

Association between intensive periodontal treatment and spontaneous intracerebral hemorrhage—a nationwide, population-based cohort study

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Abstract

Periodontal disease is a chronic inflammation of periodontium and has a high prevalence. Periodontal disease has been discovered to be a possible risk factor for cerebrovascular diseases. The available evidence are not enough to set up a causal relationship between periodontal disease and cerebrovascular diseases. Patients with spontaneous intracerebral hemorrhage have high mortality rates. The present study investigated whether intensive periodontal treatment is a protective factor of spontaneous intracerebral hemorrhage and can reduce the risk of spontaneous intracerebral hemorrhage.

In total, 64,960 patients with a history of periodontal disease were picked out from the National Health Insurance Research Databases as a case-cohort from January 01, 2000 to December 31, 2010. They were divided on the basis of whether periodontal disease patients received intensive surgical treatment (treatment cohort) or not (control cohort). The periodontal disease patients in treatment and control cohorts were selected by propensity score matching at a ratio of 1:1. Incidences of spontaneous intracerebral hemorrhage in both cohorts were analyzed and compared.

The total hazard of spontaneous intracerebral hemorrhage was significantly decreased in the treatment cohorts compared with the control cohorts (adjusted hazard ratio = 0.60, 95% confidence interval = 0.45–0.79).

Compared with the control cohort, intensive periodontal treatment may reduce the overall incidence of spontaneous intracerebral hemorrhage, particularly in elderly patients, males, and those who received more than 2 intensive treatments.

Abbreviations: aHR = adjusted hazard ratio, CAD = coronary artery disease, CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ICD-9-CM = International Classification of Diseases, ICH = intracerebral hemorrhage, NHI = National Health Insurance, NHIRD = National Health Insurance Research Databases, Ninth Revision, Clinical Modification, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus.

Keywords: epidemiology, intracerebral hemorrhage, periodontitis, public health

1. Introduction

Periodontal disease is a chronic inflammatory disease that affects the dental supporting structure, which comprises the alveolar bone, periodontal ligament, cementum, and gingiva. Periodontal disease can be classified as gingivitis or periodontitis.^[1] Gingivitis

may progress to periodontitis via damage to alveolar bone and periodontal ligaments.^[1] This is a leading reason for adult tooth loss.^[2]

Periodontal disease is highly common and affects up to 90% of the global population.^[1] In Taiwan, the prevalence of periodontal

Editor: Li Wu Zheng.

The Management Office for Health Data of China Medical University Hospital is supported in part by the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019), China Medical University Hospital, Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10501010037), NRPB Stroke Clinical Trial Consortium (MOST 104-2325-B-039 -005), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan.

The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of data; preparation, review, approval of manuscript; or decision to submit manuscript for publication.

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Medicine (2019) 98:10(e14814)

Received: 22 November 2018 / Received in final form: 10 February 2019 / Accepted: 11 February 2019

http://dx.doi.org/10.1097/MD.00000000000014814

disease in adults was approximately 94% from a short-term community-based cohort.^[3] Periodontal disease is mainly caused by dental plaque microorganisms.^[4] The major risk factors for periodontal disease are age, poor dental care, genetics, tobacco use, alcohol consumption, teeth grinding, malnutrition, obesity, psychological stress, and impaired host immune response.^[5,6] Some systemic disorders, such as diabetes mellitus, rheumatoid arthritis (RA), and hematologic diseases may induce periodontal disease.^[7–9] Periodontal disease is a prevalent chronic inflammatory disease.^[1] Periodontal disease causes a systemic inflammatory response.^[10] Chronic inflammation can induce arteriosclerotic vascular disease and specific systemic disorders, such as type 2 diabetes mellitus, cerebrovascular, and cardiovascular diseases.^[11–13]

Spontaneous intracerebral hemorrhage (ICH), also known as hemorrhagic stroke, is the second leading reason of cerebrovascular accident, second only to ischemic stroke in frequency.^[14] The overall annual standardized incidence rate of spontaneous ICH was 16 to 33 per 100,000 person-year.^[15] A median case mortality rate at 1 month was 40% (range=13–61%) and the functional independence rate was 12% to 39%.^[14] Risk factors for spontaneous ICH include hypertension, aging, male sex, *excessive alcohol consumption*, anticoagulant therapy, use of sympathomimetic drugs, intracranial tumors, arteriovenous malformations, arterial aneurysm, and amyloid angiopathy in the elderly population.^[16,17] Certain inflammatory diseases, such as *systemic lupus erythematosus* (SLE) and RA increase the risk of spontaneous ICH.^[18] Kim et al^[6] discussed that periodontal disease was an independent risk factor for spontaneous ICH. A recent series of studies have found that specific bacterial infections within the mouth increase the risk of spontaneous ICH and deep cerebral microbleeds.^[19–21]

Taiwanese National Health Insurance periodontal disease treatment projects include scaling, periodontal emergency treatment, gingivectomy, periodontal dressings, subgingival curettage, and periodontal flap operation. This retrospective cohort study used the Taiwanese National Health Insurance Research Databases (NHIRD) to investigate whether the treatment of periodontal disease with subgingival curettage or periodontal flap surgery can reduce the risk of spontaneous ICH.

2. Materials and methods

2.1. Data source

The National Health Insurance (NHI) programme is a nationwide, single-payer health insurance system in Taiwan; introduced in March 1995, it covered more than 99% of the 23.75 million Taiwanese citizens in 1998.^[22] The retrospective cohort research was conducted using data from the Longitudinal Health Insurance Database 2000. The Longitudinal Health Insurance Database 2000 has been detailed in previous studies.^[23,24] Diseases were coded according to the 2001 edition of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This research was authorized by the Institutional Review Board of China Medical University and Hospital (CMUH-104-REC2-115).

2.2. Sampled participants

All patients who had a history of periodontal disease (ICD-9-CM code 523) were included in this research. Patients with periodontal disease who underwent periodontal surgery, including subgingival curettage (scaling [claim code 91004C] and root

planning [claim codes 91006C, 91007C, and 91008C]), and periodontal flap surgery (claim codes 91009B and 91010B), during 2000 to 2010 were chosen as the treatment cohort. The index date was set as the date of receiving periodontal surgery. A control cohort was randomly selected from patients with periodontal disease who did not receive periodontal surgery during the study period. We excluded patients aged <20 years and those diagnosed with stroke (ICD-9-CM codes 430–438) before the index date from the study. The treatment and control cohorts were selected by propensity score matching at a ratio of 1:1. The propensity scores were calculated through logistic regression analysis to estimate the probability of the treatment assignment given the baseline variables: age, sex, urbanization level, monthly income, year of periodontal disease diagnosis, year of periodontal disease treatment, and comorbidities of hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), coronary artery disease (CAD; ICD-9-CM codes 410–414), chronic kidney disease (CKD; ICD-9-CM codes 580–589), chronic obstructive pulmonary disease (COPD; ICD-9-CM codes 491, 492, and 196), asthma (ICD-9-CM code 493), and alcohol-related illness (ICD-9-CM codes 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3). All participants were followed up until a diagnosis of spontaneous ICH (ICD-9-CM codes 430–432) or until censoring for loss to follow-up, death, termination of insurance, or December 31, 2011.

2.3. Statistical analysis

The distributions of demographic variables, namely age, sex, urbanization level (level 1 being the most urbanized and level 4 being the least urbanized), monthly income (New Taiwan Dollars per month), and comorbidities, were compared between the treatment and control cohorts using the chi-square test for category variables and the *t* test for continuous variables. The cumulative incidence of spontaneous ICH between the treatment and control cohorts was assessed using the Kaplan–Meier method, and differences between the curves were evaluated using a log-rank test. Incidence densities of spontaneous ICH by demographic variables and comorbidities were calculated. Univariable and multivariable Cox proportional hazards regression analyses were conducted to estimate the risk of spontaneous ICH in association with periodontal disease treatment. The multivariable models were adjusted for age, sex, urbanization level, monthly income, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, chronic kidney disease, COPD, asthma, and alcohol-related illness. The frequency of the clinical course in the treatment cohort was further analyzed to assess how responsiveness to treatment affected the risk of spontaneous ICH. All statistical analyses were conducted using SAS Version 9.4 (SAS Institute, Inc, Cary, NC), and the level of statistical significance was set at a 2-sided $P < .05$.

3. Results

Table 1 compares baseline characteristics of the treatment cohort with those of the control cohort. The treatment and control cohorts included 32,480 and 32,480 participants, respectively, during 2000 to 2010. The mean age of all participants in the treatment and control cohorts was 47.7 ± 12.7 years and 47.5 ± 14.1 years, respectively. The treatment and control cohorts had similar distributions of age, sex, urbanization level, and comorbidities, except for monthly income.

Table 1**Baseline demographic characteristics and comorbidities in treatment and control cohorts.**

	Control cohorts		Treatment cohorts		P-value
	N=32,480 n	N=32,480 %	N	%	
Age, yr					
Mean (SD)*	47.5 (14.1)	47.7 (12.7)			.06
Sex					.22
Female	16,266	50.1	16110	49.6	
Male	16,214	49.9	16370	50.4	
Urbanization level†					.35
1 (highest)	11,396	35.1	11487	35.4	
2	10,038	30.9	9837	30.3	
3	5726	17.6	5740	17.7	
4 (lowest)	5320	16.4	5416	16.7	
Monthly income‡					.001
<15,000	6554	20.2	6402	19.7	
15,000 – 19,999	14,137	43.5	13672	42.1	
≥20,000	11,789	36.3	12406	38.2	
Comorbidity					
Hypertension	6676	20.6	6765	20.8	.39
Diabetes	2172	6.69	2225	6.85	.41
Hyperlipidemia	5730	17.6	5843	18.0	.25
Coronary artery disease	3152	9.70	3201	9.86	.52
Chronic kidney disease	1471	4.53	1491	4.59	.71
Chronic obstructive pulmonary disease	2104	6.48	2144	6.60	.53
Asthma	1352	4.16	1390	4.28	.46
Alcohol-related illness	1160	3.57	1185	3.65	.60

SD, standard deviation; chi-square test.

* t test.

† The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

‡ Monthly income, new Taiwan Dollar (NTD), 1 NTD is equal to 0.03 USD.

During the mean follow-up period of 4.99 years for both cohorts, the cumulative incidence of spontaneous ICH was significantly lower in the treatment cohort than in the control cohort (log-rank test, $P < .001$). The overall incidence densities of spontaneous ICH were significantly lower in the treatment cohort than in the control cohort during the respective 179,057 and 176,340 person-years of follow-up (0.50 vs 0.86 per 1000 person-years) with an adjusted hazard ratio (aHR) of 0.60 (95% confidence interval [CI]=0.45–0.79) (Table 2). The age-specific analysis revealed that incidences of spontaneous ICH increased with age in both cohorts. However, the age-specific risk of spontaneous ICH was lower in participants aged 50 to 64 years (aHR=0.47, 95% CI=0.30–0.74) and those aged ≥ 65 years (aHR=0.52, 95% CI=0.31–0.86) in the treatment cohort compared with the control cohort. The sex-specific risk of spontaneous ICH was significantly lower in males than in females in the treatment cohort compared with the control cohort (aHR=0.50, 95% CI=0.35–0.72). The urbanization level-specific risk of spontaneous ICH was significantly lower in the third level of urbanization in the treatment cohort compared with the control cohort (aHR=0.43, 95% CI=0.22–0.83). Monthly income-specific data exhibited a lower risk of spontaneous ICH in the monthly income category of 15,000 to 19,999 (aHR=0.59, 95% CI=0.38–0.91), and $\geq 20,000$ (aHR=0.58, 95% CI=0.36–0.94) in the treatment cohort compared with the control cohort. Regardless of their clinical characteristics, patients in the treatment cohort exhibited a lower risk HR of spontaneous ICH than those in the control cohort (without comorbidity: aHR=0.59, 95% CI=0.36–0.96; with comorbidity: aHR=0.59, 95% CI=0.42–0.83).

Table 3 presents the effects of treatment responsiveness according to the frequency of clinical visits for periodontal treatment. Compared with the control cohort, the risk of spontaneous ICH decreased significantly for patients in the treatment cohort having more than 2 intensive treatment visits (aHR=0.50, 95% CI=0.35–0.71).

4. Discussion

This is the first national population-based research to investigate the relationship between periodontal disease treatment and the incidence of spontaneous ICH. Our results revealed that patients with periodontal disease who received intensive treatment exhibited a 0.6-fold lower risk of spontaneous ICH than did patients with periodontal disease who did not receive intensive treatment, after adjustment for available demographic and medical characteristics.

Spontaneous ICH represents 10% of cases with stroke, and the average *fatality rate* is approximately 50%.^[25] We discuss several risk factors for spontaneous ICH. Hypertension is the most crucial risk factor for spontaneous ICH.^[16] A systematic review demonstrated that risk factors for spontaneous ICH were aging, male sex, high alcohol consumption, and diabetes mellitus.^[17] A high cholesterol level is often associated with a low risk of spontaneous ICH.^[17] A population-based cohort study identified CKD as a risk factor for spontaneous ICH.^[26] Another cohort study demonstrated that patients with COPD were at an increased risk of spontaneous ICH.^[27] Iribarren et al reported that *asthma* was associated with an *increased* risk of spontaneous ICH.^[28] Periodontal disease and cerebrovascular accident have

Table 2

Intracerebral hemorrhage in patients with periodontal disease in treatment and control cohorts determined using a Cox proportional hazards model.

Variables	Control cohorts			Treatment cohorts			Crude HR (95% CI)	Adjusted HR [‡] (95% CI)
	Event	PY	Rate [†]	Event	PY	Rate [†]		
All	152	176,340	0.86	90	179057	0.50	0.58 (0.45, 0.76) ^{***}	0.60 (0.45, 0.79) ^{***}
Age, yr								
≤49	36	10,8201	0.33	30	107425	0.28	0.84 (0.52, 1.36)	0.83 (0.50, 1.39)
50-64	55	45,217	1.22	35	54669	0.64	0.53 (0.34, 0.80) ^{**}	0.47 (0.30, 0.74) ^{**}
≥ 65	61	22,922	2.66	25	16962	1.47	0.55 (0.34, 0.87) [*]	0.52 (0.31, 0.86) [*]
Sex								
Women	58	8625	0.67	39	88269	0.44	0.66 (0.44, 0.98) [*]	0.78 (0.51, 1.21)
Men	94	90,085	1.04	51	90788	0.56	0.54 (0.38, 0.75) ^{***}	0.50 (0.35, 0.72) ^{***}
Urbanization level [§]								
1 (highest)	39	56,330	0.69	25	57261	0.44	0.63 (0.38, 1.04)	0.61 (0.37, 1.01)
2	39	49,823	0.78	24	49632	0.48	0.62 (0.37, 1.03)	0.62 (0.37, 1.04)
3	30	28,235	1.06	13	28529	0.46	0.43 (0.22, 0.82) [*]	0.43 (0.22, 0.83) [*]
4 (lowest)	25	26,615	0.94	18	27399	0.66	0.70 (0.38, 1.28)	0.81 (0.44, 1.50)
Monthly income [†]								
< 15,000	32	30,848	1.04	20	31169	0.64	0.62 (0.36, 1.08)	0.63 (0.36, 1.10)
15,000 – 19,999	59	70,737	0.83	31	67516	0.46	0.55 (0.36, 0.85) ^{**}	0.59 (0.38, 0.91) [*]
≥ 20,000	42	59,419	0.71	29	64137	0.45	0.64 (0.40, 1.02)	0.58 (0.36, 0.94) [*]
Comorbidity								
No	44	108,212	0.41	26	102444	0.25	0.62 (0.38, 1.01)	0.59 (0.36, 0.96) [*]
Yes	89	52,791	1.69	54	60377	0.89	0.53 (0.38, 0.74) ^{***}	0.59 (0.42, 0.83) ^{**}

CI = confidence interval, HR = hazard ratio, Tx, treatment.

[†] Monthly income, new Taiwan Dollar (NTD), 1 NTD is equal to 0.03 USD. Rate[†], incidence rate per 1,000 person-years

[‡] Adjusted HR: multivariable analysis, including age, sex, urbanization level, monthly income, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, asthma, and alcohol-related illness.

[§] The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

^{||} Comorbidity[§]: Patients with any one of the comorbidities of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, asthma, and alcohol-related illness as the comorbidity group.

^{*} P < .05.

^{**} P < .01.

^{***} P < .001.

common risk factors including age,^[29] diabetes mellitus,^[30] hypertension,^[31] CKD,^[32] and COPD.^[33]

The present study revealed that comorbidities were marginally higher in the treatment cohort than in the control cohort (Table 1). There were no significant differences in means between the 2 cohorts (Table 1). Patients with comorbidity exhibited an increased risk of spontaneous ICH in both cohorts (Table 2). Periodontal disease patients with or without any comorbidity who received intensive treatment demonstrated reduced incidences of spontaneous ICH compared with the control cohort. Age is a crucial risk factor for spontaneous ICH. The incidence of spontaneous ICH doubles for each successive 10 years after the

age of 35 years.^[34] The incidence of spontaneous ICH increased with age in both cohorts (Table 2). Moreover, compared with the control cohort, the risk of spontaneous ICH was significantly decreased in patients aged 50 to 64 years (aHR = 0.47, 95% CI = 0.30–0.74) and those aged ≥65 years (aHR = 0.52, 95% CI = 0.31–0.86) among the treatment cohort. Elderly patients exhibited more favorable reduction results in the risk of spontaneous ICH in the treatment cohort compared with the control cohort.

A systematic review reported an increased incidence of spontaneous ICH in males.^[17] This observation was consistent with our study (Table 2). Furthermore, the treatment cohort

Table 3

Hazard ratios and 95% confidence intervals of the risk of intracerebral hemorrhage associated with the frequency of treatment of periodontal disease by using the Cox proportional hazard model.

	No. of event	Rate [†]	Crude HR (95% CI)	Adjusted HR [‡] (95% CI)
Control cohorts	152	0.86	1 (Reference)	1 (Reference)
Frequency of treatment of periodontal diseases				
≤1	43	0.64	0.74 (0.53, 1.04)	0.74 (0.52, 1.06)
≥2	47	0.42	0.49 (0.35, 0.67) ^{***}	0.50 (0.35, 0.71) ^{***}
P for trend			<.001	<.001

CI = confidence interval, HR = hazard ratio, Tx, treatment.

[†] Rate, incidence rate per 1000 person-years.

[‡] Adjusted HR: multivariable analysis, including age, sex, urbanization level, monthly income, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, asthma, and alcohol-related illness.

^{*} P < .05, ^{**} P < .01, ^{***} P < .001

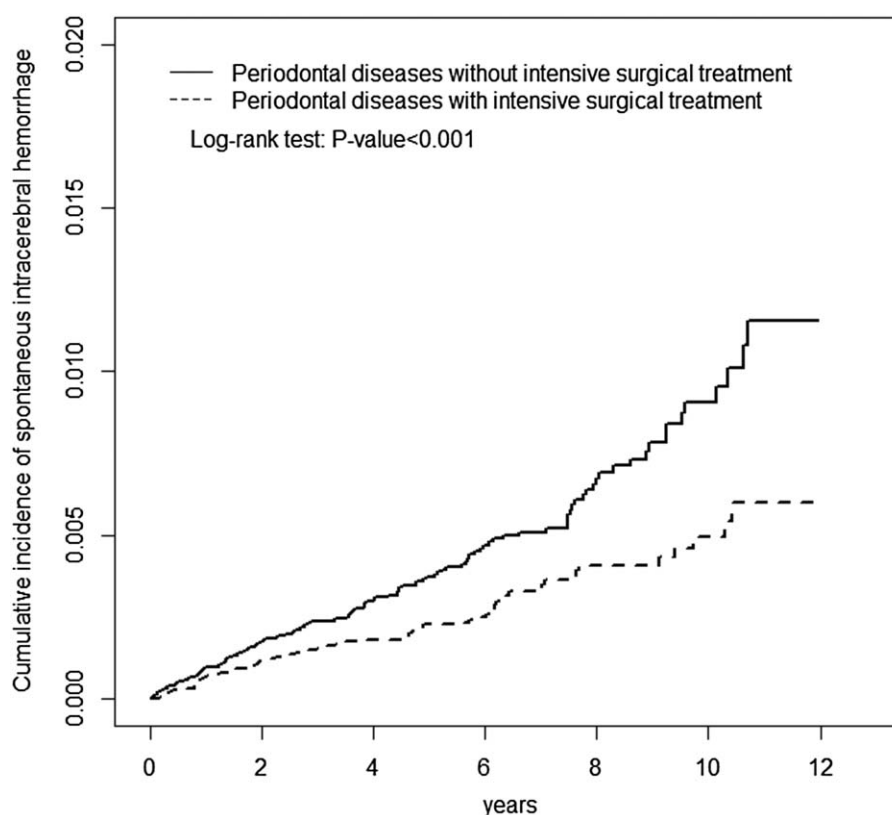


Figure 1. Comparison of cumulative incidences of spontaneous intracerebral hemorrhage in the treatment cohort (dashed line) and control cohort (solid line).

exhibited a significantly decreased incidence of spontaneous ICH in males (aHR=0.50, 95% CI=0.35–0.72) compared with females (aHR=0.78, 95% CI=0.51–1.21). The role of periodontal treatment in reducing the incidence of spontaneous ICH compared with the control cohort was *more beneficial* to males than to females. A population-based study reported the incidence of spontaneous ICH were significantly higher in the low- than in the high-income group.^[35] This observation was consistent with our study (Table 2). Compared with the control cohort, the risk of spontaneous ICH was significantly decreased in middle and high-income groups among the treatment cohort. The present study demonstrated that a single treatment for periodontal disease may reduce the incidence of spontaneous ICH compared with the control cohort (aHR=0.74, 95% CI=0.52–1.06; Table 3). The incidence of spontaneous ICH significantly decreased in patients who received more than 2 intensive treatments (aHR=0.50, 95% CI=0.35–0.71) compared with the control cohort. The cumulative incidence difference between treatment and no treatment increased with time (Fig. 1).

Several studies have discussed the correlation between periodontal disease and systemic diseases such as type 2 diabetes mellitus, CAD, COPD, ischemic stroke, and spontaneous ICH.^[6,36–41] Although no direct link between periodontal disease and systemic diseases pathology has been demonstrated, there are evidence that periodontal disease cause the overall inflammatory condition of the host. Several researchers have reported significantly elevated levels of C-reactive protein in periodontal disease patients, even after adjustment for confounding factors.^[10,42,43] A high-sensitivity C-reactive protein is an independent predictor of cerebrovascular and cardiovascular diseases.^[12,44] The researcher proposed 3 pathways that link oral

infections to systemic disorders: periodontal infection-induced platelet aggregation and acute thrombotic events, injury to cardiovascular tissue by oral microbial toxins, and periodontal infection that induces host immune dysfunction and the dysregulation of serum lipid metabolism through proinflammatory cytokines. Proinflammatory cytokines contribute to systemic diseases.

The previous studies have reported the role of chronic inflammation in the triggers vascular diseases such as arterial ectasia and microaneurysm formation in the artery.^[45,46] Other studies have also reported that patients with inflammatory disorders such as varicella-zoster virus and human immunodeficiency virus infection^[47,48] and autoimmune disorders such as RA, SLE, ankylosing spondylitis, immune thrombocytopenic purpura, psoriasis, and Wegener granulomatosis exhibit an increased risk of spontaneous ICH.^[18,49] Specific oral infections were significantly associated with ICH and increased the severity of deep brain microbes.^[19,20] We concluded that the inflammatory response of periodontal disease may increase the likelihood of cerebrovascular diseases, comprising spontaneous ICH. Further studies are needed to confirm the conclusion and determine underlying biological mechanisms.

A randomized, controlled study has reported that intensive periodontal treatment can improve oral health and vascular endothelial function, as compared with community-based periodontal care at 6 months after therapy.^[50] Some interventional studies have demonstrated that periodontal therapy can relieve chronic inflammation and lower C-reactive protein and systemic cytokine levels.^[51,52] Therefore, intensive periodontal disease treatment can reduce local (periodontal) and systemic

inflammation, thereby reducing the incidence of spontaneous ICH.

4.1. Limitations

The strength of our study was its population-based design, making our findings credible. However, we used an observational study database formed from administrative databases, resulting in some limitations.

First, the diagnostic accuracy was based on administrative data, making potential misjudging of the periodontal disease and spontaneous ICH results inevitable. However, the Bureau of NHI randomly cross-checks medical records in all medical institutions, to reduce error codes and misclassification bias. When we included patients with periodontal disease using *ICD-9-CM* diagnosis *code* from the NHIRD, we also collected the treatment codes. We selected inpatient cases of spontaneous ICH when including spontaneous ICH cases.

Second, the NHIRD does not include details of tobacco use, high alcohol consumption, body mass index, socioeconomic status, or other lifestyle-related factors that may be potential confounders. We tried to reduce these confounders, including using the COPD as a surrogate indicator for smoking, monthly income and urbanization level as a proxy of socioeconomic status, and alcohol-related illness as a proxy of alcohol consumption. In addition, such a large population-based study may have neutralized this effect. The previous study suggested that the relationship between periodontal disease and atherosclerosis may exist independently of tobacco use.^[53]

Our study was not a prospective, randomized study for determining whether periodontal disease patients receive adequate periodontal treatment. Although avoiding inherent selection bias is impossible, the severity of periodontal disease in a cohort study is uncertain. However, patients with an increased frequency of intensive periodontal disease treatment exhibited a significant reduction in the risk of spontaneous ICH compared with those without intensive periodontal disease treatment. This further proved the important role of aggressive periodontal disease treatment. Despite these potential limitations, our data sufficiently achieved the purpose of the study. Nevertheless, future research on prospective, randomized interventions is warranted to reduce these limitations and facilitate clarifying the causal relationship between periodontal disease and spontaneous ICH.

5. Conclusions

In this population-based, retrospective cohort study, we provided real-world evidence that in patients with periodontal disease, intensive periodontal treatment may reduce the overall risk of spontaneous ICH compared with the control cohort, particularly for males and elderly patients. Further prospective randomized intervention studies are needed to confirm the causal relationship between periodontal disease and spontaneous ICH.

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