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Factors Associated with Withdrawal from Dialysis Therapy in Very-Elderly Incident Hemodialysis Patients

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Abstract

Objectives: Among very-elderly kidney disease patients progressing to end-stage renal disease, there is growing interest in conservative non-dialytic management approaches. However, among those who have initiated hemodialysis, little is known about the impact of withdrawal from dialysis on mortality, nor the patient characteristics associated with withdrawal from dialysis.

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Study Design: Historical cohort study.

Setting and Participants: We examined 133,162 incident hemodialysis patients receiving care within a large national dialysis organization from 2007-2011.

Measures: We identified patients who withdrew from dialysis, either as a listed cause of death or censor reason. Incidence-rates and sub-distribution hazard-ratios for withdrawal from dialysis as well as four other censoring reasons were examined across age groups. In addition, demographic and clinical characteristics associated with withdrawal from dialysis therapy among patients in the very elderly age range (≥ 80 years old) was assessed using logistic regression analysis.

Results: Incident-rates of withdrawal from dialysis were markedly higher compared to other censoring reasons for each age group. Additionally, compared to the youngest age group, incidence of withdrawal from dialysis incrementally increased across older age groups. Among patients ≥ 80 years, factors associated with higher odds of dialysis withdrawal included non-Hispanic white ethnicity, having Medicare/Medicaid insurance, dementia, mid-west geographic region, and less favorable markers associated with malnutrition-inflammation-cachexia syndrome (MICS) such as high white blood cell counts and low body mass index, albumin, and normalized protein catabolic rate.

Conclusion/Implications: Among incident hemodialysis patients, dialysis therapy withdrawal was associated with older age, non-Hispanic white race, dementia, mid-west region and less favorable MICS status. Further studies examining withdrawal from dialysis in elderly patients are needed.

Summary of the article

Withdrawal from dialysis was associated with older age, non-Hispanic white race, dementia, mid-west region and less favorable markers for malnutrition-inflammation-cachexia syndrome among incident hemodialysis patients.

Keywords

Withdrawal from hemodialysis; very-elderly; mortality; hemodialysis

INTRODUCTION

There is an escalated risk of end-stage renal disease (ESRD) in the elderly in part due to the physiologic decline of kidney function related to aging, as well as the high prevalence of concurrent comorbidities such as diabetes and hypertension.¹⁻³ Indeed, among patients with advanced chronic kidney disease (CKD), incidence rates of dialysis initiation are highest among those ≥ 75 years of age, with a three-fold higher risk compared to those in younger age groups (i.e., 45-64 years of age).^{4, 5} Furthermore, there is added complexity in administering dialysis treatment to elderly patients, given their high comorbidity burden, frail status, and short life expectancy.⁶ Nonetheless, there has been sparse study of the management of ESRD patients in the very-elderly age range (i.e., ≥ 80 years), and there remains considerable uncertainty regarding the optimal approach to dialysis care in this population.

There has been growing recognition that withdrawal from dialysis is an increasingly frequent occurrence in the United States ESRD population. For example, United States Renal Data System (USRDS) data has shown that the proportion of deaths due to withdrawal from dialysis increased from 19% to nearly 25% from 1994 to 2007, respectively, and is now the third leading cause of death among dialysis patients, following cardiovascular and infectious etiologies.^{7, 8} Examining the factors associated with withdrawal from dialysis among patients age 80 years who have initiated hemodialysis may be particularly relevant given the high incidence of ESRD in this population.^{9–11} In the current study, we sought to determine the characteristics associated with withdrawal from hemodialysis in particular for the elderly ESRD population of age 80 years.

METHODS

Study Cohort

We conducted a historical cohort study of 208,820 incident hemodialysis patients receiving care from a large dialysis organization (LDO) outpatient facilities in the United States over a five-year period (January 2007 to December 2011). Patients who received hemodialysis treatment for at least 60 days, and had available data reporting reasons for cessation of follow-up were included. Patients were excluded if they were receiving a dialysis treatment modality other than thrice weekly in-center hemodialysis at study entry. The study was approved by the Institutional Review Committee

Assessment for Withdrawal from Hemodialysis

For the primary outcome, withdrawal from hemodialysis was defined as (1) the cessation of follow-up due to discontinuation of hemodialysis treatment or (2) death due to withdrawal from dialysis/uremia (Supplemental Figure 1). For both criteria, date of withdrawal from hemodialysis was defined according to the actual date of discontinuation of hemodialysis treatment (as opposed to the date of death due to withdrawal from hemodialysis for the latter criterion). Causes of death were ascertained from the LDO database. Patients were followed from study entry (i.e., date of first dialysis treatment) until discontinuation of hemodialysis, death, or censoring for kidney transplantation, transfer to a non-affiliated dialysis unit, recovery from dialysis treatment, or at end of the study period (December 31, 2011). As noted above, patients who died due to withdrawal from hemodialysis were censored at the time of discontinuation of hemodialysis treatment.

In secondary analysis, censoring reasons were categorized into five groups, namely, withdrawal from hemodialysis, death from reasons other than withdrawal, kidney transplantation, transfer to another dialysis facility, renal recovery from dialysis treatment. Additionally, death outcomes were categorized according to cause of death including cardiovascular disease, infectious cause, withdrawal from dialysis/uremia, hemodialysis complication and other.

Socio-Demographic, Clinical, and Laboratory Data

Information for self-reported race/ethnicity, primary insurance, access type, and the presence of comorbid conditions were obtained from the LDO electronic database. Data on comorbid

conditions were obtained from International Classification of Diseases-9 codes and included: diabetes mellitus, hypertension, atherosclerotic heart disease, congestive heart failure, other cardiac diseases (pericarditis and cardiac arrhythmia), cerebrovascular disease, chronic obstructive pulmonary disease, history of cancer, liver disease, depression, dementia and Deyo-modified Charlson Comorbidity Index (CCI) by excluding presence or absence of kidney disease.^{12, 13}

Laboratory tests were measured from blood samples that were collected before dialysis except for post-dialysis serum urea nitrogen using standardized techniques in all dialysis clinics, and were transported to a central laboratory in Deland, Florida typically within 24 hours, where they were measured using automated and standardized methods. Most laboratory tests were measured monthly, including serum creatinine, albumin, peripheral white blood cell (WBC) count, total iron binding capacity (TIBC), calcium, phosphorus, and bicarbonate. Hemoglobin was measured weekly to biweekly in most patients. Delivered dialysis dose was calculated by single-pool Kt/V (spKt/V) using urea kinetic modeling. Renal urea clearance and normalized protein catabolic rate (nPCR) were calculated. To minimize measurement variability, all repeated measures for each 91-day interval from date of dialysis initiation were averaged and the quarterly mean values in each quarter were used in all analyses.

Statistical Analyses

Patients aged 18-80 years were stratified according to whether they withdrew from hemodialysis, namely withdrawal vs. non-withdrawal (defined as patients who had received dialysis treatment continuously until the time of being censored). Baseline characteristics of the withdrawal vs. non-withdrawal from hemodialysis groups were summarized as proportions, mean \pm SD, and median (interquartile range: IQR) depending upon data type. Crude incidence rates for each censoring reason or cause of death category were expressed as the number of outcome events in the numerator divided by the sum duration of dialysis treatment time (person-time). Age groups were categorized as <50, 50-<65, 65-<80, and 80 years. We examined associations of age group category with incidence rate ratios of censor reasons and cause of death categories using age<50 years as the reference. Associations with age group as an ordinal variable with incident rate ratios of outcomes were examined to test for trend across age group. Poisson regression analysis was used to estimate the incidence rate ratios with and without adjustment for case-mix covariates which included socio-demographics and comorbidities such as age, sex, race/ethnicity, primary insurance, initial vascular access type, twelve comorbid conditions (e.g., diabetes mellitus, hypertension, atherosclerotic heart disease, congestive heart failure, other-cardiovascular disease, cerebrovascular disease, dyslipidemia, chronic obstructive pulmonary disease, liver disease, and history of malignancy), and dialysis dose (i.e., spKt/V). There was <1% missing data for all covariates, except spKt/V (16%). Missing data were addressed using multiple imputations.

We then calculated the subdistribution hazard ratios of withdrawal from hemodialysis compared to the likelihood for censoring due to other causes using competing risk regression with and without adjustment for case-mix covariates across age groups. These associations

were also examined across strata of sex (male and female) and racial/ethnic group (Whites and non-Whites). Unadjusted and adjusted logistic regression analysis using demographic data, comorbidities and clinical and laboratory values were used to reveal the characteristics associated with withdrawal from hemodialysis, and to compare the odds of withdrawal from hemodialysis across geographic regions. All analyses were carried out with STATA MP, version 13.1 (StataCorp College Station, TX, USA).

RESULTS

Baseline Characteristics Stratified by Withdrawal Status and Age Group

Among the total cohort of incident hemodialysis patients, the proportion of patients who underwent withdrawal from hemodialysis was higher amongst those ≥80 years of age (10%; N=1,730 among 17,296 patients ≥80 years of age) compared to those <80 years of age (3%; N=3,359 among 115,866 patients <80 years of age). Table 1 shows the baseline characteristics of patients aged ≥80 years according to withdrawal from hemodialysis status (i.e., withdrawal vs. non-withdrawal). Among patients ≥80 years of age, the withdrawal from hemodialysis group tended to be older and were more likely to be non-Hispanic white; have Medicare/Medicaid as their primary insurance; initiate dialysis with a central venous catheter; have diabetes, cardiac disease, or dementia; and have less favorable nutritional and inflammatory profiles at hemodialysis initiation based on laboratory surrogates (i.e., higher WBC counts and lower body mass index [BMI], serum albumin, creatinine, TIBC, and nPCR levels).

Comparison of Cause-Specific Cessation of Follow-up and Mortality Across Age Groups

Among the five censor reason categories, death due to reasons other than withdrawal from hemodialysis was the most common across all age groups. Incidence rates of withdrawal from hemodialysis and death due to reasons other than withdrawal from hemodialysis increased incrementally across older age groups. Additionally, incidence rate ratios for these two outcomes were incrementally higher with increasing age even after adjustment for socio-demographics and comorbidities, with a much steeper rise was observed for withdrawal from hemodialysis outcome: adjusted incidence rate ratios for withdrawal from hemodialysis: 1.0, 2.3, 5.2, and 10.3 for age categories <50, 50-<65, 65-<80, and ≥80 years, respectively (p-for-trend<0.001; Figures 1A and 1B). Rates of withdrawal from hemodialysis in patients age ≥80 years was 58/1000 patient-years on hemodialysis, which was more than three-fold higher than that of patients age <80 years (13/1000 patient-years on hemodialysis). Duration from the last hemodialysis treatment to death was 10 [6, 16] days among 923 patients who had available data after withdrawal from hemodialysis to death.

The crude incidence rate and the incidence rate ratios for each cause of death were also calculated among deceased patients. Among the different etiologies of death (e.g. cardiovascular disease, infectious cause, withdrawal from dialysis/uremia, hemodialysis complication and others), incidence rates for cardiovascular causes were the highest across all age groups. However, the incidence rate ratios for death due to withdrawal from dialysis/uremia were increasingly higher with incrementally older age groups: adjusted incidence

rate ratios for death due to withdrawal from dialysis/uremia: 1.0, 1.5, 2.5 and 3.4 for age categories <50, 50-<65, 65-<80, and ≥80 years, respectively ($p<0.001$; Figure 1C and 1D). For causes of death outcomes, withdrawal from dialysis/uremia was the second and third most common cause of death among patients age ≥80 years and <80 years of age, respectively. Incidence rate ratios for death due to cardiovascular or infectious causes were similar or only showed marginal increases with increasing older age categories: cardiovascular diseases, 1.0, 0.9, 1.0 and 1.1; infectious causes, 1.0, 1.1, 1.2 and 1.2 for age categories <50, 50-<65, 65-<80, and ≥80 years, respectively.

Likelihood of Withdrawal from Hemodialysis Across Age Groups

When withdrawal from hemodialysis was examined in consideration of competing risk due to other reasons for censoring across age groups, incrementally higher risk of withdrawal from hemodialysis was observed with increasingly older age even after adjustment with case-mix covariates which included socio-demographics and comorbidities (Figure 2A). Similar trends were observed across different sex and racial/ethnic groups (Figures 2B and 2C).

Clinical Characteristics Associated with Withdrawal Among Very-elderly Patients

Table 2 shows the clinical characteristics associated with odds of withdrawal from hemodialysis among patients aged ≥80 years. Older age; non-Hispanic white race/ethnicity; dementia comorbidity and having higher WBC and hemoglobin levels were associated with higher odds of withdrawal from hemodialysis both unadjusted and adjusted logistic regression analysis. Whereas African-American, Hispanic, or Asian race/ethnicity; having insurance other than Medicare or Medicaid; having arteriovenous fistula as their vascular access for initiation of hemodialysis; and having more favorable nutritional and inflammatory profiles (i.e., higher BMI, serum albumin, or nPCR levels) were associated with lower odds of withdrawal from hemodialysis. Clinical aspects known as implicated with malnutrition-inflammation-cachexia syndrome were closely associated with the probability of withdrawal from hemodialysis. For example, higher serum albumin was associated with lower withdrawal odds (odds ratio [OR]: 0.61, 95% confidence interval [CI] 0.53-0.70), so that each 1 g/dL *lower* serum albumin was associated with 64% higher odds of dialysis therapy withdrawal (OR: 1.64, 95%CI: 1.43-1.89).

Geographic regional variation for the odds of withdrawal from hemodialysis were examined between regions categorized according to 17 ESRD Networks (in which ESRD Networks 17 and 18 were merged into one region to collectively represent state of California) using logistic regression analysis. In the original analysis, region one was used as a reference, then using a contrast statement each network or region was compared to the global estimated odds of withdrawal from hemodialysis among the overall study population of patients age ≥80 years. Unadjusted and adjusted odds of withdrawal from hemodialysis are presented in Table 3. In adjusted analyses, patients who received treatment in ESRD Networks 11, 12, and 15 had a higher odds of withdrawal from hemodialysis compared to the global odds of hemodialysis withdrawal for patients age ≥80 years. However, patients in ESRD Network 2 had significant lower odds of withdrawal from hemodialysis. In general, most Midwest states including those in ESRD Network 11 and ESRD Network 12 appeared to exhibit 45 to

48% higher odds of dialysis withdrawal, whereas patients in ESRD Network 2 (New York) had by far the lowest odds dialysis therapy withdrawal (63% lower odds compared to the global odds of dialysis withdrawal for patients > 80 years).

DISCUSSION

In the present study, we observed that (1) the incidence rate of withdrawal from hemodialysis was markedly higher in elderly incident hemodialysis patients > 80 years, and accounted for the second most common cause of death in this elderly population; and that both (2) patient-related characteristics (e.g., socio-demographics, comorbidity burden, nutritional/inflammatory status) as well as non-patient related factors (e.g., geographic location) were associated with likelihood of withdrawal from hemodialysis, particularly among those > 80 years of age.

There has been a dramatic rise in the incidence of ESRD among patients > 80 years of age, which has more than doubled in the last decade. This surge in the number of very-elderly ESRD patients has introduced a number of questions and uncertainties amongst clinicians regarding the optimal management strategy of this unique patient population.^{5, 14} While dialysis treatment may prolong the survival of the very-elderly ESRD population,^{3, 15, 16} there remains wide debate as to whether dialysis treatment *vs.* conservative strategies offer greater benefit with respect to patient-centered outcomes such as quality of life in this population.^{17–20} Given their complex comorbidities and unique physical and mental/cognitive health profiles, further studies are needed to determine optimal management strategies informed by outcomes as well as patient preferences among the very-elderly ESRD population. As epidemiologic data have shown a rising frequency in patient-driven cessation from dialysis (e.g., withdrawal) over the past three decades^{21, 22} particularly amongst patients of older age,²³ we sought to determine the impact of withdrawal from dialysis upon outcomes of very-elderly hemodialysis patients, as well as factors (patient *vs.* non-patient driven) associated with withdrawal from dialysis in this population.

In our study, the odds of withdrawal from hemodialysis was substantially higher in the very-elderly group (patients aged > 80 years) even after accounting for case-mix characteristics including socio-demographics and comorbidities. The incremental increase in odds of withdrawal from hemodialysis across age group was much steeper than the increase of incidence rate ratio across age group for other censoring reasons or causes of death. While withdrawal from hemodialysis has been reported to be the third most common cause of death among US hemodialysis patients,⁷ we found that it was the second most frequent cause of death among patients > 80 years of age. Previous studies have shown a link between race/ethnicity and likelihood of withdrawal from hemodialysis, although these associations have not been examined according to age strata,^{9, 10, 24, 25}. In our cohort, odds of withdrawal from hemodialysis differed according to race/ethnicity among patients > 80 years of age. Similar to aforementioned studies, patients of minority racial/ethnic background (e.g., African-American, Hispanic, Asian) were less likely to undergo withdrawal from hemodialysis compared to non-Hispanic white hemodialysis patients in patients both > 80 *vs.* <80 years of age groups. While it has been hypothesized that socio-cultural (e.g., availability of social support networks, religious beliefs) as opposed to biologic factors may account for

these differences, further studies are warranted to more deeply understand the driving forces for these differing trajectories following hemodialysis initiation, particularly among those who are very-elderly.

Another notable observation was the differential association between patient comorbidity profile and likelihood of withdrawal from hemodialysis among patients ≥ 80 years of age. The presence of comorbidities have been found to be potent predictors for withdrawal from hemodialysis across many studies,^{9–11, 26, 27}. Those findings may lead to clinical practice guidelines favoring avoidance of dialysis among stage 5 chronic kidney disease (CKD) patients ≥ 75 years with high comorbidity burden and poor prognostic factors (e.g., impaired functional status, malnutrition).^{28–30} However, we did not observe a significant association between presence of most comorbidities with withdrawal from hemodialysis among patients ≥ 80 years; These findings may potentially be explained by prior data demonstrating that ESRD patients' perceived quality of life was not per se correlated with their comorbidity burden.³¹ Our study population consisted of elderly patients who were well enough to receive thrice weekly in-center hemodialysis treatments at an outpatient clinic of an LDO, and therefore reported depression and dementia comorbidity prevalence may have been relatively lower than for most ESRD patients age ≥ 80 years. Additional studies examining odds of hemodialysis withdrawal in consideration of these comorbidities may be needed.

However, we did observe an association between markers for malnutrition and inflammation with higher odds of withdrawal from hemodialysis. Although there have been prior reports of malnutrition markers such as low serum albumin or BMI linked with withdrawal from hemodialysis,²⁶ here we examined comprehensively the role of multiple concomitant markers for malnutrition and inflammatory complex syndrome in dialysis patients upon withdrawal from hemodialysis. It is well known that malnutrition and inflammation is associated with poor survival,³² as well as physical and psychological discomfort in dialysis patients.^{33, 34} These factors may explain the underlying link between markers for malnutrition and inflammation and withdrawal from hemodialysis observed in this study. Future studies are needed to determine the impact of mental and physical health upon decisions to pursue withdrawal from dialysis in the very-elderly population.

With respect to non-patient related factors, our study also found that there were geographic differences in odds of withdrawal from hemodialysis among patients ≥ 80 years, which was robust even after accounting for differences in case-mix characteristics such as demographic data and comorbidities. Although geographic differences in withdrawal from hemodialysis have previously been reported in studies non-stratified by age^{35, 36}, here we examined the likelihood of withdrawal from hemodialysis across ESRD Networks, particularly among the very-elderly population using adjusted logistic regression analysis accounting for socio-demographic and comorbidity characteristics. More extensive studies exploring how differences in practice patterns and local health care policies across geographic regions influence likelihood of withdrawal from hemodialysis in the very-elderly hemodialysis population are needed.

The strengths of our study include its examination of a large, nationally representative cohort of United States dialysis patients; comprehensive availability of detailed, longitudinal data

on patients' comorbidity, laboratory, and dialysis-treatment characteristics; and use of sophisticated analytic techniques such as competing risk regression. However, several limitations should be noted. First, while our study sought to rigorously define withdrawal from hemodialysis by incorporating data that (1) directly indicated discontinuation of dialysis treatment and (2) identified patients who were lost to follow-up or experienced death due to withdrawal from hemodialysis, there remains a lack of a uniform definition of withdrawal from hemodialysis from dialysis in the literature and therefore potential misclassification of this outcome is possible. Indeed, prior studies have typically defined withdrawal from hemodialysis as death preceded by discontinuation of dialysis treatment using data adapted from the ESRD death notification form (hence only restricting analyses to deceased patients),^{9, 35, 37} whereas our study also considers patients who pursued withdrawal from hemodialysis without subsequent death. Second, we lacked information about symptom burden and mental/physical health status, such as depression severity, pain, insomnia, and functional status, which are likely important determinants of withdrawal from hemodialysis. Third, we did not have data regarding date or cause of death among patients who were lost to follow-up due to discontinuation of dialysis. Fourth, our study also lacked information regarding patients' interactions with medical providers and decision processes such as describing who had the initiative for the decision of dialysis withdrawal and whether there were available advance directives. Therefore, further studies are needed to determine how patient and provider-level factors influence the decision-making process in pursuing withdrawal from hemodialysis. Fifth, provided end-of life care and patients' quality of life around the decision of withdrawal from dialysis could not be described due to the lack of regarding data. Lastly, as our study excluded patients who received hemodialysis treatment <60 days, our findings may have under-captured a sizeable proportion of very-elderly and ill incident ESRD patients who may have pursued withdrawal from hemodialysis or died prior to meeting this criteria for study entry.

Conclusions and Implications

In conclusion, among incident hemodialysis patients, we found that the likelihood of withdrawal from hemodialysis was markedly higher with increasingly older age, and that socio-demographic factors (e.g., race/ethnicity, insurance status), some markers of physical health (e.g., nutritional and inflammatory status), and geographic regions of patients' dialysis clinics were potent predictors of the odds of withdrawal from hemodialysis among very-elderly hemodialysis patients. At this time, further studies are needed to identify the best approaches for managing the very unique elderly advanced CKD population progressing to ESRD (i.e., incident ESRD patients) as well as prevalent dialysis patients that are informed by patient preferences and the impact upon their physical and mental health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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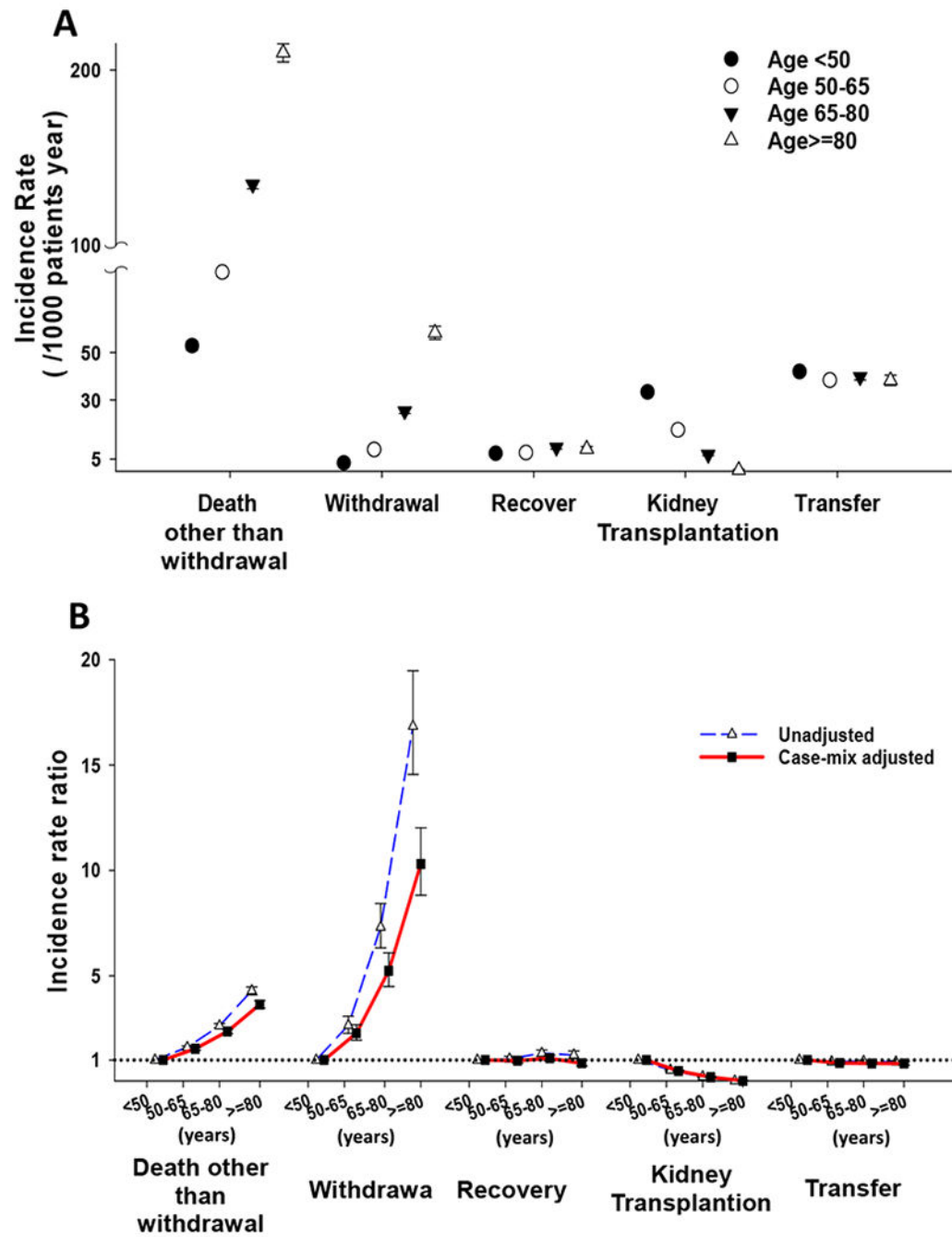
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REFERENCES

1. Coresh J, Astor BC, Greene T et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2003; 41:1–12.
2. Krishnan M, Lok CE, Jassal SV. Epidemiology and demographic aspects of treated end-stage renal disease in the elderly. *Semin Dial* 2002; 15:79–83. [PubMed: 11952930]
3. Peri UN, Fenves AZ, Middleton JP. Improving survival of octogenarian patients selected for haemodialysis. *Nephrol Dial Transplant* 2001; 16:2201–2206. [PubMed: 11682668]
4. US Renal Data System: 2013 USRDS Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. *Am J Kidney Dis* 2014; 63:supplment e1–e478.
5. Lertdumrongluk P, Rhee CM, Park J et al. Association of serum phosphorus concentration with mortality in elderly and nonelderly hemodialysis patients. *J Ren Nutr* 2013; 23:411–421. [PubMed: 23631888]
6. Kurella Tamura M Incidence, management, and outcomes of end-stage renal disease in the elderly. *Curr Opin Nephrol Hypertens* 2009; 18:252–257. [PubMed: 19374012]
7. Hackett AS, Watnick SG. Withdrawal from dialysis in end-stage renal disease: medical, social, and psychological issues. *Semin Dial* 2007; 20:86–90. [PubMed: 17244129]
8. US Renal Data System 2007 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States. *Am J Kidney Dis* 2008; 51:Supplement S1–S320.
9. Leggat JE Jr, Bloembergen WE, Levine G et al. An analysis of risk factors for withdrawal from dialysis before death. *J Am Soc Nephrol* 1997; 8:1755–1763. [PubMed: 9355079]
10. Chan HW, Clayton PA, McDonald SP et al.. Risk factors for dialysis withdrawal: an analysis of the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, 1999–2008. *Clin J Am Soc Nephrol* 2012; 7:775–781. [PubMed: 22461540]
11. Mailloux LU, Bellucci AG, Napolitano B et al. Death by withdrawal from dialysis: a 20-year clinical experience. *J Am Soc Nephrol* 1993; 3:1631–1637. [PubMed: 8507820]
12. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; 45:613–619. [PubMed: 1607900]
13. Beddhu S, Bruns FJ, Saul M et al. A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. *Am J Med* 2000; 108:609–613. [PubMed: 10856407]
14. Kurella M, Covinsky KE, Collins AJ et al. Octogenarians and nonagenarians starting dialysis in the United States. *Ann Intern Med* 2007; 146:177–183. [PubMed: 17283348]
15. Carson RC, Juszczak M, Davenport A et al.. Is maximum conservative management an equivalent treatment option to dialysis for elderly patients with significant comorbid disease? *Clin J Am Soc Nephrol* 2009; 4:1611–1619. [PubMed: 19808244]
16. Chandna SM, Da Silva-Gane M, Marshall C et al. Survival of elderly patients with stage 5 CKD: comparison of conservative management and renal replacement therapy. *Nephrol Dial Transplant* 2011; 26:1608–1614. [PubMed: 21098012]
17. Shah A, Molnar MZ, Kalantar-Zadeh K. It is not polite to ask a dialysis patient his age! *Int Urol Nephrol* 2011; 43:1101–1105. [PubMed: 21547468]
18. Brown EA. Non-dialysis therapy: a better policy than dialysis followed by withdrawal? *Semin Dial* 2012; 25:26–27. [PubMed: 22273525]
19. Germain MJ. Should dialysis be offered to all elderly patients? *Blood Purif* 2015; 39:55–57. [PubMed: 25661421]

20. Murtagh FE, Marsh JE, Donohoe P et al. Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. *Nephrol Dial Transplant* 2007; 22:1955–1962. [PubMed: 17412702]
21. Neu S, Kjellstrand CM. Stopping long-term dialysis. An empirical study of withdrawal of life-supporting treatment. *N Engl J Med* 1986; 314:14–20. [PubMed: 3079619]
22. Birmele B, Francois M, Pengloan J et al. Death after withdrawal from dialysis: the most common cause of death in a French dialysis population. *Nephrol Dial Transplant* 2004; 19:686–691. [PubMed: 14767027]
23. Germain MJ, Cohen LM, Davison SN. Withholding and withdrawal from dialysis: what we know about how our patients die. *Semin Dial* 2007; 20:195–199. [PubMed: 17555480]
24. Fissell RB, Bragg-Gresham JL, Lopes AA et al. Factors associated with “do not resuscitate” orders and rates of withdrawal from hemodialysis in the international DOPPS. *Kidney Int* 2005; 68:1282–1288. [PubMed: 16105062]
25. Kurella Tamura M, Goldstein MK, Perez-Stable EJ. Preferences for dialysis withdrawal and engagement in advance care planning within a diverse sample of dialysis patients. *Nephrol Dial Transplant* 2010; 25:237–242. [PubMed: 19734137]
26. Ellwood AD, Jassal SV, Suri RS et al. Early dialysis initiation and rates and timing of withdrawal from dialysis in Canada. *Clin J Am Soc Nephrol* 2013; 8:265–270. [PubMed: 23085725]
27. Findlay MD, Donaldson K, Doyle A et al. Factors influencing withdrawal from dialysis: a national registry study. *Nephrol Dial Transplant* 2016; 31:2041–2048. [PubMed: 27190373]
28. Moss AH, Renal Physicians A, American Society of Nephrology Working G. A new clinical practice guideline on initiation and withdrawal of dialysis that makes explicit the role of palliative medicine. *J Palliat Med* 2000; 3:253–260. [PubMed: 15859665]
29. Moss AH. Revised dialysis clinical practice guideline promotes more informed decision-making. *Clin J Am Soc Nephrol* 2010; 5:2380–2383. [PubMed: 21051749]
30. National Kidney Foundation TPSC: Initiation or Withdrawal of Dialysis in End Stage Renal Diseases: Guidelines for the Health Care Team. In.; 1996.
31. Evans RW, Manninen DL, Garrison LP Jr. et al. The quality of life of patients with end-stage renal disease. *N Engl J Med* 1985; 312:553–559. [PubMed: 3918267]
32. Kalantar-Zadeh K, Kopple JD, Block G et al. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. *Am J Kidney Dis* 2001; 38:1251–1263. [PubMed: 11728958]
33. Caravaca F, Gonzales B, Bayo MA et al. Musculoskeletal pain in patients with chronic kidney disease. *Nefrologia* 2016; 36:433–440. [PubMed: 27267921]
34. Ko GJ, Kim MG, Yu YM et al. Association between depression symptoms with inflammation and cardiovascular risk factors in patients undergoing peritoneal dialysis. *Nephron Clin Pract* 2010; 116:c29–35. [PubMed: 20460938]
35. Gessert CE, Haller IV, Johnson BP. Regional variation in care at the end of life: discontinuation of dialysis. *BMC Geriatr* 2013; 13:39. [PubMed: 23635315]
36. van Biesen W, van de Luijngaarden MW, Brown EA et al. Nephrologists’ perceptions regarding dialysis withdrawal and palliative care in Europe: lessons from a European Renal Best Practice survey. *Nephrol Dial Transplant* 2015; 30:1951–1958. [PubMed: 26268713]
37. Murphy E, Germain MJ, Cairns H et al. International variation in classification of dialysis withdrawal: a systematic review. *Nephrol Dial Transplant* 2014; 29:625–635. [PubMed: 24293659]



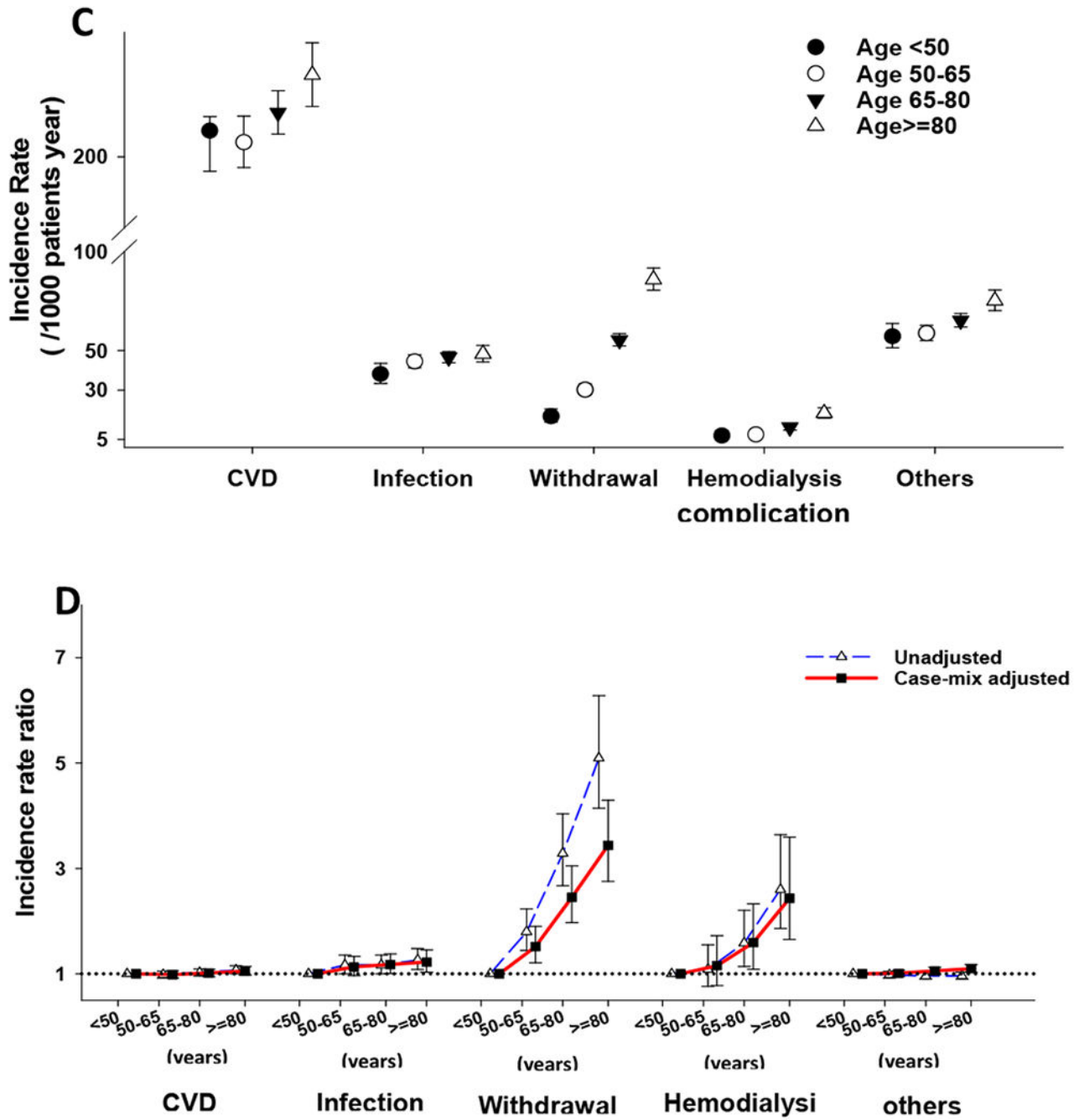


Figure 1. Comparisons of the causes of censorship based upon crude incidence rates (A) and incidence rate ratios (B) with and without adjustment for socio-demographics and comorbidities across age groups, and Comparisons of the causes of death based upon crude incidence rates (C) and incidence rate ratios (D) with and without adjustment across age groups.

Patients age <50 years old served as the reference group. Abbreviation: withdrawal, withdrawal from hemodialysis; CVD, cardiovascular disease.

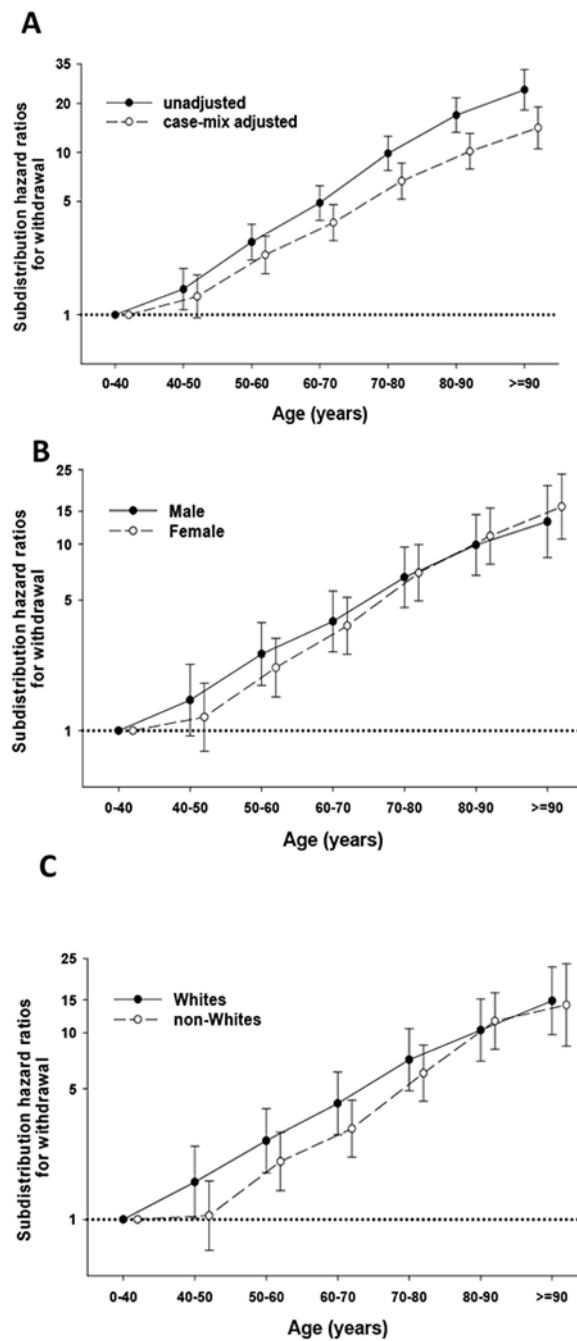


Figure 2. Subdistribution hazard ratios (SHRs) for withdrawal from hemodialysis vs. other censoring reasons across age groups assessed by competing risk regression analysis with and without adjustment for for socio-demographics and comorbidities (Panel A), as well as stratified by sex (Panel B) and race/ethnicity (Panel B).

Table 1.

Comparison of baseline characteristics according to withdrawal status in patients aged ≥ 80 years (N= 17,296).

	Withdrawal group	Non-withdrawal group	P
Number (%)	1,730(10)	15,566(90)	
Age, years	84.4±3.5	83.9±3.3	<0.001
Female, %	46	46	0.71
Race/ethnicity, %			
Non-Hispanic Caucasian	79	67	<0.001
African-American	11	18	<0.001
Hispanic	5	9	<0.001
Asian	2	4	<0.001
Primary insurance, %			
Medicare	79	73	<0.001
Medicaid	1	1	0.96
Other	20	26	<0.001
Vascular access, %			
Arteriovenous fistula	11	15	<0.001
Arteriovenous graft	4	5	0.17
Central venous catheter	79	74	<0.001
Comorbidities, %			
Diabetes mellitus	48	45	0.01
Hypertension	57	60	0.07
Atherosclerotic heart disease	18	16	0.09
Congestive heart failure	33	32	0.68
Cerebrovascular disease	2	2	0.53
Dyslipidemia	25	25	0.49
Cancer	4	4	0.47
Chronic obstructive pulmonary disease	6	6	0.90
Liver disease	1	1	0.29
Depression	1.6	2.1	0.16
Dementia	1.8	2.5	0.03
Body Mass Index	25.1 [21.8, 29.8]	26.7 [23.0, 31.9]	<0.001
Predialysis systolic/diastolic blood pressure, (mmHg)	138±19/68±9	139±9/68±9	0.03/0.18
Interdialytic weight gain, % increase	3.1±1.7	3.1±1.5	0.85
Serum Hemoglobin, g/dL	11.4±1.0	11.2±1.1	<0.001
White blood cell counts, ×10 ³ /μL	8.3±3.5	7.8±2.9	<0.001
Serum Albumin, g/dL	3.4±0.4	3.5±0.4	<0.001
Serum Creatinine, mg/dL	4.6±1.5	4.7±1.5	<0.001
Serum Bicarbonate, mmol/dL	24.5±2.6	24.3±2.6	0.01
Serum Calcium, mg/dL	8.7±0.6	8.7±0.6	0.24
Serum Phosphorus, mg/dL	4.4±1.0	4.4±1.0	0.97
Total iron binding capacity, mg/dL	208±48	216±47	<0.001

	Withdrawal group	Non-withdrawal group	<i>P</i>
Normalized protein catabolic rate, g/kg/day	0.76±0.20	0.78±0.21	<0.001
Single pool Kt/V	1.53±0.31	1.54±0.31	0.66

Values for categorical variables are given as number (percentage); values for continuous variables, mean± standard deviation.

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Table 2.

Unadjusted and adjusted odd ratios (ORs) for the odds of withdrawal from hemodialysis using logistic regression analysis.

	Unadjusted			Adjusted		
	OR	95% CI	p value	OR	95% CI	p value
Age (each + 5 years)	1.19	1.11-1.28	<0.001	1.14	1.05-1.23	0.002
Female sex (Reference: male)	1.02	0.92-1.13	0.711	1.06	0.94-1.20	0.32
Race/Ethnicity (Reference: non-Hispanic White)						
African-American	0.53	0.46-0.62	<0.001	0.52	0.44-0.62	<0.001
Hispanic	0.49	0.39-0.61	<0.001	0.47	0.37-0.60	<0.001
Asian	0.45	0.32-0.64	<0.001	0.44	0.30-0.65	<0.001
Initial vascular access (Reference: central venous catheter using group)						
Arteriovenous fistula	0.69	0.58-0.81	<0.001	0.83	0.70-0.99	0.04
Arteriovenous graft	1.06	0.87-1.28	0.58	0.92	0.70-1.20	0.53
Insurance (Reference: Medicare/Medicaid)						
Other insurance	0.74	0.66-0.84	<0.001	0.75	0.66-0.86	<0.001
Comorbidities						
Diabetes	1.13	1.03-1.25	0.014	1.09	0.97-1.22	0.13
Hypertension	0.91	0.82-1.10	0.072	0.92	0.82-1.03	0.19
Atherosclerotic heart disease	1.12	0.98-1.27	0.092	1.04	0.90-1.21	0.56
Congestive heart failure	1.02	0.92-1.14	0.68	1.03	0.91-1.16	0.68
Cerebrovascular disease	1.11	0.80-1.56	0.53	0.97	0.66-1.43	0.87
History of cancer	1.10	0.85-1.92	0.47	0.98	0.73-1.31	0.88
Chronic obstructive pulmonary disease	0.99	0.80-1.22	0.90	0.83	0.64-1.08	0.17
Liver disease	1.29	0.81-2.02	0.29	0.83	0.41-1.69	0.61
Depression	1.28	0.90-1.83	0.16	1.13	0.68-1.89	0.64
Dementia	1.43	1.03-1.98	0.03	1.66	1.08-2.54	0.02
Clinical and laboratory variables						
Body mass index (each +5 kg/m ²)	0.91	0.87-0.96	<0.001	0.91	0.86-0.96	0.001
Serum Hemoglobin (each +1 g/dl)	1.16	1.10-1.21	<0.001	1.20	1.14-1.27	<0.001
White blood cells (each +10 ³ /μL)	1.04	1.03-1.06	<0.001	1.03	1.02-1.05	<0.001
Serum Albumin (each +1 g/dl)	0.63	0.56-0.71	<0.001	0.61	0.54-0.70	<0.001
Serum Creatinine (each +1 mg/dl)	0.94	0.90-0.97	<0.001	1.00	0.97-1.04	0.85
Normalized protein catabolic rate (each +1 g/kg/day)	0.60	0.46-0.78	<0.001	0.61	0.46-0.83	0.001
Single pool Kt/V (each +0.2)	0.99	0.92-1.06	0.73	0.97	0.89-1.05	0.45

Abbreviation: CI, confidence interval

Table 3.

Unadjusted and adjusted odd ratios (ORs) for the odds of withdrawal from hemodialysis (HD) for each ESRD network among incident HD patients ≥ 80 years (reference: global odds of HD withdrawal among all incident HD patients ≥ 80 years).

ESRD network region	Unadjusted analysis			Adjusted analysis		
	OR	95% CI	p	OR	95% CI	p
1 (CT, MA, NH)	1.25	1.05-1.50	0.01	1.01	0.77-1.33	0.96
2 (NY)	0.81	0.70-0.93	0.003	0.37	0.25-0.55	<0.001
3 (NJ)	0.35	0.24-0.51	<0.001	0.92	0.67-1.28	0.62
4 (DE, PA)	0.96	0.71-1.29	0.78	0.84	0.67-1.06	0.14
5 (DC, MD, VA, WV)	1.23	0.94-1.59	0.13	0.80	0.63-1.02	0.07
6 (GA, NC, SC)	1.03	0.77-1.34	0.83	1.14	0.91-1.43	0.24
7 (FL)	0.99	0.73-1.35	0.94	0.84	0.69-1.02	0.07
8 (AL, MS, TN)	0.75	0.60-0.93	0.01	1.03	0.73-1.46	0.86
9 (IN, KY, OH)	0.97	0.80-1.20	0.85	1.12	0.92-1.36	0.25
10 (IL)	0.98	0.80-1.21	0.87	1.14	0.86-1.51	0.36
11 (MI, MN, ND, SD, WI)	0.86	0.69-1.08	0.19	1.45	1.22-1.74	<0.001
12 (IA, KS, MO, NE)	0.94	0.79-1.11	0.46	1.48	1.18-1.86	<0.001
13 (AR, LA, OK)	1.49	1.20-1.84	<0.001	0.98	0.70-1.36	0.88
14 (TX)	1.23	0.99-1.51	0.06	1.01	0.80-1.28	0.91
15 (AZ, CO, NM, NV, UT)	1.11	0.88-1.41	0.37	1.32	1.05-1.65	0.02
16 (ID, OR, WA)	1.46	1.24-1.73	<0.001	1.33	0.94-1.89	0.11
17 & 18 (CA)	1.36	0.99-1.67	0.06	0.91	0.78-1.07	0.27

* Adjusted analysis included case-mix covariates accounting for socio-demographic and comorbidities such as age, sex, race/ethnicity, primary insurance, initial vascular access type, ten comorbid conditions (e.g., diabetes mellitus, hypertension, atherosclerotic heart disease, congestive heart failure, other-cardiovascular disease, cerebrovascular disease, dyslipidemia, dementia, depression, chronic obstructive pulmonary disease, liver disease, and history of malignancy), and dialysis dose (i.e., spKt/V). Abbreviations for regions represent each state; CI, confidence interval. The mean of all regions was used as a reference group. Data from six states (AK, HI, ME, MT, RI, VT) were not available in the present study.

* AL: Alabama; AK: Alaska; AZ: Arizona; AR: Arkansas; CA: California; CO: Colorado; CT: Connecticut; DE: Delaware; DC: District of Columbia; FL: Florida; GA: Georgia; HI: Hawaii; ID: Idaho; IL: Illinois; IN: Indiana; IA: Iowa; KS: Kansas; KY: Kentucky; LA: Louisiana; ME: Maine; MD: Maryland; MA: Massachusetts; MI: Michigan; MN: Minnesota; MS: Mississippi; MO: Missouri; MT: Montana; NE: Nebraska; NV: Nevada; NH: New Hampshire; NJ: New Jersey; NM: New Mexico; NY: New York; NC: North Carolina; ND: North Dakota; OH: Ohio; OK: Oklahoma; OR: Oregon; PA: Pennsylvania; RI: Rhode Island; SC: South Carolina; SD: South Dakota; TN: Tennessee; TX: Texas; UT: Utah; VT: Vermont; VA: Virginia; WA: Washington; WV: West Virginia; WI: Wisconsin; WY: Wyoming.