STATE OF THE ART REVIEWS

Prevalence of restless legs syndrome in chronic kidney disease: a systematic review and meta-analysis of observational studies

Zhenchuan Lin, Chen Zhao, Qimei Luo, Xi Xia, Xueqing Yu and Fengxian Huang

Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health, Guangzhou, China

ABSTRACT

Introduction: Nowadays prevalence of restless legs syndrome (RLS) in chronic kidney disease (CKD) patients was reported in many studies, while the results varied. The aim of our study was to investigate the prevalence of RLS in this population, considering different data collecting measures and diagnostic criteria.

Methods: MEDLINE, Embase, PsycINFO, and Scopus databases were searched for relevant studies. We limited the analyses to studies using clinical interview or questionnaire for diagnosis. Univariate meta-regression analysis was preformed to assess the effects of the disease-related covariates on prevalence estimates. Comprehensive Meta-Analysis 2.0 was used to perform the meta-analysis.

Results: Fifty-one studies were included in the analysis. Prevalence of RLS was varied by renal function and diagnostic methods. Overall prevalence in CKD populations was 24.2% (95%CI, 20.1–28.7). Pooled prevalence of RLS was higher in patients diagnosed by questionnaire than by clinical interview [26.2% (95%CI, 17.9–36.5) vs. 23.6% (95%CI, 19.6–28.1)]. When grouped by CKD setting, the prevalence was 28.4% (95%CI, 24.6–32.6) in dialysis patients, followed by early stages patients [9.9% (95%CI, 5.4–17.5)], and kidney transplant recipients [6.7% (95%CI, 5.6–7.8)].

Conclusions: Our meta-analysis suggested that more than one-quarter of CKD sufferers, especially those who were on dialysis, were plagued by RLS. Higher sensitivity of diagnostic criteria in interview may be valuable for timely treatment.

Introduction

Chronic kidney disease (CKD), that includes abnormal kidney structure or function, is estimated to affect nearly 10% of the global population.1–3 CKD is responsible for poor outcomes, and creating serious financial burdens on both individuals and public health services system.4,5 Restless legs syndrome (RLS), a sensory motor disorder with an impulse to move the limbs, is common in the general population.6,7 It can be an idiopathic, primary, inherited disorder, or secondary to a variety of chronic diseases, for instance, CKD.8 Many CKD patients complain about the unpleasant experience of RLS. As a disorder aggravating during rest and especially in the evening, RLS is associated with poor sleep quality, low quality of life, and high risk for the cardiovascular disease.9 In addition, RLS may in turn affect the prognosis of CKD patients, including lower survival and higher short-term mortality.10

Due to the increasing attention in clinic, nowadays the prevalence of RLS is widely investigated in CKD populations. However, in existing studies, investigators primarily focused their attention about the disorder to dialysis populations (CKD 5D).11 Much remains unknown about populations in early stages of CKD (CKD stages 1–5) or kidney transplant recipients. Furthermore, although the diagnostic criteria for RLS, which are published and updated by International Restless Legs Syndrome Study Group (IRLSSG), are generally accepted and widely used in recent years, there are still many patients diagnosed by other methods. In those studies basing on the IRLSSG criteria, some investigators neglected the update of version, and used the old version for clinical diagnosis and scientific research. Even in studies using the same version of criteria, there are still differences in prevalence. For example, according to the IRLSSG criteria of version 1995, Collado-Seidel et al. reported that the prevalence of RLS in hemodialysis patients was 23.5%.12 Another study on hemodialysis, based on version 2003, reported that the prevalence was 31.0%.9 While Tuncel et al. reported that the
prevalence was 12.3% in hemodialysis patients with the same version. In conclusion, data of RLS in CKD population are insufficient, and no agreement has been reached about the overall prevalence of RLS in this population.

Despite extensive researches in this field, the results of prevalence varied. A more popular and acceptable value of RLS prevalence is imperative. Better understanding of the epidemiology of RLS in CKD populations would potentially contribute to the formulation of strategies in further clinical intervention. Furthermore, comprehensive comparisons of diagnostic efficiency in different criteria or questionnaires would be as references when making clinical diagnosis. Therefore, we performed a systematic review and meta-analysis to evaluate the prevalence of RLS in CKD populations, and compare the efficiency of different data collecting methods and diagnostic criteria.

**Methods**

This systematic review and meta-analysis was carried out according to the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. The statement is a combined checklist of items, relating to the article's title and abstract, introduction, methods, results and discussion sections. It is intended to better report analytical epidemiologic studies.

**Search strategy**

The literature search for the meta-analysis was designed to include published studies. A comprehensive search was conducted in MEDLINE (via PubMed); Embase (via Ovid); the PsycINFO, and Scopus from January 1995 to December 2015, looking for studies that paired words related to CKD (i.e., chronic kidney disease, end-stage renal disease, uremia, dialysis, hemodialysis, peritoneal dialysis, renal transplantation) with words related to RLS (i.e., restless legs syndrome, Willis Ekbom Disease, Wittmaack Ekbom Syndrome). Both medical subject headings (MeSH) terms and free text terms, including synonyms and alternative spellings were combined. Reference lists of all articles included were screened for potentially eligible studies.

**Inclusion and exclusion criteria**

Studies were included if they met the following criteria: (1) observational studies (cross-sectional, case-control or cohort studies) related to RLS in CKD patients, (2) all study participants were adults (aged 18 or older), (3) study participants had a definite diagnosis of CKD, (4) RLS was diagnosed through questionnaires or clinical interviews, (5) studies had to provide point prevalence of RLS and/or sufficient data to calculate it. If more than one study evaluated the same population, the one with the most complete data was included. Studies with the following criteria were excluded: (1) discussions, editorials, research overviews, case-reports, letters, literature reviews, or commentaries and critiques; (2) studies did not present sufficient data, and the author could not be successfully contacted; (3) studies were unrelated to exposure (CKD participants) and outcome (RLS). There was no restriction on publication date or language.
with a score of 7–13 were considered as high quality. Any disagreements were resolved through discussion with the arbitrator.

**Statistical analyses**

Statistical heterogeneity was quantified using the Cochran’s $Q$ test and $I^2$ test. A value of significance at 10% ($p < .10$) or a high value of $I^2$ ($I^2 > 75\%$) was considered high-level heterogeneity. If heterogeneity among studies was high, a random effect model was used for pooling the results from individual studies; otherwise, the fixed effect model was used. In addition, subgroup analyses would be conducted when heterogeneity was high. Univariate meta-regression analysis was performed to assess the effects of the following demographic and disease-related covariates on prevalence estimates. As the covariates chosen were not expected to explain all the heterogeneity of the studies, mixed effects regression model was used. The regression coefficients, 95% confidence interval, and $p$ values were calculated in the meta-regression analyses. To assess the stability of the RLS pooled prevalence values, sensitivity analysis was conducted to estimate the influence of each study on the pooled prevalence by removing one study at a time. Funnel plots and Egger’s test were used to detect publication bias. Asymmetry of funnel plots and $p_{\text{Egger's test}}$ less than .05 suggested the possibility of publication bias. For all analyses, a two-tailed $p < .05$ indicated statistical significance. All statistical analyses were conducted using Comprehensive Meta-Analysis (Version 2.0, 2005; Biostat, Englewood, NJ).

**Results**

**Study flow and quality assessment**

Figure 1 depicts the flowchart of studies screening. The combined searches from MEDLINE, Embase, PsycINFO, and Scopus identified 530 abstracts after duplication removal, and 346 studies were excluded after reviewing the titles and abstracts. After full-text screening of the remaining 184 studies, 143 were removed. Ten eligible studies were added after reviewing the reference lists. Finally, 51 studies, with 48 full texts and 3 abstracts, were included in our meta-analyses.

Figure 2 depicts the quality of assessment of the included studies. The average score of quality assessment in the 51 studies was 8.98. When considering full-text studies only, the average score rose to 9.38. Nine studies were considered poor quality. The methods, period and place of sample recruitment were mentioned in 41 studies (80.4%), and the selection criteria were mentioned in 28 studies (54.9%). Baseline data were recorded in 43 studies (84.3%).

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**Figure 1.** Flowchart showing number of citations retrieved by database searching and the number and type of studies included in this review. RLS: restless legs syndrome; CKD: chronic kidney disease.
Study characteristics

The baseline characteristics of each included study in our meta-analysis are shown in Table 1. Sample sizes of these included studies ranged from 12 to 1130. Sixteen studies were small sample size (<100 participants). Sample sizes of nine studies were greater than or equal to 500. Studies were primarily conducted in dialysis settings (40 studies), followed by CKD stages 1–5 (6 studies) and kidney transplantation (3 studies). In addition, there were two studies investigating mixed populations. One focused on kidney transplant recipients and dialyzed patients on transplantation waiting list. The other one included CKD patients in different stages, with and without dialysis. In the dialysis studies, 29 studies were in hemodialysis (HD) setting, and three studies were in peritoneal dialysis (PD) setting. Eight studies investigated both HD and PD patients. Geographically, according to the World Health Organization (WHO) regions, about half of the studies (25 studies) were conducted in Europe, whereas 7 in the Americas, 8 in the Western Pacific, 8 in the Eastern Mediterranean, and 3 in the South-East Asia.

Most of the investigators (38 studies) considered RLS as the only research emphasis in their studies. In the other cases, researchers investigated RLS as a part of sleep disorders questionnaires or life quality researches. Questionnaires and clinical interviews were widely used for data collection. Questionnaire-investigations were adopted in 19 studies. All questionnaires were designed according to the diagnostic criteria of IRLSSG. Most of them were self-administered questionnaires filled by the patients during the dialysis treatment or follow-up period. In some studies, questionnaires were explained and completed with the help of investigators. Clinical interviews were conducted in 32 studies. In these studies, the diagnoses were made by neurologists in 11 studies, physicians in 4 studies, and trained interviewers in 5 studies. The IRLSSG diagnostic criteria, especially the minimum standard, were widely used for clinical diagnosis. With the update of IRLSSG diagnostic criteria, the versions used in studies were slightly different. Eleven studies used the 1995 version, while 20 studies used the 2003 version. In addition, one study used the latest version in 2012. Moreover, the severity of RLS was assessed by IRLSSG Severity Scale (IRLSSGSS) in five studies, and by the John Hopkins Restless Legs Severity Scale (JHRLSS) in two studies.

Prevalence

The prevalence of RLS diagnosed by questionnaire and clinical interview are showed in Table 2 and Table 3. DerSimonian-Laird random-effects meta-analysis was used to summarize the point prevalence due to high-level heterogeneity among the studies ($I^2 = 96.1\%$, $p < .001$). Point prevalence among the 51 studies ranged from 1.5% to 69.8%, and the overall prevalence was 24.2% (95%CI, 20.1–28.7%). Geographical differences in the prevalence of RLS among CKD patients were observed. Patients in the East Mediterranean suffered from the highest rates (35.1%, 95%CI, 25.1–46.6%),
followed by the Western Pacific (26.8%, 95%CI, 18.6–37.0%), then the Americas (26.4%, 95%CI, 15.4–41.5%), and the European (22.4%, 95%CI, 16.7–29.2%). Lower rates were found in the Southeast Asia (8.5%, 95%CI, 1.9–31.2%). When grouped by age, there was no significant difference between the prevalence among the old (age ≥65 years) (24.1%, 95% CI, 14.7–37.1) and the other patients (24.2%, 95%CI, 19.8–29.2). The pooled prevalence in questionnaire group was 26.2% (95%CI, 17.9–36.5), which was statistically different in different stages of CKD (p for subgroup differences <.001).

In the setting of earlier stages of CKD, prevalence of RLS ranged from 1.5 to 23.6%, and the pooled prevalence was 9.9% (95%CI, 5.4–17.5) with high heterogeneity ($I^2 = 92.74$, $p < .001$). In the setting of kidney transplantation, the pooled prevalence was 6.7% (95%CI, 5.6–7.8). Three of these studies were from the Transplantation and Quality of Life-Hungary Study (TransQoL-HU Study), a cross-sectional study focusing on investigating sleep, mood disorders, and quality of life. In the setting of dialysis, the prevalence of RLS in individual studies ranged from 6.6 to 69.8%, and the pooled prevalence was 28.4% (95%CI, 24.6–32.6)

Table 1. Characteristics of included studies in this meta-analysis.

| First author, year | Origin nation | Method for data collection | CKD stages | Mean age | RLS/Total | Quality |
|--------------------|---------------|---------------------------|------------|----------|-----------|---------|
| Goffredo, 2003     | Brazil        | Interview                 | CKD 5D     | 52 ± 13.9| 26/176    | 10      |
| Libório, 2013      | Brazil        | Interview                 | CKD 1–5    | 36.2 ± 11.8| 18/99     | 12      |
| Araujo, 2010       | Brazil        | Interview                 | CKD 5D     | 51.6 ± 15.5| 400/86    | 10      |
| Oliveira, 2011     | Brazil        | Interview                 | CKD SD     | NR       | 34/183    | 1       |
| Ricardo, 2015      | Brazil        | Questionnaire             | CKD SD     | NR       | 45/166    | 9       |
| Lee, 2013          | Canada        | Interview                 | Mix        | NR       | 120/500   | 11      |
| Loewen, 2009       | Canada        | Questionnaire             | CKD SD     | 58 ± 11  | 7/12      | 6       |
| Li, 2014           | China         | Interview                 | CKD SD     | 61.5 ± 12.7| 12/42     | 9       |
| Telarovic, 2007    | Croatia       | Interview                 | CKD SD     | NR       | 49/82     | 11      |
| Sabry, 2010        | Egypt         | Questionnaire             | CKD SD     | 41.59 ± 16.3| 37/88     | 7       |
| Ibrahim, 2011      | Egypt         | Questionnaire             | CKD SD     | 50.82 ± 14.4| 19/264    | 11      |
| Collado-Seidel, 1998 | Germany       | Interview                 | CKD SD     | 59       | 32/136    | 9       |
| Stefanids, 2013    | Greece        | Interview                 | CKD SD     | 65 ± 13  | 154/579   | 11      |
| Giannaki, 2011     | Greece        | Interview                 | CKD SD     | 54.1 ± 16.9| 30/70     | 13      |
| Hui, 2002          | HK            | Questionnaire             | CKD SD     | 49.5 ± 11.3| 30/43     | 8       |
| Hui, 2000          | HK            | Questionnaire             | CKD SD     | 56.7 ± 12  | 124/201   | 5       |
| Molnar, 2007(1)    | Hungary       | Questionnaire             | Transplant | 49 ± 13  | 35/785    | 9       |
| Molnar, 2007(2)    | Hungary       | Questionnaire             | Transplant | 49 ± 13  | 38/804    | 1       |
| Mucsi, 2005        | Hungary       | Questionnaire             | CKD SD     | 54 ± 15  | 45/333    | 10      |
| Szentkiralyi, 2009 | Hungary       | Questionnaire             | Mix        | T: 48 ± 12 D: 49 ± 13| 55/949    | 11      |
| Pavan, 2014        | India         | Interview                 | CKD SD     | 64.3 ± 14 | 14/50     | 9       |
| Bhowmik, 2003      | India         | Interview                 | CKD SD     | 34.5 ± 11.1| 8/121     | 8       |
| Bhowmik, 2004      | India         | Interview                 | CKD 1–5    | 42.4 ± 14.9| 1/65      | 7       |
| Razeghi, 2017      | Iran          | Questionnaire             | CKD SD     | 56 ± 15  | 35/108    | 7       |
| Emami, 2017        | Iran          | Questionnaire             | CKD SD     | 54.2 ± 15.2| 26/90     | 6       |
| Mohammad, 2015     | Iran          | Interview                 | CKD SD     | 61.3 ± 13.3| 61/167    | 7       |
| Quinn, 2011        | Ireland       | Interview                 | CKD 1–5    | NR       | 55/301    | 12      |
| La Manna, 2011     | Italy         | Interview                 | CKD SD     | 65.0 ± 14.2| 31/100    | 13      |
| Cinigotto, 2002    | Italy         | Questionnaire             | CKD SD     | 63.6 ± 12.7| 38/114    | 7       |
| Pizza, 2012        | Italy         | Interview                 | CKD SD     | 65.6 ± 14.3| 51/162    | 11      |
| Gigli, 2004        | Italy         | Questionnaire             | CKD SD     | 64 ± 13  | 127/601   | 5       |
| Merlino, 2012      | Italy         | Interview                 | CKD SD     | NR       | 14/86     | 10      |
| Merlino, 2006      | Italy         | Questionnaire             | CKD SD     | 64.95 ± 12.8| 152/883   | 9       |
| Merlino, 2010      | Italy         | Interview                 | CKD 1–5    | 69.8 ± 11.7| 15/138    | 11      |
| Aritake-Okada, 2011 | Japan         | Interview                 | CKD 1–5    | 59.5 ± 16.5| 18/514    | 12      |
| Kawauuchi, 2006    | Japan         | Interview                 | CKD SD     | 60       | 53/228    | 9       |
| Takaki, 2003       | Japan         | Questionnaire             | CKD SD     | NR       | 60/490    | 9       |
| Kim, 2000          | Korea         | Questionnaire             | CKD SD     | 62.2 ± 12.7| 46/164    | 12      |
| Rijsman, 2004      | Netherlands   | Interview                 | CKD SD     | 55 ± 12  | 28/48     | 10      |
| Al-Jahdali, 2009   | Saudi Arabia  | Interview                 | CKD SD     | 55.7 ± 17.2| 114/227   | 10      |
| Siraj, 2015        | Saudi Arabia  | Interview                 | CKD SD     | 48.5 ± 15.4| 69/355    | 6       |
| Sladojevic, 2012   | Serbia        | Questionnaire             | CKD SD     | NR       | 60/490    | 9       |
| Chrustina, 2015    | Slovakia      | Interview                 | Transplant | 51.14 ± 11.1| 30/75     | 7       |
| Jesus, 2015        | Spain         | Interview                 | CKD 1–5    | 68 ± 13.3 | 5/110     | 6       |
| Salman, 2011       | Syria         | Interview                 | CKD SD     | 41.59 ± 15.1| 25/123    | 8       |
| Lin, 2013          | Taiwan        | Interview                 | CKD SD     | 61.9 ± 12.6| 286/1130  | 13      |
| Erdogan, 2012      | Turkey        | Questionnaire             | CKD SD     | 51.4 ± 14.8| 40/112    | 11      |
| Tuncer, 2011       | Turkey        | Interview                 | CKD SD     | NR       | 10/81     | 5       |
| Dikici, 2014       | Turkey        | Interview                 | CKD SD     | 59.7 ± 14.0| 113/246   | 12      |
| Soyoral, 2010      | Turkey        | Interview                 | CKD SD     | 52.28 ± 18.1| 11/76     | 10      |
| Siddiqi, 2005      | UK            | Interview                 | CKD SD     | NR       | 127/277   | 12      |

CKD: chronic kidney disease; CKD 1–5: CKD patients not treated with dialysis; CKD 5D: estimated glomerular filtration rate <15 and treated with dialysis; NR: not reported; Mix: study investigated more than one population.
with high heterogeneity ($I^2 = 94.26, p < .001$). Among dialysis studies, the pooled prevalence was numerically lower in the clinical-interview group than that in the questionnaire group [27.7% (95%CI, 23.3–32.5) vs. 31.8% (95%CI, 23.8–41.1), $p$ for subgroup difference = .402], which was unable to demonstrate statistically significant difference between them. Similarly, among the 32 studies focused on only one type of dialysis, the pooled prevalence was numerically lower in hemodialysis patients than that in peritoneal dialysis [27.9% (95%CI, 23.7–32.6) vs. 42.3% (95%CI, 23.3–63.9), $p$ for subgroup difference = .168].

**Subgroup analyses, meta-regression analysis, sensitivity analyses, and publication bias**

Heterogeneity among the studies was considerable ($I^2 = 96.1%$), so subgroup analyses and meta-regression analysis were conducted to determine the possible sources of heterogeneity. Subgroup analyses based on these variables: (1) sample size (<100, 100–499, or ≥500); (2) WHO region (European, Americas, Western Pacific, East Mediterranean, and Southeast Asia); (3) versions of IRLSSG criteria (version 1995, 2003, or 2012); (4) study quality [poor (0–6), or high (7–13)]. In these analyses, we found no significant difference in estimated prevalence based on study quality ($p$ for subgroup difference = .948) and region ($p$ = .079). But difference in sample size [32.8% (95%CI, 24.5–42.4) vs. 25.7% (95%CI, 20.4–31.8) vs. 11.8% (95%CI, 7.5–18.1), $p$ for subgroup difference < .001] and version [19.6% (95%CI, 14.2–26.5) vs. 25.1% (95%CI, 19.7–31.4) vs. 40.0% (95%CI, 29.6–51.4), $p$ for subgroup difference = .004] show significant source of heterogeneity.

**Table 4** depicts the univariate meta-regression analyses. As shown in the table, serum iron, blood urea nitrogen (BUN), creatinine, and complication (peripheral neuropathy) did not modify the estimate of prevalence. We noticed that the prevalence of RLS increased slightly for each one year increase in the age of study participants ($p$ = .001). The prevalence of RLS numerically increased with an increasing proportion of women in the study populations ($p$ < .001). When it came to factors related to dialysis, the prevalence grew with the dialysis vintage ($p$ < .001) and $Kt/V$ ($p$ = .002). In the laboratory feature, the prevalence increased 0.256% for each 1 mg/dL increase in the level of serum phosphate ($p$ < .001). There were numerical decreases when the
Table 3. Prevalence of RLS diagnosed by clinical interview.

| Study                          | Stage of CKD | Number of participants | Prevalence of interview-based RLS random effects (95%CI) |
|-------------------------------|--------------|------------------------|----------------------------------------------------------|
| Bhowmik et al., 2004          | CKD 1–5      | 1/65                   | 1.5% (0.2–10.1)                                          |
| Aritake-Okada et al., 2011    | CKD 1–5      | 18/514                 | 3.5% (2.2–5.5)                                           |
| Jesus et al., 2015            | CKD 1–5      | 5/110                  | 4.5% (1.9–10.5)                                          |
| Bhowmik et al., 2003          | Dialysis     | 8/121                  | 6.6% (3.3–12.7)                                          |
| Merlino et al., 2010          | CKD 1–5      | 15/138                 | 10.9% (6.7–17.2)                                         |
| Tuncel et al., 2011           | Dialysis     | 10/81                  | 12.3% (6.8–21.4)                                         |
| Soyoral et al., 2010          | Dialysis     | 11/76                  | 14.5% (8.2–24.3)                                         |
| Goffredo et al., 2003         | Dialysis     | 26/176                 | 14.8% (10.3–20.8)                                        |
| Liborio et al., 2013          | CKD 1–5      | 18/99                  | 18.2% (11.8–27.0)                                        |
| Quinn et al., 2011            | CKD 1–5      | 55/301                 | 18.3% (14.3–23.0)                                        |
| Oliveira et al., 2011         | Dialysis     | 34/183                 | 18.6% (13.6–24.9)                                        |
| Siraj et al., 2015            | Dialysis     | 69/355                 | 19.4% (15.6–23.9)                                        |
| Collado-Seidel et al., 1998   | Dialysis     | 32/136                 | 23.5% (17.2–31.4)                                        |
| Lin et al., 2013              | CKD 1–5+     | 121/500                | 24.2% (20.6–28.1)                                        |
| Stefanidis et al., 2013       | Dialysis     | 286/1130               | 25.3% (22.9–27.9)                                        |
| Pavan and Sathesh, 2014       | Dialysis     | 154/579                | 26.6% (23.2–30.3)                                        |
| Li et al., 2014               | Dialysis     | 14/50                  | 28.0% (17.3–41.9)                                        |
| La Manna et al., 2011         | Dialysis     | 31/100                 | 31.0% (22.7–40.7)                                        |
| Pizza et al., 2012            | Dialysis     | 51/162                 | 31.5% (24.8–39.0)                                        |
| Mohammad et al., 2015         | Dialysis     | 61/163                 | 37.4% (30.3–45.1)                                        |
| Chrustina et al., 2015        | Transplant   | 30/75                  | 40.0% (29.6–51.4)                                        |
| Giannaki et al., 2011         | Dialysis     | 30/70                  | 42.9% (31.8–54.6)                                        |
| Siddiqui et al., 2005         | Dialysis     | 127/277                | 45.8% (40.1–51.7)                                        |
| Dikici et al., 2014           | Dialysis     | 113/246                | 45.9% (39.8–52.2)                                        |
| Al-Jahdali et al., 2009       | Dialysis     | 114/227                | 50.2% (43.7–56.7)                                        |
| Rijman et al., 2004           | Dialysis     | 28/48                  | 58.3% (44.1–71.3)                                        |
| Telarovic et al., 2007        | Dialysis     | 49/82                  | 59.8% (48.8–69.8)                                        |
| Combined                      |              | 1701/6943              | 23.6% (19.6–28.1)                                        |

Heterogeneity Cochran Q = 470.18, I² = 93.41%, p < .001

CKD 1–5: earlier stages of chronic kidney disease; Dialysis: estimated glomerular filtration rate < 15 and treated with dialysis; Transplant: kidney transplant recipients.

Table 4. Univariate random-effects meta-regression analysis for the prevalence of RLS in CKD populations.

| Covariate          | Number of studies reporting one or more events | Scale | Proportional change in prevalence (95%CI) | p Values |
|--------------------|-----------------------------------------------|-------|-------------------------------------------|----------|
| Age                | 42                                            | Per 1-year increase | 0.012 (0.005 to 0.019) | .001     |
| Proportion of women| 51                                            | Per 1% increase     | 3.351 (2.612 to 4.090) | <.001    |
| Dialysis vintage   | 31                                            | Per 1-month increase| –0.012 (–0.015 to 0.010) | <.001    |
| Kt/V               | 9                                             | Per 1 increase      | 1.058 (0.404 to 1.712) | .002     |
| Ca                 | 9                                             | Per 1 mg/dL increase| –0.474 (–0.747 to –0.201) | <.001    |
| P                  | 12                                            | Per 1 mg/dL         | 0.256 (0.122 to 0.390) | <.001    |
| iPTH               | 10                                            | Per 1 pg/mL increase| 0.002 (0.002 to 0.003) | <.001    |
| Iron               | 5                                             | Per 1 ug/dL increase| –0.001 (–0.020 to 0.001) | .067     |
| BUN                | 7                                             | Per 1 mg/dL increase| –0.001 (–0.003 to 0.002) | .913     |
| Creatinine         | 8                                             | Per 1 mg/dL increase| 0.037 (–0.020 to 0.093) | .202     |
| Hemoglobin         | 42                                            | Per 1 g/dL increase | –0.382 (–0.455 to –0.309) | <.001    |
| Proportion with diabetes | 33                                | Per 1% increase     | 0.761 (0.423 to 1.098) | <.001    |
| Proportion with hypertension | 20                                 | Per 1% increase     | 0.907 (0.561 to 1.253) | <.001    |
| Proportion with peripheral neuropathy | 4 | Per 1% increase | –0.037 (–0.446 to 0.392) | .866     |
| Proportion with insomnia | 13                               | Per 1% increase     | 2.608 (2.254 to 2.982) | <.001    |
| Proportion with OSAS | 10                                  | Per 1% increase     | –0.668 (–1.330 to –0.006) | .048     |
| Proportion with depression | 5                                   | Per 1% increase     | –0.024 (–1.017 to 0.968) | .962     |
| Proportion with EDS | 12                                   | Per 1% increase     | 3.047 (2.611 to 3.482) | <.001    |

CI: confidence interval; Ca: serum calcium; P: serum phosphorus; BUN: blood urea nitrogen; iPTH: intact parathyroid hormone; Kt/V: urea clearance index; OSAS: obstructive sleep apnea syndrome; EDS: excessive daytime sleepiness.
level of serum calcium ($p < .001$) and hemoglobin ($p < .001$) dropped. Moreover, the prevalence of RLS was associated with some common chronic complications, for example, diabetes ($p < .001$), and hypertension ($p < .001$). We also found that the prevalence of RLS increased with the growth of the proportions in some other sleep disorders, such as insomnia ($p < .001$) and excessive daytime sleepiness (EDS) ($p < .001$).

The sensitivity analysis results suggested none of the studies significantly affected the pooled prevalence. Figure 3 depicts the publication biases of the studies with funnel plots. No significant publication bias was detected on both vision and statistics (the funnel plot was visually symmetrical; Egger regression: intercept = $-0.564$, 95%CI, $-4.047$ to $2.919$, $t = 0.326$, $p = .746$).

**Discussion**

Our study indicates that RLS is highly prevalent in CKD patients. In our meta-analysis, the overall prevalence of RLS among CKD populations is 24.2%, which is much higher than that in general population.24

According to our study, there are nearly one-third of dialysis patients diagnosed as RLS. Compared with dialysis, there are far fewer studies about RLS in early stages of CKD or kidney transplant recipients. In consequence, sparse data and small sample size are partially responsible for the less precise estimated prevalence in these two settings. For example, there are only four studies in transplant populations, three of which are from the TransQoL-HU Study. It is a cross-sectional study with large sample size. In this population, the prevalence of RLS is around 5%, which is close to the prevalence of general population. However, another study about transplant patients in Slovak reported a higher prevalence (40.54%).25 For the lack of related studies, to understand the real situation of RLS in transplant population, more investigations are needed. In dialysis setting, peritoneal dialysis patients suffer a higher prevalence (42.3%) than hemodialysis patients (27.9%) do. Similar result was found in the study from Rijksman et al. (Pearson’s $\chi^2$ test, $p = .03$).26 PD patients were more easily than HD patients to suffer from severe RLS and have poor sleep quality. Many RLS patients also experienced periodic limb movement disorder (PLMD) during sleep. However, an opposite conclusion was drew by Emami et al., expressing that RLS was more frequent in HD than PD patients (35.5% vs. 17.7%, $p = .048$). Another two studies showed that there was no statistically significant difference between PD and HD patients.27,28 Furthermore, a study showed that continuous ambulatory peritoneal dialysis (CAPD) treatment did not have any effect in triggering RLS symptoms. Thus, there is a hypothesis that CAPD could not induce RLS, based on the theory that the physiological membrane peritoneum does not cause any problem concerning biocompatibility.29 In the respect of dialysis adequacy, Ibrahim et al. and Chen et al. reported that RLS was significantly related to inadequate dialysis (lower level of $Kt/V$).30,31 While another study found that there was no significant correlation between RLS and dialysis adequacy.32 Likewise, the association between RLS and long dialysis history is still controversial. Three studies had provided evidence that longer history of dialysis was a risk factor of RLS.28,33,34 One suggested that RLS was caused by the accumulation of a middle molecule in dialysis-related amyloid, which was similar to the accumulation of $\beta_2$-microglobulin.31 However, longer duration of dialysis was reported not to affect the risk in another three studies. Further studies are required to explore the association between different aspects of dialysis and RLS.
The method used to diagnose RLS is partially responsible to the variable prevalence. When questionnaires were used to identify RLS, the pooled prevalence of RLS was 26.2%. After carefully re-reading every included study, we found that most of the questionnaires were done by self-rating, without necessary explanation and quality control. Sometimes participants would misunderstand the questions. For those assessed by clinical interview based on IRLSSG criteria, more adults were considered to experience RLS, with a higher prevalence of 27.7%. Among patients diagnosed by IRLSSG criteria, the prevalence of RLS was higher (25.1%) when basing on the criteria of version 2003 than those basing on the previous version. The ambiguous concept in previous criterion two, motor restlessness, was eliminated in 2003. And clearer explanation about the criterion three, worsening of symptoms at rest with at least temporary relief by activity, was assigned to two criteria in the latter version in criterion two and three. Emphasis was added to the primacy of the urge to move, and separate symptom provocation by rest from symptom relief by activity. Some supportive clinical features (such as positive family history of RLS, positive response to dopaminergic therapy and periodic limb movements), which were not essential but helpful to the diagnosis of RLS, were added to the new version of diagnostic criteria. Compared with the previous version, the version 2003 was widely promoted by IRLSSG for its higher sensitivity in finding potential patients. For example, some patients might not correspond with the former criteria, because the symptom was so severe that they cannot relief the urge by movement. However, in this later version, patients once obtained relief with movement earlier in the course of their disease were also included. Clinicians were able to describe the disease to patients in a more clear way. The quality of clinical diagnosis, particularly the sensitivity, would be improved at some degree. In the latest version, the IRLSSG revised the essential diagnostic criteria adding a fifth point allowing a diagnosis of RLS solely if the typical RLS symptoms were not accounted for by symptoms in the context of other medical of behavioral conditions. Since the new version is not widely used yet in published studies, it is not included in our discussion.

In order to study RLS prevalence in relation to the CKD course, we next sought supportive clinical features of IRLSSG criteria in the studies enrolled. We found that some studies had collected the positive family history of RLS. The response to medical treatment was also characterized in the identified studies. Maybe the majority of studies included are epidemiologic studies. Most of the investigators recorded whether the medicines were used in participants, but ignored the effect of these medicines. Despite periodic limb movements in sleep (PLMS) occurred in more than 80% of the people with RLS in general population; it was rarely reported in CKD population. In conclusion, the application of supportive clinical features in 2003 IRLSSG criteria has not yet been universal in studies about CKD population. The lack of clinical feature data may affect the diagnosis of RLS and exploration of risk factors, to which the further investigators should pay attention.

Investigators have yet to find the precise pathogenic mechanism of RLS in CKD populations. Iron-deficiency anemia is a well-known risk factor for idiopathic RLS, and the association between the level of serum ferritin and RLS suggests a close relationship between iron metabolism and pathogenetic mechanism of RLS. However, one of the included studies in our work showed no statistically significant difference in serum iron and ferritin between CKD patients with and without RLS. Related studies mentioned above are in dialysis setting. This conflicting conclusion is in part because of the routine use of iron supplementation in dialysis patients. Although Kim et al. noticed the confounding factor and tried to alleviate its effect by regular iron supplementation in almost all participants, the conclusion remained the same. The imbalance of calcium and phosphate is another widely accepted cause of RLS in CKD population, attested in some of the articles included in our study. Takaki et al. emphasized that hyperphosphatemia was associated with the presence of RLS. Hyperphosphatemia might be related to a disturbance of dopaminergic system, which mediated phosphate excretion in kidney and was also reported to be linked with RLS.

Although the quality of studies involved was relatively high (the average quality score was 8.98 in an assessment whose maximum score was 13), it did not cover up the methodological deficiencies of the review. Firstly, three abstracts, in which some essential data were insufficient, were included in our review. Secondly, inclusion or exclusion criteria were mentioned in only half of the studies (28/51 studies). The lack of inclusion/exclusion criteria might be most likely to influence the specificity of studies. In addition, more than three quarters of studies were from Europe and North America, reporting the prevalence of Caucasian and African–American. The paucity of data from other regions prevented the extension of the result in other populations.

Our study is the first study focusing on the prevalence of RLS in the whole CKD population, including the early stages and kidney transplantation recipients that have never enrolled before. Standardized methods conducted by two independent investigators and
comprehensive search for individual studies are the strengths of our review. In addition to the methodological deficiencies mentioned above, limitations of this review include insufficient data of certain populations and some findings without appropriate clinical explanation. First, comparing to the dialysis populations, the results in populations of early stages of CKD (including those with advanced diseases but not treated with dialysis) and transplantation were less certain. Fewer studies and relatively sparse data prevented us from drawing conclusions as convincing as dialysis group. Second, the prevalence of young patients (children and adolescents), which was a special group that mentioned in IRLSSG criteria, was not included in our review. It was reported that CKD in childhood had an incidence of 1.5–5 per million.\(^4\) The complications of CKD in these young patients not only affected their quality of life, but also influenced their performance at school. Third, although the prevalence was lower in the questionnaire group, the spotty quality of diagnostic criteria in various questionnaires prevented us from determining a relatively objective and credible prevalence in this group. Finally, in our meta-regression, we concluded that prevalence of RLS would increase with the increasing level of \(Kt/V\). However, as we all know, \(Kt/V\) is used to roughly estimate the adequacy of dialysis. High level of \(Kt/V\) usually means a satisfactory dialysis effect. We could not find any theoretical supports for such a result from previous studies and clinical experience. In addition, we did not analyze the long-term objective and credible prevalence in this group. Moreover, risk factors, which were not widely investigated in previous studies, might have important implications for diagnosis and prevention.

In conclusion, our study suggests that approximately one-quarter of patients with CKD suffer from RLS. Patients in dialysis treatment may be more susceptible to this sensorimotor disorder, to which both the clinical doctors and the patients should pay close attention. For more objective and accurate estimated prevalence data, further multicenter randomized clinical trials of large sample size for RLS in CKD based on clinical interview are needed. Investigators should pay more attention to the prevention and treatment of this disease.

**Disclosure statement**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

**References**

1. Chadban SJ, Briganti EM, Kerr PG, et al. Prevalence of kidney damage in Australian adults: The AusDiab kidney study. *J Am Soc Nephrol*. 2003;14:5131–5138.
2. Chen J, Wildman RP, Gu D, et al. Prevalence of decreased kidney function in Chinese adults aged 35 to 74 years. *Kidney Int*. 2005;68:2837–2845.
3. Coresh J, Byrd-Holt D, Astor BC, et al. Chronic kidney disease awareness, prevalence, and trends among U.S. adults, 1999 to 2000. *J Am Soc Nephrol*. 2005;16:180–188.
4. Singh NP, Ingle GK, Saini VK, et al. Prevalence of low glomerular filtration rate, proteinuria and associated risk factors in North India using Cockcroft-Gault and Modification of Diet in Renal Disease equation: An observational, cross-sectional study. *BMC Nephrol*. 2009;10:4.
5. Zhang L, Wang F, Wang L, et al. Prevalence of chronic kidney disease in China: A cross-sectional survey. *Lancet*. 2012;379:815–822.
6. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. *Arch Intern Med*. 2000;160:2137–2141.
7. Aurora RN, Kristo DA, Bista SR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults—an update for 2012: Practice parameters with an evidence-based systematic review and meta-analyses: An American Academy of Sleep Medicine Clinical Practice Guideline. *Sleep*. 2012;35:1039–1062.
8. Takagi J, Nishi T, Nangaku M, et al. Clinical and psychological aspects of restless legs syndrome in uremic patients on hemodialysis. *Am J Kidney Dis*. 2003;41:833–839.
9. La Manna G, Pizza F, Persici E, et al. Restless legs syndrome enhances cardiovascular risk and mortality in patients with end-stage kidney disease undergoing long-term hemodialysis treatment. *Nephrol Dial Transplant*. 2011;26:1976–1983.
10. Unruh ML, Levey AS, D’Ambrosio C, Fink NE, Powe NR, Meyer KB. Restless legs symptoms among incident dialysis patients: Association with lower quality of life and shorter survival. *Am J Kidney Dis*. 2004;43:900–909.
11. Stefanidis I, Vainas A, Dardiotis E, et al. Restless legs syndrome in hemodialysis patients: An epidemiologic survey in Greece. *Sleep Med*. 2013;14:1381–1386.
12. Collado-Seidel V, Kohnen R, Samtleben W, Hillebrand GF, Oertel WH, Trenkwalder C. Clinical and biochemical findings in uremic patients with and without restless legs syndrome. *Am J Kidney Dis*. 1998;31:324–328.
13. Tuncel D, Orhan FO, Sayarlioglu H, Isik UL, Dinc A. Restless legs syndrome in hemodialysis patients: Association with depression and quality of life. *Sleep Breath*. 2011;15:311–315.
14. von EE, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12:1495–1499.
15. Palmer S, Vecchio M, Craig JC, et al. Prevalence of depression in chronic kidney disease: Systematic review.
and meta-analysis of observational studies. *Kidney Int.* 2013;84:179–191.

16. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med.* 2006;144:427–437.

17. Navaneethan SD, Vecchio M, Johnson DW, et al. Prevalence and correlates of self-reported sexual dysfunction in CKD: A meta-analysis of observational studies. *Am J Kidney Dis.* 2010;56:670–685.

18. Szentkiralya A, Molnar MZ, Czira ME, et al. Association between restless legs syndrome and depression in patients with chronic kidney disease. *J Psychosom Res.* 2009;67:173–180.

19. Lee J, Nicholl DD, Ahmed SB, et al. The prevalence of restless legs syndrome across the full spectrum of kidney disease. *J Clin Sleep Med.* 2013;9:455–459.

20. Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov Disord.* 1995;10:634–642.

21. Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med.* 2003;4:121–132.

22. Molnar MZ, Novak M, Szeifiant L, et al. Restless legs syndrome, insomnia, and quality of life after renal transplantation. *J Psychosom Res.* 2007;63:591–597.

23. Molnar MZ, Szentkiralya A, Lindner A, et al. Restless legs syndrome and mortality in kidney transplant recipients. *Am J Kidney Dis.* 2007;50:813–820.

24. Allen RP, Bharmal M, Calloway M. Prevalence and disease burden of primary restless legs syndrome: Results of a general population survey in the United States. *Mov Disord.* 2011;26:114–120.

25. Chrastina M, Martinkova J, Minar M, Zilinska Z, Valkovic P, Breza J. Impact of kidney transplantation on restless legs syndrome. *Bratisl Lek Listy.* 2015;116:404–407.

26. Rijsman RM, de Weerd AW, Stam CJ, Kerkhof GA, Rosman JB. Periodic limb movement disorder and restless legs syndrome in dialysis patients. *Nephrology (Carlton).* 2004;9:353–361.

27. Kutner NG, Zhang R, Huang Y, Bliwise DL. Racial differences in restless legs symptoms and serum ferritin in an incident dialysis patient cohort. *Int Urol Nephrol.* 2012;44:1825–1831.

28. Gigli GL, Adorati M, Dolso P, et al. Restless legs syndrome in end-stage renal disease. *Sleep Med.* 2004;5:309–315.

29. Merlino G, Lorenzut S, Romano G, et al. Restless legs syndrome in dialysis patients: A comparison between hemodialysis and continuous ambulatory peritoneal dialysis. *Neurol Sci.* 2012;33:1311–1318.

30. Ibrahim JM, Wegdan OM. Epidemiology of sleep disorders in patients with chronic renal disease in Cairo, Egypt. *J Egypt Public Health Assoc.* 2011;86:68–72.

31. Chen WC, Lim PS, Wu WC, et al. Sleep behavior disorders in a large cohort of Chinese (Taiwanese) patients maintained by long-term hemodialysis. *Am J Kidney Dis.* 2006;48:277–284.

32. Al-Jahdali HH, Al-Qadhi WA, Khogeer HA, Al-Hejali FF, Al-Ghamdi SM, Al SAA. Restless legs syndrome in patients on dialysis. *Saudi J Kidney Dis Transpl.* 2009;20:378–385.

33. Telarovic S, Relja M, Trkulja V. Restless legs syndrome in hemodialysis patients: Association with calcium antagonists. A preliminary report. *Eur Neurol.* 2007;58:166–169.

34. Siddiqui S, Kavanagh D, Traynor J, Mak M, Deighan C, Geddes C. Risk factors for restless legs syndrome in dialysis patients. *Nephron Clin Pract.* 2005;101:c155–c160.

35. Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. *Sleep Med.* 2014;15:860–873.

36. Kavanagh D, Siddiqui S, Geddes CC. Restless legs syndrome in patients on dialysis. *Am J Kidney Dis.* 2004;43:763–771.

37. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapiere O, Lesperance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: A study of 133 patients diagnosed with new standard criteria. *Mov Disord.* 1997;12:61–65.

38. Quinn C, Uzbeck M, Saleem I, et al. Iron status and chronic kidney disease predict restless legs syndrome in an older hospital population. *Sleep Med.* 2011;12:295–301.

39. Kim JM, Kwon HM, Lim CS, Kim YS, Lee SJ, Nam H. Restless legs syndrome in patients on hemodialysis: symptom severity and risk factors. *J Clin Neurol.* 2008;4:153–157.

40. de Toledo FG, Thompson MA, Bolliger C, Tyce GM, Dousa TP. Gamma-L-glutamyl-L-DOPA inhibits Na(+)-phosphate cotransport across renal brush border membranes and increases renal excretion of phosphate. *Kidney Int.* 1999;55:1832–1842.

41. Applebee GA, Guillot AP, Schuman CC, Teddy S, Attarian HP. Restless legs syndrome in pediatric patients with chronic kidney disease. *Pediatr Nephrol.* 2009;24:545–548.

42. Li Y, Wang W, Winkelman JW, Malhotra A, Gao X. Iron status and chronic kidney disease predict restless legs syndrome in hemodialysis patients. *Kidney Int.* 2007;71:1727–1732.

43. Libório AB, Santos JP, Minete NF, de Diógenes CA, Farias LA, de Bruin VM. Restless legs syndrome and quality of sleep in patients with glomerulopathy. *BMC Nephrol.* 2013;14:113.

44. Araujo SM, de Bruin VM, Nepomuceno LA, et al. Restless legs syndrome in hemodialysis patients: Do biochemical findings distinguish them? *Movement Disorders. 15th International Congress of Parkinson’s Disease and Movement Disorders, Toronto, ON, Canada, June 5–9, 2011.*
47. Ricardo LML, Gisele RM, Miguel CR. Sleep disorders in patients with end-stage renal disease undergoing dialysis: comparison between hemodialysis, continuous ambulatory peritoneal dialysis and automated peritoneal dialysis. *Int Urol Nephrol.* 2015;47:369–375.

48. Loewen A, Siemens A, Hanly P. Sleep disruption in patients with sleep apnea and end-stage renal disease. *J Clin Sleep Med.* 2009;5:324–329.

49. Li H, Li X, Feng S, et al. Sleep disorders and its related risk factors in patients undergoing chronic peritoneal dialysis. *Chin Med J (Engl).* 2014;127:1289–1293.

50. Sabry AA, Abo-Zenah H, Wafa E, et al. Sleep disorders in hemodialysis patients. *Saudi J Kidney Dis Transpl.* 2010;21:300–305.

51. Giannaki CD, Sakkas GK, Karatzafiri C, et al. Evidence of increased muscle atrophy and impaired quality of life parameters in patients with uremic restless legs syndrome. *PLoS One.* 2011;6:e25180.

52. Pavan M, Sathish J. Restless legs syndrome in patients with end-stage renal failure on maintenance hemodialysis. *Med Sci Monit.* 2002;8:CR331–336.

53. Razeghi E, Sahraian MA, Heidari R, Bagherzadeh M. Association of inflammatory biomarkers with sleep disorders in hemodialysis patients. *Acta Neurol Belg.* 2012;112:45–49.

54. Emami N, Mosoumi M, Mortazavi M, et al. Restless legs syndrome in patients on maintenance hemodialysis and peritoneal dialysis. *J Res Med Sci.* 2012;17:5264–5271.

55. Mohammad R, Mahbubeh A, Arya J, et al. Restless legs syndrome in hemodialysis in Iran. *Neurol Sci.* 2015;36:723–727.

56. Cirignotta F, Mondini S, Santoro A, Ferrari G, Gerardi R, Buzzi G. Reliability of a questionnaire screening restless legs syndrome in patients on chronic dialysis. *Am J Kidney Dis.* 2002;40:302–306.

57. Pavan M, Sathish J. Restless legs syndrome in patients with end-stage renal disease undergoing dialysis therapy. *Nephrol Dial Transplant.* 2006;21:184–190.

58. Mohammad R, Mahbubeh A, Arya J, et al. Restless legs syndrome in nondialyzed patients with chronic renal failure. *Mov Disord.* 2010;25:1019–1025.

59. Emami N, Masoumi M, Mortazavi M, et al. Restless legs syndrome among dialysis patients with uremic restless legs syndrome. *Int Urol Nephrol.* 2013;45:1025–1030.

60. Mohammad R, Mahbubeh A, Arya J, et al. Restless legs syndrome in hemodialysis in Iran. *Neurol Sci.* 2015;36:723–727.