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Intensive Periodontal Treatment Reduces Risk of Infection-Related Hospitalization in Hemodialysis Population

A Nationwide Population-Based Cohort Study

Shih-Ting Huang, MD, Cheng-Li Lin, MSc, Tung-Min Yu, MD, Ming-Ju Wu, MD, PhD, and Chia-Hung Kao, MD

Abstract: Periodontal disease (PD) is prevalent and correlated with malnutrition and inflammation in patients on hemodialysis (HD). Periodontal therapy improves systemic inflammatory and nutritional markers in HD population. The relationship between intensive PD therapy and clinical infectious outcomes in patients on HD remains unclear.

In total, 4451 patients who underwent HD and intensive PD treatment between January 1, 1998 and December 31, 2010 were selected from the National Health Insurance Research Database as the case cohort. The comparison cohort was selected by matching a patient without PD with each PD treated patient at a 1:1 ratio according to a propensity score. The rates of hospitalizations for infectious diseases for both cohorts were analyzed and compared.

Compared with the comparison cohort, the hazard ratio (HR) of hospitalization for overall infectious diseases was 0.72 (95% confidence interval [CI] = 0.66–0.78, $P < 0.001$) for the intensive PD treatment cohort. The intensive PD treated cohort had a significantly lower risk of acute and subacute infective endocarditis (HR = 0.54, 95% CI = 0.35–0.84, $P < 0.01$), pneumonia (HR = 0.71, 95% CI = 0.65–0.78, $P < 0.001$), and osteomyelitis (HR = 0.77, 95% CI = 0.62–0.96, $P < 0.05$) than did the comparison cohort.

The intensive PD treatment of patients with HD was associated with reduced risks of overall infectious diseases, acute and subacute infective endocarditis, pneumonia, and osteomyelitis. Our study concurs the role of a conventional intervention in enhancing infectious diseases outcomes.

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Abbreviations: CI = confidence interval, ESRD = end stage renal disease, HD = Hemodialysis, HRs = hazard ratios, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, IRR = incidence rate ratio, NHIRD = National Health Insurance Research Database, PD = Periodontal disease, SDs = standard deviations.

INTRODUCTION

Infections are leading causes of death among patients with end-stage renal disease (ESRD), accounting for 15% of mortalities.[1] Infectious complications are the second leading cause of hospitalization in the ESRD population.[2] In addition to infections associated with dialysis access devices, ESRD may be susceptible to nonaccess-related infections. Among them, the most important infections include respiratory infections, Infections of the central nervous system, gastrointestinal infections, genitourinary tract infections, cellulitis, and osteomyelitis. Among them, respiratory infections are the second leading cause of infection-related deaths.[1]

Numerous measures have been used for infection prevention. Recommendations for vaccination, blood-borne virus management, and environmental cleaning are valued.[3,4] Despite these prevention measures, infection hospitalization rates in the first months of dialysis were still almost equal to rates of cardiovascular hospitalization.[2] Additional modifiable determinants of infection prevention in dialysis patients are needed to be identified and evaluated.

Periodontal diseases (PD) are prevalent in dialysis population, with prevalence rate reaching 80.6%.[5] ESRD patients exhibited higher plaque and calculus indices and lower salivary secretion than did healthy controls.[6] Diseases with at least minimal evidence of an association with periodontitis include pneumonia, chronic kidney disease, metabolic syndrome, and cancer.[7] Periodontitis severity was correlated with malnutrition and inflammatory status in dialysis patients.[5] Evidence showed that PD adversely affects all-cause or cardiovascular survival in HD population.[8,9]

Regarding periodontal therapy, studies have reported improvements in endothelial function and inflammation among

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From the Division of Nephrology, Department of Medicine, Taichung Veterans General Hospital, Taichung, Taiwan (S-T,H, T-M,Y, M-J,W); Graduate Institute of Clinical Medicine Science, School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan (S-T,H, T-M,Y, C-H,K); Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan (C-L,L); School of Medicine, China Medical University, Taichung, Taiwan (C-L,L); and Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan (C-H,K)
Correspondence: Chia-Hung Kao, Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 404, Taiwan (email: d10040@mail.cmuh.org.tw).
Author contributions: Conception and design: S-T,H and C-H,K.
Administrative support: C-H,K.
Collection and assembly of data: S-T,H, C-L,L, and C-H,K.
Data analysis and interpretation: S-T,H, C-L,L, and C-H,K.
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patients with significant PD.[10,11] In clinical setting, frequent and regular dental scaling was associated with a significant decrease in infective endocarditis (IE).[12] In dialysis population, PD therapy was suggested to improve systemic inflammation, nutritional status, and erythropoietin responsiveness.[13,14]

However, the clinical effects of intensive PD therapy on infection prevention in dialysis patients are largely unknown. Our study investigated how intensive PD therapy affects the risks of major infections and examined the trends of outcome risks that were modified by the frequency of intensive periodontal therapy in HD population.

METHODS

Data Source

This retrospective cohort study used data extracted from the Registry of Catastrophic Illness Database (RCID) in Taiwan, a part of the National Health Insurance Research Database (NHIRD). The Bureau of National Health Insurance (BNHI) established the universal NHI program in 1995. More than 99% of the population in Taiwan, approximately 23.72 million people, is enrolled in the program, which provides comprehensive medical coverage (http://www.nhi.gov.tw/english/index.aspx). The BNHI entrusted the National Health Research Institutes (NHRI) to establish and maintain the release of comprehensive NHI-related administrative claims data for research. The RCID includes all patients who satisfy the BNHI criteria for a catastrophic illness certificate. Catastrophic illnesses are defined as severe illnesses requiring advanced health care, such as malignancies, posttransplantation status, and ESRD. Patients with a catastrophic illness certificate are exempt from medical care copayments, and physicians review all certificate requests. The NHIRD identifies diseases on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The accuracy and validity of NHIRD diagnosis codes has been documented.[15] According to the Personal Information Protection Act, all researchers must formally declare that they have no intention of violating patient privacy. This study was approved by the Institutional Review Board of China Medical University (CMU-REC-101-012).

Sampled Participants

Figure 1 shows the process of selecting participants for the study cohorts. Patients newly diagnosed with ESRD (ICD-9-CM 585) between January 1, 1998 and December 31, 2010 and who underwent dialysis for at least 3 months were identified from the RCID. Patients with prior major infectious diseases, survived fewer than 90 days after the first dialysis date, were undergoing transplantation, were younger than 20 years, or whose information was missing were excluded. Patients with PD (ICD-9-CM code 523) who underwent intensive periodontal treatment (included subgingival curettage [scaling (91004C) and root planning (91006C, 91007C, 91008C)] and periodontal flap surgery [91009B, 91010B]) in the study period were included in the treatment cohort. The comparison cohort included HD patients without diagnosis of PD. The treatment and comparison cohorts were matched at a 1:1 ratio according to a propensity score.[16] The propensity score was calculated using logistic regression to estimate the probability of periodontal assignment according to baseline variables, namely age, sex, urbanization level, monthly income (in New Taiwan dollars), Charlson comorbidity index (CCI), and comorbidities of chronic obstructive pulmonary disease (COPD), hyperlipidemia, diabetes, hypertension, congestive heart failure, liver cirrhosis, and dementia. The C-statistic of the logistic regression model was 0.51.

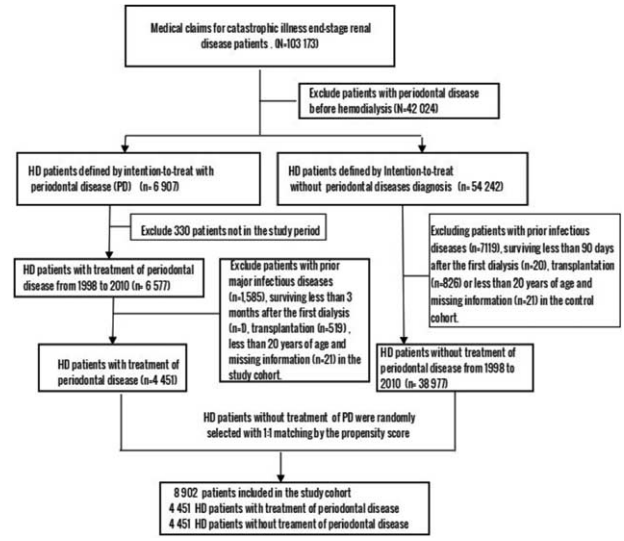

FIGURE 1. Flow diagram of patient enrollment in the study cohorts.

The index date was defined as the date of intensive PD therapy for the treatment cohort and the 15th day of the same month for the comparison cohort.

Outcome Measurements

Both cohorts were observed from the index date to the date of hospitalization for an infectious disease, including acute and subacute IE (ICD-9-CM codes 421.0, 421.1, and 421.9), bacteremia (ICD-9-CM code 790.7), pneumonia (ICD-9-CM codes 487.0, 486, 481, 480.8, 482, and 484), brain abscess (ICD-9-CM code 324.0), osteomyelitis (ICD-9-CM code 730), renal and perinephric abscess (ICD-9-CM code 590.2), withdrawal from the insurance system, or the end of the follow-up period (December 31, 2010).

Independent Variables

Sociodemographic and comorbidity data, with age, sex, urbanization level, and monthly income as the covariates, were obtained from the claims data. The NHRI urbanization categories were adopted; these comprised 7 strata, with level 1 denoting the most urbanized communities and level 7 denoting the least urbanized communities. Factors in classification included population density (people/km^2); ratios of elderly people, agricultural workers, and people with different educational levels; and the number of physicians per 100,000 people. The urbanization levels were divided into 2 categories on the basis of an NHRI report (levels 1 and 2 represented cities, and levels 3–7 represented rural areas). The monthly costs of patients for insurance premiums were classified into 3 groups, $<$NT\$15,000, NT\$15,000 to NT\$19,999, and $\geq$NT\$20,000 (US\$1 is approximately NT\$30). Comorbidities diagnosed before the index date included COPD (ICD-9-CM codes 491, 492, and 496), hyperlipidemia (ICD-9-CM code 272), diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401-405), congestive heart failure (ICD-9-CM code 428), liver cirrhosis (ICD-9-CM code 571), and dementia (ICD-9-CM code 290).

TABLE 1. Baseline Demographic Status and Comorbidity in Hemodialysis Patients With PD Treatment and Patient Without PD

	Controls, No (n = 4451)	Periodontal Diseases After Treatment, Yes (n = 4451)	*P* Value
Age (yr), mean ± SD	58.3 ± 13.7	58.5 ± 12.2	0.64
Gender			0.83
Women	2435 (54.7)	2425 (54.5)	
Men	2016 (45.3)	2026 (45.5)	
Dialysis duration, yr	2.50 (2.25)	2.47 (2.24)	0.51
Urbanization level*			0.90
1	1152 (25.9)	1156 (26.0)	
2	1388 (31.2)	1405 (31.6)	
3	801 (18.0)	810 (18.2)	
≥4	1110 (24.9)	1080 (24.3)	
Monthly income (NTD)			0.001
<15,000	1323 (29.7)	1186 (26.7)	
15,000–19,999	2297 (51.6)	2244 (50.4)	
≥20,000	831 (18.7)	1021 (22.9)	
Charlson comorbidity index (CCI)			0.95
0	326 (7.32)	336 (7.55)	
1	65 (1.46)	60 (1.35)	
2	1681 (37.8)	1678 (37.7)	
3+	2379 (53.5)	2377 (53.4)	
Comorbidity			
COPD	13 (0.29)	18 (0.40)	0.37
Hyperlipidemia	1537 (34.5)	1527 (34.3)	0.82
Diabetes	1437 (32.3)	1419 (31.9)	0.68
Hypertension	3827 (86.0)	3818 (85.8)	0.78
CHF	841 (18.9)	849 (19.1)	0.83
Liver cirrhosis	1263 (28.4)	1242 (27.9)	0.62
Dementia	57 (1.28)	64 (1.44)	0.52

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; NTD = New Taiwan dollars; PD = periodontal disease; SD = standard deviation.

* Urbanization status was categorized into 7 levels according to the population density of the residential area, with level 1 as the most urbanized and level 7 as the least urbanized.

Statistical Analysis

The baseline characteristics and comorbidities of the cohorts were compared. Chi-squared and Student *t* tests were performed for categorical and continuous variables, respectively. The incidence density of each outcome disease per 1000 person-years was calculated according to sex, age, and comorbidity status. Cox proportional hazard models were used to estimate the risk of infection outcomes in the treatment cohort compared with those in the untreated cohort. Baseline characteristic variables, such as age, sex, comorbidities, urbanization level, and monthly income, were adjusted for in the multivariate model. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox model.

We further analyzed the frequency of clinical course in the intensive treatment cohort to assess how the responsiveness to the treatment affected outcome risks. The cumulative incidences of outcome diseases were computed using the Kaplan–Meier method, and the differences between the cohorts were examined using the log-rank test. All statistical analyses were performed using SAS Version 9.3 (SAS Institute, Inc., Carey, NC). Results with a 2-tailed *P* value of <0.05 were considered statistically significant.

RESULTS

A total of 103,173 ESRD patients receiving HD were included in our catastrophic illness group (Figure 1). Among them, 42,024 HD patients who had prior diagnosis of PD before HD enrollment were excluded. Patients undergoing HD were categorized into: with PD and received intensive periodontal therapy (n = 6577); and without PD diagnosis (n = 54,242) between January 1, 1998 and December 31, 2010. After excluding patients on the basis of the aforementioned criteria, the treatment and comparison cohorts were selected and matched at a 1:1 ratio, according to propensity scores, to reduce selection bias and approximate a randomized trial. Finally, each cohort comprised 4451 patients.

Table 1 compares the baseline characteristics of patients undergoing HD and intensive periodontal treatment with those of the propensity score-matched comparison cohort. The mean dialysis duration was 2.47 ± 2.24 years and 2.50 ± 2.25 years for the treatment and comparison cohorts, respectively. The distribution of sex, age, urbanization level, and CCI was similar in both cohorts. Of the baseline comorbidities, hypertension, hyperlipidemia, and diabetes were prevalent in both cohorts. Notably, the proportions of liver cirrhosis were high,

TABLE 2. Outcomes of Periodontal Disease Patients With Treatment and Controls, as Determined Using a Matched Cox Proportional Hazards Model

	Controls			Periodontal Diseases After Treatment			
Outcome	**Event**	**PY**	**Rate**[†]	**Event**	**PY**	**Rate**[†]	**HR**[‡] **(95% CI)**
Overall infectious diseases	1191	19,068	62.5	1195	24,687	48.4	0.72 (0.66, 0.78)***
Acute and subacute infective endocarditis	50	21,448	2.33	37	27,789	1.33	0.54 (0.35, 0.84)**
Bacteremia	159	21,304	7.46	195	27,441	7.11	0.83 (0.68, 1.03)
Pneumonia	975	19,580	49.8	976	25,351	38.5	0.71 (0.65, 0.78)***
Brain abscess	13	21,524	0.60	12	27,848	0.43	0.68 (0.31, 1.50)
Osteomyelitis	157	21,196	7.41	170	27,447	6.19	0.77 (0.62, 0.96)*
Renal and perinephric abscess	15	21,536	0.70	11	27,848	0.40	0.53 (0.24, 1.17)

CI = confidence interval; HR = relative hazard ratio; PY = person-years.
[†] Incidence rate per 1000 person-years.
[‡] Multivariable analysis including age, sex, comorbidities, urbanization level, and monthly income. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

approximately 27.9% and 28.4% in the treatment and comparison cohorts, respectively. None of the baseline characteristics differed significantly between the cohorts, except stratified monthly income.

The overall incidence density of hospitalization for infectious diseases was lower in the intensive treated cohort than in the comparison cohort (48.4 vs 62.5 per 1000 person-years, respectively) (Table 2). We used matched Cox proportional hazards model to analyze the influence of PD therapy on infections. The treated patients exhibited a significantly lower risk of overall infectious diseases than did the comparison cohort, with an HR of 0.72 (95% CI = 0.66–0.78, $P < 0.001$). Among the infectious diseases for which patients were hospitalized, pneumonia, osteomyelitis, and bacteremia were the primary causes in both cohorts. The incidence rates of pneumonia, osteomyelitis, and bacteremia were 38.5, 6.19, and 7.11 events per 1000 person-years, respectively, in the treated cohort. The treated cohort exhibited a significantly lower risk for acute and subacute IE (HR = 0.54, 95% CI = 0.35–0.84, $P < 0.01$), pneumonia (HR = 0.71, 95% CI = 0.65–0.78, $P < 0.001$), and osteomyelitis (HR = 0.77, 95% CI = 0.62–0.96, $P < 0.05$) than did the comparison cohort. Although the incidence rates of bacteremia, brain abscess, renal and perinephric abscess were lower in the treated cohort, the risks did not differ significantly between the cohorts.

We further stratified patients according to age, gender, and comorbidities to estimate the risk difference (Table 3). The intensive treated patients in the age 50 to 64 group exhibited the significantly lower age-specific relative risk of IE (HR = 0.42; 95% CI = 0.22–0.80). In addition, the lower risk for IE was observed in female patients (HR = 0.41, 95% CI = 0.23–0.75), and those with comorbidities (HR = 0.54, 95% CI = 0.35–0.85). Except patients without comorbidity, the risk of pneumonia in patients with PD treatment in whichever stratification was significantly lower than that of the comparison cohort.

The patients aged elder than 65 years exhibited the lower age-specific relative risk of osteomyelitis (HR = 0.53; 95% CI = 0.34–0.81). For men, the incidence of osteomyelitis were 6.07 and 8.28 per 1000 person-years between the 2 cohorts, with a 0.66-fold relative risk of developing osteomyelitis (95% CI = 0.48–0.92). The risk of osteomyelitis was 0.77-fold lower in the treated patients with comorbidities than in the corresponding comparison cohort patients (95% CI = 0.62–0.96).

Table 4 presents the effects of treatment responsiveness according to frequency of clinic visit for intensive periodontal treatment. Compared to that in the patients without PD, the risk of hospitalization for overall infectious diseases tended to increase in PD patients who underwent therapy in <1 clinic course, and decreased significantly in patients having more than 2 infective treatment visits, with an HR of 0.52 (95% CI = 0.48–0.58, $P < 0.001$). The risk of hospitalization for overall infectious diseases decreased as frequency of treatment visit increased (P value for trend was <0.001). The treatment responsiveness of clinic visit for intensive treatment of PD on IE, bacteremia, pneumonia, and osteomyelitis were evident in the treated cohort.

Because periodontal patients may not have always been treatment during the study period and this may in fact overestimate the effect of treatment, we also used the Cox proportional hazard model with time-dependent exposure covariates to estimate the risk for each outcome disease in order to reduce this bias (Table 5).

The cumulative incidences of major infectious diseases were shown as Kaplan–Meier plot for major infections after 10 years of follow-up (Figure 2). Compared with the control cohort, the treated cohort exhibited a significantly lower cumulative incidence of IE (Figure 2A) (log-rank test $P = 0.008$), and pneumonia (Figure 2C) (log-rank test $P < 0.001$).

DISCUSSION

Primary Results

Our study was the first to demonstrate that PD treatment plays a role in the primary prevention of infectious diseases in patients on HD. We found association between PD therapy and major infectious complications in HD patients. HD patients with PD therapy had a 0.72-fold decrease in overall infectious diseases compared with HD patients without PD, after adjusting for available demographic and medical characteristics.

In Table 1, we observed high comorbidity burden in both cohorts, with over 90% patients having CCI score ≥2. This finding may be explained by the bidirectional relationship between chronic kidney disease and PD, for they share common risk factors such as aging and diabetes.[17] In Table 2, among major infectious complications in both cohorts, the highest

TABLE 3. Outcomes of Patients With Periodontal Disease After Treatment and Patient Without PD by Age, Gender, and Comorbidity, as Determined Using a Matched Cox Proportional Hazards Model

	Controls			Periodontal Diseases After Treatment			
Variables	**Event**	**PY**	**Rate**[†]	**Event**	**PY**	**Rate**[†]	**HR**[‡] **(95% CI)**
Acute and subacute infective endocarditis							
Age, yr							
≤49	10	7848	1.27	8	7950	1.01	0.81 (0.32, 2.07)
50–64	24	8146	2.95	16	12,302	1.30	0.42 (0.22, 0.80)**
≥65	16	5454	2.93	13	7537	1.72	0.55 (0.26, 1.16)
Gender							
Women	30	12,013	2.50	17	15,608	1.09	0.41 (0.23, 0.75)**
Men	20	9435	2.12	20	12,181	1.64	0.72 (0.39, 1.36)
Comorbidity[§]							
No	5	2281	2.19	3	2611	1.15	0.50 (0.12, 2.11)
Yes	45	19,168	2.35	34	25,178	1.35	0.54 (0.35, 0.85)*
Pneumonia							
Age, yr							
≤49	181	7294	24.8	126	7541	16.7	0.66 (0.52, 0.83)***
50–64	368	7503	49.1	414	11,184	37.0	0.73 (0.64, 0.84)***
≥65	426	4784	89.1	436	6626	65.8	0.70 (0.61, 0.80)***
Gender							
Women	508	11,006	46.2	512	14,264	35.9	0.73(0.65, 0.83)***
Men	467	8574	54.5	464	11,087	41.9	0.68 (0.60, 0.78)***
Comorbidity[§]							
No	63	2165	29.1	52	2471	21.0	0.71 (0.49, 1.03)
Yes	912	17,415	52.4	924	22,880	40.4	0.72 (0.65, 0.79)***
Osteomyelitis							
Age, yr							
≤49	32	7799	4.10	35	7865	4.45	0.94 (0.58, 1.53)
50–64	76	8009	9.49	97	12,096	8.02	0.82 (0.61, 1.11)
≥65	49	5388	9.09	38	7486	5.08	0.53 (0.34, 0.81)**
Gender							
Women	80	11,899	6.72	97	15,421	6.29	0.87 (0.64, 1.17)
Men	77	9297	8.28	73	12,026	6.07	0.66 (0.48, 0.92)*
Comorbidity[§]							
No	5	2308	2.17	4	2620	1.53	0.71 (0.19, 2.68)
Yes	152	18,888	8.05	166	24,827	6.69	0.77 (0.62, 0.96)*

CI = confidence interval; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; HR = relative hazard ratio; PD = periodontal disease; PY = person-years.

[†] Incidence rate per 1000 person-years.

[‡] Multivariable analysis including age, sex, comorbidities, urbanization level, and monthly income.

[§] Comorbidity: Patients with any one of the comorbidities (including COPD, hyperlipidemia, diabetes, hypertension, CHF, liver cirrhosis, and dementia) were classified as the comorbidity group. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

incidence rates were observed in pneumonia, bacteremia, and osteomyelitis, respectively. In Table 3, the risks of IE, pneumonia, and osteomyelitis in patients with comorbidities were simultaneously lower in PD patients with treatment compared with those of the control cohort.

In Table 4, we observed that the risks among overall infectious diseases, IE, bacteremia, pneumonia, brain abscess, and osteomyelitis were highest in PD patients with frequency of PD therapy <1 compared to that of control and patients with frequency of PD therapy more than 2. Moreover, the risks among overall infectious diseases, IE, bacteremia, pneumonia, brain abscess, and osteomyelitis were significantly lower in patients with frequency of intensive PD therapy more than 2 compared to that of the control group.

The higher frequency of clinic visit for intensive PD therapy in patients may represent more completed treatment course or more complex PD burden. In either situation, the HRs of infectious diseases in those who received higher treatment frequency (≥2) were lowest compared to that in both control (no PD diagnosis) and lower treatment frequency (≤1) patients. These findings further underline the association between the effect of intensive PD therapy and infections in HD patients.

Explanation for the Findings

Pneumonia

Mounting evidence suggests that a causal relationship exists between PD and respiratory infections such as bacterial

TABLE 4. Associations Between Outcome Events and the Frequency of Clinic Visit for Intensive Periodontal Disease Treatment, as Determined Using a Matched Cox Proportional Hazards Model

	N	No. of Event	Rate[†]	HR (95% CI)[‡]
Overall infectious diseases				
Controls	4451	1191	62.5	1 (Reference)
Frequency of treatment of periodontal disease				
≤1	1486	565	94.4	1.18 (1.07, 1.31)**
≥2	2965	630	33.7	0.52 (0.48, 0.58)***
P for trend				<0.001
Acute and subacute infective endocarditis				
Controls	4451	50	2.33	1 (Reference)
Frequency of treatment of periodontal disease				
≤1	1486	17	2.19	0.84 (0.48, 1.46)
≥2	2965	20	1.00	0.42 (0.25, 0.71)**
P for trend				0.001
Bacteremia				
Controls	4451	159	7.46	1 (Reference)
Frequency of treatment of periodontal disease				
≤1	1486	87	11.4	1.21 (0.92, 1.57)
≥2	2965	108	5.44	0.67 (0.52, 0.86)**
P for trend				0.002
Pneumonia				
Controls	4451	975	49.8	1 (Reference)
Frequency of treatment of periodontal disease				
≤1	1486	468	73.7	1.16 (1.03,1.29)*
≥2	2965	508	26.7	0.52 (0.47, 0.58)***
P for trend				<0.001
Brain abscess				
Controls	4451	13	0.60	1 (Reference)
Frequency of treatment of periodontal disease				
≤1	1486	6	0.77	1.06 (0.40, 2.84)
≥2	2965	6	0.30	0.50 (0.19, 1.32)
P for trend				0.17
Osteomyelitis				
Controls	4451	157	7.41	1 (Reference)
Frequency of treatment of periodontal disease				
≤1	1486	89	11.8	1.26 (0.97, 1.64)
≥2	2965	81	4.07	0.54 (0.41, 0.70)***
P for trend				<0.001
Renal and perinephric abscess				
Controls	4451	15	0.70	1 (Reference)
Frequency of treatment of periodontal disease				
≤1	1486	5	0.64	0.92 (0.33, 2.56)
≥2	2965	6	0.30	0.39 (0.15, 1.02)
P for trend				0.06

CI = confidence interval; HR, relative hazard ratio.
[†] Rate, incidence rate per 1000 person-years.
[‡] Multivariable analysis including age, sex, comorbidities, urbanization level, and monthly income. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

pneumonia and COPD.[7] Case–control studies have reported an increased risk of nosocomial and community-acquired pneumonia and respiratory infections, including COPD exacerbation, in patients with periodontal infections. The risks remained even after adjustment for possible confounding factors, including age and smoking habits.[18,19]

The mechanism of pneumonia could be the aspiration of pneumonia-causing oral pathogens.[20] Alternatively, the mechanism may be the colonization of the upper airway with the assistance of periodontal pathogens, which modify the respiratory epithelium, making the airway more susceptible to the colonization process.[21]

Oral care strategies for medically compromised patients were devised to prevent aspiration pneumonia.[22] Oral care was believed to reduce lower respiratory tract infections in elderly patients.[23] Our study demonstrated that PD therapy was associated with a 29% reduction in the risk of hospitalization for pneumonia. The potential effectiveness of PD therapy in preventing pneumonia was comparable to that of influenza vaccination.[24]

TABLE 5. Hazard Risk and 95% Confidence Intervals (CIs) for Outcome in Time-Depended Model

Outcome	Crude HR (95% CI)	HR† (95% CI)
Infectious diseases	0.75 (0.69, 0.81)***	0.75 (0.69, 0.82)***
Acute and subacute infective endocarditis	0.65 (0.42, 1.00)	0.65 (0.42, 1.01)
Bacteremia	0.85 (0.69, 1.06)	0.85 (0.69, 1.05)
Pneumonia	0.75 (0.69, 0.82)***	0.75 (0.69, 0.83)***
Brain abscess	0.88 (0.40, 1.96)	0.91 (0.41, 2.03)
Osteomyelitis	0.70 (0.56, 0.87)**	0.71 (0.56, 0.88)**
Renal and perinephric abscess	0.75 (0.34, 1.65)	0.76 (0.34, 1.66)

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; Crude HR = relative hazard ratio.
† Multivariable analysis including age, sex, urbanization level, and monthly income Charlson comorbidity index, and comorbidities of COPD, hyperlipidemia, diabetes, hypertension, CHF, liver cirrhosis, and dementia. ** $P < 0.01$.

Infective Endocarditis

Bacteremia in patients with PD tends to be sustained[25] and is a major cause of IE in elderly patients with valvular heart disease.[26] Recommendations emphasize the use of antimicrobial prophylaxis before dental procedures to prevent bacterial endocarditis in susceptible patients with periodontitis.[27]

Studies on intervention therapies, such as decolonization to ameliorate infectious complications in patients on dialysis, further support our findings. A recent population-based study reported that regular dental scaling (at least once per year) reduced the risk of IE by 33%,[12] probably because scaling can reduce the bacterial load and cause a shift in the subgingival flora.[28] Although our study did not reveal a significant reduction in the risk of bacteremia in the treated group, the incidence rates were lower than that of the control cohort.

Osteomyelitis

ESRD is a comorbidity that predisposes patients to vertebral osteomyelitis (VO).[28] HD has been associated with the highest rate of in-hospital mortality in patients with VO.[29] VO occurrence was associated with antecedent infections, DM, and immunosuppression[30]; however, few studies have examined the relationship between periodontal infection and VO.

Although the primary entry sites of the hematogenous pathogens in osteomyelitis included soft tissue, vascular access sites, and endocarditis; the pathogens were identified in only 51% of patients.[31] Our result revealed that the risk of bacteremia tended to decrease in HD patient with PD treatment, and it might infer that oral cavity being another potential route of entry in VO patients.

Limitations

The strengths of our study are that we used longitudinal, population-based data to demonstrate the demographic characteristics of patients undergoing HD with PD. Our study is the first to demonstrate an association between intensive PD intervention and major infectious diseases in high-risk patients with HD. These findings can be generalized to the overall ESRD population and may be aid in alerting clinicians or policy makers to the role of intensive PD therapy in the primary prevention of infectious diseases.

This observational study was performed using administrative databases and has inherent limitations.

First, our study was not a prospective, randomized study of hemodialysis (HD) patients with PD who did or did not receive adequate periodontal care. Although inherent selection bias could not be avoided, the significant risk reductions in the patients with higher frequency of intensive PD treatment compared with that of the patients without PD further confirm the role of PD therapy in the primary prevention of infectious diseases. Nevertheless, future studies involving well-designed, controlled interventions are required.

Second, we are uncertain as to the PD status of the control cohort. In HD patient without PD diagnosis coding, the reasons might be: patients did not have PD; or patients were underdiagnosed for PD. According to a prospective observational incenter study conducted by Chen et al, 80.6% of prevalent HD patients have PD,[1] which further confirms our control cohort as a mixed population of whom up to 80% had undiagnosed (and untreated) peridontal disease. Oral disease may be underdiagnosed in patients treated with dialysis due to the lower uptake of public dental service.[32,33] As we can see in our study, the CCI $\geq$3 were approximately 53% in both cohorts (Table 1). The high prevalence of comorbidities might prevent patients from dental care. This is the reason we chose patients without PD diagnosis (n = 54,242) in our database as control cohort.

Finally, the NHIRD does not contain detailed smoking habit, weight, or other lifestyle factors that could be potential confounders. However, recent evidence has indicated that the observed association between PD and atherosclerotic vascular disease may exist independently of smoking.[34] We adopted other important variables such as socioeconomic status and access to dental facilities (urbanization level) to strengthen the validity of our result.

CONCLUSION

Our study confirm that intensive periodontal treatment is associated with a significant risk reduction in major infectious complications in HD patient with PD. PD therapy is a potential modifiable factor in the primary prevention of infections in HD patients, especially in patients with multiple comorbidities. Therefore, the diagnosis and management of PD in HD population deserve better awareness.

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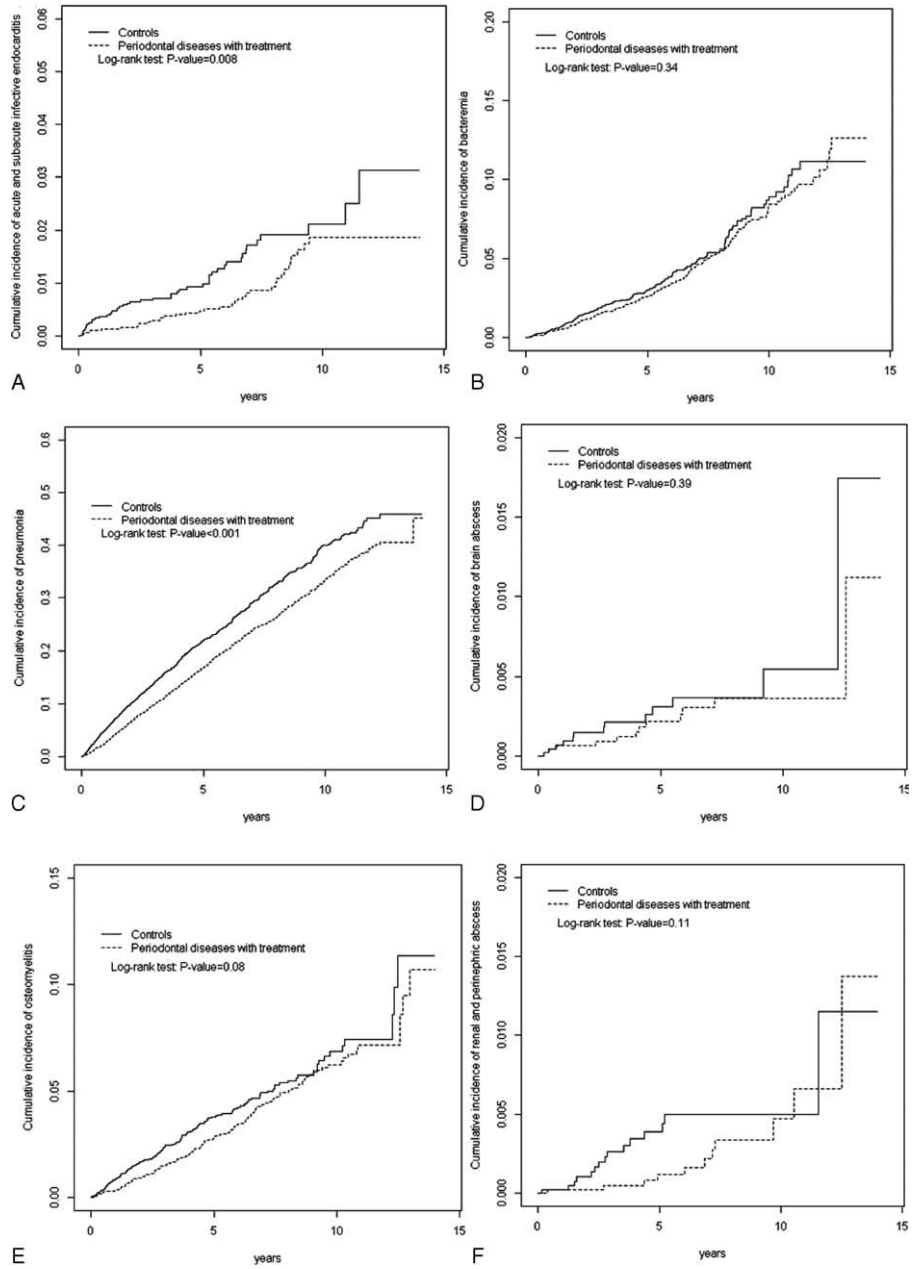

FIGURE 2. Cumulative incidence of infectious diseases in patients with PD treatment and patient without PD. PD = periodontal disease.

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