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

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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 who started dialysis between 2006 and 2008 and were registered in the United States Renal Data System in order to describe geographic variation in eGFR at dialysis initiation and determine its association with mortality. Patients were grouped into 804 health service areas (HSAs) by zip code. Individual eGFR at dialysis initiation averaged 10.8 ml/min per 1.73 m² but varied geographically. Only 11% of the variation in mean HSA-level eGFR at dialysis initiation was accounted for by patient characteristics. We calculated demographic-adjusted mean eGFR at dialysis initiation in the HSAs 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 two-stage residual inclusion method.

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

Received 20 September 2013; revised 7 February 2014; accepted 20 February 2014; published online 30 April 2014

Among 89,547 patients starting dialysis in 2008 with eGFR 5–20 ml/min per 1.73 m², eGFR at initiation was not associated with mortality over a median of 15.5 months (hazard ratio, 1.025 per 1 ml/min per 1.73 m² for eGFR 5–14 ml/min per 1.73 m²; and 0.973 per 1 ml/min per 1.73 m² for eGFR 14–20 ml/min per 1.73 m²). Thus, there was no associated harm or benefit with early dialysis initiation in the United States.

Kidney International (2014) **86**, 798–809; doi:10.1038/ki.2014.110; published online 30 April 2014

KEYWORDS: dialysis; end-stage renal disease; epidemiology and outcomes; glomerular filtration rate

The optimal time to initiate dialysis has been debated over the last two decades.^{1–5} Clinical practice guidelines published in the United States in 1997 advocated initiating dialysis when the glomerular filtration rate (GFR) was ~10.5 ml/min per 1.73 m² 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 the US clinical practice guidelines to suggest dialysis initiation at GFR < 15 ml/min per 1.73 m² in the presence of signs or symptoms of uremia.⁷ Over this time, mean GFR at dialysis initiation in the United States rose from 8.1 in 1997 to 10.8 ml/min per 1.73 m² in 2007.⁸

To date, the impact of early vs. 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 United States 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 have an impact on the outcome through its effect on treatment, but it 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 United States, explore how it relates to regional characteristics, and use 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 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 included 310,932 dialysis patients who initiated dialysis between 2006 and 2008 from 804 small geographic areas in the United States, known as health service areas (HSAs).¹⁰ Subsequent mortality analyses split the study population into two cohorts: one cohort of patients who initiated dialysis between 2006 and 2007 with an eGFR between 5 and 20 ml/min per 1.73 m² was used to create the instrumental variable (demographic-adjusted mean eGFR at dialysis initiation within the HSA); and one cohort involving 89,547 patients who initiated dialysis in 2008 with an eGFR between 5 and 20 ml/min per 1.73 m² 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, 50–339). Nationally, the mean eGFR at dialysis initiation was 10.82 ± 4.92 ml/min per 1.73 m². Mean eGFR at initiation and other patient characteristics are presented according to six national regions (Pacific, Mountain, Midwest, South, Mid-Atlantic, and New England) in Supplementary Table S1 online. We identified a geographic pattern (Figure 2a) with higher mean eGFR

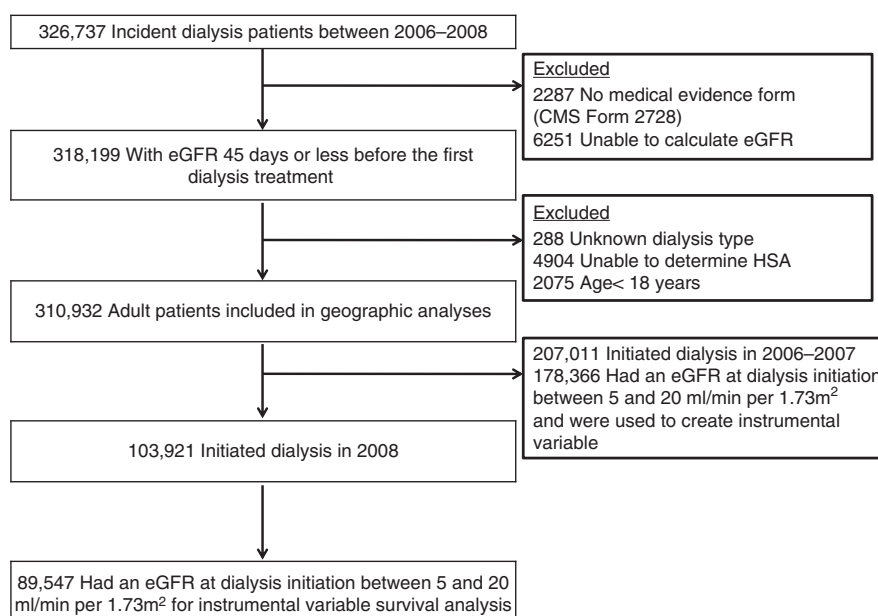


Figure 1 | Participant flow diagram. Medical evidence form refers to Centers for Medicare and Medicaid Services (CMS) Medical Evidence Form 2728. eGFR, estimated glomerular filtration rate; HSA, health service area.

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