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

A Nationwide Population-Based Cohort Study

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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.

(Medicine 94(34):e1436)

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.8 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

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.
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 confidentiality. 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.

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, 481.8, 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/km²); 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 ≥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).
**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 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<sup>a</sup> | | | 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.

<sup>a</sup>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.
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 (48.4 vs 62.5 per 1000 person-years, respectively) (Table 2). We used matched Cox proportional hazard model with time-dependent exposure covariates to estimate the effect of treatment, we also used the Cox proportional hazard model with time-dependent exposure covariates to estimate the risk difference (Table 3). The findings 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 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 treated during the study period and this may in fact over-estimate 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. In Table 2, among major infectious complications in both cohorts, the highest

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

| Outcome                      | Controls Event | Controls PY | Controls Rate (95% CI) | Periodontal Diseases After Treatment Event | Periodontal Diseases After Treatment PY | Periodontal Diseases After Treatment Rate (95% CI) | 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)   |

Cl = confidence interval; HR = relative hazard ratio; PY = 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.

In conclusion, PD patients exhibited a significantly lower age-specific relative risk of 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).
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...
pneumonia and COPD.\textsuperscript{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.\textsuperscript{18,19}

The mechanism of pneumonia could be the aspiration of pneumonia-causing oral pathogens.\textsuperscript{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.\textsuperscript{21}

Oral care strategies for medically compromised patients were devised to prevent aspiration pneumonia.\textsuperscript{22} Oral care was believed to reduce lower respiratory tract infections in elderly patients.\textsuperscript{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.\textsuperscript{24}

### 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\textsuperscript{1} | HR (95% CI)\textsuperscript{1} |
|----|--------------|-------------------------|-------------------------------|
|    | 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)\textsuperscript{**} |
|    | ≥2 | 2965 | 630 | 33.7 | 0.52 (0.48, 0.58)\textsuperscript{***} |
|    | 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)\textsuperscript{**} |
|    | 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)\textsuperscript{**} |
|    | 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)\textsuperscript{*} |
|    | ≥2 | 2965 | 508 | 26.7 | 0.52 (0.47, 0.58)\textsuperscript{***} |
|    | 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)\textsuperscript{***} |
|    | 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 |       |

\textsuperscript{CI} = confidence interval; HR, relative hazard ratio.\textsuperscript{1} Rate, incidence rate per 1000 person-years.\textsuperscript{1} Multivariable analysis including age, sex, comorbidities, urbanization level, and monthly income.\textsuperscript{7} P < 0.05, ** P < 0.01, *** P < 0.001.
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.

**References**

1. United States Renal Data System. Excerpts from the USRDS 2009 annual data report: Atlas of end-stage renal disease in the United States. Am J Kidney Dis. 2010;55:S1.
2. Collins AJ, Foley RN, Gilbertson DT, et al. The state of chronic kidney disease, ESRD, and morbidity and mortality in the first year of dialysis. Clin J Am Soc Nephrol. 2009;4:S5–S11.
FIGURE 2. Cumulative incidence of infectious diseases in patients with PD treatment and patient without PD. PD = periodontal disease.

3. CDC. *CDC Guidelines for Vaccinating Kidney Dialysis Patients and Patients with Chronic Kidney Disease*. December 2012. Available from: http://www.cdc.gov/vaccines/pubs/downloads/dialysis-guide-2012.pdf

4. Department of Health. Centre for Healthcare Related Infection Surveillance and Prevention & Tuberculosis Control. *Guideline: Prevention and Control of Infections in Dialysis Settings*. Version 3, May 2013. Australia. Available from: http://www.health.qld.gov.au/chrisp/policy_framework/renal_guideline.pdf

5. Chen LP, Chiang CK, Chan CP, et al. Does periodontitis reflect inflammation and malnutrition status in hemodialysis patients? *Am J Kidney Dis.* 2006;47:815–822.

6. Gavaldà C, Bagán J, Scully C, et al. Renal hemodialysis patients: oral, salivary, dental and periodontal findings in 105 adult cases. *Oral Dis.* 1999;5:299–302.

7. Linden GI, Herzberg MC. Working Group 4 of the Joint EFP/AAP Workshop. Periodontitis and systemic diseases: a record of discussions of Working Group 4 of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Periodontol.* 2013;84:S20–S23.

8. Kshirsagar AV, Craig RG, Moss KL, et al. Periodontal disease adversely affects the survival of patients with end-stage renal disease. *Kidney Int.* 2009;75:746–751.
9. Chen LP, Chiang CK, Peng YS, et al. Relationship between periodontal disease and mortality in patients treated with maintenance hemodialysis. Am J Kidney Dis. 2011;57:276–282.
10. Demmer RT, Trinquart L, Zuk A, et al. The influence of anti-infective periodontal treatment on C-reactive protein: a systematic review and meta-analysis of randomized controlled trials. PLoS ONE. 2013;8:e77441.
11. Elter JR, Hinderliter AL, Offenbacher S, et al. The effects of periodontal therapy on vascular endothelial function: a pilot trial. Am Heart J. 2006;151:47.
12. Chen SJ, Liu CJ, Chao TF, et al. Dental scaling and risk reduction in infective endocarditis: a nationwide population-based case–control study. Can J Cardiol. 2013;29:429–433.
13. Siribamrungwong M, Puangpanngam K. Treatment of periodontal diseases reduces chronic systemic inflammation in maintenance hemodialysis patients. Ren Fail. 2012;34:171–175.
14. Siribamrungwong M, Yothasamutr K, Puangpanngam K. Periodontal treatment reduces chronic systemic inflammation in peritoneal dialysis patients. Ther Apher Dial. 2014;18:305–308.
15. Lee CF, Lin CL, Lin MC, et al. Surgical treatment for patients with periodontal disease reduces risk of end-stage renal disease: a nationwide population-based retrospective cohort study. J Periodontol. 2014;85:50–56.
16. Parsons LS. Performing a 1: N Case–Control Match on Propensity Score. SUGI29 Seattle, WA: Ovation Research Group; 2001:165–169. http://www2.sas.com/proceedings/sugi29/165-29.pdf
17. Fisher MA, Taylor GW, West BT, et al. Bidirectional relationship between chronic kidney and periodontal disease: a study using structural equation modeling. Kidney Int. 2011;79:347–355.
18. Gomes-Filho JS, de Oliveira TF, da Cruz SS, et al. Influence of periodontitis in the development of nosocomial pneumonia: a case control study. J Periodontol. 2014;85:e82–e90.
19. de Melo Neto JP, Melo MS, dos Santos-Pereira SA, et al. Periodontal infections and community-acquired pneumonia: a case–control study. Eur J Clin Microbiol Infect Dis. 2013;32:27–32.
20. Richards AM, Abu Kwaik Y, Lamont RJ. Code blue: Acinetobacter baumannii, a nosocomial pathogen with a role in the oral cavity. Mol Oral Microbiol. 2015;30:2–15.
21. Bansal M, Khati M, Taneya V. Potential role of periodontal infection in respiratory diseases—a review. J Med Life. 2013;6:244–248.
22. Pace CC, McCullough GH. The association between oral microorganisms and aspiration pneumonia in the institutionalized elderly: review and recommendations. Dysphagia. 2010;25:307–322.
23. El-Solh AA. Association between pneumonia and oral care in nursing home residents. Lung. 2011;189:173–180.
24. Wang IK, Lin CL, Lin PC, et al. Effectiveness of influenza vaccination in patients with end-stage renal disease receiving hemodialysis: a population-based study. PLoS ONE. 2013;8:e58317.
25. Takai S, Kuriyama T, Yanagisawa M, et al. Incidence and bacteriology of bacteremia associated with various oral and maxillofacial surgical procedures. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;99:292–298.
26. Durante-Mangoni E, Bradley S, Selton-Suty C, et al. Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study. Arch Intern Med. 2008;168:2095–2103.
27. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116:1736–1754.
28. Mylona E, Samarkos M, Kakalou E, et al. Pyogenic vertebral osteomyelitis: a systematic review of clinical characteristics. Semin Arthritis Rheum. 2009;39:10–17.
29. Akiyama T, Chikuda H, Yasunaga H, et al. Incidence and risk factors for mortality of vertebral osteomyelitis: a retrospective analysis using the Japanese diagnosis procedure combination database. BMJ Open. 2013;3:e002412.
30. Beronius M, Bergman B, Andersson R. Vertebral osteomyelitis in Göteborg, Sweden: a retrospective study of patients during 1990–95. Scand J Infect Dis. 2001;33:527–532.
31. McHenry MC, Easley KA, Locker GA. Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Clevelandarea hospitals. Clin Infect Dis. 2002;34:1342–1350.
32. Griffin SO, Barker LK, Griffin PM, et al. Oral health needs among adults in the United States with chronic diseases. J Am Dent Assoc. 2009;140:1266–1274.
33. Grubbs V, Plantinga LC, Tuot DS, et al. Chronic kidney disease and use of dental services in a United States public healthcare system: a retrospective cohort study. BMC Nephrol. 2012;13:16.
34. Beck JD, Eke P, Heiss G, et al. Periodontal disease and coronary heart disease: a reappraisal of the exposure. Circulation. 2005;112:19–24.