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

Masatoshi Hara¹, Shigeru Tanaka¹,², Masatomo Taniguchi³, Kiichiro Fujisaki¹, Kumiko Torisu¹,⁴, Toshiaki Nakano¹, Kazuhiko Tsuruya⁵ and Takanari Kitazono¹

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

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-
verse events. 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−0.008x10) + (4−3.5xR) xΔV/BWpost, 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 BWpost 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 collected from the patients’ medical records. All outcomes were collected from the patients’ medical records.

**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
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 Inc., Cary, NC, 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

Table 1. Baseline Characteristics of Study Subjects.

| Variable                             | All (n=3,450) | Quartile 1 (n=856) | Quartile 2 (n=574) | Quartile 3 (n=1142) | Quartile 4 (n=878) | p for trend |
|--------------------------------------|--------------|--------------------|--------------------|--------------------|--------------------|-------------|
| Age (years)                          | 63.7 (12.8)  | 62.5 (12.5)        | 63.9 (12.5)        | 64.4 (12.8)        | 63.7 (12.3)        | 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 (days)             | 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/m²)              | 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/m²)                      | 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.

ESAs: erythropoiesis-stimulating agent, nPCR: normalized protein catabolic rate, VDRAs: vitamin D receptor activator
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        | 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 |
| Q1 (Kt/V<1.42)       | 36/856           | 1.94 (1.02-3.75) | 0.04  | -      | 1.84 (0.93-3.67) | 0.08  | -     | 1.77 (0.88-3.63) | 0.11 | -     |
| Q2 (1.42≤Kt/V<1.55)  | 20/574           | 1.90 (1.09-3.46) | 0.02  | -      | 1.82 (1.02-3.36) | 0.04  | -     | 1.89 (1.04-3.56) | 0.04 | -     |
| Q3 (1.56≤Kt/V<1.70)  | 38/1,142         | 1.00 (reference) | -     | -      | 1.00 (reference) | -     | -     | 1.00 (reference) | -   | -     |
| Q4 (Kt/V≥1.71)       | 17/878           | 1.00 (reference) | -     | -      | 1.00 (reference) | -     | -     | 1.00 (reference) | -   | -     |
| Every 0.1 increase in |                  |                  |      |         |                  |      |         |                  |      |         |
| Kt/V                 | 1.00 (reference) | 0.90 (0.84-0.97) | 0.003 | 0.90 | 0.007 (0.84-0.97) | 0.092 | 0.049 | 0.85 (0.85-0.99) | 0.049 | 0.99 |

*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.

| Cancer death | Age- and sex-adjusted model | Multivariable-adjusted model* |
|--------------|-----------------------------|-------------------------------|
| No of events/| HR (95% CI) | p value | p for trend | HR (95% CI) | p value | p for trend |
| No of patients | | | | | | |
| All | 862/2,605 | 2.50 (1.23-5.09) | 0.01 | 0.003 | 1.92 (0.87-4.24) | 0.11 | 0.18 |
| Q1 (Kt/V<1.42) | 24/543 | 1.89 (0.89-4.00) | 0.10 | - | 1.67 (0.76-3.67) | 0.20 | - |
| Q2 (1.42≤Kt/V<1.56) | 16/432 | 1.86 (0.98-3.53) | 0.06 | - | 1.70 (0.87-3.32) | 0.12 | - |
| Q3 (1.56≤ Kt/V<1.71) | 31/909 | 1.00 (reference) | - | - | 1.00 (reference) | - | - |
| Q4 (Kt/V ≥1.71) | 15/721 | 0.87 (0.40-1.89) | 0.003 | 0.90 (0.45-1.79) | 0.04 | - |
| 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
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

| Variable                  | No. of Events | No. of Patients | Cancer death | HR (95% CI) | P-value | Interaction |
|---------------------------|---------------|-----------------|--------------|-------------|---------|-------------|
| Age                       |               |                 |              |             |         |             |
| Younger (<65 years)       | 27            | 1785            |              |             |         |             |
| Older (≥65 years)         | 84            | 1855            |              |             |         |             |
| Sex                       |               |                 |              |             |         |             |
| Women                     | 39            | 1439            |              |             |         |             |
| Men                       | 71            | 2041            |              |             |         |             |
| Diabetes mellitus         |               |                 |              |             |         |             |
| Absent                    | 71            | 2447            |              |             |         |             |
| Presence                  | 40            | 1003            |              |             |         |             |
| Dialysis session length   |               |                 |              |             |         |             |
| Shorter (<5 hours)        | 54            | 1314            |              |             |         |             |
| Longer (≥5 hours)         | 57            | 2136            |              |             |         |             |
| Dialysis vintage          |               |                 |              |             |         |             |
| Shorter (<5 years)        | 56            | 1719            |              |             |         |             |
| Longer (≥5 years)         | 55            | 1731            |              |             |         |             |
| Blood hematocrit          |               |                 |              |             |         |             |
| Lower (<0.5 g/dL)         | 72            | 1721            |              |             |         |             |
| Higher (≥0.5 g/dL)        | 39            | 1729            |              |             |         |             |
| Serum albumin             |               |                 |              |             |         |             |
| Lower (<3 g/dL)           | 82            | 1451            |              |             |         |             |
| Higher (≥3 g/dL)          | 29            | 1939            |              |             |         |             |
| Body mass index           |               |                 |              |             |         |             |
| Smaller (<20 kg/m²)       | 49            | 1700            |              |             |         |             |
| Larger (≥20 kg/m²)        | 62            | 1750            |              |             |         |             |
| Use of ESA                |               |                 |              |             |         |             |
| Absence                   | 15            | 549             |              |             |         |             |
| Presence                  | 101           | 2901            |              |             |         |             |
| Use of VDRA               |               |                 |              |             |         |             |
| Absence                   | 38            | 1033            |              |             |         |             |
| Presence                  | 73            | 2417            |              |             |         |             |

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 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 quintile. 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).**

**Acknowledgement**

We would like to express our appreciation to the participants in the Q-Cohort Study, and members of the Society for the Study of Kidney Disease. The following personnel (institutions) participated in the study: Takashi Ando (Hakozaki Park Internal Medicine Clinic), Takashi Ariyoshi (Ariyoshi Clinic), Koichiro Goto (Goto Clinic), Fumitada Hattori (Nagao Hospital), Harumichi Higashi (St Mary’s Hospital), Tadasu Hirano (Hakujuji Hospital), Kei Hori (Munakata Medical Association Hospital), Takashi Inenaga (Ekisaikai Moji Hospital), Hitodoshi Kanai (Kokura Memorial Hospital), Shigemi Kiyama (Kiyama Naika), Tetsuo Komota (Komota Clinic), Hiromasa Kuma (Kuma Clinic), Toshiro Maeda (Kozenkai-Maeda Hospital), Junichi Makino (Makino Clinic), Dai Matsuo (Hirao Clinic), Chiaki Miishima (Miishima Clinic), Koji Mitsuki (Japanese Red Cross Fukuoka Hospital), Kenichi Motomura (Motomura Naika Clinic), Sadatoshi Nakamura, Hitodoshi Nakamura (Kokura Daiichi Hospital), Koichi Nakashima (Ohashi Internal Circulatory Clinic), Nobumitsu Okita (Shiroishi Kyoritsu Hospital), Shinichiro Osato (Osato Jin Clinic), Sakura Sakamoto (Fujiyamato Spa Hospital), Keiko Shigematsu (Shigematsu Clinic), Kazumasa Shimamatsu (Shimamatsu Naika Iin), Yoshito Shogakuchi (Shin-Ai Clinic), Hiroaki Takamura (Hara Hospital), Kazuhiro Takeda (Izuka Hospital), Asuka Terai (Chidoribashi Hospital), Hideyoshi Tanaka (Mojiko-Jin Clinic), Suguru Tomooka (Hakozaki Park Internal Medicine Clinic), Jiro Toyonaga (Fukuoka Renal Clinic), Hiroaki Tsuruta.
(Steel Memorial Yawata Hospital), Rytaro Yamaguchi (Shiseikai Hospital), Taihei Yanagida (Saiseikai Yahata General Hospital), Tetsuro Yanase (Yanase Internal Medicine Clinic), Tetsuhiko Yoshida (Hamamomachi Hospital), Takahiro Yoshimitsu (Gofuku-machi Kidney Clinic, Harasanshin Hospital), and Koji Yoshitomi (Yoshitomi Medical Clinic). We also thank Edanz Group (www.edanzediting.com/ac) for editing English drafts of our manuscript.

**FUNDING**
This study was supported by the Kidney Foundation (H19 JKFB 07-13, H20 JKFB 08-8, H23 JKFB 11-11) and the Japan Dialysis Outcome Research Foundation (H19-076-02, H20-003). The funders of this study had no role in the study design; collection, analysis, and interpretation of data; writing the report; or decision to submit the report for publication.

**References**

1. Maisonneuve P, Agodoa L, Gellert R, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 354: 93-99, 1999.
2. Lin HF, Li YH, Wang CH, Chou CL, Kuo DJ, Fang TC. Increased risk of cancer in chronic dialysis patients: a population-based cohort study in Taiwan. Nephrol Dial Transpl 27: 1585-1590, 2012.
3. Wakasugi M, Kazama JJ, Yamamoto S, Kawanura K, Narita I. Cause-specific excess mortality among dialysis patients: Comparison with the general population in Japan. Ther Apher Dial 17: 299-304, 2013.
4. Vogelzang JL, van Stralen KJ, Noordzij M, et al. Mortality from infections and malignancies in patients treated with renal replacement therapy: Data from the ERA-EDTA registry. Nephrol Dial Transplant 30: 1028-1035, 2015.
5. United States Renal Data System 2012 Annual Data Report. Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States. Am J Kidney Dis 61 (1 Suppl1): A7, e1-e476, 2013.
6. Masakane I, Nakai S, Ogata S, et al. An Overview of Regular Dialysis Treatment in Japan. Ther Apher Dial 19: 540-574, 2015.
7. Pruthi R, Steenkamp R, Feest T. UK Renal Registry 16th annual report: chapter 8 survival and cause of death of UK adult patients on renal replacement therapy in 2012: national and centre-specific analyses. Nephron Clin Pract 125: 139-169, 2013.
8. Holley JL. Screening, diagnosis, and treatment of cancer in long-term dialysis patients. Clin J Am Soc Nephrol 2: 604-610, 2007.
9. Janus N, Thyss A, Boulanger H, Dray G, Launay-Vacher V. Management of anticancer treatment in patients under chronic dialysis: results of the multicentric CANDY ( CANcer and DialYsis ) study. Ann Oncol 24: 501-507, 2013.
10. Charra B, Calendard E, Ruffet M, et al. Survival as an index of adequacy of dialysis. Kidney Int 41: 1286-1291, 1992.
11. Shinzato T, Nakai S, Akiba T, et al. Survival in long-term haemodialysis patients: results from the annual survey of the Japanese Society for Dialysis Therapy. Nephrol Dial Transplant 12: 884-888, 1997.
12. Kimata N, Karaboyas A, Bieber BA, et al. Gender, low Kt / V, and mortality in Japanese hemodialysis patients: Opportunities for improvement through modifiable practices Data source. Hemodial Int 18: 596-606, 2014.
13. Bloembergen WE, Stannard DC, Port FK, et al. Relationship of dose of hemodialysis and cause-specific mortality. Kidney Int 50: 557-565, 1996.
14. Yotsuwa R, Taniguchi M, Tanaka S, et al. Cardiovascular and All-Cause Mortality and Cardiovascular Disease Events in Hemodialysis Patients: The Q-Cohort Study. Am J Kidney Dis 70: 84-92, 2017.
15. Tanaka S, Ninomiya T, Taniguchi M, et al. Comparison of oral versus intravenous vitamin D receptor activator in reducing infection-related mortality in hemodialysis patients: the Q-Cohort Study. Nephrol Dial Transplant 31: 1152-1160, 2016.
16. Eriguchi R, Taniguchi M, Ninomiya T, et al. Hyporesponsiveness to erythropoiesis-stimulating agent as a prognostic factor in Japanese hemodialysis patients: the Q-Cohort study. J Nephrol 28: 217-225, 2015.
17. Daugirdas JT. The post: pre dialysis plasma urea nitrogen ratio to estimate Kt/V and NPCR: validation. Int J Artif Organs 12: 420-427, 1989.
18. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 347: 2010-2019, 2002.
19. Bloembergen WE, Hakim RM, Stannard DC, et al. Relationship of dialysis membrane and cause-specific mortality. Am J Kidney Dis 33: 1-10, 1999.
20. Maduell F, Ramos R, Varas J, et al. Hemodialysis patients receiving a greater Kt dose than recommended have reduced mortality and hospitalization risk. Kidney Int 90: 1332-1341, 2016.
21. Mandayam S, Sahinian VB. Are chronic dialysis patients at increased risk for cancer? J Nephrol 21: 166-174, 2008.
22. Kita Y, Matsubara T, Funakoshi T, Horimitsu T, Muto M, Yanagita M. Cancer screening and treatment in patients with end-stage renal disease: remaining issues in the field of oncophrology. Ren Replace Ther 2: 33, 2016.
23. Vaziri ND, Norris K. Role of Urea in Intestinal Barrier Dysfunction and Disruption of Epithelial Tight Junction in Chronic Kidney Disease. American J Nephrol 37: 1-6, 2013.
24. Vaziri ND, Zhao YY, Pahl MV. Altered intestinal microbial flora and impaired epithelial barrier structure and function in CKD: The nature, mechanisms, consequences and potential treatment. Nephrol Dial Transplant 31: 737-746, 2016.
25. Shefflin AM, Whitney AK, Weir TL. Cancer-promoting effects of microbial dysbiosis. Curr Oncol Rep 16: 406, 2014.
26. Zitvogel L, Galluzzi L, Vialud S, et al. Cancer and the gut microbiota: An unexpected link. Sci Transl Med 21:7 (271): 271ps1, 2015.
27. Hague A, Elder DJ, Hicks DJ, Paraskeva C. Apoptosis in colorectal tumour-cells—induction by the short-chain fatty-acids butyrate, propionate and acetate and by the bile-salt deoxycholate. Int J Cancer 60: 400-406, 1994.
28. Fujisaki K, Tanaka S, Taniguchi M, et al. Study on Dialysis Session Length and Mortality in Maintenance Hemodialysis Patients: The Q-Cohort Study. Nephron 139: 305-312, 2018.
29. Pfeffer MA, Burdmann EA, Chen CY, et al. A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease. N Engl J Med 361: 2019-2032, 2009.
30. René É, Lazrak HH, Laurin LP, Elftouh N, Vallée M, Lafrance JP. Association of erythropoiesis-stimulating agents and the incidence risk of cancer diagnosis among chronic dialysis patients: a nested case-control study. Nephrol Dial Transplant 32: 1047-1052, 2017.
31. Bohlius J, Schmidlin K, Brillant C, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. Lancet 373: 1532-1542, 2009.
32. Cao Y. Erythropoietin in cancer: A dilemma in risk therapy. Trends Endocrinol Metab 24: 190-199, 2013.
33. Chon KK, Matchett KB, Coulter JA, et al. Erythropoietin drives breast cancer progression by activation of its receptor EPOR. Oncotarget 8: 38251-38263, 2017.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/)
