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23-valent pneumococcal polysaccharide vaccine improves survival in dialysis patients by preventing cardiac events

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ABSTRACT

Background: Immunodeficient patients are recommended to receive pneumococcal vaccination. However, there is limited evidence showing effectiveness of the polysaccharide vaccine. Polysaccharide vaccination has shown an association with cardiovascular event risk reduction. We assessed the efficacy of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) in relation to the risk of hospitalization and death due to pneumonia and acute cardiac events.

Methods: The medical records of all dialysis patients attending our 8 study centers in 2010 were studied, and we selected 1038 consecutive patients. One-to-one propensity score matching was used to correct for potential selection bias in a PPSV23-vaccinated group versus a non-vaccinated group, and a total of 510 patients were identified for outcome analysis. Time to first admission, or deaths due to all-cause pneumonia or cardiac events until 2015 were compared between both groups.

Results: The all-cause death rate was significantly decreased in the PPSV23-vaccinated group, (hazard ratio [HR] 0.62, 95% confidence interval [CI]; 0.46–0.83, P = 0.002). All-cause death was considered to be a competing risk for the other outcomes. Further outcomes were evaluated by competing risk analysis adjusting for mortality. There was no statistically significant difference in the hospitalization rate for pneumonia; however, the hospitalization rate due to cardiac events was significantly lower in the PPSV23-vaccinated group than in the non-vaccinated group (HR 0.44, 95% CI; 0.20–0.96, P = 0.040). There was no statistically significant difference in the death rate due to pneumonia; however, the rate of cardiac death was significantly lower in the PPSV23-vaccinated group than in the non-vaccinated group (HR 0.36, 95% CI; 0.18–0.71, P = 0.003).

Conclusions: The PPSV23 vaccination is associated with a good prognosis and a low-risk of cardiac events in dialysis patients; however, there was no evidence indicating enhanced protective efficacy against pneumonia, suggesting the PPSV23 vaccination might improve the prognosis by directly preventing cardiovascular events.

1. Introduction

Infection is a major cause of morbidity and mortality among patients with end-stage renal disease (ESRD). Pneumonia is a common and serious infectious disease. Patients treated with dialysis have higher pulmonary infectious mortality rates than the general population [1]. *Streptococcus pneumoniae* (*S. pneumoniae*) is the most frequent cause of community-acquired pneumonia in adults [2], and more than half of the cases of pathogen-causing pneumonia among dialysis patients are reported to be due to *S. pneumoniae* [3]. As *S. pneumoniae* infections have become more severe, several pneumococcal polysaccharide vaccines have been developed. Older polysaccharide vaccines prevented the incidence of pneumococcal pneumonia and all-cause pneumonia in 1970s [4,5], and PPSV23

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was approved for use in 1988. PPSV23 has proven protective against invasive pneumococcal diseases (IPD) in immunocompetent adults [6–8]; however, its preventive effect on pneumococcal pneumonia without IPD remains unclear. PPSV23 is recommended for IPD prevention among all adults aged ≥65 years, and for immunosuppressed patients aged between 2 and 64 years, including those with chronic renal failure, by the Advisory Committee on Immunization Practices (ACIP) [9]. Although the ACIP recommends pneumococcal vaccination, there have been conflicting reports on the efficacy of vaccination in immunocompromised patients. The PPSV23 vaccination for HIV-infected patients was shown to be ineffective for pneumococcal infection in one prospective study, suggesting that immunodeficiency might attenuate the efficacy of PPSV23 [10]. It has also been reported that the PPSV23 vaccination reduced the rate of acute coronary syndrome (ACS) [11], which is one of the most important mortality events for ESRD. The aim of this study was to evaluate the incidence of pneumonia and cardiac events and the prognosis in PPSV23-vaccinated dialysis patients.

2. Methods

2.1. Study design and study population

We conducted a retrospective cohort study in a group of dialysis units (1 hospital and 7 clinics) in Japan. We included consecutive patients undergoing dialysis at any one of the study centers between January 1 and December 31, 2010. Study participants were followed-up until December 31, 2015. Based on the ACIP recommendations, all regularly attending patients aged ≥18 years were asked to confirm whether they had requested a PPSV23 inoculation, and we then administered the vaccine to all patients who provided informed consent in 2010. Commercially available PPSV23 (Pneumovax NP, MSD, Tokyo, Japan), containing 25 mg of each of the 23 capsular polysaccharide types was used. Each patient received a single subcutaneous dose of the vaccine (0.5 mL) in their upper arm. All patients received appropriate supportive care and regular clinical and laboratory monitoring. A seasonal influenza vaccination was administered to patients who requested inoculation prior to the onset of winter.

2.2. Outcome measures

The outcome measures comprised the time to first admission, or deaths from all-cause pneumonia or cardiac events. We comprehensively identified cause and date of hospitalization and deaths, respectively, using medical records and examination data at the centers. Pneumonia was diagnosed based on clinical symptoms (cough, sputum or fever) plus an increased white blood cell count or serum C-reactive protein, and the appearance of a new infiltration on a plain chest radiograph or a computed tomography (CT) scan. Cardiac events were defined as cardiac death, myocardial infarction, and unstable angina. Cardiac death was defined as sudden unexpected death within 1 h of a witnessed onset of symptoms, or within 24 h of having been observed alive and symptom-free. All patients suspected of acute cardiac disease were examined using plain chest radiographs, electrocardiograms, and blood tests, including cardiac enzyme tests.

2.3. Statistical analysis

Continuous variables were compared using the Student's or Welch's *t*-test. Categorical variables were compared using the chi-square test. Cox regression analyses were performed to measure outcomes between the vaccinated and non-vaccinated groups. All statistical tests were two-tailed and we considered $P < 0.05$ as a statistically significant difference.

To avoid confounding differences due to baseline variables between the vaccinated and the non-vaccinated group, we performed propensity score matching for the baseline characteristics. A multivariate logistic regression analysis was performed to estimate the propensity scores for these patients. The following 10 variables were included in the model: age, sex, body mass index (BMI), duration of dialysis, serum level of albumin, influenza vaccination in 2010, history of arteriosclerotic heart disease, chronic heart failure, peripheral vascular disease, and diabetes mellitus (DM). Matching of patients in the two groups at a one to one ratio was performed by nearest available matching with a caliper of $0.2 \times SD$, where SD is the SD of logit values of all patients in both groups. Multivariable Cox proportional hazard model was adjusted for the same 10 variables. Stata (version 14.2, StataCorp, TX, USA) was used to perform competing risk regression and other statistical analyses were performed using the SPSS software program (version 24, IBM Japan, Tokyo, Japan).

3. Results

The patient inclusion processes are illustrated in Fig. 1. A total of 1084 patients with chronic renal failure underwent dialysis at our study centers in 2010. We excluded 46 patients: 21 patients who did not attend clinic regularly, 24 patients who had been treated with the PPSV23 vaccination prior to 2000, and 1 patient with partially missing data. A total of 1038 patients were analyzed. Only 24 patients were vaccinated with PPSV23 before 2010 among all cohorts, since PPSV23 was approved in Japan in 2006 and the Japanese Ministry of Health recommended the vaccine in 2010. Table 1 showed the characteristics of study participants and matched groups. Characteristics of study participants were found to be imbalanced between the vaccinated group and the non-vaccinated group. After adjustment for confounding factors, a multivariable Cox proportional hazard model showed that PPSV23 vaccination associated with a lower incidence of death (HR 0.84, 95% CI; 0.74–0.97, P = 0.017). During follow-up, there were 178

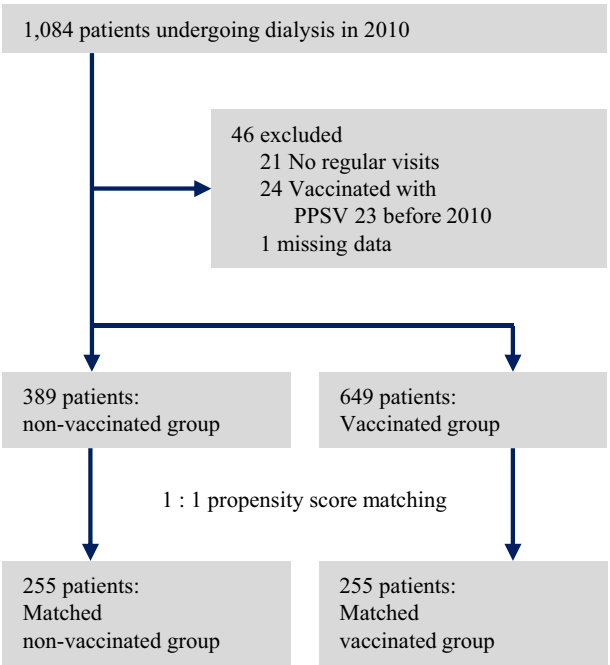

Fig. 1. Flowchart of included and excluded procedures in the study cohort.

Table 1
Patient characteristics in the study cohorts.

	Before Matched			Propensity Score-Matched		
	Non-vaccinated (n = 349)	Vaccinated (n = 689)	P value	Non-vaccinated (n = 255)	Vaccinated (n = 255)	P value
Age, median (range) (years)*	62 (26–91)	67 (28–92)	<0.001	64 (31–91)	64 (28–92)	0.35
Sex, male*	274 (70.4)	384 (59.2)	<0.001	172 (67.5)	174 (68.2)	0.85
BMI (kg/m^2)*	21.6 (3.6)	21.7 (3.9)	0.71	21.7 (3.6)	21.8 (3.8)	0.72
Influenza vaccination in 2010*	199 (51.2)	594 (91.5)	<0.001	191 (74.9)	200 (78.4)	0.35
Comorbidity						
Arteriosclerotic heart disease*	98 (25.2)	183 (28.2)	0.29	74 (29.0)	67 (26.3)	0.49
Chronic heart failure*	90 (23.1)	162 (25.0)	0.51	68 (26.7)	61 (23.9)	0.48
Cerebrovascular disease	84 (21.6)	129 (19.9)	0.51	60 (23.5)	52 (20.4)	0.39
Peripheral vascular disease*	80 (20.6)	120 (18.5)	0.41	58 (22.7)	55 (21.6)	0.75
Liver disease	18 (4.6)	22 (3.4)	0.32	14 (5.5)	5 (2.0)	0.035
Malignancy	75 (19.3)	123 (19.0)	0.90	58 (22.7)	45 (17.6)	0.15
Diabetes mellitus*	234 (60.2)	356 (54.9)	0.095	156 (61.2)	153 (60.0)	0.79
Number of comorbidities	2.1 (1.5)	2.1 (1.4)	0.86	2.2 (1.5)	2.1 (1.4)	0.31
Duration of dialysis (years)*	8.3 (8.2)	10.1 (8.8)	0.001	8.5 (8.2)	8.6 (8.0)	0.86
Cause of renal failure, DM	136 (35.0)	190 (29.3)	0.056	92 (36.1)	86 (33.7)	0.58
Kt/V	1.3 (0.3)	1.4 (0.2)	<0.001	1.3 (0.3)	1.4 (0.3)	0.084
White blood cells ($\times 10^2/\mu l$)	61.7 (20.4)	58.6 (18.1)	0.015	62.7 (21.7)	60.8 (17.9)	0.29
Hemoglobin (g/dl)	10.2 (1.3)	10.2 (1.0)	0.49	10.2 (1.3)	10.3 (1.0)	0.45
Albumin (g/dl)*	3.6 (0.4)	3.6 (0.3)	0.12	3.5 (0.4)	3.6 (0.4)	0.073
Blood urea nitrogen (mg/dl)	65.0 (15.6)	66.7 (13.8)	0.079	63.5 (15.8)	67.1 (14.2)	0.008
Creatinine (mg/dl)	11.0 (3.2)	11.3 (2.7)	0.15	10.7 (3.2)	11.5 (2.8)	0.006
Sodium (mEq/l)	138.3 (3.0)	138.9 (2.8)	0.001	138.2 (3.1)	138.7 (2.9)	0.041
Potassium (mEq/l)	5.0 (0.8)	5.2 (0.7)	<0.001	4.9 (0.8)	5.1 (0.6)	0.002
Chloride (mEq/l)	103.1 (3.4)	103.9 (3.0)	<0.001	103.1 (3.4)	103.6 (3.1)	0.068
Calcium (mg/dl)	9.0 (0.7)	9.2 (0.7)	<0.001	9.0 (0.7)	9.1 (0.6)	0.055
Phosphorus (mg/dl)	5.8 (1.5)	5.8 (1.3)	0.53	5.7 (1.5)	5.9 (1.5)	0.16
iPTH (pg/ml)	298.5 (253.8)	261.0 (210.1)	0.015	286.2 (220.6)	269.8 (233.2)	0.42
Concomitant medications						
ACIs	30 (7.7)	28 (4.3)	0.021	23 (9.0)	13 (5.1)	0.084
ARBs	187 (48.1)	272 (41.9)	0.053	120 (47.1)	118 (46.3)	0.86
Statins	42 (10.8)	66 (10.2)	0.75	30 (11.8)	24 (9.4)	0.40
Corticosteroids	10 (2.6)	15 (2.3)	0.79	5 (2.0)	8 (3.1)	0.40
Erythropoietin	325 (83.5)	552 (85.1)	0.52	217 (85.1)	220 (86.3)	0.70

Abbreviations: BMI, body mass index; DM, diabetes mellitus; iPTH, intact parathyroid hormone; ACIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.
* Adjusted factors by propensity score matching and multivariable Cox proportional hazard model.

(32.9%) mortality events, comprising 71 in the vaccinated group and 107 in the non-vaccinated group. The rate of all-cause death was significantly decreased in the vaccinated group (HR 0.62, 95% CI; 0.46–0.83, P = 0.002) (Fig. 2A). All-cause death was considered to be a competing risk for the other outcomes. Further outcomes were evaluated by competing risk analysis adjusting for mortality (Table 2). There were hospitalizations due to all-cause pneumonia in 54 of the 510 matched patients (10.6%), comprising 30 patients in the vaccinated group and 24 patients in the non-vaccinated group. Between the two groups, there was no statistically significant difference in the rate of hospitalization for pneumonia (HR 1.28, 95% CI; 0.75–2.19, P = 0.37) (Fig. 2B). There were 29 (5.7%) patients hospitalized due to cardiac events comprising 9 patients in the vaccinated group and 20 in the non-vaccinated group, and the rate of hospitalization due to cardiac events was significantly reduced due to the PPSV23 vaccination (HR 0.44, 95% CI; 0.20–0.96, P = 0.040) (Fig. 2C). There were a total of 12 (1.2%) deaths due to pneumonia, comprising 6 deaths in the vaccinated group and 6 deaths in the non-vaccinated group. No significant difference was observed in the death rate due to pneumonia (HR 1.00, 95% CI; 0.32–3.10, P = 1.00) (Fig. 2D). There were 41 (8.0%) deaths due to cardiac events, comprising 11 deaths in the vaccinated group and 30 deaths in the non-vaccinated group. The rate of cardiac death was significantly reduced in the vaccinated group (HR 0.36, 95% CI; 0.18–0.71, P = 0.003) (Fig. 2E). These data suggest that PPSV23 vaccination reduced the rate of mortality events, not through pneumonia prevention but through prevention of cardiovascular events. Although some patients had multiple episodes of pneumonia or cardiac events, only the first admission was counted in the statistical analysis. Pneumonia-causing organisms were detected in 53.7% (29/54) of patients, and pneumococcal pneumonia was diagnosed in 3 patients. IPD was observed in 1 patient diagnosed with an iliopsoas abscess. The cause of hospitalization for cardiac events included myocardial infarction (n = 14), unstable angina (n = 11), and sudden cardiac arrest (n = 4). Table 3 showed the cause of death in matched pairs. Only 1 death was detected due to pneumococcal pneumonia. Death due to cardiac events comprised 10 ACS deaths and 31 cardiac sudden deaths. Table 4 showed that the number of patients with influenza vaccination decreased every year depending on decrease of the study population. 73 patients (25 patients in the PPSV23-vaccinated group and 48 patients in the non-vaccinated group) did not get influenza vaccination through study periods among matched groups. The rate of all-cause death in the limited population was significantly decreased in the vaccinated group (HR 0.45, 95% CI; 0.23–0.85, P = 0.015). Fig. 3 shows forest plots of mortality between the vaccinated and the non-vaccinated groups. The PPSV23 vaccination was associated with a good prognosis in patients aged ≥65 years; who were male; who did not have DM; who underwent dialysis for more than 1 year; or who had 2 or more complications.

4. Discussion

PPSV23 vaccination is recommended for all adults aged ≥65 years, adults at high-risk, and especially, immunosuppressed

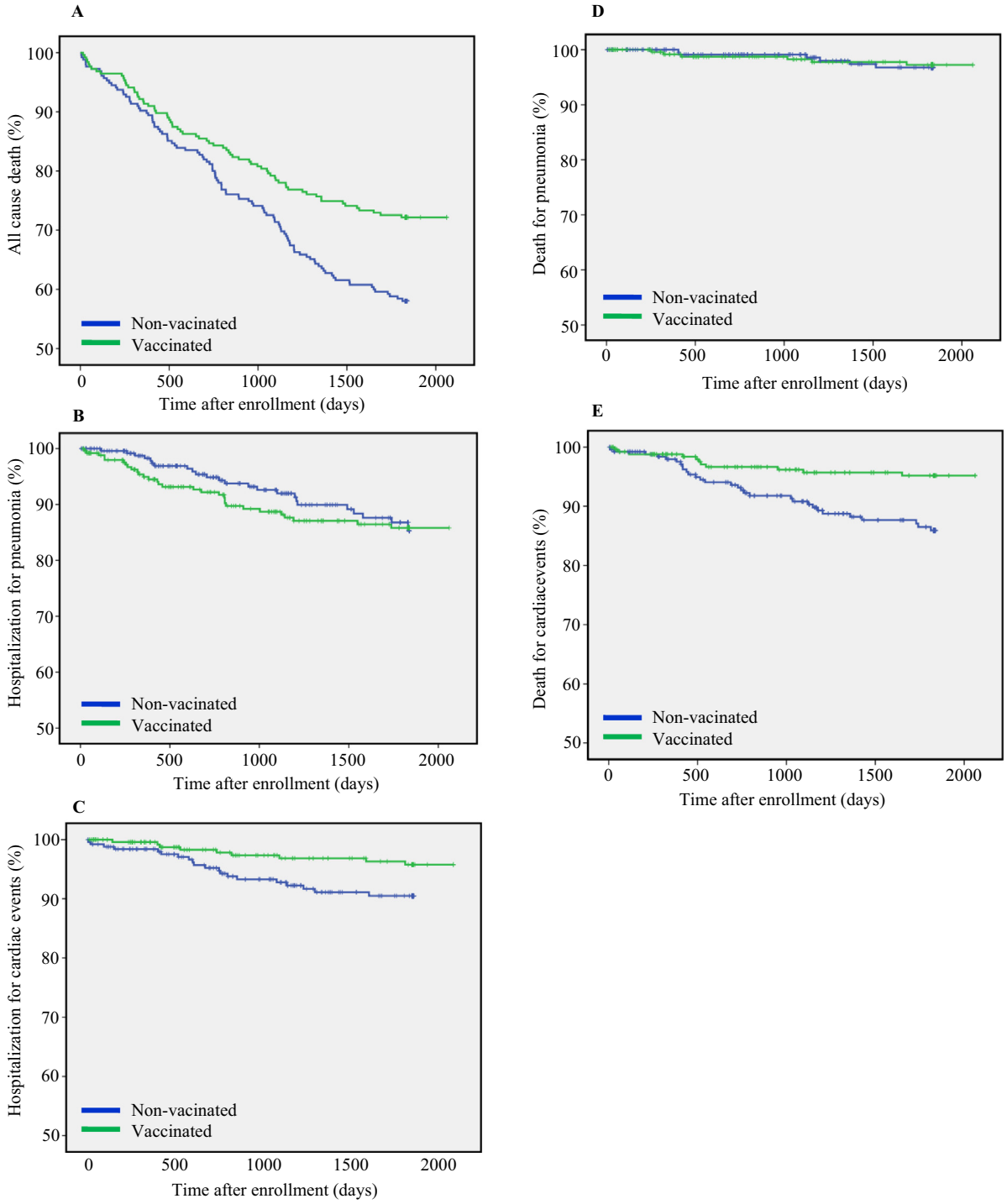

Fig. 2. Kaplan-Meier curves among matched groups (A) for all-cause mortality; (B) for time to first hospitalization due to pneumonia; (C) for time to first hospitalization due to cardiac events; (D) for death due to pneumonia; (E) for death due to cardiac events.

Table 2
Results of statistical models for the effect of PPSV23.

	Model 1 (Unadjusted model)		Model 2 (Treating all cause death as competing risk)	
	HR (95% CI)	P-value	HR (95% CI)	P-value
All cause death (A)	0.62 (0.46–0.83)	0.002		
Hospitalization for pneumonia (B)	1.17 (0.68–2.00)	0.56	1.28 (0.75–2.19)	0.37
Hospitalization for cardiac events (C)	0.42 (0.19–0.92)	0.031	0.44 (0.20–0.96)	0.040
Death for pneumonia (D)	0.91 (0.29–2.83)	0.87	1.00 (0.32–3.10)	1.00
Death for cardiac events (E)	0.34 (0.17–0.68)	0.002	0.36 (0.18–0.71)	0.003

Table 3
Causes of death throughout the study period.

	Non-vaccinated (n = 107)	Vaccinated (n = 71)
Pneumonia	6	6
Cardiac events	30	11
Renal failure	4	2
Heart failure	16	12
Cerebrovascular disease	7	5
Peripheral vascular disease	5	6
Liver disease	2	1
Malignancy	14	8
Infection other than pneumonia	7	9
Gastroduodenal ulcers	1	1
Extrinsic death	2	1
Others	6	3
Unknown	7	6

individuals aged between 2 and 64 years [9]; however, there are few reports supporting this recommendation. In a large-scale retrospective cohort study that enrolled 47,365 senior adults [7], receipt of PPSV23 was reported to have been involved in the reduction of IPD incidence (HR, 0.56; 95% CI; 0.33–0.93), but did not improve the risk of hospitalization for pneumonia (HR, 1.14; 95% CI; 1.02–1.28) and the mortality rate (HR, 0.96; 95% CI; 0.91–1.02). Furthermore, IPD in an immunocompromised host was not prevented through PPSV23 treatment (HR, 0.78; 95% CI; 0.32–1.87). A Cochrane review evaluating the efficacy of pneumococcal polysaccharide vaccines showed that the IPD incidence was strongly reduced (odds ratio [OR] 0.26; 95% CI; 0.14–0.45), but the incidence of all-cause pneumonia could not be evaluated because there was a high level of statistical heterogeneity present among the included studies. Additionally, there was no evidence of protective efficacy against all-cause pneumonia in patients with chronic illness (OR 0.93; 95% CI; 0.73–1.19) [12]. As such, the established efficacy of PPSV23 is limited to the prevention of IPD among immunocompetent adults, and no consensus has been reached on whether PPSV23 vaccination protects against the incidence of pneumonia and infectious disease in immunocompromised persons. In our study, no significant difference was observed in the rate of hospitalization due to pneumonia between the vaccinated and non-vaccinated groups. However, regarding the ESRD patients on dialysis, the PPSV23 vaccination significantly improved prognosis. It is possible that the effect of pneumococcal polysaccharide vaccines is not only specific to pneumonia and IPD.

Several studies have reported that patients with respiratory infections, including pneumococcal pneumonia, had an increased risk of acute cardiac events and stroke [13–15], and that pneumococcal polysaccharide vaccines reduced the incidence of atherosclerotic disease. In a prospective cohort study of patients aged ≥65 years with chronic illness, the vaccinated group experienced significantly fewer deaths (HR, 0.65; 95% CI; 0.55–0.77), ischemic stroke (HR, 0.67; 95% CI; 0.54–0.83), and acute myocardial infarction (HR, 0.52; 95% CI; 0.38–0.71) [16]. A large case-controlled study targeting patients with a high risk of coronary disease showed that myocardial infarctions in the PPSV23-vaccinated group were significantly lower than for the non-vaccinated group (HR 0.53, 95% CI; 0.40–0.70) [17]. A systematic review concerning the effect of pneumococcal polysaccharide vaccines on cardiovascular disease showed that receipt of the vaccine was associated with a lower incidence of ACS in patients aged ≥65 years (OR, 0.83; 95% CI; 0.71–0.97) [11]. Previously, the pneumococcal polysaccharide vaccine had been considered to prevent acute cardiac events through reducing *S. pneumoniae* infections, as acute infections trigger ACS for eliciting coronary and systemic inflammation, promoting a thrombogenic state, and increasing metabolic demand of oxygen [18]. However, several reports have shown that the pneumococcal polysaccharide vaccine might directly suppress the progression of atherosclerosis. Immunization with *S. pneumoniae* led to a reduction of atherosclerosis in mice through an immunological cross-reaction between phosphorylcholine antigens on the cell wall polysaccharide of *S. pneumoniae* and oxidized low density lipoprotein (LDL) [19,20]. In one clinical study, a significant association between pneumococcal immunoglobulin (IgG) and anti-oxidized LDL antibody titers was found [21]. Furthermore, a retrospective study of a pneumococcal vaccination among dialysis patients supported this hypothesis. This study showed that pneumococcal vaccination significantly decreased mortality (HR, 0.94; 95% CI; 0.90–0.98) and the rate of cardiac death (HR 0.91, 95% CI; 0.85–0.97), although no significant difference was noted in the pneumonia hospitalization rate [22]. It appears from both of these reports and our results that the PPSV23 vaccination possibly prolongs survival in patients on dialysis, and in high-risk cardiac patients, through directly reducing cardiovascular events.

Our study has several limitations. First, we did not analyze the immune response in the study cohorts. Patients with chronic renal failure have lower immune function, and frequently develop infectious disease. Pneumococcal vaccination for renal failure is recommended, but conflicting data exist regarding the immune response. Previous studies have reported that antibody levels in patients with chronic renal failure requiring dialysis are considerably lower and decline rapidly compared with those in healthy vaccinated adults [23–26]. These reports suggested that not all ESRD patients acquired sufficient antibody levels during the study period. In our study, patients with a history of DM and immunodeficiency responded less effectively to vaccination, meaning that low antibody levels may be associated with a low effect on survival. Fur-

Table 4
The number of patients with influenza vaccination in PPSV23-vaccinated and non-vaccinated groups in each year, respectively.

	Before Matched		Propensity Score-Matched	
	Non-vaccinated (total, %)	Vaccinated (total, %)	Non-vaccinated (total, %)	Vaccinated (total, %)
2010	199 (349, 57.0)	594 (689, 86.2)	191 (255, 74.9)	200 (255, 78.4)
2011	195 (330, 59.1)	518 (655, 79.1)	161 (237, 67.9)	176 (241, 73.0)
2012	142 (304, 46.7)	396 (613, 64.6)	115 (213, 54.0)	148 (220, 67.3)
2013	129 (280, 46.1)	355 (588, 60.4)	96 (189, 50.8)	131 (207, 63.3)
2014	119 (251, 47.4)	376 (553, 68.0)	88 (163, 54.0)	137 (193, 71.0)
2015	111 (236, 47.0)	336 (531, 63.3)	80 (152, 52.6)	127 (185, 68.6)

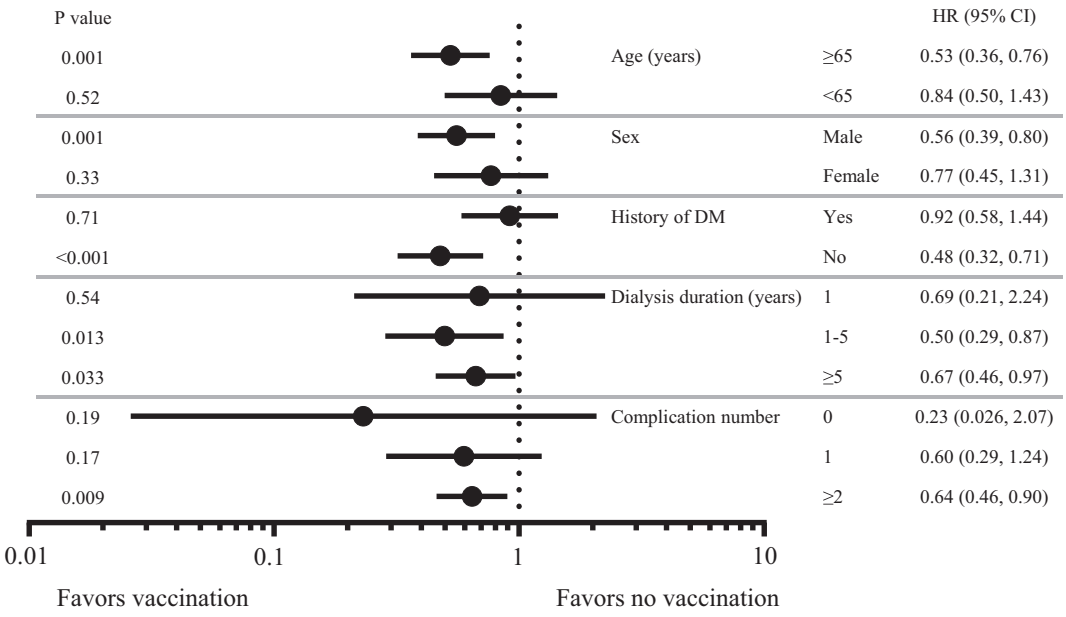

Fig. 3. Forest plot of mortality rate among matched groups.

ther analyses are needed to evaluate the association between antibody titers and mortality events. Second, endpoint events were mainly determined based on medical records held by primary doctors rather than by physicians, so the diagnoses may have been less specific. Third, in our study, only cardiac events were evaluated as atherosclerotic disease; however, it has been suggested that the polysaccharide vaccine also inhibits brain infarction. Assuming that formation of arteriosclerosis was prevented due to the pneumococcal vaccination, not only cardiovascular events but also cerebrovascular disease were reduced. We could not analyze the incidence of cerebrovascular disease because of a lack of diagnostic equipment; therefore, an additional investigation is required to reveal the efficacy of PPSV23 on stroke. Fourth, we cannot evaluate influence of some important factors (e.g. activities of daily living function, severity of cardiovascular disease or cerebrovascular disease), because the states of these factors are variable through study period.

In conclusion, PPSV23 vaccination in renal failure patients requiring dialysis is associated with a good prognosis and a decreased incidence of ACS without prevention of pneumonia. Our results suggest that the vaccine might be directly responsible for inhibiting cardiovascular events. Further investigation is required to establish whether pneumococcal antibodies can prevent the progression of arteriosclerosis in dialysis patients. Future studies may show that the polysaccharide vaccine suppresses the incidence of atherosclerotic disease in all high-risk adults.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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