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Original Article

Prevalence of Restless Legs Syndrome in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Restless legs syndrome (RLS) is a common sensorimotor sleep disorder, and rheumatoid arthritis (RA) is an inflammatory autoimmune disease that causes disability. Previous studies showed that the prevalence of RLS varies in different populations of RA (13.2 – 68.4%). It raises the need for a pooled meta-analysis to determine a more reliable estimate. Therefore, we aimed to perform a meta-analysis to assess the pooled prevalence of RLS in RA patients.
Methods: Meta-analysis was performed according to the PRISMA checklist. Embase, MEDLINE, Ovid, Web-of-Science, and Scopus databases were used for the systematic search, and eligible studies were analyzed using R version 4.0.3. For further review, we performed sensitivity analyzes to identify influential studies.
Results: Of a total of 763 studies, 11 studies (3 were from Europe, 4 from North America, and 4 from Asia) were suitable for synthesis. A total of 931 RA patients were identified, 300 of whom had symptoms of RLS. The pooled prevalence of RLS among people with RA from 11 studies was 34% (95% CI: 26-43%). The pooled prevalence of RLS in Europe, Asia, and North America was 48% (95% CI: 32-65%), 32% (95% CI: 18-45%), and 28% (95% CI: 15-42%), respectively. RLS prevalence was dramatically high in RA women patients (32% CI: 23-41%) than RA men patients (3%; 95% CI: 2-5%).
Conclusion: This systematic review and meta-analysis indicates that the risk of RLS in RA patients was 34% and female patients with RA were more prone to having RLS than male patients.

Introduction

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a common sensorimotor sleep disorder whose main feature is the urge to move the legs.[1] Previous literature has extensively discussed the epidemiology of RLS.[2-4] In summary, symptoms worsen with inactivity or rest (especially in the evening or at night). Increasing movement relieves the symptoms partly (or totally). RLS has a prevalence rate of 5-15% in the general

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population, is more common in women, and is associated with conditions such as Parkinson's disease, renal failure, diabetes mellitus, headaches, pregnancy, hypertension, and rheumatoid arthritis (RA). RLS also has significant interaction with the overall aspect of the immune system.[5]

RA is an inflammatory autoimmune disease that causes disability. It typically results in warmth, swelling, muscle wasting, joint involvement, and painful joints.[6] In addition, women are at least 2 times more likely to be affected by RA than men.[6, 7] As of 2015, RA had caused 3,000 deaths[8] and affected 24.5[9] million people worldwide. The cause of RA is unknown, but SOKKA et al. have suggested that inactivity may be an influential factor in the prevalence of RA, which was traditionally known as a treatment to improve rheumatic diseases.[10] Therefore, the association between RLS and RA could probably be explained by the changes in immunomodulation and inactivity in patients.

In the last two decades, several studies have reported the prevalence of RLS in people with RA based on different RLS diagnostic criteria (questionnaire and clinical criteria).[11-21] From these studies, the prevalence of RLS varies in different populations of RA (13.2 – 68.4%). It raises the need for a pooled meta-analysis to determine a more reliable estimate. Therefore, we performed a meta-analysis to assess the pooled prevalence of RLS in RA patients.

Materials and Methods

This meta-analysis was performed according to the PRISMA checklist (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[22]

Search strategy

The five databases (Embase, PubMed, Ovid, Web-of-Science, and Scopus) were systematically searched for the search terms "restless legs syndrome" and "rheumatoid arthritis" through February 2022. The search was limited to humans, with no restrictions on age, date, or language.

Include and exclude criteria

The inclusion criteria for the present meta-analysis were: RLS occurred after the prevalence of RA, it had to be possible to calculate the prevalence of RLS in RA patients, RLS had to be diagnosed by a standard method (questionnaires, clinical criteria, or clinical interviews), and studies had to be observational.

Exclusion criteria included: RA patients without RLS symptoms or vice versa; unrelated publication type (such as letter, correspondence, review, editorial, etc.); incomplete data or inability to calculate the prevalence of RLS in RA patients; diagnosed RLS before diagnosis RA.

Data collection

Two authors (M. Bagherpour-Kalo and P. Darabi) conducted the literature search independently and extracted the data. Disagreements were resolved by a third author (M. Hosseini). First author name, year of publication, country, method of RLS diagnosis, sample size, age of RA patients, number of RA patients with and without RLS, number of RLS and RA by sex, and prevalence of RLS in RA patients.

Statistical analysis

The prevalence of RLS in patients with RA was evaluated by sex and continent using the metafor and meta packages in R version 4.0.3 (https://www.r-project.org). In all analysis, a p-value of less than 0.05 is considered a significant threshold.

We use the Q-test and the I^2 index to assess heterogeneity and homogeneity. The Q-test is used to identify heterogeneity, and $I^2$is a good index to identify the quantified homogeneity of studies. Heterogeneity was considered as homogeneity (I^2<25), low heterogeneity (25%≤I^2<50%), moderate heterogeneity (50%≤ I^2 <75%), and substantial heterogeneity (I^2≥75%)(23). Identifying heterogeneity helps us to use appropriate models (I^2<50%:fixed-effect; I^2≥75%: random-effect) to determine the pooled analysis.[24] Forest plots were used to visually represent the results. We also used Begg's regression test (statistical) and funnel plot (visual) to assess publication bias,[25] and sensitivity analysis was performed by leaving out of each study.

To evaluate the robustness of our findings, we conducted a sensitivity analysis using several methods. We used the leaving out method and Cook's distance to identify any studies that had a particularly strong influence on the results. We also used standardized residuals and other criteria, which are presented in the supplementary file, to check for outliers. After identifying any outliers or influential studies, we refitted the model by leaving them out one at a time to determine the robustness of our results.

Results

Study characteristics

After removing duplicates, a total of 607 unique studies were identified. Of these, 596 studies did not meet all inclusion criteria and were excluded from the meta-analysis (Figure 1).

Of the 11 remaining eligible studies,[11-21] 3 were from Europe, 4 from North America, and 4 from Asia. A total of 931 RA patients were identified, 300 of whom had symptoms of RLS (Table 1). Seven studies diagnosed RLS according to International RLS Study Group (IRLSSG) criteria, and 4 studies used other diagnostic methods. Six studies (599 participants) reported prevalence by sex. Only one or two studies provided information on factors associated with RLS (including age, laboratory indices, family history, etc.). Therefore, no meta-analysis was performed for these factors.

Prevalence of RLS in RA patients

Because of the high heterogeneity (I^2=87%, P < 0.01) among studies, we used a random-effect model based on DerSimonian and Laird method. The result showed that the pooled prevalence of RLS among people with RA from 11 studies was 34% (95% CI: 26-43%; Figure 2).

The funnel plot and Begg's test suggested a significant publication bias in the meta-analysis (Kendall's tau = 0.49, P = 0.040; Figure 3).

The sensitivity analysis showed that two of the studies[3, 15] affected results (Supplementary Figure S1 and Figure S2). When we excluded these two studies, the pooled prevalence of RLS was 29% (95% CI: 22-36%; Supplementary

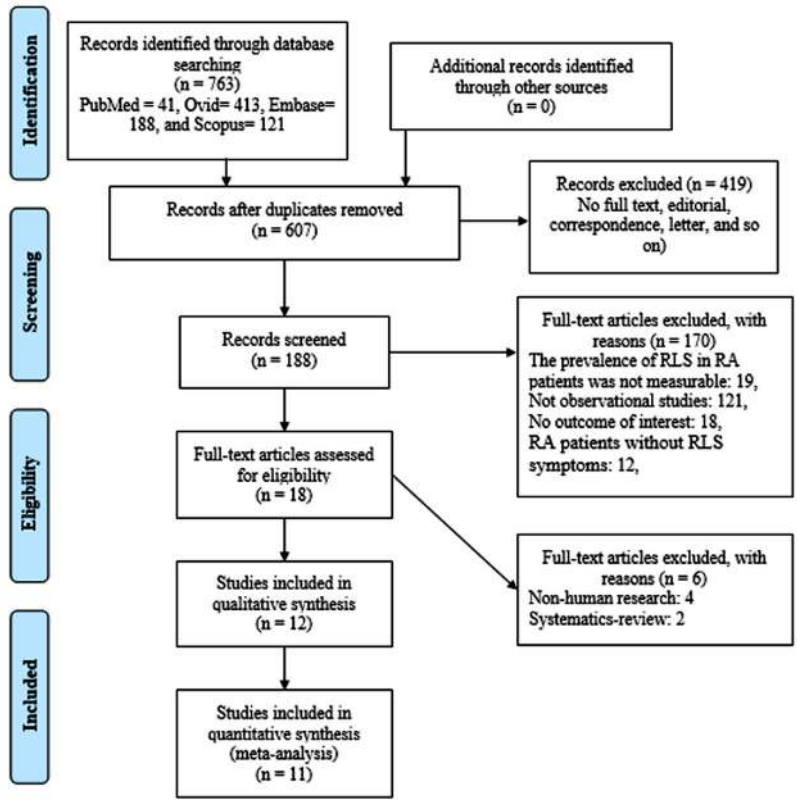

Figure 1. Flow diagram of selecting eligible studies.

Figure S3).

Subgroup analysis

Although we found differences in geographical areas in the prevalence of RLS in RA patients, it was not significant (χ^2 = 3.72, df = 2; P = 0.16). The pooled prevalence of RLS in Europe, Asia, and North America was 48% (95% CI: 32-65%; Supplementary Figure S4), 32% (95% CI: 18-45%; Supplementary Figure S4), and 28% (95% CI: 15-42%; Supplementary Figure S4), respectively.

There were differences in RLS's diagnosis method in the prevalence of RLS among people with RA, but it also was not significant (χ^2 = 0.60, df = 1; P = 0.44). The pooled prevalence with the IRLSSG method was 32% (95% CI: 21-43%; Supplementary Figure S5), and another diagnostic method was 39% (95% CI: 25-54%; Supplementary Figure S5).

A significant sex difference was observed in the meta-analysis, which had a very high prevalence in females (χ^2 = 38.01, df = 1; P < 0.01). In female patients, the pooled prevalence in Europe, Asia, and North America was 44% (95% CI: 33-56%; Figure 4), 25% (95% CI: 20-29%; Figure 4), and 24% (95% CI: 11-37%; Figure 4), respectively, and in male patients, the pooled prevalence in Europe, Asia, and North America was 8% (95% CI: 3-13%; Figure 5), 2% (95% CI: 1-4%; Figure 5), and 5% (95% CI: 0-11%; Figure 5), respectively.

Table 1. Characteristics of the eligible studies.

Study	Country	Diagnosis Method	Sample Size	RLS	Male with RLS	Female with RLS	Male with RA	Female with RA	Prevalence	Ref.
Reynolds (1986)	British	Standard questionnaire	70	21	0	21	10	60	30%	(16)
Salih (1994)	British	Gibb and Lees criteria	87	46	8	38	16	25	52.87%	(17)
Hirsch (1994)	France	Clinical Assessment: duration of morning stiffness (in minutes), number of nocturnal awakenings, number of tender joints, number of swollen joints, Ritchie articular index, and Lee functional index	19	13	1	12	1	18	68.42%	(13)
Yunus (1996)	USA	Standardized questionnaire	54	8	0	8	0	54	14.82%	(21)
Auger (2005)	Canada	Questionnaire based on the IRLSSG criteria.	100	31	NR	NR	35	65	31%	(11)
Regina (2009)	Canada	Questionnaire based on the IRLSSG criteria.	148	41	NR	NR	NR	NR	27.8%	(5)
Ishaq (2013)	Pakistan	Questionnaire based on the IRLSSG criteria.	240	65	5	60	NR	NR	27.08%	(14)
Regina (2014)	Canada	Questionnaire based on the IRLSSG criteria and Physical Activity Monitor	57	23	3	20	9	48	40.35%	(18)
Mustafa (2019)	Saudi Arabia	Questionnaire based on the IRLSSG criteria.	41	26	NR	NR	5	96	63.41%	(15)
Urashima (2020)	Japan	Questionnaire based on the IRLSSG criteria.	43	5	NR	NR	NR	NR	11.63%	(20)
Demir (2021)	Turkey	Questionnaire based on the IRLSSG criteria.	72	21	4	17	13	59	29.17%	(12)

RLS, Restless Legs Syndrome; RA, Rheumatoid Arthritis; IRLSSG, International RLS Study Group

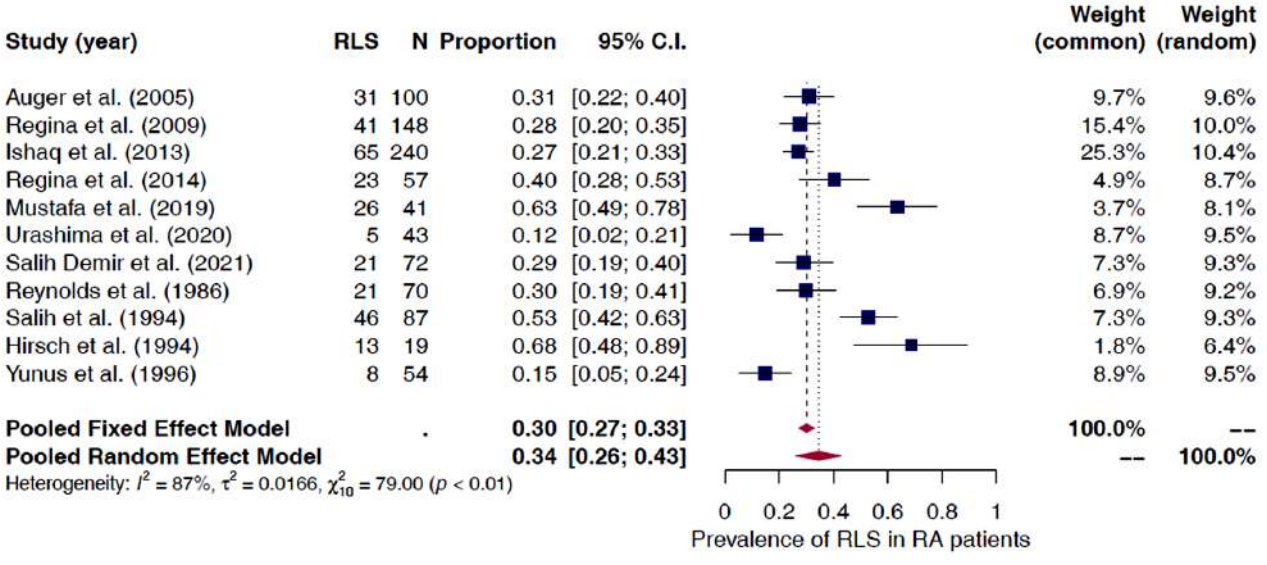

Figure 2. Forest plot of the prevalence of RLS in RA patients.

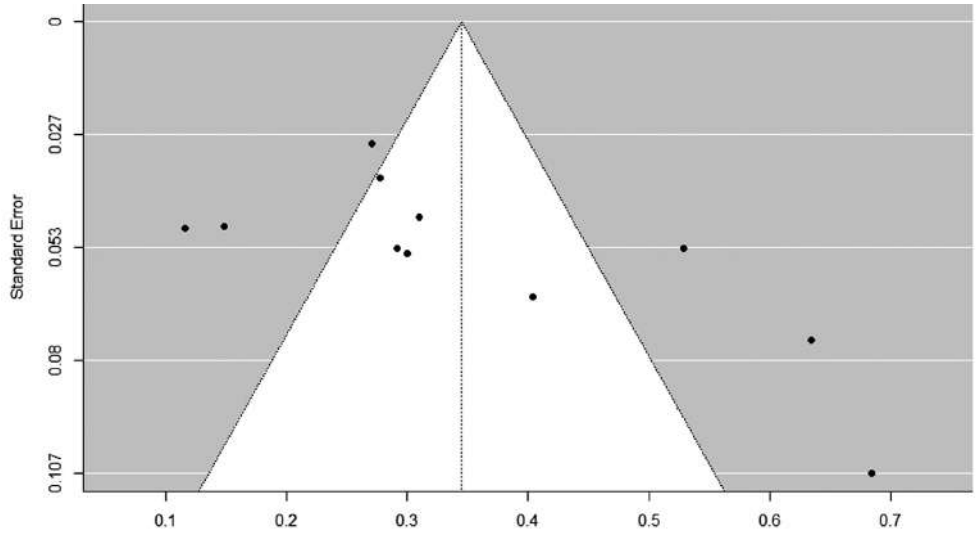

Figure 3. Funnel plot for 11 eligible studies include in meta-analysis.

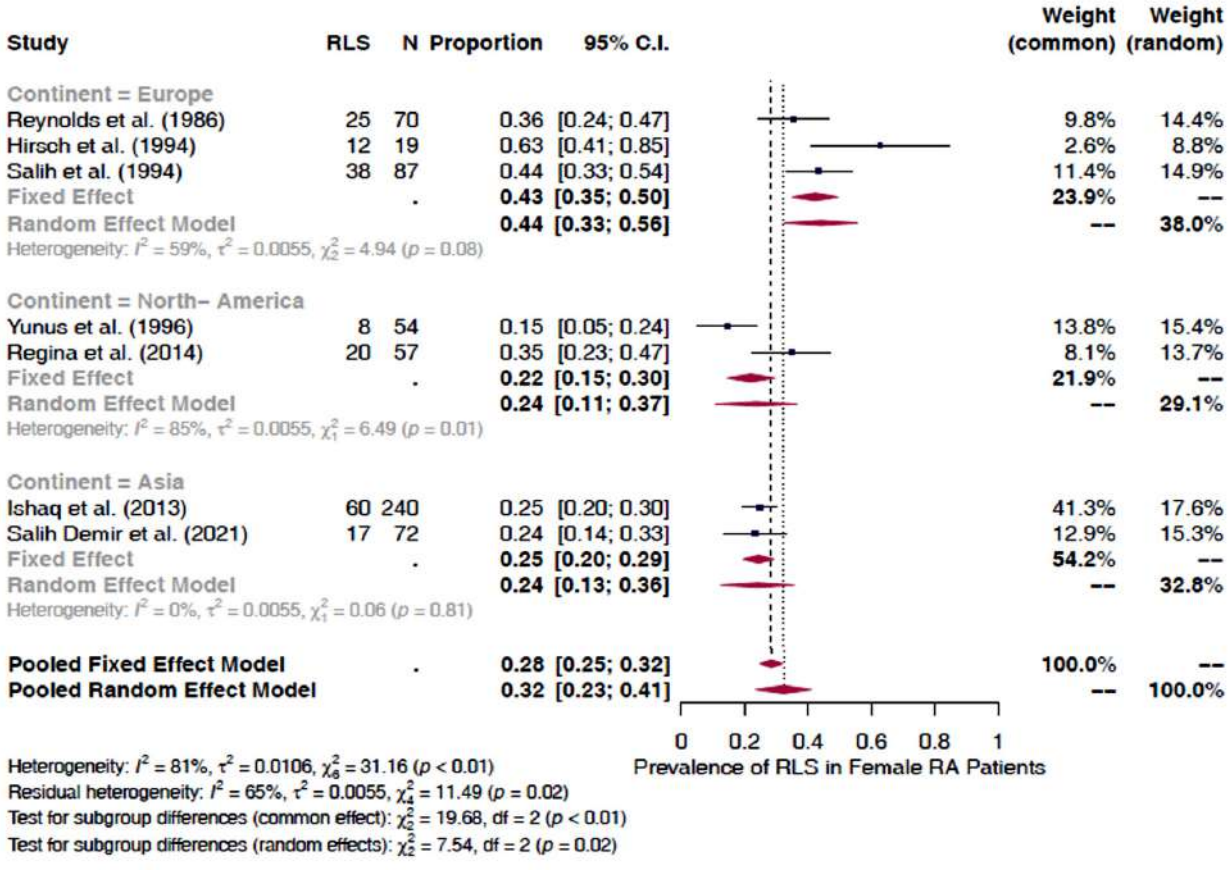

Figure 4. Forest plot of pooled prevalence of RLS in female RA patients.

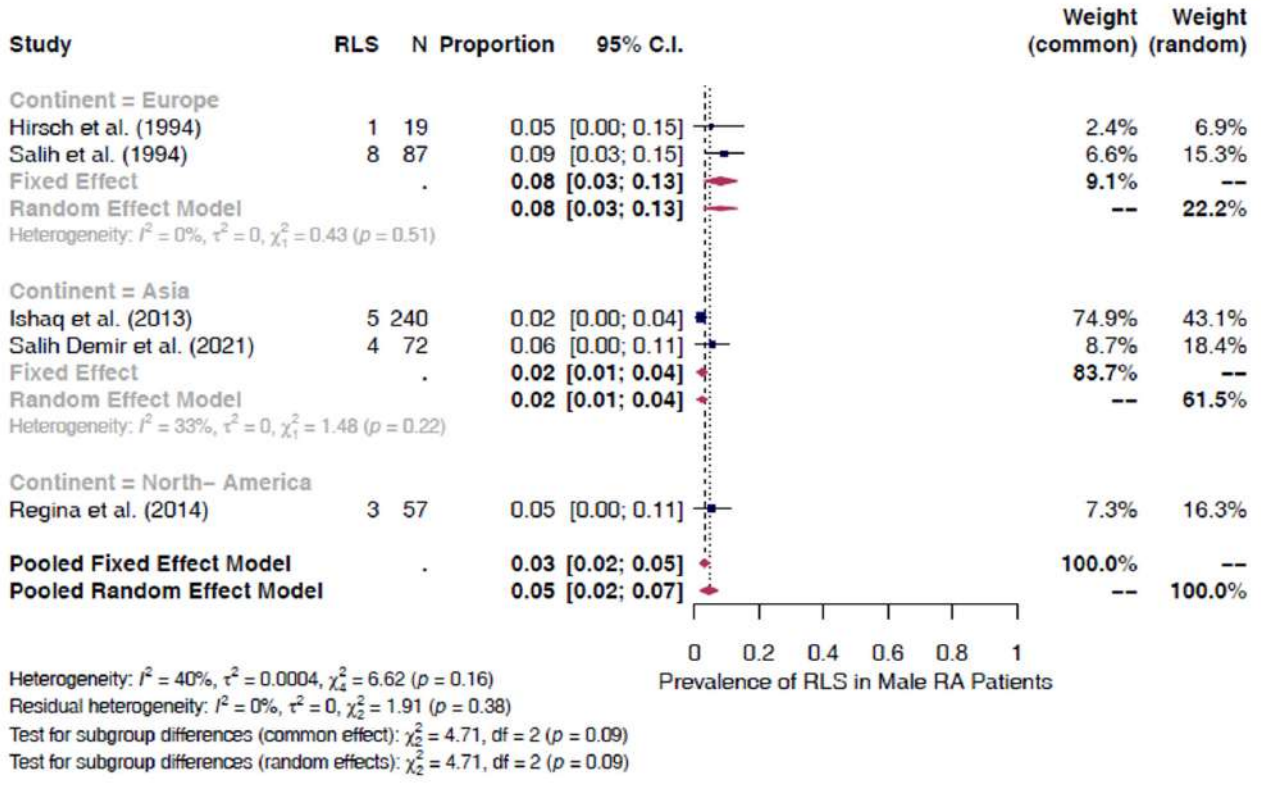

Figure 5. Forest plot of pooled prevalence of RLS in male RA patients.

Discussion

In the present study, due to high heterogeneity, we used a random-effect model to conduct the meta-analysis in 931 rheumatoid arthritis patients, of whom 300 had symptoms of restless legs syndrome.

According to 11 eligible studies, the pooled prevalence of RLS in RA patients was 34% and varied across different geographical areas (the prevalence of RLS among RA patients in Europe was relatively high) and diagnostic methods (the prevalence of RLS among RA patients using the IRLSSG method was low).

One problem that clinicians struggle with is that RLS patients do not visit rheumatology centers out of ignorance. Therefore, the exact cause and pathogenesis of RLS in rheumatoid patients had unknown for many years. For example, Ondo et al., showed in a population of 68 RLS patients that showed that RA does not play a significant role in the pathogenesis of RLS patients.[26]

In the past two decades, efforts have been made to identify risk factors for RLS in RA patients. As a result, fatigue,[12] total iron binding capacity,[12] serum ferritin,[15, 17] sleep quality,[27] periodic limb movements,[18] and hemoglobin[7] were identified as influencing factors. In another study, Taylor-Gjevre et al. examined the sleep parameters of 12 individuals with RA and found that sleep efficiency could be improved by antitumor necrosis factor alpha therapy.[28] Thus, clinicians consider neuropathies to be an important factor in the development of RLS in RA patients.

This meta-analysis also found that an important factor affecting the prevalence of

RLS in RA patient was gender. Compared with men, RLS prevalence was dramatically high in RA women patients ($P < 0.01$). It confirms the findings of previous studies. Berger et al.[29] and Smolen et al.[30] showed that RLS prevalence and RA prevalence were at least twice as high in women in the general population. Therefore, a dominant role of sex hormones could be suspected as the main cause of sex differences. Combining three genome-wide association studies from 2003 to 2017, Schormair et al. showed that MEIS1 is a strong genetic risk factor for RLS.[31] Because MEIS1 interacts with estrogen receptors,[32] this may raise a hypothesis for its differential involvement in RA patients with RLS.

A subgroup analysis showed that RA patients in Europe were more likely to have RLS compared with other geographic areas. The difference could be due to genetics, environment, lifestyle, or race. The previous study aimed to evaluate the association between lifestyle factors and the risk of RLS, suggested that obesity, physical activity, or smoking affect RLS prevalence.

Two strengths of this systematic review and meta-analysis included the following. First, to our knowledge, this is the first study applying meta-analysis to evaluate overall RLS prevalence in RA patients. Second, using sensitivity analysis to reduce the risk of bias and identify influential studies.

This meta-analysis included two limitations. First, few studies have shown the effect of risk factors (such as age, body mass index, and family history) on RLS prevalence among RA patients. The positive and significant impact of these factors on RLS has been shown in previous studies.[29] Accordingly, body mass index (above 30) and family history were seen in at least 28.5%[29] and 50%[33] of RLS patients, respectively. Forasmuch as some other characteristics such as the age of onset, treatment and therapies, and sleep quality were not included in the present meta-analysis. Therefore, evaluate of RLS risk factors in RA patients who suffer from RLS is emphasized. Second, the pooled estimate was affected by publication bias. Therefore, more research is required to examine the variation in detail.

Conclusion

This study indicates that the risk of RLS in RA patients was 34% and female patients with RA were more prone to having RLS than male patients. The pooled analysis provides a reliable estimate of the prevalence of RLS among RA patients. Further studies are needed to understand the association between RA and RLS and clarify the role of various factors among different populations.

Abbreviations

RLS, Restless Legs Syndrome; RA, Rheumatoid Arthritis; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses, IRLSSG, International RLS Study Group;

Authors' contributions

Investigation: MH, MBK, PD;
Pre-processing and conduct analyzes: MBK;
Frame work of paper: MH, MBK, PD;
Writing: MH, MBK, PD;
Approval of manuscript: MH, MBK, PD.

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Competing interests

The authors declare that they have no competing interests.

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