HHS Public Access

Author manuscript

Kidney Int. Author manuscript; available in PMC 2015 April 01.

Published in final edited form as:

Kidney Int. 2014 October ; 86(4): 798–809. doi:10.1038/ki.2014.110.

An instrumental variable approach finds no associated harm or benefit from early dialysis initiation in the United States

Julia J. Scialla, MD, MHS[1], **Jiannong Liu, PhD**[2], **Deidra C. Crews, MD, ScM**[3,4], **Haifeng Guo, MS**[2], **Karen Bandeen-Roche, PhD**[5], **Patti L. Ephraim, MPH**[4,6], **Navdeep Tangri, MD, PhD**[7], **Stephen M. Sozio, MD, MHS**[3,4], **Tariq Shafi, MBBS, MHS**[3,4], **Dana C. Miskulin, MD**[8], **Wieneke M. Michels, MD, PhD**[3,4,9], **Bernard G. Jaar, MD, MPH**[3,4,6,10], **Albert W. Wu, MD**[3,6], **Neil R. Powe, MD, MPH, MBA**[11], and **L. Ebony Boulware, MD, MPH**[3,4,6] **for The DEcIDE Network Patient Outcomes in End Stage Renal Disease Study Investigators**

[1]Department of Medicine, University of Miami Miller School of Medicine, Miami, FL [2]Chronic Disease Research Group, Minneapolis, MN [3]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD [4]Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, MD [5]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD [6]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD [7]Department of Medicine, Seven Oaks General Hospital, University of Manitoba, Winnipeg, Manitoba, Canada [8]Division of Nephrology, Tufts University School of Medicine, Boston, MA [9]Department of Medicine, Academic Medical Center, Amsterdam, The Netherlands [10]Nephrology Center of Maryland, Baltimore, MD [11]San Francisco General Hospital and University of California San Francisco, San Francisco, CA

Abstract

The estimated glomerular filtration rate (eGFR) at dialysis initiation has been rising. Observational studies suggest harm, but may be confounded by unmeasured factors. As instrumental variable methods may be less biased we performed a retrospective cohort study of 310,932 patients starting dialysis between 2006 to 2008 and registered in the United States Renal Data System in order to describe geographic variation in eGFR at dialysis initiation and determine its association with

Correspondence should be addressed to: Julia J. Scialla, MD, MHS, 1120 NW 14th Street, Suite 815, Miami, FL 33136, phone (305) 243-4991, fax (305) 243-8914, jscialla@med.miami.edu.

Disclosures:

AHRQ: Identifiable information, on which this report, presentation, or other form of disclosure is based, is confidential and protected by federal law, Section 903(c) of the Public Health Service Act, 42 USC 299a-1(c). Any identifiable information that is knowingly disclosed is disclosed solely for the purpose for which it has been supplied. No identifiable information about any individual supplying the information or described in it will be knowingly disclosed except with the prior consent of that individual. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

USRDS: The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

Portions of this work were presented in abstract form at the American Society of Nephrology's Kidney Week in San Diego, CA on November 3, 2012.

mortality. Patients were grouped into 804 health service areas by zip code. Individual eGFR at dialysis initiation averaged 10.8 ml/min/1.73m^2 but varied geographically. Only 11% of the variation in mean health service areas-level eGFR at dialysis initiation was accounted for by patient characteristics. We calculated demographic-adjusted mean eGFR at dialysis initiation in the health service areas using the 2006 and 2007 incident cohort as our instrument and estimated the association between individual eGFR at dialysis initiation and mortality in the 2008 incident cohort using the 2 stage residual inclusion method. Among 89,547 patients starting dialysis in 2008 with eGFR 5 to 20 ml/min/1.73m^2, eGFR at initiation was not associated with mortality over a median of 15.5 months [hazard ratio 1.025 per 1 ml/min/1.73m^2 for eGFR 5 to 14 ml/min/1.73m^2; and 0.973 per 1 ml/min/1.73m^2 for eGFR 14 to 20 ml/min/1.73m^2]. Thus, there was no associated harm or benefit from early dialysis initiation in the United States.

Introduction

The optimal time to initiate dialysis has been debated over the last two decades[1–5]. Clinical practice guidelines published in the United States (US) in 1997 advocated initiating dialysis when the glomerular filtration rate (GFR) was approximately 10.5 ml/min/1.73m^2 based on extrapolation from optimal dialytic clearance[6]. Subsequent concern regarding malnutrition, reduced quality of life and potential risks of emergent dialysis in patients delaying initiation led to revision of US clinical practice guidelines to suggest dialysis initiation at GFR <15 ml/min/1.73m^2 in the presence of signs or symptoms of uremia[7]. Over this time, mean GFR at dialysis initiation in the US rose from 8.1 in 1997 to 10.8 ml/min/1.73m^2 in 2007[8].

To date, the impact of early versus later dialysis initiation on patients' health outcomes remains unclear. A recent randomized trial conducted in Australia and New Zealand found no benefit or harm of early dialysis initiation, but was limited by a high rate of cross-over between groups of patients assigned to early or later initiation[9]. Furthermore, the results may not translate well to patients with end-stage renal disease (ESRD) in the US who are more likely to use hemodialysis, to have indwelling central venous catheters for dialysis access, and to have diabetes and other comorbid illnesses[10]. On the contrary, a growing body of observational research studies in the US dialysis population suggests that earlier initiation is associated with increased mortality[11–15], but may be limited by residual confounding due to factors such as health status[16,17].

Statistical methods, such as instrumental variable analyses, may help overcome confounding and improve the estimation of treatment effects from observational comparative effectiveness studies[18,19]. An instrumental variable affects the likelihood of receiving a particular treatment strategy, and therefore may impact the outcome through its effect on treatment, but is not directly associated with the outcome through any other causal pathway[20]. Variables meeting these conditions may be able to provide improved control for confounding, including unobserved confounding, although identifying suitable instrumental variables is a challenge[21]. In this study, we describe geographic variation in GFR at dialysis initiation in the US, explore how it relates to regional characteristics, and utilize the local practice pattern, reflected by the mean GFR at dialysis initiation within small geographic

areas, as an instrumental variable to estimate the association of patients' GFR at dialysis initiation and mortality.

Results

Study overview

We used nationally representative data from the United States Renal Data System (USRDS), the US registry of patients receiving treatment for ESRD[10], to accomplish two goals: (1) to explore geographic variation in the estimated GFR (eGFR) at dialysis initiation; and (2) to evaluate the relationship between patients' eGFR at dialysis initiation and risk of mortality using the observed geographic variation as an instrumental variable. The geographic analyses include 310,932 incident dialysis patients initiating dialysis between 2006–2008 from 804 small geographic areas in the US, known as health service areas (HSAs)[10]. Subsequent mortality analyses split the study population into two cohorts: one cohort of incident dialysis patients initiating dialysis between 2006–2007 was used to create the instrumental variable (demographic-adjusted mean eGFR at dialysis initiation within the HSA); and one cohort involving 89,547 patients initiating dialysis in 2008 with an eGFR between 5–20 ml/min/1.73m^2 was studied in survival analyses (Figure 1). We restricted the patients' eGFR at dialysis initiation to this range because it is a range commonly targeted by nephrologists for initiation[22].

Geographic variation in mean eGFR at dialysis initiation

The number of incident participants per HSA varied from 1 to 14,632 (median 148; interquartile range 50 to 339). Nationally, the mean eGFR at dialysis initiation was 10.82 ± 4.92 ml/min/1.73m^2. Mean eGFR at initiation and other patient characteristics are presented according to 6 national regions (Pacific, Mountain, Midwest, South, Mid-Atlantic and New England) in Supplemental Table 1. We identified a geographic pattern (Figure 2a) with higher mean eGFR at dialysis initiation in the Midwest and Mountain regions and lower mean eGFR at dialysis initiation in the South, New England, Mid-Atlantic and Pacific regions compared with the national average (Figure 2b; each $p<0.001$).

The geographic patterns were similar after additional adjustment for age, sex, race and ethnicity (Figure 3), and with further adjustment for comorbid illnesses, income and pre-dialysis insurance status (Supplemental Figure 1). After adjustment for all patient-level characteristics, mean eGFR at initiation was lowest in New England follow by the South and Mid-Atlantic and highest in Mountain, followed by Midwest and Pacific regions (Figure 2b; each $p <0.001$ compared to national average). The standard deviation of mean eGFR at dialysis initiation across HSAs was minimally attenuated by adjustment for age (9% attenuation), sex (0.1%), race (4%) and Hispanic ethnicity (2%) or 11% after full demographic adjustment. There was no further attenuation after adjustment for other patient characteristics (data not shown).

The geographic distribution of selected HSA-level characteristics is depicted in Supplemental Figure 2. Overall, eGFR at dialysis initiation was associated with many HSA-level characteristics, but associations were small in magnitude with inconsistent trends

across categories (Figure 4). The largest and most consistent trends observed were earlier dialysis initiation in areas with greater market competition or younger median age of nephrologists.

Instrumental Variable Analysis

Due to geographic differences in dialysis timing that were independent of patient characteristics, we hypothesized that the demographic-adjusted mean eGFR at dialysis initiation within the HSA (i.e. adjusted HSA-level mean eGFR) represents the local practice pattern and could be used as an instrumental variable to evaluate the association between patients' individual eGFR at initiation (i.e. patient-level eGFR) and mortality (Supplemental Figure 3). We calculated the instrumental variable using the 2006–2007 incident cohort and evaluated the relationship between patients' eGFR at dialysis initiation and mortality in 89,547 patients initiating dialysis in 2008 with an eGFR between 5–20 ml/min/1.73m^2. Patient characteristics according to eGFR at dialysis initiation below, within and above this range, which is commonly targeted by nephrologists for dialysis initiation[22], are presented in Supplemental Table 2. Adjusted HSA-level mean eGFR ranged from 8.91 to 12.52 with a median of 10.61 ml/min/1.73m^2. Patient characteristics were better balanced when classified according to adjusted HSA-level mean eGFR at dialysis initiation (> vs. ≤ median) as opposed to classification by patient-level eGFR at dialysis initiation (Table 1). Race was the only patient level covariate with a standardized difference >10% across HSA-level eGFR groups. HSA-level characteristics are presented by levels of the instrumental variable in Table 2. Some HSA-level characteristics show large standardized differences across levels of the instrument. Based on our framework (see Supplemental Figure 3), we conceptualized these factors as influencing the local physician practice patterns with regard to the types and timing of renal replacement therapy initiated, but not as causes of the outcome. HSA-level mean eGFR at dialysis initiation from the 2006–2007 incident cohort was robustly associated with patient-level eGFR at dialysis initiation from the 2008 incident cohort overall and among all subgroups tested as indicated by a high F-statistic, well above previously published cutpoints[23]. This indicates that our instrumental variable strongly predicted the treatment of interest overall and in a variety of important subgroups, a critical feature of an effective instrument (Table 3).

Over a median follow up of 15.5 months (interquartile range 9.9–19.8 months), 24,761 patients died (23.2 per 100 patient years). Using piecewise linear splines, patients' eGFR at dialysis initiation was not associated with mortality using the 2 stage residual inclusion method for instrumental variable analyses[24] (Figure 5a). Estimates for the hazard associated with eGFR across the range from 5–20 ml/min/1.73m^2 were similar in sensitivity analyses including a broader range of eGFR at dialysis initiation (Supplemental Figure 4). In a multivariable Cox model that did not incorporate the instrumental variable approach, the hazard ratio associated with higher patient-level eGFR at initiation was highly statistically significant and graded across the full range of eGFR (HR 1.033; 95% CI 1.030–1.036 for each 1 ml/min/1.73m^2 higher eGFR or HR 1.176; 95% CI 1.159–1.193 for each 5 ml/min/1.73m^2 higher eGFR; p<0.001; Figure 5b). The result was unchanged if the model incorporated clustering effect within HSAs (data not shown).

Discussion

In this study, we identified geographic variation in the timing of dialysis initiation across the US that is independent of case-mix and is associated with provider and market characteristics. These findings not only highlight opportunities to standardize care across the US but also support the use of local area mean eGFR at dialysis initiation as an instrumental variable to evaluate the relationship between early versus later dialysis initiation and mortality. Our instrumental variable analyses, which employed methodology that may be able to better control for confounding compared to standard multivariable adjustment, demonstrated no association between patients' GFR at initiation and subsequent mortality in the 2008 US incident dialysis population. Although confidence limits for the instrumental variable analyses were wide, striking differences in the shape of the association yielded by the instrumental variable analyses compared with more conventional analyses suggest that prior observational results may have substantial confounding bias. Furthermore, while not associated with mortality in this study, early initiation of dialysis increases cost to the health care system[25] and could be related to other harms, such as risk of infections, hospitalizations and worse quality of life.

Randomized controlled trials are the gold-standard for estimating treatment efficacy in the setting of idealized care delivery. However, trial results may not reliably measure the effectiveness of treatment strategies when care is delivered to patients who may not have been eligible for trials and when care is delivered under real-world constraints[26]. Comparative effectiveness studies, such as this, are designed to fill these gaps and provide more generalizable treatment estimates to complement knowledge obtained from randomized trials[26,27]. Our results are consistent with those from the IDEAL study, the only randomized controlled trial examining risks of mortality with earlier versus later dialysis initiation[9]. As IDEAL was performed in New Zealand and Australia, our similar findings may increase confidence that the findings from this trial can be extrapolated to a more diverse US dialysis population and to patients initiating dialysis in real-world clinical practice settings. On the contrary, our results may not generalize as well to patients on dialysis treated outside of the US given differences in patient characteristics.

Instrumental variable analyses attempt to control unmeasured confounding by examining the impact of differences in treatment that are due to a purely exogenous variable (i.e. the instrument) and controlling for the variation in the patients treatment that is determined by other unmeasured characteristics (i.e. the residual). For this reason, results from instrumental variable analyses generalize only to patients whose treatment was affected by the instrumental variable, a group often referred to as the "marginal" patient population[28]. In this analysis, our instrument, the local dialysis initiation practice pattern, contributed to the variation in patients' GFR at dialysis initiation across all subgroups tested, including elderly patients, those with diabetes, congestive heart failure and those without insurance, suggesting that our findings generally apply to these subgroups that were inadequately represented in the IDEAL trial[9]. Diabetic patients comprise 45%, and adults 75 years of age and older comprise 26% of patients initiating dialysis therapy in the US in 2010[10], making reliable treatment estimates that apply to these patient groups critically important. It is important to emphasize that our survival analyses focused on patients with an eGFR within

the range widely targeted by nephrologists for initiation, eGFR 5–20 ml/min/1.73m^2.[22] We were not able to evaluate for a survival advantage or disadvantage for patients initiating with eGFR outside of this range.

Although our instrumental variable impacted the average eGFR at dialysis initiation in all subgroups tested, our results would not apply to any individual patient who would have been treated the same no matter where they lived, such as a patient with refractory uremic symptoms or electrolyte abnormalities. We did not have information on the clinical reasons for dialysis initiation in this study. A number of important patient characteristics contribute to the medical decision to start dialysis earlier or later, including age and the presence of comorbid medical conditions[15,29,30]. However, in surveys many nephrologists report using GFR as a primary factor determining when to start[22]. Furthermore, although creatinine-based estimates of eGFR can be inaccurate in the setting of abnormal body composition, creatinine-based eGFR is currently the most widely monitored clinical measure of GFR in the US, and therefore reflects the information that providers use at the time of clinical decision-making. The serum creatinine measurements used in this study reflect information collected administratively from clinicians, and we do not know whether all laboratories used IDMS-traceable methods. However, the bias induced by error in serum creatinine measurement is likely to be negligible within this low range of eGFR[31] and the measurements represent the information treating physicians had available to them at the time and in the environment in which they made medical decisions.

Findings from our standard Cox models replicated those reported in prior observational studies of the association of early versus later dialysis initiation with mortality[11], suggesting that our instrumental variable was effective in accounting for additional unobserved confounding. Nonetheless, our findings should be interpreted with caution due to relatively wide confidence intervals and inherent difficulties with confirming critical assumptions of the instrumental variable approach. The validity of our findings depends upon our selection of an appropriate instrument and the soundness of our assumptions in selecting the instrument. We assumed the instrument (i.e. the local practice pattern as reflected in the demographic-adjusted HSA-level mean eGFR at dialysis initiation) only affects survival by impacting subsequent patients' eGFR at dialysis initiation, and not via any other pathway. It is possible that areas where dialysis tends to be initiated earlier may have correlated practice patterns that impact patient outcomes through alternative pathways other than their influence on patients' individual eGFRs at dialysis initiation. However, this may be less of a concern in instances, such as this, when optimal treatment practices are not known[32]. It is also possible that geographic patterns in eGFR at dialysis initiation may mirror patterns in health care quality, access to medical care, and socioeconomic status, all of which have been associated with patients' outcomes. We adjusted for median income and rurality of the patient's zip code and pre-dialysis insurance status in our analyses, but we may not have been able to fully measure and account for these differences. We considered other instruments, such as distance to the nearest dialysis facility, however these alternative variables did not adequately balance several important patient characteristics[33]. Our instrument balanced most patient characteristics to an acceptable extent, but race remained unbalanced. Although blacks tend to survive longer on dialysis compared to whites[34], this variable is relatively easily captured and controlled for in our survival models; therefore, we

wouldn't expect this to contribute to residual confounding. Further, it may have been preferable to utilize the practice patterns of a patient's specific nephrologist as an instrument, as opposed to regional practice patterns, but information linking patients with specific nephrologists was not available. Finally, in this analysis survival is measured from the time of dialysis initiation, whereas the decision about timing of dialysis initiation occurs in the setting of advanced chronic kidney disease, before dialysis is initiated. Similar to most observational studies of this subject, we were not able to account for lead time or survival bias with this study design. Novel study designs attempting to account for these factors are available, but require information on patients' pre-dialysis health history which was not available in our USRDS data[35].

In conclusion, we found geographic variation in the timing of dialysis initiation across the US that was only partially explained by patient-level demographic and clinical factors and was influenced by non-patient factors, including median nephrologist age in the HSA and local dialysis market characteristics. Although earlier initiation of dialysis incurs substantial costs to the health system[25] and may increase burdens on patients, our analyses suggest there is no meaningful impact on post-initiation outcomes in the US dialysis population, consistent with findings from a recent clinical trial. Future clinical practice guidelines in the US should discourage early dialysis initiation based exclusively on renal clearance.

Methods

Study population

We studied adults (≥18 years old) initiating dialysis in the US from 2006–2008. The USRDS maintains data on demographics, medical history and laboratory tests at the time of initial treatment for ESRD ascertained through mandated reporting by ESRD care providers [Centers for Medicare and Medicaid Services (CMS) Medical Evidence Form 2728]. The USRDS also collects information on dialysis facilities through the annual ESRD Facility Survey.

We excluded participants who were missing CMS Form 2728 or data needed to calculate eGFR, had an unknown dialysis type, or who had inadequate geographic information. We grouped patients into HSAs by zip code of residence[10], and grouped HSAs into 6 national regions (New England, Mid-Atlantic, South, Midwest, Mountain and Pacific) to test larger regional differences. We defined regions based on boundaries of US Census Regions and Divisions. If the standardized difference in mean eGFR at dialysis initiation was >0.05 ml/min/1.73m^2 between Divisions within a given Census Region, then these Regions were split into their respective Census Divisions. For instance, the Northeast Census Region was divided into the New England and Mid-Atlantic Divisions (standardized mean difference= 0.09 ml/min/1.73m^2), and the West was divided into Mountain and Pacific Divisions (standardized mean difference= 0.11 ml/min/1.73m^2). The South and Midwest Census Regions were not further divided.

Patient characteristics

Because creatinine-based eGFR is the most widely utilized measure of kidney function in clinical practice, eGFR at dialysis initiation was calculated using the 4-variable MDRD study equation[36]. We quantified comorbidity using a previously validated index[37]. We used public data sources to describe characteristics of each patients' residential zip code, including median household income from the 2000 US Census[38], and rurality, using Rural Urban Commuting Area (RUCA) codes from 2000[39]. To summarize confounders, we created a propensity score for early initiation of dialysis (eGFR ≥10ml/min/1.73m^2) using all patient level characteristics in a logistic regression model (Supplemental Methods).

HSA-level characteristics

We hypothesized that local factors, such as the availability of renal replacement therapy, characteristics of nephrologists, and the dialysis market would influence timing of dialysis initiation. Using additional data from the USRDS facility files and 2006 American Medical Association's Physician Masterfile[40], we calculated the following for each HSA: (1) the ratio of prevalent in-center hemodialysis patients to available hemodialysis beds; (2) the proportion of prevalent dialysis patients treated with peritoneal dialysis; (3) the proportion of incident ESRD patients treated with pre-emptive renal transplantation; (4) the number of practicing nephrologists per 100 prevalent dialysis patients; (5) median age of practicing nephrologists in the HSA; (6) a measure of market competition among dialysis centers in the HSA, known as the Herfindahl index[41]; and (7) the percentage of prevalent dialysis patients treated in for-profit facilities. Details of variable creation are provided as supplementary material.

Statistical analysis of geographic variation

We directly calculated the mean eGFR at initiation within each HSA. To delineate geographic patterns, we used a Bayesian hierarchical model to smooth estimates spatially assuming neighboring HSAs were similar[42]. We explored the geographic distribution of HSA-level characteristics using the same methodology.

To facilitate adjustment, we also modeled the mean eGFR at dialysis initiation with a general linear model including a random effect for each HSA and using the national population as the reference[43]. We adjusted our estimates with fixed effects for each demographic characteristic separately [age (categorized as 18–34, 35–44, 45–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and ≥85 years); sex; race (categorized as black, white, Asian or other); and Hispanic ethnicity], followed by full demographic adjustment. To evaluate if other patient characteristics influenced the variability, we adjusted for comorbidity score (categorized as 0; 1–2; 3–5; ≥6), diabetes, congestive heart failure, median income in the patient's zip code (categorized as missing; 0–24,999; 25,000–37,999; 38,000–48,999; ≥49,000), insurance status (categorized as Medicare, Medicaid, private versus none), dialysis modality at initiation, vascular access at initiation (categorized as arteriovenous fistula, arteriovenous graft, central venous catheter, peritoneal dialysis or unknown), and RUCA code of the patient's residence (categorized as metropolitan [0–3], micropolitan [4–6], rural [7–10], or missing). We tested for regional differences by adding fixed region effects with and without adjustment for patient characteristics. Finally, we used

linear regression to determine the association between each HSA-level characteristic and eGFR at initiation after adjustment for patient characteristics. These models did not include random effects for each HSA.

Instrumental variable analysis

To avoid artificial correlation between HSA-level mean eGFR at dialysis initiation (i.e. the instrumental variable) and patient-level eGFR at dialysis initiation (i.e. the treatment of interest), we split the study population and calculated the instrumental variable using demographic-adjusted random effects models described above among those that initiated dialysis in 2006–2007. We evaluated outcomes among those that initiated dialysis in 2008 with an eGFR within the "typical" eGFR range (5–20 ml/min/1.73m^2) targeted by nephrologists for dialysis initiation[22] (n=89,547). This cohort was followed until December 31, 2009 or until censoring at the time of kidney transplantation (n=2973) or recovery of renal function (n=4017).

To evaluate the association of patients' eGFR at dialysis initiation and mortality, we used the two-stage residual inclusion approach[24]. In stage one we fit a general linear regression model of patient-level eGFR at dialysis initiation using the instrumental variable and all patient-level characteristics as covariates [age, sex, race, ethnicity, comorbidity index, congestive heart failure, diabetes, insurance status, zip code level median income and RUCA code, modality and vascular access at dialysis initiation, primary cause of end-stage renal disease (diabetes, hypertension, glomerulonephritis or other/unknown) and categories of serum albumin, hemoglobin and body mass index]. We evaluated the strength of our instrumental variable overall and in subpopulations by age, race, insurance status, modality/vascular access and presence of diabetes or congestive heart failure. To assess the validity of our instrumental variable, we considered whether: (1) it was independent from the residual of the first stage model; (2) it was a predictor of patient-level eGFR at initiation; and, (3) it affected outcomes only through initiation eGFR[20]. Conditions (1) and (2) were directly verified. The HSA-level adjusted mean eGFR and the residual from stage 1 were not correlated ($p>0.99$). Our instrumental variable was a predictor of patient-level eGFR at dialysis initiation (Table 3). Condition (3) cannot be directly assessed. We verified condition (3) to the extent possible by assessing characteristics of patients who initiated dialysis in 2008 according to categories of HSA-level mean eGFR at initiation, the instrumental variable (Table 1).

In the second stage we fit a Cox proportional hazards model for all-cause mortality including the patient's eGFR at dialysis initiation, all patient-level characteristics and the residual from stage one. We incorporated penalized splines to allow flexible relationships between patient-level eGFR, stage 1 residuals and log hazard of mortality. Based on results from exploratory spline analyses, we performed analyses using piecewise linear splines with a knot at eGFR of 14 ml/min/1.73m^2 for patient-level eGFR to quantify the effect of eGFR at dialysis initiation on hazard of mortality within ranges of eGFR. The proportionality assumption was checked by Schoenfeld residual plots. Analyses were performed using R 2.15.2 and SAS 9.2.

Sensitivity Analyses

We repeated our instrumental variable analyses among the less restricted population with eGFR <20 ml/min/1.73m^2. We compared our main results to those from a multivariable Cox model adjusted for all patient-level characteristics, but without adjustment for the stage 1 residual.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Support:

The Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network Patient Outcomes in ESRD Study was supported by the Agency for Healthcare Research and Quality (AHRQ) contract HHSA290200500341I, Task Order #6. J Scialla was supported in part by K23 DK095949. D Crews was supported by the Amos Medical Faculty Development Program of the Robert Wood Johnson Foundation, Princeton NJ. W Michels was supported by a Postdoctoral Full Fellowship Abroad Grant (KFB 11.005) of the Dutch Kidney Foundation (Nierstichting). T Shafi was supported by K23 DK083514.

The DEcIDE Network Patient Outcomes in End-Stage Renal Disease Study Team consists of members from the Johns Hopkins University, Baltimore (L. Ebony Boulware, Karen Bandeen-Roche, Courtney Cook, Josef Coresh, Deidra Crews, Patti Ephraim, Bernard Jaar, Jeonyong Kim, Yang Liu, Jason Luly, Aidan McDermott, Wieneke Michels, Paul Scheel, Tariq Shafi, Stephen Sozio, Albert Wu, Jing Zhou); University of California, San Francisco (Neil R. Powe); the Chronic Disease Research Group, Minneapolis (Allan Collins, Robert Foley, David Gilbertson, Haifeng Go, Joseph Grill, Charles Herzog, Jiannong Liu, Wendy St. Peter); Cleveland Clinic Foundation (Joseph Nally, Susana Arrigain, Stacey Jolly, Vicky Konig, Xiaobo Liu, Sankar Navaneethan, Jesse Schold,); Dialysis Clinic, Incorporated, Nashville (Karen Majchrzak, Phil Zager); Tufts University, Boston (Dana Miskulin, Klemens Meyer); University of Miami (Julia J. Scialla); University of Manitoba (Navdeep Tangri); and Academic Medical Center, The Netherlands (Wieneke Michels).

References

1. Ledebo I, Kessler Ml, van Biesen W, et al. Initiation of dialysis-opinions from an international survey: Report on the Dialysis Opinion Symposium at the ERA-EDTA Congress, 18 September 2000, Nice. Nephrol Dial Transplant. 2001; 16:1132–1138. [PubMed: 11390711]
2. Obrador GT, Pereira BJ. Initiation of dialysis: current trends and the case for timely initiation. Perit Dial Int. 2000; 20:S142–149. [PubMed: 10911660]
3. Pollock CA, Cooper BA, Harris DC. When should we commence dialysis? The story of a lingering problem and today's scene after the IDEAL study. Nephrol Dial Transplant. 2012; 27:2162–2166. [PubMed: 22649211]
4. Korevaar JC, Jansen MAM, Dekker FW, et al. When to initiate dialysis: effect of proposed US guidelines on survival. Lancet. 2001; 358:1046–1050. [PubMed: 11589934]
5. Rosansky SJ. The Sad Truth About Early Initiation of Dialysis in Elderly Patients. JAMA. 2012; 307:1919–1920. [PubMed: 22570459]
6. National Kidney Foundation. NKF-KDOQI Clinical Practice Guidelines. Am J Kidney Dis. 1997; 30:S67–S136.
7. National Kidney Foundation. KDOQI Clinical practice guidelines and clinical practice recommendations for 2006 updates: hemodialysis adequacy, peritoneal dialysis adequacy and vascular access. Am J Kidney Dis. 2006; 48:S1–S322. [PubMed: 17045862]
8. O'Hare A, Choi A, Boscardin W, et al. Trends in timing of initiation of chronic dialysis in the United States. Arch Intern Med. 2011; 171:1663–1669. [PubMed: 21987197]
9. Cooper BA, Branley P, Bulfone L, et al. A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med. 2010; 363:609–619. [PubMed: 20581422]

10. United States Renal Data System. USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda, MD: 2011.
11. Susantitaphong P, Altamimi S, Ashkar M, et al. GFR at initiation of dialysis and mortality in CKD: a meta-analysis. Am J Kidney Dis. 2012; 59:829–840. [PubMed: 22465328]
12. Traynor JP, Simpson K, Geddes CC, et al. Early Initiation of Dialysis Fails to Prolong Survival in Patients with End-Stage Renal Failure. J Am Soc Nephrol. 2002; 13:2125–2132. [PubMed: 12138145]
13. Beddhu S, Samore MH, Roberts MS, et al. Impact of Timing of Initiation of Dialysis on Mortality. J Am Soc Nephrol. 2003; 14:2305–2312. [PubMed: 12937307]
14. Kazmi WH, Gilbertson DT, Obrador GT, et al. Effect of Comorbidity on the Increased Mortality Associated With Early Initiation of Dialysis. Am J of Kidney Dis. 2005; 46:887–896. [PubMed: 16253729]
15. Rosansky SJ, Eggers P, Jackson K, et al. Early start of hemodialysis may be harmful. Arch Intern Med. 2011; 171:396–403. [PubMed: 21059968]
16. Bao Y, Dalrymple L, Chertow G, et al. Frailty, dialysis initiation, and mortality in end-stage renal disease. Arch Intern Med. 2012; 172:1071–1077. [PubMed: 22733312]
17. Lassalle M, Labeeuw M, Frimat L, et al. Age and comorbidity may explain the paradoxical association of an early dialysis start with poor survival. Kidney Int. 2010; 77:700–707. [PubMed: 20147886]
18. Fang G, Brooks JM, Chrischilles EA. Comparison of instrumental variable analysis using a new instrument with risk adjustment methods to reduce confounding by indication. Am J Epidemiol. 2012; 175:1142–1151. [PubMed: 22510277]
19. Brunelli SM, Rassen JA. Emerging Analytical Techniques for Comparative Effectiveness Research. Am J Kidney Dis. 2012; 61:13–17. [PubMed: 23021799]
20. Brookhart M, Rassen J, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. Pharmacoepidemiol Drug Saf. 2010; 19:537–554. [PubMed: 20354968]
21. Angrist J, Imbens G, Rubin D. Identification of causal effects using instrumental variables. J Am Stat Assoc. 1996; 91:444–472.
22. van de Luijtgaarden M, Noordzij M, Tomson C, et al. Factors influencing the decision to start renal replacement therapy: Results of a survey among European nephrologists. Am J Kidney Dis. 2012; 60:940–948. [PubMed: 22921638]
23. Staiger D, Stock J. Instrumental variables regression with weak instruments. Econometrica. 1997; 65:557–586.
24. Terza JV, Basu A, Rathouz PJ. Two-stage residual inclusion estimation: addressing endogeneity in health econometric modeling. J Health Econ. 2008; 27:531–543. [PubMed: 18192044]
25. Harris A, Cooper BA, Li JJ, et al. Cost-effectiveness of initiating dialysis early: a randomized controlled trial. Am J Kidney Dis. 2011; 57:707–715. [PubMed: 21349618]
26. McKee M, Britton A, Black N, et al. Methods in health services research. Interpreting the evidence: choosing between randomised and non-randomised studies. BMJ. 1999; 319:312–315. [PubMed: 10426754]
27. Sox HC, Greenfield S. Comparative Effectiveness Research: A Report From the Institute of Medicine. Ann Intern Med. 2009; 151:203–205. [PubMed: 19567618]
28. Harris KM, Remler DK. Who is the marginal patient? Understanding instrumental variables estimates of treatment effects. Health Serv Res. 1998; 33:1337–1360. [PubMed: 9865223]
29. Wright S, Klausner D, Baird B, et al. Timing of dialysis initiation and survival in ESRD. Clin J Am Soc Nephrol. 2010; 5:1828–1835. [PubMed: 20634325]
30. Crews D, Scialla J, Liu J, et al. Predialysis health, dialysis timing, and outcomes among older United States adults. J Am Soc Nephrol. 2014; 25:370–379. [PubMed: 24158988]
31. Myers G, Miller W, Coresh J, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem. 2006; 52:5–18. [PubMed: 16332993]

32. Brookhart MA, Schneeweiss S. Preference-based instrumental variable methods for the estimation of treatment effects: assessing validity and interpreting results. Int J Biostat. 2007; 3:Article 14. [PubMed: 19655038]
33. Thompson S, Gill J, Wang X, et al. Higher mortality among remote compared to rural or urban dwelling hemodialysis patients in the United States. Kidney Int. 2012; 82:352–359. [PubMed: 22592186]
34. Robinson BM, Joffe MM, Pisoni RL, et al. Revisiting survival differences by race and ethnicity among hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study. J Am Soc Nephrol. 2006; 17:2910–2918. [PubMed: 16988065]
35. Sjolander A, Nyren O, Bellocco R, et al. Comparing different strategies for timing of dialysis initiation through inverse probability weighting. Am J Epidemiol. 2011; 174:1204–1210. [PubMed: 21984655]
36. Levey AS, Coresh J, Greene T, et al. Using Standardized Serum Creatinine Values in the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate. Ann Intern Med. 2006; 145:247–254. [PubMed: 16908915]
37. Liu J, Huang Z, Gilbertson DT, et al. An improved comorbidity index for outcome analyses among dialysis patients. Kidney Int. 2010; 77:141–151. [PubMed: 19907414]
38. US Census Bureau. Census 2000 Data for the United States. 2000. http://wwwcensusgov/census2000/states/ushtml
39. Rural Health Research Center. [Accessed July 26, 2012] Rural-Urban Commuting Area Codes (RUCAs). http://deptswashingtonedu/uwruca/
40. American Medical Association. AMA Physician Masterfile. 2013. http://wwwama-assnorg/ama/pub/about-ama/physician-data-resources/physician-masterfilepage?
41. Baker LC. Measuring competition in health care markets. Health Serv Res. 2001; 36:223–251. [PubMed: 11327175]
42. Waller L, Carlin B, Xia H, et al. Hierarchical spatio-temporal mapping of disease rates. J Am Stat Assoc. 1997; 92:607–617.
43. Liu J, Louis TA, Pan W, et al. State-level adjusted ESRD incident rates: use of observed vs model-predicted category-specific rates. Kidney Int. 2006; 69:1459–1463. [PubMed: 16531980]

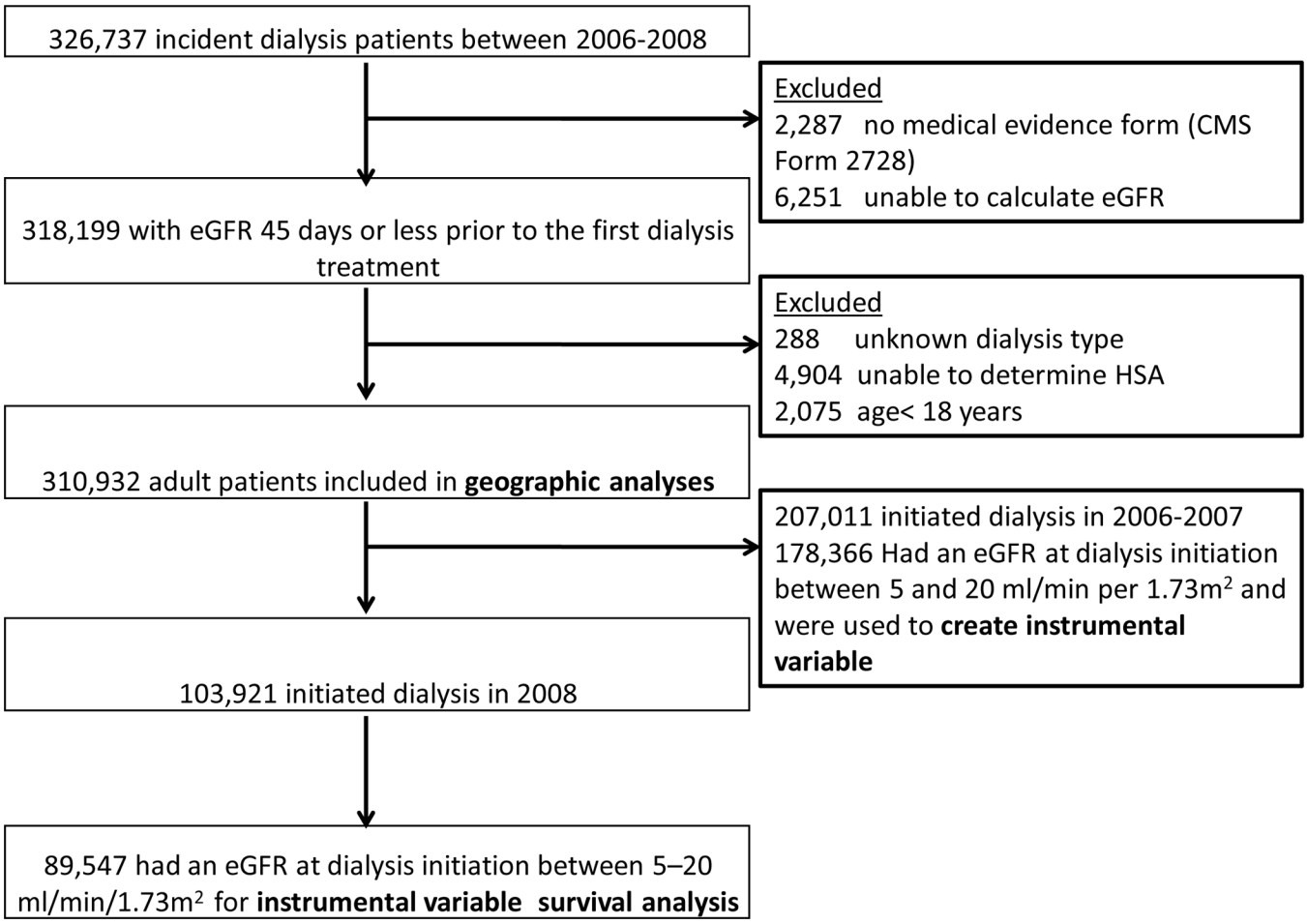

Figure 1. Participant flow diagram

Medical evidence form refers to Centers for Medicare and Medicaid Services (CMS) Medical Evidence Form 2728; eGFR, estimated glomerular filtration rate; HSA, health service area. Differences are displayed relative to the overall national mean eGFR at dialysis initiation (10.8 ml/min per 1.73 m2)

Figure 2a.

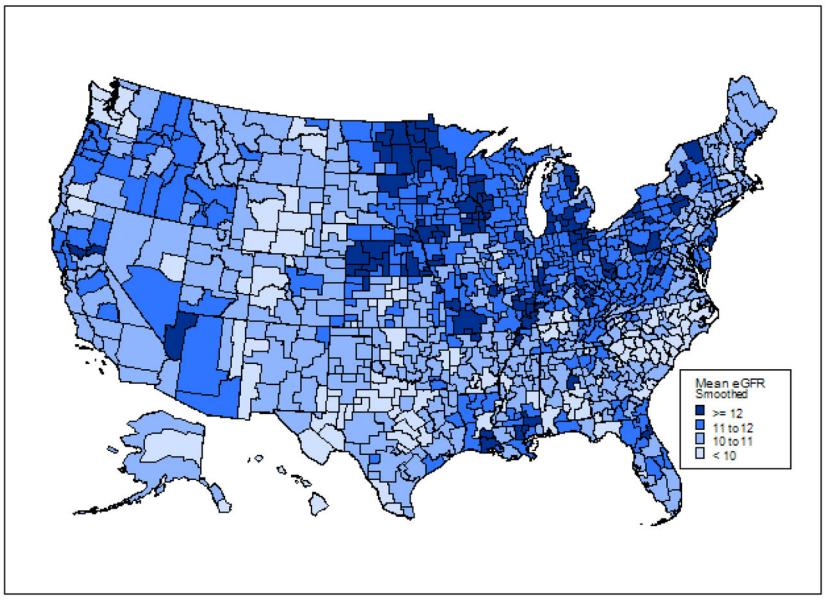

Figure 2b.

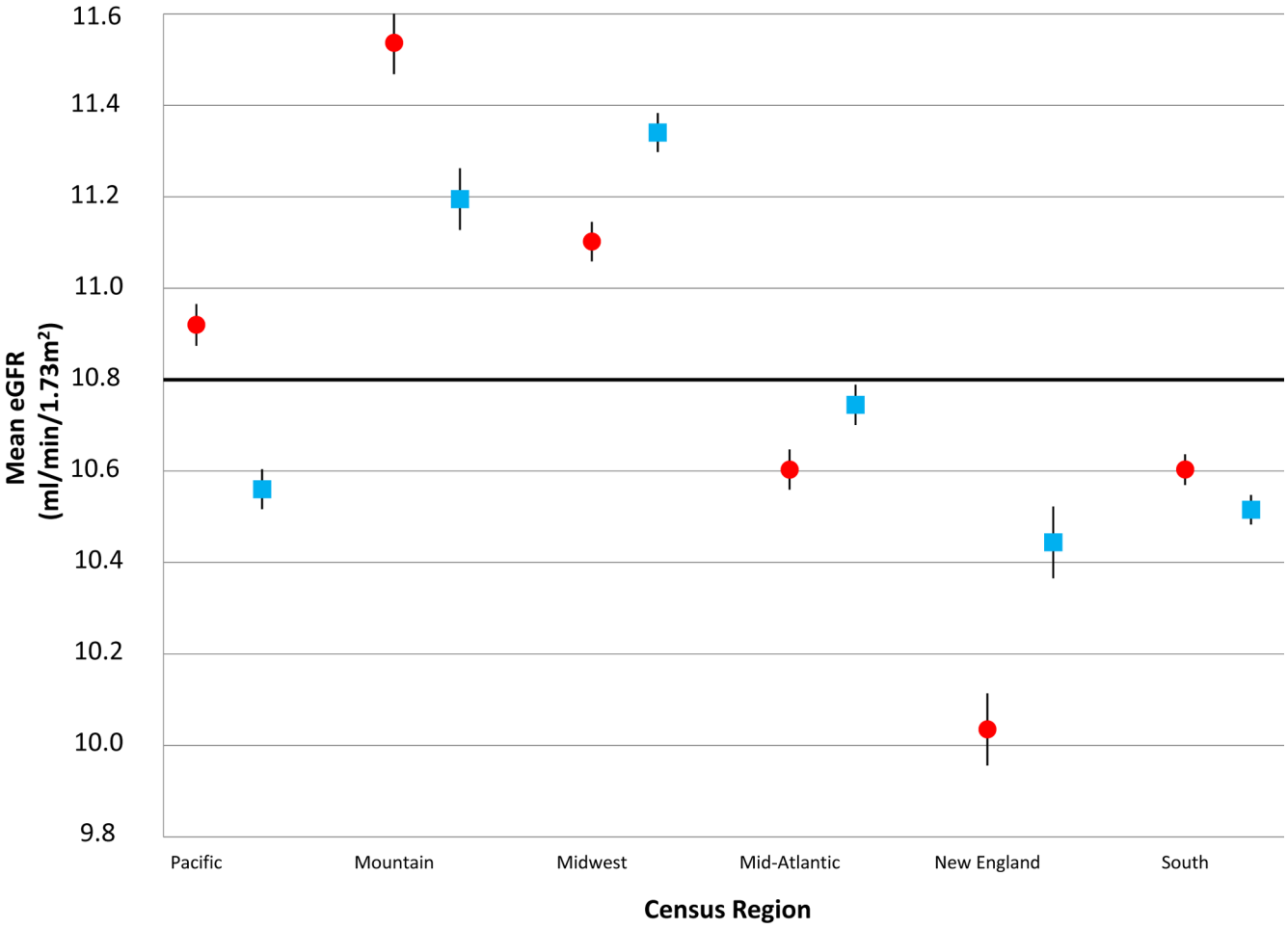

Figure 2. Variation in the timing of dialysis initiation by Health Service Area and Region

(A), mean estimated glomerular filtration rate (eGFR) at dialysis initiation smoothed by a Bayesian model.

(B), Difference between mean eGFR in the region and the national average. Differences were tested without adjustment (blue square) and with adjustment for age, sex, race, Hispanic ethnicity, comorbidity index, diabetes, congestive heart failure, median income in the patient's zip code, insurance status, modality/vascular access at dialysis initiation, and RUCA code of the patient's residence (red circle). Bars represent 95% confidence interval.

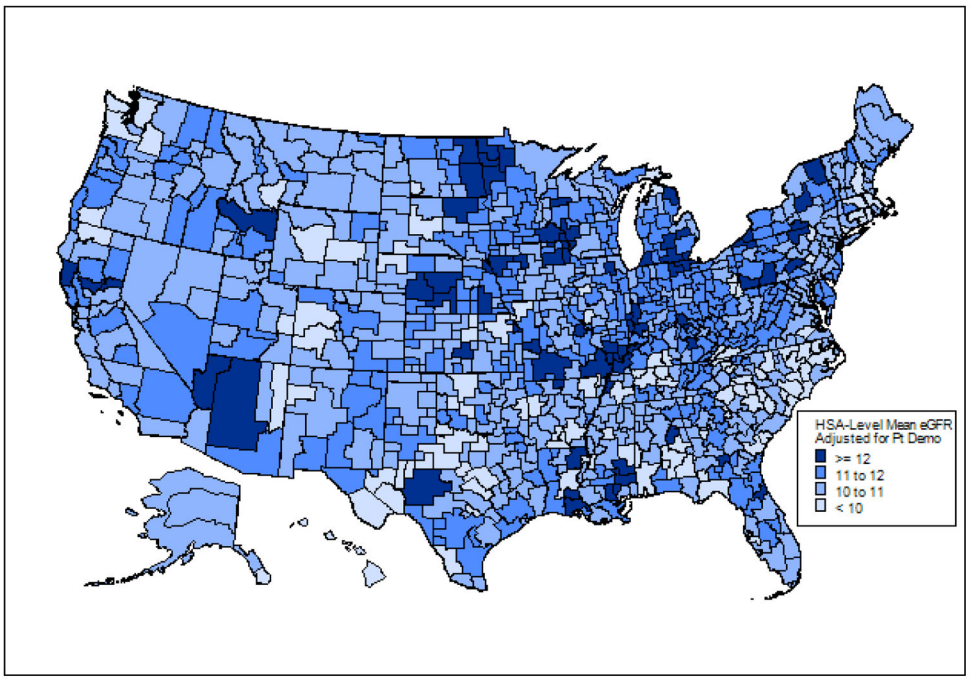

Figure 3. Variation in the timing of dialysis initiation by Health Service Area after demographic adjustment

Map depicts mean estimated glomerular filtration rate at dialysis initiation by Health Service Area (HSA) after adjusting for age, sex, race and Hispanic ethnicity using a random effects model and followed by Bayesian smoothing.

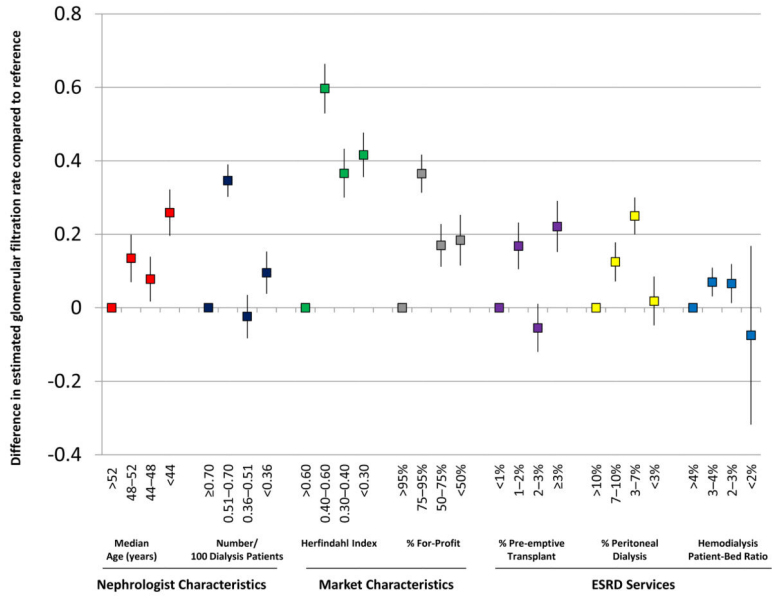

Figure 4. Difference in patients' estimated glomerular filtration rate (eGFR) at dialysis initiation according to health service area (HSA)-level characteristics

Estimates are adjusted for patient age, sex, race, Hispanic ethnicity, comorbidity index, diabetes, congestive heart failure, median income in the patient's zip code, insurance status, modality/vascular access at dialysis initiation, and rural urban commuting area (RUCA) code of the patient's residence. Herfindahl index is a measure of market competition calculated as the sum of squares of the market share of each provider type. % for-profit is referring to the percentage of prevalent hemodialysis patients treated in for-profit dialysis facilities in the HSA. % pre-emptive transplant referred to the percentage of incident end-stage renal disease patients treated with a kidney transplant prior to any dialysis modality. % peritoneal dialysis refers to the percentage of prevalent dialysis patients in the HSA treated with peritoneal dialysis. Hemodialysis patient-bed ratio refers to the total number of prevalent in-center hemodialysis patients relative to the number of available dialysis beds in all facilities in the HSA.

Figure 5a.

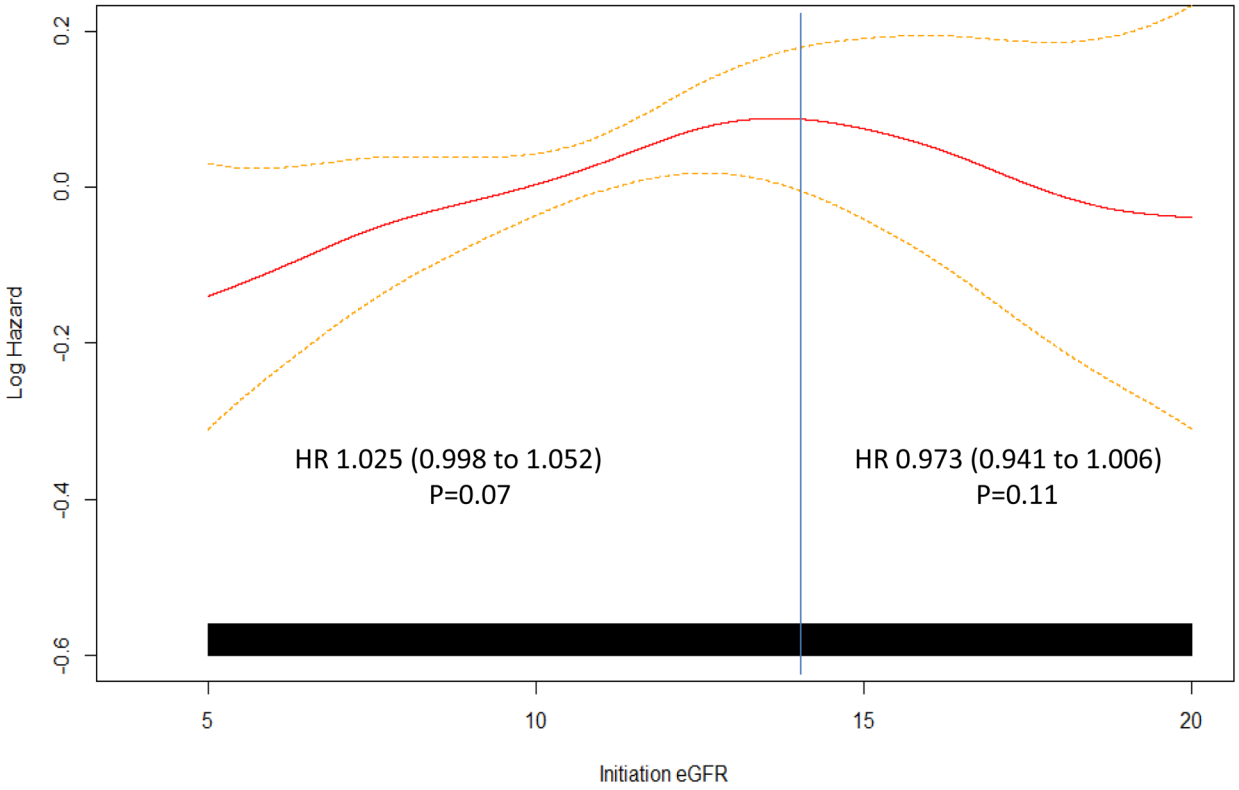

Figure 5b.

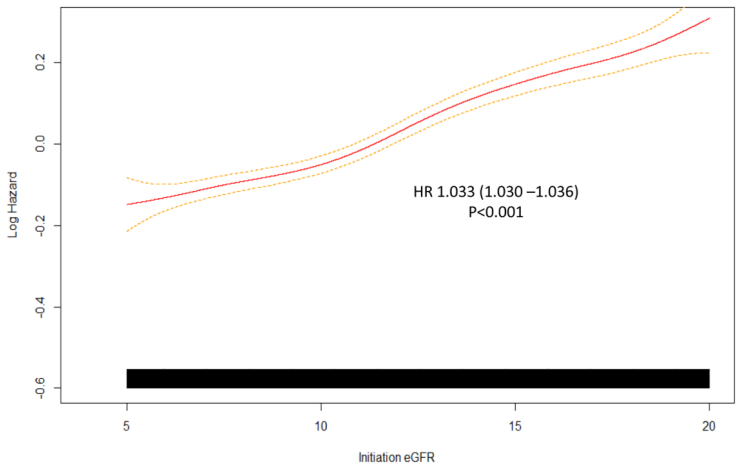

Figure 5. Relationship between patients' estimated glomerular filtration rate (eGFR) at dialysis initiation and log hazard of mortality incorporating a penalized spline

(A), Instrumental variable analysis result obtained using the two-stage residual inclusion model with demographic-adjusted mean health service area (HSA)-level eGFR at dialysis initiation as the instrumental variable. Model is adjusted for patient-level variables (age, sex, race, Hispanic ethnicity, comorbidity index, diabetes, congestive heart failure, median income and rural urban commuting area (RUCA) code in the patient's zip code, insurance status, modality and vascular access at dialysis initiation, primary cause of end-stage renal disease, serum albumin, hemoglobin and body mass index). Reference is set at the mean eGFR and log hazard ratio is indicated by the red line with 95% confidence intervals (95% CI) indicated by dashed yellow lines. Hazard ratios for mortality per 1 ml/min/1.73m^2 higher eGFR at dialysis initiation obtained from piecewise linear spline analysis with a knot at eGFR of 14 ml/min/1.73m^2 are reported above the corresponding line segment.
(B), Cox proportional hazard model result with adjustment for patient-level variables (age, sex, race, Hispanic ethnicity, comorbidity index, diabetes, congestive heart failure, median income and rural urban commuting area (RUCA) code in the patient's zip code, insurance status, modality and vascular access at dialysis initiation, primary cause of end-stage renal disease, serum albumin, hemoglobin and body mass index). Reference is set at the mean eGFR and log hazard ratio is indicated by the red line with 95% CI indicated by dashed yellow lines. Hazard ratios for mortality per 1 ml/min/1.73m^2 higher eGFR at dialysis initiation obtained from a simplified linear model is reported above the spline function. A piecewise linear spline is not used for this estimate because a knot at eGFR=14 ml/min/1.73m^2 was not significant (p=0.7).

Table 1

Patient characteristics according to their estimated glomerular filtration rate (eGFR) at dialysis initiation (patient-level) and the demographic-adjusted mean eGFR at dialysis initiation in their health service area (HSA-level).

	All N=89,549	Patient-level		HSA-level		
		eGFR ≥10.61 N=42,642	eGFR <10.61 N=46,907	eGFR ≥10.61 N=44,834	eGFR <10.61 N=44,713	Standardized difference[§]
eGFR at dialysis initiation (ml/min/1.73m^2)[*]	10.83 ± 3.58	13.94 ± 2.43	8.01 ± 1.55	11.21 ± 3.63	10.45 ± 3.50	21.0
Age (years)						
18–44	11.4%	9.0%	13.6%	11.1%	11.7%	1.4
45–64	38.3%	35.3%	40.9%	37.9%	38.6%	1.0
65–74	23.8%	24.9%	22.8%	23.8%	23.8%	−0.1
75–84	20.6%	23.5%	17.9%	21.1%	20.1%	−1.8
≥85	6.0%	7.2%	4.8%	6.1%	5.8%	−0.8
Male	55.9%	59.4%	52.7%	55.5%	56.3%	1.1
Race						
White	66.0%	67.8%	64.3%	71.8%	60.2%	−17.5
Black	28.6%	27.8%	29.4%	23.2%	34.1%	17.1
Other	5.4%	4.4%	6.3%	5.0%	5.8%	2.5
Hispanic ethnicity	12.8%	11.4%	14.2%	14.5%	11.2%	−7.0
Median income in zip code[**]						
<$25,000	9.2%	8.7%	9.6%	8.9%	9.5%	1.6
$25,000–37,999	38.0%	37.9%	38.0%	38.4%	37.5%	−1.2
$38,000–48,999	25.5%	25.9%	25.1%	26.4%	24.6%	−3.1
≥$49,000	23.9%	24.0%	23.9%	22.9%	24.9%	3.3
Rurality of zip code[†]						
Metropolitan	78.6%	78.1%	79.1%	76.8%	80.5%	6.4
Micropolitan	10.8%	11.0%	10.5%	12.0%	9.5%	−5.9
Rural	10.2%	10.4%	9.9%	10.7%	9.7%	−2.3
Insured prior to ESRD	92.9%	94.5%	91.4%	93.1%	92.6%	−1.4
Vascular access/modality at dialysis initiation						
Peritoneal dialysis	6.2%	6.5%	5.9%	6.0%	6.3%	0.9

	All N=89,549	Patient-level		HSA-level		
		eGFR ≥10.61 N=42,642	eGFR <10.61 N=46,907	eGFR ≥10.61 N=44,834	eGFR <10.61 N=44,713	Standardized difference[§]
Arteriovenous fistula	13.9%	13.8%	14.1%	13.4%	14.5%	2.1
Arteriovenous graft	3.3%	3.4%	3.1%	2.8%	3.7%	3.3
Central catheter	75.5%	75.0%	75.9%	76.4%	74.5%	−3.2
Cause of end-stage renal disease						
Diabetes	46.6%	50.3%	43.1%	47.2%	45.9%	−1.9
Hypertension	28.6%	28.2%	28.9%	28.1%	29.0%	1.5
Glomerulonephritis	10.8%	8.5%	12.9%	10.5%	11.0%	1.1
Other/unknown	14.1%	13.0%	15.1%	14.2%	14.1%	−0.2
Comorbity Score						
0	19.3%	14.4%	23.9%	19.1%	19.6%	0.9
1–2	31.5%	29.8%	33.0%	31.9%	31.0%	−1.5
3–5	31.3%	33.9%	28.9%	31.0%	31.5%	0.7
≥6	18.0%	22.0%	14.3%	17.9%	18.0%	0.1
Congestive Heart Failure	32.4%	38.0%	27.3%	32.0%	32.7%	1.0
Diabetes	59.3%	64.1%	55.0%	59.9%	58.8%	−1.5
Serum albumin (g/dl)						
<3.0	34.2%	34.3%	34.1%	33.7%	34.7%	1.6
Hemoglobin (g/dl)						
≤10	48.6%	44.7%	52.2%	46.7%	50.6%	5.6
Body mass index (kg/m^2)						
<18.5	3.5%	3.5%	3.4%	3.4%	3.6%	0.8
18.5–24.9	30.0%	30.2%	29.9%	29.3%	30.7%	2.2
25–29.9	27.9%	27.5%	28.2%	27.8%	27.9%	0.2
≥30	37.0%	37.1%	36.8%	37.7%	36.2%	−2.3
Propensity score[‡*]	0.54 ± 0.11	0.56 ± 0.11	0.51 ± 0.11	0.54 ± 0.11	0.54 ± 0.11	0.03
Mortality						
Total number of deaths	24,761	13,651	11,110	12,619	12,141	--
Incidence rate (per 100 patient years)	23.2	27.8	19.3	23.8	22.6	--

[*] presented as mean ± standard deviation

** defined based on the median household income in the patient's zip code of residence from the US Census 2000 data

† defined by rural urban commuting area (RUCA) codes; metropolitan (1–3), micropolitan (4–6) and rural (7–10)

‡ Indicates propensity score for "early" dialysis initiation (i.e. with eGFR >10 ml/min/1.73m^2) created using logistic regression

§ Indicates the standardized difference in percent of participants in each group based on classification by HSA-level timing of dialysis initiation

Table 2

Health service area (HSA)-level characteristics according to demographic-adjusted mean estimated glomerular filtration rate (eGFR) at dialysis initiation within the HSA (HSA-level mean eGFR at initiation)

	HSA-level mean eGFR at initiation (ml/min/1.73m^2)			
	All pts with eGFR 5 – 20 N=89,549	**eGFR < 10.61 N=44,713**	**eGFR ≥ 10.61 N=44,834**	**Standardized difference (%)***
Median age of nephrologists (years)				
Missing	4.6%	4.9%	4.4%	1.5
0 – 43	26.5%	21.4%	31.6%	−16.6
44 – 47	35.2%	41.8%	28.6%	19.7
48 – 51	22.8%	20.6%	25.0%	−7.5
≥52	10.9%	11.5%	10.4%	2.5
Number of nephrologists per 100 dialysis patients				
Missing	4.6%	4.9%	4.4%	1.5
< 0.36	11.6%	9.6%	13.7%	−9.0
0.36 – 0.51	11.1%	11.2%	10.9%	0.5
0.51 – 0.70	22.4%	17.7%	27.1%	−16.0
>0.70	50.3%	56.7%	43.9%	18.2
Herfindahl Index				
< 0.3	49.9%	47.6%	52.3%	−6.6
0.3 – 0.4	21.9%	27.7%	16.2%	19.7
0.4 – 0.6	17.4%	12.3%	22.5%	−19.3
>0.6	10.8%	12.5%	9.0%	8.0
Percent of profit				
<50	11.4%	11.6%	11.2%	0.7
50 – 75	22.7%	20.5%	24.9%	−7.5
75 – 95	50.1%	52.5%	47.8%	6.6
>95	15.8%	15.5%	16.1%	−1.1
Percent of pre-emptive transplant				
<1	9.9%	9.4%	10.3%	−2.4
1 – 2	38.5%	36.7%	40.4%	−5.4
2 – 3	31.7%	38.9%	24.5%	22.1

	HSA-level mean eGFR at initiation (ml/min/1.73m^2)			
	All pts with eGFR 5 – 20 N=89,549	**eGFR < 10.61 N=44,713**	**eGFR ≥ 10.61 N=44,834**	**Standardized difference (%)***
>3	20.0%	15.1%	24.8%	−17.2
Percent using peritoneal dialysis				
Missing	1.4%	1.5%	1.2%	2.3
<3	11.6%	14.5%	8.8%	12.8
3 – 7	44.8%	39.0%	50.6%	−16.5
7 – 10	24.8%	26.5%	23.1%	5.6
>10	17.4%	18.4%	16.4%	3.7
Hemodialysis patient-bed ratio				
Missing	1.3%	1.5%	1.2%	2.2
<2	0.5%	0.5%	0.5%	−0.1
2 – 3	16.2%	13.5%	18.8%	−10.2
3 – 4	45.1%	47.9%	42.3%	8.0
>4	36.9%	36.6%	37.2%	−0.9

* Indicates the standardized difference in percent of participants in each group based on classification by HSA-level timing of dialysis initiation

Table 3

Difference in individual patients' estimated glomerular filtration rate (eGFR) at dialysis initiation per 1 ml/min/1.73m^2 higher demographic-adjusted mean eGFR at dialysis initiation within the health service area (HSA-level mean eGFR at dialysis initiation) across subgroups[†]

Group	N	Patient-level eGFR difference (ml/min/1.73m^2)	95% CI		F-statistic	Partial r^2
Overall	**89,547**	**1.00**	**0.95**	**1.04**	**1784.72**	**0.018**
Age categories						
18–44 years	**10,226**	**0.92**	**0.79**	**1.06**	**177.60**	**0.016**
45–64 years	**34,260**	**0.98**	**0.90**	**1.05**	**670.95**	**0.018**
65–74 years	**21,299**	**1.07**	**0.98**	**1.17**	**495.42**	**0.022**
75–84 years	**18,426**	**0.98**	**0.88**	**1.09**	**350.21**	**0.018**
≥85 years	**5,336**	**1.07**	**0.86**	**1.27**	**105.84**	**0.018**
Race/ethnicity						
Non-hispanic white	**48,131**	**0.97**	**0.91**	**1.03**	**981.09**	**0.019**
Non-hispanic black	**25,298**	**1.03**	**0.94**	**1.12**	**483.60**	**0.018**
Hispanic	**11,495**	**1.06**	**0.92**	**1.21**	**202.14**	**0.016**
Insured prior to ESRD						
Yes	**83,171**	**1.01**	**0.96**	**1.06**	**1710.21**	**0.019**
No	**6,376**	**0.79**	**0.62**	**0.97**	**75.63**	**0.011**
Diabetes						
Yes	**53,138**	**1.07**	**1.01**	**1.13**	**1228.76**	**0.021**
No	**36,409**	**0.88**	**0.81**	**0.96**	**569.22**	**0.014**
Congestive heart failure						
Yes	**28,983**	**1.05**	**0.96**	**1.13**	**627.93**	**0.020**
No	**60,564**	**0.97**	**0.92**	**1.03**	**1154.19**	**0.018**
Modality/Access						
Hemodialysis with AVF	**12,479**	**0.96**	**0.85**	**1.07**	**283.23**	**0.020**
Hemodialysis with AVG	**2,910**	**1.06**	**0.81**	**1.31**	**67.79**	**0.021**
Hemodialysis with CVC	**67,522**	**0.98**	**0.93**	**1.04**	**1247.88**	**0.017**
Peritoneal dialysis	**5,503**	**1.25**	**1.08**	**1.43**	**199.90**	**0.032**

AVF, arteriovenous fistula; AVG, arteriovenous graft; CVC, central venous catheter

† These regression results indicate the strength of the instrumental variable (reflected by the demographic-adjusted mean eGFR at dialysis initiation within the HSA) on the treatment of interest (patients' individual eGFR at dialysis initiation) among the entire patient population and among clinically important subgroups. HSA-level mean eGFR at initiation was calculated in the 2006–2007 incident cohort and applied to patients in the 2008 incident cohort.