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Original Article

Risk of deep vein thrombosis in patients with periodontitis: A nationwide population-based cohort study in Taiwan

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KEYWORDS
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Male

Abstract *Background/purpose:* Deep vein thrombosis (DVT) constitutes the considerable morbidity worldwide. However, no studies have specifically evaluated the association between DVT and periodontitis. This study aimed to explore the potential correlation between periodontitis and the likelihood of developing DVT with a comprehensive population-based analysis.

Materials and methods: A retrospective cohort study was implemented from Taiwan's National Health Insurance Research Database. Adult individuals with newly diagnosed periodontitis between 2000 and 2019 were matched in a 1:1 ratio with non-periodontitis counterparts, employing propensity scores to harmonize the baseline characteristics. Multivariable Cox proportional hazard model was employed to assess the risk of DVT with periodontitis.

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Results: Totally, 1426 and 1177 DVT were found in the periodontitis group and non-periodontitis group, respectively. Kaplan–Meier analysis revealed a borderline statistical significant cumulative incidence of DVT in periodontitis group (log-rank test, $P = 0.054$). Subgroup analyses unveiled a 1.13-fold risk of DVT with periodontitis among age ≥65-year group (95 % confidence intervals (CI): 1.02–1.25; $P = 0.024$). Male patients increased 1.12-fold risk of DVT with borderline significance in periodontitis group (95 % CI: 1.00–1.25; $P = 0.060$). The significant age and sex interaction were observed (P for interaction $= 0.001$).
Conclusion: The results demonstrated not overall increased risk of DVT among Taiwanese patients with periodontitis. The interplay between periodontitis and the risk of DVT was modulated by age and sex. In summary, periodontitis patients' age ≥65 years old and men were found to have a significant higher risk of DVT, respectively.

Introduction

As the leading global cause of mortality, thrombosis poses a major public health challenge.[1] Deep vein thrombosis (DVT), one of the manifestations of venous thromboembolism characterized by the formation of blood clots in deep venous system, is a primary contributor to this burden. The clinical importance of DVT is highlighted by its severe complications, including the potential for fatal pulmonary embolism and post-thrombotic syndrome.[2,3] In addition to well-recognized risk factors for DVT including advanced age, malignancy, major surgery, and the use of benzodiazepines, the growing evidences suggest that the chronic inflammatory conditions may also contribute to the pathogenesis of venous thromboembolism through systemic inflammation and prothrombotic mechanism.[4–6]

Periodontitis is a chronic, multifactorial inflammatory disease involving microbial dysbiosis, dysregulated host immune response, and environmental factors.[7] Periodontitis is associated with systemic conditions, such as diabetes, chronic obstructive pulmonary disease, metabolic syndromes, and thromboembolic disorders.[8–10] While its connection to atherosclerotic disease is better characterized, the mechanisms linking periodontitis to venous thromboembolism are not well-established. Proposed pathways include the induction of systemic inflammation, transient bacteremia, and endothelial dysfunction, which may promote to pro-thrombotic condition.[11]

Some studies have suggested an increased risk of venous thromboembolism among individuals with periodontitis.[12–14] Improved oral hygiene, including tooth brushing as well as dental scaling, may be associated with a decreased risk of venous thromboembolism. However, the inconsistent results were also noted.[15] Therefore, the role of periodontitis in the development of thromboembolic events remains insufficiently characterized. To address this gap, the present study utilized a nationwide population-based cohort with well-established statistical approaches. By assessing effect modification and conducting stratified subgroup analyses, this study aimed to clarify the potential association between periodontitis and the risk of DVT in Taiwan.

Materials and methods

Data source

Longitudinal Health Insurance Database (LHID), the sub-data bank of Taiwan's National Health Insurance Research Database, included a sample of two million beneficiaries, selected at random from the beneficiary registry in 2000, representing the entire Taiwanese population. It contained all medical claims for outpatient and inpatient services, including drug prescriptions, medical procedures, and associated fees from 2000 to 2019.[5,16,17] Ethical approval was secured from the Institutional Review Board of Chung Shan Medical University Hospital (CS2-23031; Approval date: 13 March 2023). The reporting of this observational study complies with the STROBE (strengthening the reporting of observational studies in epidemiology) guidelines.

Study design and outcome

This retrospective cohort study investigated the individuals with newly diagnosed periodontitis between 2002 and 2018, identified by using International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes 523.4, 523.5 and ICD-10-CM codes K05.30, K05.31, K05.32, K05.4. To ensure the diagnostic accuracy, inclusion required either at least two outpatient visits with the diagnosis of periodontitis. The index date was defined at date of the first qualifying diagnosis of periodontitis. Individuals with a prior diagnosis of DVT before the index date were excluded to ensure the new-onset cases. The comparison group comprised individuals with no record of periodontitis from 2000 to 2019. The primary outcome was the occurrence of newly diagnosed DVT, as defined in Supplementary Table 1. Both cohorts were followed from the index date until the diagnosis of DVT, mortality, or 31 December 2019, whichever occurred first.

Comorbidities and matching

Baseline characteristics included age, sex, and comorbidities such as hypertension, hyperlipidemia, chronic liver disease, chronic kidney disease, diabetes, chronic

obstructive pulmonary disease, rheumatoid arthritis, ankylosing spondylitis, hepatitis B, hepatitis C, herpes zoster, and psoriasis (ICD codes illustrated in Supplementary Table 1). These comorbidities were identified based on at least two outpatient visits or one hospitalization within one year prior to the index date. Initially, a 1:1 matching by age and sex was conducted to assign an index date to individuals without periodontitis. This was followed by propensity score matching between periodontitis and non-periodontitis cohorts, using logistic regression based on age, sex, and comorbidities. The purpose of propensity score matching was to reduce baseline differences between the two groups.

Statistical analysis

The comparison between subjects with and without periodontitis was conducted using absolute standardized differences (ASD), with values below 0.1 indicating acceptable balance between groups.[18] The relative risk (RR) was estimated through Poisson regression. The cumulative incidence of DVT was assessed using Kaplan–Meier analysis, and differences between groups were tested with the log-rank test. Hazard ratios (HRs) with 95 % confidence intervals (CI) were calculated using a multivariable Cox proportional hazards model. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

In total, 969,527 individuals diagnosed with periodontitis and 244,305 individuals without any record of periodontitis were identified from the LHID. After excluding patients with a prior diagnosis of DVT before the index date, 964,884 individuals remained in periodontitis cohort. To evaluate the risk of DVT, both periodontitis and non-periodontitis cohorts underwent a 1:1 matching by age and sex. Subsequently, a second round of 1:1 propensity score matching was performed based on age, sex, and comorbidities. Finally, a total of 185,799 matched pairs for the final analysis as illustrated in Fig. 1. The demographic characteristics of matched cohorts are presented in Table 1. The mean age was 47.28 years in periodontitis group and 47.51 years in non-periodontitis group, with the majority being male. After matching, ASDs were below 0.1 which indicated a good balance in baseline characteristics between two groups.

As shown in Table 2 1,426 and 1,177 DVT were found in the periodontitis cohort and non-periodontitis cohort, respectively. Poisson regression demonstrated the relative risk of DVT was 1.08-fold in periodontitis group as compared to non-periodontitis group (95 % CI: 1.004–1.17). However, Kaplan–Meier analysis revealed a borderline statistical significant cumulative incidence of DVT in periodontitis group (log-rank test, $P = 0.054$) as illustrated in Fig. 2.

As shown in Table 3, Cox proportional hazard regression showed that periodontitis was not significantly associated with an increased risk of DVT after adjusting for covariates (HR = 0.98; 95 % CI: 0.90–1.06; $P = 0.552$). Female group demonstrated the lower risk of DVT as compared with male group (HR = 0.77; 95 % CI: 0.71–0.83; $P < 0.001$). However, the age ≥65 years old group was found to strongly associated with increased DVT risk up to 31.95 fold as compared to age <20 years old group (CI: 20.03–50.99, $P < 0.001$). In addition, comorbidities including hypertension, chronic

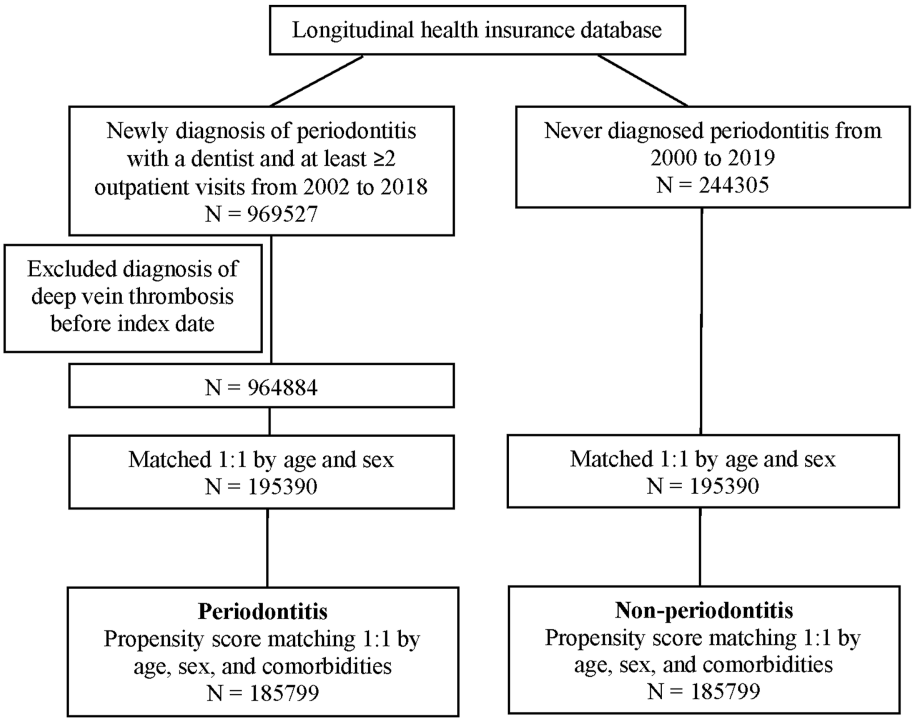


Figure 1 Study flow chart of participant selection.

Table 1 Demographic characteristics of periodontitis and non-periodontitis.

	Before PSM matching			After PSM matching		
	Non-Periodontitis	Periodontitis		Non-Periodontitis	Periodontitis	
	(N = 195390)	(N = 195390)	ASD	(N = 185799)	(N = 185799)	ASD
Age			0			0.026
<20	22942 (11.74)	22942 (11.74)		22856 (12.30)	22884 (12.32)	
20-39	47580 (24.35)	47580 (24.35)		46506 (25.03)	46529 (25.04)	
40-64	77609 (39.72)	77609 (39.72)		71020 (38.22)	71916 (38.71)	
≥65	47259 (24.19)	47259 (24.19)		45417 (24.44)	44470 (23.93)	
Mean ± SD	47.78 ± 20.48	47.78 ± 20.48	0	47.51 ± 20.71	47.28 ± 20.63	0.011
Sex			0			0.007
Female	75304 (38.54)	75304 (38.54)		72660 (39.11)	72067 (38.79)	
Male	120086 (61.46)	120086 (61.46)		113139 (60.89)	113732 (61.21)	
Hypertension	30958 (15.84)	38663 (19.79)	0.103	30349 (16.33)	32519 (17.50)	0.031
Hyperlipidemia	9721 (4.98)	15749 (8.06)	0.125	9704 (5.22)	10183 (5.48)	0.011
Chronic liver disease	5747 (2.94)	8256 (4.23)	0.069	5702 (3.07)	6267 (3.37)	0.017
Chronic kidney disease	2595 (1.33)	2071 (1.06)	0.025	2244 (1.21)	1997 (1.07)	0.013
Diabetes	15753 (8.06)	16251 (8.32)	0.009	14826 (7.98)	15212 (8.19)	0.008
Chronic obstructive pulmonary disease	6241 (3.19)	6556 (3.36)	0.009	5936 (3.19)	6149 (3.31)	0.006
Rheumatoid arthritis	581 (99.70)	711 (0.36)	0.012	571 (99.69)	603 (0.32)	0.003
Ankylosing spondylitis	179 (0.09)	300 (0.15)	0.018	179 (0.10)	174 (0.09)	0.001
Hepatitis B	1187 (0.61)	2038 (1.04)	0.048	1184 (0.64)	1153 (0.62)	0.002
Hepatitis C	956 (0.49)	1206 (0.62)	0.017	928 (0.50)	1017 (0.55)	0.007
Herpes zoster	808 (0.41)	1241 (0.64)	0.031	808 (0.43)	811 (0.44)	<0.001
Psoriasis	444 (0.23)	656 (0.34)	0.020	442 (0.24)	447 (0.24)	0.001

PSM: propensity scores matching.
N: number.
ASD: absolute standardized differences.
SD: standard deviation.

Table 2 Poisson regression of the relative risk for periodontitis and non-periodontitis.

	Non-periodontitis	Periodontitis
N	185799	185799
Person-years	1760344.74	1966918.7
N of DVT	1177	1426
ID (95 % CI)	0.67 (0.63–0.71)	0.72 (0.69–0.76)
Relative risk (95 % CI)	Reference	1.08 (1.004–1.17)

N:number.
DVT: deep vein thrombosis.
ID: incidence density (per 1000 person-years).
CI: confidence intervals.

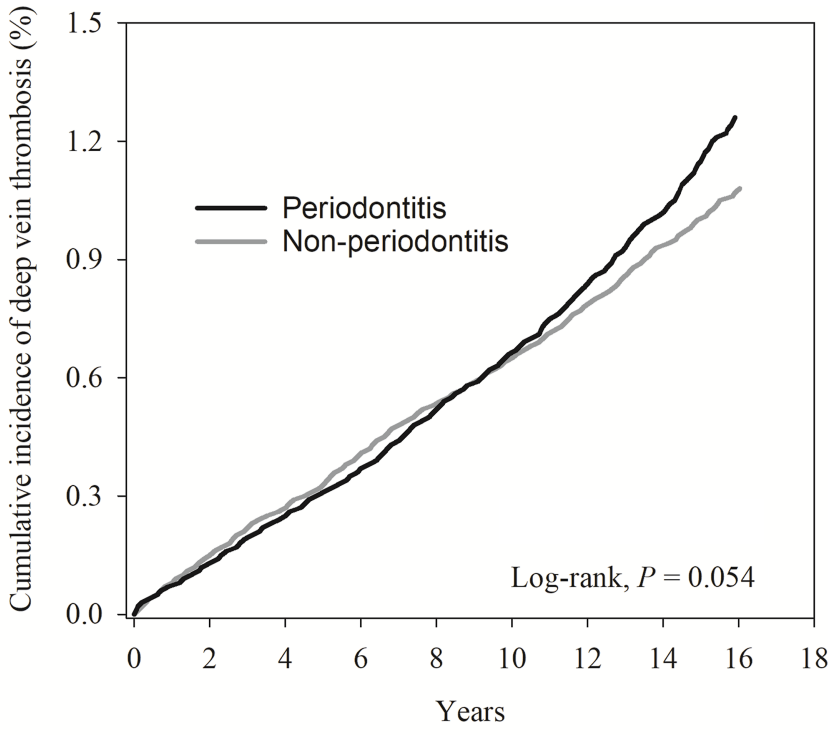
kidney disease, diabetes, chronic obstructive pulmonary disease, rheumatoid arthritis, and herpes zoster were shown as the risk factors of DVT, respectively ($P < 0.05$).

Subgroup analyses were further conducted in Table 4. Among individuals aged ≥65 years, periodontitis was significantly associated with an increased risk of DVT (HR = 1.13; 95 % CI: 1.02–1.25; $P = 0.024$). The significant age interaction effect was noted (P for interaction = 0.019). Male patients had higher risk of DVT with borderline significance in periodontitis group (HR = 1.12; 95 % CI: 1.00–1.25; $P = 0.060$). A significant sex difference was also observed (P for interaction = 0.001). Taken together, the association between periodontitis and DVT was found to be varied by age and sex, respectively.

Discussion

Recently, one systematic review suggested the positive association between periodontal disease and the incidence of thromboembolic disease.[9] However, most of the included studies are case series and case reports, the strength of evidence is relative weak. Some epidemiologic studies with small sample size restricted the ability to perform a comprehensive multivariate adjustment.[12,13] In addition, they focused on a specific high-risk population with recurrent venous thromboembolism that could limit the generalizability of findings for DVT incidents. Previously, a large-scale prospective study from 8,092 participants to examine periodontal disease and venous thromboembolism revealed no statistically significant associations after adjustment.[14] Therefore, evidence generated from well-designed longitudinal controlled clinical trials and nationwide population may be helpful to further assess the association between periodontitis and risk of DVP.

To the best of our knowledge, this is the first nationwide population propensity score matched cohort study to report the association between periodontitis exposure and the risk of DVT. In this study, Poisson regression showed a



No. at risk									
Non-periodontitis	185799	169545	151379	132679	112803	91925	68915	43795	16877
Periodontitis	185799	178234	164824	148891	130157	108785	83578	54274	21407

Figure 2 Kaplan—Meier curves for the cumulative incidence of deep vein thrombosis.

statistically significant increase of 1.08 fold in DVT incidence among individuals with periodontitis. In contrast, there was not significant between periodontitis and DVT after adjusting for age, sex, and comorbidities using a multivariate Cox model. This discrepancy may reflect the differences in model assumptions, particularly the ability of Cox regression to account for varying follow-up durations and censoring, providing a more time-sensitive assessment of risk.

In this study, further subgroup analyses revealed the heterogeneity that among those who aged ≥65 years, periodontitis was significantly linked to the increased risk of DVT about 1.13-fold. The possible reasons may be explained by the underlying biological mechanisms involving inflammation, coagulation, and individual susceptibility. In elder adults, immune aging and chronic low-grade inflammation may amplify the systemic prothrombotic pathways.[19] Increased levels of inflammatory mediators such as interleukin-6 and tumor necrosis factor-alpha in the elderly population have been shown to promote endothelial dysfunction as well as hypercoagulability.[20,21]

In this study, the elevated risk of DVT among male patients were borderline significant about 1.12 fold in periodontitis group. Moreover, sex difference was significantly noted. Consistently, past literature has indicated that men had the higher risk of DVT than women.[22] A compressive review concluded that men have an unexplained higher intrinsic venous thromboembolism risk than women.[23] Exogenous use of testosterone was associated with a slightly increased venous thromboembolism risk in men.[23] Inflammation and dysregulation of metabolism seem also of interest with respect to underlying mechanisms in venous thromboembolism risk. Taken together, these findings support the hypothesis that periodontitis may trigger the thrombo—inflammatory reactions and modulated by age and sex.

This study has several notable strengths, including the use of a large, nationally representative cohort and careful adjustment through matching as well as multivariable analysis. However, several limitations should be noted. First, both exposure (periodontitis) and outcome (DVT) were identified using administrative claims data, which may involve some errors in diagnosis such as mistakes in coding or differences in clinical judgment might still exist. Second, lack of the information regarding the severity and duration of periodontitis form NHIRD can limit the ability to examine whether more severe or long-standing disease leads to a higher risk of DVT. Third, although we adjusted for many health conditions, we could not account for certain important factors that were not obtained in this database, such as smoking, obesity, physical activity, or diet which might affect both periodontal and vascular health. Fourth, since this was an observational study, further long-term follow-ups, basic researches are needed to better understand this potential link between periodontitis and DVT.

In spite of study limitations, our findings may have significant clinical and hypothetic implications. This large-scale

Table 3 Cox proportional hazard model analysis for the risk of deep vein thrombosis.

	Univariate		Multivariate[a]	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Group				
Non-periodontitis	Reference		Reference	
Periodontitis	1.08 (1.00–1.17)	0.055	0.98 (0.90–1.06)	0.552
Age				
<20	Reference		Reference	
20–39	3.60 (2.21–5.85)	<0.001	3.50 (2.15–5.69)	<0.001
40–64	14.73 (9.25–23.47)	<0.001	12.52 (7.85–19.97)	<0.001
≥65	48.19 (30.30–76.65)	<0.001	31.95 (20.03–50.99)	<0.001
Sex				
Female	Reference		Reference	
Male	0.61 (0.56–0.66)	<0.001	0.77 (0.71–0.83)	<0.001
Hypertension	4.18 (3.86–4.52)	<0.001	1.52 (1.39–1.67)	<0.001
Hyperlipidemia	2.91 (2.59–3.28)	<0.001	1.09 (0.96–1.24)	0.182
Chronic liver disease	1.95 (1.65–2.32)	<0.001	1.15 (0.96–1.38)	0.127
Chronic kidney disease	11.80 (10.03–13.88)	<0.001	5.00 (4.24–5.91)	<0.001
Diabetes	3.39 (3.07–3.75)	<0.001	1.32 (1.18–1.48)	<0.001
Chronic obstructive pulmonary disease	2.95 (2.53–3.45)	<0.001	1.24 (1.06–1.45)	0.009
Rheumatoid arthritis	3.36 (2.25–5.02)	<0.001	1.70 (1.14–2.54)	0.010
Ankylosing spondylitis	1.39 (0.45–4.29)	0.573	1.19 (0.38–3.70)	0.761
Hepatitis B	1.88 (1.24–2.83)	0.003	1.36 (0.90–2.08)	0.146
Hepatitis C	1.53 (0.91–2.59)	0.112	0.72 (0.42–1.23)	0.233
Herpes zoster	2.96 (2.03–4.33)	<0.001	1.47 (1.00–2.14)	0.048
Psoriasis	2.09 (1.16–3.78)	0.014	1.46 (0.81–2.64)	0.210

HR: hazard ratio.
CI: confidence intervals.
[a] Adjusted for age, sex, and comorbidities.

Table 4 Subgroup analysis for risk of deep vein thrombosis.

	Non-periodontitis		Periodontitis			
	N	N of DVT	N	N of DVT	HR (95 % CI)	*P* Value
Age[a]						
<20	22856	6	22884	12	1.90 (0.71–5.08)	0.200
20-39	46506	88	46529	75	0.80 (0.59–1.08)	0.148
40-64	71020	458	71916	480	0.89 (0.78–1.01)	0.070
≥65	45417	625	44470	859	1.13 (1.02–1.25)	0.024
		P For interaction =				0.019
Sex[b]						
Female	72660	675	72067	695	0.87 (0.78–0.97)	0.012
Male	113139	502	113732	731	1.12 (1.00–1.25)	0.060
		P For interaction =				0.001

DVT: deep vein thrombosis.
N: number.
HR: hazard ratio.
CI: confidence intervals.
a: adjusted for age, sex, and chronic obstructive pulmonary disease.
b: adjusted for age, sex, hypertension, hyperlipidemia, chronic liver disease, chronic kidney disease, diabetes, chronic obstructive pulmonary disease, rheumatoid arthritis, hepatitis B, hepatitis C, herpes zoster, and psoriasis.

population-based cohort study revealed that the association between periodontitis and the risk of DVT appeared to vary across specific subgroups, particularly among older adults and the potential within male patients. Therefore, the importance of maintaining better periodontal health should be considered in the prevention of DVT. Further prospective, clinical, and experimental studies are required to confirm the positive association between periodontitis and DVT concurrence.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2025.08.011.

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