Frailty in patients on dialysis surviving for more than 40 years is common and severe: A nationwide cross-sectional study

Suguru Yamamoto[1#*], Kakuya Niihata[2#], Tatsunori Toida[3#], Masanori Abe[4], Norio Hanafusa[5], Noriaki Kurira[2, 6]

[1]Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.

[2]Department of Clinical Epidemiology, Graduate School of Medicine, Fukushima Medical University, Fukushima City, Japan.

[3]School of Pharmaceutical Sciences, Kyushu University of Health and Welfare, Miyazaki, Japan.

[4]Division of Nephrology, Hypertension and Endocrinology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan.

[5]Department of Nephrology, Tokyo Women's Medical University, Tokyo, Japan.

[6]Department of Innovative Research and Education for Clinicians and Trainees (DiRECT), Fukushima Medical University Hospital, Fukushima, Japan.

[#]These authors contributed equally to the manuscript.

[*]**Corresponding author:**

Suguru Yamamoto

Division of Clinical Nephrology and Rheumatology

Niigata University Graduate School of Medical and Dental Sciences

1-757 Asahimachi-dori, Niigata, 951-8510, Japan

E mail: yamamotos@med.niigata-.ac.jp

Tel: +81-25-227-2200 FAX: +81-25-227-0775

Abstract

Background

The number of patients with end-stage kidney disease (ESKD) with prolonged dialysis is increasing. Recently, the Japan Society for Dialysis Therapy (JSDT) survey reported that there were patients who had been undergoing dialysis for ≥40 years. Herein, we examined the clinical pathophysiology of such patients, and the association between dialysis vintage and frailty. Moreover, we also analyzed the association between dialysis vintage and bedridden status.

Methods

This cross-sectional study used data from the JSDT Renal Data Registry database. The analysis included data of 227,136 patients aged > 50 years who underwent dialysis in 2018. Dialysis vintage exposure was categorized as: 0–<5, 5–<10, 10–<20, 20–< 30, 30–<40, and >40 (40–) years. The primary and secondary outcomes were frailty and being bedridden, which were defined as ≥grade 2 and grade 4 on the Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale, respectively. Modified Poisson regression models adjusted for potential covariates were used to estimate the adjusted prevalence ratios (aPRs) for frailty and bedridden status. Clinical characteristics of patients undergoing dialysis for > 40 years were also described.

Findings

A total of 809 (0.4%) patients with ESKD had undergone dialysis for ≥40 years. Individuals belonging to this group were malnourished and had a frequent history of fractures and carpal tunnel syndrome. The prevalence of frailty was highest in the 40–

years group (54.6%). Similarly, the prevalence of being bedridden was also highest in this group (9.9%). Dialysis vintage (40- years vs. 0-<5 years) was associated with increased frailty (aPRs [95% confidence intervals]:2.40 [2.24-2.57]), and bedridden status (aPRs [95% confidence intervals]:2.09 [1.68-2.59]).

Interpretation

This large nationwide study revealed an association between dialysis vintage and frailty in patients undergoing dialysis. Long-term dialysis therapy, particularly for more than 40 years, may accelerate the decline in physical function, probably due to unmeasured dialysis-related factors.

Fundings

This study did not receive any funding.

Research in context

Evidence before this study

The number of patients with end-stage kidney disease (ESKD) with an extended history of dialysis has been increasing steadily. Recently, a survey conducted by the Japan Society for Dialysis Therapy revealed that there were patients who had been undergoing dialysis for ≥40 years. To gather relevant information, we conducted a thorough search on PubMed database using the keywords "dialysis (title and abstract)" and "frailty (title and abstract),". The search focused on studies published in English language from the inception of the database up to September 20, 2023. A meta-analysis examining frailty in patients undergoing hemodialysis revealed an association between average age, but not dialysis vintage, and an increased prevalence of frailty. A study involving kidney transplant recipients found a relationship between duration of dialysis before transplantation and development of frailty. However, this association was only observed in patients with less than 20 years of dialysis experience.

Added value of this study

This study investigated the clinical pathophysiology of Japanese patients who underwent dialysis for ≥40 years. We explored the connection of dialysis vintage with frailty and being bedridden using a comprehensive nationwide study in Japan. Our findings revealed that 809 patients with ESKD had undergone dialysis for ≥40 years. Frailty was most prevalent in the group with dialysis vintage ≥40 years (54.6%). Similarly, the prevalence of being bedridden (9.9%) was also the highest in this group. Notably, we established a significant association of dialysis vintage with an increased likelihood of frailty and bedridden status.

Implications of all the available evidence

This large nationwide study revealed an association between dialysis vintage and frailty in patients undergoing dialysis. Long-term dialysis therapy, particularly for those with dialysis vintage ≥40 years, may accelerate the decline in physical function, probably due to unmeasured dialysis-related factors.

Introduction

There has been an increase in the number of long-term dialysis patients with end-stage kidney disease (ESKD) as a result of reduction in the mortality rate due to advances in dialysis treatment.[1-4] Although it is a desirable achievement, it results in wasting and physical functioning decline in patients. While some patients lead independent lives,[5] others experience a marked decline in physical function due to joint pain and destructive spondyloarthropathy associated with the long-term uremic milieu.[6,7] Frailty is a clinical syndrome characterized by increased vulnerability and lack of functional reserve over time.[8] It has been highlighted as a risk factor for hospitalization and death among patients with ESKD.[9,10] Pathophysiological mechanisms of frailty in patients with ESKD may include wasting and uremic complications.[9,10] However, the effect of dialysis duration is not well understood.

A meta-analysis of frailty among hemodialysis patients showed an association between mean age and increased frailty, but failed to show an association with mean dialysis duration.[10] However, this finding was based on meta-regression and not analyzed at an individual level. A study on kidney transplant recipients reported that the duration of dialysis before transplantation was associated with frailty.[11] However, this association was only supported up to <20 years of dialysis. On the other hand, according to a survey by the Japanese Society for Dialysis Therapy (JSDT), the number of patients on dialysis for more than 20 years has been increasing over the years. The survey revealed that one in 12 (8.6%) patients was on dialysis for ≥20 years as of 2021, and that 1386 patients had been on dialysis for ≥40 years.[12] Information regarding changes in physical function related to long-term dialysis is particularly pertinent for younger patients commencing dialysis as they aim to adequately prepare themselves to

attain and sustain what matters to them throughout their course of life while undergoing dialysis therapy. Thus, understanding the clinical presentation of patients with ESKD with ultra-long dialysis vintage is required. Moreover, examining the association between dialysis vintage and frailty would reveal issues that need to be resolved for better dialysis care.

In this study, we examined the clinical pathophysiology of Japanese dialysis patients on dialysis for ≥40 years and the association between dialysis vintage and frailty using the JSDT Renal Data Registry (JRDR) database. Moreover, we also analyzed the association between dialysis vintage and bedridden status.

Methods

Study design and participants

This cross-sectional study used data from the JRDR database, which includes anonymized data of patients undergoing dialysis. The database comprises information retrieved by the JSDT from almost all the dialysis facilities in Japan at the end of each year. Details of the JRDR have been described previously.[1] For this study, we used the dataset of patients registered in 2018. However, the patient data set of 2018 did not include data on vascular access type and β_2-microglobulin (β2MG). Therefore, data for these variables were used from the 2017 data set. According to the JSDT, the response rate of patients' survey-questionnaires in 2018 was 94.7% from 4222 of 4458 facilities distributed nationwide.[1] Patients were excluded according to the following exclusion criteria: 1) treatment with peritoneal dialysis alone or an unknown treatment status in 2018, 2) age <50 years, and 3) absence of exposure and outcome data. The reason for excluding individuals <50 years of age was that our interest was dialysis vintage for primary exposure, and for this they

should have been alive for at least the longest vintage in our dataset, which was 49 years. We changed the values of the considered outliers to missing values. The investigators (SY, KN, TT, and NK) discussed and finalized the criteria to judge the ranges of outliers according to the clinical expertise and previous study,[13] as follows: 1) serum phosphorus <0.5 mg/dL, 2) height < 80 cm or >200 cm, 3) body weight <20 kg or >150 kg, 4) serum creatinine <3.0 mg/dL or >20 mg/dL, 5) blood urea nitrogen <10 mg/dL or >250 mg/dL, 6) single pool Kt/V <0.5 or >4.0, 7) β2MG <5.0 mg/dL or >100 mg/dL, 8) serum albumin <0.5 mg/dL or >5.0 mg/dL, 9) serum C-reactive protein >50 mg/dL, 10) hemoglobin <5.0 g/dL or 20 g/dL, and 11) normalized protein catabolic rate <0.3 g/kg/day or 2.0 g/kg/day.

Ethical considerations

The JRDR survey was conducted in accordance with the Japanese Ethical Guidelines for Epidemiological Studies published by the Ministry of Education, Science and Culture, and the Ministry of Health, Labor, and Welfare.[14] The study protocol was approved by the Ethics Committee of the JSDT (Approval No.68) and the study was conducted in accordance with the tenets of Declaration of Helsinki. The need for informed consent was waived as the data contained no identifying personal information.

Exposure and outcome

The exposure was dialysis vintage, which was categorized as: 0-<5, 5-<10, 10-<20, 20-<30, 30-<40, and ≥40 years. The primary outcome was prevalence of frailty, which was defined as ≥grade 2 on the Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale.[15,16] Grade 2 is considered a level of functional disability that precludes light work and requires occasional assistance, and has been used as an indicator of frailty

in another study.[17] The secondary outcome was bedridden status, which was defined as Grade 4 on the ECOG PS scale.

Covariates

Covariates were defined as variables considered to be determinants of dialysis vintage and functional disability. These were identified based on the evidence from literature and clinical expertise through discussions among the investigators (SY, KN, TT, and NK). We selected minimally sufficient covariates to estimate the total effects of dialysis duration on functional disability using the established analysis rule with the Dagitty web application (www.dagitty.net) on the basis of the directed acyclic graph model.[18,19] The following variables were selected as covariates: age, sex, types of vascular access, serum albumin, corrected serum calcium, serum phosphorus, intact parathyroid hormone (PTH), β2MG and creatinine index, and history of diabetes, dementia, ischemic heart disease, cerebral hemorrhage, cerebral infarction, limb amputation, carpal tunnel syndrome (CTS), and hip fracture.

Corrected serum calcium was calculated as follows:

Corrected serum calcium = serum calcium + (4- serum albumin), if serum albumin was <4 mg/dl.

Furthermore, the creatinine index, which is considered the muscle mass in patients undergoing hemodialysis, was calculated according to a previous report,[20] as follows:

Creatinine index = 16.21+1.12×sex (0 if female and 1 if male) -0.06×age (years) -0.08×single pool Kt/V+0.009×88.4×serum creatinine (mg/dL).

Construction of statistical models using these covariates is described below in the sub-section of statistical analysis. The serum levels of corrected calcium, phosphorus and intact PTH were categorized into three categories, according to the JSDT guideline,[21] as follows: <8.4 mg/dL, 8.4-10.0 mg/dL, 10.0< mg/dL for corrected calcium; <3.5 mg/dL, 3.5-6.0 mg/dL, 6.0< mg/dL for phosphorus; and <60 pg/mL, 60-240 pg/mL, 240 pg/mL< for intact PTH.

Statistical analysis

For descriptive statistics, continuous variables were summarized as medians (interquartile ranges), and categorical variables as frequencies and percentages. To examine the total effects of dialysis vintage and outcomes, we estimated prevalence ratios (PRs) using fitting modified Poisson regression models.[22] The rationale for this model is that using odds ratios overestimates the PRs due to the high prevalence of primary outcome. Model 1 included both age and sex. Model 2 included the levels of corrected serum calcium, serum phosphorus, intact PTH, and β2MG, in addition to the covariates used in model 1. Model 3 included the levels of serum albumin and creatinine index along with history of diabetes, dementia, cerebral hemorrhage, cerebral infarction, and limb amputation, in addition to the covariates used in Model 2. Moreover, we estimated the partial effects of dialysis vintage independent of the effects of hip fracture, CTS, and vascular access type, which were considered as intermediate variables in the relationship between dialysis vintage and functional disability. To estimate this partial effect, Model 4 included a history of hip fracture, CTS, and types of vascular access, in addition to the covariates in Model 3. Missing values were imputed using a multiple imputation method, creating 30

datasets by conditional chained equations, and combining them according to Rubin's rule.[23] Statistical significance was set at P<0.05. All analyses were performed using STATA (version 14, Stata LP, College Station, TX, USA).

Sensitivity analysis

To determine robustness, we conducted sensitivity analysis of two different populations. First, we conducted the same analysis as described above for all patients, excluding those whose dialysis vintage was < 1 year from the population for primary analysis. Moreover, we also performed the abovementioned analysis for patients who had never been treated with peritoneal dialysis from the population for primary analysis, wherein we excluded patients treated with peritoneal dialysis alone in 2018.

Results

Patient characteristics

A total of 319,967 patients aged ≥20 years who underwent hemodialysis were identified (Figure 1). Patients aged <50 years (n=26,009) and those with missing exposures and outcomes (n=66,822) were excluded. Eventually, 227,136 patients were included in the analysis.

Patient characteristics are presented in Table 1. The mean age of the study population was 71 years, and the mean age at the time of dialysis initiation was 65 years. Among the patients, 64.8% were men, 52.9% had diabetes, 3.8% had undergone limb amputation, 5.5% had a history of hip fractures, and 11.6% had dementia. The mean dialysis vintage was 7.5 years, and the median (interquartile range) was 5 (2-10) years. The longest dialysis vintage was 49 years. The dialysis vintage was divided into six categories (0-<5

years [n =105142, 46.3%]; 5-<10 years [n =56956, 25.1%]; 10-<20 years [n =45192, 19.9%]; 20-< 30 years [n =14336, 6.3%]; 30-<40 years [n =4701, 2.1%]; 40- years [n =809, 0.4%]).

The mean age of patients with a dialysis vintage of > 40 years was 68 years, and the mean age at the time of dialysis initiation was 26 years. Among the patients, 50.1% were men, 6.0% had diabetes, 5.9% had undergone limb amputation, 13.2% had a history of hip fractures, and 2.8% had dementia. A total of 25.5% of the patients had non-arteriovenous fistulas, i.e., 17.2% had arteriovenous grafts, 4.7% had superficialized arteries, and 3.3% had long-term catheters.

Patients with dialysis vintage < 40 years were older for commencing dialysis, more likely to be male, more likely to have higher body mass index (BMI) and increased prevalence of diabetes and dementia. They had a lower prevalence of history of hip fractures and CTS.

These characteristics were similar to the target age group being expanded to ≥20 years (Supplemental table 1).

Association of dialysis vintage with frailty

Frailty was most common among individuals with dialysis vintage >40 years (54.6%). The correlation between dialysis vintage and frailty status are presented in Table 2. In the age- and sex-adjusted model (Model 1), the PRs were significantly higher in the other categories than in the reference category (0–<5 years). The greatest PR was observed in the 40- years category (PR [95% confidence interval (CI)] 2.40 [2.25-2.56]), followed by the 30–<40 years category (PR [95% CI] 1.46 [1.40-1.52]). In Model 2, the greatest PR was observed in the 40- years category, similar to model 1. However, the 20-< 30 years

category had statistically significant lower PRs. In Model 3, the PRs (95% CI) were 1.07 (1.06-1.09), 1.11 (1.09-1.13), 1.16 (1.13-1.19), 1.63 (1.57-1.70), and 2.40 (2.24-2.57) for 5-<10, 10-<20, 20-< 30, 30-<40, 40- years categories, respectively (Figure 2). These results were similar to those of Model 4.

Association between dialysis vintage and bedridden status

Bedridden status was most common in patients belonging to the 40 years group (9.9%). The correlations between dialysis vintage and bedridden status are presented in Table 3. In Model 1, compared to the reference category (0–<5 years), PRs were significantly higher in other categories, except for the 20-< 30 years category. The greatest PR was observed in the 40- years category (PR [95% CI] 2.25 [1.83-2.78]). In Model 2, PRs were significantly higher in the 10-<20 years, 30-<40 years, and 40 years categories (PR [95% CI] 1.06 [1.01-1.10], 1.14 [1.01-1.28], and 1.92 [1.55-2.37], respectively) and significantly lower in the 20-< 30 years category (PR [95% CI] 0.85 [0.79-0.92]). In Model 3, the PRs were significantly higher for the reference category. The PRs (95% CI) were 1.17 (1.13-1.22), 1.26 (1.20-1.31), 1.14 (1.06-1.23), 1.42 (1.27-1.60), and 2.09 (1.68-2.59) for 5-<10, 10-<20, 20-< 30, 30-<40, 40- years categories, respectively (Figure 3). These results were similar to those of model 4.

Sensitivity analysis

Patients with dialysis vintage < 1 year were excluded from the primary analysis. Furthermore, the patients were limited to those who had never been treated with peritoneal dialysis from the population for primary analysis, wherein we excluded patients treated using peritoneal dialysis alone in 2018. Associations of dialysis vintage

with frailty status (Supplemental figure 1) and bed-ridden status (Supplemental figure 2) were similar to those in the primary analysis.

Discussion

This study investigated the association between dialysis vintage and frailty, focusing specifically on patients with dialysis vintage exceeding 40 years. We showed that more than half of these patients were frail and that the adjusted prevalence of frailty or being bedridden was more than two-fold.

Clinical features of patients with dialysis vintage >40 years were characterized by younger age at the time of dialysis initiation, primary kidney disease dominated by chronic glomerulonephritis, fewer cardiovascular complications and less incidence of dementia, more dialysis-related amyloidosis, and poorer nutritional indices. These distinct clinical features suggest difficulties in achieving long-term dialysis for >40 years in patients with diabetes, ischemic heart disease, or cerebrovascular disease. This less frequent vascular complication is consistent with autopsy findings of mild aortic calcification among patients with ESKD who underwent dialysis for >40 years.[7,24]

Considering the survival advantage of arteriovenous fistulas in patients undergoing hemodialysis,[25] the paucity of AV fistulas in this population indicates that they may experience multiple vascular access failures during long-term dialysis and require vascular access reconstruction using other access points than AV fistulas.

Relatively low BMI, albumin, and creatinine indices suggest that protein energy wasting (PEW) results from reduced dietary intake and factors associated with long-term dialysis.

Demonstration of the association of prolonged dialysis duration, especially >40 years, with a two-fold increase in frailty and bedridden status could serve as useful prognostic information for dialysis treatment decision-making and pose further questions about the mechanisms of frailty as a complication associated with long-term dialysis.

First, both the dialysis providers and patients with ESKD should not only consider the pre-treatment physical functioning, but also the expected physical functioning, if dialysis is to be continued for an extended period. These considerations are particularly important in younger patients. Awareness of not only the expected life expectancy, but also the changes in physical function resulting from long-term dialysis, may help patients and their caregivers plan and realize their valuable life plans.

Second, the dose-response relationship between long-term dialysis and frailty suggests the existence of unmeasured or unknown and unresolved factors that potentially affect patients' physical function during the course of long-term dialysis. This idea is supported by the fact that the magnitude of association remained unchanged after adjusting for intermediate factors, such as CTS and hip fracture. The increased risk of frailty with long-term dialysis, which is independent of CTS and high β2MG, may to some extent be associated with progressive amyloidosis due to unmeasured β2MG accumulation. For example, destructive spondyloarthropathy, a phenotype of dialysis-related amyloidosis, has also been reported to be common in patients who undergo long-term dialysis,[6,7] which may contribute to frailty. Unlike dialysis-related amyloidosis, uremic toxins that are poorly removed even with current dialysis therapies may contribute to frailty.[26] In particular, indoxyl sulfate, a protein-bound uremic toxin,[27]

has been reported to cause a decline in muscle mass by impairing mitochondrial function in muscle cells.[28]

Third, other nutritional disturbances may mediate the influence of long-term dialysis on frailty and bedridden status, although this is independent of the clinical phenotypes of PEW, such as low albumin level and low creatinine index. For example, dysgeusia and poor dietary intake can contribute to PEW and may also contribute to frailty independent of PEW.

This study has several strengths. First, using nationwide registry data covering almost all the Japanese dialysis facilities enabled us to ensure sufficient power to demonstrate associations between frailty and prolonged dialysis duration, including a large number of patients who underwent long-term dialysis for ≥40 years. In addition, we were able to build models while considering important confounding (age and nutritional status) and intermediate factors (CTS, hip fracture, and vascular access type), and thus provide analytical results that are necessary to discuss the mechanisms of frailty and bedridden status associated with long-term dialysis. This study also had a few limitations that need to be taken into consideration. First, due to the cross-sectional study design, we could not establish a causal relationship between dialysis duration and frailty or bedridden status. However, it is biologically implausible that frailty confers long-term continuation of dialysis. Second, frailty and bedridden were defined using the ECOG PS scale.[29] However, given the characteristics of a nationwide registry including more than two hundred thousand participants, we believe that this scale is a feasible and practical instrument for assessing frailty in these participants. Third, long-term dialysis patients may have fewer unmeasured comorbidities (e.g., heart failure and malignant disease) in comparison to short-term dialysis patients due to survival bias. However, the

failure to adjust for these unmeasured factors underestimated the association between dialysis duration and frailty, indicating that the association shown in the current study could be more robust. Fourth, since serum β2MG levels and vascular access were not reported in the same year, we substituted the previous year's data. Thus, misclassification of the data may have occurred. Finally, the risk factors for frailty and being bedridden, such as vertebral fractures associated with osteoporosis, were not measured. However, since osteoporosis is unlikely to be the cause of long-term dialysis history, we do not believe that it confounds the association between long-term dialysis and frailty or being bedridden.

In conclusion, our findings suggest that dialysis vintage is associated with frailty in patients with ESKD. Long-term dialysis therapy, particularly for more than 40 years, may contribute to an accelerated decline in physical function, potentially due to unmeasured and unresolved dialysis-related factors.

Authors' contributions

Conceptualization was performed by S. Y., K. N., T. T., M. A., N. H., and N. K. Data curation and formal analyses were performed by K. N., T. T., and N. K. This study did not require funding. Investigation and methodology were performed by S. Y., K. N., T. T., and N. K. Project administration was performed by S. Y. Supervision was provided by M.A. and N.H. The original draft was written by S.Y., K.N., T.T., and N.K. Review and editing were performed by S.Y., K.N., T.T., M.A., N.H., and N.K. S.Y., K.N., T.T., and N.K. directly accessed and verified the underlying data reported in the manuscript.

Declaration of interests

S. Y. received honoraria from Kyowa Kirin, research findings from Toray Medical Co., Ltd, and Kaneka Medix Co., Ltd. T.T. received consulting fees from Astellas Pharma Inc., and payments for speaking and educational events from Torii Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., AstraZeneca K.K., and Nobel Pharma Co., Ltd. MA received honoraria from Kyowa Kirin Co. Ltd, Eli Lilly Japan K.K., Otsuka Pharmaceutical Co., Ltd., Bayer Yakuhin, Ltd., Astellas Pharma Inc., and Astra Zeneca K.K.. N.K. received consulting fees from GlaxoSmithKline. K.K. received payments for speaking and educational events from Taisho Pharmaceutical Co. Ltd. and Eisai Co. Ltd.. K.N, and N.H. had no declaration of interest.

Acknowledgments

We owe the completion of this survey to the efforts of the members of the subcommittee for JRDR Regional Cooperation and staff members of the dialysis facilities who participated in the survey and responded to the questionnaires.

Funding source

None

Data sharing statement

Data will be available immediately after publication with no end date. Data will be shared upon reasonable request to the corresponding author with permission from the JRDR

investigators. Restrictions apply to the availability of the data analyzed in this study to preserve patient confidentiality. Proposals should be directed to yamamots@med.niigata-u.ac.jp to gain access.

References

1. Nitta K, Goto S, Masakane I, Hanafusa N, Taniguchi M, Hasegawa T, et al. Annual dialysis data report for 2018, JSDT Renal Data Registry: survey methods, facility data, incidence, prevalence, and mortality. Renal Replacement Therapy. 2020;6:41.

2. Lai TS, Hsu CC, Lin MH, Wu VC, Chen YM. Trends in the incidence and prevalence of end-stage kidney disease requiring dialysis in Taiwan: 2010-2018. J Formos Med Assoc. 2022;121 Suppl 1:S5-S11.

3. Harding JL, Morton JI, Shaw JE, Patzer RE, McDonald SP, Magliano DJ. Changes in excess mortality among adults with diabetes-related end-stage kidney disease: a comparison between the USA and Australia. Nephrol Dial Transplant. 2022;37(10):2004-13.

4. Johansen KL, Chertow GM, Foley RN, Gilbertson DT, Herzog CA, Ishani A, et al. US Renal Data System 2020 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2021;77(4 Suppl 1):A7-A8.

5. Malgaj Vrecko M, Ponikvar R, Gubensek J, Buturovic Ponikvar J. Clinical and dialysis-related characteristics of extremely long-term hemodialysis survivors: Three case reports. Hemodial Int. 2021;25(3):E29-32.

6. Yamamoto S, Kazama JJ, Maruyama H, Nishi S, Narita I, Gejyo F. Patients undergoing dialysis therapy for 30 years or more survive with serious osteoarticular disorders. Clin Nephrol. 2008;70(6):496-502.

7. Okubo N, Suwabe T, Oba Y, Ikuma D, Mizuno H, Sekine A, et al. A Half-Century Dialysis Survivor: Clinical and Autopsy Findings. Kidney Med. 2023;5(4):100612.

8. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14(6):392-7.

9. Kennard A, Glasgow N, Rainsford S, Talaulikar G. Frailty in chronic kidney disease: challenges in nephrology practice. A review of current literature. Intern Med J. 2022.

10. Zhao Y, Liu Q, Ji J. The prevalence of frailty in patients on hemodialysis: a systematic review and meta-analysis. Int Urol Nephrol. 2020;52(1):115-20.

11. Kosoku A, Uchida J, Iwai T, Shimada H, Kabei K, Nishide S, et al. Frailty is associated with dialysis duration before transplantation in kidney transplant recipients: A Japanese single-center cross-sectional study. Int J Urol. 2020;27(5):408-14.

12. Hanafusa N AM, Joki N, Hoshino J, Wada A, Kikuchi K, Goto S, Ogawa T, Kanda E, Taniguchi M, Nakai S, Naganuma T, Hasegawa T, Miura K, Takemoto Y. 2021 Annual Dialysis Data Report, JSDT Renal Data Registry. J Jpn Soc Dial Ther. 2022;55:665-723.

13. Hoshino J, Yamagata K, Nishi S, Nakai S, Masakane I, Iseki K, et al. Significance of the decreased risk of dialysis-related amyloidosis now proven by results from Japanese nationwide surveys in 1998 and 2010. Nephrol Dial Transplant. 2016;31(4):595-602.

14. Eba J, Nakamura K. Overview of the ethical guidelines for medical and biological research involving human subjects in Japan. Jpn J Clin Oncol. 2022;52(6):539-44.

15. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

16. West HJ, Jin JO. JAMA Oncology Patient Page. Performance Status in Patients With Cancer. JAMA Oncol. 2015;1(7):998.

17. Kenis C, Decoster L, Flamaing J, Debruyne PR, De Groof I, Focan C, et al. Incidence of falls and fall-related injuries and their predictive factors in frail older persons

with cancer: a multicenter study. BMC Geriatr. 2022;22(1):877.

18. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. Epidemiology. 2011;22(5):745.

19. Etminan M, Collins GS, Mansournia MA. Using Causal Diagrams to Improve the Design and Interpretation of Medical Research. Chest. 2020;158(1S):S21-S8.

20. Canaud B, Granger Vallee A, Molinari N, Chenine L, Leray-Moragues H, Rodriguez A, et al. Creatinine index as a surrogate of lean body mass derived from urea Kt/V, pre-dialysis serum levels and anthropometric characteristics of haemodialysis patients. PLoS One. 2014;9(3):e93286.

21. Fukagawa M, Yokoyama K, Koiwa F, Taniguchi M, Shoji T, Kazama JJ, et al. Clinical practice guideline for the management of chronic kidney disease-mineral and bone disorder. Ther Apher Dial. 2013;17(3):247-88.

22. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-6.

23. Austin PC, White IR, Lee DS, van Buuren S. Missing Data in Clinical Research: A Tutorial on Multiple Imputation. Can J Cardiol. 2021;37(9):1322-31.

24. Suwabe T, Ubara Y, Inoue M, Kitajima I, Oohashi K, Nakano I, et al. What can we learn from a patient on dialysis for 42 years? Clin Nephrol. 2014;81(6):427-34.

25. Pisoni RL, Arrington CJ, Albert JM, Ethier J, Kimata N, Krishnan M, et al. Facility hemodialysis vascular access use and mortality in countries participating in DOPPS: an instrumental variable analysis. Am J Kidney Dis. 2009;53(3):475-91.

26. Rosner MH, Reis T, Husain-Syed F, Vanholder R, Hutchison C, Stenvinkel P, et al. Classification of Uremic Toxins and Their Role in Kidney Failure. Clin J Am Soc Nephrol. 2021;16(12):1918-28.

27. Itoh Y, Ezawa A, Kikuchi K, Tsuruta Y, Niwa T. Protein-bound uremic toxins in hemodialysis patients measured by liquid chromatography/tandem mass spectrometry and their effects on endothelial ROS production. Anal Bioanal Chem. 2012;403(7):1841-50.

28. Enoki Y, Watanabe H, Arake R, Fujimura R, Ishiodori K, Imafuku T, et al. Potential therapeutic interventions for chronic kidney disease-associated sarcopenia via indoxyl sulfate-induced mitochondrial dysfunction. J Cachexia Sarcopenia Muscle. 2017;8(5):735-47.

29. Stedman MR, Watford DJ, Chertow GM, Tan JC. Karnofsky Performance Score-Failure to Thrive as a Frailty Proxy? Transplant Direct. 2021;7(7):e708.

Table 1. Patient characteristics (N=227,136)

	Dialysis vintage						
	0- <5 years n=105,142	5- <10 years n=56,956	10- <20years n=45,192	20- <30 years n=14,336	30- <40 years N=4,701	≥40 years N=809	Total N=227,136
Demographics							
Age (year)	73 (65-80)	71 (64-79)	70 (63-76)	69 (62-74)	67 (62-72)	68 (63-71)	71 (64- 79)
Age at the time of initiation of dialysis (year)	71 (63-79)	64 (57-72)	56 (49-63)	45 (38-51)	33 (27-39)	26 (21-29)	65 (54- 74)
Male sex	71,391 (67.9)	37,663 (66.1)	27,562 (61.0)	7,714 (53.8)	2,416 (51.4)	405 (50.1)	147,151 (64.8)
Cause of ESKD							
Diabetic kidney disease	46,356 (49.7)	24,924 (48.5)	14,216 (34.6)	1,019 (7.7)	57 (1.3)	4 (0.5)	86,576 (42.4)
Glomerulonephritis	15,572 (16.7)	11,212 (21.8)	14,890 (36.3)	8,397 (63.7)	3,335 (76.2)	599 (79.9)	54,005 (26.5)
Hypertensive nephrosclerosis	15,911 (17.1)	6,440 (12.5)	3,439 (8.4)	462 (3.5)	57 (1.3)	7 (0.9)	26,316 (12.9)
Polycystic kidney disease	2,696 (2.9)	2,042 (4.0)	2,261 (5.5)	652 (4.9)	85 (1.9)	7 (0.9)	7,743 (3.8)
RPGN	876 (0.9)	373 (0.7)	214 (0.5)	52 (0.4)	16 (0.4)	5 (0.7)	1,536 (0.8)
Others	11,861 (12.7)	6,432 (12.5)	6,020 (14.5)	2,605 (19.8)	828 (18.9)	128 (17.1)	27,874 (13.7)
missing, n	*11,870*	*5,533*	*4,152*	*1,149*	*323*	*59*	*23,086*
BMI (kg/m^2)	21.6 (19.4- 24.2)	21.5 (19.2- 24.1)	20.8 (18.7- 23.2)	19.9 (18.0- 22.0)	19.5 (17.8- 21.6)	19.3 (17.5- 21.2)	21.2 (19.0-23.8)
Missing, n	*7,075 (6 converted to missing)*	*2,073 (5 converted to missing)*	*1,367 (No converted to missing)*	*459 (No converted to missing)*	*168 (No converted to missing)*	*37 (No converted to missing)*	*11,179 (11 converted to missing)*
SBP (mmHg)	151 (135-166)	153 (137-169)	150 (135-166)	145 (130-161)	141 (123- 157)	132 (116- 150)	150 (135- 166)
Missing, n	*2,079*	*1,060*	*874*	*333*	*112*	*15*	*4,473*
ECOG Performance Status							
0	39,820 (37.9)	21,048 (37.0)	17,614 (39.0)	5,775 (40.3)	1,431 (30.4)	128 (15.8)	85,816 (37.8)
1	32,847 (31.2)	17,984 (31.6)	14,058 (31.1)	4,939 (34.5)	1,717 (36.5)	239 (29.5)	71,784 (31.6)
2	16,400 (15.6)	8,523 (15.0)	6,340 (14.0)	1,858 (13.0)	821 (17.5)	224 (27.7)	34,166 (15.0)
3	9,407 (9.0)	5,330 (9.4)	4,042 (8.9)	1,067 (7.4)	462 (9.8)	138 (17.1)	20,446 (9.0)
4	6,668 (6.3)	4,071 (7.2)	3,138 (6.9)	697 (4.9)	270 (5.7)	80 (9.9)	14,924 (6.6)
Dialysis prescription							

With or without PD							
Without PD	104,646 (99.5)	56,560 (99.3)	45,041 (99.7)	14,317 (99.9)	4,699 (99.9)	808 (99.9)	226,071
With PD	494 (0.5)	394 (0.7)	151 (0.3)	17 (0.1)	2 (0.1)	1 (0.1)	1,059
Unknown	2	2	0	2	0	0	6
Modality							
HD	70,506 (67.1)	34,452 (60.5)	25,985 (57.5)	7,260 (50.6)	2,055 (43.7)	322 (39.8)	140,580 (61.9)
HDF	34,163 (32.5)	22,117 (39.6)	18,884 (41.8)	6,617 (46.2)	2,244 (47.7)	374 (46.2)	84,399 (37.2)
β2MG-absorption column	1 (0.0)	7 (0.0)	177 (0.4)	441 (3.1)	399 (8.5)	112 (13.8)	1,137 (0.5)
Other HF	3 (0.0)	0	2 (0.0)	1 (0.0)	1 (0.0)	0	7 (0.0)
Others	469 (0.5)	380 (0.7)	144 (0.3)	17 (0.1)	2 (0.0)	1 (0.1)	1,013 (0.5)
Missing, n	*0*	*0*	*0*	*0*	*0*	*0*	*0*
Vascular access							
Arteriovenous fistula	66,706 (90.9)	48,257 (91.0)	37,576 (88.7)	11,469 (85.0)	3,589 (81.1)	573 (74.6)	168,170 (89.7)
Arteriovenous graft	3,985 (5.4)	3,616 (6.8)	3,781 (8.9)	1,549 (11.5)	600 (13.6)	132 (17.2)	13,663 (7.3)
Superficial artery	1,254 (1.7)	711 (1.3)	619 (1.5)	326 (2.4)	149 (3.4)	36 (4.7)	3,095 (1.7)
Long-term catheter	1,034 (1.4)	395 (0.7)	333 (0.8)	108 (0.8)	65 (1.5)	25 (3.3)	1,960 (1.1)
Others	423 (0.6)	66 (0.1)	73 (0.2)	37 (0.3)	20 (0.5)	2 (0.3)	621 (0.3)
Missing, n	*31,740*	*3,911*	*2,810*	*847*	*278*	*41*	*39,627*
Single-pool Kt/V	1.38 (1.19-1.57)	1.49 (1.32-1.68)	1.56 (1.39-1.76)	1.63 (1.45-1.84)	1.64 (1.43-1.85)	1.60 (1.42-1.85)	1.47 (1.28- 1.67)
Missing, n	*6,848*	*3,044*	*2,281*	*755*	*255*	*46*	*13,229*
Past medical history and comorbidities							
Diabetes	60,934 (60.8)	32,343 (59.4)	18,584 (43.5)	1,900 (14.3)	311 (7.2)	45 (6.0)	114,117 (52.9)
Missing, n	*4,899*	*2,520*	*2,499*	*1,035*	*378*	*61*	*11,392*
Dementia	12,814 (12.8)	6,797 (12.5)	4,278 (9.9)	918 (6.7)	190 (4.2)	22 (2.8)	25,019 (11.6)
Missing, n	*4,889*	*2,725*	*2,033*	*565*	*195*	*34*	*10,441*
Ischemic heart disease	22,548 (23.8)	14,355 (27.8)	11,240 (27.4)	3,326 (25.3)	1,100 (25.6)	194 (26.3)	52,763 (25.7)
Missing, n	*10,195*	*5,399*	*4,147*	*1,191*	*397*	*72*	*21,401*
Cerebral bleeding	4,921 (5.0)	3,698 (7.2)	3,636 (8.9)	1,156 (8.9)	278 (6.5)	44 (6.0)	13,529 (6.6)
Missing, n	*10,891*	*5,896*	*4,476*	*1,292*	*425*	*81*	*23,061*
Cerebral infarction	16,280 (17.2)	11,201 (21.7)	9,053 (22.0)	2,383 (18.1)	607 (14.1)	84 (11.5)	39,608 (19.2)
Missing, n	*10,218*	*5,248*	*4,047*	*1,184*	*400*	*77*	*21,174*

Limb amputation	2,650 (2.8)	2,491 (4.8)	2,202 (5.4)	345 (2.6)	120 (2.6)	43 (5.9)	7,821 (3.8)
Missing, n	*10,234*	*5,583*	*4,217*	*1,246*	*423*	*74*	*21,777*
Hip fracture	4,220 (4.5)	3,221 (6.3)	2,591 (6.4)	706 (5.4)	324 (7.6)	97 (13.2)	11,159 (5.5)
Missing, n	*10,657*	*5,818*	*4,437*	*1,286*	*423*	*76*	*22,697*
Carpal tunnel syndrome	659 (0.7)	563 (1.1)	1,574 (3.9)	2,571 (20.0)	2,079 (49.0)	466 (64.6)	7,912 (3.9)
Missing, n	*11,698*	*6,347*	*4,953*	*1,465*	*455*	*88*	*25,006*
Laboratory investigations							
Albumin (mg/dL)	3.6 (3.3-3.8)	3.6 (3.3-3.8)	3.6 (3.3-3.8)	3.6 (3.3-3.8)	3.5 (3.3-3.8)	3.4 (3.2-3.7)	3.6 (3.3- 3.8)
Missing, n	*1,582 (37 converted to missing)*	*686 (20 converted to missing)*	*490 (11 converted to missing)*	*181 (4 converted to missing)*	*67 (3 converted to missing)*	*12 (No converted to missing)*	*3,018 (75 converted to missing)*
BUN (mg/dL)	59 (49-69)	59 (49-69)	59 (49-70)	61 (51-71)	62 (52-71)	60 (50-71)	59 (49- 69)
Missing, n	*1,149*	*430*	*318*	*112*	*38*	*8*	*2,055*
Cr (mg/dL)	8.8 (7.0-10.6)	10.0 (8.3-11.7)	10.2 (8.6-11.9)	10.2 (8.7-11.7)	9.5 (8.1-11.0)	8.4 (7.1-9.7)	9.5 (7.7- 11.3)
Missing, n	*2,359*	*613*	*429*	*125*	*46*	*10*	*3,582*
Corrected calcium	9.0 (8.6-9.4)	9.1 (8.7-9.6)	9.2 (8.8-9.7)	9.2 (8.8-9.7)	9.2 (8.7-9.7)	9.2 (8.7-9.6)	9.1 (8.7-9.5)
<8.4 mg/dL	17,888 (17.3)	7,217 (12.9)	5,249 (11.8)	1,805 (12.8)	691 (14.9)	109 (13.7)	32,009 (14.3)
8.4-10.0 mg/dL	79,284 (76.8)	43,851 (78.1)	34,034 (76.3)	10,622 (75.2)	3,402 (73.5)	589 (74.0)	172,732 (77.2)
>10.0 mg/dL	6,122 (5.9)	5,086 (9.1)	5,334 (12.0)	1,697 (12.0)	539 (11.6)	98 (12.3)	18,876 (8.4)
Missing, n	*1,848 (37 converted to missing)*	*802 (20 converted to missing)*	*575 (11 converted to missing)*	*212 (4 converted to missing)*	*69 (3 converted to missing)*	*13 (No converted to missing)*	*3,519 (75 converted to missing)*
Phosphorus	5.0 (4.2-5.9)	5.1 (4.2-6.0)	5.1 (4.3-6.0)	5.1 (4.3-5.9)	5.0 (4.3-5.9)	4.9 (4.1-5.7)	5.1 (4.2-6.0)
<3.5 mg/dL	10,462 (10.1)	5,291 (9.4)	4,172 (9.3)	1,187 (8.4)	426 (9.1)	82 (10.2)	21,620 (9.6)
3.5- 6.0 mg/dL	70,250 (67.6)	37,483 (66.4)	30,188 (67.3)	10,002 (70.4)	3,245 (69.6)	583 (72.7)	151,751 (67.5)
>6.0 mg/dL	23,238 (22.4)	13,707 (24.3)	10,480 (23.4)	3,025 (21.3)	990 (21.2)	137 (17.1)	51,577 (22.9)
Missing, n	*1,192 (17 converted to missing)*	*475 (9 converted to missing)*	*352 (5 converted to missing)*	*122 (No converted to missing)*	*40 (No converted to missing)*	*7 (No converted to missing)*	*2,188 (31 converted to missing)*
Intact PTH	133 (74-209)	139 (80-216)	152 (90-236)	141 (77-224)	118 (55-200)	93 (32-178)	139 (79-217)
<60 pg/mL	18,290 (18.6)	8,896 (16.3)	5,866 (13.5)	2,526 (18.3)	1,209 (26.8)	281 (36.3)	37,068 (17.2)
60- 240 pg/mL	62,402 (63.3)	35,023 (64.3)	27,166 (62.5)	8,292 (60.2)	2,509 (55.7)	382 (49.3)	135,774 (63.0)
>240 pg/mL	17,932 (18.2)	10,451 (19.4)	10,451 (24.0)	2,966 (21.5)	788 (17.5)	112 (14.5)	42,810 (19.9)
Missing	*6,518*	*2,476*	*1,709*	*552*	*195*	*34*	*11,484*

β2MG (mg/L)	23.7 (19.4- 28.2)	27.7 (24.4- 31.3)	28.8 (25.9- 32.1)	27.9 (25.1- 31.0)	24.7 (21.2- 28.4)	20.8 (17.8- 24.9)	26.7 (22.8- 30.5)
Missing, n	*43,779 (76 converted to missing)*	*10,986 (35 converted to missing)*	*8,341 (24 converted to missing)*	*2,654 (3 converted to missing)*	*865 (No converted to missing)*	*146 (1 converted to missing)*	*66,771 (139 converted to missing)*
Cr index (mg/kg/day)	19.5 (17.8- 21.4)	20.6 (18.8- 22.4)	20.7 (19.0- 22.5)	20.7 (19.1- 22.4)	20.2 (18.7- 21.8)	19.3 (17.9- 20.6)	20.1 (18.4-22.0)
Missing, n	*8,429 (1,521 converted to missing)*	*3,441 (231 converted to missing)*	*2,578 (155 converted to missing)*	*836 (28 converted to missing)*	*268 (11 converted to missing)*	*49 (3 converted to missing)*	*14,544 (1,949 converted to missing)*
Hemoglobin (g/dL)	10.8 (10.1- 11.6)	10.9 (10.2- 11.6)	10.9 (10.2- 11.7)	11.0 (10.2- 11.7)	10.9 (10.2- 11.6)	10.8 (10.0- 11.5)	10. 9 (10.1- 11.6)
Missing, n	*1,666 (No converted to missing)*	*740 (No converted to missing)*	*622 (No converted to missing)*	*188 (No converted to missing)*	*72 (No converted to missing)*	*11 (No converted to missing)*	*3,299 (No converted to missing)*
Total cholesterol (mg/dL)	151 (130-177)	151 (129-176)	156 (133-181)	162 (139-187)	162 (139-186)	154 (133-185)	153 (131-178)
Missing, n	*18,921*	*9,842*	*7,766*	*2,513*	*878*	*123*	*40,043*
nPCR (g/kg/day)	0.81 (0.70- 0.93)	0.84 (0.73- 0.95)	0.86 (0.75- 0.97)	0.89 (0.78- 1.00)	0.89 (0.78- 1.00)	0.87 (0.76- 1.00)	0.83 (0.72- 0.95)
Missing, n	*6,434 (6 converted to missing)*	*2,945 (2 converted to missing)*	*2,166 (2 converted to missing)*	*714 (No converted to missing)*	*242 (1 converted to missing)*	*43 (No converted to missing)*	*12,544 (11 converted to missing)*
CRP (mg/dL)	0.14 (0.06- 0.45)	0.16 (0.06- 0.49)	0.16 (0.06- 0.50)	0.15 (0.06- 0.48)	0.20 (0.08- 0.60)	0.29 (0.10- 0.87)	0.15 (0.06- 0.48)
Missing, n	*14,279 (7 converted to missing)*	*7,758 (4 converted to missing)*	*6,196 (6 converted to missing)*	*1,979 (1 converted to missing)*	*674 (No converted to missing)*	*85 (No converted to missing)*	*30,971 (18 converted to missing)*
HBV antigen	1,250 (1.2)	752 (1.4)	712 (1.6)	276 (2.0)	92 (2.0)	18 (2.3)	3,100 (1.4)
Unknown or missing, n	*5,765*	*2,915*	*2,174*	*696*	*266*	*42*	*11,858*
HCV antibody	4,258 (4.2)	2,580 (4.7)	2,015 (4.6)	663 (4.8)	887 (19.8)	320 (41.4)	10,723 (4.9)
Unknown or missing, n	*6,329*	*3,192*	*2,432*	*798*	*290*	*54*	*13,095*

Abbreviations: β2MG, β_2-microglobulin; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; ECOG, Eastern

Cooperative Oncology Group; ESKD, end-stage kidney disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HD, hemodialysis; HDF, hemodiafiltration; HF, hemofiltration; nPCR, normalized protein catabolic rate; PD, peritoneal dialysis; PTH, parathyroid hormone; RPGN, rapidly progressive glomerulonephritis; SBP, systolic blood pressure.

Table 2. Association between dialysis vintage and frailty (N=227,136)

	Model 1			Model 2			Model 3			Model 4		
	PR	**95% CI**		**PR**	**95% CIs**		**PR**	**95% CI**		**PR**	**95% CI**	
Dialysis vintage												
<5 years	Ref.			Ref.			Ref.			Ref.		
5- <10 years	1.07	1.06-	1.09	1.01	0.99-	1.02	1.07	1.06-	1.09	1.07	1.05-	1.08
10- <20 years	1.11	1.09-	1.13	1.02	0.999-	1.03	1.11	1.09-	1.13	1.10	1.08-	1.12
20- <30 years	1.04	1.01-	1.07	0.96	0.93-	0.979	1.16	1.13-	1.19	1.13	1.10-	1.17
30- <40 years	1.46	1.40-	1.52	1.38	1.33-	1.44	1.63	1.57-	1.70	1.55	1.49-	1.62
≥40 years	2.40	2.25-	2.56	2.29	2.15-	2.45	2.40	2.24-	2.57	2.23	2.08-	2.40
Biomarkers												
β2MG (per mg/L)				1.02	1.01-	1.02	1.02	1.01-	1.02	1.02	1.01-	1.02
Albumin (per mg/dL)							0.72	0.71-	0.73	0.72	0.71-	0.73
Cr index (per mg/kg/day)							0.85	0.85-	0.85	0.85	0.85-	0.85
Comorbidities												
Diabetes							1.22	1.20-	1.23	1.22	1.20-	1.23
Dementia							1.63	1.60-	1.64	1.62	1.60-	1.64
Ischemic heart disease							1.04	1.02-	1.04	1.03	1.02-	1.04
Cerebral hemorrhage							1.40	1.37-	1.42	1.39	1.37-	1.42
Cerebral infarction							1.34	1.32-	1.35	1.33	1.32-	1.35
Limb amputation							1.57	1.53-	1.61	1.55	1.51-	1.58
Hip fracture										1.20	1.18-	1.23

Carpal tunnel syndrome										1.05	1.01-	1.09

Model 1: Adjusted for age and sex.

Model 2: Adjusted for variables included in Model 1 along with corrected calcium, phosphorus, parathyroid hormone and β2MG.

Model 3: Adjusted for variables included in Model 2 along with creatinine index, albumin, diabetes, dementia, ischemic heart disease, cerebral hemorrhage, cerebral infarction, and limb amputation.

Model 4: Adjusted for variables included in Model 3 along with carpal tunnel syndrome, hip fracture, and vascular access type.

Abbreviations: PR, prevalence ratio; CI, confidence interval; β2MG, β_2-microglobulin; Cr, creatinine

Table 3. Association between dialysis vintage and bed-ridden status (N=227,136)

	Model 1			Model 2			Model 3			Model 4		
	PR	95% CI		PR	95% CI		PR	95% CI		PR	95% CI	
Dialysis vintage												
<5 years	Ref.			Ref.			Ref.			Ref.		
5- <10 years	1.19	1.15-	1.24	1.03	0.99-	1.07	1.17	1.13-	1.22	1.17	1.13-	1.22
10- <20 years	1.28	1.23-	1.33	1.06	1.01-	1.10	1.26	1.20-	1.31	1.26	1.21-	1.32
20- <30 years	1.01	0.94-	1.09	0.85	0.79-	0.92	1.14	1.06-	1.23	1.17	1.08-	1.26
30- <40 years	1.31	1.16-	1.47	1.14	1.01-	1.28	1.42	1.27-	1.60	1.55	1.37-	1.75
≥40 years	2.25	1.83-	2.78	1.92	1.55-	2.37	2.09	1.68-	2.59	2.30	1.83-	2.88
Biomarkers												
β2MG (per mg/L)				1.03	1.03-	1.03	1.03	1.02-	1.03	1.02	1.02-	1.03
Albumin (per mg/L)							0.45	0.43-	0.46	0.45	0.43-	0.46
Cr index (per mg/kg/day)							0.71	0.70-	0.72	0.72	0.71-	0.73
Comorbidities												
Diabetes							1.09	1.06-	1.13	1.09	1.05-	1.13
Dementia							2.90	2.80-	3.01	2.87	2.77-	2.98
Ischemic heart disease							0.89	0.86-	0.92	0.88	0.85-	0.91
Cerebral hemorrhage							1.79	1.71-	1.88	1.78	1.70-	1.86
Cerebral infarction							1.54	1.49-	1.60	1.53	1.48-	1.58
Limb amputation							1.50	1.41-	1.60	1.47	1.38-	1.57
Hip fracture										1.18	1.12-	1.25
Carpal tunnel syndrome										0.77	0.69-	0.86

Model 1: Adjusted for age and sex.

Model 2: Adjusted for variables included in Model 1 along with corrected calcium, phosphorus, parathyroid hormone and β2MG.

Model 3: Adjusted for variables included in Model 2 along with creatinine index, albumin, diabetes, dementia, ischemic heart disease, cerebral hemorrhage, cerebral infarction, and limb amputation.

Model 4: Adjusted for variables included in Model 3 along with carpal tunnel syndrome, hip fracture, and vascular access type.

Abbreviations: PR, prevalence ratio; CI, confidence interval; β2MG, β_2-microglobulin; Cr, creatinine

Figure legends

Figure 1. Flow chart depicting patient selection in the study.

Abbreviations: JRDR, the Japanese Society for Dialysis Therapy Renal Data Registry.

Figure 2. Association between dialysis vintage and frailty.

Model 1: Adjusted for age and sex. Model 2: Adjusted for variables included in Model 1 along with calcium, phosphorus, parathyroid hormone and β_2-microglobulin. Model 3: Adjusted for variables included in Model 2 along with creatinine index, albumin, diabetes, dementia, and comorbidities (ischemic heart disease, cerebral hemorrhage, cerebral infarction, and limb amputation). Model 4: Adjusted for variables included in Model 3 along with carpal tunnel syndrome, hip fracture and vascular access type. Frailty was defined as grade 2 or higher on the Eastern Cooperative Oncology Group Performance Status scale. We estimated the PRs by fitting modified Poisson regression models using the Japanese Society for Dialysis Therapy Renal Data Registry database (N=227,136)

Abbreviations: PRs. prevalence ratios.

Figure 3. Association between dialysis vintage and bedridden state.

Model 1: Adjusted for age and sex. Model 2: Adjusted for variables included in Model 1 along with calcium, phosphorus, parathyroid hormone and β_2-microglobulin. Model 3: Adjusted for variables included in Model 2 along with creatinine index, albumin, diabetes, dementia, and comorbidities (ischemic heart disease, cerebral hemorrhage, cerebral infarction, and limb amputation). Model 4: Adjusted for variables included in Model 3 along with carpal tunnel syndrome, hip fracture and vascular access type. Bed-redden status was defined as grade 4 on the Eastern Cooperative Oncology Group Performance

Status scale. We estimated the PRs by fitting modified Poisson regression models using the Japanese Society for Dialysis Therapy Renal Data Registry database (N=227,136)

Abbreviations: PRs. prevalence ratios.