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REVIEW ARTICLE

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Periodontitis and risk of mortality in patients with chronic kidney disease: A systematic review with meta-analysis

Hong Wu[1] | Shengpeng Wang[2] | Zhenhui Wei[3]

[1]Department of Orthodontic Teaching and Research Office, College of stomatology, Shenyang Medical College, Shenyang, China

[2]Clinical Medicine Class 2020, Medical College of Jinzhou Medical University, Jinzhou, China

[3]Department of stomatology, Air Force Hospital from Northern Theater of Chinese People's Liberation Army, Shenyang, China

Correspondence
Zhenhui Wei, Department of stomatology, Air Force Hospital of Northern Theater of Chinese People's Liberation Army, No 46 Xiaoheyan Road, Shenyang 110000, China.
Email: 18642086090@163.com

Abstract

Studies examining the link between periodontitis and survival outcomes have yielded conflicting results in patients with chronic kidney disease (CKD). This systematic review with meta-analysis aims to assess the association between periodontitis and cardiovascular or all-cause mortality in CKD patients. A thorough search was conducted on the PubMed, Web of Science, and Embase databases for studies investigating the association between periodontitis and survival outcomes in CKD patients. Two authors independently scanned the titles or abstracts and then identified the eligible full-text article based on the PECOS criteria: Participants (CKD patients), Exposure (periodontitis), Comparison (mild/no periodontitis), Outcomes (cardiovascular or all-cause mortality), and Study design (retrospective or prospective cohort). Six cohort studies, including 7731 patients, were identified. The included studies had low-to-moderate risk of bias. The mean/median follow-up duration ranged from 18.1 months to 8.67 years. The all-cause mortality rate was 44.8% for patients with periodontitis and 28.0% for controls. Meta-analysis showed that periodontitis, defined through clinical attachment loss (CAL), was significantly associated with an increased risk of all-cause (adjusted hazard ratio [HR] 1.24; 95% confidence intervals [CI] 0.89–1.72; $I^2 = 80.9\%$) and cardiovascular mortality (HR 1.57; 95% CI 1.08–2.27; $I^2 = 34.0\%$). Additionally, a significant association between periodontitis and the risk of cardiovascular or all-cause mortality was observed in studies with a predominance of females, follow-up duration ≥5 years, all stages of CKD, and low risk of bias subgroups. Periodontitis is significantly associated with an increased risk of all-cause and cardiovascular mortality in CKD patients within low risk of bias subgroup or based on defining periodontitis through CAL. **Registration number:** PROSPERO CRD42018512391.

KEYWORDS
all-cause mortality, cardiovascular mortality, chronic kidney disease, hemodialysis, meta-analysis, periodontitis

1 | INTRODUCTION

Chronic kidney disease (CKD) is a significant global public health concern,[1] with an estimated prevalence of around 9.1% in the general population.[2] In China alone, the Global Burden of Disease Study 2019 reported 150.5 million cases and 196 726 deaths from CKD.[3] The diagnosis of CKD requires a combination of a reduced estimated glomerular filtration rate (eGFR) and evidence

of kidney injury for at least 3 months.[4] According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines,[5] CKD stages are typically categorized as stages 1–2 (eGFR>60 mL/min/1.73 m^2), stages 3–4 (eGFR 15–59 mL/min/1.73 m^2), and stage 5 (eGFR<15 mL/min/1.73 m^2), also known as end-stage renal disease (ESRD). Individuals with CKD, especially those who advance to ESRD, are at a higher risk of morbidity and mortality. Cardiovascular disease is the primary cause of death in this population. Therefore, it is crucial to identify other modifiable risk factors for reduced survival in CKD.

Chronic kidney disease has been recognized as a systemic inflammatory syndrome.[6] Persistent low-grade chronic inflammation contributes to a poorer prognosis in CKD patients.[7] Periodontitis, a chronic inflammation of the dental supporting tissues induced by microbes, has been shown to have a bidirectional relationship with CKD.[8,9] Several studies[10–13] have assessed periodontitis as a predictor of reduced survival in adult patients with CKD. However, the association between periodontitis and cardiovascular or all-cause mortality in CKD patients is still a matter of debate.

Only one meta-analysis[14] examined the association between periodontitis and mortality in patients with CKD. However, this well-designed meta-analysis did not specifically focus on periodontitis. Since then, new publications[15–18] have provided additional evidence regarding the association between periodontitis and survival outcomes in CKD patients. To address this contentious issue, we conducted a systematic review with meta-analysis to assess whether periodontitis is a significant predictor of cardiovascular or all-cause mortality in patients with CKD. Given the potential impact of subclinical local and systemic inflammation caused by periodontitis on CKD outcomes, we hypothesize that periodontitis may independently predict reduced survival outcomes in this population.

2 | MATERIALS AND METHODS

2.1 | Search strategy

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist[19] and retrospectively registered in PROSPERO database (CRD42018512391). An extensive literature search was conducted until December 2023 in the database of PubMed, Web of Science, and Embase databases using the combination of keywords (Text S1): (periodontitis OR pericementitis OR probing pocket depth OR clinical attachment loss OR alveolar bone loss) AND (hemodialysis OR peritoneal dialysis OR end-stage renal disease OR chronic kidney disease OR renal insufficiency OR renal failure OR kidney failure OR kidney transplant OR kidney transplantation) AND (survival OR mortality OR death). Additionally, a manual search was conducted in the reference lists of the included studies and relevant articles. There were no language restrictions in the literature search.

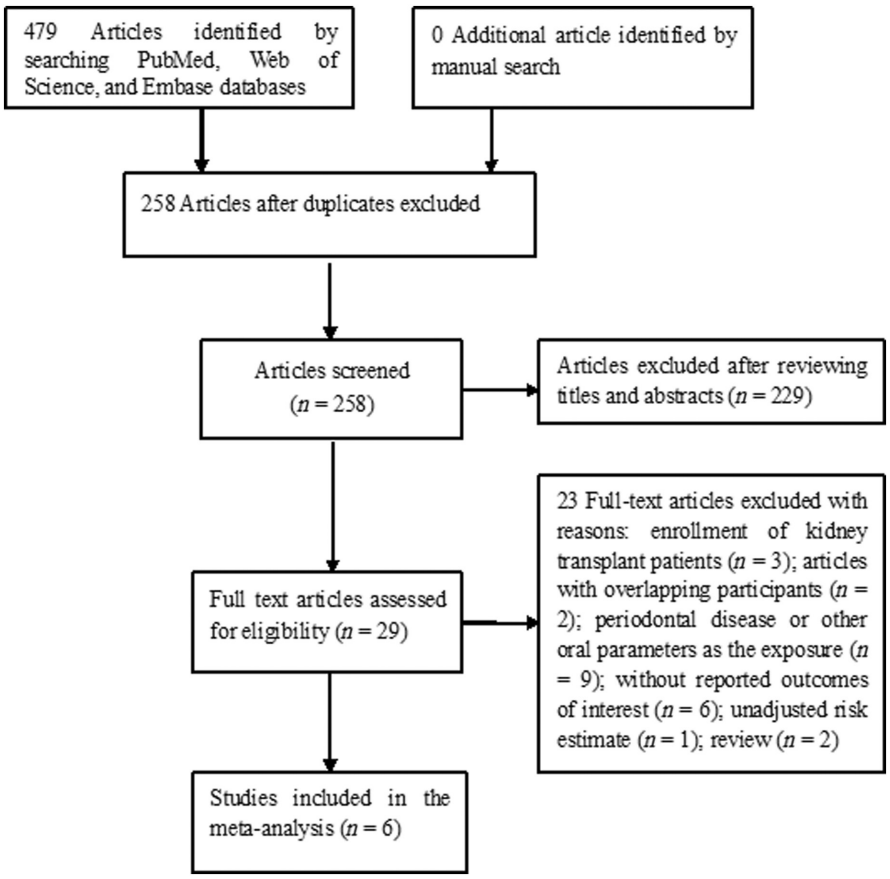

FIGURE 1 Flow chart showing the study selection process.

2.2 | Inclusion and exclusion criteria

Two independent authors scanned the titles and/or abstracts and then identified the potentially eligible full-text articles according to the PECOS criteria: (1) Participants: patients with a diagnosis of CKD stages 3–5 (an estimated glomerular filtration rate <60 mL/min/1.73 m^2 and/or urinary albumin/creatinine ratio ≥30 mg/g), including those requiring hemodialysis or peritoneal dialysis; (2) Exposure: periodontitis, as defined by probing pocket depth, clinical attachment loss, or alveolar bone loss; (3) Comparison: mild/no periodontitis as the reference group: (4) Outcomes: cardiovascular or all-cause mortality as the outcome of interest: (5) Study design: retrospective or prospective cohort that published in a peer-review journal; and (6) reported multivariable adjusted risk estimate of the

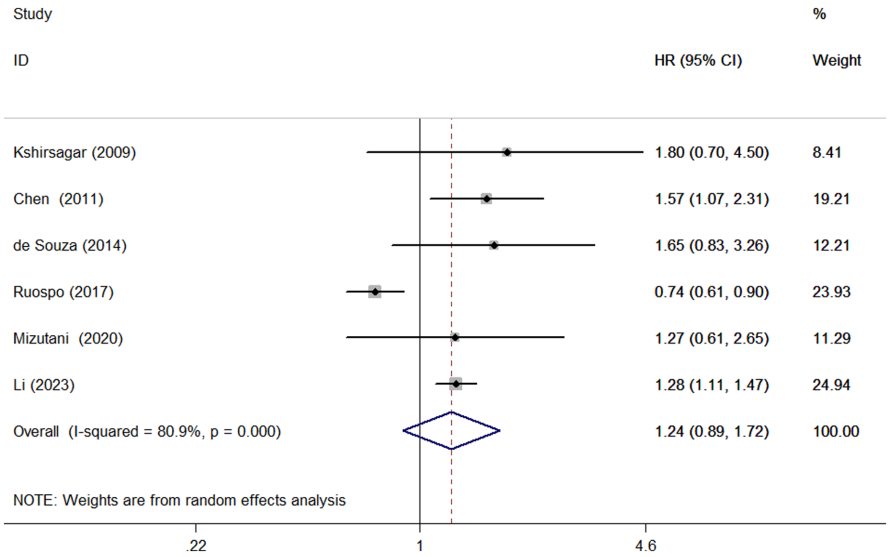

FIGURE 2 The pooled HR and 95% CI of all-cause mortality associated with periodontitis.

TABLE 1 Baseline characteristic of the included studies.

Author/year	Study design	Region	Study setting	Patients (% men)	Age (years)	Definition of periodontitis
Kshirsagar 2009[11]	R	USA	Hospital	Dialysis 168 (45.9)	53.6 ± 13.2	≥2 teeth with at least 6 mm CAL and at least 1 site with PPD >5 mm
Chen 2011[12]	P	Taiwan	Hospital	Hemodialysis 253 (46.2)	58.8 ± 0.8	PDI score >3
de Souza 2014[13]	P	Brazil	Hospital	Hemodialysis 122 (64.8)	50 ± 13	CAL≥5 mm in at least three teeth in at least 2 quadrants
Ruospo 2017[16]	P	Europe	Hospital	Hemodialysis 2710 (62.4)	61.5 ± 14.5	WHO-CPI 3–4 scores
Mizutani 2020[17]	P	Japan	Hospital	Hemodialysis 207 (65.2)	65.9 ± 12.1	At least 1 site PPD ≥3.0 mm and CAL ≥3.0 mm
Li 2023[19]	P	USA	Community	CKD 4271 (45.2)	60.02 ± 0.36	≥1 site CAL ≥4 mm, or at least 1 site PPD ≥5 mm

Abbreviations: BMI, body mass index; CAL, clinical attachment loss; CCI, Charlson Comorbidity Index; CI, confidence interval; CKD, chronic kidney disease; CPI, community periodontal index; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HR, hazard ratio; P, prospective; PDI, periodontal disease index; PPD, probing pocket depth; R, retrospective; WHO, World Health Organization.

[a]Results from pooling the subgroups.

[b]Results from propensity-matched analysis.

aforementioned outcomes. When multiple articles had overlapping participants, only the article with the most recent data was selected. The exclusion criteria included: (1) inclusion of kidney transplantation patients, (2) reported unadjusted risk summary, and (3) absence of risk estimates for death related to periodontitis. Any disagreements during the study selection process were resolved through discussion between the two authors until a consensus was reached.

2.3 | Data extraction and risk of bias assessment

From eligible studies, two authors independently recorded the following data: the first author's name, year of publication, geographical region, study design, type of patients (severity of CKD), sample size, gender distribution, baseline age, definition of periodontitis, outcome of interest, study duration, fully adjusted risk estimate, and adjusted factors. The risk of bias assessment was conducted using the Newcastle-Ottawa Scale (NOS) for cohort studies.[20] This scale assessed the selection of study participants, comparability, verification of exposure, and ascertainment of outcomes. Studies with a total score of 4–6 points were categorized as moderate risk of bias, while those with 7–9 points were categorized as low risk of bias. Disagreements in the process of data extraction and risk of bias assessment were resolved through discussion between the two authors until a consensus was reached.

2.4 | Statistical analysis

The association between periodontitis and survival outcomes was assessed by combining adjusted hazard ratios (HR) and their corresponding 95% confidence intervals (CI). The degree of heterogeneity among studies was assessed using Cochran's Q test and the I^2 statistic. If the p-value from Cochran's Q test was less than 0.1 and/or the I^2 statistic was greater than 50%, significant heterogeneity was deemed to be present. Due to the apparent clinical heterogeneity in defining periodontitis, a random effects model was selected for all meta-analyses. To assess the reliability of the overall risk estimate, a sensitivity analysis was conducted by omitting one study at a time. Subgroup analyses were carried out based on the study design, severity of CKD, patients' age, gender, sample sizes, definition of periodontitis, duration of follow-up, reference population, and study risk of bias. Publication bias was assessed using funnel plot, Beg's test, and Egger's test, with a p-value of less than 0.1 indicating the presence of publication bias. All meta-analyses were performed using Stata 12.0 (StataCorp, TX, USA).

Definition of controls	Number of periodontitis/controls	Follow-up	Outcomes, event number, HR (95% CI)	Variables used in adjusted models
None/mild periodontitis (All the remaining cases)	68/100	18 months	Total death: 22 1.8 (0.7–4.5) CV death: 14 5.0 (1.2–19.1)	Age, center, sex, dialysis vintage, smoking, cause of ESRD, DM, cause of ESRD, hypertension
None/mild periodontitis (All the remaining cases)	149/104	6 years	Total death: 102 1.57 (1.07–2.31)[a] CV death: 52 1.45 (0.83–2.52)[a]	Age, serum albumin, high-sensitivity CRP, CCI score, education, smoking
No periodontitis (All the remaining cases)	73/49	64.1 months	Total death: 34 1.65 (0.83–3.26)[a]	Age, sex, DM, hypertension, CRP, use of dental floss, frequency of visits to the dentist
None/mild periodontitis (All the remaining cases)	1355/1355	22.1 months	Total death: 556 0.74 (0.61–0.90)[b] CV death: 280 0.91 (0.64–1.29)	Age, sex, income, smoking, serum phosphorus, myocardial infarction, DM, mean arterial pressure, time on dialysis, number of teeth
No periodontitis (All the remaining cases)	194/13	3 years	Total death: 38 1.27 (0.61–2.65)	Age, sex, current smoking, BMI, DM, CVD, serum albumin, high-sensitivity CRP
None/mild periodontitis (All the remaining cases)	2213/2058	8.67 years	Total death: 2146 1.28 (1.11–1.47) CV death: 805 1.44 (1.14–1.81)	Age, sex, race/ethnicity, socioeconomic status, smoking, drinking, dietary quality, physical activity, BMI, hypercholesterolemia, hypertension, CVD, cancer, DM

3 | RESULTS

3.1 | Search results and study characteristics

Figure 1 illustrates the flowchart of the study selection process. The initial database search yielded 439 records, of which 258 remained after removing duplicates. After screening of titles and abstracts, 229 articles were removed, primarily because they were not relevant to the topic. Subsequently, 23 articles were excluded after the full-text assessment, mainly due to the enrollment of kidney transplant patients, articles with overlapping participants, other oral parameters as the exposure, or lack of outcomes of interest. Finally, six cohort studies[10–12,15,16,18] included in the qualitative synthesis. The *agreement between* the *authors* in the process of study selection was 87%.

Table 1 presents the baseline characteristics of the studies included in the analysis. These included studies were published between 2009 and 2023 and were conducted in Europe,[15] USA,[10,18] Brazil,[12] Taiwan,[11] and Japan.[16] One study[11] enrolled patients in all stages of CKD, while the others enrolled patients receiving dialysis. All the studies included a total sample size of 7731 patients, with a mean age ranging from 50 to 65.9 years. The follow-up period ranged from 18.1 months to 8.67 years. In the studies that reported such data, the all-cause mortality rate was 44.8% for patients with periodontitis and 28.0% for controls. According to the NOS criteria, two[10,15] of the included studies were deemed to be of moderate risk of bias, while the remaining studies were considered low risk of bias (Table S1).

3.2 | All-cause mortality

All the studies included in the analysis provided data on the association between periodontitis and all-cause mortality. A pooled analysis revealed that periodontitis was not significantly associated with a higher risk of all-cause mortality (adjusted HR 1.24; 95% CI 0.89–1.72; Figure 2) in patients with CKD. Significant heterogeneity was found ($I^2 = 80.9\%$, $p < .001$). The pooled HR ranged from 1.18 to 1.33 and the lower 95% confidence interval varied from 0.80 to 1.17 in the leave-one-out sensitivity analysis. This suggests that the pooled risk summary may be unreliable. Particularly, the study conducted by Ruospo et al[15] had a significant effect on the overall risk summary. However, periodontitis significantly predicts all-cause mortality based on defining periodontitis through CAL (adjusted HR 1.33; 95% CI 1.17–1.51).

Moreover, subgroup analysis revealed that the association between periodontitis and all-cause mortality was also influenced by the patients' age, gender, severity of CKD, follow-up duration, and risk of bias (Table 2). No evidence of publication bias was observed based on the results of the Beg's test ($p = .452$), Egger's test ($p = .605$), and the funnel plot (Figure 3).

3.3 | Cardiovascular mortality

Four studies[10,11,15,18] provided the data on the association between periodontitis and cardiovascular mortality. A pooled analysis revealed no significant association between periodontitis and an increased risk of cardiovascular mortality (adjusted HR 1.31; 95% CI 0.74–2.32; Figure 4) in patients with CKD. Significant heterogeneity was found ($I^2 = 87.2\%$, $p < .001$). Sensitivity analysis showed that the pooled HR ranged from 1.10 to 1.57 and the lower 95% confidence interval varied from 0.62 to 1.08. These findings suggest that the pooled risk summary may be unreliable. When we excluded the study conducted by Ruospo et al[15] from the overall analysis, the heterogeneity was significantly reduced ($I^2 = 34.0\%$, $p = .220$). Periodontitis significantly predicts cardiovascular mortality based on defining periodontitis through CAL (adjusted HR 1.57; 95% CI 1.08–2.27). Moreover, subgroup analysis indicated that the association between periodontitis and cardiovascular mortality was also influenced by the study design, gender, severity of CKD, follow-up duration, and risk of bias (Table 3).

4 | DISCUSSION

The present systematic review with meta-analysis indicates that periodontitis, defined through CAL, is associated with all-cause and cardiovascular mortality among patients with CKD. The overall pooled results are unreliable in the sensitivity analyses, probably due to the heterogeneity of the included studies. In addition, the association of periodontitis with cardiovascular or all-cause mortality seemed to be also influenced by factors, such as gender, severity of CKD, follow-up duration, or study risk of bias. Therefore, caution should be exercised when interpreting these findings because of the limited number of studies included and heterogeneity between these studies.

A previously well-designed meta-analysis[21] has assessed the association between periodontitis and CKD. The authors concluded that periodontitis was associated with an increased risk of CKD after adjusting for multiple variables. However, the impact of periodontitis on survival outcomes remains controversial in CKD patients. An early meta-analysis revealed a significant association between periodontitis and all-cause mortality in patients with CKD.[14] It is noteworthy that this meta-analysis did not specifically examine periodontitis. In contrast, our meta-analysis exclusively assessed CKD patients with periodontitis, while excluding renal transplant patients, thereby significantly reducing clinical heterogeneity.

Similar results were also reported in a study that did not meet our inclusion criteria. Ruokonen et al. found that moderate periodontitis was significantly associated with all-cause mortality in CKD patients when analyzed using univariate Cox proportional hazards regression. However, it did not show any independent relationship with death in multivariate analysis.[22] Chen et al. found no correlation

TABLE 2 Subgroup analysis on all-cause mortality.

Subgroup	Number of studies	Pooled HR	95% CI	*p*-value for HR	Heterogeneity between studies
Study design					
Prospective	5	1.20	0.85–1.69	.216	$I^2=84.1\%$; $p<.001$
Retrospective	1	1.80	0.71–4.56	.307	–
Patients' age					
≥60 years	3	1.03	0.65–1.62	.896	$I^2=90.1\%$; $p<.001$
<60 years	3	1.61	1.18–2.21	.003	$I^2=0.0\%$; $p=.962$
Gender distribution					
Male predominant	3	1.06	0.62–1.84	.823	$I^2=68.9\%$; $p=.040$
Female predominant	3	1.32	1.16–1.50	<.001	$I^2=0.0\%$; $p=.499$
Severity of CKD					
All CKD	1	1.28	1.11–1.47	.001	–
Dialysis	5	1.26	0.80–2.01	.322	$I^2=77.5\%$; $p=.001$
Sample sizes					
≥2000	2	0.98	0.57–1.67	.934	$I^2=95.0\%$; $p<.001$
<2000	4	1.55	1.16–2.08	.003	$I^2=0.0\%$; $p=.936$
Definition of periodontitis					
Defining through CAL	5	1.33	1.17–1.51	<.001	$I^2=0.0\%$; $p=.772$
Defining not use CAL	1	0.74	0.61–0.90	.002	–
Reference population					
Mild/no periodontitis	4	1.19	0.80–1.76	.402	$I^2=87.9\%$; $p<.001$
No periodontitis	2	1.46	0.89–2.41	.138	$I^2=0.0\%$; $p=.609$
Follow-up duration					
>5 years	3	1.32	1.16–1.50	<.001	$I^2=0.0\%$; $p=.503$
≤5 years	3	1.04	0.60–1.79	.896	$I^2=60.4\%$; $p=.080$
Study quality					
Moderate risk of bias	2	1.02	0.44–2.36	.959	$I^2=70.2\%$; $p=.067$
Low risk of bias	4	1.32	1.16–1.50	<.001	$I^2=0.0\%$; $p=.709$

Abbreviations: CAL, clinical attachment loss; CI, confidence intervals; CKD, chronic kidney disease; HR, hazard ratio.

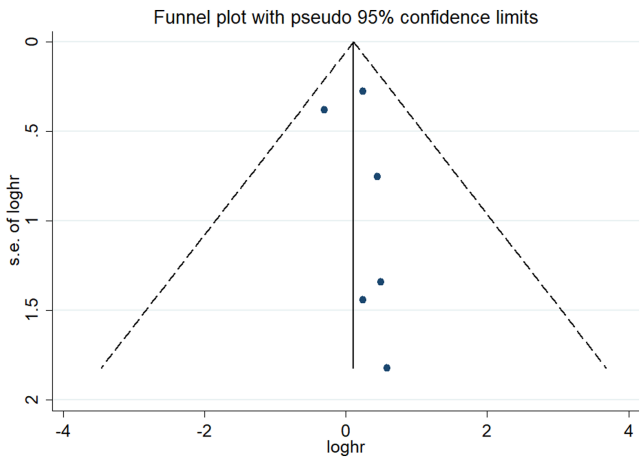

FIGURE 3 Funnel plot for detecting publication bias.

between periodontal parameters, such as probing depth or clinical attachment loss, and cardiovascular and cerebrovascular events among peritoneal dialysis patients.[23] Moreover, advanced chronic periodontitis was not linked to overall mortality and cardiovascular death in kidney transplant recipients.[24]

Periodontitis was found to be a significant predictor of cardiovascular or all-cause mortality in the studies that defined periodontitis through the clinical attachment loss subgroup. This finding suggests that the definition of periodontitis may affect its impact on cardiovascular or all-cause mortality. Additionally, a significant association between periodontitis and the risk of cardiovascular or all-cause mortality was also observed in studies with a predominance of females, a follow-up duration of more than 5 years, all stages of CKD, and low risk of bias study subgroups. Our subgroup analysis also revealed that studies with smaller sample sizes (<2000) and larger sample sizes (≥2000) have a distinct impact on the association

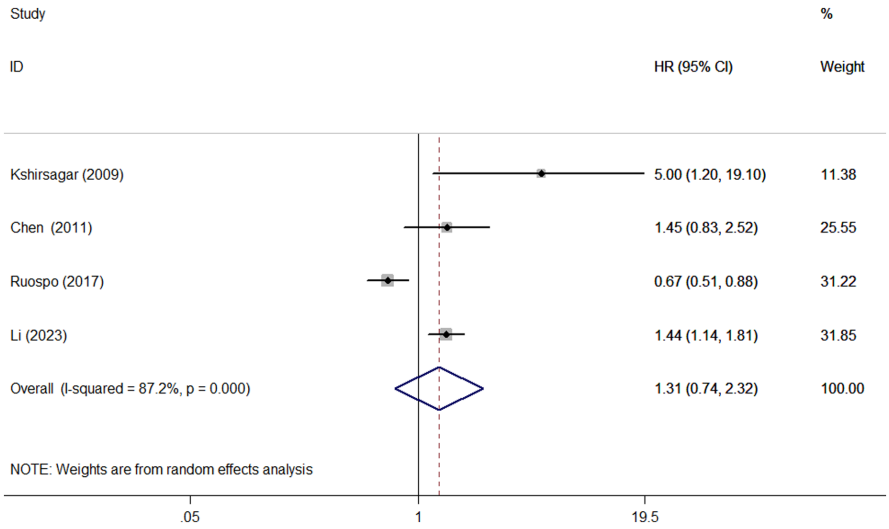

FIGURE 4 The pooled HR and 95% CI of cardiovascular mortality associated with periodontitis.

TABLE 3 Subgroup analysis on cardiovascular mortality.

Subgroup	Number of studies	Pooled HR	95% CI	*p*-value for HR	Heterogeneity between studies
Study design					
Prospective	3	1.10	0.62–1.94	.743	$I^2 = 89.4\%$; $p < .001$
Retrospective	1	5.00	11.20–19.10	.023	–
Patients' age					
≥60 years	2	0.99	0.47–2.09	.168	$I^2 = 62.2\%$; $p = .104$
<60 years	2	2.27	0.71–7.31	.970	$I^2 = 94.3\%$; $p < .001$
Gender distribution					
Male predominant	1	0.67	0.51–0.88	.004	–
Female predominant	3	1.57	1.08–2.27	.018	$I^2 = 34.0\%$; $p = .220$
Severity of CKD					
All CKD	1	1.44	1.14–1.81	.002	–
Dialysis	3	1.36	0.57–3.27	.493	$I^2 = 84.3\%$; $p = .001$
Sample sizes					
≥2000	2	0.99	0.47–2.09	.970	$I^2 = 94.3\%$; $p < .001$
<2000	2	2.27	0.71–7.31	.168	$I^2 = 62.2\%$; $p = .104$
Definition of periodontitis					
Defining through CAL	3	1.57	1.08–2.27	.018	$I^2 = 34.0\%$; $p = .220$
Defining not use CAL	1	0.67	0.51–0.88	.004	–
Follow-up duration					
>5 years	3	1.44	1.16–1.78	.001	$I^2 = 0.0\%$; $p = .982$
≤5 years	3	1.62	0.23–11.49	.627	$I^2 = 60.4\%$; $p = .005$
Study quality					
Moderate risk of bias	2	1.62	0.23–11.49	.627	$I^2 = 87.2\%$; $p = .005$
Low risk of bias	2	1.44	1.16–1.78	.001	$I^2 = 0.0\%$; $p = .982$

Abbreviations: CAL, clinical attachment loss; CI, confidence intervals; CKD, chronic kidney disease; HR, hazard ratio.

between periodontitis and the risk of cardiovascular or all-cause mortality in CKD patients. It should be noted that larger sample sizes generally yield more reliable and precise estimates. However, factors, such as patients' age, gender distribution, severity of CKD, definition of periodontitis, and length of follow-up in individual studies should also be taken into consideration. Additional prospective cohort studies should further investigate the predictive value of periodontitis, considering factors such as age, gender, early stage of

CKD, definition of periodontitis, and follow-up duration in patients with CKD.

One important consideration when interpreting the current findings is the potential impact of periodontal treatment. However, one of the studies included in the analysis reported a lack of evidence for an association between treated or untreated periodontitis and all-cause mortality in patients undergoing hemodialysis.[12] Additionally, in patients with type 2 diabetes, coronary heart disease (CHD), or cerebrovascular disease, there was no significant difference in the cardiovascular events or overall mortality between those who received periodontal treatment or maintenance care and those who did not.[25] It is important to note that the variation in treatment approaches may have influenced the outcomes of the treated patients. Furthermore, there is insufficient evidence to support the idea that periodontal treatment can improve survival outcomes in patients with CKD.[26] Future randomized controlled trials are necessary to assess whether CKD patients with concurrent periodontitis will derive benefits from periodontal treatment.

Several potential mechanisms could explain the link between periodontitis and mortality in CKD patients. First, microorganisms related to periodontitis may contribute to hypercoagulability and platelet aggregation,[27] accelerating the progression of pre-existing cardiovascular disease. Secondly, periodontitis was found to be associated with malnutrition–inflammation–atherosclerosis syndrome, especially in hemodialysis patients,[28] leading to inflammatory cardiovascular events.[29] Thirdly, chronic systemic inflammation caused by periodontitis may worsen renal dysfunction and contribute to the progression of kidney disease in patients with CKD. Finally, localized infections associated with periodontitis can further weaken the immune system.

This meta-analysis has several methodological limitations. First, the varying definitions of periodontitis used in the included studies were a major concern. Using different criteria for diagnosing periodontitis may have led to a potential selection bias. In particular, the severity of periodontitis was not considered in the subgroup analysis due to insufficient data on this aspect. Therefore, the influence of periodontitis severity on the predictive value could not be evaluated. Secondly, 2 out of 6 of the included studies were categorized as moderate risk of bias, which could potentially impact the accuracy of the pooled results. Thirdly, most of the studies included did not consider periodontal treatments, which could potentially affect the connections between periodontitis and the risk of mortality. Fourthly, there was certain heterogeneity among studies in terms of survival outcomes, which could not be fully explained in the subgroup analysis. The varied diagnostic criteria used to define periodontitis may be a significant source of heterogeneity. Fifthly, the findings from the subgroup analysis may be potentially unreliable due to the small number of studies analyzed. Finally, the failure to adjust for important factors, such as edentulism,[30] diabetes, hypertension, and CHD may have biased the pooled risk summary. Furthermore, the exclusion of studies that only reported risk estimates from the univariate analysis may have biased the combined results.

5 | CONCLUSIONS

Periodontitis is significantly associated with an increased risk of all-cause and cardiovascular mortality in CKD patients within low risk of bias subgroup or based on defining periodontitis through CAL. These findings indicate that overall pooled result is not reliable, probably due to the heterogeneity of the included studies.

AUTHOR CONTRIBUTIONS

Study conception/design and interpretation of data: ZH Wei. Literature search, study selection, data extraction, quality assessment, statistical analysis: H Wu, SP Wang. Writing (draft): SP Wang. Writing (editing): H Wu. All the authors reviewed and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The available data and materials section refers to the raw data used in this study are included in manuscript.

ORCID

Zhenhui Wei https://orcid.org/0009-0006-3319-5520

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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