Sleep and Biological Rhythms
https://doi.org/10.1007/s41105-024-00513-4

ORIGINAL ARTICLE

Association between Chronic kidney disease and restless leg syndrome (RLS): a systematic review and meta-analysis

Nur Aini[1,2] · Ollyvia Freeska Dwi Marta[1] · Erma Wahyu Mashfufa[1] · Lilis Setyowati[1]

Received: 20 May 2023 / Accepted: 23 January 2024

Abstract

Restless leg syndrome (RLS) is characterized by unpleasant nocturnal sensations in the lower limbs, and it has emerged as the fourth leading cause of insomnia and is often an underdiagnosed medical condition among sleep disorders. The symptoms of RLS are more common in chronic kidney disease patients than in the general population. Therefore, we performed the first meta-analysis to estimate the risk of RLS among chronic kidney disease patients. We conducted a comprehensive search in Embase, Ovid-MEDLINE, PubMed, Scopus, Web of Science, and CINAHL databases. Data were analyzed with the random-effects model using Comprehensive Meta-Analysis (CMA) software to find the odds ratio (OR). The heterogeneity was checked with the I^2 test and Cochran's Q-statistic, and we performed the moderator analysis to find potential sources of heterogeneity. The study quality was assessed using the Newcastle–Ottawa Scale. Of 1175 studies, we found nine studies, with a total of 18,983 participants. The pooled OR of RLS among chronic kidney disease was 5.64 (95%CI 2.70–11.78). Regarding moderator analysis results, it was observed that higher body mass index and abnormal laboratory results would increase the risk of RLS; however, the statistical test was not significant in the current study. The findings reveal a substantial sixfold increase in the likelihood of RLS when compared to the general population. Therefore, health professionals should encourage patients to adhere to the treatment and practice a healthy lifestyle to manage their condition and reduce the risk of RLS. Moreover, future research can develop an intervention to reduce RLS symptoms.

Keywords Chronic kidney disease · Restless leg syndrome · Odds ratio · Meta-analysis

Introduction

Chronic kidney disease (CKD) is defined as kidney damage or glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 for a period of three months or more [1]. Studies worldwide have increasingly reported the prevalence of CKD, with diabetes and hypertension as its primary causes [1, 2]. Recent data indicates that CKD affects 9.1% to 13.4% of the worldwide population [3]. Patients with CKD often suffer from various sleep disorders [4, 5]. According to Ogna et al., [6], up to 80% of CKD patients have poor sleep quality, sleep-disordered breathing (SDB), and restless legs syndrome (RLS). In the context of hemodialysis patients, RLS has been identified to be highly prevalent [6], with a meta-analysis, revealing a prevalence rate of 24.2% [7]. In the general population, RLS symptoms are more commonly reported in individuals over the age of 45 years, with 38% of sufferers reporting the onset of symptoms before the age of 20 years [5]. Moreover, in hemodialysis patients, the prevalence of RLS is 20–30%, compared to 3–7% in the general population [5]. This risk increases with the presence of additional comorbidities [8], making symptoms of RLS more common in patients with CKD than in the general population [8].

Restless leg syndrome, also known as Willis–Ekbom syndrome, is a sensory–motor disorder manifested by unpleasant nocturnal sensations in the lower limbs that are relieved by movement [5]. Movements, such as walking, stretching, or bending the legs, relieve the discomfort at least temporarily and partially [9]. Restless leg syndrome causes a disturbance in sleep through an inexplicable desire to move one's legs [4], a phenomenon that can manifest at any stage

✉ Nur Aini
nuraini_fikes@umm.ac.id

[1] Nursing Department, Faculty of Health Sciences, University of Muhammadiyah Malang, Bendungan Sutami Street, 188 A, Malang, East Java, Indonesia

[2] School of Nursing, College of Nursing, Taipei Medical University, Taipei, Taiwan

Published online: 02 March 2024

of chronic kidney disease [6]. Despite symptoms of RLS being more common at night, they can occur at any time during periods of rest or inactivity. Patients frequently report unpleasant achy, creeping, crawling, or itchy sensations in the lower legs [8]. Additionally, RLS is frequently associated with involuntary, rhythmic, and brief contractions of the legs during sleep, known as periodic limb movements [10]. Symptoms may occur at least twice a week, with their severity and frequency of symptoms varying widely [10]. Increasing RLS severity is associated with worse sleep quality, lower quality of life (QoL), daytime sleepiness, depressive symptoms, anxiety, cardiovascular risk, and mortality [8, 11]. Patients with severe RLS symptoms report deficits in physical functioning, bodily pain, general health, vitality, social functioning, role-physical, and role-emotion [9]. Moreover, RLS has become the fourth leading cause of insomnia and is often an underdiagnosed medical condition among various sleep disorders [12].

Brain iron dysregulation plays a significant role in RLS, potentially during its transport across the blood–brain barrier. Given iron is an essential cofactor in dopamine production, low iron levels could explain the changes in dopamine metabolism observed in RLS [5]. Low brain iron gives pathophysiological consequences in hypoxia and demyelination as iron is crucial for oxygen transport. Consequently, a decreased level of iron in the brain can lead to hypoxia. A direct consequence of the activation of hypoxic pathways would be an increase in dopaminergic activity, which is indubitable in RLS patients [12]. Furthermore, the synthesis of myelin sheaths is also dependent on iron; thus, a deficiency in brain iron would lead to suboptimal myelin [12].

Previous studies have reported various factors associated with RLS in chronic kidney disease, including age [7], female [13], alcohol intake [13], increased levels of serum phosphate, decreased serum calcium and hemoglobin levels, disease complications (such as hypertension and diabetes) [7], iron deficiency [5], and body mass index (BMI) [14]. A meta-analysis by Mao et al. [15] revealed the association between RLS with diabetes and hemoglobin. However, some factors are inconsistent with the findings of Rohani et al. [11], who reported no significant association between RLS and gender, marital status, education, drug usage, drug abuse, alcohol intake, smoking, and BMI. The study by Lin et al. [13] also reported that age, BMI, weeks on hemodialysis, frequency of hemodialysis, dialysis solution temperature, diabetes mellitus type 2, family history of RLS, smoking, tea intake, coffee intake, and other routine laboratory blood test showed no relationship with RLS. To our knowledge, there has been no previous meta-analysis which explores RLS in chronic kidney disease patients in comparison to other populations [15]. Therefore, we performed the first comprehensive meta-analysis to (1) explore the association between chronic kidney disease and RLS, (2) analyze the risk of RLS in chronic kidney disease compared to the general populations, and (3) examine the associated risk factors of RLS in chronic kidney disease patients to address the current research gap.

Methods

Reporting standards and literature searching

We utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in reporting study [16], and this study has been registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022340985). In July 2022, we performed a comprehensive literature search without time and language restrictions on the Embase, Ovid-MEDLINE, PubMed, Scopus, Web of Science, and CINAHL databases. Moreover, we conducted a manual search using Google Scholar, and we also assessed previously published systematic reviews and meta-analyses to retrieve potential studies. The combinations of keywords used were as follows: "Chronic Renal Insufficiency OR Chronic Kidney Disease OR kidney disease", Restless Leg Syndrome OR Willis–Ekbom Syndrome OR 'Wittmaack-Ekbom syndrome (Appendix 1).

Eligibility criteria and data extraction

Published studies were included if they met any of the following criteria: (1) The study reported data derived from observational studies with cohort, cross-sectional, and case–control designs; (2) The study presented outcomes related to RLS; (3) RLS was diagnosed using an instrument, for instance, the international restless legs syndrome study group rating scale (IRLSSG), or other RLS questionnaires; (4) The study reported original data on odds ratio (OR), or detailed information on cases and control events; (5) The study included a control group (non-renal disease patients).

Studies were excluded if they met any of the following criteria: (1) Pertained to irrelevant topics; (2) Included irrelevant populations; (3) Used irrelevant study designs; (4) were meta-analyses or reviews; (5) Represented a study protocol; (6) Were non-research articles; (7) Contained insufficient data (which remained insufficient even after attempts to contact the study authors), and (8) included participants identical to those in another study.

Two authors independently selected and extracted the included studies, gathering information on authors, country of origin, study design, target population, diagnosis methods, sample size, RLS events, population characteristics, risk factors, and risk of bias (Table 1).

Table 1 Characteristics included studies of the association between chronic kidney disease and restless leg syndrome (RLS)

No	Author (Year), Country	Study design	Population, Diagnosis	Sample size, RLS event, Instrument for diagnosing RLS	Study characteristics (*n*, %; *M*, SD)	Risk factors (Data in kidney disease cases) (*n*, %; *M*, SD)	Risk of bias
1	Aritake-Okada et al. (2011), Japan [23]	Case-control	Adult, CKD	Sample size Case: 514 Control: 535 RLS event: Case: 18 Control: 8 Instrument: IRLSSG	Age: 59.1 (16.8) Duration of disease (years): NI Gender (case) Male: 353 (68.7%) Female: 161 (31.3%) Gender (control) Male: 353 (65.9%) Female: 182 (34.1%)	Creatinine (mg/dl): 3.9 (3.8) BUN (mg/dl): 38.6 (21.5)	8–L
2	Bambini et al. (2019), Brazil [24]	Case-control	Adult, ERSD	Sample size Case: 25 Control: 75 RLS event: Case: 14 Control: 11 Instrument: IRLSSG	Age: 47 (10.8) Duration of disease (years): NI Gender (case) Male: 7 (28%) Female: 18 (72%) Gender (control) Male: 30 (40%) Female: 45 (60%)	Hypertension: 14 (100%) Smoking: 2 (14.3%) BMI: 25.7 (4.8) Creatinine (mg/dl): 8.4 (2.3) Albumin (g/dl): 4 (0.6) Hemoglobin (g/dl): 11.2 (2.3) Vitamin D: 22.8 (7.8) Calcium (mg/dl): 9.8 (0.8) Ferritin (ng/ml): 359 (107.6) Iron (ng/ml): 57 (15)	8–L
3	Bhowmik et al. (2004), India [25]	Case-control	Adult, CKD	Sample size Case: 65 Control: 99 RLS event: Case: 1 Control: 0 Instrument: IRLSSG	Age: 42.4 (14.9) Duration of disease (years): NI Gender (case) Male: 50 (76.9%) Female: 15 (23.1%) Gender (control) Male: 32 (32.3%) Female: 67 (67.7%)	BMI: 21.5 (1.9) Creatinine (mg/dl): 6.6 (2.2) BUN (mg/dl): 134.8 (51.6) Albumin (g/dl): 3.6 (0.7) Hemoglobin (g/dl): 8.5 (2.2) Calcium (mg/dl): 8.7 (1.1) Ferritin (ng/ml): 157.6 (109.9) GFR (mL/min): 10.4 (2.9)	8–L
4	Bliwise et al. (2014), USA [26]	Case-control	Adult, ESDR	Sample size Case: 3,234 Control: 12,931 RLS event: Case: 3,234 Control: 3,231 Instrument: IRLSSG	Age: 61.4 (14.9) Duration of disease (years): NI Gender (case) Male: 1,572 (48.6%) Female: 1,662 (51.4%) Gender (control) Male: 6,284 (48.6%) Female: 6,647 (51.4%)	Diabetes: 852 (54.2%) Hemoglobin (g/dl): 10.1 (1.6)	8–L

Table 1 (continued)

No	Author (Year), Country	Study design	Population, Diagnosis	Sample size, RLS event, Instrument for diagnosing RLS	Study characteristics (*n*, %; *M*, SD)	Risk factors (Data in kidney disease cases) (*n*, %; *M*, SD)	Risk of bias
5	Darwish et al. (2016), Egypt [27]	Case-control	Children, CKD	Sample size Case: 54 Control: 41 RLS event: Case: 11 Control: 1 Instrument: The RLS questionnaire, derived from the standard criteria for diagnosis of RLS in children	Age: 9.9 (2.9) Duration of disease (years): 2.2 (2.2) Gender (case) Male: 31 (57.4%) Female: 23 (42.6%) Gender (control) Male: 23 (42.6%) Female: 18 (57.4%)	BMI: 17.8 (3.2) Creatinine (mg/dl): 3.5 (0.7) Hemoglobin (g/dl): 10.9 (1.2) Calcium (mg/dl): 9.9 (0.7) GFR (mL/min): 46.4 (10.1)	8–L
6	Merlino. G et al. (2010), Italy [28]	Case-control	Adult, CKD	Sample size Case: 138 Control: 151 RLS event: Case: 15 Control: 5 Instrument: IRLSSG	Age: 69.8 (11.7) Duration of disease (years): 6.2 (6.6) Gender (case) Male: 85 (61.6%) Female: 53 (38.4%) Gender (control) Male: 64 (42.4%) Female: 87 (57.6%)	Creatinine (mg/dl): 2.3 (1.4) BUN (mg/dl): 51.5 (32.3) Albumin (g/dl): 4.1 (0.6) Hemoglobin (g/dl): 12.7 (1.6) Calcium (mg/dl): 2.2 (0.4) Ferritin (ng/ml): 50.8 (29.8) Iron (ng/ml): 66.1 (18.6)	8–L
7	Riar et al. (2013), USA [29]	Cross-sectional	Children, CKD	Sample size Case: 124 Control: 85 RLS event: Cases: 19 Control: 5 Instrument: IRLSSG	Age: 13.4 (3.1) Duration of disease (years): 8.2 (4.5) Gender (case) Male: 80 (64.5%) Female: 44 (35.5%) Gender (control) Male: 32 (37.7%) Female: 53 (62.3%)	BMI: 22.2 (6.2) GFR (mL/min): 61.5 (30.8)	8–L
9	Stefanidis et al. (2013), Greece [30]	Cross-sectional	Adult, CKD	Sample size Case: 579 Control: NI RLS event: Case: 154 Control: NI (OR: 5.40; 95%CI: 4.60—6.30) Instrument: IRLSSG	Age: 65 (13) Duration of disease (years): 3.6 (3.7) Gender (case) Male: 343 (59.4%) Female: 236 (40. 6%) Gender (control) Male: NI Female: NI	Diabetes: 30 (22.2%) BMI: 25.4 (4.2) Albumin (g/dl): 4.1 (0.3) Hemoglobin (g/dl): 11.2 (1.3) Calcium (mg/dl): 8.8 (0.8) Ferritin (ng/ml): 254 (286) Iron (ng/ml): 45.2 (25.5)	9–L

Table 1 (continued)

No	Author (Year), Country	Study design	Population, Diagnosis	Sample size, RLS event, Instrument for diagnosing RLS	Study characteristics (*n*, %; *M*, SD)	Risk factors (Data in kidney disease cases) (*n*, %; *M*, SD)	Risk of bias
9	Winkelman et al. (1996), USA [31]	Cross-sectional	Adult, ESDR	Sample size Case: 204 Control: 129 RLS event: Case: NI Control: NI (OR: 1.59; 95%CI: 1.22—2.06) Instrument: IRLSSG	Age: 56.8 (15.8) Duration of disease (years): NI Gender (case) Male: 96 (47.1%) Female: 108 (52.9%) Gender (control) Male: 77 (59.7%) Female: 52 (40.3%)	BUN (mg/dl): 66 (9) Hemoglobin (g/dl): 9.8 (1.4) Calcium (mg/dl): 9 (1.3) Iron (ng/ml): 54.9 (29.3)	6–M

NI no information, *M* Mean, *SD* standard deviation, *BMI* body mass index, *BUN* blood urea nitrogen, *GFR* glomerular filtration rate, *OR* odds ratio, *IRLSSG* the international restless legs syndrome study group rating scale, *RLS* restless legs syndrome, Risk of bias (*L*: low, *M*: moderate)

Risk of bias and statistical analysis

The quality of the included studies was evaluated independently by two raters using the Newcastle–Ottawa Scale (NOS) [17]. This is a risk-of-bias assessment tool for observational studies that is recommended by the Cochrane Collaboration [18]. The NOS consists of nine or eight questions: (1) selection of study groups (four items); (2) comparability of groups (two items); and (3) ascertainment of exposure and outcomes (three items) for case–control and cohort studies, whereas cross-sectional study has two items [17, 18]. The overall score indicates the overall risk of bias in the study: scores of $\geq$ 7–9, 4–6, and $<$ 4 indicate low, moderate, and high risk of bias, respectively [17, 18]. We determined the interrater agreement between the two assessors using Cohen's kappa coefficient (κ) test and the results were interpreted as follows: a κ of $\leq$ 0, 0.01 to 0.20, 0.21 to 0.40, 0.41 to 0.60, 0.61 to 0.80, and 0.81 to 1.00 indicated no, none to slight, fair, moderate, substantial, and almost perfect agreement, respectively [19]. A third expert reviewer was consulted to resolve through discussion any interrater differences and disagreements.

Statistical synthesis and publication bias

The data were analyzed using a random-effects model in the presence of heterogeneity with the Comprehensive Meta-Analysis CMA tool (version 3.0) [20]. Heterogeneity was measured using the I^2 and Cochran's Q tests; here, an I^2 of $\geq$ 30%, a small Q value, and p-value of $<$ 0.1 indicated significant heterogeneity [21]. The main outcomes are presented as odds ratio (OR) with a 95% confidence interval (95% CI). For OR effect measures, a value of 1 represents no difference between the groups, OR $>$ 1 indicates the occurrence of an event, and OR $<$ 1 indicates decreased occurrence of an event [21]. In the presence of heterogeneity, subgroup and meta-regression were used to determine the moderator variables, including gender, age, duration of disease, population, body mass index (BMI), smoking status, laboratory test results [ferritin, iron, creatinine, blood urea nitrogen (BUN), albumin, hemoglobin, calcium, ferritin, glomerular filtration rate (GFR), vitamin D], and medical comorbidities (hypertension, diabetes). A p-value of $<$ 0.05 demonstrated that a moderator variable was significant among groups.

Furthermore, sensitivity analysis was performed based on the sample size and risk of bias. The sensitivity analysis results were compared with those of the initial odds ratio analysis and assessed for consistency to ensure robust study findings [21]. To detect the presence of publication bias, we employed a funnel plot for visual assessment and used Egger's regression intercept and Begg and Mazumdar rank correlation [20]. An asymmetric funnel plot shape, that is, one with no points on one side of the plot, would suggest the presence of publication bias [22]. A p-value of $>$ 0.1 was considered to indicate the absence of publication bias; if publication bias was detected, the trim-and-fill method was used to correct it [22].

Results

Overview of the included studies

We began our study by initially identifying a total of 1175 studies from various databases, of which 396 duplicate studies were excluded. Next, the remaining 779 studies were screened based on their titles and abstracts, and 68 studies were identified to meet the eligibility criteria for further full-text checks. Of the 68 eligible studies, 61 were excluded because they did not measure the outcomes of interest. This left us with the remaining seven studies [23–29] that

were deemed suitable for inclusion in our meta-analysis. Additionally, we conducted a manual search on Google Scholar, identifying two [30, 31] more eligible studies. In the end, our comprehensive meta-analysis encompassed a total of nine studies with 18,983 participants and was published between 1996 and 2019 (Fig. 1, Appendix 2).

The majority of participants were males (50.1%). The mean age of the participants was 47.2 (11.5) years old, with the age range spanned from 9.9 to 69.8 years old. On average, participants had been living with the disease for approximately 5.1 years, and the majority of individuals were diagnosed with RLS using the International Restless Legs Syndrome Group (IRLSSG) questionnaire. In terms of the population breakdown, 77.8% of the patients were adults, while 22.2% were children. Moreover, identified risk factors included BMI (22.5 + 4.1), creatinine (4.9 + 2.1), hemoglobin (10.7 + 1.7), albumin (3.9 + 0.6), calcium (8.1 + 0.9), ferritin (205.4 + 133.3), iron (55.8 + 22.1), and GFR (39.4 + 14.6) (Table 1). In general, eight out of the nine studies had a low risk of bias, while one study had a moderate risk of bias (Appendix 3). The Cohen's *k* test showed substantial agreement between the two raters ($k = 0.63$, p-value = 0.005).

Meta-analysis results

The analysis revealed a pooled odds ratio of RLS among chronic kidney disease patients of 5.64 (95%CI 2.70–11.78), which means that chronic kidney disease patients are more likely to have the risk of RLS 5.64 compared to the general population. We also observed statistical heterogeneity, with $Q = 101.70$, $I^2 = 92.13$, and p-value < 0.001 (Fig. 2). Regarding population, the pooled odds ratio of RLS among children with chronic kidney disease was 3.70 (95% CI 1.47–9.30). In contrast, among adult patients, the odds ratio was 6.07 (95% CI 2.61–14.15) (Fig. 3). The results of Begg and Mazumdar rank correlation and Egger's regression intercept showed no significant publication bias (p-value = 0.46, and 0.71, respectively) (Appendix 4).

Moderator analysis and sensitivity analysis

Subgroup and meta-regression analyses were conducted to identify the potential sources of heterogeneity. Both subgroup and meta-regression analyses revealed that there were no significant differences in the odds ratio of RLS regarding age, gender, population, duration of disease, BMI, laboratory tests (ferritin, iron, creatinine, BUN, albumin, hemoglobin, calcium, ferritin, and GFR) (Table 2). However, according to the Cochrane Handbook, for performed moderator analysis, at least ten studies should be available for each characteristic or variable being analyzed [21]. Thus, the moderator analysis results in this study are less robust and require further research.

Sensitivity analysis was conducted based on the risk of bias and study sample size. First, we independently analyzed the studies with a moderate risk of bias and excluded one such study. This resulted in a slight change in the odds ratio from 5.64 (95% CI 2.70–11.78) to 7.45 (95% CI 3.20–17.33). Second, we performed sensitivity analysis by excluding one

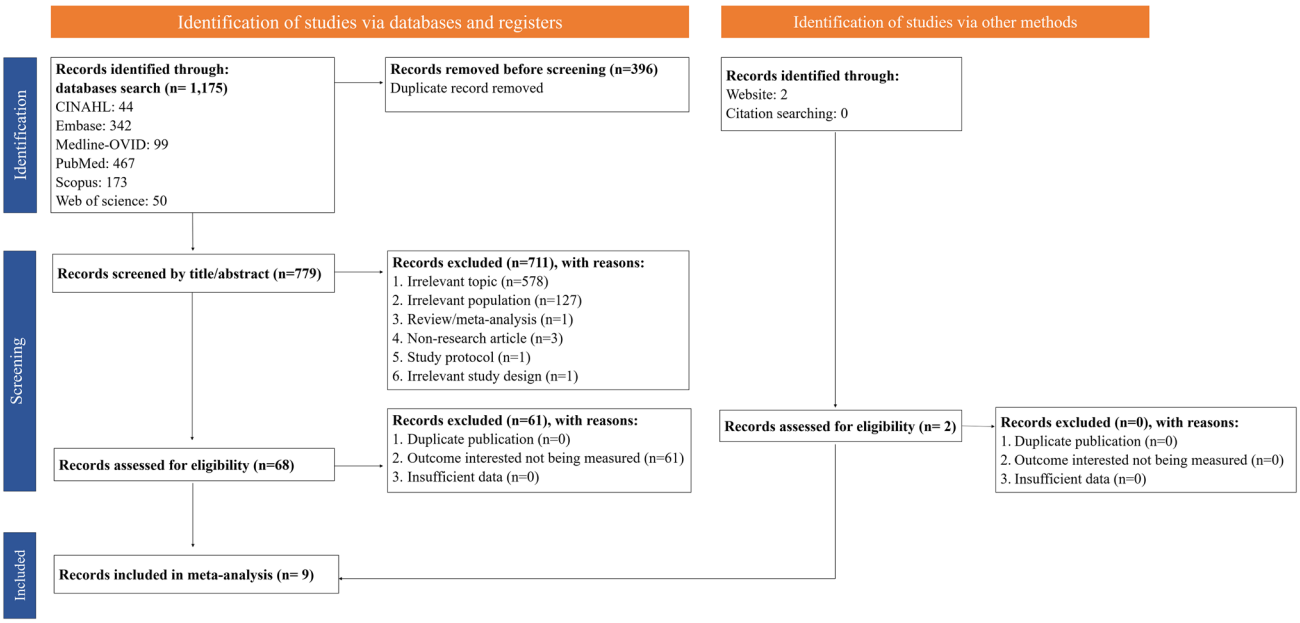


Fig. 1 PRISMA flow chart

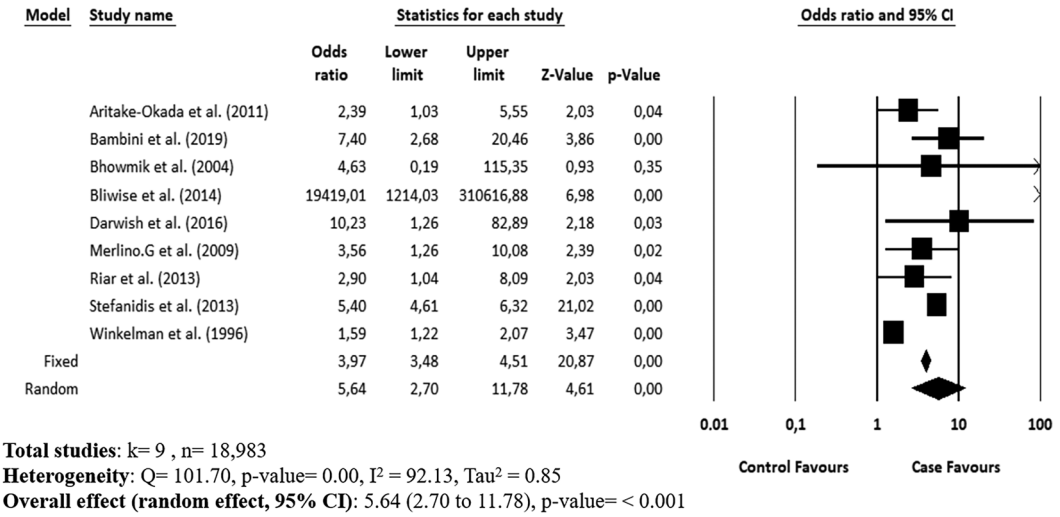
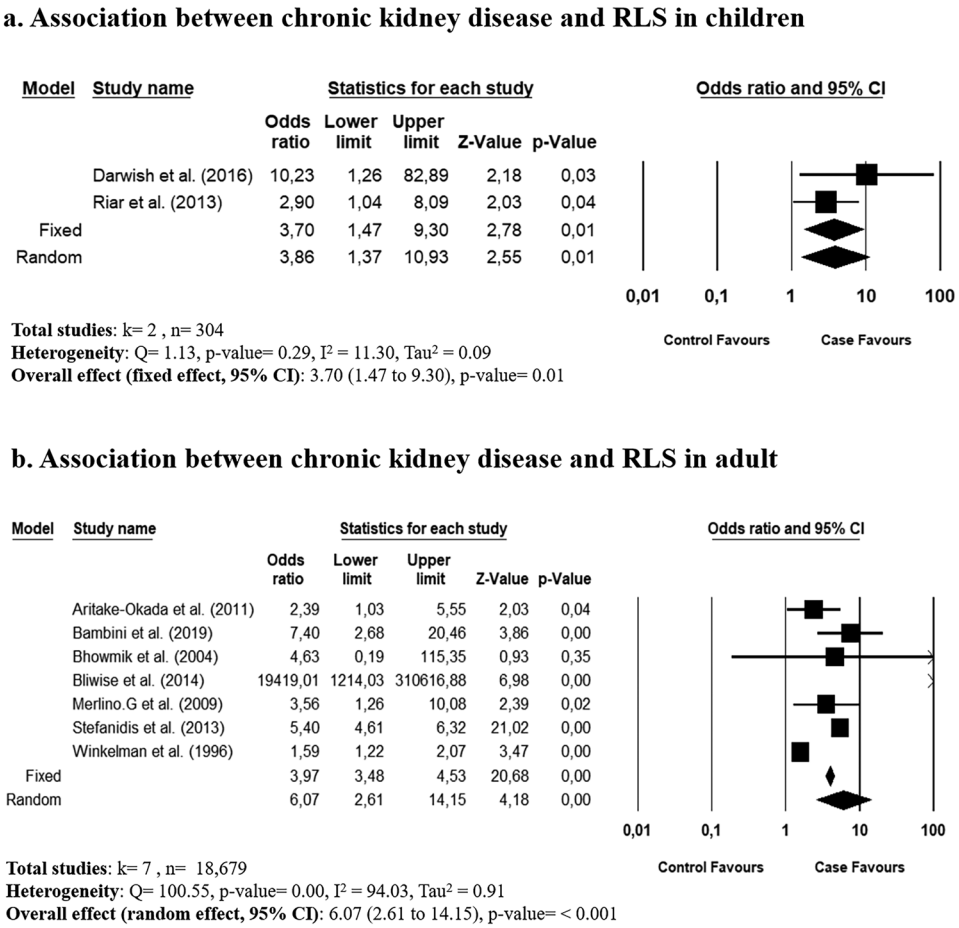


Fig. 2 Forest plot of pooled odds ratio of restless leg syndrome (RLS) among chronic kidney disease patients

Fig. 3 Forest plot of restless leg syndrome (RLS) based on population



study with a sample size of < 30 in the case group or control group. Likewise, the odds ratio changed slightly from 5.64 (95% CI 2.70–11.78) to 5.50 (95% CI 2.47–12.27). Both sensitivity results indicated a minimal difference in the measurements in the odds ratio. Thus, the results of the current meta-analysis could be considered robust.

Table 2 Moderator analysis of association between chronic kidney disease and restless leg syndrome (RLS)

Variable	*k* of study (sample size)	Subgroup analysis			Meta-regression analysis			
		OR	95% CI	*p* value	Coefficient	Standard Error	95% CI	*p* value
Age	9 (18,983)	–	–	–	0.02	0.03	− 0.07 to 0.10	0.70
BMI	5 (1147)	–	–	–	0.04	0.10	− 0.17 to 0.24	0.71
Duration of disease	4 (1172)	–	–	–	0.15	0.10	− 0.34 to 0.05	0.14
Laboratory result								
Creatinine	5 (1697)	–	–	–	0.14	0.11	− 0.09 to 0.36	0.23
BUN	4 (1835)	–	–	–	0.00	0.02	− 0.03 to 0.03	0.78
Hemoglobin	6 (1560)	–	–	–	0.28	0.29	− 0.29 to 0.86	0.33
Albumin	4 (1132)	–	–	–	0.70	2.79	− 6.18 to 4.77	0.80
Calcium	6 (1560)	–	–	–	0.04	0.14	− 0.23 to 0.31	0.77
Ferritin	4 (1132)	–	–	–	0.00	0.00	− 0.00 to 0.01	0.33
Iron	4 (1301)	–	–	–	0.02	0.06	− 0.13 to 0.10	0.78
GFR	3 (468)	–	–	–	NA	NA	NA	NA
Population								
Children	2 (304)	3.86	1.37–10.93	0.51	–	–	–	–
Adult	7 (18,679)	6.07	2.61 to 14.15		–	–	–	–
Gender								
Male	7 (3179)	6.76	6.20–7.37	0.06	–	–	–	–
Female	6 (3347)	2.98	1.29–6.89		–	–	–	–

OR odds ratio, *BMI* body mass index, *BUN* blood urea nitrogen, *GFR* glomerular filtration rate, *NA* not applicable, data cannot be analyzed due to limited number of studies

Discussion

Main findings

To our knowledge, this study is the first meta-analysis that estimated the risk of RLS among chronic kidney disease patients when compared to the general population. While previous meta-analyses have addressed related topics, they differ in scope and focus. For instance, Mao, Shen [15] identified potential risk factors for the susceptibility to RLS among dialysis patients, without making direct comparisons to the general population. Similarly, Lin, Zhao [7] investigated the prevalence of RLS in chronic kidney disease patients but exclusively included studies involving adult participants. In contrast, our current meta-analysis took a broader approach and examined the risk of RLS and associated factors in chronic kidney disease patients. We included all studies related to chronic kidney disease, including end-stage renal disease (ESRD), from children to adult population, and critically compared the risk of RLS among chronic kidney disease patients with the general population. Although the exact cause of RLS among CKD patients is not clearly understood, there are identified factors, such as anemia, iron deficiency, and elevated serum calcium, which may contribute to an increased likelihood of RLS in those patients than the general population [32].

The findings of this meta-analysis revealed a substantial sixfold increase in the likelihood of RLS development among chronic kidney disease patients when compared to the general population. Notably, despite the presence of study heterogeneity, our sensitivity analysis confirmed these associations, and importantly, we found no evidence of publication bias. Furthermore, previous research findings showed that 15–55% of kidney patients presented RLS [14, 32, 33]. Moreover, a study by Stefanidis et al. [30] and Winkelman et al. [31] showed that chronic kidney disease patients have a higher odds ratio of RLS than the general population. However, the included studies in this meta-analysis had case–control and cross-sectional designs. While both study designs provide valuable insights into the associations between CKD and RLS, neither can elucidate the causal relationship. It is difficult to determine whether CKD causes RLS or if RLS causes CKD. As a result, longitudinal studies or experimental designs are required in future research.

The pathophysiology of RLS remains enigmatic, with iron and dopamine emerging as the most extensively studied factors in understanding the physiologic mechanisms underlying RLS [5, 33]. Iron plays an essential role as a cofactor for the electron-transporting enzyme tyrosine hydroxylase in oxidative metabolism and serves as an oxygen transporter to various body organs, including the brain [33]. Tyrosine hydroxylase stands as

the rate-limiting enzyme responsible for the production of dopamine. Therefore, iron deficiency can indirectly reduce dopamine production in the brain [34]. Dopamine, on the other hand, modulates the function of motor and sensory spinal cord neurons and decreases dopamine levels in the nervous system, contributing to symptoms of RLS [34].

In addressing the issue of heterogeneity, we performed moderator analysis. It was observed that increasing age, duration of disease, higher body mass index, and abnormal laboratory results would increase the risk of RLS; however, we found no statistically significant results for meta-regression and subgroup analysis in the current study. This result was corroborated by a study by Beladi et al. [32], which revealed no significant associations between RLS and age, gender, dialysis shift, and hemoglobin, calcium, and phosphate levels. A study by Lin et al. [13] also found no relationship between laboratory tests (creatinine, albumin, calcium, hemoglobin, ferritin, and total iron binding capacity); however, this study identified that female sex and alcohol intake were significant risk factors of RLS [13]. Moreover, it is important to note that no significant association exists between RLS and gender, alcohol intake, smoking, and BMI [11]. In contrast, a meta-analysis found associations between RLS and diabetes, low levels of hemoglobin or iron, but no association in females, age, duration of dialysis, BMI, BUN, creatinine, albumin, phosphorus, and calcium [15].

We posit that the cause of non-significant moderator analysis and different results from the previous meta-analysis in the current study may be that in the current study, the mean of some laboratory results was still within the normal threshold. For instance, the average levels of iron and ferritin were measured at 56 ng/ml and 205.45 ng/ml, respectively. According to Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines, serum ferritin levels < 30 ng/mL indicate a severe iron deficiency in CKD [35]. Similarly, most calcium levels in the current meta-analysis were found to be within the normal range. According to McCann [36], the normal calcium level is 8.4–9.5 mg/dL. It is noteworthy that both, increased serum concentrations of calcium [37] and calcium deficiency were associated with RLS [38, 39]. However, calcium represents just one of among many possible causes of RLS, and it may not even be the main factor for a majority of people who suffer from RLS [39]. Another factor contributing to our findings is the fact that in the current study, each moderator variable had fewer than 10 studies. Thus, the results of moderator analysis might be less robust and less valid because to conduct moderator analysis, at least 10 studies should be available for each characteristic or variable [21].

Strengths and limitations

Our meta-analysis has several strengths: (1). This is the first meta-analysis to provide an association between chronic kidney disease and RLS, and analyze the odds ratio of RLS among chronic kidney disease patients compared to the general population; (2). This study identified and analyzed risk factors associated with RLS among chronic kidney disease patients, for instance, gender, age, disease duration, BMI, and laboratory test results (ferritin, iron, creatinine, BUN, albumin, hemoglobin, calcium, GFR); (3). Our research is supported by a comprehensive search of six databases supported by a manual search on Google Scholar without time and language restrictions; (4). The study adhered to stringent methodological procedures, including independent screening, meticulous data extraction, and the study protocol registered on PROSPERO; (5). Sensitivity analyses were performed to support the robustness of the current study. However, the limitations of our study are (1). We were only able to identify nine relevant studies for inclusion in our meta-analysis; (2). The presence of heterogeneity within the included studies prompted us to conduct moderator analysis to determine potential sources of this heterogeneity; (3). The limited number of characteristics of variables available in the included studies somewhat constrained the robustness of our moderator analysis results; and (4). The cross-sectional and case–control design cannot elucidate the causal relationship. Thus, longitudinal studies or experimental designs for further research, are needed to provide more robust causal inferences between CKD and RLS.

Conclusion

Chronic kidney disease patients are sixfold more likely to develop RLS compared to the general population. Both populations, adults, and children with chronic kidney disease, have an odds ratio of more than one, which indicates a high risk of RLS. After we performed a moderator analysis, the results of moderator analysis were not statistically significant, although the results showed that abnormal body mass index and abnormal laboratory test results would increase the risk of RLS. Therefore, future research should include more studies, and advance an intervention to reduce the RLS symptoms in chronic kidney disease patients. Moreover, health professionals should actively motivate patients to adhere to their treatment plans and practice a healthy lifestyle, in order to reduce the risk of RLS.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41105-024-00513-4.

Acknowledgements The findings and conclusions in this document are those of the authors, who are responsible for its contents.

Author contributions NA: conceptualization, methodology, writing—original draft, supervision. OFDM: conceptualization, formal analysis & data curation. EWM: Validation, writing—review & editing. lilis setyowati: validation, writing—review & editing.

Funding The authors received financial support for the research grant from the Faculty of Health Sciences University of Muhammadiyah Malang (Grant number: E.6/266a/FIKES-UMM/III/2022).

Declarations

Conflict of interest The authors declare no conflict of interest in this study.

References

1. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl. 2022;12(1):7–11. https://doi.org/10.1016/j.kisu.2021.11.003.
2. Aini N, Wahyu AC. The correlation between family support and psychological well-being in patients with end-stage renal disease. Kontakt. 2020;22(4):291–6. https://doi.org/10.32725/kont.2020.041.
3. Vart P, Heerspink HJL. Progress and opportunities in measuring the burden of chronic kidney disease. Lancet Reg Health Eur. 2022;20: 100447. https://doi.org/10.1016/j.lanepe.2022.100447.
4. Nigam G, Camacho M, Chang ET, Riaz M. Exploring sleep disorders in patients with chronic kidney disease. Nat Sci Sleep. 2018;10:35–43. https://doi.org/10.2147/NSS.S125839.
5. Maung SC, El Sara A, Chapman C, Cohen D, Cukor D. Sleep disorders and chronic kidney disease. World J Nephrol. 2016;5(3):224–32. https://doi.org/10.5527/wjn.v5.i3.224.
6. Ogna A, Forni Ogna V, Haba Rubio J, Tobback N, Andries D, Preisig M, et al. Sleep characteristics in early stages of chronic kidney disease in the hypnoLaus cohort. Sleep. 2016;39(4):945–53. https://doi.org/10.5665/sleep.5660.
7. Lin Z, Zhao C, Luo Q, Xia X, Yu X, Huang F. Prevalence of restless legs syndrome in chronic kidney disease: a systematic review and meta-analysis of observational studies. Ren Fail. 2016;38(9):1335–46. https://doi.org/10.1080/0886022X.2016.1227564.
8. Novak M, Winkelman JW, Unruh M. Restless legs syndrome in patients with chronic kidney disease. Semin Nephrol. 2015;35(4):347–58. https://doi.org/10.1016/j.semnephrol.2015.06.006.
9. Guo S, Huang J, Jiang H, Han C, Li J, Xu X, et al. Restless legs syndrome: from pathophysiology to clinical diagnosis and management. Front Aging Neurosci. 2017. https://doi.org/10.3389/fnagi.2017.00171.
10. Silber MH, Buchfuhrer MJ, Earley CJ, Koo BB, Manconi M, Winkelman JW, et al. The management of restless legs syndrome: an updated algorithm. Mayo Clin Proc. 2021;96(7):1921–37. https://doi.org/10.1016/j.mayocp.2020.12.026.
11. Rohani M, Aghaei M, Jenabi A, Yazdanfar S, Mousavi D, Miri S. Restless legs syndrome in hemodialysis patients in Iran. Neurol Sci. 2015;36(5):723–7. https://doi.org/10.1007/s10072-014-2026-8.
12. Vlasie A, Trifu SC, Lupuleac C, Kohn B, Cristea MB. Restless legs syndrome: an overview of pathophysiology, comorbidities and therapeutic approaches (Review). Exp Ther Med. 2022;23(2):185. https://doi.org/10.3892/etm.2021.11108.
13. Lin XW, Zhang JF, Qiu MY, Ni LY, Yu HL, Kuo SH, et al. Restless legs syndrome in end stage renal disease patients undergoing hemodialysis. BMC Neurol. 2019;19(1):47. https://doi.org/10.1186/s12883-019-1265-y.
14. ZadehSaraji N, Hami M, Boostani R, Mojahedi MJ. Restless leg syndrome in chronic hemodialysis patients in Mashhad hemodialysis centers. J Renal Inj Prev. 2017;6(2):137–41. https://doi.org/10.15171/jrip.2017.27.
15. Mao S, Shen H, Huang S, Zhang A. Restless legs syndrome in dialysis patients: a meta-analysis. Sleep Med. 2014;15(12):1532–8. https://doi.org/10.1016/j.sleep.2014.07.017.
16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71. https://doi.org/10.1136/bmj.n71.
17. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2021 [Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
18. Lo CK-L, Mertz D, Loeb M. Newcastle-Ottawa scale: comparing reviewers to authors assessments. BMC Med Res Methodol. 2014;14(45):1–5. https://doi.org/10.1186/1471-2288-14-45.
19. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med. 2012;22(3):276–82.
20. Serghiou S, Goodman SN. Random-effects meta-analysis: Summarizing evidence with caveats. JAMA. 2019;321(3):301–2. https://doi.org/10.1001/jama.2018.19684.
21. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane handbook for systematic reviews of interventions, version 6.3. 2022 2022 [Available from: https://training.cochrane.org/handbook/current].
22. Ahn E, Kang H. Introduction to systematic review and meta-analysis. Korean J Anesthesiol. 2018;71(2):103–12. https://doi.org/10.4097/kjae.2018.71.2.103.
23. Aritake-Okada S, Nakao T, Komada Y, Asaoka S, Sakuta K, Esaki S, et al. Prevalence and clinical characteristics of restless legs syndrome in chronic kidney disease patients. Sleep Med. 2011;12(10):1031–3. https://doi.org/10.1016/j.sleep.2011.06.014.
24. Bambini BBM, Moyses RMA, Batista LCD, Coelho BBSS, Tufik S, Elias RM, et al. Restless legs syndrome in patients on hemodialysis: Polysomnography findings. Hemodial Int. 2019;23(4):445–8. https://doi.org/10.1111/hdi.12781.
25. Bhowmik D, Bhatia M, Tiwari S, Mahajan S, Gupta S, Agarwal SK, et al. Low prevalence of restless legs syndrome in patients with advanced chronic renal failure in the Indian population: a case controlled study. Ren Fail. 2004;26(1):69–72. https://doi.org/10.1081/JDI-120028557.
26. Bliwise DL, Zhang RH, Kutner NG. Medications associated with restless legs syndrome: a case-control study in the US renal data system (USRDS). Sleep Med. 2014;15(10):1241–5. https://doi.org/10.1016/j.sleep.2014.05.011.
27. Darwish AH, Abdel-Nabi H. Sleep disorders in children with chronic kidney disease. Int J Pediatr Adolesc Med. 2016;3(3):112–8. https://doi.org/10.1016/j.ijpam.2016.06.001.
28. Merlino G, Lorenzut S, Gigli GL, Romano G, Montanaro D, Moro A, et al. A case-control study on restless legs syndrome in nondialyzed patients with chronic renal failure. Mov Disord. 2010;25(8):1019–25. https://doi.org/10.1002/mds.23010.
29. Riar SK, Leu RM, Turner-Green TC, Rye DB, Kendrick-Allwood SR, McCracken C, et al. Restless legs syndrome in children with

chronic kidney disease. Pediatr Nephrol. 2013;28(5):773–95. https://doi.org/10.1007/s00467-013-2408-9.
30. Stefanidis I, Vainas A, Dardiotis E, Giannaki CD, Gourli P, Papadopoulou D, et al. Restless legs syndrome in hemodialysis patients: an epidemiologic survey in Greece. Sleep Med. 2013;14(12):1381–6. https://doi.org/10.1016/j.sleep.2013.05.022.
31. Winkelman JW, Cheftow GM, Lazarus JM. Restless legs syndrome in end-stage renal disease. Am J Kidney Dis. 1996. https://doi.org/10.1016/s0272-6386(96)90494-1.
32. Beladi-Mousavi SS, Jafarizade M, Shayanpour S, Bahadoram M, Moosavian SM, Houshmand G. Restless legs syndrome: associated risk factors in hemodialysis patients. Nephrourol Mon. 2015;7(6): e31967. https://doi.org/10.5812/numonthly.31967.
33. de Menezes AF, Motta D, de Carvalho FO, Santana-Santos E, de Andrade Junior MP, Figueiroa MF, et al. Restless legs syndrome in dialysis patients: does the dialysis modality influence its occurrence and severity? Int J Nephrol. 2018. https://doi.org/10.1155/2018/1414568.
34. Hamed SA. Neurologic conditions and disorders of uremic syndrome of chronic kidney disease: presentations, causes, and treatment strategies. Expert Rev Clin Pharmacol. 2019;12(1):61–90. https://doi.org/10.1080/17512433.2019.1555468.
35. Pergola PE, Fishbane S, Ganz T. Novel oral iron therapies for iron deficiency anemia in chronic kidney disease. Adv Chronic Kidney Dis. 2019;26(4):272–91. https://doi.org/10.1053/j.ackd.2019.05.002.
36. McCann L. Calcium in chronic kidney disease: recommended intake and serum targets. Adv Chronic Kidney Dis. 2007;14(1):75–8. https://doi.org/10.1053/j.ackd.2006.10.011.
37. Jiménez-Jiménez FJ, Ayuso P, Alonso-Navarro H, Calleja M, Díez-Fairén M, Álvarez I, et al. Serum trace elements concentrations in patients with restless legs syndrome. Antioxidants (Basel). 2022. https://doi.org/10.3390/antiox11020272.
38. Alnaaim S, Alghirash F, Alenzi A, Zahirah MOA, Tashari T, Hakami F, et al. The prevalence of restless legs syndrome among pregnant women in Saudi Arabia. Cureus. 2023. https://doi.org/10.7759/cureus.42883.
39. Neves PD, Graciolli FG, Oliveira IB, Bridi RA, Moysés RM, Elias RM. Effect of mineral and bone metabolism on restless legs syndrome in hemodialysis patients. J Clin Sleep Med. 2017;13(1):89–94. https://doi.org/10.5664/jcsm.6396.