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Effect Of The Expanded Prospective Payment System On Dialysis Initiation, The Usage Of Erythropoiesis-Stimulating Agents, And Medicare Expenditures

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EFFECT OF THE EXPANDED PROSPECTIVE PAYMENT SYSTEM ON DIALYSIS INITIATION, THE USAGE OF ERYTHROPOIESIS-STIMULATING AGENTS, AND MEDICARE EXPENDITURES

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In January 2011, the U.S. Centers for Medicare & Medicaid Services (CMS) implemented the expanded prospective payment system (PPS) for financing the management of end-stage renal disease (ESRD). Expanded PPS may not only change healthcare providers' decisions about patient care by removing the financial incentives associated with the previous composite rate payment methodology, but also change the Medicare expenditures associated with various treatment patterns by using a constant base rate for all dialysis modalities. This study aimed to examine the effect of the expanded PPS on providers' decisions on timing of dialysis initiation and ESA utilizations in ESRD patients as well as the association between different dialysis treatment patterns and Medicare expenditures. Incident ESRD patients were identified using the United States Renal Data System (USRDS) data between 2006 and 2016. We performed interrupted time-series analysis to examine the effect of the expanded PPS on timing of dialysis initiation and ESA utilizations in ESRD patients. We performed intention-to-treat analysis and as-treated analysis to examine the association between treatment pattern

and cumulative 3-year Medicare expenditures of ESRD patients after expanded PPS implementation. The treatment pattern was characterized by initial dialysis modality type and subsequent modality changes. We found significant decrease in the odds of early dialysis initiation following expanded PPS implementation. We also found that the odds of using ESAs and the cumulative 6-month doses of ESAs in pre-and post-dialysis initiation periods decreased following expanded PPS implementation; the magnitude of decrease in ESA utilization in the post-dialysis initiation period was larger than that in the pre-dialysis initiation period after expanded PPS implementation. In addition, the study found that patients who initiated peritoneal dialysis (PD) and stayed on PD had lower cumulative 3-year Medicare expenditure compared with patients who initiated hemodialysis (HD) and stayed on it. However, PD patients who switched to HD had a significantly higher cumulative 3-year Medicare expenditure than those who initiated HD and stayed on it or switched to PD, regardless of when the switch to HD occurred during the first 3 years after dialysis initiation. Our findings suggest that 1) The 2011 expanded PPS reduced the odds of early dialysis initiation and dis-incentivized the volume and intensity of ESA utilization in the post-dialysis initiation period; and 2) After the implementation of expanded PPS, steady use of PD remains a better dialysis option than HD in terms of costs. However, patients who initiated PD and switched to HD may lose this economic advantage.

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BACKGROUND

Prevalence and treatments of end-stage renal disease

ESRD is the last stage of chronic kidney disease (CKD). Patients are considered to have end-stage renal disease (ESRD) when their kidneys cease to function permanently. ESRD patients need renal replacement treatments such as dialysis or kidney transplantation for survival (Rodger 2012). ESRD poses a significant health and economic burden in the United States. The annual incidence rate of ESRD rose from 72.3 per million in 1980 to 373.4 per million in 2016 with 726,331 prevalent cases living with ESRD in2016. Although ESRD patients account for less than 1% of the total Medicare population, they account for more than 7% of the overall Medicare costs since 2004. In 2016, the Medicare ESRD expenditure was $35.4 billion (USRDS annual data report 2018).

Majority of the ESRD patients in the United States receive either forms of dialysis as opposed to kidney transplantation (Jian 2019). In 2016, 87.3% of incident ESRD patients started with HD, 9.7% started with PD, and 2.8% received a kidney transplant. Consequently, more than 90% of the Medicare ESRD expenditure in 2016 was spent on dialysis therapy (USRDS annual data report 2018). HD filters waste products from the blood, which is typically performed 3 times per week for 3–4 hours per treatment (National institute of diabetes and digestive and kidney diseases 2018). There are two types of HD, in-center HD and home HD. Among HD patients, 98.0% used in-center HD in 2016(USRDS annual data report 2018). PD, a home-based therapy, relies on the insertion of dialysate in the abdomen (Peppelenbosch 2008). As a renal replacement treatment for ESRD patients, PD is equivalent to HD in terms of survival and quality of life (Brown 2010, Liem 2007, Mehrotra 2011,

Nadeau-Fredette 2015, Yang 2015, Weinhandl 2010). Modality selection is influenced by both patients and providers.

Anemia that results from reduction of erythropoietin production is common in patients with CKD (Sargent 2004). The incidence rate of anemia is about 47.7% in patients with CKD and 76% in patients with ESRD (Coyne 2017). Prior to 1990, anemia of patients with CKD and ESRD was managed with oral and occasional i.v. iron administration, occasional use of androgens, and blood transfusions. However, blood transfusion has severe complications including transfusion reactions, sensitization, and iron overload (Coyne 2017). After that, Erythropoiesis-stimulating agents (ESAs) is primarily used for CKD and ESRD-related anemia (National Kidney Foundation 2006). These agents are used to raise hemoglobin (Hb) (The U.S. Recombinant Human Erythropoietin Pre-dialysis Study 1991), to reduce the need for red blood cell (RBC) transfusion and to improve symptoms (Butler 2015).

Policy context for ESRD patients receiving dialysis

Prior to January 2011, Medicare used a composite rate payment methodology to reimburse facilities that provide renal dialysis services to Medicare beneficiaries with ESRD. The composite rate payment methodology was adjusted by basic case-mix adjustment factors including age, body size, and geographic differences, and by drug add-on payment accounting for changes in the drug pricing methodology that occurred in 2005. This payment methodology paid for dialysis treatment costs and certain routinely used ESRD-related drugs, laboratory tests, and supplies collectively as a bundle once dialysis was initiated. This bundle did not include many other ESRD-related injectables drugs, such as ESAs used to treat CKD and ESRD related anemia, as well as non-routine laboratory tests. (CMS 2010). These unincluded items and services were separately billed and paid for in a fee-for-service (FFS) basis during the post-dialysis initiation period.

Under the composite rate payment methodology, dialysis facilities could maximize reimbursement and financial returns by increasing the volume and intensity of services that were not included in the bundle after dialysis initiation (MedPAC 2011). Office of Inspector General reported that dialysis facilities could obtain financial benefit from prescribing injectable drug erythropoietin (EPO), injectable iron and vitamin D (Kleinke 2004). Medicare expenditure for separately billed items and services had increased dramatically. In 2007, Medicare paid approximately $9.2 billion for dialysis-related services, of which 38% was paid for separately billed items and services (CMS 2010). Patients receiving home dialysis tend to use substantially fewer ESAs and other injectable ESRD drugs. For example, the average

Medicare Payment per treatment for separately billed services was $52 lower for PD (Turenne 2018).

In order to address the exponentially growing healthcare costs, U.S. Centers for Medicare & Medicaid Services (CMS) implemented a new expanded prospective payment system (PPS), and expanded the bundle payment in January 2011. Under the expanded PPS, dialysis services as well as formerly separately billed items and services (such as the injectable ESAs), were now included in an expanded bundled amount. The expanded PPS pays dialysis treatment with case-mix adjustments for age, body surface area, low body mass index, four comorbidity categories (two acute and two chronic), and the onset of renal dialysis. Adjustments also are made for area wages, facility size, self-dialysis training and outlier cases (CMS 2010). 2011 expanded PPS made the revenue of dialysis facilities no longer dependent on the use of formerly separately billed medications and laboratory tests by bundling these items and thus, removed the incentive for inefficiency in the use of these medications and laboratory tests.

Literature review

With the implementation of expanded PPS, the treatment pattern and Medicare expenditure of patients with ESRD have been changing. We reviewed the literature on changes in treatment pattern and Medicare expenditure that occurred after expanded PPS implementation, and studies on the impact of CMS expanded PPS on these changes.

Timing of dialysis initiation

Glomerular filtration rate (GFR) is the measure of kidney function and can represent the dialysis initiation timing. Generally, GFR is measured in research settings and transplant centers, which requires experienced personnel. Thus, the estimated GFR (eGFR) is usually used and the predominant method to represent the timing of dialysis initiation. The eGFR is a calculation based on blood. When kidney function decreases, less creatinine is eliminated and thus eGFR decreases. (Leurs 2015). Earlier dialysis initiation was defined as initiation at eGFR≥10 ml/min per 1.73 m (O'Hare 2011, Leurs 2015, Slinin 2014). The percent of incident ESRD patients had early dialysis initiation rose from 12.9% in 1996 to 42.6% in 2010. After expanded PPS implementation, the percent of early dialysis decreased to 38.6% in 2016 (USRDS annual report 2018).

Factors associated with dialysis initiation timing have been well explored. Some studies reported that presence of concomitant medical conditions and poor functional status were associated with early dialysis initiation (Lassalle 2010, Kausz 2000, Kinchen2002, Navaneethan 2008); Women, older patients, Hispanics and Asians, and uninsured patients were more likely to initiate dialysis later (Obrador 1999, Kausz 2000, Kinchen2002,

Navaneethan 2008). Kausz et al. stated that African American patients may initiate dialysis later at a higher creatinine level because they had a higher eGFR for the same creatinine level (Kausz,2000). However, some other studies had different findings that African Americans are more likely to have poor quality of pre-dialysis care and presence of comorbid conditions and therefore, have initiated dialysis early (Winkelmayer 2001, Gadegbeku 2002). Slinin et al. suggested that patients who received pre-dialysis nephrologist care are more likely to initiate dialysis early, and greater provider experience is associated with lower likelihood of early initiation (Slinin 2014). A study conducted in Canada reported there was a small amount of variation in timing at facility level and no variation among geographic regions (Sood 2014). Yu et al. found that physicians who would not profit from the dialysis facility were not inclined to initiate dialysis early (Yu 2015).

ESA utilization in patients with chronic kidney disease

ESAs is the largest single Medicare drug expenditure in the US in 2004 which costed $1.8 billion and comprised 11% of all Medicare ESRD cost (Mae 2007). Since 2006, findings from several clinical trials and the change of FDA label have raised concerns about the safety of ESAs (Drüeke 2006, Pfeffer 2009, Singh 2006) and suggested reducing ESAs utilization. In 2011, ESAs used in dialysis period was included in expanded PPS. The safety concerns and expanded PPS may have influenced ESAs utilization in patients with CKD and ESRD.

Several studies estimated the trend of ESA utilization prior to dialysis initiation. Winkelmayer et al. conducted a closed cohort study in the United States using ESRD registry data of patients 67 years or older from 1995 to 2010, they described the trends of the use of ESAs, I.V. iron supplements and blood transfusion in the 2 years prior to ESRD. The results

showed that the proportion of patients with incident ESRD receiving any ESAs in the 2 years prior to dialysis initiation increased from 3.2% in 1995 to 40.8% in 2007; thereafter, ESAs use decreased to 35.0% in 2010 (Winkelmayer 2014). Coyne et al. reported that the proportion of patients receiving ESA prior to dialysis initiation kept increasing until 2006, after that it started to decrease and the proportion was below 15% in 2012 in the United States (Coyne 2017). Park et al. conducted a retrospective cohort analysis using Truven MarketScan Commercial and Medicare Supplemental databases. They examined the monthly rates and types of anemia treatment in non-dialysis patients with CKD from 2006 to 2015, and evaluated the impact of TREAT study results (October 2009) and FDA's (June 2011) safety warnings and guidelines on the anemia management. Their results showed that prevalent CKD patients were increasingly less likely to be treated with ESAs from 2006 to 2015(Park 2018).

The trend of ESA utilization following dialysis initiation has been well described. USRDS measured the percent of HD adult patients who had a claim for ESA utilization during any single month, and reported that there was no obvious change in percent between 2006 and 2010, but the percent declined sharply from 2010 to 2016 (USRDS annual report 2018). Wetmore et al. performed a restrospective analysis using Medicare claims to examine the anemia management in prevalent patients receiving PD and HD between 2007 and 2011.They reported that dose and frequency of ESA utilization decreased during the period 2007-2011 (Wetmore 2015). Coritsidis et al. estimated the trend of ESA utilization in patients receiving HD from hospital-based dialysis centers by using Electronic medical records. They reported that from 2010 to 2013, median cumulative 4-week doses of darbepoetin alfa and epoetin alfa declined 38.8% and 24%, respectively (Coritsidis 2014). Karaboyas et al. calculated the monthly ESA dose from July1, 2009 to September 30, 2013 by using data from United States

Dialysis Outcomes and Practice Patterns Study, and found that Mean ESA dose declined throughout the study (Karaboyas 2015).

Some studies evaluated the impact of expanded PPS on the ESA utilization following dialysis initiation. Swaminathan et al. evaluated the impact of expanded PPS on the ESA utilization of HD patients by using data from renal management information system between January 1, 2009 and June 30, 2011. They reported that the expanded PPS was associated with an immediate and substantial decline in the use of ESAs among patients with hematocrit >36 percent and little change in the use of ESAs among patients with hematocrit ≤36 percent (Swaminathan 2015). Turenne et al. estimated the change of erythropoietin (EPO) dose in prevalent HD patients using data from the dialysis outcomes and practice pattern study between August 2010 to December 2011. They reported that mean EPO dose declined from 20,506 to 14,777 U/wk and suggested that there was no immediate indication of racial disparities in anemia management resulting from expanded PPS(Turenne 2015). Wang et al. examined the association between expanded PPS and ESA utilization in HD patients older than 66 years and having Medicare as primary payer. They reported that 92% of patients received an ESAs in the pre-policy period (January 1, 2008, to December 31, 2009) compared with 72% of patients in the post-policy period (July 1, 2011, to June 30, 2013); among patients receiving an ESA, the monthly ESA dose was also markedly lower following expanded PPS(Wang 2016).

Dialysis modality and related Medicare expenditure

PD and HD are the two types of dialysis modality usedin the US. Instead of using a single dialysis modality, some patients require a sequential use of different modalities because of changes in medical conditions, occurrence of complications, and patient preference (Guo 2003). For example, almost 50% of patients transferred to other types of dialysis therapies in the second or third year after PD initiation (Chan 2017, Kolesnyk 2010, Kumar 2014, Lan 2015, Perl 2012, Pajek 2014), whereas the transfer rate from HD to PD is about 10% (Chui 2013). The transfer between modalities incurs additional costs which eventually increases the overall expenditures related to the care of patients (Prichard 1997). Two studies have estimated the direct economic consequences of dialysis modality change (Chui 2013, Shih 2005). Chui et al. (2013) conducted a retrospective study using administrative records from the Northern and Southern Alberta Renal Programs, and reported that the cumulative 3-year costs of patients who initiated PD and transferred to HD (PD-HD)in the first year of dialysis were similar to those of patients who initiated and remained on HD therapy (HD only); the cumulative3-year costs of patients who initiated HD and transferred to PD (HD-PD) in the first year of dialysis were smaller than those of patients who initiated and remained on HD therapy (HD only). Shih et al. (2005) estimated the Medicare expenditure of dialysis patients using USRDS data from 1996 to 1997,accounting for dialysis modality changes that occurred in the first 3 years following dialysis initiation. They reported that PD-HD in the first year following dialysis initiation was associated with increased Medicare expenditure, comparing with HD only, whereas Medicare expenditure was lower for patients who transferred from PD to HD after the first year. To our knowledge, no study has evaluated the Medicare expenditure after expanded PPS implementation accounting for the dialysis type and transfers.

Study significance

Financial relationships commonly exist between dialysis facilities and nephrologists; for example, nephrologists often derive income from co-ownership, employee-ship, or medical directorship of dialysis facilities (Berns 2018, Ozar 2013). Hence, although expanded PPS was aimed at influencing treatments provided during dialysis period, it may also affect treatments provided before and at dialysis initiation. Before 2011 expanded PPS implementation, dialysis facilities and nephrologists had no direct financial incentive to delay dialysis, and could prescribe separately billed services and products after dialysis initiation, in order to benefit from the reimbursement of the volume and intensity of these items. However, after the 2011 expanded PPS implementation, providers might benefit from initiating dialysis late and prescribing certain services and products before dialysis initiation to keep them out of the post-dialysis capitated period. eGFR at dialysis initiation which indicates the timing of dialysis initiation began to decrease after year 2010 (USRDS annual data report 2018), in other words, providers started to initiate dialysis late since 2010. This reduction might potentially be due to the 2011 expanded PPS implementation. Therefore, this study examined the association between the change in eGFR and expanded PPS, to assess whether expanded PPS has affected the dialysis initiation timing.

Expanded PPS aimed to dis-incentivize volume and intensity of treatments during the dialysis period by eliminating FFS billing and bundling more services. Nephrologists and dialysis facilities may decide to decrease the ESA utilization in dialysis period to reduce the provider-expense per patient. In addition, ESA utilization could be used both before and after dialysis initiation and might be shifted more to the pre-dialysis period, after the 2011 expanded

PPS, to avoid the utilization in post-dialysis capitated period. As mentioned above, previous studies showed declining use in ESA utilization over time both before and after dialysis initiation. This is likely because of safety concerns about ESAs that apply to both periods. However, along with growing safety concerns were the economic incentives caused by the expanded PPS, which created incentives to further reduce ESA utilization during the dialysis period. The effect of the 2011 expanded PPS on nephrologists' and dialysis facilities' decisions regarding ESA utilizations remains unclear. The majority of studies focused on describing the trend change of ESAs. No study has estimated the impact of expanded PPS on ESA utilization prior to dialysis initiation. Some studies found the decrease in ESA utilization during the dialysis period was associated with expanded PPS, however, these studies had some limitations, such as using data collected within the first year following expanded PPS implementation, focusing on certain specific groups, and unable to isolate the effect of expanded PPS from the influence of safety concerns. This study examined whether the decline in ESA utilization was more prominent in patients after the onset of dialysis compared to patients prior to the onset of dialysis in order to isolate the effect of the economic incentives caused by expanded PPS from the broader influence of safety concerns.

As mentioned above, instead of using a single dialysis modality during treatment, some patients require a sequential use of different dialysis modalities because of changes in medical conditions, occurrence of complications, or patient preference (Guo 2003, Chan 2017, Kolesnyk 2010, Kumar 2014, Lan 2015, Perl 2012, Pajek 2014). Dialysis transfer incurs additional costs and eventually increases the overall expenditures related to ESRD care (Prichard 1997). Therefore, it is necessary to examine the healthcare expenditures in

ESRD patients taking into account the dialysis transfer. Previous studies found that PD maintained the economic advantage even when dialysis transfer occurred (Chui 2013, Shih 2005). The reason might be that the significant difference in cost between PD and HD counteracted the impact of dialysis transfer on healthcare expenditure. However, previous findings may not be applicable to represent recent Medicare expenditure in the United States. Patients receiving HD have higher requirements for formerly separately billed services and items than those receiving PD, which made PD cheaper than HD. The expanded PPS added formerly separately billed services to the bundle and made payment on a per treatment basis with same base rate for all dialysis treatment modalities (HD and PD). Consequently, the expanded PPS made the difference in cost between PD and HD smaller than before (CMS 2017). Given the implementation of expanded PPS, patients initiating on PD may lose the economic advantage when dialysis transfer occurs because of the extra cost caused by dialysis transfer and the shrink of difference in cost between PD and HD. Hence, this study estimated the Medicare expenditure of ESRD patients taking into account the dialysis modality type and dialysis transfer after expanded PPS implementation.

Study aims and hypotheses

Aim 1: Evaluate the effect of the 2011 expanded PPS on timing of dialysis initiation measured by eGFR level at dialysis initiation

Hypothesis 1 : the decrease of eGFR at dialysis initiation may be caused by 2011 expanded PPS. In other words, nephrologists and dialysis facilities may be inclined to initiate dialysis later after expanded PPS implementation.

Aim 2: Evaluate the effect of the 2011 expanded PPS on utilization of ESAs during pre-dialysis and post-dialysis initiation periods

Hypothesis 2: ESA utilization for anemia management in pre-and post-dialysis period may be affected by expanded PPS.

Hypothesis 2.1: The probability of using ESAs and the doses of ESAs may decrease in both pre-and post-dialysis initiation periods

Hypothesis 2.2: the decline in ESA utilization may be more prominent in pre-dialysis initiation period compared to post-dialysis initiation period.

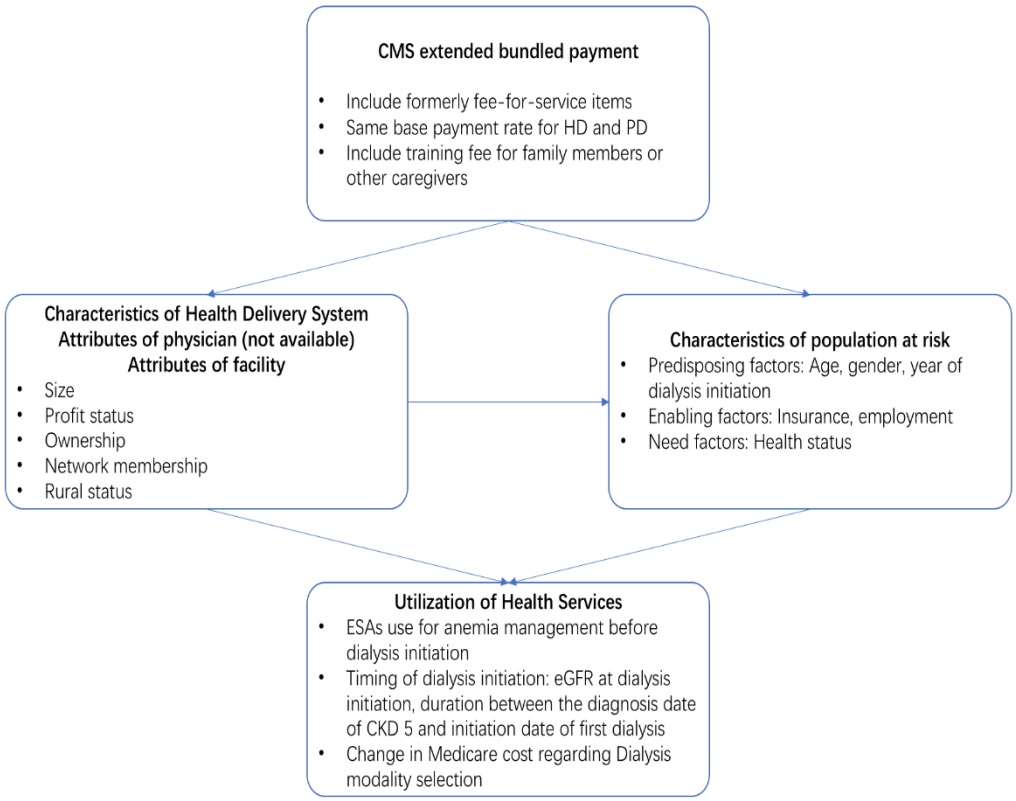
Aim 3: Examine the association between 3-year Medicare expenditure and treatment modalities

Hypothesis 3: the 3-year Medicare expenditure of patients who had dialysis transfer may be higher than that of patients who initiate and maintain on HD.

Conceptual model

This study used the conceptual model of access to medical care designed by Lu Ann Aday and Ronald Andersen. This framework can be conceptualized as proceeding from health policy objectives through the characteristics of the health care system and of the populations at risk to the outcomes (Aday and Anderson 1974). Consumer satisfaction will not be considered in this study. The detailed conceptual model of this study is as follows:

Figure 1 conceptual model



METHODS

Data source

This retrospective observational analysis used the United States Renal Data System (USRDS) data for the period 2006-2016. USRDS provides information about chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the United States. It is a national data system that collects, analyzes, and distributes information from Centers for Medicare & Medicaid Services (CMS), the United Network for Organ Sharing (UNOS), and the ESRD networks. This database contains several datasets which can be linked using USRDS_ID, facility ID and UPIN. The datasets used in this study are as follows:

a. CORE DATASET

The Core Standard Analysis Files include Patient Profile, Medical Evidence Form, CMS/CDC ESRD Annual Facility Survey, Pre-ESRD payer history, Payer History.

b. ESRD MEDICARE CLAIMS

ESRD Medicare claims include Part A, Part B and Part D claims. Part A claims contain claims of inpatient, outpatient, skilled nursing facility, home health agency, and hospice.. Part B claims contain claims of physician/supplier and durable medical equipment. Part D claims contain details of prescriptions filled by Part D beneficiaries.

c. PRE-ESRD MEDICARE CLAIMS

The pre-ESRD claims include Medicare Part A, Part B and Part D claims incurred in the 2 years prior to the ESRD onset.

d. PROVIDER ID CROSSWALK FILE

This file contains crosswalk of CMS provider ID and USRDS assigned provider ID.

Aim 1: Assess the impact of CMS expanded PPS on the timing of dialysis initiation

a. Study design and population

ESRD patients, who initiated dialysis as their first treatment modality for ESRD between January 1, 2006 to December 31, 2016, were identified from USRDS. Dialysis initiation date was the index date for patient inclusion as well as study design. This study only included those who were equal to or older than 18 years old, who had medical evidence form filled within 45 days of dialysis initiation, who did not have date of death erroneously recorded as being before dialysis initiation date, who had both Medicare parts A and B coverage (with Medicare as the primary payer) on the dialysis initiation date and during the 6 months before dialysis initiation, who did not have missing values for any variables used in the regression, and who received dialysis from a non-VA facility. Patients without both Medicare parts A and B as primary payer at and during the 6 months before dialysis initiation date were excluded because this period was used to develop the baseline Charlson comorbidity index. We excluded patients who received dialysis from a VA facility because VA patients could be receiving ESRD-related services from the VA health administration, and USRDS will not have information about those services for the purposes of a consistent analysis.

b. Measures

1) Dependent variable

Early dialysis initiation

The dependent variable of aim 1 measured timing of dialysis initiation in terms of eGFR level at dialysis initiation. This variable defined as "early dialysis initiation" was a binary variable indicating eGFR at dialysis initiation ≥10.0 mL/min/1.73m2 (coded as 1) (Cooper 2010, Yu 2015, Matthew 2017), and eGFR at dialysis initiation <10.0 mL/min/1.73m2 (coded as 0).

2) Independent variables

The analysis of aim 1 had three independent variables of interest. The first was a binary pre-post variable "expanded-PPS" capturing the 2011 expanded PPS implementation, and coded as 1 for all patients initiating dialysis at or after 2011 and as 0 for all patients initiating dialysis before 2011. The second is "dialysis initiation time-period", which was measured as a continuous variable indicating the time period to which a patient's dialysis initiation date belonged (for the purposes of interrupted time series analysis). Dialysis initiation time-period ranged from 1 to 22, and each consecutive number represented 6 calendar months starting from January 2006 to December 2016. This time-period variable was created using 6 month intervals instead of indicators based on 12 months because a minimum of 8 time periods before and 8 after an intervention are needed to statistically evaluate changes in an interrupted time series analysis(Penfold 2013). The third was the interaction between the expanded-PPS and dialysis initiation time-period variable. This interaction term was coded as 0 during the pre-2011 composite rate payment period. It was coded as 1 to 12 for every 6-month time interval from January 1, 2006 to December 31, 2016.

Other independent variables controlled for were patient- and facility-level characteristics. Patient-level characteristics were collected at the time of dialysis initiation date (index date), except for the Charlson Comorbidity Index (CCI) score, which was calculated using the Medicare claims data from the 6 months period before the dialysis initiation date. Four types of patient-level characteristics were controlled for: sociodemographic, clinical, behavioral, and treatment. Patient sociodemographic characteristics included age at dialysis initiation (continuous variable measured in years); gender (female, male); race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other); education, measured as a percentage of adults with high school education or more, in the patient's ZIP code area (continuous variable in percent); income measured as median household income for the patient's ZIP code area (continuous variable in USD); employment status at dialysis initiation (unemployed, employed); and residential urbanicity at dialysis initiation (large metropolitan, medium or small metropolitan, micropolitan, and non-core). Education and income were obtained for each patient at the ZIP code level as suggested in previous studies (Berkowitz 2015, Krieger 2005), since personal information on these were not present in the data; they were obtained by linking the patient's ZIP code in the USRDS to the 2010 U.S. Census data. Residential urbanicity was identified for each patient by linking the patient's FIPS code in the USRDS to the 2010 Rural Urban Commuting Area codes. Patient clinical characteristics included nephrologist care prior to dialysis initiation (no, <6 months, 6-12 months, and >12 months); primary cause of ESRD (diabetes, hypertension, glomerulonephritis/cystic renal disease, and others); CCI score at dialysis initiation (continuous variable); serum albumin at dialysis initiation (albumin <3 g/dL, 3 g/dL≤ albumin <3.5 g/dL, and albumin ≥3.5 g/dL); disability at dialysis initiation (yes, no); and BMI at dialysis initiation (continuous variable). Patient behavioral characteristics included

smoking status at dialysis initiation (yes, no), drug dependence at dialysis initiation (yes, no), and alcohol dependence at dialysis initiation (yes, no). Patient treatment characteristic only included dialysis type at dialysis initiation (HD, PD). Facility-level characteristics included unit affiliation (chain, independent); number of facility stations (continuous variable); non-profit designation (yes, no); ownership (hospital-based, free-standing); and regional ESRD network identifiers (Network 1 to Network 17). Variable name, format and description of patient level and facilities level characteristics were listed in appendix table S1.

c. Statistical analysis

Descriptive statistics were performed to compare baseline characteristics between patients who initiated dialysis before and after the 2011 expanded PPS implementation using *t* tests for continuous variables and Pearson's chi-square tests for categorical variables. All P values are two-sided, and statistical significance was defined as P less than 0.05. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC) and Stata (version 13; Stata Corp., College Station, TX).

To analyze if the 2011 expanded PPS implementation was temporally associated with early dialysis initiation, an interrupted time-series analysis was conducted using multivariable logistic regression. As mentioned above the three main independent variables of interest in this regression were the binary pre-post "expanded-PPS" variable, the continuous "dialysis initiation time-period", and the interaction of these two variables. In addition to the three independent variables, patient-level and facility-level characteristics listed in appendix Table

S1 were adjusted for in the regression. Based on specification tests and model fit, the square of age and square of BMI were also included in the regression analyses, and the continuous income variable was logarithmically transformed. In order to adjust for clustering of patients within the facility, cluster-robust adjustment of standard errors were performed in the regression (Abadie 2017). All P values reported are two-sided; statistical significance was defined as P values less than 0.05. The equation of interrupted time-series logistic regression was as follows:

$$\log\left(\frac{p(early\ dialysis\ initiation = 1)}{1 - p(early\ dialysis\ initiation = 1)}\right) = \alpha + \beta_1 expanded\ PPS + \beta_2 dialysis\ initiation\ time - period + \beta_3 interaction\ term + \gamma other\ independent\ variables$$

The coefficient of expanded-PPS estimates the level change in the outcome immediately after the implementation of expanded PPS; the coefficient of dialysis initiation time-period estimates the change in the outcome that occurred over each time interval before the expanded PPS implementation; and the coefficient of interaction term estimates the change in the trend in outcome after the expanded PPS implementation, compared with the trend before the expanded PPS implementation (Wagner 2002).

Aim 2: Assess the impact of CMS expanded PPS on ESA utilization among patients with CKD and ESRD.

a. Study design and population

In aim2, the effect of the 2011 expanded PPS was examined on ESA utilization six months pre and post dialysis initiation. ESRD patients, who initiated dialysis as their first treatment modality for ESRD from July 1, 2008, to June 30, 2010, and from July 1, 2011, to June 30, 2016, were identified from USRDS. The reasons are: 1) Medicare only required dialysis facilities to report each separately billed service as a separate revenue center line item with individual dates of service since January 1, 2008. Hence accurate information on ESA utilization in patients who received ESAs before January 1, 2008 was unavailable; 2) patients who initiated dialysis before July 1, 2008 and after June 30, 2016 were excluded because 6-month claims filed before and after dialysis initiation were needed to capture ESA utilization; 3) patients, who initiated dialysis between July 1st, 2010, and June 30th, 2011, were excluded because the ESA utilization period examined pre and post dialysis initiation for these patients, did not strictly fall in the pre January 2011 composite rate payment period, or the post January 2011 expanded PPS period, to facilitate development of two clean comparison groups before and after the 2011 expanded PPS implementation. The Charlson comorbidity for this aim was developed using claims filed 12 months before dialysis initiation up to six month before dialysis initiation so the baseline comorbidity index period does not overlap with the period during which the dependent variable was captured. Consequently, for this aim this study excluded patients without uninterrupted Medicare part A and B coverage from 12 months before dialysis initiation to 6 months after dialysis initiation. Moreover, to ensure each patient had the same provider access to receive ESAs

before dialysis initiation, patients who did not have at least 6 months of nephrology care prior to dialysis initiation were excluded. Patients who received transplantation during the 6 months following dialysis initiation were excluded because the ESA utilization of these patients were not affected by expanded PPS. This study also excluded patients who were younger than 18 years old, who did not have medical evidence form filled within 45 days of dialysis initiation, who had date of death erroneously recorded as being before dialysis initiation date, who had missing values for any variables used in the regression and who received dialysis from a non-VA facility. We excluded patients who received dialysis from a VA facility because VA patients could be receiving ESRD-related services from the VA health administration, and USRDS will not have cost information about those services for the purposes of a consistent analysis.

b. Measures

1) Dependent variables

Three dependent variables were analyzed in aim 2. The first and second dependent variables measured ESA utilization and cumulative 6-month doses of ESA pre and post dialysis initiation. ESA utilization was measured using two binary variables indicating any ESA utilization during the 6 months before and 6 months following dialysis initiation. Cumulative 6-month doses of ESAs was measured using two continuous variables indicating the total doses of ESAs during the 6 months before and 6 months following dialysis initiation. The Healthcare Common Prodecure Coding System (HCPCS) codes for the three

types of ESAs, epoetin alfa or beta (EPO) ('J0885', 'J0886', 'Q4081', 'Q0136','Q4055','0634','0635'), darbepoetin alfa (DPO) ('C1774', 'J0880', 'Q4054', 'Q0137', 'J0881', 'J0882'), and epoetin beta pegol (PEG) ('Q2047', 'J0890','J0887', 'J0888', 'Q9972','Q9973'), were used to identify ESA utilization from Medicare claims. Dose of DPO and PEG were converted to that of EPO using a dose conversion ratio (EPO:DPO:PEG = 200:1:0.93) (Kuwahara 2015, Kuwahara 2013). The third dependent variable was the ratio of the cumulative doses of ESAs utilized during the 6 months before dialysis initiation period divided by the cumulative doses of ESAs utilized during the 6 months following dialysis initiation period. To ensure that the denominator of the ratio was greater than zero, we excluded patients who did not receive ESAs during the 6 months following dialysis initiation.

2) Independent variables

The analysis of aim 2 had three independent variables of interest. The first was a binary pre-post variable "expanded-PPS" capturing the 2011 expanded PPS implementation, and coded as 1 for all patients initiating dialysis at or after 2011 and as 0 for all patients initiating dialysis before 2011. The second is "dialysis initiation time-period", which was measured as a continuous variable indicating the time period to which a patient's dialysis initiation date belonged. Dialysis initiation time-period ranged from 1 to 28, and each consecutive number represented 3 calendar months starting from July 1, 2008 to June 30, 2016 (with the exclusion of patients who initiated dialysis between July1st 2010-June30th 2011). This time-period variable was created using 3 month intervals instead of indicators based on 12 months because a minimum of 8 time periods before and 8 after an intervention are needed to statistically evaluate changes in an interrupted time series analysis (Penfold

2013). The third was the interaction between the expanded-PPS and dialysis initiation time-period variable. This interaction term was coded as 0 during the pre-2011 composite rate payment period. It was coded as 1 to 20 for every 6-month time interval in aim 2. The other independent variables were the same as those in aim 1, except for nephrologist care prior to ESRD onset. This study did not include it in aim 2 because every patient included in the corresponding analytic sample had received at least 6 months of pre-dialysis nephrology care.

c. Statistical analysis

Descriptive statistics were performed to compare baseline characteristics between patients who initiated dialysis before and after the 2011 expanded PPS implementation using t tests for continuous variables and Pearson's chi-square tests for categorical variables. All P values are two-sided, and statistical significance was defined as P less than 0.05. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC) and Stata (version 13; Stata Corp., College Station, TX).

To analyze ESA utilization during the 6 months before and following the dialysis initiation, interrupted time-series analyses were conducted using two sets of two-part models, in addition to a third linear regression analysis. Cumulative 6-month doses of ESA was a positive variable with a large number of zero values. Two-part models statistically decompose the density of the outcome into a process that generates zeros and a process that generates positive values (Beeuwkes and Zaslavsky 2004). The first two-part model evaluated ESA utilization during the 6 months before dialysis initiation. The first part of this model was a logistic regression evaluating the binary dependent variable indicating whether

or not ESAs were utilized during the 6 months before dialysis initiation, and the second part was a linear regression evaluating the dependent variable capturing the cumulative dose of ESAs utilized during the 6 months before dialysis initiation. A similar two-part model was performed for the 6-months following dialysis initiation. Based on the distribution of the cumulative dose dependent variables and results of the BoxCox specification tests, these variables were logarithmically transformed before the linear regressions were estimated in the second parts. The third and final linear regression analysis evaluated the ratio of the cumulative dose of ESAs utilized during the 6 months before the dialysis initiation divided by the cumulative dose of ESAs utilized during the 6 months following the dialysis initiation. As mentioned above, the three main independent variables of interest in these regressions evaluating ESA utilization were, the binary pre-post "expanded-PPS" variable, the continuous "dialysis initiation time-period", and the interaction of these two variables.

The equation of two-part models were as follows:

In the first part, the binary outcome of 'any' versus 'zero' was modeled.

$$\log\left(\frac{p(ESA\ utilization = 1)}{1 - p(ESA\ utilization = 1)}\right) = \alpha + \beta_1 expanded - PPS + \beta_2 dialysis\ initiation\ time - period + \beta_3 interaction\ term + \gamma other\ independent\ variables$$

In the second part, the cumulative 6-month doses of ESAs among patients receiving ESAs was modeled.

$$Cumulative\ 6 - month\ doses\ of\ ESAs = \alpha + \beta_1 expanded - PPS + \beta_2 dialysis\ initiation\ time - period + \beta_3 interaction\ term + \gamma other\ independent\ variables + \varepsilon$$

In addition to report the coefficients of variables in the two-part models and explain the meaning of coefficients, overall marginal effect which estimates the effect of covariate on the marginal mean of dependent variable for the combined population of ESA users and non-users (smith 2015).

Ratio of ESA utilization was calculated as:

$$Ratio = \frac{cumulative\ 6-month\ doses\ of\ ESA\ in\ pre-dialysis\ initiation\ period}{cumulative\ 6-month\ doses\ of\ ESA\ in\ post-dialysis\ initiation\ period}$$

The equation of the interrupted time-series analysis of the ratio was:

$$Ratio = \alpha + \beta_1 expande - PPS + \beta_2 dialysis\ initiation\ time - period + \beta_3 interaction\ term + \gamma other\ independent\ variables + \varepsilon$$

Since there are no formal clinical guidelines establishing the dose conversion ratio for ESAs, and EPO is the most commonly used ESA in the United States, a sensitivity analysis was performed by excluding patients who used DPO or PEG and redoing the analyses for all regressions examining ESA utilizations.

Aim 3: Assess the association between cumulative 3-year Medicare expenditure and dialysis modality pattern

a. Study design and population

This study identified ESRD patients, from the USRDS, who initiated HD and PD as their first treatment modality for ESRD between January 1, 2011 and December 31, 2013. Patients initiating dialysis after 2013 were excluded because this study estimates cumulative 3-year Medicare expenditure. The beginning date of follow-up was de fined as dialysis initiation date, and the ending date of follow-up was defined as the date of death, transplantation, recovered function, or loss to follow-up, whichever occurred first. Medicare claims in the 6 months before and 3 years following dialysis initiation were used to calculate Charlson comorbidity index and Medicare expenditure, respectively. Consequently, this study only included patients who had both Medicare parts A and B coverage (with Medicare as the primary payer) during the 6 months before and 3 years following dialysis initiation. This study excluded patients who were younger than 18 years old, who did not have medical evidence form filled within 45 days of dialysis initiation, who had missing values for any variables used in the regressions and received dialysis from a non-VA facility. We excluded patients who received dialysis from a VA facility because VA patients could be receiving ESRD-related services from the VA health administration, and USRDS will not have cost information about those services for the purposes of a consistent analysis.

b. Measures

1) Dependent variable

The dependent variable in aim 3 measured the cumulative Medicare expenditure during the 3-year period following dialysis initiation. The cumulative Medicare expenditure consisted of the costs paid by Medicare Parts A, B, and D. It was calculated as the sum of the plan payment amount and the low-income subsidy. Costs paid by other types of insurance or related nonmedical costs were excluded to focus on Medicare expenditure only. All costs were inflated to the 2017 U.S. dollars using the medical care component of the consumer price index.

2) Independent variables

The two independent variables of interest were initial dialysis type and dialysis modality pattern. Initial dialysis type was a binary variable indicating HD (coded as 0) and PD (coded as 1). Dialysis modality pattern was a categorical variable characterized by the dialysis modality transfer type (HD-PD and PD-HD), count of transfer, and time to transfer. Count of transfer was defined as the total number of transfers in the first 3 years of dialysis. To capture the count of transfer, we followed the CMS "60-day rule" which indicates that any change in modality lasting at least 60 days is recorded as a transfer (USRDS 1999). Time to transfer was defined as the interval between dialysis initiation date and first transfer date. Dialysis modality pattern had nine categories: HD only (initiated and maintained on HD in the first 3 years); PD only (initiated and maintained on PD in the first 3 years); PD- HD in first year (initiated PD and transferred to HD in the first year of dialysis, PD-HD in second

year, and PD-HD in third year; HD--PD (initiated HD and then transferred to PD in the first year of dialysis) in first year, HD-PD in second year, and HD-PD in third year; and more than one transfer.

Other independent variables were patient- and facility-level characteristics. Patient-level characteristics were collected at the time of ESRD onset, except for the Charlson Comorbidity Index (CCI) score. Four types of patient-level characteristics were controlled for: treatment, sociodemographic, clinical, behavioral. Treatment characteristic was the year of dialysis initiation (2011, 2012,2013). The other three types of independent variables have been described in aim1.

c. Statistical analysis

Intent-to-treat and as-treated analyses were conducted following the recommendations from previous studies (Vonesh 2000, Shih 2005). Given any subsequent modality changes were unknown, an intent-to-treat analysis can provide useful information for decision makers to choose or make recommendations on an initial dialysis modality. We conducted an intent-to-treat analysis to examine the association between initial dialysis type with cumulative 3-year Medicare expenditure, and conducted an as-treated analysis to assess the association between dialysis modality pattern in the first three years of dialysis and cumulative 3-year Medicare expenditure.

Patient- and facility-level characteristics were compared between initial dialysis type (HD versus PD) by T test for continuous variables and Pearson's chi-square test for categorical variables. Due to the highly skewed distribution of Medicare expenditure,

generalized linear model (GLM) with gamma distribution and log link function was used to estimate the 3-year Medicare expenditure (Basu 2004). Because the observations within a facility could be related with each other, in all analyses we used cluster-robust standard errors to account for this correlation (Abadie 2017). All P values reported were two-sided; statistical significance level was set at P value less than 0.05.

The equation of intent to treat analysis is:

$$Medicare\ expenditure = \alpha + \beta M \quad + \gamma other\ independent\ variables + \varepsilon$$

The dependent variable is the cumulative 3-year Medicare expenditure following dialysis initiation. M is a dummy variable indicating initial dialysis type.

The equation of as-treated analysis is:

$$\begin{aligned} &Medicare\ expenditure \\ &\quad = \alpha + \beta_1 M_1 + \beta_2 M_2 + \beta_3 M_3 + \beta_4 M_4 + \beta_5 M_5 + \beta_6 M_6 + \beta_7 M_7 + \beta_8 M_8 \\ &\quad + \gamma other\ independent\ variables + \varepsilon \end{aligned}$$

The dependent variable is the cumulative 3-year Medicare expenditure following dialysis initiation. Since dialysis modality pattern had 9 categories, 8 dummy variables were created to indicate the categories of dialysis modality pattern with HD only as the reference group.

JOURNAL ARTICLE

Change in healthcare providers' decisions on timing of dialysis initiation and ESA utilization in ESRD patients after the implementation of expanded prospective payment system

ABSTRACT

Background

In 2011, the U.S. Centers for Medicare & Medicaid Services (CMS) implemented a new expanded prospective payment system (PPS) for end-stage renal disease (ESRD) which may have changed healthcare providers' decisions about ESRD care. We examined the association between the 2011 expanded PPS and healthcare providers' decisions on timing of dialysis initiation and use of erythropoiesis-stimulating agents (ESAs).

Method

We identified incident dialysis patients in the United States Renal Data System and performed interrupted time-series analysis to examine the effect of the 2011 expanded PPS. Multivariable logistic regression and two-part models were conducted to analyze timing of dialysis initiation and ESA utilization, respectively.

Results

A total of 209,522 patients were included in the analysis of dialysis initiation timing and 57,312 were included in the analysis of ESA utilization. We found that the odds of early dialysis initiation decreased immediately by 19% following the 2011 expanded PPS; the odds of ESA utilization decreased immediately by 15% and 47% following the 2011 expanded PPS in the pre-and post-dialysis initiation periods, respectively; the cumulative 6-month

doses of ESAs decreased immediately by 19% and 39% following the 2011 expanded PPS in the pre-and post-dialysis initiation periods, respectively.

Conclusion

Our findings suggest that 2011 expanded PPS may reduce the probability of early dialysis initiation and ESA utilization after dialysis initiation. Future studies are needed to examine the extent to which clinical causes and expanded policy contributed.

INTRODUCTION

End-stage renal disease (ESRD) poses a significant health and economic burden in the United States. The annual incidence rate of ESRD rose from 72.3 per million in 1980 to 373.4 per million in 2016, with 726,331 prevalent cases living with ESRD in 2016 (USRDS annual data report 2018). Although ESRD patients account for less than 1% of the total Medicare population, they account for more than 7% of the overall Medicare costs since 2004. In 2016, the Medicare expenditure for ESRD was $35.4 billion. ESRD patients need renal replacement therapies such as hemodialysis (HD), peritoneal dialysis (PD) or kidney transplantation for survival (Rodger 2012). Majority of the ESRD patients in the United States receive either forms of dialysis as opposed to the kidney transplantation (Jian 2019). Consequently, more than 90% of the Medicare ESRD expenditure is spent on dialysis therapy (USRDS annual data report 2018).

Prior to January 2011, Medicare used a composite rate payment methodology to reimburse facilities that provided renal dialysis services to Medicare beneficiaries with ESRD. This payment methodology paid for dialysis treatment costs and certain routinely used ESRD-related drugs, laboratory tests, and supplies collectively as a bundle once dialysis was initiated (post-dialysis initiation period). The bundle did not include many other ESRD-related injectable drugs, such as erythropoiesis-stimulating agents (ESAs) used to treat CKD and ESRD related anemia, as well as non-routine laboratory tests. Medicare paid for these items and services, not included in the bundle, separately, during the post-dialysis initiation period. In addition, all ESRD related items and services were billed separately and paid for on a fee-for-service (FFS) basis before dialysis initiation (pre-dialysis initiation period).

Payments for items and services, which were separately billed during the post-dialysis initiation period, had increased dramatically before 2011. In 2007, Medicare paid approximately $9.2 billion for dialysis-related services, of which 38% was paid for separately billed items and services (CMS 2010).

In order to address the exponentially growing healthcare costs, U.S. Centers for Medicare & Medicaid Services (CMS) implemented a new expanded prospective payment system (PPS), and expanded the bundle payment in January 2011. Under the 2011 expanded PPS, dialysis services as well as formerly separately billed items and services (such as the injectable ESAs), were now included in an expanded bundled amount during the post-dialysis initiation period (CMS 2010, CMS 2018). CKD and ESRD related items and services during the pre-dialysis initiation period were still paid for separately on a FFS basis.

The 2011 expanded PPS was aimed at influencing healthcare providers' decisions about ESRD-related treatment utilizations, and consequently containing costs. Financial relationships commonly exist between dialysis facilities and nephrologists; for example, nephrologists often derive income from co-ownership, employee-ship, or medical directorship of dialysis facilities (Berns 2018, Ozar 2013). Hence, prior to 2011, dialysis facilities and their associated nephrologists could maximize reimbursement and consequently financial returns, by increasing the prescribed volume and intensity of separately billed items and services during the post-dialysis initiation period (MedPAC 2011). The 2011 expanded PPS aimed to dis-incentivize volume and intensity of treatment during the post-dialysis initiation period, by eliminating FFS billing, and bundling more services. However, the effect of the 2011 expanded PPS on nephrologists' and dialysis facilities' decisions regarding

utilizations of ESRD-related drugs and services remains unclear. Studies suggest that healthcare providers generally respond to financial incentives and payment strategy changes, though there is limited evidence specific to kidney disease and dialysis (Gabel 2008, Mulley 2009, Wennberg 1982).

The 2011 expanded PPS might influence the decision of dialysis facilities and nephrologists in two broad ways: 1) by influencing the timing of the dialysis initiation; and 2) by influencing the volume of products and services used before and after dialysis initiation. Before the 2011 expanded PPS, dialysis facilities and nephrologists had no direct economic incentive to delay dialysis, and could prescribe separately billed services and products during the post-dialysis initiation period, in order to benefit from the reimbursement of the volume and intensity of these items during that period. However, after the 2011 expanded PPS implementation, providers might benefit from initiating dialysis late and prescribing certain services and products during the pre-dialysis initiation period to keep them out of the post-dialysis capitated period. The timing of dialysis initiation is typically determined by the estimated glomerular filtration rate (eGFR) level at dialysis initiation, with early dialysis initiation defined as an eGFR $\geq$ 10.0 ml/min/1.73m^2 (Cooper 2010, Yu 2015, Matthew 2017). In the United States, the mean eGFR at dialysis initiation increased from 7.7 mL/min/1.73m^2 in 1996 to 10.4 mL/min/1.73m^2 in 2010, but subsequently decreased to 9.7 mL/min/1.73m^2 in 2016 (USRDS annual report 2018); this reduction might potentially be due to the 2011 expanded PPS implementation. Utilization of certain services and products that could be used both before and after dialysis initiation might be shifted more to the pre-dialysis initiation period, after the 2011 expanded PPS, to keep them out of the post-dialysis

capitated period. One such product is the ESA, which is primarily used for CKD and ESRD related anemia (hemoglobin level ≤12 g/dL). Nephrologists and dialysis facilities may decide to manage anemia more aggressively during the pre-dialysis initiation period. To our knowledge, no study has evaluated the effect of the 2011 expanded PPS on the timing of dialysis initiation or change in extent of use of products before and after dialysis initiation, once they were bundled with dialysis services after 2011.

In the current study, we evaluated the effect of the 2011 expanded PPS on (1) timing of dialysis initiation measured by eGFR level at dialysis initiation (where a lower eGFR score indicates delayed dialysis initiation); and (2) utilization of ESAs during pre-dialysis and post-dialysis initiation periods, given the payment mechanisms before and after dialysis initiation were different pre and post 2011.

METHODS

Data Sources

This retrospective observational analysis used the United States Renal Data System (USRDS) data for the period 2006-2016. USRDS is a national data system that provides information on all patients with CKD and ESRD in the United States. Data were extracted from the following eight USRDS datasets: Patient Profile, Medical Evidence Form, CMS/CDC ESRD Annual Facility Survey, Pre-ESRD payer history, Payer History, Pre-ESRD Medicare claims, ESRD Medicare claims, and Provider crosswalk.

Study design and study population

This study only included ESRD patients, from the USRDS, who initiated dialysis as their first treatment modality for ESRD between January 1, 2006 and December 31, 2016. Dialysis initiation date was the index date for patient inclusion as well as study design. The study only included those who were equal to or older than 18 years old, who had medical evidence form filled within 45 days of dialysis initiation, who did not have date of death erroneously recorded as being before dialysis initiation date, who had both Medicare parts A and B coverage (with Medicare as the primary payer) on the dialysis initiation date and during the 6 months before dialysis initiation, who had all the eight USRDS datasets mentioned above, who did not have missing values for any variables used in the regressions, and who received dialysis from a non-VA facility. Patients without both Medicare parts A and B as primary payer at and during the 6 months before dialysis initiation date were excluded because this period was used to develop the baseline Charlson comorbidity index. We excluded patients who received dialysis from a VA facility because physicians working in the VA system are salary-paid, hence would have little financial gain from modifying service usage based on reimbursement changes (Yu 2015). In addition, VA patients could be receiving ESRD-related services from the VA health administration, and this data will not have information about those services for the purposes of a consistent analysis.

In addition to the above inclusion and exclusion rules, additional exclusions were made while examining the impact of the 2011 expanded PPS on ESA utilization. The effect of the 2011 expanded PPS was examined on ESA utilization six months pre and post dialysis initiation. Hence, the Charlson comorbidity for this aim was developed using claims filed 12

months before dialysis initiation up to six month before dialysis initiation so the baseline comorbidity index period does not overlap with the period during which the dependent variable was captured. Consequently, for this aim only patients with uninterrupted Medicare part A and B coverage from 12 months before dialysis initiation to 6 months after dialysis initiation were included. Patients who received kidney transplantation in the six months following dialysis initiation were excluded because the 2011 expanded PPS applies to ESRD patients who are receiving dialysis. Moreover, to ensure each patient had the same provider access to receive ESAs before dialysis initiation, patients who did not have at least 6 months of nephrology care prior to dialysis initiation were excluded. Finally, only patients who initiated dialysis from July 1, 2008, to June 30, 2010, and from July 1, 2011, to June 30, 2016 were included when examining ESA utilization. Medicare only required dialysis facilities to report each separately billed service as a separate revenue center line item with individual dates of service since January 1, 2008. Hence accurate information on ESA utilization in patients who received ESAs before January 1, 2008 was unavailable, consequently only patients who initiated dialysis before January 1st 2008 were excluded. Patients who initiated dialysis before July 1, 2008 and after June 30, 2016 were excluded because 6-month claims filed before and after dialysis initiation were needed to capture ESA utilization. Patients who initiated dialysis between July 1st, 2010, and June 30th, 2011, were excluded because the ESA utilization period examined pre and post dialysis initiation for these patients, did not strictly fall in the pre January 2011 composite rate payment period, or the post January 2011 expanded PPS period, to facilitate development of two clean comparison groups before and after the 2011 expanded PPS implementation.

Dependent variables

Four dependent variables were analyzed in this study. The first dependent variable measured timing of dialysis initiation in terms of eGFR level at dialysis initiation. This variable defined as "early dialysis initiation" was a binary variable indicating eGFR at dialysis initiation ≥10.0 mL/min/1.73m2 (coded as 1) (Cooper 2010, Yu 2015, Matthew 2017), and eGFR at dialysis initiation <10.0 mL/min/1.73m2 (coded as 0).

The second and third dependent variables measured ESA utilization, and cumulative 6-month doses of ESA pre and post dialysis initiation. ESA utilization was measured using two binary variables indicating any ESA utilization during the 6 months before and 6 months following dialysis initiation. Cumulative 6-month doses of ESA was measured using two continuous variables indicating the total doses of ESAs during the 6 months before and 6 months following dialysis initiation. The Healthcare Common Prodecure Coding System (HCPCS) codes for the three types of ESAs, epoetin alfa or beta (EPO), darbepoetin alfa (DPO), and epoetin beta pegol (PEG), were used to identify ESA utilization from Medicare claims. Dose of DPO and PEG were converted to that of EPO using a dose conversion ratio (EPO:DPO:PEG = 200:1:0.93) (Kuwahara 2015, Kuwahara 2013). The fourth dependent variable was the ratio of the cumulative 6-month doses of ESAs during the pre-dialysis initiation period divided by the doses of ESAs during the post-dialysis initiation period.

Independent variables

The analyses had three independent variables of interest. The first was a binary pre-post variable "expanded-PPS" capturing the 2011 expanded PPS implementation, and coded

as 1 for all patients initiating dialysis at or after 2011 and as 0 for all patients initiating dialysis before 2011. The second is "dialysis initiation time-period", which was measured as a continuous variable indicating the time period to which a patient's dialysis initiation date belonged (for the purposes of interrupted time series analysis) (Erickson 2016). For the first analysis on timing of dialysis initiation this variable ranged from 1 to 22, and each consecutive number represented 6 calendar months starting from January 2006 to December 2016. For the second analysis on ESA utilization this variable ranged from 1 to 28, and each consecutive number represented 3 calendar months starting from July 1, 2008 to June 30, 2016 (with the exclusion of patients who initiated dialysis between July1st 2010-June30th 2011). This time-period variable was created using 3 and 6 month intervals instead of indicators based on 12-calendar months because a minimum of 8 time periods before and 8 time periods after an intervention are needed to statistically evaluate changes in an interrupted time series analysis (Penfold 2013). The third was the interaction between the expanded-PPS and dialysis initiation time-period variable. This interaction term was coded as 0 during the pre-2011 composite rate payment period. It was coded as 1 to 12 for every 6-month time interval during the post-2011 expanded PPS period in the first analysis on timing of dialysis initiation, and 1 to 20 for every 3-month time interval in the second analysis on ESA utilization.

Other independent variables controlled for in the analyses were patient- and facility-level characteristics. Patient-level characteristics were collected at the time of dialysis initiation date (index date), except for the Charlson Comorbidity Index (CCI) score, which was calculated using the Medicare claims data from the period before the dialysis initiation

date, as described above. Four types of patient-level characteristics were controlled for: sociodemographic, clinical, behavioral, and treatment. Patient sociodemographic characteristics included age at dialysis initiation (continuous variable measured in years); gender (female, male); race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other); education, measured as a percentage of adults with high school education or more, in the patient's ZIP code area (continuous variable in percent); income measured as median household income for the patient's ZIP code area (continuous variable in USD); employment status at dialysis initiation (unemployed, employed); and residential urbanicity at dialysis initiation (large metropolitan, medium or small metropolitan, micropolitan, and non-core). Education and income were obtained for each patient at the ZIP code level as suggested in previous studies (Berkowitz 2015, Krieger 2005), since personal information on these were not present in the data; they were obtained by linking the patient's ZIP code in the USRDS to the 2010 U.S. Census data. Residential urbanicity was identified for each patient by linking the patient's FIPS code in the USRDS to the 2010 Rural Urban Commuting Area codes. Patient clinical characteristics included nephrologist care prior to dialysis initiation (no, <6 months, 6-12 months, and >12 months); primary cause of ESRD (diabetes, hypertension, glomerulonephritis/cystic renal disease, and others); CCI score at dialysis initiation (continuous variable); serum albumin at dialysis initiation (albumin <3 g/dL, 3 g/dL≤ albumin <3.5 g/dL, and albumin ≥3.5 g/dL); disability at dialysis initiation (yes, no); and BMI at dialysis initiation (continuous variable). Nephrologist care prior to dialysis initiation was not included in the analysis of ESA utilization because every patient included in the corresponding analytic sample had received at least 6 months of pre-dialysis nephrology care. Patient behavioral characteristics included smoking status at dialysis

initiation (yes, no), drug dependence at dialysis initiation (yes, no), and alcohol dependence at dialysis initiation (yes, no). Patient treatment characteristic only included dialysis type at dialysis initiation (HD, PD). Facility-level characteristics included unit affiliation (chain, independent); number of facility stations (continuous variable); non-profit designation (yes, no); ownership (hospital-based, free-standing); and regional ESRD network identifiers (Network 1 to Network 17).

Statistical analysis

Descriptive statistics were performed to compare baseline characteristics between patients who initiated dialysis before and after the 2011 expanded PPS implementation using t tests for continuous variables and Pearson's chi-square tests for categorical variables. To analyze if the 2011 expanded PPS implementation was temporally associated with early dialysis initiation, an interrupted time-series analysis was conducted using multivariable logistic regression analysis with the binary eGFR-based "early dialysis initiation" variable as the dependent variable. As mentioned above the three main independent variables of interest in this regression were the binary pre-post "expanded-PPS" variable, the continuous "dialysis initiation time-period" created by dividing the 11-year study period (January 1, 2006-December 31, 2016) into 22 six-month intervals and classifying patients into these 22 time intervals based on their dialysis initiation dates, and the interaction of these two variables.

To analyze ESA utilization during the 6 months before and following the dialysis initiation, interrupted time-series analyses were conducted using two sets of two-part models, in addition to a third linear regression analysis (Deb 2018). The first two-part model

evaluated ESA utilization during the 6 months before dialysis initiation. The first part of this model was a logistic regression evaluating the binary dependent variable indicating whether or not ESAs were utilized during the 6 months before dialysis initiation, and the second part was a linear regression evaluating the dependent variable capturing the cumulative dose of ESAs utilized during the 6 months before dialysis initiation. A similar two-part model was performed for the 6-months following dialysis initiation. Based on the distribution of the cumulative dose dependent variables and results of the BoxCox specification tests, these variables were logarithmically transformed before the linear regressions were estimated in the second parts. In addition to report the coefficients of variables in the two-part models, overall marginal effect which estimates the effect of covariate on the marginal mean of dependent variable for the combined population of ESA users and non-users (smith 2015). The third and final linear regression analysis evaluated the ratio of the cumulative dose of ESAs utilized during the 6 months before the dialysis initiation divided by the cumulative dose of ESAs utilized during the 6 months following the dialysis initiation. To ensure that the denominator of the ratio was greater than zero, we excluded patients who did not receive ESAs during the 6 months following dialysis initiation. As mentioned above, the three main independent variables of interest in these regressions evaluating ESA utilization were, the binary pre-post "expanded-PPS" variable, the continuous "dialysis initiation time-period" created by dividing the study period (July 1, 2008-June 30, 2010, and July 1, 2011-December 31, 2016) into 28 three-month intervals and classifying patients into these 28 time intervals based on their dialysis initiation dates, and the interaction of these two variables.

In addition to the three independent variables patient-level and facility-level characteristics listed in Table 1 were adjusted for in all the regressions. Based on specification tests and model fit the square of age and square of BMI were also included in the regression analyses, and the continuous income variable was logarithmically transformed. In order to adjust for clustering of patients within the facility, cluster-robust adjustment of standard errors were performed in all regressions (Abadie 2017). As mentioned above, for computing the cumulative doses of the three types of ESAs used in the data, doses of two of the ESAs (DPO and PEG) were converted using a dose conversion ratio to dose equivalents of the third ESA (EPO) (Kuwahara 2015). Since there are no formal clinical guidelines establishing the dose conversion ratio for ESAs, and EPO is the most commonly used ESA in the United States, a sensitivity analysis was performed by excluding patients who used DPO or PEG and redoing the analyses for all regressions examining ESA utilizations. All statistical significance tests were two-sided, and statistical significance was defined as p-value<0.05. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC) and Stata (version 13; Stata Corp., College Station, TX).

RESULTS

Baseline characteristics

The first analysis involving dialysis initiation timing included 209,522 patients ,with 115,531 patients initiating dialysis before the 2011 expanded PPS implementation (pre-expanded PPS cohort) and 93,991 patients initiating dialysis at or after the expanded PPS

implementation (post-expanded PPS cohort). The post-expanded PPS cohort had a lower proportion of patients who were disabled, had nephrologist care prior to dialysis initiation, underwent HD, received dialysis from independent and hospital-based facilities, as compared with the pre-expanded PPS cohort. However, this cohort had a higher proportion of patients who were male, were non-Hispanic white, had diabetes as the primary cause of ESRD, had serum albumin level less than 3g/dl, and received dialysis from for-profit facilities. Patients in the post-expanded PPS cohort also had significantly higher CCI scores and BMI values than patients in the pre-expanded PPS cohort (Table 1).

The second analysis involving ESA utilization included 57,312 patients, with 21,053 patients initiating dialysis before the 2011 expanded PPS implementation and 36,259 patients initiating dialysis at or after the expanded PPS implementation. Compared with the pre-expanded PPS cohort, the post-expanded PPS cohort had a lower proportion of patients who were from a large metropolitan area, underwent HD, and received dialysis from independent, non-profit and hospital-based facilities; however, this cohort had a higher proportion of patients who were non-Hispanic white, had diabetes as the primary cause of ESRD, and had serum albumin level lower than 3 g/dl. Patients in the post-expanded PPS cohort also had significantly higher CCI scores and BMI values (Table 1).

Dialysis initiation timing

The percentage of pre-expanded PPS cohort who initiated dialysis early was significantly higher than that of post-expanded PPS cohort who initiated dialysis early (54.26% vs. 53.03%, respectively; Table 1). After adjusting for patient-level and facility-

level characteristics, the odds of early dialysis initiation increased by approximately 3% every 6 months in the pre-2011 composite rate payment period (odds ratio [OR], 1.028; 95% confidence interval [CI], 1.024-1.033), whereas the odds of early dialysis initiation decreased immediately by 19% following the 2011 expanded PPS implementation (OR, 0.813; 95% CI, 0.786-0.853). The trend towards increasing odds of early dialysis initiation over time reversed in the post 2011 expanded PPS period (Table 2).

ESA utilization

As described above, we used two-part models to analyze ESA utilization. Multivariate logistic regression was conducted in the first part, and OLS linear regression was conducted in the second part. The results of the BOXCOX test suggested applying log transformation to the dependent variable in the second part.

The percentage of post-expanded PPS cohort who used ESAs before dialysis initiation was significantly lower than that of pre-expanded PPS cohort (31.47% vs. 41.16%, respectively; Table 1). Among patients who used ESAs before dialysis initiation, the cumulative 6-month doses of ESAs in the pre-dialysis initiation period were significantly lower for post-expanded PPS cohort than for pre-expanded PPS cohort (63,411 units vs.83,829 units, respectively; table 1). Table 2 shows the results of the interrupted time series analyses of ESA utilization. After adjusting for patient-level and facility-level characteristics, the odds of using ESAs before dialysis initiation decreased by approximately 1.1% every 3 months (OR, 0.983; 95% CI, 0.971-0.995) before expanded PPS implementation. The odds

of using ESAs before dialysis initiation decreased immediately by 15% following the 2011 expanded PPS implementation (OR, 0.845; 95% CI, 0.788-0.907). However, there was no significant change in downward trend of reduced ESAs over time occurred following the 2011 expanded PPS implementation (OR, 0.994; 95% CI, 0.981-1.007). Among patients who used ESAs before dialysis initiation, there was no significant change in the cumulative 6-month doses of ESAs before dialysis initiation in the pre-2011 composite rate payment period. The cumulative 6-month doses of ESAs decreased significantly by 19% (95% CI, 25%-12%) following the 2011 expanded PPS implementation. In addition, no significant change in the downward trend of reduced ESA doses over time following the 2011 expanded PPS implementation was observed. The overall marginal effect that combines both parts of the two-part model showed that the cumulative 6-month doses of ESAs before dialysis initiation in the post 2011 expanded PPS period was significantly lower (9,116 units, 95% CI, 5,469units- 12,763 units) than that in the pre-2011 composite rate payment period.

The percentage of post-expanded PPS cohort who used ESA after dialysis initiation was significantly lower than that of pre-expanded PPS cohort (91.26% vs. 96.49%, respectively; Table 1). Among patients who used ESAs after dialysis initiation, the cumulative 6-month doses of ESAs in the post-dialysis initiation period was significant lower for post-expanded PPS cohort compared with that for pre-expanded PPS cohort (267,441 units vs.484,311 units ,respectively; table 1). After adjusting for patient-level and facility-level characteristics, there was no significant change in the odds of using ESAs in the pre-2011 composite rate payment period. The odds of using ESAs after dialysis initiation decreased immediately by 47% following the 2011 expanded PPS implementation (OR,

0.528; 95% CI, 0.452-0.617; table 2). There was no significant change in the downward trend of reduced ESA utilization in the post dialysis initiation period, following expanded PPS implementation. Among patients who used ESAs after dialysis initiation, the cumulative 6-month doses of ESAs decreased by approximately 0.56% (95% CI, 0.06% -1.06%; table 2) every 3 months in the pre-2011 composite rate payment period. The cumulative 6-month doses of ESAs decreased significantly by 39% (95% CI, 38%-41%; table 2) following the 2011 expanded PPS implementation. In addition, there was significant decrease in the slope following expanded PPS implementation, suggesting that the magnitude of decrease in the cumulative 6-month doses of ESAs increased over time (95% CI, 0.69%-1.77%). The overall marginal effect showed that the cumulative 6-month doses of ESAs in the dialysis period was significantly lower (208,308 units, 95% CI, 192,469 units-224,147 units; table 2) in post 2011 expanded PPS period than that in the pre- 2011 composite rate payment period.

We also examined the trend of the ratio of ESA doses in the pre-dialysis initiation period to that in the post-dialysis initiation period for patients who used ESAs in the post-dialysis initiation period. Before 2011 expand PPS implementation, there was no significant change in the ratio. However, the ratio increased immediately by 0.05 following the 2011 expanded PPS implementation (95% CI, 0.22, 0.078), which suggesting an increase in ESA utilization before dialysis initiation relative to after dialysis initiation.

Sensitivity analysis

Compared with the main model of ESA utilization, the direction and significance of the estimates of expanded-PPS remained the same in the sensitivity analysis. We found

immediately decrease in the odds of EPO use and the cumulative 6-month EPO doses in both pre- and post-dialysis initiation periods following the 2011 expanded PPS implementation. Although the interaction term of cumulative 6-month EPO doses in pre-dialysis initiation period was significant in the sensitivity analysis, which was different from that in the main model, the direction of the interaction term remained the same. The ratio of cumulative 6-month EPO doses increased immediately by 0.005 following the 2011 expanded PPS implementation (Table 3). None of our findings were sensitive to the dose conversion ratio.

DISCUSSION

The 2011 expanded PPS implementation may have influenced healthcare providers' decisions related to ESRD care. In the current study, we examined the association between the 2011 expanded PPS and healthcare providers' decisions on timing of dialysis initiation and ESAs utilization in ESRD patients. Previous studies have examined the factors associated with eGFR at dialysis initiation, and found that eGFR at dialysis initiation is associated with provider characteristics such as experience and education, receipt of pre-dialysis nephrology care, patient preference, distance to facility, economic motivation etc. (Li 2017, Slinin 2014, van de Luijtgaarden 2012, Yu 2015). Our study is the first one to estimate the effect of 2011 expanded PPS on dialysis initiation timing. After adjusting for patient-level and facility-level characteristics, we observed an immediate decrease in the odds of early dialysis initiation and a decreasing trend over time following the 2011 expanded PPS implementation. These findings support our hypothesis that nephrologists and dialysis

facilities are inclined to initiate dialysis late rather than early because the 2011 expanded PPS reduces their motivation to initiate dialysis early. Although this is an important finding, the decrease in early dialysis initiation may have other explanations. Other contributors may be driving this trend change. For example, the landmark clinical trial IDEAL published in 2010 found that early dialysis initiation lacks a clinical benefit (Cooper 2010). In addition, the most recent clinical practice guidelines, such as NKF-KDOQI and KDIGO, recommend that the decision to initiate dialysis should be based on an assessment of the complications of CKD rather than simply on the eGFR level (KDIGO 2013). Future research will need to determine whether the PPS or these other factors explain the shift in timing of dialysis initiation.

The trends of ESA utilization in the pre-dialysis and post-dialysis initiation periods have been well described (Wetmore 2015, Coritsidis 2014, Karaboyas 2015, Winkelmayer 2014, Coyne 2017, Park 2018). To our knowledge, no study has evaluated the impact of the 2011 expanded PPS on ESA utilization in the pre dialysis initiation period. Some studies evaluated the impact of the 2011 expanded PPS on the ESA utilization in the post-dialysis initiation period. Swaminathan et al. reported that the 2011 expanded PPS was associated with an immediate and substantial decline in the use of ESAs, however, this study only examined the ESA utilization between January 2009 and June 2011(Swaminathan 2015). Turenne et al. estimated the change of EPO dose by using data of HD patients from August 2010 to December 2011 and reported that mean EPO dose declined from 20,506 U/wk to 14,777 U/wk (Turenne 2015). Wang et al. examined the association between expanded PPS and ESA utilization in HD patients older than 66 years and having Medicare as primary

payer. They reported that 92% of patients received an ESAs in the pre-policy period (January 1, 2008, to December 31, 2009) compared with 72% of patients in the post-policy period (July 1, 2011, to June 30, 2013); among patients receiving an ESA, the monthly ESA dose was also markedly lower following expanded PPS(Wang 2016). Our study is the first comprehensive study using data of HD and PD patients from 2008 to 2016 to estimate the effect of 2011 expanded PPS on the ESA utilization in the 6 months before and 6 months after dialysis initiation simultaneously, and to compare the relative differences in utilization change due to expanded PPS between pre-and post-dialysis initiation periods.

We observed decreasing trends in both pre-dialysis initiation and post-dialysis initiation periods as previous studies. The reason might be the growing safety concerns of ESAs. Since 2006, several key randomized clinical trials published in 2006 and 2009 suggest that high doses of ESAs should be avoided (Drüeke 2006, Pfeffer 2009, Singh 2006). Moreover, the U.S. Food and Drug Administration issued safety alerts in 2006, required pharmaceutical companies to add safety warnings to ESAs labels (i.e., "black box" warnings) in 2007-2008, and revised the ESAs labels and clinical guidelines in 2011. Furthermore, a landmark study, the Trial to Reduce cardiovascular Events With Aranesp Therapy (TREAT), which examined use of ESAs therapy to treat anemia among CKD patients, reported no clinical benefit of ESAs compared with placebo. All these findings have raised concerns about the safety of ESAs and may led to lower use of ESAs in CKD and ESRD patients since 2006 (zhang 2011, Miskulin 2013, Winkelmayer 2014).

We also observed that the decline in ESA utilization was more prominent in post-dialysis initiation period compared to pre-dialysis initiation period. The immediately

decrease in the odds of ESAs utilization was greater in post-dialysis initiation period compared with pre-dialysis initiation period; the decrease in the cumulative 6-month doses of ESAs used in the post-dialysis initiation period became greater following expanded PPS, whereas the change in decreasing trend was not significant in the pre-dialysis initiation period; the ratio of ESA doses in pre-dialysis initiation period divided by ESAs doses in post-dialysis initiation period increased significantly following expanded PPS. There are two reasons for the greater decrease in post-dialysis initiation period and the increasing ratio of ESA doses. One reason is that nephrologists and dialysis facilities may decide to manage anemia more aggressively during the pre-dialysis initiation period to reduce the ESA utilization in the post-dialysis capitated period. Another reason is that ESA utilization during the dialysis period was affected by 2011 expanded PPS and safety concerns of ESAs, whereas ESA utilization before dialysis initiation was affected only by the safety concerns. Thus, expanded PPS further reduced ESA utilization in the post-dialysis initiation period. Both reasons indicate that expanded PPS affected healthcare providers' decisions on ESA utilization. Previous studies have demonstrated sharp declines in ESA utilization after 2011, none has been able to disentangle the economic causes from clinical causes. By examining ESA utilization in pre-dialysis initiation period relative to ESA utilization in post-dialysis initiation period, we were able to isolate the economic incentives. Further study is needed to estimate how much of the ESAs decrease in post-dialysis initiation period can be attributed to the expanded PPS.

This study has several limitations. First, the CCI score only represents conditions at the time of study initiation. However, we do not expect that changes in comorbid conditions over time would impact the ESAs utilization and dialysis initiation timing. Second, similar to all other observational studies, there were some unobservable confounding factors that we were not be able to adjust for. Third, our findings were not generalized to other ESRD population without Medicare Parts A and B as primary payer.

CONCLUSION

We found that the 2011 expanded PPS implemented was associated with significant decrease in the odds of early dialysis initiation and the decline in ESA utilization was more prominent in post-dialysis initiation period compared with pre-dialysis initiation period. These findings suggest that 2011 expanded PPS may reduce the probability of early dialysis initiation and dis-incentivize the volume and intensity of ESAs utilization in post-dialysis initiation period. Future studies are needed to examine the extent to which clinical causes and expanded policy contributed.

Table 1 Baseline characteristics of pre- and post-expanded PPS cohorts

	Dialysis initiation timing analysis			ESA utilization analysis		
	Pre-expanded PPS cohort (n=115,531)	Post-expanded PPS cohort (n=93,991)	P-value	Pre-expanded PPS cohort (n= 21,053)	Post-expanded PPS cohort (n=36,259)	P-value
Dependent variables						
Early dialysis initiation (%)	54.26	53.03	<0.001			
Pre-dialysis initiation period						
ESA utilization(%)				41.16	31.47	<0.001
Cumulative 6-month doses of ESAs among patients using ESAs (mean, unit)				83,829	63,411	<0.001
Post-dialysis initiation period						
ESA utilization (%)				96.49	91.26	<0.001
Cumulative 6-month doses of ESAs among patients using ESAs (mean, unit)				484,311	267,441	<0.001
Ratio of Cumulative 6-month ESAs before dialysis initiation to that after dialysis initiation (mean)				0.1911	0.1182	0.017
Independent variable						
Patient sociodemographic characteristics						
Age at ESRD onset(mean), y	72.97	72.61	<0.001	72.64	72.78	0.1389
Gender (%)						
Male	53.82	55.14	<0.001	55.07	55.75	0.114
Female	46.18	44.86		44.93	44.25	
Race/ethnicity (%)						
Non-Hispanic white	66.88	67.61	<0.001	66.99	69.6	<0.001
Non-Hispanic Black	20.83	19.07		19.89	18.33	
Hispanic	8.49	9.27		8.7	8.16	
Others	3.79	4.05		4.42	3.9	
Employment status (%)						
Unemployed	98.29	98.25	0.463	97.79	97.96	0.158
Employed	1.71	1.75		2.21	2.04	
Residential urbanicity (%)						
Large metropolitan	44.02	43.82	<0.001	42.45	41.27	0.001
Medium or small metropolitan	32.53	33.52		34.21	35.75	
Micropolitan	14.02	13.12		14.08	13.5	
Non-core	9.42	9.53		9.25	9.48	
Median household income (mean)	51,557	51,992	<0.001	52,298	52,534	0.2211
Education (mean)	48.38	48.08	0.0004	48.45	48.32	0.3351
Patient clinical characteristics						
Primary cause of ESRD (%)						
Diabetes	45.18	46.57	<0.001	48.83	49.78	<0.001
Hypertension	32.54	32.49		32.83	33.35	
Glomerulonephritis/cystic renal disease	6.68	5.90		7.65	6.63	
Others	15.60	15.05		10.69	10.24	
Serum Albumin (%)						
albumin<3 g/dl	30.90	38.73	<0.001	29.35	30.27	<0.001
3g/dl <=albumin< 3.5g/dl	28.45	29.42		28.73	29.91	
albumin≥3.5g/dl	33.80	31.85		41.92	39.82	
CCI score (mean)	7.43	8.12	<0.001	6.19	7.87	<0.0001
Disabled (%)						
No	89.70	88.71	<0.001	93.64	93.39	0.246
Yes	10.30	11.29		6.36	6.61	
BMI (mean)	28.48	28.99	<0.001	28.99	29.24	0.0001
Nephrologist care prior to ESRD onset (%)						
No	30.92	27.18	<0.001			
<6 months	13.65	15.94				
6-12 months	24.78	21.30				
>12 months	30.65	35.58				

Patient behavioral characteristics						
Current smoking status (%)						
No	94.66	94.11	<0.001	94.42	94.10	0.119
Yes	5.34	5.89		5.58	5.90	
Drug dependence (%)						
No	99.47	99.42	0.191	99.61	99.65	0.432
Yes	0.53	0.58		0.39	0.35	
Alcohol dependence (%)						
No	98.96	98.83	0.003	99.28	99.35	0.305
Yes	1.04	1.17		0.73	0.65	
Patient treatment characteristic						
Dialysis type (%)						
HD	95.55	93.73	<0.001	93.40	90.09	<0.001
PD	4.45	6.27		6.60	9.91	
Facility characteristics						
Unit affiliation (%)						
Independent	32.13	22.49	<0.001	30.39	22.50	<0.0001
Chain	67.87	77.51		69.61	77.50	
Number of dialysis station	20.69	20.50	<0.001	21.01	20.65	<0.0001
Non-profit designation (%)						
No	77.57	83.85	<0.001	77.49	83.90	<0.0001
Yes	22.43	16.15		22.51	16.10	
Ownership (%)						
Hospital-based	14.08	8.39	<0.001	13.12	8.35	<0.001
Free-standing	85.92	91.61		86.88	91.65	
Network						
Network 1 (CT, ME, MA, NH, RI, VT)	4.81	4.14	<0.001	6.27	5.33	<0.001
Network 2 (NY)	7.31	6.7		7.14	6.72	
Network 3 (NJ, PR, VI)	5.02	5.16		5.03	4.31	
Network 4 (DE, PA)	4.51	4.62		3.77	4.6	
Network 5 (DC, MD, VA, WV)	4.94	5.36		4.49	5.52	
Network 6 (GA, NC, SC)	9.13	8.77		10.32	9.74	
Network 7 (FL)	4.69	5.09		4.78	4.93	
Network 8 (AL, MS, TN)	6.12	6.18		5.39	6.14	
Network 9 (IN, KY, OH)	8.69	8.48		7.01	8.51	
Network 10 (IL)	4.22	4.54		3.02	4.27	
Network 11 (MI, MN, ND, SD, WI)	8.1	6.5		8.72	6.81	
Network 12 (IA, KS, MO, NE)	4.46	4.66		4.18	4.77	
Network 13 (AR, LA, OK)	4.63	4.53		4.97	4.46	
Network 14 (TX)	8.03	8.97		9.94	8.64	
Network 15 (AZ, CO, NV, NM, UT, WY)	4.2	4.67		4.43	4.8	
Network 16 (AK, ID, MT, OR, WA)	2.66	2.58		3.79	3.22	
Network 17 (AS, Guam, HI, Mariana Islands, Northern CA, Southern CA)	8.48	9.03		6.76	7.23	

Table 2 Results of interrupted time-series analyses for dialysis initiation timing and ESA utilization

Independent variable of interest	Early dialysis initiation	ESA utilization in pre-dialysis initiation period		ESA utilization in post-dialysis initiation period		Ratio of Cumulative 6-month ESAs before dialysis initiation to that after dialysis initiation
		First part	Second part	First part	Second part	
	OR(95% CI)	OR(95% CI)	Dose %(95% CI)	OR(95% CI)	Dose %(95% CI)	
Expanded-PPS	0.815* (0.786, 0.853)	0.845* (0.788, 0.907)	-18.833* (-25.318,-11.785)	0.528* (0.452,0.617)	-39.487* (-41.343, -37.573)	0.050* (0.022,0.078)
Dialysis initiation time	1.028* (1.024, 1.033)	0.983* (0.971, 0.995)	-0.705 (-2.122,0.731)	0.974 (0.943,1.007)	-0.558* (-1.058,-0.056)	-0.002 (-0.006, 0.001)
Interaction between expanded-PPS and dialysis initiation time	0.976* (0.969, 0.982)	0.994 (0.981, 1.007)	-0.486 (-1.981,1.032)	1.002 (0.969,1.036)	-1.231* (-1.766,-0.694)	0.000 (-0.004, 0.004)
Average marginal effect (95% CI)		-9116.304 (-12763.51, -5469.101)		-208308.4 (-224147.1,-192469.7)		

Table 3 Results of sensitivity analysis for EPO use

Independent variable of interest	EPO use in pre-dialysis initiation period		EPO use in post-dialysis initiation period		Ratio of Cumulative 6-month EPO before dialysis initiation to that after dialysis initiation
	First part	Second part	First part	Second part	
	OR(95% CI)	Dose %(95% CI)	OR(95% CI)	Dose %(95% CI)	
Expanded-PPS	0.849* (0.772,0.933)	-21.484* (-27.989,-14.394)	0.703* (0.596,0.829)	-43.757* (-45.695,-41.751)	0.005* (0.002, 0.009)
Dialysis initiation time	0.982* (0.965,0.998)	1.031 (-0.380,2.464)	0.968 (0.935,1.001)	-0.297 (-0.876,0.287)	-0.0004 (-0.001, 0.0003)
Interaction between expanded-PPS and dialysis initiation time	0.996 (0.978,1.014)	-1.813* (-3.338,-0.263)	0.969 (0.936,1.004)	-0.667* (-1.306,-0.025)	0.0003 (-0.0004, 0.001)
Average marginal effect (95% CI)	-2077.65 (-2936.816, -1218.484)		-224705.1 (-248693.2, -200717.1)		

Appendix

Table S1 Interrupted time-series analysis for dialysis initiation timing and ESA utilization

	Early dialysis initiation	ESA utilization in pre-dialysis initiation period		ESA utilization in post-dialysis initiation period		Ratio of Cumulative 6-month ESAs before dialysis initiation to that after dialysis initiation
		First part	Second part	First part	Second part	
	OR(95% CI)	OR(95% CI)	Dose %(95% CI)	OR(95% CI)	Dose %(95% CI)	
Independent variable of interest						
Expanded-PPS	0.815*	0.845*	-18.833*	0.528*	-39.487*	0.050*
	(0.786, 0.853)	(0.788, 0.907)	(-25.318,-11.785)	(0.452,0.617)	(-41.343, -37.573)	(0.022,0.078)
Dialysis initiation time	1.028*	0.983*	-0.705	0.974	-0.558*	-0.002
	(1.024, 1.033)	(0.971, 0.995)	(-2.122,0.731)	(0.943,1.007)	(-1.058,-0.056)	(-0.006, 0.001)
Interaction between expanded-PPS and dialysis initiation time	0.976*	0.994	-0.486	1.002	-1.231*	0.000
	(0.969, 0.982)	(0.981, 1.007)	(-1.981,1.032)	(0.969,1.036)	(-1.766,-0.694)	(-0.004, 0.004)
Independent variable						
Patient sociodemographic characteristic						
Age at ESRD onset, y	0.956*	1.024*	3.546*	0.967*	0.462	0.004*
	(0.950, 0.962)	(1.010, 1.039)	(1.803,5.320)	(0.941,0.993)	(-0.106,1.032)	(0.001, 0.007)
Age2 at ESRD onset	1.0004*	0.99995	-0.022*	1.000*	-0.005	-0.00002
	(1.0003, 1.0004)	(0.9998, 1.00006)	(-0.034,-0.009)	(1.000,1.001)	(-0.009,0.000)	(-0.0005, 0.00001)
Gender (reference: Male)						
Female	0.604*	1.346*	-0.645	2.014*	0.790	0.012
	(0.593, 0.616)	(1.298, 1.396)	(-4.880,3.778)	(1.869,2.171)	(-0.684,2.286)	(-0.001,0.026)

Race/ethnicity (reference: Non-Hispanic white)						
Non-Hispanic black	1.253* (1.219, 1.287)	1.063* (1.004, 1.125)	-2.731 (-9.244,4.248)	1.354* (1.211,1.515)	18.083* (15.450,20.776)	-0.009 (-0.021,0.004)
Hispanic	0.895* (0.861, 0.931)	0.896* (0.823, 0.977)	-25.592* (-33.091,-17.251)	1.316* (1.137,1.522)	-1.680 (-4.817,1.560)	-0.007 (-0.053,0.039)
Others	0.758* (0.717, 0.800)	0.804* (0.709, 0.911)	-15.113* (-26.257,-2.286)	1.290* (1.053,1.581)	4.766* (0.693,9.003)	-0.027 (-0.054,0.001)
Employment status (reference: Unemployed)						
Employed	0.781* (0.729, 0.837)	1.226* (1.083, 1.388)	11.348 (-4.135,29.332)	1.024 (0.830,1.264)	3.072 (-2.004,8.411)	0.011 (-0.016,0.038)
Residential urbanicity (reference: large metropolitan)						
Medium or small metropolitan	1.043* (1.007, 1.080)	1.005 (0.946,1.067)	12.439* (3.738,21.871)	0.842* (0.765,0.927)	-6.732* (-9.287,-4.105)	0.020* (0.002,0.038)
Micropolitan	1.034 (0.991, 1.079)	0.972 (0.897, 1.053)	5.515 (-5.107,17.325)	0.720* (0.637,0.814)	-6.199* (-9.252,-3.044)	0.003 (-0.018,0.023)
Non-core	0.954* (0.912, 0.999)	0.877* (0.804, 0.957)	-1.345 (-11.837,10.395)	0.757* (0.659,0.869)	-6.755* (-10.225,-3.150)	0.013 (-0.017,0.043)
Log transform of Median household income	1.075* (1.038, 1.114)	1.318* (1.225, 1.418)	8.507 (-0.700,18.568)	1.126 (0.989,1.282)	-0.683 (-3.544,2.262)	0.024* (0.001,0.047)
Education (mean)	1.0005 (0.999,1.001)	1.233* (1.088, 1.396)	0.270* (0.091,0.449)	1.001 (0.999,1.003)	0.099* (0.038,0.161)	0.0003 (-0.0002, 0.0008)
Patient clinical characteristic						
Primary cause of ESRD (reference: diabetes)						
Hypertension	0.835* (0.816, 0.854)	0.923* (0.883, 0.966)	4.224 (-1.084,9.817)	0.983 (0.906,1.068)	1.912* (0.035,3.825)	-0.013* (-0.026,-0.001)

Glomerulonephritis/ cystic renal disease	0.693* (0.667, 0.720)	1.119* (1.041, 1.202)	10.803* (1.607,20.831)	0.960 (0.839,1.099)	4.226* (1.058,7.494)	0.033* (0.000,0.067)
Others	0.751* (0.730, 0.772)	0.943 (0.886, 1.004)	14.602* (6.187,23.684)	1.063 (0.941,1.201)	7.885* (4.823,11.037)	0.004 (-0.014,0.022)
Serum Album (reference: albumin>=3.5 g/dl)						
albumin<3 g/dl	0.908* (0.887, 0.930)	0.888* (0.848, 0.931)	-2.614 (-8.048,3.140)	1.571* (1.433,1.721)	16.581* (14.281,18.927)	-0.042* (-0.057,-0.026)
3g/dl<=albumin<3.5 g/dl	0.924* (0.903, 0.946)	0.976 (0.935, 1.020)	2.034 (-2.959,7.284)	1.230* (1.131,1.336)	10.975* (8.941,13.047)	-0.019* (-0.036,-0.002)
CCI score	1.115* (1.112, 1.118)	1.012* (1.007, 1.017)	0.643* (0.077,1.212)	1.042* (1.033,1.052)	0.658* (0.464,0.851)	0.001 (-0.003, 0.003)
Disabled (reference: No)						
Yes	1.219* (1.181, 1.259)	0.688* (0.636, 0.745)	-12.323* (-21.301,-2.320)	0.962 (0.817,1.132)	4.067* (0.886,7.349)	-0.016 (-0.046, 0.014)
BMI	0.986* (0.980, 0.992)	0.960* (0.947, 0.972)	1.828* (0.294,3.387)	0.906* (0.883,0.931)	0.556* (0.002,1.114)	-0.002 (-0.006, 0.012)
BMI2	1.0003* (1.0002, 1.0004)	1.0004* (1.000, 1.001)	-0.018 (-0.040, 0.004)	1.001* (1.001,1.002)	0.002 (-0.006,0.010)	0.00002 (-0.00003, 0.00006)
Nephrologist care prior to ESRD onset (reference: No)						
<6 months	1.168* (1.133, 1.204)					
6-12 months	1.156* (1.127, 1.186)					
>12 months	1.124* (1.096, 1.153)					
Patient behavioral characteristics						

Current smoking status (reference: No)						
Yes	0.940*	0.658*	-14.202*	0.697*	-16.143*	-0.042*
	(0.904, 0.979)	(0.604, 0.717)	(-23.023,-4.372)	(0.613,0.793)	(-19.107,-13.070)	(-0.056, -0.029)
Drug dependence (reference: No)						
Yes	1.020	0.576*	12.727	0.894	-8.867	-0.012
	(0.901, 1.154)	(0.391, 0.849)	(-29.205,79.497)	(0.534,1.495)	(-19.368,3.001)	(-0.045, 0.020)
Alcohol dependence (reference: No)						
Yes	1.141*	0.992	3.226	0.874	-0.999	0.041
	(1.045, 1.246)	(0.783, 1.257)	(-23.701,39.656)	(0.592,1.291)	(-9.941,8.830)	(-0.024, 0.106)
Patient treatment characteristics						
Dialysis type (reference: PD)						
HD	0.725*	0.877	8.163	3.826*	75.161*	-0.091*
	(0.688, 0.759)	(0.815, 0.945)	(-1.179,18.388)	(3.482,4.205)	(68.630,81.945)	(-0.118,-0.063)
Facility characteristics						
Unit affiliation (reference: independent)						
Chain	0.997	1.015	-14.070*	1.038	24.885*	-0.045*
	(0.956, 1.039)	(0.940, 1.097)	(-22.343,-4.917)	(0.922,1.169)	(19.885,30.093)	(-0.067,-0.022)
Number of dialysis station	0.993*	1.006	0.273	1.006*	0.192*	-0.0003
	(0.991, 0.995)	(1.002, 1.009)	(-0.132, 0.680)	(1.002,1.010)	(0.039,0.345)	(-0.001, 0.0006)
Non-profit designation (reference: Profit)						
Non-profit	0.929*	1.179*	-4.941	1.066	-5.000*	-0.002
	(0.879, 0.981)	(1.040, 1.335)	(-15.777,7.289)	(0.915,1.241)	(-8.691,-1.159)	(-0.025, 0.022)
Ownership (reference: Free standing)						
Hospital-based	1.033	0.983	10.969	0.991	-9.583*	0.074
	(0.955, 1.118)	(0.896, 1.080)	(-6.307, 31.430)	(0.803,1.224)	(-15.521,-3.227)	(-0.002,0.151)
Network (reference : Southeastern kidney council)						

Network 1 (CT, ME, MA, NH, RI, VT)	0.804* (0.732, 0.882)	0.999 (0.872, 1.146)	30.076* (7.875,56.847)	1.166 (0.928,1.464)	-4.960 (-10.545,0.974)	0.018 (-0.015,0.050)
Network 2 (NY)	1.028 (0.939, 1.128)	0.632* (0.541,0.738)	-10.470 (-25.417,7.473)	1.021 (0.804,1.297)	-6.012 (-11.979,0.359)	-0.042* (-0.070,-0.014)
Network 3 (NJ, PR, VI)	1.230* (1.116, 1.354)	0.636* (0.552,0.733)	20.679 (-0.840,46.868)	1.563* (1.173,2.083)	1.761 (-4.474,8.402)	0.001 (-0.053,0.054)
Network 4 (DE, PA)	1.157* (1.056, 1.267)	0.719* (0.628,0.823)	-0.616 (-17.314,19.455)	0.909* (0.738,1.119)	-6.853 (-13.362,0.145)	-0.016 (-0.041,0.010)
Network 5 (DC, MD, VA, WV)	1.212* (1.120, 1.311)	0.799* (0.699,0.913)	1.795 (-13.000,19.105)	0.935 (0.726,1.203)	-0.559 (-6.081,5.287)	-0.013 (-0.032,0.006)
Network 7 (FL)	1.171* (1.075, 1.275)	0.974 (0.859,1.104)	12.967 (-4.957,34.271)	1.053 (0.833,1.329)	-11.246* (-16.721,-5.412)	0.008 (-0.022,0.039)
Network 8 (AL, MS, TN)	0.957 (0.877, 1.044)	0.935 (0.817,1.070)	29.107* (9.735,51.899)	1.036 (0.861,1.246)	-7.774* (-12.301,-3.012)	0.018 (-0.001,0.037)
Network 9 (IN, KY, OH)	1.369* (1.273, 1.473)	0.760* (0.679,0.851)	48.371* (26.725,73.716)	0.807* (0.669,0.973)	-8.847* (-13.242,-4.230)	0.024 (-0.001,0.049)
Network 10 (IL)	1.248* (1.133, 1.374)	0.842* (0.740,0.957)	17.192 (-6.263,46.516)	0.692* (0.554,0.865)	-17.597* (-25.375,-9.009)	0.072* (0.011,0.134)
Network 11 (MI, MN, ND, SD, WI)	1.535* (1.419, 1.662)	0.749* (0.660,0.851)	55.347* (32.308,82.398)	0.810* (0.670,0.980)	-16.368* (-20.616,-11.893)	0.028 (-0.012,0.068)

Network 12 (IA, KS, MO, NE)	1.480*	1.018	62.638*	0.743*	-12.059*	
	(1.356, 1.622)	(0.898,1.154)	(34.317,96.930)	(0.609,0.906)	(-17.314,-6.469)	0.088*
						(0.044,0.132)
Network 13 (AR, LA, OK)	1.147*	0.815*	1.887	1.069	-8.988*	
	(1.048, 1.255)	(0.706,0.940)	(-16.762,24.714)	(0.855,1.337)	(-15.906,-1.502)	-0.003
						(-0.028,0.022)
Network 14 (TX)	1.105*	0.827*	27.067*	0.849	-13.262*	
	(1.027, 1.189)	(0.742,0.923)	(9.875,46.951)	(0.706,1.021)	(-17.248,-9.084)	0.019
						(-0.008,0.045)
Network 15 (AZ, CO, NV, NM, UT, WY)	1.687*	0.705*	-2.045	0.501*	-31.980*	
	(1.549, 1.834)	(0.619,0.803)	(-18.284,17.422)	(0.412,0.608)	(-35.875,-27.849)	0.038
						(-0.013,0.088)
Network 16 (AK, ID, MT, OR, WA)	1.248*	0.996	54.799*	0.690*	-20.143*	
	(1.120, 1.391)	(0.841,1.180)	(26.200,89.879)	(0.554,0.859)	(-26.012,-13.809)	0.133
						(-0.032,0.298)
Network 17 (AS, Guam, HI, Mariana Islands, Northern CA, Southern CA)	1.340*	0.642*	-5.798	0.818*	-14.024*	
	(1.242, 1.446)	(0.563,0.731)	(-21.114,12.490)	(0.674,0.993)	(-18.342,-9.479)	-0.011
						(-0.039,0.016)

Table S2 Sensitivity analysis for EPO use

	EPO use in pre-dialysis initiation period		EPO use in post-dialysis initiation period		Ratio of Cumulative 6-month EPO before dialysis initiation to that after dialysis initiation
	First part	Second part	First part	Second part	
	OR(95% CI)	Dose %(95% CI)	OR(95% CI)	Dose %(95% CI)	
Independent variable of interest					
Expanded-PPS	0.849*	-21.484*	0.703*	-43.757*	0.005*
	(0.772,0.933)	(-27.989,-14.394)	(0.596,0.829)	(-45.695,-41.751)	(0.002, 0.009)
Dialysis initiation time	0.982*	1.031	0.968	-0.297	-0.0004
	(0.965,0.998)	(-0.380,2.464)	(0.935,1.001)	(-0.876,0.287)	(-0.001, 0.0003)
Interaction between expanded-PPS and dialysis initiation time	0.996	-1.813*	0.969	-0.667*	0.0003
	(0.978,1.014)	(-3.338,-0.263)	(0.936,1.004)	(-1.306,-0.025)	(-0.0004, 0.001)
Independent variable					
Patient sociodemographic characteristic					
Age at ESRD onset, y	1.038*	3.564*	0.971*	0.359	0.0005
	(1.018,1.058)	(1.467,5.704)	(0.945, 0.999)	(-0.325,1.048)	(-0.0001, 0.001)
Age2 at ESRD onset	0.9999	-0.022*	1.0003*	-0.004	-1.88e-06
	(0.9997, 1.000)	(-0.037,-0.007)	(1.0001,1.0005)	(-0.009,0.001)	(-6.23e-06, 2.47e-06)
Gender (reference: Male)					
Female	1.365*	-0.631	1.928*	1.639	0.003*
	(1.301,1.433)	(-5.149,4.102)	(1.783,2.085)	(-0.165,3.475)	(0.001, 0.005)
Race/ethnicity (reference: Non-Hispanic white)					
Non-Hispanic black	1.041	0.177	1.395*	19.111*	-0.002*
	(0.969,1.120)	(-6.103,6.879)	(1.243,1.565)	(16.040,22.263)	(-0.005, 0.000)

Hispanic	0.930	-20.455*	1.404*	-2.968	-0.002
	(0.832,1.039)	(-28.340,-11.703)	(1.207,1.632)	(-6.552,0.753)	(-0.006, 0.001)
Others	0.785*	-18.010*	1.362*	5.160*	-0.005*
	(0.660,0.934)	(-29.148,-5.121)	(1.104,1.680)	(0.520,10.013)	(-0.010, 0.0003)
Employment status (reference: Unemployed)					
Employed	1.100	-1.463	0.952	1.292	-0.005*
	(0.934, 1.296)	(-15.447,14.833)	(0.763, 1.189)	(-4.668, 7.624)	(-0.008, 0.001)
Residential urbanicity (reference: large metropolitan)					
Medium or small metropolitan	0.937	-0.587	0.796*	-6.526*	-0.002
	(0.861,1.020)	(-6.592,5.804)	(0.717,0.884)	(-9.388,-3.575)	(0.005, 0.000)
Micropolitan	0.923	-9.202*	0.684*	-5.664*	-0.001
	(0.825,1.033)	(-17.478,-0.097)	(0.598,0.783)	(-9.329,-1.851)	(-0.005, 0.002)
Non-core	0.818*	-13.764*	0.738*	-5.454*	-0.003
	(0.720,0.930)	(-22.774,-3.703)	(0.636,0.858)	(-9.673,-1.037)	(-0.008, 0.001)
Log transform of Median household income	1.346*	17.246*	1.086	-2.029	0.006*
	(1.219,1.485)	(7.371,28.029)	(0.946,1.246)	(-5.218,1.267)	(0.003, 0.010)
Education (mean)	1.000	0.035	1.001	0.078*	-0.00003
	(0.998, 1.002)	(-0.151,0.223)	(0.998,1.003)	(0.005,0.151)	(-0.0001, 0.0005)
Patient clinical characteristic					
Primary cause of ESRD (reference: diabetes)					
Hypertension	0.907*	6.326*	0.999	1.099	-0.002
	(0.855,0.962)	(0.640,12.333)	(0.916, 1.090)	(-1.109,3.356)	(-0.003, 0.0004)
Glomerulonephritis/ cystic renal disease	1.134*	11.814*	0.954	2.457	0.004*
	(1.030,1.249)	(2.152,22.390)	(0.828,1.100)	(-1.377,6.441)	(0.000, 0.009)
Others	0.921	12.102*	1.057	5.000*	0.003
		(2.956,22.061)	(0.932,1.198)	(1.331,8.802)	(0.002, 0.008)

	(0.846,1.004)				
Serum Album (reference: albumin>=3.5 g/dl)					
albumin<3 g/dl	0.897*	-3.069	1.615*	16.640*	-0.005*
	(0.844,0.955)	(-8.714,2.925)	(1.467,1.779)	(13.945,19.399)	(-0.007, -0.003)
3g/dl<=albumin<3.5 g/dl	0.959	1.031	1.228*	9.651*	-0.004*
	(0.906,1.015)	(-4.512,6.897)	(1.125,1.340)	(7.247,12.108)	(-0.007, -0.002)
CCI score	1.014*	0.4588	1.042*	0.524*	0.0003
	(1.008, 1.020)	(-0.144,1.065)	(1.032, 1.052)	(0.286, 0.762)	(0.0001, 0.0005)
Disabled (reference: No)					
Yes	0.734*	-10.873	1.005	5.474*	-0.007
	(0.660, 0.816)	(-20.964,0.505)	(0.848, 1.192)	(1.683, 9.406)	(-0.009, -0.005)
BMI	0.955*	0.549	0.904*	0.296	-0.0005
	(0.939, 0.971)	(-1.071,2.196)	(0.880, 0.928)	(-0.351,0.947)	(-0.001, 0.0002)
BMI2	1.0005*	-0.001	1.001*	0.006	3.86E-06
	(1.0002, 1.0007)	(-0.025,0.022)	(1.0008,1.0016)	(-0.003,0.016)	(-4.92E-06, 0.00001)
Patient behavioral characteristics					
Current smoking status (reference: No)					
Yes	0.658*	-11.833*	0.742*	-15.215**	-0.005*
	(0.587, 0.737)	(-21.880,-0.494)	(0.648, 0.850)	(-18.739,-11.538)	(-0.007, -0.002)
Drug dependence (reference: No)					
Yes	0.662	18.174	0.888	-3.920	-0.003
	(0.399, 1.099)	(-29.307,97.546)	(0.521, 1.514)	(-16.120,10.054)	(-0.008, 0.003)
Alcohol dependence (reference: No)					
Yes	0.777	-15.836	0.875	4.669	-0.006*
		(-44.090, 26.694)	(0.576, 1.328)	(-5.961,16.501)	(-0.009, 0.002)

	(0.560, 1.077)				
Patient treatment characteristics					
Dialysis type (reference: PD)					
HD	0.916	3.921	3.788*	79.808*	-0.024*
	(0.825, 1.017)	(-4.304,12.854)	(3.426, 4.189)	(72.094, 87.867)	(-0.029, -0.018)
Facility characteristics					
Unit affiliation (reference: independent)					
Chain	1.180*	9.544	1.283*	24.997*	-0.004*
	(1.054,1.323)	(-0.674,20.814)	(1.128, 1.460)	18.999,31.296)	(-0.010, -0.002)
Number of dialysis station	1.007*	0.183 (-0.097,0.464)	1.003	0.219*	0.00006
	(1.002, 1.012)		(0.998, 1.008)	(0.057,0.381)	(-0.00005, 0.0001)
Non-profit designation (reference: Profit)					
Non-profit	0.966	-7.938	0.975	-6.465*	-0.001
	(0.839,1.113)	(-17.399,2.606)	(0.831,1.143)	(-10.540,-2.205)	(-0.005, 0.002)
Ownership (reference: Free standing)					
Hospital-based	1.156	3.141	0.501	3.550	0.011*
	(0.924, 1.446)	(-13.339,22.755)	(0.379,0.663)	(-7.434,15.838)	(0.001, 0.021)
Network (reference : Southeastern kidney council)					
Network 1 (CT, ME, MA, NH, RI, VT)	0.897	6.494	1.094	-7.232*	0.003
	(0.747,1.077)	(-6.085,20.758)	(0.846,1.416)	(-13.335,-0.698)	(-0.003, 0.009)
Network 2 (NY)	0.624*	-6.352	0.957	-3.428	-0.007*
	(0.500,0.779)	(-21.790,12.133)	(0.735,1.247)	(-10.327,4.002)	(-0.013, -0.000)
Network 3 (NJ, PR, VI)	0.536*	-0.156	1.788*	2.759	-0.007*
	(0.445,0.646)	(-15.218,17.584)	(1.324,2.413)	(-4.229,10.258)	(-0.013, -0.001)
Network 4 (DE, PA)	0.743*	-5.342	0.998	-7.423	-0.001

	(0.611,0.904)	(-17.856,9.076)	(0.791,1.259)	(-14.650,0.416)	(-0.006, 0.005)
Network 5 (DC, MD, VA, WV)	0.786*	-11.762	0.974	-2.189	-0.006*
	(0.658,0.939)	(-21.705,0.557)	(0.733,1.296)	(-8.180,4.192)	(-0.010, -0.002)
Network 7 (FL)	0.908	1.893	1.078	-13.700*	0.009
	(0.749,1.101)	(-10.076,15.456)	(0.846,1.374)	(-19.936,-6.979)	(0.001, 0.017)
Network 8 (AL, MS, TN)	0.844	3.965	0.975	-8.262*	-0.001
	(0.709,1.004)	(-8.682,18.364)	(0.801,1.187)	(-13.114,-3.140)	(-0.005, 0.003)
Network 9 (IN, KY, OH)	0.525*	-4.054	0.720*	-8.906*	-0.007*
	(0.446,0.617)	(-16.077,9.690)	(0.591,0.877)	(-14.002,-3.508)	(-0.011, -0.003)
Network 10 (IL)	0.758*	-23.924*	0.640*	-13.343*	0.0117
	(0.630,0.913)	(-36.105,-9.421)	(0.501,0.819)	(-22.224,-3.447)	(0.0116, 0.035)
Network 11 (MI, MN, ND, SD, WI)	0.487*	-0.137	0.648*	-15.566*	-0.005*
	(0.399,0.595)	(-12.696,14.226)	(0.525,0.800)	(-20.910,-9.861)	(-0.010, 0.000)
Network 12 (IA, KS, MO, NE)	0.708*	-3.415	0.660*	-12.493*	-0.003
	(0.580,0.865)	(-16.282,11.429)	(0.533,0.818)	(-18.570,-5.962)	(-0.008, 0.003)
Network 13 (AR, LA, OK)	0.806*	-6.567	1.138	-8.556*	-0.003
	(0.663,0.979)	(-19.336,8.221)	(0.904,1.433)	(-16.220,-0.191)	(-0.008, 0.001)
Network 14 (TX)	0.701*	-1.775	0.853	-13.024*	-0.002
	(0.600,0.818)	(-13.289,11.267)	(0.702,1.036)	(-17.506,-8.298)	(-0.007, 0.002)
Network 15 (AZ, CO, NV, NM, UT, WY)	0.629*	-14.366*	0.474*	-33.690*	-0.001
	(0.521,0.759)	(-26.148,-0.706)	(0.384,0.586)	(-38.113,-28.950)	(-0.006, 0.004)
Network 16 (AK, ID, MT, OR, WA)	0.540*	-22.372*	0.569*	-20.524*	-0.006
	(0.407,0.716)	(-37.979,-2.838)	(0.445,0.728)	(-27.984,-12.292)	(-0.014, 0.002)
Network 17 (AS, Guam, HI, Mariana Islands,	0.626*	-12.657*	0.979	-14.505*	-0.003
	(0.527,0.742)	(-23.231,-0.625)	(0.797,1.203)	(-19.243,-9.489)	(-0.007, 0.001)

Northern CA,
Southern CA)

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The association between dialysis modality pattern and cumulative 3-year Medicare expenditure

ABSTRACT

Background

In 2011, the U.S. Centers for Medicare & Medicaid Services (CMS) implemented the expanded prospective payment system for end-stage renal disease (ESRD). ESRD patients often require a sequential use of dialysis modalities which incurs additional costs that may eventually increase the overall costs associated with ESRD care. We estimated the Medicare expenditure following payment reform by examining the dialysis modality types and transfers.

Methods

We identified incident dialysis patients from the United States Renal Data System, and categorized them by initial dialysis modality type (peritoneal dialysis [PD] or in-center hemodialysis [HD]) and subsequent modality transfer. We used generalized linear models to estimate the 3-year cumulative Medicare expenditure by dialysis modality patterns.

Results

Compared with those who initiated and maintained on HD, PD patients who transferred to HD had a significantly higher adjusted cumulative 3-year Medicare expenditure regardless of when the transfer occurred during the first 3 years of dialysis, HD patients who transferred to PD in the first 2 years of dialysis had a significantly lower Medicare expenditure.

Conclusion

In terms of cost, PD remains a better initial dialysis option than HD for ESRD patients. However, patients who initiate PD and transfer to HD lose this economic advantage. Patients who initiate HD and transfer to PD may preserve this advantage, but transferring from HD to PD may be associated with adverse health outcomes. Strategies are needed to prevent the transfer from PD to HD and to minimize initial HD use in ESRD patients who are eligible for PD.

INTRODUCTION

End-stage renal disease (ESRD), the last stage of chronic kidney disease (CKD), has posed significant economic burden to the United States. Between 2004 and 2016, the Medicare fee-for-service expenditure for ESRD rose from $18 billion to $35 billion. Since 2004, although ESRD patients have accounted for less than 1% of the total Medicare population, they have accounted for more than 7% of the overall Medicare expenditure. Most ESRD patients in the United States receive dialysis therapy, with hemodialysis (HD) and peritoneal dialysis (PD) being the most commonly used dialysis modalities. In 2016, 87.3% of incident ESRD patients initiated renal replacement therapy with HD, whereas 9.7% initiated with PD. Consequently, about 90.4% of the ESRD Medicare expenditure in 2016 was spent on dialysis therapy. (USRDS annual data report 2018).

As a renal replacement treatment for ESRD patients, PD is equivalent to HD in terms of survival and quality of life (Brown 2010, Liem 2007, Mehrotra 2011, Nadeau-Fredette 2015, Yang 2015, Weinhandl 2010). In addition, PD is associated with lower costs than HD due to the lower cost of therapy delivery and the fewer requirements of patients for expensive medications such as erythropoietin (Atapour 2015, Berger 2009, Makhele 2019, Snyder 2004, Sinnakirouchenan 2011). Therefore, there is a strong economic rationale for choosing PD over HD as the initial dialysis for ESRD. However, instead of using a single dialysis modality during treatment, some patients require a sequential use of different modalities because of changes in medical conditions, occurrence of complications, or patient preference (Guo 2003, Chan 2017, Kolesnyk 2010, Kumar 2014, Lan 2015, Perl 2012, Pajek 2014). The dialysis transfer incurs additional costs and eventually increases the overall expenditures

related to ESRD care (Prichard 1997). Therefore, it is necessary to examine the healthcare expenditures in ESRD patients taking into account the dialysis transfer.

Majority of dialysis transfers occur in the first three years of dialysis. More than 70% of PD-to-HD transfers occurred in the first two years of dialysis and 89% of HD-to-PD transfers occurred in the first year of dialysis (Nessim 2015, Yang 2015). Therefore, previous studies estimated the healthcare expenditure in a 3-year study period to account for the impact of dialysis transfer on healthcare expenditure (Chui 2013, Shih 2005). Chui et al supported the PD-first policy in all eligible patients because patients initiating on PD still had an economic advantage over patients initiating on HD no matter whether dialysis transfer occurred (Chui 2013). Shih et al reported patients who initiated PD and transferred to HD in the first year of dialysis lost the economic advantage, however, patients whose transfers occurred in the second and third year of dialysis sustained this economic advantage. Consequently, they suggested choosing PD as initial dialysis option for ESRD and maintaining on PD for a longer time (Shih 2005). The results of the two studies showed that PD maintains the economic advantage even though dialysis transfer incurs additional cost. The reason might be the significant difference in cost between PD and HD which counteracts the impact of dialysis transfer on healthcare expenditure.

Previous findings may not be applicable to represent recent Medicare expenditure in the United States because U.S. Centers for Medicare & Medicaid Services (CMS) implemented a new expanded prospective payment system (PPS) in January 2011. Medicare

used a composite rate payment methodology to reimburse dialysis facilities before January 2011. This payment methodology paid for dialysis treatment costs and certain routinely used ESRD-related drugs, laboratory tests, and supplies collectively as a bundle, but did not include many other ESRD-related injectable drugs and non-routine laboratory tests. As mentioned above, patients receiving HD have higher requirements for these services and items than those receiving PD, which made PD cheaper than HD. The 2011 expanded PPS included all formerly separately billed services in the bundle and made payment on a per treatment basis with same base rate for all dialysis treatment modalities (HD and PD). Consequently, the 2011 expanded PPS made the difference in cost between PD and HD smaller than before (CMS 2017). The 2015 USRDS annual report showed that the Medicare expenditure per year per patient of HD was 44% higher than that of PD in 2003, and the percent decreased to 21% in year 2013 (2015 USRDS annual report). Given the implementation of expanded PPS, we hypothesized that the patients initiating on PD may lose the economic advantage over patients initiating on HD when dialysis transfer occurs because of the extra cost caused by dialysis transfer and the shrink of difference in cost between PD and HD. This study aimed to estimate the 3-year Medicare expenditure of ESRD patients taking into account the dialysis modality type and dialysis transfer.

METHODS

Data

This retrospective cohort study used data for the period 2011–2016 from the USRDS, which provides information about chronic kidney disease and ESRD in the United States. The USRDS is a national data system that collects, analyzes, and distributes information from CMS, the United Network for Organ Sharing (UNOS), and the ESRD networks. This database contains several datasets that can be linked using USRDS_ID, facility ID, and UPIN. We extracted data from the following USRDS datasets: Patient Profile, Medical Evidence Form, Pre-ESRD claims, ESRD claims, and CMS/CDC ESRD Annual Facility Survey.

Study design and population

This study estimated the 3-year Medicare expenditure of dialysis patients after expanded PPS implementation. To be eligible for this study, patients had to initiate dialysis as the first treatment modality for ESRD between January 1, 2011 and December 31, 2013, had to be equal to or older than 18, had to have a completed Medical Evidence Form filled within 45 days of dialysis initiation, and had to have both Medicare parts A and B coverage (with Medicare as the primary payer) during the 6 months before and 3 years following dialysis initiation. Medicare parts A and B coverage was required because Medicare claims in the 6 months before and 3 years following dialysis initiation were used to calculate Charlson comorbidity index and Medicare expenditure, respectively. This study excluded patients who had missing values for any variables used in the regressions, who received a preemptive kidney transplant as initial treatment for ESRD, who received dialysis from a

non-VA facility, who had date of death was erroneously recorded as being before dialysis initiation date, and who had less than 3-year follow-up. The beginning date of follow-up was defined as dialysis initiation date, and the ending date of follow-up was defined as the date of death, transplantation, recovered function, or loss to follow-up, whichever occurred first. Patients who received dialysis from a VA facility were excluded because VA patients could be receiving ESRD-related services from the VA health administration, and USRDS will not have cost information about those services.

Dependent variable

The dependent variable was the cumulative Medicare expenditure during the 3-year period since dialysis initiation. The cumulative Medicare expenditure consisted of the costs paid by Medicare Parts A, B, and D, and was calculated as the sum of the plan payment amount and the low-income subsidy. To focus only on Medicare expenditure, costs paid by other types of insurance or related nonmedical costs were excluded. All costs were inflated to 2017 U.S. dollars using the medical care component of the consumer price index.

Independent variables

The two independent variables of interest were initial dialysis type and dialysis modality pattern. Initial dialysis type was a binary variable indicating HD and PD. Patients beginning with in-center HD were assigned to the HD group (coded as 0), whereas patients who initiated continuous ambulatory PD (CAPD) or continuous cycling PD (CCPD) were assigned to the PD group (coded as 1). Dialysis modality pattern was a categorical variable that was created based on the information of the dialysis transfer type, count of transfer, and

time to transfer. Only two types of transfers, HD-to-PD and PD-to-HD, were considered because HD and PD are the most commonly used dialysis modalities in the United States. Count of transfer was defined as the total number of transfers in the first 3 years of dialysis. To capture the count of transfer, the CMS "60-day rule," which indicates that any change in modality lasting at least 60 days is recorded as a transfer, was applied (USRDS 1999). Time to transfer was defined as the interval between the date of dialysis initiation and the date when first transfer occurred. Dialysis modality pattern had nine categories: HD only (initiated and maintained on HD in the first 3 years); PD only (initiated and maintained on PD in the first 3 years); PD-to-HD (initiated PD and then transferred to HD in the first year, PD-to-HD in the second year, and PD-to-HD in the third year); HD-to-PD (initiated HD and then transferred to PD in the first year, HD-to-PD in the second year, and HD-to-PD in the third year); and more than one transfer.

Other independent variables were patient- and facility-level characteristics. Patient-level characteristics were collected at the time of dialysis initiation, except for the Charlson Comorbidity Index (CCI) score, which was calculated using the Medicare claims data in the 6 months prior to dialysis initiation. Four types of patient-level characteristics were controlled for: treatment, sociodemographic, clinical, and behavioral. Treatment characteristic was the year of dialysis initiation (2011, 2012, and 2013). Sociodemographic characteristics included age at dialysis initiation (in years); gender (female, male); race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other); employment status (unemployed, employed); residential urbanicity (large metropolitan, medium or small metropolitan, micropolitan, and non-core); education, measured as a percentage of adults

with at least a high school education in the patient's zip code area; and log transformation of median household income for the patient's zip code area. Rural status was identified for each patient by linking the patient's FIPS code in the USRDS to the 2010 Rural Urban Commuting Area codes. Education and median household income were defined for each patient by linking the patient's zip code in the USRDS to the U.S. Census tract data. Clinical characteristics included primary cause of ESRD (diabetes, hypertension, glomerulonephritis/cystic renal disease, and others); serum albumin level (0.6 g/dL≤ albumin <3 g/dL, 3 g/dL≤ albumin <3.5 g/dL, and 3.5 g/dL≤ albumin ≤6 g/dL); CCI score; disabled (yes, no); body mass index (BMI); and nephrologist care prior to ESRD onset (no, <6 months, 6-12 months, and >12 months). Behavioral characteristics included current smoking status (yes, no); drug dependence (yes, no); and alcohol dependence (yes, no). Facility-level characteristics included unit affiliation (chain, independent); number of facility stations; profit designation (yes, no); ownership type (hospital-based, free-standing); and network (network1-network17).

Statistical analysis

Intent-to-treat and as-treated analyses were conducted based on recommendations from previous studies (Vonesh 2000, Shih 2005). Because any subsequent modality changes were unknown, an intent-to-treat analysis can provide useful information for decision makers to choose or make recommendations on an initial dialysis modality. An intent-to-treat analysis was conducted to examine the association between initial dialysis type and cumulative 3-year Medicare expenditure, and an as-treated analysis was conducted to assess

the association between dialysis modality pattern and cumulative 3-year Medicare expenditure.

Patient- and facility-level characteristics were compared between initial dialysis type (HD vs. PD) by *t* test for continuous variables and Pearson's chi-square test for categorical variables. Due to the highly skewed distribution of Medicare expenditure, generalized linear model (GLM) with gamma distribution and log link function was used to estimate the 3-year Medicare expenditure (Basu 2004). Because the observations within a facility could be related with each other, in all analyses we used cluster-robust standard errors to account for this correlation (Abadie 2017). All P values reported were two-sided; statistical significance level was set at P value less than 0.05. All analyses were conducted using SAS v. 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics

This study included 16,884 ESRD patients with 1425 initiating with PD and with 15495 initiating with HD in the period 2011–2013. Compared to the HD group, the PD group had a significantly higher proportion of patients who were non-Hispanic white, who were employed, who were from places with higher median family income, and who had at least a high school education. In terms of patient-level characteristics, the PD group had a lower proportion of patients with diabetes as the primary cause of ESRD, but a higher proportion of patients with glomerulonephritis as the primary cause. The proportion of patients with hypertension and other diseases as the primary cause of ESRD was similar between the two

groups. Compared to HD group, the PD group had a significantly higher proportion of patients who received nephrology care prior to dialysis initiation and who had an albumin level greater than 3.5, but a significantly lower proportion of patients who were disabled. The CCI score of patients in the PD group was significantly lower than that of patients in the HD group. In terms of facility-level characteristics, compared with the HD group, the PD group had a significantly higher proportion of patients receiving dialysis from chain, free-standing, and non-profit facilities. Treatment characteristics differed significantly between the PD and HD groups. Approximately 40% of ESRD patients who initiated PD experienced at least one transfer within 3 years following dialysis initiation, compared with less than 5% of ESRD patients who initiated HD. Over 7% of the PD group experienced more than one dialysis transfer, compared with less than 3% of the HD group. Compared with the HD group, the PD group had a significantly lower proportion of patients experiencing the first dialysis transfer in the first year following dialysis initiation (table 1).

Intent-to-treat multivariate regression

Results from the GLM model of the intent-to-treat analysis are presented in Table 2. The cumulative 3-year Medicare expenditure of patients who initiated PD was 7.84% significant lower than that of patients who initiated HD (95% CI, 5.46%-10.16%). In addition, a variety of factors were found to affect Medicare expenditure independently. Medicare expenditure was found to be significantly higher in patients who were younger, were female, were non-Hispanic black, were from a large metropolitan area, had diabetes as the primary cause of ESRD, had no nephrologist care prior to dialysis initiation, were

disabled, had lower albumin levels, had higher CCI scores, had higher BMI values, and received dialysis from free-standing facility.

As-treated multivariate regression

Table 3 presents the results from the as-treated analysis of the association between dialysis modality pattern and Medicare expenditure. As shown, there was a similar pattern of effects of patient demographic characteristics, patient clinical characteristics, and facility-level characteristics. The cumulative 3-year Medicare expenditure of patients in PD-only group was 20.04% significant lower than that of patients in HD-only group (95% CI, 17.45%-22.54%). The cumulative 3-year Medicare expenditure of patients who initiated PD and experienced one transfer in the follow-up period was significantly higher than that of patients in HD-only group, regardless of when the transfer occurred during follow-up ($P<0.05$). The cumulative 3-year Medicare expenditure of patients who initiated HD and experienced one transfer in the first two years of dialysis was significantly lower than that of patients in HD-only group ($P<0.05$). Patients who experienced more than one transfer had a significantly higher Medicare expenditure than those in HD-only group ($P<0.001$).

Table 4 presents the adjusted cumulative 3-year Medicare expenditure. After adjusting for the other patient- and facility-level characteristics, the cumulative 3-year Medicare expenditure was $268,821 and $247,756 for patients who initiated HD and PD, respectively. The adjusted cumulative 3-year Medicare expenditure for the HD-only and PD-only groups was $269,090 and $215,174, respectively. The cumulative 3-year Medicare expenditure of patients in the HD-to-PD group in the first two years following dialysis

initiation was significantly lower than that of patients in the HD-only group ($P<0.05$). The cumulative 3-year Medicare expenditure of patients in the HD-to-PD group in the third year following dialysis initiation ($272,638) was higher than that of patients in the HD-only group, although the difference was not significant ($P=0.7653$). The adjusted cumulative 3-year Medicare expenditures of patients who initiated PD and transferred to HD were $306,018 for first year, $305,254 for second year, and $298,164 for third year.

DISCUSSION

In this study, we evaluated the cumulative 3-year Medicare expenditure after the 2011 implementation of the expanded PPS, and compared Medicare expenditure among various treatment pathways for ESRD patients. We found that the cumulative 3-year Medicare expenditure was lower for patients who initiated PD, compared with those who initiated HD, which is consist with previous studies (Atapour 2015, Berger 2009, Makhele 2019, Sinnakirouchenan 2011). Specifically, we found that the cumulative 3-year Medicare expenditure for patients initiating on HD was approximate 7.8% higher than that of patients initiating on PD. Although the difference in cost between HD and PD has been decreasing in recent years, patients initiating on PD still have an economic advantage over patients initiating on HD. Thus, collectively, our findings, along with those previous studies (Chaudhary 2011, Chui 2013), support the widespread use of PD as initial dialysis modality in eligible ESRD patients.

As mentioned above, some ESRD patients require a sequential use of different dialysis modalities during treatment (Guo 2003, Chan 2017, Kolesnyk 2010, Kumar 2014, Lan 2015, Perl 2012, Pajek 2014), and the transfer among these modalities may incur additional costs (Prichard 1997). After accounting for the impact of dialysis modality transfer on the Medicare expenditure, as hypothesized, we found that patients who initiated PD and transferred to HD had a significantly higher Medicare expenditure than those who initiated and maintained on HD, regardless of when the transfer occurred during follow-up, which differs from the findings of previous studies. For example, Chui et al. (2013) found that the 3-year cost of patients initiating on PD and transferring to HD in the first year of treatment was lower than that of patients who underwent only HD in the first 3 years of treatment. Furthermore, Shin et al. (2005) found that patients who initiated and maintained on PD or transferred to HD after the first year of treatment had a lower 3-year Medicare expenditure than patients who underwent only HD, whereas patients who initiated PD and transferred to HD in the first year of treatment lost this economic advantage. The reason for this discrepancy in findings is that the implementation of the expanded PPS in 2011 may have been reducing the difference in initial cost between HD and PD and further increased the influence of dialysis modality change on total cost. We also found that the economic advantage of PD was offset by additional cost associated with dialysis modality change. The USRDS annual report showed that the utilization of PD as initial dialysis modality has increased following payment reform (USRDS annual report 2017). Therefore, with the increasing use of PD, more attention is needed to avoid the occurrence of PD-to-HD transfer in order to maintain the economic advantage of PD. Given the scope of this study, we did not examine the reasons for HD-to-PD transfers, although research has shown that reasons for

PD-to-HD transfer include patient preference, peritonitis and catheter-related infections, ultrafiltration failure, and catheter malfunction (Chaudhary et al. 2011). Research has also revealed that very few quantitative data are available on PD-to-HD transfer with regard to health outcomes (Chan et al. 2019). In their narrative systematic review, Chan et al. (2019) noted that some studies found that the rate of PD-to-HD transfer remained stable and that mortality associated with this transfer decreased over time; however, most of these studies are limited by a single-center design, lack of covariates adjustment, and poor generalizability. Regardless of whether a PD-to-HD transfer is associated with adverse health outcomes, it is associated with a high Medicare expenditure. Therefore, future studies are needed to identify effective prevention strategies to avoid PD-to-HD transfers.

Compared with that of the transfer from PD to HD, the incident rate of transfer from HD to PD was much lower. We found that only 2.38% of patients had one transfer and 2.31% had more than one transfer during the follow-up period; 68.04% of the first transfers occurred in the first year of treatment. The reasons that patients transferred from HD to PD include lack of pre-dialysis care or renal replacement treatment education; late referral; change in patient, family, or caregiver preference; change in health status; and ongoing HD-related treatment complications (Nessim 2015). We also found that the Medicare expenditure of HD patients who transferred to PD in the first year and second year of treatment was lower than that of HD patients who maintained on HD in the follow-up period, which is consistent with the previous findings (Chui et al. 2013). However, we found that the Medicare expenditure of HD patients who transferred to PD in the third year of treatment was higher than that of HD patients who maintained on HD in the follow-up period. Thus, the cost-

savings of the HD-to-PD transfer were offset when the transfer occurred in the third year of treatment. Although the transfer occurring in the first 2 years of treatment reduced Medicare expenditure, it may be inappropriate to suggest transferring from HD to PD during this period given the potential adverse health outcomes associated with this transfer, such as increasing the risk of technique failure and death on PD (Chidambaram 2011, Lobbedez 2012, Mujais 2006, Nessim 2015). Future studies are needed to examine the association between HD-to-PD transfers and adverse health outcomes, and to develop interventions to minimize initial HD use in patients who are eligible for PD.

This study has some important limitations. First, it may have underestimated costs because we captured costs only where Medicare was the primary payer. We were not able to include patients' copayments, deductibles, and indirect costs for ESRD patients and their family caregivers, because the USRDS does not contain these data. Second, our study period was limited to 3 years, so we were not able to capture the impact of dialysis modality transfers that occurred after 3 years of treatment. However, our study period captures the time when the vast majority of dialysis modality transfers occur. Third, it only considered conventional in-center HD and PD, so other types of dialysis modalities, such as home-based HD and in-center self-HD, were not included. However, less than 8% of patients initiating on HD undergo home-based HD and in-center self-HD (USRDS annual report 2017), so our study captures the vast majority of ESRD patients undergoing HD. Finally, similar to all other observational studies, our study has some unobservable confounding factors that we were not be able to adjust for.

CONCLUSION

We found that the 3-year cumulative Medicare expenditure was significantly lower for patients who initiated and maintained on PD, compared with that of patients who initiated and maintained on or transferred to another dialysis modality. For patients who initiated PD and transferred to HD, the Medicare expenditure was higher than that of patients who underwent only HD, regardless of when the transfer occurred during the first 3 years of treatment. Our findings suggest that PD is a better initial dialysis modality than HD in terms of costs and that PD-to-HD transfers should be prevented. For patients who initiated HD and transferred to PD in the first and second year of treatment, the 3-year cumulative Medicare expenditure was lower than that of patients who underwent only HD. However, given the potential adverse health outcomes associated with HD-to-PD transfers, initial HD use in patients who are eligible for PD should be minimized.

Table 1. Baseline patient characteristics

Number (%)	PD 1425(8.44)	HD 15459 (91.56)	P-value
Patient sociodemographic characteristics			
Age (mean), y	69.72	70.03	0.3407
Gender (%)			
Male	55.02	53.09	0.1623
Female	44.98	46.91	
Race/ethnicity (%)			
Non-Hispanic White	68.56	58.04	<.0001
Non-Hispanic Black	16.42	25.59	
Hispanic	9.33	11.36	
Other	5.68	5.01	
Employment status (%)			
Unemployed	94.18	98.15	<0.001
Employed	5.82	1.85	
Residential urbanicity (%)			
Large metropolitan	42.47	45.39	0.0776
Medium or small metropolitan	33.85	32.09	
Micropolitan	13.17	13.42	
Non-core	10.51	9.09	
Median household income (mean)	53895	50957	<0.001
Education (mean)	48.70	47.46	0.0035
Patient clinical characteristics			
Primary cause of ESRD (%)			<0.001
Diabetes	44.57	51.40	
Hypertension	33.78	31.95	
Glomerulonephritis	12.12	6.45	
Other	9.53	10.20	
Nephrologist care prior to dialysis initiation (%)			
No	5.40	22.32	<0.001
<6 months	16.54	16.54	
6-12 months	24.46	21.43	
>12 months	53.61	39.71	
Disabled (%)			
Yes	1.40	6.82	<0.001
No	98.60	93.18	
Serum Albumin (%)			
album<3 g/dL	12.40	33.72	<0.001
3 g/dL <=album<3.5 g/dL	23.13	29.58	
album>=3.5 g/dL	64.47	36.70	
BMI (mean)	28.83	29.91	<0.001
CCI score (mean)	6.36	8.02	<0.001
Patient behavioral characteristics			
Current smoker (%)			
Yes	5.05	5.72	0.2926
No	94.95	94.28	
Presence of alcohol dependence (%)			
Yes	0.21	1.04	0.0022
No	99.79	98.96	
Presence of drug dependence (%)			
Yes	0.28	0.52	0.2239
No	99.72	99.48	
Patient treatment characteristics			
Year of dialysis initiation (%)			
2011	36.30	40.68	0.0019
2012	33.99	33.10	
2013	29.71	26.22	
Count of transfer (%)			
No transfer	62.58	95.31	<0.001
One transfer	29.99	2.38	

More than one transfer	7.43	2.31	
First transfer pattern (N)			
HD to PD	NA	726	
PD to HD	534	NA	
Time-to-first transfer among patients with dialysis transfer (%)			
First year of dialysis	37.08	68.04	<0.001
Second year of dialysis	33.15	21.49	
Third year of dialysis	29.78	10.47	
Facility-level characteristics			
Unit affiliation (%)			
Independent	20.74	24.36	0.0022
Chain	79.62	75.64	
Number of dialysis stations	20.63	20.89	0.2961
Facility ownership (%)			
Hospital-based	5.54	9.89	<0.001
Free-standing	94.46	90.11	
Profit designation (%)			
No	87.46	81.99	<0.001
Yes	12.54	18.01	
Network			
Network 1 (CT, ME, MA, NH, RI, VT)	3.78	4.30	<0.001
Network 2 (NY)	3.57	6.78	
Network 3 (NJ, PR, VI)	2.66	5.08	
Network 4 (DE, PA)	4.20	4.26	
Network 5 (DC, MD, VA, WV)	4.48	5.83	
Network 6 (GA, NC, SC)	10.23	9.12	
Network 7 (FL)	4.48	4.48	
Network 8 (AL, MS, TN)	8.41	7.03	
Network 9 (IN, KY, OH)	7.57	7.80	
Network 10 (IL)	5.19	3.94	
Network 11 (MI, MN, ND, SD, WI)	4.63	6.71	
Network 12 (IA, KS, MO, NE)	5.12	4.03	
Network 13 (AR, LA, OK)	5.54	4.25	
Network 14 (TX)	8.97	9.45	
Network 15 (AZ, CO, NV, NM, UT, WY)	6.59	4.67	
Network 16 (AK, ID, MT, OR, WA)	3.01	2.88	
Network 17 (AS, Guam, HI, Mariana Islands, Northern CA, Southern CA)	11.56	9.40	

Note: NA indicates not applicable.

Table 2. Multivariate regression: the intent-to-treat approach

	3-year Medicare expenditure %	95% Confidence Interval
Patient treatment characteristics		
Initial dialysis type (reference: HD)		
PD	-7.836*	(-10.156, -5.456)
Year of dialysis initiation (reference: 2011)		
2012	-1.430	(-2.965, 0.14)
2013	-0.985	(-2.586, 0.642)
Patient demographic factors		
Age	-0.807*	(-0.866, -0.737)
Gender (reference: Male)		
Female	7.186*	(5.77, 8.611)
Race (reference: Non-Hispanic white)		
Non-Hispanic black	4.415*	(2.48, 6.386)
Hispanic	1.939	(-0.618, 4.571)
Other	-0.339	(-3.401, 2.819)
Employment (reference: Unemployed)		
Employed	-3.546	(-7.974, 1.106)
Residential urbanicity (reference: Large metro)		
Medium or Small metro	-8.899*	(-10.488, -7.291)
Micropolitan	-9.787*	(-12.041, -7.476)
Non-core	-8.112*	(-10.658, -5.484)
Log transform of median household income ($10,000)	-1.745	(-4.036, 0.602)
Education	0.030	(-0.02, 0.08)
Patient clinical factors		
Primary cause of ESRD (reference: Diabetes)		
Hypertension	-1.813*	(-3.391, -0.21)
Glomerulonephritis	-5.257*	(-7.799, -2.635)
Other	4.216*	(1.765, 6.727)
Nephrologist care prior to dialysis initiation (reference: no)		
<6 months	-3.892*	(-6.087, -1.646)
6-12 months	-2.196*	(-4.18, -0.17)
>12 months	-4.151*	(-5.927, -2.332)
Disabled (reference: No)		
Yes	18.199*	(15.096, 21.373)
Serum albumin (reference: 3.5 g/dL <=album<6 g/dL)		
0.6 g/dL <=album<3g/dL	9.955*	(8.156, 11.784)
3g/dL <=album<3.5 g/dL	4.404*	(2.737, 6.099)
BMI	0.341*	(0.25, 0.431)
CCI score	2.521*	(2.347, 2.696)
Patient behavioral characteristics		
Current smoker (reference: No)		
Yes	-1.074	0.5350
Presence of alcohol dependence (reference: No)		
Yes	-4.868	(-11.45, 2.204)
Presence of drug dependence (reference: No)		
Yes	8.026	(-2.79, 20.045)
Facility-level characteristics		
Unit affiliation (reference: independent)		
Chain	-0.469	(-2.537, 1.643)
Number of dialysis stations		
Facility ownership (reference: Free-standing)		
Hospital-based	-4.648*	(-8.066, -1.104)
Profit designation (reference: No)		
Yes	-0.965	(-3.738, 1.888)
Network (reference: Trans-pacific)		
Network 1 (CT, ME, MA, NH, RI, VT)	1.015	(-3.382, 5.622)
Network 2 (NY)	-1.872	(-5.88, 2.306)
Network 3 (NJ, PR, VI)	2.696	(-1.489, 7.047)
Network 4 (DE, PA)	-11.255*	(-15.066, -7.263)
Network 5 (DC, MD, VA, WV)	-14.624*	(-18.053, -11.059)
Network 7 (FL)	-16.573*	(-19.708, -13.325)
Network 8 (AL, MS, TN)	-14.015*	(-17.692, -10.174)
Network 9 (IN, KY, OH)	-19.740*	(-22.872, -16.49)
Network 10 (IL)	-11.591*	(-15.194, -7.836)

Network 11 (MI, MN, ND, SD, WI)	-13.826*	(-17.552, -9.932)
Network 12 (IA, KS, MO, NE)	-14.067*	(-17.428, -10.569)
Network 13 (AR, LA, OK)	-21.054*	(-24.278, -17.684)
Network 14 (TX)	-19.780*	(-23.049, -16.364)
Network 15 (AZ, CO, NV, NM, UT, WY)	-15.600*	(-18.592, -12.497)
Network 16 (AK, ID, MT, OR, WA)	-18.356*	(-21.643, -14.939)
Network 17 (AS, Guam, HI, Mariana Islands, Northern CA, Southern CA)	-16.623*	(-20.26, -12.829)

Table 3. Multivariate regression: the as-treated approach

	3-year Medicare expenditure	95% Confidence Interval
Patient treatment characteristics		
Dialysis modality pattern (reference: HD only)		
PD only	-20.037*	(-22.539, -17.445)
HD to PD, year 1	-17.271*	(-21.022, -13.342)
HD to PD, year 2	-8.817*	(-15.245, -1.892)
HD to PD, year 3	1.319	(-8.415, 12.086)
PD to HD, year 1	13.724*	(6.535, 21.397)
PD to HD, year 2	13.440*	(6.684, 20.611)
PD to HD, year 3	10.805*	(4.05, 17.998)
More than one transfer	9.122*	(5.127, 13.258)
Year of dialysis initiation (reference: 2011)		
2012	-1.509	(-3.033, 0.04)
2013	-0.757	(-2.352, 0.854)
Patients sociodemographic factors		
Age	-0.797*	(-0.856, -0.727)
Gender (reference: Male)		
Female	7.219*	(5.813, 8.643)
Race (reference: Non-Hispanic white)		
Non-Hispanic Black	4.279*	(2.357, 6.226)
Hispanic	1.949	(-0.598, 4.561)
Other	-0.449	(-3.449, 2.655)
Employment (reference: Unemployed)		
Employed	-3.584	(-7.891, 0.924)
Residential urbanicity (reference: large metro)		
Medium or Small metro	-8.808*	(-10.39, -7.207)
Micropolitan	-9.986*	(-12.208, -7.698)
Non-core	-8.038*	(-10.569, -5.427)
Log transform of median household income ($10,000)	-1.607	(-3.873, 0.723)
Education	0.040	(-0.01, 0.09)
Patient clinical factors		
Primary cause of ESRD (reference: Diabetes)		
Hypertension	-1.745*	(-3.314, -0.15)
Glomerulonephritis	-4.763*	(-7.291, -2.166)
Other	4.216*	(1.796, 6.695)
Nephrologist care prior to dialysis initiation (reference: no)		
<6 months	-3.863*	(-6.049, -1.636)
6-12 months	-2.284*	(-4.257, -0.27)
>12 months	-4.276*	(-6.04, -2.479)
Disabled (reference: No)		
Yes	18.246*	(15.142, 21.422)
Serum Albumin (reference: 3.5 g/dL <=album<6 g/dL)		

0.6 g/dL <=album<3g/dL	9.856*	(8.069, 11.672)
3g/dL <=album<3.5 g/dL	4.248*	(2.603, 5.919)
BMI	0.321*	(0.23, 0.411)
CCI score	2.501*	(2.337, 2.675)
Patient behavioral characteristics		
Current smoker (reference: No)		
Yes	-1.134	(-4.075, 1.898)
Presence of alcohol dependence (reference: No)		
Yes	-4.744	(-11.29, 2.296)
Presence of drug dependence (reference: No)		
Yes	7.004	(-3.555, 18.708)
Facility-level characteristics		
Unit affiliation (reference: independent)		
Chain	-0.469	(-2.508, 1.603)
Number of dialysis stations	0.000	(-0.08, 0.07)
Facility ownership (reference: Free-standing)		
Hospital-based	-4.496*	(-7.891, -0.965)
Profit designation (reference: No)		
Yes	-1.213	(-3.959, 1.603)
Network (reference: Trans-pacific)		
Network 1 (CT, ME, MA, NH, RI, VT)	1.258	(-3.111, 5.823)
Network 2 (NY)	-2.000	(-6.002, 2.173)
Network 3 (NJ, PR, VI)	2.316	(-1.853, 6.663)
Network 4 (DE, PA)	-11.130*	(-14.964, -7.124)
Network 5 (DC, MD, VA, WV)	-14.530*	(-17.979, -10.944)
Network 7 (FL)	-17.0818*	(-20.22, -13.817)
Network 8 (AL, MS, TN)	-14.273*	(-17.955, -10.426)
Network 9 (IN, KY, OH)	-19.940*	(-23.08, -16.682)
Network 10 (IL)	-11.636*	(-15.253, -7.864)
Network 11 (MI, MN, ND, SD, WI)	-13.972*	(-17.684, -10.102)
Network 12 (IA, KS, MO, NE)	-14.050*	(-17.42, -10.542)
Network 13 (AR, LA, OK)	-21.156*	(-24.369, -17.799)
Network 14 (TX)	-19.660*	(-22.941, -16.239)
Network 15 (AZ, CO, NV, NM, UT, WY)	-15.583*	(-18.592, -12.453)
Network 16 (AK, ID, MT, OR, WA)	-18.143*	(-21.424, -14.726)
Network 17 (AS, Guam, HI, Mariana Islands, Northern CA, Southern CA)	-16.431*	(-20.06, -12.637)

Table 4. Adjusted cumulative 3-year Medicare expenditure by initial dialysis type and dialysis modality pattern

	Mean	95% CI	P-value
Intent-to-treat			
HD	$ 268,821	$ 266,839 – $ 270,790	<.0001
PD	$ 247,756	$ 241,784 – $ 253,876	
As-treated			
HD	$ 269,090	$ 267,079 – $ 271,143	
PD	$ 215,174	$ 208,647 – $ 221,926	<.0001
HD to PD, year 1	$ 222,615	$ 212,628 – $ 233,095	<.0001
HD to PD, year 2	$ 245,389	$ 228,159 – $ 263.893	0.0138
HD to PD, year 3	$ 272,638	$ 246,520 – $ 301,523	0.7653
PD to HD, year 1	$ 306,018	$ 286,731 – $ 326,603	0.0001
PD to HD, year 2	$ 305,254	$ 287,219 – $ 324,422	<.0001
PD to HD, year 3	$ 298,164	$ 280,127– $ 317,363	0.0013
More than one transfer	$ 293,637	$ 283,084 – $ 304,583	<.0001

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CONCLUSION

This study evaluated the impact of CMS expanded PPS on dialysis initiation timing and ESA utilization in pre-and post-dialysis initiation periods, and compared cumulative 3-year Medicare expenditures among different dialysis modalities. Our findings suggest that 1) expanded PPS may reduce the probability of early dialysis initiation and ESA utilization in the post-dialysis initiation period; 2) PD remains a better initial dialysis option than HD in terms of costs, however, patients who initiate PD and transfer to HD lose this economic advantage. This study has several limitations. First, we cannot exclude the alternative explanations that contributed to the patterns in dialysis initiation timing. Second, we may have underestimated costs because we captured costs only where Medicare was the primary payer. Third, we only considered conventional in-center HD and PD, so other types of dialysis modalities such as home-based HD and in-center self-HD were not included in our analysis. Finally, similar to all other observational studies, there were some unobservable confounding factors that we were not be able to adjust for. Future studies are needed to isolate the alternative explanations that contributed to the patterns in dialysis initiation timing, to assess how much of the ESA decrease in post-dialysis initiation period can be attributed to the expanded PPS, and to evaluate the costs paid by other types of insurance for ESRD.

APPENDICES

Table S1 Patient level and facility level characteristics

Variable name	format	description	Source	Variable name in database
Patient demographics				
Age	Continuous	Age at first ESRD service	PATIENTS	INC_AGE
Race and ethnicity	Categorical 0 non-Hispanic White 1 non-Hispanic Black 2 Hispanic 3 others	Race and ethnicity of patient	PATIENTS, CMS-2728	RACE and ETHN
Gender	Categorical 0 female 1 male	Sex of patient	PATIENTS	SEX
Employment status	Categorical 0 unemployed 1 employed	Summarizes the patients employment status at time of 2728 filing	CMS-2728	EMPCUR
Median family income	Continuous		PATIENTS Census data	ZIPCODE
The percent of people with high school diploma	Continuous		PATIENTS Census data	ZIPCODE
Location of patient	Categorical 0 Large metro 1 Medium or Small metro 2 Micropolitan 3 Non-core		PATIENTS Census data	ZIPCODE
Patient clinical characteristics				
Disabled	Categorical 0 no 1 yes	Inability to transfer, Inability to ambulate	CMS-2728	COMO_INTRANS, NOAMBUL
Primary cause of ESRD	Categorical 0 diabetes 1 hypertension 2 Glomerulonephritis/cystic renal disease 3 others	Primary Cause of Renal Failure	CMS-2728	PDIS
Albumin	Categorical 0 albumin<3 g/dl 1 3g/dl <=albumin< 3.5g/dl 2 albumin≥3.5g/dl	Serum Albumin Value (g/dl).	CMS-2728	ALBUM
BMI	Continuous	Body Mass Index - Calculated	CMS-2728	BMI

Charlson comorbidity score	Continuous		Claims	
Pre-dialysis treatment	Categorical 0 no 1 <6 months 2>6-12 months 3 >12 months	Was patient under care of a nephrologist? If Yes,6-12 or >12 months; Was patient under care of a nephrologist?	CMS-2728	NEPHCARERANGE, NEPHCARE
Patient treatment characteristics				
Dialysis modality	Categorical 0 HD 1 PD 2 HHD	First ESRD event modality type	PATIENTS	FIRST_MODALITY
Patient behavioral characteristics				
Current smoker	Categorical 0 no 1 yes	Tobacco use (current smoker).	CMS-2728	COMO_TOBAC
Drug dependence	Categorical 0 no 1 yes	drug dependence	CMS-2728	COMO_DRUG,DRUG
Alcohol dependence	Categorical 0 no 1 yes	Alcohol dependence	CMS-2728	ALCOH, COMO_ALCHO
Facility level characteristics				
Unit affiliation	Categorical 0 independent 1 chain		Annual facility survey	Chain ID
Non- profit status	Categorical 0 non-profit 1 profit	Type of facility	annual facility survey	SURVCERT
Facility ownership	Categorical 0 free-standing 1 hospital-based	Type of ownership	annual facility survey	TYPOWNER
Network membership	Continuous	ESRD Network Number	annual facility survey	NETWORK
Number of dialysis station	Categorical 1 New England; 2 New York; 3 Trans-Atlantic R.C.; 4 PA and DE; 5 Mid Atlantic R. C.; 6 Southeastern Kidney Council; 7 Florida; 8 AL,MS and TN; 9 Tri-state R. N.; 10 Illinois; 11 Upper Midwest; 12 IA,KS,MO and NE; 13 AR,LA,and OK; 14 Texas; 15 Inter-mountain; 16 Northwest	Total Number of Dialysis Stations	annual facility survey	TOTSTAS

	Renal Net; 17 Trans-pacific and South California			

Figure S1 The unadjusted percentage of ESAs use in the 6-month prior to dialysis initiation

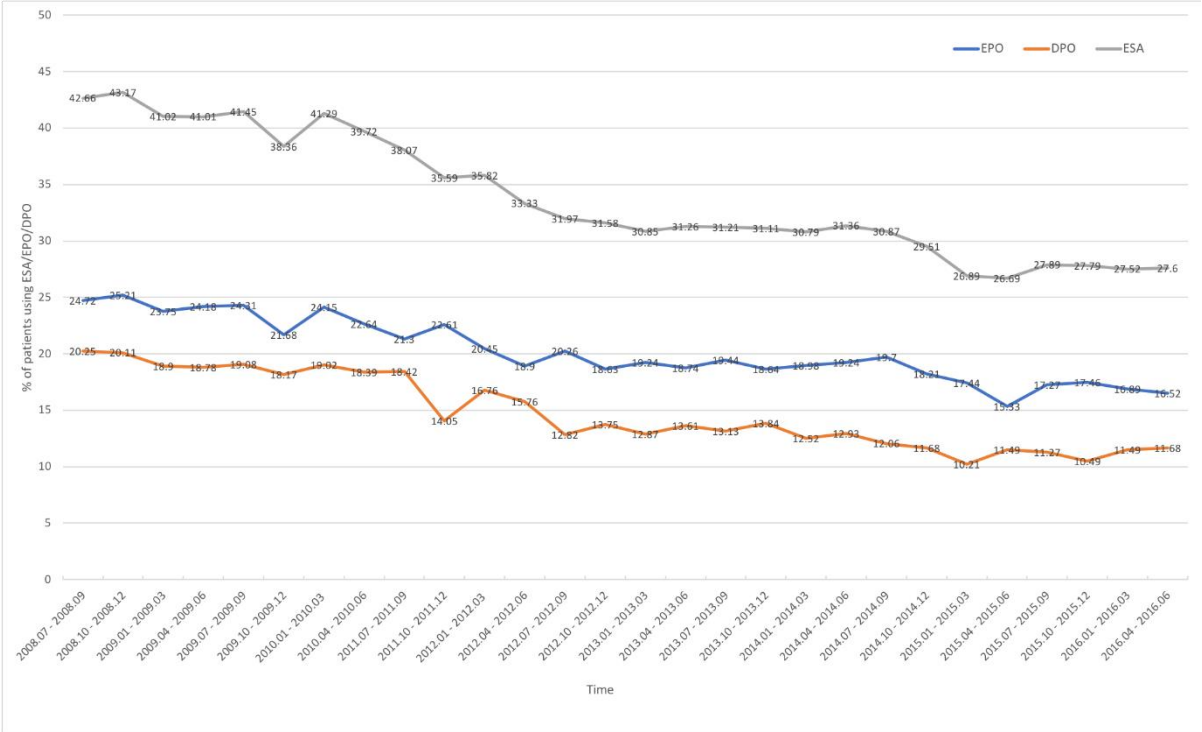
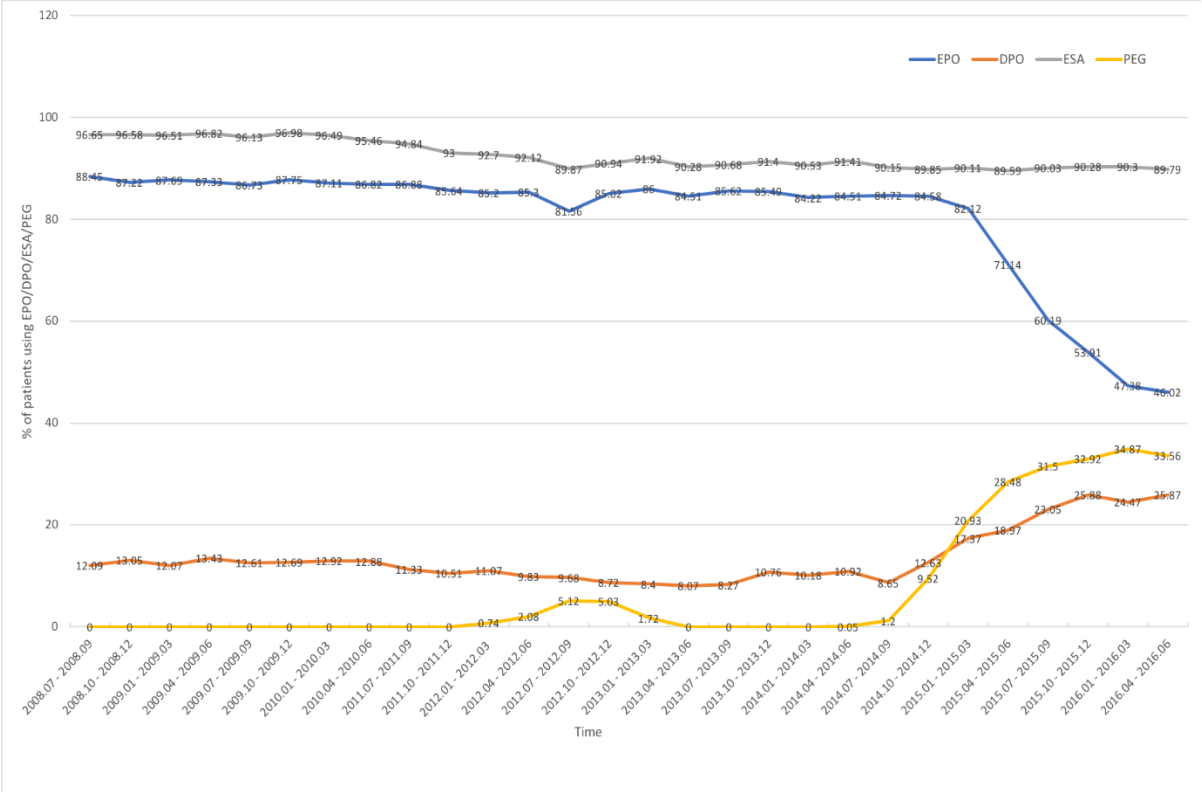


Figure S2 The unadjusted percentage of ESAs use in the 6-month following dialysis initiation



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