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Higher dental care is positively associated with key prognosis factors in peritoneal dialysis patients: findings from a retrospective study

Takeyuki Hiramatsu^{*} , Shota Okumura, Daiki Iguchi and Hiroshi Kojima

Abstract

Background: Oral disease may be increased in people with end-stage renal disease and associated with inflammation, cardiovascular disease, and mortality. Moreover, oral disease may be essential to decide the prognosis of peritoneal dialysis (PD) patients. However, only a few reports have explored the effects of dental care (DC) on cardiovascular diseases and mortality in PD patients. Thus, we aimed to investigate the association of DC with the prognosis of PD patients.

Methods: In this single-center, retrospective study, we enrolled 165 incident PD patients aged ≥ 20 years. We classified patients based on their dental care score, assessed using a self-reported questionnaire into the better dental care group (Group A, score ≥ 7) or the worse dental care group (Group B, score < 7). Demographic, clinical, hospitalization, hospital admission, comorbidities (including congestive heart failure, acute coronary syndrome, stroke, peripheral artery disease, and pneumonia), and mortality (including specific causes) data were extracted from the patient's medical records. Data were analyzed using one-way ANOVA, Wilcoxon t-test, Kruskal–Wallis, Mann–Whitney U-test, chi-square test, Fisher's exact test and multiple regression when appropriate. We compared the survival distributions among groups using the long-rank test.

Results: Of the 165 patients, 75 were allocated to group A and 90 to group B. PD patients with better dental care (group A) had significantly lower levels of C-reactive protein (CRP) and higher levels of serum albumin compared to PD patients with worse dental care (group B). Hospital admissions due to congestive heart failure, acute coronary syndrome, pneumonia, and peritonitis were also lower in group A than group B. Mortality rates due to congestive heart failure, acute coronary syndrome, pneumonia, and sepsis were lower in group A than in group B.

Conclusions: The study highlights the importance of good dental care, particularly for PD patients. Nephrologists and dental professions should design and implement oral health education strategies to improve PD patients' dental care.

Keywords: Peritoneal dialysis, Dental care, Cardiovascular event

Background

Cardiovascular disease and infection are the most important predictors of survival in patients on dialysis in Japan [1]. In recent decades, it has been found that frequently people with end-stage renal disease (ESRD) have a higher prevalence of oral disease, which may be associated with malnutrition, inflammation, cardiovascular diseases, and mortality [2–6].

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Poor dental care (DC) is the main factor for developing dental diseases, while good dental hygiene may prevent oral diseases and improve appetite. Thus, a good DC may help maintain a good nutrition state and improve chronic inflammation and malnutrition, as reported previously [2]. Studies have also reported that dental care is associated with severe infections [7, 8], including in peritoneal dialysis (PD) patients [9]. In frail older adults, results from a systematic review showed that good oral health care could reduce aspiration pneumonia incidence [10].

Some studies showed better DC decreased cardiovascular disease [5, 11, 12]. Although oral health hygiene has undeniable importance to PD patient's health, studies exploring the association between DC and the incidence of cardiovascular events, such as congestive heart failure (CHF) or acute coronary syndrome (ACS), are scarce.

In the present study, we aimed to investigate whether DC in PD patients might affect the incidence of cardiovascular diseases and infection, especially peritonitis.

Methods

Study design and participants

We conducted this retrospective observational study in the Konan-Kosei Hospital in Japan from January 2010 to December 2019 ($n = 189$). Patients between the ages of 20 and 80 years were included if they started PD after January 2010. The exclusion criteria were as follows: (1) patients who could not do PD therapy by themselves; and (2) follow-up time less than 3 months after starting PD. Data on 165 incident PD patients who met these criteria and agreed to participate in the present study were extracted from medical records. All patients gave written informed consent. The study protocol was approved by the ethics committee at the Konan-Kosei Hospital and was conducted following the ethical principles stated in the Declaration of Helsinki and the Japanese Ministry of Health, Labor, and Welfare. The reporting of the study follows the STROBE statement and the broader EQUATOR guidelines.

Demographic and clinical data

Data regarding patient's background, such as age, sex, height, weight, background diseases of ESRD, PD vintage, continuous ambulatory PD (CAPD) or automated PD (APD), serum levels of albumin and C-reactive protein (CRP), Kt/V as total dialysis, and blood pressure were collected once a year at every last visit of the year. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Moreover, biochemical examinations were done once a year at every last visit of the year.

Self-administered DC questionnaire

After January 2010, we started suggesting DC to all patients on PD. The DC recommendation included brushing teeth three or more times per day, good oral hygiene, outpatient dental visits every 3 months, and prophylactic antibiotics treatment before scaling or caries treatment. Moreover, patients undertook a self-reported questionnaire including the DC performance at the last visit of every year. The DC questionnaire used in this study (Table 1) was a modified version from Japan Dental Association and the questionnaire used in the Oral Diseases in Hemodialysis (ORAL-D) study [13]. The total dental score ranged from zero to thirteen (higher values represented better oral hygiene habits). According to the dental care score, patients were divided into two groups: Group A (better dental health group, score ≥ 7), Group B (low dental health group, score < 7).

Hospital admissions, comorbidities, and mortality

We identified all admissions to the hospital during the study period, excluding those required for dialysis initiation. Each admission was categorized into the following categories: all cases, cases of infectious peritonitis, case of peritonitis with *Streptococcus species* (*sp.*), and cases of peritonitis with *Staphylococcus sp.* We also evaluated the incidence of peritonitis, especially due to peritonitis with *Streptococcus sp.*, CHF, ACS, stroke, peripheral artery disease (PAD), and pneumonia.

Further, we collected information on all-cause mortality and the causes of death (allocated into the following categories: CHD, ACS, pneumonia, sepsis, and stroke).

Statistical analysis

The admission rate was defined as the total incident number/cumulative treatment year. The mortality rate was defined as the incidence divided by cumulative PD patients (/person year). Data were presented as the mean \pm standard deviation for normally distributed variables, while asymmetrically distributed variables were presented as the median and interquartile range. Comparison between the two groups was performed by one-way analysis of variance (ANOVA) testing, followed by an appropriate post hoc analysis including Wilcoxon t-test, Kruskal–Wallis, Mann–Whitney U-test, chi-square test and Fisher's exact test. A multiple regression analysis was used to test the factors related to hospitalization risk in all patients. A $p < 0.05$ was considered to be statistically significant. Statistical analyses were performed using SPSS version 23 statistical software for Windows (SPSS, Inc., Chicago, IL, USA).

Table 1 Dental care questionnaire (modified from ORAL-D study questionnaire)

Question	Score	Description
How many times in a day do you brush your teeth?	0	Less than one
	1	One
	2	Two
	3	Three or more
Do you use dental floss?	0	No
	1	Sometimes
	2	Every day
Do you use mouse wash?	0	No
	1	Sometimes
	2	Every day
How many teeth do you have?	0	Less than 20
	1	20 and more
When did you make the latest dental visit?	0	Do not remember
	1	Over 1 year ago
	2	Less than 1 year ago
	3	Less than 6 months ago
How often do you change your toothbrush?	0	Less than 2 times per year
	1	Every 6 months
	2	Every 3 months
	3	Every 1 month
Do you use prophylactic antibiotics before a dental procedure?	0	No
	1	Yes

Results

Patient groups and characteristics

According to the inclusion and exclusion criteria, from the eligible 189 patients, 24 patients were excluded (22 were unable to do the PD by themselves, and two were moved to other clinics). Thus, 165 patients were retrieved from the medical record and split into two groups based on their dental care score. The patient's dental scores ranged between 0 and 13, the average score was 6.93 ± 1.33 , and the median value was 7. Therefore, patients' data were divided into two groups: Group A (dental care score ≥ 7 ; $n = 268$) and Group B (dental care score < 7 ; $n = 302$). Mean observational period was 58.9 ± 40.0 months in Group A and 49.8 ± 32.8 months in Group B ($p = 0.001$).

Both groups had similar characteristics, as the only significant differences were observed in serum levels of CRP (known to correlate with the magnitude of the inflammatory response), serum albumin, and BMI. Patients in group A had significantly lower CRP levels and significantly higher serum albumin and BMI (reflecting the nutritional status or inflammatory state of the whole body) compared with patients in group B (Table 2).

Our data showed a significant correlation between dental care score (DCS) with both serum CRP levels

($r = -0.401$, $p = 0.001$) and albumin levels ($r = 0.367$, $p = 0.001$).

Comparison of patients' hospitalization and admission rates by cause-specific between oral hygiene levels

Overall, the frequency of hospitalization and the admission rate due to all complications were significantly higher in group B patients than in group A (Fig. 1). From all the recorded complications that lead to hospital admission, CHF and ACS were the two conditions with a particularly high incidence in patients from group B compared with group A. Only hospital admission rates due to stroke and PAD was similar between the two groups. Similar results are depicted in Fig. 2, comparing the time distribution until the event of interest in the two independent groups using the log-rank test.

In summary, prevalence rates for all complications, except for stroke (Fig. 2c) and PAD (data not shown), were significantly higher in group B than in group A (Fig. 2a, b, d, e, f). Thus, compared with PD patients with better dental care (group A), the peritonitis-free period was significantly shorter in PD patients with worse dental care group B. Participants in Group B had lower toothbrushing frequency than those in Group A (1.33 ± 0.58 vs. 2.54 ± 0.50 ($p = 0.001$)). Moreover, the multiple regression analysis (Table 3) revealed that toothbrushing frequency

Table 2 Patient characteristics

	Group A (n = 75)	Group B (n = 90)	p value
Dental care score	9.2 ± 1.2	4.0 ± 1.1	0.001**
Age (year)	63.9 ± 12.0	64.2 ± 10.5	0.875
Male sex, n (%)	42 (56.0)	53 (58.9)	0.829
PD vintage (month)	58.9 ± 40.0	49.8 ± 32.8	0.001**
Type of PD			0.715
CAPD, n (%)	29 (38.6)	36 (40.0)	
APD, n (%)	49 (61.4)	54 (60.0)	
Kidney disease due to ESRD			0.892
CGN, n (%)	34 (45.3)	42 (46.7)	
DM, n (%)	15 (20.0)	18 (20.0)	
NS, n (%)	21 (28.0)	24 (26.7)	
Other CKDs, n (%)	5 (6.7)	6 (6.7)	
BMI (kg/m ²)	23.5 ± 3.2	22.7 ± 2.3	0.048*
Smoking status			0.848
Never, n (%)	44 (58.7)	54 (60.0)	
Past, n (%)	25 (33.3)	27 (30.0)	
Current, n (%)	6 (8.0)	9 (10.0)	
CRP (mg/dL)	0.19 ± 0.04	0.21 ± 0.05	0.045*
Albumin (g/dL)	3.41 ± 0.15	3.23 ± 0.20	0.001**
LDL-cholesterol (mg/dL)	108.2 ± 23.9	110.2 ± 31.5	0.738
HDL-cholesterol (mg/dL)	50.3 ± 9.4	49.8 ± 10.9	0.556
SBP (mmHg)	150.4 ± 11.6	151.1 ± 14.2	0.653
DBP (mmHg)	85.2 ± 4.2	86.2 ± 5.1	0.140
Kt/V	1.88 ± 0.25	1.83 ± 0.30	0.071

Data are expressed as mean ± standard deviation

APD automated peritoneal dialysis, BMI body mass index, CAPD continuous ambulatory peritoneal dialysis, CGN chronic glomerulonephritis, CRP C-reactive protein, DBP diastolic blood pressure, DM diabetes mellitus, NS nephrosclerosis, PD peritoneal dialysis, SBP systolic blood pressure

* $p < 0.05$; ** $p < 0.001$

was the most important factor for all-cause peritonitis (t value = -2.182 , $p = 0.048$), Streptococcal peritonitis (t value = -2.739 , $p = 0.006$), CHF (t value = -1.739 , $p = 0.059$) and pneumonia (t value = -2.916 , $p = 0.004$) for all participants. Also, dental visit was another main factor associated with CHF (t value = -2.463 , $p = 0.014$) and with ACS (t value = -2.094 , $p = 0.037$).

We also evaluated the hospitalization for all participants according to the changes in DCS compared with that of the baseline by dividing PD patients into three groups (decreased [$n = 26$], no change [$n = 73$], increased [$n = 18$]). The admission rates were higher in decreased DCS groups, on the other hand, lower in the increased DCS groups except for stroke or PAD (Table 4). Moreover, we found that the distribution of the patients by DCS group differed based on the following characteristics: all peritonitis ($\chi^2 = 8.54$, $p = 0.013$), Streptococcal peritonitis ($\chi^2 = 11.89$, $p = 0.003$), CHF ($\chi^2 = 8.80$, $p = 0.012$), and ACS ($\chi^2 = 10.12$, $p = 0.006$). No association was found

between DCS group and the remaining characteristics (pneumonia, infection, stroke, and PAD). Moreover, Fisher's exact analysis was used to compare the risk of respective hospitalization between decreased and increased group. The findings revealed hospitalization in decreased group had a higher risk in all peritonitis ($p = 0.006$), Streptococcus ($p = 0.001$), CHF ($p = 0.013$), and ACS ($p = 0.041$) than those in increased group, but in Staphylococcus ($p = 0.536$), stroke ($p = 0.151$), PAD ($p = 0.133$), pneumonia ($p = 0.439$), or other infection ($p = 0.682$), there were no relationship between the two groups.

Mortality rates in PD by oral hygiene level

All-cause mortality rates were significantly higher in PD patients with worse dental care (group B) than in patients with better dental care (group A; $p = 0.001$). In the stratified analysis by cause of death (Fig. 3), PD patients in group B also had significantly higher mortality due to CHF, ACS, pneumonia, and sepsis than PD patients in group A. Only the mortality rates due to stroke were similar among the two groups ($p = 0.805$). None of the patients died from peritonitis. Moreover, patients who died from sepsis had no evidence of pneumonia or other infectious focuses, except for bacteremia on admission. Multiple regression analysis showed that dental visit frequency was the major factor in mortality due to CHF (t value = -1.993 , $p = 0.050$) and ACS (t value = -1.883 , $p = 0.062$) (other data not shown). The survival curves using log-rank analysis (Fig. 4) showed similar results, indicating that worse oral hygiene was significantly associated with decreased survival rate in patients with CHF, ACS, and pneumonia. Our findings revealed that dental health might improve the survival rate in sepsis, but without significance. Nevertheless, there was no effect on the survival rate of stroke patients (Fig. 4a, b, d, e, f).

Discussion

This study showed that serum albumin values were significantly higher, and CRP values were significantly lower among the patients with better DC services. Notably, CRP and serum albumin levels were correlated with DC scores. That is to say, better dental care health might induce a higher value of serum albumin and a lower value of CRP. These findings suggest that dental hygiene may improve chronic inflammation and nutritional state in PD patients. In addition, we found that dental hygiene is associated with reduced admission rates due to peritonitis, pneumonia, cardiovascular events and is also associated with mortality due to cardiovascular events.

In previous reports, dental diseases were shown to be associated with a higher risk of malnutrition, inflammation, and cardiovascular events in ESRD patients [5], with possible positive implications in other frequent

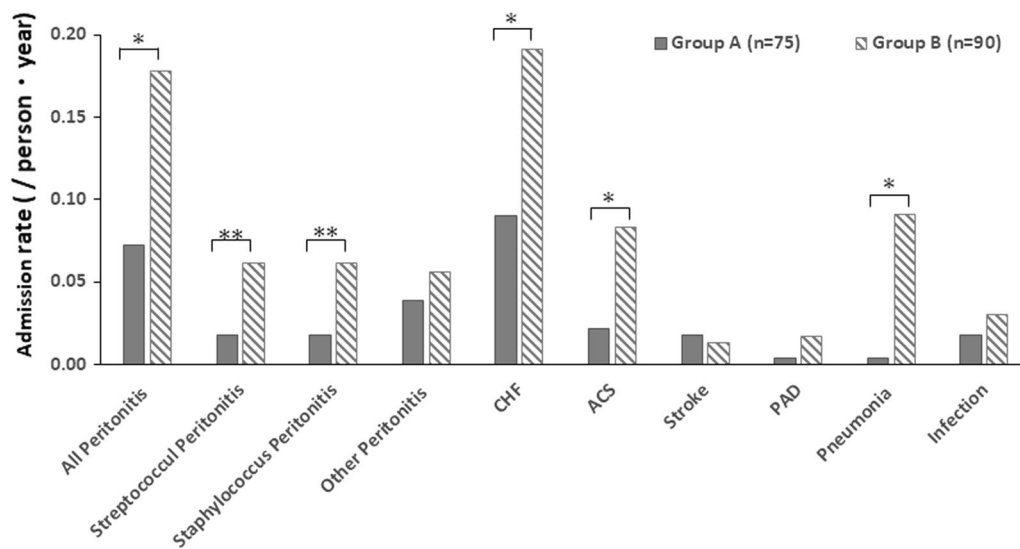


Fig. 1 Comparison of hospital admission rates by cause-specific admission between Group A and B. According to all hospitalization, acute coronary syndrome, congestive heart failure, peritonitis (all, *Streptococcus* or *Staphylococcus* related), and pneumonia, admission rates were significantly lower in group A than B. Nevertheless, the admission rate due to stroke and PAD were similar between groups A and B. * $p < 0.01$; ** $p < 0.05$

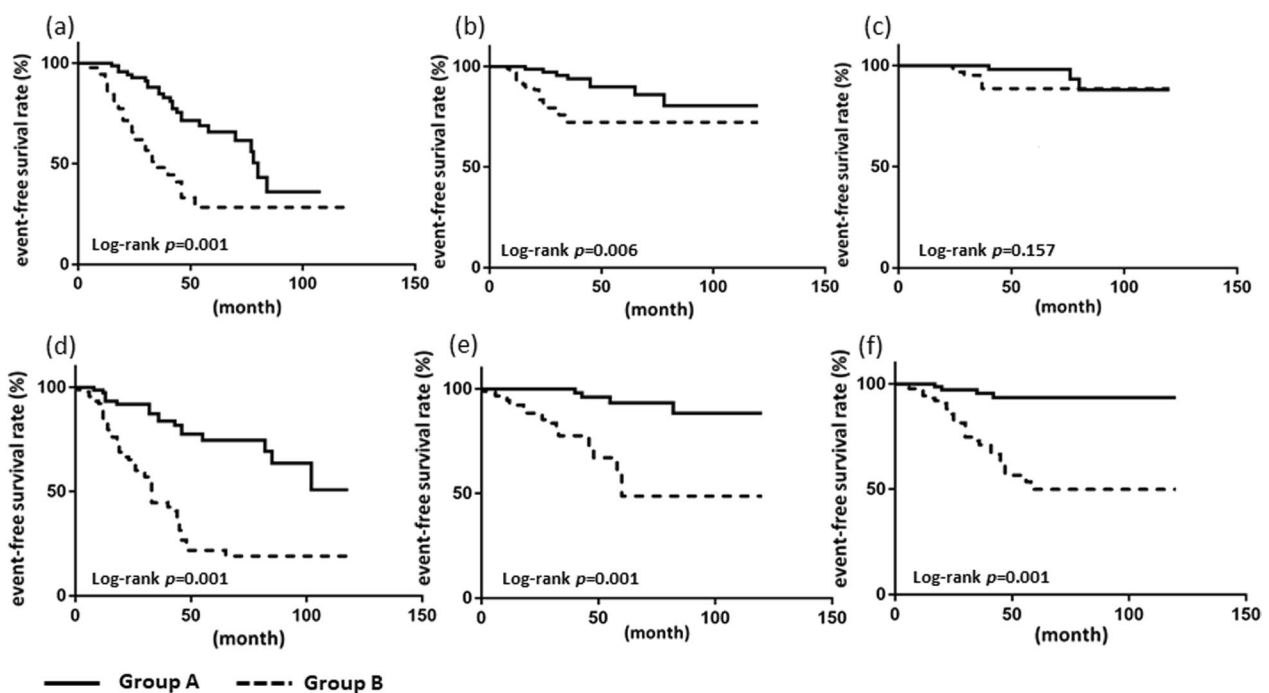


Fig. 2 Event-free survival for patients with higher (Group A—solid line) and lower (Group B—dashed line) dental care scores according to the cause of hospital admission. **a** Admission due to congestive heart failure (CHF); **b** Admission due to acute coronary syndrome; **c** Admission due to stroke; **d** Admission due to peritonitis; **e** Admission due to *Streptococcus* peritonitis; **f** Admission due to pneumonia. Log-rank analysis revealed that hospitalization in group B had a high prevalence risk of CHF, ACS, all peritonitis, *Streptococcus* peritonitis, and pneumonia ($p = 0.001$)

Table 3 Multiple regression analysis of risk factors related to hospitalization risk in all patients

Question	Complication	t value	p value
How many times in a day do you brush your teeth?	All peritonitis	−2.182	0.048*
	Streptococcal peritonitis	−2.739	0.006**
	Staphylococcal peritonitis	−1.787	0.075
	CHF	−1.739	0.056
	ACS	−1.332	0.183
	Stroke	0.731	0.465
	PAD	0.324	0.746
	Pneumonia	−2.916	0.004**
	Other infection	−0.143	0.886
Do you use dental floss?	All peritonitis	0.368	0.713
	Streptococcal peritonitis	1.018	0.309
	Staphylococcal peritonitis	−0.013	0.989
	CHF	1.518	0.098
	ACS	−1.608	0.106
	Stroke	0.694	0.488
	PAD	−0.875	0.382
	Pneumonia	1.016	0.310
	Other infection	0.266	0.791
Do you use mouse wash?	All peritonitis	0.577	0.564
	Streptococcal peritonitis	2.050	0.041*
	Staphylococcal peritonitis	−0.321	0.749
	CHF	0.051	0.959
	ACS	−0.373	0.709
	Stroke	−0.337	0.736
	PAD	−0.176	0.860
	Pneumonia	−0.617	0.537
	Other infection	−0.681	0.496
How many teeth do you have?	All peritonitis	1.635	0.103
	Streptococcal peritonitis	0.458	0.647
	Staphylococcal peritonitis	1.686	0.098
	CHF	0.585	0.559
	ACS	1.448	0.148
	Stroke	1.220	0.102
	PAD	−0.975	0.330
	Pneumonia	−1.810	0.071
	Other infection	0.283	0.777
When did you make the latest dental visit?	All peritonitis	−1.525	0.132
	Streptococcal peritonitis	−0.502	0.616
	Staphylococcal peritonitis	−1.891	0.059
	CHF	−2.463	0.014*
	ACS	−2.094	0.037*
	Stroke	0.038	0.970
	PAD	0.200	0.842
	Pneumonia	−1.368	0.172
	Other infection	−1.110	0.268

Table 3 (continued)

Question	Complication	t value	p value
How often do you change your toothbrush?	All peritonitis	− 1.568	0.118
	Streptococcal peritonitis	− 2.895	0.004**
	Staphylococcal peritonitis	− 1.697	0.090
	CHF	1.895	0.044*
	ACS	− 2.203	0.028*
	Stroke	− 1.000	0.318
	PAD	1.239	0.216
	Pneumonia	− 0.754	0.451
	Other infection	− 1.515	0.130
Do you use prophylactic antibiotics before a dental procedure?	All peritonitis	− 0.753	0.452
	Streptococcal peritonitis	− 0.394	0.694
	Staphylococcal peritonitis	1.061	0.289
	CHF	− 1.935	0.048*
	ACS	− 0.721	0.472
	Stroke	− 1.727	0.085
	PAD	− 0.894	0.372
	Pneumonia	− 0.381	0.703
	Other infection	− 1.065	0.288

ACS acute coronary syndrome, CHF congestive heart failure

* $p < 0.05$; ** $p < 0.001$ **Table 4** Comparison of hospital admission rates according to DCS change in all patients

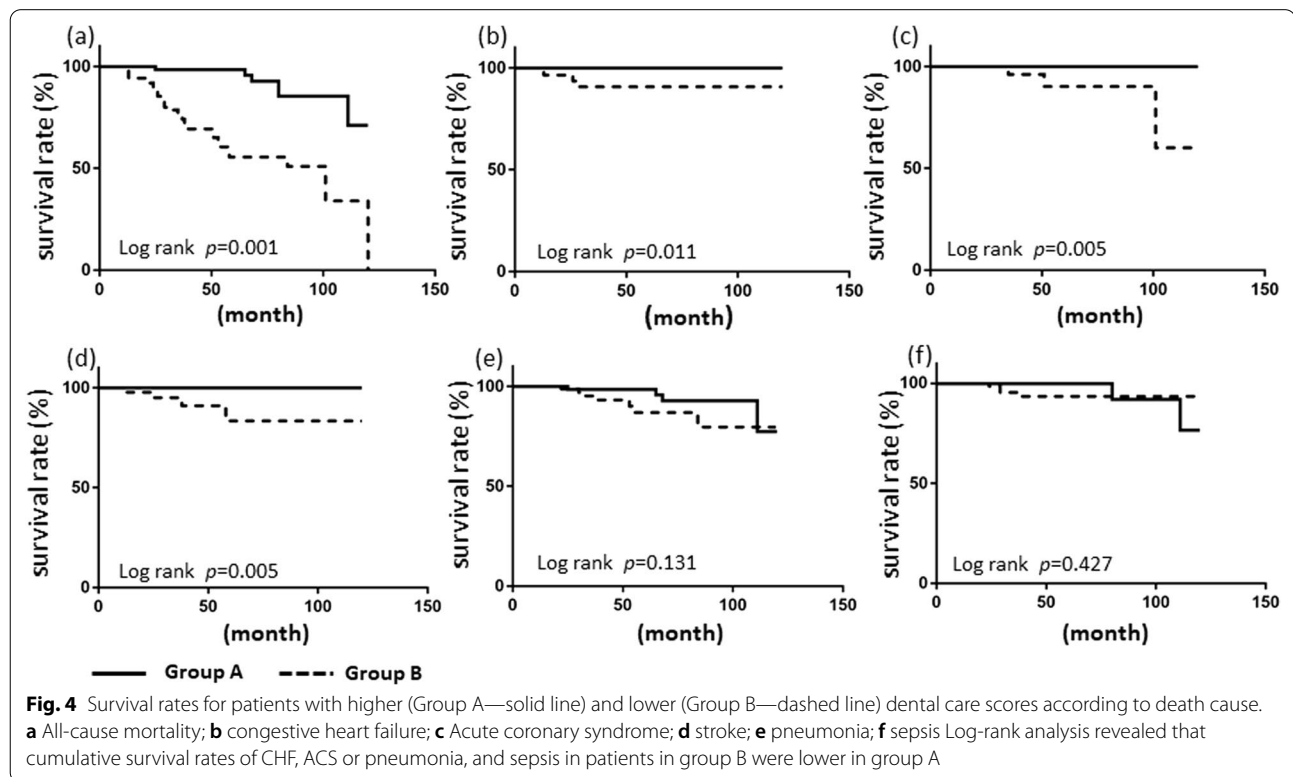
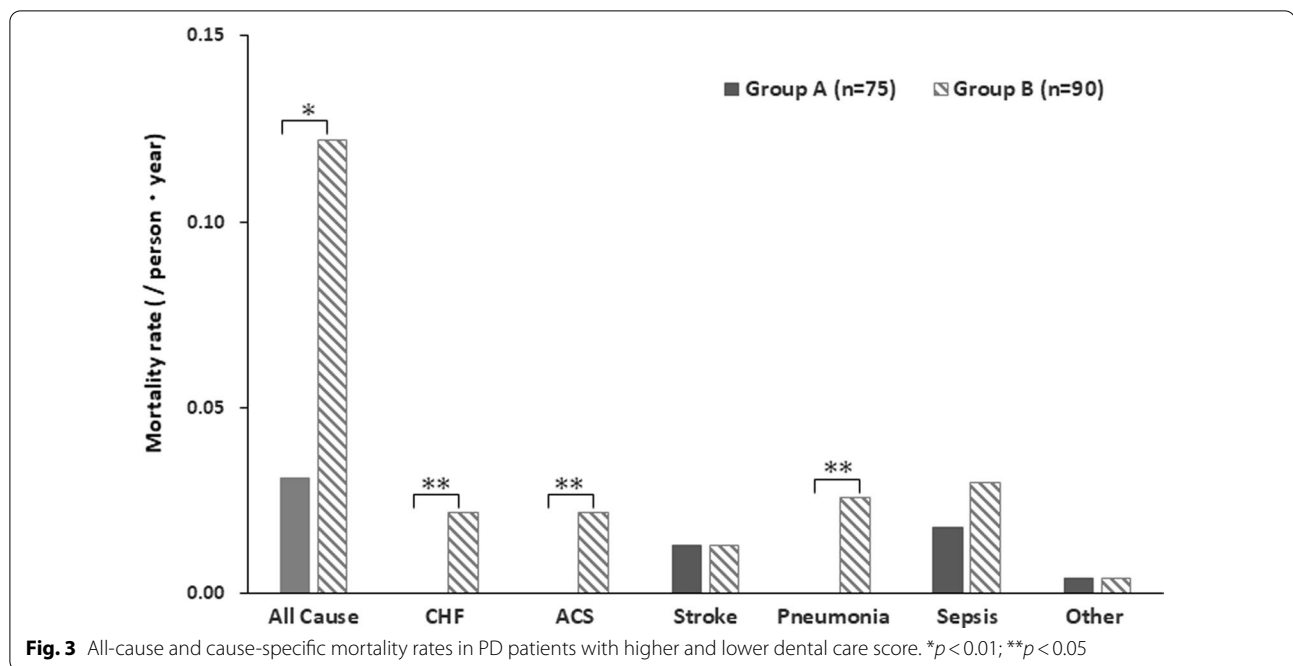
Cause of hospitalization	DCS			χ^2 value	p value
	Decreased (n = 26)	No change (n = 73)	Increased (n = 18)		
All peritonitis [n (%)]	20 (76.9)	39 (53.4)	6 (33.3)	8.54	0.013*
Streptococcal peritonitis [n (%)]	11 (42.3)	14 (19.2)	0 (0.0)	11.89	0.003**
Staphylococcal peritonitis [n (%)]	8 (30.8)	24 (32.9)	4 (22.2)	0.79	0.676
ACS [n (%)]	14 (53.8)	39 (53.4)	3 (16.7)	8.80	0.012*
CHF [n (%)]	8 (30.8)	19 (26.0)	1 (5.6)	10.21	0.006**
Stroke [n (%)]	4 (15.4)	7 (9.6)	6 (33.3)	5.31	0.070
PAD [n (%)]	4 (15.4)	5 (6.8)	0 (0.0)	4.22	0.121
Pneumonia [n (%)]	6 (23.1)	19 (26.0)	2 (11.1)	1.98	0.372
Other infection [n (%)]	5 (19.3)	8 (11.0)	2 (11.1)	1.06	0.588

ACS acute coronary syndrome, CHF congestive heart failure, PAD peripheral artery disease

* $p < 0.05$; ** $p < 0.001$

health issues, such as frailty or sarcopenia. In line with another previous report [3], our results support that dental hygiene could improve chronic inflammation and malnutrition. In addition, our finding showed that regular toothbrushing and prophylactic antibiotics treatment might reduce the microorganism in the oral cavity, followed by a reduced risk of peritonitis or pneumonia. Moreover, several dental visits might improve oral health, reducing the risk of CHF or ACS.

To improve the prognosis and quality of life of PD patients, it is imperative to reduce the incidence of peritonitis, pneumonia, CHF, and ACS. Although preventing these complications is challenging and complex, our study may suggest that maintaining good oral hygiene and care could help prevent infectious diseases, including peritonitis and pneumonia, and some cardiovascular diseases, such as CHF and ACS. The mechanisms explaining this effect may reduce chronic inflammation



and malnutrition, as supported by other findings. Also, gingival inflammation might play an essential role in the pathogenesis of atherosclerosis and represent a higher risk for cardiovascular disease [13–15]. It was reported

that accumulated dental plaque drove neutrophil-based inflammation and metastatic immunologic response to oral microorganisms [16] and that subgingival biofilm in periodontal pockets enabled translocation of oral

bacteria into the circulation system [17]. In hemodialysis patients, periodontitis was also associated with increased malnutrition and systemic inflammation [18]. Frequent dental visits and frequent change of toothbrush might maintain a better oral health condition, such as reducing dental plaque, which might reduce the risk of CHF or ACS, as our results showed.

Previous studies have described some of the adverse outcomes in chronic kidney disease patients that might be caused due to poor oral care, including endothelial dysfunction [19], atherosclerosis [20], thrombosis [21], vascular injury, and endotoxemia [22]. Septicemia may induce bacterial translocation from subgingival biofilm, and poor dental health may also injure the immune response during sepsis [13, 22]. Then, better dental care may reduce the risk of cardiovascular events and reduce the hospitalization of PD patients [23].

Peritonitis is a leading factor associated with the withdrawal of PD in our region, in Japan [23], and globally [24, 25]. However, our findings showed that peritonitis was not a cause of death in the study population, suggesting that DC could have lowered peritonitis incidence. Educating patients in improving their oral hygiene will likely be beneficial for preventing systematic diseases, including cardiovascular disease.

Oral disease is a common complication in adults with chronic kidney disease [14]. Simple strategies to improve oral health include increasing the frequency of brushing and dental visits. Frequent brushing and removal of tartar prevent subgingival bacterial biofilm formation in periodontal pockets [15], which may decrease the risk of cardiovascular events. Moreover, regular teeth brushing might reduce *Streptococcal* peritonitis incidence by preventing bacterial translocation into the circulation system. Our findings revealed that sepsis (due to *Streptococcal peritonitis*) was associated with an increased mortality rate in PD patients with poor DC (group B).

This study had some limitations. First, it is a retrospective observational single-center study. Thus, a multicenter, double-blind prospective study would be recommended based on the evidence in this study. Second, all patients in the study had already received dental care recommendations, such as frequent brushing, careful oral hygiene, regular dental visits, and prophylactic antibiotics treatment before scaling or caries treatment. Thus, the patients with poor DC (group B) do not represent the typical level of oral hygiene in PD patients. Third, aside from hospitalization cases, many outpatients have similar complications, but those cases were not evaluated. Finally, we used a self-reported questionnaire to determine the DC level.

Conclusions

Our study revealed that DC is beneficial not only for hospitalization cases due to cardiovascular disease (including CHF or ACS) but also in cases of peritonitis, especially *Streptococcal peritonitis*. Given the importance of DC in improving quality of life and treatment survival, it is vital to encourage and educate PD patients to improve their oral health. Although successful educational or intervention strategies can be implemented to improve oral hygiene, those would greatly benefit from the cooperation between the nephrologists and dental professionals.

Abbreviations

ACS: Acute coronary syndrome; ANOVA: Analysis of variance; APD: Automated peritoneal dialysis; BMI: Body mass index; CAPD: Continuous ambulatory peritoneal dialysis; CHF: Congestive heart failure; CRP: C-reactive protein; DC: Dental care; ESRD: End-stage renal disease; PAD: Peripheral artery disease; PD: Peritoneal dialysis.

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Authors' contributions

All authors discussed the study protocol and participated in data collection. Data analysis was done by TH and HK. After that, the study findings were discussed by all authors. TH wrote the manuscript draft. All authors approved the final manuscript version.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The Ethics Committee of the Konan-Kosei Hospital approved this study (Konan-Kosei Rinsho Kenkyu 2020-036(0403)Ver2.0), and it was conducted following the ethical principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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