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Review Article

Association of sleep disorders, chronic pain, and fatigue with survival in patients with chronic kidney disease: a meta-analysis of clinical trials

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ABSTRACT

Objective: Sleep disorders, chronic pain, and fatigue have been long-standing torments in most patients with chronic kidney disease (CKD). In this review, we attempted to explore whether these nontraditional cardiovascular risk factors are associated with increased mortality in patients with CKD.
Method: Electronic searches were performed in MEDLINE (PubMed, 1966–2018), EMBASE (1974–2018), ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials databases. All prospective or retrospective studies were considered eligible if they were cohort or observational studies and the final outcome was all-cause death or mortality.
Results: We ultimately included 18 studies (12 studies on sleep disorders, three studies on chronic pain, and three studies on fatigue) in our review. Pooled analysis of all studies indicated that patients with sleep disorders, chronic pain, and fatigue had increased risks of all-cause mortality (risk ratio [RR] = 1.47, 95% confidence interval [CI] = 1.30–1.66, $p < 0.0001$; RR = 1.29, 95% CI = 1.27–1.31, $p < 0.0001$; RR = 1.45, 95% CI = 1.23–1.70, $p < 0.0001$, respectively). Pooled results from four studies indicated that dialysis patients with sleep-disordered breathing had increased cardiovascular disease outcomes (RR = 2.45, 95% CI = 1.74–3.44, $p < 0.0001$).
Conclusion: Sleep disorders, chronic pain, and fatigue are remarkably associated with increased all-cause mortality in patients with CKD. Large clinical randomized controlled trials are required to further confirm the results of our meta-analysis.

1. Introduction

Patients with chronic kidney disease (CKD), especially those on hemodialysis (HD), are at high risk for various complications, such as cardiovascular disease (CVD), bleeding and ischemic stroke, hypertension, and bone mineral metabolic disorders [1–3]. However, some clinical manifestations and symptoms such as sleep disorders, chronic pain, and fatigue often exert negative effects on these patients. Sleep disorders, including reduced sleep duration and sleep efficiency at night, excessive daytime sleepiness, periodic limb movements in sleep, sleep-disordered breathing (SDB), and sleep apnea syndrome, occur with increased frequency in patients with CKD. It has been reported that 80% of dialysis patients with CKD are affected by sleep disorders. These patients have short, fragmented sleep with a total sleep duration between 260 and 360 min and sleep efficiencies between 66% and 85% [4]. Chronic pain and fatigue are significant factors associated with CKD that have received increasing recognition in recent years and commonly result in increased depression and diminished quality of life. To date, some small clinical trials have assessed whether sleep disorders, chronic pain, and fatigue are associated with survival in patients with CKD or HD patients; however, these studies have reported inconsistent results [5–22]. Considering these inconsistent results in regard to the association of sleep disorders, chronic pain, and fatigue with

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survival in dialysis or nondialysis patients with CKD, we believe that it is important to attempt to resolve the issue. Therefore, we conducted a meta-analysis of published clinical trials to pool the results and, thus, improve the statistical power of the analysis.

2. Methods

2.1. Search strategy

The relevant literature was searched in MEDLINE (PubMed, 1966–2018), EMBASE (1974–2018), ClinicalTrials.gov, and Cochrane Central Register of Controlled Trials databases using the following terms: "sleep OR pain OR fatigue" AND "chronic kidney disease (CKD) OR end stage renal disease (ESRD)" AND "all-cause death OR all-cause mortality OR survival OR mortality." Manual searches of references cited by the identified original studies and relevant review articles were attempted. All studied papers were on human subjects and were published in the English language. The detailed steps are presented in Fig. 1. A total of 18 studies were included in our meta-analysis, which are listed in Tables 1 and 2. These 18 studies met the following inclusion criteria adopted for our meta-analysis: duration of more than six months; average patient age of less than 75 years; use of a control group; and availability of outcome data on mortality in patients with CKD.

2.2. Data collection

Three reviewers (H,M.J., X.H.Y., B.L.Z.) performed the search and reviewed the results. Data were collected by all authors and independently extracted by three reviewers (H.M.J., H.X.Y., B.L.Z.), who reviewed all the study characteristics (ie, first author's surname, year of publication, study design, sample, follow-up, outcomes, and assessment of study quality). Any disagreement in data extraction was resolved through a discussion between these two reviewers in consultation with the other authors (H.Y.G., X.L.Z., L.L.G.).

2.3. Quality assessment for individual studies

The two previously mentioned reviewers assessed the quality of each selected study using the Newcastle–Ottawa Scale [23], which assigns a maximum of nine stars to a study based on the quality of patient selection, study design, comparability, exposure, and outcome. We considered a study to be of "high quality" if it scored nine stars on this scale and "medium quality" if it scored seven or eight stars. Any discrepancies were resolved through a discussion between these two reviewers.

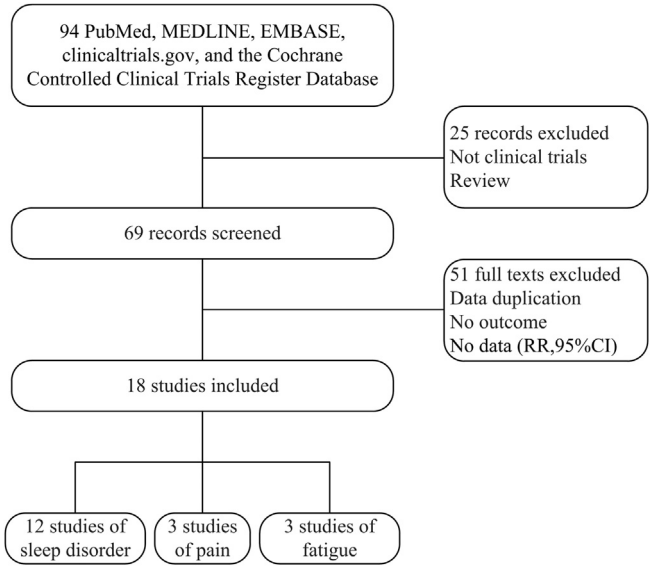

Fig. 1. Study selection process.

2.4. Summary measures and synthesis of results

The risk ratios (RRs) for sleep disorders, chronic pain, and fatigue associated with mortality were extracted from each study or calculated by a reviewer (X.H.Y.). Four studies reported that sleep disorders are associated with CVD outcomes; thus, we used subgroup analysis to assess the effect of sleep disorders on the relative risk of CVD. We provided the following baseline characteristics of all included studies: study design, method(s) of assessment, subjects, mean follow-up time, age, sex, pre-existing conditions, outcomes, and quality. To assess the potential for publication bias, we constructed funnel plots for each outcome in which the log RRs were plotted against their standard errors. We also conducted a sensitivity analysis in which each study was extracted in turn to evaluate the effect of the study on the estimate.

2.5. Statistical analyses

Risk ratios represented a valid approach to assess the risks of mortality associated with sleep disorders, chronic pain, and fatigue. Statistical heterogeneity across various studies was tested using Cochran's Q test. A p value of more than the nominal level of 0.05 indicated a lack of heterogeneity across the studies. Because the studies used a variety of assessments of sleep disorders, pain, and fatigue, which would lead to heterogeneity, RRs and 95% confidence intervals (CIs) were calculated using a random effects model. We also performed subgroup analysis to evaluate the association of sleep disorders with CVD outcomes. We used the Egger test to examine the presence of publication bias. Data were analyzed using STATA 14.0 (StataCorp, College Station, TX, USA). Statistical significance was set at $p < 0.05$ for all analyses.

3. Results

3.1. Study flow and study characteristics

The decision process that was used to differentiate the studies considered for inclusion is displayed in Fig. 1. Overall, as previously mentioned, we ultimately included 18 studies (12 studies on sleep disorders, three studies on chronic pain, and three studies on fatigue). Table 1 shows the characteristics of the 12 included studies on sleep disorders. All studies recorded all-cause mortality, and four studies recorded CVD outcome. Of the selected clinical trials, nine and three focused on dialysis and nondialysis patients, respectively. Table 2 presents the characteristics of the six studies on chronic pain and fatigue associated with mortality. All studies recorded all-cause mortality; of the selected clinical trials, five and one focused on dialysis and nondialysis patients, respectively. The results of quality assessment indicated that 11 and seven studies were of high and medium quality, respectively. The seven medium-quality studies lacked detailed descriptions of the study design.

3.2. Association of mortality with sleep disorders, chronic pain, and fatigue in patients with CKD

Exploratory data analysis of all studies indicated that patients with sleep disorders, chronic pain, and fatigue had increased risks of all-cause mortality, as shown in Figs. 2–4 (RR = 1.47, 95% CI = 1.30–1.66, $p < 0.0001$; RR = 1.29, 95% CI = 1.27–1.31, $p < 0.0001$; RR = 1.45, 95% CI = 1.23–1.70, $p < 0.0001$, respectively).