidence derived from any observational cohort study is generally less robust than that obtained from randomised control trials since cohort studies are subject to various biases related to confounding effects. Despite our careful efforts to maintain adequate control of confounding factors, unpredictable biases could still remain if they stem from unmeasured or unknown confounders. Notwithstanding these limitations, the strengths of this study must also be acknowledged and these include the immediate availability of data, the comprehensiveness of the database and the statistical power derived from the samples' large sizes. In addition, this retrospective 15-year cohort study allowed us to clearly determine if the symptoms of depression exacerbated the risk of stroke for those with RA, and the corresponding findings could serve as a reference for future treatment strategies.

In conclusion, this study demonstrated that patients with RA and comorbid depression were more than twice as likely to have a stroke than were those of the healthy controls. We further found that the factors contributing to the high risk of stroke included being male, older as well as having depression and a comorbid condition such as hypertension, diabetes or heart disease. Healthcare providers may therefore be able to better recognise those demographic and diseases characteristics that contribute to the risk of stroke among patients with RA from this population-based study. Findings also supported that the routine screening of depression and the institution of patient-centred interventions may represent an important strategy for improving clinical outcomes for patients with RA.

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Contributors All the authors approved the contents of the submitted article. M-CL and H-RG contributed equally to this work. T-YT and S-YC conceived and designed the experiments. T-YT and H-RG analysed the data. T-YT, N-SL, M-CL and H-RG contributed in reagents/materials/analysis tools. TYT, HL and H-RG wrote the paper. T-YT, N-SL, HL, S-YC, M-CL, H-RG contributed in the final approval of manuscript.

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