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ORIGINAL RESEARCH

Depression Risk in Patients with Rheumatoid Arthritis in the United Kingdom

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) is one of the most common chronic inflammatory diseases. The goal of this study was to analyze the risk of depression in patients diagnosed with RA and treated by general practitioners in the UK.

Methods: The present study included patients first diagnosed with RA between 2000 and 2014 (index date). Individuals were excluded if they had also been diagnosed with depression or if they had received therapy for depression at or prior to the index date. The primary outcome measure was the rate of patients with depression (ICD 10: F32, 33) within 5 years of the RA diagnosis. Demographic data included gender and age. Furthermore, a revised version of the Charlson comorbidity index was used as a generic marker of comorbidity.

Results: A total of 4187 patients were included in the study. After 5 years of follow-up, 23.7% of men and 36.5% of women had developed depression (log rank p value <0.001). Women were more likely to develop depression than men (HR 1.61, 95% CI 1.42–1.84). Age and Charlson comorbidity score had no significant impact on the risk of being diagnosed with this psychiatric disorder.

Conclusion: Around 30% of RA patients developed depression within 5 years of the RA diagnosis. The depression risk was higher in women than in men. The current findings also indicate that improved detection and treatment of patients with both RA and depression are important.

Keywords: Depression; Rheumatoid arthritis; Risk factors; United Kingdom

INTRODUCTION

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory diseases [1, 2]. RA can affect joints, connective tissues, muscles, tendons, and fibrous tissues [3]. This disorder has a prevalence of 0.3–1% and is known to be more common in women and in developed countries [2]. In the United Kingdom (UK), at least 1.16% of women and 0.44% of men were found to be affected by RA [4].

Rheumatoid arthritis is considered a chronic condition and has a major impact on the quality of life of patients [5], thus underlying the

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importance of personalized management and treatment of people affected by this disease. In 2013, Matcham and colleagues discovered in a systematic review and meta-analysis that the prevalence of major depressive disorder was around 17% in patients diagnosed with RA [6]. They further estimated that this prevalence was significantly associated with age, with younger patients being at a higher risk of developing depression than older patients. Some have reported that gender is a risk factor for the development of depression in individuals diagnosed with RA. In 2005, Ramjeet et al. estimated that women with recent-onset inflammatory polyarthritis exhibited higher levels of anxiety and depression than men [7]. However, Mostafa and Radwan later found no significant relationship between gender and depression in RA patients [8]. Finally, a Taiwanese study showed that women with RA had a greater risk of depression than men with RA [9].

Since these findings are controversial, we decided to analyze the risk of depression in patients diagnosed with RA and treated by general practitioners (GPs) in the UK.

METHODS

Database

The Disease Analyzer database (IMS HEALTH) compiles drug prescriptions, diagnoses, and basic medical and demographic data obtained directly and in anonymous format from computer systems used in GP practices [10].

This database recorded multiple patient characteristics (e.g., age, gender) and comorbidities (e.g., myocardial infarction, stroke, cancer, diabetes) with sufficient data to allow the calculation of the Charlson index, which examines 22 comorbidities and demographic factors (see below).

Diagnoses (ICD-10), prescriptions (Anatomical Therapeutic Chemical (ATC) Classification System), and the quality of reported data are monitored by IMS based on a range of criteria (e.g., completeness of documentation, linkage between diagnoses, and prescriptions).

In the UK, the sampling methods used to select physicians' practices were appropriate to obtain a representative database of people with RA [10]. The sampling method for the Disease Analyzer database is based on statistics from all doctors in the UK. These statistics are used to determine the panel composition according to the following strata: region, community size category, and age of physician.

Study Population

Patients who were first diagnosed with RA (ICD-10: M05, M06) between 2000 and 2014 were included in the present study. The date of first RA diagnosis documentation by a GP was considered the index date. Individuals were excluded if they had also been diagnosed with depression based on the ICD-10 criteria (F32, F33) or if they had received therapy for depression (ATC: N06A) at or prior to the index date.

Formal ethical approval was not required for this study according to German law (§15 BOÄ, Medical Association's professional code of conduct), as the study was based on anonymized data. It was not possible to identify individual patients. Therefore, informed consent was not required (nor could it be received).

Study Outcome Measures and Independent Variables

The primary outcome measure was the proportion of patients diagnosed with depression within 5 years of the diagnosis of RA. Patients were followed up from January 2010 until June 2016. Demographic data included gender and age. Furthermore, a revised version of the Charlson comorbidity index (CCI) was used as a generic marker of comorbidity [11]. The Charlson comorbidity index describes 22 comorbid conditions where each condition is assigned a score from 1 to 6 depending on the risk of dying from it. Clinical conditions and associated scores in the CCI are as follows: myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes, hemiplegia, moderate or severe kidney disease, diabetes with end-organ damage, tumor,

leukemia, lymphoma, moderate or severe liver disease, malignant tumor, metastasis, and AIDS [11]. CCI was included in order to estimate if a higher RA patient comorbidity status is associated with a higher risk of depression.

Statistical Analysis

Descriptive analyses were obtained for all demographic and clinical variables, and the mean ± SD was calculated for normally distributed variables. Kaplan–Meier curves were used to analyze the proportion of RA patients diagnosed with depression. The Kaplan–Meier curve is defined as the probability that an event (for example, diagnosis) will occur within a given length of time when time is discretized into many small intervals. It provides a visual representation of this probability in two or more groups. The strength of Kaplan–Meier analysis is that it includes patients who could not be followed for the complete study duration (for example, 5 years); these patients are assumed to have the same event probability as those who continue to be followed [12, 13]. Finally, a multivariate Cox regression model was created to determine the impact of demographic and clinical variables on the risk of being diagnosed with depression. In a Cox regression model, the parameter of interest is the time until the occurrence of an event (for example, disease). Like Kaplan–Meier analyses, Cox regression analyses also include patients who could not be observed throughout the entire study duration. The Cox regression uses a proportional hazards model to calculate the hazard ratio (HR), which shows the ratio of event probabilities in the two groups [14]. p values <0.005 were considered statistically significant. Analyses were carried out using SAS version 9.3.

RESULTS

A total of 4187 patients were included in this study. The mean age was 59.1 years (SD 17.8 years), and 34.3% were men. The mean Charlson comorbidity score was 1.4 (SD 1.1).

Figure 1 displays Kaplan–Meier curves for the time to depression diagnosis by gender, with 23.7% of men and 36.5% of women developing depression within the 5-year follow-up period (log rank p value <0.001).

Table 1 displays the results of the multivariate Cox regression model. Women were more likely to develop depression than men (HR 1.61, 95% CI 1.42–1.84). Age and Charlson comorbidity score had no significant impact on the risk of being diagnosed with this psychiatric disorder.

DISCUSSION

In the present retrospective study, around 30% of patients developed depression within 5 years of RA diagnosis. We also found a 1.6-fold increase in the risk of developing depression in women compared to men.

RA is a chronic condition that has a substantial impact on health. In 2007, Haroon and colleagues investigated 136 RA patients and 75 age-matched controls and discovered that quality of life was compromised in individuals diagnosed with RA [15]. The authors further found a significant inverse correlation between the activity of the disease and the physical and psychological domains of quality of life. More recently, a 2013 study performed in Brazil estimated that moderate to severe RA was associated with major functional disability and morbidity, with work and activity impairment increasing with disease severity [16].

The impact of RA on depression has been the focus of several works in the past decade. In 2002, Dickens et al. discovered in a systematic review and meta-analysis of the literature that depression was more frequent in individuals with RA than in healthy individuals [17]. This may be partially explained by the levels of pain experienced by RA patients, thus clearly underlying the importance of personalized treatments and management for these patients. In 2013, another meta-analysis of 72 studies that included 13,189 patients found that the prevalence of major depression was 16.8% (95% CI 10–24%) [6]. According to the PHQ-9 test questionnaire, depression prevalence was even

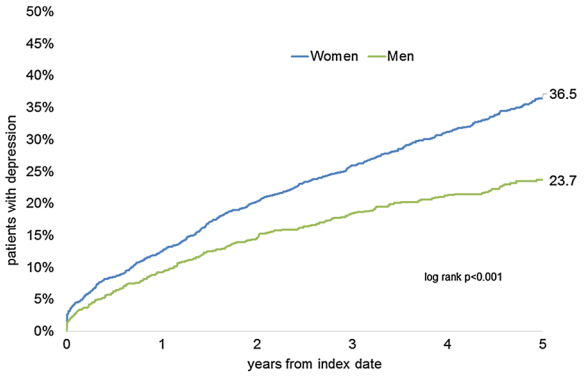

Fig. 1 Kaplan–Meier curves for time to depression diagnosis in newly diagnosed RA patients by gender

Table 1 Association of depression with predefined variables in RA patients: results of the multivariate Cox regression analysis

Characteristics	Hazard ratio (95% CI)	*p* value
Women vs men	1.61 (1.42–1.84)	<0.001
Age ≤40 vs >70 years	0.88 (0.74–1.05)	0.165
Age 41–50 vs >70 years	1.10 (0.92–1.32)	0.298
Age 51–60 vs >70 years	1.14 (0.96–1.34)	0.129
Age 61–70 vs >70 years	0.91 (0.77–1.09)	0.299
Charlson comorbidity index	1.04 (0.97–1.15)	0.159

higher and reached 38.8% (95% CI 34–43%). Finally, the authors showed a significant relationship between mean age and the rate of depression, with lower age being associated with increased rates. In line with these findings, the present study discovered that approximately 30% of patients were depressed within 5 years after the diagnosis of RA.

Such results are of particular concern because depression is known to increase the risk of mortality in RA patients [18]. The identification of predictors of depression in this population is very important and has been the focus of several recent works [19–21]. In 2006, Covic and colleagues estimated that 12 variables correctly classified around 80% of RA individuals into depressed and nondepressed groups [19]. The strongest predictors of this psychiatric condition were high tension, low self-esteem, and the perceived impact of RA. Interestingly, fatigue, passive coping, pain, and physical disability had additional effects on the risk of developing depression. Later, an American study of 172 patients found that disease severity (calculated using the Health Assessment Questionnaire, HAQ) and ethnicity were significantly associated with depression [20]. Finally, Lin and colleagues discovered in 2015 that women, younger patients, and people with comorbidities such as stroke, chronic kidney disease, or cancer were at a particular risk of depression [22]. The present retrospective study, which included more than 4000 patients, also showed that women were more likely to be diagnosed with depression within the 5 years following RA diagnosis compared to men. Recently, the relationship between gender and depression in RA has been the focus of several studies. A 2005 UK analysis including 112 individuals affected by recent-onset inflammatory polyarthritis showed that 36% of the population was at risk of depressive symptoms [7]. Furthermore, it was also found that women displayed higher levels of depression than men, although gender had no impact on levels of disability or pain. Later, Mostafa and Radwan discovered that the prevalence of depression in an Egyptian population with RA was 15.29% [8]. The authors notably found positive correlations between depression and age, disease duration, and disease activity. In contrast, there was no significant association with gender. More recently, it was estimated in a Taiwanese analysis that included 3698 adults newly diagnosed with RA that women, the elderly, and patients with comorbidities were at a higher risk of developing depression than men, younger individuals, and patients free of comorbidities [7, 9]. The association between gender and depression or anxiety in RA might be explained by the fact that men tend to adjust better to their disease than women. Another possibility is that male RA patients are less likely to reveal their depressive symptoms to their doctor than female RA patients. Finally, in the present study, age and comorbidity had no significant impact on depression. This difference may be explained by the fact that the multivariate

regression model was adjusted for inflammation, which is known to play a key role in both depression and RA.

In general, retrospective primary care database analyses are limited by the validity and completeness of the data on which they are based. The present study is subject to the following limitations. The assessment of diagnoses was based solely on ICD codes entered by general practitioners, and no information was available regarding the procedure by which depression diagnoses were made. Information about whether depression diagnoses were made by GPs themselves or by psychiatrists was unavailable. Data on potential confounding variables such as socioeconomic status, marital status, educational level, social support, psychosocial stressors, and lifestyle-related risk factors (body mass index, smoking status, etc.) were also unavailable. Unfortunately, no data on the severity of inflammation were available. The strength of the study is the large number of patients available for analysis. Another strength is the use of real-world data in primary care practices where diagnoses are continuously documented, allowing for unbiased exposure assessment (no recall bias).

CONCLUSIONS

Around 30% of RA patients developed depression within 5 years of the diagnosis of RA. Women had a higher risk of being diagnosed with depression in the 5 years following the index date compared to men.

The current findings also indicate that improved detection and treatment of patients with RA and depression is needed.

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Compliance with Ethics Guidelines. Formal ethical approval is not required according to German law (§15 BOÄ, Medical Association's professional code of conduct), as the study is based on anonymized data. Identification of individual patients was not possible. Therefore, informed consent was not required; nor could it be received.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due data protection rules but are available from the corresponding author on reasonable request.

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