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【 ORIGINAL ARTICLE 】

The Association between Dialysis Dose and Risk of Cancer Death in Patients Undergoing Hemodialysis: The Q-Cohort Study

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Abstract:

Objective Uremic toxins are known risk factors for cancer in patients undergoing hemodialysis (HD). Although adequate removal of uremic toxins might reduce the cancer risk by improving subclinical uremia, the relationship between the dialysis dose and risk of cancer death in patients undergoing HD remains unclear.

Methods In this prospective observational study, 3,450 patients undergoing HD were followed up for 4 years. The primary outcome was cancer death. Patients were divided into quartiles according to their baseline Kt/V levels. The association between the Kt/V levels and risk of cancer death was estimated using the Kaplan-Meier method and Cox proportional-hazards model.

Results A total of 111 patients (3.2%) died from cancer during the 4-year observational period. The 4-year survival rate decreased linearly with decreasing Kt/V. The multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer death were 2.23 (95% CI, 1.13-4.56), 1.77 (0.88-3.63), and 1.89 (1.04-3.56) in quartile (Q)1, Q2, and Q3, respectively, compared with patients in the highest Kt/V category (Q4) (p for trend = 0.06). Every 0.1 increase in Kt/V was associated with a reduction of 8% in cancer death (HR 0.92, 95% CI, 0.85-0.99).

Conclusion A lower dialysis dose might be associated with a higher risk of cancer death in patients undergoing HD. Kt/V is a simple indicator of dialysis dose used in clinical practice and might be a useful modifiable factor for predicting the risk of cancer death. Further basic and interventional studies are needed to confirm the apparent reduction in cancer death associated with increasing the dialysis dose.

Key words: dialysis dose, cancer death, uremic toxin, urea, dysbiosis

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Introduction

Recent advances in dialysis technology have led to an increase in the life expectancy of patients undergoing hemodialysis (HD). However, the consequent aging of patients undergoing HD is associated with an increased incidence of cancer death, in addition to cardiovascular deaths. Several reports have indicated a higher incidence of cancer among patients undergoing HD compared with the general population (1, 2). Furthermore, the cancer-related mortality is also higher in patients undergoing HD than in the general population (3, 4). Although the incidence of cancer death among patients undergoing HD has remained around 4.0-10.0% in recent years (5-7), it still represents the major cause of death in this population.

There are concerns that the cancer diagnosis and interventions in patients undergoing HD are inadequate compared with the general population because of the costs and the vulnerability of this patient group to treatment-related ad-

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verse events (8, 9). It is therefore necessary to identify predictors of or modifiable factors related to future cancer death among patients undergoing HD. Some observational studies showed that a higher Kt/V value, as an indicator of the dialysis dose, was associated with reduced all-cause (10-12) and cardiovascular mortalities (13). However, few studies have examined the specific relationship between the dialysis dose and cancer death. One observational study reported that the risk of cancer death increased when the Kt/V was <1.6 (10), while another study reported no association between cancer death and Kt/V value (13). The relationship between the dialysis dose and risk of cancer death thus remains controversial.

The present study assessed the association between the dialysis dose and cancer death in a large-scale longitudinal cohort of patients undergoing HD.

Materials and Methods

Design of the Q-cohort study and study population

The Q-Cohort Study was a multicenter, prospective, longitudinal observational cohort study of 3,598 outpatients ≥18 years old undergoing HD in 39 dialysis facilities in Saga and Fukuoka Prefectures, Kyushu, Japan. The details of this study have been described previously (14-16). Patients were enrolled from December 2006 to December 2007. Patients with missing clinical variables (n=53) and for whom clinical outcomes were missing (n=95) were excluded. The remaining 3,450 patients were enrolled in this study.

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research (Approval No. 20-31) and was registered in the University Hospital Medical Information Network (UMIN) clinical trial registry (UMIN000000556). This study was performed according to the Ethics of Clinical Research (Declaration of Helsinki) requirements. Informed consent was obtained prior to participation from all patients.

Exposure variable

The main exposure variable was the dialysis dose, assessed by single-pool Kt/V (spKt/V) levels at baseline, determined using the Daugirdas method (17). In brief, spKt/V=−ln (R−0.008×t) + (4−3.5×R) ×ΔV/BW_{post}, where R is the post-/pre-dialysis plasma urea nitrogen ratio, t is the dialysis session length (in hours), ΔV is the ultrafiltration volume (in liters), and BW_{post} is the post-dialysis body weight (in kilograms). To avoid the effect of recirculation on the post-dialysis urea determination, ultrafiltration and the dialysis fluid flow were stopped before the sample was drawn.

Potential confounders

Demographic data, including the age, sex, dialysis session length (DSL), dialysis vintage, and presence of diabetes mellitus, and clinical data, including the hemoglobin, serum albumin (Alb), serum calcium (Ca), serum phosphate, serum total cholesterol, serum C-reactive protein (CRP), serum ferritin, normalized protein catabolic rate (nPCR), Kt/V, and body mass index (BMI), were gathered from the patients' medical records at baseline. Blood samples were collected via vascular access at dialysis initiation on the first dialysis day of the week (Monday or Tuesday, depending on patients' dialysis shifts). The corrected serum Ca value was obtained from the serum Ca value and serum albumin value using Pyne's formula, as follows: corrected Ca (mg/dL) = observed total Ca (mg/dL) + [4.0 - serum albumin concentration (g/dL)]. The BMI (kg/m^2) was calculated from the body height and weight measured in light clothing without shoes. The physicians at each dialysis facility checked the current use of erythropoiesis-stimulating agents (ESAs) and vitamin D receptor activators (VDRAs).

Outcome assessment

The primary outcome was cancer death, defined as death with cancer as the primary cause. All outcomes were collected from the patients' medical records.

Statistical analyses

The patients were divided into four groups according to Kt/V quartiles: quartile 1 (Q1), Kt/V <1.42; Q2, Kt/V 1.42-1.55; Q3, Kt/V 1.56-1.70; and Q4, Kt/V ≥1.71. Data are presented as the mean ± standard deviation for normally distributed continuous variables, median and interquartile range for non-normally distributed continuous variables, and percentage for categorical variables, as appropriate. To evaluate trends in continuous and categorical values across the quartiles of Kt/V categories, the Jonckheere-Terpstra and Cochran-Armitage tests, respectively, were used. The incidence rates for cancer death according to the Kt/V quartile categories were plotted by the Kaplan-Meier method and compared by the log-rank test. Unadjusted, age- and sex-adjusted, and multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for cancer death according to the Kt/V level were estimated using a Cox proportional-hazards model. Because an association between a low Kt/V level and high rate of cancer death was assumed, we chose the highest quartile of Kt/V category (Q4) as the reference for the Cox model. In the multivariable-adjusted model, adjustments were made for the following clinically or biologically plausible risk factors for outcome, or based on the findings of previous studies: age, sex, diabetes mellitus, dialysis vintage, DSL, BMI, hemoglobin level, serum albumin, serum total cholesterol, serum CRP, serum ferritin, nPCR, and use of ESAs and VDRAs. The effect of heterogeneity in Kt/V on the risk of cancer death across baseline characteristics was tested by adding an interaction term to the relevant Cox proportional-hazard model.

To explore the functional form of the multivariable-adjusted relationship between Kt/V as a continuous predictor and the risk of cancer death, smoothing splines were applied. We used the software package called *smoothHR* which provides flexible hazard ratio curves and make it possible to

Table 1. Baseline Characteristics of Study Subjects.

Variable	All (n=3,450)	Kt/V				p for trend
		Quartile 1 (n=856) <1.42	Quartile 2 (n=574) 1.42-1.55	Quartile 3 (n=1,142) 1.56-1.70	Quartile 4 (n=878) ≥1.71	
Age (years)	63.7 (12.8)	62.5 (12.5)	63.9 (12.5)	64.4 (12.8)	63.7 (13.2)	0.008
Male patients (%)	59.2	83.9	74.2	60.9	22.9	<0.001
Diabetes (%)	29.1	41.1	30.0	28.2	17.9	<0.001
Dialysis duration (years)	5.5 [2.1, 11.5]	3.6 [1.0, 8.0]	5.0 [2.1, 12.0]	6.1 [2.5, 11.6]	7.1 [3.3, 14.3]	<0.001
Dialysis session length (hours)	5.0 [4.0, 5.0]	5.0 [4.0, 5.0]	5.0 [4.5, 5.0]	5.0 [4.0, 5.0]	5.0 [5.0, 5.0]	<0.001
Body mass index (kg/m^2)	21.1 (3.1)	22.5 (3.5)	21.5 (2.8)	21.0 (2.9)	19.8 (2.6)	<0.001
Pre-dialysis systolic blood pressure (mmHg)	152.9 (23.4)	157.3 (23.3)	155.2 (22.4)	150.9 (23.5)	149.9 (23.3)	<0.001
Hemoglobin (g/dL)	10.5 (1.2)	10.7 (1.3)	10.5 (1.1)	10.6 (1.2)	10.4 (1.1)	<0.001
Serum albumin (g/dL)	3.8 (0.4)	3.8 (0.5)	3.8 (0.4)	3.8 (0.5)	3.8 (0.4)	0.97
Serum corrected calcium (mg/dL)	9.4 (0.8)	9.3 (0.8)	9.4 (0.8)	9.4 (0.8)	9.5 (0.7)	<0.001
Serum phosphorus (mg/dL)	4.9 (1.2)	5.1 (1.2)	4.9 (1.2)	4.9 (1.2)	4.9 (1.1)	<0.001
Serum intact parathyroid hormone (pg/mL)	106 [48, 216]	110 [49, 216]	106 [44, 213]	108 [51, 220]	102 [46, 212]	0.51
Serum C-reactive protein (mg/dL)	0.13 [0.06, 0.30]	0.13 [0.06, 0.32]	0.13 [0.06, 0.34]	0.13 [0.08, 0.30]	0.10 [0.04, 0.29]	0.002
Serum total cholesterol (mg/dL)	155.7 (36.6)	150.5 (36.0)	152.5 (36.8)	154.0 (35.8)	165.2 (36.5)	<0.001
Serum ferritin (ng/mL)	163 [68, 299]	163 [66, 295]	164.5 [69, 328]	163 [67, 282]	167 [73, 316]	0.68
nPCR (mg/kg/m^2)	0.96 (0.19)	0.87 (0.18)	0.92 (0.14)	1.00 (0.20)	1.02 (0.19)	<0.001
Use of VDRAs (%)	70.1	70.1	70.6	68.4	71.9	0.68
Use of ESAs (%)	84.1	81.1	81.7	85.4	86.9	<0.001

Values are presented as mean (standard deviation) for normally distributed continuous variables, median [interquartile range] for non-normally distributed continuous variables, and percentage for categorical variables. The Cochran-Armitage test was used to determine p for trend of categorical variables. The Jonckheere-Terpstra test was used to determine p for trend of continuous variables. A two-tailed p value<0.05 was considered statistically significant.

ESA: erythropoiesis-stimulating agent, nPCR: normalized protein catabolic rate, VDRA: vitamin D receptor activator

identify non-linear relationships between continuous predictors and survival. The multivariable-adjusted model was adjusted for the same variables as the fully adjusted Cox model. Age, sex, diabetes mellitus, dialysis vintage, DSL, BMI, hemoglobin level, serum albumin, serum total cholesterol, serum CRP, serum ferritin, nPCR, and the use of ESAs and VDRAs were treated as spline terms. The third quartile of Kt/V (1.71) was chosen as the reference for the spline plot. All analyses were conducted using the software programs JMP, version 11 for Windows (SAS Institute, Cary, USA), and R statistical software, version 3.3.0 (R Foundation for Statistical Computing). A two-tailed value of p<0.05 was considered statistically significant.

Results

Baseline characteristics according to quartiles of Kt/V levels

The baseline clinical characteristics of the study population according to Kt/V quartile are shown in Table 1. Patients with the lower Kt/V category had a significantly younger mean age, higher proportion of men, higher prevalence of diabetes mellitus, shorter median dialysis vintage, higher BMI, and higher pre-dialysis systolic blood pressure than the higher Kt/V category. The mean hemoglobin concentrations, serum phosphate, and serum CRP levels were significantly higher, and the mean serum corrected Ca and total cholesterol levels were significantly lower in subjects with the lower Kt/V category. In addition, the proportion of patients using ESAs was significantly lower among those in the lower KT/V category than in the higher Kt/V category.

The association between Kt/V and the risk of cancer death

During the 4-year follow-up period, 111 (3.2%) patients died of cancer, with a crude incidence rate of 10.3 per 1,000 patient-years. The median survival time of patients who died of cancer was 616 (316-915) days. The cumulative incidence rates of all-cause mortality and cancer death according to the Kt/V level are shown in Fig. 1A and B, respectively. The event-free survival rate for cancer death decreased linearly with decreasing Kt/V (p=0.03; Fig. 1B). The unadjusted, age- and sex- adjusted, and multivariable-adjusted HRs associated with Kt/V categories are shown in Table 2. In an age- and sex- adjusted model, the HR increased linearly with decreasing Kt/V (p for trend =0.01; Table 2), and patients in the lowest Kt/V category (Q1) had the highest HR for the incidence of cancer death compared with the reference category (Q4) [HR (95% CI), 2.40 (1.30-4.57); p= 0.005; Table 2]. This association remained after adjusting for potential confounding factors, including age, sex, diabetes mellitus, dialysis vintage, DSL, BMI, hemoglobin level, serum albumin, serum total cholesterol, serum CRP, serum

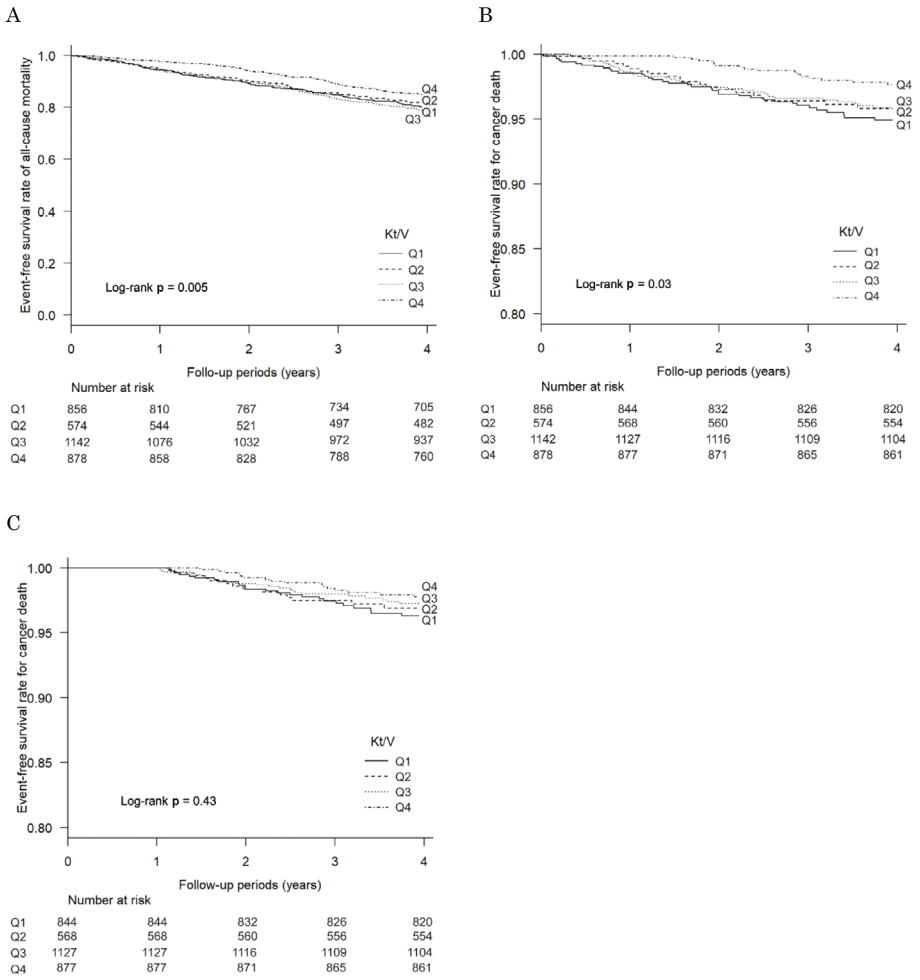

Figure 1. **Event-free survival rate for (A) all-cause mortality and (B) cancer death according to the Kt/V quartile during the four-year follow-up period. (C) Event-free survival rate for cancer death according to the Kt/V quartile during the four-year follow-up period, excluding patients who died of cancer within one year after registration. Two-tailed p<0.05 was considered statistically significant. Q: quartile**

Table 2. **Hazard Ratios for Cancer Death according to Kt/V Quartiles.**

		Unadjusted model			Age- and sex-adjusted model			Multivariable-adjusted model*		
	Number of events/ number of patients	HR (95% CI)	p value	p for trend	HR (95% CI)	p value	p for trend	HR (95% CI)	p value	p for trend
Cancer death										
All	111/3,450									
Q1 (Kt/V<1.42)	36/856	2.32 (1.32-4.23)	0.003	0.008	2.40 (1.30-4.57)	0.005	0.01	2.23 (1.13-4.56)	0.02	0.06
Q2 (1.42≤Kt/V<1.55)	20/574	1.94 (1.02-3.75)	0.04		1.84 (0.93-3.67)	0.08		1.77 (0.88-3.63)	0.11	
Q3 (1.56≤ Kt/V<1.70)	38/1,142	1.90 (1.09-3.46)	0.02		1.82 (1.02-3.36)	0.04		1.89 (1.04-3.56)	0.04	
Q4 (Kt/V ≥1.71)	17/878	1.00 (reference)	-		1.00 (reference)	-		1.00 (reference)	-	
Every 0.1 increase in Kt/V		0.90 (0.84-0.97)	0.003		0.90 (0.84-0.97)	0.007		0.92 (0.85-0.99)	0.049	

*Adjusted for age, sex, diabetes mellitus, dialysis duration, dialysis session length, body mass index, hemoglobin level, serum albumin, serum total cholesterol, serum C-reactive protein, serum ferritin, normalized protein catabolic rate, and use of erythropoiesis-stimulating agents and vitamin D receptor activators. A two-tailed p value<0.05 was considered statistically significant.

CI: confidence interval, HR: hazard ratio, Q: quartile

Table 3. Hazard Ratios for Cancer Death according to Kt/V Quartiles Restricted to Longer Dialysis Duration.

		Age- and sex-adjusted model			Multivariable-adjusted model*		
	No of events/ No of patients	HR (95% CI)	p value	p for trend	HR (95% CI)	p value	p for trend
Cancer death							
All	86/2,605						
Q1 (Kt/V<1.42)	24/543	2.50 (1.23-5.09)	0.01	0.003	1.92 (0.87-4.24)	0.11	0.18
Q2 (1.42≤Kt/V<1.56)	16/432	1.89 (0.89-4.00)	0.10		1.67 (0.76-3.67)	0.20	
Q3 (1.56≤ Kt/V<1.71)	31/909	1.86 (0.98-3.53)	0.06		1.70 (0.87-3.32)	0.12	
Q4 (Kt/V ≥1.71)	15/721	1.00 (reference)	-		1.00 (reference)	-	
Every 0.1 increase in Kt/V		0.87 (0.80-0.95)	0.003		0.90 (0.81-0.99)	0.04	

*Adjusted for age, sex, diabetes mellitus, dialysis duration, dialysis session length, body mass index, hemoglobin level, serum albumin, serum total cholesterol, serum C-reactive protein, serum ferritin, normalized protein catabolic rate, and use of erythropoiesis-stimulating agents and vitamin D receptor activators. A two-tailed p value<0.05 was considered statistically significant.

CI: confidence interval, HR: hazard ratio, Q: quartile

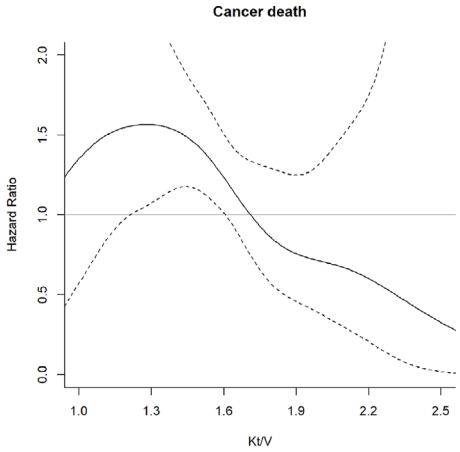

Figure 2. Functional form of the multivariable-adjusted relationship between the Kt/V levels and risk of cancer death using smoothing splines. The solid line represents the hazard ratio, the dotted line represents the 95% confidence interval, and the horizontal gray line corresponds to reference hazard ratio (1.0). The third quartile of Kt/V (1.71) was chosen as the reference. The multivariable-adjusted model was adjusted for the age, sex, diabetes mellitus, dialysis vintage, dialysis session length, body mass index, hemoglobin level, serum albumin, serum total cholesterol, serum C-reactive protein, serum ferritin, normalized protein catabolic rate, and use of erythropoiesis-stimulating agents and vitamin D receptor activators.

ferritin, nPCR, and use of ESAs and VDRAs. In the multivariable-adjusted model, the HR increased marginally linearly with decreasing Kt/V (p for trend =0.06; Table 2), and patients with the lowest Kt/V category (Q1) had the highest HR for the incidence of cancer death compared with the reference category (Q4) [HR (95% CI), 2.23 (1.13-4.56); p=0.02; Table 2]. Every 0.1 increase in Kt/V was associated with a 0.92-fold (95% CI 0.84-0.99) decrease in the risk of cancer death after adjusting for potential confounding factors.

To account for any malignancies carried over from the non-dialysis period, we also performed an analysis restricted to participants with a longer dialysis duration. We analyzed those with a dialysis duration longer than the first quartile category (2.1 years). Although the difference was no longer significant due to the decreased statistical power, the tendency towards increased cancer death with the lowest Kt/V category remained (Table 3). Furthermore, to reduce the effect of the presence of cancer at baseline, we performed an analysis excluding patients who died of cancer within one year after registration. Although the difference was no longer significant due to the decreased statistical power, the survival rate decreased linearly with decreasing Kt/V (Fig. 1C). The continuous multivariable-adjusted association between the Kt/V levels and the risk of cancer death showed a similar relationship. The lower Kt/V tended to increase the risk of cancer death and it was significant when Kt/V was lower than around 1.6 (Fig. 2).

Subgroup analyses stratified by baseline characteristics

We assessed the consistency of the association between Kt/V and the risk of cancer death by examining the effect in subgroups stratified by potential confounders (Fig. 3). However, subgroup analyses showed no significant interactions between the Kt/V level and other baseline characteristics (p ≥0.05 for all interactions; Fig. 3).

Discussion

The present prospective cohort study conducted in 3,450 HD patients indicated that Kt/V, as an indicator of the dialysis dose, was independently associated with the risk of cancer death, even after adjusting for potential confounders. A cubic spline analysis showed that the relationship was almost linear, and the risk increased significantly when the Kt/V was lower (around 1.6). These findings suggest that removing uremic toxins by optimal modification of the dialysis dose may help prevent future cancer death among patients undergoing HD.

The randomized Hemodialysis (HEMO) Study compared

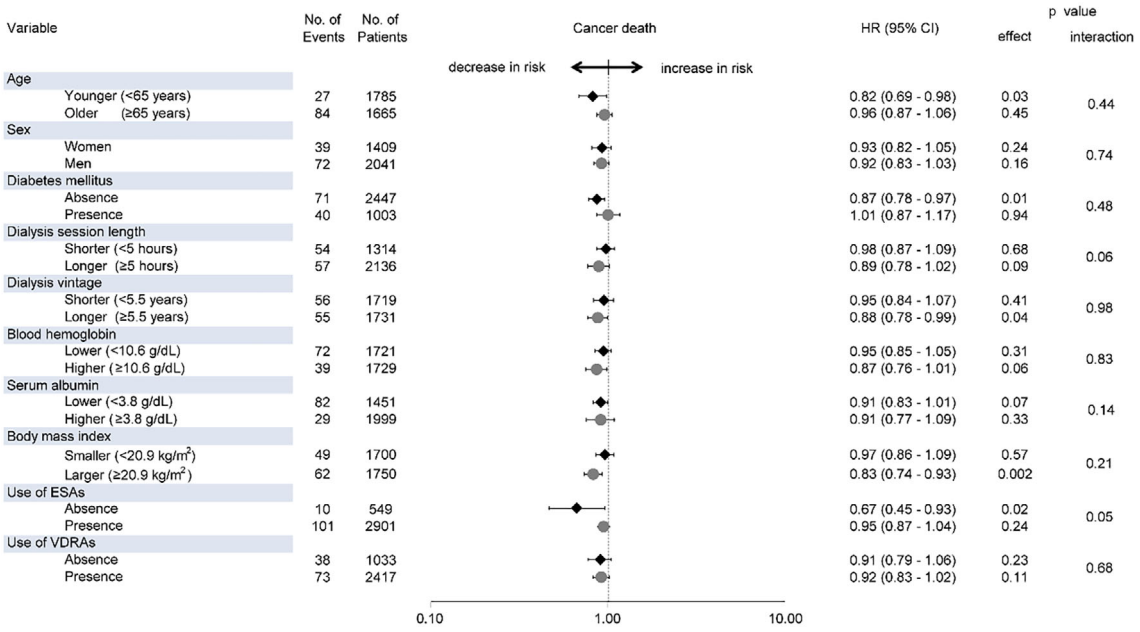

Figure 3. Multivariable-adjusted hazard ratios and 95% confidence intervals for cancer death for every 0.1 increase in Kt/V level in subgroups stratified according to the baseline characteristics and treatment. The multivariable-adjusted model was adjusted for the age, sex, diabetes mellitus, dialysis vintage, dialysis session length, body mass index, hemoglobin level, serum albumin, serum total cholesterol, serum C-reactive protein, serum ferritin, normalized protein catabolic rate, and use of erythropoiesis-stimulating agents and vitamin D receptor activators. Gray circles and filled rhombi denote point estimates of the hazard ratio, and error bars represent 95% confidence intervals. Results were adjusted using the final selected model. Variables relevant to the subgroups were excluded from each model. Two-tailed p<0.05 was considered statistically significant.

the prognoses of patients receiving a high dialysis dose (target spKt/V approximately 1.65) and a standard dialysis dose (target spKT/V approximately 1.25) and showed no significant differences in all-cause, cardiovascular, or infection-related deaths (18). However, this previous study described different dialysis conditions from those in Japan and did not examine the specific relationship between the dialysis dose and cancer death. Another previous observational study reported that the risk of cancer death increased when Kt/V was <1.6 (10), which agreed with the current results, although the mechanism was not shown. In contrast, another study reported no association between cancer death and the Kt/V levels (13). Although the reason for this discrepancy is not clear, it may be related to the limited statistical power of the analyses due to the small number of cancer deaths. An increasing Kt/V might be expected to reduce the mortality rate (12, 13, 19, 20), as an adequate dialysis dose might improve subclinical uremia by removing uremic toxins (13).

Uremic toxins are known risk factors for cancer in patients undergoing HD (21, 22). Urea, as one such toxin, has been reported to impair the intestinal barrier function and alter the microbial flora, causing dysbiosis (23, 24), which has in turn demonstrated an important role in the initiation and progression of some kinds of cancer (25). Dysbiosis might modulate the risks of cancer development and progression by enhancing the production of protumor inflammatory mediators [such as tumor necrosis factor-α, interleukin (IL)-6, IL-1β, and IL-23] and genotoxic reactive oxygen species, damaging DNA and inducing chromosomal instability, and promoting cell proliferation (26). Furthermore, butyrate has shown anti-tumorigenic and anti-proliferative effects due to its regulation of genes that inhibit cell proliferation and induce apoptosis via histone deacetylase inhibition (27). Butyrate-producing bacteria are decreased in dysbiosis, which may also contribute to the increased risks of cancer development and progression. The current findings support a role for urea (which uses spKt/V as an index for removal) in cancer development and progression, and some strategies aimed at lowering urea levels might improve dysbiosis in patients with advanced chronic kidney disease (CKD) (24). Increasing the removal of urea by increasing Kt/V might thus improve the dysbiosis status and reduce the risk of cancer progression.

The current subgroup analysis suggested that several factors modified the relationship between the Kt/V level and cancer death. The effect of Kt/V on the risk of cancer death tended to be lower in patients with a longer DSL (p for interaction=0.06; Fig. 3); indeed, we recently revealed that patients who underwent HD for ≥5 hours had a significantly lower risk of all-cause death than those with HD <5 hours after adjusting for confounding risk factors (28). This association between a longer DSL and lower risk of cancer death may suggest an antitumor effect of an increased dialysis dosage. In addition, the effect of Kt/V levels on reducing

the risk of cancer death was more prominent in patients without ESAs than in those receiving ESAs (p for interaction=0.05; Fig. 3). Indeed, several epidemiological studies suggested that the risk of cancer death was increased with ESA therapy (29-31), and the landmark Trial to Reduce Cardiovascular Events with Aranesp Therapy in patients with a history of malignancy found that those taking ESAs had a significantly higher risk of cancer death than those not taking ESAs (29). A recent control study also showed that ESA use was associated with an increased risk of developing a new cancer (30). There are several possible explanations for the link between ESAs and cancer risk. ESAs have been shown to increase tumor angiogenesis and growth and stimulate the tumor expression of erythropoietin receptors, which promote cancer proliferation, resulting in increased cancer death (32, 33). Our current results support the suggestion that patients without ESAs have a lower risk of cancer death than those taking ESAs.

This study had several strengths, including a large sample size and homogeneous patient characteristics in terms of cancer death. Furthermore, the data were collected prospectively.

However, the study also had several limitations. First, we were unable to adjust for some very important confounding factors such as the history of cancer, analgesic use, smoking, alcohol consumption, immunosuppressive treatment, hepatitis B or C, human papillomavirus, *Helicobacter pylori* infection, and occupation, because of a lack of data. Information on smoking status is indispensable for examining the risk for cancer. Furthermore, our finding of the highest prevalence of men in the low dialysis dose (Q1 quartile) group suggests that the prevalence of smoking is highest in this quartile. However, no significant interaction was observed between the Kt/V level and sex in relation to the risk of cancer death, suggesting that these findings might have been unchanged even if the smoking habit had been considered. Second, data on the presence or absence of cancer at the time of registration and the kinds, types, sites, and stages of cancer were also unavailable. To rule out the possibility that some malignancies may have been present before the dialysis period, we analyzed participants with longer dialysis durations. Furthermore, to reduce the effect of the presence of cancer at baseline, we also performed an analysis excluding patients who died of cancer within one year after registration. Although the difference was no longer significant due to the reduced statistical power, the tendency towards increased cancer death in patients with the lowest Kt/V remained. Third, the Kt/V values were obtained at a single time point (baseline examination), which might have caused patients to be misclassified, potentially weakening the identified association between Kt/V and the risk of cancer death, and biasing the results towards the null hypothesis. Furthermore, we were unable to obtain data of the residual kidney function when evaluating the Kt/V. However, since the average dialysis vintage was 5.5 years, there may have been little residual kidney function (RKF). In addition, the influence of the RKF is thought to have been negligible. To rule out any effect of the RKF, we analyzed participants with a relatively long dialysis duration (>2.1 years). Although the significance of the difference disappeared due to the reduced statistical power, cancer death still tended to be associated with the lowest Kt/V category. Fourth, although we obtained Kt/V data, we were unable to obtain separate pre- and post-dialysis blood urea nitrogen data and could therefore not calculate the urea reduction rate. Our results would have been more robust if we had been able to confirm the same tendency with the urea reduction rate. Fifth, this study did not examine the incidence of cancer. Although we speculated that dysbiosis induced by the low dialysis dose increased the development and progression of cancer, it is difficult to determine whether or not a low dialysis dose does indeed increase the incidence of cancer. Finally, we did not collect or analyze any microbes and/or their metabolites, which would have helped elucidate the mechanism responsible for the observed relationship.

In conclusion, our findings suggest that a lower dialysis dose might be associated with a higher risk of cancer-related death in patients undergoing HD. Kt/V is a simple indicator of the dialysis dose used in clinical practice and might be a useful modifiable factor for predicting the risk of cancer-related death in patients undergoing HD. Further basic and interventional studies are needed to confirm the apparent reduction in cancer death associated with increasing the dialysis dose in patients undergoing HD.

The authors state that they have no Conflict of Interest (COI).

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