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Original Article

Is periodontitis a potential risk factor of rhegmatogenous retinal detachment? A population-based retrospective cohort study of Taiwan

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Abstract *Background/Purpose:* Periodontitis, a common inflammatory disease, has been linked to various systemic and ocular conditions. However, its connection to rhegmatogenous retinal detachment (RRD), a vision-threatening condition, remains uncertain. This study aimed to investigate the association between periodontitis and RRD.
Materials and methods: From 2000 to 2015, 1,936,512 participants were recruited from Taiwan's National Health Insurance Research Database, including 29,970 with chronic periodontitis, defined by at least three outpatient visits within a year. A matched 1:1 comparison group was selected based on sex, age, and index year. The periodontitis group was divided into two subgroups: those who received root planing and/or surgical therapy (subgroup 1) and those who did not (subgroup 2).
Results: At the end of the follow-up, 2165 participants in the periodontitis group and 1259 in the comparison group developed RRD. The cumulative risk of RRD was increased in the

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periodontitis group, and the two subgroups, compared to the comparison group. After adjustment with the covariates of sociodemographic factors, systemic diseases, RRD comorbidities, and smoking/alcohol habits, the increased risk of developing RRD remained significant (adjusted hazard ratio: 1.49, 95 % CI: 1.12−1.83, $P < 0.001$). Subgroups 1 and 2 also had increased risks, with adjusted hazard ratios of 1.70 and 1.34, respectively. These results persisted even when excluding the first 1 or 5 years of data.

Conclusion: This nationwide retrospective study showed that patients with chronic periodontitis, regardless of whether they received periodontal treatment, had a higher risk of developing RRD, suggesting a potential association between periodontitis and RRD.

Introduction

Retinal detachment, characterized by the separation of the neurosensory retina from the underlying retinal pigment epithelium, is a sight-threatening condition.[1] There are four major types of retinal detachment: rhegmatogenous, traction, exudative or serous, and combined traction-rhegmatogenous.[1] Among these, rhegmatogenous retinal detachment (RRD) is the most common type of retinal detachment and can lead to blindness without proper and timely treatment.[2] In RRD, liquefied vitreous pockets can lead to currents in the vitreous cavity and dynamic traction at sites where the vitreous is adhered to the retina.[3] This traction can result in the formation of retinal breaks.[3] Certain risk factors have been suggested to be involved with the detachment, such as myopia, previous ocular trauma, and previous eye disease.[4,5] However, the precise pathogenesis of the separation between the neurosensory retina and the underlying epithelium is still uncertain.

Periodontitis is a renowned bacteria-induced inflammatory disease that affects humans worldwide, characterized by inflammation and destruction of the periodontium.[6] There is substantial evidence suggesting a link between periodontitis and systemic diseases, including diabetes mellitus, coronary artery disease, and neurodegenerative disease,[7,8] through the inflammatory, immune, or proteolytic pathways. A recent *in vitro* study demonstrated that the dysbiotic periodontal pathogen *Porphyromonas gingivalis* can effectively invade retinal pigment epithelial cells, replicate within them, and persist over time.[9] Study further shows that the outer membrane vesicles derived from *Porphyromonas gingivalis* can cause retinal endothelial dysfunction and is associated with diabetic retinopathy.[10] Although the exact pathogenesis is unknown, the hydrolysis of endothelial monolayers after treatment with activated gingipains of *Porphyromonas gingivalis*.[11] Recently, using epidemiology, the potential relationship between periodontal diseases and eye diseases, including glaucoma, age-related macular degeneration (AMD), infectious scleritis, and uveitis, has also been discovered.[12−14] While alterations in the blood-retinal barrier are associated with diabetic retinopathy and AMD,[15] due to retinal microvascular endothelial dysfunction, the blood-aqueous barrier-induced intravitreal currents may have also been linked to RRD.[3,16−18] In this study, by retrieving data from the National Health Insurance Research Database (NHIRD) of Taiwan, we retrospectively investigated the risk of RRD in patients with chronic periodontitis with a 15-year follow-up period.

Materials and methods

Database

Data were retrieved from the NHIRD of Taiwan from 2000 to 2015. On March 1, 1995, the Taiwanese government began the National Health Insurance (NHI) Program, which offers centralized health insurance to more than 90 % of the population.[19] The NHIRD is a representative sample of the total population of 23,000,000 people in Taiwan. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes were used to record the diagnoses. The diagnosis of RRD was performed by a board-certified ophthalmologist, and chronic periodontitis was validated by dentists. This study was exempted from review by the Institutional Review Boards of Taipei Tzu Chi Hospital (No. 10-W-003) and the Institutional Review Board of the Tri-Service General Hospital, National Defense Medical Center (No. E202316018).

Study design

The present study was designed as a retrospective matched cohort study. Patients who had received their first-time diagnosis of chronic periodontitis (ICD-9-CM codes 523.4, chronic periodontitis) were selected from January 1, 2000, to December 31, 2015. Based on the dentistry database, patients who underwent at least three outpatient visits within the 1-year claim period for chronic periodontitis, according to the ICD-9-CM code, were enrolled in the periodontitis group. The estimation algorithm of propensity score matching was used logistic regression, matching algorithm was taken nearest neighbor matching, and the tolerance of matching score was set 0.2. The option for nearest neighbor was set as random matching order, replacement, no caliper, and 1 to 1 matching by sex, age, and index year. A total of 29,970 individuals who had the dental visit(s) but lacked the periodontitis diagnosis were therefore included in the comparison group. Furthermore,

the patients with chronic periodontitis were categorized into the subgroup 1, which included those who received root planning and/or surgical therapy, and the subgroup 2, which consisted of those who did not receive these periodontal therapies, based on previous studies.[20,21] Periodontal therapies were identified according to the NHI order codes (the sub-gingival curettage/root planing of 91,006–91008C and periodontal flap operation of 91009B–91010B). The exclusion criteria were as follows: (a) those diagnosed with chronic periodontitis and therapy from January 1, 1998, to December 31, 1999, (b) those diagnosed with RRD from 1998 to 1999 or before the first visit for periodontitis, and (c) those aged <35 years. Of 1,936,512 individuals, 29,970 who were diagnosed with chronic periodontitis were included in periodontics group and subdivided into subgroup 1 and 2 (11,482 and 18,488 in subgroup 1 and 2, respectively) (Fig. 1).

Covariate assessment

The covariates in our analysis included the following: age group (35–54 and ≥ 55 years), urbanization level of residence (levels 1–4), monthly insurance premium, level of care (hospital center, regional hospital, and local hospital/clinics), and comorbidities. Urbanization levels were characterized into four levels according to population and specific designation.[22] The baseline comorbidities included hypertension (ICD-9-CM codes: 401.1, 401.9, 402.10, 402.90, 404.10, 404.90, 405.1, and 405.9), diabetes mellitus (ICD-9-CM code: 250.0–250.3 and 250.7), stroke (ICD-9-CM codes: 433, 434, and 436), hyperlipidemia (ICD-9-CM code: 272), depression (ICD-9-CM codes: 296.2–296.3, 300.4, and 311), traumatic brain injury (ICD-9-CM codes: 310.2, 800–804, 850–854, 905.0–950.1, 950.3, 907.0, 959.01, 959.9, and V15.52), coronary artery disease (ICD-9-

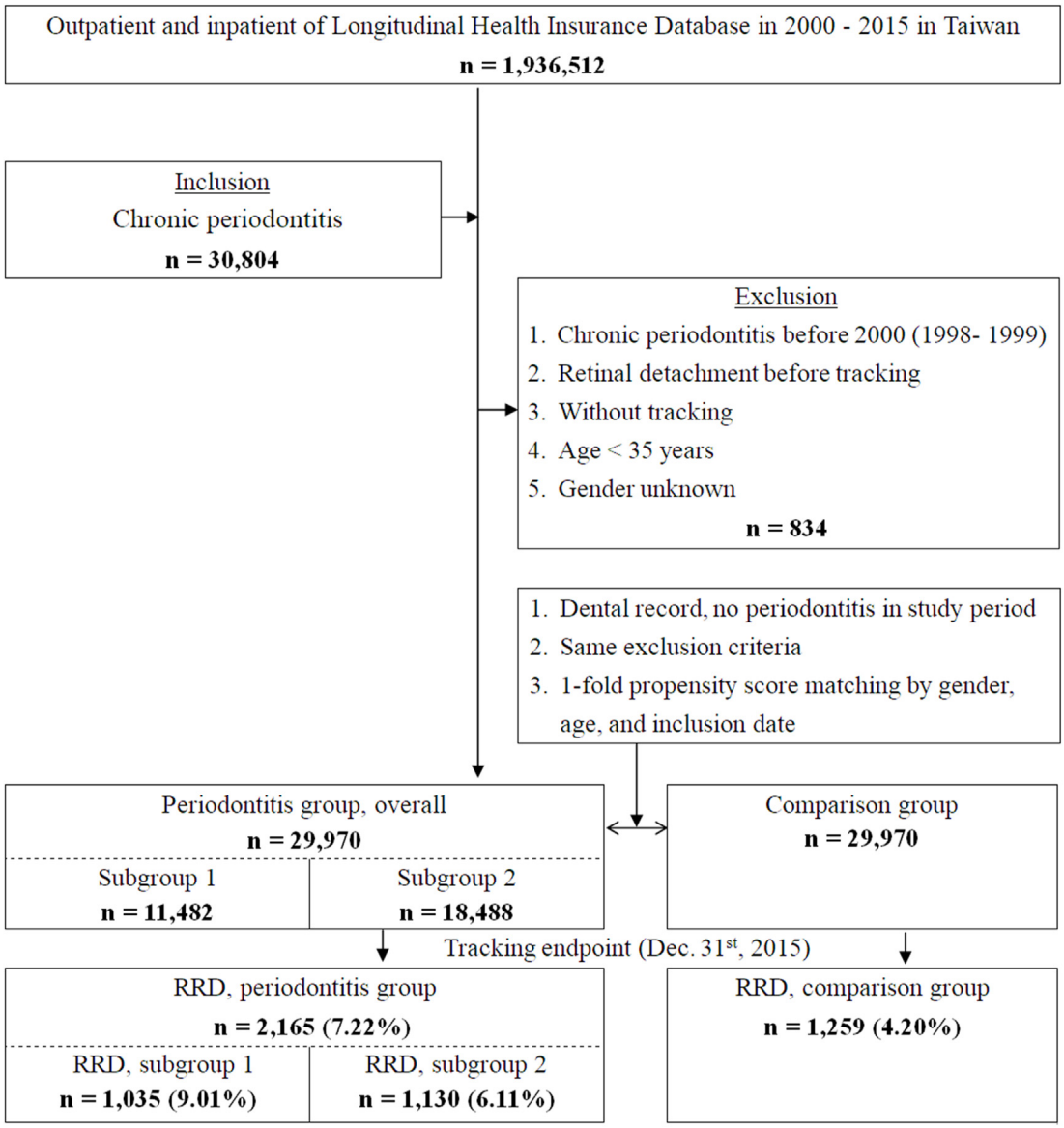

Figure 1 Flowchart of study sample selection from the NHIRD in Taiwan.

Table 1 Characteristics of the study groups at baseline.

Variables	Total		Periodontitis		Comparison		*P*
	n	%	n	%	n	%	
Gender, male	30,944	51.62	15,472	51.62	15,472	51.62	0.999
Age (yrs)	55.16 ± 10.05		55.12 ± 9.96		55.19 ± 10.14		0.394
Age group (yrs)							0.999
35—54	29,120	48.58	14,560	48.58	14,560	48.58	
≧55	30,820	51.42	15,410	51.42	15,410	51.42	
IP (10^3 NT$)							**< 0.001**
<18	18,251	30.45	8465	28.24	9786	32.65	
18—35	25,806	43.05	12,016	40.09	13,790	46.01	
>35	15,883	26.50	9489	31.66	6394	21.33	
Urbanization level							**< 0.001**
1 (The highest)	17,320	28.90	9306	31.05	8014	26.74	
2	15,791	26.34	7971	26.60	7820	26.09	
3	12,136	20.25	5802	19.36	6334	21.13	
4 (The lowest)	14,693	24.51	6891	22.99	7802	26.03	
Level of care							**< 0.001**
Hospital center	21,250	35.45	11,872	39.61	9378	31.29	
Regional hospital	20,539	34.27	9786	32.65	10,753	35.88	
Local hospital/clinics	18,151	30.28	8312	27.73	9839	32.83	
Comorbidities							
Myopia, with	11,325	18.89	5798	19.35	5527	18.44	**0.005**
Previous eye surgery, with	7597	12.67	3845	12.83	3752	12.52	0.254
Previous ocular trauma, with	7433	12.40	3782	12.62	3651	12.18	0.104
Previous eye disease, with	15,840	26.43	7976	26.61	7864	26.24	0.300
Hypertension, with	15,576	25.99	7874	26.27	7702	25.70	0.109
Diabetes mellitus, with	11,903	19.86	6024	20.10	5879	19.62	0.138
Stroke, with	5409	9.02	2784	9.29	2625	8.76	**0.023**
Hyperlipidemia, with	10,534	17.57	5520	18.42	5014	16.73	**< 0.001**
Depression, with	2251	3.76	1237	4.13	1014	3.38	**< 0.001**
TBI, with	3455	5.76	1672	5.58	1783	5.95	0.052
CAD, with	7724	12.89	3972	13.25	3752	12.52	**0.007**
COPD, with	5999	10.01	3014	10.06	2985	9.96	0.693
CCI_R	1.08 ± 0.84		1.13 ± 0.88		1.02 ± 0.79		**< 0.001**
Obesity, with	527	0.88	303	1.01	224	0.75	**0.001**
Tobacco, with	366	0.61	202	0.67	164	0.55	0.052
Alcoholism, with	3192	5.33	1672	5.58	1520	5.07	**0.006**

P value: Chi-square/Fisher exact test on category variables and one-way ANOVA with Scheffe post hoc on continuous variables. Bold: significant difference at $P < 0.05$. IP: monthly insurance premium in New Taiwan Dollars; TBI: traumatic brain injury; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; Tobacco: tobacco use disorder; CCI-R: Charlson comorbidity index revised.

CM codes: 410—414), obesity (ICD-9-CM codes:278), chronic obstructive pulmonary disease (ICD-9-CM codes: 490—496), tobacco use disorder (ICD-9-CM codes: 305.1), alcoholism (ICD-9-CM codes: 303, 305.0), and Charlson comorbidity index revised (CCI_R). Moreover, comorbidities such as myopia (ICD-9-CM codes: 367.1), previous ocular trauma (ICD-9-CM codes: 871, 921), previous eye diseases (ICD-9-CM codes: 360.00, 360.11, 360.12, 361.10, 361.12, 362.63, 363.05, 363.08, 363.21), and previous eye surgeries (NHI order codes: 86006C, 86007C, 86008C, 86206C, 86207B, 86213B, 86214C, 86407B, 86408B) were included and utilized in our analysis for RRD comorbidities.

Outcome measures

We conducted a follow-up with all the study participants from the index date, until the onset of RRD (ICD-9-CM code: 361.0) or the end of 2015.

Statistical analysis

The distributions of categorical and continuous variables were analyzed using the chi-square- and t-tests, respectively. Fisher's exact test was used to examine the

differences between two groups for categorical variables. Multivariate Cox proportional hazards regression analysis was used to calculate hazard ratio (HR) with 95 % confidence interval (CI). Four models for adjusted analysis were used. Kaplan–Meier curves were generated to assess the risk of RRD, and log-rank tests were performed to determine the statistical significance among groups. Sensitivity analysis was performed by excluding the RRD diagnosis within the first 1 or 5 years to eliminate potential protopathic bias. Statistical significance was defined as a two-tailed *P*-value of <0.05. Data analysis was conducted using IBM Statistical Product and Service Solutions (SPSS) software version 22 (IBM, Chicago, IL, USA).

Results

Demographic characteristics at the baseline and endpoint

At baseline, the patients between the comparison and periodontitis groups showed statistical differences in the various factors, including monthly insurance premium, urbanization lever, care level, myopia, stroke, hyperlipidemia, depression, coronary artery disease, the level of CCI_R, obesity, and alcoholism ($P < 0.05$) (Table 1).

At the end of follow-up, 1259 (4.20 %) patients in the comparison group, and 2165 (7.22 %) in the periodontitis

Table 2 Characteristics of the groups at the end of follow-up.

Variables	Total		Periodontitis		Comparison		*P*
	n	%	n	%	n	%	
Subjects enrolled	59,940		29,970		29,970		
RRD, with	3424	5.71	2165	7.22	1259	4.20	**< 0.001**
Gender, male	30,944	51.62	15,472	51.62	15,472	51.62	0.999
Age (yrs)	59.18 ± 19.56		58.91 ± 19.26		59.44 ± 19.86		**0.001**
Age group (yrs)							**< 0.001**
35–54	26,811	44.73	13,109	43.74	13,702	45.72	
≧55	33,129	55.27	16,861	56.26	16,268	54.28	
IP(10^3NTD) < 18	18,251	30.45	8465	28.24	9786	32.65	**< 0.001**
18–35	25,806	43.05	12,016	40.09	13,790	46.01	
>35	15,883	26.50	9489	31.66	6394	21.33	
Urbanization level							**< 0.001**
1 (The highest)	17,254	28.79	9248	30.86	8006	26.71	
2	16,013	26.72	8082	26.97	7931	26.46	
3	12,735	21.25	6011	20.06	6724	22.44	
4 (The lowest)	13,938	23.25	6629	22.12	7309	24.39	
Level of care							**< 0.001**
Hospital center	21,153	35.29	11,888	39.67	9265	30.91	
Regional hospital	20,658	34.46	9760	32.57	10,898	36.36	
Local hospital/clinics	18,129	30.25	8322	27.77	9807	32.72	
Comorbidities							
Myopia, with	11,745	19.59	6024	20.10	5721	19.09	**0.002**
Previous eye surgery, with	7685	12.82	3894	12.99	3791	12.65	0.208
Previous ocular trauma, with	7513	12.53	3802	12.69	3711	12.38	0.262
Previous eye disease, with	15,987	26.67	8013	26.74	7974	26.61	0.719
Hypertension, with	15,747	26.27	7936	26.48	7811	26.06	0.246
Diabetes mellitus, with	12,031	20.07	6125	20.44	5906	19.71	**0.026**
Stroke, with	5680	9.48	2883	9.62	2797	9.33	0.230
Hyperlipidemia, with	10,761	17.95	5534	18.47	5227	17.44	**0.001**
Depression, with	2594	4.33	1376	4.59	1218	4.06	**0.002**
TBI, with	3565	5.95	1735	5.79	1830	6.11	0.101
CAD, with	7893	13.17	4022	13.42	3871	12.92	0.068
COPD, with	6090	10.16	3086	10.30	3004	10.02	0.268
CCI_R	1.10 ± 0.86		1.15 ± 0.91		1.05 ± 0.80		**0.041**
Obesity, with	557	0.93	305	1.02	252	0.84	**0.027**
Tobacco, with	392	0.65	209	0.70	183	0.61	0.205
Alcoholism, with	3310	5.52	1712	5.71	1598	5.33	**0.041**

P value: Chi-square/Fisher exact test on category variables and one-way ANOVA with Scheffe post hoc on continuous variables. Bold: significant difference at $P < 0.05$. RRD: rhegmatogenous retinal detachment; IP: monthly insurance premium in New Taiwan Dollars; TBI: traumatic brain injury; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; Tobacco: tobacco use disorder; CCI-R: Charlson comorbidity index revised.

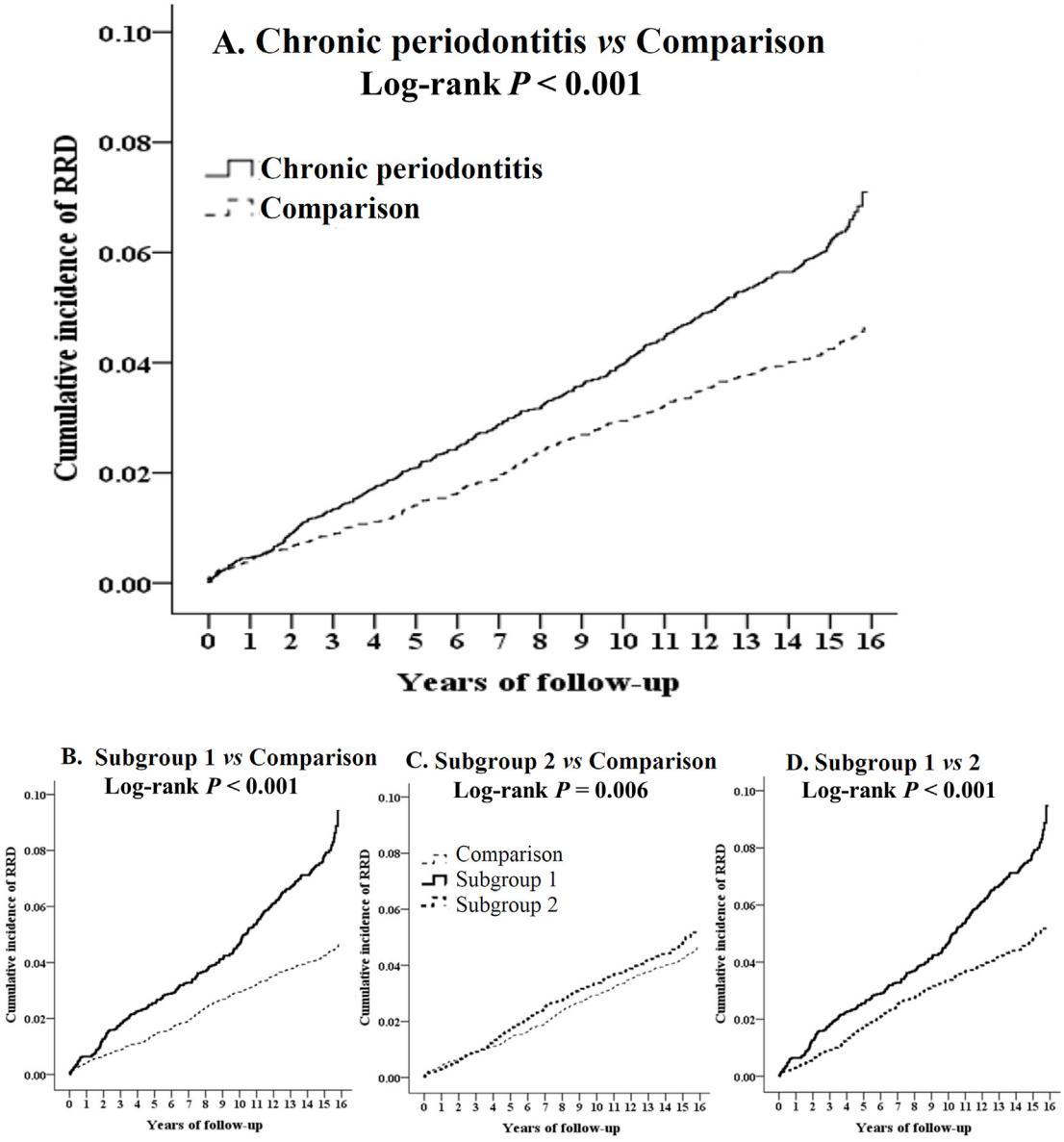

Figure 2 Cumulative risks of rhegmatogenous retinal detachment (RRD) in the examined groups by Kaplan—Meier analysis and log-rank test. The cumulative incidences of RRD: periodontitis group *vs* comparison group (A), subgroup 1 *vs* comparison group (B), subgroup 2 *vs* comparison group (C), and subgroup 1 *vs* subgroup 2 (D).

group developed RRD (Fig. 1 and Table 2). The rates of RRD development between the two groups were statistically different ($P < 0.001$). Significant differences were also observed in variables such as age, age groups, monthly insurance premium, urbanization level, care level, myopia, diabetes, hyperlipidemia, depression, CCI_R, obesity, and alcoholism (Table 2). The cumulative risk for RRD in the periodontitis group was significantly higher than that in the comparison group (log-rank test, $P < 0.001$) (Fig. 2A).

For the two periodontitis subgroups, 9.01 % (1035 out of 11,482) of patients in the subgroup 1 developed RRD, while in the subgroup 2, 6.11 % (1130 out of 18,488) of patients developed RRD (Fig. 1). Both subgroups showed significantly increased cumulative risks (*vs* comparison group) (Fig. 2B and C). Besides, the risk was greater in the subgroup 1 compared to the subgroup 2 (Fig. 2D).

Risk factors for developing rhegmatogenous retinal detachment

The crude HRs for developing RRD in periodontitis group (with the comparison group as the reference) were 1.80 (95 % CI: 1.38—2.11, $P < 0.001$) (Table 3). The increased risk of developing RRD remained significant even after adjusting for sociodemographic factors (Model 1, adjusted HR: aHR = 1.70), sociodemographic factors and RRD comorbidities (Model 2, aHR = 1.53), and sociodemographic factors, systemic diseases, and smoking/alcohol habits (Model 3, aHR = 1.68). In model 4, the increased risk of developing RRD remained significant even after adjusting for all above factors (aHR = 1.49, 95 % CI: 1.12—1.83). Besides, patients having the following characteristics: aged ≥55 years, urbanization levels of 1—3, at

Table 3 Risks of retinal detachment in groups determined by the Cox regression.

Variables	Crude	Model 1	Model 2	Model 3	Model 4
	HR (95 % CI)	aHR (95 % CI)	aHR(95 % CI)	aHR(95 % CI)	aHR(95 % CI)
Group (comparison, reference)					
Periodontitis	1.80 (1.38–2.11)*	1.70 (1.29–2.03)*	1.53 (1.18–1.96)*	1.68 (1.30–2.07)*	1.49 (1.12–1.83)*
Male (F‡, reference)	1.29 (0.86–1.48)	1.21 (0.84–1.47)	1.27 (0.80–1.48)	1.31 (0.80–1.58)	1.28 (0.72–1.44)
Age (years old) (35–54, reference)					
≧ 55 yrs	1.57 (1.37–1.77)*	1.53 (1.31–1.72)*	1.47 (1.20–1.66)*	1.49 (1.22–1.66)*	1.46 (1.23–1.68)*
IP (NTD10^3) (<18, reference)					
18–35	1.20 (0.57–1.55)	1.20 (0.59–1.59)	1.21 (0.48–1.70)	1.18 (0.46–1.71)	1.11 (0.44–1.69)
>35	1.28 (0.79–1.76)	1.26 (0.77–1.77)	1.31 (0.56–1.87)	1.24 (0.56–1.80)	1.21 (0.53–1.79)
Urbanization (level 4§, reference)					
1 (highest)	1.69 (1.35–2.06)*	1.53 (1.32–1.78)*	1.46 (1.30–1.67)*	1.51 (1.31–1.72)*	1.43 (1.30–1.52)*
2	1.63 (1.31–1.99)*	1.51 (1.31–1.63)*	1.39 (1.28–1.59)*	1.49 (1.29–1.60)*	1.39 (1.23–1.48)*
3	1.58 (1.30–1.91)*	1.48 (1.28–1.59)*	1.37 (1.20–1.53)*	1.43 (1.23–1.58)*	1.34 (1.18–1.43)*
Level of care (local hospital/clinics, reference)					
Hospital center	2.10 (1.69–2.60)*	1.63 (1.47–1.89)*	1.57 (1.44–1.79)*	1.61 (1.47–1.86)*	1.43 (1.34–1.48)*
Regional hospital	1.98 (1.60–2.42)*	1.56 (1.43–1.83)*	1.51 (1.41–1.73)*	1.54 (1.43–1.81)*	1.41 (1.33–1.50)*
Comorbidities					
Myopia, with‖	2.17 (1.61–2.97)*		2.05 (1.60–2.91)*		2.01 (1.51–2.85)*
Previous eye surgery, with‖	1.90 (1.45–2.68)*		1.77 (1.41–2.63)*		1.72 (1.39–2.56)*
Previous ocular trauma, with‖	1.97 (1.34–2.70)*		1.87 (1.30–2.66)*		1.81 (1.24–2.57)*
Previous eye disease, with‖	2.03 (1.56–2.84)*		1.91 (1.52–2.71)*		1.89 (1.49–2.69)*
Hypertension, with‖	1.45 (1.22–1.69)*			1.43 (1.28–1.69)*	1.40 (1.22–1.69)*
Diabetes mellitus, with‖	1.58 (1.31–1.71)*			1.53 (1.31–1.71)*	1.51 (1.34–1.70)*
Stroke, with‖	1.38 (1.17–1.54)*			1.38 (1.14–1.53)*	1.33 (1.10–1.69)*
Hyperlipidemia, with‖	1.41 (1.26–1.68)*			1.41 (1.28–1.67)*	1.40 (1.20–1.69)*
Depression, with‖	1.53 (1.13–2.20)*			1.53 (1.12–2.06)*	1.51 (1.10–2.03)*
Traumatic brain injury, with‖	1.37 (1.18–1.68)*			1.33 (1.12–1.60)*	1.31 (1.10–1.58)*
Coronary artery disease, with‖	1.46 (1.10–2.01)*			1.43 (1.09–1.99)*	1.42 (1.04–1.92)†
COPD, with‖	1.70 (1.30–2.12)*			1.62 (1.28–2.06)*	1.61 (1.26–2.00)*
CCI_R	1.28 (1.24–1.30)*			1.28 (1.23–1.30)*	1.27 (1.23–1.29)*
Obesity, with‖	1.97 (0.87–2.88)			1.90 (0.81–2.78)	1.80 (0.79–2.69)
Tobacco, with‖	1.39 (1.00–1.66)			1.28 (0.73–1.59)	1.26 (0.71–1.51)
Alcoholism, with‖	1.40 (1.01–1.68)†			1.30 (0.90–1.61)	1.29 (0.84–1.58)

HR = hazard ratio, CI = confidence interval, aHR = adjusted HR; IP: monthly insurance premium in New Taiwan Dollars; COPD: chronic obstructive pulmonary disease; Tobacco: tobacco use disorder; CCI-R: Charlson comorbidity index revised. *, $P < 0.001$. †, $P < 0.05$. ‡**: female as the reference,** §**: level 4 (the lowest urbanization level),** ‖**: without as the reference.**

Model 1: Adjusted for sex, age, insured premium, urbanization level, and level of care (sociodemographic factors).
Model 2: Adjusted for Model 1 and rhegmatogenous retinal detachment comorbidities.
Model 3: Adjusted for Model 1, systemic diseases, and smoking/alcoholism.
Model 4: Adjusted for Model 1, rhegmatogenous retinal detachment comorbidities systemic diseases, and smoking/alcoholism.

the care level in central/regional hospitals, with the four RRD comorbidities (myopia, previous eye surgeries, previous ocular trauma, and previous eye diseases), as well as the systemic conditions of hypertension, diabetes mellitus, stroke, hyperlipidemia, depression, traumatic brain injury, coronary artery disease, chronic obstructive pulmonary disease, and CCI_R, were found to be at high risk of developing RRD.

Sensitivity test

The risk of developing RRD was significantly higher in the periodontitis group, as well as in the two subgroups, compared to the comparison group, despite the adjustments (e.g., in model 4: aHR = 1.49, $P < 0.001$; 1.70, $P < 0.001$; and 1.34, $P = 0.041$; for periodontitis group and two subgroups, respectively) (Table 4). Moreover, the

Table 4 Sensitivity for factors of retinal detachment by using Cox regression.

				Crude	Model 1	Model 2	Model 3	Model 4
	Events	Years	Rate‡	HR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Overall								
Periodontitis	2,165	1,898,250.91	114.05	1.80 (1.38-2.11)*	1.70(1.29-2.03)*	1.53 (1.18-1.96)*	1.68(1.30-2.07)*	1.49 (1.12-1.83)*
Subgroup 1	1,035	755,172.43	137.05	2.01 (1.55-2.39)*	1.92(1.47-2.31)*	1.74 (1.35-2.23)*	1.91(1.47-2.36)*	1.70 (1.27-2.08)*
Subgroup 2	1,130	1,143,078.48	98.86	1.60 (1.23-1.90)*	1.51(1.15-1.83)*	1.38 (1.07-1.77)*	1.51(1.17-1.86)*	1.34 (1.01-1.64)†
Comparison	1,259	1,984,552.66	63.44	Reference	Reference	Reference	Reference	Reference
1Y-Excluded								
Periodontitis	2,022	1,873,255.52	107.94	1.72 (1.32-2.06)*	1.63 (1.24-2.00)*	1.48 (1.15-1.90)*	1.62 (1.26-2.01)*	1.45 (1.09-1.77)*
Subgroup 1	932	688,346.99	135.40	1.91 (1.46-2.27)*	1.82 (1.38-2.20)*	1.65 (1.28-2.11)*	1.80 (1.40-2.23)*	1.61 (1.21-1.97)*
Subgroup 2	1,090	1,184,908.53	91.99	1.59 (1.22-1.89)*	1.51 (1.14-1.81)*	1.37 (1.06-1.75)*	1.50 (1.16-1.85)*	1.33 (1.00-1.63)†
Comparison	1,215	1,940,136.87	62.62	Reference	Reference	Reference	Reference	Reference
5Y-Excluded								
Periodontitis	1,081	1,549,695.64	69.76	1.71 (1.32-2.05)*	1.64 (1.24-1.97)*	1.48 (1.15-1.90)*	1.62 (1.25-2.01)*	1.44 (1.09-1.78)*
Subgroup 1	535	717,410.35	74.57	1.74 (1.34-2.08)*	1.65 (1.27-2.00)*	1.50 (1.16-1.93)*	1.64 (1.27-2.03)*	1.46 (1.10-1.79)*
Subgroup 2	546	832,285.29	65.60	1.69 (1.30-2.03)*	1.61 (1.23-1.94)*	1.46 (1.13-1.88)*	1.60 (1.24-1.98)*	1.43 (1.07-1.75)*
Comparison	628	1,668,748.10	37.63	Reference	Reference	Reference	Reference	Reference

*$P < 0.00^{a}$. †, $P \leq 0.05$.

Model 1: Adjusted for sex, age, insured premium, urbanization level, and level of care (sociodemographic factors).

Model 2: Adjusted for Model 1 and rhegmatogenous retinal detachment comorbidities.

Model 3: Adjusted for Model 1, systemic diseases, and smoking/alcoholism.

Model 4: Adjusted for Model 1, rhegmatogenous retinal detachment comorbidities systemic diseases, and smoking/alcoholism.

aHR, adjusted hazard ratio; CI = confident interval. 1Y-Excluded = data in the first year were excluded for analysis; 5Y-Excluded = data in the first 5 years were excluded for analysis.

‡ : Rate,/15 person-years.

increased risk of having RRD persisted in the periodontitis group and the two subgroups (*vs* the comparison group) even after excluding the first 1 or 5 years (Table 4).

Discussion

In this study, using the NHIRD in Taiwan, participants were screened and categorized into a periodontitis group and a comparison group (29,970 in each group). At the end of the follow-up period, 2165 participants in the periodontitis group and 1259 in the comparison group developed RRD. Kaplan–Meier analysis and Cox regression model demonstrated that the risk of developing RRD was higher in the periodontitis group compared to the comparison group. After adjusting for sociodemographic factors, RRD comorbidities, systemic diseases, and smoking/alcoholism habits, the aHRs for developing RRD in the periodontitis group was 1.49 (95 % CI: 1.12–1.83, $P < 0.001$). In the context of RRD, several factors are commonly acknowledged as risk factors, including myopia, ocular trauma, and cataract-related surgery.[4] Additionally, inflammatory eye diseases, such as endophthalmitis and uveitis, have been linked to retinal detachment.[1,23,24] Retinoschisis and lattice degeneration are also considered risk factors, while a history of previous ocular surgery may contribute to vitreoretinal traction and retinal detachment.[24,25] Furthermore, aging compromises the integrity of the blood-ocular barrier and diminishes the immune regulatory function of retinal neurons.[26] In the present study, nevertheless, these factors were considered as covariates to validate the elevated risk of retinal detachment associated with chronic periodontitis.

To date, an association between periodontitis and RRD remains lacking. Nonetheless, recent studies have shown a significant association between periodontitis and neurodegenerative conditions.[7,8] The entry of periodontal pathogens into the bloodstream through compromised periodontal tissue is suggested as a key pathogenic mechanism.[27,28] Periodontal pathogens, along with the released lipopolysaccharide endotoxins, might not only remain confined to the oral cavity but also spread to distant organs.[29] Inflammatory responses and toxins, such as gingipains, might further exacerbate the connection between periodontal and neurodegenerative diseases by disrupting endothelial cell junctions, thus increasing blood–brain barrier permeability.[30,31]

The underlying mechanisms related to the association between periodontitis and RRD have not been explored; however, a potential link between periodontal disease and eye diseases or retinal microcirculation was suggested.[32,33] Recent reports have highlighted associations between periodontitis and certain eye diseases, including glaucoma, AMD, and various ocular infectious diseases, suggesting that the oral microbiota altered by periodontitis may trigger immune responses that promote the development of ocular diseases.[12–14] Moreover, the dysfunction of endothelial cells resulting from periodontitis may contribute to the pathophysiology of ocular diseases.[13] The relationship between blood-ocular-barrier breakdown and poor periodontal status has recently been emphasized.[34] The blood-ocular barrier, comprising the blood-aqueous barrier and the blood-retinal barrier, plays a crucial role in safeguarding the eye from the entry of toxic substances and maintaining the physiology ocular homeostasis.[15] However, these barriers can be compromised by surgical trauma or inflammatory/infectious diseases, leading to increased vascular permeability and potential detachment of the retina from the retinal pigment epithelium, possibly due to misdirected aqueous flow.[3]

Periodontal microorganisms can trigger the expression of matrix metalloproteinases (MMPs).[35] Studies have also shown that MMP-2, MMP-9 and their latent pro-forms (proMMP-2, -9) are significantly higher in the subretinal fluid and vitreous of RRD patients, while MMP-8 levels were higher in RRD patients' subretinal fluid.[36] In the vitreous of retinal detachment patients, the cytokines including interleukin (IL)-6, IL-7 and IL-8 were significantly upregulated compared with controls of macular hole or vitreomacular traction.[37] Animal studies have also reported similar findings, including the MMP-2 and -9 activity increased concurrently[38] and the IL-1β and tumor necrosis factor-α expressions elevated in rats with retinal detachment.[39]

Indeed, this study faced several limitations. First, similar to previous studies using the NHIRD for periodontal diseases,[20,21] there was a lack of precise clinical data on periodontitis. The accuracy of the codes used may be affected by coding errors or up-coding, although the Bureau of National Health Insurance conducts routine inspections and reviews of claims. To increase the diagnostic accuracy of the coding system, the inclusion of patients with more than three records of periodontal diagnosis was selected.[40] Secondly, many other medical-related factors, such as nutritional status, physical activity, family history, genetic, psychosocial, and detailed environmental factors, were unavailable in the dataset. Third, selection bias is an inherent limitation of retrospective studies. Fourth, the reasons for the greater risk in subgroup 1 compared to subgroup 2 were not explored in the study. Various factors, including delayed treatment, disease severity, and post-treatment maintenance, should be further evaluated comprehensively. Therefore, caution should be exercised in interpreting the results of this study due to its retrospective population-based cohort design and associated limitations.

In conclusion, we observed the development of RRD in the periodontitis and comparison groups for 15 years using the NHIRD of Taiwan. The risk of RRD was higher in the periodontitis group than in the comparison group (aHR = 1.49). The study findings suggest an association between chronic periodontitis and RRD. Further detailed investigations may be necessary to clarify the nature of this relationship.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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