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Is hemodialysis itself a risk factor for dementia? An analysis of nationwide registry data of patients on maintenance hemodialysis in Japan

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Abstract

Background: Chronic kidney disease is a major risk factor for dementia, but the influence of hemodialysis itself on the development of dementia remains unclear. We previously reported that non-diabetic patients on maintenance hemodialysis have preserved cognitive function; hemodialysis removes blood amyloid β (Aβ), which is a major cause of Alzheimer's disease in the brain; and the number of Aβ deposits in the postmortem brains of hemodialysis patients was significantly less compared to that in age-matched controls not undergoing hemodialysis. We aimed to evaluate the influence of hemodialysis on the development of dementia.

Methods: We accessed the Japanese Society for Dialysis Therapy Renal Data Registry between December 31, 2009, and December 31, 2010. Dementia was identified in 120,101 patients undergoing maintenance hemodialysis. The association between hemodialysis duration and dementia risk was analyzed using logistic regression analysis.

Results: There was a significant decrease in the dementia risk with an increase in the hemodialysis duration, with odds ratios (95% confidence intervals) of 0.78 (0.74–0.82) and 0.88 (0.78–0.99) for every 10 years in non-diabetic and diabetic patients, respectively. However, in diabetic patients, the correlation between hemodialysis duration and dementia risk was not consistent.

Conclusion: A longer hemodialysis duration was correlated with a lower dementia risk, but the correlation between hemodialysis duration and dementia risk in diabetic patients was much weaker and vaguer than that in non-diabetic patients. This finding does not appear to contradict greatly the assumption that the reduction in dementia risk with a prolonged hemodialysis duration in non-diabetic patients was caused not only by the survivor effect but also by hemodialysis itself.

Keywords: Dementia, Dialysis, Epidemiology, Hemodialysis duration, Amyloid β

Background

Chronic kidney disease (CKD) is a major risk factor for dementia [1, 2]. Fukunishi et al. [3] reported that the annual incidence rate of dementia among elderly patients was 7.4 times higher in those on hemodialysis than in those from the general population. Lin et al. [4] showed that there is no significant difference in dementia risk between patients undergoing hemodialysis and those undergoing peritoneal dialysis. However, the influence of long-term hemodialysis itself on the development of dementia remains unclear.

Alzheimer's disease (AD) is a major cause of dementia [5], and the accumulation of amyloid β (Aβ) protein in the brain in this condition was thought to cause cognitive impairment [6]. Moreover, the metabolic degradation of Aβ and its clearance from the brain are impaired in patients with AD [7]. If Aβ clearance from the brain can be increased, it is considered that AD could be prevented or even treated. To this end, treatment with antibodies

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against Aβ has been shown to result in cognitive improvement and reduced Aβ burden in the brain among patients with AD [8]. Furthermore, in a current human clinical trial, patients with AD are being treated with peripheral administration of albumin, which is an Aβ-binding substance, and this phase 2 trial already has reported improved cognitive function in patients with AD [9]. Kato et al. [10] showed that hemodialysis removes Aβ, and Kitaguchi et al. [11] showed that cognitive function was maintained or improved in most patients undergoing maintenance non-diabetic hemodialysis over a period of 18 to 36 months. Sakai et al. [12] reported that the deposition of Aβ in postmortem brain tissue was decreased significantly in patients who had undergone hemodialysis compared to that in age-matched patients who had not undergone hemodialysis. Reusche et al. [13] reported similar results. These reports suggest that hemodialysis itself may prevent development of AD through removal of Aβ from the blood.

The Japanese Society for Dialysis Therapy (JSDT) has been conducting epidemiologic studies in dialysis facilities throughout Japan since 1968. Since 1983, more than 700,000 patients have been registered in an electronic database, including those who have died (JSDT Renal Data Registry [JRDR]) [14]. The influence of hemodialysis therapy itself on the development of dementia is unclear. Therefore, we evaluated the influence of hemodialysis therapy itself on the development of dementia using data from the JRDR.

Methods

Database search

The JSDT has been conducting annual surveys at dialysis facilities in Japan since 1968, and since 1983, all patients undergoing dialysis at the target facilities have been registered in the JRDR for monitoring [14]. The present study used the JRDR.

Subjects

Data from 282,010 patients undergoing chronic hemodialysis therapy at the end of 2009 were extracted from the JRDR (JRDR09002 dataset). At first, we selected the target patients based on their status at the end of 2009. To ensure uniformity of treatment conditions of the target patients, we excluded patients who underwent treatments other than hemodialysis. Cerebrovascular disease (CVD) is known to be a major risk factor for the development of dementia [5], but the type of dementia expected to be responsive to the preventive effects of hemodialysis is AD [10, 11]. Therefore, we excluded patients with preexisting brain infarction or brain hemorrhage. Furthermore, to analyze the dementia incidence, we excluded patients with preexisting dementia and those with missing data at the end of 2009. A total of 149,534 patients were included in the baseline dataset. Next, based on the data obtained at the end of 2010, we excluded patients who had died, were lost to follow-up, and had an unclear history of dementia. To avoid the influence of dementia caused by CVD, we excluded those with newly developed brain infarction or hemorrhage and those without information regarding these conditions. Finally, 120,101 patients were included in the analysis.

Diabetic patients are regarded as a high-risk group for AD and vascular dementia (VaD) [15]. Therefore, we speculated that the effect of blood Aβ removal by hemodialysis might be weakened by diabetes with strong risk of dementia, particularly AD. Further, some parts of dementia among diabetic patients are reported as independent diseases because dementia developed in these patients has unique pathologic conditions [16]. Thus, we analyzed not only the whole target patient group but also patients without (non-diabetic group, $n = 80,207$) and with (diabetic group, $n = 39,894$) diabetes separately.

The baseline characteristics of these patients are summarized in Tables 1 and 2. The selection process for the target patients is summarized in Fig. 1.

Dementia survey

The presence or absence of concomitant dementia, brain infarction, and brain hemorrhage was investigated through surveys conducted in 2009 and 2010 [14, 17]. The questions and possible answers are shown in Table 3.

A note stating, “A patient’s primary doctor should answer this question” was added. When assessing the dementia risk, patients designated as “with dementia (requiring no care)” and “with dementia (requiring care)” at the end of 2010, but not in 2009, were recorded as patients with newly developed dementia.

Covariates

Among the items included in the 2009 and 2010 surveys, the following were used as covariates in a logistic regression analysis: Kt/V for urea calculated with a single pool model (Kt/V) [18]; body mass index (BMI), predialysis serum albumin level (albumin level), predialysis serum C-reactive protein level (CRP level), and predialysis whole blood hemoglobin level (hemoglobin level); history of myocardial infarction, limb amputation, or hip fracture; activities of daily living (ADLs); and place of residence. The response options for the questions regarding history of brain infarction, brain hemorrhage, myocardial infarction, limb amputation, and hip fracture were “Yes” and “No.” The response options for the items on ADLs and place of residence are presented in the footnotes of Tables 1 and 2.

Table 1 Baseline characteristics of non-diabetic patients

		Hemodialysis duration (year)															
		0~ 1	(%)	2~4	(%)	5~9	(%)	10~14	(%)	15~19	(%)	20~24	(%)	25~	(%)	Total	(%)
Total		14,787	(100.0)	17,293	(100.0)	19,984	(100.0)	12,479	(100.0)	7452	(100.0)	4138	(100.0)	4074	(100.0)	80,207	(100.0)
Sex	Male	9106	(61.6)	10,515	(60.8)	11,814	(59.1)	7144	(57.2)	4169	(55.9)	2275	(55.0)	2251	(55.3)	47,274	(58.9)
	Female	5681	(38.4)	6778	(39.2)	8170	(40.9)	5335	(42.8)	3283	(44.1)	1863	(45.0)	1823	(44.7)	32,933	(41.1)
Age (years old)	15–64	5980	(40.4)	7584	(43.9)	10,258	(51.3)	7245	(58.1)	4654	(62.5)	2635	(63.7)	2732	(67.1)	41,088	(51.2)
	65–74	4066	(27.5)	4900	(28.3)	5612	(28.1)	3499	(28.0)	2092	(28.1)	1196	(28.9)	1133	(27.8)	22,498	(28.0)
	< 75	4741	(32.1)	4809	(27.8)	4114	(20.6)	1735	(13.9)	706	(9.5)	307	(7.4)	209	(5.1)	16,621	(20.7)
With history of myocardial infarction		630	(4.3)	780	(4.5)	767	(3.8)	467	(3.7)	314	(4.2)	187	(4.5)	190	(4.7)	3335	(4.2)
With history of limb amputation		101	(0.7)	101	(0.6)	137	(0.7)	100	(0.8)	44	(0.6)	33	(0.8)	48	(1.2)	564	(0.7)
With history of hip fracture		181	(1.2)	279	(1.6)	310	(1.6)	175	(1.4)	104	(1.4)	89	(2.2)	190	(4.7)	1328	(1.7)
ADL	No symptoms[†]	8122	(54.9)	10,072	(58.2)	12,140	(60.7)	7742	(62.0)	4553	(61.1)	2282	(55.1)	1733	(42.5)	46,644	(58.2)
	Moderate symptoms[‡]	4512	(30.5)	5153	(29.8)	5896	(29.5)	3641	(29.2)	2269	(30.4)	1414	(34.2)	1518	(37.3)	24,403	(30.4)
	≥ 50% sitting up[§]	1333	(9.0)	1307	(7.6)	1174	(5.9)	704	(5.6)	370	(5.0)	257	(6.2)	466	(11.4)	5611	(7.0)
	≥ 50% in bed[#]	496	(3.4)	429	(2.5)	416	(2.1)	176	(1.4)	125	(1.7)	96	(2.3)	206	(5.1)	1944	(2.4)
	Whole day in bed[¶]	154	(1.0)	100	(0.6)	115	(0.6)	58	(0.5)	42	(0.6)	32	(0.8)	87	(2.1)	588	(0.7)
Place of residence	Homes[ʛ]	13,836	(93.6)	16,614	(96.1)	19,359	(96.9)	12,138	(97.3)	7250	(97.3)	4022	(97.2)	3838	(94.2)	77,057	(96.1)
	Care facilities[^]	164	(1.1)	203	(1.2)	162	(0.8)	76	(0.6)	38	(0.5)	16	(0.4)	27	(0.7)	686	(0.9)
	Hospitals[ɻ]	694	(4.7)	335	(1.9)	316	(1.6)	170	(1.4)	106	(1.4)	62	(1.5)	163	(4.0)	1846	(2.3)
With dementia at the end of 2010		669	(4.5)	681	(3.9)	599	(3.0)	285	(2.3)	108	(1.4)	58	(1.4)	39	(1.0)	2439	(3.0)
Age (years old)*		66.2	± 14.0	65.1	± 13.8	63.0	± 13.4	61.2	± 12.5	60.2	± 11.4	60.4	± 10.1	60.8	± 8.5	63.3	± 13.1
Kt/V*		1.25	± 0.3	1.39	± 0.3	1.46	± 0.3	1.52	± 0.3	1.54	± 0.3	1.56	± 0.3	1.57	± 0.3	1.43	± 0.3
Body mass index (kg/m^2)*		21.4	± 3.3	21.5	± 3.4	21.3	± 3.3	20.8	± 3.0	20.4	± 2.9	20.2	± 2.7	19.8	± 2.7	21.0	± 3.2
Serum albumin level (g/dl)*		3.70	± 0.4	3.77	± 0.4	3.79	± 0.4	3.80	± 0.3	3.80	± 0.4	3.77	± 0.3	3.71	± 0.4	3.77	± 0.4
Serum CRP level (mg/dl)*		0.46	± 1.6	0.38	± 1.2	0.36	± 1.2	0.36	± 1.3	0.39	± 1.4	0.38	± 1.4	0.47	± 1.4	0.39	± 1.3
Hemoglobin level (g/dl)*		10.5	± 1.3	10.6	± 1.2	10.6	± 1.2	10.7	± 1.2	10.7	± 1.2	10.7	± 1.2	10.6	± 1.3	10.6	± 1.2

ADLs activities of daily living, *CRP* C-reactive protein

*Data are presented as mean ± standard deviation

[†]No symptoms (the patient can perform social activities without symptoms and behave without restrictions)

[‡]Moderate symptoms (the patient has mild symptoms and has trouble with physical work, but can walk and do light and sedentary work, such as light domestic and clerical work)

[§]≥ 50% sitting up (the patient can walk and take care of him/herself, but sometimes requires care. The patient can sit up at least half of the day, but cannot do light work)

[#]≥ 50% in bed (the patient can take care of him/herself to some extent, but often requires care and is in bed at least half of the day)

[¶]Whole day in bed (the patient cannot take care of him/herself and requires constant care. The patient must be in bed all day)

[ʛ]Patients' own home

[^]Care facilities (e.g., homes with care services; nursing homes, such as private nursing homes without national aid and nursing homes for families with financial difficulties; group homes; vocational centers; or relief facilities)

[ɻ]Hospitals (e.g., health service facilities for the elderly; beds for general patients, patients at chronic stage, patients requiring rehabilitation, and patients with mental illness and infectious diseases, such as tuberculosis)

Table 2 Baseline characteristics of diabetic patients

		Hemodialysis duration (year)															
		0~1	(%)	2~4	(%)	5~9	(%)	10~14	(%)	15~19	(%)	20~24	(%)	25~	(%)	Total	(%)
Total		12,756	(100.0)	13,342	(100.0)	10,273	(100.0)	2785	(100.0)	605	(100.0)	98	(100.0)	35	(100.0)	39,894	(100.0)
Sex	Male	8949	(70.2)	9215	(69.1)	6819	(66.4)	1767	(63.4)	369	(61.0)	61	(62.2)	18	(51.4)	27,198	(68.2)
	Female	3807	(29.8)	4127	(30.9)	3454	(33.6)	1018	(36.6)	236	(39.0)	37	(37.8)	17	(48.6)	12,696	(31.8)
Age (years old)	15–64	6378	(50.0)	6495	(48.7)	5040	(49.1)	1415	(50.8)	276	(45.6)	57	(58.2)	23	(65.7)	19,684	(49.3)
	65–74	3940	(30.9)	4434	(33.2)	3518	(34.2)	970	(34.8)	234	(38.7)	28	(28.6)	8	(22.9)	13,132	(32.9)
	< 75	2438	(19.1)	2413	(18.1)	1715	(16.7)	400	(14.4)	95	(15.7)	13	(13.3)	4	(11.4)	7078	(17.7)
With history of myocardial infarction		913	(7.2)	1154	(8.6)	896	(8.7)	241	(8.7)	57	(9.4)	12	(12.2)	2	(5.7)	3275	(8.2)
With history of limb amputation		383	(3.0)	571	(4.3)	638	(6.2)	220	(7.9)	66	(10.9)	8	(8.2)	5	(14.3)	1891	(4.7)
With history of hip fracture		201	(1.6)	250	(1.9)	251	(2.4)	65	(2.3)	21	(3.5)	4	(4.1)	1	(2.9)	793	(2.0)
ADL	No symptoms[†]	6419	(50.3)	6685	(50.1)	4942	(48.1)	1277	(45.9)	234	(38.7)	43	(43.9)	9	(25.7)	19,609	(49.2)
	Moderate symptoms[‡]	4121	(32.3)	4323	(32.4)	3323	(32.3)	906	(32.5)	193	(31.9)	28	(28.6)	12	(34.3)	12,906	(32.4)
	≥ 50% sitting up[§]	1425	(11.2)	1401	(10.5)	1244	(12.1)	375	(13.5)	100	(16.5)	20	(20.4)	8	(22.9)	4573	(11.5)
	≥ 50% in bed[#]	471	(3.7)	562	(4.2)	496	(4.8)	151	(5.4)	51	(8.4)	3	(3.1)	2	(5.7)	1736	(4.4)
	Whole day in bed[¶]	155	(1.2)	184	(1.4)	133	(1.3)	51	(1.8)	16	(2.6)	3	(3.1)	2	(5.7)	544	(1.4)
Place of residence	Homes[ʃ]	11,912	(93.4)	12,656	(94.9)	9769	(95.1)	2617	(94.0)	557	(92.1)	93	(94.9)	29	(82.9)	37,633	(94.3)
	Care facilities[^]	136	(1.1)	141	(1.1)	107	(1.0)	29	(1.0)	9	(1.5)	1	(1.0)	0	(0.0)	423	(1.1)
	Hospitals[ɻ]	619	(4.9)	438	(3.3)	324	(3.2)	125	(4.5)	33	(5.5)	3	(3.1)	5	(14.3)	1547	(3.9)
With dementia at the end of 2010		512	(4.0)	578	(4.3)	375	(3.7)	97	(3.5)	24	(4.0)	4	(4.1)	2	(5.7)	1592	(4.0)
Age (years old)*		64.0	± 11.5	64.2	± 11.1	64.4	± 10.5	63.9	± 10.0	64.5	± 9.9	62.9	± 9.8	60.5	± 10.5	64.2	± 11.0
Kt/V*		1.18	± 0.3	1.32	± 0.3	1.38	± 0.2	1.45	± 0.3	1.49	± 0.3	1.49	± 0.3	1.52	± 0.2	1.30	± 0.3
Body mass index (kg/m^2)*		22.5	± 3.5	22.7	± 3.6	22.4	± 3.5	21.7	± 3.3	20.7	± 3.3	20.6	± 3.4	19.8	± 3.1	22.4	± 3.5
Serum albumin level (g/dl)*		3.66	± 0.4	3.77	± 0.4	3.77	± 0.3	3.74	± 0.4	3.69	± 0.4	3.73	± 0.3	3.63	± 0.4	3.73	± 0.4
Serum CRP level (mg/dl)*		0.45	± 1.5	0.39	± 1.3	0.43	± 1.5	0.53	± 2.0	0.47	± 1.4	0.39	± 0.9	1.02	± 2.3	0.43	± 1.5
Hemoglobin level (g/dl)*		10.5	± 1.3	10.6	± 1.2	10.6	± 1.2	10.6	± 1.3	10.6	± 1.3	10.6	± 1.4	10.6	± 1.4	10.6	± 1.3

ADLs activities of daily living, *CRP* C-reactive protein

*Data are presented as mean ± standard deviation

[†]No symptoms (the patient can perform social activities without symptoms and behave without restrictions)

[‡]Moderate symptoms (the patient has mild symptoms and has trouble with physical work, but can walk and do light and sedentary work, such as light domestic and clerical work)

[§]≥ 50% sitting up (the patient can walk and take care of him/herself, but sometimes requires care. The patient can sit up at least half of the day, but cannot do light work)

[#]≥ 50% in bed (The patient can take care of him/herself to some extent, but often requires care and is in bed at least half of the day)

[¶]Whole day in bed (The patient cannot take care of him/herself and requires constant care. The patient must be in bed all day)

[ʃ]Patients' own home

[^]Care facilities (e.g., homes with care services; nursing homes, such as private nursing homes without national aid and nursing homes for families with financial difficulties; group homes; vocational centers; relief facilities)

[ɻ]Hospitals (e.g., health service facilities for the elderly; beds for general patients, patients at chronic stage, patients requiring rehabilitation, and patients with mental illness and infectious diseases, such as tuberculosis)

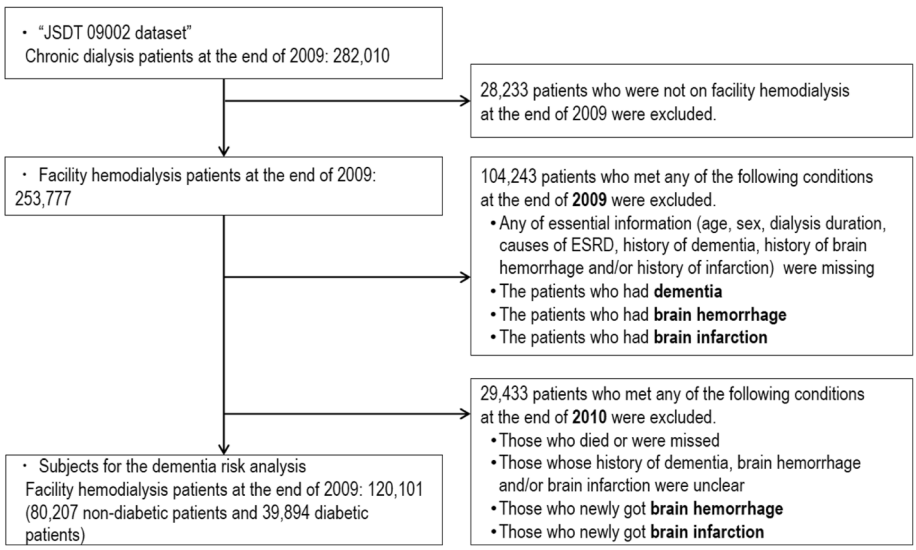

Fig. 1 Selection process for patients. Data from the Japanese Society for Dialysis Therapy (JSDT) Registry were used

Statistical analysis

All analyses were performed using the Statistical Analysis System, version 9.4 (SAS Institute, Inc., Cary, NC, USA). The incidence rate of dementia from the end of 2009 to the end of 2010 was calculated using the following formula: incidence rate of dementia (cases/1000 person-years) = the number of patients with newly developed dementia during the observation period (cases)/the total person-years of the target patients during the observation period (person-years) × 1000.

The time of dementia onset was not recorded in this survey. Therefore, the length of follow-up for patients who suffered dementia during 2010 was assumed to be 0.5 years when the incidence rate of dementia was calculated.

Because of the lack of data on the time of dementia onset, for the analyses of dementia risk, logistic regression models were constructed. All *P* values were two sided. In all models, the hemodialysis duration at the end of 2009 was used as the independent variable and the prevalence of dementia at the end of 2010 was used as the dependent variable. In these analyses, age-adjusted and multifactor models were used.

The age and hemodialysis duration values used in this report were calculated as of the end of 2009. As age is the most independent risk factor of dementia, the age-adjusted model included only age and hemodialysis duration as independent variables. The multifactor model included baseline factors from the age-adjusted model plus additional clinical covariates (i.e., sex; comorbidity of diabetes; Kt/V; BMI; albumin level; CRP level; hemoglobin level; history of myocardial infarction, limb amputation, or hip fracture; ADLs; and place of residence). Age, hemodialysis duration, Kt/V, BMI, albumin level, CRP level, and hemoglobin level were incorporated as continuous variables, whereas the other factors were incorporated as stratified categorical variables (Tables 1 and 2). A missing value of each covariate was treated as "a missing value group" and was analyzed.

In the multifactor model analysis, we analyzed not only the whole target patients but also non-diabetic and diabetic patients separately, to compare the tendency of dementia risk of these two patient groups. In these separated analyses, we incorporated hemodialysis duration as a stratified variable into the analytic model to confirm the dementia risk trend associated with elongation of hemodialysis duration. The hemodialysis duration was stratified into the following intervals: 0 to 1, 2 to 4, 5 to 9, 10 to 14, 15 to 19, 20 to 24, and ≥ 25 years. Because patients initiated on hemodialysis within 2 years frequently have significant residual renal function, we considered hemodialysis duration of < 2 years as a separate category. The mean value of age, which is the

Table 3 The questions and answer options in the dementia survey

• Questions
Please indicate the presence or absence of dementia in the patient.
Please provide as much information as you can about the conditions of the patient during dialysis treatment or consultation.
(Note that the primary doctor should provide the answer.)
• Answer options
Without dementia
Without dementia (requiring no care)
Without dementia (requiring care)
Unspecified

most independent risk factor, was quite similar between the hemodialysis duration groups (Tables 1 and 2).

Finally, to evaluate how the exclusion of patients by the end of 2010 affected the results (Fig. 1, $n = 29,433$), we conducted the following sensitivity analyses. We analyzed the dementia risk under the assumptions that none of the excluded patients suffered dementia (negative analysis) and that all excluded patients suffered dementia (positive analysis). These analyses were conducted on the non-diabetic and diabetic patients separately, using the multifactor model.

Results

Diabetes and dementia risk

The overall dementia incidence was higher in diabetic than in non-diabetic patients (35.5 cases/1000 person-years; 95% confidence interval [CI], 33.8–37.3 vs. 30.9 cases/1000 person-years, 95% CI, 29.7–32.1; Table 4). In the multifactor model analysis, the diabetic patients did not have significant risk of dementia compared with non-diabetic patients. (Table 5).

Covariates and dementia risk

The associations between the covariates and dementia risk, which were obtained from the whole patient analysis using the multifactor model, are shown in Table 5. Female sex, elder age, and higher CRP level were associated with higher dementia risk. The dementia risk was higher in those with than in those without a history of hip fracture, whereas the risk was lower in those with than in those without a history of amputation. Predictably, reduced ADLs and residence at a hospital or care facility were associated with dementia.

Hemodialysis duration and dementia risk

As shown in Table 4, there was a decrease in the dementia incidence with an increase in hemodialysis duration in non-diabetic patients, but there was no such association in diabetic patients.

When we analyzed the whole target patient group, which included those without and with diabetes simultaneously, longer hemodialysis duration was associated significantly with lower dementia risk in the age-adjusted and multifactor model analyses (Fig. 2a).

On the other hand, when we analyzed patients without and with diabetes separately, the analytic results were different. In non-diabetic patients, longer hemodialysis duration was associated significantly with lower dementia risk in the age-adjusted and multifactor model analyses, similar to the whole patient group analyses (Fig. 2b). However, in diabetic patients, we found no significant association between hemodialysis duration and dementia risk in the age-adjusted model analysis. The multifactor model analysis showed a significant correlation between hemodialysis duration and dementia risk, but the correlation was much weaker than that found in non-diabetic patients (Fig. 2c).

Figure 3 shows the results of the analyses in which hemodialysis duration was treated as a stratified but not as a continuous variable. These analyses were done using a multifactor model. Non-diabetic patients had a consistent decrease in dementia risk with an increase in hemodialysis duration from the shortest to the longest duration strata (Fig. 3a). However, in contrast, diabetic patients had only a vague association between hemodialysis duration and dementia risk. The association between hemodialysis duration and dementia risk was not consistent along with the elongation of hemodialysis duration (Fig. 3b). At less than 5 years of hemodialysis

Table 4 Dementia incidence according to hemodialysis duration

Hemodialysis duration (year)	Non-diabetic patients				Diabetic patients			
	Number of patients	Person-years	Number of patients who developed dementia	Incidence rates of dementia (cases/1000 person-year) (95% CI)	Number of patients	Person-years	Number of patients who developed dementia	Incidence rates of dementia (cases/1000 person-year) (95% CI)
0–1	14,787	14,452.5	669	46.3 (42.9 – 49.9)	12,756	12,500.0	512	35.8 (32.9 – 39.1)
2–4	17,293	16,952.5	681	40.2 (37.3 – 43.3)	13,342	13,053.0	578	39.1 (36.1 – 42.4)
5–9	19,984	19,684.5	599	30.4 (28.1 – 33.0)	10,273	10,085.5	375	32.2 (29.1 – 35.6)
10–14	12,479	12,336.5	285	23.1 (20.6 – 25.9)	2785	2736.5	97	30.1 (24.7 – 36.8)
15–19	7452	7398.0	108	14.6 (12.1 – 17.6)	605	593.0	24	34.5 (23.1 – 51.4)
20–24	4138	4109.0	58	14.1 (10.9 – 18.3)	98	96.0	4	34.9 (13.1 – 93.1)
25–	4074	4054.5	39	9.6 (7.0 – 13.2)	35	34.0	2	50.6 (12.7 – 202.5)
Total	80,207	78,987.5	2439	30.9 (29.7 – 32.1)	39,894	39,098.0	1592	35.5 (33.8 – 37.3)

Incidence rate of dementia (cases/1000 person-years) = the number of patients with newly developed dementia during the observation period (cases)/the total person-years of the target patients during the observation period (person-years) × 1000. The length of follow-up for patients with dementia was assumed to be 0.5 years

CI confidence interval

Table 5 ORs of dementia with covariates

Covariates	Number of patients	Incident number*	OR for development of dementia	(95% CI)	*p* value	Covariates	Number of patients	Incident number*	OR for development of dementia	(95% CI)	*p* value
Age						History of myocardial infarction					
For every 10 years old	120,101	4031	1.05	(1.02 ~ 1.07)	0.0003	No	113,283	3762	1.00	Reference	
Sex						Yes	6610	265	1.02	(0.91 ~ 1.14)	0.7
Male	74,472	2112	1.00	Reference		No information available	208	4	0.61	(0.30 ~ 1.25)	0.2
Female	45,629	1919	1.14	(1.08 ~ 1.21)	0.0001	History of limb amputation					
Comorbidity of diabetes						No	117,449	3911	1.00	Reference	
Without diabetes	80,207	2439	1.00	Reference		Yes	2455	111	0.66	(0.56 ~ 0.77)	0.0001
With diabetes	39,894	1592	1.00	(0.94 ~ 1.07)	0.9	No information available	197	9	1.03	(0.53 ~ 2.00)	0.9
Kt/V						History of hip fracture					
For every 0.1 increase	112,533	3690	1.00	(0.99 ~ 1.01)	0.5	No	117,467	3789	1.00	Reference	
No information available	7568	341	1.00	(0.83 ~ 1.19)	1.0	Yes	2121	219	2.38	(2.10 ~ 2.71)	0.0001
Body mass index						No information available	513	23	1.26	(0.82 ~ 1.93)	0.3
For every 1 kg/m^2 increase	105,234	3390	0.99	(0.98 ~ 1.00)	0.2	Activities of daily living					
No information available	14,867	641	1.01	(0.81 ~ 1.25)	1.0	No symptoms[†]	66,253	1009	1.00	Reference	
Serum albumin level						Moderate symptoms[‡]	37,309	1159	1.13	(1.05 ~ 1.22)	0.001
For every 1.0 g/dl increase	116,318	3923	0.96	(0.89 ~ 1.04)	0.3	≥ 50% sitting up[§]	10,184	1050	4.49	(4.14 ~ 4.88)	0.0001
No information available	3783	108	0.76	(0.55 ~ 1.06)	0.1	≥ 50% in bed[#]	3680	548	9.60	(8.69 ~ 10.6)	0.0001
CRP level						Whole day in bed[¶]	1132	224	21.70	(18.7 ~ 25.2)	0.0001
For every 1.0 mg/dl increase	58,498	2276	1.02	(1.00 ~ 1.04)	0.03	No information available	1543	41	0.95	(0.66 ~ 1.37)	0.8
No information available	61,603	1755	0.94	(0.88 ~ 1.02)	0.1	Place of residence					

Table 5 ORs of dementia with covariates *(Continued)*

Covariates	Number of patients	Incident number*	OR for development of dementia	(95% CI)	*p* value	Covariates	Number of patients	Incident number*	OR for development of dementia	(95% CI)	*p* value
Hemoglobin level						Homes[¶]	114,690	3286	1.00	Reference	
For every 1.0 g/dl increase	118,829	3967	0.99	(0.97 ~ 1.01)	0.5	Care facilities[^]	1109	191	10.95	(9.53 ~ 12.6)	0.0001
No information available	1272	64	1.18	(0.84 ~ 1.65)	0.3	Hospitals[¥]	3393	526	5.32	(4.86 ~ 5.84)	0.0001
						No information available	909	28	1.15	(0.73 ~ 1.82)	0.5

The associations between the covariates and dementia risk, which were obtained from the whole patient group analysis using a multifactor model, are shown
ADLs activities of daily living, *CI* confidence interval, *CRP* C-reactive protein, *OR* odds ratio
*Number of patients with dementia
[†]No symptoms (the patient can perform social activities without symptoms and behave without restrictions)
[‡]Moderate symptoms (the patient has mild symptoms and has trouble with physical work, but can walk and do light and sedentary work, such as light domestic and clerical work)
[§]≥ 50% sitting up (the patient can walk and take care of him/herself, but sometimes requires care. The patient can sit up at least half of the day, but cannot do light work)
[#]≥ 50% in bed (the patient can take care of him/herself to some extent, but often requires care and is in bed at least half of the day)
[¶]Whole day in bed (the patient cannot take care of him/herself and requires constant care. The patient must be in bed all day)
[¶]Patients' own home
[^]Care facilities (e.g., homes with care services; nursing homes, such as private nursing homes without national aid and nursing homes for families with financial difficulties; group homes; vocational centers; or relief facilities)
[¥]Hospitals (e.g., health service facilities for the elderly; beds for general patients, patients at chronic stage, patients requiring rehabilitation, and patients with mental illness and infectious diseases, such as tuberculosis)

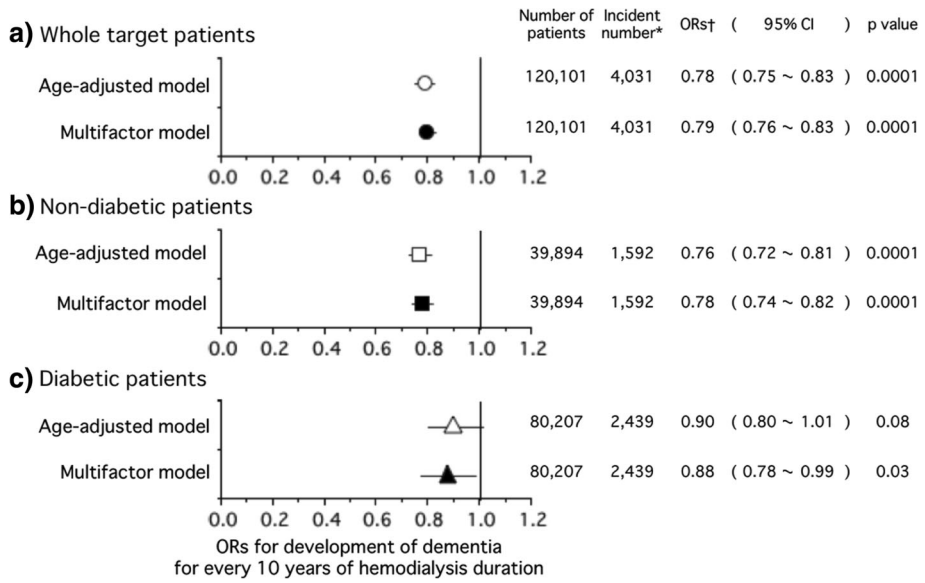

Fig. 2 Dementia risk for hemodialysis duration. The dementia risk for hemodialysis duration was analyzed for each different patient group using the age-adjusted or multifactor model. The age-adjusted model included only age and hemodialysis duration as independent variables. The multifactor model included baseline factors from the age-adjusted model plus additional clinical covariates (i.e., sex, comorbidity of diabetes, Kt/V, BMI, albumin level, CRP level, hemoglobin level, history of myocardial infarction, limb amputation, or hip fracture, ADLs, and place of residence). The duration of hemodialysis was treated as a continuous variable. Please note that the *X* axis is a linear plot. **a** The target patients of the analysis were the whole target patients. **b** The target patients of the analysis were only the non-diabetic patients. **c** The target patients of the analysis were only the diabetic patients. Asterisk indicates the number of patients who suffered dementia. Dagger indicates ORs for development of dementia for every 10 years of hemodialysis duration. ADLs activities of daily living, BMI body mass index, CI confidence interval, CRP C-reactive protein, OR odds ratio

duration, the dementia risk seemed to increase along with the elongation of the hemodialysis duration, but, on the contrary, from five to 19 years, it seemed to decrease. At over 20 years of hemodialysis duration, the dementia risk seemed to increase again along with elongation of the duration.

Figure 4 shows the result of sensitivity analysis. In the negative and positive analyses in the non-diabetic patients, the dementia risk decreased with increasing hemodialysis duration (Fig. 4a). However, in the positive analysis of diabetic patients, the risk of dementia tended to increase with prolongation of hemodialysis duration (Fig. 4b).

Discussion

Our study showed that the dementia risk in non-diabetic patients decreased with prolongation of hemodialysis duration. However, we must consider the survivor effect when analyzing the relationship between hemodialysis duration and dementia incidence.

The survivor effect is a bias caused by a prolonged period of observation for incidence in the target cohort. As the observation period increases, more patients with risk factors will drop out from the target cohort upon reaching the designated endpoints. As a result, the incidence rate tends to decrease with an increase in the observation period. In our study, hemodialysis duration also was the exposure period, with hemodialysis as a risk factor. Therefore, we must consider the survivor effect of hemodialysis duration in this study.

On the other hand, CKD is a reported risk factor of dementia [1, 2]. If we consider hemodialysis duration as the exposure period and consider CKD as a risk factor, a longer hemodialysis duration may be expected to increase dementia risk. However, in our study, the dementia risk in non-diabetic patients decreased as the hemodialysis duration increased. This result may suggest that the risk-reducing power of the survivor effect overcame the risk-enhancing power of CKD in non-diabetic patients throughout the entire hemodialysis period. However, we could not necessarily identify a clear relationship between dialysis duration and dementia risk in diabetic patients.

In general, the survivor effect appears to be stronger when more patients drop out from the target cohort as they reach the designated endpoints. For example, the dementia risk was significantly lower in patients with a history of limb amputation (odds ratio [OR], 0.66 [95% CI, 0.56–0.77]; the OR compares patients "with limb amputation history" to those "without limb amputation history"; Table 5). Moreover, previous research has shown that the survival rate was low in hemodialysis

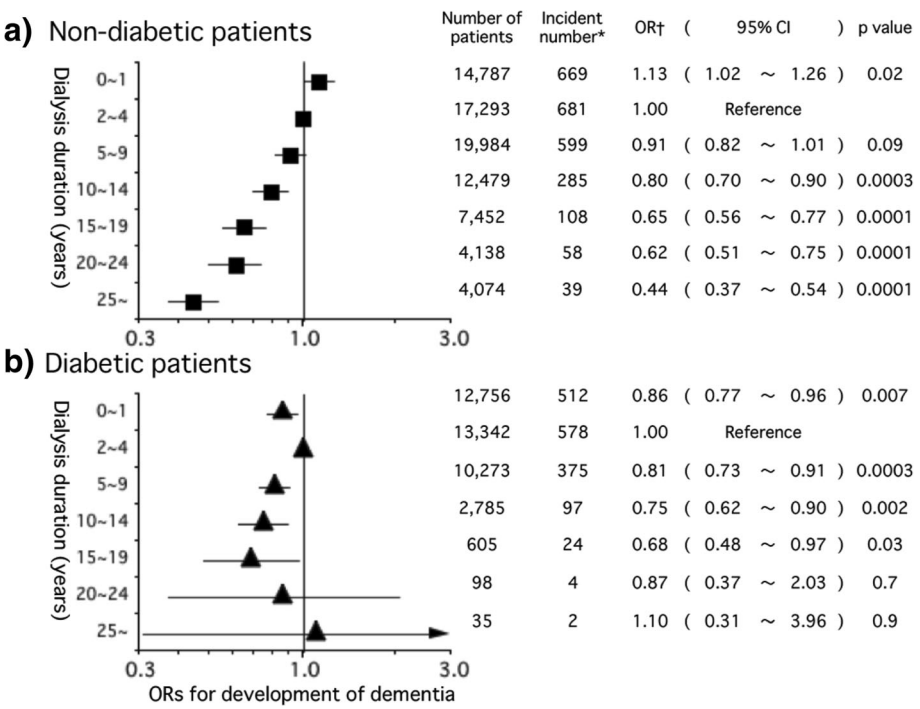

Fig. 3 Dementia risk for hemodialysis duration as a stratified variable. The dementia risk for hemodialysis duration was analyzed as a stratified variable using the multifactor model. The multifactor model included the following factors as independent variables: hemodialysis duration, age, sex, comorbidity of diabetes, Kt/V, BMI, albumin level, CRP level, hemoglobin level, history of myocardial infarction, limb amputation, or hip fracture, ADLs, and place of residence. Please note that the *X* axis is a log-linear plot. **a** The target patients of the analysis were only the non-diabetic patients. **b** The target patients of the analysis were only the diabetic patients. Asterisk indicates the number of patients who suffered dementia. Dagger indicates ORs for development of dementia. ADLs activities of daily living, BMI body mass index, CI confidence interval, CRP C-reactive protein, OR odds ratio

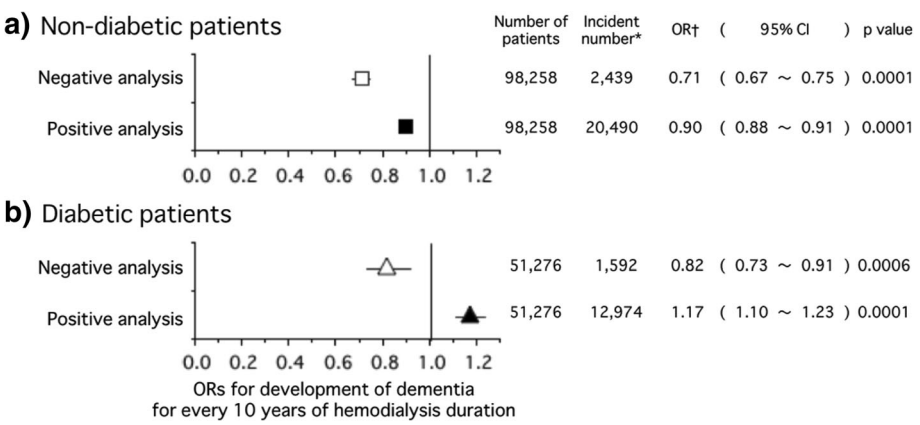

Fig. 4 Sensitivity analyses for the excluded patients' influence evaluation. The sensitivity analyses were conducted to evaluate how the exclusion of patients affected the results. We analyzed the dementia risk under the assumptions that none of the excluded patients had dementia (negative analysis) and that all the excluded patients had dementia (positive analysis). These analyses were conducted using the multifactor model, which included the following factors as independent variables; hemodialysis duration, age, sex, comorbidity of diabetes, Kt/V, BMI, albumin level, CRP level, hemoglobin level, history of myocardial infarction, limb amputation, or hip fracture, ADLs, and place of residence. Please note that the *X* axis is a linear plot. **a** The target patients of the analysis were only the non-diabetic patients. **b** The target patients of the analysis were only the diabetic patients. Asterisk indicates the number of patients with dementia. Dagger indicates ORs for development of dementia for every 10 years of hemodialysis duration. ADLs activities of daily living, BMI body mass index, CI confidence interval, CRP C-reactive protein, OR odds ratio

patients with a history of limb amputation [19]. This also is confirmed in our mortality risk analysis (Additional file 1: Table S1). The mortality risk increased significantly when hemodialysis duration increased in non-diabetic and diabetic (Additional file 1: Table S2). However, the relationship between mortality risk and hemodialysis duration was much stronger in the diabetic patients than in non-diabetic patients. Based on these findings, we may be able to assume that the survivor effect was stronger in diabetic patients than in non-diabetic patients. However, the relationship between dementia risk and hemodialysis duration in diabetic patients was much weaker or vaguer than that in non-diabetic patients (Figs. 2 and 3). Therefore, we might be able to consider that the reduction in dementia risk with prolonged hemodialysis duration in non-diabetic patients was caused not only by the survivor effect but also by some other factors, such as hemodialysis itself.

AD is a major cause of dementia [5], in which accumulation of Aβ in the brain results in cognitive impairment [6]. Moreover, in these patients, the metabolic degradation of Aβ and its clearance from the brain are impaired [7]. If Aβ clearance from the brain can be increased, AD might be prevented or even treated. It has been shown that hemodialysis removes Aβ [10] and that the cognitive function of non-diabetic patients was maintained or improved among those undergoing maintenance hemodialysis over a period of 18 to 36 months [11]. Additionally, Aβ deposition was significantly weaker in the postmortem brains of patients who had undergone hemodialysis than in age-matched controls who had not undergone hemodialysis [12], and this finding is comparable to the finding in the study by Reusche et al. [13]. Although Lin et al. [4] showed that there is no significant difference in dementia risk between patients undergoing hemodialysis and those undergoing peritoneal dialysis, Jin et al. [20] showed that Aβ removal from the blood by peritoneal dialysis also reduces Aβ in the brain interstitial fluid. These reports suggest that hemodialysis might reduce the dementia risk through removal of Aβ from the blood of patients.

It is known that hemodialysis patients have a high morbidity risk of cerebrovascular events [21], and CVD is a major risk factor for VaD. We excluded patients with a clear history of CVD (Fig. 1). Therefore, we may assume that most cases in our analysis had a type of dementia other than VaD. In the study by Sekita et al. [22] on dementia in the general population in Japan, approximately 46% of individuals had AD and 30% had VaD. If we apply this finding to our study in which patients with CVD were excluded, we might be able to assume that approximately two thirds of our patients with dementia had AD. However, we may have to consider the possibility that patients suffered VaD without presenting with clear symptoms of CVD, and it is known that patients with CKD tend to experience VaD rather than AD [23]. Therefore, we may have to consider that the patients with dementia among our target patients still include many with VaD. However, it is reported that the vascular lesion of patients with CKD also is a risk for AD [24]. Furthermore, it has been reported that many patients with cerebrovascular dementia have concomitant AD [5]; thus, we believe that hemodialysis may suppress the development of dementia in this patient group to some extent.

In this survey, despite the notification that the primary physician should determine the presence or absence of dementia, no standard criteria were specified and there was no information on dementia severity. We cannot exclude the possibility that this ambiguity of dementia diagnosis influenced the analytic results. Patients with long hemodialysis duration might be well known by their own physicians in charge. This situation might make it easier for the physicians to be aware of their patients' dementia. On the other hand, the physicians might tend to answer "without dementia" from force of habit. However, even if we suppose the possibility of "negative diagnosis bias" of long-term dialysis patients, we cannot explain the reason why the risk suppression effect of hemodialysis duration in diabetic patients is weaker than that of non-diabetic patients.

On assessing patients in this study, we found no apparent relationship between hemodialysis duration and age (Tables 1 and 2). Moreover, the influence of age was adjusted using the logistic regression analysis. Therefore, it is difficult to consider that a deviation in age with a prolonged hemodialysis duration affected the analytical results.

The discontinuation of dialysis after dementia onset by a substantial number of patients could exacerbate the survivor effect. However, among the 8367 patients excluded from our analytical cohort due to death during 2010, only 33 (0.4%) died due to discontinuation of dialysis. Thus, discontinuation of dialysis does not appear to contribute substantially to the survivor effect.

Considering the aforementioned findings, the assumption that hemodialysis itself may prevent development of AD in non-diabetic patients does not appear to have a major conflict with our results. Our results may not show clearly the dementia-preventing effect of hemodialysis therapy. However, if we can interpret this result as "the first finding," showing the dementia-preventing effect of hemodialysis therapy based on the real clinical data obtained from a large cohort of patients, this result may have important implications in the prevention of dementia. Therefore, we reported this result in this study.

Although hemodialysis is considered to be preventive against the incidence of dementia, it does not imply that

the incidence of dementia in the hemodialysis patients is absolutely lower than that in the general population. The incidence of dementia in the > 65-year-old target patients was 50.0 and 59.0 cases/1000 person-years among those without and with diabetes, respectively (Additional file 1: Table S3). On the other hand, it is reported that the incidence of dementia in the > 65-year-old Japanese general population was 30.5–35.6 cases/1000 person-years [25]. This finding suggests that the absolute value of the incidence of dementia in hemodialysis patients is still higher than that in the general population. This may suggest that the dementia risk-reducing effect of hemodialysis did not overcome the risk caused by CKD itself, which every hemodialysis patient faced.

Because it is known that renal failure patients without hemodialysis have a 2.86 times higher risk of cognitive impairment than healthy subjects [2], we consider that the high dementia risk of hemodialysis patients may not have resulted from hemodialysis therapy but from their renal failure. There may be some patients who had dementia or cognitive impairment prior to dialysis initiation. Therefore, in this study, we evaluated the relationship between dementia risk and the patients' hemodialysis duration.

In the present analysis, we found no significant risk of dementia related to Kt/V (Table 5). Kt/V is considered to be the dialysis efficiency indicator of the small substance because the target substance of Kt/V is urea and its molecular weight is only 60 Da. On the other hand, the molecular weight of Aβ, which is considered to be related to the occurrence of AD, is 4 kDa and is much heavier than urea. Recently, Kawaguchi et al. [26] reported that dialyzers remove Aβ from the blood, not by the dialysis phenomenon but by adsorption during hemodialysis therapy [26]. Kato et al. [10] also reported that the reduction rate of blood Aβ concentration of a 4-h hemodialysis session is approximately 34.9 to 53.0%. Based on these reports, we may be able to assume that the reduction rate of Aβ in our target patients was similar to that reported by Kato et al. [10]. These findings suggest that our result of Kt/V having no dementia risk does not necessarily conflict with our hypothesis that the hemodialysis prevents development of AD through removing Aβ.

Regarding removal of large molecular weight substances from the blood, the hemodiafiltration therapy, which uses dialysis and the filtration phenomenon, generally is considered to have a higher efficiency than hemodialysis. However, because the main mechanism of removing Aβ from blood is not dialysis but the adsorption phenomenon of the dialyzer membrane, we may be able to consider that the choice of blood purification method, such as hemodialysis or hemodiafiltration, may not make much difference in the dementia preventive effect.

Diabetes is a known risk factor for dementia [15]. Hanyu et al. [16] recently mentioned that dementia in diabetic patients should be regarded as an independent disease (i.e., diabetes-related dementia) because it results from pathologic conditions related to diabetes. Following their concept, we separated the target patients based on their comorbidity of diabetes in our study. A unique disease entity causing dementia also may explain the weak or absent association between hemodialysis duration and dementia risk in diabetic patients. In our analysis, the multifactor model showed no significant dementia risk in diabetic patients compared with non-diabetic patients (Table 5). When we tentatively analyzed the dementia risk for the comorbidity of diabetes using a simple analytic model that contains only age and hemodialysis duration as covariates other than comorbidity of diabetes, we showed that diabetic patients had a significant OR for dementia of 1.13 (95% CI, 1.07–1.20, $P = 0.0001$; Additional file 1: Table S4). We considered that this finding may show that the influence of the comorbidity of diabetes was confounded by other covariates in the multifactor model analysis.

We conducted a sensitivity analysis to evaluate how the exclusion of patients by the end of 2010 affected the results. In the negative and positive analyses of non-diabetic patients, the dementia risk decreased with increasing hemodialysis duration (Fig. 4a). This result suggested that the exclusion of patients by the end of 2010 did not affect the relationship between dementia risk and hemodialysis duration among the non-diabetic patients. Although the negative analysis of diabetic patients showed that the dementia risk decreased with prolongation of hemodialysis duration, the positive analysis of diabetic patients showed to the contrary that the risk of dementia increased with prolongation of hemodialysis duration (Fig. 4b). This result showed that the dementia risk possibly may increase along with prolongation of hemodialysis duration in diabetic patients. But the diabetic patients may also have a weak negative relationship between the dementia risk and their hemodialysis duration because the multifactor model analysis of the diabetic patients showed a weak but significant negative relationship between the dementia risk and hemodialysis duration (Fig. 2c).

Our analysis showed that advancing age, female sex, a high CRP level, history of hip fracture, low ADLs, and admission to facilities or hospitals were significant risk factors for dementia (Table 5). These risk factors have been reported as significant for dementia in previous studies [27–30]. Anemia has been reported to be a risk factor for cognitive impairment [31]. However, our analysis did not show a significant association between

hemoglobin level and dementia risk. We considered that the effects of hemoglobin on dementia probably were confounded by other covariates (Additional file 1: Table S5).

Our study had several limitations. First, the diagnostic criteria for dementia were not specified clearly, and the assessment of dementia was based on a simple query to the respondents at each facility. Despite the notification that the primary physician should determine the presence or absence of dementia, no standard criteria were specified and there was no information on dementia severity. Second, the database used did not include many factors, including hypertension, hyperlipidemia, low socioeconomic status, and low education status, which have been reported to affect dementia risk in patients with CKD [32]. Third, we could not completely exclude survivor bias despite our efforts to mitigate the effect by incorporating many covariates in the regression model. To resolve these problems in the future, extensive cohort studies should be performed among patients undergoing hemodialysis and care should be taken to collect detailed information related to the onset of AD.

Conclusion

A longer hemodialysis duration was correlated with a lower dementia risk in non-diabetic patients, but not in diabetic patients. This finding does not appear to contradict greatly the assumption that the reduction in dementia risk with a prolonged hemodialysis duration in non-diabetic patients was caused not only by the survivor effect but also by hemodialysis itself.

Additional file

Additional file 1: Table S1. Mortality risk analysis. **Table S2.** Mortality risk with hemodialysis duration. **Table S3.** Dementia incidence of the subjective patients of the present study whose age is more than 65 years old. **Table S4.** Dementia risk of diabetes calculated using a simple analytic model. **Table S5.** Dementia risk of hemoglobin level calculated using a simple analytic model. (DOC 13433 kb)

Abbreviations

AD: Alzheimer's disease; ADLs: Activities of daily living; Aβ: Amyloid β; BMI: Body mass index; CI: Confidence interval; CKD: Chronic kidney disease; CRP: C-reactive protein; CVD: Cerebrovascular disease; ESRD: End-stage renal disease; JRDR: Japanese Society for Dialysis Therapy Renal Data Registry; JSDT: Japanese Society for Dialysis Therapy; OR: Odds ratio; VaD: Vascular dementia

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Availability of data and materials

The data that support the findings of this study are available from JSDT but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of JSDT.

Authors' contributions

SN, KW, and NK devised the study design. SN and EK analyzed the data. KS assisted with the pathophysiologic assessment. KK assisted with the etiologic assessment. SN wrote the original draft, prepared the tables and figures, and searched the literature. All authors interpreted the data and reviewed the manuscript. All authors read and approved the final manuscript.

Authors' information

S.N. and E.K. are present members of Committee of Renal Data Registry of JSDT, and K.W. was a previous member of this committee.

Ethics approval and consent to participate

The present survey was approved by the medicine ethics committee of JSDT (approval number is 2) and was exempt from the need for informed consent. The study was performed in accordance with the relevant guidelines 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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