Clinical Oral Investigations (2021) 25:6259–6268
https://doi.org/10.1007/s00784-021-03924-6

ORIGINAL ARTICLE

Periodontal disease and risk of mortality and kidney function decline in advanced chronic kidney disease: a nationwide population-based cohort study

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Received: 4 November 2020 / Accepted: 29 March 2021 / Published online: 4 April 2021

Abstract

Objectives Periodontal disease is prevalent in patients with chronic kidney disease (CKD) and potentially associated with kidney function decline. However, it is uncertain whether periodontal disease affects the risk of mortality and morbidity in patients with advanced CKD.

Materials and methods Taiwan's National Health Insurance Research Database was used to conduct a nationwide population-based cohort study. Propensity score matching procedures were performed to select people with stage 5 CKD and to compare the long-term risk of mortality, end-stage renal disease, and major adverse cardiovascular events (MACE) between people with and without periodontal disease. Multivariable Cox regression analyses were conducted to calculate the adjusted hazard ratio (aHR) with 95% confidence interval (CI) for the outcome of interest.

Results A total of 8119 subjects with stage 5 CKD were initially included. After matching to demographic and clinical covariates, 1254 subjects with 7099 person-years of follow-up were selected for analyses. Periodontal disease was not associated with long-term risks of all-cause mortality (aHR: 0.77, 95% CI: 0.49–1.22), progression to end-stage renal disease (aHR: 0.91, 95% CI: 0.75–1.10), or MACE (aHR: 1.18, 95% CI: 0.91–1.53). These findings were generally consistent across subgroups of age, sex, comorbid diabetes, uses of systemic antibiotic, and different dental procedures.

Conclusions Periodontal disease is not a predictor for long-term mortality or morbidity in patients with advanced CKD.

Clinical relevance These results provide important evidence to elucidate the relationship between periodontitis and critical clinical outcomes of advanced CKD.

Keywords Cardiovascular event · End-stage renal disease · Gum disease · Renal failure

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Introduction

Chronic kidney disease (CKD) is a leading cause of premature mortality and disability, affecting approximately 700 million individuals and imposing a huge economic burden on healthcare system worldwide [1]. CKD is projected to increase further due to the aging population and the growing prevalence of diabetes [2]. For patients with CKD, the risks of mortality, cardiovascular events, and hospitalization increase as the glomerular filtration rate (GFR) decreases below 60 $mL{\cdot}min^{-1}$ [3]. Patients with pre-dialysis CKD have a particularly high burden of severe symptoms with life expectancies of only 4 to 6 years [4]. However, there are currently few proven treatments in improving the clinical outcomes of pre-dialysis CKD [5, 6].

Periodontal disease is common and under-recognized in patients with CKD [7, 8]. Periodontal disease may cause systemic inflammation and malnutrition, and it has been demonstrated as a potential prognostic factor for health outcomes in the context of renal failure [9, 10]. Studies have shown that periodontal disease is associated with kidney function decline [11–17], cardiovascular diseases [18], and mortality [12, 19, 20] in CKD patients. However, it is still not fully clarified whether periodontal disease associates with mortality and morbidity in advanced CKD due to several limitations of previous studies, including small patient samples (< 1000 subjects) [13, 14, 16], cross-sectional design [11, 14, 16], unmatched statistical methodology [11–17, 19–21], insufficient confounding adjustment [14, 16], and restriction to specific populations or institutions [12–14, 16]. Identifying modifiable risk factors for adverse events of CKD is crucial for reducing its burden, but evidence regarding the association between periodontal disease and CKD prognosis is limited.

Accordingly, Taiwan's National Health Insurance Research Database (NHIRD) was used to conduct a nationwide population-based cohort study to investigate the putative association of periodontal disease with the long-term risks of mortality, progression to end-stage renal disease (ESRD), and major adverse cardiovascular events (MACE) in patients with advanced CKD. Based on the existing evidence [11–20], we hypothesized that periodontal disease was associated with greater risks of mortality and morbidity in patients with advanced CKD. The predictors of critical outcomes were also investigated and potentially confounding factors were further controlled using sound analytical methodology.

Materials and methods

Source of data

Taiwan's National Health Insurance program was launched in March 1995 and covered more than 99% of 23.4 million Taiwan residents at the end of 2013. The NHIRD contains comprehensive data of the insured individuals, including demographic characteristics (date of birth, sex, and residential location) and claims data (outpatient and inpatient care, physicians' primary and secondary diagnoses, medical prescriptions, and treatment procedures). Research articles based on this database have been broadly accepted in prominent scientific journals worldwide [21–24]. For the protection of personal privacy, a unique identification number is assigned to each beneficiary and enciphered before the data are released for research purposes. In this study, the unique identification number was employed to link all the medical records of each beneficiary. We employed three Longitudinal Health Insurance Databases (LHID2000, LHID2005, and LHID2010), which randomly sampled 1 million subjects from the original NHIRD in the years 2000, 2005, and 2010, respectively. The LHIDs include the most updated medical claims of sampled beneficiaries since 1997. The representativeness of LHIDs has been validated by Taiwan's National Health Research Institutes [25].

Patient selection

Inclusion criteria were patients aged ≥ 20 years who had a record of CKD using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes and had concurrent uses of erythropoiesis-stimulating agents covered by health insurance between January 1, 2002, and June 30, 2013. (Supplementary Table 1). Only patients with the CKD diagnosis made at least 2 times were included. In the reimbursement regulations of Taiwan's National Health Insurance, erythropoiesis-stimulating agents can be initiated when non-dialyzed CKD patients have a serum creatinine level > 530 $\mu mol{\cdot}L^{-1}$ (approximately equivalent to stage 5 CKD) and anemia defined by packed-cell volume < 28%, to maintain a packed-cell volume not exceeding 36%. Study has shown that 85% of patients with non-dialyzed stage 5 CKD used erythropoiesis-stimulating agents in Taiwan [4]. Therefore, this selected cohort was highly representative of people with stage 5 CKD. We defined the date of the first prescription of erythropoiesis-stimulating agents as the index date. People receiving renal replacement therapy before the index date were excluded. Patients were further classified into two groups: those with periodontal disease and without periodontal disease (control group). The diagnosis of periodontal disease was defined by the ICD-9-CM codes 523.0, 523.1, 523.3, and 523.4 made within 24 months before the index date. In this study, we considered patients with periodontal disease who had at least two outpatient service claims from board-certified dentists. Similar approaches have been broadly adopted and validated in previous studies [26–28]. In Taiwan, dentists considered medical and dental history, findings of periodontal examination, and radiographic analysis to identify

patients with periodontal disease in the clinical settings [29]. The periodontal examination typically included measurements of gingival topography (probing depth, recession, and attachment level) and assessments of gingival inflammation, dental plaque and calculus distributions, and subgingival health (bleeding on probing and suppuration) [29]. Patients were excluded from the control group if they had undergone any subgingival curettage or other periodontal procedures within 24 months before the index date.

Covariates

Monthly premium was classified into $0–500, $501–800, and > $800 US dollars. The ICD-9-CM codes of physicians' diagnoses within 24 months before the index date were used to identify the history of the following coexisting diseases: hypertension, diabetes mellitus, ischemic heart disease, atherosclerosis, cardiac dysrhythmias, heart failure, liver cirrhosis, chronic obstructive pulmonary disease, cerebrovascular disease, dyslipidemia, malignancies, and mental disorders (Supplementary Table 1). These coexisting diseases were chosen based on data availability, physiological plausibility, and the existing literature. Proxies for lifestyle factors were smoking, alcohol abuse, malnutrition, and obesity. We also included the dental procedures performed within 24 months before the index date, including dental scaling, subgingival curettage, periodontal flap surgery, other periodontal procedures, teeth extraction, odontectomy, and emergent dental care. Four types of systemic antibiotics prescribed within 24 months before the index date were included in the analysis: amoxicillin, cephalexin, clindamycin, and metronidazole [30].

Outcome measurement

Primary outcome is all-cause mortality. Secondary outcomes include progression to ESRD, defined as the date patients began dialysis for at least 90 days. According to Taiwan's Health Insurance reimbursement regulations, patients can undergo long-term dialysis only when their estimated GFR value drops below 5 $mL \cdot min^{-1}$ per 1.73 m^2. Finally, because of the potential association of periodontal disease with cardiovascular diseases and infections [18], we also ascertained the number of patients hospitalized for MACE, acute renal failure, septicemia or sepsis, urinary tract infection, and pyelonephritis (Supplementary Table 1). MACE include acute myocardial infarction, new-onset heart failure, stroke, and cardiac dysrhythmias. The included patients were followed up until December 31, 2013.

Statistical analysis

According to Schoenfeld's formula for sample size estimation of proportional hazards regression models [31], at least 112 events are needed to attain a power of 0.8 assuming an alpha level of 0.05 and hazard ratio (HR) of mortality 1.7 [19]. Of note, a total of 179 deaths occurred during the study period (87 and 92 in periodontal disease and control groups, respectively), which has met the requirement of sample size. Matching procedures with propensity score were conducted to balance the distribution of age, sex, monthly premium, coexisting diseases, and lifestyle factors between CKD patients with and without periodontal disease. A non-parsimonious multivariable logistic regression model was applied to estimate a propensity score for subjects with or without periodontal disease. We matched subjects with periodontal disease to controls (case-control ratio 1:1) using a greedy matching algorithm within a tolerance limit of 0.05 and without replacement [32]. The distributions of baseline characteristics in propensity score–matched samples were compared between subjects with and without periodontal disease by using standardized difference [33]. The cumulative incidences of mortality and morbidity were illustrated with the Kaplan-Meier method and compared between groups using log-rank tests. Adjusted hazard ratio and 95% confidence interval (CI) of CKD outcomes associated with periodontal disease were calculated by multivariable Cox proportional hazards regression models. Stratified analyses were also conducted by age, sex, comorbid diabetes, uses of systemic antibiotic, and different dental procedures to examine the outcomes of patients with periodontal disease within these strata. Finally, we applied stepwise backward variable elimination processes with an entry probability of 0.05 and removal probability of 0.1 to identify the independent factors associated with all-cause mortality, progression to ESRD, and MACE. A two-sided level of 0.05 was considered statistically significant. All the statistical analyses were conducted using Statistics Analysis System (SAS), Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

After the matching process, a total of 627 matched pairs were selected for analyses (Fig. 1). The follow-up time was median 5.4 years (interquartile range 2.8–8.5 years), and the cumulative time at risk of all matched subjects was 7099 person-years. Table 1 shows the baseline characteristics of the included subjects with and without periodontal disease. The distributions of demographics, coexisting diseases, and lifestyle factors were well balanced after propensity score matching. Of note, people with periodontal disease were more likely to receive systemic antibiotics and dental procedures compared with control group (Supplementary Table 2).

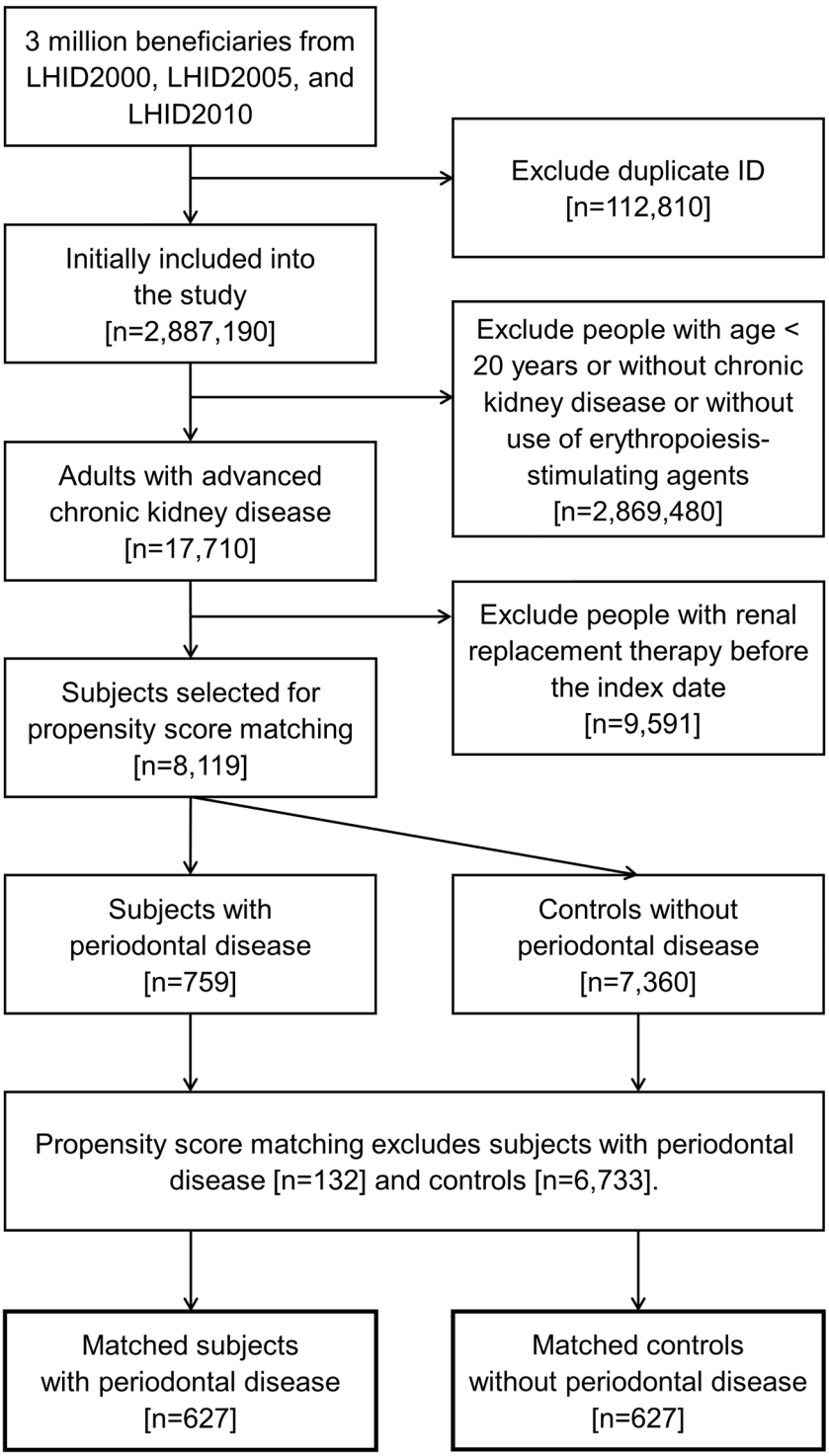

Fig. 1 Flow diagram for patient selection

Periodontal disease and all-cause mortality

One-year, 3-year, and 5-year cumulative incidences of all-cause mortality were 2.9% (95% CI: 1.5–4.3), 6.1% (4.1–8.1), and 10.2% (7.7–12.7) for people with periodontal disease, and 3.6% (2.2–5.0), 8.5% (6.1–10.9), and 12.9% (10.0–15.8) for controls (Fig. 2a). The duration between the index date and all-cause mortality was median 4.0 years (interquartile range 1.3–6.1) for people with periodontal disease and 2.8 years (1.1–5.3) for controls. The association between periodontal disease and all-cause mortality was non-significant either in the univariate model (crude HR: 0.87, 95% CI: 0.65–1.17) or in the multivariable model (adjusted HR: 0.77, 95% CI: 0.49–1.22) (Table 2). Similarly, there was no

Table 1 Baseline characteristics of CKD cases with periodontal disease and matched controls

	Periodontal disease, *n* = 627		Control, *n* = 627		Standardized difference
Age (years), mean (SD)	61.6	13.3	61.5	13.6	0.0074
Sex, male, *n* (%)	313	49.9	304	48.5	0.0317
Monthly premium (USD), *n* (%)					0.0300
0–500	366	58.4	378	60.3	
501–800	189	30.1	178	28.4	
≥ 801	72	11.5	71	11.3	
Coexisting disease, *n* (%)					
Hypertension	517	82.5	533	85.0	− 0.1035
Diabetes	306	48.8	325	51.8	− 0.0669
Ischemic heart disease	173	27.6	186	29.7	− 0.0560
Atherosclerosis	12	1.9	11	1.8	0.0489
Cardiac dysrhythmias	57	9.1	53	8.5	0.0440
Heart failure	107	17.1	116	18.5	− 0.0542
Liver cirrhosis	18	2.9	21	3.4	− 0.0877
COPD	71	11.3	79	12.6	− 0.0669
Cerebrovascular disease	115	18.3	138	22.0	− 0.1259
Dyslipidemia	233	37.2	227	36.2	0.0227
Malignancy	58	9.3	61	9.7	− 0.0307
Mental disorders	154	24.6	156	24.9	− 0.0095
Proxy for lifestyle factors, *n* (%)					
Smoking	2	0.3	3	0.5	− 0.2244
Alcohol abuse	6	1.0	5	0.8	0.1014
Malnutrition	6	1.0	6	1.0	0
Obesity	1	0.2	1	0.2	0
Systemic antibiotics, *n* (%)	234	37.3	204	32.5	0.1162

COPD, chronic obstruction pulmonary disease; *SD*, standard deviation; *USD*, United States Dollar

association between periodontal disease and mortality in the subgroups of age, sex, comorbid diabetes, uses of systemic antibiotics, or dental scaling (Table 3). Supplementary Table 3 shows the risk of all-cause mortality in patients with periodontal disease who had various dental treatments.

Periodontal disease and progression to ESRD

One-year, 3-year, and 5-year cumulative incidences of onset of ESRD were 59.9% (95% CI: 56.0–63.8), 82.6% (79.5–85.7), and 88.2% (85.3–91.1) for people with periodontal disease, and 61.4% (57.5–65.3), 82.9% (79.6–86.2), and 87.7% (84.6–90.8) for controls (Fig. 2b). The duration between the index date and onset of ESRD was median 0.6 year (interquartile range 0.2–1.2) for people with periodontal disease and 0.5 year (0.2–1.0) for controls. The association of periodontal disease with ESRD was non-significant either in the univariate model (crude HR: 1.00, 95% CI: 0.88–1.13) or in the multivariable model (adjusted HR: 0.91, 95% CI: 0.75–1.10) (Table 2). Supplementary Table 4 shows the risk of ESRD in periodontally diseased patients undergoing various dental procedures.

Periodontal disease and MACE

One-year, 3-year, and 5-year cumulative incidences of MACE were 17.4% (95% CI: 14.5–20.3), 30.6% (26.9–34.3), and 40.4% (36.1–44.7) for people with periodontal disease, and 16.4% (13.5–19.3), 30.1% (26.4–33.8), and 36.8% (32.7–40.9) for controls (Fig. 2c). The duration between the index date and MACE was median 1.5 years (interquartile range 0.5–3.9) for people with periodontal disease and 1.3 years (0.3–3.2) for controls. The association of periodontal disease with MACE was non-significant either in the univariate model (crude HR: 1.06, 95% CI: 0.89–1.27) or in the multivariable model (adjusted HR: 1.18, 95% CI: 0.91–1.53) (Table 2). Supplementary Table 5 shows the MACE risk of periodontal disease patients with different dental procedures.

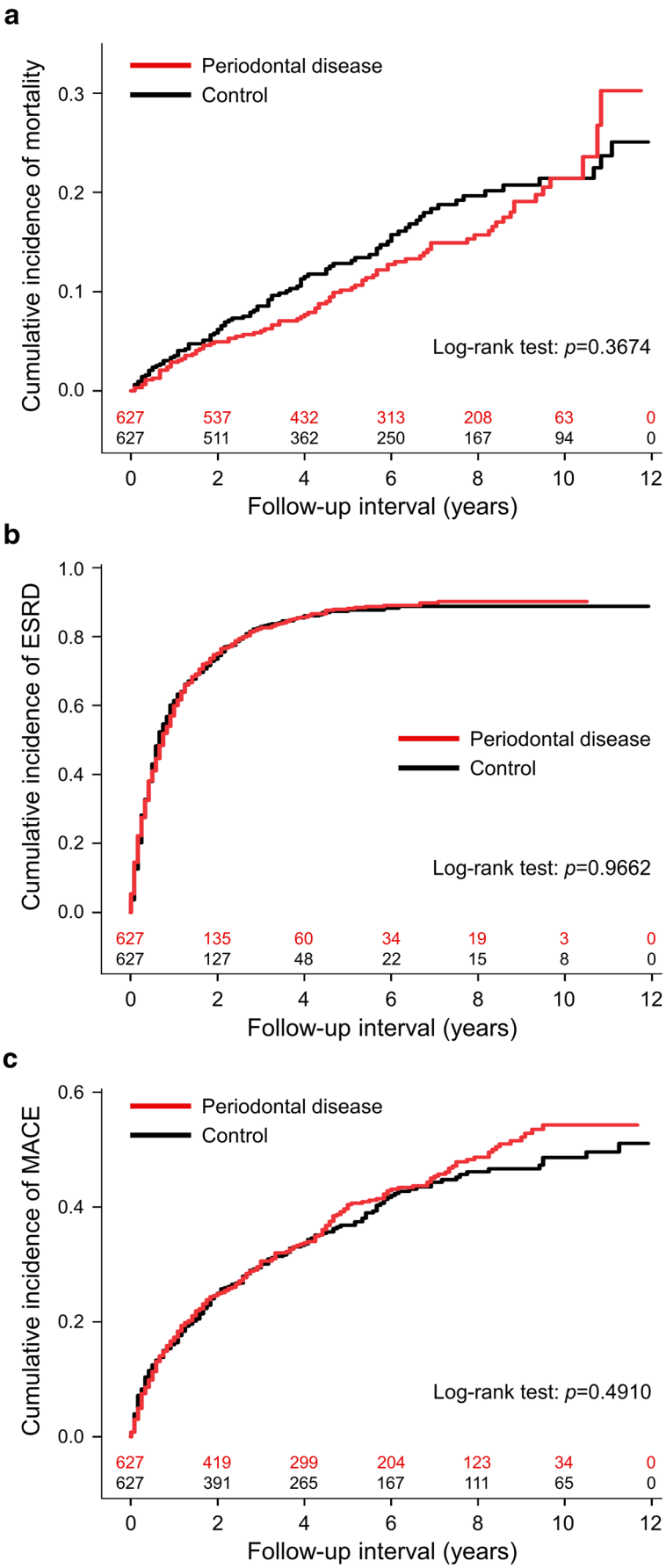

Fig. 2 Cumulative incidences of **a** all-cause mortality, **b** progression to ESRD, and **c** MACE between people with and without periodontal disease with number of subjects at risk

Table 2 Risk of all-cause mortality and morbidities for CKD cases with periodontal disease and matched controls

	Periodontal disease		Control		Outcome risk				
	Event, *n*	Crude incidence rate/1000 PY	Event, *n*	Crude incidence rate/1000 PY	IRR	cHR (95% CI)	*p*	aHR (95% CI)†	*p*
All-cause mortality	87	23.4	92	27.2	0.86	0.87 (0.65–1.17)	0.3676	0.77 (0.49–1.22)	0.2664
Morbidities									
Progression to ESRD	521	575.3	495	599.6	0.96	1.00 (0.88–1.13)	0.9673	0.91 (0.75–1.10)	0.3263
MACE‡	261	96.1	232	90.3	1.06	1.06 (0.89–1.27)	0.4939	1.18 (0.91–1.53)	0.2162
Septicemia or sepsis	180	57.5	184	64.3	0.89	0.90 (0.73–1.10)	0.3006	0.86 (0.63–1.17)	0.3364
Urinary tract infection	137	44.3	136	47.2	0.94	0.95 (0.75–1.20)	0.6640	1.21 (0.85–1.72)	0.2833
Pyelonephritis	12	3.3	16	4.8	0.68	0.69 (0.33–1.47)	0.3367	0.94 (0.28–3.14)	0.9227
Acute renal failure	80	23.7	83	26.9	0.88	0.93 (0.69–1.27)	0.6637	0.74 (0.46–1.20)	0.2195

aHR, adjusted hazard ratio; *CI*, confidence interval; *cHR*, crude hazard ratio; *ESRD*, end-stage renal disease; *IRR*, incidence rate ratio; *MACE*, major adverse cardiovascular events; *PY*, person-years

†Adjusted for age, sex, monthly premium, coexisting diseases, proxies for lifestyle factors, systemic antibiotics, and dental procedures

‡Including acute myocardial infarction, new-onset heart failure, stroke, and cardiac dysrhythmias

Periodontal disease and infection

There was no association between periodontal disease and the risk of hospitalizations for septicemia or sepsis (adjusted HR: 0.86, 95% CI: 0.63–1.17), urinary tract infection (adjusted HR: 1.21, 95% CI: 0.85–1.72), pyelonephritis (adjusted HR: 0.94, 95% CI: 0.28–3.14), or acute renal failure (adjusted HR: 0.74, 95% CI: 0.46–1.20) (Table 2).

Table 3 Subgroup analysis for risk of all-cause mortality associated with periodontal disease

		Event, *n*	Crude incidence rate/1000 PY	IRR	cHR (95% CI)†	*p*	aHR (95% CI)†	*p*
Age < 65 years	PD	32	14.5	0.78	0.80 (0.50–1.28)	0.3565	0.74 (0.38–1.46)	0.3887
	Control	40	18.5	Reference	Reference		Reference	
Age ≥ 65 years	PD	55	36.7	0.86	0.86 (0.59–1.27)	0.4526	0.82 (0.45–1.50)	0.5186
	Control	52	42.5	Reference	Reference		Reference	
Male	PD	40	22.6	0.68	0.68 (0.45–1.03)	0.0650	0.76 (0.41–1.41)	0.3780
	Control	51	33.1	Reference	Reference		Reference	
Female	PD	47	24.2	1.09	1.12 (0.74–1.71)	0.5972	1.00 (0.51–1.97)	0.9905
	Control	41	22.2	Reference	Reference		Reference	
Diabetes mellitus	PD	51	30.4	0.93	0.91 (0.62–1.36)	0.6550	0.79 (0.44–1.41)	0.4295
	Control	49	32.8	Reference	Reference		Reference	
No diabetes mellitus	PD	36	17.7	0.78	0.81 (0.52–1.27)	0.3644	0.94 (0.43–2.04)	0.8675
	Control	43	22.7	Reference	Reference		Reference	
Systemic antibiotics	PD	36	25.5	0.83	0.84 (0.52–1.37)	0.4840	0.84 (0.41–1.73)	0.6411
	Control	30	30.7	Reference	Reference		Reference	
No systemic antibiotics	PD	51	22.2	0.86	0.87 (0.60–1.26)	0.4647	0.81 (0.43–1.50)	0.4949
	Control	62	25.7	Reference	Reference		Reference	
Dental scaling	PD	60	21.0	0.73	0.72 (0.39–1.35)	0.3079	0.68 (0.34–1.37)	0.2757
	Control	12	28.9	Reference	Reference		Reference	
No dental scaling	PD	27	31.6	1.17	1.18 (0.76–1.83)	0.4613	0.83 (0.42–1.66)	0.6010
	Control	80	26.9	Reference	Reference		Reference	

aHR, adjusted hazard ratio; *CI*, confidence interval; *cHR*, crude hazard ratio; *IRR*, incidence rate ratio; *PD*, periodontal disease

†Adjusted for age, sex, monthly premium, coexisting diseases, proxies for lifestyle factors, systemic antibiotics, and dental procedures

Independent factors associated with mortality and morbidity

Supplementary Table 6 shows the results of backward variable elimination processes. Age and diabetes were both associated with the risk of all-cause mortality, progression to ESRD, and MACE. Of note, prior receipts of odontectomy and emergent dental care were linked to higher risks of ESRD (adjusted HR: 5.54, 95% CI: 2.44–12.58) and MACE (adjusted HR: 1.31, 95% CI: 1.06–1.63), respectively.

Discussion

This study found no evidence to support an association between periodontal disease and long-term risks of mortality, progression to ESRD, or MACE in patients with stage 5 CKD. Our results also suggested that periodontal disease was not associated with the risk of hospitalizations for sepsis or urinary tract infection in advanced CKD patients. Our study has two strengths to evaluate the relationship between periodontal disease and prognosis of advanced CKD. First, a nationwide dataset was used to increase the generalizability of analytical results. Second, we conducted robust statistical analyses using propensity score matching to balance the distribution of baseline characteristics. Our results provide important evidence to elucidate the relationship between periodontitis and important clinical outcomes of advanced CKD patients.

To our knowledge, this is the first study to focus on the putative impact of periodontal disease on patients with predialysis CKD, who have a particularly high burden of symptoms among populations of kidney disease [4]. In addition, propensity score matching analyses were used to minimize potential confounding effect from periodontitis-related systemic comorbidities, which have not been performed in previous studies [11–17, 19–21, 34]. Compared with previous cross-sectional studies [11, 14, 16], we used a longitudinal data with a follow-up interval up to 12 years to better examine the temporal relationship and causality. Our study found no evidence to support the hypothesis that periodontitis is an important risk factor for mortality, kidney function decline, and cardiovascular events of CKD, agreeing with one recent report [34] but not the others [11–17, 19–21]. Prior studies claimed a relationship between periodontal disease and mortality or kidney function decline in patients with old age [12, 13, 16] and diabetes mellitus [15, 20]. However, our subgroup analyses did not reveal such an association.

There might be several reasons why we did not identify an effect of periodontitis on mortality and kidney function as reported in prior studies [11–17, 19–21]. First, the etiology of CKD might vary among the included patients and possibly affect the CKD progression and mortality risk [35]. Second, the association between periodontal status and CKD outcomes might be attenuated by improvements in the medical care of CKD and periodontitis in Taiwan during the follow-up period [29, 36]. Third, our analyses have adjusted for a variety of periodontitis-related comorbidities (such as diabetes, ischemic heart disease, and atherosclerosis) in the models, which might conceal effects of periodontitis, which are (if present) only minor. Fourth, the disease in stage 5 CKD might be too advanced for periodontal disease to exert its detrimental effect on the selected outcomes [4].

Studies have shown that intensive periodontal therapy may improve clinical periodontal parameters and reduce circulating inflammatory response in ESRD patients [37, 38]. A clinical trial further showed that non-surgical periodontal treatment may benefit the kidney function, assessed by GFR using cystatin C, in patients with chronic periodontitis [39]. However, our analyses did not demonstrate an association between CKD outcomes and periodontal therapy or dental scaling. The current evidence supporting the therapeutic effect of periodontal care on kidney function and survival in CKD patients is still insufficient.

Whether periodontitis negatively influences kidney function in people without CKD remains an issue of great debate, with increased risks reported in some studies [12, 13, 17] but not in others [34]. Two studies focused on the elderly population and both reported a significant association between periodontal disease and kidney function decline [12, 13]. In contrast, the evidence regarding the relationship between periodontal disease and kidney function is conflicting among non-elderly people [17, 34]. The discrepant findings might result from the different measures of kidney function (formulas based on only serum creatinine levels or combination of serum creatinine and cystatin C levels) and potential measurement errors of periodontal disease due to increased tooth loss in elderly population.

There are limitations to our study. First, our data did not contain information about physical measures and biochemical laboratory measures that were not covered by NHIRD. Therefore, our analyses could not further adjust for GFR values [3], periodontal metrics, severity of periodontal disease [40], and level of inflammatory markers [9, 10], which might affect the risk of mortality and morbidity in CKD patients. There might exist patients with minor forms of periodontal disease or with a slower progression rate in the control group. Second, our analyses did not consider the pathophysiology of CKD and causes of death due to the difficulty of data acquisition. Third, our dataset did not include patients with periodontal disease who did not seek conventional dental care due to mild symptoms. Fourth, it is possible that our analyses could not detect a subtler effect of periodontal disease on CKD prognosis, which might be overridden by the significant comorbidities of CKD. Fifth, our results may not be applicable to non-Asian populations [41]. Finally, our cohort was followed up merely until the end of 2013 due to the regulations of NHIRD. Nevertheless, a previous study has shown that over half events of ESRD occurred within 4 years after the

diagnosis of CKD [42]. In our study, patients were followed up for median 5.4 years, and reliable estimated results can still be obtained in the context of survival analysis.

In conclusion, this study found no evidence for an association between periodontal disease and long-term mortality, progression to ESRD, or MACE in patients with stage 5 CKD in a general population examined over 12 years. Our analyses showed that periodontal disease is not an independent risk factor for mortality and morbidity in patients with advanced CKD. However, these results should be interpreted with caution because the periodontal metrics were not available. Future studies should focus on populations with early-stage CKD rather than predominantly pre-dialysis patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00784-021-03924-6.

Funding This work was supported by the grants from Shuang Ho Hospital (109IIT-02), Taipei Medical University, New Taipei City, Taiwan, and Ministry of Science and Technology (MOST109-2314-B-038-024), Taipei, Taiwan.

Declarations

Ethics approval This study was reviewed and approved by the Institutional Review Board of Taipei Medical University and Taipei Veterans General Hospital in Taiwan (TMU-JIRB-N202010040; IRB-TPEVGH-2013-04-005E).

Consent to participate Written informed consent was waived by the Institutional Review Board (chair: Professor Chung-Ming Chen of Taipei Medical University and Professor Shung-Tai Ho of Taipei Veterans General Hospital).

Conflict of interest The authors declare no competing interests.

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